OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Proposition 65

Evidence on the Carcinogenicity of Bisphenol A (BPA)

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

Proposition 65[1] requires the publication of a list of chemicals "known to the state" to cause cancer or reproductive toxicity. The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency maintains this list in its role as the lead agency for implementing Proposition 65. The Carcinogen Identification Committee (CIC) advises and assists OEHHA, and adds chemicals to the Proposition 65 list of chemicals that cause cancer, as required by Health and Safety Code section 25249.8.

The CIC serves as the state's qualified experts for determining whether a chemical has been clearly shown to cause cancer. The CIC also provides advice and consultation regarding which chemicals should receive their review. At their meeting in November 2020, the CIC recommended that Bisphenol A (BPA) be placed in the 'high' priority group for future listing consideration. OEHHA selected BPA for consideration for listing by the CIC, and in January 2022 OEHHA solicited from the public information relevant to the assessment of the evidence on its carcinogenicity. OEHHA reviewed and considered the information received in preparing this document.

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

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LIST OF ABBREVIATIONS

Abbreviation	Full name
14C-BPA	Radiocarbon-labeled BPA
3-OH-BPA-N7-Ade	3-Hydroxy-bisphenol A-N7-adenine
3-OH-BPA-N7Gua	3-Hydroxy-bisphenol A-N7-guanine
4-OHT	4-Hydroxytamoxifen
5hmC	5-Hydroxymethylcytosine
5mC	5-Methylcytosine
8-OHdG	8-Hydroxydeoxyguanosine or 8-Oxo-7,8-dihydro-2'-deoxyguanosine
8-OHG	8-Oxo-7,8-dihydroguanosine
8-oxoG	8-Oxoguanosine
8-oxoGua	8-Oxoguanine
95% CI	95% Confidence Interval
β	Regression coefficient
γ-H2AX	H2A histone family member X phosphorylated on serine 139
µg	Micrograms
µg/day	Micrograms per day
µg/g	Micrograms per gram
µg/kg	Micrograms per kilogram
µg/kg-day	Micrograms per kilogram per day
µg/l	Micrograms per liter
µg/ml	Micrograms per milliliter
µIU/ml	Micro international units per milliliter
µl	Microliters
µM	Micromolar
µmol/l	Micromoles per liter
µmol/mol	Micromoles per mole
ACS	American Cancer Society
ADHD	Attention deficit hyperactivity disorder
AhR	Aryl hydrocarbon receptor
AML	Acute myeloid leukemia
APE-1	Apurinic/apyrimidinic endonuclease 1
ARF6	ADP ribosylation factor 6
ASC	Human adipose stromal/stem cells

Abbreviation	Full name
AUC	Area under the curve
[B]	Benign
BER	Base excision repair
BEST	Biomonitoring exposures study
BMI	Body mass index
BPA	Bisphenol A
BPA-DS	BPA-disulfate
BPA-G	Bisphenol A glucuronide
BPAQ	Bisphenol-3,4-quinone or BPA-*o*-quinone
BPA-S	Bisphenol A sulfate
BRCA	BReast CAncer gene
BW	Body weight
CAR	Constitutive androstane receptor
CARE-2	California regional exposure study 2
CAS RN	Chemical Abstracts Service Registry Number
CAT	Catalase
CD	Crohn's disease
CGIs	CpG islands
CHO	Chinese hamster ovary
CIC	Carcinogen Identification Committee
CLARITY-BPA	The Consortium Linking Academic and Regulatory Insights on Bisphenol A (BPA) Toxicity
CLL	Chronic lymphocytic leukemia
cm^3	Cubic centimeters
Cmax	Maximum concentration/Peak concentration (in the plasma or other tissues)
CNV	Copy number variant
CompTox Chemical Dashboard	Computational Toxicology Chemicals Dashboard
Con A	Concanavalin A
COX-2	Cyclooxygenase 2
CPD	Cyclobutene pyrimidine dimers
CpG	Cytosine-phosphate-guanine
CRP	C-reactive protein
CYP	Cytochrome P450
d6-BPA or d16-BPA	Deuterated BPA

Abbreviation	Full name
dA	Deoxyadenine
DCIS	Ductal carcinoma in situ
DES	Diethylstilbestrol
dG	Deoxyguanosine
dGMP	Deoxyguanosine monophosphate
DHPN	N-*bis*(2-hydroxy propyl) nitrosamine
DHT	Dihydrotestosterone
DLP	Dorsolateral prostate
DMAB	3,2'-dimethyl-4-aminobiphenyl
DMBA	7,12-Dimethylbenz(a)anthracene
DMP	Differentially methylated position
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DNMT	DNA methyltransferase
DOX	Doxycycline
dpf	Days post fertilization
E_2	Estradiol or 17β-estradiol
EE_2	Ethinyl estradiol
EFSA	European Food Safety Authority
ELISA	Enzyme-linked immunosorbent assay
EMT	Epithelial-to-mesenchymal transition
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Estrogen receptor
EREs	Estrogen response elements
ERRγ	Estrogen-related receptor-gamma
ESR1, ERα	Estrogen receptor 1, estrogen receptor-alpha
ESR2, ERβ	Estrogen receptor 2, estrogen receptor-beta
EZH2	Enhancer of Zeste homolog 2
F	Female
F0	Parental generation
F1	First filial generation
F344	Fischer 344
FD	Fluorescence detection
FMV	First morning void

Abbreviation	Full name
FOX	Firefighter occupational exposures project
Fpg	Formamidopyrimidine DNA glycosylase
FXR	Farnesoid X receptor
g/mol	Grams per mole
GD	Gestation day
GHR	Growth hormone receptor
GPER/GPR30	G-protein coupled estrogen receptor
GPx	Glutathione peroxidase
GR	Glucocorticoid receptor
GR	Glutathione reductase
GSH	Glutathione, reduced form
GSSG	Glutathione disulfide
GST	Glutathione-S-transferase
GSTP1	Glutathione S-transferase pi 1
H2O2	Hydrogen peroxide
HATs	Histone acetyltransferases
HAWC	Health Assessment Workspace Collaborative
HCA	Hydroxycoumarylalcohol
hCGC	Human cumulus granulosa cells
HDAC	Histone deacetylase
HDMs	Histone lysine demethylases
HESC	Human endometrial stroma cells
HGF	Human gingival fibroblast
hMSCs	Human mesenchymal stromal stem cells
HMTs	Histone lysine methyltransferases
HOX	Homeobox containing genes
HPA-v	Human visceral preadipocytes
HPLC-MS/MS	High-performance liquid chromatography/tandem mass spectrometry
HR	Hazard Ratio
HRT	Hormone replacement therapy
hs-CRP	High-sensitivity C-reactive protein
hUM-MSC	Human uterine myoma mesenchymal stem cells
HUVEC	Human umbilical vein endothelial
i.p.	Intraperitoneal

Abbreviation	Full name
i.v.	Intravenous
IAP	Intracisternal A-particle
IARC	International Agency for Research on Cancer
IFN-α	Interferon alpha
IFN-γ	Interferon gamma
IgM	Immunoglobulin M
IL	Interleukin
iMDDCs	Immature monocyte-derived dendritic cells
iNOS	Inducible nitric oxide synthase
IPP	Isopropenylphenol
IQR	Interquartile range
JEM	Job exposure matrix
JNK	c-Jun N-terminal kinase
KCs	Key characteristics
kg	Kilogram
Kow	Octanol-water partition coefficient
LBD	Ligand binding domain
LC	Liquid chromatography
LC-HRAMMS	Liquid chromatography high-resolution accurate-mass mass spectrometry
LC-MS	Liquid chromatography coupled with mass spectrometry
LINEs	Long interspersed nucleotide elements
lncRNA	Long non-coding RNA
LOD	Limit of detection
LOQ	Limit of quantitation
LOX-2	Lipoxygenase-2
LP	Lateral prostate
LTRs	Long terminal repeats
LXR	Liver X receptor
[M]	Malignant
M	Male
MAPKs	mitogen activated protein kinases
MBP	4-Methyl-2,4-bis(p-hydroxyphenyl)pent-1-ene
MDA	Malondialdehyde
MEF	Mouse embryonic fibroblasts

Abbreviation	Full name
mg/animal-day	Milligrams per animal per day
mg/day	Milligrams per day
mg/dl	Milligrams per deciliter
mg/g	Milligrams per gram
mg/kg	Milligrams per kilogram
mg/kg bw	Milligrams per kilogram body weight
mg/kg-day	Milligrams per kilogram per day
mg/kg-week	Milligrams per kilogram per week
mg/l	Milligrams per liter
mg/ml	Milligrams per milliliter
MIEEP	Maternal and infant environmental exposure project
miRNA, miR	microRNA
MLH1	MutL homolog 1
MLL	Mixed lineage leukemia family of histone methyltransferases
mm^3	Cubic millimeters
mmHg	Millimeters of mercury
MMS	Methyl methanesulfonate
MMTV	Mouse mammary tumor virus
MN	Micronuclei
MNU	Methylnitrosourea
mol/l	Moles per liter
MPP	methyl-piperidinopyrazole
mRNA	messenger RNA
MRP	Multidrug resistance-associated protein
MS	Mass spectrometry
NBS1	Nijimegen breakage syndrome 1
NCTR	National Center for Toxicology Research
NF-κB	Nuclear Factor Kappa B
ng/µl	Nanograms per microliter
ng/dl	Nanograms per deciliter
ng/g	Nanograms per gram
ng/kg	Nanograms per kilogram
ng/kg-day	Nanograms per kilogram per day
ng/l	Nanograms per liter

Abbreviation	Full name
ng/mg	Nanograms per milligram
ng/ml	Nanograms per liter
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute of Occupational Safety and Health
NK	Natural killer
nM	Nanomolar
nmol/l	Nanomoles per liter
nmol/min/mg	Nanomoles per minute per milligram
NO	Nitric oxide
NOD	Non-obese diabetic
NOES	National Occupational Exposure Survey
NOS	Not otherwise specified
NR	Not reported
NS	Not significant
NSCLC	Non-small cell lung cancer
NTP	National Toxicology Program
ºC	Degrees Celsius
OEHHA	Office of Environmental Health Hazard Assessment
OGG1	8-Oxoguanine glycosylase
OH-BPA	Hydroxylated BPA
OR	Odds ratio
OVA	Ovalbumin
PAR	Poly(ADP-ribose)
PARP-1	Poly(ADP-ribose) polymerase 1
PBMC	Peripheral blood mononuclear cells
PBPK	Physiologically-based pharmacokinetic
PCM	Peritoneal cavity macrophage
PCNA	Proliferating cell nuclear antigen
PCOS	Polycystic ovarian syndrome
pctl	Percentile
PIN	Prostatic intraepithelial neoplasia
PKD1	Protein kinase D1
pM	Picomolar

Abbreviation	Full name
PMA	Phorbol-12-myristate-13-acetate
pmol	Picomoles
PND	Postnatal day
PPAR	Peroxisome proliferator activated receptor
ppb	Parts per billion
PPD	Periurethral prostatic ducts
ppm	Parts per million
PPRE	Peroxisome proliferator response element
PR	Progesterone receptor
PTU	6-Propyl-2-thiouracil
PVC	Polyvinyl chloride
PXR	Pregnane X receptor
QC	Quality control
qPCR	Quantitative polymerase chain reaction
r	Correlation coefficient
R	Rare
Ral	Raloxifene
RAR	Retinoic acid receptor
RCE	Relative cloning efficiency
RNA	Ribonucleic acid
RNS	Reactive nitrogen species
RoC	Report on Carcinogens
RoR	Retinoic acid receptor-related orphan receptor
ROS	Reactive oxygen species
RPE	Relative plating efficiency
RR	Relative risk
RTL	Relative telomere length
RXR	Retinoid x receptor
s.c.	Subcutaneous
SCE	Sister chromatid exchange
SD (NCTR)	NCTR Sprague-Dawley/CD23/Nctr BR
SD rats	Sprague-Dawley rats
SHE	Syrian hamster embryo
SINEs	Short interspersed nuclear elements

Abbreviation	Full name
SMD	standardized mean difference
SOD	Superoxide dismutase
STZ	Streptozotocin
SULT	Sulfotransferase
SXR	Steroid and xenobiotic receptor
T	Testosterone
T1/2	Half-life
T3	Triiodothyronine
T4	Thyroxine
TAMs	Tumor-associated macrophages
TEB	Terminal end bud
TERT	Telomerase reverse transcriptase
TET	Ten-eleven translocation
TGF-β	Transforming growth factor beta
Tmax	Time needed to reach peak concentration
TNF-α	Tumor necrosis factor alpha
TR	Thyroid hormone receptor
TRI	Toxics Release Inventory
TSH	Thyroid stimulating hormone
UDS	Unscheduled DNA synthesis
UGT	Uridine-5'-diphospo-glucuronosyltransferase
UHPLC-HRMS	Ultrahigh-performance liquid chromatography-high-resolution mass spectrometry
UHPLC-MS/MS	Ultrahigh-performance liquid chromatography with tandem mass spectrometry detection
UK	United Kingdom
US	United States
US EPA	United States Environmental Protection Agency
Vmax	Maximum velocity of an enzymatic reaction
VP	Ventral prostate
XRCC1	X-ray repair cross-complementing protein 1

SUMMARY

This document presents evidence relevant to the evaluation of the cancer hazard of bisphenol A (BPA). BPA was placed in the 'high' priority group for future listing consideration by the Carcinogen Identification Committee (CIC) at their November 2020 meeting.

BPA is a high-production-volume chemical with a wide range of consumer and industrial applications. Most BPA is used in the production of polycarbonate plastics and epoxy resins, though BPA is also used in the production of a variety of other materials. BPA can be considered ubiquitous, with levels measured in environmental media, biota, and humans. Humans are exposed to BPA predominantly through contaminated food and drinking water, with additional exposures from ingestion of dust, inhalation of indoor and outdoor air, and dermal contact with certain materials. Biomonitoring studies have shown that BPA is readily detected in Californians, though both detection frequency and levels have decreased in recent years as some uses of BPA have been reduced or prohibited. See Sections 1.2 and 1.3 for additional information on BPA sources and exposure, and Appendix A for select recent biomonitoring studies in California.

Systematic Literature Review Approach

Using a systematic approach similar to that used by the National Toxicology Program (NTP) for its Report on Carcinogens (NTP 2015), the Office of Environmental Health Hazard Assessment (OEHHA) conducted literature searches on the carcinogenicity of BPA (last comprehensive search, December 2021). The literature searches included primary searches in major biomedical databases, searches in other data sources such as reports by other health agencies, and additional focused searches. The literature searches were supplemented with a public data call-in period from January 28 to March 14, 2022. An overview of the systematic literature review approach is presented in Section 2, and more detailed information can be found in Appendix B.

Carcinogenicity Studies in Humans

Considerations for interpreting the epidemiologic evidence on BPA and cancer

The general population is likely to have been exposed to BPA across all life stages due to decades of extensive use in numerous consumer products. The level of BPA in the body varies over time and even over the course of a single day due to its short biological half-life and frequent exposures from multiple sources. Thus, BPA

measurement at a single point in time likely does not represent an individual's long term BPA exposure.

Most epidemiologic studies estimated BPA exposure from a single biological sample collected at a single point in time, and none collected samples longitudinally. Therefore, the measured BPA levels may not reflect levels in the time window relevant for cancer causation. In addition, BPA was detected in biological samples at low frequencies in some of these studies, and the approaches taken in handling data where BPA was not detected, such as imputing BPA levels or omitting individuals with non-detectable levels can introduce bias in exposure characterization.

Long-term exposure to BPA was estimated through questionnaires or a job exposure matrix in a few studies that also had limitations. Questionnaire responses have not been found to correlate well with measured urinary BPA levels, and the use of a job exposure matrix is of limited utility given widespread exposure to BPA from non-occupational sources.

Additional limitations of the studies reviewed were the inability to establish a temporal association when BPA was measured in biological samples collected at or after a cancer diagnosis, the potential for reverse causation, and the inclusion of prevalent cases in cross-sectional studies.

Summary of the epidemiologic evidence on BPA and cancer

The majority of the epidemiologic studies on the carcinogenicity of BPA investigated breast cancer. All but one of the breast cancer studies measured BPA in biological matrices (urine, serum, and breast adipose tissue), and were limited by the collection of a single biological sample at one point in time. One study used a job exposure matrix, but had limited ability to detect an effect because non-occupational sources, which contribute highly to BPA exposure, were not assessed. Results were inconsistent, though some positive associations were observed in case-control studies that measured BPA in urine, the two studies that measured BPA in breast adipose tissue reported an increase in risk in one and a decrease in the other, and the two studies that measured BPA in serum reported non-statistically significant increases in risk.

For prostate cancer, all of the three studies reviewed reported positive associations. A case-cohort analysis from Spain measured BPA in serum samples collected before disease onset, but was limited by the potential for significant exposure measurement error due to collection of a single sample and because more than a quarter of the samples were below the limit of detection and thus a level was imputed for the analyses. A hospital-based case-control study from Hong Kong reported an exposure-response trend for cumulative BPA exposure from diet estimated retrospectively from questionnaires, but other sources and routes of exposure were not considered. A cross-sectional study among urology patients in Ohio did not provide a risk estimate but

observed significantly higher urinary BPA levels in prostate cancer patients than in urology patients without prostate cancer, based on a single urine measurement at the time of diagnosis.

Positive associations between BPA and thyroid cancer were reported in two cross-sectional studies from Italy and China (Zhou et al. 2017c), but interpretation was limited by collection of a single biological sample, the use of prevalent cases, and the lack of reporting on quality control measures or limit of detection.

For other cancer sites (endometrium, bone, lymphohematopoietic system, lung, brain, bile duct/gallbladder, eye, and all-cancer mortality), there was only one published study that reported measures of association with BPA.

See Section 3 for more detailed information on carcinogenicity studies in humans.

Carcinogenicity Studies in Animals

Tumor findings from animal carcinogenicity studies

Carcinogenicity studies of BPA have been conducted in male and female F344 rats, female SD rats, male and female SD (NCTR) rats, female Wistar-Furth rats, male and female B6C3F1 mice, male and female Agouti$^{+/-}$ C57BL/6J:C3H/HeJ mice, female CD-1 mice, and male gerbils. Statistically significant tumor findings are as follows:

- Alimentary system: Hepatocellular tumors in male SD (NCTR) rats, and female Agouti$^{+/-}$ C57BL/6J:C3H/HeJ mice
- Endocrine system: Pituitary tumors in female F344 rats and male B6C3F1 mice; thyroid C-cell tumors in male SD (NCTR) rats
- Mammary gland: Fibroadenoma in male F344 rats; adenocarcinoma, and adenoma and adenocarcinoma combined in female SD (NCTR) rats
- Reproductive system (female): Clitoral gland tumors and uterine stromal polyps in female SD (NCTR) rats
- Reproductive system (male): Testicular interstitial (Leydig) cell tumors in male F344 rats
- Lymphohematopoietic system: Leukemia in male F344 rats, lymphoma in male SD (NCTR) rats and male B6C3F1 mice

In addition, multiple types of rare tumors were observed in several studies in male and female SD (NCTR) rats. Here is some more detailed information on the animal tumor findings.

Tumors in male F344 rats

- In the 103-week feeding study in BPA-treated male F344 rats, the incidence of mammary gland fibroadenoma was significantly increased in the high-dose (2000 ppm) group by pairwise comparison with controls, with a significant dose-related trend (NTP 1982).
- In the 103-week feeding study in BPA-treated male F344 rats, the incidence of testicular interstitial (Leydig) cell tumors was significantly increased in both dosing groups (1000, 2000 ppm) by pairwise comparison with controls, with a significant dose-related trend (NTP 1982).
- In the 103-week feeding study in BPA-treated male F344 rats, the incidence of leukemia (NOS) was significantly increased in the high-dose (2000 ppm) group by pairwise comparison with controls, with a significant dose-related trend (NTP 1982).

Tumors in female F344 rats

- In the 12-week oral study in BPA-treated female F344 rats, the incidence of pituitary tumors, likely adenomas of the adenohypophysis, was significantly increased in the low-dose group (50 mg/kg-day) (Hao et al. 2016).

Tumors in male SD (NCTR) rats

- In the two-year continuous-dose study in male SD (NCTR) rats exposed to BPA *in utero* and from PND1 until study termination (CLARITY-BPA core study #8), the incidence of rare hepatocellular carcinoma was increased with a significant dose-related trend (NTP 2018).
- In the two-year stop-dose study in male SD (NCTR) rats exposed to BPA *in utero* and via gavage from PND1 to PND21 (CLARITY-BPA core study #4), the incidence of thyroid gland C-cell adenoma was increased with a significant dose-related trend (NTP 2018).
- In the two-year stop-dose study in male SD (NCTR) rats exposed to BPA *in utero* and via gavage from PND1 to PND21 (CLARITY-BPA core study #4), the incidence of malignant lymphoma of the prostate (dorsal/lateral lobes) was significantly increased in the high-dose group (25000 µg/kg-day) by pairwise comparison with controls, with a significant dose-related trend. The incidence of malignant lymphoma from all sites was increased with a significant dose-related trend (NTP 2018).
- In the one- and two-year studies in male SD (NCTR) rats exposed to BPA *in utero* and after birth for different lengths of time (arms 2, 4, 6, and 8 in CLARITY-BPA core study), multiple types of rare tumors were observed in multiple organs

in treated groups in each of the study arms except for arm #6 where only one rare tumor type was observed, with none in concurrent controls (NTP 2018).

Tumors in female SD (NCTR) rats

- In the two-year stop-dose study in female SD (NCTR) rats exposed to BPA *in utero* and via gavage from PND1 to PND21 (CLARITY-BPA core study #3), the incidence of adenocarcinoma of the mammary gland, and the incidence of adenoma and adenocarcinoma combined was each significantly increased in the 2.5 µg/kg-day group (NTP 2018).
- In the one-year continuous-dose study in female SD (NCTR) rats exposed to BPA *in utero* and from PND1 until study termination (CLARITY-BPA core study #5), the incidence of uterine stromal polyps was increased with a significant dose-related trend (NTP 2018).
- In the two-year continuous-dose study in female SD (NCTR) rats exposed to BPA *in utero* and from PND1 until study termination (CLARITY-BPA core study #7), the incidence of clitoral gland adenoma, and adenoma and carcinoma combined was each increased with a significant dose-related trend (NTP 2018).
- In the one- and two-year studies in male SD (NCTR) rats exposed to BPA *in utero* and after birth for different lengths of time (arms 1, 3, 5, and 7 in CLARITY-BPA core study), multiple types of rare tumors were observed in multiple organs in treated groups in each of the study arms (NTP 2018).

Tumors in male B6C3F1 mice

- In the 103-week feeding study in BPA-treated male B6C3F1 mice, the incidence of chromophobe carcinoma of the pituitary gland was increased in the high-dose group (5000 ppm), with a significant dose-related trend (NTP 1982).
- In the 103-week feeding study in BPA-treated male B6C3F1 mice, the incidence of malignant lymphoma, and malignant lymphoma and lymphocytic leukemia combined was significantly increased in the low-dose group (1000 ppm) by pairwise comparison with controls (NTP 1982).

Tumors in female Agouti$^{+/-}$ C57BL/6J:C3H/HeJ mice

- In the 10-month study in female Agouti$^{+/-}$ C57BL/6J:C3H/HeJ mice exposed to BPA *in utero* and via lactation, then in feed from post-weaning until study termination, the incidence of hepatocellular adenoma and carcinoma combined was significantly increased in the high-dose group (50 ppm), with a significant dose-related trend (Weinhouse et al. 2014).

Tumor findings from additional animal studies

Studies using transgenic animal models

- In a female mouse mammary tumor model (MMTV-erbB2), BPA exposure (two lowest doses) reduced the median time to an animal's first mammary tumor, significantly increased mammary tumor multiplicity, increased mammary tumor volume (second lowest dose), and significantly increased lung metastases of mammary tumors (Jenkins et al. 2011).
- In a different study using the female mouse MMTV-erbB2 model, *in utero* exposure to BPA (two lowest doses) decreased tumor latency in females (statistically significant for one dose) (Ma et al. 2020).
- In a transgenic mouse model (male and female combined) with an estradiol non-responsive mutant estrogen receptor (ER)-α ligand binding domain, BPA induced "tumor-like outgrowths" in the flank muscle in six out of 15 mice (Sekar et al. 2016). Two of these six "outgrowths" were confirmed as adenocarcinomas.

Studies in xenograft, syngeneic, and regenerated organ mouse models

- Exposure to BPA starting before introduction of the xenograft increased the number of tumor-bearing mice, mean tumor volume or tumor weight following injection with human breast cancer cell lines (Kim et al. 2019a; Merzoug-Larabi et al. 2019; Weber Lozada and Keri 2011).
- Exposure to BPA after introduction of the xenograft promoted growth of established tumors with several human cancer cell lines (Hwang et al. 2013; Lee et al. 2017b; Wetherill et al. 2006; Xu et al. 2017; Zhu et al. 2009).
- Exposure to BPA starting before or at the same as introduction of syngeneic mouse cancer cells increased the resulting tumor volume (Jun et al. 2021; Nava-Castro et al. 2019; Palacios-Arreola et al. 2017).
- Exposure to BPA increased the incidence of atypical ductal hyperplasia and ductal carcinoma *in situ* in regenerated mammary glands (Wang et al. 2014a).

Studies of BPA in combination with other treatments

- In studies of BPA administered before treatment with a model carcinogen in rats and mice, statistically significant increases in tumor incidence and/or tumor multiplicity were observed in mammary glands of female rats (Betancourt et al. 2010; Jenkins et al. 2009; Leung et al. 2017; Varuzza et al. 2019) and statistically significant decreases in mammary tumor latency were observed in female rats and mice (Betancourt et al. 2010; Jenkins et al. 2009; Leung et al. 2017; Weber Lozada and Keri 2011).

- In studies of BPA administered before testosterone and 17β-estradiol treatment in male rats, statistically significant increases of microinvasive carcinoma and prostatic intraepithelial neoplasia (total PIN or high grade PIN) of the prostate were observed (Prins et al. 2011; Prins et al. 2017).
- In the study of BPA administered after tumor initiation in female rats using a mammary gland carcinogenesis model, BPA significantly increased tumors in the mammary gland (Zhang et al. 2021b).

See Section 4 for more detailed information on carcinogenicity studies in animals.

Mechanistic Considerations and Other Relevant Data

Pharmacokinetics and metabolism

BPA is rapidly absorbed in humans by the oral and dermal routes and is distributed throughout the body, crossing the blood-brain barrier and the placenta. The half-life of BPA in humans exposed by the oral route is around six hours. Excretion is also rapid and occurs primarily via urine in humans and other primates; in rodents, the main route of excretion is via feces. BPA undergoes enterohepatic circulation in rats and possibly mice, but not in humans or other primates. Despite rapid elimination, BPA is routinely detected in more than 90% of human urine samples, suggesting frequent repeated exposures, likely from multiple sources. Adipose tissues may serve as a reservoir to store BPA. The metabolism of BPA occurs primarily via conjugation, leading to the formation of BPA glucuronide and BPA-sulfate. The extent of conjugative metabolism is determined by life stage, co-exposure to xenobiotics and drugs, certain diseases, and polymorphisms of conjugative enzymes. A secondary metabolic pathway, oxidative metabolism, leads to the formation of several electrophilic, reactive, and estrogenic metabolites, as well as to the formation of reactive oxygen species, 8-hydroxydeoxyguanosine (8-OHdG) and other DNA adducts. See Section 5.1 for more detailed information on pharmacokinetics and metabolism.

Key characteristics of carcinogens

The key characteristics (KCs) of carcinogens were used to organize the data relevant to carcinogenicity from mechanistic studies of BPA. KCs are characteristics of agents that cause cancer, and can encompass many types of mechanistic endpoints. OEHHA uses this approach to systematically identify, organize, and summarize mechanistic information. The evidence from studies of BPA related to the 10 KCs of carcinogens is summarized here. See Section 5.3 for more detailed summaries of data relevant to the KCs of carcinogens.

Is electrophilic or can be metabolically activated

BPA can be metabolized by CYP enzymes and peroxidases to form electrophilic compounds, including BPA-3,4-quinone (BPAQ); its semi-quinone intermediate; an arene epoxide intermediate; an isopropenylphenol radical (which can form 4-methyl-2,4-bis(p-hydroxyphenyl)pent-1-ene, an estrogenic metabolite of BPA); and an unidentified electrophilic compound (which leads to dimerization of BPA). The metabolite BPAQ can form DNA adducts which have been identified as 3-hydroxy-bisphenol A-N7-guanine and 3-hydroxy-bisphenol A-N7-adenine. Several studies have reported the formation of DNA adducts in various systems including human *in vitro*, animal *in vivo* and *in vitro*, and cell-free systems.

BPA also induces oxidative lesions in DNA (measured as 8-OHdG), presumably through the formation of reactive oxygen species or BPAQ. The formation of 8-OHdG associated with BPA exposure has been reported in several human observational studies as well as in animal *in vivo* and *in vitro* studies. In addition, BPA can bind to cysteine residues of proteins and form protein adducts in the rat *in vivo* and in a cell-free system.

Is genotoxic

Overall, there are many studies (including studies in humans) reporting DNA damage with exposures to noncytotoxic concentrations of BPA, some studies reporting chromosomal effects, and a few studies reporting BPA-induced mutagenicity.

BPA induced mutations in a normal human cell culture and an immortalized cell line *in vitro* and in male rats *in vivo*, but not in bacteria or yeast. The mutagenicity of BPA has not been well studied in systems other than bacteria and yeast.

Several chromosomal effects induced by noncytotoxic concentrations of BPA were observed in many studies. One study in exposed humans showed a marginally positive association ($p = 0.059$) between urinary BPA levels and sister chromatid exchange frequency in peripheral blood lymphocytes collected from over a hundred Korean men and women. A number of *in vitro* studies in human cells and in animal cells, and *in vivo* studies in rodents and other animals have reported increases in micronuclei, chromosomal aberrations, and various types of chromosomal abnormalities following BPA treatment. Three studies showed that BPA significantly increased chromosomal aberrations in plants. Two studies showed that BPA induced microtubule abnormalities in acellular systems.

A substantial amount of data on BPA-induced DNA damage are available. More than ten human observational studies reported statistically significant associations between BPA and urinary or serum levels of 8-OHdG or 8-oxo-7,8-dihydroguanosine, biomarkers of oxidative damage to DNA. Two human observational studies reported positive

associations between urinary BPA concentration and sperm DNA fragmentation. Increases in DNA adduct formation, DNA strand breaks, oxidative damage to DNA, and γ-H2AX (histone 2AX phosphorylated at serine 139) were observed in multiple experimental systems treated with noncytotoxic concentrations of BPA, *i.e.*, human cells *in vitro*, animals *in vivo*, animal cells *in vitro*, and acellular systems. Increases in expression of proteins associated with DNA damage-control were observed in two studies in human cells *in vitro* and in one study in animals *in vivo*.

Alters DNA repair or causes genomic instability

Overall, a small number of studies have evaluated the ability of BPA to alter DNA repair or cause genomic instability. A few studies found that BPA decreased capacity to repair various types of DNA damage in human peripheral blood mononuclear cells, human MELN cells, mouse peritoneal macrophages, and mouse embryonic fibroblasts. Three studies found decreased expression of DNA repair enzymes (MyH, TP53, *mlh1*) and one study found small changes in copy number variants.

Induces epigenetic alterations

Overall, there is evidence from many studies that BPA exposure can induce epigenetic effects or effects on gene or protein expression that may be caused by epigenetic changes. Human observational studies in fetal tissue, mother-child pairs, children, and adults reported associations between BPA levels and altered methylation of many genes related to cancer pathways, as well as altered global DNA methylation. Similarly, BPA exposure to human cells *in vitro* altered methylation of individual genes and global methylation status. Other epigenetic effects, such as expression of microRNAs, overexpression of DNA methyltransferases, and histone modifications, were found to be altered in many studies in human cells *in vitro*. All of these observations are also supported by studies in non-human mammals *in vivo*, mammalian cells *in vitro*, and fish.

Induces oxidative stress

Evidence for BPA-induced oxidative stress comes from consistent findings in multiple biomarkers from many recent human and animal *in vivo* and *in vitro* studies. Notably, BPA consistently induces oxidative damage to DNA (measured as 8-OHdG) and increases reactive oxygen or nitrogen species production in numerous studies from human observational studies, studies using human cells *in vitro*, and rodent studies *in vivo* and *in vitro*, with concentration- or dose-dependent relationships in some studies. In addition, increases in lipid peroxidation (measured as malondialdehyde or 8-isoprostane) and reductions in GSH and antioxidant enzyme activities or levels have been reported in recent reviews and primary research articles on BPA.

Induces chronic inflammation

Overall, inflammatory effects of BPA were observed in several human observational studies and in many animal studies.

Human cross-sectional studies found a positive association between BPA levels and inflammatory biomarkers such as C-reactive protein, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). One cohort study reported that BPA was positively associated with increased levels of IL-6 in pregnant women but the other cohort study in pregnant women did not report any significant association.

In animals, longer-term BPA exposure is associated with chronic inflammation, as evidenced by histopathology in many tissues including the liver, prostate, and lungs, and significant (sometimes dose-dependent) increases in levels of pro-inflammatory biomarkers. Most studies report statistically significant increases in IL-1β, IL-6, TNF-α, and other inflammatory biomarkers. One three-month study observed dose- and time-dependent increases in serum levels of TNF-α and IL-6 in Wistar rats with concomitantly observed tissue inflammation of pancreatic islet cells, with severity of inflammation increasing with the dose. Several other studies reported concurrent chronic inflammation and increases in pro-inflammatory biomarkers, while two studies reported a negative association between BPA exposure and these biomarkers.

Is Immunosuppressive

Overall, several studies report effects on cancer-related immunosuppressive effects of BPA. Several studies observed significantly decreased T-lymphocyte and B cell populations in spleen or lymph nodes in rodents *in vivo* and a few studies observed decreased proliferation in human cells *in vitro* after exposure to BPA. Decreased macrophage phagocytotic capacity was observed in studies in humans *in vitro*, animals *in vivo*, and animal *in vitro* systems. A few studies in primary human cells and rodents *in vivo* observed reduce chemotactic capacity of neutrophils. For dendritic cells, one study observed decreased endocytotic capacity in human cells, while another study in mice observed decreased numbers of cells in spleen mesenteric lymph nodes. One study found decreased levels of splenic natural killer cells in rats. Lastly, one study in mice and one study in juvenile rock bream reported decreased IgM levels after BPA exposure.

Modulates receptor-mediated effects

Estrogen receptors (ERs)

BPA is a well-recognized xenoestrogen that is known to mimic and interfere with the actions of estrogen. There is a large body of evidence from observational studies in humans, human cells *in vitro*, and animal studies *in vivo* and *in vitro* indicating that BPA

modulates ER-mediated effects through several different ER subtypes and their downstream signaling pathways. While it is well-known that BPA binds to cytosolic ERs and activates ER nuclear translocation and binding to estrogen response elements in DNA, additional ER-related activities of BPA have been identified.

These non-canonical ER activities of BPA may explain many observations that are unexpected solely based on the classical ER pathway, such as the rapid onset of extra-nuclear responses, the low-dose effects, and the non-monotonic dose-responses, with the latter two effects also echoing the female rat mammary tumor response seen in the CLARITY-BPA core study #3. For example, BPA's effects on membrane-associated estrogen receptors (mERs), G-protein coupled estrogen receptor (GPER/GPR30), and estrogen-related receptor gamma (ERRγ, an orphan nuclear receptor) may each alter different downstream genomic and non-genomic signaling pathways in a cell-type specific fashion. In addition to these examples, BPA can also induce epigenetic changes to regulate the expression of ERα, and cancer-related ER target genes.

Estradiol (E2)

Positive correlations between BPA levels and E2 were found in some studies in subpopulations from human observational studies, such as male partners in subfertile couples, girls and female adolescents, and newborns, but the majority of studies were inconsistent. Overall, the effects of BPA on E2 levels in human cells *in vitro* and in non-human mammals *in vivo* were also inconsistent. In non-human mammalian cells *in vitro*, exposure to BPA decreased E2 levels in studies of mouse and rat ovarian granulosa cells or follicles, increased E2 levels in most studies of pig granulosa cells and in one study of sheep granulosa cells, and decreased E2 levels in one study of boar testes.

Progesterone and progesterone receptor

BPA exposure was associated with an increase in expression of the progesterone receptor in some *in vitro* studies in human cells and the majority of *in vitro* studies in non-human mammalian cells, while findings in human observational studies and *in vivo* studies in animals were inconsistent. No consistent effects of BPA exposure on progesterone levels were observed in humans or animals, or cells *in vitro*.

Androgen receptor (AR)

Some positive associations between AR and BPA levels were observed in human observational studies in women while inconsistent results were reported in men. BPA exhibited antiandrogenic activity on human AR and interfered with AR nuclear translocation in several human *in vitro* studies. Expression of AR in various tissues from mammalian *in vivo* studies performed in mice, rats, and gerbils were inconsistent. BPA

also exhibited antiandrogenic activity on mammalian AR in a few studies while expression was either increased or not changed in mammalian *in vitro* studies.

Testosterone (T)

In human observational studies, a positive association between BPA exposure and T levels was observed in women and girls with polycystic ovary syndrome. No consistent findings between BPA and T were observed in other populations. In human *in vitro* studies, treatment with BPA decreased T levels in fetal and adult testes and adrenocortical carcinoma cells. In mammalian *in vivo* studies, BPA exposure consistently decreased serum, testicular, and brain T levels in male mice, but effects were inconsistent in female mice, male and female rats, and rabbits. In mammalian *in vitro* studies, the effect of BPA on T levels was inconsistent.

Thyroid hormones and thyroid hormone receptors (TRs)

In human cells *in vitro*, BPA exposure antagonized activity of thyroid hormone receptor β (TRβ) in several cell lines (*e.g.*, kidney, liver), had some agonistic activity in one study in liver cells, and had no activity in a study of kidney cells. No associations between BPA and thyroid hormone levels were consistently observed in human observational studies or in rats *in vivo*. No consistent effects of BPA on TR expression were observed in non-human mammalian cells *in vitro*.

Prolactin

Some positive associations were observed between BPA and prolactin levels in observational studies of occupationally exposed men and women. One study found a negative association between cord blood BPA and prolactin levels, while no associations were seen in other populations. BPA exposure increased prolactin levels in several rat studies.

Other nuclear receptors

- PPARα: In animals *in vivo,* BPA altered peroxisome proliferator-activated receptor alpha (PPARα) mRNA or protein levels in mice, rats, and fish. In *in vitro* studies, BPA decreased PPARα mRNA levels in rat liver cells and increased PPARα protein levels in mouse Leydig tumor cells.
- PPARγ: BPA altered expression or activity of PPARγ in several types of human cells *in vitro,* rats and mice *in vivo,* and non-human animal cells *in vitro,* although there are no clear patterns. BPA levels were not correlated with PPARγ expression in human observational studies in men or women in Italy and India.
- AhR: In human observational studies, BPA levels were positively correlated with aryl hydrocarbon receptor (AhR) expression in infertile women and men and fertile men, but not fertile women in Italy. A study in India reported a positive

correlation of BPA levels with AhR expression. There is some evidence that BPA can activate AhR or increase its expression in human cells *in vitro,* in mice and rats *in vivo*, and in fish*.* Mixed results for AhR were found in mouse and rat cells exposed to BPA *in vitro*.

- PXR: BPA levels were positively correlated with pregnane X receptor (PXR) in human observational studies in infertile women and men and fertile men in Italy, but not fertile women. A number of studies of several types of human cells *in vitro* demonstrated that BPA activates or increases the expression of PXR. BPA increased PXR mRNA levels in female fish. In male fish, BPA increased PXR mRNA levels with short-term exposure and decreased levels after longer exposure. BPA did not affect PXR activity or transcription in animal studies *in vitro.*

Causes immortalization

There are several studies available on BPA that provide information relevant to its potential to cause immortalization. Two studies reported that BPA is able to induce cell transformation in Syrian Hamster Embryonic (SHE) cells, while two other studies in SHE cells and one in the A31-1-13 clone of BALC/c3T3 cells did not find significant alterations to cell transformation. BPA was able to increase cell invasion in three human primary cell lines. Additionally, increases in mesenchymal cell markers were observed in three human cancer cell lines and one human epithelial cell line after exposure to BPA and one study observed a decrease in a cellular senescence gene in a human cancer cell line. In one cross-sectional study, higher urinary BPA levels were associated with shorter relative telomer length in adult women. Five studies characterized alterations to telomerase expression, activity, or telomere length after BPA exposure in human cells *in vitro*. Two studies performed in primary human cells found decreases in telomerase activity, *hTERT* mRNA expression, or telomere length after exposure to BPA, while three studies performed in human cancer cell lines found increases or no alterations in telomerase expression and activity.

Alters cell proliferation, cell death or nutrient supply

BPA-induced cell proliferation has been observed in many studies using human cells *in vitro*. There are also studies reporting that BPA decreases apoptosis, increases glycolysis-based energy production, alters proteins involved in cellular replication or cell cycle control signaling pathways, and increases angiogenesis. A number of studies have reported that BPA induces hyperplasia, with observations in multiple organs in multiple strains of rats and mice.

1. INTRODUCTION

1.1 Chemical Identity of Bisphenol A

Bisphenol A (BPA) is a synthetic organic compound produced by condensation of one molecule of **a**cetone (the suffix "A" in the name, BPA) and two molecules of phenol in the presence of an acid catalyst (Figure 1). BPA has a symmetrical chemical structure comprised of two phenol rings connected by a methyl bridge (Figure 2).

BPA is a solid at room temperature and has an extremely low vapor pressure. BPA is completely soluble in organic solvents (such as acetic acid or alcohol) and moderately soluble in water. Selected chemical properties of BPA are listed in Table 1.

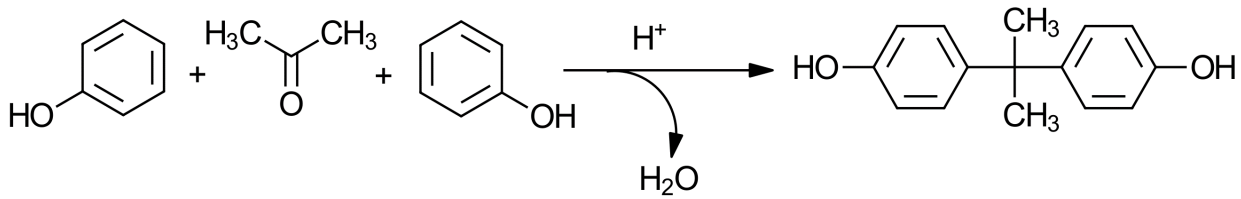


Figure 1 Synthesis of bisphenol A

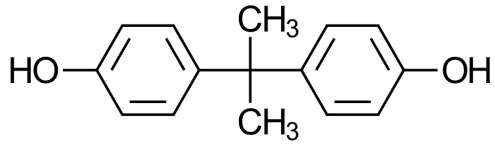


Figure 2 Chemical structure of bisphenol A

Table 1 Selected chemical properties of bisphenol A[a]

Chemical name	Bisphenol A (BPA)
Synonyms	4,4′-(propane-2,2-diyl)diphenol; phenol, 4,4'-(1-methylethylidene)*bis*-; 2,2-*bis*(4-hydroxyphenyl)propane; p,p'-isopropylidenebisphenol
Chemical Abstracts Service Registry Number (CAS RN)	80-05-7
Molecular formula	$C_{15}H_{16}O_2$
Molecular weight (g/mol)	228.29
Boiling point (ºC)	200
Melting point (ºC)	155
Vapor pressure (mmHg)	$6.78 \times 10^{-8} – 2.59 \times 10^{-6}$
Water solubility (mol/l)	8.55×10^{-4}
Octanol-water coefficient (Log K_{ow})	3.32

[a] Values are from US EPA's CompTox Chemical Dashboard (https://comptox.epa.gov/dashboard/chemical/details/DTXSID7020182; accessed March 22, 2022).

1.2 Production, Sources, and Use

BPA is a high production volume chemical, with over 13 billion pounds estimated to have entered the global marketplace in 2021 (Research and Markets 2022). Aggregate annual US production volumes (including manufacture and import) for 2012–2019, the most recent years for which such data are available, are reported only as ranges; annual production in each of these years is reported to be between one and five billion pounds (US EPA 2022a). Annual US production volumes have been relatively consistent for over a decade; US EPA has previously reported domestic production volumes of 2.25 billion pounds in 2011 and 2.4 billion pounds in 2007 (US EPA 2022a).

First synthesized in the late 19th century, widespread industrial use of BPA began decades later following discovery of its utility as a monomer in the manufacture of polymeric materials (Vogel 2009). Most BPA is used in the production of polycarbonate plastics and epoxy resins. BPA monomer is also used in the manufacture of other specialty plastics (e.g., polyester, polysulfone, polyacrylate, and polyetherimide), and as

a chemical intermediate, developer, additive, or processing aid in the production of other materials (e.g., a precursor in the synthesis of tetrabromobisphenol-A, a developer in a number of thermal paper applications, an end-of-polymerization inhibitor in PVC plastics, an antioxidant or stabilizer for various plasticizers, and an intermediate in the manufacture of antioxidants for textile finishing and of certain dyes) (European Commission Scientific Committee on Consumer Safety 2021; United Nations Environment Program 2020; US EPA 2010). In the United States, the use of BPA in the manufacture of baby bottles, sippy cups, and infant formula packaging has been prohibited (US FDA 2018) and the use of BPA-containing epoxy resins as coatings for canned foods has decreased in recent years.[2]

Sources of BPA include emissions from its manufacture and industrial use, as well as releases from products and materials containing BPA during use and after disposal (United Nations Environment Program 2020; US EPA 2010). Emissions from facilities manufacturing or processing BPA and BPA-containing materials and products can be substantial (Corrales et al. 2015; Cousins et al. 2002; Flint et al. 2012; Klecka et al. 2009; Staples et al. 1998; Tsai 2006; Vasiljevic and Harner 2021). According to the US EPA, releases of BPA to the environment exceed one million pounds per year (US EPA 2022b). In 2020, a total of 2,478,712 pounds of BPA were reported to US EPA as having been disposed of or released by the top 100 reporting facilities in the Toxics Release Inventory (TRI) program; four facilities in California reported a total of 223,470 pounds of BPA disposed or released (US EPA 2022c). There are also postconsumer sources associated with consumer product disposal or waste. These include BPA-containing leachates from landfills, discharges of effluents containing BPA from wastewater treatment plants, and degradation of BPA-containing materials in the environment (Corrales et al. 2015; Flint et al. 2012; Fu and Kawamura 2010; Teuten et al. 2009; Vasiljevic and Harner 2021).

1.3 Occurrence and Exposure

BPA has been measured in environmental media, biota, and humans. Though BPA is not considered to be a persistent chemical based on its physical properties (see Table 1), BPA can be considered ubiquitous as a result of high levels of production, use, and subsequent environmental introduction. Global environmental occurrence and environmental fate of BPA have been reviewed broadly (Corrales et al. 2015; Cousins

[2] Can Manufacturers Institute. 2020. CMI Washington State Canned Food Market Basket Survey. Available: https://www.cancentral.com/sites/cancentral.com/files/public-documents/CMI%20Washington%20State%20Canned%20Food%20Market%20Basket%20Report%20%2B%20Raw%20Data.pdf.; Center for Environmental Health. 2022. Canned Foods. Available: https://ceh.org/products/canned-foods/, accessed on July 19 2022.

et al. 2002) and by environmental medium, including a recent review of BPA in indoor and outdoor air (Vasiljevic and Harner 2021).

Briefly, BPA has been identified in sediments, soils, and biosolids, including those in California (Careghini et al. 2015; Maruya et al. 2022; United Nations Environment Program 2020). BPA has also been identified in drinking water, ground water, and surface waters, including various water bodies in California (Barnes et al. 2008; Maruya et al. 2022; United Nations Environment Program 2020).

BPA has been shown to be taken up by plants, including edible crops, and has also been measured in animals and in raw animal products (Flint et al. 2012; Repossi et al. 2016; Santonicola et al. 2019; Tao et al. 2021). BPA has been detected in foods; its presence is generally attributed to contact of the food with BPA-based processing materials or food packaging materials (Almeida et al. 2018; Vilarinho et al. 2019; Wang et al. 2022). BPA has been detected in indoor dust samples from businesses and homes, including in California (Caban and Stepnowski 2020; Mitro et al. 2016; Shin et al. 2020; Wang et al. 2015b)

Humans are exposed to BPA through ingestion of contaminated food and water, ingestion of dust, inhalation of indoor and outdoor air, and dermal contact with BPA-containing materials. Studies investigating the relative contribution of these exposure pathways have consistently identified ingestion of contaminated food and beverages as the predominant contributor to exposure for most individuals (Covaci et al. 2015; Huang et al. 2018b; Martínez et al. 2018; US FDA 2018). BPA has been detected in breast milk in the US and other countries, which contributes to dietary intake for infants and toddlers (Dualde et al. 2019; Nakao et al. 2015; Sayıcı et al. 2019; Zimmers et al. 2014). The relative importance of dietary intake to BPA exposure is further supported by intervention studies and randomized cross-over dietary studies that have demonstrated dietary modifications such as removal of canned or packaged foods or incorporation of more fresh foods result in decreases in urinary BPA levels by 50% or more (Carwile et al. 2011; Kim et al. 2020; Peng et al. 2019b; Rudel et al. 2011).

Other exposure pathways, e.g., dust ingestion, inhalation in indoor environments, or dermal contact can also contribute substantially to overall BPA exposure for certain individuals, such as some older infants and young children (Geens et al. 2011; Healy et al. 2015; Morgan et al. 2018; Wang et al. 2019d). Developing fetuses may also be exposed via *in utero* transfer; BPA has been detected in fetal cord blood, fetal liver, amniotic fluid, and the placenta (Dreshaj and Pasha 2021; Gerona et al. 2013; Lee et al. 2018b).

BPA has a short half-life in the body (approximately 6 hours) (see Section 5.1) and the general population is frequently exposed from multiple sources, resulting in BPA levels that vary widely within an individual, even within the span of a 24-hour period. Thus,

biomonitoring approaches at best reflect an individual's short-term exposure to BPA. However, recent population biomonitoring studies of BPA report detection frequencies of over 90%, demonstrating that exposure in humans remains widespread (Centers for Disease Control and Prevention 2021; Colorado-Yohar et al. 2021; Huang et al. 2018b). Total BPA, which typically represents the sum of BPA and at least the two major conjugated metabolites (BPA glucuronide [BPA-G] and BPA sulfate [BPA-S]) following enzymatic hydrolysis, measured in urine using a liquid chromatography (LC) and tandem mass spectrometry (MS), is widely recognized as the standard biomonitoring measure. This is the approach currently used by major biomonitoring programs including Biomonitoring California and the US National Health and Nutrition Examination Survey (NHANES) (Calafat et al. 2015; Gavin et al. 2014; LaKind et al. 2019).

Several biomonitoring studies have reported total BPA levels in urine of California residents in recent years, including studies conducted by the Biomonitoring California program (https://biomonitoring.ca.gov) (Gerona et al. 2016; Harley et al. 2016; Kim et al. 2021; Lin et al. 2020; Smith et al. 2022; Waldman et al. 2016). Table A1 in Appendix A presents urinary BPA levels in Californians from select studies with urine samples collected between 2007 and 2020. Generally, both detection frequency and BPA levels in Californians have decreased in recent years, as some uses of BPA, such as its use in epoxy-resin linings of cans and bottles, have been reduced (Table A1).

1.4 Review by Other Health Agencies

BPA has not been reviewed or classified as to its potential carcinogenicity by the International Agency for Research on Cancer (IARC), the US Environmental Protection Agency (US EPA), the National Institute for Occupational Safety and Health (NIOSH), the National Toxicology Program (NTP) Report on Carcinogens, or the US Food and Drug Administration (US FDA).

2. OVERVIEW OF SYSTEMATIC LITERATURE REVIEW APPROACH

2.1 Literature Search Process

Literature searches on the carcinogenicity of BPA were conducted mainly in December 2021. The goal was to identify peer-reviewed journal articles, print and digital books, reports, and gray literature that potentially reported toxicological and epidemiologic information on the carcinogenicity of this chemical.

As described below, we used an approach similar to that recommended by the National Toxicology Program (NTP) Handbook for Preparing Report on Carcinogens (RoC) Monographs (NTP 2015).

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:

- Three submissions received during the data call-in period (January 28 – March 14, 2022) (https://oehha.ca.gov/proposition-65/comments/comment-period-request-relevant-information-carcinogenicity-bisphenol-bpa)

Primary searches for BPA were executed using chemical synonyms in combination with search terms for human cancer studies, animal cancer studies, toxicokinetic studies, and mechanistic studies for genotoxicity and other key characteristics. There were no restrictions in the searches on exposure route or duration of exposure on cancer studies in humans, cancer studies in animals or mechanistic studies, or on publication language.

For detailed information on the literature search process, please see Appendix B.

2.2 Literature Screening Process

Due to the large volume of literature on BPA identified from the primary searches, SWIFT (Sciome Workbench for Interactive Computer-Facilitated Text-mining) Active Screener (SWIFT AS) (Howard et al. 2020) was used as a tool to facilitate the initial

screening of references from the primary searches. The literature from primary searches was organized by evidence streams; five distinct SWIFT AS projects were created and completed between December 2021 to February 2022 (https://www.sciome.com/swift-activescreener/). In each of the five projects, two OEHHA scientists independently completed the screening for a decision to be made on each title and abstract, following predefined inclusion and exclusion criteria. This initial screening in SWIFT AS allowed for efficient initial literature inclusion and exclusion with the help of artificial intelligence.

After initial screening in SWIFT AS, HAWC (Health Assessment Workspace Collaborative, https://hawcproject.org) was used as a tool to further screen and tag the literature. First, citations retrieved from SWIFT AS screening projects were uploaded to EndNote libraries, and duplicates were removed. Next, these EndNote libraries were uploaded to HAWC for multi-level screening using specific inclusion and exclusion criteria (see Appendix B). For example, certain citations identified by the literature search as epidemiologic studies were later excluded, and the reasons for exclusion are provided in Appendix C.

In Level 1 screening in HAWC, each citation was first screened by at least one OEHHA scientist, based solely on titles and abstracts, to eliminate studies or articles that do not contain information on BPA on any of the key topics covered in this cancer hazard identification document, such as cancer studies in humans and animals, toxicokinetics, metabolism, genotoxicity, or other cancer-associated mechanisms. The Level 1 screen was intended to identify all studies deemed to have a reasonable possibility of containing information that could be useful for the review process. Papers identified for inclusion during Level 1 screening were tagged in HAWC according to key topics.

In Level 2 screening, full-text papers for all citations that passed the Level 1 screening were obtained and screened by at least one OEHHA scientist, using similar inclusion/exclusion criteria as was used in the Level 1 screening.

Following Level 2 screening, the tagging of articles according to key topics was updated in HAWC. Level 1 and 2 screenings were conducted and HAWC search results were updated if additional relevant studies in addition to those cited in the original set of publications (“secondary citations”) were identified.

Table Builder (Shapiro et al. 2018), a web-based application, was applied to systematically extract and analyze the data that were included in Section 3, Carcinogenicity studies in humans. Additionally, Table Builder was used as a custom-made database to generate Word tables in this document.

More than 4000 references, including peer-reviewed journal articles and government reports, were identified for inclusion through these search strategies. Among these, over 1300 references were cited in this document.

3. CARCINOGENICITY STUDIES IN HUMANS

3.1 Introduction

The epidemiologic literature on the carcinogenicity of BPA was identified through a systematic search of several databases. Appendix B provides a description of the details of the epidemiologic literature search strategy and literature search terms.

3.1.1 Methods

All human epidemiologic studies of cancer that measured or estimated BPA levels were eligible for inclusion. A total of 23 articles were excluded for the following reasons: reviews without original data (n = 11); studies reported only as conference abstracts since the results reported in such abstracts are considered preliminary and subject to change and have not been peer-reviewed (n = 10), and studies where the outcome was uterine leiomyoma, which are benign conditions that do not progress to malignancy (except in extremely rare situations) (Bulun 2013) (n = 2) (see Appendix Table C2 for list of excluded studies). There were no exclusions based on study location, language, or statistical adjustments. When screening articles for inclusion, we first screened based on title and abstract, then full article review.

Twenty-eight articles published in peer-reviewed journals on the carcinogenicity of BPA were included for this review for the following sites: breast cancer (n = 14, including 2 publications of the same data), prostate cancer (n = 4, including 2 publications of the same data), thyroid cancer (n = 2), endometrial cancer (n = 1), bone cancer (n = 1), lung cancer (n = 2), brain cancer (n = 1), lymphohematopoietic cancers (n = 1), extrahepatic bile duct/gallbladder cancer (n = 1), eye cancer (n = 1), and all cancers combined (n = 1). One publication reported on both breast and prostate cancer (Salamanca-Fernández et al. 2021).

Strengths and limitations of each study were carefully assessed. Each study included in this review was systematically evaluated for study quality and informativeness for cancer hazard assessment using a domain-based approach guided by the NTP RoC handbook (NTP 2015) and principles outlined in the IARC Monograph Preamble (IARC 2019a). The domains evaluated were selection bias, information bias due to errors in measurement of exposure or outcome, confounding bias, and analysis bias. Limitations and strengths in each domain are presented in the study descriptions and tables, only when notable for the interpretation of studies. The potential magnitude and direction of bias (towards the null, away from the null, unknown) was also considered (Steenland et al. 2020). The domains of information bias due to errors in exposure measurement and confounding bias are presented in further detail below (see Section 3.1.2 for further

considerations). There were also several considerations specific to assessing the epidemiologic literature on BPA and cancer, which are discussed briefly below.

3.1.2 Key issues in the consideration of the epidemiologic data on BPA and cancer

3.1.2.1 Exposure assessment limitations

Human exposure to BPA has been widespread due to its extensive use and ubiquitous presence. As discussed in Section 1.3 it is routinely detected in more than 90% of human urine samples. BPA has a short half-life in the body and the general population is frequently exposed from multiple sources, resulting in BPA levels that vary widely within an individual, even within the span of a 24-hour period, Thus, a single measurement of BPA cannot reliably characterize long term exposure, and the collection of biological samples at a single point in time in most epidemiologic studies is a major limitation. Additionally, questionnaire responses have not been found to correlate well with measured urinary BPA levels. The latency period between first exposure to a chemical carcinogen and observation of cancer is on the order of years, and for some chemicals, decades. The reviewed cancer epidemiology studies assessed exposure by either measurement of BPA in biological matrices without longitudinal samples, questionnaire, or job exposure matrix (JEM). For these reasons, it is difficult to correctly assign individuals in these studies to categories or levels of BPA exposure and to detect associations with chronic disease outcomes, such as cancer.

Limitations in the characterization of BPA exposure associated with use of questionnaires, JEMs, and biological measurements, which can affect the ability of a study to detect an association with BPA exposure, are discussed below.

Questionnaires and JEMs

The questionnaire approach, as used to assess ingested sources of BPA in a study of prostate cancer (Tse et al. 2017; Tse et al. 2018), is limited in the ability to accurately characterize BPA exposure. Given the many varied sources of exposure (see sections 1.2 and 1.3) that are not typically sufficiently incorporated into questionnaires and, in many cases, are unknown to the participant (Gerona et al. 2016; Nomura et al. 2016), non-differential exposure misclassification is possible, which may bias risk estimates towards the null and attenuate any dose-response relationships.

Studies demonstrating limitations of questionnaire data in characterizing BPA exposure include Gerona et al. (2016) and Nomura et al. (2016). Gerona et al. (2016) assessed both dietary and non-dietary BPA exposure in pregnant women with an extensive questionnaire and determined that longer-term dietary scores (*e.g.*, weekly consumption of canned beverages, canned and paper-packaged foods) were not associated with a

one-time measurement of BPA in urine, and that respondents with reported knowledge of BPA or taking action to avoid BPA had similar levels of BPA as those who did not. Nomura et al. (2016) attempted to validate a BPA dietary exposure assessment module comprised of a food frequency questionnaire targeting known sources of BPA exposure with three 24-hour food records and BPA measurements of pooled spot urine samples collected on three days in healthy adults. Dietary BPA intake from the questionnaire was not associated with urinary BPA levels. These authors concluded that the known dietary sources of BPA exposure explained less than half the variability in urinary BPA levels, regardless of diet assessment method, and suggested a questionnaire approach was likely insufficient and that additional important sources of BPA exposure likely exist.

Given widespread exposure to BPA from non-occupational sources, the use of a JEM in characterizing BPA exposure, as was done in four case-control studies of BPA and cancer (Ahrens et al. 2007; Aschengrau et al. 1998; Behrens et al. 2012; Costas et al. 2015), represents a significant limitation to the characterization of exposure in these studies. Moreover, few participants in these case-control studies were occupationally exposed to BPA, severely reducing the power of these studies to detect an association with BPA.

Biological measurements

Number and timing of measurements

The greatest limitation in the majority of the epidemiology studies was the collection of a single biological sample per participant. As discussed below, this single measurement at one point in time is unlikely to provide accurate estimates of long-term exposure to BPA, and may also not reflect BPA levels within the critical time window of susceptibility for cancer causation (LaKind et al. 2019; Reeves et al. 2014; Townsend et al. 2013). None of the studies collected samples longitudinally.

The collection of a single biological sample (one sample per matrix) contributes to considerable imprecision in characterizing BPA exposure, as multiple studies have demonstrated that measurement of BPA in a single urine sample is unlikely to provide accurate estimates of long-term exposure to BPA (Calafat et al. 2015; Calafat 2016; Fisher et al. 2015; LaKind et al. 2019; Morgan et al. 2018; Reeves et al. 2014; Townsend et al. 2013). None of the epidemiology studies included in this review analyzed longitudinal samples. Moreover, it is likely that multiple longitudinal samples would be required to improve confidence in BPA exposure classification, as several studies have reported poor reproducibility of repeated measurements of urinary BPA (Aylward et al. 2017; Braun and Hauser 2011; Braun et al. 2012; Cox et al. 2016; Meeker et al. 2013; Morgan et al. 2018; Philippat et al. 2013; Pollack et al. 2016; Reeves et al. 2014; Townsend et al. 2013; Ye et al. 2011a). Thus, non-differential exposure misclassification is possible in each of the epidemiology studies reviewed

here, which may bias risk estimates towards the null and attenuate any dose-response relationships.

Animal toxicokinetic studies indicate that fetal exposures may represent a critical time period in which BPA exposure results in an increased risk of cancer (see Section 5.1 Pharmacokinetics and Metabolism). Though the general population are expected to have been exposed *in utero* as well as throughout childhood, every epidemiologic study in this review assessed BPA exposure in adults. Typically, if exposures during important time windows of susceptibility have not been assessed in a study, this is expected to result in decreased sensitivity to detect an effect; given that the general population is expected to have had exposure during the window of susceptibility, this is not expected to be a significant issue in epidemiologic studies of BPA. Similarly, of studies in which BPA exposure was assessed using biomonitoring, only a few collected biological samples prospectively (Bao et al. 2020; Salamanca-Fernández et al. 2021; Sarink et al. 2021; Wu et al. 2021). In most studies, samples were collected after diagnosis, with many collected during or after cancer treatment. Though the possibility of reverse causation cannot be disregarded and it is also possible that diagnosis may have modified exposure related behaviors such as diet (Maskarinec et al. 2001), BPA exposure of some magnitude is expected to have occurred prior to diagnosis in each study population.

Biological matrix

Most epidemiologic studies in this review assessed BPA using urine samples, which is widely considered the optimal biological matrix for measurement of BPA in humans (Calafat et al. 2015; Ougier et al. 2021). Urine samples analyzed in these studies include random spot samples as well as samples that reflect specific time periods, such as first morning voids and 12-hour overnight samples. To enable comparisons between individuals, urinary concentrations of chemicals such as BPA are often adjusted, most commonly by creatinine adjustment (Barr et al. 2005). Some studies reported only unadjusted urinary levels (Bao et al. 2020; Duan et al. 2013a; López-Carrillo et al. 2021) and may therefore introduce bias (Christensen et al. 2014; O'Brien et al. 2016).

Urine was the most frequently used biological matrix in the studies reviewed. Two studies measured BPA in serum (Marotta et al. 2019; Zhou et al. 2017c) and two studies measured BPA in breast adipose tissue samples (Keshavarz-Maleki et al. 2021; Reeves et al. 2018). Two of these studies also measured BPA in urine (Keshavarz-Maleki et al. 2021; Zhou et al. 2017c). Quantification of BPA in serum is considered to be more challenging than urine; serum levels are typically orders of magnitude lower than those in urine (Calafat et al. 2013; Koch et al. 2012; Ougier et al. 2021; Thayer et al. 2015). While some studies suggest that adipose tissues may serve as a reservoir for BPA (see Section 5.1 Pharmacokinetics and Metabolism), additional studies are needed

to verify this and better characterize the intraindividual variability in BPA measurements in breast adipose tissue.

BPA analytes

In the epidemiologic studies reviewed, the analyte most commonly used to assess BPA exposure is “total BPA”, a measure which comprises free BPA and at least one BPA metabolite (typically the glucuronide and/or the sulfate conjugate of BPA, measured following enzymatic hydrolysis). Measures of total BPA that comprise free BPA and the glucuronide conjugate (BPA-G) and the sulfate conjugate (BPA-S) are currently used to assess BPA exposure in urine samples in major biomonitoring programs including Biomonitoring California and NHANES (Calafat et al. 2015; CDC 2019; Gavin et al. 2014; LaKind et al. 2019; Zhou et al. 2014b).

Two of the epidemiologic studies of BPA and cancer measured free BPA (López-Carrillo et al. 2021; Reeves et al. 2018), and one directly measured BPA-G (Trabert et al. 2014), these single analyte approaches are not considered as optimal as measurement of total BPA in most circumstances. Limitations associated with the selection of free BPA as the single analyte to biomonitor include the likelihood of underestimating exposure, and the possibility of sample contamination with environmental sources of BPA. More specifically, pharmacokinetic studies in humans have demonstrated that BPA is rapidly metabolized and excreted mainly as BPA-G and BPA-S (Teeguarden et al. 2015b; Thayer et al. 2015; Völkel et al. 2002; Völkel et al. 2005). Measurement of the free (unconjugated) form of BPA, typically a small fraction of total BPA in the body, is therefore expected to underestimate BPA exposure. Analytical measurement of free (unconjugated) BPA is also particularly susceptible to environmental contamination during sample collection or processing, and can result in exposure misclassification (Longnecker et al. 2013; Ougier et al. 2021; Ye et al. 2013). Few studies reported efforts to limit BPA contamination during sampling and/or analysis (e.g., use of BPA-free sampling materials) or robust quality assurance measures to support validity of BPA measurements. Nondifferential BPA contamination of samples could bias risk estimates towards the null.

On the other hand, direct measurement of a single conjugated metabolite like BPA-G can also result in exposure misclassification, because there is considerable interindividual variability in enzymatic conjugation capacity within the population as a result of a number of factors, including genetic polymorphisms and disease states (see Section 5.1 Pharmacokinetics and Metabolism).

Detection method and limits of detection and quantification

Most of the epidemiology studies utilized MS-based methods to measure BPA and/or BPA metabolites; methods utilizing LC or gas chromatography (GC) coupled with high resolution mass spectrometry (HRMS) or tandem mass spectrometry (MS/MS) are the

most sensitive and specific. The limits of detection (LOD) and quantification (LOQ) for total BPA in any matrix (urine, serum, or breast adipose tissue) in the epidemiology studies using such a method were all below 0.5 nanograms per milliliter (ng/ml) or ng per gram (ng/g), with many studies reporting LODs in urine below 0.05 ng/ml. Four studies (López-Carrillo et al. 2021; Marotta et al. 2019; Muthusamy et al. 2021; Yang et al. 2009a) used LC with fluorescence detection (FD)-based methods for analysis of BPA that can be less sensitive than the preferred MS-based methods. One study used an enzyme-linked immunosorbent assay (ELISA), for measurement of BPA in urine and breast adipose tissue (Keshavarz-Maleki et al. 2021). While some ELISA-based methods can be less specific for the analyte due to potential for cross-reactivity with other substances, these authors reported LODs below 0.01 ng/ml.

Low detection frequency and handling of non-detects

The LOD refers to the lowest chemical concentration that can be distinguished from a concentration of zero with reasonable confidence; detection limits vary between assay methods, laboratories, and even within a laboratory over time (Barr et al. 2006). In studies using less sensitive methods to detect BPA, or in studies of populations with relatively low recent BPA exposure, the number of participants with levels of BPA below the LOD can be substantial. For example, López-Carrillo et al. (2021) reported an LOD of 2.78 ng/ml, the highest reported LOD in any epidemiologic study reviewed, and only 14.8% of samples tested in this study were above this LOD. Studies in which BPA is detected at relatively low frequencies either lose statistical power by omitting samples below the LOD or by imputing samples below the LOD (e.g., assigning a value of zero, the LOD, or some function of the LOD), which can introduce artificial patterns into the data (Barr et al. 2006; Helsel 2010; Helsel 1990; Lubin et al. 2004). Both approaches introduce bias into the analysis to varying degrees, based on the sample size, proportion of observations below the LOD, and the imputation approach used (Barr et al. 2006; Chen et al. 2011; Helsel 2010; Helsel 1990; Helsel 2005; Lubin et al. 2004; US EPA 2000). Some of the epidemiology studies (López-Carrillo et al. 2021; Muthusamy et al. 2021; Parada et al. 2019; Reeves et al. 2018; Salamanca-Fernández et al. 2021; Yang et al. 2018) did impute BPA levels when more than 15% of samples (in total or in either cases or controls) fell below the LOD. Of most substantial concern are two studies where detection rates were very low: López-Carrillo et al. (2021) detected free BPA in less than 15% of urine samples, and Reeves et al. (2018) detected free BPA in breast adipose tissue in less than 27% of samples from cases and less than 39% of samples from controls.

3.1.2.2. Study design limitations

Due to its ubiquitous presence, it is reasonable to assume that the general population has been continuously and widely exposed to BPA across all life stages, including the prenatal period and certainly for years preceding a cancer diagnosis (Braun and Hauser

2011; Ikezuki et al. 2002; Mendonca et al. 2014; Sayıcı et al. 2019). This, taken together with the limitations discussed above inherent in characterizing BPA exposure, provide useful context when evaluating epidemiologic studies.

Cross-sectional studies and case-control studies with a cross-sectional design (e.g., BPA measured at or after cancer diagnosis) were therefore reviewed despite the inherent limitation of these designs to establish a temporal sequence between exposure and disease, especially for studies of chronic diseases with long latency periods using short lived biomarkers that are not necessarily reflective of long term exposure histories (Savitz and Wellenius 2022; US EPA 2005, 2020). Additional limitations of cross-sectional studies pertain to the prevalent cases captured in these studies, which are "vulnerable to length-biased sampling in which individuals with the longest lasting disease (due to any combination of extended survival or failure to recover) are more likely to be selected as prevalent cases in the study" (Savitz and Wellenius 2022). Prevalent cases could also differ in characteristics related to BPA levels (exposure patterns or metabolism) that could affect their survival compared to the incident cases captured in case-control, nested case-control, or cohort designs.

The potential for reverse causation could not be ruled out in the studies with cross-sectional design (few studies collected samples prospectively before disease diagnosis). BPA levels obtained post-treatment could increase from use of certain medical equipment containing BPA (EFSA 2015; Genco et al. 2020; Vandentorren et al. 2011). On the other hand, indirect evidence suggests that BPA levels could decrease post-diagnosis due to dietary changes. Cancer patients have been shown to modify exposure related behaviors such as diet post-diagnosis or post-treatment (Maskarinec et al. 2001; Pedersini et al. 2021; Thomson et al. 2002) and some intervention studies have demonstrated that changes in diet quality (e.g., reduction of canned and processed foods and an increase in fresh foods) result in decreases in urinary BPA levels of 50% or more (Kim et al. 2020; Peng et al. 2019b; Rudel et al. 2011).

3.1.2.3 Confounding bias

The risk estimates in each study were carefully examined to determine the potential for bias due to confounding. A confounder is a variable that may distort the association between the exposure and outcome of interest (Porta 2014; Rothman et al. 2008). It is related to the exposure and causally related to the outcome. A variable is considered as a confounder when evaluating the relationship between an exposure (e.g., BPA) and outcome (e.g., cancer) when three requirements are met:

1. The variable can cause or prevent the outcome of interest.
2. It is not an intermediate variable in the causal pathway between exposure and the outcome.
3. It is associated with the exposure under investigation.

The correct identification of confounders “requires substantive knowledge about the causal network of which exposure and outcome are part (e.g., pathophysiological and clinical knowledge). Attempts to select confounders solely based on observed statistical associations may lead to bias” (Porta 2014).

Furthermore, over-adjustment of additional variables that are not considered potential confounders can introduce bias (a systematic error) where none was present to begin (Greenland and Rothman 2008).

Potential confounders in the association between BPA and cancer, by target organ

The discussion of confounders here focuses on hormonally related cancers, specifically breast, endometrial, prostate, and thyroid cancer. Risk factors for these cancer sites were identified from IARC (IARC 2019b), the American Cancer Society (ACS 2019, 2020a, b, 2021a, b), and the World Cancer Research Fund (WCRF 2022a, b, c). Of the risk factors identified, several are also associated with BPA exposure and therefore may be considered potential confounders (Table 2). Of the risk factors for endocrine cancers in general, there is evidence that BPA is associated with obesity (Carwile and Michels 2011; Liu et al. 2017a; Trasande et al. 2012) and diabetes (Lang et al. 2008; Ning et al. 2011; Sun et al. 2014).

Of the breast cancer risk factors, there is evidence that BPA is associated with obesity (Do et al. 2017; Liu et al. 2017a; Wang et al. 2012b; Wu et al. 2020c), tobacco smoke exposure (Geens et al. 2014), race/ethnicity (Lakind and Naiman 2011), and age (Lakind and Naiman 2011). Obesity/BMI may be an important potential confounder in the association between BPA exposure and breast cancer, which was adjusted for in all but three studies (Aschengrau et al. 1998; He et al. 2022; López-Carrillo et al. 2021). It is also important to note that some studies on breast cancer stratify their results by hormone receptor subtype (estrogen or progesterone receptors) (Trabert et al. 2014; Wu et al. 2021).

Of the risk factors for endometrial cancer, there is evidence that BPA is associated with polycystic ovarian syndrome (PCOS) (Vandenberg et al. 2007), obesity (Wu et al. 2020c), type 2 diabetes (Provvisiero et al. 2016), and age (Lakind and Naiman 2011).

Possible confounders for prostate and thyroid cancer are obesity (Wu et al. 2020c), age (Lakind and Naiman 2011), and race/ethnicity (prostate cancer only) (Lakind and Naiman 2011).

Table 2 Risk factors and potential confounders for selected cancer sites

Cancer site	Risk factors	Potential Confounders
Breast	Established: Alcohol consumption, ionizing radiation, estrogen-progestogen oral contraceptives (combined), estrogen-progestogen menopausal therapy (combined), diethylstilbestrol, age, race/ethnicity, low physical activity, overweight/obese status, early menarche, late menopause, post-menopausal status, tall height, breast density, greater birthweight, not breast feeding, not having children/parity, genetic risk factors (mutations in BRCA1, BRCA2, PALB2, TP53, PTEN), family history IARC limited evidence: dieldrin, aldrin metabolized to dieldrin, digoxin, postmenopausal estrogen therapy, ethylene oxide, night shift work, polychlorinated biphenyls, tobacco smoking	Obesity, tobacco smoke exposure, race/ethnicity, age
Endometrium	Established: Tamoxifen, estrogen-progestogen menopausal therapy (combined), postmenopausal estrogen therapy, obesity, tall height, PCOS, age, type 2 diabetes, family history of endometrial or colorectal cancer, not having children/ parity, early menarche, late menopause, history of breast or ovarian cancer, history of endometrial hyperplasia, radiation therapy in pelvic area IARC limited evidence: diethylstilbestrol Protective: oral contraceptive use, IUD use, coffee consumption	PCOS, obesity, type 2 diabetes, age
Prostate	Established: Age, race/ethnicity, family history of prostate cancer, genetic markers (BRCA1, BRCA2, Lynch Syndrome), overweight/obesity, tall height, geographical location IARC limited evidence: androgenic (anabolic) steroids, arsenic and inorganic arsenic compounds, cadmium	Obesity, age, race/ethnicity

Cancer site	Risk factors	Potential Confounders
	and cadmium compounds, firefighting, malathion, night shift work, red meat consumption, rubber manufacturing industry, thorium-232 and its decay products, X- and gamma-radiation	
Thyroid	Established: Exposure to ionizing radiation (especially during childhood), radioisotopes of iodine (including iodine-131), overweight/obesity, too much or not enough iodine in diet, age, female sex, genetic risk factors (APC mutation, PTEN mutation, PRKAR1A mutation), family history of thyroid cancer	Obesity, age

3.2 Human Epidemiology Studies by Cancer Site

Human epidemiology studies assessing the association between BPA exposure and cancer are discussed below, organized by cancer site. Cancer sites are ordered by the number of studies available. The text presents an expanded synthesis of the findings to enhance readability, whereas the details of the studies are mostly presented in tables. Study details are highlighted in both text and table only when they are remarkable or key for interpretation. Tables for breast, prostate, and thyroid cancers are presented below, while tables for all other sites are presented in appendix Table C1. To facilitate comparison of the results across studies, the BPA level is noted, if it was available from the publication.

3.2.1 Breast cancer

Thirteen epidemiologic studies (Aschengrau et al. 1998; He et al. 2022; Keshavarz-Maleki et al. 2021; López-Carrillo et al. 2021; Morgan et al. 2017; Muthusamy et al. 2021; Parada et al. 2019; Reeves et al. 2018; Salamanca-Fernández et al. 2021; Trabert et al. 2014; Wu et al. 2021; Yang et al. 2009a; Yang et al. 2018) were identified. Of these, three (Muthusamy et al. 2021; Yang et al. 2009a; Yang et al. 2018) did not present a risk estimate and are not reviewed in detail. In addition, one meta-analysis of studies of breast cancer was identified (Liu et al. 2021a). This meta-analysis reported a meta-OR of 0.85 (95% CI: 0.69–1.05) based on a crude analysis of the highest versus lowest BPA levels and breast cancer risk, but is not discussed further because it was based on only five of the epidemiologic studies included in this review (Liu et al. 2021a).

Most studies do not specify a subtype of breast cancer, however two case-control studies were of postmenopausal breast cancer (Trabert et al. 2014; Wu et al. 2021).

The breast cancer studies are grouped for discussion here based on the exposure assessment method (biomonitoring of urine, tissue, serum; JEM), timing of sample collection (before or at/after diagnosis), and author (alphabetical), with studies that did not report measures of association included after studies within the same exposure assessment method that did report measures of association. Details of study design and epidemiologic findings for studies that reported measures of association are presented in Table 4.

BPA was measured in urine in nine of these studies (He et al. 2022; Keshavarz-Maleki et al. 2021; López-Carrillo et al. 2021; Morgan et al. 2017; Muthusamy et al. 2021; Parada et al. 2019; Trabert et al. 2014; Wu et al. 2021; Yang et al. 2018), in breast adipose tissue in two studies (Keshavarz-Maleki et al. 2021; Reeves et al. 2018), in serum in two studies (Salamanca-Fernández et al. 2021; Yang et al. 2009a), and assessed through a JEM in one study (Aschengrau et al. 1998). BPA was detected by liquid chromatography mass spectrometry methods in the majority of studies.

All but two of the studies that measured BPA in biological samples (Keshavarz-Maleki et al. 2021; Reeves et al. 2018) collected a single biological sample per participant and none collected samples longitudinally, resulting in significant limitations for interpretation. The majority of studies were of case-control design, collected samples at or after diagnosis, and could not rule out reverse causation. Two studies collected samples prospectively before disease diagnosis (Salamanca-Fernández et al. 2021; Wu et al. 2021) but were still limited in interpretation by the single sample.

Table 3 summarizes the exposure characterization of BPA in these epidemiologic studies of breast cancer.

Table 3 Exposure assessment details for studies of BPA and breast cancer by study design and author (alphabetical)

Reference, location, study design	BPA levels[a]	Exposure assessment method / matrix	Exposure assessment timing
BPA assessed for time periods before diagnosis			
Aschengrau et al. (1998); USA: Cape Cod, Massachusetts Case-control	Ever/never exposure. 0.8% of study population (2 people) exposed to BPA only (without other xenoestrogens examined); 9.6% (25 people) exposed to BPA (with or without other xenoestrogens)	JEM based on NIOSH /NOES database, chemical production and usage information, and expert judgment of certified industrial hygienist	Retrospective, after diagnosis (diagnosis: 1983–1986)
Salamanca-Fernández et al. (2021); Spain: Gipuzkoa, Granada, Murcia and Navarra Case-cohort	Geometric mean unadjusted total BPA: 1.12 ng/ml (cases), 1.10 ng/ml (subcohort) for breast cancer; 1.33 ng/ml (cases), 1.29 ng/ml (subcohort) for prostate cancer *36.6% of controls and 24.3% of cases below the LOD imputed for analyses*	Biomonitoring: serum (one sample)	1992–1996, before diagnosis (diagnosis: 2011–2013)
Wu et al. (2021); United States: California and Hawaii (HI) Nested case-control	Geometric mean creatinine-adjusted total BPA (95% confidence interval [CI]): 1.17 (1.08–1.28) ng/mg (cases), 1.15 (1.06–1.25) ng/mg (controls)	Biomonitoring; urine (one first morning void [FMV] or overnight sample)	2001–2006, before diagnosis (diagnosis: 2001–2014)
BPA assessed in a case-control study of cross-sectional design, or a cross-sectional study			
He et al. (2022); China: Wuhan Case-control	Geometric mean unadjusted total BPA (without deconjugated BPA-S): 3.00 ng/ml [3.00 µg/l] (median: 2.63 ng/ml [2.63 µg/l]; interquartile range (IQR): 0.98–7.16 ng/ml [0.98–7.16 µg/l]) (cases), 1.55 ng/ml [1.55 µg/l] (median: 1.50 ng/ml [1.50 µg/l]; IQR: 0.71–3.12 ng/ml [0.71–3.12 µg/l]) (controls). Geometric mean creatinine-adjusted total BPA (without	Biomonitoring; urine (one spot sample)	2016–2019, at/after diagnosis

Reference, location, study design	BPA levels[a]	Exposure assessment method / matrix	Exposure assessment timing
	deconjugated BPA-S): 2.45 ng/mg [2.45 µg/g] (median: 1.95 ng/mg [1.95 µg/g]; IQR: 0.87–6.15 ng/mg [0.87–6.15 µg/g]) (cases), 1.19 ng/mg [1.19 µg/g] (median: 1.01 ng/mg [1.01 µg/g]; IQR: 0.60–2.15 ng/mg [0.60–2.15 µg/g]) (controls)		
Keshavarz-Maleki et al. (2021); Iran: Tehran Case-control	Geometric mean unadjusted total BPA: 1.69 ng/ml (cases); 0.83 ng/ml (controls). In adipose tissue: 0.0035 ng/mg [3.50 ng/g] (cases), 0.0015 ng/mg [1.50 ng/g] (controls).	Biomonitoring: urine (one FMV sample), breast adipose tissue (one sample)	2018–2019, at/after diagnosis (during treatment)
López-Carrillo et al. (2021); Mexico: Five states in Northern Mexico Case-control	Geometric mean unadjusted free BPA for samples >LOD: 20.81 ng/ml [20.81 µg/l] (all), 28.11 ng/ml [28.11 µg/l] (cases), 13.42 ng/ml [13.42 µg/l] (controls) *85.2% of samples below the LOD imputed for analyses*	Biomonitoring: urine (one FMV sample)	2007–2011, at/after diagnosis
Morgan et al. (2017); United States: various states (NHANES) Cross-sectional	Geometric mean creatinine-adjusted total BPA: 1.06 (cases), 1.16 (controls) *LOD not reported but available from NHANES. Unspecified % of samples below LOD*	Biomonitoring: urine (one spot sample)	2005–2010, at/after diagnosis
Parada et al. (2019); United States: Long Island, New York Case-control	Median creatinine-adjusted total BPA: 1.53 ng/mg [1.53 µg/g] (cases), 1.69 ng/mg [1.69 µg/g] (controls) *18.3% of samples below the LOD imputed for analyses*	Biomonitoring: urine (one spot sample)	2007 or 2010, at/after diagnosis
Reeves et al. (2018); United States: Springfield, Massachusetts Case-control	Mean free BPA for samples >LOQ of 0.38 ng/g: 0.00071 ng/mg [0.71 ng/g] (cases), 0.00066 ng/mg [0.66 ng/g] (controls) *62.5% of controls and 73.9% of cases below the LOQ imputed for analyses*	Biomonitoring: breast adipose tissue (one or more samples)	2014–2015, at/after diagnosis (during treatment)

Reference, location, study design	BPA levels[a]	Exposure assessment method / matrix	Exposure assessment timing
Trabert et al. (2014); Poland: Lodz, Warsaw Case-control	Geometric mean creatinine-adjusted BPA-G: 4.11 ng/mg (cases), 3.92 ng/mg (controls), 4.88 ng/mg (Warsaw site), 2.29 ng/mg (Lodz site), 4.30 ng/mg (ER+), 3.83 ng/mg (ER-)	Biomonitoring: urine (one 12 hour overnight sample)	2000–2003, at/after diagnosis
BPA assessed in a cross-sectional study or case-control study of cross-sectional design (no risk estimate presented)			
Muthusamy et al. (2021); India Case-control/cross-sectional	Mean BPA: 5.76 ng/ml (cases), 1.18 ng/ml (controls) *26% of samples below the LOD (approach to data analysis not specified)*	Biomonitoring: urine (one spot sample)	years NR, at/after diagnosis
Yang et al. (2009); Korea Case-control	Mean BPA: 1.69 ng/ml [1.69 µg/l] (median: 0.043 ng/ml [0.043 µg/l]) *49.2% of samples below the LOD imputed for analyses*	Biomonitoring: serum (one sample)	1994–1997, at/after diagnosis
Yang et al. (2018); Taiwan Case-control	Mean creatinine-adjusted BPA: 14.17 µg/g (cases), 5.95 µg/g (controls) *Participants without detectable levels of any chemical of interest (including BPA) were excluded from analyses (3 cases, 80 controls),*	Biomonitoring: urine (one spot sample)	2013–2014, at/after diagnosis

[a] unless otherwise specified, number of samples reported below LOD was not a major concern.

Studies measuring BPA in urine

Nine studies of breast cancer and BPA exposure relied on measurement of BPA in a single urine sample for each participant. Of these studies, six used LC with MS (He et al. 2022; Morgan et al. 2017; Parada et al. 2019; Trabert et al. 2014; Wu et al. 2021; Yang et al. 2018), two used a LC method with fluorescence detection (López-Carrillo et al. 2021; Muthusamy et al. 2021), and one used ELISA (Keshavarz-Maleki et al. 2021) to detect BPA. Only one study collected urine samples prospectively (Wu et al. 2021), which is presented first below, followed by six studies that collected a single urine sample per person at or after disease diagnosis (He et al. 2022; Keshavarz-Maleki et al. 2021; López-Carrillo et al. 2021; Morgan et al. 2017; Parada et al. 2019; Trabert et al. 2014). The studies that do not present a risk estimate of BPA with breast cancer are presented last in this section (Muthusamy et al. 2021; Yang et al. 2018).

Wu et al. (2021) conducted a nested case-control study of postmenopausal breast cancer within the Multiethnic Cohort in which BPA was measured in urine samples collected at enrollment into the cohort, prospectively before disease diagnosis. Urine was sampled at different time points across participants (first morning from CA, overnight and first morning from Hawaii), which was adjusted for in the analyses. Creatinine-adjusted BPA levels were analyzed in tertiles of exposure (≤0.84, >0.84 to ≤1.76, >1.76 ng/mg) (Wu et al. 2022). BPA was correlated with several other chemicals: methyl paraben, ethyl paraben, propyl paraben, butyl paraben, benzyl paraben, and total paraben. There was no association between the highest category of BPA exposure and postmenopausal breast cancer; however, there was a non-significant inverse association with the 2nd tertile of BPA exposure (OR: 0.84; 95% CI: 0.67–1.06). This general pattern of association did not change in several sensitivity analyses stratified by hormone receptor positivity (“ER+ or PR+” or “ER– and PR–”), BMI waist-hip ratio at urine collection, years of follow-up after urine collection, stage at diagnosis (invasive and in situ combined vs invasive breast cancers only), or by use of hormone replacement therapy (HRT) at urine collection. When the analyses were stratified by race/ethnicity, the results were generally null except for an inverse association in Japanese Americans. Although BPA exposure was assessed using an appropriate analytical method for which the authors provided at least one validation measure, within-batch variability was 21.9%. [Exposure assessment limitations: single sample; spot urine samples collected at different times across participants (though collection type was controlled for in analyses); high within-batch variability; co-exposures to other chemicals.]

He et al. (2022) reported positive associations with creatinine-adjusted BPA levels in a case-control study of breast cancer from Wuhan, China; the OR per µg/g unit increase in BPA was 1.54 (95% CI: 1.34–1.77). The ORs were also elevated in analyses of the interaction of high and low BPA levels with genotypes of CYP19A1 rs1902580, CYP1A1

rs1048943, CYP1A1 rs4646422, CYP17A1 rs743572, CYP2E1 rs3813867 and CYP24A1 rs2296241. A urine sample was collected post-diagnosis for each participant, but before any medical treatments. A number of other considerations further limit interpretation of the positive associations, including potential for false positive results due to multiple comparisons. There were also severe limitations in reporting study details and analyses. For example, it was difficult to assess the potential for selection bias due to lack of detailed description of the differences between people included in the study versus those who were eligible, limited detail on sociodemographic characteristics, and no information on response rates. This study matched controls to cases by abortion status, which was not further defined. The authors may have used the term 'abortion' to signify 'miscarriage', which is the same word in the Chinese language. Matching on abortion is not appropriate; it is not a risk factor for breast cancer and therefore not a confounder in the BPA/breast cancer association. Analyses were not adjusted for BMI, an important potential confounder in the association between BPA exposure and breast cancer. For the analyses of the main effect of BPA exposure on breast cancer, the 1st and 2nd tertiles of BPA exposure were combined and compared to the last tertile, which could bias risk estimates towards the null. For stratified analyses that assessed the interaction between BPA exposure and a third variable (*e.g.*, age, age at menarche, menopause status, and abortion status), the reference categories were not appropriate (low BPA exposure and no exposure to a third variable was not used as the reference category), complicating the interpretation of these results. [Exposure assessment limitations: single sample; collection of spot urine samples; and no QC measures reported.]

Keshavarz-Maleki et al. (2021) conducted a hospital-based case-control study in Tehran, Iran that enrolled 41 breast cancer mastectomy patients and 11 reduction mammoplasty patients, all lifetime non-smokers. A first morning spot urine was collected prior to obtaining a breast adipose tissue sample. BPA was detected in approximately 93% of cases and 82% of controls using ELISA. BPA concentrations in urine and tissue were collinear in cases (r = 0.896, p-value < 0.001), but there was no association in controls (p-value > 0.05, correlation coefficient not presented). After adjusting for age and BMI, the OR for BPA in urine was 10.59 (95% CI: 1.62–65.7). Study participants were not matched on potential confounders; the lack of matching in the design does not ensure comparability between the case and control groups. [Exposure assessment limitations: single sample per matrix; use of ELISA which may not be specific for BPA; and not reporting how samples below LOD were treated.]

A population-based case-control study in Mexico that measured only free BPA reported positive associations between BPA levels and breast cancer (López-Carrillo et al. 2021). Urine samples were collected for each participant before treatment or surgery. The OR for the highest exposure category (>12.05 µg/l BPA) was 2.31 (95% CI: 1.43–3.74). The increased risk remained in sensitivity analyses among women whose urinary

BPA had a recovery ≥ 80% (OR: 1.66; 95% CI: 1.28–2.14) and after excluding women with undetectable BPA (OR: 4.43; 95% CI: 1.89–10.42). The analyses were only adjusted for age and creatinine levels but not obesity or other potential confounders. Those BPA levels that were reported in samples above the LOD in this study are 7–10 times greater than other studies that measured total BPA in urine (He et al. 2022; Keshavarz-Maleki et al. 2021). It is unclear if the contrast between studies is due to actual differences between exposures or measurement error. [Exposure limitations: single sample; BPA analyte (free BPA) present only in trace amounts and susceptible to contamination; collection of spot urine samples; no adjustment of BPA for urine volume; BPA recovery in quality control (QC) samples up to 148.22% (indicating potential for contamination); high LOD; and imputation of exposure levels for 85.2% of samples below the LOD.]

A cross-sectional study (Morgan et al. 2017) using NHANES data on urinary BPA reported inverse associations between creatinine-adjusted urinary BPA levels and self-report of ever being diagnosed with breast cancer (OR for 50% above LOD: 0.73; 95% CI: not reported; adjusted for BMI, race, age/age at menarche). [Exposure limitations: single sample; collection of spot urine samples; no specification of number of samples below the LOD for which exposure levels were imputed.]

Parada et al. (2019) reported non-significant inverse associations with creatinine-adjusted BPA levels both overall and in a subset of these women with a BMI <25 kg/m² in a case-control study from Long Island, New York. Creatinine-adjusted BPA was analyzed as a continuous log-transformed variable and in quintiles. The OR for the association between log-transformed BPA and breast cancer incidence was 0.91 (95% CI: 0.8–1.02) overall, 0.78 (95% CI: 0.66–0.93) in women with a BMI <25 kg/m², and 1.04 (0.87–1.24) in overweight women (BMI ≥25 kg/m²). There was no internal consistency in the analyses reported by quintile of BPA exposure, and there did not appear to be an exposure-response relationship (*p*-value for test for trend was not reported). Results were similar when restricting the outcome to breast cancer-specific mortality. [Exposure assessment limitations: single sample; collection of spot urine samples; no QC measures reported; relatively high LOD; and imputation of exposure levels for 18.3% of samples below LOD.]

Trabert et al. (2014) conducted a population-based case-control study of postmenopausal breast cancer from two centers in Poland (Lodz, Warsaw). Urine samples were collected either before or after treatment and/or surgery in the cases; all samples reflected a 12 hour collection period. Timing of sample collection with respect to surgery did not affect creatinine-adjusted BPA-G levels; the geometric means of samples collected before and after treatment or surgery were comparable. Although BPA-G levels were higher in Warsaw than in Lodz, there was no association with breast cancer in Warsaw, but an increased risk was observed in Lodz. The ORs for

creatinine-adjusted log-transformed continuous BPA-G (ng/mg) were 0.94 (95% CI: 0.81–1.11) in Warsaw and 1.32 (95% CI: 1.00–1.73) in Lodz. The inconsistencies in these results, despite matching cases and controls by recruitment center, poses challenges for interpreting this study. Overall, there was a roughly 2-fold increased risk of breast cancer (OR: 1.7; 95% CI: 1.15–2.52) in the 2nd quartile of BPA exposure (2.06–4.16 creatinine-adjusted BPA-G (ng/mg)) and also in all exposure categories (quartiles) when restricted to ER-negative breast cancer. [Exposure assessment limitations: single sample; choice of BPA analyte (BPA-G) susceptible to interindividual variability in metabolism; no QC measures reported; and no LOD reported.]

In India, Muthusamy et al. (2021) reported a significantly higher concentration of BPA in the urine of cases (5.76 ng/ml ± 6.00, n = 50) than in controls (1.18 ng/ml ± 2.11, n = 50) (*p*-value < 0.0001). No risk estimate for BPA with breast cancer was presented, and this study is not included in Table 4. It is not clear whether incident or prevalent cases were included. [Exposure assessment limitations: single sample; the BPA analyte (free BPA, present only in trace amounts and susceptible to contamination); the biological matrix analyzed (spot urine without creatinine-adjustment); recovery of the internal standard of 79.12%; not reporting how samples below LOD (26%) were treated.]

In a case-control study in Taiwan, Yang et al. (2018) reported a significantly higher concentration of BPA in the urine of incident cases (14.17 µg/g creatinine, 95% CI: 8.75–22.93, n = 44) than community controls (5.95 µg/g creatinine, 95% CI: 3.39–10.46, n = 22) (*p*-value: 0.033). No risk estimate for BPA with breast cancer was presented, and this study is not included in Table 4. [Exposure assessment limitations: single sample; did not specify the BPA analyte (assumed total BPA); the biological matrix analyzed (spot urine); no QC measures reported; no LOD reported (participants without detectable levels of BPA and other chemicals of interest were excluded from analyses).]

Studies measuring BPA in Breast Adipose Tissue

Two hospital-based case-control studies measured BPA in tissue (Keshavarz-Maleki et al. 2021; Reeves et al. 2018), and one of these studies measured BPA in both tissue and urine samples (Keshavarz-Maleki et al. 2021). Both studies took measures to limit contamination (including use of BPA-free sampling materials), were limited in sample size by a small number of breast cancer mastectomy cases and even fewer breast reduction mammoplasty controls, and by few sociodemographic variables presented (making it difficult to evaluate the potential for selection bias). Furthermore, the selection of all participants from a single referral center may not reflect the underlying study population. Keshavarz-Maleki et al. (2021) reported difficulty in enrolling healthy controls from the same referral center. Neither study matched study participants on potential confounders; the lack of matching in the design does not ensure comparability between the case and control groups. In fact, controls were younger than cases in both

studies. Fluctuations in BPA levels could not be taken into account and non-differential exposure misclassification is likely, which would bias risk estimates towards the null.

Keshavarz-Maleki et al. (2021) measured BPA in urine as well as breast adipose tissue using ELISA; study details are presented above in the discussion of studies measuring BPA in urine. After adjusting for age and BMI, the OR for BPA in breast adipose tissue was 54.96 (95% CI: 2.08–1372.55). A strength of this study was the exposure assessment. BPA was measured in most participants in two biological matrices; however, in cases, the breast adipose tissue sample was collected in proximity to the tumor, therefore it may not approximate the normal tissue physiology for comparison to the controls. [Exposure assessment limitations: single sample per matrix; biological matrix analyzed (breast adipose tissue); use of ELISA which may not be specific for BPA and not reporting how samples below LOD were treated.]

In a case-control study from Massachusetts, Reeves et al. (2018) reported an OR of 0.9 (95% CI: 0.4–2) for cases with detectable BPA (>LOQ of 0.38 ng/g) in breast adipose tissue. This study was difficult to interpret as it is not clear how the ORs were calculated. All cases were compared to controls (the referent), rather than assessing the effect of the exposure (as a continuous or categorical variable, with the lowest exposure category serving as the reference category) on the outcome. In cases, a normal tissue sample away from the tumor was collected and a subset of cases also provided a tissue sample from the unaffected breast, making it more comparable to the tissue samples collected in controls. A subset of cases and controls had two samples collected from the same breast. BPA levels were highly variable both within-breast and between breasts, with coefficients of variation ranging from 8.9% to 141.4% in replicate samples with BPA >LOQ. [Exposure assessment limitations: single sample for most (a subset of participants had an additional tissue sample collected simultaneously); BPA analyte (free BPA); the biological matrix analyzed (breast adipose tissue); highly variable BPA levels both within-breast and between breasts; relatively high LOQ; and imputation of exposure levels for a 69.4% of samples below the LOQ.]

Studies measuring BPA in serum

In the Spanish arm of the EPIC cohort (Salamanca-Fernández et al. 2021), BPA was measured in a serum sample collected prospectively, before diagnosis. Every 5 ng/ml increase in BPA level was associated with a 4.7% increase in the risk of breast cancer (HR: 1.047; 95% CI: 0.98–1.12). [Exposure assessment limitations: single sample; biological matrix analyzed (serum); relatively high LOD; and imputation of exposure levels for 30.6% of participants below the LOD.]

A study from Korea (Yang et al. 2009a) reported the median level of conjugated BPA in serum in breast cancer cases (0.61 µg/l, n = 70) was higher (not statistically significant) than in controls (0.03 µg/l, n = 82). No risk estimate for BPA with breast cancer was

presented, and this study is not included in Table 4. [Exposure assessment limitations: the BPA analyte (conjugated BPA); the biological matrix analyzed (serum); imputation of exposure levels for 49.2% of samples below the LOD.]

Studies measuring BPA using a job exposure matrix

In a population-based case-control study, Aschengrau et al. (1998) reported an OR of 0.8 (95% CI: 0.5–1.4) for both the categories of 'any BPA exposure' and 'BPA plus other xenoestrogens'. This is the only breast cancer study that assessed BPA using a job exposure matrix (JEM). The effect of BPA from other co-exposures could not be disentangled. Analyses were not adjusted for BMI, an important potential confounder in the association between BPA exposure and breast cancer. Another limitation is that non-occupational sources of BPA exposure (e.g., dietary exposure via contaminated food or food packaging materials) were not assessed. The general population is not highly exposed to BPA through occupation; therefore, the design and methods are not ideal to assess the carcinogenicity of BPA exposure. [Exposure assessment limitations: the JEM doesn't capture widespread BPA exposure from non-occupational sources].

Table 4 Breast cancer studies with measures of association, ordered by exposure assessment method (biomonitoring of urine, tissue, serum; JEM), timing of collection (before or at/after diagnosis), and author

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Wu et al. (2021) Nested Case-Control Hawaii, California (LA county), USA **Enrollment or follow-up:** 1993–1996	**Population:** Postmenopausal women from the Multiethnic Cohort Study Cases: 1032; Controls: 1030 **Exposure assessment method:** urine; BPA measured in a prospectively collected (2001–2006) single urine sample before case ascertainment (2001–2014). No measures to limit BPA contamination reported. Exposure proxy: total BPA following enzymatic hydrolysis, analyzed by LC-HRAMMS. Creatinine adjusted. Samples below LOQ were imputed as the LOQ/2.	Post-menopausal: OR, BPA (ng/g creatinine)			Education, number of children, age at menarche, menopausal status at urine collection, BMI at urine collection, neighborhood SES at urine collection, smoking at urine collection, alcohol intake, Mediterranean energy-adjusted total score	**Exposure information:** LOQ: 0.001 ng/ml. Geometric mean total BPA of 1.17 ng/g creatinine, 95% CI: 1.08–1.28 (cases), 1.15 ng/g creatinine, 95% CI: 1.06–1.25 (controls) **Strengths:** Urine samples prospectively collected before cancer diagnosis. Several sensitivity analyses were conducted, stratified by hormone receptor positivity ("ER+ or PR+", or "ER– and PR–"), BMI waist-hip ratio at urine collection, years of follow-up after urine collection, stage at diagnosis (invasive and in situ combined vs invasive breast cancers only), use of hormone replacement therapy (HRT) at urine collection, race/ethnicity. **Limitations:** Single urine sample does not account for within-person variability over time and may limit ability to detect an effect. Spot urine samples were collected at different times across participants. Exposure proxy (deconjugated BPA-G and BPA-S + BPA) may be affected by
		≤0.84	1	372		
		>0.84 to ≤1.76	0.84 (0.67–1.06)	313		
		>1.76	0.95 (0.75–1.21)	347		
		Trend-test *p*-value: 0.53				
		Post-menopausal, HR positive (ER+ or PR+): OR, BPA (ng/g creatinine)				
		≤0.84	1	305		
		>0.84 to ≤1.76	0.87 (0.69–1.09)	265		
		>1.76	0.98 (0.78–1.24)	289		
		Trend-test *p*-value: 0.73				
		Post-menopausal, HR negative (ER– and PR–): OR, BPA (ng/g creatinine)				
		≤0.84	1	47		
		>0.84 to ≤1.76	0.78 (0.49–1.24)	35		
		>1.76	1 (0.64–1.59)	42		
		Trend-test *p*-value: 0.84				
		Post-menopausal: OR, Categorized BPA (ng/g) creatinine adjusted among BMI ≤25 kg/m²				
		≤0.84	1	141		
		>0.84 to ≤1.76	0.77 (0.56–1.06)	119		
		>1.76	0.99 (0.72–1.36)	146		
		Trend-test *p*-value: 0.73				
		Post-menopausal: OR, Categorized BPA (ng/g) creatinine adjusted among BMI >25 kg/m²				
		≤0.84	1	231		
		>0.84 to ≤1.76	0.94 (0.7–1.25)	194		
		>1.76	0.96 (0.72–1.28)	201		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
		Trend-test *p*-value: 0.98				background contamination. Within-batch variability in BPA analysis of 21.9%. Samples collected from postmenopausal women but time window of exposure susceptibility may occur much earlier.
He et al. (2022) Case-Control Wuhan, China **Enrollment or follow-up:** November 2016–October 2019	**Population:** Cases: 302; Controls: 302 **Exposure assessment method:** urine; BPA measured in a single morning mid-stream urine sample collected post-diagnosis (2016–2019), but before any medical treatments. Reported use of sample collection material to limit BPA contamination. Exposure proxy: total BPA following enzymatic hydrolysis analyzed by UHPLC-HRMS[3]. Creatinine adjusted. Samples below LOD were imputed as the LOD/√2.	OR, BPA (adjusted for creatinine)			Age, age at menarche, menopausal status, smoking status, abortion status	**Exposure information:** LOD: 0.031 ng/ml. Total BPA: Low level (≤1.71 µg/g); high level (>1.71 µg/g) **Strengths:** The authors reported some measures to validate the analytical method. **Limitations:** Severe limitations in reporting study details and analyses. No detailed description of the analyzed vs target population, no information on response rates, no reason for matching by abortion status (which was not further specified). The first and 2nd tertiles of BPA exposure were combined and compared to the 3rd and highest category - this would bias risk estimates towards the null. Stratified analyses had reference categories that were not appropriate (low BPA exposure and no exposure to a third variable was not used as the reference category), complicating the interpretation of
		BPA per µg/g unit increment (continuous)	1.54 (1.34–1.77)	302		
		≤1.71 µg/g BPA	1	138		
		> 1.71 µg/g BPA	2.48 (1.78–3.49)	164		
		CYP19A1 rs1902580 interaction: Adjusted OR, Urinary BPA, µg/g				
		GG, low exposure	1	NR		
		GG, high exposure	2.6 (1.75–3.89)	NR		
		GA + AA, low exposure	1.58 (0.98–2.54)	NR		
		GA + AA, high exposure	3.71 (2.13–6.62)	NR		
		CYP1A1 rs1048943 interaction: Adjusted OR, Urinary BPA, µg/g				
		TT, low exposure	1	NR		
		TT, high exposure	2.73 (1.74–4.34)	NR		
		CT + CC, low exposure	1.13 (0.72–1.76)	NR		
		CT + CC, high exposure	2.49 (1.55–4.01)	NR		
		CYP1A1 rs4646422 interaction: Adjusted OR, Urinary BPA, µg/g				
		CT +TT, low exposure	1	NR		

[3] Ultrahigh-performance liquid chromatography-high-resolution mass spectrometry

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
		CT + TT, high exposure	3.12 (1.64–6.03)	NR		these results. A single spot urine sample collected after breast cancer diagnosis could not account for within person variability in BPA levels nor rule out reverse causation. No QC measures reported. Did not report efforts to mitigate contamination from other sources besides collection material.
		CC, low exposure	1.5 (0.9–2.52)	NR		
		CC, high exposure	3.46 (2.04–5.97)	NR		
		CYP17A1 rs743572 interaction: Adjusted OR, Urinary BPA, µg/g				
		GG, low exposure	1	NR		
		GG, high exposure	1.64 (0.9–3.04)	NR		
		GA + AA, low exposure	0.84 (0.52–1.36)	NR		
		GA + AA, high exposure	2.49 (1.57–4.19)	NR		
		CYP2E1 rs3813867 interaction: Adjusted OR, Urinary BPA, µg/g				
		CG + CC, low exposure	1	NR		
		CG + CC, high exposure	2.52 (1.4–4.61)	NR		
		GG, low exposure	1.04 (0.65–1.66)	NR		
		GG, high exposure	2.56 (1.57–4.19)	NR		
		CYP24A1 rs2296241 interaction: Adjusted OR, Urinary BPA, µg/g				
		GG, low exposure	1	NR		
		GG, high exposure	2.69 (1.5–4.89)	NR		
		AG + AA, low exposure	1.2 (0.74–1.96)	NR		
		AG + AA, high exposure	2.9 (1.75–4.87)	NR		
Keshavarz-Maleki et al. (2021) Case-Control	**Population:** Surgery patients at the university hospital of Imam Khomeini,	OR, Concentration of BPA (ng/ml)			Age, BMI	**Exposure information:** LOD < 10 pg/ml (0.065 pg/g tissue) Geometric mean total BPA in urine: 1.69 ng/ml (cases); 0.83 ng/ml
		BPA in breast adipose tissue (ng/ml)	54.96 (2.08–1372.55)	NR		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Tehran, Iran **Enrollment or follow-up:** 2018–2019	Tehran, Iran Cases: 41; Controls: 11 **Exposure assessment method:** urine and breast adipose tissue; BPA measured in adipose breast tissue samples collected during surgery and first morning spot urine (collected within 24 hours of surgery). Reported use of sample collection material to limit BPA contamination. Exposure proxy: total BPA assessed using ELISA[4]. Did not report how samples below LOD were treated.	BPA in urine (ng/ml)	10.59 (1.62–65.7)	NR		(controls) Geometric mean BPA in breast adipose tissue: 3.50 ng/g (cases), 1.50 ng/g (controls) **Strengths:** Measured BPA in both urine and breast adipose tissue samples. **Limitations:** Single sample in each matrix does not account for within-person variability over time and may limit ability to detect an effect. Small sample size. Limited number of sociodemographic variables presented, selection of all subjects from single referral center which may not reflect the underlying study population. Reported difficulty in enrolling healthy controls from same referral center. Did not match study subjects on potential confounders; does not ensure comparability between the case and control groups. Did not report how samples below LOD were treated. Did not adjust urinary BPA levels for creatinine. Exposure method (ELISA) may not be specific to BPA.
López-Carrillo et al. (2021) Case-Control Mexico (5 northern	**Population:** 1045 patients with histologically confirmed breast cancer, matched by	OR, Free BPA (µg/l)			Age (years), creatinine (mg/dl)	**Exposure information:** LOD: 2.78 ng/ml [µg/l] in all samples: Geometric mean BPA ng/ml [µg/l]: 3.16 in cases, 2.47 controls
		All women ≤1.39	1	319		
		All women 1.40–12.05	0.73 (0.39–1.35)	18		
		All women >12.05	2.31 (1.43–3.74)	57		

[4] Enzyme-linked immunosorbent assay

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
states) **Enrollment or follow-up:** 2007–2011	age with 1030 women without cancer and residing in the same study area. Cases identified in public tertiary hospitals in study region (n = 17 hospitals). Cases: 394; Controls: 404 **Exposure assessment method:** urine; single first-morning void urine sample (collected 2007–2011) (pre-treatment for cases). Collection material selected that limits BPA contamination reported. Exposure proxy: BPA analyzed by HPLC/FD[5]. BPA concentrations corrected by recovery percentage. Samples below the LOD were imputed as 1.97 µg/l (LOD/√2). Creatinine adjusted.	Women with BPA <80% of recovery, ≤1.39	1	185		Geometric mean BPA in samples >LOD: 20.81 ng/ml [20.81 µg/l] (all), 28.11 ng/ml [28.11 µg/l] (cases), 13.42 ng/ml [13.42 µg/l] (controls) **Strengths:** Use of population-based controls. **Limitations:** The analyses were only adjusted for age and creatinine levels but not obesity or other potential confounders. Single urine sample does not account for within-person variability over time and may limit ability to detect an effect. The detection limit was at least one order of magnitude higher than in other studies, which captures only those highly exposed. BPA was imputed for the majority of cases (82%) and controls (88%), therefore decreasing capacity to characterize exposure. The ORs are based on creatinine-adjusted BPA categories but only unadjusted values of BPA levels were given. This is a concern because after adjusting for creatine, some samples may move into a different category.
		Women with BPA <80% of recovery, 1.40–12.05	1.42 (0.5–4)	11		
		Women with BPA <80% of recovery, >12.05	1.18 (0.62–2.27)	28		
		Women with BPA ≥80% of recovery, ≤1.39	1	134		
		Women with BPA ≥80% of recovery, 1.40–12.05	0.54 (0.22–1.32)	7		
		Women with BPA ≥80% of recovery, >12.05	4.59 (2.17–9.74)	29		
		Women with BPA ≥LOD (2.78 µg/l), ≤12.83	1	13		
		Women with BPA ≥LOD (2.78 µg/l), >12.83	4.43 (1.89–10.42)	57		
Morgan et al. (2017)	**Population:** NHANES	OR, Categorized BPA (ng/g) creatinine adjusted			Race/ethnicity, age	**Exposure information:** LODs not reported but available
		< LOD to 50%	1	44		

[5] High-pressure liquid chromatography equipped with a fluorescence detector

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Cross-sectional United States **Enrollment or follow-up:** 2005–2010	Cases: 78; Controls: 2067 **Exposure assessment method:** urine; BPA measured in a single spot urine sample collected after breast cancer diagnosis. No measures to limit BPA contamination reported. Number of samples below LOD not reported. Exposure proxy: total BPA following enzymatic hydrolysis, analyzed by HPLC-MS/MS at the CDC; creatinine adjusted.	≥ 50% (0.42–1.23)	0.76 (0.45–1.3)	34	Race/ethnicity, BMI, age at menarche	from NHANES. Geometric mean: controls = 1.16 ng/g; cases = 1.06 ng/g (log transformed and creatinine adjusted) **Strengths:** Large sample size. NHANES dataset. **Limitations:** Did not report confidence interval for the risk estimate from the most adjusted model. Use of self-reported cancer diagnosis makes outcome subject to misclassification through possible over or underreporting. A single spot urine sample collected after breast cancer diagnosis could not account for within person variability in BPA levels nor rule out reverse causation.
		OR, Categorized BPA (ng/g) creatinine adjusted				
		< LOD to 50%	1	44		
		≥ 50% (0.42–1.23)	0.73	34		
Parada et al. (2019) Case-Control Long Island, NY USA **Enrollment or follow-up:** 1996–1997	**Population:** Subjects from Long Island Breast Cancer Study Project (LIBCSP), a population-based study of breast cancer which included 1,508 women with a first diagnosis of in situ or invasive breast cancer and 1,556	OR, BPA (µg/g creatinine)			Menopausal status, use of hormone replacement therapy, age at menarche, parity/lactation history, family history of breast cancer, BMI, lifetime alcohol intake, age, education	**Exposure information:** LOD: 0.04 ng/ml. Median total BPA concentration: 1.53 µg/g (cases), 1.69 µg/g (controls) **Strengths:** Large sample size. Urine samples taken before chemotherapy for most participants. BPA analyses conducted by CDC laboratory. **Limitations:** Relatively high LOD. A single spot urine sample collected after breast cancer diagnosis could not account
		Ln(BPA)	0.91 (0.8–1.02)	NR		
		< LOD–0.950	1	174		
		0.958–1.38	0.76 (0.53–1.09)	132		
		1.38–2.04	0.76 (0.53–1.09)	135		
		2.05–3.63	0.8 (0.56–1.15)	142		
		3.63–388	0.75 (0.52–1.08)	128		
		Trend-test *p*-value: 0.11				
		OR, BPA (µg/g creatinine), BMI < 25 kg/m²				
		Ln(BPA)	0.78 (0.66–0.93)	NR		
		< LOD–1.23	1	119		
		1.24–2.44	0.8 (0.53–1.19)	105		
		2.45–388	0.65 (0.44–0.98)	92		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
	women without breast cancer. Cases: 711; Controls: 598 **Exposure assessment method:** urine; BPA measured in a single spot urine sample collected after breast cancer diagnosis (2007 & 2010). 79.1% of urine samples were collected prior to the initiation of chemotherapy. No QC measure reported. No measures to limit BPA contamination reported. Exposure proxy: total BPA following enzymatic hydrolysis, analyzed by HPLC-MS/MS at the CDC; Creatinine adjusted. Samples below LOD were imputed as the LOD/√2.	OR, BPA (µg/g creatinine), BMI ≥25 kg/m²				for within person variability in BPA levels nor rule out reverse causation. Approximately 20% of samples were below the limit of detection, therefore decreasing capacity to characterize exposure. No QC measure reported. Exposure proxy (deconjugated BPA-G and BPA-S + BPA) may be affected by background contamination.
		Ln(BPA)	1.04 (0.87–1.24)	NR		
		< LOD–1.23	1	139		
		1.24–2.44	0.93 (0.63–1.39)	124		
		2.45–388	1.07 (0.71–1.6)	130		
		Breast cancer-specific mortality: OR, BPA (µg/g creatinine)				
		Ln(BPA)	1.02 (0.82–1.28)	NR		
		< LOD–0.950	1	26		
		0.958–1.38	0.78 (0.41–1.47)	16		
		1.38–2.04	0.77 (0.41–1.44)	16		
		2.05–3.63	1.03 (0.57–1.85)	22		
		3.63–388	0.93 (0.5–1.73)	18		
		Trend-test *p*-value: 0.85				
		Breast cancer-specific mortality: OR, BPA (µg/g creatinine), BMI <25 kg/m²				
		Ln(BPA)	0.85 (0.55–1.3)	NR		
		< LOD–1.23	1	11		
		1.24–2.44	1.33 (0.59–2.99)	14		
		2.45–388	1.05 (0.42–2.64)	8		
		Breast cancer-specific mortality: OR, BPA (µg/g creatinine), BMI ≥25 kg/m²				
		Ln(BPA)	1.11 (0.85–1.44)	NR		
		< LOD–1.23	1	25		
		1.24–2.44	0.54 (0.27–1.07)	13		
		2.45–388	1.2 (0.68–2.1)	27		
Trabert et al. (2014) Case-Control Poland **Enrollment or follow-up:**	**Population:** Cases: 575; Controls: 575 **Exposure assessment method:** urine; BPA	Post-menopausal: OR, Creatinine-adjusted BPA-G (ng/mg)			Conditioned on age and study site, education, BMI, age at menarche, parity, years	**Exposure information:** LOD: NR (cited method reports LOD of 0.005 ng/ml) BPA-G geometric mean: 4.11 ng/mg creatinine (cases), 3.92 ng/mg creatinine (controls)
		Log-transformed continuous	1.04 (0.91–1.17)	575		
		< 2.06	1	123		
		2.06–4.16	1.7 (1.15–2.52)	176		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
2000–2003	measured in a single 12-hour overnight urine sample collected after diagnosis (2000–2003), with some samples collected after treatment or surgery. No measures to limit BPA contamination reported. Exposure proxy: Unconjugated BPA and BPA-G were analyzed by HPLC/MS/MS[6]. Creatinine adjusted. Samples below LOD were imputed as 0.1 g /mg creatinine for continuous exposure and included in first quartile for categorical exposure.	4.17–7.80	1.02 (0.67–1.55)	130	since menopause, duration of menopausal hormone therapy use, family history of breast cancer, history of benign breast disease, ever had screening mammogram	**Strengths:** Measurement of the conjugated form of BPA, which reflects BPA metabolism, reduces potential BPA contamination of samples that may arise during processing or laboratory analyses. **Limitations:** Potential for reverse causation as all samples collected post-diagnosis, and some post treatment or surgery. No QC measures reported. Measurement of urinary BPA-G may not adequately reflect exposure to BPA, due to the inter-individual variability in BPA glucuronidation. Analysis of a single urine sample per person does not account for within-person variability over time and may limit ability to detect an effect. Models may have over-adjusted for covariates and could result in a loss of precision.
		> 7.80	1.09 (0.73–1.63)	143		
		Trend-test *p*-value: 0.59				
		Post-menopausal, ER+ tumors: OR, Creatinine-adjusted BPA-G (ng/mg)				
		ER+, Log-transformed continuous	0.99 (0.85–1.14)	384		
		ER+, < 2.06	1	76		
		ER+, 2.06–4.16	1.34 (0.83–2.17)	113		
		ER+, 4.17–7.80	0.86 (0.51–1.43)	91		
		ER+, > 7.80	0.84 (0.51–1.36)	102		
		Trend-test *p*-value: 0.84				
		Post-menopausal, ER– tumors: OR, Creatinine-adjusted BPA-G (ng/mg)				
		ER–, Log-transformed continuous	1.12 (0.89–1.43)	191		
		ER–, < 2.06	1	47		
		ER–, 2.06–4.16	2.89 (1.41–5.93)	63		
		ER–, 4.17–7.80	1.53 (0.69–3.39)	39		
		ER–, > 7.80	2.11 (0.94–4.74)	41		
		Trend-test *p*-value: 0.34				
Reeves et al. (2018)	**Population:** Participants recruited	Adjusted OR, Detectable BPA (>LOQ of 0.38 ng/g)			BMI	**Exposure information:** LOQ: 0.38 ng/g
		Controls	1	14		

[6] High-performance liquid chromatography/tandem mass spectrometry

Case-Control Springfield, MA **Enrollment or follow-up:** 2014–2015	at Baystate Medical Center, Springfield, MA who were enrolled in the Rays of Hope Center for Breast Research Registry. Cases: 36; Controls: 14 **Exposure assessment method:** breast adipose tissue; BPA measured in 1 or more breast adipose tissue samples collected during surgery (2014–2015). Exposure proxy: BPA analyzed by HPLC-MS/MS. Measures taken to minimize BPA contamination. Reported BPA measures were blank-corrected. Samples below LOQ were imputed as “0”.	Cases	0.9 (0.4–2)	36	Mean BPA for samples > LOQ: 0.71 ng/g (cases), 0.66 ng/g (controls) **Strengths:** This was the only study to use generalized estimating equation models to account for repeated measurements. BPA levels were blank-corrected. **Limitations:** Small sample size. This study was difficult to interpret as it is not clear how the ORs were calculated. All cases were compared to controls (the referent), rather than assessing the effect of the exposure (as a continuous or categorical variable, with the lowest exposure category serving as the reference category) on the outcome. High LOQ. BPA levels were highly variable both within-breast and between breasts; coefficients of variation ranged 8.9% to 141.4% in replicate samples with BPA>LOQ. Approximately 70% of samples were below the LOQ, therefore decreasing capacity to characterize exposure. Lacked urine samples to correlate breast adipose tissue levels. Analysis of tissue samples collected at the same time does not account for within-person variability over time and may limit ability to detect an effect. Potential for bias in control selection; reduction mammoplasty patients may not represent the source population.

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Salamanca-Fernández et al. (2021) Case-cohort Spain (Gipuzkoa, Granada, Murcia, Navarra) **Enrollment or follow-up:** 1992–1996	**Population:** EPIC (case-cohort) Cases: 547; Controls: 1918 **Exposure assessment method:** serum; BPA measured prospectively in a single serum sample collected at recruitment (1992–1996) before case ascertainment (2011–2013); no measures to limit BPA contamination reported; exposure proxy: total BPA following enzymatic hydrolysis analyzed by UHPLC-MS/MS[7]. Samples below LOD were imputed as the LOD/√2.	HR			Stratified by center and age group, education level, BMI, physical activity, smoking status, alcohol consumption, menopause, number of pregnancies, breastfeeding, oral contraceptive use, HRT, age	**Exposure information:** LOD: 0.2 ng/ml total Geometric mean BPA in serum: 1.12 ng/ml (cases), 1.10 ng/ml (subcohort) **Strengths:** Prospective sample collection. Adequate follow-up time (median 16.9 years). Population is large. Used previously-validated questionnaires to characterize covariates. **Limitations:** High LOD. BPA detection in serum generally underestimates the levels of BPA excreted. Analysis of a single sample per person does not account for within-person variability over time and may limit ability to detect an effect. Exposure proxy (deconjugated BPA-G and BPA-S + BPA) may be affected by background contamination. Approximately 30% of samples were below the limit of detection, therefore decreasing capacity to characterize exposure.
		BPA levels (for 5 ng/ml increase)	1.047 (0.98–1.12)	2306		
		Log2(BPA)	1.011 (0.97–1.06)	2306		
		HR, Categorized BPA (values in ng/ml)				
		< LOD	1.047 (0.98–1.12)	705		
		Tertile 1 [0.2–1.8)	0.82 (0.61–1.1)	562		
		Tertile 2 [1.8–5.1)	0.875 (0.65–1.18)	556		
		Tertile 3 [5.1–68.9]	1.127 (0.84–1.5)	483		
Aschengrau et al. (1998) Case-Control Cape Cod, MA USA **Enrollment or**	**Population:** Cases: 261; Controls: 753 **Exposure assessment method:** JEM;	Adjusted OR			Age at diagnosis or index year, vital status at interview, family history of	**Exposure information:** probable occupational exposure to bisphenol A: 9.6% of cases, 11.6% of controls **Strengths:** Industrial hygienist-based exposure
		Unexposed to xenoestrogens	1	158		
		Any BPA	0.8 (0.5–1.4)	25		
		BPA plus other xenoestrogens	0.8 (0.5–1.4)	23		

[7] Ultra-high performance liquid chromatography with tandem mass spectrometry detection

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
follow-up: 1983–1986	exposure assessment based on data from the NIOSH National Occupational Exposure Survey, chemical production and usage information, and the expert judgment of a certified industrial hygienist.	Only BPA	–	2	breast cancer, age at first birth, personal history of prior breast cancer, benign breast disease	assessment combined with subject specific information on job tasks and calendar years of employment to increase specificity of NIOSH/NOES matches. Selection bias unlikely: participation rates high and similar demographic characteristics between cases and controls. Exposure assessment was blinded to outcome status and independent of the interview. **Limitations:** Information bias possible: exposure assessment relied on interview data from study subjects and their next-of-kin. Crude exposure assessment: exposure assignments were for any versus no exposure and no information on exposure intensity. Non-occupational BPA exposure was not assessed (e.g., BPA from food) which could bias risk estimates towards the null. The general population is not highly exposed to BPA through jobs, therefore the design and methods are not ideal to assess BPA exposure. Could not account for other occupational co-exposures; there were 2 cases exposed to 'only BPA' and a risk estimate could not be calculated.
		Unadjusted OR			None	
		1–5 years any BPA	0.2 (0.1–0.7)	NR		
		6–10 years any BPA	2 (0.5–7)	NR		
		>10 years any BPA	1.5 (0.6–3.3)	NR		

3.2.2 Prostate cancer

Both of the epidemiologic studies that assessed the association between BPA exposure and prostate cancer found evidence of an association. One cross-sectional study did not provide a risk estimate but is reported briefly below (Tarapore et al. 2014).

In a case-cohort analysis, Salamanca-Fernández et al. (2021) included 575 prostate cancer cases and 3690 cancer free members of the Spanish EPIC cohort (1772 men) with available data on BPA exposure (Table 5). Total BPA was measured in serum samples collected prospectively at recruitment. There were no significant differences in serum BPA levels (p = 0.809) in prostate cancer cases (1.33 ng/ml) compared with the subcohort (1.29 ng/ml). BPA was not associated with prostate cancer in linear models (hazard ratio [HR] for 5 ng/ml increase in BPA: 0.989; 95% CI: 0.92–1.06). However, when BPA was analyzed as a $\log_2$ transformed continuous variable, there was a 3.5% increase in risk of prostate cancer with every ng/ml increase in BPA level (HR: 1.035; 95% CI: 0.99–1.08). The increases in risk were also observed when BPA was analyzed in tertiles compared to those below the limit of detection: HR tertile 1, 1.404 (95% CI: 1.05–1.88); HR tertile 2, 1.365 (95% CI: 1.02–1.82); HR tertile 3, 1.305 (95% CI: 0.98–1.74). [Exposure assessment limitations: single sample; biological matrix analyzed (serum); relatively high LOD; and imputation of exposure levels for 28.3% of participants below the LOD.]

Tse et al. conducted a case-control study in Hong Kong among 431 incident prostate cancer cases and 402 age-matched controls (Tse et al. 2017; Tse et al. 2018). Cumulative BPA exposure through ingestion was assessed using a tool reconstructed through questionnaire data and a literature review of BPA levels, similar to construction of a JEM. Detailed data were collected on habitual use of specific types of food or beverage container including what the container is made of, the frequency of use (e.g., daily, weekly, etc.), the handling practice (e.g., for storing hot water, heating by microwave), and years of usage. The BPA assessment tool ranked specific items of food or beverage containers in terms of concentrations of BPA according to the literature review. Increasing cumulative BPA exposure was associated with prostate cancer (OR high exposure vs low exposure: 1.88; 95% CI: 1.24–2.86), with evidence of an exposure-response (p-value for trend = 0.014). The study adjusted for age, marital status, and unemployment status and therefore may have been over-adjusted. Hospital controls were recruited, which may differ in lifestyle habits from the general population. Misclassification of BPA exposure was possible as there were no considerations of exposure variations over time. Other routes of BPA exposure such as direct skin contact or inhalation were not measured by the index. The assessment tool was further validated by two experts in environmental hygiene and food safety who blindly rated the exposure intensity of BPA based on the same master list and same rating scale. High

inter-rater and inter-method agreement was obtained with interclass correlation coefficients of 0.86 and 0.90, indicating a good replication of the tool for evaluating environmental BPA exposure via ingestion. [Exposure assessment limitations: this tool was limited to certain sources of dietary exposure and didn't capture other sources or routes.]

Tarapore et al. (2014) also assessed total BPA exposure and prostate cancer in a cross-sectional study, but did not present a risk estimate. Among the 60 urology patients included in this study, creatinine-adjusted urinary BPA levels in prostate cancer patients (5.74 mg/g [95% CI: 2.63, 12.51]) were significantly higher than in urology patients without prostate cancer (1.43 mg/g [95% CI: 0.70, 2.88]) (p = 0.012). This study is not included in Table 5. [Exposure assessment limitations: single sample; collection of spot urinary samples.]

Table 5 Prostate cancer

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Salamanca-Fernández et al. (2021) Case-cohort Spain **Enrollment or follow-up:** EPIC cohort enrollment 1992–1996; 2011–2013 for case ascertainment	**Population:** Participants of subcohort from 4 EPIC centers in Spain: Gipuzkoa, Granada, Murcia and Navarra Cases: 575; Controls: 1772 **Exposure assessment method:** serum; BPA measured prospectively in a single serum sample collected at recruitment (1992–1996) before case ascertainment (2011–2013); no measures to limit BPA contamination reported; exposure proxy: total BPA following enzymatic hydrolysis analyzed by UHPLC-MS/MS. Samples below LOD were imputed as the LOD/√2.	HR, Serum BPA levels (Categorized (ng/ml) and continuous)			Age, education level, BMI, physical activity, smoking status, alcohol consumption	**Exposure information**: LOD: 0.2 ng/ml total BPA levels: 1.33 ng/ml in prostate cancer cases and 1.29 ng/ml in the subcohort **Strengths:** Prospective sample collection. Adequate follow-up time (median 16.9 years). Population is large. Used previously-validated questionnaires to characterize covariates. **Limitations:** High LOD. BPA detection in serum generally underestimates the levels of BPA excreted. Analysis of a single sample per person does not account for within-person variability over time and may limit ability to detect an effect. Exposure proxy (deconjugated BPA-G and BPA-S + BPA) may be affected by background contamination. Approximately 30% of samples were below the limit of detection, therefore decreasing capacity to characterize exposure.
		BPA levels (for 5 ng/ml increase)	0.989 (0.92–1.06)	NR		
		Log2(BPA)	1.035 (0.99–1.08)	NR		
		< LOD (0.2 ng/ml)	1	NR		
		Tertile 1 (0.2–1.8)	1.404 (1.05–1.88)	NR		
		Tertile 2 (1.8–5.1)	1.365 (1.02–1.82)	NR		
		Tertile 3 (5.1–68.9)	1.305 (0.98–1.74)	NR		
Tse et al. (2017; 2018) Case-Control Hong Kong **Enrollment or follow-up:**	**Population:** Cases: 431; Controls: 402 **Exposure assessment method:** questionnaire;	OR, Cumulative BPA Index (Categorical, main model)			Age, marital status, unemployment status	**Exposure information:** dietary exposure scores calculated from questionnaire responses using a literature review **Strengths:** Chronic BPA exposure via
		Low	1	75		
		Middle	1.66 (1.15–2.4)	232		
		High	1.88 (1.24–2.86)	124		
		Trend-test *p*-value: 0.014				

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
2011–2016	Exposure was assessed using a tool that reconstructed BPA exposure through questionnaire data (use of specific types of food and beverage containers and handling conditions) and a literature review of BPA levels, similar to construction of a JEM. The BPA assessment tool rankings were validated against exposure intensity assessments by two experts.	OR, Cumulative BPA Index (Categorical, full model)			Age at interview, marital status, unemployment status, family prostate cancer history, consumption of deep fried food, consumption of pickled vegetable, green tea drinking habits, nightshift work, cumulative BPA exposure index	ingestion assessed using a validated tool with high interrater agreement. **Limitations:** Potential for selection bias: Use of hospital controls which may differ in lifestyle habits from the general population. Misclassification of BPA exposure possible: no considerations of exposure variations over time, exposure through sources other than specific types of food and beverage containers, or of exposure contributions through nondietary routes
		Low	1	75		
		Middle	1.54 (1.05–2.26)	232		
		High	1.57 (1.01–2.44)	124		
		Trend-test *p*-value: 0.057				

3.2.3 Thyroid cancer

Positive associations between BPA and thyroid cancer were reported in two cross-sectional studies (Table 6).

Marotta et al. (2019) reported a crude OR of 3.71 (95% CI: 0.67–20.34) for the association between serum BPA levels and differentiated thyroid carcinoma in a study that included 5 centers in Italy. [Exposure assessment limitations: single sample; biological matrix analyzed (serum); no QC measures reported; no LOD reported (participants without detectable levels of BPA and other chemicals of interest were excluded from analyses).]

Zhou et al. (2017c) reported an OR of 3.57 (95% CI: 1.37–9.3) for papillary thyroid carcinoma associated with higher urinary BPA (>2.84 ng/ml) in a study conducted in Shandong Province, China. BPA was measured in both serum and urine, but ORs were calculated only for urine. [Exposure assessment limitations: single sample per matrix; not reporting how samples below LOD (17%) were treated.]

Both studies are limited by the cross-sectional design, as discussed above.

Table 6 Thyroid cancer

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Marotta et al. (2019) Cross-sectional Italy **Enrollment or follow-up:** January–April 2017	**Population:** Cases: 28; Controls: 27 **Exposure assessment method:** serum; BPA measured in a single sample collected at or after diagnosis; exposure proxy: BPA (analyte not specified, method reference not provided) analyzed by LC/FD/UV; no QC measures reported; no measures to limit BPA contamination reported; no LOD reported; number of samples below LOD not reported.	Differentiated thyroid carcinoma: Unadjusted OR			None	**Exposure information:** Median BPA in serum: 666.52 ng (differentiated thyroid carcinoma cases), 763.27 ng (benign nodules) **Limitations:** Cross-sectional design. BPA detection in serum generally underestimates the levels of BPA excreted. Participants without measurable serum levels of chemicals of interest, including BPA, were excluded from analyses. No QC measures reported and no LOD reported. Exposure proxy (analyte not specified) may be affected by background contamination. Potential for reverse causation as all samples collected at or after diagnosis. Analysis of a single serum sample per person does not account for within-person variability over time and may limit ability to detect an effect.
		Unexposed to BPA	1	2		
		Exposed to BPA	3.71 (0.67–20.34)	26		
Zhou et al. (2017c) Cross-sectional Shandong Province, China **Enrollment or follow-up:** February–September 2013	**Population:** Cases: 53; Controls: 65 **Exposure assessment method:** urine and serum; single sample collected after diagnosis; QC measures reported. Exposure proxy: total BPA following enzymatic hydrolysis, analyzed by HPLC-MS/MS; creatinine-adjusted. No measures to limit BPA contamination reported.	Papillary thyroid carcinoma: OR			Unclear	**Exposure information:** LOQ: 0.1 ng/ml (urine); 0.2 ng/ml (serum). Geometric mean urinary BPA, adjusted for creatinine: 4.68 µg/g (cases), 1.06 µg/g (controls). Geometric mean serum BPA: 7.61 ng/ml (cases) 7.62 ng/ml (controls) **Limitations:** Cross-sectional design. Treatment of samples below LOD (17%) was not reported. Analysis of a single sample per matrix (urine and serum) per person does not account for within-person
		Urinary BPA >2.84 ng/ml (not adjusted for creatinine)	3.57 (1.37–9.3)	NR		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
	Treatment of samples below LOD not reported.					variability over time and may limit ability to detect an effect. Creatinine-adjusted urine not used in regression analysis. Unclear which confounders were adjusted for in analyses. No OR reported for BPA in serum and thyroid cancer.

3.2.4 Endometrial cancer

Sarink et al. (2021) conducted a case-control study of post-menopausal endometrial cancer nested within the Multiethnic Cohort (Appendix Table C1). Creatinine-adjusted BPA was measured in urine samples collected at enrollment into the cohort, prospectively before disease diagnosis. Each woman provided a single overnight (CA and HI) or first morning urine sample (HI). Cancer was diagnosed a median of 6.6 years after urine collection. There was no association between BPA exposure and endometrial cancer in this study: OR tertile 2, 0.86 (95% CI: 0.44–1.67); OR tertile 3, 1.21 (95% CI: 0.6–2.44), *p*-value for trend = 0.5. [Exposure assessment limitations: single sample, collection of different types of spot urine samples (e.g., overnight, first morning void) across participants (though collection type was controlled for in analyses), and 22% within-batch variability.]

3.2.5 All cancer mortality

Bao et al. (2020) evaluated the association of BPA exposure with cancer mortality (defined as death from malignant neoplasms, ICD codes C00-C97) in the NHANES cohort with urinary BPA levels measured between 2003 and 2008 (Appendix Table C1). Mortality data was obtained through 2015 for a median follow-up time of 9.6 years. There was no association of urinary BPA levels with cancer mortality (HR: 0.98; 95% CI: 0.40–2.39) for the third tertile compared to the first tertile, with adjustment for age, sex, race/ethnicity, urinary creatinine levels, educational level, family income status, smoking, alcohol drinking, physical activity, total energy intake, Healthy Eating Index 2010 score, and BMI. [Exposure assessment limitations: single sample, collection of spot urine samples; no adjustment of BPA measure for urine volume (though analyses were adjusted for creatinine level).]

3.2.6 Bone cancer

A hospital-based case-control study in Wuhan, China found an association between urinary BPA levels above 7.01 ng/ml (creatinine-adjusted) with risk of osteosarcoma overall (OR: 1.41; 95% CI: 1.01–1.72; 63 cases), osteosarcoma affecting the hip (OR: 2.00; 95% CI: 1.30–3.17; 22 cases), and osteosarcoma affecting the knee (OR: 1.66; 95% CI: 1.14–2.49; 36 cases) (Jia et al. 2013) (Appendix Table C1). The authors also performed stratified analyses by genotype (GG [wild-type], and GC or CC [variants]) of the –22G>C polymorphism of the lysyl oxidase (LOX) gene, which has been shown to be related to the development of osteosarcoma with the CC genotype giving the highest risk. Participants with BPA levels above 7.01 ng/ml who carried a -22G>C polymorphism of LOX (GC or CC) had significantly increased risk of osteosarcoma

overall (*p*-value for interaction = 0.036), osteosarcoma affecting the hip (*p*-value for interaction = 0.024), and osteosarcoma affecting the knee (*p*-value for interaction = 0.017) compared to participants without the polymorphism. Cases and controls were matched by age and sex, but analyses did not adjust for additional confounders. [Exposure assessment limitations: single sample; BPA analyte not specified; type of urine sample collected not specified; relatively high LOD; no QC measures reported; number of samples below LOD not reported.]

3.2.7 Lung cancer

A hospital-based case-control study in Wuhan, China found an association between urinary BPA levels above 1.32 µg/g creatinine with risk of non-small cell lung cancer (NSCLC) (OR: 1.91; 95% CI: 1.39–2.62; 257 cases) compared to the reference group with BPA levels ≤0.29 µg/g creatinine (Li et al. 2020b) (Appendix Table C1). The study also evaluated the role of a single nucleotide polymorphism (SNP) involved in regulating estrogen signaling, rs2046210 at 6q25.1 (located upstream of the estrogen receptor-1 [ESR1] gene). A significant association between high levels of BPA and risk of NSCLC was observed in people carrying the rs2046210 A allele (OR: 3.02; 95% CI: 1.89–4.83; 132 cases), but not in those carrying the rs2046210 GG wild-type allele (OR: 1.68; 95% CI: 0.94–3.01; 69 cases). [Exposure assessment limitations: single sample; collection of spot urine samples.]

A small cross-sectional study from South Korea (Pamungkas et al. 2016) designed to identity potential metabolomic biomarkers of lung cancer did not present a risk estimate for serum BPA levels and lung cancer, but did report significantly higher BPA concentrations, as approximated from relative abundance of ions (confirmed with an external standard), in cases (n = 35) ($p < 0.05$) compared to controls (n = 70). This study is not included in Appendix Table C1. [Exposure assessment limitations: single sample; not specifying the BPA analyte (assumed it is free BPA, which is present in trace amounts and susceptible to contamination); the biological matrix analyzed (serum); no quantification of BPA levels; no QC measures reported; no LOD reported.]

3.2.8 Brain cancer

A hospital-based case-control study in Wuhan, China observed an association between urinary BPA levels and risk of meningioma, with a positive trend (*p*-value, 0.003) (Duan et al. 2013a) (Appendix Table C1). Quartiles 2, 3, and 4 of BPA exposure were all significantly increased compared to quartile 1, with the highest OR in quartile 4 (OR: 1.57; 95% CI: 1.12–2.09). Analyses were also stratified by BMI categories and HRT use. [Exposure assessment limitations: single sample; type of urine sample collected

not specified; no adjustment of BPA measure for urine volume; no QC measures reported; no LOD reported.]

3.2.9 Lymphohematopoietic cancer

A case-control study within the Epilymph study, a multi-center study conducted in six European countries, analyzed the association between multiple endocrine disrupting chemicals with risk of lymphoma and its subtypes (Costas et al. 2015) (Appendix Table C1). Controls were selected from population registers in two countries and from the same hospitals as cases in the other four countries. Probability of exposure to chemicals was determined by a JEM. Exposure probability scores were assigned by experts who determined the probability that occupational exposure levels exceeded the background level in the general population (through diet, environment, or consumer products). The association between ever exposure to BPA and lymphoma or its subtypes was not statistically significant (OR for lymphoma: 1.55; 95% CI: 0.78–3.08; 19 cases) (Costas et al. 2015). This study was limited by the small number of participants exposed to BPA, which reduces the power to detect an effect. [Exposure assessment limitations: the JEM doesn't capture widespread BPA exposure from non-occupational sources].

3.2.10 Eye cancer

Behrens et al. (2012) investigated uveal melanoma within the Study of Occupational Causes of Rare Cancers of Unknown Aetiology, which included populations from nine European countries (Appendix Table C1). Population, hospital, or cancer controls were matched by region, sex, and age. Exposure was determined through a JEM, which was calculated by combining exposure duration, exposure intensity, and probability into a weighted exposure score. Probability was assessed based on information of personal protective equipment use. There was no association between BPA exposure and risk of uveal melanoma. [Exposure assessment limitations: the JEM doesn't capture widespread BPA exposure from non-occupational sources].

3.2.11 Extrahepatic bile duct/gallbladder cancers

Ahrens et al. (2007) conducted a case-control study in men in six European countries investigating the relationship between occupational exposures and gallbladder carcinoma, cancer of the extrahepatic bile duct, and cancer of the ampulla of Vater (Appendix Table C1). Exposure was determined through a JEM. Exposure was quantified by probability, intensity, and duration based on job-specific questionnaires. The OR was 2.1 (95% CI: 1.0–4.3; 9 exposed cases) for the association between BPA

exposure and these cancers (combined). [Exposure assessment limitations: the JEM doesn't capture widespread BPA exposure from non-occupational sources].

3.3 Summary of Epidemiologic Studies

Epidemiologic studies of BPA and cancer outcomes with two or more published studies reporting measures of association with BPA are summarized below (breast, prostate and thyroid cancers). Results were not summarized for cancer outcomes for which only one such study was available (endometrium, bone, lymphohematopoietic system, lung, brain, bile duct/gallbladder, eye, and all cancer mortality).

3.3.1 Considerations for interpreting epidemiologic studies of BPA and cancer

BPA has been extensively used for decades in numerous consumer products and industrial applications and the general population can reasonably be assumed to have been exposed to BPA across all life stages. The level of BPA in the body varies over time and even over the course of a single day, due to its short biological half-life and frequent exposures from multiple sources. Thus, the collection of biological samples at a single point in time cannot reliably characterize an individual's long term BPA exposure. This represents a major limitation of all the epidemiologic studies that relied on biological samples to characterize BPA exposure, as none collected samples longitudinally. In addition, BPA was detected in biological samples at low frequencies in some of these studies, and the approaches taken in handling data where BPA was not detected, such as imputing BPA levels or omitting individuals with non-detectable levels can introduce bias in exposure characterization. The studies that did not rely on biological sampling, but used questionnaires or a JEM also had limitations. Questionnaire responses have not been found to correlate well with measured urinary BPA levels, and the use of a JEM is of limited utility given widespread exposure to BPA from non-occupational sources. Therefore, it is difficult for the reviewed epidemiologic studies to correctly assign individuals to categories or levels of BPA exposure.

Temporality is an important consideration for causal inference, but none of the biomarker studies demonstrate that the measured BPA levels reflected levels at the critical time window of susceptibility for cancer causation, even in the few studies that measured BPA before disease diagnosis. Studies with cross-sectional designs, including case-control studies that detected biomarkers of BPA exposure at the time of cancer diagnosis, could not rule out reverse causation. Missing the critical exposure period and failure to account for latency effects, which is on the order of years or decades for most carcinogens, can result in true causal effects being missed. Cross-sectional studies were additionally limited by the enrollment of prevalent cases that

represent individuals with the longest lasting disease, where factors related to survival may also be associated with BPA exposure levels.

Such considerations affect interpretation of all studies reviewed; there are additional limitations specific to each study as well.

3.3.2 Breast cancer

The majority of the epidemiologic studies on the carcinogenicity of BPA investigated breast cancer. Results are inconsistent in these studies and interpretation is challenging given several limitations. All but one of the breast cancer studies measured BPA in biological matrices (urine, serum, and breast adipose tissue), while one used a JEM.

Most breast cancer studies measured BPA in urine, which is considered to be the optimal biologic matrix, but BPA exposure was estimated in each of these studies from a single sample, and single samples are limited in their ability to estimate longer-term exposure. In the only study that collected urine samples prospectively, no association was observed with postmenopausal breast cancer in the Multiethnic Cohort (Wu et al. 2021). The time window of susceptibility may not have been captured, as samples were collected from women in their 60s.

Positive associations with urinary BPA levels were reported in some case-control studies, but there were several limitations that affect interpretation of these findings. Among hospital patients in China, a positive dose-response trend was reported, as well as interactions between ‘high BPA exposure’ and polymorphisms in several cytochrome P450 genes, but the study had limitations in methodology and reporting (He et al. 2022). Among breast cancer mastectomy patients and unmatched reduction mammoplasty controls in a hospital in Iran, a positive association was reported (Keshavarz-Maleki et al. 2021), but selection bias was a potential concern. A population-based study from Mexico reported positive associations, but BPA levels in over 85% of the collected urine samples were below the LOD and analyses were based on imputed levels, which can contribute to exposure measurement error (López-Carrillo et al. 2021). A population-based study of postmenopausal women in two cities in Poland reported some positive associations in one city but no association in the other (Trabert et al. 2014). A case-control study conducted in Long Island, New York reported inverse associations both overall and in a subset of women with a BMI of less than 25 kg/m² (Parada et al. 2019), but no quality control measures were reported.

Results from three cross-sectional studies that analyzed spot urine samples were similarly inconsistent. An analysis using NHANES data reported an inverse association and higher BPA levels in controls (Morgan et al. 2017). Two studies did not report risk estimates, but reported significantly higher BPA levels in cases than controls in India (Muthusamy et al. 2021) and Taiwan (Yang et al. 2018). However, the Indian study

reported that BPA was not detected in a fourth of the samples and the Taiwanese study excluded participants without detectable levels of any chemical of interest (including BPA).

Results from two hospital-based case-control studies that measured BPA in breast adipose tissues were also inconsistent. While there is some suggestion from studies of bariatric surgery patients (see Section 5.1) that adipose tissues may serve as a reservoir for BPA, additional studies are needed to verify this and to characterize intra-individual variability. A study from Massachusetts reported inverse associations (Reeves et al. 2018), while the study from Iran observed increases in risk with higher adipose levels of BPA (Keshavarz-Maleki et al. 2021). In the Massachusetts study, BPA levels were imputed for over two-thirds of samples (Reeves et al. 2018). Selection bias was of particular concern in both studies and it was unclear if the participants were representative of the source population: all participants were enrolled from a single referral center, controls were younger than cases, and few sociodemographic variables were presented. These studies were also limited in sample size by a small number of breast cancer mastectomy cases and even fewer breast reduction mammoplasty controls.

BPA was measured in serum in two studies, only one of which reported a measure of association. A case-cohort analysis of the Spanish arm of the EPIC cohort found a non-significant increase in risk with increasing levels of serum BPA collected before breast cancer diagnosis, but BPA levels were imputed for over a quarter of serum samples below the LOD (Salamanca-Fernández et al. 2021). A small case-control study from Korea reported a higher (not statistically significant) median level of total serum BPA in breast cancer cases than in controls (Yang et al. 2009a) but did not present a risk estimate. In addition, BPA levels were imputed for approximately half of serum samples below the LOD.

A population-based case-control study was the only breast cancer study that used a JEM to estimate BPA exposure (Aschengrau et al. 1998). Inverse associations were reported for both the categories of ‘any BPA exposure’ and ‘BPA plus other xenoestrogens.’ However, this study had limited ability to detect an effect because non-occupational sources, which contribute highly to BPA exposure, were not assessed.

3.3.3 Prostate cancer

Positive associations between BPA and prostate cancer were reported. A case-cohort analysis within the Spanish EPIC cohort observed an increase in the risk of prostate cancer with every unit increase in serum BPA and in tertiles of BPA levels compared to those below the LOD (Salamanca-Fernández et al. 2021). This study collected a single serum sample before cancer diagnosis; BPA levels in over a quarter of the samples

were below the LOD and analyses were based on imputed levels, which can contribute to exposure measurement error. In a hospital-based case-control study in Hong Kong, increased cumulative dietary BPA exposure within a five year period before diagnosis/recruitment was associated with prostate cancer, with evidence of an exposure-response trend (Tse et al. 2017; Tse et al. 2018). However, cumulative dietary BPA exposure was estimated retrospectively based on questionnaire data and a literature review of BPA levels; other sources and routes of exposure were not captured. A cross-sectional study among urology patients in Ohio observed significantly higher urinary BPA levels in prostate cancer patients than in urology patients without prostate cancer, but did not report a risk estimate (Tarapore et al. 2014).

3.3.4 Thyroid cancer

Positive associations between BPA and thyroid cancer were reported in two cross-sectional studies from Italy (Marotta et al. 2019) and China (Zhou et al. 2017c). The interpretation of these studies was limited by collection of a single biologic sample, the use of prevalent cases, and the lack of reporting on quality control measures or LOD.

4. CARCINOGENICITY STUDIES IN ANIMALS

4.1 Studies Exposing Rodents Beginning at or after 4 Weeks of Age

4.1.1 Overview of available studies

Carcinogenicity studies of BPA in rodents were identified by the literature search. Eight studies exposed rodents (rats, mice, and gerbils) to BPA starting at four to 14 weeks of age (Study # 1–8) (Table 7). Four out of these eight studies were two-year studies in rats and mice with BPA administered in feed (NTP 1982). Four studies with short study durations were conducted in female rats (12, 64 weeks) and male gerbils (24, 29 weeks) (Facina et al. 2018; Facina et al. 2021; Hao et al. 2016; Zhang et al. 2017a). The interpretation of data is limited for the last four studies because of less-than-lifetime study durations, small group size (≤ 10 per group), and the fact that only one organ/tissue was examined in those studies.

Table 7 Overview of studies exposing rodents to BPA beginning at or after four weeks of age

Study No.	Species, strain	Sex, group size	Study duration (weeks)	Route, age at first exposure (weeks)	Administered concentration or dose	Exposure duration (weeks)	Reference
1	Rat, F344	M, 50	108	Feed, 5	0, 1000, 2000 ppm	103	NTP (1982), Huff (2001)
2	Rat, F344	F, 50	108	Feed, 5	0, 1000, 2000 ppm	103	NTP (1982), Huff (2001)
3	Rat, F344	F, 7–10	64	Gavage, 6	0, 250, 1000 µg/kg-day	64	Zhang et al. (2017a)
4	Rat, F344	F, 10	12	Oral, 4	0, 50, 200, 400 mg/kg-day	12	Hao et al. (2016)
5	Mouse, B6C3F1	M, 50	107	Feed, 5	0, 1000, 5000 ppm	103	NTP (1982), Huff (2001)
6	Mouse, B6C3F1	F, 50	107	Feed, 5	0, 5000, 10000 ppm	103	NTP (1982), Huff (2001)
7	Gerbil, (strain not specified)	M, 6	24	Drinking water, 14	0, 50 µg/kg-day	24	Facina et al. (2018)
8	Gerbil, (strain not specified)	M, 7	29	Drinking water, 14	0, 50 µg/kg-day	29	Facina et al. (2021)

M, male; F, female; ppm, parts per million

4.1.2 Rats

4.1.2.1 Two-year feeding studies in male and female F344 rats (NTP 1982)

The results from these NTP studies were later published in a peer-reviewed journal article (Huff 2001).

Male Rats

Five-week-old male Fischer 344 (F344) rats (50 per group) were administered BPA in feed at 0, 1000, or 2000 ppm for 103 weeks. NTP calculated the average daily doses to be 0, 74, and 148 mg/kg-day, respectively. There was no significant difference in survival between the control and the treated groups. Mean bodyweight in the low and high dose groups were 95.5% and 91.3% of control values, respectively. Mean food consumption in treated males was approximately 90% of the controls.

Increases in leukemia (not otherwise specified, or NOS) of the hematopoietic system, fibroadenoma of the mammary gland, and interstitial (Leydig) cell tumors of the testis were observed in BPA-treated male rats (Table 8). The increase in the incidence of leukemia (NOS) was statistically significant in the high-dose group compared to the controls, and there was a significant trend (p = 0.021). The incidence of mammary gland fibroadenoma was significantly increased in the high-dose group compared to the controls, with a significant trend (p = 0.008). Statistically significant increases in interstitial (Leydig) cell tumors of the testis were observed in both treated groups, with a significant trend (p = 0.0015).

Table 8 Tumor incidence in male F344 rats administered BPA in feed for 103 weeks (NTP 1982)

Tumor site	Tumor type (week of first tumor)	Concentration in feed (ppm)			Trend test *p*-value
		0	1000	2000	
		Average daily dose (mg/kg-day)			
		0	74	148	
Hematopoietic system	Leukemia (NOS) (9 weeks)[1]	13/50	12/50	23/50*	0.021
Mammary gland	Fibroadenoma (106 weeks)[2]	0/36	0/40	4/34*	0.008
Testis	Interstitial (Leydig) cell tumor (86 weeks)[1]	35/47	48/48***	46/49**	0.0015

Treatment group tumor incidence with asterisks indicates significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Exact trend test conducted by OEHHA. NOS, not otherwise specified.
[1]Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site.
[2]Tumor incidence is expressed as the number of animals with the specified tumor over the number of animals examined at the specific tissue microscopically (NTP 1982).

Female Rats

Five-week-old female F344 rats (50 per group) were administered BPA in feed at 0, 1000, or 2000 ppm for 103 weeks. NTP calculated the average daily doses to be 0, 74, and 135 mg/kg-day, respectively. There was no significant difference in survival between the controls and the treated groups. Mean bodyweights in the low and high dose groups were 93.7% and 89.1% of control values, respectively. Food consumption in treated females was approximately 70–80% of the controls.

Marginal, non-significant increases of leukemia (NOS) were observed in BPA-treated groups (control, 7/50; 1000 ppm, 13/50; 2000 ppm, 12/50) compared to controls (Huff 2001; NTP 1982).

4.1.2.2 64-week gavage study in female F344 rats (thyroid gland only) (Zhang et al. 2017a)

Six-week-old female F344 rats were administered BPA (0, 250, 1000 µg/kg-day) via gavage for 64 weeks. Thyroid glands were removed for histological examination at 70 weeks of age. No significant difference in survival was observed between the controls and the treated groups. Mean bodyweights in treated females were lower than those of the controls but the decrease was not statistically significant.

No neoplastic lesions of the thyroid were observed in BPA treated groups (control, 0/10; BPA250, 0/7; BPA1000, 0/8). One animal of the 250 µg/kg-day BPA group developed thyroid focal hyperplasia (control, 0/10; BPA250, 1/7).

4.1.2.3 12-week oral study in female F344 rats (pituitary gland only) (Hao et al. 2016)

Four-week-old female F344 rats were administered BPA (dissolved in corn oil) orally at 0, 50, 200, or 400 mg/kg-day for 12 weeks. Pituitary glands were removed for histological examination. Pituitary tumors of the adenohypophysis were reported in BPA treated groups (control, 0/10; BPA50, 4/10; BPA200, 1/10; BPA400, 3/10). The increase was statistically significant in the low-dose group compared to the controls ($p < 0.05$). These tumors were likely adenomas of the *pars distalis*, based on the increased immunohistochemical staining of prolactin.

4.1.3 Mice

4.1.3.1 Two-year feeding studies in male and female B6C3F1 mice (NTP 1982)

The results of these NTP studies were later published in a peer-reviewed journal article (Huff 2001).

Male mice

Five-week-old male B6C3F1 mice (50 per group) were administered BPA in feed at 0, 1000, or 5000 ppm for 103 weeks. The average daily dose information (mg/kg-day) was not reported by NTP (1982) because of a lack of accurate measure of food consumption due to excessive spilling. There was no significant difference in survival between the controls and the treated groups. In treated male mice, mean bodyweights were decreased by no more than approximately 10% compared to controls. NTP (1982) reported that food consumption appeared to be similar among all groups.

In male mice, increases in malignant lymphomas (at all sites) and chromophobe carcinomas of the pituitary gland were observed (Table 9). The increase of malignant lymphomas was statistically significant in the low-dose group compared to the controls. One lymphocytic leukemia developed in the low-dose group and two leukemias (NOS) occurred in the high-dose group. Leukemias are rare in male B6C3F1 mice by the oral/feed route in NTP historical controls (0/952 among 20 studies) conducted between 1984 and 1994 (NTP 1999a). According to McConnell et al. (1986), it is appropriate to combine the incidences of malignant lymphomas with lymphocytic leukemia. The combined incidence of such lymphoma and leukemia in the low-dose group was significantly higher compared to the controls. Three animals in the high-dose group developed rare pituitary chromophobe carcinomas (trend test, $p = 0.047$).

Table 9 Tumor incidence in male B6C3F1 mice administered BPA in feed for 103 weeks (NTP 1982)

Tumor Site	Tumor Type (week of first tumor)	Concentration in feed (ppm)			Trend test *p*-value
		0	1000	5000	
Hematopoietic system[1]	Malignant lymphomas (77 weeks)	2/47	8/47*	3/45	NS
	All leukemias (91 weeks) [rare][2]	0/44	1/46	2/45	NS
	Malignant lymphomas and lymphocytic leukemia combined (77 weeks)[3]	2/47	9/47*	3/45	NS
Pituitary[4]	Chromophobe carcinoma (97 weeks) [rare]	0/37	0/36	3/42	0.0465

Treatment group tumor incidence with asterisks indicates significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
Exact trend test conducted by OEHHA. NS, not significant ($p \geq 0.05$).
[1]Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor and examined at the site.
[2]NTP historical controls (studies conducted between 1984 and 1994) for leukemia (lymphocytic, monocytic, mononuclear, or undifferentiated) were 0/952 in male mice. Leukemia is a rare tumor type in male mice (NTP 1999a).
[3]Malignant lymphomas and lymphocytic leukemia are combined based on McConnell et al. (1986)
[4]Tumor incidence is expressed as the number of animals with the specified tumor over the number of animals examined microscopically at the specific tissue as reported by NTP (1982). Chromophobe carcinoma is a rare tumor type in male mice. In the NTP historical control database of 19 studies conducted from 1984 to 1994 (NTP 1999a), the incidence of pituitary *pars distalis* neoplasms (adenoma and carcinoma combined) in male B6C3F1 mice was 0.6% (5/899, range 0–6.3%).

Female mice

Five-week-old female B6C3F1 mice (50 per group) were administered BPA in feed at 0, 5000, or 10000 ppm for 103 weeks. The average daily dose information (mg/kg-day) was not reported by NTP (1982) because of a lack of accurate measure of food consumption due to excessive spilling. There was no significant difference in survival between the controls and the treated groups. In treated female mice, mean bodyweights were decreased by more than 20% in both dosed groups at week 8 compared to controls, and decreases of 15% or more continued throughout the study. NTP (1982) reported that food consumption appeared to be similar among all groups.

No treatment-related tumors were observed in female mice.

4.1.4 Gerbils: 24-week and 29-week drinking water studies in males (prostate only)

Two studies examined the effects of BPA on prostate tumor induction in male gerbils (Facina et al 2018; 2021). Both studies are limited due to small group size, only one BPA dose level tested, short study duration, examination of only prostate, and imprecise reporting of tumor incidence.

Facina et al. (2018)

100-day-old male gerbils (n = 6) were administered 50 µg/kg-day BPA in drinking water (water given *ad libitum*) for 24 weeks. Prostates were removed at the end of the study (> 9-month-old) for histological analysis. The BPA dosed group exhibited non-significant weight gain compared with the control group. Malignant microinvasive carcinomas were found in BPA-treated animals (incidence reported as imprecise percentages with bar graphs; statistical significance not reported) in the dorsolateral prostate (DLP) and ventral prostate (VP), with none observed in controls. Premalignant lesions or prostatic intraepithelial neoplasia (PIN) were observed in the DLP and VP in both control and BPA-dosed animals, with a small increase in the DLP in the BPA-dosed animals. BPA-treated animals exhibited statistically significant increases in PIN multiplicity (number of lesions per animal) ($p < 0.05$).

Facina et al. (2021)

100-day-old male gerbils (n = 7) were administered 50 µg/kg-day BPA in drinking water for 29 weeks (Facina et al. 2021). At the end of the study, the BPA dosed group exhibited non-significant weight gain compared with the control group. Malignant MCs were observed in BPA-treated animals (incidence reported as imprecise percentages with bar graphs; statistical significance not reported) in the DLP and VP, with none observed in controls. Increases (*p*-value not reported) of premalignant PIN were observed in the DLP and VP in BPA-dosed animals compared to the controls. BPA-treated animals exhibited significant (as stated by the authors; *p*-value not provided) increases in PIN multiplicity compared to controls.

4.2 Studies Exposing Rodents Beginning *In Utero* or within the First Week of Life

4.2.1 CLARITY-BPA studies in rats (NTP 2018, 2021a)

4.2.1.1 Introduction to the CLARITY-BPA studies

The Consortium Linking Academic and Regulatory Insights on Bisphenol A (BPA) Toxicity (CLARITY-BPA) is a research program involving the National Institute of

Environmental Health Sciences (NIEHS), the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA), and several laboratories in academia (grantees).

CLARITY-BPA has two components, first, core guideline-compliant chronic studies conducted at NCTR from 2012 to 2015 (referred to as core studies in this document), and second, studies of various endpoints conducted by NIEHS-funded researchers (referred to as grantee studies). In the core studies, animals were exposed *in utero* and via gavage from gestation day 6 (GD6) through either postnatal day (PND) 21, or one or two years of age. The grantees were sent tissues from animals treated at NCTR in a similar manner as the animals included in the core studies. Animal numbers for the core studies were typically 20–50 per sex per treatment group, whereas numbers of animals and/or tissues provided for grantee studies were smaller (around 4–12 per sex per treatment group). The core studies are published as a National Toxicology Program (NTP) report, titled "A Perinatal and Chronic Extended-Dose-Range Study of Bisphenol A in Rats" (NTP 2018) and summarized in a peer-reviewed publication (Camacho et al. 2019). The grantee studies have been published in 17 peer-reviewed papers and summarized in an NTP report, titled "NTP research report on the consortium linking academic and regulatory insights on bisphenol A toxicity (CLARITY-BPA): a compendium of published findings" (NTP 2021a). Additionally, Heindel et al. (2020) conducted an integrated analysis of the findings from eight published peer-reviewed papers. Some unpublished grantee studies can be found in the NTP Chemical Effects in Biological Systems database (https://cebs.niehs.nih.gov/cebs/program/CLARITY-BPA).

The rat strain used by CLARITY-BPA, NCTR Sprague-Dawley/CD23/Nctr BR (SD (NCTR)), is a unique breeding colony of Sprague-Dawley (SD) rats maintained at NCTR. This colony originated from Charles River SD founders in the late 1970s and has been used in testing with hormonally active agents since then (NTP 2018). The colony was selectively bred for rapid growth and susceptibility to obesity (Uchtmann et al. 2020). The genetic background of this strain and its biological responses to BPA are quite different from other SD rats, such as Harlan SD rats used in chronic 2-year NTP carcinogenicity studies (Bansal and Zoeller 2019; Gileta et al. 2021).

4.2.1.2 CLARITY-BPA core studies, with in utero and gavage exposures (GD6 through PND21, or 1 or 2 years of age) and long-term observational periods in rats (Camacho et al. 2019; NTP 2018)

BPA (0, 2.5, 25, 250, 2500, and 25000 µg/kg-day) was administered daily by gavage in 0.3% carboxymethylcellulose vehicle to pregnant SD (NCTR) rats (dams) from GD6 through the start of parturition and then directly to male and female pups from the day after birth (PND1) until PND21 (stop-dose arm) or continuously until termination at one or two years of age (continuous-dose arm) (Figure 3). All animals were fed a soy- and

alfalfa-free diet to minimize phytoestrogen content, and were housed in polysulfone cages and drinking water was provided in glass water bottles to minimize unintentional background exposures to BPA. As shown below and in Figure 3, there are eight arms of studies in the CLARITY-BPA core studies. Additionally, a positive control, ethinyl estradiol (EE_2) (0.05, 0.5 µg/kg-day), was also included in the four continuous-dose arms to assess the sensitivity of the test system to low doses of an estrogen.

1. Stop-dose, 1-year, female (n = 20–22)
2. Stop-dose, 1-year, male (n = 19–22)
3. Stop-dose, 2-year, female (n = 46–50)
4. Stop-dose, 2-year, male (n = 46–50)
5. Continuous-dose, 1-year, female (n = 20–24)
6. Continuous-dose, 1-year, male (n = 20–24)
7. Continuous-dose, 2-year, female (n = 46–50)
8. Continuous-dose, 2-year, male (n = 46–50)

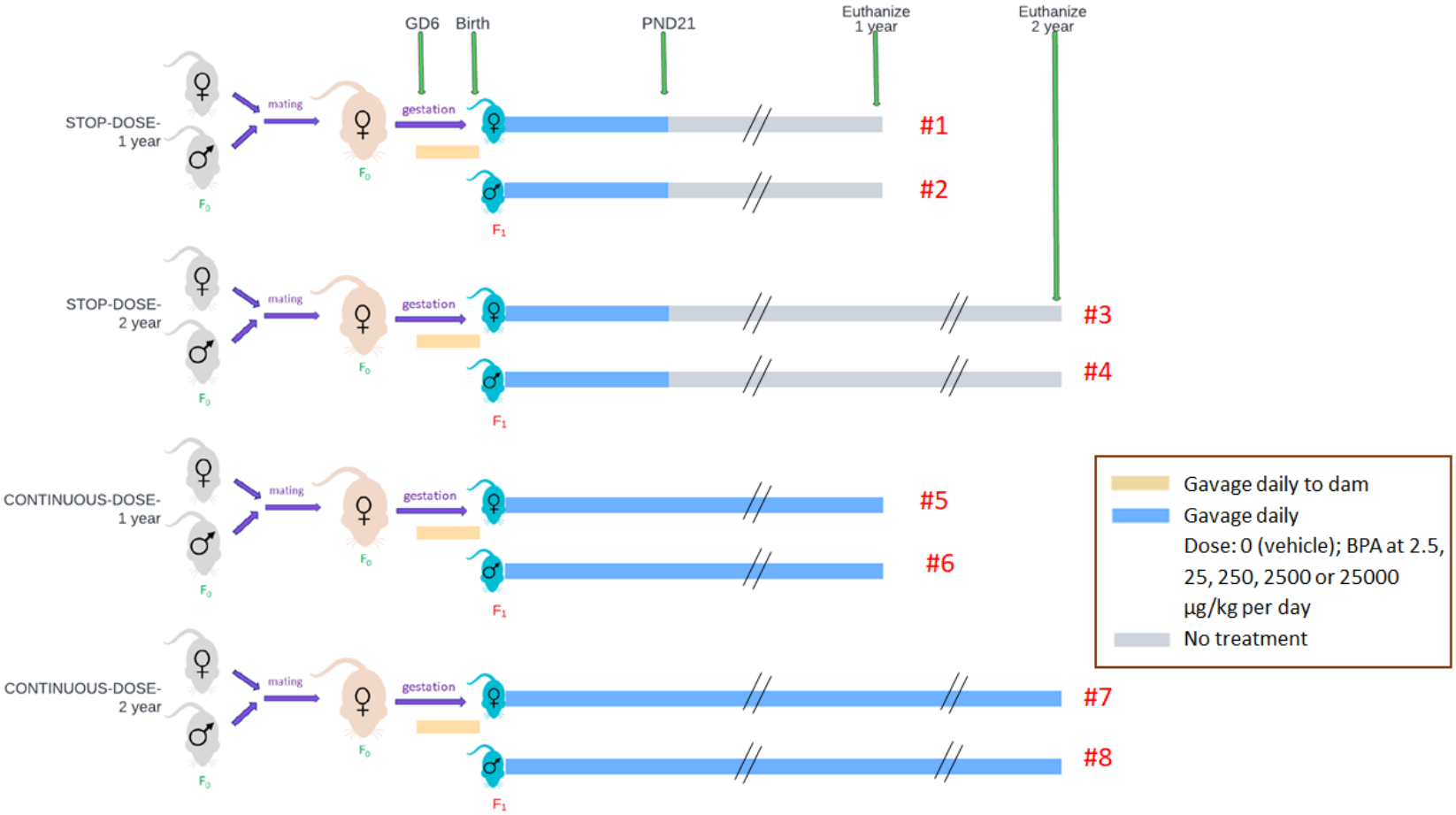


Figure 3 Design of the CLARITY-BPA core studies.

There are eight arms within the core studies. The dosing periods are indicated with orange (gavage to the F0 dams) and blue (gavage to the F1 pups) shadings. GD6, gestational day 6; PND21, postnatal day 21; F0, the parent generation; F1, offspring from F0.

NTP (2018) described the rationale for dose selection in the core studies. At a series of meetings in late 2011 and early 2012, scientists from NTP, NIEHS's Division of Extramural Research and Training, NCTR, and other FDA product centers, and NIEHS-funded CLARITY-BPA grantees discussed issues of study design, including dose selection. NTP (2018) noted:

> *"For discussion of dose selection, a summary of data obtained from the NCTR BPA subchronic study was presented and discussed. It was initially agreed that a vehicle control and six log-spaced doses between 2.5 and 250,000 µg BPA/kg bw/day would provide an adequate dose range from reasonably close to human exposure on the low end to a dose expected to produce clear adverse effects at the high end. Serum measurements of BPA across the postnatal life span of animals in the subchronic study showed that the high dose of 300,000 µg BPA/kg bw/day gave rise to approximately 50 µM active unconjugated BPA in PND 4 animals and approximately 1 µM in PND 80 animals, which were clearly out of the range of attainable human internal exposure from dietary sources, estimated to be in the low to sub-pM range. There was general agreement that the current concern was restricted to a lower dose range, below the previously reported no-observed-adverse-effect level in guideline-compliant regulatory toxicity assays, which was 5,000 µg/kg bw/day. The 250,000 µg BPA/kg bw/day dose group would provide little additional information to influence regulatory action. A high dose of 25,000 µg BPA/kg bw/day was viewed as providing an adequate margin of human exposure, greater than 25,000-fold based on the aggregate human exposure estimates of < 0.5 µg BPA/kg bw/day mentioned above. The low dose selected, 2.5 µg BPA/kg bw/day, provided a margin of exposure at least 10-fold higher than the maximum allowed background dietary exposure".*

The report indicated that the lowest dose, 2.5 µg/kg-day, is a dose reasonably close to human exposure levels and approximately 10-fold above the level that could potentially result from consumption of background BPA in the laboratory rodent diet. The highest dose, 25000 µg/kg-day, is a dose at least 50000-fold higher than the estimated 95th percentile human dietary exposures.

NTP (2018) and Camacho et al. (2019) stated the following conclusions from the CLARITY-BPA core studies:

> *"There was a possible relationship between the increased incidences of lesions in the female reproductive tract and the male pituitary and exposure to the 25,000 µg BPA/kg bw-day dose level."*

Available historical control databases

Historical control data enables the identification of rare spontaneous tumor types in an animal strain. The most appropriate historical control data come from control animals of the same strain, sex, animal colony, and laboratory, fed the same diet, housed under the same conditions, and from studies employing the same method of test substance administration and conducted within two or three years of the study in question[8]. Rare tumor types are defined as those with tumor incidence less than 1% in historical control animals.

No historical control data on spontaneous tumor incidences meeting all the factors listed above were identified for the CLARITY-BPA studies. Here, in identifying and discussing the rare tumor findings from CLARITY-BPA core studies (#1–#8), the following three databases of historical control tumor incidence for Sprague-Dawley rats were used:

- NTP (2008, 2010) (dietary/feed administration, SD (NCTR) rats, 1999 to 2003),
- Charles River (2013) (oral routes, Crl:CD®(SD)BR rats, 2001 to 2009), and
- NTP (2021b) (all routes, Hsd SD rats, 2007 to 2012).

Each of the three databases is relevant for comparing with the CLARITY-BPA core studies, yet each has its own unique set of strengths and limitations. The NTP (2008, 2010) studies were conducted by the same laboratory (NCTR) using SD rats from the same animal colony as those used in the CLARITY-BPA studies, Charles River (2013) is the original source of the SD rats that founded the NCTR strain, and NTP (2021b) offers studies that were conducted closer to the time period when the CLARITY-BPA core studies were conducted, albeit in a different colony of SD rats. Regarding limitations, some of the studies used by these databases to calculate the historical control data were conducted outside of the recommended time period (within 2 or 3 years of initiation of the CLARITY-BPA core studies) per the US EPA (2005) guidance[9]. Other limitations include non-gavage exposure routes, and usage of a SD rat colony that is different from the one used by the CLARITY-BPA core studies. Often, the individual animal studies within these databases fulfill some criteria but fail others. To retrieve a sufficient number of studies and animals for comparison, it was not possible to find a single set of historical control data that were considered as ideal. Therefore, all three databases are used as references in this document. Rare tumor types that are found in BPA treated animals and in less than 1% in historical control animals in each of the three sets of historical control data, with no occurrence in the concurrent controls,

[8] US EPA (2005) states "[t]he most relevant historical data come from the same laboratory and the same supplier and are gathered within 2 or 3 years one way or the other of the study under review; other data should be used only with extreme caution."

[9] *Ibid.*

are presented in this document. A detailed comparison of relevant study design elements of the CLARITY-BPA core studies to these three historical control databases is shown in Table 10.

Table 10 Comparison of study design elements between the CLARITY-BPA core studies and three selected historical control databases

Study design elements	CLARITY-BPA	NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Species and strain	SD/CD23/ Nctr BR [SD (NCTR)] rats	SD/CD23/ Nctr BR [SD (NCTR)] rats	Crl:CD®(SD)BR rats	Hsd SD rats
Study initiation date	Studies initiated in 2012 (ended in 2015)	Studies initiated between 1999–2003	Studies initiated between 2001–2009	Studies initiated between 2007–2012
Route of administration and exposure length	*In utero* (F0 oral gavage) plus oral gavage in F1 for 21 days, 1 year or 2 years	*In utero* and via lactation (F0 dietary) plus dietary in F1 for 21 days, 140 days or 2 years	Oral routes (7 gavage and 13 dietary studies) for 2 years	All routes (3 gavage, 7 dietary, 1 drinking water, and 2 inhalation studies) for 2 years
Feed	Purina 5K56 (soy- and alfalfa-free)	Purina 5K56 (soy- and alfalfa-free)	Purina PMI No. 5002	NIH-07 or NTP-2000
Cage and water bottle material	Polysulfone[1], glass	Polycarbonate, unknown	Not specified	Polycarbonate, unknown
Age at study termination	1 year or 2 years	2 years	2 years	2 years
Number of male rat controls	Various, see text above	207	1205	639
Number of female rat controls	Various, see text above	210	1205	640

[1] As mentioned in section 1.2, BPA monomer is also used in the manufacture of various specialty plastics including polycarbonate and some polysulfone plastic. Testing of a small number of polysulfone cages used in the CLARITY-BPA core studies did not detect the presence of measurable levels of BPA above background (laboratory blanks).

Stop-dose arms (#1, #2, #3, #4)

F1 female (#1, #3) and male (#2, #4) SD (NCTR) rats were exposed to BPA *in utero* from GD6 to birth and directly via gavage from PND1 through PND21. These rats were then observed for up to one (#1, #2) or two years (#3, #4). The BPA exposure for these stop-dose arms ceased at weaning (before puberty), to assess the potential for effects caused solely by developmental/early life BPA exposure. No positive control groups (treatment with EE_2) were included in the four stop-dose arms.

Stop-dose one-year studies (#1, #2)

Stop-dose one-year study in female rats (20–22 animals per group) (#1)

No significant difference in body weight or survival rate between the control and treated groups was reported.

Single occurrences of six types of rare tumors were observed in this study in BPA-treated females (see Table 11). In addition, two uterine stromal polyps were observed in BPA-treated females (1/22 [5%] in the 2.5 µg/kg-day dose group and 1/22 [5%] in the 250 µg/kg-day dose group) compared to none in the vehicle control. While these benign tumors are not rare in SD (NCTR) rats, a statistically significant increase in the incidence of these tumors (by trend) was observed in BPA-treated females in the one-year continuous-dose study (#5).

Table 11 Number of animals with rare tumors[1] in the stop-dose one-year study in female rats (#1), where female F1 SD (NCTR) rats were exposed to BPA during gestation[2] and via gavage from PND1 to PND21, and observed until study termination at one year of age (NTP 2018)

Tumor site	Tumor type	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=106)	Historical control[3]		
		0 (n=20)	2.5 (n=22)	25 (n=20)	250 (n=22)	2500 (n=20)	25000 (n=22)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Uterus	Adenoma	0	0	0	1	0	0	1	2/210 (0.95%) [0–2%]	6/1205 (0.5%) [0–3.08%]	3/500 (0.6%) [0–4%]
Zymbal's gland	Carcinoma	0	0	0	1	0	0	1	0/210	NR	0/640
Parathyroid	Adenoma	0	0	0	1	0	0	1	0/210	6/1205 (0.5%) [0–4%]	1/580 (0.17%) [0–2%]
Skin	Fibrosarcoma	0	0	0	1	0	0	1	0/210	6/1205 (0.5%) [0–2%]	4/640 (0.62%) [0–2%]
Brain	Malignant meningioma	0	0	0	0	0	1	1	0/210	1/1205 (0.08%) [0–2%]	1/590 (0.17%) [0–2%]
	Malignant schwannoma	0	0	0	0	0	1	1	1/210 (0.48%) [0–2%]	2/1205 (0.17%) [0–2%]	1/590 (0.17%) [0–2%]

NR: not reported.
[1]Rare tumors with historical control incidence of less than 1% and no occurrence in concurrent controls are presented.
[2]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.
[3]Three sets of historical control data are reported: NTP (2008, 2010) dietary route (SD (NCTR) rats, 1999–2003), Charles River (2013) oral routes (Crl:CD®(SD)BR rats, 2001–2009), and NTP (2021b) all routes (Hsd SD rats, 2007–2012). Brackets, range.

Non-neoplastic pathology findings

In the uterus, there was a statistically significant increase in cystic endometrial hyperplasia relative to vehicle controls at 25000 µg/kg-day (32% versus 10% in control, $p < 0.05$). Additionally, a statistically significant increase of squamous metaplasia in the uterus was observed in the 25000 µg/kg-day group (18% versus 0% in control, $p < 0.01$). There was a statistically significant increase in thyroid C-cell hyperplasia in the 2.5 µg/kg-day group (73% versus 50% in control, $p < 0.05$ [10]).

Stop-dose one-year study in male rats (19–22 animals per group) (#2)

No significant difference in body weight or survival rate between the control and treated groups was reported.

Single occurrences of three types of rare tumors were observed in this study in BPA-treated males (see Table 12).

Table 12 Number of animals with rare tumors[1] in the stop-dose one-year study in male rats (#2), where male F1 SD (NCTR) rats were exposed to BPA during gestation[2] and via gavage from PND1 to PND21, and observed until study termination at one year of age (NTP 2018)

Tumor site	Tumor type[3]	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=101)	Historical control[4]		
		0 (n=20)	2.5 (n=20)	25 (n=20)	250 (n=19)	2500 (n=20)	25000 (n=22)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Small intestine, jejunum	Adenoma	0	1	0	0	0	0	1	0/207	NR	NR
	Adenocarcinoma	0	0	1	0	0	0	1	1/207 (0.48%) [0–2%]	NR	NR
All sites	Granulocytic leukemia	0	1	0	0	0	0	1	1/207 (0.5%) [0–2%]	7/1205 (0.58%) [0–6%]	2/639 (0.31%) [0–2%]

NR: not reported.
[1]Rare tumors with historical control incidence of less than 1% and no occurrence in concurrent controls are presented.
[2]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.
[3]One heart malignant schwannoma, which is rare in NTP (2008, 2010) and Charles River (2013) reports, but not in NTP (2021b) report, was observed in 250 µg/kg-day dose group.
[4]Three sets of historical control data are reported: NTP (2008, 2010) dietary route (SD (NCTR) rats, 1999–2003), Charles River (2013) oral routes (Crl:CD®(SD)BR rats, 2001–2009), and NTP (2021b) all routes (Hsd SD rats, 2007–2012). Brackets, range.

[10] $p < 0.05$ vs. controls by secondary, but not primary, statistical test (reported in Camacho et al. 2019). Secondary test (JT/SW), which was run to include information on lesion severity together with the incidence data, was conducted by Jonckheere-Terpstra test to test for monotonic dose trends, followed by Shirley's test for pairwise comparisons to controls.

Non-neoplastic pathology findings

A statistically significant increase in hyperplasia in bone marrow myeloid cells was observed in the 25 µg/kg-day dose group as compared with vehicle control group ($p < 0.05$).

Stop-dose two-year studies (#3, #4)

Stop-dose two-year study in female rats (46–50 animals per group) (#3)

No significant difference in survival rate between the control and treated groups was reported. At week 4, the mean body weight was statistically significantly decreased (by trend) in BPA-treated groups as compared to the vehicle control group, but no difference was observed after week 4.

Statistically significant increases in the incidences of mammary gland adenocarcinoma and adenoma and adenocarcinoma combined were observed at the lowest dose tested (2.5 µg/kg-day) by pairwise comparison with vehicle control (Table 13).

Table 13 Tumor incidence in the stop-dose two-year study in female rats (#3), where female F1 SD (NCTR) rats were exposed to BPA during gestation[1] and via gavage from PND1 to PND21, and observed until study termination at two years of age (NTP 2018)

Tumor site	Tumor type	Day of first tumor [PND]	Dose (µg/kg-day)						Exact trend test *p*-value
			0	2.5	25	250[2]	2500	25000	
Mammary gland	Adenoma	464	1/48	1/44	0/43	3/45	0/47	1/40	NS
	Adenocarcinoma	451	3/48	11/44*	5/45	7/48	9/47	5/41	NS
	Adenoma or adenocarcinoma	451	4/48	12/44*	5/45	9/48	9/47	6/41	NS

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor. Treatment group tumor incidence with asterisks indicates significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$. Exact trend test conducted by OEHHA. NS, not significant ($p \geq 0.05$). PND, postnatal day.
[1]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.
[2]One animal in the 250 µg/kg-day group was found dead on day 630 and autolysis of the mammary glands precluded diagnosis; therefore, the animal was censored.

Additionally, four types of rare tumors were observed in the BPA-treated groups and these are summarized in Table 14.

Table 14 Number of animals with rare tumors[1] in the stop-dose two-year study in female rats (#3), where female F1 SD (NCTR) rats were exposed to BPA during gestation[2] and via gavage from PND1 to PND21, and observed until study termination at two years of age (NTP 2018)

Tumor site	Tumor type	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=194)	Historical control[3]		
		0 (n=50)	2.5 (n=50)	25 (n=48)	250 (n=50)	2500 (n=50)	25000 (n=46)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Pancreatic islets	Carcinoma	0	0	0	0	1	0	1	0/210	NR	5/638 (0.78%) [0–2%]
Pancreatic acinar cell	Adenoma	0	0	0	0	1	0	1	0/210	NR	NR
Ovary	Malignant thecoma	0	0	0	0	1	0	1	0/210	0/1205	0/640
Skin	Fibrosarcoma	0	1	2	0	2	0	5	0/210	6/1205 (0.5%) [0–2%]	4/640 (0.62%) [0–2%]

NR: not reported.
[1]Rare tumors with historical control incidence of less than 1% and no occurrence in concurrent controls are presented.
[2]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.
[3]Three sets of historical control data are reported: NTP (2008, 2010) dietary route (SD (NCTR) rats, 1999–2003), Charles River (2013) oral routes (Crl:CD®(SD)BR rats, 2001–2009), and NTP (2021b) all routes (Hsd SD rats, 2007–2012). Brackets, range.

Non-neoplastic pathology findings

There was a significant dose-related positive trend in cystic endometrial hyperplasia and the incidences in the 2500 and 25000 µg/kg-day groups were significantly higher than that in the vehicle control (57% and 52%, respectively, vs 37% in control, $p < 0.05$ for both). The incidence of hyperplasia in the pituitary pars distalis was statistically significantly increased in the 2.5 and 25 µg/kg-day groups (64% and 71%, respectively, vs 51% in control, $p < 0.05$ for both).

Stop-dose two-year study in male rats (46–50 animals per group) (#4)

The survival of the treated animals in two dose groups (250 and 25000 µg/kg-day) was more than 15% less than that of vehicle controls by week 71. At week 4, the mean body weights were statistically significant decreased (by trend) in BPA-treated groups as compared to the vehicle control group but no difference was observed after week 4.

As shown in Table 15, a statistically significant increase in the incidence of malignant lymphoma of prostate (dorsal/lateral lobes) was observed at the highest dose (by pairwise comparison), with a significant trend. The incidence of malignant lymphoma at

all sites was statistically significantly increased (by trend) as was the incidence of thyroid gland C-cell adenoma.

Table 15 Tumor incidence in the stop-dose two-year study in male rats (#4), where male F1 SD (NCTR) rats were exposed to BPA during gestation[1] and via gavage from PND1 to PND21, and observed until study termination at two years of age (NTP 2018)

Tumor site	Tumor type	Day of first tumor [PND]	Dose (µg/kg-day)						Exact trend test *p*-value
			0	2.5	25	250	2500	25000	
Prostate (dorsal/ lateral lobes)	Malignant lymphoma	254	0/49	0/48	0/48	3/50	2/49	4/45*	$p < 0.01$
All sites	Malignant lymphoma	254	1/49	0/48	1/48	3/50	2/49	5/45	$p < 0.01$
Thyroid gland	C-cell adenoma	609	0/37	1/31	0/33	0/26	1/34	3/23	*$p < 0.05$*

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor. Treatment group tumor incidence with asterisks indicates significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$. Exact trend test conducted by OEHHA. NS, not significant ($p \geq 0.05$). PND, postnatal day.
[1]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.

Additionally, multiple types of rare tumors were observed in the BPA-treated groups and these are summarized in Table 16.

Table 16 Number of animals with rare tumors[1] in the stop-dose two-year study in male rats (#4), where male F1 SD (NCTR) rats were exposed to BPA during gestation[2] and via gavage from PND1 to PND21, and observed until study termination at two years of age (NTP 2018)

Tumor site	Tumor type[4]	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=192)	Historical control[3]		
		0 (n=50)	2.5 (n=48)	25 (n=48)	250 (n=50)	2500 (n=50)	25000 (n=46)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Kidney	Lipoma	0	1	0	0	1	0	2	0/189	7/1205 (0.58%) [0–4%]	2/639 (0.31%) [0–2%]
	Liposarcoma	0	2	1	1	0	0	4	0/189	3/1205 (0.25%) [0–2%]	2/639 (0.31%) [0–2%]
	Lipoma and liposarcoma, combined	0	3	1	1	1	0	6	0/189	7/1205 (0.58%) [0–4%]	2/639 (0.31%) [0–2%]
	Malignant mesenchymal tumor	0	1	0	0	0	0	1	0/189	NR	NR
Nose	Adenoma (NOS)	0	0	0	0	0	1	1	1/191 (0.5%) [0–2%]	NR	NR
	Squamous cell carcinoma	0	0	2	0	1	0	3	0/191	NR	NR
Liver	Hepatocellular carcinoma	0	1	1	2	0	1	5	1/198 (0.5%) [0–2%]	11/1205 (0.91%) [0–2.5%]	2/639 (0.31%) [0–2%]
Spleen	Sarcoma	0	1	1	0	0	0	2	1/199 (0.5%) [0–2%]	NR	NR
	Liposarcoma	0	1	0	0	0	0	1	0/199	NR	NR
Stomach, glandular	Adenoma	0	1	0	0	0	0	1	0/93	NR	NR
	Malignant Schwannoma	0	0	0	1	0	0	1	0/93	NR	NR
Pituitary gland	Carcinoma	0	0	1	0	0	0	1	0/195	8/1205 (0.66) [0–4%]	1/637 (0.17%) [0–2%]
	Cranio-pharyngioma	0	0	0	0	0	1	1	0/195	NR	NR
Testis	Benign/ malignant seminoma	0	1 [B]	0	0	1 [M]	0	2	1/200 (0.5%) [0–2%]	NR	NR
Prostate (dorsal/ lateral lobes)	Adeno-carcinoma	0	0	1	0	0	0	1	2/201 (0.995%) [0–4%]	5/1205 (0.41%) [0–3.33%]	NR
Preputial gland	Carcino-sarcoma	0	0	0	0	0	1	1	0/197	NR	NR

Tumor site[3]	Tumor type[4]	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=192)	Historical control[3]		
		0 (n=50)	2.5 (n=48)	25 (n=48)	250 (n=50)	2500 (n=50)	25000 (n=46)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Seminal vesicle	Carcino-sarcoma	0	0	0	0	1	0	1	0/177	NR	NR
Bone	Osteosarcoma	0	0	0	0	0	1	1	1/207 (0.5%) [0–2%]	7/1205 (0.58%) [0–2%]	1/639 (0.16%) [0–2%]
Lung	Sarcoma	0	0	0	0	0	1	1	0/190	NR	0/638 (0%)
All sites	Granulocytic leukemia	0	1	1	0	0	1	3	1/207 (0.5%) [0–2%]	7/1205 (0.58%) [0–6%]	2/639 (0.31%) [0–2%]

NR: not reported. [B], benign. [M], malignant. NOS, not otherwise specified.
[1]Rare tumors with historical control incidence of less than 1% and no occurrence in concurrent controls are presented.
[2]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.
[3]Three sets of historical control data are reported: NTP (2008, 2010) dietary route (SD (NCTR) rats, 1999–2003), Charles River (2013) oral routes (Crl:CD®(SD)BR rats, 2001–2009), and NTP (2021b) all routes (Hsd SD rats, 2007–2012). Brackets, range.
[4]Heart malignant schwannoma, which is rare in NCTR and Charles River (2013) reports, but not in NTP (2021b) report, was observed in one animal each in the 2.5 and 25000 µg/kg-day dose groups.

Non-neoplastic pathology findings

The incidence of pituitary pars distalis hyperplasia was statistically significantly increased in the 25000 µg/kg-day group relative to vehicle controls (44% versus 26%, $p = 0.02$). The incidence of adrenal medulla hyperplasia was statistically significantly increased in the 2500 µg/kg-day group relative to vehicle controls (34% versus 17%, $p = 0.03$). The incidence of spleen lymphoid hyperplasia was statistically significantly increased in the 250 and 2500 µg/kg-day groups relative to vehicle controls (12% and 12%, respectively, versus 2%, $p = 0.039$).

Continuous-dose arms (#5, #6, #7, #8)

In these arms, BPA was administered daily via oral gavage to F0 dams from GD6 through parturition and then by oral gavage to pups (F1) from PND1 until termination at one year or two years. Positive controls (EE_2 at 0.05 or 0.5 µg/kg-day) were included in these four continuous-dose arms.

Continuous-dose one-year studies (#5, #6)

F1 female (#5) and male (#6) SD (NCTR) rats were exposed to BPA in utero from GD6 to birth and directly via gavage from PND1 through one year.

Continuous-dose one-year study in female rats (20–24 animals per group) (#5)

No significant difference in survival rate between the vehicle control and treated groups was reported. The mean body weight was 10–13% higher (not statistically significant) in the 2.5 µg/kg-day group in weeks 36–52 compared with vehicle control group. No other differences in mean body weights between any treatment group and vehicle control were reported.

A statistically significant dose-related increasing trend in the incidence of uterine stromal polyps was observed (Table 17). No increase in uterine stromal polyps was observed in the EE_2-treated positive control groups.

Table 17 Tumor incidence in the continuous-dose one-year study in female rats (#5), where female F1 SD (NCTR) rats were exposed to BPA during gestation[1] and via gavage from PND1 until study termination at one year of age (NTP 2018)

Tumor site	Tumor type	Day of first tumor [PND]	Dose (µg/kg-day)						Exact trend test *p*-value
			0	2.5	25	250	2500	25000	
Uterine	Stromal polyps	361	1/20	0/20	1/21	0/22	3/20	3/24	$p < 0.05$

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor. Exact trend test conducted by OEHHA. PND, postnatal day.
[1]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.

Single occurrences of two types of rare tumors were observed in this study in BPA-treated females (Table 18).

Table 18 Number of animals with rare tumors[1] in the continuous-dose one-year study in female rats (#5), where female F1 SD (NCTR) rats were exposed to BPA during gestation[2] and via gavage from PND1 until study termination at one year of age (NTP 2018)

Tumor site	Tumor type	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=112)	Historical control[3]		
		0 (n=23)	2.5 (n=22)	25 (n=22)	250 (n=24)	2500 (n=20)	25000 (n=24)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Pancreatic islets	Carcinoma	0	0	0	1	0	0	1	0/209	NR	5/638 (0.78%) [0–2%]
Thyroid gland follicular cell	Adenoma	0	0	0	0	0	1	1	1/210 (0.48%) [0–2%]	13/1205 (1%) [0–4%]	1/638 (0.16%) [0–2%]

NR: not reported.

[1]Rare tumors with historical control incidence of less than 1% and no occurrence in concurrent controls are presented.

[2]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.

[3]Three sets of historical control data are reported: NTP (2008, 2010) dietary route (SD (NCTR) rats, 1999–2003), Charles River (2013) oral routes (Crl:CD®(SD)BR rats, 2001–2009), and NTP (2021b) all routes (Hsd SD rats, 2007–2012). Brackets, range.

In addition, non-significant increases in mammary gland fibroadenoma (three in the 2.5 µg/kg-day, three in 25 µg/kg-day, one in the 250 µg/kg-day, two in the 2500 µg/kg-day, and six in the 25000 µg/kg-day dose groups) were observed in BPA-treated females compared to two in the vehicle control, and mammary gland adenocarcinomas (one each in the 2.5 and 25 µg/kg-day dose groups) were observed in BPA-treated females compared to none in the vehicle control. As noted earlier, statistically significant increases in mammary gland adenocarcinoma and combined adenoma and adenocarcinoma were observed in the 2.5 µg/kg-day dose group in the 2-year stop-dose study in female rats (#3).

Non-neoplastic pathology findings

There was a statistically significant increase in mammary ductal dilatation in the 25 µg/kg-day group (32% versus 9% in vehicle control, $p < 0.001$). Uterine endometrial hyperplasia was statistically significantly increased in the 2.5 and 250 µg/kg-day dose groups (32% and 29%, respectively, versus 9% in vehicle control, $p < 0.05$). The incidence of vaginal epithelial hyperplasia was increased in the 2500 and 25000 µg/kg-day dose groups [30% ($p > 0.05$) and 33% ($p < 0.05$), respectively, versus 13% in vehicle control]. All three lesions (mammary ductal dilatation, endometrial hyperplasia, and vaginal epithelial hyperplasia) were also observed in EE_2-treated positive controls.

Increases in mammary gland lobular hyperplasia and uterine squamous metaplasia were also observed in the positive controls.

Continuous-dose one-year study in male rats (20–24 animals per group) (#6)

No significant difference in body weight or survival rate between the control and treated groups was reported.

One rare adenocarcinoma of the small intestine (jejunum) was observed in the highest dose group.

Non-neoplastic pathology findings

Hematopoietic cell proliferation in the spleen was increased in the highest dose group compared to vehicle controls (9% versus 0%, $p < 0.05$).

Increased lymphocyte infiltration in the dorsal/lateral prostate was observed in the 2.5 µg/kg-day group (46% versus 18% in vehicle control, $p < 0.05$), and suppurative inflammation in the dorsal/lateral prostate was increased over a high background (82% in vehicle control) in the 2.5, 250, 2500, and 25000 µg/kg-day dose groups (91%, 92%, 90%, and 86%, respectively).

Two-year terminal continuous-dose studies (#7, #8)

F1 female (#7) and male (#8) SD (NCTR) rats were exposed to BPA *in utero* from GD6 to birth and directly via gavage from PND1 through two years.

Continuous-dose two-year study in female rats (46–50 animals per group) (#7)

No significant difference in survival rate between the control and treated groups was reported. The sole difference in comparisons between treatment groups and vehicle control was for the mean body weights in the 250 µg/kg-day dose group, which were statistically significantly higher by 16–18% than those of the vehicle control group for weeks 96–104.

As shown in Table 19, there were statistically significant increases in clitoral gland adenoma and adenoma or carcinoma combined (by trend). Two rare fibrosarcomas of the clitoral gland were also observed, one at 2.5 and one at 250 µg/kg-day. The animals with clitoral gland fibrosarcoma were distinct from those that had clitoral gland adenoma or carcinoma.

Table 19 Tumor incidence in the continuous-dose two-year study in female rats (#7), where female F1 SD (NCTR) rats were exposed to BPA during gestation[1] and via gavage from PND1 until study termination at two years of age (NTP 2018)

Tumor site	Tumor type	Day of first tumor [PND]	Dose (µg/kg-day)						Exact trend test *p*-value
			0	2.5	25	250	2500	25000	
Clitoral gland	Fibrosarcoma [R]	607	0/32	1/32	0/24	1/28	0/24	0/28	NS
	Adenoma	531	0/40	0/38	0/32	0/41	0/33	2/36	$p < 0.05$
	Carcinoma	426	1/50	1/44	1/43	1/47	4/47	1/45	NS
	Adenoma or Carcinoma	426	1/50	1/44	1/43	1/47	4/47	3/45	$p < 0.05$

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor. Exact trend test conducted by OEHHA. NS, not significant ($p \geq 0.05$). R, rare. PND, postnatal day. Specifically, the incidence of clitoral gland fibrosarcoma in untreated female rats is 0% (NTP 2021b), 0% (Charles River 2013) and 0% (0/210) (NTP 2008, 2010). NTP (2021b): all routes (Hsd SD rats, 2007–2012), Charles River (2013): oral routes (Crl:CD®(SD)BR rats, 2001–2009), and SD (NCTR): rat data are from NTP (2008, 2010) (dietary feed studies conducted in 1999 to 2003).

[1]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.

Additionally, several rare tumors were observed in the BPA-treated groups, and these are summarized in Table 20.

Table 20 Number of animals with rare tumors[1] in the continuous-dose two-year study in female rats (#7), where female F1 SD (NCTR) rats were exposed to BPA during gestation[2] and via gavage from PND1 until study termination at two years of age (NTP 2018)

Tumor site	Tumor type	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=189)	Historical control[3]		
		0 (n=50)	2.5 (n=48)	25 (n=46)	250 (n=49)	2500 (n=50)	25000 (n=46)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Pancreatic islets	Carcinoma	0	0	1	0	0	0	1	0/209	NR	5/638 (0.78%) [0–2%]
Small intestine, jejunum	Adenocarcinoma	0	0	1	1	0	0	2	0/207	NR	NR
Brain	Malignant oligodendroglioma	0	1	0	0	0	0	1	1/210 (0.5%) [0–2%]	NR	2/590 (0.34%) [0–2%]
	Malignant glioma	0	0	1	1	0	0	2	1/210 (0.5%) [0–2%]	NR	2/590 (0.34%) [0–2%]
Vagina	Squamous cell carcinoma	0	1	0	0	0	0	1	0/102	NR	NR
Lung	Alveolar/ bronchiolar adenoma	0	0	1	0	0	0	1	1/210 (0.5%) [0–2%]	3/1205 (0.25%) [0–2%]	1/638 (0.16%) [0–2%]
Ear	Benign neural crest tumor	0	0	0	1	0	0	1	0/210[4]	NR	NR
Nose	Osteosarcoma	0	0	0	0	1	0	1	0/210	NR	NR
Parathyroid	Adenoma	0	0	1	0	0	0	1	0/142	6/1205 (0.5%) [0–4%]	1/580 (0.17%) [0–2%]
Ovary	Benign thecoma	0	1	0	0	0	0	1	0/209	6/1205 (0.5%) [0–4%]	1/640 (0.16%) [0–2%]
	Yolk sac carcinoma	0	0	0	1	0	0	1	0/209	NR	NR
Skin	Fibrosarcoma	0	1	0	0	1	1	3	0/210	6/1205 (0.5%) [0–2%]	4/640 (0.62%) [0–2%]
Zymbal's gland	Adenoma/ carcinoma	0	1	0	0	2	2	5	0/210[4]	NR	0
All sites	Histiocytic sarcoma	0	0	0	0	0	1	1	0/210	7/1205 (0.58%) [0–3.08%]	1/639 (0.16%) [0–2%]

NR: not reported.

[1]Rare tumors with historical control incidence of less than 1% and no occurrence in concurrent controls are presented.

[2]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.

[3]Three sets of historical control data are reported: NTP (2008, 2010) dietary route (SD (NCTR) rats, 1999–2003), Charles River (2013) oral routes (Crl:CD®(SD)BR rats, 2001–2009), and NTP (2021b) all routes (Hsd SD rats, 2007–2012). Brackets, range.

[4]In the case of the historical control data for tumors of the Zymbal's gland and ear, tissues were not examined microscopically unless gross lesions were detected. The denominator represents the number of animals examined, either macroscopically or microscopically.

In addition, non-significant increases in mammary gland adenocarcinoma (17 in the 2.5 µg/kg-day, 11 in 25 µg/kg-day, 12 in the 250 µg/kg-day, 18 in the 2500 µg/kg-day, and seven in the 25000 µg/kg-day dose) were observed in BPA-treated females compared to seven in the vehicle control. As noted earlier, statistically significant increases in mammary gland adenocarcinoma and combined adenoma and adenocarcinoma were observed in the 2.5 µg/kg-day dose group in the two-year stop dose study in female rats (#3). Non-significant increases in thyroid gland C-cell adenomas/carcinomas (one carcinoma in the 2.5 µg/kg-day, one adenoma in the 25 µg/kg-day, and two adenomas in the 25000 µg/kg-day dose) were observed in BPA-treated females compared to none in the vehicle control. As noted earlier, a statistically significant increase in thyroid gland C-cell adenomas with a significant trend were observed in the two-year stop dose study in male rats (#4).

Statistically significant increases in mammary gland adenocarcinoma, benign pheochromocytoma of the adrenal medulla, and thyroid gland C cell adenoma were observed in the EE_2-treated positive controls.

Non-neoplastic pathology findings

The incidences of mammary gland atypical foci were higher in some treatment groups than in vehicle controls, and for the 2.5 µg/kg-day group the increase was statistically significant (15% versus 4% in the vehicle controls, $p < 0.05$). An increased incidence of uterine squamous metaplasia occurred in BPA-treated groups with a statistically significant trend ($p < 0.05$). The incidence of vaginal epithelium hyperplasia was significantly increased at each of the dose groups from 25–25000 µg/kg-day (incidences of 8% in vehicle controls and 27%, 20%, 22%, and 26% for the 25, 250, 2500, and 25000 µg/kg-day dose groups, respectively, $p < 0.05$ for each dose group compared to control). There was a statistically significant increase in thyroid follicular cell hyperplasia in the highest dose group as compared to the vehicle controls (12% versus 3%, $p < 0.05$). Statistically significant increases in the above mentioned non-neoplastic lesions were also observed in EE_2-treated positive controls.

Continuous-dose two-year study in male rats (46–50 animals per group) (#8)

No significant difference in body weight or survival rate between the control and treated groups was reported.

As shown in Table 21, a statistically significant increase (by trend) in rare hepatocellular carcinoma was observed in BPA-treated male rats.

Table 21 Tumor incidence in the continuous-dose two-year study in male rats (#8), where male F1 SD (NCTR) rats were exposed to BPA during gestation[1] and via gavage from PND1 until study termination at two years of age (NTP 2018)

Tumor site	Tumor type	Day of first tumor [PND]	Dose (µg/kg-day)						Exact trend test *p*-value
			0	2.5	25	250	2500	25000	
Liver	Hepatocellular carcinoma [R]	656	0/24	0/25	0/24	2/24	1/24	3/19	$p < 0.01$

Tumor incidence is expressed as the number of tumor-bearing animals over the number of animals alive at the time of first occurrence of the tumor. Exact trend test conducted by OEHHA. R, rare. PND, postnatal day. The incidence of hepatocellular carcinoma in untreated male Hsd SD rats is 0.31% (range 0–2%) (NTP 2021b), in untreated male Crl:CD®(SD)BR rats is 0.91% (range 1.67–2.5%) (Charles River 2013), and in untreated male SD (NCTR) rats is 0.5% (range 0–2%) (NTP 2008, 2010).
[1]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.

Additionally, several other rare tumors were observed in the BPA-treated groups, and these are summarized in Table 22.

Table 22 Number of animals with rare tumors[1] in the continuous-dose two-year study in male rats (#8), where male F1 SD (NCTR) rats were exposed to BPA during gestation[2] and via gavage from PND1 until study termination at two years of age (NTP 2018)

Tumor site	Tumor type	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=189)	Historical control[3]		
		0 (n=50)	2.5 (n=48)	25 (n=46)	250 (n=49)	2500 (n=50)	25000 (n=46)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Kidney	Benign oncocytomas	0	0	1	0	0	0	1	0/189	NR	2/639 (0.31%) [0–2%]
Zymbal's gland	Adenoma	0	0	2	0	0	1	3	0/207[4]	NR	1/639 (0.16%) [0–2%]
Large intestine, colon	Adenoma	0	0	0	0	1	0	1	2/207 (0.97%) [0–4%]	NR	NR
Large intestine, rectum	Leiomyosarcoma	0	0	0	0	0	1	1	1/207 (0.5%) [0–3%]	1/1205 (0.08%) [0–2%]	NR
Small intestine, jejunum	Adenocarcinoma	0	0	0	0	1	1	2	1/207 (0.5%) [0–3%]	NR	NR
Brain	Carcinoma	0	0	0	0	1	0	1	0/194	NR	NR
Bladder	Carcinoma	0	0	0	1	0	0	1	0/186	NR	NR
	Papilloma	0	0	0	0	0	1	1	0/186	4/1205 (0.33%) [0–2%]	NR
Nose	Squamous cell carcinoma	0	0	1	0	2	0	3	0/191	NR	NR
Liver	Hemangiosarcoma	0	1	0	1	1	0	3	0/198	7/1205 (0.58%) [0–5%]	NR
	Lipoma	0	0	0	1	0	0	1	0/198	NR	NR
Spleen	Sarcoma	0	2	1	0	0	0	3	1/207 (0.5%) [0–2%]	NR	NR
	Hemangiosarcoma	0	0	0	0	1	0	1	0/207	4/1205 (0.33%) [0–2%]	3/639 (0.47%) [0–3%]
Stomach, glandular	Squamous cell papilloma	0	0	1	0	0	0	1	0/135	NR	NR
Pituitary gland	Carcinoma	0	0	0	0	1	0	1	0/195	8/1205 (0.66) [0–4%]	1/637 (0.17%) [0–2%]
Testis	Malignant seminoma	0	1	0	0	0	0	1	1/200 (0.5%) [0–2%]	NR	NR
Peritoneum	Paraganglioma	0	0	0	0	0	1	1	0/207[4]	NR	NR

Tumor site	Tumor type	Dose (µg/kg-day)						Tumors from all BPA-treated groups (n=189)	Historical control[3]		
		0 (n=50)	2.5 (n=48)	25 (n=46)	250 (n=49)	2500 (n=50)	25000 (n=46)		NTP (2008, 2010)	Charles River (2013)	NTP (2021b)
Tongue	Squamous cell papilloma	0	0	0	0	0	1	1	0/207[4]	NR	NR
Skin, sebaceous gland	Adenoma	0	0	0	0	0	1	1	0/201	6/1205 (0.5%) [0–3%]	2/639 (0.31%) [0–2%]
Thyroid gland follicular cell	Carcinoma	0	1	1	0	0	0	2	0/188	2/1205 (0.17%) [0–1.67%]	0/637 (0%)
Seminal vesicle	Adenoma	0	0	0	1	0	0	1	1/207 (0.5%) [0–2%]	NR	NR
Lung	Alveolar/ bronchiolar carcinoma	0	1	0	0	0	0	1	1/207 (0.5%) [0–2%]	5/1205 (0.41%) [0–3.33%]	3/638 (0.47%) [0–2%]
Epididymis or testis	Malignant mesothelioma	0	0	0	2	0	1	3	0/200	2/1205 (0.16%) [0–1.67%]	NR
All sites	Histiocytic sarcoma	0	0	0	0	0	1	1	0/207	12/1205 (1%) [0–4%]	2/639 (0.31%) [0–2%]
Oral mucosa	Fibrosarcoma	0	0	0	0	1	0	1	0/207[4]	NR	NR

NR: not reported.
[1]Rare tumors with historical control incidence of less than 1% and no occurrence in concurrent controls are presented.
[2]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.
[3]Three sets of historical control data are reported: NTP (2008, 2010) dietary route (SD (NCTR) rats, 1999–2003), Charles River (2013) oral routes (Crl:CD®(SD)BR rats, 2001–2009), and NTP (2021b) all routes (Hsd SD rats, 2007–2012). Brackets, range.
[4]In the case of the historical control data for tumors of the Zymbal's gland, tongue, peritoneum, and oral mucosa, tissues were not examined microscopically unless gross lesions were detected. The denominator represents the number of animals examined, either macroscopically or microscopically.

In addition, non-significant increases in malignant lymphomas (all sites) (one in the 2.5 µg/kg-day, three in 25 µg/kg-day, three in the 250 µg/kg-day, three in the 2500 µg/kg-day, and three in the 25000 µg/kg-day dose) were observed in BPA-treated males compared to two in the vehicle control. As noted earlier, a statistically significant increase in malignant lymphoma (all sites) by trend, as well as a statistically significant increase in the incidence of malignant lymphoma of prostate at the highest dose (by pairwise comparison), with a significant trend were observed in the two-year stop dose study in male rats (#4). Non-significant increases in thyroid gland C-cell adenomas/carcinomas (one carcinoma in the 2.5 µg/kg-day, one carcinoma in the 250 µg/kg-day, and two adenomas in the 2500 µg/kg-day dose) were observed in BPA-treated males compared to none in the vehicle control. As noted earlier, a statistically significant increase in thyroid gland C-cell adenomas with a significant trend was observed in the two-year stop dose study in male rats (#4).

Non-neoplastic pathology findings

There were statistically significant increases of pituitary gland (*pars distalis*) hyperplasia relative to vehicle controls in the 25 and 25000 µg/kg-day dose groups (40% and 42% respectively, versus 23% in vehicle controls, $p < 0.05$). There were statistically significant increases of parathyroid gland hyperplasia relative to vehicle control in the 25 and 250 µg/kg-day groups [61% ($p < 0.01$) and 47% ($p < 0.05$), respectively, versus 30% in vehicle controls]. In the ventral prostate, a significant increase of epithelial hyperplasia relative to vehicle control was observed in the 250 µg/kg-day group (37% versus 20% in vehicle controls, $p < 0.05$). In kidney, a significant increase of transitional epithelium hyperplasia relative to control was observed in the 25 µg/kg-day group (35% versus 9% in vehicle controls, $p < 0.01$). Statistically significant increases of pituitary gland (pars distalis) hyperplasia and kidney transitional epithelium hyperplasia were also observed in EE_2-treated positive controls.

4.2.1.3 CLARITY-BPA grantee studies (NTP 2021a)

"Grantee studies" were conducted by 14 NIEHS-funded university-based research groups that were provided tissues from animals treated at NCTR in a similar manner as the animals included in the core studies, to pursue hypothesis-driven research focused on specific organ systems. Depending on the end points evaluated, some grantees requested and were provided with tissues collected at ages other than those assessed in the core studies (*e.g.*, PND90, 6 months of age). The sample sizes of tissues and animals provided for grantee studies were smaller than those in the core studies (*e.g.*, n = 4–12). Nineteen peer-reviewed publications from these grantee studies have been summarized in NTP (2021b). Two of these publications, Prins et al. (2018) and Montevil et al. (2020), included data on neoplastic and preneoplastic findings in the prostate and mammary gland, respectively, in BPA-treated animals. These findings are briefly summarized below.

Grantee studies of the prostate

<u>Stop-dose one-year exposure study in male rats: Prins et al. (2018) and summarized in NTP (2021b)</u>

F1 male SD (NCTR) rats (4–10 animals per group) were exposed to BPA via *in utero* exposure (from GD6 to the birth) and gavage at 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day from PND1 to PND21 (same treatment protocol as core study #2). Animals were sacrificed at one year of age for pathology analyses of the prostate. The entire prostatic complex was provided to the grantee researchers for these analyses. As distinct from core studies in which only dorsolateral and ventral prostate were examined, this study conducted histopathological examination of the entire prostatic complex, *i.e.*, the anterior prostate (comprised of the seminal vesicles and coagulating gland), the ventral

prostate, the dorsal/lateral section, and the periurethral dorsolateral prostatic ducts. Due to the small number of animals in each treatment group (*i.e.*, n < 18), the authors noted that the study had less than 80% power to detect a significant increase in lesion incidence by BPA over background at a significance level of 0.05.

Prins et al. (2018) did not report any BPA-treatment related neoplastic or preneoplastic effects in any region of the prostate. Supplemental data reported by the authors in Table S4 was further examined by OEHHA. As shown in Table 23, a statistically significant increase of preneoplastic high-grade prostatic intraepithelial neoplasia (PIN) lesions in the lateral prostate is apparent by trend test (when the six vehicle control animals co-housed with the high-dose BPA group were excluded from the analyses). Non-significant increases in PIN lesions in the periurethral dorsolateral prostatic ducts were also observed in the three lowest BPA dose groups. No treatment-related findings were observed in the anterior or ventral prostate.

Table 23 Incidence of preneoplastic PIN in male F1 SD (NCTR) rats exposed to BPA during gestation[1] and via gavage from PND1 to PND21 and then held without further treatment until termination at one year of age (Prins et al. 2018)

Lesion site	Lesion type	Dose (µg/kg-day)						Exact trend test *p*-value
		0[2]	2.5	25	250	2500	25000	
Lateral prostate	PIN	0/4 (0/10)	0/8	0/8	0/10	1/10	2/10	$p < 0.05$
Periurethral dorsolateral prostatic ducts	PIN	1/4 (4/10)	3/8	4/8	5/10	1/10	1/10	NS

Lesion incidence is expressed as the number of lesion-bearing animals over the number of animals examined in each experimental group (Prins et al. 2018). Exact trend test conducted by OEHHA with data from the subset (n = 4) of vehicle controls. NS, not significant ($p \geq 0.05$). PIN, prostatic intraepithelial neoplasia.

[1]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.

[2]6 out 10 vehicle controls were co-housed with the 25000 µg/kg BPA rats. These rats may have background BPA contamination; therefore, a subset of vehicle controls was selected (n = 4) within those that were not co-housed with the high-dose BPA group. Data for all 10 vehicle controls given in parentheses.

<u>Continuous-dose one-year exposure study in male rats: Prins et al. (2018) and summarized in NTP (2021b)</u>

F1 male SD (NCTR) rats (7–10 animals per group) were exposed to BPA via *in utero* exposure (from GD6 to birth) and via oral gavage at 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day from PND1 to one year of age (same treatment protocol as core study #6).

Animals were sacrificed at one year of age for pathology analyses of the prostate. As described above, the entire prostatic complex was provided to the grantee researchers for histopathologic analyses of the anterior and ventral prostate, the dorsal/lateral section, and the periurethral dorsolateral prostatic ducts. Due to the small number of animals in each treatment group (*i.e.*, n < 18), the authors noted that the study had less than 80% power to detect a significant increase in lesion incidence by BPA over background at a significance level of 0.05.

No BPA-treatment related neoplastic or preneoplastic effects were observed in any region of the prostate (Prins et al. 2018; see also supplemental data reported by the authors in Table S3).

Stop-dose one-year exposure study in male rats with testosterone and 17β-estradiol (T+E2) capsule implantation on PND90: Prins et al. (2018) and summarized in NTP (2021b)

F1 male SD (NCTR) rats (5–20 animals per group) were exposed to BPA via *in utero* exposure (from GD6 to birth) and oral gavage at 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day from PND1 to PND21. In order to test for prostatic susceptibility to hormonally induced carcinogenesis, these animals were implanted with Silastic capsules containing testosterone and 17β-estradiol (T+E2) on PND90 to simulate the hormonal changes associated with aging and prostate carcinogenesis in humans. Prins et al. (2018) noted the unequal distribution of animals in the treatment groups in this study, with n = 19–20 animals in the vehicle and EE_2 positive controls, n = 4 animals in the 25 and 2500 µg/kg-day groups, and n = 5–15 animals in the remaining BPA treatment groups. Due to the small number of animals in each treatment group (*i.e.*, n < 18), the authors noted that the study had less than 80% power to detect a significant increase in lesion incidence by BPA over background at a significance level of 0.05.

Animals were sacrificed at one year of age for pathology analyses of the prostate. As described above, the entire prostatic complex was provided to the grantee researchers for histopathologic analyses of the anterior and ventral prostate, the dorsal/lateral section, and the periurethral dorsolateral prostatic ducts.

Implantation of all animals on PND90 with T+E2 -containing Silastic capsules increased the incidences of PIN and adenocarcinoma of the prostate in all treatment groups, including vehicle controls. In this study BPA treatment had no discernable effect on the incidences of PIN or adenocarcinoma in any region of the prostate. However, as shown in Table 24, statistically significant increases in the lateral prostate PIN severity score were observed in the 2.5, 250, and 25000 µg/kg-day groups compared to vehicle controls ($p < 0.01$, $p < 0.05$, $p < 0.05$, respectively). In addition, a statistically significant increase in adenocarcinoma multiplicity in the periurethral dorsolateral prostatic ducts

was observed in the 2.5 µg/kg-day group compared to controls ($p < 0.01$) (Prins et al. 2018).

Table 24 Incidence of PINs and adenocarcinoma in the prostate in male F1 SD (NCTR) rats exposed to BPA during gestation[1] and via gavage from PND1 to PND21, treated with T+E2 implants at PND90[2], and terminated at one year of age (Prins et al. 2018)

Lesion site	Lesion type	BPA Dose[3] (µg/kg-day)						Exact trend test *p*-value
		0	2.5	25	250	2500	25000	
Lateral prostate	PIN[4], (severity score)[5]	14/16 (1.3 ± 0.2)	6/6 (3.0 ± 0.4)**	2/4	11/12 (2.3 ± 0.3)*	4/4	9/9 (2.4 ± 0.4)*	NS
Periurethral dorsolateral prostatic ducts	Adenocarcinoma[4], (tumor multiplicity)[6]	8/16 (1.1 ± 0.1)	3/6 (5.3 ± 1.5)**	1/4	4/12 (1.8 ± 0.5)	1/4	3/9 (2.0 ± 0.6)	NS

[1]F0 dams were exposed to various doses of BPA (0, 2.5, 25, 250, 2500, 25000 µg/kg-day) from gestation day 6 to the start of labor via gavage.
[2]All dose groups, including the control received implants with T+E2.
[3]Animals in all groups received T+E2 implants on PND90.
[4]Lesion incidence is expressed as the number of lesion-bearing animals over the number of animals examined in each experimental group (Prins et al. 2018). Exact trend test conducted by OEHHA. NS, not significant ($p \geq 0.05$).
[5]Severity score indicated as level of abnormality of PIN lesions. The score is based on the system as follow: "0" = no abnormalities detected; "0.5" = extremely minimal; "1" = minimal (or one); "2" = slight (or a couple); "3" = moderate (or a few); "4" = marked (or several); "5" = severe (or many). Statistical analysis by ANOVA with Dunnett's posttest with controls was conducted by Prins et al. (2018), * $p < 0.05$, ** $p < 0.01$. Only the severity scores were shown for the 2.5, 250, and 25000 µg/kg-day dose groups were significant compared with the control. Data from the 25 and 2500 µg/kg-day dose groups were not evaluated due to each having a small sample size (n = 4).
[6]Tumor multiplicity represents the number of adenocarcinomas per rat. It was calculated as the mean ± SEM per group. **p <0:01 vs. controls as determined by Fischer Exact test with Bonferroni correction for multiple comparisons (conducted by Prins et al. 2018). Data from the 25 and 2500 µg/kg-day dose groups were not evaluated due to each having a small sample size (n = 4).

Grantee studies of the mammary gland

In the grantee studies of Montevil et al. (2020), mammary glands obtained from 90-day- and 6-month-old F1 female SD (NCTR) rats were examined for the presence of a number of types of lesions, including lobular or ductular alveolar dilatations, lobular hyperplasia, periductular fibrosis, ductal epithelial necrosis with lymphocytic infiltration, fibroadenomas, adenomas, ductal carcinoma *in situ* (DCIS), and adenocarcinoma.

Stop-dose 90-day exposure study in female rats: Montevil et al. (2020) and summarized in NTP (2021b)

Female F1 SD (NCTR) rats (8–10 animals per group) were exposed to BPA via *in utero* exposure (from GD6 to the birth) and oral gavage at 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day from PND1 to PND21 (same treatment protocol as core study #1, although animals were terminated early, at PND90). Two EE_2 positive control groups (0.05 or 0.5 µg/kg-day) were also included in the study. Animals were sacrificed on PND90 and the fourth inguinal mammary glands were provided to the grantee researchers for pathology analyses.

Two DCIS (2/10 vs. 0/10 in vehicle controls) were observed in the BPA 250 µg/kg-day group, with none in any other groups (See Table S5A in Montevil et al (2020) supplemental data). One fibroadenoma (1/9) and one observation of lobular hyperplasia (1/9) was reported in the EE_2 0.05 µg/kg-day positive control group, with none in the vehicle control.

One observation of periductular fibrosis with lymphocytic infiltration (1/10) was reported in the BPA 25 µg/kg-day dose group, with none in the vehicle control.

Stop-dose six-month exposure study in female rats: Montevil et al. (2020) and summarized in NTP (2021b)

Female F1 SD (NCTR) rats (10 animals per group) were exposed to BPA via *in utero* exposure (from GD6 to the birth) and gavage at 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day from PND1 to PND21 (same treatment protocol as core study #1, although animals were terminated early, at 6 months). Two EE_2 positive control groups (0.05 or 0.5 µg/kg-day) were also included in the study. Animals were sacrificed at 6 months of age and the fourth inguinal mammary glands were provided to the grantee researchers for pathology analyses.

No neoplastic findings were observed in BPA-treated animals in this study (See Table S5B in Montevil et al. (2020) supplemental data). One fibroadenoma, one adenoma and two adenocarcinomas were observed in the EE_2 0.5 µg/kg-day positive control group, with none observed in other groups.

Lobulo/ductular-alveolar dilatations were observed in 1/10 animals in the BPA 2.5 µg/kg-day dose group and 4/10 animals in the EE_2 0.5 µg/kg-day dose group, with none in the vehicle control. Periductular fibrosis was observed in one animal each in the BPA 25000 µg/kg-day dose group and the EE_2 0.5 µg/kg-day dose group (with lymphocytic infiltration) with none in the vehicle control.

Continuous-dose 90-day exposure study in female rats: Montevil et al. (2020) and summarized in NTP (2021b)

Female F1 SD (NCTR) rats (9–10 animals per group) were exposed to BPA via *in utero* exposure (from GD6 to the birth) and oral gavage at 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day from PND1 to PND90 (same treatment protocol as core study #5, although animals were terminated early, at PND90). Two EE_2 positive control groups (0.05 or 0.5 µg/kg-day) were also included in the study. Animals were sacrificed at PND90 and the fourth inguinal mammary glands were provided to the grantee researchers for pathology analyses.

No neoplastic findings were observed in BPA-treated animals in this study (See Table S5A in Montevil et al. (2020) Supplemental data). One DCIS (1/10 vs. 0/10 in vehicle control) was observed in the EE_2 0.5 µg/kg-day positive control group.

Periductular fibrosis with lymphocytic infiltration was observed in one animal each in the 25 µg/kg-day (1/10) and 25000 µg/kg-day (1/10) BPA dose groups, with none in vehicle or positive controls. One ductal epithelial necrosis with inflammatory infiltrate was observed in the 25000 µg/kg-day dose group, with none in vehicle or EE_2 positive controls.

Continuous-dose six-month exposure study in female rats: Montevil et al. (2020) and summarized in NTP (2021b)

Female F1 SD (NCTR) rats (10 animals per group) were exposed to BPA via *in utero* exposure (from GD6 to the birth) and gavage at 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day from PND1 to 6 months (same treatment protocol as core study #5, although animals were terminated early, at 6 months). Two EE_2 positive control groups (0.05 or 0.5 µg/kg-day) were also included in the study. Animals were sacrificed at 6 months and the fourth inguinal mammary glands were provided to the grantee researchers for pathological analyses.

Fibroadenoma was observed in one animal each in the 2.5 µg/kg-day (1/10) and 25 µg/kg-day (1/10) BPA dose groups, with none in vehicle controls (1/10) and two in the EE_2 0.5 µg/kg-day positive control group (2/10) (See Table S5B in Montevil et al. (2020) Supplemental data). Three adenomas and one adenocarcinoma were observed in the EE_2 0.5 µg/kg-day positive control group.

Periductular fibrosis was observed in one animal in the vehicle control group, and lobulo/ductular-alveolar dilatation was observed in four animals in the EE_2 0.5 µg/kg-day positive control group.

Conclusions stated from Montevil et al. (2020) are quoted as follows:

"At all time points, lower doses resulted in larger effects [than higher doses of BPA], consistent with the core study (NTP 2018), which revealed a significant increase of mammary adenocarcinoma incidence in the stop-dose animals at the lowest BPA dose tested."

4.2.1.4 Overall results and issues associated with the CLARITY-BPA core studies

Overall findings from CLARITY-BPA core studies

As shown in Table 25, several types of rare tumors and statistically significant tumor findings were observed in the CLARITY-BPA core studies (arms #3, #4, #5, #7, and #8). In brief,

- Stop-dose two-year study in female rats (#3): Statistically significant increases in the incidences of mammary gland adenocarcinoma and adenoma and adenocarcinoma combined were observed at the lowest dose. Five rare skin fibrosarcomas were observed in BPA-treated animals.
- Stop-dose two-year study in male rats (#4): A statistically significant increase in the incidence of malignant lymphoma of the prostate (dorsal/lateral lobes) was observed at the highest dose, with a significant trend. Statistically significant dose-related trends were observed for malignant lymphoma at all sites and thyroid gland C-cell adenoma. Multiple types of rare tumors, including granulocytic leukemia, kidney lipoma, kidney liposarcoma, hepatocellular carcinoma, nasal squamous cell sarcoma, and spleen sarcoma, were observed in BPA-treated animals.
- Continuous-dose one-year study in female rats (#5): A statistically significant dose-related trend in uterine stromal polyps was observed.
- Continuous-dose two-year study in female rats (#7): Statistically significant dose-related trends in clitoral gland adenoma and combined adenoma or carcinoma were observed. Several types of rare tumors were observed in BPA-treated animals, including two rare fibrosarcomas of the clitoral gland (see Table 25).
- Continuous-dose two-year study in male rats (#8): A statistically significant dose-related trend in rare hepatocellular carcinoma was observed. In addition, several other rare tumors were observed in the BPA-treated animals (see Table 25).

Table 25 Summary of rare tumors and statistically significant tumor findings observed in CLARITY-BPA studies in rats (all tumors are rare unless otherwise specified) (NTP 2018)

Tumor site	Tumor type	Female-1y-cont. (#5)	Female-2y-stop (#3)	Female-2y-cont. (#7)	Male-2y-stop (#4)	Male-2y-cont. (#8)
All sites	Granulocytic leukemia				✓ (3)	
	Malignant lymphoma [rare in females only]				Positive trend	
Brain	Malignant glioma			✓ (2)		
Kidney	Lipoma				✓ (2)	
	Liposarcoma				✓ (4)	
	Lipoma and liposarcoma, combined				✓ (6)	
Liver	Hepatocellular carcinoma				✓ (5)	Positive trend
	Hemangiosarcoma					✓ (3)
Mammary gland	Adenoma or adenocarcinoma [not rare]		* in low dose			
Nose	Squamous cell carcinoma				✓ (3)	✓ (3)
Skin	Fibrosarcoma		✓ (5)	✓ (3)		
Small intestine, jejunum	Adenocarcinoma			✓ (2)		✓ (2)
Spleen	Sarcoma				✓ (2)	✓ (3)
Thyroid gland	C-cell adenoma [not rare]				Positive trend	
	Follicular cell carcinoma					✓ (2)
Zymbal's gland	Carcinoma			✓ (4)		
	Adenoma					✓ (3)
Clitoral gland	Adenoma or Carcinoma [not rare]			Positive trend		
	Fibrosarcoma			✓ (3)		
Uterus	Stromal polyps [not rare]	Positive trend				
Prostate (dorsal/ lateral lobes)	Malignant lymphoma [not rare]				* in high dose with positive trend	
Testis or epididymis	Malignant mesothelioma					✓

All tumors are rare unless otherwise specified.
Checkmarks (✓) indicate the rare tumor occurred in at least two BPA-treated groups; however, the incidence was not statistically significant by Fisher pairwise comparison or trend test. Total number of animals with the rare tumor in all treatment groups combined is given in paratheses.
Asterisks indicate statistically significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$. Positive trend, $p < 0.05$ or $p < 0.01$ with Exact trend test conducted by OEHHA.
Gray shading indicates the sites are not applicable (sex-specific reproductive tissues).

Issues associated with the CLARITY-BPA core studies

Several issues associated with the CLARITY-BPA core studies have been raised by multiple scientists. These issues include possible exposure of controls to BPA as a result of environmental BPA contamination, the lack of responsiveness of the SD (NCTR) rat colony to estrogenic chemicals and chemicals that affect thyroid gland function, and the lack of appropriate historical control data on spontaneous tumor incidences for this rat colony. These issues are considered to be significant and may have limited the sensitivity of these studies, and thereby affect the ability of these studies to detect carcinogenic effects.

Concern regarding possible exposure of controls to BPA via environmental contamination

Both Hunt et al. (2014) and Vandenberg et al. (2019) raised concerns over data indicating BPA exposure to control animals in a 90-day subchronic pilot study conducted in part to demonstrate the efficacy of the CLARITY-BPA project (Churchwell et al. 2014; Delclos et al. 2014). Churchwell et al. (2014) reported that serum analyses revealed that two sets of controls (vehicle-only gavage and naive or untreated) had significant background contamination with BPA in the pilot study. Both total BPA (free (unconjugated) BPA + BPA-glucuronide) and BPA-glucuronide were measured in the serum of vehicle and naive control animals. The levels of BPA-glucuronide in the serum of vehicle and naive control animals ranged from around 2 to 10 nM and were similar to serum levels detected in the lowest BPA exposure group (2.5 µg/kg-day, 7–10 nM BPA-G) (Churchwell et al. 2014; Delclos et al. 2014). The authors stated that it is impossible to get an accurate measure of the free, unconjugated BPA due to the ever present, unavoidable contamination post sample collection; therefore, BPA-G, a metabolite that is not expected be prone to contamination, was used to compare with levels in the serum of the low dose group.

Churchwell et al. (2014) concluded that:

> *"Direct measurements of BPA-glucuronide in vehicle and naive control serum (2–10nM) indicated unintentional exposure and metabolism at levels similar to those produced by 2.5 g/kg bw/day BPA (7–10nM), despite careful attention to potential BPA inputs (diet, drinking water, vehicle, cages, bedding, and dust) and rigorous dosing solution certification and delivery. The source of this exposure could not be identified.*"

Because of the unknown nature of the contamination source in the pilot study, it was not possible to effectively address this issue in the CLARITY-BPA core studies and therefore, contamination remains a possibility in the core studies.

Although Heindel et al. (2015) later reported that internal dosimetry data collected in 46 vehicle-exposed controls at (one year of age) indicate that serum levels of BPA in these

animals were lower than in animals in the BPA 2.5 and 25 µg/kg-day dose groups, the study authors still could not rule out the possibility of background BPA contamination occurring in the rest of the control animals (n = 246) at one year, or in earlier time periods in these studies.

There appears to be a high incidence of several rare tumors in the vehicle control animals in several arms of the CLARITY-BPA core studies, including rare small intestine adenocarcinomas in male rats (core study #4), and rare ovary granulosa cell tumors (core studies #3 and #7) and heart schwannomas (core studies #3 and #7) in female rats. These observations may result from the unexplained BPA contamination.

Thus, it seems possible that contamination of animals with BPA was not adequately controlled for in the CLARITY-BPA core studies and this may have reduced the ability to detect differences in adverse outcomes (*e.g.,* cancer, hyperplasia) between control and BPA-treated animals.

Concerns regarding responsiveness of the SD (NCTR) rat colony to estrogenic chemicals and chemicals that affect thyroid gland function

Rat strains differ markedly in their sensitivity to BPA treatment (Kurebayashi et al. 2003; Snyder et al. 2000; Steinmetz et al. 1998). Steinmetz et al. (1998) reported that Fischer 344 (F344) rats have been shown to be more sensitive to BPA than Sprague–Dawley (SD) rats in some responses, including increases in the weight of the uterus and other reproductive organs. The specific SD rat colony used for the CLARITY-BPA core studies, SD (NCTR), was founded decades ago, and may differ from other SD rat colonies in sensitivity to BPA.

Vandenberg et al. (2019) also stated that the SD (NCTR) rat strain used in the CLARITY-BPA studies was insensitive to known estrogens, such as EE_2. For example, in the CLARITY-BPA core studies, several established estrogen-sensitive outcomes were not observed in the EE_2 positive control groups, such as any effects on the timing of vaginal opening in female SD (NCTR) rats undergoing puberty, or on testes weight, or chronic inflammation in the prostate in male SD (NCTR) rats. The lack of responsiveness of SD (NCTR) rats to estrogenic chemicals represents a significant limitation of the CLARITY-BPA studies.

In a CLARITY grantee study (Bansal and Zoeller 2019), the authors suggested the possibility that the SD (NCTR) rat strain is uniquely insensitive to thyroid hormone insufficiency. In this study, a well-known thyroid peroxidase inhibitor, 6-propyl-2-thiouracil (PTU) was used to induce T4 suppression and act as a positive control chemical in SD (NCTR) rats. However, PTU only weakly affected a subset of well-known thyroid-sensitive endpoints in male pups and no endpoints affected in female brain were observed. The authors concluded that

"NCTR SD rats appear to be particularly insensitive to the thyroidal effects of BPA exposure. Thus, they do not appear to be a useful system in which to study BPA effects on thyroid endocrinology or physiology, and it is not clear the degree to which this is generalizable to chemical effects on other endocrine systems."

Concerns regarding the available historical control data on spontaneous tumor incidence for the SD (NCTR) rat colony

In the CLARITY-BPA core studies, NTP (2018) identified two sets of prior studies conducted in this strain of rat, NTP (2008) and NTP (2010), to be used as historical controls. There are some differences on how the animals were treated in these two sets of studies compared to the CLARITY-BPA studies, including the use of different methods of test substance administration (diet, vs gavage in the CLARITY-BPA studies) and different types of cages (polycarbonate, vs polysulfone in the CLARITY-BPA studies). Vandenberg et al. (2020) pointed out and stated that these issues make the NTP (2008) and NTP (2010) studies inappropriate historical controls for the CLARITY-BPA studies, as the animals were not gavaged, suggesting a different background level of stress, and they were housed in polycarbonate cages, suggesting a different background level of BPA exposure.

In addition, as mentioned above, the studies (namely NTP 2008 and 2010) used by NTP (2018) to calculate historical control data were initiated several years earlier than the CLARITY-BPA studies. US EPA's 2005 Guidelines for carcinogen risk assessment (US EPA 2005) state that "[t]he most relevant historical data come from the same laboratory and the same supplier and are gathered within 2 or 3 years one way or the other of the study under review; other data should be used only with extreme caution". The CLARITY-BPA studies were conducted from 2012 to 2015, while the NTP (2008) and NTP (2010) studies were conducted from 1999 to 2003. It is possible that part of the differences between spontaneous tumor incidence in controls of CLARITY-BPA and these earlier NTP studies reflect natural experimental drift over time.

Besides the above limitations, the numbers of control animals in the NTP (2008) and NTP (2010) studies are low (~210 per sex). The limitations of these historical control data were acknowledged in NTP (2018) (*e.g.*, limited numbers of control animals of each sex in the NTP (2008) and NTP (2010) studies, use of different methods of administration, and the potential for drift in neoplasm incidence over time to occur).

Additional concerns about the design of the CLARITY-BPA studies were raised by Vandenberg et al. (2020) and Uchtmann et al. (2020), such as the lack of an unhandled, non-gavaged control group and lack of EE_2-treated positive controls in the stop-dose arms of the core studies. A previous pre-CLARITY study showed oral gavage procedures created a significant difference in the potential stress-related endpoints

relative to the unhandled control group (Vandenberg et al. 2014b). Thus, animal stress might have diminished the power of the study to find any effects from BPA.

4.2.2 Other studies in rats

Four other early life exposure studies (e.g., *in utero* with or without lactational exposures) were identified in rats (Table 26). One study was conducted in males and three studies were conducted in females (Acevedo et al. 2013; Ichihara et al. 2003; Murray et al. 2007).

These studies examined the effects of BPA on the development of neoplastic and/or preneoplastic lesions with broad ranges of doses and study durations, and via different early life exposures. In the male rat study (Ichihara et al. 2003), group sizes were small (12 animals per group) and only the prostate was examined. In the three female rat studies, the mammary gland was the only tissue examined (Acevedo et al. 2013; Murray et al. 2007). Other limitations of the studies in female rats included small group size (4–12 animals per group) and short study durations (PND50 to PND200).

Studies of short exposure duration and less than lifetime study duration may reduce the power to detect significant treatment-related effects. Such study designs render these studies inadequate for assessing the carcinogenic potential of BPA. Thus, studies of less than one year study duration are not included in Section 4.2.2, unless neoplasms were observed. Excluded studies include Ho et al. (2006), Durando et al. (2007), and Takashima et al. (2001).

Table 26 Overview of other studies exposing rats to BPA beginning *in utero*

Strain	F1 sex, group size	Study duration	Exposure route and design	Administered dose (µg/kg-day) to F0 dams	Exposure duration	Reference
F344	M, 12	65 weeks	*In utero*, and via lactation, F0 dams via gavage	0, 50, 7500, 120000	GD1 to PND21	Ichihara et al. (2003)
Sprague-Dawley	F, 5–12	PND50, 90, 140, 200	*In utero,* F0 dams via *s.c.* injections	0, 0.25, 2.5, 25, or 250	GD9 to birth	Acevedo et al. (2013)
Sprague-Dawley	F, 5–12	PND50, 90, 140, 200	*In utero* and via lactation, F0 dams via gavage	0, 0.25, 2.5, 25, or 250	GD9 to PND21	Acevedo et al. (2013)
Wistar-Furth	F, 4–6	PND50, 95	*In utero,* F0 dams via *s.c.* injections	0, 2.5, 25, 250, 1000	GD9 to PND1	Murray et al. (2007)

M, male; F, female; PND, postnatal day; GD, gestation day; *s.c.*, subcutaneous

65-week study in male F1 F344 rats exposed in utero and via lactation (Ichihara et al. 2003)

Pregnant female F344 rats (F0 dams) were administered BPA at 0, 0.05, 7.5, or 120 mg/kg-day (0, 50, 7500, or 120000 µg/kg-day, as presented in Table 26) via gavage (in 0.5% carboxymethyl cellulose sodium salt) from gestation day (GD) 1 to PND21. F1 pups (12 animal per group) were weaned on PND21. F1 males were terminated for histological examination at 65 weeks of age.

No treatment-related tumors were observed in male rats. Seminal vesicles and ventral and anterior lobes of the prostate were examined for preneoplastic lesions, and none were observed in either the BPA-treated or control groups.

50- to 200-day study in female F1 Sprague-Dawley rats exposed in utero (mammary gland only) (Acevedo et al. 2013)

Pregnant female dams (F0) were administered BPA (0, 0.25, 2.5, 25, or 250 µg/kg-day in 50% DMSO) *s.c.* via osmotic pump implants from GD9 to birth. Mammary glands of F1 females (5–12 animals per group, each litter was represented only once) were removed on PND50, PND90, PND140, and PND200 for histological analysis. On PND50, no neoplastic lesions of the mammary gland were observed. Preneoplastic lesions were observed on PND50 only in BPA treatment groups, and included atypical ductal hyperplasia (control, 0/5; BPA0.25, 3/5; BPA2.5, 1/5; BPA25, 0/5; BPA250, 2/5). At later timepoints adenocarcinomas of the mammary gland were observed only in BPA treatment groups, on PND90 (one at BPA2.5), PND140 (one at BPA250) and PND200 (one at BPA0.25). In addition, one lobular alveolar hyperplasia was observed in the BPA250 group on PND90.

50- to 200-day study in female F1 Sprague-Dawley rats exposed in utero and via lactation (mammary gland only) (Acevedo et al. 2013)

Pregnant female dams (F0) were administered BPA (0, 0.25, 2.5, 25, or 250 µg/kg-day in 50% DMSO) *s.c.* via osmotic pump implants from GD9 to birth and through lactation (PND1 to PND21). Mammary glands of F1 females (5–12 animals per dose per exposure group, each litter was represented only once) were removed on PND50, PND90, PND140, and PND200 for histological analysis. On PND50, ductal carcinoma *in situ* was observed in one BPA-treated animal (control, 0/5; BPA25, 1/5). Atypical ductal hyperplasia was also observed on PND50 in BPA-exposed groups (control, 0/5; BPA2.5, 1/5; BPA25, 1/5; BPA250, 1/6). On PND90, lobular alveolar hyperplasia was observed in one BPA25 animal. On PND140, adenocarcinomas were observed in two BPA-exposed animals (one at BPA2.5, and one at BPA25) and one lobular alveolar hyperplasia was observed in the BPA0.25 group. On PND200, one fibroadenoma was observed in the BPA2.5 group.

50- and 95-day study in female F1 Wistar-Furth rats exposed in utero (mammary gland only) (Murray et al. 2007)

Pregnant female dams (F0) were administered BPA (0, 2.5, 25, 250, 1000 µg/kg-day) in 50% DMSO via osmotic pump implants from GD9 until PND1. F1 pups were weaned on PND21, and then fed normal diet. Female F1 animals were sacrificed on PND50 or PND95 and mammary glands were removed. Only one F1 from a given litter was assigned to each group for histopathological examinations. On PND50, significant (3–4-fold, $p < 0.05$) increases in the incidence of hyperplastic ducts of the mammary gland were observed in each of the treated groups compared to controls, and mammary gland carcinoma *in situ* was observed in one animal in each of the two highest dose groups (control, 0; BPA250, 1/4; BPA1000, 1/4). On PND95, a significant increase in mammary hyperplastic lesions was observed in the 2.5 µg/kg-day group compared to controls ($p = 0.032$), and mammary gland carcinoma *in situ* was observed in two animals in each of the two highest dose groups (control, 0; BPA250, 2/6; BPA1000, 2/6).

4.2.3 Mice

Five studies exposing mice to BPA beginning *in utero* or within the first week of life were identified in mice. Table 27 presents an overview of the designs of these studies. One study was conducted in males and four were conducted in females (Newbold et al. 2007; Newbold et al. 2009; Tucker et al. 2018; Weinhouse et al. 2014). The studies had limitations including small group sizes (all studies, 5–23 animals per group), short exposure duration (three studies, *in utero* or neonatal only), and limited examination of tissues (mammary gland, one study; female reproductive tract, one study; female reproductive tract or mammary gland, one study; liver, two studies). A three-month study in female mice with small group sizes (20 per group) examined only the pelvic organs and found no neoplasms, and is not included in section 4.2.3 (Signorile et al. 2010).

Table 27 Overview of studies exposing mice to BPA beginning *in utero* or within the first week of life

Strain	F1 Sex, group size	Study duration (months)	Exposure route and design	Administered dose (µg/kg-day) to F0 dams, unless otherwise noted	Exposure duration	Reference
CD-1	F, 16–23	18	*s.c.* injections	0, 10, 100, 1000 (to neonates)	PND1 to PND5	Newbold et al. (2007)
CD-1	F, 13–16	18	*In utero*, F0 dams via *s.c.* injections	0, 0.1, 1, 10, 100, or 1000	GD9 to GD16	Newbold et al. (2009)
CD-1	F, 5–14	3, 8, 14	*In utero*, F0 dams via gavage twice daily	0, 1000, 10000, 100000	GD10 to GD17	Tucker et al. (2018)[1]
Agouti$^{+/-}$ C57BL/6J: C3H/HeJ	M, 9–11	10	*In utero* and via lactation, F0 dams & F1 via feed	0, 5×10^{-5}, 0.05, 50 ppm in feed	GD0.5–5 to PND22, F1 PND22 to 10-month-old	Weinhouse et al. (2014)
Agouti$^{+/-}$ C57BL/6J: C3H/HeJ	F, 9–10	10	*In utero* and via lactation, F0 dams & F1 via feed	0, 5×10^{-5}, 0.05, 50 ppm in feed	GD0.5–5 to PND22, F1 PND22 to 10-month-old	Weinhouse et al. (2014)

M, male; F, female; PND, postnatal day; GD, gestation day; *s.c.*, subcutaneous

[1]F0 dams were dosed with BPA (0, 500, 5000, 50000 µg/kg bw) twice daily and reported as 0, 1000, 10000, 100000 µg/kg-day in the table. F0 dams observed to have a copulatory plug the following morning after mating were considered to be at gestation day (GD) 0.5 or GD0 (Tucker et al. 2018). *In utero* dosing days reported in the publication as GD10.5 to GD17.5 are presented here as GD10 to GD17.

18-month study in female CD-1 mice exposed to BPA from PND1 to PND5 via s.c. injection (reproductive tissues only) (Newbold et al. 2007)

Female newborn CD-1 [Crl:CD-1 (ICR) BR] mice (24 per treatment group) were administered BPA (0, 10, 100, or 1000 µg/kg-day) in corn oil by daily subcutaneous (*s.c.*) injection from PND1 to PND5. Female newborns from all dams were pooled and randomly standardized before the treatment. Animals were sacrificed for histopathological examination of reproductive tissues (uterus, ovary/oviduct) at 18 months.

In the uterus, benign leiomyomas were observed in all BPA-dose groups but the increases were not significant compared to the controls (control, 0/18; BPA10, 1/23; BPA100, 2/20; BPA1000, 1/16). Uterine stromal polyps were increased at BPA100, but the increase was not statistically significant (control, 1/18; BPA10, 1/23; BPA100, 5/20; BPA1000, 1/16).

Preneoplastic lesions were observed in the uterus. A statistically significant increase of cystic endometrial hyperplasia was observed in the 100 µg/kg-day BPA group (control,

1/18; BPA10, 5/23; BPA100, 9/20, $p < 0.01$; BPA1000, 4/16). Atypical hyperplasia of the endometrium was observed in one animal each in the BPA10 and BPA100 dose groups (control, 0/18; BPA10, 1/23; BPA100, 1/20; BPA1000, 0/16). No neoplastic or preneoplastic lesions were observed in the ovary/oviduct.

18-month study in female F1 CD-1 mice exposed to BPA in utero (reproductive and mammary tissues only) (Newbold et al. 2009)

Thirty pregnant female CD-1 [Crl:CD-1 (ICR) BR] mice (F0) (five per group) were administered BPA (0, 0.1, 1, 10, 100, or 1000 µg/kg-day) in corn oil via *s.c.* injection from GD9 to GD16. F1 were delivered on GD19. F1 pups were pooled from all litters within each dose group and females were sacrificed for histopathological examination of reproductive tissues at 18 months. Histopathology was also performed on mammary tumors identified by gross examination.

Non-significant increases of neoplastic lesions were observed in female reproductive tissues. In the ovary, cystadenomas developed in several BPA groups, but the increases were not statistically significant compared to the control group (control, 0/16; BPA0.1, 0/14; BPA1, 0/12; BPA10, 1/14; BPA100, 1/14; BPA1000, 1/13). Uterine stromal polyps were noted in some BPA-treated groups, with none in controls (one at BPA0.1, one at BPA1 and one at BPA10). One stromal sarcoma of the cervix occurred in the BPA100 group (1/14), with none in controls.

Multiple types of preneoplastic lesions were observed. Increases in uterine cystic endometrial hyperplasia, which did not reach statistical significance, were observed in the BPA1 and BPA 100 groups (control, 2/16; BPA0.1, 0/14; BPA1, 5/13; BPA10, 1/14; BPA100, 5/14; BPA1000, 1/13). Adenomatous hyperplasia of the endometrium was seen in some BPA-treated animals (one at BPA1, two at BPA100, none in controls), and atypical hyperplasia of the endometrium was also observed in some BPA-treated animals (three at BPA0.1, two at BPA1, one at BPA1000, none in controls). Squamous metaplasia was also observed in some BPA treated animals (one at BPA1, two at BPA100, none in controls).

3–14 month study in female F1 CD-1 mice exposed to BPA in utero (mammary gland only) (Tucker et al. 2018)

Pregnant female CD-1 mice (F0) were administered BPA at 0 (n = 12), 0.5 (n = 13), 5 (n = 12), or 50 (n = 11) mg/kg in sesame oil via gavage twice daily (0, 1000, 10000, 100000 µg/kg-day, as presented in Table 27) from GD10 to GD17. Female F1 mice were sacrificed at 3, 8, or 14 months of age and mammary glands were removed for histological analysis.

At 14 months, one mammary lipoma was observed in the mid-dose BPA group, with none in controls (control, 0/13; low-dose, 0/14; mid-dose, 1/11; high-dose, 0/6). No

mammary gland tumors were observed in mice examined at 3 or 8 months of age. At 14 months, preneoplastic lobuloalveolar hyperplasia was observed in one or more mice in each of the BPA-treated groups, with none in controls (control, 0/13; low-dose, 3/14, mid-dose, 2/11; high-dose, 1/6). In addition, lobuloalveolar hyperplasia was observed in one animal in the mid-dose group at 8 months of age (control, 0/5; low-dose, 0/8; mid-dose, 1/5; high-dose, 0/5).

10-month studies in male and female F1 Agouti$^{+/-}$ C57BL/6J:C3H/HeJ mice exposed to BPA in utero, via lactation and in feed (liver only) (Weinhouse et al. 2014)

Weinhouse et al. (2014) examined the effects of BPA on induction of liver tumors in studies with 10-month perinatal and postnatal exposure in male and female Agouti$^{+/-}$ C57BL/6J:C3H/HeJ mice. The wild type (a/a) C57BL/6J:C3H/HeJ dams (F0) were administered BPA (0, 5×10^{-5}, 0.05, 50 mg/kg diet-day or ppm) in phytoestrogen-free diets for two weeks before mating while Agouti C57BL/6J:C3H/HeJ sires were exposed to BPA during mating period. F0 sires were briefly exposed to diets containing BPA during the mating period (0.5 to 5 days). Male and female F1 mice (9–11 animals per dose per group) were exposed to BPA via F0 dams from GD1 to birth (PND1), and through lactation until weaning on PND22. Then male and female F1 mice were fed on the same BPA containing diets as those for the F0 dams. At 10 months of age, animals were sacrificed, and livers were removed for histopathological examinations.

Male mice

In males, two hepatocellular adenomas were found in the high-dose group (control, 0/10; 5×10^{-5} ppm, 0/10; 0.05 ppm, 0/11; 50 ppm, 2/9) (trend test $p = 0.046$). No treatment-related differences were observed in the incidences of hepatocellular carcinoma (control, 2/10; 5×10^{-5} ppm, 1/10; 0.05 ppm, 2/11; 50 ppm, 2/9) or hepatocellular adenoma or carcinoma combined (control, 2/10; 5×10^{-5} ppm, 1/10; 0.05 ppm, 2/11; 50 ppm, 4/9).

Female mice

In females, as shown in Table 28, one hepatocellular adenoma was observed in the high-dose group. Hepatocellular carcinomas were observed in all BPA-treated groups, with none in the controls. A significant increase in the incidence of hepatocellular adenoma or carcinoma combined was observed in the 50 ppm group by pairwise comparison to the controls ($p < 0.05$), with a significant trend ($p = 0.0185$).

Table 28 Liver tumor incidence in female Agouti$^{+/-}$ C57BL/6J:C3H/HeJ mice exposed to BPA *in utero*, via lactation, and post-weaning in feed until 10 months of age (Weinhouse et al. 2014)

Tumor Site	Tumor Type	Administered concentration (ppm)[1]				Trend test *p*-value
		0	5×10^{-5}	0.05	50	
Liver	Hepatocellular adenoma	0/9	0/10	0/10	1/9	NS
	Hepatocellular carcinoma	0/9	2/10	1/10	3/9	NS
	Combined hepatocellular adenoma or carcinoma	0/9	2/10	1/10	4/9*	0.0185[2]

Tumor incidence is expressed as the number of animals with the specified tumors over the number of animals examined microscopically as reported by study authors (Weinhouse et al. 2014). Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (conducted by OEHHA): * $p < 0.05$. Exact trend test conducted by OEHHA. NS, not significant.
[1] ppm is parts per million of BPA in feed (1 ppm = 1 mg/kg).
[2] The presented value is from the Exact trend test conducted by OEHHA. The authors reported the *p*-value of 0.056 using the Cochran-Armitage exact trend test (Weinhouse et al. 2014).

4.3 Studies Using Transgenic Animal Models

Three transgenic studies in mice (Jenkins et al. 2011; Ma et al. 2020; Sekar et al. 2016) and one in zebrafish (Yang et al. 2019a) were identified.

Female mouse mammary tumor virus (MMTV)-erbB2/neu transgenic mice [FVB/N/TgN (MMTV-neu202Mul)], referred to as MMTV-erbB2 from this point on] were exposed to BPA (0, 2.5, 25, 250, and 2500 µg/l) via drinking water beginning at 56 days old with continued exposure until 252 days old or when tumors exceeded 10% bodyweight (Jenkins et al. 2011). All lesions were examined pathologically and those classified as invasive mammary adenocarcinomas were used in the final analysis of tumor latency, volume and multiplicity. Lung metastases of mammary tumors were also quantified. A subset of mice were selected for sacrifice at 112 days of age for cell proliferation mechanism studies, which are discussed in Section 5.3.10. Exposure to 2.5 and 25 µg/l BPA in drinking water reduced the median time to an animal's first mammary tumor compared to controls (*p*-values for reduced tumor onset not given), significantly increased mammary tumor multiplicity ($p = 0.01$ for both doses), and increased mammary tumor volume (25 µg/l: $p < 0.05$; 2.5 µg/l dose: not significant). Significant increases of lung metastases of mammary tumors were observed in mice treated with either 2.5 µg/l ($p < 0.01$) or 25 µg/l BPA ($p < 0.05$). No treatment-related neoplastic effects were observed at the higher doses of BPA.

In a separate study, MMTV-erbB2 transgenic mice were used to investigate the effects of *in utero* BPA exposure on mammary tumors (Ma et al. 2020). Pregnant mice were exposed via *s.c.* injection of BPA (0, 50, 500 ng/kg and 250 µg/kg bw) daily from GD11–19 and female offspring were observed for mammary tumorigenesis, mammary morphogenesis and other reproductive or endocrine-related endpoints. BPA decreased the tumor latency period in the offspring from an average of 37.6 weeks in the control to 35.1 and 32.3 weeks for the 50 and 500 ng/kg groups, respectively ($p < 0.05$ pairwise comparison between the 500 ng/kg group and control). Low doses of BPA (50 and 500 ng/kg) also significantly ($p < 0.01$) increased the number of terminal end buds and epithelial cell proliferation in mammary glands at PND35. The high dose of BPA (250 µg/kg) did not decrease the mammary tumor latency period in female offspring and did not increase the number of terminal end buds or epithelial cell proliferation in mammary glands at PND35.

To investigate estrogen receptor alpha (ERα)-binding ligands, Sekar et al. (2016) developed a transgenic mouse model that constitutively expresses a firefly luciferase split reporter complementation biosensor (NFLuc-ER-LBD$_{G521T}$-CFLUC) to screen for ER function and ligand binding affinity and potency. The E2 non-responsive mutant ER-α ligand binding domain (LBD) utilized in this study is not responsive to various E2 analogs but is responsive to other ER ligands, such as diethylstilbestrol, 4-hydroxytamoxifen (4-OHT), methyl-piperidinopyrazole and raloxifene. Male and female transgenic mice, ten to twelve-weeks old in groups of 5–15, were exposed to BPA in drinking water at 0, 2.8 and 5.6 nM for six months. Mice were imaged every two weeks for bioluminescent signals. "Tumor-like outgrowths" in the flanks were identified in six out of 15 female mice treated with 5.6 nM BPA for six months. Outgrowths in two of these animals were confirmed by histopathology to be adenocarcinomas. No tumor growths were observed in low-dose or control females, or in any male mice.

A *kras* transgenic zebrafish model for hepatocellular carcinoma was used to investigate the effects of BPA and other environmental toxicants on liver tumorigenesis and inflammation (Yang et al. 2019a). In this model, the hepatic specific expression of *kras^{G12V}* can be induced by treatment with doxycycline (DOX). Here, larvae were treated with DOX (20 µg/ml) and BPA (5 µg/ml-day) from three to seven days post fertilization (dpf 3 – 7). On dpf 8, larvae were anesthetized and imaged for liver size and neutrophil quantification. Both liver size and intrahepatic neutrophil number were significantly ($p < 0.01$) increased with BPA treatment compared to the DOX-only control group. This study did not confirm if the increased liver size was due to neoplastic growth, but the authors indicated that previous experiments using this model had shown that “histologically these livers show apparent hyperplasia, a precursor of carcinogenesis”.

4.4 Studies in Xenograft, Syngeneic, and Regenerated Organ Mouse Models

BPA has been studied in ten studies using xenograft mouse models, four studies using syngeneic mouse models, and one study using regenerated mammary gland mouse model (Appendix Table D1).

In studies with xenograft models:

- Exposure to BPA starting before introduction of the xenograft increased the number of tumor-bearing mice following injection with human breast carcinoma MCF-7 cells in one study (Weber Lozada and Keri 2011) and injection with MCF-7 cells that overexpressed protein kinase D1 (PKD1), but not MCF-7 cells that did not overexpress PKD1 in another study (Merzoug-Larabi et al. 2019).
- Exposure to BPA starting before introduction of the xenograft increased mean tumor volume following injection with MCF-7 cells with both normal expression and overexpression of PKD1 (Merzoug-Larabi et al. 2019) and increased mean tumor weight following injection with human breast cancer MCF10DCIS.com/Luc-GFP cells (low-dose BPA only) (Kim et al. 2019a).
- Exposure to BPA after introduction of the xenograft promoted growth of established tumors with MCF-7 cells (Lee et al. 2017b), human breast adenocarcinoma MDA-MB-231 cells (Xu et al. 2017), human ovarian adenocarcinoma BG-1 cells (Hwang et al. 2013), human prostate cancer LNCaP cells (Wetherill et al. 2006), and human neuroblastoma SK-N-SH cells (Zhu et al. 2009).
- Exposure to BPA suppressed growth of established tumors formed by ERα-negative, ERβ-positive human B-cell lymphoma (Granta-519) cells (Yakimchuk et al. 2018).
- Exposure to BPA either during the preparation of normal human prostate epithelium xenografts or after introduction of the xenograft increased the incidence of high grade prostatic intraepithelial neoplasia (PIN) in the xenograft after hormonal carcinogenesis was initiated by implantation of pellets containing testosterone and E2 (Prins et al. 2014).

In studies with syngeneic models:

- Exposure to BPA starting before introduction of syngeneic mouse mammary adenocarcinoma 4T1 cells increased the resulting tumor volume (Nava-Castro et al. 2019; Palacios-Arreola et al. 2017).
- Exposure to BPA at the same time as introduction of syngeneic mouse colorectal carcinoma CT-26-Luc cells increased the resulting tumor volume (Jun et al. 2021).

- Exposure to BPA suppressed growth of established tumors formed by ERα-negative, ERβ-positive mouse T-cell lymphoma (EG-7) cells (Yakimchuk et al. 2018).

In the study of a regenerated mammary gland model:

- Pretreatment of mice with BPA prior to isolation of mammary stem cells that were used to regenerate mammary glands resulted in increased incidences of atypical ductal hyperplasia (ADH) and ductal carcinoma *in situ* (DCIS) in the regenerated glands (Wang et al. 2014a).

4.5 Studies of BPA in Combination with Other Treatments

4.5.1 Studies of BPA administered before treatment with a model carcinogen

Ten publications reported tumor findings observed in studies of BPA administered before treatment with a model carcinogen, with 10 studies in rats and one study in mice. BPA exposure routes included *in utero* and/or lactation, drinking water and *s.c.* injection. Animals were administered BPA in early life (*in utero* through lactation) except one study of BPA exposure in young rats (from PND21 to PND51) (Varuzza et al. 2019).

Prenatal or early postnatal BPA exposure followed by postnatal exposure to the carcinogens 7,12-dimethylbenz(a)anthracene (DMBA) or methylnitrosourea (MNU) had an effect on mammary gland tumor development in mice and rats. Statistically significant findings included increases of mammary gland tumor incidence (Betancourt et al. 2010; Leung et al. 2017; Varuzza et al. 2019), and tumor multiplicity (Jenkins et al. 2009; Varuzza et al. 2019), and decreases of tumor latency (Betancourt et al. 2010; Jenkins et al. 2009; Leung et al. 2017; Weber Lozada and Keri 2011). In one study with small group size (≤ 15 animals per group) a non-statistically significant increase in ductal carcinoma *in situ* was observed with prenatal exposure to BPA (Durando et al. 2007), while in another study a protective effect of early postnatal BPA exposure was observed (Yin et al. 2006).

Early-life administration of BPA had no effect in other studies and organs, including the uterus, prostate, thyroid gland, lung, liver, thymus, and esophagus (Ichihara et al. 2003; Takashima et al. 2001; Yoshida et al. 2004).

The major limitations of these studies included small group sizes in many studies (≤19 animals per group), short BPA exposure duration, and examination of only one organ or tissue type in many studies. For more information on the treatment plan and study findings of these studies, see Appendix D, Table D2.

4.5.2 Studies of BPA administered before testosterone and 17β-estradiol treatment (prostate only)

Three publications (Prins et al. 2011; Prins et al. 2017; Wong et al. 2015) reported neoplastic and/or preneoplastic lesions in the prostates of male SD rats in studies of BPA administered before testosterone (T) and 17β-estradiol (E2) treatment. In these studies, neonatal rats were exposed to BPA on PND1, 3 and 5 by oral or *s.c.* injection routes. T+E2 capsules were implanted in animals starting on PND70 or PND90 until study termination. The major findings included statistically significant increases of microinvasive carcinoma in the LP and total PIN (low-grade (LG-) and high-grade (HG-) PIN combined) or HG-PIN in LP, DP, and periurethral prostatic ducts (PPDs) of the prostate (Prins et al. 2011; Prins et al. 2017). Exposure of male rats to BPA alone significantly increased PIN (LG- and HG-PIN combined, or HG-PIN) in the LP in these 28-week and 12-month studies (Prins et al. 2011; Prins et al. 2017). The major limitations of these studies of BPA administered before T+E2 treatment included small group sizes (≤ 28 animals per group), shorter than lifetime exposure (12 months or shorter), and examination of only prostate tissues. For more information on the treatment plan and study findings of these studies, see Appendix Table D3.

4.5.3 Studies of BPA administered after tumor initiation

Three publications investigated the effects of BPA administered after tumor initiation in female rats. BPA significantly increased tumors in the mammary gland after initiation with diethylnitrosamine, MNU, and N-bis (2-hydroxy propyl) nitrosamine (DHPN) (Zhang et al. 2021b). BPA either significantly reduced or had no effect on thyroid carcinomas or adenomas after initiation with DHPN (Takagi et al. 2001; Zhang et al. 2017a). For more information on the treatment plan and study findings of these studies, see Appendix Table D4.

5. MECHANISTIC CONSIDERATIONS AND OTHER RELEVANT DATA

5.1 Pharmacokinetics and Metabolism

Hundreds of studies have investigated the pharmacokinetics and metabolism of BPA in humans and animals, and the subject has been reviewed in multiple publications (*e.g.*, Chapin et al. (2008); Gramec Skledar and Peterlin Mašič (2016); Kang et al. (2006); Michałowicz (2014); Nachman et al. (2014)). OEHHA did not review all available studies on the pharmacokinetics and metabolism of BPA. Since humans and animals share many of the reported metabolic pathways for, and metabolites of, BPA, data from animal studies are included when human data are unavailable or incomplete, or when data from animal studies is useful to complement human data and to highlight route, species, and gender differences observed. We excluded studies conducted in non-mammalian animals, microbes, or plants. Review of animal studies focused on those conducted in rodents and primates.

OEHHA also reviewed a number of human and animal studies that provide relevant information on (i) enzymes involved in BPA metabolism, (ii) reactive metabolites of BPA and (iii) human polymorphisms in some of these key enzymes. Overall, OEHHA reviewed over 500 studies on BPA pharmacokinetics and metabolism.

BPA is rapidly absorbed in humans by oral and dermal routes (Liu and Martin 2017; Sasso et al. 2020; Teeguarden et al. 2015a), and studies in animals indicate rapid absorption by oral, dermal, subcutaneous (*s.c.*), intravenous (*i.v.*), and intraperitoneal (*i.p.*) routes. BPA is distributed throughout the body, crossing the blood-brain barrier and the placenta. It is rapidly excreted, primarily via urine in humans and other primates. In rodents, feces is the main route of excretion. BPA undergoes enterohepatic circulation in rats and possibly mice, but not in humans, chimpanzees or cynomolgus monkeys. In spite of a short half-life (less than 6 hours for humans by oral route) and fast excretion, total BPA was detected in spot urine samples of more than 90% of 8498 participants in NHANES 2005–2014 (Ward et al. 2020), suggesting frequent daily exposures to BPA and continual presence in the body. The metabolism of BPA occurs primarily via conjugation by glucuronidation or sulfo-conjugation, but oxidative metabolism also occurs and leads to the production of several electrophilic, reactive, and/or estrogenic metabolites, as well as formation of DNA adducts. Polymorphisms of key enzymes, life stage, co-exposure to xenobiotics and certain diseases determine the extent of conjugative metabolism in individuals.

The following subsections on BPA absorption, distribution, and excretion will focus on studies by oral or dermal routes, which are more relevant than other routes for exposures to humans, and on studies using radiolabeled BPA, *e.g.*, deuterated- (d6- or

d16-BPA) or radiocarbon-labeled BPA (^{14}C-BPA), regardless of route. Studies using radiolabeled BPA are informative because labeled BPA can be distinguished from unlabeled background BPA (*e.g.*, exposure from other non-experimental routes or contamination concerns in sample collection and preparation). Metabolism of BPA is discussed after absorption, distribution, and excretion.

In most of the studies discussed in this section, BPA levels are reported as "free" BPA (unconjugated) or "total" BPA (unconjugated and conjugated). Although BPA can bind non-covalently with proteins, including plasma proteins, most studies have not specified whether the BPA levels measured include some portion (or all) of the BPA that was bound to proteins at the time of sample collection. Some studies did report the sample preparation procedures used; for example, a protein denaturation step followed by solvent extraction (Ho et al. 2017a), or just a solvent extraction step using methanol (Patterson et al. 2013; Sasso et al. 2020) or acetonitrile (Teeguarden et al. 2011; Vandenberg et al. 2014a). Each of these example sample preparation procedures would be expected to release some (or possibly all) protein-bound BPA.

Examples of pharmacokinetic studies of BPA conducted in nonhuman mammals are provided below to illustrate the breadth of routes and species studied, organized by route and species. Some of these studies are discussed further in this section.

- oral
    - Rats (Diel et al. 2004; Doerge et al. 2011a; Domoradzki et al. 2003; Domoradzki et al. 2004; Knaak and Sullivan 1966; Miyakoda et al. 2000; Pottenger et al. 2000; Sakamoto et al. 2002; Snyder et al. 2000; Sun et al. 2002; Yoo et al. 2001)
    - Mice (Doerge et al. 2011b; Izzotti et al. 2009; Miyaguchi et al. 2015; Sieli et al. 2011; Taylor et al. 2011; Zalko et al. 2003)
    - Others:
        - Rhesus monkeys (Patterson et al. 2013; Vom Saal et al. 2014)
        - Cynomolgus monkeys and chimpanzees (Negishi et al. 2004)
        - Dogs (Gayrard et al. 2013)
        - Pigs (Gayrard et al. 2019)
- *s.c.* or dermal
    - Rats (Marquet et al. 2011)
    - Mice (Mita et al. 2012)
    - Others:
        - Sheep (Viguié et al. 2013)
        - Pigs (Zalko et al. 2011)
- *i.v.*
    - Rats (Doerge et al. 2010a; Doerge et al. 2011a; Moors et al. 2006; Shin et al. 2002; Sun et al. 2002; Upmeier et al. 2000)
    - Mice (Doerge et al. 2012)

- *i.p.*
    - Rats (Atkinson and Roy 1995b; Yoo et al. 2000; Yoo et al. 2001)

5.1.1 Absorption

After oral dosing, approximately 0.2%, 2.8%, 0.94% and 10% of the applied dose enters the systemic circulation in adult mice, rats, rhesus monkeys and humans, respectively, with subsequent first pass metabolism in the liver (Doerge et al. 2010a; Doerge et al. 2010b; Doerge et al. 2012; Mielke and Gundert-Remy 2012). Dermal absorption bypasses this first pass metabolic step, leading to higher bioavailability of "free (unconjugated)" BPA (Sasso et al. 2020). Following absorption, BPA is extensively metabolized (Domoradzki et al. 2004; Gramec Skledar et al. 2015), and more than 90% of the unmetabolized BPA is thought to be non-covalently bound to plasma protein (Chapin et al. 2008), leaving the remaining 5–10% unbound in humans and rats (Teeguarden et al. 2005).

Absorption of BPA is rapid with oral administration. In a study with human volunteers, the maximum concentration (Cmax) of free BPA in blood (0.43 nM) was reached within 1.6 hours after ingestion of d6-BPA. Reported half-lives ($T_{1/2}$) of free BPA and BPA-G (BPA-glucuronide, a major BPA metabolite, discussed under Metabolism section below) were short, with 0.45 and 0.28 hours, respectively (Teeguarden et al. 2015a). In a different study with human volunteers, Cmax of BPA-G in the blood was reached at 80 minutes (= Tmax, time to reach Cmax) after oral administration of 5 mg d16-BPA; no free BPA was detected (Völkel et al. 2002). The half-life for BPA-G in the blood was estimated to be 5.3 hours. Thayer et al. (2015) also reported a short Tmax of 1.3 hours for total BPA in the serum in volunteers receiving an oral dose of 100 µg/kg d6-BPA.

Dermal absorption is less rapid compared to the oral route, based on human studies conducted with thermal paper containing up to 20 mg BPA per gram of paper (Adeyemi et al. 2020; Biedermann et al. 2010; Hormann et al. 2014; Lv et al. 2017). After dermal dosing with 100 µg/kg over a 12-hour period in 10 volunteers, free (unconjugated) and total (unconjugated plus conjugated) d6-BPA in serum were first detected at 2.8 and 1.4 hours in serum, respectively. Cmax values for free and total d6-BPA were 0.272 and 3.26 nM, respectively (Sasso et al. 2020). The serum half-lives of free and total d6-BPA by the dermal route were 17.6 and 21.4 hours, respectively (Sasso et al. 2020). BPA transfer and absorption increases when hands are wet or greasy, or with the use of hand sanitizer (Biedermann et al. 2010; Hormann et al. 2014).

In vitro dermal absorption/penetration studies with radiolabeled BPA reported varying levels of absorption, with longer incubation time generally resulting in greater absorption or penetration, and different vehicles resulting in different absorption rates. The following absorption rates were observed: 1.7–3.6% over 24 hours in fresh human skin

(Toner et al. 2018), 45.6% in viable human skin over 72 hours (Zalko et al. 2011), and 3–41% with different vehicles (3%: sebum; 6%: acetone; 41%: water) in human skin over 40 hours (Champmartin et al. 2020). In non-viable human skin, absorption rates were 8.6% over 24 hours (Demierre et al. 2012), and 13% over 48 hours (Mørck et al. 2010).

Half-lives of BPA can vary by route and species (Collet et al. 2015; Doerge et al. 2010a; Poet and Hays 2018). In general, plasma half-lives are longer in mice than rats with the same doses and administration route. Species comparisons of plasma half-lives of BPA by oral route were reviewed by Poet and Hays (2018): reported half-lives were 5.5 hours in humans (Teeguarden et al. 2015a), 0.63–34 hours in mice, with a lower dose having a longer half-life (Doerge et al. 2011b; Taylor et al. 2011), 3 hours in rats (Doerge et al. 2010a), and 0.39–8.9 hours in monkeys (Doerge et al. 2010b; Taylor et al. 2011). Species comparison of half-lives in plasma following an *i.v.* dose of 5 mg/kg was reported by Collet et al. (2015): 13.3 hours for mice, 5.6 hours for rats, 1.3 hours for sheep, 0.97 hours for pigs, 0.94 hours for horses and 0.62 hours for dogs.

The route of BPA administration affects the level of free (unconjugated) BPA in blood. Species and route differences (oral and *s.c.*) between rats, chimpanzees and monkeys were studied by Tominaga et al. (2006). In all species, the oral route led to lower levels of free BPA in the blood compared to the *s.c.* route. Similarly, route comparisons (oral, *i.v.* and *s.c.*) on the bioavailability of ^{14}C-BPA in male and female F344 rats showed that there was a marked difference in the levels of free BPA in the plasma, with the oral route having the lowest free BPA compared with the *s.c.* or *i.v.* routes (Pottenger et al. 2000). This is consistent with the assumption that BPA undergoes first pass metabolism in the liver following oral exposure (Doerge et al. 2010a). The major metabolite in the plasma after oral exposure was glucuronide conjugated BPA (BPA-G), accounting for 68–100% of plasma radioactivity (Pottenger et al. 2000). By contrast, lower BPA-G levels were observed following *s.c.* (17–49%) or *i.p*. (27–69%) administration, with higher free BPA (65–76% for *s.c.* and 21–51% for *i.p*., respectively) in plasma (Pottenger et al. 2000). Similar to the findings in rats, levels of free BPA were higher in the plasma of mice with the *s.c.* route compared with oral administration (Draganov et al. 2015).

5.1.2 Distribution

BPA is distributed throughout the body in humans and animals. In humans, BPA has been detected in the liver (Geens et al. 2012), brain (Charisiadis et al. 2018; Geens et al. 2012), adipose tissues (Artacho-Cordón et al. 2017; Artacho-Cordón et al. 2018; Charisiadis et al. 2018; Fernandez et al. 2007; Geens et al. 2012), placenta (Jimenez-Diaz et al. 2010; Lee et al. 2018b), hair (Katsikantami et al. 2020; Lee et al. 2017a), and in various body fluids including breast milk and colostrum (Azzouz et al. 2016; Hartle et

al. 2018; Hines et al. 2015; Migeot et al. 2013; Schönfelder et al. 2002; Tateoka 2015), cord blood (Aris 2014; Lee et al. 2018b; Schönfelder et al. 2002), amniotic fluid (Dreshaj and Pasha 2021; Engel et al. 2006), peritoneal fluid (Aris 2014) and semen (Inoue et al. 2002). BPA was also detected in the brain in humans (Charisiadis et al. 2018; Geens et al. 2012) and rats (Kim et al. 2004; Sun et al. 2002) thus BPA crosses the blood-brain barrier and the placenta.

In autopsies of 11 patients, the highest average BPA concentrations were detected in adipose tissue (3.78 ng/g) followed by liver (1.48 ng/g) and brain (0.91 ng/g) (Geens et al. 2012). Adipose tissues may serve as a reservoir to store BPA (Stahlhut et al. 2009). This is supported by the observation that excretion of BPA increases as bariatric surgery patients lose weight (Dambkowski et al. 2018). In NHANES data from 1999–2006, urinary BPA levels were inversely associated with lean mass in men, not in women, after adjusting for potential confounders like body mass index (BMI) (Corbasson et al. 2016). Storage of BPA in adipose tissues is likely dependent on continuous or frequent exposure to BPA. A study in mice found that a single dose of BPA was rapidly absorbed in adipose tissue of mice and was eliminated within 24 hours (Doerge et al. 2012). However, no repeated or continuous exposure occurred in these experiments, which is not representative of dietary and environmental exposure in humans.

Similar to distribution in humans, orally administered ^{14}C-BPA was distributed throughout the body in female F344 rats, with the gastrointestinal tract (86.7 µg) and liver (29.6 µg) having the highest level, followed by plasma (6.97 µg), fat (1.95 µg) and kidney (1.66 µg) 48 hours after dosing (Kim et al. 2004). In another study with male and female F344 rats (^{14}C-BPA by the oral route), radioactivity was detected in all organs 30 minutes after dosing, with some sex differences. In male rats, levels of BPA in various tissues 30 minutes after dosing were distributed as follows (with levels ranking from highest to lowest): kidney, liver, pituitary gland, adrenal gland, blood, lung and thyroid gland. In female rats at 30 minutes, the highest radioactivity was in the liver, followed by kidney, blood, adrenal gland, uterus and lung. At 72 hours, only kidney and liver showed radioactivity in both male and female rats (Kurebayashi et al. 2005).

Breast milk

BPA is detected in breast milk, including colostrum (Azzouz et al. 2016; Cao et al. 2015; Chemek and Nevoral 2019; Nakao et al. 2015; Sayıcı et al. 2019; Tateoka 2015; Zimmers et al. 2014). A recent study (Dualde et al. 2019) reported over 77% and 83% of 120 human breast milk samples (in Valencia, Spain) have detectable levels of free (unconjugated) and total (conjugated and unconjugated) BPA, with geometric means of 0.15 ng/ml and 0.29 ng/ml, respectively.

Distribution of BPA to breast milk occurs rapidly, as demonstrated in a study with breastfeeding women, where BPA was detected in the milk within one hour of consumption of a canned coffee drink from a BPA-containing can (an estimated 37.4 µg BPA intake) (Tateoka 2015).

BPA was also detected in the milk of rats (Doerge et al. 2010c; Okabayashi and Watanabe 2010) and mice (Snyder et al. 2000; Taylor et al. 2011). In lactating CD rats receiving a single ^{14}C-BPA dose by gavage, a small percentage of BPA also rapidly transferred to the milk within one hour. BPA-G was the dominating metabolite in the milk and plasma in rat pups (Snyder et al. 2000).

Placenta and fetal compartments

Free BPA can cross the placenta in humans and animals (Corbel et al. 2013; Corbel et al. 2015; Gauderat et al. 2016; Kolatorova et al. 2018). In rats, small amounts of BPA-G can cross the placenta (Domoradzki et al. 2003; Nishikawa et al. 2010). Some metabolism such as deconjugation of BPA-G can occur in the fetus (see Metabolism section). Paired mother-fetus biomonitoring measurements show how maternal BPA levels affect levels in fetuses and neonates (Corbel et al. 2014; Dreshaj and Pasha 2021; Engel et al. 2006; Gounden et al. 2021; Kolatorova et al. 2018; Lee et al. 2018b; Liu et al. 2017b; Schönfelder et al. 2002; Troisi et al. 2014). For example, in samples from 318 maternal-neonatal pairs from Korea (Lee et al. 2018b), the median BPA concentrations were highest in the neonatal urine (4.75 ng/ml), followed by maternal urine (2.86 ng/ml), cord serum (1.71 ng/ml), maternal serum (1.56 ng/ml), breast milk (0.74 ng/ml) and placenta (0.53 ng/ml). As reviewed by Dreshaj and Pasha (2021), BPA levels in fetal cord blood, fetal liver, and amniotic fluids range from 0.14 to 9.2, 1.3 to 50.5, and 0.36 to 5.62 ng/g, respectively. Biomonitoring studies of BPA in Japan measured 0.62–1.37 ng/ml in umbilical cord blood, 0.56 ng/ml in amniotic fluid, and 0.26–1.32 ng/ml in maternal serum (Tateoka 2015). On average, total BPA measured in umbilical cord serum was comprised of 36% free BPA (range: 4–100%), 45% BPA-sulfate (BPA-S) (range: 2–96%) and 19% BPA-G (range: 0.1–82%) in 85 Californian samples (Gerona et al. 2013). As reviewed by Gerona et al. (2013), free BPA was also detected in the umbilical cord serum in other studies (e.g., Schönfelder et al. (2002); Chou et al. (2011)). Levels of BPA in cord blood were sometimes higher than maternal blood in the paired samples (Kolatorova et al. 2018; Liu et al. 2017b; Schönfelder et al. 2002), suggesting potential deconjugation or less effective detoxification/conjugation (e.g., immature enzyme system or presence of β-glucuronidase; see Metabolism for details) in the fetal compartment, thus leading to greater amounts of free BPA in the fetus. Statistically higher blood BPA levels were observed in male compared to female fetuses in 37 samples taken in Germany (Schönfelder et al. 2002).

BPA can also cross the placenta in animals, as has been shown in studies with pregnant animals using radiolabeled BPA and various administration routes: F344 rats

(Takahashi and Oishi 2000), SD rats (Doerge et al. 2011a), mice (Zalko et al. 2003), and sheep (Corbel et al. 2013; Gauderat et al. 2016; Gingrich et al. 2019). In sheep, 4.5% of the administered *i.v.* dose, 5 mg/kg, can be transferred to the fetus (Gauderat et al. 2016). On average, 67% of BPA entering the fetal circulation was eliminated though fetal-to-maternal clearance with a short half-life of 20 minutes (Gauderat et al. 2016). A much longer half-life for BPA was observed in fetal (52 hours) vs maternal (5.3 hours) circulation in a pregnant sheep by *s.c.* injection of 0.5 mg/kg BPA (Ginsberg and Rice 2009). Conjugated BPA cannot cross the placenta back into the maternal circulation (Corbel et al. 2014; Vom Saal et al. 2014).

In pregnant CD1 mice dosed with 25 µg/kg ^{3}H-BPA by *s.c.* injection at gestation day 17, the highest percentage of radioactivity after 24 hours was detected in the digestive tract (defined by authors as "from duodenum to rectum, including the digestive tract content"; 45.3%), followed by feces (21.2%), urine (5.7%), fetus/litter (4.1%), carcass (2.8%), liver (2.5%), bile (1.9%) and placenta (0.6%) (Zalko et al. 2003).

5.1.3 Excretion

BPA is excreted in urine, feces, breast milk, and sweat. From a maternal perspective, excretion also occurs by passing BPA on to the fetus via placental transfer (see section on Placenta and fetal compartments). The primary excretion in humans is via urine and usually occurs within 24 hours, with more than 90% of orally administered BPA excreted (Thayer et al. 2015; Völkel et al. 2002). Urine is also the major excretion route for non-human primates such as cynomolgus monkeys (Doerge et al. 2011b; Kurebayashi et al. 2002).

The elimination half-life of total d6-BPA (oral dose of 100 µg/kg in ten volunteers) was estimated to be 7.8 hours (free BPA: 5.5 hours, BPA-G: 7.3 hours and BPA-S: 5 hours, respectively) (Teeguarden et al. 2015a). Völkel et al. (2005) reported the elimination half-life of 4 hours in six volunteers receiving 25 µg d16-BPA. BPA is excreted mainly as conjugated metabolites, the largest amount being BPA-G (with an average of 85% in males and 75% in females), followed by BPA-S (Li et al. 2022; Teeguarden et al. 2015a; Völkel et al. 2002; Völkel et al. 2005; Ye et al. 2005). This is consistent with human biomonitoring data, where the majority of urinary metabolites were BPA-G (69.5%) followed by BPA-S (21%) and free BPA (9.5%) (Ye et al. 2005). Only 10% of the 30 urinary samples in the study by (Ye et al. 2005) had detectable free BPA. Free BPA was also detected in 11% of 100 newborn urine samples collected at birth or up to one month after birth from Canada (Arbuckle et al. 2015).

Sweat is a minor excretion pathway for humans. BPA was detected in sweat in two studies: in sweat samples collected from 16 out of 20 individuals while in a sauna or

during exercise (Genuis et al. 2012), and in sweat patches worn for 7 days from 3 out of 50 individuals (Porucznik et al. 2015).

In rats (Knaak and Sullivan 1966) and mice (Zalko et al. 2003) (data presented earlier in the placenta and fetal compartments section), BPA is excreted primarily in feces, followed by urine. Radioactivity in fecal and urinary excretion in rats accounted for 84% of the oral ^{14}C-BPA dose in Knaak and Sullivan (1966), 91% in Snyder et al. (2000), 88% in males and 64% in females (feces only) in Kurebayashi et al. (2005) and over 95% (higher urinary portion in females) in Pottenger et al. (2000). The majority of the orally administered ^{14}C-BPA dose was excreted within 24 hours, with an average of 56% of radioactivity detected in feces and 28% in urine over an 8-day period (Knaak and Sullivan 1966). Radioactivity was not detected in the exhaled CO_2 (Knaak and Sullivan 1966). Similar patterns of excretion were observed for the oral, *i.v.* and *s.c*. routes (Pottenger et al. 2000).

In one earlier study conducted in an unspecified strain of rats (Knaak and Sullivan 1966), about a 35% free BPA, 35% hydroxylated BPA, and 30% conjugated BPA were detected in feces following oral administration. Later studies reported more consistent results; free BPA was the predominant form in feces from rats treated with an oral dose of 100 mg/kg radiolabeled-BPA (14C- or d6-BPA), 61% in F344 rats (Kurebayashi et al. 2003), 98% in SD rats (Twaddle et al. 2010), and 98% in F344 and CD rats (Snyder et al. 2000). Pottenger et al. (2000) did not identify hydroxylated BPA in the feces, as reported by Knaak and Sullivan (1966), but hydroxylated BPA was detected in mouse feces in a study by Zalko et al. (2003) (free BPA was still the predominant form, accounting for over 95% of the fecal excretion). Gramec Skledar and Peterlin Mašič (2016) suggest that high levels of free BPA in feces are likely due to microbial metabolism of the conjugated form in the digestive tract based on findings from Knaak and Sullivan (1966) and Zalko et al. (2003).

In rat urine, BPA was excreted primarily as BPA-G. Strain differences in excretion between female F344 and CD rats (in the urine and feces) were reported by Snyder et al. (2000) following administration of 14C-BPA via gavage. For CD rats, 70% of radioactivity was found in feces and 21% in urine over 6 days. For F344 rats, 50% of radioactivity was in feces and 42% in urine. BPA-G was the major urinary metabolite for both rat strains, though low levels of free BPA were detected, ranging from 2.2% to 10% of total ^{14}C-BPA dose at different time points (24–96 hours).

Some sex or route differences in excretion were observed in rats (Kurebayashi et al. 2003; Pottenger et al. 2000), mice (Zalko et al. 2003) and monkeys (Doerge et al. 2010b). For example, female rats have higher urinary excretion (21–34%), about 2-fold greater than male rats (13–16%), across all administration routes (oral, *i.v.* and *s.c.*) and doses tested (Pottenger et al. 2000). Route comparison shows that urinary excretion of a 10 mg/kg dose in female rats is lowest by the *s.c.* route (54.40%), compared to oral

(71.65%) and *i.v.* (64.07%) routes. Major urinary metabolites identified were BPA-G, followed by free BPA and BPA-S across these routes, doses, and sexes.

Biliary excretion and enterohepatic circulation

Biliary excretion occurs in rats and mice and enterohepatic circulation occurs in rats (Doerge et al. 2010a; Inoue et al. 2001; Inoue et al. 2004; Kurebayashi et al. 2003) and possibly mice (Miyaguchi et al. 2015), but not in humans or other primates (Tominaga et al. 2006). Inoue et al. (2001) suggest that BPA absorbed by the intestine in rats is probably glucuronidated exclusively in the liver and the conjugate is excreted mainly into the bile. Infusion studies with 7.5 μM BPA into the liver via the portal vein showed that 91% of BPA was absorbed by the liver tissue, and 65% of the absorbed BPA was glucuronidated within 60 minutes. Approximately 65% of the BPA-G was excreted into the bile, and about 35% into the hepatic vein (Inoue et al. 2001). Using higher BPA concentrations (0.01, 0.05, and 0.1 mM), free BPA was also excreted but only into the vein at 5.6%, 9.3%, and 14.6%, respectively, of the total BPA (Inoue et al 2001). Biliary excretion of ^{14}C-BPA in F344 rats accounted for 45–50% of the radioactivity administered by the oral route and 58–66% administered by the *i.v*. route six hours after dosing (Kurebayashi et al. 2003). In pregnant rats, biliary excretion of BPA-G is reduced by approximately 50% compared to non-pregnant rats, and venous excretion of BPA-G was increased three-fold. This may be due to reduced multidrug resistance-associated protein (MRP)2-mediated transport, the mechanism that facilitates excretion of the glucuronide into the bile (Inoue et al 2004). Biliary excretion has also been observed in CD1 mice, where biliary extracts consisted of more than 90% BPA-G (Zalko et al. 2003).

Enterohepatic circulation was observed in rats. Following oral or *i.v.* administration of radiolabeled BPA, individual rat serum concentration-time profiles showed a secondary peak of total, but not unconjugated, BPA, suggesting that enterohepatic circulation occurs (Doerge et al. 2010a, 2012). Miyaguchi et al. (2015) suggested that enterohepatic circulation may also occur in mice based on the slow urinary clearance from plasma. Enterohepatic circulation has not been observed in cynomolgus monkeys, chimpanzees (Doerge et al. 2010b; Tominaga et al. 2006) or humans (Völkel et al. 2002).

5.1.4 Metabolism

The metabolism of BPA occurs primarily in the liver (Inoue et al. 2016; Völkel et al. 2002), although other tissues are able to metabolize BPA. For example, BPA was metabolized via conjugation in human and pig skin (Zalko et al. 2011). Overall, metabolism is largely similar in humans and laboratory animals, with many of the same metabolites detected in both (reviewed in (Gramec Skledar and Peterlin Mašič 2016)).

The primary metabolic route is the conjugation of BPA with either glucuronic acid or sulfate, forming BPA-glucuronide (BPA-G) or BPA-sulfate (BPA-S), respectively. Conjugation allows for rapid excretion of these metabolites via urine in humans and cynomolgus monkeys (Kurebayashi et al. 2002; Völkel et al. 2002) and via bile and feces in rats (Inoue et al. 2001; Knaak and Sullivan 1966; Kurebayashi et al. 2003; Pottenger et al. 2000) (see Section 5.1.3 Excretion). A second metabolic pathway is the oxidation of BPA by cytochrome P450 (CYP) enzymes, leading to the formation of reactive metabolites such as BPAQ. An overview of the proposed metabolism of BPA is shown in Figure 4 to illustrate the major pathways and key enzymes. Not all metabolites, conjugates or CYP enzymes are shown in this figure.

BPA-G is the main metabolite formed in humans and animals, followed by BPA-S (Knaak and Sullivan 1966; Pottenger et al. 2000; Snyder et al. 2000; Ye et al. 2005). In humans, BPA-G constitutes approximately 69% and BPA-S about 21% of excreted metabolites (Ye et al. 2005). Because BPA-G (Matthews et al. 2001) and BPA-S (Shimizu et al. 2002) both lack estrogenic activity, these conjugation pathways are generally considered as detoxification pathways with regards to estrogenic effects.

The oxidative pathway mediated via CYP enzymes is a quantitatively minor pathway for BPA. However, this pathway leads to the formation of several bioactive, reactive and electrophilic metabolites, including *ortho*-hydroxy-BPA (*ortho*-OH-BPA, BPA catechol), BPAQ, carbocations, and the estrogenic metabolites 4-methyl-2,4-*bis*(*p*-hydroxyphenyl)pent-1-ene (MBP) and hydroxycoumyl alcohol (HCA) (Atkinson and Roy 1995a, b; Gramec Skledar and Peterlin Mašič 2016; Jaeg et al. 2004; Knaak and Sullivan 1966; Michałowicz 2014; Nakamura et al. 2011; Yoshihara et al. 2004; Zalko et al. 2003). Some of these metabolites are formed via reactive intermediates and thus may contribute to the formation of reactive oxygen species (ROS) and oxidative stress. BPA metabolites have been shown to form DNA adducts *in vitro* and *in vivo* (Atkinson and Roy 1995a, b; De Flora et al. 2011; Edmonds et al. 2004; Izzotti et al. 2009; Wu et al. 2017; Zhao et al. 2018).

In humans, factors that affect metabolism and susceptibility to BPA toxicity include genetic polymorphisms associated with key enzymes involved in metabolic activation and detoxification, deconjugation reactions, metabolic competition, certain diseases, and life stage. This is discussed in more detail below.

Conjugation pathway: glucuronidation

As mentioned above, BPA is extensively metabolized in the liver, primarily via conjugation with either glucuronic acid or sulfate, which increases the water solubility of BPA and thus allows for faster urinary excretion, usually within 24 hours or less (Hanioka et al. 2008; Kurebayashi et al. 2002; Kurebayashi et al. 2003; Stowell et al. 2006; Thayer et al. 2015; Trdan Lušin et al. 2012; Völkel et al. 2002). Conjugated

metabolites can account for more than 80% of urinary metabolites, with BPA-G accounting for the majority of excreted metabolites in humans (about 70%) (Landolfi et al. 2017; Quesnot et al. 2014; Ye et al. 2005). BPA-G is generally the main metabolite formed in both humans and animals (Gramec Skledar and Peterlin Mašič 2016; Knaak and Sullivan 1966; Nakagawa and Tayama 2000; Pottenger et al. 2000; Völkel et al. 2002; Zalko et al. 2003). One study with 30 individuals reported gender differences for conjugated metabolites, with men having significantly higher levels of BPA-G compared to women, and women having significantly higher levels of BPA-S (Kim et al. 2003).

In a dosimetry study conducted as part of the Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity (CLARITY-BPA), SD rats were given d6-BPA on PND4 or PND25 by gavage at 2.5, 25, or 250 µg/kg. Free (unconjugated) d6-BPA was detected in the serum of all treated groups, and ranged from 0.5–7.7% of the total d6-BPA measured (Camacho et al. 2019).

A minor metabolite, a BPA diconjugate with glucuronide and sulfate has been identified in male but not female rats at high dose application (Inoue et al. 2016) and in *in vitro* studies with human, rat, and mice microsomal fractions (Pritchett et al. 2002). Zalko et al. (2003) reported diconjugates of BPA in pregnant mice and possibly a diconjugate of BPA with glucuronic acid and N-acetyl galactosamine in the placenta.

Glucuronidation can vary between species, strains, and sexes (see Pritchett et al. (2002). For example, in one study female rat liver microsomes were more effective with glucuronidation of BPA compared to human microsomes (Elsby et al. 2001).

UDP-glucuronosyltransferases (UGTs) are a family of major phase II enzymes that catalyze the conjugation of BPA with glucuronic acid from the cofactor UDP-glucuronic acid to form BPA glucuronide. In humans, UGT2B15 and UGT1A9 have the highest activity of glucuronidation of BPA among the hepatically expressed UGTs (Gramec Skledar et al. 2015; Hanioka et al. 2008; Street et al. 2017). UGT2B15 contributes over 80% of glucuronidation of BPA at lower concentrations (below 5 µM), whereas UGT1A9 contributes up to 50% at higher concentrations (50 µM) (Street et al. 2017). Other human isoforms of UGTs that can glucuronidate BPA include UGT1A1, UGT1A3, UGT2B4, and UGT2B7 (Hanioka et al. 2008). Extra-hepatic UGTs, such as UGT1A1 in kidney, intestine, and breast tissue, as well as UGT2A1 (which is mainly expressed in the airways), can also glucuronidate BPA (Gramec Skledar et al. 2015; Street et al. 2017; Trdan Lušin et al. 2012). In rats, BPA is conjugated via hepatic UGT2B1 (Yokota et al. 1999).

In mice, enzymes of both the UGT1 and UGT2 families are able to glucuronidate BPA (Fay et al. 2015). While lacking estrogenic activity, BPA-G is a bioactive molecule which has been shown to induce human and murine adipocyte differentiation (Boucher et al. 2015) and depression of mitogen activated protein kinases (MAPKs) in rat prolactinoma cells (Vinas et al. 2013).

Many studies have shown that human UGTs carry significant genetic polymorphisms which can result in different (mostly lower and in some cases complete loss of) enzyme activities (Kasteel et al. 2020). These UGT polymorphisms may explain the inter-individual variability of BPA glucuronidation. Human UGT polymorphisms have been reported for enzymes UGT1A1, UGT1A9, and UGT2B15, where differences in genotype may account for inter-individual variability in the clearance of BPA. For example, UGT1A9*22/*22 had a two-fold higher glucuronidation rate compared to genotype *1/*1 or *1/*22 (Street et al. 2017), and UGT1A1*28/*28 had 80% lower glucuronidation compared to the *1/*1 genotype (Trdan Lušin et al. 2012). For information on UGT polymorphisms and BPA glucuronidation activity, see Appendix Table E1.

Besides studies that measured the effect of UGT polymorphisms on BPA glucuronidation, one study attempted to examine the correlation between UGT variant genotypes and serum BPA levels in a Chinese population, although the interpretation of this study is very limited due to the lack of information on BPA intake/exposure (Luo et al. 2020). This study compared the serum levels of BPA between women who were wildtype for UGT1A1, UGT2B7, or UGT2B15 with women who carried the respective variants (UGT1A1*6, UGT2B7*2, and UGT2B15*2), and found no statistically significant difference except for a small decrease in carriers of the UGT2B15*2 variant.

Reduced glucuronidation of BPA has also been associated with certain diseases, for example, Parkinson's disease, where patients had lower glucuronidation of BPA compared to healthy controls (Landolfi et al. 2017).

Co-exposure of BPA with other xenobiotics or some commonly used drugs can inhibit BPA conjugation and metabolism. Co-exposures to triclosan, tetrabromobisphenol A, or bisphenol S significantly inhibited BPA conjugation metabolism, with the amount of BPA-G, BPA-S, and OH-BPA-S decreasing with rising doses of other added xenobiotics (Peng et al. 2019a). Similarly, some commonly used drugs (for example, carbamazepine, mefenamic acid, salicylic acid, naproxen, and valproic acid) inhibit BPA metabolism in rat hepatocytes. BPA glucuronidation was inhibited by naproxen and carbamazepine in incubations with rat microsomes (Verner et al. 2010).

Glucuronidation is also dependent on life stage. Changes in phase II drug-metabolizing enzyme expression during development can significantly alter the pharmacokinetics for a given drug or toxicant (Dreshaj and Pasha 2021; McCarver and Hines 2002). As reviewed by McCarver and Hines (2002), UGT1A1 is absent from the fetal liver, and UGT2B15 is active at reduced levels in the human fetus. These findings are supported by a study with human fetal liver samples, where mRNA expression of UGT2B15 and SULT1A1 were significantly reduced in fetal liver compared to gender-matched healthy adult liver samples (Nahar et al. 2013). Similarly, in a study on ontogeny of human UGT2B15 expression investigators found that fetal UGT2B15 protein expression begins with the onset of the 3rd trimester, with levels reaching approximately 18% of adult

values. The greatest increase in expression occurred during the first postnatal weeks (Divakaran et al. 2014). Similar results were observed in rats, where low levels of UGT2B1 were observed in fetuses (Nishikawa et al. 2010). In a different animal model, the Vmax (maximum velocity of an enzymatic reaction) of glucuronidation of BPA in ovine sheep fetuses increased from approximately 500-fold lower in early fetuses to 13-fold lower in near-term fetuses, as compared to adult sheep (Corbel et al. 2015).

In the fetus, the balance between conjugation of BPA and deconjugation of BPA-G may impact the internal levels of free BPA. Deconjugation of BPA-G by fetal *β*-glucuronidases has been observed, leading to higher levels of free BPA in the fetus. Fetal levels of *β*-glucuronidase can reach adult levels, as observed in a study by Nahar et al. (2013), where the expression of *β*-glucuronidase mRNA in human fetal liver was comparable to levels in adult liver.

In rats, BPA-G can pass through the placenta where it is subsequently deconjugated by *β*-glucuronidase, leading to free BPA in the rat fetus and amniotic fluid (Nishikawa et al. 2010). Similarly, placental tissue from ewes hydrolyzed BPA-G into BPA, suggesting glucuronidase activity in placental tissues (Corbel et al. 2015). A study with chronically catheterized fetal sheep measured the contribution of BPA-G hydrolysis to BPA to the elimination of BPA-G from the fetal compartment and its resulting effect on the overall fetal exposure to free BPA. Using data on levels of BPA and BPA-G in the fetus and maternal blood and PBPK modeling, the authors estimated that deconjugation reactions resulted in a 43% increase in the overall fetal exposure to free BPA, compared to a hypothetical scenario with no deconjugation (Gauderat et al. 2016). Conversely, Patterson et al. (2013) observed that levels of conjugated BPA remained steady and at higher levels in fetuses of Rhesus monkeys compared to the mothers. However, the authors only measured total conjugates and did not distinguish between sulfated and glucuronidated BPA (Patterson et al. 2013).

In some cases (discussed below), sulfoconjugation rather than glucuronidation can be the dominant process (Liu et al. 2017b). Hence, a conclusion regarding de-glucuronidation in the fetus cannot be drawn for the Patterson et al. (2013) study.

Deconjugation also occurs in adult animals. A study in rats found that after oral administration of BPA, BPA-G was found in the contents of the upper and lower part of the small intestine, but only free BPA was found in the content of the cecum. The authors observed a high *β*-glucuronidase activity in extracts prepared from the cecum content (Sakamoto et al. 2002).

Conjugation pathway: sulfoconjugation

BPA can also be conjugated with sulfate to form BPA-sulfate. In humans, BPA is sulfated by cytosolic sulfotransferases (SULTs), several of which are found in liver cytosol (Nishiyama et al. 2002). Using recombinant sulfotransferases, Nishiyama et al.

(2002) found that SULT1A1, SULT2A1, and SULT1E were able to conjugate BPA, with SULT1A1 having the highest activity. Similar to the de-conjugation of BPA-G, BPA sulfate conjugates can be de-conjugated by sulfatases, such as estrone sulfatase (arylsulfatase C) (Stowell et al. 2006).

Sulfoconjugation of BPA is often, but not always, a lesser pathway compared to glucuronidation, with BPA-S constituting about 21% of metabolites in human urine (Ye et al. 2005). However, sulfoconjugation can be higher or lower compared to glucuronidation, depending on the tissue and specific population examined, co-exposures to xenobiotics, disease status of individuals, life stage, or polymorphisms. For example, in a study with healthy Chinese adults, BPA-S was significantly higher than BPA-G in both serum and whole blood (Li et al. 2022). The authors acknowledged that this observation is different from studies in several other studies in humans and rodents where BPA-G is shown as the predominant metabolite, and mentioned enzyme activities, gut microbes, and different exposure pathways as possible explanations.

The developmental expression of sulfotransferases may also play a role in the sulfoconjugation of BPA. As reviewed by McCarver and Hines (2002), higher SULT1A3 activity in fetal liver and kidney tissues (ranging in gestational age from 18 to 25 weeks) was observed compared to adult tissues. In contrast, SULT1A1 activity was higher in adult tissues. A study conducted with second trimester pregnant women in California (Gerona et al. 2013) found that umbilical cord serum, on average, had greater amounts of BPA-S (45%; range 2–96%) than BPA-G (19%; range 0.1–82%). A similar result was found in a study in China where BPA-S was the dominant metabolite and was significantly higher than BPA-G in both maternal and cord sera (Liu et al. 2017b). The higher sulfoconjugation in cord blood may be due to limited UGT activity in the fetus and earlier ontogeny of sulfotransferases, which is the main conjugation pathway prior to birth (Liu et al. 2017b; McCarver and Hines 2002; Nachman et al. 2014). This is in agreement with results from another study (briefly mentioned in the previous section on glucuronidation (Divakaran et al. 2014)), where UGT2B15 protein expression was not observed in the first and second trimester in microsomes from fetal liver. A study in sheep also supports sulfoconjugation as the main conjugation pathway prior to birth. Sulfoconjugation of BPA, but not glucuronidation, was observed with placental tissues of ewes that were incubated with BPA (Corbel et al. 2015). The Vmax of sulfoconjugation by hepatic cytosols was in a similar range in early stage and near term fetuses but was about one fifth of the Vmax calculated for adult ewes (Corbel et al. 2015).

As mentioned above, co-exposure of BPA with other phenolic xenobiotics can inhibit the formation of BPA-S, due to competitive enzyme binding with SULTs (Peng et al. 2019a). Thus, sulfoconjugation of BPA was significantly inhibited by co-exposure to triclosan, tetrabromobisphenol A, and bisphenol S.

Certain diseases may also impact sulfate conjugation of BPA. For example, BPA sulfoconjugation may be reduced in humans with liver disease. Tissues from patients with steatosis, diabetes, diabetes cirrhosis, or cirrhosis showed decreased hepatic sulfate conjugation of BPA, ranging from 8–23% of levels seen with tissues from healthy adults with non-fatty livers (Yalcin et al. 2016). Similarly, in transgenic obese mice (Lep−/−(B6.V-Lepob/J, ob/ob), sulfoconjugation was 23% less compared to wildtype (C57BL/6) mice (Yalcin et al. 2016).

Like BPA-G, BPA-S can also undergo deconjugation. Experiments with human and animal cell lines indicate that conjugation and de-conjugation reactions of BPA can be cell specific, and can determine BPA toxicity. For example, mouse mammary epithelial HC11 cells did not show any biotransformation capability with BPA, while human liver HepG2 and mammary MCF-7 cells were able to form BPA-S and BPA-G (Bursztyka et al. 2008; Pritchett et al. 2002). BPA-S is unable to permeate the membrane of Hep2G cells (Suiko et al. 2000). However, in cells that have high levels of estrone sulfatase, such as MCF-7 cells, uptake may occur. Estrone sulfatase is located on the outer leaflet of the cell membrane of breast cancer cells. Thus, MCF-7 cells that were incubated with BPA-S or BPA-disulfate (BPA-DS) were able to deconjugate BPA-S via estrone sulfatase, resulting in uptake of BPA and subsequent cellular effects, observed as cell proliferation of MCF-7 cells (Stowell et al. 2006).

Oxidative metabolism

In addition to conjugation with glucuronide or sulfate, BPA is also metabolized via oxidation, primarily via CYP enzymes (Nakamura et al. 2011; Ousji et al. 2020; Schmidt et al. 2013). Oxidation of BPA leads to the formation of several electrophilic and reactive metabolites such as quinones and various radicals, which can contribute to the formation of ROS and oxidative stress (Gassman 2017). Other oxidative metabolites identified have estrogenic and/or cell proliferative properties as described in more detail below (Nakagawa and Suzuki 2001; Nakamura et al. 2011). Many of these reactive metabolites are unstable and therefore difficult to isolate or detect *in vivo*. Hence, the majority of oxidative metabolism studies have been conducted *in vitro,* and only a few *in vivo* studies are available (*in vivo* studies: (Atkinson and Roy 1995a; Izzotti et al. 2009; Zalko et al. 2003). *In vitro* studies (Elsby et al. 2001; Jaeg et al. 2004; Nakagawa and Suzuki 2001; Nakamura et al. 2011; Okuda et al. 2011; Schmidt et al. 2013; Ye et al. 2011b; Yoshihara et al. 2001; Yoshihara et al. 2004)) have been conducted with human or animal hepatocytes, S9 fractions, microsomes, and recombinant human enzymes to allow for detection and identification of reactive metabolites, especially when nucleophilic trapping agents such as reduced glutathione (GSH) are added (Ousji et al. 2020; Schmidt et al. 2013). Broadly, oxidative metabolism results in the formation of hydroxylated metabolites, dimers, metabolites of carbon bridge cleavage, and their corresponding GSH conjugates (Schmidt et al. 2013). This section summarizes the

main oxidative pathways and metabolites that have been identified, and describes enzymes and mechanisms that lead to their formation. Aspects of oxidative metabolism that relate to specific key characteristics (KCs) of carcinogens (KC1, KC2, KC5, KC8, or KC10) are noted but are discussed in more detail in their respective sections.

Ortho-OH-BPA

In CYP-catalyzed reactions with the presence of NADPH, BPA is hydroxylated to *ortho*-hydroxy-BPA (*ortho*-OH-BPA, also referred to as 3-OH- or 5-OH-BPA), a catechol (Ousji et al. 2020). *Ortho*-OH-BPA has been identified in rats and mice *in vivo* (Knaak and Sullivan 1966; Zalko et al. 2003)), and *in vitro* in reactions with rat hepatocytes, human or rodent liver microsomes, and human recombinant CYP enzymes (Elsby et al. 2001; Jaeg et al. 2004; Nakagawa and Suzuki 2001; Nakamura et al. 2011; Okuda et al. 2011; Ousji et al. 2020; Schmidt et al. 2013; Ye et al. 2011b; Yoshihara et al. 2001; Yoshihara et al. 2004). The human recombinant CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 enzymes can oxidize BPA to *ortho*-OH-BPA, with CYP1A2 and CYP2C9 having the highest activity (Schmidt et al. 2013). In addition to detection in rat feces, *ortho*-OH BPA has been detected in the placenta, amniotic fluid, fetus, maternal plasma and liver in mice (Knaak and Sullivan 1966; Zalko et al. 2003)). In other enzymatic reactions, *ortho*-OH-BPA can be conjugated with sulfate via sulfotransferase and undergo further hydroxylation by CYP enzymes (Ousji et al. 2020). O*rtho*-OH-BPA has been shown to induce proliferation of human MCF-7 breast cancer cells (Nakagawa and Suzuki 2001). *Ortho*-OH-BPA has some slight estrogenic activity and is about 10-fold less potent than BPA in the yeast estrogenicity assay (Elsby et al. 2001). This is further discussed in Section 5.3.8 KC 8 and Section 5.3.10 KC10.

BPA-3,4-quinone (BPAQ)

In subsequent oxidative reactions by CYP enzymes, *ortho*-OH-BPA is oxidized to BPA-3,4-quinone (BPAQ), a reactive and electrophilic metabolite that can covalently bind to DNA and form adducts (Nakamura et al. 2011; Ousji et al. 2020; Qiu et al. 2004; Schmidt et al. 2013; Wu et al. 2017). The formation of DNA adducts (see below) by BPAQ has been reported in several studies, including *in vivo* studies in rats and mice (Atkinson and Roy 1995a; Izzotti et al. 2009), and in several *in vitro* studies (Atkinson and Roy 1995a, b; Edmonds et al. 2004; Izzotti et al. 2009; Nakamura et al. 2011; Ousji et al. 2020; Qiu et al. 2004; Wu et al. 2017; Zhao et al. 2018). Quinones are also highly redox active molecules, with the catechol-quinone couple being capable of redox cycling, thereby generating ROS and oxidative stress (Kovacic 2010; Xiong et al. 2021). This is further discussed under KC5 (Section 5.3.5).

BPAQ-DNA adducts were identified in several studies. In an earlier study, Atkinson and Roy (1995a, 1995b) demonstrated that rats exposed to BPA via a single *i.p.* injection or via multiple gavage treatments formed DNA adducts in the liver. These adducts had

identical chromatographic migration patterns compared to adducts formed from incubations of synthesized BPAQ with rat liver DNA, and to adducts formed in enzymatic reactions with peroxidase, as well as those formed from incubations of BPAQ with deoxyguanosine monophosphate (dGMP). In later studies with DNA and/or individual deoxynucleosides, BPAQ reaction products with deoxyguanosine (dG) and deoxyadenine (dA) were identified as 3-OH-BPA-N7-Gua and 3-OH-BPA-N7-Ade respectively, each formed via an intermediate (3-OH-BPAN7-dG and 3-OH-BPAN7-dA, respectively) (Qiu et al. 2004; Wu et al. 2017; Zhao et al. 2018). One other study identified BPA-3,4-quinone-guanine-N7 as the adduct in reaction with BPAQ and herring testes DNA or dG (Edmonds et al. 2004). Adduct formation was inhibited when rat liver microsomes were incubated with BPA in the presence of CYP inhibitors, indicating oxidative reactions via CYP enzymes are involved (Atkinson and Roy 1995a). DNA adducts were also observed in the liver and mammary tissue of female CD-1 mice receiving BPA via drinking water, and DNA adduct formation was concentration-dependent *in vitro* (Izzotti et al. 2009). BPAQ induced the formation of oxidatively modified DNA bases, measured as 8-hydroxydeoxyguanosine (8-OHdG), in rat hepatocytes (Sakuma et al. 2010). This is further discussed under KC5. Adducts were also observed in BPA-treated human prostatic non-tumorigenic epithelial PNT1a cells and prostatic metastatic carcinoma PC3 cells (De Flora et al. 2011). Adduct formation is also discussed under KC1 (Section 5.3.1) and KC2 (Section 5.3.2).

Metabolism of oxidative reaction products and other oxidative reactions

GSH-conjugation of oxidative reaction products. Incubation of BPA or *ortho*-OH-BPA with human liver microsomes or human recombinant CYP enzymes, in the presence of NADPH and GSH, results in the formation of glutathione conjugates, e.g., mono- and di-GSH conjugate of BPA (CYP2C9, CYP2C19) and *ortho*-OH-BPA (CYP2E1, CYP2C9). Formation of the GSH conjugate of BPA required CYP activity, as BPA-GSH did not form in the absence of NADPH. The formation of BPA-GSH may involve GSH binding to an arene epoxide intermediate product of CYP-catalyzed oxidative metabolism (See Figure 4) (Schmidt et al. 2013).

C-C bond cleavage. The cleavage of the parent BPA molecule may occur via an unstable quinol intermediate after oxidation by CYP enzymes (See Figure 4) (Nakamura et al. 2011; Schmidt et al. 2013). Cleavage of the C-C bond is thought to result in formation of hydroquinone and a carbocation intermediate, which can give rise to hydroxycumyl alcohol (HCA) and its GSH conjugate, isopropylphenol (IPP) and its GSH conjugate, 4-methyl-2,4-*bis*(*p*-hydroxyphenyl)pent-1-ene (MBP), and phenol and its GSH conjugate (Jaeg et al. 2004; Nakamura et al. 2011; Ousji et al. 2020; Schmidt et al. 2013; Yoshihara et al. 2004).

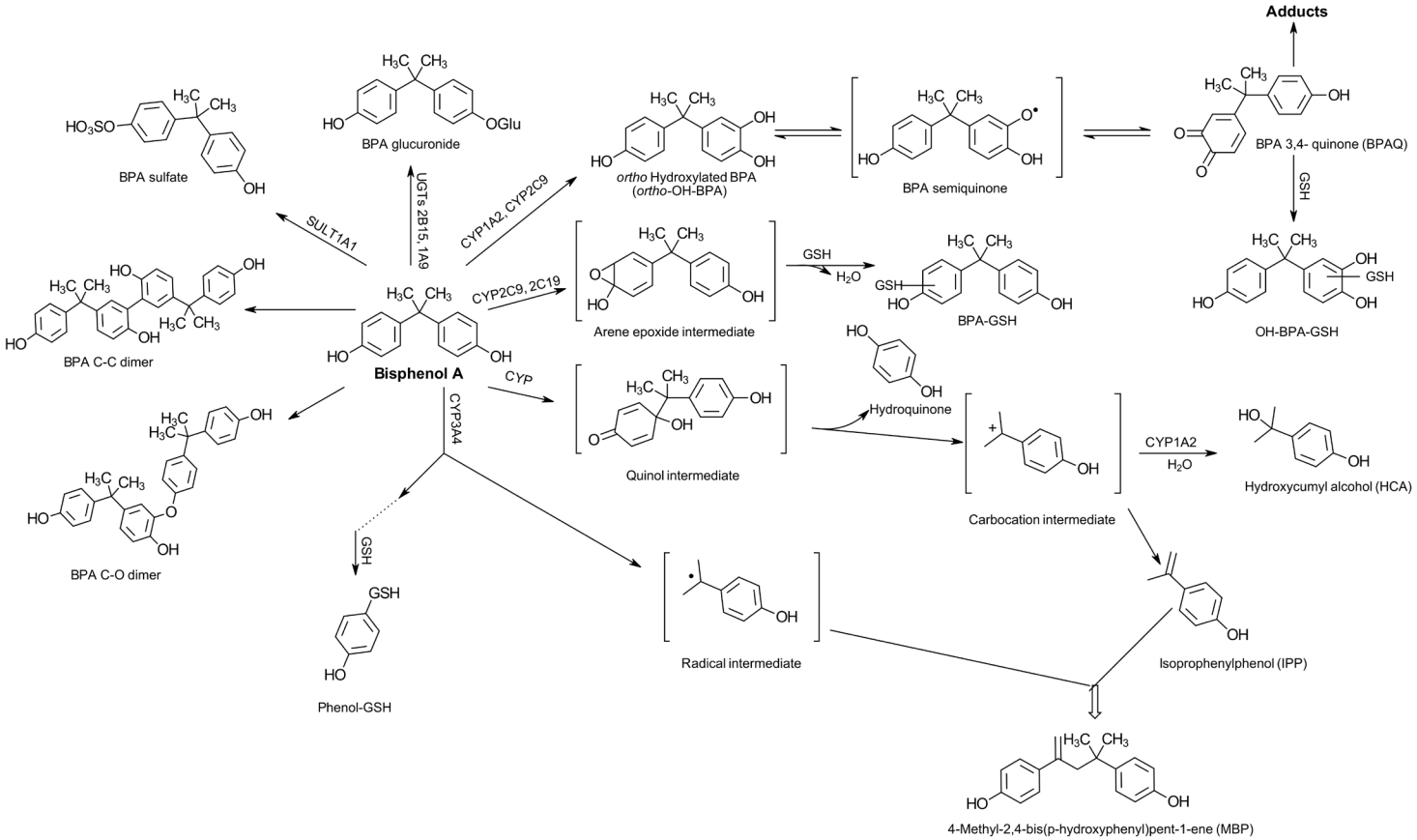
These reactive metabolites resulting from C-C bond cleavage and subsequent reactions have been observed in incubations with human, rat, or mouse S9 fractions,

microsomes, and with recombinant human P450 enzymes (Jaeg et al. 2004; Nakamura et al. 2011; Ousji et al. 2020; Schmidt et al. 2013). One cleavage metabolite, HCA, is estrogenic and demonstrates greater estrogenicity compared to BPA (Nakamura et al. 2011). Another cleavage metabolite, MBP, which is formed in incubations of BPA with rat liver S9 fractions, and may be produced via radical IPP fragments(Gramec Skledar and Peterlin Mašič 2016; Jaeg et al. 2004; Yoshihara et al. 2004)), is also estrogenic and has shown greater estrogenicity than BPA (Ishibashi et al. 2005; Okuda et al. 2010; Yoshihara et al. 2004). MBP (0.1 nM–10 μM) also stimulated cell proliferation of human MCF-7 breast cancer cells at concentrations up to 25 nM (Hirao-Suzuki et al. 2019). There is indirect evidence that MBP is formed with human, monkey, and mouse S9 fractions, as incubations with respective S9 fractions and BPA lead to increased estrogenicity compared to controls using BPA and denatured S9 fractions (Yoshihara et al. 2004). Radical metabolites of BPA are further discussed in Section 5.3.1.

Dimerization. BPA can form dimers in reactions with mouse liver S9 fractions, human, rat, and mouse liver microsomes, and human CYP3A4 (Jaeg et al. 2004; Ousji et al. 2020). Jaeg et al. (2004) tentatively characterized a few BPA dimers, the amount of which was proportional to the amount of BPA added. Jaeg et al. (2004) suggested that BPA dimerization may be a two-step metabolic process consisting of enzymatic oxidation of BPA into an unidentified reactive intermediate followed by a nonenzymatic reaction between the reactive compound and parent compound. Ousji et al. (2020) detected two linear dimers, one formed via C-C linkage and the second one formed via C-O linkage. These authors proposed an aromatic radical pathway (an aryl radical of a hydroxyl group of BPA) with the involvement of a CYP enzyme.

Additional metabolites. Several other minor metabolites such as oxidized sulfate and glucuronide conjugates, disaccharide conjugates, and others have been identified and are described in Gramec Skledar and Peterlin Mašič (2016), Ousji et al. (2020), Zalko et al. (2003), and Jaeg et al. (2004). Zalko et al. (2003) identified several methoxylated BPA conjugates *in vivo*, isolated mainly from the digestive tract, urine and livers of pregnant CD-1 mice. It is unclear through which pathways they were generated. Hu et al. (2022) identified a GSH di-oxygenated BPA in incubations with recombinant human glutathione S-transferase pi 1 (GSTP1) and rat microsomes. These minor metabolites are not presented in the metabolism Figure 4.

Figure 4 Proposed biotransformation of BPA, modified from Gramec Skledar and Peterlin Mašič (2016)[11], Ousji et al. (2020) and Schmidt et al. (2013)



[11] There appears to be a typographic error in Gramec Skledar and Peterlin Masic (2016) regarding the key CYP enzyme involved in BPA hydroxylation. It is named as CYP2A1 in Figure 2 of Gramec Skledar and Peterlin Masic (2016), while the original citation, Schmidt et al 2013 (quoted by Gramec Skledar and Peterlin Masic 2016), listed it as CYP1A2.

5.1.5 Summary of pharmacokinetics and metabolism

BPA is rapidly absorbed in humans by the oral and dermal routes and is distributed throughout the body, crossing the blood-brain barrier and the placenta. The half-life of BPA in humans exposed by the oral route is around 6 hours. Excretion is also rapid and occurs primarily via urine in humans and other primates; in rodents, the main route of excretion is via feces. BPA undergoes enterohepatic circulation in rats and possibly mice, but not in humans or other primates. Despite rapid elimination, BPA is routinely detected in more than 90% of human urine samples, suggesting frequent repeated exposures, likely from multiple sources. Adipose tissues may serve as a reservoir to store BPA. The metabolism of BPA occurs primarily via conjugation, leading to the formation of BPA-G and BPA-S. The extent of conjugative metabolism is determined by life stage, co-exposure to xenobiotics and drugs, certain diseases, and polymorphisms of conjugative enzymes. A secondary metabolic pathway, oxidative metabolism, leads to the formation of several electrophilic, reactive, and estrogenic metabolites, as well as to the formation of ROS, 8-OHdG and other DNA adducts.

5.2 Animal Tumor Pathology

This section describes the relevant pathology for many of the tumor types observed in animal cancer studies of BPA discussed in Sections 4.1 and 4.2.

5.2.1 Rat

5.2.1.1. Hematopoietic system neoplasms (malignant lymphoma or leukemia)

Malignant lymphoma

In the NTP CLARITY-BPA core study #4 (two-year stop-dose study) in F1 male SD (NCTR) rats, the incidence of malignant lymphomas of the prostate (dorsal/lateral lobes) was statistically significantly increased in the 25000 µg/kg-day BPA group, with a statistically significant trend. The incidence of malignant lymphomas at all sites was also statistically significantly increased by trend (NTP 2018).

Malignant lymphoma is an uncommon neoplasm in SD rats (Rebelatto 2018). Malignant lymphomas may be lymphocytic, lymphoblastic, mixed, or histiocytic types (Ward et al. 1990). In the historical control database of Crl:CD (SD)BR rats reported by Charles River Laboratories (Charles River 2013), the spontaneous rate of malignant lymphomas (including lymphomas and lymphocytic leukemias) in male rats from 20 studies conducted between 2001 and 2009 was 0.7% (8/1205, range: 1.5–4%). In the NTP

historical control database of Hsd SD (Hsd:Sprague Dawley) rats (NTP 2021b), the spontaneous rate of malignant lymphomas from 12 studies conducted between 2007 and 2012 was 1.6% (10/639, range: 0–4%). In the CLARITY-BPA core study #4 (NTP 2018), which was conducted between 2012 and 2015, the incidence rate of malignant lymphomas from all sites in the untreated males was 2% (1/49) and within the historical range for SD rats.

Leukemia

In the two-year feeding study of BPA in male F344 rats, leukemias (NOS) were statistically significantly increased in the high-dose group (2000 ppm BPA) compared with the controls, and with a statistically significant trend (NTP 1982). First occurrence of leukemia was observed in a 9-week-old male of the low-dose group. The next leukemia was observed at 84 weeks (approximately 19.6 months) in the high-dose group (NTP 1982).

The incidence of leukemia in untreated control males was 26% (13/50) in this two-year feeding study of BPA, which was conducted between 1977 and 1979 (NTP 1982), and was within the range of 10–50% reported for untreated male rats of this strain (Ward et al. 1990).

5.2.1.2. Testicular interstitial (Leydig) cell tumor

In the two-year feeding study of BPA in male F344 rats, interstitial (Leydig) cell tumors of the testis were statistically significantly increased in both BPA-exposed groups (1000 and 2000 ppm) and with a statistically significant trend. The first occurrence of the tumor in males was observed at 86 weeks (NTP 1982).

Interstitial (Leydig) cell neoplasms of the testis are common in untreated aging F344 rats, with most being benign. There is a continuum of Leydig cell proliferative response, ranging from hyperplasia to adenomas and carcinomas (Boorman et al. 1990b). In the NTP historical database, the spontaneous rate for testicular adenomas in male F344 rats was 88.6% (889/1003, range: 74–96%, from 20 studies conducted between 1984 and 1994) (NTP 1999b). In the current study, conducted between 1977 and 1979, the first occurrence of this tumor was at 86 weeks in one control animal and the incidence in controls of 74.5% (35/47) was within the historical control range (NTP 1982).

5.2.1.3. Mammary gland tumors

Fibroadenoma of the mammary gland

In the two-year feeding study of BPA in male F344 rats, fibroadenomas of the mammary gland were statistically significantly increased in the high-dose group (2000 ppm BPA), and with a statistically significant trend. The first occurrence of the tumor in males was at 106 weeks (NTP 1982).

Fibroadenomas are the most common benign neoplasms of the mammary gland in rats, and they consist of ductal and/or alveolar epithelium and fibrous connective tissue. Spontaneously occurring fibroadenomas generally are end-stage benign neoplasms (Eighmy et al. 2018). The incidence of fibroadenomas in females (27–29%) is about 7–10 times greater than the incidence in males (3–4%) (Eighmy et al. 2018). In the current study, no fibroadenoma was observed in males of the control group (NTP 1982). Fibroadenomas can arise from adenomas, and can progress to adenocarcinomas (Eighmy et al. 2018).

Adenoma or adenocarcinoma of the mammary gland

In the NTP CLARITY-BPA core study #3 (two-year stop-dose study) in F1 female SD (NCTR) rats, adenocarcinomas, or combined adenomas and adenocarcinomas of the mammary gland were statistically significantly increased in the 2.5 µg/kg-day BPA group. The first occurrence of the tumor was observed on day 451 (NTP 2018).

Mammary gland adenomas are benign tumors consisting primarily of glandular epithelium, with little connective tissue. Mammary adenomas may progress to fibroadenomas, and to adenocarcinomas (Boorman et al. 1990a). Mammary gland fibroadenomas, adenomas and adenocarcinomas are typically aggregated for study evaluation (McConnell et al. 1986). Both mammary adenomas and adenocarcinomas are common in female SD rats. In the historical control database of Crl:CD (SD)BR rats (Charles River 2013), the spontaneous rate of adenomas in female rats was 5.2% (62/1205, range: 0.8–13.3%, from 20 studies conducted between 2001 and 2009). The spontaneous rate of adenomas in female SD (NCTR) rats was 1% (2/210, range: 0–3.7%) (NTP 2008, 2010). The spontaneous rate of adenocarcinomas in female Crl:CD (SD)BR rats was 9.2% (111/1205, range: 1.7–27.7%, from 20 studies conducted between 2001 and 2009) (Charles River 2013). The spontaneous rate of adenocarcinomas in the SD (NCTR) rats was 11% (23/210, range: 9–13%) (NTP 2008, 2010). In the concurrent controls of the current study, which was conducted between 2012 and 2015, the rates of adenomas (2.1%, 1/48) and adenocarcinomas (6.3%, 3/48) were within the historical ranges (NTP 2018).

5.2.1.4. Thyroid C-cell adenoma

In the NTP CLARITY-BPA core study #4 (two-year stop-dose study) in F1 male SD (NCTR) rats, the incidence of C-cell adenomas of the thyroid gland was increased with a statistically significant trend. The first occurrence of C-cell adenoma was observed on day 609 (NTP 2018).

C-cell adenoma of the thyroid gland is a common lesion in aging SD rats. The C cells (parafollicular or calcitonin-producing cells) are located within the thyroid follicle between the follicular basement membrane and the follicular epithelium (Mense and

Boorman 2018). Preneoplastic focal proliferative lesions may progress to benign adenomas and to malignant carcinomas (Mense and Boorman 2018).

5.2.1.5. Uterine stromal polyps

In the NTP CLARITY-BPA core study #5 (one-year continuous-dose study) in F1 female SD (NCTR) rats, uterine stromal polyps were increased with a statistically significant trend. The first occurrence of the lesion was on day 361 (NTP 2018).

Stromal polyps of the uterus are common benign neoplasms in aged rats and the spontaneous rate is 5–6.8% (Dixon et al. 2018). Stromal polyps may be expected to progress to stromal sarcomas in rats (Dixon et al. 2018; McConnell et al. 1986).

5.2.1.6. Clitoral gland adenoma and carcinoma

In the NTP CLARITY-BPA core study #7 (two-year continuous-dose study) in F1 female SD (NCTR) rats, adenomas, or combined adenomas and carcinomas of the clitoral gland were increased with a statistically significant trend. The first occurrence of clitoral adenoma was on day 531 and carcinoma was on day 426 (NTP 2018).

Neoplastic lesions of the preputial/clitoral glands comprise a morphological continuum, including hyperplasia (a pre-neoplastic lesion), adenoma, and carcinoma (or adenocarcinoma) (Yoshizawa 2018). Transition from a benign to a malignant neoplasm can be expected for clitoral gland neoplasms in rats (McConnell et al. 1986). Spontaneous adenomas of the clitoral gland are extremely rare in rats (Rudmann et al. 2012). The available historical controls in SD (NCTR) rats indicate a spontaneous rate of clitoral gland adenomas in this rat colony of 1% (2/200, range: 0–4%) (NTP 2008, 2010). In the NTP historical control database of Hsd SD rats, no spontaneous clitoral gland adenoma was observed (0/626). The spontaneous rate of carcinoma or adenoma and carcinoma combined was 0.16% (1/626, range: 0–2%, from 13 studies conducted between 2007 and 2012) (NTP 2021b).

5.2.1.7 Liver hepatocellular carcinoma

In the NTP CLARITY-BPA core study #8 (two-year continuous-dose study) in F1 male SD (NCTR) rats, hepatocellular carcinomas of the liver were increased with a statistically significant trend. The first occurrence of the lesion was on day 656 (NTP 2018).

Hepatocellular carcinomas and adenomas are of the same tissue origin, and carcinomas are believed to arise out of benign adenomas (McConnell et al. 1986). In the current study, few adenomas were observed (one at control; one at BPA25, two at BPA250 and two at BPA2500) with no adenoma observed at the high dose (25000 µg/kg-day) (NTP 2018). The analysis of the spontaneous occurrence of hepatocellular carcinomas in male SD rats from three historical control datasets indicates that it is a

rare tumor type (less than 1% spontaneous occurrence). The spontaneous rate of hepatocellular carcinoma was 0.31% (2/639, range: 0–2%, from 13 studies conducted between 2007 and 2012) in Hsd SD rats (NTP 2021b), 0.91% (11/1205, range: 1.67–2.5%, from 20 studies conducted between 2001 and 2009) in Crl:CD (SD)BR rats (Charles River 2013), and 0.5% (1/198, range: 0–2%) in SD (NCTR) rats (NTP 2008, 2010).

5.2.1.8 Pituitary tumor of the pars distalis

In the 12-week study of female F344 rats, the incidence of pituitary tumors of the *pars distalis* was statistically significantly increased in the low-dose BPA group (50 mg/kg-day) compared to the controls. The tumors are believed to be prolactinomas (a term used by Hao et al. but also known as adenomas of the *pars distalis*) based on immuno-histochemical staining for prolactin (Hao et al. 2016).

Adenoma of the *pars distalis* (one of the three areas in the pituitary adenohypophysis) is the most common type of pituitary adenoma (Remick and Brown 2018). Spontaneous tumors of the *pars distalis* are common in rats and may be related to endocrine imbalances with aging. The incidence of adenoma of the *pars distalis* is reported to be 45% in untreated F344 females (Remick and Brown 2018).

5.2.2 Mouse

5.2.2.1 Hematopoietic system neoplasms (malignant lymphoma or lymphocytic leukemia)

In the two-year feeding study of BPA in male B6C3F1 mice, malignant lymphomas, or malignant lymphomas and lymphocytic leukemia combined, were statistically significantly increased in the 1000 ppm BPA group. The first occurrence of these tumors was observed at 77 weeks (NTP 1982). Hematopoietic neoplasms were observed in multiple organs in both control and BPA-treated mice. Among the male mice that had malignant lymphomas, two mice from the control group had the mixed type, while eight mice from the low-dose group had the following: five mixed, two histiocytic, and one lymphocytic type, and three mice from the high-dose group had the mixed type (NTP 1982).

Malignant lymphomas are common in B6C3F1 mice (Ward 1999). The spontaneous rate of malignant lymphomas in male B6C3F1 mice was 8.3% (113/1355, range: 2–20%) from NTP carcinogenicity studies, as summarized by Haseman (1999). Leukemia is a rare tumor type in male mice. There was no spontaneous leukemia (0/1355) found among the studies (Haseman 1999). In the NTP (1982) study, there was one lymphocytic leukemia (1/46) in the low-dose group (1000 ppm BPA), two leukemias (NOS) (2/45) in the high-dose group (5000 ppm BPA), and none in the control group

(0/44). Malignant lymphomas and lymphocytic leukemia were combined based on recommendations by McConnell et al. (1986).

5.2.2.2 Pituitary chromophobe carcinoma

In the two-year feeding study of BPA in male B6C3F1 mice, chromophobe carcinomas of the pituitary gland were increased in the high-dose group (5000 ppm BPA) with a statistically significant trend (NTP 1982).

In the NTP historical control database, the incidence of neoplasms (adenoma and carcinoma combined) in pituitary *pars distalis* of male B6C3F1 mice was 0.6% (5/899, range: 0–6.3%, from 19 studies conducted between 1984 and 1994) (NTP 1999a). Thus, being one type of pituitary *pars distalis* neoplasm, chromophobe carcinoma is a rare tumor type (less than 1% occurrence).

5.2.2.3 Hepatocellular adenoma and carcinoma

In the 10-month study where female Agouti$^{+/-}$ C57BL/6J:C3H/HeJ mice were exposed to BPA *in utero*, via lactation and post-weaning in feed until 10 months of age, the incidence of combined hepatocellular adenomas and carcinomas was statistically significantly increased in the high-dose group (50 ppm BPA) with a statistically significant trend (Weinhouse et al. 2014).

C3H/HeJ mice are prone to spontaneous hepatocellular neoplasms while C57BL/6J mice are relatively resistant (Maronpot 2009). Historical controls of spontaneous liver tumors in the Agouti$^{+/-}$ C57BL/6J:C3H/HeJ strain used by Weinhouse et al. (2014) are not available. Hepatocellular adenomas are expected to progress to carcinomas as both tumor types arise from the same cell type, and it is appropriate to combine them (Harada et al. 1999; McConnell et al. 1986).

5.3 Key Characteristics of Carcinogens

A comprehensive review of the more than 100 agents known to cause cancer in humans identified 10 key characteristics (KCs) of carcinogens (IARC 2020; Smith et al. 2016). As the name implies, KCs are characteristics of agents that cause cancer, in contrast to the hallmarks of cancer (Hanahan and Weinberg 2000, 2011), which are properties of cancer cells and neoplasms, and also in contrast to modes of action, which are sequences of key events that transform normal cells into malignant tumors. Mode of action analysis depends on prior knowledge sufficient to hypothesize how an agent might cause cancer, knowledge that too often is incomplete. The KCs can encompass many types of mechanistic endpoints and are not constrained to previously formulated hypotheses, allowing a broader consideration of multiple mechanistic pathways and

hypotheses. OEHHA uses this approach to systematically identify, organize, and summarize information on mechanisms of carcinogenesis for BPA.

Table 29 Key characteristics of carcinogens

Key characteristic	Example of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (*e.g.,* epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, UDS), intercalation, gene mutations, cytogenetic changes (*e.g.,* CAs, MN)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (*e.g.,* topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (*e.g.,* DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor inactivation/activation (*e.g.,* ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Source: Smith et al. (2016) and IARC (2020)

AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (*e.g.*, oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

5.3.1 Is electrophilic or can be metabolically activated

Electrophiles are reactive, electron-seeking molecules capable of binding to electron-rich cellular macromolecules including DNA, RNA, lipids, and proteins, thereby forming covalent adducts. The measurement of covalent adducts on DNA and proteins is the most common method of assessing electrophilic activity (Smith et al. 2020). BPA can be metabolized by CYP enzymes and peroxidases to form electrophilic compounds (see Section 5.1.4, metabolism, and Figure 4). These electrophilic metabolites of BPA include bisphenol-*o*-quinone (BPAQ) and its semi-quinone intermediate, an arene epoxide intermediate (Schmidt et al. 2013), an isopropenylphenol (IPP) radical (which can form MBP) (Yoshihara et al. 2004), and an unidentified electrophilic compound (which leads to dimerization of BPA) (Ousji et al. 2020). Available studies for electrophilic metabolites of BPA have focused on quinone-derived DNA adducts.

Quinones can bind to, or modify, the nucleobases of DNA (Xiong et al. 2021). BPAQ, formed from BPA in enzymatic reactions, such as those mediated by microsomes or S9, can form DNA adducts with calf thymus and MCF-7 cell DNA, and with deoxyguanosine (dG) and deoxyadenine (dA) (Atkinson and Roy 1995b; Izzotti et al. 2009; Zhao et al. 2018). These adducts have been identified as 3-hydroxy-bisphenol A-N7-guanine (3-OH-BPA-N7Gua) and 3-hydroxy-bisphenol A-N7-adenine (3-OH-BPA-N7-Ade) (Qiu et al. 2004; Zhao et al. 2018). Another study identified the formation of a BPAQ N7-guanine- adduct in a cell-free herring sperm DNA system (Edmonds et al. 2004). The *in vitro* formation of DNA adducts from BPA (in the presence of S9) with calf thymus DNA was concentration-dependent (Izzotti et al. 2009). Adduct formation can be inhibited by cytochrome P450 enzyme inhibitors (Atkinson and Roy 1995a).

BPA may also induce oxidative lesions in DNA (measured as 8-OHdG), presumably through the formation of ROS or BPAQ (see Section 5.1; Steffensen et al. (2020)). The formation of 8-OHdG associated with BPA exposure has been reported in several human observational studies as well as in animals *in vivo and in vitro* studies. These studies of BPA and 8-OHdG DNA adducts are discussed in more detail in KC2 and KC5 (Sections 5.3.2 and 5.3.5).

Following enzymatic activation, BPA can also bind to cysteine residues of proteins and form protein adducts, as seen in rats *in vivo* and in a cell-free system (Hu et al. 2022).

Below is a brief summary of available studies on the formation of DNA and protein adducts.

DNA adducts*:*

- Human *in vitro*
    - Significant levels of DNA adducts were formed in prostate cell lines (PNT1a non-tumorigenic epithelial cells [$p < 0.05$] and PC3 metastatic

carcinoma cells [$p < 0.01$]) treated with BPA (200–250 nM) for 24 hours (De Flora et al. 2011). When PNT1a cells were treated with a low concentration (1 nM) of BPA for two months, DNA adducts were increased, although not significantly ($p = 0.08$).

- Animal *in vivo*
    - DNA adducts were formed in the liver of male CD1 rats exposed to BPA (200 mg/kg bw) via a single *i.p.* injection or via multiple day gavage (Atkinson and Roy 1995a).
    - Administration of BPA to female Swiss CD-1 albino mice via drinking water (200 mg/kg-day for eight consecutive days) resulted in the formation of DNA adducts in the liver and in mammary epithelial cells (Izzotti et al. 2009).
- Animal *in vitro*
    - BPA (50, 100, 200 µM) increased DNA adduct formation in a dose-dependent manner in cultured Syrian hamster embryo (SHE) cells (Tsutsui et al. 1998).
- Cell-free systems
    - BPA (100 µM) formed BPAQ following microsomal activation and bound covalently to rat liver DNA. The two major BPAQ-DNA adducts also matched chromatographically to the two adducts identified in the rat *in vivo* study (Atkinson and Roy 1995a, b).
    - Adduct formation was markedly reduced when deoxyguanosine monophosphate (dGMP) and rat liver microsomes were incubated with BPA in the presence of CYP inhibitors (Atkinson and Roy 1995a).
    - BPAQ reacted with calf thymus DNA, MCF-7 cell DNA, and dG to form the DNA adduct 3-OH-BPA-N7Gua (Zhao et al. 2018).
    - BPA (6.2 to 100 µM), in the presence of rat S9 mix, reacted with calf thymus DNA and formed multiple DNA adducts in a dose-dependent manner (Izzotti et al. 2009).

Protein adducts:

- Animal *in vivo*
    - The reactive metabolites of BPA covalently bind to cysteine residues of liver proteins in female SD rats. BPA-derived cysteine adducts were detected in the livers of rats exposed to either a single oral dose of 100 mg/kg BPA or daily doses of 10 mg/kg BPA for 15 days. Proteomics

analysis identified 24 BPA-modified proteins from the liver of exposed rats, and pathway analysis indicated they were mainly enriched for proteins associated with oxidative stress-related pathways (Hu et al. 2022).

- Cell-free system
    - BPA (49.3 μM) covalently binds to cysteine 47 of the human recombinant glutathione S-transferase pi 1 (GSTP1) in the presence of microsomal activation (Hu et al. 2022).

Summary of evidence for KC1

BPA can be metabolized by CYP enzymes and peroxidases to form electrophilic compounds, including BPAQ; its semi-quinone intermediate; an arene epoxide intermediate; an isopropenylphenol radical (which can form MBP, an estrogenic metabolite of BPA); and an unidentified electrophilic compound (which leads to dimerization of BPA). The metabolite BPAQ can form DNA adducts which have been identified as 3-OH-BPA-N7Gua and 3-OH-BPA-N7-Ade. Several studies have reported the formation of DNA adducts in various systems including human *in vitro*, animal *in vivo* and *in vitro*, and cell-free systems.

BPA also induces oxidative lesions in DNA (measured as 8-OHdG), presumably through the formation of reactive oxygen species or BPAQ. The formation of 8-OHdG associated with BPA exposure has been reported in several human observational studies as well as in animal *in vivo* and *in vitro* studies. In addition, BPA can bind to cysteine residues of proteins and form protein adducts in the rat *in vivo* and in a cell-free system.

5.3.2 Is genotoxic

Genotoxicity refers to the ability of a chemical or other type of agent or biological process to damage DNA or induce changes in the DNA sequence. The link between genotoxicity and carcinogenesis is well established (Smith et al. 2016; Smith et al. 2020). Changes in the DNA sequence include gene or point mutations such as base substitutions, frameshifts, and small deletions or insertions, and chromosomal effects such as chromosomal aberrations, micronuclei, and aneuploidy. Examples of DNA damage include DNA adducts, DNA strand breaks, and oxidative damage to DNA.

Studies on the genotoxicity of BPA have been reviewed and summarized in detail by Chapin et al. (2008), part of an NTP report (CERHR 2008). Overall, Chapin et al. (2008) concluded:

> "In *in vitro* genetic toxicity studies reviewed by the European Union (2003) and/or Haighton et al. (2002), evidence of aneugenic potential, chromosomal aberration, micronuclei formation, and DNA adducts was observed (Table 57). Because of the lack of chromosomal effects in *in vivo* studies (Table 58) and unknown relevance of DNA adduct formation, which only occurred at high-doses, both groups concluded that bisphenol A is not likely to have genotoxic activity *in vivo*."

Two tables with summaries of BPA genotoxicity studies from Chapin et al. (2008) (identified as Table 58 and Table 57 in the quote above) are attached in this document as Appendix Table F2 and Table F3. Over a hundred additional genotoxicity studies not included in the review by Chapin et al (2008) were identified by the literature search. These additional genotoxicity studies were reviewed to supplement the genotoxicity evaluations in Chapin et al. (2008). To sum up, BPA has been tested for a variety of genotoxicity endpoints in human observational studies, human cells *in vitro,* animals *in vivo*, animal cells *in vitro*, and in bacteria, yeast, plants, and acellular systems.

Overall, findings from these genotoxicity studies of BPA include evidence of

(i) In human observation studies: induction of sister chromatid exchange (SCE) (Table 30), oxidative damage to DNA (see Section 5.3.5 Induces oxidative stress and Appendix Table H1), and damage to sperm DNA (Table 30),
(ii) In human cells *in vitro*: induction of mutations, micronuclei (MN) formation, chromosomal aberrations (CA), centrosomal abnormalities, microtubule abnormalities, DNA strand breaks, formation of DNA adducts, oxidative damage to DNA, and an increase in unscheduled DNA synthesis (UDS) (Appendix Tables F1 and H2)
(iii) In animals *in vivo*: induction of mutations, MN, CA, meiotic chromosome abnormalities, DNA strand breaks, formation of DNA adducts, and oxidative damage to DNA (Appendix Table F2)
(iv) In animal cells *in vitro*: inducing of MN, CA, chromosome misalignment and spindle abnormalities, and aneuploidy, DNA strand breaks, and formation of DNA adducts and, oxidative damage to DNA (Appendix Tables F3 and H2)
(v) In plants and acellular systems: CA in onion and pea roots, and formation of DNA adducts and microtubule abnormalities in acellular systems (Appendix Table F3).

These studies are briefly discussed below. Detailed information on the study design and results are given in Table 30 (section (i) human observational studies), Table F1, Table F2 and Table F3 [also known as Table 57 and Table 58 in Chapin et al. (2008)], Table H1, and Table H2.

(i) Human observational studies

Twenty-six publications reporting genotoxicity endpoints of BPA in exposed humans were identified [none were reviewed by Chapin et al. (2008)]. Among these, twenty-one publications reported data on oxidative damage to DNA, and the evidence is summarized and discussed in Section 5.3.5, Oxidative Stress. One publication reported data on sister chromatid exchange (SCE), and four publications reported data on damage to sperm DNA; these five studies are summarized in Table 30. Below is a brief summary of all 26 studies.

Oxidative damage to DNA (details in Section 5.3.5)

Of the 19 studies (reported by 21 publications) that report data on oxidative damage to DNA in humans (See Section 5.3.5 Oxidative Stress for details),13 studies (two cohort studies, three case-control studies, and eight cross-sectional studies) report statistically significant associations between BPA and urinary or serum levels of 8-hydroxydeoxyguanosine (8-OHdG) or 8-oxo-7,8-dihydroguanosine (8-OHG), recognized biomarkers of oxidative damage to DNA, in various populations from different geographic regions, at various ages, and from both sexes. Four cross-sectional studies and one cohort study found no association, and one cross-sectional study found a significant negative association.

SCE

One study showed a marginally positive (not statistically significant) association between urinary BPA levels (range: 0.03–62.4 µg/l) and SCE frequency in peripheral blood lymphocytes collected from 172 Korean men and women (Yang et al. 2006). The least squares regression coefficient was 0.052 (p = 0.059).

DNA fragmentation/damage in human sperm

Four publications reporting on three studies (one cross-sectional, one case-control, one prospective cohort) evaluated the association between BPA and DNA fragmentation/damage in human sperm (Goldstone et al. 2015; Meeker et al. 2010b; Meeker et al. 2011; Omran et al. 2018). Two publications on one set of data from a cross-sectional study of subfertile male partners in Massachusetts showed that urinary BPA levels correlated with higher damage in sperm DNA measured by the neutral comet assay (p trend = 0.03) (Meeker et al. 2010b; Meeker et al. 2011). One case-control study in Egypt found significantly higher damage (measured by the alkaline comet assay) in sperm DNA in both infertile men and fertile controls (Omran et al. 2018). A statistically significant negative association between urinary BPA concentration and sperm DNA fragmentation ($\beta = -0.0544$, p = 0.035) was reported in 418 men enrolled in a prospective cohort study of couples intending to become pregnant in Michigan and Texas, using a sperm chromatin structure assay (Goldstone et al. 2015).

The geometric mean urinary BPA concentration detected in this study (0.55 µg/l) is lower than that of the other studies [1.7 µg/l (mean) from Meeker et al. (2010b); Meeker et al. (2011), and 24.2 µg/l (median) from Omran et al. (2018)].

Table 30 Genotoxicity studies of BPA in humans (see Section 5.3.5 and Appendix Table H1 for additional studies in humans on oxidative damage to DNA)

Test endpoint	Study population (sample size)	BPA exposure metric	Results	Reference
Sister chromatid exchange (SCE)	Peripheral blood lymphocytes collected from 172 Koreans (51% male, 49% female). Urine samples collected from 81 males and 79 females.	Urinary levels of conjugated BPA ranged from 0.03–62.4 µg/l (median: 7.86 µg/l).	Positive association (not significant). BPA exposure showed a marginal association with SCE [least squares regression coefficient = 0.052; *p* = 0.059].	Yang et al. (2006)
Sperm DNA damage	Cross-sectional study of 132 male partners (ages 18–55) in subfertile couples seeking treatment between 2000 and 2004 in Boston, MA. 3 urine samples and at least one semen sample were collected from each participant.	Urinary BPA quartiles (µg/l) were used as the levels of BPA exposure: I: < 0.8, II: 0.8-1.3, III: 1.3-2.5, IV: > 2.5 Geometric mean of urinary BPA, specific gravity-corrected = 1.7 µg/l (n = 190).	Positive association. IQR increase in urinary BPA was associated with a 10% (95% CI: 0.03–19%) increase in sperm DNA damage. Significant trend (*p* for trend = 0.03), measured as tail DNA% by the neutral comet assay.	Meeker et al. (2010b); Meeker et al. (2011)
	Prospective cohort study (LIFE Study), recruited participants from 2005–2009 in Michigan and Texas. 418 men (aged 18+ years) who were partners in couples interested in becoming pregnant. Participants provided a urine sample and at least one semen sample.	Geometric mean of urinary BPA concentration was 0.55 µg/l (95% CI: 0.49–0.63 µg/l).	Negative association. Increasing urinary BPA concentration associated with lower DNA fragmentation (measured by SCSA analysis) in both unadjusted (β = −0.0649, *p* = 0.002) and adjusted (β = −0.0544, *p* = 0.035) linear regression models (adjusted for age, abstinence time, alcohol consumption, BMI, creatinine, education, income, previously fathered pregnancy, serum cotinine, study site, race/ethnicity).	Goldstone et al. (2015)
	Hospital-based case-control study in Egypt, 50 infertile men and 50 healthy fertile men as matched controls.	BPA concentrations detected in urine samples from all infertile cases and fertile	Positive association. Several significant associations of BPA with higher levels of sperm DNA damage parameters (tail DNA%, tail meanX and tail moment) in controls, infertile men, and in all	Omran et al. (2018)

Test endpoint	Study population (sample size)	BPA exposure metric	Results	Reference
	One time urine and semen sample were collected from each participant.	controls, with median values of 24.2 µg/l and 20.9 µg/l, respectively.	subjects combined ($p < 0.001$). An alkaline comet assay was implemented to identify sperm DNA damage.	

IQR, interquartile range; CI, confidence interval; tail DNA%, the percent of total DNA that is present in the tail in a comet assay; LIFE, the Longitudinal Investigation of Fertility and the Environment; SCSA, sperm chromatin structure assay; tail meanX, center of gravity of DNA in the tail (x coordinate) in a comet assay; tail moment, defined as the product of the tail length and the fraction of total DNA in the tail (tail moment = tail length x % of DNA in the tail) in a comet assay.

(ii) Human cells in vitro

Around 50 publications on genotoxicity studies conducted in human cells *in vitro* were identified via OEHHA's literature searches (Section 2 and Appendix B). Selected study endpoints from only two of these publications (Iso et al. 2006; Takahashi et al. 2001) were included in the review by Chapin et al. (2008). Findings from these genotoxicity studies performed in human cells *in vitro* are summarized as follows (See Appendix F, Table F1 for details on study designs and findings).

Mutations

- Increases in mutations were observed in an immortalized embryonic kidney (HEK 293T) cell line (Hu et al. 2021) and in cultured normal embryo-derived fibroblast (RSa) cells treated with various noncytotoxic concentrations of BPA [Takahashi et al. (2001), also reported in Chapin et al. (2008)].

Chromosomal effects

Micronuclei (MN)

Normal cells

- Statistically significant increases in MN were observed in isolated lymphocytes (Santovito et al. 2018), umbilical vascular endothelial (HUVEC) cells (Ribeiro-Varandas et al. 2013), and an embryo-derived hepatic cell line (Zheng et al. 2012) exposed to noncytotoxic concentrations of BPA. Significant concentration-dependent increases in MN were also observed in two normal lymphoblastoid cell lines (AHH-1 and MCL-5 cells) (Hernandez et al. 2013; Johnson and Parry 2008; Parry et al. 2002) exposed to various noncytotoxic concentrations of BPA.
- Exposure to up to 250 µM BPA for 12 hours did not increase MN in primary foreskin fibroblasts (Lehmann and Metzler 2004).

Cancer cells

- Statistically significant increases in MN were observed in a breast cancer cell line (MCF-7 cells) exposed to a noncytotoxic concentration of BPA (Kabil et al. 2008).
- Exposure to up to 4.4 μM BPA in colon adenocarcinoma cells (Ribeiro-Varandas et al. 2013) and up to 60 μM BPA in hepatoma cells (Quesnot et al. 2016) did not increase MN.

Chromosome aberrations (CA)

Normal cells

- Statistically significant increases in CA were observed in isolated peripheral blood mononuclear cells (Di Pietro et al. 2020), and in male and female amniocyte cells (Aghajanpour-Mir et al. 2016) and a significant concentration-dependent increase in CA was observed in isolated lymphocytes (Santovito et al. 2018) treated with various noncytotoxic concentrations of BPA.

Cancer cells

- Significant increases in CA were observed in MCF-7 cells treated with noncytotoxic concentrations of BPA (Aghajanpour-Mir et al. 2016).

Chromosomal segregation issues, including centrosomal and microtubule abnormalities

Normal cells

- Concentration-responsive increases in centrosomal abnormalities were observed in two immortalized normal prostate epithelial cells (NPrEC and RWPE-1 cell lines) and a statistically significant increase in the formation of microtubule asters was also observed in RWPE-1 cells (Tarapore et al. 2014),
- Increase in kinetochore-positive MN, indicating chromosome loss, and significant concentration-dependent increases in chromosome non-disjunction in MCL-5 cells (Parry et al. 2002) treated with noncytotoxic concentrations of BPA.

Cancer cells

- Statistically significant increases in unaligned chromosomes and mitotic cells with multipolar spindles, and several other types of microtubule abnormalities were observed in a cervical adenocarcinoma (HeLa) cell line (Kim et al. 2019c), and concentration-responsive increases in centrosomal abnormalities were observed in multiple prostate cancer cell lines (LNCaP, 22Rv-1, C4-2, and PC-3) treated with noncytotoxic concentrations of BPA (Tarapore et al. 2014).

DNA damage

A large number of studies have investigated BPA-induced DNA damage in human cells *in vitro*. Appendix Table F1 presents the findings from all studies, and those using non-cytotoxic concentrations of BPA are discussed below.

DNA adducts

- Increased 8-OHdG DNA adducts in spermatozoa (Barbonetti et al. 2016), and increased DNA adducts (measured by ^{32}P postlabeling) in two prostate cell lines (De Flora et al. 2011) following treatment with BPA.

DNA strand breaks measured by comet assays

The comet assay, also known as the single cell gel electrophoresis (SCGE) assay, detects DNA strand breaks and alkali-labile sites in a single cell (Langie et al. 2015). The assay can be conducted under alkaline conditions (pH > 13), to detect single and double strand breaks and alkali-labile sites (Langie et al. 2015; Mokra et al. 2017), or under neutral conditions (pH 7 – 9) to detect only double strand breaks (Mokra et al. 2017). The alkaline comet assay can also be modified by addition of the repair endonucleases such as formamidopyrimidine DNA glycosylase (Fpg), which induces strand breaks after recognizing and targeting oxidized bases (*e.g.*, purines) (Collins et al. 1996).

Single strand and double strand breaks (alkaline comet assay)

Normal cells

- Significant concentration-dependent increases in DNA strand breaks were observed in peripheral blood mononuclear cells in two studies after exposure to various noncytotoxic concentrations of BPA. One study involved a chronic 22-day exposure at a low concentration (Herz et al. 2017) and the exposed cells for four hours (Mokra et al. 2017).
- Statistically significant increases in DNA strand breaks were observed in cultured human gingival fibroblast (HGF) and bone marrow stem (MSC) cells (Ebrahimi et al. 2021), breast epithelial MCF-10A cells (Jalal et al. 2019), and prostate epithelial RWPE-1 cells (Kose et al. 2020) after exposure to various noncytotoxic concentrations of BPA.
- Exposure to up to 4.4 µM BPA did not increase DNA strand breaks in sperm (Sharma et al. 2018) or embryo-derived lung fibroblast MRC-5 cells (Ramos et al. 2019).

Cancer cells

- Statistically significant increases in DNA strand breaks were observed in colon cancer MKN45 cells (Ebrahimi et al. 2021), in hepatoma HepG2 cells (Balabanic

et al. 2021; Li et al. 2017b), in breast cancer MDA-MB-231 cells (Jalal et al. 2019), and in a Hep-2 laryngeal carcinoma cell line (*p*-value was not provided) (Ramos et al. 2019) after exposure to various non-cytotoxic concentrations of BPA. In addition, a significant concentration-dependent increase in DNA strand breaks was observed in breast cancer MCF-7 cells [Iso et al. (2006), also reported in Chapin et al. (2008)] after exposure to non-cytotoxic concentrations of BPA.

Double strand breaks (neutral comet assay)

- Statistically significant increases in DNA strand breaks were observed in isolated peripheral blood mononuclear cells (Mokra et al. 2017), and cultured normal breast epithelial 184A1 cells (Pfeifer et al. 2015), and a significant concentration-dependent increase in DNA strand breaks was observed in cultured embryo hepatocyte L-02 cells (Zheng et al. 2012) after exposure to various noncytotoxic concentrations of BPA.

Oxidative stress-induced strand breaks (modified alkaline comet assay with Fpg enzyme) (details in Section 5.3.5 and Appendix Table H2)

- Statistically significant increases in oxidative damage to DNA were observed in isolated peripheral blood mononuclear cells (Durovcova et al. 2018; Mokra et al. 2018), prostate epithelial RWPE-1 cells (Kose et al. 2020), and cultured embryo-derived lung fibroblast MRC-5 cells (Ramos et al. 2019) after exposure to noncytotoxic concentrations of BPA.
- Exposure to up to 4.4 µM BPA did not increase levels of oxidative damage to DNA in Hep-2 laryngeal carcinoma cells (Ramos et al. 2019).

<u>γ-H2AX</u>

γ-H2AX, a phosphorylated form of the histone protein H2AX, is a marker for DNA double-strand breaks (Noubissi et al. 2021). Findings from several of the studies included in Appendix F Table F1 are summarized below.

Normal cells

- Significant increases in γ-H2AX were observed in isolated peripheral blood mononuclear cells (PBMC), and phytohemagglutinin stimulated PBMC CD3+ T cells and CD4+ T cells (Di Pietro et al. 2020), cultured fetal lung fibroblasts (Mahemuti et al. 2018), immortalized IMR-90 lung fibroblasts and embryonic kidney HEK 293T cells (Hu et al. 2021), normal breast epithelial HME1 cells (*p*-value not provided) (Nair et al 2020), 184A1 and MCF-10A breast epithelial cell lines (Pfeifer et al. 2015), and immortalized NKNT-3 hepatocytes (*p*-value not provided) (Kim et al. 2018) after exposure to noncytotoxic concentrations of BPA.

- Exposure to 50 nM BPA for 48 hours did not increase γ-H2AX in phytohemagglutinin stimulated PBMC CD8+ T cells and CD19+ B cells (Di Pietro et al. 2020).

Cancer cells

- Increases in γ-H2AX were observed in various hepatoma cell lines or spheroids in five of seven studies after exposure to various noncytotoxic concentrations of BPA (Hercog et al. 2019; Hu et al. 2021; Kim et al. 2018; Quesnot et al. 2016) (spheroids, (Kim et al. 2018)). Concentration-dependent increases were observed three of these studies with hepatoma cell lines (Hu et al. 2021; Kim et al. 2018; Quesnot et al. 2016), and in studies with HCT116 colorectal carcinoma (p53 wild-type and null) cell lines (Kim et al. 2018).
- Additionally, statistically significant increases in γ-H2AX were observed in MCF-7 (ER+) and MDA-MB-231(ER−) breast epithelial cell lines (Pfeifer et al. 2015), in the ACHN renal cell adenocarcinoma cell line (Audebert et al. 2011), and in MCF-7 cells (*p*-value was not provided) (Iso et al. 2006; Nair et al. 2020) treated with noncytotoxic concentrations of BPA.
- Exposure to up to 100 μM BPA did not increase levels of γ-H2AX relative to controls in colorectal epithelial adenocarcinoma LS174T cells or HepG2 cells in one study (Audebert et al. 2011), while in another study exposure to 43 μM BPA did not increase γ-H2AX in HepG2 cells (Hercog et al. 2020).

Unscheduled DNA synthesis (UDS)

- UDS was increased in embryo-derived fibroblast RSa cells, which are doubly infected with Simian virus 40 and Rous sarcoma virus, after exposure to 1 μM BPA, but not at higher or lower concentrations (Takahashi et al. (2001), also reported in Chapin et al. (2008)).

DNA damage response (measured as increases in certain phosphorylated protein markers, or gene expression)

- Long-term exposure to a low concentration of BPA increased the levels of several DNA damage markers, *e.g.,* phospho-checkpoint kinase 1 (p-Chk1), phospho-checkpoint kinase 2 (p-Chk2), phospho- tumor protein P53 (p-p53) in cultured normal mammary epithelial HME1 cells and breast cancer MCF-7 cells (Nair et al. 2020).
- Exposure of hepatoma HepG2 cells to 43 μM BPA for 24 hours did not increase expression of the following DNA damage response genes: TP53, MDM2, CDKN1A, GDD45A, CHEK1, ERCC4 (Hercog et al. 2019).

(iii) Animals in vivo

Ten genotoxicity studies of BPA conducted in animals *in vivo* were reviewed by Chapin et al. (2008) [See Appendix F, Table F2, *In vivo* genetic toxicity studies of bisphenol A, excerpted from CERHR (2008) Appendix II, Table 58]. More than 30 publications on this topic have been published since 2008, and the findings from these publications are briefly discussed below.

Mutations

- A statistically significant increase in dominant lethal mutation rate during the fourth (22–28 days post BPA exposure) and sixth (36–42 days post BPA exposure) week of mating intervals was observed in male Holtzman rats treated with oral low-dose BPA (Tiwari and Vanage 2013).
- Administration of BPA did not cause dominant lethal mutations in germ cells in male SD rats, and did not induce mutations in the germ cells of *Drosophila melanogaster* (offspring) measured by the sex-linked recessive lethal test [abstract only reported in Bond et al. (1980) and Foureman et al. (1994), both also reported in Chapin et al. (2008), Haighton et al. (2002), and EU (2003)].

Chromosomal effects

<u>Micronuclei (MN)</u>

- Rats
    - Significant dose-dependent increases in MN were observed in the bone marrow cells of Holtzman and Wistar rats treated with noncytotoxic doses of BPA in two studies (Srivastava and Gupta 2016; Tiwari et al. 2012).
    - Exposure to up to 2500 mg/kg-day of BPA to male Fischer 344 and SD rats did not increase MN in bone marrow cells in two studies (De Flora et al. 2011; NTP 1995).
- Mice
    - Statistically significant increases in MN were observed in peripheral blood reticulocytes of female mice treated with noncytotoxic doses of BPA (Gajowik et al. 2013).
    - Administration of BPA to ICR [Gudi and Krsmanovic (1999), aka Shell Oil Co. (1999); Masuda et al. (2005), both also reported in Chapin et al. (2008), Haighton et al. (2002), and EU (2003)] and Swiss albino (Naik and Vijayalaxmi 2009) mice did not increase MN formation in bone marrow cells (both studies) or in peripheral blood cells (Gudi and Krsmanovic 1999).
- Other species

- Statistically significant increases in MN formation were observed in the peripheral erythrocytes of turbot fish (*Scophthalmus maximus*) [Bolognesi et al. (2006), also reported in Chapin et al. (2008)], and in the embryonic cells of freshwater snails (*Physa acuta*) (positive dose-dependent relationship) (Sánchez-Argüello et al. 2012) treated with noncytotoxic doses of BPA.

Chromosome aberrations (CA)

- A significant dose-dependent increase in the frequency of CA was observed in the bone marrow cells of male Holtzman rats treated with noncytotoxic doses of BPA (Tiwari et al. 2012).
- Exposure to a single oral dose (10 – 100 mg/kg) or a repeat oral dose for five days (10 mg/kg) of BPA to Swiss albino mice did not increase the frequency of CA in bone marrow cells (Naik and Vijayalaxmi 2009).

Meiotic chromosome abnormalities, including congression failure, aneuploidy, hyperploidy, and meiotic delay

- Significant dose-dependent increases in meiotic chromosome abnormalities, including congression failure, aneuploidy, or hyperploidy were observed in oocytes of juvenile female mice [Hunt et al. (2003), also reported in Chapin et al. (2008)], in sperm of juvenile male mice (Vrooman et al. 2015), and in oocytes of pregnant mice and their female offspring [Susiarjo et al. (2007), also reported in Chapin et al. (2008)] treated with noncytotoxic doses of BPA.
- Exposure to BPA did not induce aneuploidy in oocytes and zygotes of female mice [Pacchierotti et al. (2008), also reported in Chapin et al. (2008)] and in spermatocytes of male mice (also no delay of meiotic divisions) [Pacchierotti et al. (2008), also reported in Chapin et al. (2008)].

DNA damage

DNA adducts (details in section 5.3.1)

- DNA adducts were formed in the liver of BPA-treated male rats [Atkinson and Roy (1995b), also reported in Chapin et al. (2008)], and in the liver and mammary cells of BPA-treated female mice (Izzotti et al. 2009).

Oxidative damage to DNA/RNA, measured by oxidized nucleotides (details in section 5.3.5 and Appendix H)

- Increases of 5-hydroxymethyl-2′-deoxyuridine and 8-hydroxy-2′-deoxyguanosine in female rats (Cho et al. 2009), 8-oxoG in female rats (Li et al. 2019b), and 8-OHdG in male and female rats (Tiwari et al. 2012), in the germinal epithelium of male F1 rats (Chianese et al. 2018), and in common carp (Gu et al. 2020).

- No significant increases of 8-OHdG were found in zebrafish or fathead minnow treated with BPA (Corrales et al. 2017).

DNA strand breaks, measured by alkaline comet assays

- Rats
    - Statistically significant increases in DNA strand breaks were observed in pachytene spermatocytes of adult male rats (Liu et al. 2013; Wu et al. 2013a), blood lymphocytes of male and female rats (Tiwari et al. 2012), peripheral blood cells of adult male rats (Ulutas et al. 2011), heart cells of adult rats (Amin 2019), sperm of male rats (Tiwari and Vanage 2013), and hepatic tissue of female rats (Abdel-Rahman et al. 2018) treated with noncytotoxic doses of BPA.
    - Exposure to 200 mg/kg-day of BPA to adult SD male rats did not increase DNA strand breaks in peripheral blood lymphocytes (De Flora et al. 2011).
- Mice
    - Significant increases in DNA strand breaks were observed in sperm, lymphocytes and cells from spleen, kidneys, and lung of male mice (Dobrzyńska and Radzikowska 2013), lung cells of female mice (Gajowik et al. 2013), liver cells of male mice (Elhamalawy et al. 2018), and testicular cells of male mice (Sharma et al. 2018), and a significant dose-dependent increase was observed in brain cells of juvenile male mice (Zhou et al. 2017b) treated with noncytotoxic doses of BPA.
- Other species
    - Statistically significant increases in DNA strand breaks were observed in freshwater crustaceans (*Daphnia magna*) (Park and Choi 2009), aquatic midge (*Chironomus riparius*) (Martínez-Paz et al. 2013; Park and Choi 2009), and wild type Oregon-R *Drosophila melanogaster* (Anet et al. 2019) treated with noncytotoxic doses of BPA.

DNA strand breaks, measured by γ-H2AX

- Statistically significant increases in γ-H2AX were observed in pachytene spermatocytes of adult male rats in two studies (Liu et al. 2013; Liu et al. 2014a), spermatocytes of male rats (Wu et al. 2013a), spermatid of male F1 rats (*p*-value not provided) (Chianese et al. 2018), hippocampal microglia of rats (Di Pietro et al. 2020), and liver of juvenile male and female rats (Kim et al. 2018) treated with noncytotoxic doses of BPA.

Expression of poly(ADP-ribose) polymerase 1 (PARP-1, a marker of genotoxicity)

- Direct cutaneous exposure to low-dose BPA significantly increased the expression of PARP-1 in adult earthworms (*Eisenia fetida*), compared to controls (Novo et al. 2018).

(iv) Animal cells in vitro

Sixteen *in vitro* genotoxicity studies conducted in animal cells were reviewed by Chapin et al. (2008) [See Appendix Table F3, *In vitro* genetic toxicity studies of bisphenol A, excerpted from CERHR (2008) Appendix II, Table 57 (*i.e.*, Chapin et al. 2008, pp. 224 – 225) in Appendix F], and more than 10 additional studies were identified through the literature search OEHHA conducted. Findings from these studies are briefly summarized as follows.

Mutations

- BPA did not induce mutations in four studies in rodent cells. Specifically, BPA did not induce mutations in the hypoxanthine-guanine phosphoribosyltransferase (*hprt*) locus in Chinese hamster lung fibroblast V79 cells in one study, in the heterozygous thymidine kinase ($tk^{+/-}$) locus in mouse lymphoma L5178Y cells in two studies, or in the Na+/K+ ATPase and *hprt* loci in Syrian hamster embryo (SHE) cells in another study (Chapin et al. (2008), see Appendix Table F3 of this document).

Chromosomal effects

Micronuclei (MN)

- Increases in MN were observed in five studies at noncytotoxic concentrations of BPA, including three in Chinese hamster lung fibroblast V79 cells (Pfeiffer et al. (1997), also reported in Chapin et al. (2008), see Appendix Table F3; Parry et al. (2002); Hernandez et al. (2013)), one in Chinese hamster ovary (CHO) cells (Xin et al. 2015), and one in bovine lymphocytes (Šutiaková et al. 2014).

Chromosomal aberrations (CA)

- Increases in CA were observed in cultured CHO cells treated with noncytotoxic concentrations of BPA (Xin et al. 2015) in one study, and with cytotoxic concentrations of BPA in three studies [Galloway et al. (1998) and Hilliard et al. (1998), both as reported in Chapin et al. (2008), see Appendix Table F3; Tayama et al. (2008)].
- BPA did not induce CA in four studies, one in cultured CHO cells [Chapin et al. (2008), see Appendix Table F3], one in an epithelial-type rat liver (RL1) cell line (EU (2003), also reported in Chapin et al. (2008), Table F3), and two in cultured SHE cells [Tsutsui et al. (1998), also reported in Chapin et al. (2008), Table F3; Tsutsui et al. (2000)].

Sister chromatid exchange (SCE)

- BPA did not induce SCE in one study in cultured CHO cells with or without metabolic activation [Ivett et al. (1989), Tennant et al. (1986), as reported in Chapin et al. (2008), see Appendix Table F3].

Chromosome misalignment and spindle abnormalities, including microtubule abnormalities and aneuploidy

- An increase in aneuploidy was observed in SHE cells at non-cytotoxic doses [Tsutsui et al. (1998), also reported in Chapin et al. (2008), see Appendix Table F3].
- Increases in aneuploidogenic potential as assessed by microtubule assays were observed in Chinese hamster V79 cells treated with noncytotoxic concentrations of BPA [Pfeiffer et al. (1997) and Ochi (1999), both also reported in (Chapin et al. 2008), see Appendix Table F3].
- Statistically significant increases in chromosome misalignment and spindle abnormalities were observed in isolated bovine oocytes from heifers in two studies (Campen et al. 2018; Ferris et al. 2015) treated with various noncytotoxic concentrations of BPA, and increased spindle and centrosome abnormalities were observed in isolated mouse oocytes exposed to noncytotoxic concentrations of BPA [Can et al. (2005), as reviewed in (Chapin et al. 2008), see Appendix Table F3].

DNA damage

DNA adducts

- Noncytotoxic concentrations of BPA increased DNA adduct formation in a dose-dependent manner in cultured SHE cells [Tsutsui et al. (1998), also reported in Chapin et al. (2008), see Appendix Table F3].

Oxidative damage (details in section 5.3.5 and Appendix H Table H2)

- Statistically significant increases of 8-OHdG were observed in isolated primary rat hepatocytes treated with noncytotoxic concentrations of the BPA metabolite BPAQ (Sakuma et al. 2010), and in cultured mouse embryonic fibroblast NIH3T3 cells treated with a noncytotoxic concentration of BPA (Chen et al. 2016).
- Statistically significant increases of other oxidized nucleotides were observed in cultured mouse embryonic fibroblasts treated with BPA (Gassman et al. 2015).

DNA strand breaks

- Statistically significant increases in DNA strand breaks measured by alkaline comet assays were observed in isolated fish sperm from sterlet (*Acipenser ruthenus*) (Hulak et al. 2013), an immortalized mouse microglial (BV2) cell line

(Jalal et al. 2019), and a rat insulinoma (INS-1) cell line (Xin et al. 2014) treated with noncytotoxic concentrations of BPA.
- A statistically significant increase in γ-H2AX, a marker of DNA double strand breaks, was observed in cultured NIH3T3 cells treated with a noncytotoxic concentration of BPA (Chen et al. 2016).
- Noncytotoxic concentrations of BPA did not increase DNA strand breaks measured by alkaline elution assays in cultured primary rat hepatocytes [Storer et al. (1996), also reported in (Chapin et al. 2008), see Appendix Table F3].

(v) Bacteria, yeast, plants, and acellular systems

Twelve genotoxicity studies conducted in bacteria, yeast, and acellular systems were reviewed by Chapin et al. (2008) [See Appendix Table F3, *In vitro* genetic toxicity studies of bisphenol A, excerpted from CERHR (2008) Appendix II, Table 57 (*i.e.*, Chapin et al. 2008, pp. 224 – 225)]. Additional publications, including studies conducted in plants, have been published since 2008. Many of these studies are briefly summarized as follows.

Bacteria

- BPA did not increase reverse mutations in Ames *Salmonella* mutagenicity assays in multiple tester strains [Dean and Brooks (1978), JETOC (1996), Masuda et al. (2005), Haworth et al. (1983), Schweikl et al. (1998), Takahata et al. (1990), all as reported in (Chapin et al. 2008), Appendix Table F3; Ikhlas and Usman (2022); Tiwari et al. (2012); Zemheri and Uguz (2016)], and also tested negative in *Salmonella* SOS/umuC assays (Balabanic et al. 2021).
- BPA did not increase reverse mutations in *Escherichia coli* strains WP2 and WP2uvrA (EU 2003).

Yeast

- BPA did not increase mutations in *Saccharomyces cerevisiae* strain JDI [Dean and Brooks (1978), as reported in (Chapin et al. 2008), Appendix Table F3].

Plants

- Statistically significant increases in chromosomal aberrations were observed in onion root cells of *Allium cepa* in two studies (Jadhav et al. 2012; Oliveira et al. 2021), and in pea root tip cells of *Pisum. Sativum* (Siddiqiui et al. 2021) treated with noncytotoxic concentrations of BPA.

Acellular systems

- BPA increased DNA adduct formation in purified rat DNA incubated with rat liver microsomes [(Atkinson and Roy 1995a), also reported in (Chapin et al. 2008),

Table F3], and in calf thymus DNA incubated with rat S9 (Izzotti et al. 2009). (see details in Section 5.3.1)

- BPA inhibited microtubule polymerization in bovine brain microtubule proteins, which disrupted microtubule formation and resulted in chromosomal abnormalities [Pfeiffer et al. (1997), Pfeiffer (1996), Metzler and Pfeiffer (1995), all as reported in (Chapin et al. 2008), Appendix Table F3].

Summary of evidence for KC2

Overall, there are many studies (including studies in humans) reporting DNA damage with exposures to noncytotoxic concentrations of BPA, some studies reporting chromosomal effects, and a few studies reporting BPA-induced mutagenicity.

BPA induced mutations in a normal human cell culture and an immortalized cell line *in vitro* and in male rats *in vivo*, but not in bacteria or yeast. The mutagenicity of BPA has not been well studied in systems other than bacteria and yeast.

Several chromosomal effects induced by noncytotoxic concentrations of BPA were observed in many studies. One study in exposed humans showed a marginally positive association (p = 0.059) between urinary BPA levels and SCE frequency in peripheral blood lymphocytes collected from over a hundred Korean men and women. A number of *in vitro* studies in human cells and in animal cells, and *in vivo* studies in rodents and other animals have reported increases in MN, CAs, and various types of chromosomal abnormalities following BPA treatment. Three studies showed that BPA significantly increased CAs in plants. Two studies showed that BPA induced microtubule abnormalities in acellular systems.

A substantial amount of data on BPA-induced DNA damage are available. More than ten human observational studies reported statistically significant associations between BPA and urinary or serum levels of 8-OHdG or 8-OHG, biomarkers of oxidative damage to DNA. Two human observational studies reported positive associations between urinary BPA concentration and sperm DNA fragmentation. Increases in DNA adduct formation, DNA strand breaks, oxidative damage to DNA, and γ-H2AX were observed in multiple experimental systems treated with noncytotoxic concentrations of BPA, *i.e.*, human cells *in vitro*, animals *in vivo*, animal cells *in vitro*, and acellular systems. Increases in expression of proteins associated with DNA damage-control were observed in two studies in human cells *in vitro* and in one study in animals *in vivo*.

5.3.3 Alters DNA repair or causes genomic instability

Maintaining genomic stability and repairing damaged DNA are essential for normal cell function. Exogenous agents may interfere with DNA repair processes, which can lead to

mutations and/or genomic instability. Alterations in DNA repair that lead to an increase in mutations can occur, for example, through suppression of high-fidelity DNA repair enzymes or enhancement of error-prone enzymes. Genomic instability can manifest as alterations in copy number variants, increases in chromosomal translocations, or microsatellite instability. Both alterations in DNA repair and genomic instability induced by exogenous agents can contribute to tumorigenesis (Smith et al. 2020).

Few studies have evaluated the ability of BPA to alter DNA repair or cause genomic instability. Some studies have found that BPA decreases the expression of DNA repair enzymes. Other studies have shown that BPA exposure alters a cell's ability to fully repair DNA damage. One *in vitro* study reported that BPA treatment resulted in small changes in copy number variants. Findings from these studies are briefly summarized below.

Studies using human cells in vitro

- DNA repair in human peripheral blood mononuclear cells was measured by comet assay after 4 hours of exposure to 10 µg/ml BPA (a concentration associated with a 5% decrease in cell viability) and up to 120 minutes of recovery period in clean media immediately after BPA exposure. While evidence of repair of BPA-induced DNA damage was observed over the course of the 120-minute recovery period, residual or unrepaired, DNA damage remained after 120 minutes of recovery (Mokra et al. 2017).
- Human MELN cells (a MCF-7 derived breast carcinoma cell line stably transfected with the ER responsive gene ERE-βGlob-Luc-SVNeo) treated with UVB radiation followed by exposure to 10^{-5} M BPA for 24 hours were unable to repair cyclobutane pyrimidine dimers (CPD) relative to irradiated dimethyl sulfoxide (DMSO) vehicle controls or irradiated culture medium controls. On the other hand, cells treated with 10^{-5} BPA for 24 hours prior to irradiation were able to repair CPD lesions to similar levels as DMSO and medium controls (Cargouët et al. 2006).
- The gene expression of MyH, a MutY homolog that is involved in base excision repair (BER), was significantly decreased ($p < 0.05$) in RWPE-1 human prostate epithelial cells after exposure to 45 µM BPA (a concentration associated with a 20% decrease in cell viability) for 24 hours. Decreases in gene expression of 8-oxoguanine glycosylase (OGG1) and apurinic/apyrimidinic endonuclease 1 (APE-1), two repair enzymes also involved in BER, were observed but were not statistically significant (Kose et al. 2020).
- Significant decreases ($p < 0.05$) in TP53 expression levels were observed in RL95-2 human endometrial carcinoma cells exposed to 10 or 10^3 nM BPA, but not at 10^5 nM BPA, as measured by quantitative PCR (qPCR). No significant

decreases in TP53 levels were observed at any BPA concentration when measured by mRNA Chip. In a separate experiment, RL95-2 cells transfected with vehicle miRNA showed significant decreases in TP53 expression levels after exposure to 10^3 or 10^5 nM BPA, but not at 10 nM BPA. While TP53 is often associated with cell cycle regulation, studies have shown that a lack of TP53 can impair various types of DNA repair (Williams and Schumacher 2016). Levels of ADP ribosylation factor 6 (ARF6) were also decreased after exposure to 10 or 10^3 nM BPA as measured by qPCR; however, the role of ARF6 in DNA repair is unclear (Chou et al. 2017).

- Changes in copy number variants (CNVs) were reported in human neuronal progenitor cells derived from embryonic stem cells after exposure to 10 nM BPA relative to DMSO vehicle controls (Du et al. 2018). Specifically, the number of CNV gain (duplications) was 5 for control and 6 for the BPA-treated cells, and the number of CNV loss (deletions) was 8 for control and 10 for BPA-treated cells. There are limitations to the reporting of data (*e.g.*, lack of reporting standard deviation or number of measurements), and there is no discussion of biological or statistical significance of the effects.

Studies using non-human experimental systems

- Peritoneal macrophages isolated from male C57BL/6 mice exposed to 0 or 250 µg/L BPA via drinking water for 30 weeks were treated with methyl methanesulfonate (MMS) and allowed to recover for 3 or 6 hours. Residual DNA damage was measured by comet assay or H2A histone family member X phosphorylated on serine 139 (γ-H2AX). A significantly higher amount of residual DNA damage, a sign of impaired DNA repair, was observed after MMS treatment in the macrophages from the BPA-treated mice compared to those from control mice. Additionally, gene expression of Nijmegen breakage syndrome 1 (NBS1), which is involved in double-strand break repair, was significantly decreased ($p < 0.01$) after MMS treatment in the macrophages from BPA-exposed mice compared to those from control mice (Yang et al. 2021b).
- The effects of BPA on BER were examined in mouse embryonic fibroblasts. BPA was found to suppress BER based on data from several experiments (Gassman et al. 2015).
    - In the first experiment, cells proficient or deficient for OGG1, an enzyme that initiates BER, were treated with $KBrO_3$ to induce oxidative damage. OGG1-proficient cells treated with only $KBrO_3$ resulted in increased cytotoxicity, which was ameliorated by pretreatment with 150 µM BPA. The reduced cytotoxicity was considered a result of BPA's suppression of OGG1-mediated DNA repair. On the contrary, cytotoxicity was not

observed in Ogg-1 deficient cells treated with $KBrO_3$ with or without BPA pretreatment, indicating a key role of OGG1-mediated, BER-induced strand breaks in the cell death observed in Ogg1-proficient MEFs.

- In a second experiment, Ku70-proficient and -deficient MEFs were pretreated with or without BPA followed by exposure to $KBrO_3$. As Ku70 is an enzyme involved in non-homologous end joining, Ku70-deficient cells rely on BER to repair damaged DNA. In Ku70-deficient cells, $KBrO_3$ caused a dose-dependent decrease in cell growth. When cells were pretreated with 150 µM BPA, $KBrO_3$-induced cytotoxicity was reduced. The reduced cytotoxicity was considered a result of BPA's suppression of BER.
- In a third experiment, Ku70-deficient MEFs were treated with or without BPA and then micro-irradiated to induce strand breaks and oxidative damage. With pretreatment of BPA, two factors of BER were reduced in these MEFs compared to untreated, irradiated Ku70-deficient controls. These factors were recruitment of x-ray cross-complementing protein 1 (XRCC1) and synthesis of poly(ADP-ribose) (PAR) to sites of the micro-irradiation.

- A decrease in MutL homolog 1 (*mlh1*) gene expression, which is involved in mismatch repair, was observed in the ovaries of female wild-type (Oregon R) *Drosophila melanogaster* exposed to 10 mg/l BPA. In the ovaries of *mlh1* heterozygous mutant (*mlh1*^{e00130}*/CyO)* female *Drosophila melanogaster*, *mlh1* gene expression was significantly decreased ($p < 0.05$) after exposure to 1 or 10 mg/l BPA (Vimal et al. 2019).

Summary of evidence for KC3

Overall, a small number of studies have evaluated the ability of BPA to alter DNA repair or cause genomic instability. A few studies found that BPA decreased capacity to repair various types of DNA damage in human peripheral blood mononuclear cells, human MELN cells, mouse peritoneal macrophages, and mouse embryonic fibroblasts. Three studies found decreased expression of DNA repair enzymes (MyH, TP53, *mlh1*) and one study found small changes in copy number variants.

5.3.4 Induces epigenetic alterations

The potential for exposure to BPA to result in epigenetic effects or effects on gene or protein expression that may be caused by epigenetic changes has been investigated in many human and animal *in vivo* and *in vitro* studies. Epigenetic changes are

“hypothesized to serve as mediators of cancer etiology and progression, in many cases preceding cancer” (Smith et al. 2020). “The epigenome of a cancer cell is characterized by site-specific DNA hypermethylation, a global pattern of DNA hypomethylation, alterations in miRNA [microRNA] profile, and histone modifications” (Kanwal et al. 2015). Table 31 briefly describes some of the terms and concepts relevant to evaluating epigenetic studies.

Table 31 Epigenetic terminology

Term	Definition	Reference(s)
DNA methylation	Occurs when a methyl group is added at a cytosine nucleotide that precede guanines (CpG dinucleotides); influences DNA function by activating or repressing transcriptional activity of a gene and by altering chromatin accessibility and remodeling. Alterations in DNA methylation include hypermethylation, hypomethylation, hydroxymethylation, and loss of imprinting. • DNA hypermethylation occurs mainly in promoter CpG islands. Modifications are catalyzed by the enzyme DNA methyltransferase (DNMT). • DNA hypomethylation is associated with genomic instability and cancer progression. • Loss of imprinting is the loss of parental allele-specific monoallelic expression of genes due to altered DNA hypomethylation and can increase risk of cancer. • Genome-wide hypomethylation of repetitive elements and decreases in 5-methylcytosine are frequently observed in cancer. • Hydroxymethylation is the process of converting 5-methylcytosine into 5-hydroxymethylcytosine by TET (ten-eleven translocation) enzymes. • The global loss of cytosine hydroxymethylation has been observed in a wide range of solid tumors.	Kanwal et al. (2015); Pappalardo and Barra (2021); Pfeifer et al. (2014)
Altered expression of microRNAs	MicroRNAs (miRNAs) are a class of noncoding RNAs that play a role in RNA silencing and modulate chromatin regulation and post-	Aure et al. (2021); Dong et al. (2016);

Term	Definition	Reference(s)
	transcriptional gene expression. It has been hypothesized that miRNAs regulate the translation rate of more than 60% of protein-coding genes and participate in the regulation of cellular processes. Altered miRNAs are involved in cancer initiation and metastasis and can act as either oncogenes or tumor suppressors. miRNAs play crucial roles in the regulation of cancer-associated processes, including proliferation, differentiation, and apoptosis. Effects on miRNAs depend on exposure time and dose, and vary across species, tissues, and developmental stages.	Kanwal et al. (2015); Li et al. (2019a); Wang et al. (2015a)
Altered expression of long non-coding RNAs	Long non-coding RNAs (lncRNA) are a class of noncoding transcripts longer than 200 nucleotides. They play a role in the regulation of gene transcription and post-transcriptional mRNA processing.	Mercer et al. (2009)
Histone modifications	Histones are large groups of protein complexes that help DNA condense into chromatin. Modifications includes methylation and acetylation of lysine residues on histone tails, which can affect gene expression by altering chromatin structure and accessibility. Histone methylation is mediated by histone lysine methyltransferases (HMTs) and histone lysine demethylases (HDMs). Histones acetylation is maintained by the interplay of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Histone modifications may affect both tumor initiation and progression by altering gene expression and affecting genome integrity or chromosomal segregation.	Bannister and Kouzarides (2011); Gerhauser (2013); Wen et al. (2016)

The following sections summarize relevant epigenetic data on BPA from human observational studies, studies in human cells *in vitro*, studies in animals *in vivo*, studies in mammalian cells *in vitro*, and studies in fish.

Epigenetic and related observations in human studies

Many studies have evaluated changes in DNA methylation in BPA-exposed individuals. Altered DNA methylation is understood to be a major early event in tumor development characterized by widespread genome hypomethylation that leads to chromosome instability and localized DNA hypermethylation. “This unique pattern of individual gene methylation is the characteristic commonly observed in various tumor suppressor genes in most types of human cancers and serve as a surrogate for point mutations or deletions that cause transcriptional silencing of tumor-suppressor genes” (Kanwal et al. 2015). The first part of this section describes the studies that reported effects on individual genes, while the next section describes studies that reported global methylation effects. Appendix Table G1 lists the genes evaluated in the human studies reviewed in this section, along with brief descriptions of the functions of the genes. Details of the methylation studies assessing individual genes can be found in Appendix Table G2–Table G5.

Effects on methylation of individual genes in human studies

Epigenetic alterations were measured in fetal tissue, mother-child pairs, children, and adults. Appendix Table G2 provides details of the individual studies. Most epigenetic studies selected candidate genes or pathways, often related to a non-cancer outcome of interest (*e.g.*, asthma, neurodevelopmental diseases), and do not report comprehensive effects of methylation on the entire genome. Findings discussed here are of genes with DNA methylation changes that were found to be associated with increased BPA levels and with cancer or cancer-related pathways, often determined by a brief search of gene databases (*e.g.*, GeneCards) or the literature.

DNA methylation changes were measured in 50 fetal liver tissue samples from the University of Washington Laboratory for the Study of Human Embryology fetal tissues bank in two studies (Faulk et al. 2015; Weinhouse et al. 2015). BPA levels in the tissue were associated with hypomethylation of specific CpG sites of IL-6ST and hypermethylation of STAT3 (Weinhouse et al. 2015). Faulk et al. (2015) scanned the entire genome, conducted pathway analyses, and found strong enrichment of genes downregulated in response to estrogen, including BCAS4 and BCAR3.

Studies of four cohorts of mother-child pairs investigated the association between BPA measured in maternal urine during pregnancy with methylation of DNA from the placenta (Song et al. 2021b) or cord blood (Junge et al. 2018; Montrose et al. 2018; Song et al. 2020b). The top affected genes were HLA-DRB6, HLA-DRB1, HDAC4, FAM59B, ARHGAP9, RFX7, P2RX5 (Song et al. 2021b), CAPS2, TNRFSF25, HKR1 (Song et al. 2020b), MEST, RAB40B (Junge et al. 2018), PPARα, and IGF2 (Montrose et al. 2018) (see Appendix Table G1 for more information on these genes). Three cohort studies of mother-child pairs measured BPA in maternal urine and DNA methylation in

offspring at ages 2 and 6 (Choi et al. 2020c), 7 (Alavian-Ghavanini et al. 2018), or 8-14 (Goodrich et al. 2016) years old. Compared to children with low maternal BPA, children with high maternal BPA had altered methylation of CpG sites on IGF2R and SVIL at age 2 and SVIL at age 6 in Korea (Choi et al. 2020c). Hypermethylation of IGF2 was also reported in Swedish children with higher prenatal BPA exposure in Goodrich et al. (2016). In 7-year-old Mexican children, prenatal BPA levels were associated with methylation of a CpG site of GRIN2B in girls but not boys (Alavian-Ghavanini et al. 2018).

A cross-sectional study in Taiwan found that BPA levels were negatively correlated with MAPK1 promoter methylation in 3-year-old children (Yang et al. 2020). In a cross-sectional study in Denmark, children were examined every 6 months between the ages of approximately 6 and 15 (Almstrup et al. 2020). Methylation of several genes was associated with BPA in samples collected the same day (BAALC, FBXO47, TAPBP) and BPA averaged over a year (BAALC, FBXO47, TAPBP, FAM83A, PNOC). In a Spanish cohort, BPA was measured in urine from boys aged 9–11 years and DNA was collected when they were 15–17 years old (Mustieles et al. 2022). The BDNF gene was found to be hypermethylated in those with higher BPA levels. In a cross-sectional study, NDN and HOXA10 genes were found to be hypomethylated in 10–13 year old girls in Egypt (Kim et al. 2013).

In cross-sectional studies in adults, the ESR1 gene was hypermethylated in men exposed to a middle tertile of BPA in Lebanon (Awada et al. 2019a) and the TSP50 gene was hypermethylated in women undergoing IVF with higher BPA levels (Hanna et al. 2012).

Effects on global methylation or hydroxymethylation

Global DNA hypomethylation has been associated with the development of several types of cancer, including breast cancer (Awada et al. 2019a). Global methylation was measured in seven studies in humans (details in Appendix Table G3). BPA and DNA methylation was measured in fetal tissue from the University of Washington fetal tissues bank in several studies. Higher BPA levels in fetal liver tissue were positively associated with methylation in CpG islands and negatively associated with methylation in CpG shores, shelves, and repetitive regions (Faulk et al. 2015). LINEs (Long Interspersed Nucleotide Elements), LTRs (Long Terminal Repeats), DNA elements, and satellite repeats were hypomethylated in the medium BPA exposure group compared to the low exposure group in the fetal liver tissue (Faulk et al. 2016). Free and total BPA levels were positively associated with global methylation at LINE-1 in fetal placenta tissue, but not kidney or liver tissue (Nahar et al. 2015).

In a cohort study, BPA in maternal urine was positively associated with LINE-1 methylation in infant cord blood in an adjusted model (Navarro-Lafuente et al. 2022).

BPA in maternal urine was slightly positively associated with LINE-1 methylation in cord blood leukocytes of infant boys (although not statistically significant), but not infant girls (Montrose et al. 2018). A study that measured urinary BPA in pregnant mothers and LINE-1 methylation in 8–14 year-old offspring did not find an association (Goodrich et al. 2016). LINE-1 methylation in sperm was significantly lower in Chinese workers exposed to BPA, but LINE-1 methylation in peripheral blood was not (Miao et al. 2014). Additional analyses of this same cohort found that spermatic LINE-1 was more highly hydroxymethylated in the BPA-exposed group than the unexposed group in pooled (Zheng et al. 2017) and individual samples (Tian et al. 2018). In these occupational cohort studies, both hypomethylation of LINE-1 and increased hydroxymethylation were observed in sperm DNA of BPA-exposed workers. Tian et al. (2018) states that hydroxymethylation is present at actively transcribed genes and involved in activating gene expression, while methylation is associated with repression of gene expression. They speculate that hydroxymethylation may be a more sensitive biomarker than methylation.

Epigenetic and related observations in human cells in vitro

Methylation of individual genes

Numerous studies of human cells *in vitro* have found that BPA can alter methylation of individual genes, many of which are involved in cancer pathways (see Appendix Table G4 for study details).

Awada et al. (2019a) stated that BPA has a profound impact on the DNA methylome, based on examination of several epigenetic markers in MCF-7 cells. Pathway analysis of differentially methylated genes in BPA treated MCF-7 cells identified several subsets of cancer pathways that were affected (*e.g.*, pathways linked to endometrial cancer, acute myeloid leukemia, colorectal cancer, and proteoglycans in cancer). Additionally, many of these differentially methylated sites or regions are in ER (estrogen receptor)-responsive genes; 25 of the 47 pathways of the differentially methylated position (DMP)-derived genes affected by BPA treatment were ER-dependent (Awada et al. 2019a). Other studies using human mammary cells also reported methylation changes for many genes involved in cancer pathways following BPA exposure, including those in estrogen-dependent MCF-7 cells (Nair et al. 2020; Wang et al. 2018b), estrogen-independent MCF-10 cells (Fernandez et al. 2012), and other mammary epithelial cells (Nair et al. 2020; Qin et al. 2012).

In prostate adenocarcinoma PC-3 cells, increased methylation was observed in the promoter region of the tumor suppressor gene p16 (Fatma Karaman et al. 2019). Of the 94 other tumor suppressor genes examined, nine were hypermethylated (BCR, CDKN2A, LOX, MGMT, PTGS2, PYCARD, TIMP3, TSC2, ZMYDN10) and three were hypomethylated (STP1, NEUROG1, PDLIM4) in PC-3 cells.

Altered methylation of several other genes related to cancer processes were also observed in human embryonic stem cells (Huang et al. 2017a) and placenta cells (Cao et al. 2022), while Senyildiz et al. (2016) did not observe methylation changes in HepG2 cells.

Global methylation or hydroxymethylation patterns

Global alterations in methylation status have also been studied in many human *in vitro* studies. BPA increased the percent of global DNA methylation in two neuroblastoma cell lines (Senyildiz et al. 2017; Suchkova et al. 2019) but not in the third cell line (Bastos Sales et al. 2013). In human mesenchymal bone marrow stem cells, embryonic kidney HEK293 cells, and hepatocellular carcinoma HepG2 cells, BPA increased or decreased the percentage of global DNA methylation, varying by time and dose (Senyildiz et al. 2016; Suchkova et al. 2019) but had no effect on differentiated embryonic kidney cells (Patkin et al. 2017). In human embryonic stem cells, BPA decreased global DNA methylation (Du et al. 2018). BPA significantly decreased global hydroxymethylation in one study (Senyildiz and Ozden 2015) in MCF-7 cells, but had no effect in another (Wang et al. 2018b). In prostate cancer cells, BPA exposure decreased the percentage of DNA methylation and increased the percentage of hydroxymethylation (Fatma Karaman et al. 2019). BPA increased methylation of LINE-1 repeats in colon carcinoma cells and umbilical vein endothelial cells (Ribeiro-Varandas et al. 2014) and decreased methylation of LINE-1 in colorectal Caco-2 cells (Oldenburg et al. 2021) and MCF-7 cells (Awada et al. 2019a).

miRNAs

Expression of miRNAs was altered in many studies in human cells *in vitro*. In human endometrial cancer cells exposed to 0.01, 1, or 100 μM BPA, 82 miRNAs were dysregulated (Chou et al. 2017). Thirteen of these miRNAs were related to the progression of endometrial carcinoma, as identified from the literature. BPA inhibited miR-381-3p expression, which promotes high PTTG1 expression and alters the cell cycle to enhance proliferation in MCF-7 cells (Deng et al. 2021). BPA altered levels of many miRNAs in MCF-7 cells (Oldenburg et al. 2021; Tilghman et al. 2012; Verbanck et al. 2017). In particular, levels of miR-21, an “estrogen-regulated onco-miR in breast cancer” (Tilghman et al. 2012), were suppressed in BPA treated MCF-7 cells. An increase in miR-21 expression was observed with BPA treatment in ERα-negative and estrogen-resistant MCF-7F cells, demonstrating that BPA has both estrogen-dependent and -independent activity (Tilghman et al. 2012). BPA significantly upregulated miR-146 in Caco-2 cells, and miR-24, miR-155, miR-21, and miR-146 in human lung fibroblasts (HLFs) (Oldenburg et al. 2021). Pathway analysis of these miRNAs by Oldenburg et al. (2021) revealed that cancer pathways were among the top-ranked. BPA exposure significantly reduced miR-181b and miR-27b expression in primary human endometrial

stromal cells (Reed et al. 2018). In primary pre-adipocytes, BPA altered many miRNAs and lncRNAs, many of which were enriched in cancer pathways (Verbanck et al. 2017).

DNMTs

DNMTs are key enzymes that regulate the DNA methylation machinery; overexpression can lead to reduced expression of tumor suppressor genes (Hegde and Joshi 2021). BPA induced modest increases in DNMT1 RNA expression in MCF-7 cells (Awada et al. 2019a). These effects were estrogen-dependent, as demonstrated by inhibition in the presence of an estrogen receptor inhibitor. There were also estrogen-dependent modest increases in expression of TET2 and TET3 RNA (Awada et al. 2019a). In ER-positive MCF-7 cells and ERα$^{-/-}$ knockout MCF-7 cells, BPA induced increases in DNMT1, DNMT3A, and DNMT3B expression (except there was no significant change in DNMT3A expression in ER-knockout cells) (Li et al. 2020d). In human trophoblast BeWo cells, BPA downregulated DNMT1 expression and upregulated DNMT3a and DNMT3b expression (Cao et al. 2022). In human embryonic stem cells, BPA decreased methylation of DNMT1, DNMT3A, and DNMT3B (Du et al. 2018; Huang et al. 2017a).

Histone modifications

In three studies in MCF-7 cells, BPA exposure increased histone acetylation and H3K4 trimethylation, through enrichment of MLL2, MLL3 (mixed lineage leukemia family of histone methyltransferases) and CBP/p300 (HATs) in promoter regions, to increase expression of several genes associated with breast cancer and other cancers. These affected genes include *HOXB9* (Deb et al. 2016), *HOXC6* (Hussain et al. 2015), and *EZH2* (Bhan et al. 2014). *HOX* genes (homeobox containing genes) regulate transcription of many genes and play critical roles in tumor proliferation, metastasis, and angiogenesis (Hussain et al. 2015). *EZH2* (enhancer of Zeste homolog 2) gene product possesses H3K27-specific methyltransferase activity and is closely associated with gene silencing and chromatin condensation (Bhan et al. 2014). *In vitro* exposure to BPA increased *EZH2* expression in another study in MCF-7 cells (Doherty et al. 2010) and in primary human endometrial cells (Xiong et al. 2020). In addition, BPA induced significant alterations of global histone acetylation and methylation in normal cells (endometrial stromal cells) and some cancer cell lines (head and neck cancer cells, hepatocellular carcinoma cells, colorectal cancer cells, and colon cancer cells) (Almeida et al. 2021; Fatma Karaman et al. 2019; Senyildiz et al. 2016; Sowers et al. 2020; Xiong et al. 2020). BPA up- or down-regulated mRNA expression of a number of HDACs or HATs in endometrial stromal cells (Xiong et al. 2020), keratinocytes, head and neck cancer cells (Almeida et al. 2021), prostate cancer cells (Fatma Karaman et al. 2019), and epithelial colorectal cancer cells (Sowers et al. 2020).

Epigenetic and related observations in mammalian studies

Methylation of individual genes

BPA has many epigenetic effects on individual genes in mice and rats exposed *in vivo*, several of which were observed in estrogen receptor genes (see Appendix Table G5). *In utero* BPA exposure significantly increased methylation of CpG sites in Esr1 and/or Esr2 in the brain in BALB/c mice (Kundakovic et al. 2013), prostate in CD-1 mice (Bhandari et al. 2019), and testis in Kunming mice (Wei et al. 2020b). BPA exposure *in utero* decreased methylation of Esr1 binding genes in the uterus of CD-1 mice (Jorgensen et al. 2016). *In utero* and/or lactational exposure to BPA also decreased methylation of Mest in BALB/c mice (Junge et al. 2018) and Hoxa10 in CD-1 mice (Bromer et al. 2010), altered methylation of Il-6st and Stat3 in C57BL/6J mice (Weinhouse et al. 2015), and increased methylation of H10/Igf2 in Kunming mice (Wei et al. 2020b). Genomic DNA isolated from the liver was enriched in statistically significantly differentially methylated regions in cancer-related pathways in male and/or female a/a wild-type mice (Anderson et al. 2017; Kim et al. 2014b).

In rats, BPA exposure also altered methylation of several sites. BPA increased methylation of CpG sites in Esr1 and Esr2 in testis of Holtzman rats exposed as adults (Doshi et al. 2011). BPA exposure *in utero* and/or through lactation increased Esr1 methylation in the testis of Wistar rats (El Henafy et al. 2020) and in the hippocampus of SD rats (Chang et al. 2016b). One study in SD rats observed hypomethylation of Esr1 in mammary tissue following lactational exposure (Jadhav et al. 2017). In addition to the estrogen receptor, several genes involved in prostate cancer processes demonstrated alterations in methylation status in SD rats following postnatal BPA exposure (e.g., Pde4d4, Tpd52, Creb3L4, Sox2, Nsbp1, Scgb2a1) (Ho et al. 2006; Prins et al. 2017; Tang et al. 2012; Wong et al. 2015). Genes related to other cancer pathways were also hypo- or hypermethylated following lactational BPA exposure to SD rats (Jadhav et al. 2017).

Global methylation or hydroxymethylation patterns

In mice exposed to BPA *in utero*, global DNA methylation in heart tissue was increased in male and decreased in female C56BL/6N mice (Patel et al. 2013), and increased in tail tissue of a/a and A^{vy}/a mice (Anderson et al. 2012). BPA exposure had no effect on repetitive elements LINE-1 or Intracisternal A-particle in two studies in 10-month-old mice exposed *in utero* and through lactation (Kochmanski et al. 2017; Kochmanski et al. 2018). In male rats, BPA exposure induced a decrease in global DNA methylation in liver (Ma et al. 2013) and global hydroxymethylation in testes (Abdel-Maksoud et al. 2015).

miRNAs

Studies have also demonstrated that BPA affects expression of miRNAs in animals *in vivo. In utero* BPA exposure to California mice (*Peromyscus californicus*) caused increases or decreases in expression of over 25 different miRNAs, including an increase in miR-146 (Kaur et al. 2021), which is a key modulator of development of some tumor types (Testa et al. 2017). Expression of miR-146 (specifically miR-146a-5p) was also induced in interstitial Leydig cells by BPA exposure (Gao et al. 2018).

DNMTs

Male Sprague Dawley rats exposed to BPA via *s.c.* injection on PND1, 3, and 5 demonstrated significantly decreased DNMT1 and increased DNMT3A expression at day 10 (not days 90 or 200) and significantly increased DNMT3B at days 10, 90, and 200 in prostate tissue (Tang et al. 2012). Male Holtzman rats exposed to BPA via *s.c.* injection on PND1-5 and sacrificed on PND125 showed an increase in DNMT3A and DNMT3B expression in the testes (Doshi et al. 2011). When male Holtzman rats exposed to BPA via *s.c.* injection on PND1-5 were mated with untreated females, and viable and resorbed embryos were analyzed on GD20, DNMT1, DNMT3A, and DNMT3B expression was significantly decreased in BPA-treated resorbed embryos compared to control embryos. No changes were observed in BPA-treated viable embryos (Doshi et al. 2012). Male CD-1 mouse fetuses exposed to BPA *in utero* demonstrated a significant decrease in expression of DNMT1 and DNMT3a in urogenital sinus mesenchyme (and a non-significant increase in DNMT3b) (Bhandari et al. 2019).

Histone modifications

Histone modifications were observed in many *in vivo* animal studies in mice, rats, and gerbils. For example, increases in *EZH2* expression were observed in female rats (Altamirano et al. 2017; Bhan et al. 2014), mice (Doherty et al. 2010; Hong et al. 2016), and gerbils (Ruiz et al. 2021). Alterations of methylation and/ or acetylation status in histone H3 or H4 in promoters of several genes were observed in rat liver (Strakovsky et al. 2015), pancreas (Chang et al. 2016a), mammary gland (Altamirano et al. 2017; Dhimolea et al. 2014), and testes (Chen et al. 2017b) and in mouse mammary gland (Doherty et al. 2010) and testes (Hong et al. 2016; Shi et al. 2019b). Alterations in expression of other histone modification enzymes (DNMTs, HATs, HDACs) were observed in several studies in rats and mice (Altamirano et al. 2017; Bhan et al. 2014; Chen et al. 2017b; Shi et al. 2018; Shi et al. 2019b; Strakovsky et al. 2015).

Epigenetic and related observations in animal cells in vitro

Methylation of individual genes

Only one study was identified that observed alterations in methylation of individual genes in animal cells *in vitro* (Longo et al. 2020). Decreased methylation of the promoter and CpG sites upstream of the transcription start site of the *Pparγ* gene was observed in mouse 3T3-L1 preadipocytes and mouse embryonic NIH3T3 fibroblasts exposed to 1 nM BPA for 8 days *in vitro* (Longo et al. 2020).

Global methylation patterns

Global DNA methylation was significantly increased in mouse spermatocyte-derived GC-2 cells treated with BPA (Sidorkiewicz et al. 2018; Yin et al. 2016). Significant decreases of global methylation levels were observed in a number of mouse cells exposed to BPA *in vitro*, including cultured embryos, bone marrow derived cells, preadipocyte fibroblasts, spermatogonia, and neuroblastoma cells (Bastos Sales et al. 2013; Li et al. 2018c; O'Brien et al. 2014; Patkin et al. 2017), and in normal rat kidney cells (Tuzcuoglu and Ozden 2020).

miRNAs

Chen et al. (2013) exposed mouse embryonic stem cells to BPA for 24 hours and mouse embryoid bodies to BPA for up to six days and observed decreases in expression levels of miR-134, a possible tumor suppressor (Pan et al. 2017), in both cell types. Another study exposed mouse Sertoli cells to BPA and found that 59 and 78 miRNAs were up- or down-regulated after three and 24 hours, respectively (Cho et al. 2010). Many of these miRNAs were related to genes associated with DNA repair, DNA replication, cell proliferation, and other cancer-related processes.

DNMTs, TET2, and histone modifications

In mouse spermatocytes, BPA exposure increased DNMT1 protein levels and decreased DNMT3a and DNMT3b protein levels (Yin et al. 2016). In mouse embryonic hypothalamic cells, DNMT1 and DNMT3a mRNA levels were decreased, while DNMT3b levels were increased (Warita et al. 2013). In mouse hypothalamic GT1-7 cells following BPA exposure, TET2 localization shifted from the nucleus to the cytoplasm and reduced H3K4me3 abundance at the GnRH gene promoter was observed (Kurian et al. 2016). Tet (ten-eleven translocation) enzymes initiate active DNA demethylation and play a role in promotion of histone 3 lysine 4 trimethylation. Modifications of methylation or acetylation of histone H3 or H4 in promoters of several genes were observed in rat myoblasts (Escarda-Castro et al. 2021), mouse macrophages (Li et al. 2018b), GnRH neurons (Kurian et al. 2016), mouse oocytes (Trapphoff et al. 2013), mouse spermatogonial cells (Li et al. 2018c), and porcine oocytes (Wang et al. 2016b). Altered

expression of HATs and several HDACs were observed in rat pheochromocytoma cells and myoblast cells (Bi et al. 2022; Escarda-Castro et al. 2021). In mouse cells, changes in expression of histone deacetylase, histone methyltransferase, and histone demethylase were observed in macrophages, T cells, and spermatogonial cells (Li et al. 2018b; Li et al. 2018c; Sowers et al. 2020). Increases of histone methyltransferase expression were reported in porcine oocytes (Wang et al. 2016b).

Epigenetic and related observations in fish

Methylation of individual genes

Three studies were identified that measured methylation of individual genes in fish (see Appendix Table G6 for details). In zebrafish exposed to BPA, hypomethylation of CpG sites was observed in *esr1* in liver and *cyp19a1a* in testes (Zhao et al. 2017). Hypomethylation of *cyp19a2* was observed in zebrafish embryos (Bouwmeester et al. 2016). In rare minnows, BPA exposure induced hypermethylation of CpG sites of star and *hsd11b2* and hypomethylation of *hsd3b* (Zhang et al. 2018a).

Global methylation, DNMTs and histone modifications

Global hypomethylation was observed in testes and ovaries of BPA-exposed zebrafish (Laing et al. 2016; Liu et al. 2016b).

Several studies reported alterations in DNMTs in zebrafish and rare minnows exposed to BPA (Gyimah et al. 2021; Santangeli et al. 2016; Zhang et al. 2018a; Zhu et al. 2020; Zhu et al. 2021).

Histone modifications, including altered histone methylation or acetylation and alterations in expression or levels of HDACs, were reported in zebrafish liver cells (Blanc et al. 2019), zebrafish embryos (Blanc et al. 2019; Lombo et al. 2019a; Lombo et al. 2019c; Lombo and Herraez 2021; Santangeli et al. 2016), zebrafish larvae (Torres et al. 2021), zebrafish testes and testicular cells (Gonzalez-Rojo et al. 2019), zebrafish spermatozoa (Lombo et al. 2019a; Lombo et al. 2019b), zebrafish ovaries (Santangeli et al. 2016), rare minnow ovaries (Liu et al. 2020b; Zhu et al. 2021), and rare minnow testes (Zhu et al. 2020) exposed to BPA.

Summary of evidence for KC4

Overall, there is evidence from many studies that BPA exposure can induce epigenetic effects or effects on gene or protein expression that may be caused by epigenetic changes. Human observational studies in fetal tissue, mother-child pairs, children, and adults reported associations between BPA levels and altered methylation of many genes related to cancer pathways, as well as altered global DNA methylation. Similarly, BPA exposure to human cells *in vitro* altered methylation of individual genes and global methylation status. Other epigenetic effects, such as expression of miRNAs,

overexpression of DNA methyltransferases, and histone modifications, were found to be altered in many studies in human cells *in vitro*. All of these observations are also supported by studies in non-human mammals *in vivo*, mammalian cells *in vitro*, and fish.

5.3.5 Induces oxidative stress

Oxidative stress refers to an imbalance between the production and elimination of reactive oxygen and nitrogen species (ROS, RNS). Oxidative stress may contribute to the carcinogenic process by causing DNA mutations, chromosomal damage, genomic instability, and altered cell cycle regulation (Reuter et al. 2010). ROS can be formed during the metabolism of BPA, either via redox cycling or oxidative reactions involving various metabolic intermediates such as quinones and other reactive radicals [see Section 5.1.4 on Metabolism; Gassman (2017)].

Biomarkers for oxidative stress include 8-OHdG (8-hydroxydeoxyguanosine; indicative of oxidative damage to DNA that is linked to mutagenesis and carcinogenesis; also discussed in Section 5.3.2 KC2), ROS or RNS production, malondialdehyde (MDA) or 8-isoprostane (two common markers for lipid peroxidation), total antioxidant capacity, glutathione status [*e.g.*, reduced glutathione (GSH), glutathione disulfide (GSSG), GSH/GSSG ratio; glutathione-S-transferase (GST), and glutathione reductase (GR), glutathione peroxidase (GPx)], and other antioxidant enzyme activities and expression levels [*e.g.*, superoxide dismutase (SOD), catalase (CAT)].

Over 500 studies that investigated whether BPA induced oxidative stress were identified by the literature search. Original studies on humans and rodents with a focus on oxidative damage to DNA, as well as ROS or RNS generation were reviewed, as these are more robust and direct evidence of oxidative stress. Findings from BPA studies of other biomarkers of oxidative stress, such as increased lipid peroxidation and alterations in glutathione status or antioxidant enzyme activities or levels, are also discussed and are mainly based on four recent review papers on BPA by Steffensen et al. (2020), Zhang et al. (2022), Amjad et al. (2020), and Gassman (2017). The main findings of these review papers are briefly summarized below as an overview on BPA-induced oxidative stress.

Steffensen et al. (2020) reviewed 27 human observational studies conducted from 2008 to 2019 on various oxidative stress biomarkers from BPA exposure in different populations. The most common biomarkers for BPA-related oxidative stress in human observational studies are 8-OHdG, 8-isoprostane, and MDA; all of which predominantly showed positive associations with BPA exposure (Steffensen et al. 2020). A systematic review of rodent studies *in vivo* on BPA oxidative stress (Zhang et al. 2022) identified relevant English-language publications up to July 2020 (excluding studies with *in utero* or lactational BPA exposures), and the authors conducted a meta-analysis. This meta-

analysis found that exposure to BPA is significantly associated with increased MDA, reduced GSH and reduced antioxidant enzymes, such as GR, CAT, GPx, and SOD, based on data from rodent studies. Zhang et al. (2022) proposed that the degree of oxidative damage may be related to dose and duration of BPA exposure, as well as target tissues. Similar findings on reduced GSH levels and antioxidant enzyme activities or levels (e.g., CAT) from *in vivo* rodent studies were reported in another review (Amjad et al. 2020). Gassman (2017) reviewed the evidence of effects on ROS, GSH, and antioxidant enzyme activities or levels in rodents *in vivo*, and *in vitro* in cultured human and rodent cells, and concluded that BPA can induce complex oxidative stress, depending on the cell type or cellular microenvironment. Possible interactions between oxidative stress and other KCs (such as genotoxicity, DNA repair capacity, receptor-mediated effects, or cell proliferation) were also discussed by Gassman (2017).

Evidence for BPA-induced oxidative stress is summarized below, including evidence on oxidative damage to DNA (study details in Appendix Table H1 and Table H2), followed by ROS or RNS generation (Appendix Table H3–Table H5), lipid peroxidation, and changes in GSH and antioxidant enzyme activities or levels.

Oxidative damage to DNA

8-Hydroxydeoxyguanosine (8-OHdG) is a free radical-induced oxidative lesion formed in nuclear and mitochondrial DNA. 8-OHdG is a biomarker for measuring the direct effect of oxidative damage to DNA and has been used to estimate the DNA damage in humans after exposure to cancer-causing agents, such as tobacco smoke, asbestos fibers, heavy metals, and polycyclic aromatic hydrocarbons (Valavanidis et al. 2009). 8-OHdG is formed during the repair of DNA damage *in vivo* by exonucleases and is excreted in urine without further metabolism (Panpatil et al. 2020).

Over 30 studies, all published since 2009, investigated whether BPA induces oxidative damage to DNA, including 19 observational studies in humans (Table H1), 5 *in vitro* studies using human cells and 3 using animal cells (Table H2), and 5 *in vivo* animal studies. Overall, human observational studies of various study designs demonstrated a consistent positive association between BPA exposure and 8-OHdG in various study populations (e.g., life stage, gender, geographic location). Four animal studies *in vivo* (three in rodents and one in fish) showed positive associations between BPA exposure and oxidative damage to DNA or RNA. In eight studies using different mammalian cells *in vitro*, exposure to BPA or BPAQ (a BPA metabolite) also showed increases in biomarkers for oxidative damage to DNA. Findings from these original studies are briefly summarized by study type.

Human observational studies

All 19 human studies measured 8-OHdG in urine. Seventeen studies measured BPA in urine, while two studies (Gao et al. 2021; Metwally et al. 2018) measured BPA levels in

serum. Thirteen studies (eight cross-sectional studies, three case-control studies and two cohort studies) reported statistically significant positive associations ($p < 0.05$) between urinary or serum BPA and urinary 8-OHdG levels. Four cross-sectional studies and one cohort study reported no association between BPA and 8-OHdG, and one cross-sectional study reported a significant negative correlation. BPA levels were often measured in single serum or urine samples, collected at a single point in time. Single biological measurements of BPA are subject to the limitations described in Section 3.1.2 (*i.e.*, key issues in epidemiologic studies section) and may not reflect the usual exposure, although this concern is not as significant for oxidative damage to DNA as for cancer, which has a much longer latency period. Given this limitation (non-differential exposure misclassification usually biases the results towards the null), positive associations between BPA and 8-OHdG were still observed in multiple human studies. Studies are summarized by the findings (grouped by positive association, no association, and negative association) and by life stage (details in Appendix Table H1).

Positive association between BPA and 8-OHdG

BPA was significantly associated with increased 8-OHdG in multiple studies with study populations in different life stages or study locations.

- In children
    - Significant positive association between serum BPA and 8-OHdG was found in 49 children with autism spectrum disorders in Egypt (Metwally et al. 2018), and in 465 children (including 250 healthy children and 215 children with attention-deficit hyperactivity disorder) in China (Li et al. 2018d).
    - In children without medical conditions, significant positive associations were also found between urinary BPA and 8-OHdG levels in three studies: in 96 children aged 3 to 6 years old in China (Lv et al. 2016), and in 300 children (6–14 years old) in Brazil (Rocha et al. 2018). An interquartile range (IQR) increase in urinary BPA was significantly associated with 12.9% increase in 8-OHdG and 19.4% increase in 8-OHG (8-oxo-7,8-dihydroguanosine, a marker for RNA damage) in 275 school children in China (Zhou et al. 2019).
- In pregnant women
    - An IQR increase in urinary BPA was significantly associated with a 9% increase of 8-OHdG in 461 pregnant women in Massachusetts, adjusted for potential confounding factors (Ferguson et al. 2016). A second study in Puerto Rico also showed that an IQR increase in urinary BPA was significantly associated with a 21% increase of 8-OHdG levels in 54 pregnant women (Watkins et al. 2015).
- In adults and children/infants without medical conditions

- Positive associations between urinary BPA and 8-OHdG were observed in 130 urine samples from 67 healthy persons aged 1–87 years old in Saudi Arabia (Asimakopoulos et al. 2016), in 32 healthy adults in Singapore (Liu et al. 2019), and in 416 participants recruited from a hospital in China (adjusted for potential confounders) (Zhong et al. 2022), and in 116 residents living near an e-waste recycling region in China and in the residents living in the reference areas (Zhang et al. 2016). Two-fold increases in urinary BPA were significantly associated with a 3.8% increase in 8-OHdG in 512 repeated urine samples collected over three months in 11 healthy men in China (Wang et al. 2019f).
- Urinary BPA was significantly positively associated with 8-OHdG, adjusted for potential confounders in 134 post-menopausal women in Korea (Yang et al. 2009b). No association was found in in 259 men or 92 pre-menopausal women from the same study.

<u>No association between BPA and 8-OHdG</u>

- No associations were observed between BPA and 8-OHdG levels in the third trimester in pregnant women (Chang et al. 2019).
- No associations between BPA and 8-OHdG were found in 618 children and adolescents with chronic kidney disease (Jacobson et al. 2020), or in 111 women with unexplained recurrent spontaneous abortion, adjusted for potential confounders (Liang et al. 2020).
- In healthy adults, urinary BPA concentrations were not significantly associated with 8-OHdG in 14 women who participated in a 2-week intervention study given wheat sprout juice (Yi et al. 2011), or in 960 urban adult residents, after adjusting for age, sex, weight, smoking, and exercise (Hong et al. 2009). In the study by Hong et al. (2009), urinary BPA was weakly positively correlated with 8-OHdG ($\beta = 0.04$; $p = 0.011$) by simple regression without adjusting for any confounders.

<u>Negative association between BPA and 8-OHdG</u>

- One study showed a significant negative correlation between BPA and 8-OHdG in 100 workers in Shenzhen, Guangdong without adjusting for any confounding factors (Gao et al. 2021).

Animal studies in vivo

- Significant dose-dependent and time-dependent increases in oxidized nucleotides (5-hydroxymethyl-2′-deoxyuridine and 8-OHdG) in female SD rats were observed following *i.p*. injections of BPA (10 or 50 mg/kg-day for 4 days) ($p < 0.001$) (Cho et al. 2009).
- Significant increases in 8-OHdG were found in the plasma of healthy adult male and female Holtzman rats treated with 5 mg/kg-day for six days by the oral route

($p < 0.001$); 8-OHdG was not significantly increased in lower dose groups receiving 2.4 or 10 µg/kg-day (Tiwari et al. 2012).
- Increases of 8-OHdG were observed by immunofluorescence (without statistical test) at postnatal day 45 in the germinal epithelium of male offspring of Wistar rats exposed to BPA via *in utero* exposure, lactation and drinking water (0.1 mg/l); no 8-OHdG was observed in controls (Chianese et al. 2018).
- Significant increases in 8-OHdG were observed in gills of common carp that were exposed to 2 mg/l BPA in water for 30 days (dosing range: 0.01, 0.1, 0.5, and 2 mg/l BPA) (Gu et al. 2020).
- No significant increases of 8-OHdG were found in zebrafish or fathead minnows exposed to 0.64 to 5.12 mg/l BPA in water (equivalent to 5% to 40% of the lethal concentration 50 (LC50), 12.8 mg/l) (Corrales et al. 2017).

Oxidative damage to RNA from rat study *in vivo*

- Significant increases of urinary 8-oxoguanosine (8-oxoG, a marker for oxidative damage to RNA; $p < 0.001$) in female SD rats treated with 50 mg/kg bw by gastric gavage for 4 days were observed. No significant increases were found in rats treated at lower doses (10 or 30 mg/kg bw) (Li et al. 2019b).

Studies using mammalian cells in vitro

- *Human spermatozoa*. Exposure to BPA (300 µM for 20 hours) produced oxidative damage in spermatozoa and led to a significant increase of the percentage of human spermatozoa with 8-OHdG DNA adduct formation (3.5-fold; $p < 0.05$) compared to controls (Barbonetti et al. 2016).
- *Human lymphocytes*. Exposure to BPA at 0.001, 0.1, and 2.5 mM for one hour was associated with statistically significant increases of oxidative damage to DNA, measured by a modified Comet assay, at all doses tested ($p < 0.01$) (Durovcova et al. 2018).
- *Human peripheral blood mononuclear cells.* Significant concentration-dependent increases of oxidized pyridines and purines were observed ($p < 0.05$) in cells exposed to 0.001–1 µg/ml BPA for 4 or 48 hours (Mokra et al. 2018).
- *Human laryngeal carcinoma*, *epithelial type 2 (Hep-2) cells and human lung fibroblast (MRC-5) cells.* Authors reported significant increases in oxidative damage to DNA in MRC-5 cells after treatment with 4.4 nM and 4.4 µM BPA for 48 hours, compared to untreated control. Statistically significant decreases were observed in Hep-2 cells treated with 0.44 nM and 4.4 nM, compared to untreated control (Ramos et al. 2019). (No comparison between treated group and vehicle control was done)
- *Immortalized human prostate epithelial (RWPE-1) cells.* Increases of oxidative damage to DNA were observed in cells treated with 45 µM BPA for 24 hours (not assessed via statistical test) (Kose et al. 2020).

- *Primary rat hepatocytes*. Cells were exposure to BPA (10 µM) or BPAQ (BPA-3,4-quinone, a metabolite of BPA; at 1, 5 or 10 µM). Statistically significant increases of 8-OHdG were observed in cells exposed to 10 µM of BPAQ, not in other test conditions ($p < 0.05$) (Sakuma et al. 2010).
- *Mouse embryonic fibroblast (NIH3T3) cells*. Cells were exposed to 2, 10, or 50 µM BPA for 24 hours. A significant increase in 8-OHdG ($p < 0.01$) was observed in cells treated with 50 µM BPA ($p < 0.01$) (Chen et al. 2016).
- *Mouse embryonic fibroblasts.* Statistically significant increases of 5-hydroxycytosine and thymine glycol were observed ($p < 0.05$) in cells exposed to 150 µM BPA, but no significant increase in 8-oxoguanine (8-oxoGua) was observed (Gassman et al. 2015).

ROS and RNS generation

More than 100 publications were identified with data on ROS or RNS generation associated with BPA exposure in human cells *in vitro*, rodents *in vivo*, and rodent cells *in vitro* (details in Appendix Tables H3–H5). No human observational studies were identified on ROS or RNS generation associated with BPA exposure. Overall, BPA was consistently associated with increased ROS (both intracellular and mitochondrial) or RNS levels in the majority of these studies. These findings are consistent with the earlier review [see Tables 1 and 2 in Gassman (2017)].

Among the studies using human cells *in vitro* (Table H3), statistically significant increases of ROS (*e.g.*, hydrogen peroxide, H_2O_2) or RNS (*e.g.*, nitric oxide, NO) associated with BPA exposure were reported consistently in about 30 studies, with no changes in ROS or RNS levels reported in three studies (Kang et al. 2013; Lee et al. 2018a; Wang et al. 2020a) and one study showing statistically significant decreases in ROS (Chepelev et al. 2013). BPA exposure was often associated with statistically significant increases of ROS and/or RNS in normal human cells (e.g., peripheral blood mononuclear cells or hepatocytes) (Michalowicz et al. 2015; Oh and Lim 2008) and in human cancer cells (*e.g.*, MCF-7 or hepatoma HepG2 cells) (Güzel et al. 2020; Huc et al. 2012). For example, significant concentration-dependent increases of ROS were observed in human neutrophils exposed to BPA at 1, 3, 10, 30 and 100 µM for 2 hours (Balistrieri et al. 2018). Several other studies also observed concentration-dependent increases of ROS, including studies in neurons derived from human embryonic stem cells (hESCs), and human granulosa-like tumor (KGN) cells (Huang et al. 2020; Huang et al. 2021; Wang et al. 2019f). Increases in ROS were also reported with exposure to low concentrations of BPA. For example, in LAPC-4 (androgen-dependent) human prostate cancer cells, but not in PC-3 (androgen independent) human prostate cancer cells, exposure to 1 nM BPA (an “environmentally relevant low dose” per authors) for 15 minutes resulted in statistically significant increases in ROS (Koong and Watson 2015).

Among the rodent studies *in vivo*, most (more than 35) showed statistically significant increases of ROS and RNS with BPA exposure (Table H4), with a few exceptions that reported significant decreases of NO (Aboul Ezz et al. 2015), or no changes of ROS or RNS (Nagarajan et al. 2021; Ogo et al. 2018; Quan et al. 2017). Significant increases of ROS or RNS were observed in different strains of rats (e.g., Wistar or SD) and mice (e.g., CD-1 or Swiss), often in both sexes [e.g., Banerjee et al. (2018); Ozaydin et al. (2018b); D'Cruz et al. (2012b); Wang et al. (2019c)]. For example, in male Wistar rats exposed to 0.005, 0.5, 50 and 500 µg/kg-day BPA for 45 days by gavage, statistically significant dose-dependent increases of H_2O_2 were observed at all doses. The dosing scheme in this study is similar to human exposure scenarios with low doses (0.005 or 0.5 µg/kg-day for 45 days) that are well below the LOAEL (lowest observed adverse effect level, 50 µg/kg-day) set by US EPA (1988). Significant increases of H_2O_2 were observed starting at the lowest dose of 0.005 µg/kg-day. A few studies (Ahmed et al. 2018; D'Cruz et al. 2012b; Khan et al. 2016; Kobroob et al. 2018; Ozaydin et al. 2018b) also showed dose-dependent increases of ROS or NO at higher doses than those tested in D'Cruz et al. (2012b). Other studies reported significant increases of ROS in male Wistar rat offspring associated with paternal (pre-mating) BPA exposure (Jiang et al. 2014; Olukole et al. 2019), significant increases of NO in Swiss rats associated with paternal exposure in both F1 and F0 animals (Al-Griw et al. 2021), and significant increases of ROS in CD-1 mice associated with exposure during gestation in F1 and F0 (but not F2 or F3) animals (Rahman et al. 2020). No changes in levels of superoxide anion were observed in SD rat offspring exposed to BPA during gestation (Quan et al. 2017).

Among the studies using rodent cells *in vitro* (Table H5), consistent positive associations between BPA exposure and ROS or RNS were observed in more than 30 studies; only one reported no increases in ROS with BPA exposure (Yoshida et al. 2002). For example, significant increases of ROS were observed in mouse hippocampal HT-22 cells exposed to concentrations of BPA as low as 1 nM (Pang et al. 2019). Concentration-dependent increases of ROS were observed in two studies (Kobroob et al. 2018; Lee et al. 2008).

Lipid peroxidation (measured by 8-isoprostane or MDA)

Two review papers have established that BPA increases lipid peroxidation in human observational studies (Steffensen et al. 2020) and in rodent *in vivo* studies (Zhang et al. 2022). Additional evidence from recent *in vitro* human studies strengthens this relationship between BPA and lipid peroxidation.

As reviewed in Tables 1–2 by Steffensen et al. (2020), BPA exposure in humans was consistently associated with significant increases of lipid peroxidation measured by 8-isoprostane or malondialdehyde. All five studies reviewed with 8-isoprostane data showed a significantly positive correlation with BPA (Bono et al. 2019; Chang et al.

2019; Ferguson et al. 2016; Wang et al. 2019f; Watkins et al. 2015). Results with MDA measurements varied by the analytical methods. Consistent positive associations between BPA and MDA measured with chromatographic separation to exclude other aldehydes were reported in different populations (Kim and Hong 2017; Yang et al. 2009b; Yi et al. 2011). As reviewed by Steffensen et al. (2020), no consistent findings were observed between BPA and MDA measured by TBARS (2-thiobarbituric (TBA) reactive substances, a colorimetric analysis that may include other aldehydes): two studies showed positive associations (Dallio et al. 2018; Omran et al. 2018) and two studies showed no association (Erden et al. 2014; Hong et al. 2009). Additional human studies published since Steffensen et al. (2020) also reported statistically significant associations between BPA exposure and increased MDA (Gao et al. 2021; Haq et al. 2020b) or increased 8-isoprostane (Liang et al. 2020). For example, in women with unexpected recurrent spontaneous abortion (Liang et al. 2020), urinary BPA was significantly associated with increases in 8-isoprostane levels, adjusted for age, body mass index and other confounders (β = 0.74, 95% CI: 0.07, 1.41; p = 0.031).

Zhang et al. (2022) conducted a systematic review on BPA-induced oxidative stress in rodent *in vivo* studies and identified 20 papers published before 2020 for a meta-analysis. In this meta-analysis, the authors reported that BPA exposure was significantly associated with increased MDA. The standard mean difference (SMD) for MDA was 16.88 (95% CI: 12.06, 21.71; I^2 (heterogenicity): 94.7%; 13 studies). [SMD is a summary statistic for the meta-analysis, see Higgins et al. (2022) for more details.] This increase (SMD) was higher in groups with higher BPA dose (≥ 50 mg/kg vs. < 50 mg/kg), longer exposure duration (≥ 30 days vs. < 30 days), and in tissues other than the reproductive system [see Tables 3, 4, 6 and 7 of Zhang et al. (2022)].

Neither Steffensen et al. (2020) nor Zhang et al. (2022) reviewed evidence from human *in vitro* studies. Many *in vitro* studies using human cells also reported significant increases of MDA associated with BPA exposure and a few recent publications are given as examples (Abdullah and Rashid 2020; Dallio et al. 2018; Ebrahimi et al. 2021; Güzel et al. 2020; Huang et al. 2020; Lama et al. 2019; Wang et al. 2021a; Zhao et al. 2019). For example, concentration-dependent increases of MDA were observed in three human cell lines treated with 5, 50, or 100 µg/ml BPA, including a normal human gingival fibroblast cell line, a colon cancer cell line (MKN45), and a bone marrow stem cell line (Ebrahimi et al. 2021).

GSH and antioxidant enzyme activities or levels

Four reviews have examined the effect of BPA on GSH and antioxidant enzyme activities or levels (Amjad et al. 2020; Gassman 2017; Steffensen et al. 2020; Zhang et al. 2022). Findings in the limited number of available human studies are not consistent; more consistent results of reduced antioxidant enzymes are observed in rodent *in vivo* and *in vitro* studies.

Inconsistent results between BPA exposure and antioxidant enzyme activities were reported from three human observational studies, based on BPA levels and enzyme activities in blood, reviewed in Tables 1 and 2 by Steffensen et al. (2020). Specifically, a positive association between BPA and antioxidant enzyme activities was reported in Dallio et al. (2018), no association was reported by Kondolot et al. (2016), and a negative association was reported by Huang et al. (2017b).

Findings from rodent *in vivo* studies are more consistent: decreased antioxidant enzyme activities or levels were shown in rodent *in vivo* studies based on three reviews (Amjad et al. 2020; Gassman 2017; Zhang et al. 2022). In a review of 14 rodent studies [Table 2 in Gassman (2017)], 11 showed decreased GSH levels or antioxidant enzyme activities or levels with BPA exposure [e.g., Chitra et al. (2003); Hassan et al. (2012);Jain et al. (2011); Moon et al. (2012); Tiwari et al. (2012)]; two showed organ-specific changes of decreased or increased enzyme activities (Kabuto et al. 2003; Kabuto et al. 2004), and one showed no changes (Zhou et al. 2015). Another review by Amjad et al. (2020) showed similar findings: reduced activities/levels of SOD (3 studies), CAT (3 studies) and GSH (3 studies). In the meta-analysis of 20 rodent studies *in vivo* identified from a systematic review, Zhang et al. (2022) reported that BPA was statistically significantly associated with reduced levels of GSH (SMD = –10.64, 95% CI: –13.96, –7.33; I^2 = 90.1%; 13 studies), and reduced antioxidant enzymes, specifically GR (SMD = –10.46; 95% CI: –13.91, –7.02; I^2 = 56.7%; 4 studies), CAT (SMD = –8.48; 95% CI: –11.66, –5.3; I^2= 92.3%; 14 studies), GPx (SMD = –9.37; 95% CI: –11.95, –6.8; I^2 = 90.9%;15 studies), GST (SMD = –7.59; –14.51, –0.67; I^2 = 95.3%; 5 studies), and SOD (SMD = –6.48; 95% CI: –8.37, –4.58; I^2 = 92%; 17 studies) [see Table 3 in Zhang et al. (2022)]. Similar to their findings on MDA, changes of antioxidant enzymes may depend on the BPA dose, duration or tissue type [Tables 4, 6, 7 in Zhang et al. (2022)]. Organ- or tissue-specific responses of BPA-induced changes in antioxidant enzymes were also discussed in Gassman (2017). For example, Kabuto et al. (2004) reported organ-specific increases of SOD, CAT, and GPx activities in male ICR mice from *in utero* exposure, including a significant dose-dependent increase in SOD in the liver but not in the kidney, brain or testis, and a significant decrease in GPx in the kidney, not in liver, brain, or testis.

In vitro evidence in rodent cells has shown reduced activity or levels of CAT and GSH, and inconsistent results for SOD [See Table 2 in Amjad et al. (2020)].

Summary of KC5 evidence

Evidence for BPA-induced oxidative stress comes from consistent findings in multiple biomarkers from many recent human and animal *in vivo* and *in vitro* studies. Notably, BPA consistently induces oxidative damage to DNA (measured as 8-OHdG) and increases reactive oxygen or nitrogen species (ROS or RNS) production in numerous studies from human observational studies, studies using human cells *in vitro*, and

rodent studies *in vivo* and *in vitro*, with concentration- or dose-dependent relationships in some studies. In addition, increases in lipid peroxidation (measured as MDA or 8-isoprostane) and reductions in GSH and antioxidant enzyme activities or levels have been reported in recent BPA reviews and publications.

5.3.6 Induces chronic inflammation

Chronic inflammation associated with the development of cancer is a prolonged response to persistent infections or irritants that inflict cell death and tissue injury. For example, chronic inflammation, if linked with inflammatory bowel disease such as ulcerative colitis and Crohn's disease, can increase the risk of colorectal cancer by 10-fold, whereas the control of colitis by certain anti-inflammatory agents reduces colon cancer incidence (Lu et al. 2006).

Chronic inflammation can trigger cellular events associated with carcinogenesis, such as cellular transformation, promotion and survival of transformed cells, proliferation, invasion, angiogenesis, and metastasis (Aggarwal et al 2006; Sethi et al 2008; Smith et al 2020). Several pro-inflammatory molecules have been identified, including the cytokines tumor necrosis factor-alpha (TNF-α), transforming growth factor-β (TGF-β) and several interleukins (ILs) such as IL-1α, IL-1β, IL-6, IL-8, IL-18, chemokines, and others (Aggarwal et al. 2006; Landskron et al. 2014). The expression of these molecules is mainly regulated by the transcription factor NF-κB, which is present in an inactive state in most cells, and which can be induced by a wide variety of inflammatory stimuli and carcinogens (Aggarwal et al. 2006). Cytokines mediate cell-to-cell communication and regulate proliferation, cell survival, differentiation, immune cell activation, cell migration, and death. Chemokines can play several roles in cancer progression and have a well-known role in regulating the recruitment and trafficking of leukocytes to sites of inflammation (Aggarwal et al. 2006). During chronic inflammation, cytokines can induce cell transformation and malignancy, conditional on the balance of pro- and anti-inflammatory cytokines, their relative concentrations, cytokine receptor expression levels, and the activation state of surrounding cells (Landskron et al. 2014).

Regarding the measurement of chronic inflammation, Smith et al. (2020) states the following:

> "Due to the short-term nature of most *in vitro* assays, it is difficult to assess persistent, chronic inflammatory responses in these systems. Some 'long-term' *in vitro* co-culture models better mimic chronic inflammation, especially in regard to cytokine/chemokine profiles, but it is difficult to model inflammatory cell recruitment."

Thus, longer-term studies with histopathological examination of tissues that can visualize inflammatory changes, and/or studies that measure inflammatory biomarkers after prolonged exposure, can more directly assess chronic inflammation.

Over 200 studies that investigated inflammation due to BPA exposure in humans and animals were identified by the literature search. Of these studies, human studies that measured inflammatory biomarkers in BPA exposed populations and animal studies with longer-term (≥ 28 days) exposure that either observed inflammation directly via histopathology or measured changes in inflammation biomarkers, or both, were selected for review. Short term studies using mammalian cells *in vitro* were excluded from further review.

A brief overview of some cytokines and their functions is provided in Table 32 below.

Table 32 Some common cytokines, chemokines, and key enzymes involved in chronic inflammation and carcinogenesis

Cytokine or Chemokine	Roles in chronic inflammation and carcinogenesis	References
Tumor necrosis factor alpha (TNF-α)	TNF-α is a multifunctional cytokine that plays a role in cell survival, proliferation, differentiation, and death; it can either enhance or inhibit tumor progression. • TNF-α activates other inflammatory actors which in turn participate in the inflammatory response. • TNF-α has been linked to all steps involved in tumorigenesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis. • TNF-α may contribute to immune escape and tumor progression by facilitating the biological activity and/or expansion of immune-suppressive cells such as regulatory T cells, B cells, and myeloid-derived suppressor cells. • TNF-α activates Nuclear Factor kB (NF-κB), which in turn leads to the expression of inflammatory genes, including cyclooxygenase-2 (COX-2), lipoxygenase-2 (LOX-2), cell-adhesion molecules, anti-apoptotic proteins, inflammatory cytokines, chemokines, and inducible nitric oxide synthase (iNOS). • TNF-α can activate other signaling pathways such as nuclear factor p38 and c-Jun N-terminal kinase (JNK), which can result in the induction of oncoproteins. For example, TNF-α up-regulated the oncoprotein HBXIP, resulting in the enhanced growth of breast cancer cells.	Aggarwal (2003); Aggarwal et al. (2006); Cai et al. (2017); Cruceriu et al. (2020); Montfort et al. (2019); Sethi et al. (2008); Wang and Lin (2008); Woo et al. (2000)

Cytokine or Chemokine	Roles in chronic inflammation and carcinogenesis	References
	• TNF-α has also been shown to stimulate reactive oxygen species (ROS) *in vitro*.	
TGF-β	TGF-β's role in cancer is context dependent. "TGF-β can contribute to the differentiation of both regulatory (suppressive) T cells (Tr cells) and inflammatory Th17 cells."	Prud'homme (2007)
Interleukin (IL)-1 (including IL-1α and IL-1β)	IL-1 induces the recruitment of tumor-associated macrophages (TAMs) and tumor immunosuppressive myeloid-derived suppressor cells (MDSCs), which may promote tumor development in breast cancer. In human breast cancer, higher expression of IL-1β has been associated with tumor invasiveness and aggressiveness. Expression of IL-1α, IL-1β, and their receptors in human breast cancer tissues results in the activation of a population of cells and subsequently contributes to angiogenesis, tumor proliferation, and tumor invasion in the microenvironment.	Kaneko et al. (2019)
IL-6	IL-6 is involved in the activation of T helper cells, the inhibition of T-regulatory cells, and the differentiation of B cells. IL-6 can affect tumor cell proliferation. In some cancers such as lung cancer, IL-6 can have a preventative role in tumor initiation, but it has also been linked to tumor progression.	Unver and McAllister (2018)
IL-8	IL-8 has been reported to promote growth, angiogenesis, and metastasis of several types of tumors. Additionally, polymorphisms in the IL-8 gene are associated with a higher risk of some cancers in specific populations.	Aggarwal et al. (2006)
IL-10	IL-10 can suppress antigen presentation by myeloid cells and inhibit the production of interferon gamma (IFN-γ)-promoting cytokines, especially IL-12, thereby hindering the induction of strong anti-tumor immunity by these cells. IL-10 can inhibit the synthesis of IL-1, IL-6, and TNF-α and can also inhibit NF-κB signaling, leading to a downregulation of pro-inflammatory cytokine expression.	Kumar and Creery (2000); Landskron et al. (2014); Ouyang and O'Garra (2019)
IL-17A	IL-17A, is a pro-inflammatory cytokine that plays an essential role in host defense against microbial infections and is implicated in various inflammatory conditions such as autoimmune diseases, metabolic disorders, and cancer. IL-17A can propagate cascades of events that lead to neutrophil recruitment, inflammation, and host defense.	Gu et al. (2013)

Cytokine or Chemokine	Roles in chronic inflammation and carcinogenesis	References
IL-18	IL-18 is a pro-inflammatory cytokine in the IL-1 family that regulates immune functions such as T helper (Th) 1 and Th2 responses and NK cell activation. The role of IL-18 in carcinogenesis is context-dependent, as its activation can either promote tumor development and progression or enhance anti-tumor immunity and limit tumor growth.	Fabbi et al. (2015); Vecchié et al. (2021)
IL-22	IL-22 is a "mediator in inflammation, mucous production, protective role against pathogens, wound healing, and tissue regeneration". "Accumulating evidence suggests a pivotal role of IL-22 in instigation of various cancers due to its pro-inflammatory and tissue repairing activity".	Arshad et al. (2020)
IL-23	IL-23 is a pro-inflammatory cytokine. IL-23 has tumor-promoting properties and has been shown suppress the antitumor function of T cells and the anti-metastatic function of NK cells. Together with proinflammatory cytokine IL-12, IL-23 plays a key role in shaping the development of antitumor or protumor immunity, respectively.	Yan et al. (2018)
Interferon alpha (IFN-α)	IFN-α mediates diverse immune responses to tumors. IFN-α may have "dual opposing roles in cancer development based on the mutational status of its signaling components, which determines the expression of anti- or pro-tumorigenic IFN stimulated genes".	Vidal (2020)
Interferon gamma (IFN-γ)	IFN-γ is critical to both innate and adaptive immunity and plays a pivotal function in cancer immune surveillance, stimulating antitumor immunity and promoting tumor recognition and elimination. It is a primary activator of macrophages. However, recent studies suggest that IFN-γ may also be a tumor promoter.	Castro et al. (2018b)
Cyclooxygenase-2 (COX-2)	COX-2 is "a key enzyme in fatty acid metabolism, is upregulated during both inflammation and cancer. COX-2 is induced by proinflammatory cytokines at the site of inflammation and enhanced COX-2-induced synthesis of prostaglandins stimulates cancer cell proliferation, promotes angiogenesis, inhibits apoptosis and increases metastatic potential".	Desai et al. (2018)
Chemokines	Chemokines are "synthesized by various types of cells, including monocytes, macrophages, T lymphocytes, neutrophils, and fibroblasts, as well as neural, endothelial, and epithelial cells. Chemokines and their receptors play important roles in the development of various tumors by	Groblewska et al. (2020); Hughes and Nibbs (2018)

Cytokine or Chemokine	Roles in chronic inflammation and carcinogenesis	References
	promoting proliferation, survival, metastasis, and neoangiogenesis". (Groblewska et al. 2020) See also Hughes and Nibbs (2018) for a review on chemokines.	
C-reactive protein (CRP)	• "C-reactive protein (CRP) is an evolutionarily conserved multimeric protein of innate immunity. In humans, its blood levels change acutely and quantitatively in response to the severity of tissue damage and the inflammatory response that ensues". • "Bound CRP can activate endothelial cells, platelets and leukocytes and the complement system and influence the overall inflammatory response that results from the inciting threat to homeostasis". • "Blood levels of CRP are used to monitor the presence and extent of inflammation in cancer patients".	Potempa et al. (2021)

Studies in humans measuring inflammatory biomarkers

Several human studies have found a positive association between BPA exposure and inflammatory biomarkers. Ten studies in humans that measured BPA levels in urine or blood and inflammation markers such as CRP and cytokines in blood were identified in the literature search. There were eight cross-sectional studies, and two cohort studies conducted in pregnant women. The cross-sectional studies were performed in newborns or adults, including adults with Type 2 diabetes mellitus (Soundararajan et al. 2019), premenopausal women with polycystic ovary syndrome (PCOS) (Tarantino et al. 2013), and individuals with Crohn's Disease (Linares et al. 2021). BPA levels were mostly measured at a single point in time. Single biological measurements of BPA are subject to the limitations described in Section 3.1.2 (*i.e.*, key issues in epidemiologic studies section).

These cross-sectional studies found a positive association between BPA levels and inflammatory biomarkers such as CRP, IL-6, TNF-α, and other interleukins. One cohort study reported that BPA was positively associated with increased levels of IL-6 in pregnant women (Ferguson et al. 2016), while the other cohort study in pregnant women reported a weak, non-significant association with IL-6, and no significant association between BPA and several other cytokines (Watkins et al. 2015).

A brief summary of these studies is provided below.

- Cross-sectional study in 76 men in Italy (Savastano et al. 2015). Significant correlation was found between plasma levels of BPA and inflammatory markers such as IL-6 (r = 0.320, p = 0.005) and TNF-α (r = 0.248, p = 0.031).
- Cross-sectional study in 200 healthy adults in Korea (Choi et al. 2017). The urine levels of BPA were significantly (p = 0.018) higher in participants with high plasma levels of high-sensitivity C-reactive protein (hs-CRP) (≥ 2 mg/l) than participants with low-hs-CRP (< 2 mg/l).
- Nested case-control study in 482 pregnant women in the USA (Ferguson et al. 2016). Non-significant positive associations were observed between total BPA in urine and plasma levels of the inflammatory biomarkers IL-1B, IL-10, and TNF-α, while a non-significant negative association was observed with CRP. A significant positive association was found with IL-6. An interquartile range (IQR) increase of BPA was associated with a 10.9% increase in IL-6 (95% CI: 3.97, 18.4) for model 1, a 9.77% increase (95% CI: 2.58, 17.5) for model 2, and a 8.95% increase (95% CI: 1.81, 16.6) for model 3 [number of covariates adjusted: model 3 > model 2 > model 1].
- Cross-sectional study in 176 healthy newborns in Cyprus (Yuruker et al. 2021). Significantly higher IL-22 levels (p = 0.007) and increased ratio of IL-22/TGFβ (p = 0.04) were detected in cord blood of participants with BPA levels above the 75th percentile (>19.16 ng/ml) compared to those with BPA levels below the 75th percentile.
- Cross-sectional study in 40 premenopausal women with PCOS and 20 controls (non-PCOS) in Italy (Tarantino et al. 2013). Within women with PCOS, women with higher BPA levels (defined as higher than the 95th percentile of the BPA in the non-PCOS controls) in their serum samples showed significantly higher CRP (p = 0.038) and IL-6 (p = 0.054) serum levels than women with PCOS and lower BPA levels (defined as not higher than the 95th percentile of the BPA in the non-PCOS controls).
- Cross-sectional study in 400 adults with or without diabetes mellitus in Pakistan (Haq et al. 2020b). Within the diabetic group, significantly higher levels of CRP (p < 0.05) and IL-6 (p < 0.001) were observed in participants with BPA detected in urine, compared to participants without BPA detected in urine. Similarly, within the non-diabetic individuals, significantly higher levels of CRP (p < 0.05) and IL-6 (p < 0.001) were observed in participants with BPA detected in urine, compared to those with BPA not detected.
- Cross-sectional study in 60 adults in South India (Soundararajan et al. 2019). Serum BPA levels were significantly associated with serum IL-6 (r = 0.294, p = 0.024) and TNF-α (r = 0.309, p = 0.017) among study participants.
- Cross-sectional study in 485 adults in Korea (Yang et al. 2009b). Urinary BPA concentrations were positively associated with CRP levels in postmenopausal

women (β = 0.113, p = 0.029) in the model adjusted for age, BMI, cotinine, alcohol, and exercise. However, such associations did not exist in men and premenopausal women.

- Cross-sectional study in 200 Crohn's disease (CD) patients in Spain (Linares et al. 2021). Positive correlations between serum BPA and IL-23 (r = 0.807, p = 0.001), and between serum BPA and IL-17A (r = 0.743, p = 0.001) in CD patients with or without bacterial DNA were reported.
- Cohort study among pregnant women in Puerto Rico (Watkins et al. 2015). Serum markers of inflammation (CRP, IL-1β, IL-6, IL-10, and TNF-α) were measured twice during pregnancy (187 measurements from 105 participants). An IQR (interquartile range) increase in BPA was positively (but not significantly, p = 0.06 with the baseline model, and p = 0.11 with the adjusted model) associated with an increase in serum IL-6 (reported as percent difference with IQR increase and natural log transformed exposure). There were no significant associations between BPA and IL-1β, IL-10, TNF-α, or CRP.

Animal studies with observed tissue inflammation

Many mammalian animal studies observed chronic tissue inflammation in animals exposed to BPA, with exposure duration ranging from 4 to 52 weeks (See Table 33 below). Species examined in studies reporting on chronic tissue inflammation include rats (Wistar, Albino, SD, Noble), mice (CD-1, C57BL/6, BALB/c, MRL/lpr), Mongolian gerbils, "minipigs", and Dutch-belted rabbits. Doses given ranged from 0.1 µg/kg-day to 500 mg/kg-day, with oral/gavage administration being the most common route, and *i.p*. and *s.c*. administration being less common.

Inflammation was generally characterized as inflammatory cell invasion, necrosis, and fibrosis and/or other structural changes. Most of these studies focused on one or two tissues of interest. Collectively from these studies, inflammation was reported in the following tissues: liver, lung, brain, mammary gland, prostate, epididymis, kidney, pancreas, small intestine, colon, and Achilles tendon. Many studies concomitantly also observed changes in tissue levels of pro-inflammatory cytokines, thus complementing histopathological findings with biochemical data. For example, Haq et al. (2020a) observed dose-dependent increases of inflammation of pancreatic islet cells along with dose-dependent increases in TNF-α and IL-6 in a 90-day study in rats (with doses ranging from 50 – 5000 µg/kg-day). Shorter exposure duration (6 and 12 weeks; 25 mg/kg-day) in rats also resulted in tissue inflammation (*e.g.*, lung), with severity of inflammation increasing with the dose. Gene expression of TNF-α was also increased in this study and was significantly higher in the high dose group compared to controls (Rehman et al. 2021).

Table 33 BPA-induced tissue inflammation (with changes in biomarkers of inflammation, if assessed) in animal studies *in vivo*

Species, strain, and sex	Length of exposure	Dose and Route	Tissues examined and findings of inflammation[1]	Biomarkers of inflammation measured	Reference
Rat, Wistar albino, sex not reported	90 days, with TNF-α and IL-6 measured at the end of each month.	0, 50, 500, 2500, or 5000 µg/kg-day; oral	**Pancreas:** dose-dependent increase of inflammation of pancreatic islet cells	**Serum:** time- and concentration-dependent increases of TNF-α and IL-6 ($p < 0.001$ for both biomarkers at all concentrations and time points, except that the increase in TNF-α was not significant at 50 µg/kg-day after one month).	Haq et al. (2020a)
Rat, Wistar, M	6 and 12 weeks	10 or 25 mg/kg-day; gavage	**Small intestine:** Inflammation of the small intestine (intestinal lesions, epithelial necrosis, neutrophilic infiltrations, and disruption of villi structure) observed in all but the low dose 6-week exposure group.	**Liver:** Significant increase in mRNA of IFN-α for both doses at 6 weeks ($p < 0.001$) and 12 weeks ($p < 0.001$ for low-dose, $p < 0.01$ for high-dose)	Ambreen et al. (2019)
Rat, Wistar, M	6 and 12 weeks	10 or 25 mg/kg-day; gavage	**Lung:** dose-dependent increase of observed tissue inflammation.	**Lung:** Significant increases in TNF-α mRNA expression at both doses and after both 6 and 12 weeks; the increases appear to be time- and concentration-dependent.	Rehman et al. (2021)
Rat, Wistar, M	30 days	500 mg/kg-day; gavage	**Lung:** inflammation was observed, including edematous thickening of the alveolar walls, marked	**Lung:** Increase in mRNA expression of IL-18	Abedelhaffez et al. (2017)

Species, strain, and sex	Length of exposure	Dose and Route	Tissues examined and findings of inflammation[1]	Biomarkers of inflammation measured	Reference
			lymphocytic infiltration, and multiple fibrotic areas.	(statistical tests not reported)	
Rat, Wistar albino, F	4 weeks	150 mg/kg-day; *i.p.* injection	**Cortex and hippocampus of the brain:** neuroinflammation with perivascular inflammatory infiltrate was observed	**Brain (cortex & hippocampus):** Significant increase in IL-1β and TNF-α. Significant decrease in IL-10 and TGF-β. ($p < 0.001$ for all biomarkers)	Abdel-Rafei and Thabet (2020)
Rat, albino (strain unspecified), M	30 days	100 mg/kg-day; oral	**Liver:** inflammatory cell infiltration was observed	**Liver:** significant increases of NF-κB; TNF-α; IL-6; IL-1β and COX-2 ($p < 0.05$ for all biomarkers)	Ijaz et al. (2021)
Rat, albino (strain unspecified), M	70 days	50 mg/kg-day; oral	**Liver:** inflammatory cell infiltration was observed	**Liver:** Significantly increased mRNA expression of hepatic IL-6 and TNF-α ($p < 0.01$ for all biomarkers)	Lebda et al. (2020)
Rat, SD (NCTR), M	Beginning *in utero* GD6 through the start of parturition and then directly to male pups from PND1 continuously until one year of age[2]	2.5, 25, 250, 2500 and 25000 µg/kg-day; gavage	**Epididymis:** lymphocyte infiltration at highest dose only (CLARITY-BPA core study #6, continuous-dose, one-year) (not characterized further) **Liver:** mononuclear cell infiltration at multiple doses (study #6) (not characterized further) **Prostate:** lymphocyte infiltration in the dorsolateral lobe at lowest dose	Not measured	Camacho et al. (2019)

Species, strain, and sex	Length of exposure	Dose and Route	Tissues examined and findings of inflammation[1]	Biomarkers of inflammation measured	Reference
			only (study #6) (not characterized further)		
Rat, SD (NCTR), F	Beginning *in utero* GD6 through the start of parturition and then directly to female pups from PND1 until PND21; observed at one year of age[2]	2.5, 25, 250, 2500 and 25000 µg/kg-day; gavage	**Liver:** mononuclear cell infiltration at the lowest and highest doses (CLARITY-BPA core study #1, stop-dose, one-year) (not characterized further)	Not measured	Camacho et al. (2019)
Rat, SD (NCTR), F	Beginning *in utero* GD6 through the start of parturition and then directly to female pups from PND1 continuously until one year of age[2]	2.5, 25, 250, 2500 and 25000 µg/kg-day; gavage	**Pancreas:** lymphocyte infiltration at the lowest dose only (CLARITY-BPA core study #5, continuous-dose, one-year) (not characterized further)	Not measured	Camacho et al. (2019)
Rat, Sprague-Dawley (Crl:CD), M and F	90 days	0, 0.5, 5, 50, or 250 mg/kg-day from PND6 to PND96; gavage	**Liver:** inflammatory cell infiltration in bile duct and multi focal lymphocytic inflammatory cell infiltration in liver parenchyma (only males examined; results reported for 0.5 and 5 mg/kg-day treatment groups)	Not measured	Jeong et al. (2017)

Species, strain, and sex	Length of exposure	Dose and Route	Tissues examined and findings of inflammation[1]	Biomarkers of inflammation measured	Reference
Rat, SD albino, M	4 weeks	10 mg/kg-day; oral	**Liver:** inflammatory cell infiltration increased in the areas around the portal tract.	**Serum:** significant increase in levels of IL-6 and CRP (measured with a commercially available kit detecting human CRP) ($p < 0.001$ for both biomarkers)	Ahmed Zaki et al. (2021)
Rat, SD, M	60 days	25 mg/kg-day; oral	**Liver:** inflammatory cell accumulation around the vena centralis was observed	Not measured	Akçay et al. (2020)
Rat, Wistar, M	PND36–66	20 or 200 µg/kg-day; gavage	**Epididymis:** qualitative increase in the inflammatory infiltrate of stroma and epididymal lumen in the BPA 200 group compared to that of the control and BPA 20 groups. Inflammatory foci in caput and cauda epididymis.	**Epididymis:** Significant increase ($p < 0.05$) of IL-6 immunoreactivity at both doses in the epididymal epithelium (no IL-6 was detected in the epididymal stromal cells)	Ogo et al. (2018)
Rat, SD, M	*In utero* GD10–21; male offspring euthanized on PND21 and 180	25 or 250 mg/kg-day; gavage	**Prostate:** at PND180, increase in multifocal inflammation in prostatic ventral lobe observed at both doses	Not measured	Bernardo et al. (2015)
Rat, SD albino, F	3 days/week for 5 weeks	BPA group received 500 BPA mg/kg-day, 3 days/week for 5 weeks via *i.p.* injection; control group received daily	**Lung:** mononuclear cell infiltration, also described by the authors as peribronchial leukocytic aggregation, was observed	**Lung:** Significant increases in IL-6, TNF-α, and TGF-β ($p < 0.05$ for all three cytokines)	Moustafa et al. (2021)

Species, strain, and sex	Length of exposure	Dose and Route	Tissues examined and findings of inflammation[1]	Biomarkers of inflammation measured	Reference
		gavage of distilled water for 9 weeks			
Rat, Noble (NBL), M	32 weeks	Co-exposure[3]. 15 (low) or 320 (high) mg BPA with 30 mg testosterone (T) or T + 15 mg estrogen (E2) implanted capsules *s.c.* (the capsules were renewed every 8 weeks until sacrifice)	**Prostate:** Significantly ($p < 0.05$) elevated infiltration of both CD4+ and CD8a+ cells into the PIN epithelium of the lateral prostate lobes was observed in the T + low- or high-BPA-treated groups, compared with the control, T only, or T + E2 groups. Histology shows massive infiltration of both CD4+ and CD8a+ cells in the dysplastic epithelium but not in the adjacent periglandular stroma, histologically normal acini, or hyperplastic glands.	Not measured	Lam et al. (2016)
Mouse, C57Bl/6J, sex not specified	2 and 5 weeks	120 mg/kg-day, 5 days/week; *i.p.* injection	**Kidney:** interstitial inflammatory cell infiltration in the kidney was observed at 2 and 5 weeks	**Kidney:** significant increases in mRNA expression of IL-6 at 2 and 5 weeks ($p < 0.05$); significant increase in mRNA expression of CCL-2 at 2 weeks ($p < 0.001$), and decrease at 5 weeks ($p < 0.05$)	Priego et al. (2021)
Mouse, MRL/lpr, F	6 weeks	0.1 or 0.2 µg/ml; drinking water	**Kidney:** interstitial inflammatory cell infiltration was observed	**Kidney:** Significant increases in the protein expression of NF-κB at 0.2 µg/kg-day ($p < 0.05$)	Dong et al. (2020)

Species, strain, and sex	Length of exposure	Dose and Route	Tissues examined and findings of inflammation[1]	Biomarkers of inflammation measured	Reference
Mouse, BALB/c, M and F	8 weeks	50 mg/kg-day; gavage	**Lung:** perivascular inflammatory cellular Infiltrates were observed in the BPA treated group, with 20% showing Grade 2 inflammatory infiltration and 80% showing Grade 3, compared to none in control	Not measured	Shaukat et al. (2017)
Gerbil, M	6 months	50 µg/kg-day; drinking water	**Prostate:** (dorsolateral and ventral lobes) intraluminal and subepithelial inflammation; extensive periductal inflammation was observed	Not measured	Facina et al. (2018)
Gerbil, M	29 weeks	50 µg/kg-day; drinking water	**Prostate:** (dorsolateral and ventral lobes) intraluminal and periductal inflammation was observed. BPA treatment significantly increased the multiplicity of intraluminal inflammation in dorsolateral and ventral lobes.	**Prostate:** Increased staining intensity for IL-6 was observed in both the dorsolateral and ventral lobes of BPA treated gerbils. Increased staining for IL-10 was reported in acinar epithelium near PIN and intraductal inflammation in both lobes of BPA treated group.	Facina et al. (2021)
Gerbil, M	Single injection on study day 45; Examined on day 52 and 120	50 mg/kg bw; single *s.c.* injection	**Prostate:** inflammatory infiltrate cells were observed in the lumen on day 120. Only the ventral lobes were examined.	Not measured	Colleta et al. (2017)
Gerbil, F	*In utero*, lactation.	50 or 5000 µg/kg-day; gavage	**Mammary gland:** inflammatory cells in conjunctive tissues or	Not measured	Leonel et al. (2020a)

Species, strain, and sex	Length of exposure	Dose and Route	Tissues examined and findings of inflammation[1]	Biomarkers of inflammation measured	Reference
	GD8 through lactation by gavage to dams; euthanized on day 180		epithelial structures were observed in F1 offspring at the low doses.		
"Minipig", strain and sex not specified	4 months	1 mg/kg-day; oral	**Achilles tendon:** inflammatory fibroblastic cells were found within the tendon and near the vascular beds.	Not measured	Bellido et al. (2018)
Rabbit, Dutch-belted	*In utero*, lactation. From GD15 to PND7. Tissues were collected from dams and from 6-week-old offspring.	200 µg/kg-day; diet	**Colon & liver:** Inflammatory cell infiltration in the colonic lamina propria and hepatic periportal region were more frequent in BPA-treated dams than in the controls; Similarly, inflammation cell infiltration in the colon and liver was more frequent and of higher grades in 6-week-old BPA-exposed rabbit offspring compared to control offspring.	Not measured	Reddivari et al. (2017)

CCL, C-C motif ligand; GD, gestation day; IL, interleukin; *i.p.*, intraperitoneal; M, male; F, female; PND, postnatal day; *s.c.*, subcutaneous

[1] All tissues examined in each study are listed in this table, except for Camacho et al (2019).

[2] Part of the CLARITY-BPA core studies; for detailed exposure conditions, refer to section 4.2.1.

[3] For detailed experimental conditions, refer to Section 4.5.

Animal studies measuring inflammatory biomarkers

In addition to the studies in Table 33 that characterized both tissue inflammation as well as inflammatory biomarkers in response to BPA exposure, some studies measuring only inflammatory biomarkers were identified and summarized in Appendix Table I1. These additional studies were conducted in Wistar rats and CD-1 and C57BL/6 mice, using BPA doses ranging from 0.2 µg/kg-day to 500 mg/kg-day, with oral gavage, drinking water, and feed being the main routes of administration. Exposure duration ranged from 4 to 24 weeks and with one study utilizing *in utero* exposure. Most studies report statistically significant increases in IL-1β, IL-6, TNF-α, and other inflammatory biomarkers. Two studies in CD-1 mice (including one with *in utero* exposure) reported decreases in the levels of pro-inflammatory cytokines following BPA exposure (Fischer et al. 2016; Park et al. 2021).

Summary of evidence for KC6

Overall, inflammatory effects of BPA were observed in several human observational studies and in many animal studies.

Human cross-sectional studies found a positive association between BPA levels and inflammatory biomarkers such as CRP, IL-6, and TNF-α. One cohort study reported that BPA was positively associated with increased levels of IL-6 in pregnant women but the other cohort study in pregnant women did not report any significant association.

In animals, longer-term BPA exposure is associated with chronic inflammation, as evidenced by histopathology in many tissues including the liver, prostate, and lungs, and significant (sometimes dose-dependent) increases in levels of pro-inflammatory biomarkers. Most studies report statistically significant increases in IL-1β, IL-6, TNF-α, and other inflammatory biomarkers. One three-month study observed dose- and time-dependent increases in serum levels of TNF-α and IL-6 in Wistar rats with concomitantly observed tissue inflammation of pancreatic islet cells, with severity of inflammation increasing with the dose. Several other studies reported concurrent chronic inflammation and increases in pro-inflammatory biomarkers, while two studies reported a negative association between BPA exposure and these biomarkers.

5.3.7 Is Immunosuppressive

Immunosuppression can result in a reduction in the capacity of the immune system to respond effectively to tumor cells. Immunosuppression may allow neoplastic cells to escape immune surveillance and permit the survival and replication of these cells to form tumors (Smith et al. 2020). Both the innate and adaptive parts of the immune system participate in immune surveillance, *i.e.*, recognition and removal of malignant

cells. The innate immune system is the first line of defense, and key components of the innate (or natural) immune system include natural immunoglobulin M (IgM) antibody-producing B1 or CD5+ cells, macrophages, mast cells, dendritic cells, and natural killer (NK) cells (Vollmers and Brändlein 2009). The adaptive immune system consists of a heterogeneous population of infiltrating lymphocytes such as T cells and other immune cells to modulate the anti-tumor response (Neeve et al. 2019).

Both natural IgM (produced by B1 cells and marginal zone cells) and adaptive IgM (synthesized by B2 cells) play important roles in the cancer immune response. Natural IgM eliminates tumor cells when they begin to transform; adaptive IgM eliminates tumor cells during growth (Díaz-Zaragoza et al. 2015). Natural IgM antibodies recognize and bind to tumor-specific surface antigens and induce apoptosis via induction of cellular stress, for example by cross-linking of modified anti-complement receptors, blocking of growth-factor receptors, or by increasing the intracellular level of neutral lipids (Vollmers and Brändlein 2009). NK cells are effector lymphocytes that control several types of tumors and microbial infections by limiting their spread and subsequent tissue damage. Functions of NK cells, including the control of tumor development, can be dependent on their interaction with dendritic cells, macrophages, T cells and endothelial cells (Vivier et al. 2008). NK cells have been observed to induce tumor cell apoptosis through interferon gamma (IFN-γ) and perforin release (Neeve et al. 2019). Dendritic cells are antigen-presenting cells (*i.e.*, they capture tumor antigen) and are capable of activating naive T cells to differentiate into tumor antigen-specific CD4+ helper T cells or to CD8+ cytotoxic T cells. Neutrophils are key cellular mediators of the innate immune response (Qazi et al. 2009). Results from various studies suggest that tumor-associated neutrophils have anti-tumor properties, including the ability to induce cytotoxicity and inhibit metastasis via phagocytosis, trogocytosis, or direct cytotoxic elimination of cancer cells (Ustyanovska Avtenyuk et al. 2020). Conversely, other studies point to a tumor-supporting role of neutrophils (Shaul and Fridlender 2019; Uribe-Querol and Rosales 2015).

While numerous studies related to BPA's effects on immune cells were identified, this section is focused on and summarizes findings relevant to immune suppression (e.g., suppressed immune cell function, decreased immune cell number).

Effects on T cell and B cell cellularity or proliferation

- Human primary CD8+ T lymphocytes stimulated with IL-2 and a commercial human T Cell activation/expansion kit: 0.3 and 3 nM BPA (but not 30 nM) significantly decreased ($p < 0.05$ and $p < 0.01$, respectively) cell proliferation after exposure for 35 days *in vitro* (Tran et al. 2020).

- Human WiL2-NS B lymphoblast cells stimulated by LPS: Cell proliferation and viability were significantly decreased ($p < 0.01$ for both endpoints) after exposure to 100 µM BPA (but not 1 to 30 µM) for 48 hours *in vitro* (Jang et al. 2020).
- Male BALB/c and C57BL/6 mice: Adult male mice *s.c.* injected with 5 µM BPA (but not 0.625, 2.25, or 2.5 µM) had significantly reduced ($p < 0.05$ for both strains of mice) percentage of $CD4^+$ $CD25^+$ T cells among the $CD4^+$ T cells. In a separate experiment to assess the effects of prenatal exposure, male BALB/c mice born to mothers exposed to 10 and 100 nM BPA (but not 1 nM) via drinking water had significantly decreased ($p < 0.05$ and $p < 0.01$, respectively) percentage of $CD4^+CD25^+$ T lymphocytes (Yan et al. 2008).
- Female BALB/c mice: Exposure to 5 mg/kg bw BPA for 5 days via *s.c.* injection significantly decreased ($p < 0.01$) $CD3^+$T cell populations in spleens of female BALB/c mice measured immediately after the last dose of BPA and 3 days following the last dose. Under the same BPA treatment, splenic B220+ B cell population was significantly decreased 3 days following the last dose, but not immediately after the last dose (Sugita-Konishi et al. 2003).
- Spleen cells from ovalbumin (OVA) and BPA treated BALB/c mice and stimulated with OVA or Concanavalin A (Con A): BALB/c mice were immunized with 100 µg of alum-precipitated ovalbumin twice and administered 4 treatments of 0.1 mg/g BPA via *i.p.* injection. Isolated spleen cells were stimulated with OVA or Con A. BPA significantly reduced ($p < 0.05$) lymphocyte proliferation after Con A stimulation but not after OVA stimulation (Alizadeh et al. 2006).
- Splenic lymphocytes isolated from BALB/c mice: LPS-stimulated cell proliferation was decreased after *in vitro* exposure to 10 and 100 µM BPA exposure for 4 days [statistical significance was not reported]. BPA had no effect on Con A stimulated cell proliferation (Sakazaki et al. 2002).
- Male C57BL/6J mice treated with streptozotocin (STZ) to induce Type I diabetes: The percentages of splenic Th cells, cytotoxic T cells, and total T cells were significantly decreased ($p < 0.05$) in male C57BL/6J mice exposed to 1 mg/l BPA (but not 10 mg/l) for 5 weeks via drinking water and injected *i.p.* with STZ for 5 consecutive days and measured 11 days after first STZ injection. At day 11 after STZ, cultured splenocytes from 1 mg/l BPA treated mice had significantly higher T cell proliferation, but this effect was not seen at 10 mg/l BPA, or at either dose of BPA when cells were stimulated with Con A for 72 hours. At day 50 after STZ, cultured splenocytes from 10 mg/l BPA, but not 1 mg/l, treated mice had significantly higher T cell proliferation. At day 50 significantly higher T cell proliferation was also seen with ConA stimulation of cultured splenocytes from 10 mg/l BPA treated mice, while significantly lower T cell proliferation was seen with ConA stimulation at day 50 in cells cultured from mice treated at 1 mg/l BPA. The percentage of B cells were significantly increased ($p < 0.05$) in mice exposed to 1

mg/l BPA, but not 10 mg/l, on day 11 after STZ. No significant differences were observed for Treg cells. No significant effects on cell counts or percentages for any cell type were observed on day 50 after first STZ injection (Cetkovic-Cvrlje et al. 2017).

- Male C3H/HeN mice: In male offspring of C3H/HeN mice treated orally with 50 µg/kg-day BPA from gestation day (GD) 15 to postnatal day (PND) 21, $CD3^+$ $Tbet^+$ IFN-γ^+ Th1 cell frequency in *lamina propria* (LP) of the small intestine at PND45 and in both LP and spleen at PND170 was significantly decreased ($p < 0.05$). $CD3^+$ $Tbet^+$ IFN-γ^+ Th1 cell frequency was increased in spleen at PND45. $CD3^+$ RORγt^+ IL-17^+ Th17 cell frequency was significantly decreased in LP and increased in spleen at PND45 with no differences observed at PND170. $CD4^+$ $CD25^+$ $FoxP3^+$ Treg cell frequency was increased in LP at PND170, while no effects were observed in spleen at either PND45 or PND170 (Malaisé et al. 2017).
- Spleen and thymus leukocyte populations in SD (NCTR) rats: In females, splenic cellularity was increased and the percentage of IgM^+/IgG^+ B cells was significantly decreased ($p < 0.05$) after exposure to 25 µg/kg-day BPA for 6 months via oral gavage, but not for other exposure durations or doses. In males, the percentages of CD8+ T cells and NK T cells were increased after exposure to 25000 µg/kg-day BPA for 1 year, but not for other exposure durations or doses. No effects of BPA on thymic cellularity, assessed at PND21, were observed in either sex (Li et al. 2018a).
- Female Wistar rats: Twenty-five-day old female offspring of Wistar rats orally treated with 5 µg/kg-day BPA from GD15 to PND21 had significantly decreased ($p < 0.05$) $CD4^+$ $CD25^+$ $FoxP3^+$ Treg and $CD4^+$ $CD25^+$ Th lymphocytes in the spleen and mesenteric lymph nodes (Menard et al. 2014).
- Male Wistar rats: Compared to both untreated control and sham control, male Wistar albino rats exposed to 300 and 900 µg/kg-day BPA *in utero* had significantly decreased ($p < 0.01$) immunohistochemical staining of CD3 (T cell marker) and CD20 (B cell marker) in both spleen and mesenteric lymph nodes at PND21 and PND45 (Aydemir et al. 2020).
- Spleen cells isolated from Lewis rats and stimulated with Con A: Con A-induced proliferation of spleen cells isolated from Lewis rats was increased after *in vitro* exposure to 50 µM BPA for 72 hours, but decreased at 100, 200, or 400 µM (statistics not reported) (Jontell et al. 1995).
- Lymphocytes isolated from female goldfish (*Carassius auratus*): In peripheral blood lymphocytes isolated from female goldfish, *in vitro* BPA exposure between 0.005 to 50 mg/l significantly increased ($p < 0.05$) lymphocyte proliferation. Significantly decreased ($p < 0.05$) lymphocyte proliferation was observed at higher doses of BPA (500–1000 mg/l) (Yin et al. 2007).

Effects on Neutrophils (function)

- Human primary neutrophils: BPA significantly reduced ($p < 0.05$) the chemotactic capacity of human primary neutrophils in a Transwell chemotaxis assay at 0.1 and 1 µM and inhibited their ability to kill methicillin-resistant *Staphylococcus aureus* at 100 µM (Balistrieri et al. 2018).
- Human primary neutrophils: In a Boyden chamber chemotaxis assay, exposure to 16 nM and 1.6 µM BPA significantly ($p < 0.05$) reduced the chemotactic capacity in human primary neutrophils from men and women. While there was no significant difference in the percent of phagocytotic cells, phagocytotic activity was increased in female neutrophils, but decreased in male neutrophils, at 1.6 µM BPA (Ratajczak-Wrona et al. 2021).
- Peritoneal cavity neutrophils from female BALB/c mice: In female BALB/c mice treated with 5 mg/kg bw BPA for 5 days via *s.c.* injection and given *i.p.* injections of casein three days after the end of treatment, neutrophils from the peritoneal cavity had significantly decreased ($p < 0.01$) phagocytotic activity when incubated *in vitro* with *E. coli* despite having increased numbers after infection *in vivo*. Killing activity was significantly decreased after 20 minutes of incubation, but not different than controls after 60 minutes (Sugita-Konishi et al. 2003).

Effects on macrophages (cell number or phagocytosis function)

- Macrophages that were differentiated from the human monocytic leukemia cell line THP-1: Human monocytic leukemia cell line THP-1 cells were treated with phorbol-12-myristate-13-acetate (PMA) for differentiation into macrophages, then these macrophage-like cells were treated with 0.001 to 10 µM BPA for 24 hours and subsequently stimulated with LPS for another 24 hours before being tested for phagocytosis. At all concentrations tested, BPA significantly decreased phagocytosis ($p < 0.05$) (Couleau et al. 2015).
- Human and rat monocyte derived macrophages: Peripheral blood monocytes from male humans and rats (Wistar HanTac:WH) were differentiated *in vitro* to macrophages. The differentiation of human monocytes was achieved via stimulation with recombinant human Granulocyte Macrophage Colony Stimulating Factor, and the differentiation of rat monocytes was achieved via stimulation with rat recombinant Granulocyte Macrophage Colony Stimulating Factor. BPA (0.1 to 100 µM) exposure *in vitro* had no significant effects on phagocytosis in rat or human monocyte-derived macrophages (Berntsen et al. 2018).
- Macrophages from BALB/c mice: Exposure to 5 mg/kg bw BPA for 5 days via *s.c.* injection significantly decreased ($p < 0.01$) macrophage populations in spleens of female BALB/c mice measured immediately after the last dose of BPA and 3 days following the last dose (Sugita-Konishi et al. 2003).

- Macrophages from male C57BL/6J mice treated with STZ to induce Type I diabetes: No effects were observed on the percent or absolute number of macrophages in splenocytes from male C57BL/6J mice exposed to 1 or 10 mg/l BPA for 5 weeks via drinking water and injected *i.p.* with STZ for 5 consecutive days and measured 11 or 50 days after first STZ injection (Cetkovic-Cvrlje et al. 2017).
- Peritoneal macrophages from female CD-1 mice: Upon inflammatory activation by IFN-γ and LPS, peritoneal macrophages isolated from adult female CD-1 mice and treated with 20 ng/ml BPA *in vitro* for 2 days showed significantly decreased ($p < 0.01$) phagocytic capacity (Li et al. 2018b).
- Pancreatic macrophages from female non-obese diabetic (NOD/ShiLtJ) mice: In female NOD/ShiLtJ mice exposed to 1 mg/l BPA throughout the lifetime (starting *in utero* via dosing to dams) via drinking water, the mean number of pancreatic resident F4/80$^+$ macrophages and percentage of phagocytic macrophages were both significantly decreased ($p < 0.05$) at 7 weeks of age, but not at 11 weeks of age (Bodin et al. 2015).
- Peritoneal cavity macrophages from Wistar rats, C57BL/6 mice, and NOD mice: *In vitro* exposure to 100 µM BPA (but not 0.1, 1 or 10 µM) significantly reduced phagocytosis of peritoneal cavity macrophages (PCM) isolated from adult female and male C57Bl/6 mice and Wistar rats ($p < 0.05$ for each of the four experiments). Phagocytosis of PCM from IL-1KO (knock out) female mice and Wistar rat pups (female and male combined as one group) was decreased at 100 µM, but the decreases were not statistically significant. No effects on phagocytosis were observed in PCM from female NOD mice (Berntsen et al. 2018).
- Splenic phagocytes from fish: In splenic phagocytes isolated from spotted snakehead (*Channa punctata*), 1 nM to 1 µM BPA *in vitro* exposure significantly ($p < 0.05$) depressed percentage of phagocytosis and phagocytic index when the cells were treated with heat-killed yeast cells (Pandey et al. 2018).
- Macrophages isolated from female goldfish (*Carassius auratus*): In head kidney macrophages isolated from female goldfish, *in vitro* exposure to BPA between 0.005 and 50 mg/l significantly increased ($p < 0.05$) phytohemagglutinin (PHA)-induced proliferation[12]. Significantly decreased ($p < 0.05$) proliferation was observed at higher doses of BPA (500–1000 mg/l) (Yin et al. 2007).

[12] The data is shown in Figure 3 of Yin et al (2007) and summarized in the text. While the heading for Figure 3 stated the data is on "lymphocyte proliferation", it is likely to be a typo, as the text in the results section describes the data from Figure 3 as "macrophage proliferation". In addition, Figure 2 shows data on the lymphocyte proliferation.

Effects on dendritic cells

- Human immature monocyte-derived dendritic cells (iMDDCs) isolated from peripheral blood: Human iMDDCs exposed to 50 µM BPA for 5 days *in vitro* had significantly decreased ($p < 0.01$) endocytotic capacity toward FITC-labeled dextran relative to untreated controls (Švajger et al. 2016).
- Dendritic cells from spleen and mesenteric lymph nodes of female Wistar rats: Twenty-five-day old female offspring of rats fed 5 µg/kg-day BPA from GD15 to PND21 had significantly decreased ($p < 0.05$) $CD11b^{-}$ $CD103^{+}$ $MHCII^{+}$ $CD172^{+}$ dendritic cells in the spleen and mesenteric lymph nodes (Menard et al. 2014).

Effects on NK cells

- NK cells from spleen of C57BL/6J mice: The percentage of splenocytes that were NK cells, but not absolute cell number, was significantly decreased ($p < 0.05$) in C57BL/6J mice exposed to 1 mg/l BPA (but not 10 mg/l) for 5 weeks via drinking water and injected *i.p.* with STZ for 5 consecutive days and measured 11 days after first STZ injection. No significant differences in the percentage or absolute number of splenic NK cells were observed 50 days after first STZ injection (Cetkovic-Cvrlje et al. 2017).

Effects on IgM levels

- Female BALB/c mice: Reactivity of serum IgM antibodies in female BALB/c mice was decreased after a single injection of 250 µg/kg BPA during the neonatal stage followed by breast tumor induction via injection of the mouse breast cancer cell line 4T1 (statistical significance not reported) (Hernández Avila et al. 2019).
- Juvenile fish (rock bream *Oplegnathus fasciatus)*: In juvenile rock bream *Oplegnathus fasciatus*, *in vivo* exposure to 10 or 50 ng/l BPA for 5 days followed by 1, 3, and 5 days of green and red LED treatment of two intensities (0.3 and 0.5 W/m^2) significantly decreased plasma IgM activity (Choi et al. 2016).

Summary of evidence for KC7

Overall, several studies report effects on cancer-related immunosuppressive effects of BPA. Several studies observed significantly decreased T-lymphocyte and B cell populations in spleen or lymph nodes in rodents *in vivo* and a few studies observed decreased proliferation in human cells *in vitro* after exposure to BPA. Decreased macrophage phagocytotic capacity was observed in studies in humans *in vitro*, animals *in vivo*, and animal *in vitro* systems. A few studies in primary human cells and rodents *in vivo* observed reduce chemotactic capacity of neutrophils. For dendritic cells, one study observed decreased endocytotic capacity in human cells, while another study in mice observed decreased numbers of cells in spleen mesenteric lymph nodes. One study

found decreased levels of splenic NK cells in rats. Lastly, one study in mice and one study in juvenile rock bream reported decreased IgM levels after BPA exposure.

5.3.8 Modulates receptor-mediated effects

5.3.8.1 Estrogen receptors

BPA is a well-recognized xenoestrogen that is known to mimic and interfere with the actions of estrogen. There is a large body of evidence from observational studies in humans, human cells *in vitro*, and animal studies *in vivo* and *in vitro* indicating that BPA modulates ER-mediated effects through several different ER subtypes and their downstream signaling pathways. The evidence has been discussed in many reviews (Acconcia et al. 2015; Acconcia et al. 2017; Chapin et al. 2008; Cimmino et al. 2020; Engin and Engin 2021; Gao et al. 2015; Hafezi and Abdel-Rahman 2019; Khan et al. 2021; La Merrill et al. 2020; Li et al. 2020c; Marino et al. 2012; Romagnolo et al. 2016; Sonavane 2022; Vandenberg et al. 2009; Wang et al. 2017d; Winz and Suh 2021). For example, Chapin et al. (2008) summarizes the evidence on BPA's estrogenicity from *in vitro* (see Table 52 in Chapin et al. (2008)) and *in vivo* (see Table 53 in Chapin et al. (2008)) studies.

While it is well-known that BPA binds to cytosolic ERs and activates ER nuclear translocation and binding to estrogen response elements (EREs) in DNA, additional ER-related activities of BPA have been identified. These non-canonical ER activities of BPA may explain many observations that are unexpected solely based on the classical ER pathway, such as the observed low-dose effects, the non-monotonic dose-responses, and the rapid onset of extra-nuclear responses (Acconcia et al. 2015; Sonavane 2022). Examples of non-canonical ER related activities of BPA are briefly described here.

Membrane-bound estrogen receptors (mERs)

BPA has been found to bind to mERα (also known as the truncated ERα36) and mERβ, which were palmitoylated and localized at the plasma membrane in the caveolar domains via physical association with the membrane scaffolding protein caveolin-1 (Marino et al. 2012; Watson et al. 2007; Watson et al. 2014). Activation of mERs by BPA triggers rapid estrogenic signaling within seconds or minutes via activation of cellular kinase systems such as extracellular signal regulated kinase / mitogen-activated protein kinase (ERK/MAPK) and phosphatidylinositol-3-kinase / AKT (PI3K/AKT) (by mERα) or p38/MAPK (by mERβ) (Acconcia et al. 2015; Marino et al. 2012; Watson et al. 2007; Watson et al. 2014). The BPA-induced mERα pathway has been found to induce changes in the intracellular levels of cAMP and calcium (Acconcia et al. 2015; Khan et al. 2021; Watson et al. 2007), which can lead to changes in downstream signaling pathways, cellular proliferation, and migration (Sonavane 2022). On the other

hand, BPA can behave as an E2 antagonist, inhibiting E2 activation of mERβ and its downstream p38/MAPK signaling pathway (Acconcia et al. 2015; Bolli et al. 2010; Marino et al. 2012).

G-protein coupled estrogen receptor (GPER/GPR30)

GPER/GPR30 is a seven-transmembrane-domain receptor and has been identified in a variety of species in numerous tissues with different expression patterns (Thomas and Dong 2006). GPER/GPR30 interacts with many other proteins to mediate the activation of several kinase pathways, *e.g.*, ERK1/2, PI3K, protein kinase A (PKA), and MAPK (Dong et al. 2011; Li et al. 2020c). It is one of the most common membrane-bound ERs, and BPA has shown high binding affinity for this receptor (Acconcia et al. 2015; Cimmino et al. 2020; Sonavane 2022). Rapid signaling of GPER/GPR30 by low-dose BPA results in a number of estrogen-like responses, including cell proliferation, inhibition of apoptosis, EMT, migration, and increased expression of estrogen responsive genes (Cimmino et al. 2020; Khan et al. 2021; Pupo et al. 2012; Sonavane 2022).

Estrogen-related receptor γ (ERRγ)

The estrogen-related receptor γ (ERRγ) is one member in a subfamily of orphan nuclear receptors with sequence similarity to ERα, including ERRα, ERRβ, and ERRγ (Li et al. 2020c; Takayanagi et al. 2006). E2 is not the natural ligand of ERRs, and ERRs have constitutive transcriptional activity (Takayanagi et al. 2006). BPA in the nanomolar concentration range has been shown to bind to ERRγ with high affinity (Liu et al. 2014b; Matsushima et al. 2021; Takayanagi et al. 2006). The estrogenicity of low-dose BPA could partially be mediated through ERRγ, as ERRγ is highly expressed in the brain (especially during development), lung, reproductive tissues, and other tissues (Acconcia et al. 2015; Takeda et al. 2009), and shares many target genes with ERα (Acconcia et al. 2015).

In addition to these examples, BPA can also induce epigenetic changes to regulate the expression of ERα and cancer-related ER target genes (Khan et al. 2021; Sonavane 2022) (see Section 5.3.4).

5.3.8.2 Estradiol (E2)

Human observational studies

Some positive correlations between BPA levels and E2 were observed in a few subpopulations and the results are presented here. For the other subpopulations, no consistent patterns were observed; details of these can be found in Appendix Table J1.1.

- In male partners in subfertile couples, positive associations between BPA and E2 were observed in two studies in Egypt and Czech Republic (Shokry et al. 2020; Vitku et al. 2015), but not in a third in the US (Meeker et al. 2010a).
- In healthy children and adolescents, a positive correlation with E2 was observed in girls in one study in Korea (Lee et al. 2013a) and in female adolescents in the US (Wang et al. 2021f). No associations were observed in girls in Canada (Pollock et al. 2021).
- In newborns, positive correlations were observed with BPA measured in cord blood in males in Turkey (Sunman et al. 2019) and in males and females combined in South Africa (Gounden et al. 2021). No associations were observed in another study of newborns in Japan (Minatoya et al. 2017). When BPA was measured in maternal urine, positive correlations were observed with E2 measured in female infants at 14 days, 28 days, 42 days, and 3 months of life, and in male infants at 14 days, 28 days, and 42 days of life (Wang et al. 2017c).

Studies in human cells in vitro

Overall, the effects of BPA on E2 levels in human cells *in vitro* studies are inconsistent. Information on study design and findings for each study are given in Appendix Table J1.2, and will not be discussed further here.

Studies in non-human mammals in vivo

Overall, the effects of BPA on E2 levels in non-human mammals *in vivo* are inconsistent. Information on study design and findings for each study are given in Appendix Table J1.3, and will not be discussed further here.

Studies in non-human mammalian cells in vitro

Information on study design and findings on the effects of BPA on E2 from non-human mammalian *in vitro* studies are provided in Appendix Table J1.4. *In vitro* exposure to BPA decreased E2 levels in studies of mouse and rat ovarian granulosa cells or follicles, increased E2 levels in most studies of pig granulosa cells and in one study of sheep granulosa cells, and decreased E2 levels in one study of boar testes.

- In mouse preantral and antral follicles, E2 levels were significantly decreased after exposure to BPA (Peretz et al. 2011; Wang et al. 2018a; Ziv-Gal et al. 2013).
- In rat primary granulosa cells exposed to 1 to 100 µM BPA, E2 levels were significantly decreased (Chen et al. 2017a; Lee et al. 2019a; Zhou et al. 2008).
- In pig granulosa cells, three studies found increased E2 levels after exposure to 0.087 to 10 µM BPA (Grasselli et al. 2010; Song et al. 2019; Wu et al. 2018), while one study found that BPA treatment decreased FSH-stimulated E2 in granulosa cells (Mlynarcikovic et al. 2005).

- In sheep granulosa cells, E2 levels were significantly increased after exposure to 10 to 200 µM BPA (Teteau et al. 2020).
- One study in boar testes found decreased E2 levels after exposure to 10 nM BPA (Pawlicki et al. 2019).

5.3.8.3 Progesterone and Progesterone receptor

Progesterone (P4)

Human observational studies

Inconsistent results between BPA and progesterone levels were observed in two occupational studies (Hao et al. 2011; Miao et al. 2015). Miao et al. (2015) reported a positive association between urine BPA and progesterone, while Hao et al. (2011) reported lower progesterone in workers exposed to BPA for more than 5 years compared to workers exposed for less than 5 years. A study of newborns reported a negative correlation of cord blood progesterone and BPA measured in maternal serum or cord blood (Gounden et al. 2021). In other populations, human observational studies were not able to detect an association between BPA and progesterone levels (Aker et al. 2016; Aker et al. 2019; Minatoya et al. 2017; Pollack et al. 2018; Pollock et al. 2021; Tsai et al. 2020).

In vitro studies of human cells

Inconsistent effects on P4 levels have been observed in human cells *in vitro* exposed to BPA (see Appendix Table J2.1 for study details).

- In adrenal adenocarcinoma H295R cells treated with BPA, one study found increased P4 levels (Zhang et al. 2011) while another study found decreased P4 levels (Feng et al. 2016).
- P4 levels were increased in cumulus granulosa cells (Pogrmic-Majkic et al. 2019) but decreased in luteinized granulosa cells and granulosa KGN cells after exposure to BPA (Mansur et al. 2016; Shi et al. 2021).

Studies in mammals *in vivo*

Information on study design and findings on the effects of BPA on P4 from non-human mammalian *in vivo* studies is provided in Table J2.2 in Appendix J. Overall, levels of P4 in rodents exposed to BPA were primarily decreased or not different from controls.

- In mice treated with BPA, serum or urinary P4 levels were either significantly decreased [(Berger et al. 2008) (multiple exposures); (Tang et al. 2020; Wei et al. 2020a)] or not different from controls [(Berger et al. 2008) (single exposure); (Tucker et al. 2018; Xi et al. 2011)].

- In rats treated with BPA, serum or plasma P4 levels were mainly decreased (for example, studies by (Hamdy et al. 2018; Ijaz et al. 2020; Martínez-Pena et al. 2017). A few studies reported increased serum or plasma P4 levels in juvenile females exposed to BPA during gestation and throughout lactation (Silva et al. 2019), adult females (Osman et al. 2021), or adult males (Rashid et al. 2018). Some studies in rats did not observe any effect of BPA on serum or plasma P4 levels (Behmanesh et al. 2018; Patel et al. 2017).

In vitro studies of non-human mammalian cells

Overall, P4 levels measured from BPA treated mammalian cells *in vitro* were inconsistent (significantly decreased or increased, or not affected) at BPA concentrations ≤10 µM and consistently decreased at BPA concentrations ≥100 µM (see Table J2.3 for study details).

- P4 levels in mouse Leydig TM3 and TM4 cells and in antral follicles were decreased after exposure to BPA (Ok et al. 2017; Peretz et al. 2011).
- In granulosa cells obtained from pigs, one study found P4 levels increased at lower concentrations of BPA tested but decreased levels at the highest dose (Mlynarcikovic et al. 2005) while another study found decreased P4 levels at all BPA concentrations tested (Grasselli et al. 2010).
- In rat granulosa cells, BPA exposure decreased P4 production (Chen et al. 2017a; Samardzija et al. 2018). Another study found increased P4 levels at lower concentrations but decreased P4 levels at higher concentrations of BPA exposure (Zhou et al. 2008).
- Decreased P4 levels were observed in sheep granulosa cells exposed to BPA (Teteau et al. 2020).

Progesterone Receptor (PR)

In vitro studies of human cells or transfected or cell-free human PR

Overall, increased expression of PR was generally observed following BPA exposure of human cells *in vitro*. BPA exhibited antagonistic activity for human PR or did not bind to PR (see Appendix Table J2.4 for study details).

- Several studies in breast cancer MCF-7 cells reported increased PR mRNA or protein after treatment with BPA (Krishnan et al. 1993; Samuelsen et al. 2001; Tilghman et al. 2012). A few studies did not find effects on PR mRNA in MCF-7 cells or mammospheres after exposure to BPA (Diel et al. 2002; Lillo et al. 2017).
- PR expression was also increased in endometrial stromal cells (Mannelli et al. 2015), human endometrial ECC-1 cells (Bergeron et al. 1999), and Ishikawa endometrial adenocarcinoma cells (Aldad et al. 2011; Schaefer et al. 2010) treated with BPA. One study did not find differences in PR mRNA expression in

endometrial stromal fibroblasts isolated from patients with fibroids or pelvic organ prolapse treated with BPA (Aghajanova and Giudice 2011).

- In binding activity studies, BPA exhibited antagonistic activity for PR by reducing P4-induced activity in MCF-7 cells (Doan et al. 2020) and did not bind to human PR in breast cancer cells (Simon et al. 2016), cervical cancer cells (Grimaldi et al. 2019), or yeast cells stably transfected with human PR (Li et al. 2010).
- In cell free assays, one study reported BPA binding to human PR with an IC50 of 45 μM and a binding affinity of 0.1% (Scippo et al. 2004), while another study did not observe BPA binding to PR at concentrations of up to 10 μM (Takayanagi et al. 2006).

Studies in non-human mammals *in vivo*

Information on study design and findings on the effects of BPA on PR expression in rodent *in vivo* studies is provided in Table J2.5 in Appendix J. Overall, these studies report mixed results for the effect of BPA exposure on expression of PR, with some studies reporting similar effects in specific tissues (e.g., mammary gland, ovaries, uterus, and certain brain regions), and other studies reporting either no effect, or opposite effects.

- Increased PR expression was observed in the epithelial compartment of mammary glands of mice exposed to BPA *in utero* (Munoz-de-Toro et al. 2005).
- PR expression was increased in the ovaries of PND21 mice exposed to BPA *in utero* but decreased at PND56 (Han et al. 2020; Wei et al. 2019a; Wei et al. 2020a).
- In the uterus of BPA-exposed mice, some studies reported increased PR expression (Berger et al. 2010; Markey et al. 2005), while another study observed no effects in PR mRNA expression (Toda et al. 2002).
- In pregnant mice treated with BPA, PR mRNA expression was increased in placenta with male embryos but decreased in placentae with female embryos (Imanishi et al. 2003).
- In ovariectomized adult female rats exposed to BPA, PR mRNA or protein levels were increased in various parts of the brain, such as the medial preoptic nucleus, preoptic area, anterior pituitary, ventromedial hypothalamic nucleus, and frontal cortex. Decreased PR mRNA expression was observed in the temporal cortex and no effects were observed in the parietal cortex or mediobasal hypothalamus (Funabashi et al. 2001; Funabashi et al. 2003; Funabashi et al. 2004).
- In male rats exposed to BPA *in utero*, PR levels were increased in the medial preoptic nucleus (Fahrenkopf and Wagner 2020) and in juvenile male rats exposed to BPA, PR mRNA expression was increased in the hypothalamus (Zhang et al. 2013).

- One study found increased PR protein levels in mammary glands of rats exposed to BPA *in utero* (Jenkins et al. 2009), while another study did not find differences in PR protein levels (Durando et al. 2011).
- In the uterus, PR mRNA expression was decreased in female rats (Varayoud et al. 2011) and juvenile ovariectomized rats (Diel et al. 2000) exposed postnatally. In another study, PR mRNA expression in the uterus of rats was significantly increased 4 and 8 hours after a single administration of BPA but not significantly different 24 hours after a single dose of BPA or three daily doses of BPA. Uterine PR protein levels were increased (between 1.4- to 11.2-fold) 4, 8, and 24 hours after a single treatment with BPA and 24 hours after three daily treatments (Ashby and Odum 2004).
- In gerbils exposed to BPA *in utero* and throughout lactation, increased PR positive cells were observed in mammary gland epithelium when measured by immunohistochemistry, however, no differences in PR expression were observed when measured by Western blotting (Leonel et al. 2020b).
- In adult female gerbils exposed to BPA during pregnancy, decreased PR expression was observed in normal, hyperplastic, and carcinomic regions of mammary glands (Ruiz et al. 2021).
- BPA treatment in ovariectomized African green monkeys did not affect PR mRNA expression in endometrial glands or stromal cells (Aldad et al. 2011).

In vitro studies of non-human mammalian cells

Expression of PR in non-human mammalian cells *in vitro* was primarily increased (see Appendix Table J2.6 for study details).

- PR mRNA and protein expression was increased in embryonic stem cells and mammary organoids from mice (Altamirano et al. 2020; Lee et al. 2019c).
- PR mRNA and protein expression was increased in rat pituitary tumor GH3 cells after treatment with BPA (Kim et al. 2012; Vo et al. 2012).

No effects were observed in sheep primary granulosa cells treated with BPA (Teteau et al. 2020).

5.3.8.4 Androgen receptor

Human observational studies

Three cross-sectional studies were conducted in humans that investigated correlations between BPA levels and expression of the androgen receptor (AR) (Caserta et al. 2013b; La Rocca et al. 2015; Melzer et al. 2011). All three studies measured BPA in serum or urine and AR expression in peripheral blood mononuclear cells (PBMCs) collected at the same time and are subject to the limitations described in Section 3.1.2.

- In a cross-sectional study conducted in Italy, AR expression was measured in PBMCs of 111 infertile women and 44 fertile women. Serum BPA levels significantly positively correlated with mRNA expression of AR in both infertile women (r = 0.444; p < 0.0005) and fertile women (r = 0.378, p < 0.05) (Caserta et al. 2013b).
- In another cross-sectional study in Italy, gene expression of AR was measured in 70 infertile men and 83 fertile men. Serum BPA levels significantly positively correlated with AR expression in both fertile men (r = 0.53; p < 0.05) and infertile men (r = 0.50; p < 0.05) (La Rocca et al. 2015).
- In a third cross-sectional study of 96 men in Italy, AR gene expression did not significantly correlate with urinary BPA levels (Melzer et al. 2011).

In vitro studies of human cells or transfected human AR

While several studies report the anti-androgenic activity of BPA on wild type AR, BPA has been shown to interact differently with certain mutant forms of AR found in prostate cancer (see Appendix Table J3.1 for study details).

- In several *in vitro* studies utilizing human or mammalian cell lines stably or transiently transfected with human AR, BPA exhibited anti-androgenic activity: decreasing dihydrotestosterone (DHT)-, testosterone (T)-, or R1881-induced AR luciferase activity with half maximal inhibitory concentrations (IC_{50}) values ranging from 0.318 to 19.6 µM (for example, studies by Doan et al. (2020), Grimaldi et al. (2019), Xu et al. (2005)).
- While some studies observed no agonistic activity for AR (for example, studies by Sun et al. (2006), Xu et al. (2005)), one study reported weak agonistic activity of BPA towards AR at 10 µM (Molina-Molina et al. 2013). A few studies did not find agonistic or antagonistic activity for AR (Gaido et al. 2000; Simon et al. 2016; Takayanagi et al. 2006).
- BPA also reduced AR translocation to the nucleus in transfected osteosarcoma U2OS cells (Teng et al. 2013) and in CHO-K1 cells transiently transfected with human AR (Huang et al. 2019).
- In MCF-7 or CV-1 cells transfected with wild type AR or AR-T877A, a mutant AR found in hormone-refractory prostate cancers, BPA activated AR-T877A luciferase activity, but not wild type AR (Wetherill et al. 2002). In another study utilizing various prostate cancer cell lines comparing wild type AR in LAPC-4 cells, mutant AR-T877A in LNCaP cells, or mutant AR-H874Y in 22Rv-1 cells, BPA alone weakly induced luciferase activity at the AR-responsive probasin target gene reporter in all three cell lines. When tested with DHT, BPA enhanced DHT-induced AR-T877A and AR-H874Y activation, but not wild type AR. Additionally, the induction of luciferase activity by DHT and BPA was blocked by

an AR antagonist Casodex, indicating an AR-specific effect (Wetherill et al. 2005).

Several studies investigated the effects of BPA on AR mRNA expression in human cells *in vitro*.

- Significant increases in AR mRNA expression were observed in human primary prostate epithelial cells while significant decreases were observed in human prostate fibroblast cells exposed to BPA (Wang et al. 2021c)
- Significant increases in AR mRNA expression were observed in TK6 lymphoblast cells (Chen et al. 2021).
- No differences in AR mRNA expression were observed in MCF-7 breast cancer cells after exposure to BPA (Diel et al. 2002).
- One study observed a significant decrease in AR protein levels in human Sertoli cells exposed to 20 µM BPA; however, these cells had decreased cell viability at this concentration (de Freitas et al. 2016).

Mammalian studies in vivo

Several studies performed in mammals exposed to BPA reported alterations in AR expression in brain, mammary, prostate, and reproductive tissues (see Appendix Table J3.2 for study details).

- AR mRNA expression was significantly increased in the hypothalamus of juvenile/adult-exposed rats (Zhang et al. 2013) and pituitary gland of *in utero*-exposed rats (Oliveira et al. 2017), while a few studies found no significant differences in AR mRNA expression in the hypothalamus (Kadir et al. 2021; Oliveira et al. 2017), pituitary (Kadir et al. 2021), or medial amygdala (Ubuka et al. 2018) following early life exposures.
- Decreased AR protein expression was observed in mammary glands of male offspring exposed to BPA *in utero* and throughout lactation (Kass et al. 2015).
- AR mRNA expression was decreased in the uterus with juvenile exposure (Diel et al. 2000) and in preantral, antral, and primary ovarian follicles in females, while protein expression was increased in primordial follicles with *in utero* and lactational exposure (Santamaría et al. 2016).
- AR mRNA or protein expression was decreased in testicular tissue in males exposed *in utero* and throughout lactation (Campos et al. 2019), postnatally (Salian-Mehta et al. 2014), or as juveniles and adults (Eshak and Osman 2014; Qiu et al. 2013). One study found no difference in AR mRNA expression in testes with adult exposure (Jin et al. 2013). AR protein expression was significantly increased in seminal vesicles (Williams et al. 2001) and caput epididymis (Abdel-Maksoud et al. 2018) of rats with early life exposure.

- Prostate AR protein expression was increased in orchiectomized male rats exposed to BPA as juveniles (Nishino et al. 2006). AR protein expression in the ventral prostate was increased with adult exposure (Wu et al. 2020b) and in two studies with *in utero* exposure (Bernardo et al. 2015); non-significantly increased (Brandt et al. 2014), while decreases were reported in ventral prostate stromal cells in two studies with *in utero* exposure (Ramos et al. 2001; Ramos et al. 2003).
- In male C57BL/6J mice exposed during adulthood, AR protein expression was significantly increased in the medial preoptic area of the brain, but no significant differences were observed in the medial amygdala or bed nucleus of the stria terminalis (a region of the forebrain) (Picot et al. 2014). In male ICR mice exposed as juveniles, decreased AR protein levels were observed in the amygdala and bed nucleus of stria terminalis (Wang et al. 2021c).
- In CD-1 mice exposed to BPA *in utero*, one study found decreased AR mRNA expression levels in mammary glands of female offspring at 8 months old, but not at 14 months old (Tucker et al. 2018).
- Another study found increased binding of prostate AR to Mibolerone, an AR agonist, in mice at PND21 and PND50 after *in utero* BPA exposure (Gupta 2000). A third study found a non-statistically significant decrease in testicular AR mRNA expression in males exposed early in life (*in utero* through PND31) (Chioccarelli et al. 2021).
- In studies conducted in gerbils, increased frequencies of AR positive cells were observed in normal, hyperplastic or neoplastic tissue in mammary glands of females exposed during pregnancy and lactation (Ruiz et al. 2021). In males exposed as adults, increased frequency of AR positive cells was observed in dorsolateral and ventral prostate lobes (Facina et al. 2018; Facina et al. 2021).
- In gerbils exposed *in utero*, decreased frequency of AR positive cells was observed in periurethral mesenchyme (male and female), smooth muscle layer (male), and epithelial buds (female) while increased frequency was observed in prostate epithelium and stroma (female) (Rodríguez et al. 2016). Decreased frequency of AR positive cells was also observed in prostatic epithelial cells of orchiectomized male gerbils (Colleta et al. 2017).
- In a study in New Zealand rabbits, BPA exposure *in utero* significantly decreased AR mRNA expression in fetal testicular tissue at GD27, but increased expression at PND3 (Ortega-García et al. 2021).
- BPA had no effect on AR mRNA expression in sheep placenta (Song et al. 2020a).

In vitro studies of non-human cells or transfected rodent AR

Few studies have examined the effects of BPA on AR in non-human cells or cells transfected with rodent AR *in vitro* (see Appendix Table J3.3 for study details).

- One study in mouse prostate urogenital sinus mesenchyme cells observed a significant increase in AR mRNA expression (Richter et al. 2007).
- No differences in AR mRNA expression were observed in mouse GC-2 spermatocytes (Sidorkiewicz et al. 2018).
- No differences in AR mRNA expression were observed in mouse 3T3-L1 preadipocytes (Phrakonkham et al. 2008).
- In HeLa cells transiently transfected with mouse AR, BPA exhibited antiandrogenic activity by partially inhibiting androgen binding to AR (Lee et al. 2003).
- In isolated SD rat Sertoli cells, AR protein levels were not significantly altered after BPA exposure (Izumi et al. 2011).
- In a cell free assay, BPA had weak binding affinity for recombinant rat AR (Kim et al. 2010b).

5.3.8.5 Testosterone

Human observational studies

OEHHA identified 38 human studies examining the relationship between BPA (in serum or urine) and serum concentrations of testosterone (T, including total, free or bioavailable[13]) or FAI (free androgen index, calculated as total T divided by sex hormone binding globulin). Results are briefly summarized by gender and medical conditions [*e.g.*, polycystic ovary syndrome (PCOS) or infertility] (see Appendix Table J4.1 for details). Detection of BPA's effects in humans is challenging because BPA levels were often measured in single serum or urine samples, collected at a single point in time. Single biological measurements of BPA are subject to the limitations described in Section 3.1.2 (*i.e.*, key issues in epidemiologic studies section). In addition, detection of any chemical's effects on T in humans is challenging because biosynthesis and metabolism of T is dynamic and complicated, affected by many pathways and enzymes (Schiffer et al. 2019). Overall, BPA levels are associated with increased T in females with PCOS. Findings on the relationship between BPA and T are inconsistent in other populations, or limited to a small number of studies, as are findings on the relationship between BPA and FAI.

[13] Bioavailable T refers to free T plus T weakly bound to serum albumin.

Women or girls with PCOS, girls with precocious puberty, or pregnant women

- In women or girls with PCOS, serum BPA was significantly associated/correlated with increased total T or free T in seven studies (Akin et al. 2015; Kandaraki et al. 2011; Kawa et al. 2019; Konieczna et al. 2018; Luo et al. 2020; Takeuchi and Tsutsumi 2002; Takeuchi et al. 2004), while urinary BPA was significantly correlated with decreased total T or free T in one study (Lazúrová et al. 2021). A significant positive correlation was observed between serum BPA and FAI in women with PCOS (Konieczna et al. 2018; Tarantino et al. 2013).
- In one study of girls with precocious puberty, higher BPA was significantly correlated with increased T (Lee et al. 2014).
- A non-significant negative association of urinary BPA with T was observed in one study of pregnant women (Aker et al. 2019).

Male partners in subfertile couples

- In male partners in subfertile couples, urinary BPA were significantly correlated with decreased total T in two studies (Den Hond et al. 2015; Shokry et al. 2020), but not in a third study (Meeker et al. 2010a), and a fourth study found no significant association of plasma BPA with total T (Vitku et al. 2016). A significant positive correlation was observed between urinary BPA and FAI in one of these studies (Meeker et al. 2010a), while no correlation between plasma BPA and FAI was reported in another (Vitku et al. 2016).

Children with ADHD

- In children (boys and girls) with attention-deficit/hyperactivity disorder (ADHD), no association was found between BPA and total T or free T (Tsai et al. 2020).

Children and adolescents

- In a study of boys (8–14 years old), no significant association between urinary BPA and total T or free T was observed (Ferguson et al. 2014). BPA was associated with statistically significant dose-dependent increases of T in adolescent girls (13–19 years old), dose-dependent decreases of T in adolescent boys, and no association in children (6–12 years old) from NHANES 2011–2012 survey (Scinicariello and Buser 2016). Two studies using different NHANES populations (2013–2016) both reported no significant associations in children or adolescents (Pollock et al. 2021; Wang et al. 2021f). Significant negative association between BPA and FAI was observed in female adolescents, but not in male adolescents or children (Wang et al. 2021f). No association of urinary BPA with T was found in pre-adolescent girls (Lee et al. 2013a). In boys (aged 9–11 years old), urinary BPA was significantly associated with dose-dependent increases of total T (Mustieles et al. 2018).

Maternal BPA exposure and association with T in infants, children, or adult men

- In newborn boys, maternal urinary BPA levels in the 3rd trimester were significantly associated with dose-dependent decreases of total T in cord blood, after adjustment for confounding variables (Liu et al. 2016a). Gounden et al. (2021) reported significant negative correlations between maternal or cord blood BPA (and BPA-G) and cord blood total T in newborn boys and girls. In another study of newborn boys and girls, no significant association was found between cord blood BPA and T, after adjusting for confounding variables (Minatoya et al. 2017). Wang et al. (2017b) reported significantly positive associations between BPA and T at 3 months after birth for all infants or female infants, but not males.
- Maternal urinary BPA in the 2nd trimester, but not in the 1st or 3rd trimester, was significantly associated with increased T in 8–13 years old girls, after adjusting for confounding variables (Watkins et al. 2017). In a study of 8–14 years old boys, no significant association between maternal urinary BPA in the 3rd trimester and total T or free T was observed (Ferguson et al. 2014).
- No association was found between maternal serum BPA and T in adult men (Hart et al. 2018).

Occupationally exposed male workers

- In male workers occupationally exposed to BPA, no correlation between serum or urinary BPA and total T was reported (Liu et al. 2015a; Zhou et al. 2013; Zhuang et al. 2015), and a significant negative association was observed between serum BPA and free T (Zhou et al. 2013). Urinary BPA was significantly associated with decreased FAI in occupationally exposed male workers (Liu et al. 2015a; Zhou et al. 2013).

Adults

- In men, urinary BPA was significantly associated with dose-dependent increases of total T and free T in one study (Lassen et al. 2014), significantly decreased free T or bioavailable T in one study (Manfo et al. 2019), and no significant association in four studies (Adoamnei et al. 2018; Liang et al. 2017; Mendiola et al. 2010; Takeuchi and Tsutsumi 2002). A significant negative correlation was found between BPA and FAI in fertile men in one study (Mendiola et al. 2010). No associations between BPA and T were reported in studies of men and women (average age: 61.8 years old) in China (Li et al. 2014), while Galloway et al. (2010) reported a significant positive association between BPA and total T in men after adjusting for confounding variables, and no association in women.

Human in vitro studies

Overall, human *in vitro* studies have found consistently decreased T levels after exposure to BPA (See Table J4.2 in Appendix J).

- Studies in primary fetal testes tissues obtained between gestation weeks 6 to 12 (Ben Maamar et al. 2015; Eladak et al. 2015; N'Tumba-Byn et al. 2012), human adult testes from prostate cancer patients (Desdoits-Lethimonier et al. 2017), and human adrenocortical carcinoma H295R cells (Feng et al. 2016; Wang et al. 2014b; Zhang et al. 2011) all reported that treatment with BPA significantly decreased T levels, compared to controls.
- One study in human ovarian granulosa KGN cells found no significant differences in T levels after exposure to BPA for 6 hours (Shi et al. 2021).

Mammalian in vivo studies

Information on study design and findings on the effects of BPA on T from non-human mammalian *in vivo* studies is provided in Table J4.3 in Appendix J.

- T levels in BPA-exposed male mice have also been shown to be consistently decreased. Several studies found significantly decreased serum, testicular, or brain testosterone levels in male mice exposed to BPA, either as adults or *in utero* [*e.g.*, (Chouhan et al. 2015; Hong et al. 2016; Xi et al. 2011; Xu et al. 2015b)], while two studies reported no effect on T (Shi et al. 2017a; Zou et al. 2020).
- Only one study reported an increase in T levels in mice one hour after a single *i.p.* injection of BPA (Song et al. 2002).
- Studies in female mice were less consistent, with some studies reporting no effect of BPA on T levels, and others reporting either increases or decreases.

Data on the effect of BPA on T levels in male rats is less consistent than in male mice.

- Some studies in male rats found significantly decreased levels of serum, plasma, or testicular T (Akingbemi et al. 2004; Cardoso et al. 2010; D'Cruz et al. 2012a; Jin et al. 2013), while other studies observed either significantly increased levels of T [*e.g.*, (Qiu et al. 2013; Watanabe et al. 2003)], or no significant differences after BPA exposure [*e.g.*, (Lee et al. 2013b; Wu et al. 2011)]. The effect of exposure to BPA on T levels in male rats may differ depending on the life stage at which exposure occurs, and the age at which T levels are assessed.
- The life stage of exposure and the studies in female rats reported inconsistent effects of BPA on T levels.
- One study in adult male New Zealand White rabbits found a significant and dose-dependent decrease in serum T levels (Karabulut and Gulay 2020) while in

another study in pregnant New Zealand rabbits, BPA exposure during gestation significantly increased serum T levels in offspring (Ortega-García et al. 2021).
- One study in adult male gerbils reported no effect on serum T levels (Facina et al. 2021).
- A study in field voles reported a significant increase in plasma T levels at the highest dose tested (Nieminen et al. 2002).

Mammalian in vitro studies

Information on study design and findings on the effects of BPA on T from non-human mammalian *in vitro* studies is provided in Table J4.4 in Appendix J.

- T levels were decreased after exposure to BPA in mouse fetal testes explants (Eladak et al. 2015; N'Tumba-Byn et al. 2012) and several studies with mouse TM3 Leydig cells [*e.g.*, (Goncalves et al. 2018; Jambor et al. 2019)]. One study found non-statistically significant increases in mouse primary Leydig cells (Savchuk et al. 2013) and another reported significantly increased T levels in mouse MA-10 Leydig tumor cells (Dankers et al. 2013) after exposure to BPA.
- In mouse primary antral follicles, T levels were significantly decreased when continuously exposed to BPA for 72 or 96 hours (Peretz and Flaws 2013).
- BPA treatment significantly decreased T levels in rat fetal testes explants (Ben Maamar et al. 2015; N'Tumba-Byn et al. 2012) but not adult explants (Ullah et al. 2018a).
- Decreased T levels were observed with BPA treatment in rat R2C Leydig tumor cells (Kim et al. 2010a) but not primary Leydig cells (Murono et al. 2001).
- Increased T levels were observed in rat seminiferous tubule explants (Chen et al. 2018b) and rat ovarian theca-interstitial cells treated with BPA (Zhou et al. 2008).

5.3.8.6 Thyroid hormones and thyroid hormone receptors

The relationship between thyroid hormones and various cancers has been demonstrated in many studies. Thyroid hormones such as triiodothyronine (T3) and thyroxine (T4) affect cancer cell proliferation, apoptosis, invasiveness, and angiogenesis, and mediate their effects through several pathways, as reviewed in Krashin et al. (2019). Hyperthyroidism may increase the risk of several cancers, while hypothyroidism may reduce aggressiveness of malignancies or delay the onset of cancer. Overall, increases in T3 or T4 are generally associated with increased risk of cancers, while decreases are associated with reduced risk of cancer, although these observations are not entirely consistent across different cancers (Krashin et al. 2019).

Human observational studies

The effects of BPA on thyroid hormones were measured in numerous human observational studies. All of the analyses were based on single biological measurements of BPA, which are subject to the limitations described in Section 3.1.2. The data are not consistent between studies. Differences in results may be due to different study designs (*e.g.*, timing and method of exposure assessment), study populations, or life stages (*e.g.*, pregnancy). Details of each study are given in Appendix Table J5.1, and will not be discussed further here.

In vitro studies of human cells or transfected human thyroid hormone receptor (TR)

Details of the *in vitro* studies in human cells or transfected human thyroid hormone receptor (TR) can be found in Appendix Table J5.2. Studies in human *in vitro* cells have reported antagonistic activity of BPA on T3-induced luciferase activity of TRα and TRβ transfected into TSA201 HEK293-derived cells (Moriyama et al. 2002), hepatocellular carcinoma HepG2 cells (Sun et al. 2008), CV-1 cells (Sheng et al. 2012; Sun et al. 2009) and Vero cells (Sun et al. 2012). Another study in transfected HepG2 cells found that BPA had agonistic and antagonistic activity towards TRβ at 1 μM (Hofmann et al. 2009). In ovarian COV434 cells, no differences in TRα mRNA expression were observed after exposure to BPA (Mlynarcikova and Scsukova 2020).

Mammalian studies in vivo

Overall, findings for the effect of BPA exposure on serum or plasma levels of T3, T4 and TSH were mixed in mammalian studies (See Appendix Table J5.3 for details).

- Findings for the effect of BPA exposure on serum or plasma T3 levels were mixed in studies in rats, with many reporting no effect, some reporting decreases, and one study reporting an increase. One study in adult male rats exposed early in life reported decreased T3 levels in the hippocampus and prefrontal cortex.
- Findings for the effect of BPA exposure on serum or plasma T4 levels were mixed in studies in rats, with some studies reporting increases, some reporting decreases, and some reporting no effect. One study each in mice and sheep reported decreases, and one study in voles reported an increase.
- Findings for the effect of BPA exposure on serum or plasma TSH were mixed in rats, with some studies reporting no effect, and some reporting increases.

In vitro studies of non-human cells

Several studies in rodent cells *in vitro* report effects of BPA on TR expression or activity (See Appendix Table J5.4 for details).

- In mouse isolated cerebellar granule cells, TRα and TRβ mRNA expression was significantly increased after BPA exposure (Jocsak et al. 2019).
- In rat isolated cerebellar cells TRα and TRβ mRNA expression was significantly decreased while TRα and TRβ protein levels were increased (Somogyi et al. 2016).
- In rat pituitary tumor GH3 cells, TRα and TRβ mRNA expression was significantly decreased (Lee et al. 2018c; Lee et al. 2017c).
- Two studies in rat GH3 cells reported that BPA had antagonistic activity by reducing T3-induced luciferase activity (Freitas et al. 2011), and inhibiting T3 binding to thyroid hormone receptor (Jung et al. 2007).
- In GH3 cells transfected with thyroid hormone response element (TRE), BPA significantly increased TR-mediated luciferase transcription (Zhang et al. 2018b), while weak binding activity of BPA to rat liver TR was reported in two studies (Kitamura et al. 2002; Moriyama et al. 2002).

5.3.8.7 Prolactin (PRL)

Human observational studies

Positive associations were observed between urinary BPA and prolactin levels in female workers (Hao et al. 2011; Miao et al. 2015) and male workers (Liu et al. 2015a) in China. Although there are difficulties in estimating long-term exposure to BPA (see Section 1.3), the fact that these workers were exposed to BPA at work for at least six months provides a known length of time with regular exposure. Miao et al. (2015) reported a significant positive association between urine BPA levels and prolactin in female workers, which remained statistically significant after adjusting for menstrual phase. Hao et al. (2011) reported higher prolactin levels in female workers exposed to BPA for at least one year compared to unexposed workers, as well as a significant association by logistic regression. The third study reported a positive association between urinary BPA and prolactin in male workers with occupational BPA exposure (Liu et al. 2015a).

In mother-child pairs in Japan, cord blood BPA was negatively associated with prolactin in male and female babies combined (Minatoya et al. 2017). No correlations were found in other populations (Li et al. 2014; Meeker et al. 2010a; Shokry et al. 2020; Tsai et al. 2020).

Studies in mammals in vivo

Several studies in rats reported increased serum PRL levels after exposure to BPA (see Appendix Table J6.1 for study details).

- Serum PRL levels were increased in several studies in both female and male rats treated with BPA (e.g., (Hao et al. 2011; Osman et al. 2021).
- Two studies reported decreases in serum PRL levels in female rats exposed to BPA *in utero* to adulthood or only in adulthood (Delclos et al. 2014; Srivastava and Dhagga 2019).
- A few studies reported no changes in serum PRL levels, e.g., in adult ovariectomized rats exposed to BPA either over several weeks (Maruyama et al. 1999) or administered a single *i.p.* injection of BPA and sacrificed 24 hours later (Furuta et al. 2006).

5.3.8.8 Other nuclear receptors, e.g., PPARα, PPARγ, PXR, CAR, and others

Other nuclear receptors have either been shown or hypothesized to be involved in mechanisms of cancer development or progression. For nuclear receptors such as the aryl hydrocarbon receptor (AhR), modulation of activity or expression contributes to carcinogenic phenotypes, such as cell invasion, migration, and survival (Wang et al. 2020d). Activation of peroxisome proliferator-activated receptor alpha (PPARα) and constitutive androstane receptor (CAR) are associated with liver tumor formation in rodents, but their mechanisms in human carcinogenesis remain unclear (Corton et al. 2018; Guyton et al. 2009; Lake 2018). Several other nuclear receptors, such as pregnane X receptor (PXR) and PPARγ, are hypothesized to have both pro- and anti-tumorigenic roles depending on tissue type or disease state (Pondugula et al. 2016; Youssef and Badr 2011). The section below summarizes data related to modulation by BPA of various nuclear receptors that may be relevant to carcinogenesis.

Human observational studies

Three cross-sectional studies were conducted in humans that investigated correlations between BPA levels and expression of various nuclear receptors (Caserta et al. 2013b; La Rocca et al. 2015; Soundararajan et al. 2019). All three measured BPA in serum and nuclear receptor expression in peripheral blood mononuclear cells (PBMCs) collected at the same time and are, therefore, subject to the limitations described in Section 3.1.2.

In a cross-sectional study conducted in Italy, levels of gene expression of nuclear receptors were measured in PBMCs of 111 infertile women and 44 fertile women (Caserta et al. 2013b) [preliminary results of this study were published in (Caserta et al. 2013a)]. Serum BPA levels significantly positively correlated with the mRNA expression of the pregnane X receptor (PXR; also known as steroid and xenobiotic receptor, or SXR) (r = 0.429; p < 0.0005), and aryl hydrocarbon receptor (AhR) (r = 0.335; p < 0.005), but not peroxisome proliferator-activated receptor gamma (PPARγ), in infertile women. BPA did not significantly correlate with PXR, AhR, or PPARγ expression in fertile women. In another cross-sectional study in Italy, gene expression levels of

nuclear receptors were measured in PBMCs of 70 infertile men and 83 fertile men (La Rocca et al. 2015). Serum BPA levels significantly positively correlated with AhR (r = 0.42; $p < 0.05$) and PXR (r = 0.61; $p < 0.05$) expression in fertile men. BPA levels also correlated with AhR (r = 0.50; $p < 0.05$) and PXR (r = 0.50; $p < 0.05$) expression in infertile men. BPA was not associated with PPARγ expression in fertile or infertile men. A third cross-sectional study conducted in India measured gene expression levels of nuclear receptors in PBMCs of 30 patients with type 2 diabetes and 30 participants with normal glucose tolerance (Soundararajan et al. 2019). Serum BPA levels significantly correlated with AhR expression (r = 0.304; p = 0.019), but not PPARγ expression in the study participants.

Studies using human cells in vitro, rodents in vivo, animal cells in vitro, and fish in vivo/ex vivo

This section summarizes the many studies conducted in human cells *in vitro*, rodents *in vivo,* animal cells *in vitro,* and fish *in vivo/ex vivo* for several nuclear receptors. The details for each of these studies are presented in Table J7.1 to Table J7.15 in Appendix J. A number of studies were identified that measured alterations in genes that are not specifically related to a single receptor and are not reported here, with the exception of data on PPAR response elements (PPREs), which may reflect activity of multiple PPARs (PPARα, PPARβ/δ, or PPARγ).

PPARα

See Appendix Tables J7.1–Table J7.3 and Table J7.15 for summaries of individual studies.

- Table J7.1: Effects of BPA exposure on PPARα in human cells *in vitro*
- Table J7.2: Effects of BPA exposure on PPARα in rodents *in vivo*
- Table J7.3: Effects of BPA exposure on PPARα in animal cells *in vitro*
- Table J7.15: Effects of BPA exposure on nuclear receptors in fish and other species *in vivo/ex vivo*

Nine studies have examined the effects of BPA on peroxisome proliferator-activated receptor α (PPARα) expression and activity.

- One study in a human hepatoma cell line reported that BPA induced peroxisome proliferator response element (PPRE) reporter gene expression, an indicator of either PPARα, PPARβ/δ, or PPARγ activation (Wang et al. 2010).
- In *in vivo* studies, BPA increased PPARα mRNA and protein levels in liver and testes of male Swiss albino mice exposed as adults (Sharma et al. 2019), and decreased mRNA levels in liver of male C57BL/6J mice exposed *in utero* (Long et al. 2021).

- In rats, BPA decreased PPARα protein levels in liver of female rats exposed beginning at 7 weeks of age for four weeks (Thabet et al. 2020), had no effect on mRNA levels in liver of female SD rats exposed prenatally and through lactation (Somm et al. 2009), and decreased mRNA levels in kidney of male SD rats exposed prenatally and through lactation (Hsu et al. 2019).
- In rodent cells *in vitro*, BPA significantly decreased PPARα mRNA levels in rat hepatoma FaO cells (Grasselli et al. 2013) and increased PPARα protein levels in mouse Leydig tumor cells (Gorowska-Wojtowicz et al. 2019).
- BPA exposure to gilthead sea bream juveniles increased PPARα mRNA levels in liver (Maradonna et al. 2015). In one molecular docking study, BPA was not predicted to bind to human PPARα with significant binding efficiency (Sarath Josh et al. 2014).

PPARγ

See Table J7.4– Table J7.6, Table J7.15 for summaries of individual studies.

- Table J7.4. Effects of BPA exposure on PPARγ in human cells *in vitro*
- Table J7.5. Effects of BPA exposure on PPARγ in rodents *in vivo*
- Table J7.6. Effects of BPA exposure on PPARγ in animal cells *in vitro*
- Table J7.15. Effects of BPA exposure on nuclear receptors in fish and other species *in vivo/ex vivo*

Overall, BPA can activate and/or increase the expression of PPARγ in several types of human cells *in vitro*, including primary adipocytes and cultured adipose tissue explants (Boucher et al. 2014; Wang et al. 2013a), adipose-derived stem cells (Ohlstein et al. 2014; Salehpour et al. 2020), ovarian cumulus granulosa cells (Pogrmic-Majkic et al. 2019), and transfected liver cells (Long et al. 2021).

- BPA weakly activated PPARγ in osteosarcoma cells in two studies (Pereira-Fernandes et al. 2013; Simon et al. 2016) and weakly inhibited activity in another (Dusserre et al. 2018).
- BPA inhibited PPARγ activity in a reporter gene assay in human embryonic kidney cells (Schaffert et al. 2021).
- BPA did not affect PPARγ expression in human bone marrow-derived mesenchymal stromal stem cells (Chamorro-Garci-a et al. 2012), endometrial stromal fibroblasts (Aghajanova and Giudice 2011), or ovarian serous carcinoma cells (Hoffmann et al. 2017), and had little effect on transfected hepatoma cells (Sui et al. 2012).
- In transfected kidney cells, macrophages, and hepatoma cells, BPA increased PPRE-luciferase activity, an indicator of PPARα, PPARβ/δ, or PPARγ activity (Gao et al. 2020b; Wang et al. 2010).

In rodents *in vivo,* BPA activated PPARγ and/or increased PPARγ expression in several studies.

- Increases in PPARγ mRNA levels were observed in the livers of male and female mice exposed to BPA *in utero* (Arroyo-Salgado et al. 2018; Long et al. 2021; Sharma et al. 2019), and male mice exposed *in utero* and continuing to PND140 (Biasiotto et al. 2016).
- In female rats exposed to BPA *in utero* and during lactation, PPARγ mRNA levels were increased in the parametrial white adipose tissue in one study (Somm et al. 2009) and decreased in the perigonadal and perirenal adipose tissue in another study (Zhang et al. 2014).
- PPARγ mRNA levels were decreased in pancreatic islet cells of male rats exposed to BPA as adults (Rahmani et al. 2020).
- PPARγ mRNA levels were decreased in the uterine arteries of female rats exposed to BPA before and during pregnancy (Barberio et al. 2021).
- In addition to the rodent studies, one study in gilthead sea bream juveniles reported an increase in PPARγ mRNA expression after BPA exposure (Maradonna et al. 2015).

BPA altered PPARγ mRNA levels in animal cells *in vitro.*

- PPARγ mRNA levels were increased in mouse fibroblasts (Longo et al. 2020) and mouse hypothalamic neurons (Salehi et al. 2019), and PPARγ was activated in mouse hepatoma cells (Simon et al. 2016).
- BPA exposure significantly increased PPARγ mRNA or protein levels at some concentrations and time points in mouse 3T3-L1 preadipocytes in six studies (Ahmed and Atlas 2016) (Ariemma et al. 2016; Héliès-Toussaint et al. 2014; Longo et al. 2020; Phrakonkham et al. 2008; Zhou et al. 2017a), and no alterations were observed in one study (Atlas et al. 2014).
- BPA significantly decreased PPARγ in rat hepatoma cells (Grasselli et al. 2013), and antagonistic activity was observed in cells transfected with polar bear PPARγ (Routti et al. 2016).
- Three studies transfected cells with PPREs, an indicator of PPARα, PPARβ/δ, or PPARγ activity.
- Two studies in mouse 3T3-L1 preadipocytes (Biasiotto et al. 2016) and one in COS-7 cells (Ahmed and Atlas 2016) observed an increase in PPRE-luciferase activity, while another in 3T3-L1 cells did not (Sargis et al. 2010).

AhR

See Appendix Table J7.7– Table J7.9, Table J7.15 for summaries of individual studies.

- Table J7.7. Effects of BPA exposure on AhR in human cells *in vitro*

- Table J7.8. Effects of BPA exposure on AhR in rodents *in vivo*
- Table J7.9. Effects of BPA exposure on AhR in animal cells *in vitro*
- Table J7.15. Effects of BPA exposure on nuclear receptors in fish and other species *in vivo/ex vivo*

There is some evidence that BPA can activate AhR or increase its expression based on human cells *in vitro*.

- In hepatocytes from three human donors, 10 μM BPA caused a slight increase in AhR mRNA levels in one donor and decreases in the other two; 100 μM BPA decreased mRNA levels in one donor, with no change in the other two (Vrzal et al. 2015).
- In human cell lines, BPA exposure increased AhR protein levels in one study using HepG2 cells expressing dioxin-response elements (DREs) (Yu et al. 2021) and did not alter AhR activity in another study in human breast cancer cells expressing DREs (Doan et al. 2020).

There is also evidence that BPA can increase AhR expression in animals *in vivo.*

- Male mice exposed to BPA *in utero* and through lactation demonstrated significantly increased AhR protein levels in the testis (Meng et al. 2018) and spleen (Gao et al. 2020a).
- *In utero* BPA exposure also increased AhR mRNA levels in cerebra, cerebella, testes, and ovaries of male and female mouse embryos at various doses and days of gestation (Nishizawa et al. 2005).
- Male rats exposed to BPA *in utero* and through lactation demonstrated an increase in AhR protein levels in the kidney (Hsu et al. 2019).
- In female zebrafish, BPA exposure significantly increased AhR1 mRNA expression levels in liver (Duan et al. 2013b).

Four studies measured AhR activity in mammalian cells *in vitro.*

- In mouse hepatoma cells *in vitro*, BPA inhibited AhR activity in one study (Bonefeld-Jorgensen et al. 2007), demonstrated borderline AhR agonism in another (Kruger et al. 2008), and had no effect in a third (Simon et al. 2016).
- BPA had no effect on AhR activity in rat hepatoma cells expressing DREs (Doan et al. 2020).

<u>PXR</u>

See Appendix Table J7.10, Table J7.11, and Table J7.15 for summaries of individual studies.

- Table J7.10. Effects of BPA exposure on PXR in human cells *in vitro*
- Table J7.11. Effects of BPA exposure on PXR in animal cells *in vitro*

- Table J7.15. Effects of BPA exposure on nuclear receptors in fish and other species *in vivo/ex vivo*

Evidence for the activation or increase in expression of PXR comes primarily from studies in human cells *in vitro*.

- In primary hepatocytes from three human donors, *in vitro* exposure to 10 µM BPA increased PXR mRNA levels above negative control in two donors, but decreased or did not alter PXR in the third donor and in all donors exposed to 100 µM BPA [statistical significance was not reported] (Vrzal et al. 2015).
- BPA exposure also induced PXR activity or expression in transfected hepatoma cells (Kuzbari et al. 2013; Sui et al. 2012; Takeshita et al. 2001; Yu et al. 2021), endometrial adenocarcinoma cells (Masuyama et al. 2005), transfected embryonic kidney cells (Vrzal et al. 2015), and transfected HeLa cells (Creusot et al. 2010; Grimaldi et al. 2019; Molina-Molina et al. 2013). In the transfected HeLa cells, BPA induced PXR activity up to 40% of the activity of the positive control (SR12813).
- BPA exposure increased PXR transcriptional activity in osteoblasts and osteoblast-like cells transfected with human PXR (Miki et al. 2016).
- PXR activity was significantly increased in COS-1 cells transfected with human PXR (DeKeyser et al. 2011).

No PXR studies were identified in rodents *in vivo*.

In animal studies conducted *in vitro*, there was no effect on PXR activity in transfected rat hepatoma cells (Kuzbari et al. 2013) and PXR-mediated transcription of the *Cyp3a1* reporter gene was not affected in transfected COS-7 cells (Masuyama et al. 2000).

In rare minnows, BPA exposure significantly increased PXR mRNA levels in females. In males, PXR mRNA levels were increased in groups exposed to 5 µg/l after 14 days, but decreased in groups exposed to 15 or 50 µg/l after 14 days and 5 or 15 µg/l after 35 days (Gao et al. 2014).

<u>Other Nuclear Receptors</u>

Overall, there are a limited number of studies available on the effects of BPA on these other nuclear receptors. Studies demonstrated increased, decreased, or no change in different cell types, without clear patterns. The following paragraphs present the available data for each receptor (see Appendix Table J7.12– Table J7.15 for more details and summaries of individual studies).

- Table J7.12. Effects of BPA exposure on Constitutive Androstane Receptor (CAR), Glucocorticoid Receptor (GR), Liver X Receptor (LXR), PPARβ/δ,

Retinoic Acid Receptor (RAR), and Retinoid X Receptor (RXR) in human cells *in vitro*
- Table J7.13. Effects of BPA exposure on LXR, PPARβ, RAR, RAR-related orphan Receptor (RoR), and RXR in rodents *in vivo*
- Table J7.14. Effects of BPA exposure on GR, LXR, and PPARβ/δ in animal cells *in vitro*
- Table J7.15. Effects of BPA exposure on nuclear receptors in fish and other species *in vivo/ex vivo*

CAR

- In primary hepatocytes from three human donors, CAR mRNA levels were increased following *in vitro* exposure to 10 and 100 μM BPA in one donor and to 10 μM in another donor; CAR mRNA levels were decreased in the third donor (Vrzal et al. 2015).
- BPA exposure decreased CAR protein levels, but did not alter transcription in human HepG2 cells (Yu et al. 2021).
- In COS-1 cells transfected with human CAR1, 2, or 3, *in vitro* BPA exposure increased CAR1 and CAR3 activity, but not CAR2 (DeKeyser et al. 2011).

GR

- BPA exposure to primary hepatocytes from three human donors decreased GR mRNA levels in two donors at each dose (10, 100 μM) (Vrzal et al. 2015).
- BPA exposure did not affect GR activity in two human breast cancer cell lines (Kolšek et al. 2015; Simon et al. 2016).
- In rodent cells *in vitro*, GR activity was significantly increased in mouse 3T3-L1 preadipocytes (Sargis et al. 2010).
- GR activity was not affected in transfected mouse fibroblasts (Atlas et al. 2014) or mammary organoids (Altamirano et al. 2020).
- In rainbow trout embryos, BPA exposure increased whole body GR protein levels (Birceanu et al. 2015).

LXR

- BPA did not alter LXRα activity in transfected human HepG2 cells (Sui et al. 2012).
- BPA exposure increased LXR mRNA levels at some doses and time points in male (Ji et al. 2020) and female (Gao et al. 2020b) mouse livers.
- In female ICR mice exposed during pregnancy, LXRα mRNA levels were increased in placentae with male, but not female, embryos (Imanishi et al. 2003).

- In mouse macrophages exposed to BPA *in vitro*, LXRα mRNA and protein expression were significantly increased, but no effects were observed on LXRβ mRNA levels (Ampem et al. 2019).

PPARβ/δ

- In human cells *in vitro*, BPA increased PPARβ/δ activity in HEK293 cells (Li et al. 2021b) and did not affect PPARβ/δ expression in ovarian cells (Mlynarcikova and Scsukova 2020).
- Wang et al. (2010) reported an increase in PPRE-luciferase activity in transfected human hepatoma cells, which is an indicator of PPARα, PPARβ/δ, or PPARγ activity and may not be specific to PPARβ/δ.
- In male mice *in vivo*, BPA exposure increased PPARβ mRNA and protein levels in the liver and testes (except for a significant decrease in PPARβ protein levels in the highest dose group) (Sharma et al. 2019).
- In animal cells *in vitro*, PPARβ levels were decreased in mouse Leydig tumor cells and PPARδ mRNA levels were decreased in rat hepatoma cells (Grasselli et al. 2013).
- One study in gilthead sea bream juveniles reported an increase in PPARβ mRNA expression after BPA exposure (Maradonna et al. 2015).

RARα

- BPA did not alter RARα activity in transfected human HepG2 cells (Sui et al. 2012).
- Exposure to 2 µg/kg-day BPA *in utero* increased RARα mRNA levels in cerebella of male and female mouse embryos, and decreased RARα mRNA levels in the cerebra of males and females and testes of males (Nishizawa et al. 2003).
- In another study, exposure to 0.02, 200, or 20000 µg/kg-day BPA exposure *in utero* increased RAR*α* mRNA levels in cerebra, cerebella, ovaries, and testes in male and female mouse embryos (Nishizawa et al. 2005).

ROR

- In female ICR mice exposed during pregnancy, RoRγ mRNA levels were decreased in placentae with female, but not male, mouse embryos (Imanishi et al. 2003).

RXR

RXR activation can lead to apoptosis; thus, inactivation or a decrease in expression may inhibit apoptosis and is relevant to carcinogenesis.

- No effect on RXR was observed in human cells *in vitro*, including hepatoma (HepG2) cells (Sui et al. 2012), ovarian granulosa tumor cells (Mlynarcikova and Scsukova 2020), and COS-7 cells transfected with human RXR (Chamorro-Garci-a et al. 2012).
- Alterations in mRNA levels in mouse embryos *in vivo* were affected by dose in two studies. Specifically, exposure to 2 µg/kg-day BPA *in utero* decreased RXR*α* mRNA levels in male embryo cerebra, cerebella, and testes, and in female embryo cerebella and ovaries (Nishizawa et al. 2003).
- *In utero* exposure to 200 or 20000 µg/kg-day BPA increased RXR*α* mRNA levels in some tissues in male and female mouse embryos (Nishizawa et al. 2005).
- In *Xenopus* tail cultures, RXRγ mRNA levels were slightly decreased after BPA exposure (Iwamuro et al. 2006).
- In freshwater snails, exposure to 100 or 500 µg/l caused a decrease in RXR mRNA levels after 24 or 48 hours, and an increase after 96 hours in the 500 µg/l dose group (Morales et al. 2018).
- One study in gilthead sea bream juveniles reported an increase in RXR mRNA expression in the liver after BPA exposure (Maradonna et al. 2015).

5.3.8.9 Summary of evidence for KC8

Estrogen receptor (ER)

BPA is a well-recognized xenoestrogen that is known to mimic and interfere with the actions of estrogen. There is a large body of evidence from observational studies in humans, human cells *in vitro*, and animal studies *in vivo* and *in vitro* indicating that BPA modulates ER-mediated effects through several different ER subtypes and their downstream signaling pathways. While it is well-known that BPA binds to cytosolic ERs and activates ER nuclear translocation and binding to estrogen response elements in DNA, additional ER-related activities of BPA have been identified.

These non-canonical ER activities of BPA may explain many observations that are unexpected solely based on the classical ER pathway, such as the rapid onset of extra-nuclear responses, the low-dose effects, and the non-monotonic dose-responses, with the latter two effects also echoing the female rat mammary tumor response seen in the CLARITY-BPA core study #3. For example, BPA's effects on membrane-associated estrogen receptors (mERs), G-protein coupled estrogen receptor (GPER/GPR30), and estrogen-related receptor gamma (ERRγ, an orphan nuclear receptor) may each alter different downstream genomic and non-genomic signaling pathways in a cell-type

specific fashion. In addition to these examples, BPA can also induce epigenetic changes to regulate the expression of ERα, and cancer-related ER target genes.

Estradiol (E2)

Positive correlations between BPA levels and E2 were found in some studies in subpopulations from human observational studies, such as male partners in subfertile couples, girls and female adolescents, and newborns, but the majority of studies were inconsistent. Overall, the effects of BPA on E2 levels in human cells *in vitro* and in non-human mammals *in vivo* were also inconsistent. In non-human mammalian cells *in vitro*, exposure to BPA decreased E2 levels in studies of mouse and rat ovarian granulosa cells or follicles, increased E2 levels in most studies of pig granulosa cells and in one study of sheep granulosa cells, and decreased E2 levels in one study of boar testes.

Progesterone and progesterone receptor (PR)

BPA exposure was associated with an increase in expression of PR in some *in vitro* studies in human cells and the majority of *in vitro* studies in non-human mammalian cells, while findings in human observational studies and *in vivo* studies in animals were inconsistent. No consistent effects of BPA exposure on progesterone levels were observed in humans or animals, or cells *in vitro*.

Androgen receptor (AR)

Some positive associations between AR and BPA levels were observed in human observational studies in women while inconsistent results were reported in men. BPA exhibited antiandrogenic activity on human AR and interfered with AR nuclear translocation in several human *in vitro* studies. Expression of AR in various tissues from mammalian *in vivo* studies performed in mice, rats, and gerbils were inconsistent. BPA also exhibited antiandrogenic activity on mammalian AR in a few studies while expression was either increased or not changed in mammalian *in vitro* studies.

Testosterone (T)

In human observational studies, a positive association between BPA exposure and T levels was observed in women and girls with polycystic ovary syndrome. No consistent findings between BPA and T were observed in other populations. In human *in vitro* studies, treatment with BPA decreased T levels in fetal and adult testes and adrenocortical carcinoma cells. In mammalian *in vivo* studies, BPA exposure consistently decreased serum, testicular, and brain T levels in male mice, but effects were inconsistent in female mice, male and female rats, and rabbits. In mammalian *in vitro* studies, the effect of BPA on T levels was inconsistent.

Thyroid hormones and thyroid hormone receptors (TRs)

In human cells *in vitro*, BPA exposure antagonized activity of TRβ in several cell lines (*e.g.*, kidney, liver), had some agonistic activity in one study in liver cells, and had no activity in a study of kidney cells. No associations between BPA and thyroid hormone levels were consistently observed in human observational studies or in rats *in vivo*. No consistent effects of BPA on TR expression were observed in non-human mammalian cells *in vitro.*

Prolactin

Some positive associations were observed between BPA and prolactin levels in observational studies of occupationally exposed men and women. One study found a negative association between cord blood BPA and prolactin levels, while no associations were seen in other populations. BPA exposure increased prolactin levels in several rat studies.

Other nuclear receptors

- PPARα: In animals *in vivo,* BPA altered PPARα mRNA or protein levels in mice, rats, and fish. In *in vitro* studies, BPA decreased PPARα mRNA levels in rat liver cells and increased PPARα protein levels in mouse Leydig tumor cells.
- PPARγ: BPA altered expression or activity of PPARγ in several types of human cells *in vitro,* rats and mice *in vivo,* and non-human animal cells *in vitro,* although there are no clear patterns. BPA levels were not correlated with PPARγ expression in human observational studies in men or women in Italy and India.
- AhR: In human observational studies, BPA levels were positively correlated with AhR expression in infertile women and men and fertile men, but not fertile women in Italy. A study in India reported a positive correlation of BPA levels with AhR expression. There is some evidence that BPA can activate AhR or increase its expression in human cells *in vitro,* in mice and rats *in vivo*, and in fish. Mixed results for AhR were found in mouse and rat cells exposed to BPA *in vitro*.
- PXR: BPA levels were positively correlated with PXR in human observational studies in infertile women and men and fertile men in Italy, but not fertile women. A number of studies of several types of human cells *in vitro* demonstrated that BPA activates or increases the expression of PXR. BPA increased PXR mRNA levels in female fish. In male fish, BPA increased PXR mRNA levels with short-term exposure and decreased levels after longer exposure. BPA did not affect PXR activity or transcription in animal studies *in vitro.*

5.3.9 Causes immortalization

Carcinogens have been shown to increase the frequency of cell transformation from normal to malignant phenotypes and increase such cells' capacity for tissue invasion (Smith et al. 2020). This process can occur through the epithelial-to-mesenchymal transition (EMT), in which altered expression of the ratio of epithelial (*e.g.*, E-cadherin) to mesenchymal (*e.g.*, vimentin) genes allows cells to detach and invade surrounding tissue, a key step towards tumor metastasis (Zeisberg and Neilson 2009). Additionally, carcinogens can alter key factors that lead to cell immortalization, such as decreasing cellular senescence markers (*e.g.*, p21, p53, etc), and maintaining or extending telomere length through activation of telomerase (Smith et al. 2020). Information on BPA identified through OEHHA's literature search relevant to this KC is summarized below.

Cell invasion

- In human endometrial stroma cells (HESCs), 10 and 100 nM BPA significantly increased ($p < 0.05$) cell invasion in a Matrigel Transwell assay after 48 hours (Wen et al. 2020). No effect was seen at 1 nM BPA.
- Significantly increased ($p < 0.05$) cell invasion was observed in human uterine myoma mesenchymal stem cells (hUM-MSCs) in a Matrigel invasion assay after exposure to 10 nM BPA for two weeks (Wang et al. 2013b).
- In RWPE-1 human normal prostate cells, 20 μM BPA exposure for 48 hours significantly increased ($p < 0.001$) the number of invasive cells in a Matrigel Transwell assay (Liu et al. 2020a).

EMT markers

- In BG-1 human ovarian cancer cells, significant increases ($p < 0.05$) in both *vimentin* (an intermediate filamentous protein involved in EMT) and *snail* (a key transcription factor during EMT, with functions such as repression of E-cadherin) mRNA expression were observed after exposure to 1 μM BPA for 6 or 24 hours. Significant increases ($p < 0.05$) in protein levels of vimentin, snail, and MMP-9 (also involved in EMT) were observed after 48 hours of exposure but not 24 hours (Kim et al. 2015). No effect was observed on the mRNA expression of another EMT maker, *slug.*
- Significant increases ($p < 0.05$) in *vimentin* and *snail* mRNA and protein levels and decreases in E-cadherin mRNA and protein levels were observed in human breast cancer MCF-7 cells exposed to 100 ng/ml BPA for 48 hours (Liu et al. 2015b). No effect was observed on the mRNA expression of another EMT marker, *slug*.

- In human SK-N-SH and SiMa neuroblastoma cells, vimentin and fibronectin (another intermediate filamentous protein involved in EMT) protein levels were increased after 48 hours of exposure to 1 nM BPA, as shown by western blot (not quantified) (Xiong et al. 2017).
- In Nthy-ori 3-1 human thyroid follicular epithelial cells, exposure to 0.1 or 333 μM BPA significantly (p <0.05) and dose-dependently decreased E-cadherin protein expression and increased N-cadherin and MMP-9 protein expression. The exposure duration was not reported (Li et al. 2021c).

Cell transformation

- Significant increases (p < 0.01) in cell transformation frequency were observed in Syrian hamster embryo (SHE) cells exposed to 50, 100, or 200 μM BPA relative to vehicle controls (Tsutsui et al. 1998).
- A concentration-dependent increase in transformation frequency was observed in SHE cells exposed to 25–200 μM BPA, with significant increases (p < 0.05) at 100 and 200 μM (Kanai et al. 2001).
- Exposure to up to 50 μg/ml BPA for 24 hours or up to 30 μg/ml BPA for 7 days did not significantly increase morphological transformation frequency in SHE cells relative to controls. The relative plating efficiency (RPE) at 50 μg/ml BPA for 24 hours was 44% and at 30 μg/ml for 7 days was 61%. At all other concentrations tested, RPE values were above 77% (LeBoeuf et al. 1996).
- BPA concentrations up to 60 μg/ml did not significantly increase the number of transformed colonies in SHE cells exposed for 7 days. The relative cloning efficiency (RCE) at 60 μg/ml BPA was 3% in one trial and toxic in a second trial. At 40 μg/ml BPA, RCE values ranged from 18% to 60%. At all other concentrations tested, RCE values were above 60% (Jones et al. 1988).
- BPA was tested in transformation assays performed in the A31-1-13 clone of BALC/c3T3 mouse embryonic fibroblast cells at concentrations of up to 0.263 mM. There was a significant transformation result in one trial (out of four) at 0.131 mM. The average cytotoxic LD_{50} for BALC/c3T3 cells was 0.147 mM (Matthews et al. 1993).

Cellular senescence markers

- In C4-2 human prostate cancer cells, significantly decreased (p < 0.05) $p21^{waf1}$ mRNA expression was observed after exposure to 0.1 nM BPA for 3 weeks (Ho et al. 2017b) .

Telomerase expression, activity, or telomere length

- One cross-sectional study found that higher urinary BPA levels (adjusted for creatinine) were associated with shorter relative telomere length (RTL) in

Lebanese adult females in a multivariate model adjusted for age and waist circumference (tertile 2: OR: 2.85; 95% CI: 1.34–6.10; tertile 3: OR: 2.97; 95% CI: 1.45–6.09; *p*-value for trend, 0.005). The association was not statistically significant when BPA levels and RTL were analyzed as continuous variables (β, –0.01; 95% CI: –0.03, 0.004). There was no association in males or in subjects overall (Awada et al. 2019b). Interpretation of these results is limited by the one-time measurement of urinary BPA and the cross-sectional study design (see Section 3.1.2 for a discussion of these issues).

- In human primary peripheral blood mononuclear cells (PBMCs), a significant decrease ($p < 0.01$) in telomerase activity was observed after exposure to 1 nM BPA for up to 24 hours, but not 10, 100, or 1000 nM. Telomerase reverse transcriptase (TERT, the catalytic subunit of telomerase) mRNA levels were not significantly altered after 6 or 24 hours of exposure. In a long-term exposure experiment, telomerase activity was significantly decreased ($p < 0.01$) in cultured human primary PBMCs after exposure to 1, 3, or 10 nM BPA for 22 days (Herz et al. 2017).
- In human CD8+ T lymphocytes, significant decreases ($p < 0.01$) in telomerase activity were observed after exposure to 0.3 or 3 nM BPA (but not 30 mM) for 24 hours. Significant decreases ($p < 0.01$) in telomere length and hTERT protein expression were observed after exposure to 3 nM BPA (but not 0.3 or 30 nM) for 49 days. No significant alterations in telomerase activity were observed in exposed CD4+ T cells (Tran et al. 2020).
- Significant increases ($p < 0.001$) in telomerase mRNA expression and activity were observed in human MCF-7 breast cancer cells exposed to 1 μM BPA for 24 hours. Significant increases ($p < 0.05$) in telomerase expression, but not activity, were also observed at 10 nM. No significant alterations in telomerase expression or activity were observed in human MDA-MB-231 breast cancer cells. No significant change in RTL was observed in either cell type after exposure to 10 nM or 1 μM BPA for 24 or 48 hours (Awada et al. 2020).
- In MCF-7 cells treated with 1 μM BPA for 24 hours, a significant increase ($p < 0.05$) in *hTERT* mRNA expression was observed (Takahashi et al. 2004).
- Significant increases ($p < 0.01$) in telomerase activity were observed after exposure to 10 ng/ml BPA for 48 or 72 hours in HepG2 human hepatoma cells (no change at 24 hours) (Xu et al. 2015a).

Summary of evidence for KC9

There are several studies available on BPA that provide information relevant to its potential to cause immortalization. Two studies reported that BPA is able to induce cell transformation in SHE cells, while two other studies in SHE cells and one in the A31-1-13 clone of BALC/c3T3 cells did not find significant alterations to cell transformation.

BPA was able to increase cell invasion in three human primary cell lines. Additionally, increases in mesenchymal cell markers were observed in three human cancer cell lines and one human epithelial cell line after exposure to BPA and one study observed a decrease in a cellular senescence gene in a human cancer cell line. In one cross-sectional study, higher urinary BPA levels were associated with shorter relative telomer length in adult women. Five studies characterized alterations to telomerase expression, activity, or telomere length after BPA exposure in human cells *in vitro*. Two studies performed in primary human cells found decreases in telomerase activity, *hTERT* mRNA expression, or telomere length after exposure to BPA, while three studies performed in human cancer cell lines found increases or no alterations in telomerase expression and activity.

5.3.10 Alters cell proliferation, cell death or nutrient supply

As reviewed in Smith et al. (2016); Smith et al. (2020), carcinogens may alter cell cycle control, stimulate uncontrolled cell proliferation and angiogenesis to increase vascularity, and enable the evasion of apoptosis. Examples of effects indicative of KC10 include increased cell proliferation and hyperplasia, decreased apoptosis, changes in growth factors, changes in energetics and signaling pathways related to cellular replication or cell cycle control, and increased angiogenesis.

This section discusses findings from both published reviews and some original studies of BPA conducted in human cells *in vitro*, and findings from studies of BPA conducted in rodents *in vivo*.

Human cells in vitro

Around two hundred studies that report effects of BPA relevant to KC10 in human cells *in vitr*o were identified. In addition, three reviews were identified that provide summaries on several KC10 effects observed in human cells *in vitro*: increased cell proliferation (Chapin et al. 2008; Gassman 2017), changes in signaling pathways related to cellular replication or cell cycle control (Nomiri et al. 2019), and alteration of apoptosis (Nomiri et al. 2019). Given the rich data on KC10 and the availability of reviews, findings from the three reviews are presented here, as well as some example findings from individual studies.

Cell proliferation

BPA at noncytotoxic concentrations has been shown to induce cell proliferation *in vitro* in many different types of human cell lines, including normal, immortalized and cancer cell lines. Findings from many such studies are presented in Table I of the review by Gassman (2017) and in Table 52 of the review by Chapin et al. (2008). Findings from

some studies conducted in non-cancer human cell lines are presented below, followed by findings from some studies conducted in human cancer cell lines. See Appendix K for a list of studies examining cell proliferation in MCF-7 cells and other human cancer cell lines. A number of studies reported no increase and others reported decreases in proliferation, indicating BPA's effect on cell proliferation may be impacted by cell type, BPA concentration, and other factors.

Non-cancer human cells

- Exposure to low-dose BPA (≤ 10 µM) increased cell proliferation in four types of cultured normal/immortalized human breast epithelial cells, *i.e.* HBL-100 (Wu et al. 2012), MCF10-A (Pfeifer et al. 2015), 184A1 (Pfeifer et al. 2015), and normal human mammary epithelial cells (Qin et al. 2012).
- Exposure to low-dose BPA promoted proliferation of normal human prostate fibroblasts (0.1, 1, and 10 nM) and epithelial (0.1 and 1 nM) cells in one study (Wu et al. 2020b), and slightly increased proliferation of human prostate epithelial cells in another study (Nomura et al. 2009).
- Exposure to BPA (100 µM) increased cell proliferation in normal human osteoblasts (hFOB 1.19) with stable transfection of steroid and xenobiotic receptor (SXR) (Miki et al. 2016).
- Exposure to BPA (2 µg/ml) increased cell proliferation in normal human umbilical vein endothelial (HUVEC) cells (Zheng et al. 2006).
- Exposure to low-dose BPA increased cell proliferation in an immortalized human oral keratinocyte (NOK-SI) cell line (10 nM BPA) (Almeida et al. 2021) and in another immortalized human keratinocyte (HaCaT) cell line (0.01–1 µM BPA) (Zhang et al. 2019).
- Exposure to low-dose BPA (1 nM) (Wu et al. 2013b) and BPA (50 and 100 µM) (Gassman 2017) increased cell proliferation in an immortalized human embryonic kidney (HEK293T) cell line.

Human cancer cell lines

- Reviews on cell proliferation of human prostate or breast cancer cells
    - As reviewed in Table I of Gassman (2017), two studies (Chepelev et al. 2013; Koong and Watson 2015) showed that BPA induced cell proliferation in LAPC-4 prostate cancer cells (> 0.001 nM).
    - As reviewed by Chapin et al. (2008), the effect of BPA on cell proliferation in human breast cancer MCF-7 cells has been extensively studied. Table 52 in Chapin et al. (2008) summarizes the findings from 23 studies in which BPA increased cell proliferation in MCF-7 cells.

- An additional 34 studies not included in the review by Chapin et al. (2008) showing BPA-induced MCF-7 cell proliferation were identified by OEHHA's literature searches, and a list of these studies is provided in Appendix K.
- Several studies identified BPA-induced cell proliferation in other types of human breast cancer cells: T47D cells, SkBr-3 cells, ZR-75-1 cells, and MDA-MB-231 cells, and breast cancer stem cell 3-dimensional mammospheres. A list of these studies is provided in Appendix K.
- More evidence on BPA-induced cell proliferation in other types of human cancer cells (*e.g.,* colon, liver, thyroid, lung, prostate, ovarian, endometrial, and cervical cancer cells) was reported in many studies, and a list of these studies is provided in Appendix K.

Inhibition of apoptosis

BPA has been shown to alter apoptosis signaling pathways and decrease apoptosis in several different human cancer cell lines. Some example findings are presented below.

- See Table 4 of the review by Nomiri et al. (2019), which summarizes some studies showing that low-dose exposure to BPA upregulates anti-apoptotic proteins and downregulates pro-apoptotic proteins in several types of cancer cells, but not in acute myeloid leukemia (AML) cells. For example, low-dose exposure to BPA results in:
    - Upregulation of Bcl-2 (an anti-apoptotic protein) and proliferating cell nuclear antigen (PCNA), and downregulation of p53, BAX (a pro-apoptotic protein), and Bim (a pro-apoptotic protein) in human breast cancer cells
    - Upregulation of Bcl-xL (an anti-apoptotic protein) in a human colon cancer cell line
    - Inhibition of Caspases 3, 7, and 9 in a human ovarian cancer cell line
    - Upregulation of pro-apoptotic proteins such as Fas, TRAIL, and Caspases 8 and 9 in a human AML cell line
- BPA decreased apoptosis and activated pro-survival signaling pathways such as PI3K/AKT/mTOR in human breast cancer cells (Dairkee et al. 2013; Goodson et al. 2011; Jenkins et al. 2009).
- Co-treatment with BPA and leptin inhibited Caspase-3 expression and activity in human ovarian OVCAR-3 cancer cells (Ptak et al. 2013).
- BPA inhibited apoptosis in human choriocarcinoma BeWo cells (Ponniah et al. 2015).

Signaling pathways related to cellular replication or cell cycle control

BPA has been shown to alter signaling pathways related to cellular replication or cell cycle control in several different human cancer cell lines. Some example findings are presented below.

- See Table 2 of the review by Nomiri et al. (2019), which summarizes studies showing that BPA alters cell growth and proliferation pathways in several human cancer cell lines. For example, exposure to low-dose BPA has been shown to
    - Activate or increase levels of cyclins, CDKs, and PCNA in multiple human breast cancer cell lines
    - Inhibit p53 and p21 activity in two human breast cancer cell lines
    - Increase phosphorylation of cyclin D1 and AKT in human BG-1 ovarian cancer cells
    - Upregulate p21 and p27, and downregulate cyclin D1 and ERK in human prostate cancer LNCaP cells
- Exposure to low dose BPA (1 μM) significantly increased cyclin D1 expression levels in a human breast epithelial HBL-100 cell line (Wu et al. 2012).
- Exposure to BPA activated cyclin D1 protein and increased the percentage of cells in S and G2 phases via estrogen receptor-mediated pathways in MCF-7 cells (Zhang et al. 2012).
- Exposure to BPA (9 μM) for 72 hours increased expression of cyclin D1 and CDK4 in a human SK-N-SH neuroblastoma cell line (Zheng et al. 2011).
- Exposure to BPA increased the expression of cyclin D1 and inhibited the expression of p21 via an estrogen receptor-dependent signaling pathway in MCF-7 cells (Lee et al. 2012).

Angiogenesis

Here are a few examples of studies that examined BPA's effect on angiogenesis:

- Exposure to BPA (10 nM and 1 μM) significantly increased the growth of HUVEC cells, increasing the number of segments and nodes of vessel-like structures in one study (Almeida et al. 2021), and the number and length of endothelial tubes in another study (Andersson and Brittebo 2012).
- Exposure to BPA (3 μM) upregulated genes important for vascularization and angiogenesis of the endometrium in normal human endometrial stromal cells, such as vascular endothelial growth factor B and C (*VEGFB* and *VEGFC*) (Reed et al. 2018).
- Exposure to BPA (1 μM) resulted in a 1.8-fold induction of VEGF compared to vehicle controls in the estrogen-sensitive breast cancer MELN cell line derived from MCF-7 cells (Buteau-Lozano et al. 2008).

Glycolysis-based energy production

- Low-dose BPA (10 nM) exacerbated the metabolic switch observed in human bladder cancer-associated fibroblasts (decreased mitochondrial metabolism and increased glycolytic metabolism), leading to greater acidification of the extracellular environment (Pellerin et al. 2021).
- BPA (250 and 500 nM) statistically significantly increased glucose uptake after 20 minutes of treatment (and also increased cell proliferation) in MCF-7 cells (Norberto et al. 2017).
- Low-dose BPA (1 and 10 nM) promoted glycolysis-based metabolism (and cell proliferation) in human ovarian OVCAR-3 cancer cells through the estrogen receptor α-mediated pathway (Shi et al. 2017b).

Rodent studies in vivo

BPA has been observed to induce hyperplasia and cell proliferation in multiple rodent studies *in vivo*, as summarized below.

Rats

- One-year stop-dose study in female rats (CLARITY-BPA core #1): There was a statistically significant increase in cystic endometrial hyperplasia in the uterus in the highest BPA-dosed rats and a statistically significant increase in thyroid C-cell hyperplasia in the lowest BPA-dosed rats (NTP 2018).
- One-year stop-dose study in male rats (CLARITY-BPA core #2): A statistically significant increase in hyperplasia in bone marrow myeloid cells was observed in the BPA 25 µg/kg-day dosed rats (NTP 2018).
- Two-year stop-dose study in female rats (CLARITY-BPA core #3): There were statistically significantly increases in cystic endometrial hyperplasia and hyperplasia in the pituitary pars distalis in BPA-treated rats (NTP 2018).
- Two-year stop-dose study in male rats (CLARITY-BPA core #4): There were statistically significantly increases in pituitary pars distalis hyperplasia, adrenal medulla hyperplasia, and spleen lymphoid hyperplasia in BPA-treated rats (NTP 2018).
- One-year continuous-dose study in female rats (CLARITY-BPA core #5): There were statistically significantly increases in uterine endometrial hyperplasia and vaginal epithelial hyperplasia in BPA-treated rats (NTP 2018).
- One-year continuous-dose study in male rats (CLARITY-BPA core #6): Hematopoietic cell proliferation in the spleen was increased in the highest BPA-dosed rats (NTP 2018).

- Two-year continuous-dose study in female rats (CLARITY-BPA core #7): There were statistically significantly increases in vaginal epithelium hyperplasia and thyroid follicular cell hyperplasia in BPA-treated rats (NTP 2018).
- Two-year Continuous-dose study in male rats (CLARITY-BPA core #8): There were statistically significantly increases in pituitary gland (*pars distalis*) hyperplasia, parathyroid gland hyperplasia, epithelial hyperplasia of the ventral prostate, and kidney transitional epithelium hyperplasia in BPA-treated rats (NTP 2018).
- In a 28-week study of male Sprague-Dawley rats, a non-significant increase in prostatic intraepithelial neoplasia (control, 1/9; BPA, 2/6) was observed in rats exposed as neonates to BPA (10 µg/kg-day) via *s.c.* injection on PND1, 3, and 5 (Ho et al. 2006).
- In F1 female Wistar rats (n = 5–15) exposed to BPA *in utero*, statistically significant increases in mammary ductal hyperplasia were observed at PND110 (control, 8.2%; BPA, 18%, $p < 0.05$) and PND180 (control, 3.2%; BPA, 16.2%, $p < 0.05$) when F0 dams were exposed to BPA (0, 25 µg/kg-day) via *s.c.* injection from GD8 to GD23 (Durando et al. 2007).
- In the 25-week study of F1 male Wistar rats (n = 5–7) exposed to BPA *in utero* and via lactation, no preneoplastic lesions were reported in thyroid, lung, liver, or thymus when F0 dams were exposed to BPA (0, 10000 ppm) in feed from preconception, and GD1 to PND21 (Takashima et al. 2001).
- In the 25-week study of F1 female Wistar rats (n = 6–7) exposed to BPA *in utero* and via lactation, no preneoplastic lesions were reported in thyroid, lung, liver, and thymus when F0 dams were exposed to BPA (0, 10000 ppm) in feed from preconception, and from GD1 to PND21 (Takashima et al. 2001).
- In 40 adult female albino rats treated with BPA by gavage (50 mg/kg-day for 90 days), significantly higher scores for PCNA-positive nuclei in the myometrial layers of treated animals (n = 10.38) were observed, as compared to controls (n = 1.5, $p < 0.001$) (Othman et al. 2016b).
- In F1 female Wistar-Furth rats (n = 4–6) exposed *in utero* when F0 dams were exposed to BPA (0, 2.5, 25, 250, 1000 µg/kg-day) via *s.c.* injection from GD9 to PND1, significant (3–4 fold, $p < 0.05$) increases in the incidence of hyperplastic ducts of the mammary gland were observed in each treated group compared to controls on PND50, and a significant increase in mammary hyperplastic lesions was observed in the low-dose BPA treated group compared to controls on PND95 ($p = 0.032$) (Murray et al. 2007).
- In the 400-day study of F1 female Wistar rats (n = 13–17) exposed *in utero* and via lactation when F0 dams were exposed to BPA (0, 25, 250, 500, 5000 µg/kg-day) via gavage from GD7 to PND22, a significant increase in mammary intraductal hyperplasia was observed in the BPA250 group compared to controls on PND400 ($p < 0.05$) (Mandrup et al. 2016).

Mice

- In the 18-month study of female CD-1 [Crl:CD-1(ICR) BR] mice (n = 16–23) exposed to BPA (0, 10, 100, 1000 µg/kg-day) via *s.c.* injection on PND1 to PND5, increases (not statistically significant) in oviduct progressive proliferative lesions (control, 0/18; BPA10, 3/23; BPA100, 3/20; BPA1000, 1/16) were observed (Newbold et al. 2007).
- In the 18-month study of F1 female CD-1 mice (n = 13–16) that exposed F0 dams to BPA (0, 0.1, 1, 10, 100, or 1000 µg/kg-day) via *s.c.* injection from GD9 to GD16, increases (not statistically significant) in oviduct progressive proliferative lesions (control, 0/16; BPA0.1, 1/13; BPA1, 1/12; BPA10, 3/13; BPA100, 3/13; BPA1000, 2/13) were observed (Newbold et al. 2009).
- In the 4-month study of female Balb/c mice (n = 5) exposed to BPA (0, 25 µg/kg-day) via gavage for 3 weeks, significant increases of lateral branches ($p = 0.0004$) and percentage of hyperplasia ($p = 0.03$) compared with the controls were observed in the mammary gland (Wang et al. 2014a).
- In the 3-month study of F1 female Balb/c mice (n = 20) exposed to BPA (0, 100, 1000 µg/kg-day) *in utero* and via lactation (by *s.c.* injections to F0 dams from GD1 to PND7), significant increases of endometrial adenomatous hyperplasia in the high-dose group compared with the controls (control, 2/20; BPA100, 5/20; BPA1000, 10/20, $p < 0.01$) and increases of endometrial atypical hyperplasia by trend (control, 0/20; BPA100, 3/20; BPA1000, 4/20, $p < 0.05$ by trend) were observed. Significant increases of ovarian cysts were observed in treated groups compared with the controls (control, 2/20; BPA100, 9/20, $p < 0.01$; BPA1000, 10/20, $p < 0.01$) (Signorile et al. 2010).
- In F1 female CD-1 mice (n = 8–11) exposed to BPA (0, 1000, 10000, 100000 µg/kg-day) *in utero* (by dosing F0 dams via gavage twice daily from GD10 to GD17), mammary gland terminal end buds (TEBs) were significantly increased (control, ~ 2 TEBs/gland; BPA10000, ~ 10 TEBs/gland; $p < 0.05$) at PND20. The percentage of mammary glands with undifferentiated TEBs was higher in all treated groups (control, 25%; BPA groups, > 50%) at 3 months (Tucker et al. 2018).
- In MMTV-erbB2/neu transgenic female mice (n = 5–17) exposed to BPA (0, 2.5, 25, 250, 2500 µg/l) in drinking water from 56 to 112 days of age, statistically significant increases in the cell proliferation index in mammary gland epithelial cells were observed at 25 µg/l and above ($p \leq 0.001$ for each of the three doses), with a dose-related trend from control to 25 µg/l. The mammary gland epithelial cells from animals in the two lower doses groups also had higher ratios of “cell proliferation: apoptosis”, with the ratio at 25 µg/l being statistically significantly higher than control ($p \leq 0.001$) (Jenkins et al. 2011).

An additional four studies, reviewed in Table 1 of Seachrist et al. (2016), reported positive findings:

- In F1 female SD rats exposed to BPA (0, 25–250 µg/kg-day) *in utero* (by dosing F0 dams orally from GD10 to parturition), an increased number of TEBs, TDs and lobular structures during mammary gland development was observed (Moral et al. 2008).
- In F1 male SD rats exposed to BPA (0, 25–250 µg/kg-day) *in utero* (by dosing F0 dams via gavage from GD12 to PND21), increased incidences of multifocal hyperplasia/dysplasia and PINs in prostate glands were observed (Brandt et al. 2014).
- In F1 male Long-Evans rats exposed to BPA (0, 25–250 µg/kg-day) *in utero* and via lactation (by dosing F0 dams orally from GD10 to GD21), an increase in the number of Leydig cells in the testes was observed (Nanjappa et al. 2012).
- In F1 female C56BL/6 mice exposed to BPA (0, 0.6 µg–1.2 mg/kg-day) *in utero* and via lactation (by dosing F0 dams orally from GD1 to PND24), an increased number of TEB in mammary glands was observed (Ayyanan et al. 2011).

Summary of evidence for KC10

BPA-induced cell proliferation has been observed in many studies using human cells *in vitro*. There are also studies reporting that BPA decreases apoptosis, increases glycolysis-based energy production, alters proteins involved in cellular replication or cell cycle control signaling pathways, and increases angiogenesis. A number of studies have reported that BPA induces hyperplasia, with observations in multiple organs in multiple strains of rats and mice.

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APPENDIX A. SELECT BPA BIOMONITORING STUDIES IN CALIFORNIA (2007–2020)

Table A1 Select urinary BPA biomonitoring studies in California (2007–2020)

Region (study name)	Participants with BPA analyses	Analyte(s) measured and limit of detection[a] (µg/l)	Detection frequency (%)	Geometric mean urinary BPA concentration	Reference
Northern and Central California[b]	Pregnant women, 2nd trimester (N = 112)	BPA, LOD = 0.5; BPA-G, LOD = 0.5; BPA-S, LOD = 0.025	total BPA: 100 free BPA: 88 BPA-G: 99 BPA-S: 75	2009–2011: Creatinine-adjusted values: total BPA 6.16 µg/g (95th pctl: 196.65 µg/g) free BPA: 0.21 µg/g (95th pctl: 1.61 µg/g) BPA-G: 6.77 µg/g (95th pctl: 249.76 µg/g) BPA-S: 0.62 µg/g (95th pctl: 80.35 µg/g)	Gerona et al. (2016)
San Francisco (MIEEP)	Pregnant women (N = 89)	BPA + deconjugated BPA-G and BPA-S, LOD = 0.20	NR	2010–2011: Uncorrected values: 1.25 µg/l (90th pctl: 4.85)	Biomonitoring California[e]
Southern California (FOX)	Firefighters (N = 101)	BPA + deconjugated BPA-G and BPA-S, LOD = 0.20	94.1	2010–2011: Uncorrected values: 1.58 µg/l (95th pctl: 11.9 µg/l; max 37.4 µg/l) Creatinine-adjusted values: 1.40 µg/g (95th pctl: 5.88 µg/g; max: 21.1 µg/g)	Biomonitoring California[e]; Waldman et al. (2016)
Central Valley (BEST-1)	Adults (N = 109)	BPA + deconjugated BPA-G and BPA-S, LOD = 0.200	89.9	2011–2012: Uncorrected values: 1.40 µg/l (95th pctl: 13.3 µg/l)	Biomonitoring California[e]

Region (study name)	Participants with BPA analyses	Analyte(s) measured and limit of detection[a] (µg/l)	Detection frequency (%)	Geometric mean urinary BPA concentration	Reference
Central Valley (BEST-2)	Adults (N = 218)	BPA + deconjugated BPA-G and BPA-S, LOD = 0.100	96.3	2013: Uncorrected values: 1.40 µg/l (95th pctl: 7.18 µg/l)	
Salinas (HERMOSA)[b]	Adolescent girls aged 14–18 (N = 100)	BPA + deconjugated BPA-G and BPA-S, LOD = 0.2	81.5	2013: Uncorrected values: 0.8 µg/l [ng/ml] (95th pctl: 5.9 µg/l [ng/ml]) Specific-gravity corrected values: 1.1 µg/g (95th pctl: 5.6 µg/g)	Harley et al. (2016); Smith et al. (2022)
Northern California (MARBLES)[b]	Pregnant women (N = 218)	BPA + deconjugated BPA-G, LOD = 0.8	Overall (2007–2014): 59 2007: 67 2008: 63 2009: 58 2010: 59 2011: 55 2012: 62 2013: 62 2014: 42	Overall (2007–2014): 1.0 µg/l [ng/ml] (95th pctl: 4.5 µg/l [ng/ml]) 2007: 1.44 µg/l [ng/ml] 2008: 1.31 µg/l [ng/ml] 2009: 1.25 µg/l [ng/ml] 2010: 1.14 µg/l [ng/ml] 2011: 1.03 µg/l [ng/ml] 2012: 1.13 µg/l [ng/ml] 2013: 1.14 µg/l [ng/ml] 2014: 0.78 µg/l [ng/ml]	Kim et al. (2021)
Los Angeles[b]	Adolescent and adult college students (N = 55)	BPA + deconjugated BPA-G and BPA-S, LOD NR, LOQ = 0.011	99.5 (reported for all samples from both California and China)	Unadjusted values: 2012: 0.56 µg/l [ng/ml] 2014: 0.75 µg/l [ng/ml] 2015: 0.57 µg/l [ng/ml] 2016: 0.64 µg/l [ng/ml] 2017: 0.54 µg/l [ng/ml] Specific-gravity corrected values: 2012: 1.36 µg/g 2014: 0.56 µg/g	Lin et al. (2020)

Region (study name)	Participants with BPA analyses	Analyte(s) measured and limit of detection[a] (µg/l)	Detection frequency (%)	Geometric mean urinary BPA concentration	Reference
				2015: 0.37 µg/g 2016: 0.45 µg/g 2017: 0.31 µg/g	
Los Angeles county (CARE-LA)	Adult women (N = 60)	BPA + deconjugated BPA-G and BPA-S, LOD = 0.100	46.7	2018: Uncorrected values: NA[d] (75th pctl: 0.756 µg/l; 95th pctl: 1.96 µg/l)	Biomonitoring California[e]
Riverside, San Bernardino, Imperial, Mono, and Inyo counties (CARE-2)	Adults (N = 151)	BPA + deconjugated BPA-G and BPA-S, LOD = 0.200	69.5	2019: Uncorrected values: 0.503 µg/l (75th pctl: 1.12 µg/l; 95th pctl: 3.19 µg/l)	
San Diego and Orange counties (CARE-3)[c]	Adults (N = 90)	BPA + deconjugated BPA-G and BPA-S, LOD = 0.100	82.2	2020: Uncorrected values: 0.287 µg/l (75th pctl: 0.598 µg/l; 90th pctl: 0.895 µg/l)	

BEST, biomonitoring exposures study; CARE-LA, California regional exposure study, Los Angeles county; CARE-2, California regional exposure study, region 2 (Riverside, San Bernardino, Imperial, Mono, and Inyo counties); CARE-3, California regional exposure study, region 3 (San Diego and Orange counties); FOX, firefighter occupational exposures project; HERMOSA, health and environmental research in make-up of Salinas adolescents; LOD, limit of detection; LOQ, limit of quantification; MARBLES, markers of autism risk in babies: learning early signs; max, maximum; MIEEP, maternal and infant environmental exposure project; NA, not available; NR, not reported; pctl, percentile

[a] If no limit of detection was reported, the limit of quantification is provided.

[b] Gerona et al. (2016), Lin et al. (2020), HERMOSA, and MARBLES studies were not part of the Biomonitoring California program.

[c] Study sample collection ended in March 2020 due to the COVID19 pandemic.

[d] Geometric mean not calculated given detection frequency of 46.7%.

[e] https://biomonitoring.ca.gov/, accessed July 2022.

APPENDIX B. LITERATURE SEARCH ON THE CARCINOGENICITY OF BISPHENOL A

Literature searches on the carcinogenicity of BPA were conducted mainly in December 2021. The goal was to identify peer-reviewed journal articles, print and digital books, reports, and gray literature that potentially reported toxicological and epidemiological information on the carcinogenicity of this chemical.

As described below, we used an approach similar to that recommended by the National Toxicology Program (NTP) Handbook for Preparing Report on Carcinogens (RoC) Monographs (NTP 2015).

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:

- Three submissions received during the data call-in period (January 28 – March 14, 2022) (https://oehha.ca.gov/proposition-65/comments/comment-period-request-relevant-information-carcinogenicity-bisphenol-bpa)

Primary Search Process

1) Data Sources

Table B1 lists the data sources that were searched to find information on BPA. The list is adapted from the recommendation by the NTP Handbook for Preparing Report on Carcinogens (RoC) Monographs (NTP 2015), based on availability and suitability for this topic.

Table B1 Biomedical literature databases used in primary literature search

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/)
National Technical Reports Library (NTRL) (https://ntrl.ntis.gov/NTRL/)

2) Search Term Identification

- The US EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) was used to identify synonyms for BPA. The PubMed MeSH database (https://www.ncbi.nlm.nih.gov/mesh/) was used to find subject headings and other index terms related to the chemical.
- The PubMed Cancer filter (https://www.nlm.nih.gov/bsd/pubmed_subsets/cancer_strategy.html) was used for cancer-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 2016) was used to identify search strategies for Human Epidemiology, Experimental Animals, ADME, Key Characteristics of Carcinogenesis, and Other Mechanistic concepts.
- Additional strategies for Key Characteristics of Carcinogenesis were drawn from those used by IARC (Barupal et al. 2021).

3) Primary Search Execution

Searches were executed in PubMed, Embase, Scopus, SciFinder-N, and NTRL in December 2021. Four separate searches were done in PubMed, Embase and Scopus. These searches were for:

- Human cancer studies
- Animal cancer studies
- ADME studies
- Studies on key characteristics of carcinogens and other mechanistic concepts.

The basic structure used for each search is shown in Table B2 through Table B5.

Table B2 Human cancer studies search structure (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	BPA terms
#2	Cancer terms (PubMed Cancer Filter)
#3	Human Epidemiological Study terms (RoC Strategy)
#4	#1 AND #2 AND #3

Table B3 Animal cancer studies search structure (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	BPA terms
#2	Cancer terms (PubMed Cancer Filter)
#3	Experimental Animals terms (RoC Strategy)
#4	#1 AND #2 AND #3

Table B4 ADME studies search structure (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	BPA terms
#2	ADME terms (RoC Strategy)
#3	#1 AND #2

Table B5 Studies on key characteristics of carcinogens and other mechanistic concepts search structure (PubMed, Embase, Scopus)

Search step	Search Concepts
#1	BPA terms
#2	Cancer terms (PubMed Cancer Filter)
#3	RoC Other Mechanistic strategy
#4	#1 AND #2 AND #3
#5	IARC Key Characteristics of Carcinogens strategy
#6	RoC Key Characteristics of Carcinogens strategy
#7	#1 AND (#5 OR #6)
#8	#4 OR #7

The searches were run first in PubMed. Then the search terms and syntax were 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 Table B6 and Table B7.

Table B6 Human cancer epidemiologic studies search structure (SciFinder-N)

Search step	Search Concepts
#1	BPA terms
#2	Limit to Journal Article
#3	Limit to human concept
#4	Limit to Database "CAplus"
#5	Search within results: epidemiology terms
#6	Search within results: cancer terms
#7	EXCLUDE Database Medline

CAplus (chemical abstract plus) is a database of chemical information that can be accessed via SciFinder-N.

Table B7 Animal studies search structure (SciFinder-N)

Search step	Search Concepts
#1	BPA terms
#2	Limit to Journal Article
#3	Limit to animal concept
#4	Limit to Database "CAplus"
#5	EXCLUDE Database Medline

CAplus, chemical abstract plus.

One search was run in the National Technical Reports Library. The basic structure used in the search is shown in Table B8.

Table B8 BPA and cancer-related data search structure (NTRL)

Search step	Search Concepts
#1	(BPA terms) AND (Cancer terms)

Results from all databases were uploaded to EndNote, maintaining separate libraries for each of the four concepts searched. Duplicates were removed. The results of the primary searches for BPA are shown in Table B9.

Table B9 BPA search results

Search	PubMed Results	Embase Results	Scopus Results	SciFinder-N Results	NTRL Results	Unique Results After Deduplication
Human cancer studies	235	325	270	14	0	527
Animal cancer studies	1536	1259	840	110	9	2390
ADME	2450	3848	2594	NA	0	4923
Studies on key characteristics of carcinogens and other mechanistic concepts	8530	10757	11990	NA	0	13086

NA, not applicable.

Other Data Source Searches

Several additional databases and websites of authoritative bodies were searched for data and additional references that may have been missed in the primary literature search.

Authoritative reviews and reports:

- International Agency for Research on Cancer (IARC) publications, including but not limited to IARC Monographs on the Identification of Carcinogenic Hazards to Humans (https://monographs.iarc.fr/)
- NTP publications, including but not limited to, technical reports, nominations for toxicological evaluation documents, RoC monographs, RoC background documents or monographs, and other NTP reports (https://ntp.niehs.nih.gov)
- US Environmental Protection Agency (US EPA) publications (https://www.epa.gov/)
- US Food and Drug Administration (US FDA) publications (https://www.fda.gov/)

- National Institute for Occupational Safety and Health (NIOSH) publications (https://www.cdc.gov/niosh/index.htm)

Other databases and web resources:

- Computational Toxicology (CompTox) Chemicals Dashboard, (https://www.epa.gov/chemical-research/comptox-chemicals-dashboard)
- Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles (https://www.atsdr.cdc.gov/toxprofiles/index.asp)
- PubChem BioAssay (National Library of Medicine) (https://www.ncbi.nlm.nih.gov/pcassay)
- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/)
- MalaCards (for gene functions) (https://www.malacards.org/)
- OMIM (for gene functions) (https://omim.org/)
- GeneCards (for gene functions) (https://www.genecards.org/)
- KEGG (for gene functions) (https://www.genome.jp/kegg/kegg2.html)
- CDC Public Health Genomics and Precision Health Knowledge Base (for gene functions) (https://phgkb.cdc.gov/PHGKB/phgHome.action?action=home)

Additional Focused Searches

In addition to the primary searches listed above, focused searches were conducted for exposure, and animal tumor pathology. Additional relevant literature was identified from citations of individual articles. Some relevant publications were also identified via updated PubMed search results after December 2021.

Exposure (section 1.2 and section 1.3)

Specific governmental databases were queried for information relevant to BPA production, sources, and exposure. BPA production volumes were identified from US EPA Chemical Data Reporting data (https://www.epa.gov/chemical-data-reporting/access-cdr-data, accessed on July 19, 2022). Quantities of BPA released or disposed by specific facilities were identified from US EPA Toxics Release Inventory data (https://www.epa.gov/toxics-release-inventory-tri-program, accessed on July 19, 2022). BPA levels in Californians and the general US population were identified, respectively, from Biomonitoring California summary data (https://biomonitoring.ca.gov/, accessed on July 19, 2022) and CDC's Fourth Report on Human Exposure to Environmental Chemicals, Updated Tables (https://www.cdc.gov/exposurereport/, accessed on July 19, 2022).

Additional focused literature searches were conducted in PubMed and Scopus to identify California-specific biomonitoring studies as well as California-specific studies reporting environmental levels of BPA.

Animal tumor pathology (section 5.2)

Focused searches were conducted using:

- Three pathology books:
  - IARC Pathology of tumors in laboratory animals: Volume 1, 1990, edited by Turusov VS and Mohr U;
  - Pathology of the mouse: edited by Maronpot RR, Boorman GA, and Gaul BW., 1999;
  - Boorman's Pathology of the Rat: edited by Suttie AW, Leininger JR, and Bradley AE., 2018.
- NTP's historical controls database (https://ntp.niehs.nih.gov/ntp/historical_controls/ntp2000_2020/r_hcrpt_allrte20201200.pdf; https://ntp.niehs.nih.gov/data/controls/index.html), and searching for information specific to species and tumor site/type.
- Historical control database by Charles River Laboratories (https://www.criver.com/sites/default/files/resources/CompilationofSpontaneousNeoplasticLesionsandSurvivalinCrlCD%C2%AESDRatsFromControlGroupsMarch2013.pdf)

Additional relevant literature was identified from citations in individual book chapters or articles.

Literature Screen Processes

Use of SWIFT (Sciome Workbench for Interactive Computer-Facilitated Text-mining) Active Screener (SWIFT AS)

Due to the large volume of literature on BPA identified from the primary searches (Table B9), SWIFT AS (Howard et al. 2020), which incorporates machine learning (i.e., artificial intelligence) was used as a tool to facilitate the initial screening of references from the primary searches. Five distinct SWIFT AS projects were created[14]:

- A pilot project was created that included just the references with first authors whose last names begin with the letter A or B (1259 references), from the "studies on key characteristics of carcinogens and other mechanistic concepts" searches. The pilot project included approximately one-tenth of the references identified in this search, as was used to fine tune the literature screening procedures in SWIFT AS.

[14] The numbers of references shown below for each project do not include the full sets of references selected and used as 'training seeds' in developing the project-specific AI models for screening in SWIFT AS.

- A project that included the remainder of the search results for “studies on key characteristics of carcinogens and other mechanistic concepts” (11780 references)
- A project that included all the search results for “human cancer studies” (511 references)
- A project that included all the search results for “animal cancer studies” (2389 references)
- A project that included all the search results for “ADME studies” (4889 references)

The five projects were completed between December 2021 to February 2022 (https://www.sciome.com/swift-activescreener/). In each of the five projects, two OEHHA scientists independently completed the screening for a decision to be made on each title and abstract, following predefined inclusion and exclusion criteria. This initial screening in SWIFT AS allowed for efficient initial literature inclusion and exclusion with the help of artificial intelligence.

Use of Health Assessment Workspace Collaborative (HAWC)

After initial screening in SWIFT AS, HAWC (https://hawcproject.org/about/) was used as a tool to further screen and tag the literature on the carcinogenicity of BPA, following the guidance provided in the NTP RoC Handbook (NTP 2015). Specifically:

- Importing the EndNote libraries into HAWC

Citations retrieved from the SWIFT AS screening projects were uploaded to EndNote libraries, and duplicates were removed. Next, these EndNote libraries were uploaded to HAWC for multi-level screening using specific inclusion and exclusion criteria. For example, certain citations identified by the literature search as epidemiological studies were later excluded, and the reasons for exclusion are provided in Appendix Table C2.

- Screening and tagging references

In Level 1 screening, each citation was first screened by at least one OEHHA scientist, based solely on titles and abstracts, to eliminate studies or articles that do not contain information on BPA on any of the key topics covered in this cancer hazard identification document, such as cancer studies in humans and animals, toxicokinetics, metabolism, genotoxicity, or other cancer-associated mechanisms. The level 1 screen was intended to identify all studies deemed to have a reasonable possibility of containing information that could be useful for the review process. Papers identified for inclusion during Level 1 screening were tagged in HAWC according to key topics. A paper can be assigned (or tagged) to one or more of the key topic(s). A positive response by only one of the reviewers was sufficient to pass a publication on to the next review level.

In Level 2 screening, the full papers were obtained for all citations that passed the Level 1 screen. These full papers were screened independently by at least one OEHHA scientist, using similar inclusion/exclusion criteria as was used in the Level 1 screening. However, Level 2 reviewers could make more accurate judgments about the relevance of the citations because they were reviewing the full text of the articles, 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 conducted and HAWC search results were updated if additional relevant studies in addition to those cited in the original set of publications ("secondary citations") were identified.

See Figure 5 for the overview of the HAWC literature screening results (literature tag tree) for the BPA HAWC project.

Use of Table Builder in the organization of epidemiologic data

Table Builder (Shapiro et al. 2018), a web-based application, was applied to systematically extract and analyze the data that were included in Section 3, Carcinogenicity studies in humans. Table Builder was also used as a custom-made database to generate Word tables in this document.

Summary

More than 4000 references, including peer-reviewed journal articles and government reports, were identified for inclusion through these search strategies. Among these, over 1300 references were cited in this document. See Figure 6 for the overall literature search and screening process employed for this HID.

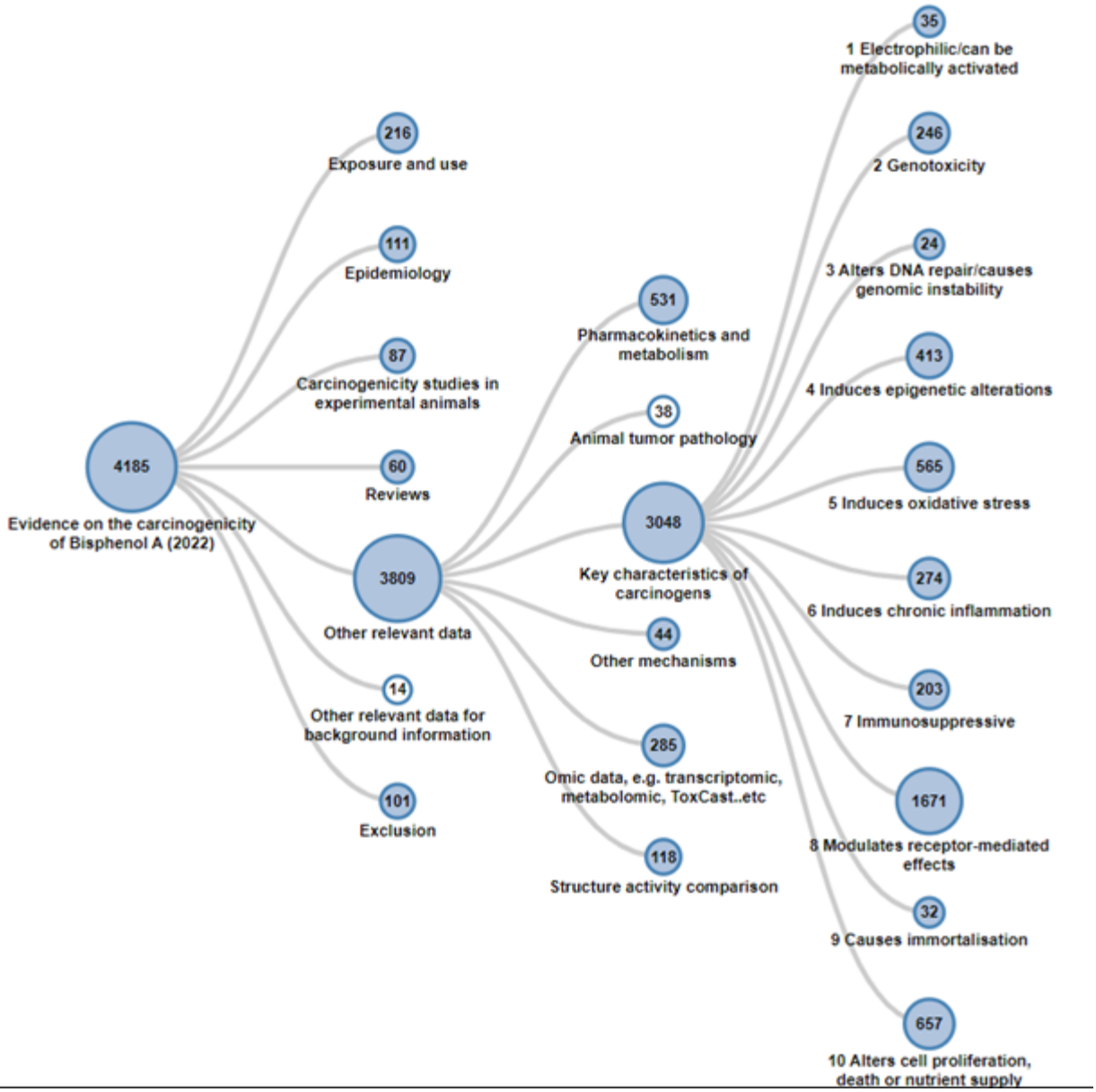

Figure 5 Overview of HAWC literature screening results (literature tag tree) for BPA (number of publications in each tag is labelled in the node)

Note: Tagging of references within most of these nodes was further refined. For example, the 111 references tagged in the epidemiology node include 25 references that were subsequently excluded, and 58 references that were subsequently identified as background or supporting references.

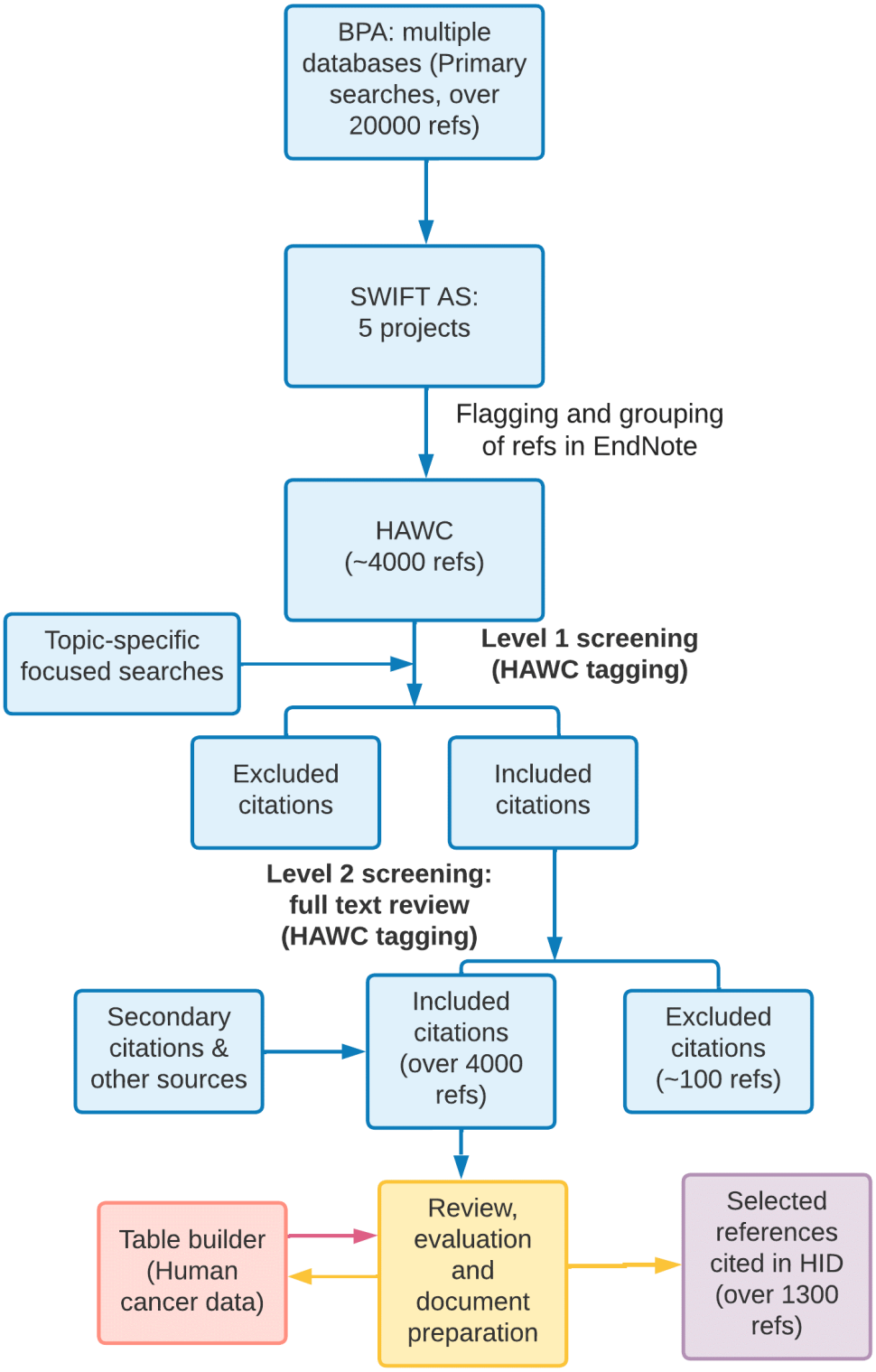

Figure 6 Overall literature search and screening process

(Refs, references)

Detailed PubMed Literature Search Strategies – Primary Searches

Table B10 PubMed search strategy for human cancer studies

Set #	Search Terms	Results	Concept Group
1	"Bisphenol A"[nm] OR 80-05-7[rn] OR 201-245-8[rn] OR "Bisfenol A"[tiab] OR "Bisphenol A"[tiab] OR "BPA"[tiab] OR "4,4'-(Propane-2,2-diyl)diphenol"[tiab] OR "4,4'-Propane-2,2-diyldiphenol"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-"[tiab] OR "2,2-Bis(4-hydroxyphenyl)propane"[tiab] OR "2,2-Bis(4'-hydroxyphenyl) propane"[tiab] OR "2,2'-Bis(4-hydroxyphenyl)propane"[tiab] OR "2,2-BIS-(4-HYDROXY-PHENYL)-PROPANE"[tiab] OR "2,2-Bis(p-hydroxyphenyl)propane"[tiab] OR "2,2-Di(4-Hydroxyphenyl) Propane"[tiab] OR "2,2-DI(4-HYDROXYPHENYL)PROPANE"[tiab] OR "2,2-Di(4-phenylol)propane"[tiab] OR "4,4'-(1-Methylethylidene)bisphenol"[tiab] OR "4,4'-Bisphenol A"[tiab] OR "(4,4'-Dihydroxydiphenyl)dimethylmethane"[tiab] OR "4,4'-DIHYDROXYPHENYL-2,2-PROPANE"[tiab] OR "4,4'-isopropilidendifenol"[tiab] OR "4,4'-Isopropylidendiphenol"[tiab] OR "4,4'-Isopropylidene bisphenol"[tiab] OR "4,4'-Isopropylidenebis[phenol]"[tiab] OR "4,4'-isopropylidenediphenol"[tiab] OR "4,4-ISOPROPYLIDENE DIPHENYL"[tiab] OR "4,4'-Methylethylidenebisphenol"[tiab] OR "Bis(4-hydroxyphenyl)dimethylmethane"[tiab] OR "BIS[PHENOL], 4,4'-(1-METHYLETHYLIDENE)-"[tiab] OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)-"[tiab] OR "Bisphenol-A"[tiab] OR "Bis(p-hydroxyphenyl)propane"[tiab] OR "Diphenol methylethylidene"[tiab] OR "Diphenylolpropane"[tiab] OR "Hidorin F 285"[tiab] OR "Isopropylidenebis(4-hydroxybenzene)"[tiab] OR "NSC 1767"[tiab] OR "NSC 17959"[tiab] OR "Parabis"[tiab] OR "Parabis A"[tiab] OR "Phenol, 4,4'-isopropylidenedi-"[tiab] OR "Pluracol 245"[tiab] OR "p,p'-Bisphenol A"[tiab] OR "p,p'-Dihydroxydiphenylpropane"[tiab] OR "p,p'-Isopropylidenebisphenol"[tiab] OR "p,p'-Isopropylidenediphenol"[tiab] OR "P,P'-ISOPROPYLIDENE DIPHENOL"[tiab] OR "Rikabanol"[tiab] OR "β,β'-Bis(p-hydroxyphenyl)propane"[tiab] OR 2444-90-8[rn] OR "Bisphenol A disodium salt"[tiab] OR "Disodium 4,4'-isopropylidenediphenolate"[tiab] OR "Disodium 4,4'-(propane-2,2-diyl)diphenolate"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, disodium salt"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, sodium salt (1:2) "[tiab] OR 94006-29-8[rn] OR "Barium(2+) 4,4'-isopropylidenebisphenolate"[tiab] OR "Barium 4,4'-(propane-2,2-diyl)diphenolate"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, barium salt (1:1)"[tiab]	13836	Bisphenol A Terms
2	cancer[sb]	6,886,274	PubMed Cancer Filter

Set #	Search Terms	Results	Concept Group
3	(("Epidemiologic Studies"[mh] OR "epidemiology"[sh] OR "Meta-Analysis"[pt] OR “Case Report”[pt] OR workmen*[tiab] OR Worker*[tiab] OR Seroepidemiologic-Stud*[tiab] OR retrospective-stud*[tiab] OR prospective-stud*[tiab] OR Mortality[tiab] OR longitudinal-stud*[tiab] OR follow-up stud*[tiab] OR ecological-study[tiab] OR ecological-studies[tiab] OR Cross-Sectional Stud*[tiab] OR Correlation-stud*[tiab] OR cohort*[tiab] OR case-control*[tiab] OR cancer-registr*[tiab] OR case-series[tiab] OR case-referent[tiab] OR record-link*[tiab])) OR ((metaanalysis[tiab] OR case-report[tiab] OR metaanalyses[tiab] OR meta-analysis[tiab]) NOT medline[sb])	5,550,034	RoC Human Epidemiological Studies Strategy
7	#1 AND #2 AND #3	235	Combine BPA + Cancer + Human Epi

Table B11 PubMed search strategy for animal cancer studies

Set #	Search Terms	Results	Concept Group
1	"Bisphenol A"[nm] OR 80-05-7[rn] OR 201-245-8[rn] OR "Bisfenol A"[tiab] OR "Bisphenol A"[tiab] OR "BPA"[tiab] OR "4,4'-(Propane-2,2-diyl)diphenol"[tiab] OR "4,4’-Propane-2,2-diyldiphenol"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-"[tiab] OR "2,2-Bis(4-hydroxyphenyl)propane"[tiab] OR "2,2-Bis(4'-hydroxyphenyl) propane"[tiab] OR "2,2'-Bis(4-hydroxyphenyl)propane"[tiab] OR "2,2-BIS-(4-HYDROXY-PHENYL)-PROPANE"[tiab] OR "2,2-Bis(p-hydroxyphenyl)propane"[tiab] OR "2,2-Di(4-Hydroxyphenyl) Propane"[tiab] OR "2,2-DI(4-HYDROXYPHENYL)PROPANE"[tiab] OR "2,2-Di(4-phenylol)propane"[tiab] OR "4,4'-(1-Methylethylidene)bisphenol"[tiab] OR "4,4'-Bisphenol A"[tiab] OR "(4,4'-Dihydroxydiphenyl)dimethylmethane"[tiab] OR "4,4'-DIHYDROXYPHENYL-2,2-PROPANE"[tiab] OR "4,4'-isopropilidendifenol"[tiab] OR "4,4'-Isopropylidendiphenol"[tiab] OR "4,4'-Isopropylidene bisphenol"[tiab] OR "4,4'-Isopropylidenebis[phenol]"[tiab] OR "4,4'-isopropylidenediphenol"[tiab] OR "4,4-ISOPROPYLIDENE DIPHENYL"[tiab] OR "4,4'-Methylethylidenebisphenol"[tiab] OR "Bis(4-hydroxyphenyl)dimethylmethane"[tiab] OR "BIS[PHENOL], 4,4'-(1-METHYLETHYLIDENE)-"[tiab] OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)-"[tiab] OR "Bisphenol-A"[tiab] OR "Bis(p-hydroxyphenyl)propane"[tiab] OR "Diphenol methylethylidene"[tiab] OR "Diphenylolpropane"[tiab] OR "Hidorin F 285"[tiab] OR "Isopropylidenebis(4-hydroxybenzene)"[tiab] OR "NSC 1767"[tiab] OR "NSC 17959"[tiab] OR "Parabis"[tiab] OR "Parabis A"[tiab] OR "Phenol, 4,4'-isopropylidenedi-"[tiab] OR "Pluracol 245"[tiab] OR "p,p'-Bisphenol A"[tiab] OR "p,p'-Dihydroxydiphenylpropane"[tiab] OR "p,p'-Isopropylidenebisphenol"[tiab] OR "p,p'-Isopropylidenediphenol"[tiab] OR "P,P'-ISOPROPYLIDENE DIPHENOL"[tiab] OR "Rikabanol"[tiab] OR "β,β'-Bis(p-hydroxyphenyl)propane"[tiab] OR 2444-90-8[rn] OR "Bisphenol A disodium salt"[tiab] OR "Disodium 4,4'-isopropylidenediphenolate"[tiab] OR "Disodium 4,4'-(propane-2,2-diyl)diphenolate"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-,	13836	Bisphenol A Terms

Set #	Search Terms	Results	Concept Group
	disodium salt"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, sodium salt (1:2) "[tiab] OR 94006-29-8[rn] OR "Barium(2+) 4,4'-isopropylidenebisphenolate"[tiab] OR "Barium 4,4'-(propane-2,2-diyl)diphenolate"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, barium salt (1:1)"[tiab]		
2	cancer[sb]	6885544	PubMed Cancer Filter
3	("Animals, Genetically Modified"[mh] OR "Animals, Inbred Strains"[mh] OR "Chimera"[mh] OR "Animals, Laboratory"[mh] OR "models, animal"[mh] OR animals[mh:noexp] OR "animal experimentation"[mh] OR "murinae"[mh]) OR ("animal stud*"[tiab] OR ape[tiab] OR apes[tiab] OR balb[tiab] OR bonobo*[tiab] OR bovine[tiab] OR C57[tiab] OR C57bl[tiab] OR callithrix[tiab] OR canis[tiab] OR capra[tiab] OR capuchin*[tiab] OR cat[tiab] OR cats[tiab] OR cattle[tiab] OR cavia[tiab] OR chicken[tiab] OR chickens[tiab] OR chimpanzee*[tiab] OR chinchilla*[tiab] OR cow[tiab] OR cows[tiab] OR cricetinae[tiab] OR "danio rerio"[tiab] OR equus[tiab] OR felis[tiab] OR ferret[tiab] OR ferrets[tiab] OR fish[tiab] OR "flying fox"[tiab] OR "Fruit bat"[tiab] OR gibbon*[tiab] OR goat[tiab] OR goats[tiab] OR guppy[tiab] OR horse[tiab] OR horses[tiab] OR jird[tiab] OR jirds[tiab] OR leontopithecus[tiab] OR "long-evans"[tiab] OR macaque*[tiab] OR marmoset*[tiab] OR medaka[tiab] OR merione[tiab] OR meriones[tiab] OR muridae[tiab] OR murinae[tiab] OR "Mustela putorius"[tiab] OR nomascus[tiab] OR "non human primate*"[tiab] OR orangutan*[tiab] OR "pan paniscus"[tiab] OR "pan troglodytes"[tiab] OR pig[tiab] OR piglet*[tiab] OR pigs[tiab] OR polecat*[tiab] OR quail[tiab] OR rhesus[tiab] OR rodent[tiab] OR rodentia[tiab] OR rodents[tiab] OR saguinus[tiab] OR sheep[tiab] OR sheeps[tiab] OR siamang*[tiab] OR "Sprague-Dawley"[tiab] OR swine[tiab] OR swines[tiab] OR symphalangus[tiab] OR tamarin*[tiab] OR vervet*[tiab] OR wistar[tiab] OR "wood mouse"[tiab] OR zebrafish[tiab]) OR ((boar[tiab] OR boars[tiab] OR dog[tiab] OR dogs[tiab] OR gerbil*[tiab] OR "guinea pig*"[tiab] OR hamster[tiab] OR hamsters[tiab] OR mice[tiab] OR monkey[tiab] OR monkeys[tiab] OR mouse[tiab] OR murine[tiab] OR "pongo pygmaeus"[tiab] OR rabbit[tiab] OR rabbits[tiab] OR rat[tiab] OR rats[tiab] OR sow[tiab] OR sows[tiab]) NOT medline[sb]) OR (("in vitro"[tiab] OR "in vitro techniques"[mh] OR "cell line*"[tiab]) AND "animals"[mh:noexp])	7472264	RoC Experimental Animal Studies Filter
4	#1 AND #2 AND #3	1,536	Combine BPA + Cancer + Animals

Table B12 PubMed search strategy for ADME

Set #	Search Terms	Results	Concept Group
1	(("Bisphenol A"[nm] OR 80-05-7[rn] OR 201-245-8[rn] OR "Bisfenol A"[tiab] OR "Bisphenol A"[tiab] OR "BPA"[tiab] OR "4,4'-(Propane-2,2-diyl)diphenol"[tiab] OR "4,4'-Propane-2,2-diyldiphenol"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-"[tiab] OR "2,2-Bis(4-hydroxyphenyl)propane"[tiab] OR "2,2-Bis(4'-hydroxyphenyl) propane"[tiab] OR "2,2'-Bis(4-hydroxyphenyl)propane"[tiab] OR "2,2-BIS-(4-HYDROXY-PHENYL)-PROPANE"[tiab] OR "2,2-Bis(p-hydroxyphenyl)propane"[tiab] OR "2,2-Di(4-Hydroxyphenyl) Propane"[tiab] OR "2,2-DI(4-HYDROXYPHENYL)PROPANE"[tiab] OR "2,2-Di(4-phenylol)propane"[tiab] OR "4,4'-(1-Methylethylidene)bisphenol"[tiab] OR "4,4'-Bisphenol A"[tiab] OR "(4,4'-Dihydroxydiphenyl)dimethylmethane"[tiab] OR "4,4'-DIHYDROXYPHENYL-2,2-PROPANE"[tiab] OR "4,4'-isopropilidendifenol"[tiab] OR "4,4'-Isopropylidendiphenol"[tiab] OR "4,4'-Isopropylidene bisphenol"[tiab] OR "4,4'-Isopropylidenebis[phenol]"[tiab] OR "4,4'-isopropylidenediphenol"[tiab] OR "4,4-ISOPROPYLIDENE DIPHENYL"[tiab] OR "4,4'-Methylethylidenebisphenol"[tiab] OR "Bis(4-hydroxyphenyl)dimethylmethane"[tiab] OR "BIS[PHENOL], 4,4'-(1-METHYLETHYLIDENE)-"[tiab] OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)-"[tiab] OR "Bisphenol-A"[tiab] OR "Bis(p-hydroxyphenyl)propane"[tiab] OR "Diphenol methylethylidene"[tiab] OR "Diphenylolpropane"[tiab] OR "Hidorin F 285"[tiab] OR "Isopropylidenebis(4-hydroxybenzene)"[tiab] OR "NSC 1767"[tiab] OR "NSC 17959"[tiab] OR "Parabis"[tiab] OR "Parabis A"[tiab] OR "Phenol, 4,4'-isopropylidenedi-"[tiab] OR "Pluracol 245"[tiab] OR "p,p'-Bisphenol A"[tiab] OR "p,p'-Dihydroxydiphenylpropane"[tiab] OR "p,p'-Isopropylidenebisphenol"[tiab] OR "p,p'-Isopropylidenediphenol"[tiab] OR "P,P'-ISOPROPYLIDENE DIPHENOL"[tiab] OR "Rikabanol"[tiab] OR "β,β'-Bis(p-hydroxyphenyl)propane"[tiab] OR 2444-90-8[rn] OR "Bisphenol A disodium salt"[tiab] OR "Disodium 4,4'-isopropylidenediphenolate"[tiab] OR "Disodium 4,4'-(propane-2,2-diyl)diphenolate"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, disodium salt"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, sodium salt (1:2) "[tiab] OR 94006-29-8[rn] OR "Barium(2+) 4,4'-isopropylidenebisphenolate"[tiab] OR "Barium 4,4'-(propane-2,2-diyl)diphenolate"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, barium salt (1:1)"[tiab]) NOT (Boronophenylalanine OR borophenylalanine OR "borono-L-phenylalanine ")	13486	Bisphenol A 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 (Skin[tiab] AND absorption[tiab]) OR (Oral[tiab] AND absorption[tiab]) OR (Injection[tiab] AND absorption[tiab]) OR (Gavage[tiab] AND	2982671	RoC ADME Terms

Set #	Search Terms	Results	Concept Group
	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]))		
3	#1 AND #2	2450	Combine BPA + ADME

Table B13 PubMed search strategy for key characteristics of carcinogens and mechanistic concepts

Set #	Search Terms	Results	Concept Group
1	(("Bisphenol A"[nm] OR 80-05-7[rn] OR 201-245-8[rn] OR "Bisfenol A"[tiab] OR "Bisphenol A"[tiab] OR "BPA"[tiab] OR "4,4'-(Propane-2,2-diyl)diphenol"[tiab] OR "4,4'-Propane-2,2-diyldiphenol"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-"[tiab] OR "2,2-Bis(4-hydroxyphenyl)propane"[tiab] OR "2,2-Bis(4'-hydroxyphenyl) propane"[tiab] OR "2,2'-Bis(4-hydroxyphenyl)propane"[tiab] OR "2,2-BIS-(4-HYDROXY-PHENYL)-PROPANE"[tiab] OR "2,2-Bis(p-hydroxyphenyl)propane"[tiab] OR "2,2-Di(4-Hydroxyphenyl) Propane"[tiab] OR "2,2-DI(4-HYDROXYPHENYL)PROPANE"[tiab] OR "2,2-Di(4-phenylol)propane"[tiab] OR "4,4'-(1-Methylethylidene)bisphenol"[tiab] OR "4,4'-Bisphenol A"[tiab] OR "(4,4'-Dihydroxydiphenyl)dimethylmethane"[tiab] OR "4,4'-DIHYDROXYPHENYL-2,2-PROPANE"[tiab] OR "4,4'-isopropilidendifenol"[tiab] OR "4,4'-Isopropylidendiphenol"[tiab] OR "4,4'-Isopropylidene bisphenol"[tiab] OR "4,4'-Isopropylidenebis[phenol]"[tiab] OR "4,4'-isopropylidenediphenol"[tiab] OR "4,4-ISOPROPYLIDENE DIPHENYL"[tiab] OR "4,4'-Methylethylidenebisphenol"[tiab] OR "Bis(4-hydroxyphenyl)dimethylmethane"[tiab] OR "BIS[PHENOL], 4,4'-(1-METHYLETHYLIDENE)-"[tiab] OR "BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)-"[tiab] OR "Bisphenol-A"[tiab] OR "Bis(p-hydroxyphenyl)propane"[tiab] OR "Diphenol methylethylidene"[tiab] OR "Diphenylolpropane"[tiab] OR "Hidorin F 285"[tiab] OR "Isopropylidenebis(4-hydroxybenzene)"[tiab] OR "NSC 1767"[tiab] OR "NSC 17959"[tiab] OR "Parabis"[tiab] OR "Parabis A"[tiab] OR "Phenol, 4,4'-isopropylidenedi-"[tiab] OR "Pluracol 245"[tiab] OR "p,p'-Bisphenol A"[tiab] OR "p,p'-Dihydroxydiphenylpropane"[tiab] OR "p,p'-Isopropylidenebisphenol"[tiab] OR "p,p'-Isopropylidenediphenol"[tiab] OR "P,P'-ISOPROPYLIDENE DIPHENOL"[tiab] OR "Rikabanol"[tiab] OR "β,β'-Bis(p-hydroxyphenyl)propane"[tiab] OR 2444-90-8[rn] OR "Bisphenol A disodium salt"[tiab] OR "Disodium 4,4'-isopropylidenediphenolate"[tiab] OR "Disodium 4,4'-(propane-	13475	Bisphenol A Terms

Set #	Search Terms	Results	Concept Group
	2,2-diyl)diphenolate"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, disodium salt"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, sodium salt (1:2) "[tiab] OR 94006-29-8[rn] OR "Barium(2+) 4,4'-isopropylidenebisphenolate"[tiab] OR "Barium 4,4'-(propane-2,2-diyl)diphenolate"[tiab] OR "Phenol, 4,4'-(1-methylethylidene)bis-, barium salt (1:1)"[tiab]) NOT (Boronophenylalanine OR borophenylalanine OR "borono-L-phenylalanine "))		
2	cancer[sb]	6897327	PubMed Cancer Filter
3	((("etiology"[sh] OR "Causality"[mh] OR "biomarkers, tumor"[mh] OR "oncogene fusion"[mh] OR"tumor necrosis factors"[mh] OR "adverse-outcome-pathway*"[tiab] OR "biological-marker"[tiab] OR "biological-markers"[tiab] OR "biomarkers"[tiab] OR "biomarker"[tiab] OR "Biotransformation"[tiab] OR "etiology"[tiab] OR "Key Event*"[tiab] OR "Mechanism-of-action"[tiab] OR "Mechanisms-of-action"[tiab] OR "Mode-of-action"[tiab] OR "modes-of-action"[tiab] OR "Molecular-Initiating-Event*"[tiab] OR "neoplastic-cell-transform*"[tiab] OR "Phosphorylation"[tiab] OR "Toxicity-Pathway*"[tiab] OR "toxicokinetic*"[tiab] OR "toxic-pathway*"[tiab]) AND (Cancer[sb])) OR ("tumor-inhibit*"[tiab] OR "tumor-promot*"[tiab] OR "tumour-inhibit*"[tiab] OR "tumour-promot*"[tiab] OR "Oncogenes"[tiab] OR "Oncogenesis"[tiab] OR "Oncogenic"[tiab] OR "pathogenesis"[tiab]))	3710816	RoC "Other Mechanistic" Search Strategy
4	#1 AND #2 AND #3	1244	Combine BPA + Cancer + Other Mechanistic

Set #	Search Terms	Results	Concept Group
5	(“Mutation”[Mesh] OR “Cytogenetic Analysis”[Mesh] OR “Mutagens”[Mesh] OR “Oncogenes”[Mesh] OR “Genetic Processes”[All Fields] OR “genomic instability”[MesH] OR chromosom*[All Fields] OR clastogen*[All Fields] OR “genetic toxicology”[All Fields] OR “strand break”[All Fields] OR “unscheduled DNA synthesis”[All Fields] OR “DNA damage”[All Fields] OR “DNA adducts”[All Fields] OR “chromatid”[All Fields] OR micronucle*[All Fields] OR mutagen*[All Fields] OR “DNA repair”[All Fields] OR “DNA fragmentation”[All Fields] OR “DNA cleavage”[All Fields]) OR (“rna”[MeSH] OR “epigenesis, genetic”[MesH] OR rna OR “rna, messenger”[MeSH] OR “rna”[All Fields] OR “messenger rna”[All Fields] OR mrna[All Fields] OR “histones”[MeSH] OR histones[All Fields] OR epigenetic[All Fields] OR miRNA[All Fields] OR methylation [All Fields]) OR (“reactive oxygen species”[MeSH Terms] OR “reactive oxygen species”[All Fields] OR “oxygen radicals”[All Fields] OR “oxidative stress”[MeSH Terms] OR “oxidative”[All Fields] OR “oxidative stress”[All Fields] OR “free radicals”[All Fields]) OR ((chronic[All Fields] AND “inflammation”[MeSH Terms]) OR (chronic inflamm*[All Fields])) OR (Immunosuppression[MH] OR “Killer Cells, Natural”[MH] OR “CD4-Positive TLymphocytes”[MH] OR immunosuppress*[tw] OR immune response*[tw] OR immune function*[tw] OR “immune status”[tw] OR “immune state*”[tw] OR “immune competence”[tw] OR “immune impairment”[tw] OR “immune dysregulation”[tw] OR “humoral immunity”[tw] OR “cell-mediated immunity”[tw] OR NK[tw] OR “Natural Killer”[tw] OR CD4[tw] OR “T4 Cell*”[tw] OR T4 Lymphocyte[tw]) OR (“Androgen Antagonists”[Mesh: NoExp] OR “Androgen Receptor Antagonists”[Mesh:NoExp] OR “Estrogen Antagonists”[MH] OR “Estrogen Receptor Modulators”[MH:NoExp] OR “Gonadal Hormones”[MH] OR “Thyroid Hormones”[MH] OR “Endocrine Disruptors”[MH] OR “Receptors, Steroid”[MH] OR “Receptors, Cytoplasmic and Nuclear”[MH] OR “Receptors, Aryl Hydrocarbon”[MH] OR Androgen* [tw] OR Estradiol[tw] OR Estrogen* [tw] OR Progesterone[tw] OR Testosterone[tw] OR thyroid[tw] OR “Endocrine disrupt*”[tw] OR “Peroxisome Proliferator-Activated Receptor”[tw] OR PPAR[tw] OR “constitutive androstane receptor”[tw] OR “farnesoid Xactivated receptor”[tw] OR “liver X receptor”[tw] OR “Retinoid X receptor”[tw] OR “Aryl hydrocarbon receptor”[tw] OR “Ah receptor”[tw]) OR (“Cell Transformation, Neoplastic”[MH:NoExp] OR “Cell Transformation, Viral”[MH] OR Telomere[MH] OR “Telomere Shortening”[MH] OR “Telomere Homeostasis”[MH] OR “cell transformation”[tw] OR “tumorigen transformation”[tw]	5817323	IARC Key Characteristics of Carcinogens Search Strategy

Set #	Search Terms	Results	Concept Group
	“tumorigenic transformation”[tw] OR “neoplastic transformation”[tw] OR “carcinogen transformation”[tw] OR “carcinogenic transformation”[tw] OR “viral transformation”[tw] OR immortalization[tw] OR Telomer* [tw]) OR (“Cell Proliferation”[MH] OR “DNA Replication”[MH] OR “Cell Cycle”[MH] OR Hyperplasia[MH] OR Metaplasia[MH:NoExp] OR “Neovascularization, Pathologic”[MH:NoExp] OR Apoptosis[MH] OR “Angiogenesis Modulating Agents”[MH:NoExp] OR “Angiogenesis Inducing Agents”[MH] OR “Heat-Shock Proteins”[MH] OR “Extracellular Matrix”[MH:NoExp] OR “Cell proliferation”[tw] OR “Cellular proliferation”[tw] OR “Cell multiplication”[tw] OR “Cell division”[tw] OR “Proliferative activity”[tw] OR “Sustained proliferation”[tw] OR “DNA replication”[tw] OR “DNA synthesis”[tw] OR “tumor growth”[tw] OR “neoplastic growth”[tw] OR “malignant growth”[tw] OR Hyperplasia[tw] OR Metaplasia[tw] OR “Apoptosis inhibition”[tw] OR Angiogenesis [tw] OR “heat shock protein”[tw] OR “extracellular matrix”[tw])		
6	(("adduct formation"[tiab] OR "DNA Adducts"[mh] OR "activation, metabolic"[mh] OR "dna breaks"[mh] OR "chromosome aberrations"[mh] OR "DNA fragmentation"[mh] OR "DNA Adduct*"[tiab] OR "electrophile"[tiab] OR "electrophilic"[tiab] OR "dna alkylating agent*"[tiab] 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 crosslinks"[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 aberrations"[tiab] OR "chromosomal abnormalit*"[tiab] OR "chromosome abnormalit*"[tiab] OR "genotoxic"[tiab] OR "SOS Response, Genetics"[mh] OR "Polyploidy"[mh] OR "Genomic Instability"[mh] OR "DNA Repair"[mh] OR "DNA end-joining repair"[mh] OR "DNA replication"[mh] OR "DNA topoisomerases"[mh] OR "Aneuploidy"[mh] OR ("DNA"[tiab] AND "Crosslink"[tiab]) OR "microsatellite instability"[tiab] OR "chromosomal instability"[tiab] OR "binucleation"[tiab] OR	6334191	RoC KC Search Strategy

Set #	Search Terms	Results	Concept Group
	"binucleated"[tiab] OR "ubiquitination"[mh] OR "Gene Expression Regulation"[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 "RNA, long noncoding"[mh] OR "CpG island Methylator"[tiab] OR "CpG island Methylation"[tiab] OR "epigenotype"[tiab] OR "epimutation*"[tiab] OR "methylation associated silencing"[tiab] OR "promoter methylation"[tiab] OR "methylated DNA"[tiab] OR "histone tail modifications"[tiab] OR "histone tail modification"[tiab] OR "chromatin organization"[tiab] OR "histone modification"[tiab] OR "epigenetic*"[tiab] OR "epigenomic*"[tiab] OR "rna interference"[tiab] OR "gene activation"[tiab] OR "proteasome"[tiab] OR "Free Radicals"[mh] OR "Reactive Oxygen Species"[mh] OR "reactive nitrogen species"[mh] OR "uncoupling agents"[mh] OR "metalloproteases"[mh] OR "Oxidative stress"[mh] OR "Oxidative phosphorylation"[mh] OR "Oxidative phosphorylation coupling factors"[mh] OR "Electron Transport"[mh] OR "Oxidative-damage*"[tiab] OR "reactive-nitrogen-species"[tiab] OR "superoxide-radical*"[tiab] OR "hydroxyl-radical"[tiab] OR "glutathione deplet*"[tiab] OR "C-reactive protein"[mh] OR "eosinophils"[mh] OR "Inflammation"[mh] OR "cell adhesion molecules"[mh] OR ("fibrinogen"[tiab] AND "Inflammation"[tiab]) OR "chronic inflammation"[tiab] OR "chronically inflamed"[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 "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 "immunosuppression"[mh] OR "immunosuppressive agents"[mh] OR "Immunologic Factors"[pa] 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 "Receptors, Aryl Hydrocarbon"[mh] OR "Transcriptional Activation"[mh] OR "Aryl hydrocarbon receptor*"[tiab] OR "receptor mediat*"[tiab] OR "transcription factor*"[tiab] OR "transcriptional activat*"[tiab] OR "Xenobiotic sensor*"[tiab] OR "xenosensor*"[tiab] OR "Ah receptor*"[tiab] OR "alternative lengthening of telomere*"[tiab] OR "cellular Immortalization"[tiab] OR "p53 inactivat*"[tiab] OR "p53 inhibit*"[tiab] OR "p53 delet*"[tiab] OR "pRb inactivat*"[tiab] OR "pRb inhibit*"[tiab] OR "pRb delet*"[tiab] OR "Rb/p16INK4a inactiv*"[tiab] OR "retinoblastoma protein"[tiab] OR "senescent"[tiab] OR "senescence"[tiab] OR "Angiogenesis Modulating Agents"[mh] OR "Angiogenesis		

Set #	Search Terms	Results	Concept Group
	Inducing Agents"[pa] OR "Angiogenesis Inducing Agents"[mh] OR "Neovascularization, Pathologic"[mh] OR "Cell Hypoxia"[mh] OR "angiogenic"[tiab] OR "cellular energetics"[tiab] OR "hypoxic cell*"[tiab] OR "cell hypoxia"[tiab] OR "cellular hypoxia"[tiab] OR "Apoptosis"[mh] OR "Cell death"[mh] OR "Cytotoxicity, Immunologic"[mh] OR "Caspases"[mh] OR "autophagy"[mh] OR "necrosis" [mh] OR "Autolysis"[mh] OR "survivin"[tiab] OR "Cytotoxin"[tiab] OR "Caspases"[tiab] OR "Cell Proliferation"[mh] OR "homeostasis"[mh] OR "Cyclin-Dependent Kinases"[mh] OR "Cyclin-Dependent Kinase Inhibitor Proteins"[mh] OR "mitogens"[mh] OR "Mitogens"[pa] OR "cell cycle control*"[tiab] OR "mitotic checkpoint*"[tiab] OR "hepatocellular proliferation"[tiab] OR "Cytogenesis"[tiab] OR "Cytogenic"[tiab] OR "cellular replication*"[tiab] OR "hyperplasia"[tiab] OR "Neoplasia"[tiab] OR "mitogenesis"[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] OR "gene silencer"[tiab] OR "gene silencing"[tiab] OR "deacetylation"[tiab] OR "DNA methylation"[tiab] OR "histone deacetylase*"[tiab] OR "ubiquitination"[tiab] OR "gene expression"[tiab] OR "microRNA*"[tiab] OR "miRNA*"[tiab] OR "non coding RNA*"[tiab] OR "SiRNA*"[tiab] OR "small inhibitory RNA*"[tiab] OR "Small interfering RNA*"[tiab] OR "electron transport chain*"[tiab] OR "reactive oxygen species"[tiab] OR "Oxidative stress*"[tiab] OR "free radical*"[tiab] OR "C reactive protein*"[tiab] OR "eosinophil*"[tiab] OR "autoimmunity"[tiab] OR "Immunomodulation"[tiab] OR "Immune modulation"[tiab] OR "cellular homeostasis"[tiab] OR "Cell Proliferat*"[tiab] OR "Cellular Proliferat*"[tiab] OR "cyclin dependent kinase*"[tiab] OR "mitogens"[tiab] OR "mitogen"[tiab] OR "Apoptosis"[tiab] OR "autophagy"[tiab] OR "necrosis "[tiab] OR "autolysis"[tiab] OR "angiogenesis"[tiab]) NOT medline[sb])		
7	#1 AND (#5 OR #6)	8417	Combine BPA + KCC (both)
8	#4 OR #7	8530	Other Mechanistic OR KCC

APPENDIX C. CARCINOGENICITY STUDIES IN HUMANS

Section C1 Tables for cancer sites with one study

Table C1 Epidemiologic studies for cancer sites with one study

Table C1: Endometrial cancer

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Sarink et al. (2021) Nested Case-Control Hawaii and California (Multiethnic Cohort) **Enrollment or follow-up:** 1993–1996	**Population:** Postmenopausal women from the Multiethnic Cohort Study Cases: 139; Controls: 139 **Exposure assessment method:** urine; BPA measured in a prospectively collected (2001–2006) single urine sample before case ascertainment (up to 2017). No measures to limit BPA contamination reported. Exposure proxy: total BPA following enzymatic hydrolysis, analyzed by LC-HRAMMS; creatinine adjusted. Samples below LOD were imputed as the LOD/2.	**Odds ratio, Categorized BPA (ng/mg creatinine)**			BMI, diabetes, Mediterranean Diet Score	**Exposure information:** Median BPA (IQR): 1.54 ng/mg creatinine (0.81–2.95) (controls); 1.62 ng/mg creatinine (1.01–2.93) (cases) **Strengths:** Urine samples prospectively collected before endometrial cancer diagnosis. **Limitations:** Single urine sample does not account for within-person variability over time and may limit ability to detect an effect. Exposure proxy may be affected by background contamination. LOD not reported. Within-batch variability in BPA analysis of 22%. Samples collected from postmenopausal women but time window of exposure susceptibility may occur much earlier.
		Tertile 1	1	44		
		Tertile 2	0.86 (0.44–1.67)	45		
		Tertile 3	1.21 (0.6–2.44)	50		
		Trend test *p*-value: 0.5				

Table C1: All cancer mortality

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Bao et al. (2020) Cohort United States **Enrollment or follow-up:** 2003–2008	**Population:** NHANES 3,883 **Exposure assessment method:** urine; BPA measured in single spot urine sample. No measures to limit BPA contamination reported. Exposure proxy: total BPA following enzymatic hydrolysis, analyzed by HPLC-MS/MS at the CDC; creatinine adjusted. Samples below the LOD were imputed as LOD/√2.	**All cancer mortality: Hazard ratio, Tertiles of BPA (mean ng/ml)**			Age, sex, race/ethnicity, urinary creatinine levels, educational level, family income status, smoking, alcohol drinking, physical activity, total energy intake, Healthy Eating Index 2010 score, BMI	**Exposure information:** LOD: 0.36 µg/l (ng/ml) (2003–2004 samples); 0.40 µg/l (ng/ml) (2005–2008 samples); Tertiles of urinary BPA (medians: 0.7, 2.1, 5.7 ng/ml) **Strengths:** Large sample size. Measured BPA in urine prior to outcome, with a median follow-up of 9.6 years. BPA analyses conducted by CDC laboratory. **Limitations:** No specific cancer sites were assessed. Single urine sample does not account for within-person variability over time and may limit ability to detect an effect. No QC measures reported.
		Tertile 1 (0.7)	1	31		
		Tertile 2 (2.1)	1.12 (0.48–2.63)	22		
		Tertile 3 (5.7)	0.98 (0.4–2.39)	22		

Table C1: Bone cancer: osteosarcoma

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Jia et al. (2013) Case-Control	**Population:** Patients at Union Hospital, Tongji	**Overall: Unadjusted odds ratio, BPA (µmol/mol creatinine)**			None	**Exposure information:** LOD: 0.5 ng/ml. Median BPA: 7.01 ng/ml.
		< 7.01	1	43		

Table C1: Bone cancer: osteosarcoma

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Wuhan, China **Enrollment or follow-up:** 2009–2011	Medical College, Huazhong University of Science and Technology, Wuhan, China. Cases: 106; Controls: 112 **Exposure assessment method:** urine; BPA measured in a single urine sample. No details reported on timing of sample. No measures to limit BPA contamination reported. Exposure proxy: BPA (analyte not specified, method reference not provided) analyzed by HPLC-MS. Creatinine adjusted. Samples below LOD imputed as 0.35 ng/ml (70% of LOD).	≥ 7.01	1.41 (1.01–1.72)	63		**Limitations:** Single urine sample does not account for within-person variability over time and may limit ability to detect an effect. No details on sample collection provided, including when samples were taken. BPA analyte is not specified and cannot be inferred from limited method details provided or referenced. Exposure proxy may be affected by background contamination. No QC measures reported. Did not control for any potential confounders. Small sample size for the interaction analysis.
		Hip: Unadjusted odds ratio, BPA (µmol/mol creatinine)				
		< 7.01	1	14		
		≥ 7.01	2 (1.3–3.17)	22		
		Knee: Unadjusted odds ratio, BPA (µmol/mol creatinine)				
		< 7.01	1	21		
		≥ 7.01	1.66 (1.14–2.49)	36		
		Other sites: Unadjusted odds ratio, BPA (µmol/mol creatinine)				
		< 7.01	1	5		
		≥ 7.01	1.22 (0.71–1.41)	8		
		Overall: Unadjusted odds ratio, BPA (µmol/mol creatinine), stratified by LOX -22G/C polymorphism				
		< 7.01, GG	1	33		
		≥ 7.01, GG	1.37 (1–7.15)	42		
		Overall: Unadjusted odds ratio, BPA (µmol/mol creatinine), stratified by LOX -22G/C polymorphism				
		BPA < 7.01, GC or CC	1	10		
		BPA ≥ 7.01, GC or CC	1.48 (1.06–7.37)	21		

Table C1: Lung cancer

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Li et al. (2020b) Case-Control Wuhan, China **Enrollment or follow-up:** 2016–2018	**Population:** Han Chinese patients at the Tongji Hospital of Huazhong University of Science and Technology, Wuhan, China. Cases: 615; Controls: 615 **Exposure assessment method:** urine; BPA measured in a single urine sample collected in polypropylene. No details reported on timing of sample. Exposure proxy: total BPA (without deconjugated BPA-S) analyzed by HPLC-MS. Use of procedure blanks, spiked samples, duplicates for accuracy. QC measures reported. Creatinine adjusted. BPA detected in 98.4% of controls and 97.2% of cases. Samples below LOD imputed as LOD/√2).	**Non-small cell lung cancer (NSCLC): Odds ratio, Quartiles of BPA (µg/g creatinine)**			Sex, age, smoking status, drinking status, BMI	**Exposure information:** LOD: 0.031 µg/l; LOQ: 0.063 µg/l Quartiles: < 0.39, 0.40–0.73, 0.74–1.32, >1.32 (µg/g creatinine) **Strengths:** Large sample size. BPA detected in 98.4% of controls and 97.2% of cases. Analyzed interaction of ESR1 gene polymorphism and BPA exposure. **Limitations:** A single spot urine sample collected after cancer diagnosis could not account for within person variability in BPA levels nor rule out reverse causation. Measure of total BPA excludes BPA-S.
		Q1 (≤0.39)	1	138		
		Q2 (0.40–0.73)	0.83 (0.58–1.17)	109		
		Q3 (0.74–1.32)	0.8 (0.57–1.14)	111		
		Q4 (>1.32)	1.91 (1.39–2.62)	257		
		Non-small cell lung cancer (NSCLC): Odds ratio, Quartiles of BPA (µg/g creatinine), by genotype				
		Q1, rs2046210 GG	1	44		
		Q2, rs2046210 GG	1.01 (0.53–1.94)	37		
		Q3, rs2046210 GG	0.7 (0.36–1.37)	27		
		Q4, rs2046210 GG	1.68 (0.94–3.01)	69		
		Non-small cell lung cancer (NSCLC): Odds ratio, Quartiles of BPA (µg/g creatinine), by genotype				
		Q1, rs2046210 GA + AA	1	77		
		Q2, rs2046210 GA + AA	0.65 (0.4–1.06)	51		
		Q3, rs2046210 GA + AA	1.22 (0.74–2.03)	56		
		Q4, rs2046210 GA + AA	3.02 (1.89–4.83)	132		

Table C1: Brain cancer

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Duan et al. (2013a) Case-Control Wuhan, China **Enrollment or follow-up:** 2009–2010	**Population:** Hospital-based case-control study at Union Hospital in Wuhan, China Cases: 247; Controls: 258 **Exposure assessment method:** urine; BPA measured in a single urine sample. No details reported on type of urine sample or timing of sample collection. No measures to limit BPA contamination reported. Exposure proxy: BPA analyzed by HPLC-MS.	**Meningioma: Odds ratio, Quartile of BPA (ng/ml)**			Sex, age, race, BMI, HRT use, family history of cancer	**Exposure information:** Quartiles of BPA: < 0.53, 0.54–0.91, 0.92–1.69, >1.69 ng/ml **Limitations:** A single spot urine sample collected after cancer diagnosis could not account for within person variability in BPA levels nor rule out reverse causation. Type of urine sample not specified. No adjustment of BPA measure for urine volume. Exposure proxy may be affected by background contamination. No QC measures reported.
		Quartile 1 (< 0.53)	1	NR		
		Quartile 2 (0.54–0.91)	1.4 (1.01–1.86)	NR		
		Quartile 3 (0.92–1.69)	1.45 (1.03–1.98)	NR		
		Quartile 4 (>1.69)	1.57 (1.12–2.09)	NR		
		Trend test *p*-value: 0.003				

Table C1: Lymphoma

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Costas et al. (2015) Case-Control Spain, France, Germany,	**Population:** Epilymph study, a multicenter case-control study carried out in six European countries	**Lymphoma: Odds ratio, Ever exposure to BPA**			Age, education, sex, country, exposure to other organic solvents	**Exposure information:** Exposed vs unexposed **Limitations:**
		Never	1	588		
		Ever	1.55 (0.78–3.08)	19		
		Multiple myeloma: Odds ratio, Ever exposure to BPA				
		Never	1	85		

Table C1: Lymphoma

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Italy, Ireland, Czech Republic **Enrollment or follow-up:** 1998–2004	Cases: 2178; Controls: 2457 **Exposure assessment method:** JEM; Three experts assigned exposure by job title based on probability that occupational exposure exceeded a background level, based on their expertise and an existing bank of coded jobs, with exposure status defined as 'unlikely', 'possible', and 'probable'. Exposure assignment was blind to the case-control status.	Ever	1.36 (0.37–4.99)	3		Low power since very few participants were exposed to BPA. Did not account for non-occupational exposure. Non-differential exposure misclassification is possible, which would likely attenuate risk estimates towards the null.
		Follicular lymphoma: Odds ratio, Ever exposure to BPA				
		Never	1	102		
		Ever	1.92 (0.53–6.95)	3		
		Diffuse large B-Cell lymphoma: Odds ratio, Ever exposure to BPA				
		Never	1	196		
		Ever	1.85 (0.73–4.68)	7		
		Chronic lymphocytic leukemia: Odds ratio, Ever exposure to BPA				
		Never	1	119		
		Ever	1.12 (0.35–3.57)	4		
		Hodgkin's lymphoma: Odds ratio, Ever exposure to BPA				
		Never	1	128		
		Ever	1.46 (0.36–5.89)	3		

Table C1: Eye cancer: uveal melanoma

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Behrens et al. (2012) Case-Control Denmark,	**Population:** Study of Occupational Causes of Rare Cancers of Unknown Aetiology: comprised of the	**Uveal melanoma: Odds ratio, Occupational exposure to BPA**			Country, sex, age, eye color, history of ultraviolet radiation ocular damage	**Exposure information:** Exposed vs unexposed
		Unexposed	1	NR		
		Ever exposed	0.67 (0.29–1.56)	6		

Table C1: Eye cancer: uveal melanoma

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Latvia, France, Germany, Italy, Sweden, Spain, Portugal, UK **Enrollment or follow-up:** 1994–1997	national populations of Denmark and Latvia; the population of certain administrative regions in France, Germany, Italy, and Sweden; hospital recruitment areas in Spain and Portugal; and a small non-representative sample from an eye clinic in the UK. Cases: 280; Controls: 3084 **Exposure assessment method:** JEM; Using job specific questionnaires, occupational exposure was characterized using a weighted exposure score calculated by combining exposure duration, exposure intensity, and exposure probability as determined by personal protective equipment use.	Ever exposed, excluding cancer controls and UK subjects	0.96 (0.4–2.27)	6		**Limitations:** Analyses based on few exposed subjects. Did not account for non-occupational exposures. Non-differential exposure misclassification is possible, which would likely attenuate risk estimates towards the null. No clear distinction between iris and ciliary melanoma was made for some cases.

Table C1: Extrahepatic bile duct/gallbladder cancer

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI)	Exposed cases/ deaths	Co-variates controlled	Comments, strengths, and limitations
Ahrens et al. (2007) Case-Control Denmark, France, Germany, Italy, Spain, Sweden **Enrollment or follow-up:** 1995–1997	**Population:** International multicenter case-control study in 6 European countries Cases: 183; Controls: 1938 **Exposure assessment method:** JEM; using job specific questionnaires, exposure was quantified by exposure duration, exposure intensity, and exposure probability as determined by protective equipment use. Exposure assessment was blinded with respect to case–control status.	**Gallbladder carcinoma, cancer of the extrahepatic bile duct, or cancer of the ampulla of Vater: Odds ratio, Occupational exposure to BPA**			Age, country, gallstones	**Exposure information:** Exposed vs. unexposed **Limitations:** Analyses based on few exposed subjects. Did not account for non-occupational exposure. Non-differential exposure misclassification is possible, which would likely attenuate risk estimates towards the null.
		Never	1	NR		
		Ever	2.1 (1–4.3)	9		

Section C2 Publications initially identified in the literature search as epidemiologic studies: Reasons for exclusion

Table C2 Publications initially identified in the literature search as epidemiologic studies: Reasons for exclusion

Full Citation	Reason for exclusion
Ahrens W, Langner I, Schmeisser N, Mester B, Behrens T. 2013. Male germ-cell cancer in car manufacturing workers: Results of a nested case-control study. European Journal of Epidemiology 28.	Conference abstract
Costas LC, Infante R, Cocco, Van T, Zock, De S. 2013. Endocrine disruptors and the risk of lymphoma in the epilymph study. Occupational and environmental medicine 70.	Conference abstract
Dumitrascu MC, Mares C, Petca RC, Sandru F, Popescu RI, Mehedintu C, et al. 2020. Carcinogenic effects of bisphenol a in breast and ovarian cancers (review). Oncology letters 20.	Review
Engin AB, Engin A. 2021. The effect of environmental bisphenol a exposure on breast cancer associated with obesity. Environmental toxicology and pharmacology 81:103544.	Review
Fischer C, Lundsberg L, Pal L. 2014. Urinary bispenol a and breast cancer: Nhanes 2005–2010. Fertility and Sterility 102.	Conference abstract
Jung KJ, Jee SH. 2019. Cohort study of serum bisphenol a, polygenetic risk score, and thyroid cancer in korea. Genetic Epidemiology 43:885.	Conference abstract
Paumgartten FJR. 2003. Adverse health consequences of environmental exposure to 'endocrine disruptors'. Annual Review of Biomedical Sciences 5:45–55.	Review
Pellerin E, Caneparo C, Chabaud S, Bolduc S, Pelletier M. 2021. Endocrine-disrupting effects of bisphenols on urological cancers. Environmental research 195.	Review
Picerno T, Borowsky ME, La Scala N, Sloan N. 2017. Urinary bisphenol a levels in women with endometrial cancer. Gynecologic Oncology 145:110–111.	Conference abstract
Plesnicar, A., Druzina B, Kovac, V., Kralj B. 2002. Environment and breast cancer - the role of xenooestrogens in breast cancer carcinogenesis. Radiology and Oncology 36.	Review
Pollack AZ, Buck Louis GM, Chen Z, Sun L, Trabert B, Guo Y, et al. 2015. Bisphenol a, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma. Environmental research 137:101–107.	Uterine leiomyoma, a benign tumor that is not expected to progress to the very rare

Full Citation	Reason for exclusion
	malignant leiomyosarcoma[15]
Prins GS. 2008. Endocrine disruptors and prostate cancer risk. Endocr Relat Cancer 15:649–656.	Review
Quagliariello V, Rossetti S, Cavaliere C, Di Palo R, Lamantia E, Castaldo L, et al. 2017. Metabolic syndrome, endocrine disruptors and prostate cancer associations: Biochemical and pathophysiological evidences. Oncotarget 8:30606–30616.	Review
Rodgers KM, Udesky JO, Rudel RA, Brody JG. 2018. Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. Environmental research 160:152–182.	Review
Roy D, Morgan M, Yoo C, Deoraj A, Roy S, Yadav VK, et al. 2015. Integrated bioinformatics, environmental epidemiologic and genomic approaches to identify environmental and molecular links between endometriosis and breast cancer. Int J Mol Sci 16:25285–25322.	Review
Sarink D, Le Marchand L, Cheng I, Wu AH, Franke AA, Wilkens LR, et al. 2019. Prospective investigation of pre-diagnostic urinary bisphenol a and phthalates in relation to endometrial cancer risk in the multiethnic cohort (mec) study. International Journal of Gynecological Cancer 29.	Conference abstract
Sarink D, Le Marchand L, Cheng I, Wu AH, Franke AA, Wilkens LR, et al. 2020. Pre-diagnostic phthalates and other endocrine disruptors in relation to endometrial cancer risk in the multiethnic cohort (mec) study. Cancer Epidemiology Biomarkers and Prevention 29.	Conference abstract
Sonnenschein C, Wadia PR, Rubin BS, Soto AM. 2011. Cancer as development gone awry: The case for bisphenol-a as a carcinogen. Journal of Developmental Origins of Health and Disease 2:9–16.	Review
Tse LA, Ng CF, Ho WM, Lee MYP, Wang F. 2016. Identifying environmental hazardous substances associated with prostate cancer risk in hong kong population. Occupational and environmental medicine 73.	Conference abstract
Wan MLY, Co VA, El-Nezami H. 2021. Endocrine disrupting chemicals and breast cancer: A systematic review of epidemiological studies. Crit Rev Food Sci Nutr:1–27.	Review
Wesselink AK, Weuve J, Hauser R, Williams PL, Bethea TN, McClean M, et al. 2019. Urinary concentrations of bisphenols in relation to uterine leiomyomata risk. Reproductive Sciences 26.	Uterine leiomyoma

[15] Bulun SE (2013). Uterine fibroids. N Engl J Med 2013;369:1344-55.

Full Citation	Reason for exclusion
Wesselink AK, Weuve J, Fruh V, Bethea TN, Claus Henn B, Harmon QE, et al. 2021. Urinary concentrations of phenols, parabens, and triclocarban in relation to uterine leiomyomata incidence and growth. Fertil Steril 116:1590–1600.	Conference abstract
Zare Jeddi M, Alipour S, Yunesian M, Ahmadkhaniha R, Rastkari N, Adli SJ, et al. 2015. Endocrine disruptors and women reproductive health: The case of bisphenol-a and breast cancer. Tropical Medicine and International Health 20:67–68.	Conference abstract

APPENDIX D. ANIMAL CARCINOGENICITY STUDIES (OTHER DESIGNS)

Table D1 Overview of BPA effects in studies using xenograft, syngeneic, and regenerated organ mouse models

Strain, sex, group size, xenografted, syngeneic, or regenerated gland/cells	Study design	Findings	Reference
BALB/c *nu*/*nu*, female, ovariectomized after tumor established, 6 per group, **xenografted BG-1 human ovarian adenocarcinoma cells**	BG-1 cells (5×10^6 per animal) mixed with Matrigel and injected *s.c.* into the back of the mice. Once tumor sizes reached 50 mm^3, the mice were ovariectomized. At 7 weeks, mice were injected *s.c.* 3 times a week for 8 weeks with one of the following: corn oil (vehicle control), E2 (20 µg/kg bw), BPA (100 mg/kg bw), E2 + GEN (E2 20 µg/kg bw + GEN 300 mg/kg bw), or BPA + GEN (BPA 100 mg/kg bw + GEN 300 mg/kg bw). The study was terminated 15 weeks after BG-1 cell injection.	Administration of BPA alone, E2 alone, or BPA plus GEN increased the tumor volume compared to that of the vehicle control group. Increased cell proliferation, cell density, and BrdU incorporation was observed in tissue sections of tumors from the mice exposed to BPA alone or E2 alone compared to the vehicle control group.	Hwang et al. (2013)
Mouse, BALB/c nude mice, male, 10 per group, **syngeneic model with BALB/c mouse colorectal carcinoma CT-26-Luc cells**	Male nude mice were injected *s.c.* with CT-26-Luc cells (5×10^6 per mouse), implanted *s.c.* with a micro-osmotic pump, and infused with either saline or BPA (100 µg/kg-day) *s.c.* for 28 days. Tumor growth was assessed after 28 days.	Tumor volume was significantly increased (4.64-fold) in BPA-treated mice compared to controls ($p < 0.05$).	Jun et al. (2021)
BALB/c nude, female, 7 per group, **xenografted with MCF10 DCIS.com/Luc-GFP cells, a human**	3-week-old female mice were administered BPA in drinking water at concentrations of 0, 2.5 µg/l, or 25 5 µg/l for 70 days. On day 31 MCF10 DCIS [ductal carcinoma *in situ*].com/Luc-GFP cells (ER, PR, and HER2-negative) resuspended in Matrigel were injected	Low-dose BPA promoted tumor cell growth (tumor volumes, $p = 0.0619$; tumor weight, $p < 0.05$ and bioluminescence, $p = 0.0083$) compared to the vehicle controls; but these effects were not observed in the high-dose BPA group.	Kim et al. (2019a)

Strain, sex, group size, xenografted, syngeneic, or regenerated gland/cells	Study design	Findings	Reference
breast cancer cell line	into the second mammary fat pad of each animal (10^6 cells per animal).		
BALB/c *nu*/*nu*, female, ovariectomized after tumor established, 7 per group, **xenografted with human breast carcinoma MCF-7 cells**	Mice were injected *s.c.* with human breast carcinoma MCF-7 cells mixed in Matrigel (3×10^6 cells per animal reported in text and figure legend, and 5×10^6 cells per animal reported in materials and methods). Once tumor volume reached 90–100 mm^3, mice were ovariectomized to exclude endogenous estrogen effects. Mice were then injected *s.c.* every 2 days for a period of 10 weeks with one of the following: corn oil control, BPA 50 mg/kg bw, E2 20 µg/kg bw (other treatment groups included in this study are not discussed here).	The tumor volumes of the mice treated with either BPA or E2 gradually increased compared to the vehicle control ($p < 0.05$ by Student's t-test) from week 3 to week 9. Tumors of mice treated with either BPA or E2 had increased expression of markers related to epithelial-mesenchymal transition and metastasis.	Lee et al. (2017b)
Swiss nude Foxn1 *nu/nu* (athymic), female, 15 per group, **xenografted with human breast carcinoma MCF-7 cells**	Mice were administered either vehicle (0.001% ethanol) or 5 µg/kg-day BPA in drinking water from 2 weeks before tumor cell injection until 60 days after injection. Mice were injected *s.c.* (1.2×10^7 cells per animal) with either human breast carcinoma MCF-7 cells overexpressing protein kinase D1 (PKD1) (clone P) or MCF-7 cells not overexpressing PKD1 (clone C).	In animals injected with MCF-7 clone P cells, BPA exposure significantly increased the number of mice developing tumors (BPA, 12/15; vehicle control, 8/15, $p < 0.01$), but not in mice injected with MCF-7 clone C cells. BPA exposure increased mean tumor volumes in mice injected with either MCF-7 clone P cells (BPA: 45.67 ± 20.74 mm^3, vehicle control: 1.44 ± 0.05 mm^3) or MCF-7 clone C cells (BPA: 10.59 ± 3.20 mm^3, vehicle control: 4.09 ± 2.89 mm^3).	Merzoug-Larabi et al. (2019)
BALB/c AnN (H2-d), male offspring, 7–9 per group, **syngeneic model with BALB/c**	0 (untreated control), 0 (ethanol vehicle control), or BPA 250 mg/kg-day F0 maternal exposure from GD11 to PND21 via drinking water. Adult (8-week-old) F1 males in each treatment group received an intrascrotal	The tumor weights in the BPA-exposed F1 males were increased significantly (by approximately 75%) compared to unexposed and vehicle controls ($p < 0.01$).	Nava-Castro et al. (2019)

Strain, sex, group size, xenografted, syngeneic, or regenerated gland/cells	Study design	Findings	Reference
mouse breast cancer 4T1 cell line	inoculation of 1 × 10^3 4T1 cancer cells. Tumor growth was assessed after 25 days.	The expression of inflammatory-related cytokines (IL-10 and TNF-α) in the tumors was significantly enhanced compared to control and vehicle groups.	
BALB/c AnN (H2-d), female, 12 per group, **syngeneic model with BALB/c mouse mammary adenocarcinoma 4T1 cells**	PND3 female mice were injected *s.c.* with 20 µl corn oil (vehicle control) or 250 µg/kg BPA. At 8 weeks of age BALB/c mouse mammary adenocarcinoma 4T1 cells (10^4 per animal) were injected into the mammary fat pad. Tumor growth was monitored for 25 days.	BPA-exposed mice developed larger tumors (tumor weight, $p < 0.01$) compared to vehicle controls. Tumor leukocytic infiltrate analysis revealed a higher proportion of regulatory T-lymphocytes in the BPA-exposed group. RT-PCR analysis of tumor samples showed a decreased expression of TNF-α, IFN- γ, and the M2 macrophage marker Fizz-1 in the BPA-exposed group.	Palacios-Arreola et al. (2017)
Nude, male, 27–42 per group, **xenografted with human prostate epithelium stem-progenitor cells combined with rat urogenital sinus mesenchyme**	Human prostate epithelium stem-progenitor cells from 19–20-year-old organ donors were cultured to form prostaspheres in the absence (groups 1, 2, and 3 below) or presence of 200 nM BPA (group 4 below). 3000 cells dispersed from 7-day prostaspheres were combined with rat urogenital sinus mesenchyme in Matrigel and grafted under the renal capsule in adult male nude mice. Groups of xenografted nude mice were treated for 2 weeks via the oral route as follows: (1) vehicle (n = 38), (2) BPA 100 µg/kg bw (n = 36), (3) BPA 250 µg/kg bw (n = 27), and (4) 200 nM BPA during *in vitro* prostasphere culture plus 250 µg/kg bw (n = 42). After 1-month, hormonal carcinogenesis was initiated by *s.c.* implantation of T+E2 pellets (25 mg of	BPA increased the incidence of high grade prostatic intraepithelial neoplasia (PIN) in human prostate epithelium xenografts (*p*-values are for pairwise comparison with vehicle control): (1) Vehicle control: 5/38 (13%) (2) BPA 100 µg/kg bw: 12/36 (36%), $p < 0.05$ (3) BPA 250 µg/kg bw: 9/27 (33%), $p < 0.05$ (4) 200 nM BPA during *in vitro* prostasphere culture plus 250 µg/kg bw *in vivo*: 19/42 (45%), $p < 0.01$	Prins et al. (2014)

Strain, sex, group size, xenografted, syngeneic, or regenerated gland/cells	Study design	Findings	Reference
	T and 2.5 mg E2). The study was terminated at 4 months post implantation.		
Balb/c, female, 10–11 per group, **regenerated mouse mammary glands**	Beginning at the age of 21 days (week 3) and continuing to week 6, mice were gavaged daily with sesame oil or BPA 25 µg/kg-day, at two months of age a subgroup of control and treated mice were given a single oral gavage of DMBA at 30 mg/kg bw. Mammary glands were harvested at 6 weeks (immediately after last BPA treatment), 2 months, or 4 months of age for preparation of murine mammary stem cells (MaSC). MaSCs were cultured to form mammospheres and then 3D structures. Solid MaSc-enriched 3D structures were *s.c.* transplanted into cleared mammary fat pads of 21-day old mice to create regenerated mammary glands.	The percentage of ADH/DCIS was increased in regenerated glands from MaSCs harvested at all time points from mice exposed to BPA during puberty, with or without exposure at 2 months to DMBA, with the highest average value found in BPA-exposed MaSCs harvested at 4 months (6.3%). Significant increases of hyperplastic lesions were observed in the regenerated glands from BPA-exposed MaSCs vs. control MaSCs harvested at 6 weeks (65.3% vs. 29.8%), 2 months (41.6% vs. 13.4%), and 4 months (72.1% vs. 30.8%), and from BPA plus DMBA exposed MaSCs vs. DMBA alone at 4 months (83.6% vs. 59%).	Wang et al. (2014a)
Ovariectomized NCR *nu/nu* (athymic), female, 6–7 per group, **xenografted with human breast carcinoma MCF-7 cells**	Mice were ovariectomized and implanted *s.c.* with 60-day release pellets containing placebo, BPA (37.5 mg), or E2 (1.7 mg). After recovery from surgery mice were injected *s.c.* with human breast carcinoma MCF-7 cells mixed in Matrigel (10^6 cells per animal).	BPA or E2 exposure significantly increased the number of mice developing tumors by 9 weeks (BPA, 5/6; E2, 5/7, placebo, 0/7).	Weber Lozada and Keri (2011)
NCR/nu/nu (athymic), male, castrated after tumor established, 11–12 per group,	Human prostate cancer LNCaP cells (2×10^6 cells per mouse, mixed with Matrigel) were injected *s.c.* into the right flank of 6–8-week-old mice. Once tumors reached 50–100 mm^3 in volume, the mice were castrated and	BPA statistically significantly accelerated tumor growth rate, measured as tumor volume, 21 and 35 days after castration and pellet implantation, as compared with	Wetherill et al. (2006)

Strain, sex, group size, xenografted, syngeneic, or regenerated gland/cells	Study design	Findings	Reference
xenografted with LNCaP human prostate cancer cells	implanted *s.c.* with either placebo or BPA 21-day time-release pellets (12.5 mg) (highest mean serum concentration = 27 ng/ml, 7 days after 21 days). The study was terminated 35 days after castration and pellet implantation.	placebo group ($p < 0.001$ and $p < 0.01$ by pairwise comparison at day 21 and 35, respectively).	
Severe combined immuno-deficiency (SCID), female, number of mice per group not reported, **xenografted with human breast adenocarcinoma MDA-MB-231 cells**	Human breast cancer MDA-MB-231 cells were suspended in 100 ml of medium mixed with Matrigel and inoculated into the left inguinal mammary fat pad at the base of the nipple (2×10^6 cells per mouse) of 5-week-old mice. When the tumor was palpable, the mice were randomly divided into four groups and injected intramuscularly with either corn oil (vehicle), BPA (150 mg/kg bw), G-15, an antagonist of the GPER estrogen receptor (370 mg/kg bw) or BPA plus G-15 every 3 days for 4 weeks.	BPA-treatment significantly increased tumor volume at 4 weeks, compared to vehicle control ($p < 0.05$). Tumor volume was not significantly different from vehicle controls in animals treated with either G-15 or BPA plus G-15. [Three tumors from each group were shown but the number of animals per group was not reported.]	Xu et al. (2017)
Immunodeficient NOD/SCID/IL2γ^{null}, male, 5 per group, **xenografted with ERα-negative, ERβ-positive human B cell lymphoma Granta-519 cells**	Male mice were injected *s.c.* with human B cell lymphoma Granta-519 cells (which express ERβ, but not ERα) (15×10^6 cells per animal). After 7 days, when *s.c.* tumors were 50–100 mm^3, mice were treated *per o.s.* once daily with BPA at 0 or 50 µg/kg bw in 10% ethanol/ 90% rapeseed oil for 19 days.	BPA 50 µg/kg-day significantly suppressed tumor growth (measured by tumor volume, mm^3) ($p < 0.01$) on days 16–19, compared to vehicle control. [The authors stated in the results section of the publication that the effect of BPA was also tested using a xenografted human Daudi lymphoma cell line and referred readers to Supplementary Fig. 2 for data showing that BPA had no effect on tumor growth. However, Supplementary Fig. 2 does not show data on BPA as claimed in the results section.]	Yakimchuk et al. (2018)

Strain, sex, group size, xenografted, syngeneic, or regenerated gland/cells	Study design	Findings	Reference
Castrated C57Bl/6J, male, 6 per group, **syngeneic model with C57Bl/6 mouse ERα-negative, ERβ-positive T cell lymphoma EG7 cells**	Male mice were castrated and injected *s.c.* with mouse T cell lymphoma EG7 cells (which express ERβ, but not ERα) (3×10^5 cells per mouse). After 7 days, when tumors were 50–100 mm^3, mice were treated *per os* once daily with BPA at 0, 0.02, 1 or 50 µg/kg bw in 10% ethanol/ 90% rapeseed oil for 18 days.	BPA 50 µg/kg-day significantly suppressed tumor growth (measured by tumor volume, mm^3) ($p < 0.05$) on days 15, 16 and 18.	Yakimchuk et al. (2018)
Ovariectomized BALB/c nu/nu (athymic), female, 9–11 per group, **xenografted with SK-N-SH human neuroblastoma cells**	All mice underwent bilateral ovariectomy, and 1-week later SK-N-SH cells (1×10^7 cells per mouse) were injected *s.c.* on the right hind flank of the mice. Once tumors were approximately 7 mm in length or width, mice were administered either E2 (500 µg/kg-day, n =11), BPA (200 mg/kg per day, n = 10), or olive oil vehicle (n = 9) by gavage for 18 days, after which the study was terminated.	Tumor volume was increased in the BPA (3.14 ± 0.6 cm^3) and E2 treatment groups (4.49 ± 0.77 cm^3) compared to controls (1.95 ± 0.28 cm^3) ($p < 0.05$). Tumor weights in the BPA- and E2-treated mice were, respectively, 57.3% and 80.4% heavier than in controls ($p < 0.05$). Tumor microvessel density was increased in the BPA (83.3%) and E2 treatment groups (50.1%), compared to controls ($p < 0.05$). VEGF protein expression was also increased in the BPA and E2 treatment groups, compared to controls. Tumor microvessel density and VEGF protein expression is both markers of angiogenesis.	Zhu et al. (2009)

F, female; M, male; F0, pregnant dams; F1, offspring from F0; GD, gestation day; PND, postnatal day; *s.c.*, subcutaneous; conc., concentration; E2, 17-β estradiol; T, testosterone; GEN, genistein; n, animal numbers; VEGF, vascular endothelial growth factor; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; PIN, prostatic intraepithelial neoplasia; PBS, phosphate-buffered saline.; *per os*, by mouth

Table D2 Studies of BPA administered before treatment with a model carcinogen

Species, strain, sex, group size	Treatment plan	Findings	Reference
Rat, SD, female, 11 per group	BPA doses and route: (to F0 dams) 0, 2.5, 25, 250, 2500 µg/kg-day *in utero*. Exposure details: F0 dams were given BPA in feed, with or without high-butter fat (HBF) during mating and throughout gestation, then on control diet after birth. F1 pups were treated with a single oral dose of 7,12-dimethylbenz(a)anthracene (DMBA) (20 mg/kg bw) on PND50. Animals were terminated on PND140 (20 weeks of age).	Mammary gland (only tissue examined) Mammary tumors (not otherwise specified): HBF+DMBA, 45.5%; BPA2.5+(HBF+DMBA), 60%, BPA25+(HBF+DMBA), 90%, $p = 0.043$; BPA250+(HBF+DMBA), 50%, BPA2500+(HBF+DMBA), 40% Tumor latency was significantly reduced in the BPA25+(HBF+DMBA) group, compared to the HBF+DMBA group, $p = 0.0422$ BPA did not increase tumor incidence in groups receiving normal diet and DMBA (data not shown)	Leung et al. (2017)
Rat, Wistar, female, 5–15 per group	BPA doses and route: (to F0 dams) 0, 25 µg/kg-day, F1 exposed *in utero.* Exposure details: F0 dams were given BPA via osmotic pump *s.c.* from GD8 to GD23. On PND50, F1 pups were given a single *i.p.* injection of 25 mg/kg N-nitroso-N-methylurea (MNU). Animals were terminated on PND110 or PND180.	Mammary gland (only tissue examined) PND110 No malignant tumors in MNU only or BPA+MNU (n = 9 per group); PND180 Ductal carcinoma in situ: MNU, 0/10; BPA+MNU, 2/15	Durando et al. (2007)

Species, strain, sex, group size	Treatment plan	Findings	Reference
Rat, SD CD/Crj, female, 17–26 per group	BPA doses and route: 0, 0.1, 10 mg/rat-day, by *s.c.* injection. Exposure details: Rats were given BPA *s.c.* on PND2, 4, and 6. At 7 weeks of age, rats were given a single dose of 50 mg/kg MNU. [The abstract indicates MNU was administered *i.p.*, while the Methods section indicates the route was *i.v.*] Animals were examined at 17 and 27 weeks of age for mammary tumors (palpitation), and terminated at 33 weeks of age.	Mammary gland tumors (only tissue examined) 17 weeks of age: MNU, 36.8%; BPA0.1+MNU, 16.7%; BPA10+MNU, 7.7% (number of animals examined not reported) 27 weeks of age: MNU, 76.5%; BPA0.1+MNU, 58.3%; BPA10+MNU, 34.6% (number of animals examined not reported) 33 weeks of age [a]: MNU, 94.1% (16/17); BPA0.1+MNU, 79.2% (16/20); BPA10+MNU, 76.9% (20/26) Mammary tumor latency (weeks): MNU, 6; BPA0.1+MNU, 6; BPA10+MNU, 10 Mammary tumor multiplicity at 33 weeks of age: MNU, 2.24; BPA0.1+MNU, 1.42; BPA10+MNU, 1.65	Yin et al. (2006)
Rat, SD, female, 11 per group	BPA doses and route: (to F1) 0, 1000 ppm in drinking water. Exposure details: F0 dams were given low protein diet (6% protein, LPD) or normal diet (17% protein) from GD1 to GD21 then were fed on normal diet during lactation. F1 pups were given BPA in drinking water from PND21 to PND51 (30 days). On PND51, rats were given a single gavage dose of 30 mg/kg DMBA. Animals were examined twice a week for mammary tumors (palpitation), and terminated on PND250.	F0 animals were fed normal diet if not noted as LPD. Mammary gland (only tissue examined) Tumor incidence (benign and malignant combined): DMBA, 18%; BPA+DMBA, 73%, $p = 0.032$; DMBA+LPD, 36%; BPA+(DMBA+LPD), 64% Tumor multiplicity (mean): DMBA, 0.18; BPA+DMBA, 1.82, $p = 0.018$; DMBA+LPD, 0/91; BPA+(DMBA+LPD), 1.64 Tumor latency (weeks): DMBA, 31; BPA+DMBA, 13; DMBA+LPD, 14; BPA+(DMBA+LPD), 12	Varuzza et al. (2019)

Species, strain, sex, group size	Treatment plan	Findings	Reference
Rat, SD CD, female, 28–30 per group	BPA doses and route: (to F0 dams) 0, 25, and 250 µg/kg-day *in utero.* Exposure details: F0 dams were given BPA via gavage from GD10 to GD21. F1 females were given a single gavage of 30 mg/kg bw DMBA on PND50 (all three treatment groups) or PND100 (control and BPA 250 µg/kg-day groups only). Animals were examined twice a week for mammary tumors (palpitation) and terminated at 12 months of age.	Mammary gland (only tissue examined) PND50 No differences in tumor latency or multiplicity between groups PND100 Increased tumor incidence: DMBA, 53.6%, n = 30; BPA250+DMBA, 83.3%, n = 28, p = 0.022 Decreased tumor latency (days): DMBA, 267; BPA250+DMBA, 189.5, p = 0.012 Tumor multiplicity: non-significant increase in BPA+DMBA group compared to DMBA control	Betancourt et al. (2010)
Rat, SD CD, female, 24–34 per group	BPA doses and route: (to F0 dams) 0, 25, 250 µg/kg-day via lactation. Exposure details: F0 dams were given BPA via gavage (5 days/week, 15 times in total) from PND2 to 20. F1 pups were given a single gavage of 30 mg/kg bw DMBA on PND50. Animals were examined twice a week for mammary tumors (palpitation) and terminated at 12 months of age.	Mammary gland (only tissue examined) Tumor multiplicity: DMBA, 2.84 ± 0.31, n = 32; BPA25+DMBA, 3.82 ± 0.43, n = 34; BPA250+DMBA, 5.00 ± 0.88, n = 24, p = 0.004 Tumor latency (median, days): DMBA, 65; BPA25+DMBA, 53; BPA250+DMBA, 56.5	Jenkins et al. (2009)
Rat, Donryu female, 24–30 per group	Uterine carcinogenesis model BPA doses and route: (to F0 dams) 0, 0.006, 6 mg/kg-day *in utero* and via lactation. Exposure details: F0 dams were given BPA via gavage from GD2 to PND21. F1 females were treated with a single intra-uterine administration of 20 mg/kg N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) at 11 weeks of age. Animals were terminated at 15 months of age.	Uterus Endometrial adenocarcinoma: (ENNG, 8/24; low-dose BPA+ENNG, 10/30; high-dose BPA+ENNG, 6/30	Yoshida et al. (2004)
Rat , Wistar, female, 5–19 per group	BPA doses and route [b]: (to F0 dams) 0, 10000 ppm *in utero* and via lactation. Exposure details: F0 dams were given BPA in basal diet or in soybean-devoid feed (SDF) with exposure started 10 weeks before mating, through mating, gestation, and	Animals were on basal diet unless noted as SDF. Thyroid Follicular cell carcinoma: BHP,1/17; BPA+BHP, 3/19; SDF+BHP, 1/16;	Takashima et al. (2001)

Species, strain, sex, group size	Treatment plan	Findings	Reference
	lactation (GD1 to PND21). F1 pups were on basal diet. At 5 weeks of age, pups were treated with 2000 ppm N-nitrosobis (2-hydroxypropyl) amine (BHP) in drinking water for 12 weeks. Animals were terminated at 25 weeks of age, and thyroid, lung, liver, thymus, and esophagus examined.	BPA+(SDF+BHP), 1/15; Follicular cell adenoma: BHP, 1/17; BPA+BHP, 2/19; SDF+BHP, 0/16; BPA+(SDF+BHP), 1/15 <u>Lung</u> Adenocarcinoma: BHP, 2/17; BPA+BHP, 3/19; SDF+BHP, 1/16; BPA+(SDF+BHP), 1/15; Adenoma: BHP, 11/17; BPA+BHP, 11/19; SDF+BHP, 7/16; BPA+(SDF+BHP), 6/15 Adenosquamous cell carcinoma: BHP, 0/17; BPA+BHP, 0/19; SDF+BHP, 1/16; BPA+(SDF+BHP), 0/15 Squamous cell carcinoma: BHP, 1/17; BPA+BHP, 1/19; SDF+BHP, 0/16; BPA+(SDF+BHP), 2/15 <u>Liver</u> Hepatocellular carcinoma: BHP, 0/17; BPA+BHP, 2/19; SDF+BHP, 1/16; BPA+(SDF+BHP), 1/15 Hepatocellular adenoma: BHP, 1/17; BPA+BHP, 4/19; SDF+BHP, 2/16; BPA+(SDF+BHP), 0/15 <u>Thymus</u> Malignant lymphoma: BHP, 1/17; BPA+BHP, 1/19; SDF+BHP, 0/16; BPA+(SDF+BHP), 0/15 <u>Esophagus</u> Squamous cell carcinoma: BHP, 0/17; BPA+BHP, 1/19; SDF+BHP, 1/16; BPA+(SDF+BHP), 1/15 Papilloma: BHP, 16/17; BPA+BHP, 17/19; SDF+BHP, 13/16; BPA+(SDF+BHP), 13/15	

Species, strain, sex, group size	Treatment plan	Findings	Reference
Rat, Wistar, male, 5–19 per group	BPA doses and route [b]: (to F0 dams) 0, 10000 ppm *in utero* and via lactation. Exposure details: F0 dams were given BPA in basal diet or in soybean-devoid feed (SDF) with exposure started 10 weeks before mating, through mating, gestation, and lactation (GD1 to PND21). F1 pups were on basal diet. At 5 weeks of age, pups were treated with 2000 ppm BHP in drinking water for 12 weeks. Animals were terminated at 25 weeks of age and thyroid, lung, liver, thymus, and esophagus examined.	Animals were on basal diet unless noted as SDF. Thyroid Follicular cell carcinoma: BHP, 16/19; BPA+BHP, 15/18; SDF+BHP, 14/14; BPA+(SDF+BHP), 14/17 Follicular cell adenoma: BHP, 15/19; BPA+BHP, 17/18; SDF+BHP, 14/14; BPA+(SDF+BHP), 15/17 Lung Adenocarcinoma: BHP, 7/19; BPA+BHP, 6/18; SDF+BHP, 6/14; BPA+(SDF+BHP), 5/17 Adenoma: BHP, 15/19; BPA+BHP, 16/18; SDF+BHP, 8/14; BPA+(SDF+BHP), 12/17 Adenosquamous cell carcinoma: BHP, 0/19; BPA+BHP, 0/18; SDF+BHP, 1/14; BPA+(SDF+BHP), 0/17 Squamous cell carcinoma: BHP, 4/19; BPA+BHP, 3/18; SDF+BHP, 2/14; BPA+(SDF+BHP), 1/17 Liver Hepatocellular adenoma: BHP, 0/19; BPA+BHP, 0/18; SDF+BHP, 2/14; BPA+(SDF+BHP), 1/17 Thymus Malignant lymphoma: BHP, 7/19; BPA+BHP, 5/18; SDF+BHP, 4/14; BPA+(SDF+BHP), 0/17 Esophagus Squamous cell carcinoma: BHP, 0/19; BPA+BHP, 1/18; SDF+BHP, 2/14; BPA+(SDF+BHP), 1/17 Papilloma: BHP, 16/19; BPA+BHP, 15/18; SDF+BHP, 12/14; BPA+(SDF+BHP), 16/17	Takashima et al. (2001)

Species, strain, sex, group size	Treatment plan	Findings	Reference
Rat, F344, male, 15–19 per group	BPA doses and route: (to F0 dams) 0, 0.05, 7.5, 30, 120 mg/kg-day via *in utero* and via lactation. Exposure details: F0 dams were given BPA via gavage from GD1 to PND21. From 5- 25 weeks of age F1 males were given 50 mg/kg 3,2'-dimethyl-4-aminobiphenyl (DMAB) by *s.c.* injection (10 total injections, at 2-week intervals). Animals were terminated at 65 weeks of age.	Prostate VP Carcinoma: DMAB, 0/19; BPA0.05+DMAB, 1/18; BPA7.5+DMAB, 2/15; BPA30+DMAB, 2/19; BPA120+DMAB, 1/19 Small intestine Adenoma & carcinoma combined: DMAB, 1/21; BPA0.05+DMAB, 3/21; BPA7.5+DMAB, 3/21; BPA30+DMAB, 2/21; BPA120+DMAB, 4/20	Ichihara et al. (2003)
Mouse, FVB/N, female, ≥10 per group[c]	BPA doses and route: (to F0 dams) 0, 25, 250 µg/kg-day *in utero.* Exposure details: F0 dams were given BPA via gavage from GD8 to birth. F1 females were dosed with 1 mg per mouse DMBA via gavage at 5 and 6 weeks (two times total). Animals were examined weekly for mammary tumors (palpitation) and terminated at 111 weeks of age.	Mammary gland (only tissue examined) Squamous cell carcinoma tumor latency (mean, weeks): DMBA, 111, BPA25+DMBA, 69.3, p <0.05; BPA250+DMBA, 50.8, p <0.05	Weber Lozada and Keri (2011)

F0, pregnant dams; F1, offspring from F0; GD, gestation day; PND, postnatal day; *s.c.*, subcutaneous; BHP, N-nitrosobis(2-hydroxypropyl)amine; MNU, N-nitroso-N-methylurea; DMBA, 7,12-dimethylbenzoanthracene; ENNG, n-ethyl-N'-nitro-N-nitrosoguanidine; DMAB, 3,2'-dimethyl-4-aminobiphenyl; VP, ventral lobes of prostate.

[a] Incidence numbers were converted by OEHHA based on reported percentage data by Yin et al. (2006).

[b] Animals were fed on 1% BPA in diet and was expressed 10000 ppm in the table. Incidence numbers were converted by OEHHA based on reported percentage data and number of animals for each treatment by Takashima et al. (2001).

[c] Each dose group has at least 10 mice from >3 litters (Weber Lozada and Keri 2011).

Table D3 Studies of BPA administered before testosterone and 17β-estradiol treatment in male rats

strain, sex, group size	Treatment plan	Findings	Reference
SD, male, 15–25 per group	BPA doses and route: 0, 10 µg/kg-day by oral route. Exposure details: Neonatal rats were given BPA orally on PND1, 3, 5. On PND90 rats were *s.c.* implanted with T+E2 (testosterone +17β-estradiol) capsules [a] for 16 weeks. The study was terminated when animals were 28 weeks of age.	Prostate (only tissue examined) LP PIN (includes low-grade or LG- and high-grade or HG-PIN): T+E2, 64%; BPA+(T+E2), 90%, p <0.05 VP PIN (LG- only, based on PIN score): T+E2, 18%; BPA+(T+E2), 40%, NS DP PIN (LG- only, based on PIN score): T+E2, 33%; BPA+(T+E2), 66%, NS	Prins et al. (2011)
SD, male, 15–25 per group	BPA doses and route: 0, 10 µg/kg-day by *s.c.* injection. Exposure details: Neonatal rats were given BPA *s.c.* on PND1, 3, 5. On PND90 rats were *s.c.* implanted with T+E2 capsules [a] for 16 weeks. The study was terminated when animals were 28 weeks of age.	Prostate (only tissue examined) LP PIN (includes LG- and HG-PIN): T+E2, 64%; BPA+(T+E2), 100%, p <0.05 VP PIN (LG- only, based on PIN score): T+E2, 18%; BPA+(T+E2), 40%, NS DP PIN (LG- only, based on PIN score): T+E2, 33%; BPA+(T+E2), 47%, NS	Prins et al. (2011)
SD, male, 8–11 per group	BPA doses and route: 0, 0.1, 1, 10, 100, 5000 µg/kg-day by *s.c.* injection. Exposure details: Neonatal rats were given BPA *s.c.* on PND1, 3, 5. On PND90, rats were *s.c.* implanted with T+E2 capsules [a] until 7-months of age (28 weeks of age).	Prostate (only tissue examined) LP HG-PIN: T+E2, 33%; BPA0.1+(T+E2), 70%; BPA1+(T+E2), 56%; BPA10+(T+E2), 67%; BPA100+(T+E2), 62%; BPA5000+(T+E2), 80%, p < 0.05 VP HG-PIN: T+E2, 0%; BPA0.1+(T+E2), 0%; BPA1+(T+E2), 11%; BPA10+(T+E2), 0%; BPA100+(T+E2), 12%; BPA5000+(T+E2), 0% DP HG-PIN: T+E2, 0%; BPA0.1+(T+E2), 20%; BPA1+(T+E2), 11%; BPA10+(T+E2), 11%;	Prins et al. (2017)

strain, sex, group size	Treatment plan	Findings	Reference
		BPA100+(T+E2), 50%, p <0.05; BPA5000+(T+E2), 20% PPD HG-PIN: T+E2, 0%; BPA0.1+(T+E2), 0%; BPA1+(T+E2), 33%, p <0.05; BPA10+(T+E2), 33%, p <0.05; BPA100+(T+E2), 40%, p <0.05; BPA5000+(T+E2), 29%	
SD, male, 17–21 per group	BPA doses and route: 0, 10 µg/kg-day by *s.c.* injection. Exposure details: Neonatal rats were given BPA *s.c.* on PND1, 3, 5. On PND90, rats were *s.c.* implanted with T+E2 capsules [a] until 12 months of age.	Prostate (only tissue examined) LP Microinvasive carcinoma: untreated, 0/17; T+E2, 3/18; BPA+(T+E2), 13/21, p <0.01 vs. untreated or T+E2 only Glandular carcinoma: control, 0/17; T+E2, 0/18; BPA+(T+E2), 3/21 PIN (includes LG- and HG PIN): untreated, 1/17; T+E2, 15/18; BPA+(T+E2), 20/21, p < 0.0001 vs. untreated VP: Microinvasive carcinoma: untreated, 0/17; T+E2, 0/18; BPA+(T+E2), 1/21 DP Microinvasive carcinoma: untreated, 0/17; T+E2, 1/18; BPA+(T+E2), 3/21 Glandular carcinoma: untreated, 0/17; T+E2, 0/18; BPA+(T+E2), 1/21 PPD Microinvasive carcinoma: untreated, 1/17; T+E2, 1/18; BPA+(T+E2), 2/21 Glandular carcinoma: untreated, 1/17; T+E2, 0/18; BPA+(T+E2), 3/21	Prins et al. (2017)
SD, male, 24–28 per group	BPA doses and route: 0, 10 µg/kg-day by *s.c.* injection Exposure details: Neonatal rats were given BPA *s.c.* on PND1, 3, 5. On PND70, rats were *s.c.* implanted with T+E2 capsules [b] until 12 months of age.	Prostate (only tissue examined) Whole gland Carcinoma: T+E2, 4/26; BPA+(T+E2), 4/28 LP Carcinoma: T+E2, 3/26; BPA+(T+E2), 1/28	Wong et al. (2015)

strain, sex, group size	Treatment plan	Findings	Reference
SD, male, 20–26 per group	BPA doses and route: 0, 2, 10, 50 µg/kg-day by oral route. Exposure details: Neonatal rats were given BPA orally on PND1, 3, and 5. On PND70, rats were *s.c*. implanted with T+E2 capsules [b] until 12 months of age.	Prostate (only tissue examined) Whole gland Carcinoma: T+E2, 4/26; BPA2+(T+E2), 3/25; BPA10+(T+E2), 5/25; BPA50+(T+E2), 3/24 LP Carcinoma: T+E2, 3/26; BPA2+(T+E2), 1/25; BPA10+(T+E2), 3/25; BPA50+(T+E2), 2/24 PPD Carcinoma: T+E2, 3/18; BPA2+(T+E2), 2/21; BPA10+(T+E2), 4/21; BPA50+(T+E2), 1/21	Wong et al. (2015)

NS, not significant; PND, postnatal day; *s.c.*, subcutaneous; PIN, prostatic intraepithelial neoplasia; LG-PIN, low-grade PIN; HG-PIN, high-grade PIN; T, testosterone; E2, 17β-estradiol; LP, lateral lobes of prostate; VP, ventral lobes of prostate; DP, dorsal lobes of prostate; DLP, dorsolateral lobes of prostate, PPD, periurethral prostatic ducts; $p < 0.05$, statistically significant

[a] Animals were implanted with Silastic capsules packed with 17β-estradiol (one 1 cm tube) and testosterone (two 2 cm tubes) for 16 weeks (replaced every 8 weeks) (Prins et al. 2011; Prins et al. 2017).

[b] Animals were implanted with one estradiol and two testosterone containing capsules to drive prostate carcinogenesis and the capsules were replaced every two months (Wong et al. 2015).

Table D4 Studies of BPA administered after tumor initiation in female rats

Strain, sex, group size	Model/Treatment plan	Findings	Reference
SD, female, 16–17 per group	Mammary gland carcinogenesis model BPA doses and route: 0, 20 mg/kg-day via gavage. Exposure details: 4–5-week-old rats were treated with a single *i.p.* injection of 100 mg/kg diethylnitrosamine (DEN) on study day1; four by *i.p*. injections of 20 mg/kg methylnitrosourea (MNU) on days 5, 8, 11, and 14, and 0.1% DHPN in drinking water during study week 1 and study week 3, (from day 1 to 7, and from day 14 to 21). From day 30 to 210, rats were administered BPA at 0 (control) or 20 mg/kg-day via gavage. Animals were terminated on study day 210.	Mammary gland Mammary tumor: control, 6/16; BPA, 10/16; $p < 0.05$ BPA treatment reduced tumor latency, compared to the controls, $p < 0.037$ Control: DEN+MNU+DHPN	Zhang et al. (2021b)
F344, female 12–15 per group	Thyroid carcinogenesis model BPA doses and route: 0, 10000 ppm in feed. Exposure details: Rats were ovariectomized at 5 weeks of age, then given a single *s.c.* injection of 2000 mg/kg N-bis (2-hydroxy propyl) nitrosamine (DHPN) at 6 weeks of age. At 7 weeks of age, rats were given 1000 ppm sulfadimethoxine (SDM) in drinking water for 8 weeks. Rats were administered 0 (control) or 10000 ppm BPA in feed from 15 weeks of age to 42 weeks of age. Animals were terminated at 42 weeks of age.	Thyroid Adenoma: control, 0/12; BPA, 0/15 Carcinoma: control, 10/12; BPA, 4/15, $p < 0.01$ Control: DHPN+SDM	Takagi et al. (2001)
F344, female, 7–10 per group	Thyroid carcinogenesis model BPA doses and route: 0, 250, 1000 µg/kg-day via gavage. Exposure details: 5-week-old rats were given a single *s.c.* injection of 2800 mg/kg DHPN. At 6 weeks of age, rats were given BPA via gavage at 0 (control), 250 µg/kg-day or 1000 µg/kg-day, with or without 1000 µg/l potassium iodine (KI) in drinking water for 64 weeks. Animals were terminated one week after BPA treatment ended (at 71 weeks of age).	Thyroid [a] Carcinoma: BPA vs control (not significant) BPA+KI vs. KI (not significant) Control: DHPN	Zhang et al. (2017a)

s.c., subcutaneous, *i.p.* intraperitoneal; DHPN, N-bis(2-hydroxypropyl)nitrosamine; SDM, sulfadimethoxine; DEN, diethylnitrosamine; MNU, methylnitrosourea

[a] Incidence were not provided for all treatment groups.

APPENDIX E. UGT POLYMORPHISM AND BPA GLUCURONIDATION

Table E1 UGT isoform polymorphisms and BPA glucuronidation

UGT isoform	Variant	UGT variant's activity compared to wildtype	Summary of UGT variant's activity	Methods of detection	Reference
UGT1A1	UGT1A1*28	Hepatic tissue intrinsic clearances for *1/*1, *1/*28, and *28/*28 microsomes were 1113, 1075, and 284 ml/min/kg body weight, respectively.	Lower	BPA glucuronidation activities were measured using 20 μM BPA and pooled human liver microsomes.	Trdan Lušin et al. (2012)
		Measured as nmol/min/mg protein. No significant differences between wildtype (2.6), *1/*28 (1.6), and *28/*28 (2.4) were observed.	No change	BPA glucuronidation activities were measured using 5 μM BPA and microsomes extracted from human liver bank samples grouped by gender, alcohol consumption, smoking, and selected UGT genotypes.	Street et al. (2017)
UGT1A9	UGT1A9*22	Measured as nmol/min/mg protein. No significant difference between wildtype (2.4) and *1/*22 (1.7), while the *22/*22 (4.4) samples had significantly higher activity than wildtype.	Higher	BPA glucuronidation activities were measured using 5 μM BPA and microsomes extracted from human liver bank samples grouped by gender, alcohol consumption,	Street et al. (2017)

UGT isoform	Variant	UGT variant's activity compared to wildtype	Summary of UGT variant's activity	Methods of detection	Reference
				smoking, and selected UGT genotypes.	
UGT2B15	UGT2B15*2	No detectable formation of BPA glucuronide	No activity	Measured by the amount of BPA glucuronide formed in HEKJ293 cells stably transfected with plasmids encoding UGT2B15-p.85D and UGT2B15-p.85Y which correspond to the UGT2B15*1 and UGT2B15*2 alleles, respectively, and treated with 5 or 50 µM BPA.	Street et al. (2017)
	UGT2B15*2	Measured as nmol/min/mg protein. Non-significant decrease in activity: wildtype (3.1), *1/*2 (1.8), and *2/*2 (2.0)	Lower	BPA glucuronidation activities were measured using 5 µM BPA and microsomes extracted from human liver bank samples grouped by gender, alcohol consumption, smoking, and selected UGT genotypes.	Street et al. (2017)
	UGT2B15*2 UGT2B15*5	The PBPK modeling shows that at both 0.05 and 1 µg/kg-day oral doses, the respective maximum blood concentrations (Cmax) and the AUCs were	Lower (*2 and *5)	Using the *in vitro* Km and Vmax data for recombinant human UGT2B15*2 and 2B15*5 from Hanioka et al.	Partosch et al. (2013)

UGT isoform	Variant	UGT variant's activity compared to wildtype	Summary of UGT variant's activity	Methods of detection	Reference
		higher than with the wild-type enzyme. Cmax was 3.9 and 4.9 times higher, and AUC was 4.9 and 5.5 times higher than wild-type, at 1 µg/kg-day for *2 and *5, respectively. Data for 0.05 µg/kg-day were not shown.		(2011), this study did PBPK modeling.	
	UGT2B15*2, UGT2B15*3, UGT2B15*4, UGT2B15*5, UGT2B15*6, UGT2B15*7	2B15*2 and 2B15*5 both showed markedly reduced Vmax ($p < 0.01$ for both), and markedly reduced intrinsic clearance ($p < 0.01$ for both) compared to the wild type. 2B15*6 had significantly lower Vmax ($p < 0.05$) but not intrinsic clearance. No change in Km or Vmax with other variants.	Lower (*2 and *5)	BPA glucuronidation activities were measured as the formation of BPA glucuronide *in vitro*, using BPA (0.5–100 µM) and membranes from Sf9 (insect) cells expressing recombinant wild-type and variant UGT2B15s.	Hanioka et al. (2011)

APPENDIX F. KC2, IS GENOTOXIC

Section F1 Genotoxicity studies of BPA – studies using human cells *in vitro*

Table F1 Genotoxicity studies of BPA in human cells *in vitro*

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
Mutations				
Mutations [Single base substitutions (SBS); double base substitutions (DBS); small insertions and deletions (InDel)]	Immortalized embryonic kidney HEK 293T cells	100 µM for 24 hours	Increased mutation frequency compared to DMSO control at a noncytotoxic concentration.	Hu et al. (2021)
Mutations [Base substitutions at K-*ras* codon 12; Ouabain resistance]	Embryo-derived fibroblasts (RSa cells) [doubly-infected with Simian virus 40 and Rous sarcoma virus]	0.01, 0.1, 1, 10 µM for 6 days [K-*ras* codon 12] 0.001, 0.01, 0.1, 1, 10 µM for 21 days [ouabain resistance]	K-*ras* codon 12: BPA ≥ 0.1 µM increased mutations in the noncytotoxic concentration range. Ouabain resistance: Increased mutation frequency compared to controls (BPA at 0.1 µM, $p < 0.005$, BPA at 10 µM, $p < 0.05$) in the noncytotoxic concentration range. No effects were observed at BPA 1 µM.	Takahashi et al. (2001), also reported in Chapin et al. (2008)
Chromosomal effects				
Micronuclei (MN) [Cytokinesis blocked micronucleus (CBMN) assay]	Embryo L-02 hepatocytes	0.1, 1, 10 µmol/l (µM) for 24 hours	Increases in MN in the noncytotoxic concentration range (BPA at 10 µM, $p < 0.05$); positive dose-response observed.	Zheng et al. (2012)
MN	Primary foreskin AG01522C fibroblasts	50, 100, 150, 200, 250 µM for 12 hours	No significant difference in MN with BPA treatment, measured in assays with or without cytokinesis blocked.	Lehmann and Metzler (2004)
MN [CBMN assay]	Lymphocytes (collected from five healthy female subjects in Italy)	0.01, 0.02, 0.05, 0.1, 0.2 µg/ml for 48 hours	Increases in MN in the noncytotoxic concentration range (BPA ≥ 0.02 µg/ml [0.09 µM], $p < 0.05$); positive dose-response observed.	Santovito et al. (2018)

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
MN [CBMN assay]	Lymphoblastoid AHH-1 cell line	20, 40, 60, 80 µM	Increases in MN (BPA ≥ 40 µM, $p < 0.05$) in a dose-dependent manner. No cytotoxicity data reported.	Hernandez et al. (2013)
MN [CBMN assay]	Lymphoblastoid AHH-1 cell line	1.5, 3.1, 6.2, 7.7, 9.2, 10.8, 12.3, 18.5, 24.6, 37 µg/ml for 24 hours	Increases in MN (BPA ≥ 12.3 µg/ml (53 µM), $p < 0.05$) in a dose-dependent manner. No cytotoxicity data reported.	Johnson and Parry (2008)
MN [CBMN assay]	Lymphoblastoid MCL-5 cell line	5, 10, 15, 20, 30 µg/ml	Increases in micronucleated binucleate cells (BPA ≥10 µg/ml [43 µM], $p < 0.05$) in a dose-dependent manner. No cytotoxicity data reported.	Parry et al. (2002)
MN	Umbilical vascular endothelial cells (HUVEC)	10 ng/ml [44 nM] and 1 µg/ml [4.4 µM] for 72 hours	Increases in MN at noncytotoxic concentrations:44 nM ($p = 0.0045$) and 4.4 µM ($p = 0.0002$).	Ribeiro-Varandas et al. (2013)
MN [CBMN assay]	Breast adenocarcinoma MCF-7 cells	5 µM for 24 hours	Increases in MN at a noncytotoxic concentration (5 µM BPA, $p < 0.05$).	Kabil et al. (2008)
MN	Colon adenocarcinoma HT29 cells	10 ng/ml [44 nM] and 1 µg/ml [4.4 µM] for 72 hours	No significant difference in MN with BPA treatment.	Ribeiro-Varandas et al. (2013)
MN	Immortalized hepatic bipotent progenitor HepaRG cells	40, and 60 µM for 1 or 7 days	No significant difference in MN with BPA treatment.	Quesnot et al. (2016)
Chromosome aberrations (CA)	Male amniocytes	0.4, 1, 4, 40, 100 µg/ml for 48 hours	Increases in CA at BPA ≥ 1 µg/ml [4.3 µM], $p < 0.05$. Cytotoxicity IC_{50} is 40 µg/ml.	Aghajanpour-Mir et al. (2016)
CA	Female amniocytes	0.4, 1, 4, 40, 100 µg/ml for 48 hours	Increases in CA (1 µg/ml [4.3 µM], 4 µg/ml [17.2 µM], $p < 0.05$). Cytotoxicity IC_{50} is 4 µg/ml.	Aghajanpour-Mir et al. (2016)
CA	Peripheral blood mononuclear cells (PBMC)	25, 50, 100 nM for 48 hours	Increases in CA at BPA ≥ 25 nM ($p < 0.001$), in the noncytotoxic concentration range.	Di Pietro et al. (2020)
CA	Lymphocytes (collected from five healthy female subjects in Italy)	0.01, 0.02, 0.05, 0.1, 0.2 µg/ml for 24 hours	Increases in CA at noncytotoxic concentrations: 0.05 µg/ml [0.22 µM] ($p = 0.002$), 0.1 µg/ml [0.43 µM] ($p = 0.001$), and 0.2 µg/ml [0.87 µM] ($p < 0.001$); dose-dependent relationship observed.	Santovito et al. (2018)
CA	Breast adenocarcinoma MCF-7 cells	0.4, 1, 4, 40, 100 µg/ml for 48 hours	Increases in CA at noncytotoxic concentrations: 4 µg/ml [17.2 µM] and 40 µg/ml [172 µM] ($p < 0.001$)	Aghajanpour-Mir et al. (2016)
Centrosomal abnormalities	Immortalized normal prostate epithelial	0.01, 0.1, 1, 10, 100 nM for 72 hours	For both cell lines: Increases in cells with more than 2 centrosomes (centrosome	Tarapore et al. (2014)

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
	NPrEC and RWPE-1 cell lines		amplification) at 0.01 and 0.1 nM ($p < 0.001$), with a non-monotonic dose-response and a maximal response at 0.1 nM. No cytotoxicity data reported.	
Centrosomal abnormalities	Cervical adenocarcinoma HeLa cell line	100 nM for 5 hours	Increases in unaligned chromosomes and mitotic cells with multipolar spindles ($p < 0.01$). No cytotoxicity data reported.	Kim et al. (2019c)
Centrosomal abnormalities	Lymphoblastoid MCL-5 cell line	5, 10, 15, 20 µg/ml	At 5 µg/ml [22 µM] and above, increases in kinetochore-positive MN, indicating chromosome loss, and concentration-related increase in chromosome non-disjunction ($p < 0.05$). No cytotoxicity data reported.	Parry et al. (2002)
Centrosomal abnormalities	Prostate cancer LNCaP, 22Rv1, C4-2, and PC-3 cell lines	0.01, 0.1, 1, 10, 100 nM for 72 hours	LNCaP and 22Rv1: Increases in cells with more than 2 centrosomes (centrosome amplification) at 0.01 and 0.1 nM ($p < 0.001$), with a non-monotonic dose-response and a maximal response at 0.1 nM. C4-2 and PC-3: Increases in centrosome amplification at all doses, with a monotonic dose-response that plateaus at 0.1 nM BPA; $p < 0.005$ for C4-2 and $p < 0.008$ for PC-3. No cytotoxicity data reported.	Tarapore et al. (2014)
Microtubule abnormalities	Immortalized normal prostate epithelial RWPE-1 cell line	0.1 nM for 2 hours or 72 hours	Increased formation of radial microtubule arrays (asters) at 2 and 72 hours. No cytotoxicity data reported.	Tarapore et al. (2014)
Microtubule abnormalities	Cervical adenocarcinoma HeLa cells	100 nM for 5 hours	BPA at 100 nM interfered with spindle microtubule (MT) attachment to kinetochores; interrupted proper localization of MT-associated proteins on the mitotic spindle; and disrupted centriole duplication cycle ($p < 0.01$). No cytotoxicity data reported.	Kim et al. (2019c)
DNA damage				
DNA adducts (8-OHdG)	Spermatozoa (collected from	300 µM for 20 hours	Increased 8-OHdG DNA adduct formation at a	Barbonetti et al. (2016)

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
	healthy 25–30-year-old males)		noncytotoxic concentration (3.5-fold; $p < 0.05$).	
DNA adducts	Non-tumorigenic prostate epithelial PNT1a cell line	200–250 nM for 24 hours, or 1 nM for 2 months	Increased DNA adducts detected by ^{32}P postlabeling (with acute exposure for 24 hours, $p < 0.05$, and with chronic exposure for 2 months, $p = 0.08$).	De Flora et al. (2011)
DNA adducts	Metastatic prostate carcinoma PC3 cell line	200–250 nM for 24 hours	Increased DNA adducts detected by ^{32}P postlabeling, $p < 0.01$.	De Flora et al. (2011)
DNA strand breaks [Alkaline comet assay]	Normal bronchial epithelial cells (BEAS-2B cell line)	12.5, 25, 50, 100, 200 µM for 24 hours	Increased DNA strand breaks at a cytotoxic concentration (200 µM, $p < 0.05$). Cytotoxicity IC_{50} is approximately 100 µM.	George and Rupasinghe (2018)
DNA strand breaks [Alkaline comet assay]	Normal gingival fibroblast (HGF cell line)	0.5, 5, 50, 100 µg/ml	Increase in DNA strand breaks (5 µg/ml [22 µM], $p < 0.001$; 50 [220 µM] and 100 µg/ml [440 µM], $p < 0.0001$) in a dose-dependent manner; cytotoxicity IC_{50} is 10 µg/ml [44 µM].	Ebrahimi et al. (2021)
DNA strand breaks [Alkaline comet assay]	Normal embryo-derived lung fibroblast MRC-5 cell line	0.44, 4.4 nM, and 4.4 µM for 48 hours	No increase in treated groups compared to vehicle control.	Ramos et al. (2019)
DNA strand breaks [Alkaline comet assay]	Bone marrow stem cell line (MSC)	0.5, 5, 50, 100 µg/ml	Increase in DNA strand breaks (5 µg/ml [22 µM], 50 [220 µM], and 100 µg/ml [440 µM], $p < 0.0001$) in a dose-dependent manner; cytotoxicity IC_{50} is 10 µg/ml [44 µM].	Ebrahimi et al. (2021)
DNA strand breaks [Alkaline comet assay]	Peripheral blood mononuclear cells	1, 3, 10 nM for 24 hours or 22 days	Increased DNA strand breaks at 22 days (1, 3, and 10 nM, $p < 0.01$) in the noncytotoxic concentration range. No significant effect at 24 hours.	Herz et al. (2017)
DNA strand breaks [Alkaline comet assay]	Peripheral blood mononuclear cells	0.01, 0.1, 1, 10 µg/ml for 1 or 4 hours	Increases in DNA strand breaks at ≥0.1 µg/ml [0.43 µM] for 1 hour ($p < 0.05$) and at ≥0.01 µg/ml [0.043 µM] for 4 hours ($p < 0.05$); in the noncytotoxic concentration range and in a dose-dependent manner.	Mokra et al. (2017)
DNA strand breaks [Alkaline comet assay]	MCF-10A cells	2 and 4 µg/ml for 3, 6, 24, 48 hours	Increased DNA strand breaks [measured by tail length] at 2 [8.7 µM] and 4 µg/ml [17.5 µM] after 3, 6, 24, and 48 hours, $p < 0.01$.	Jalal et al. (2019)

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
DNA strand breaks [Alkaline comet assay]	Sperm (from Nordic Cryobank)	1, 1.5, 2, 3 µmol/l (µM)	No significant difference in DNA strand breaks with BPA treatment.	Sharma et al. (2018)
DNA strand breaks [Alkaline comet assay]	Immortalized prostate epithelial RWPE-1 cell line	45 µM for 24 hours	Increased DNA strand breaks at 45 µM, $p < 0.05$. Cytotoxicity IC_{20} is 45 µM, IC_{50} is 113.74 µM.	Kose et al. (2020)
DNA strand breaks [Alkaline comet assay]	Colon cancer MKN45 cell line	0.5, 5, 50, 100 µg/ml	Increase in DNA strand breaks at 5 µg/ml [22 µM], 50 [220 µM], and 100 µg/ml [440 µM] ($p < 0.0001$), in a dose-dependent manner; cytotoxicity IC_{50} is 10 µg/ml [44 µM].	Ebrahimi et al. (2021)
DNA strand breaks [Alkaline comet assay]	HepG2 cells	1, 10, 100, 1000 µg/l for 4 or 24 hours	Increase in DNA strand breaks at ≥ 10 µg/l [43.5 nM], $p < 0.05$ for 4 hours and $p < 0.001$ for 24 hours, in the noncytotoxic concentration range in a dose-dependent manner.	Balabanic et al. (2021)
DNA strand breaks [Alkaline comet assay]	HepG2 cells	0.01, 0.1, 1 µM for 24 hours	Increase in DNA strand breaks at 0.01, 0.1, and 1 µM ($p < 0.01$) in the noncytotoxic concentration range in a dose-dependent manner.	Li et al. (2017b)
DNA strand breaks [Alkaline comet assay]	Laryngeal carcinoma (Hep-2) cells	0.44, 4.4 nM, and 4.4 µM for 48 hours	Increase in DNA strand breaks at 0.44 nM compared to vehicle control (p-value not provided), but not at 4.4 nM or 4.4 µM.	Ramos et al. (2019)
DNA strand breaks [Alkaline comet assay]	MCF-7 cells	0.01, 1, 100 µM (0.002–23 mg/l), without metabolic activation for 3 hours	Increase in DNA strand breaks at ≥ 1 µM ($p < 0.01$) in the noncytotoxic concentration range in a dose-dependent manner.	Iso et al. (2006), also reported in Chapin et al. (2008)
DNA strand breaks [Alkaline comet assay]	MCF-7 cells	2 and 4 µg/ml for 3, 6, 24, 48 hours	Increase (not statistically significant) in DNA strand breaks, measured by tail length, at 2 [8.7 µM] and 4 µg/ml [17.5 µM] for 3, 6, 24, or 48 hours.	Jalal et al. (2019)
DNA strand breaks [Alkaline comet assay]	MCF-7 cells	1, 10, 25, 50, 100 µM for 24 hours	Increase in DNA strand breaks at cytotoxic concentrations (10, 25, 50 µM, $p < 0.001$). Cytotoxicity IC_{50} is 10 µM.	Lei et al. (2017)
DNA strand breaks [Alkaline comet assay]	Breast cancer (ER-negative) MDA-MB-231 cell line	100 µM (23 mg/l) without metabolic activation for 3 hours or 24 hours	Increase in DNA strand breaks at a noncytotoxic concentration ($p < 0.05$).	Iso et al. (2006), also reported in Chapin et al. (2008)

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
DNA strand breaks [Alkaline comet assay]	MDA-MB-231 cell line	2 and 4 µg/ml for 3, 6, 24, 48 hours	Increase in DNA strand breaks, measured by tail length, at 2 [8.7 µM] and 4 µg/ml [17.5 µM] for 6, 24, or 48 hours ($p < 0.001$) and at 2 µg/ml [8.7 µM] for 3 hours ($p < 0.001$).	Jalal et al. (2019)
DNA strand breaks [Alkaline comet assay]	HeLa cell line	8.96, 17.9, 35.8 µM for 24 hours	Increase in DNA strand breaks at a cytotoxic concentration (35.8 µM, $p < 0.05$). Cytotoxicity IC_{50} is 35.8 µM.	Park and Choi (2007)
DNA double strand breaks [Comet assay with neutral condition]	Embryo L-02 hepatocytes	0.1, 1, 10 µmol/l (µM) for 24 hours	Increase in DNA double strand breaks at ≥1 µM ($p < 0.05$) in the noncytotoxic concentration range, in a dose-dependent manner.	Zheng et al. (2012)
DNA double strand breaks [Comet assay with neutral condition]	Normal breast epithelial (ER-negative) cell line (184A1 cells)	100 nM for 3 or 24 hours	Increase in DNA double strand breaks at a noncytotoxic concentration (100 nM for 3 hours, $p < 0.0001$; for 24 hours, $p < 0.001$).	Pfeifer et al. (2015)
DNA double strand breaks [Comet assay with neutral condition]	PBMCs	0.01–10 µg/ml for 1 or 4 hours	Increase in DNA double strand breaks at 1 µg/ml [4.3 µM] and 10 µg/ml [43 µM] for 1 hour ($p < 0.05$), and at 10 µg/ml [43 µM] for 4 hours ($p < 0.05$), in the noncytotoxic concentration range.	Mokra et al. (2017)
DNA strand breaks [Modified comet assay with Fpg enzyme]	Normal embryo-derived lung fibroblast MRC-5 cell line	0.44, 4.4 nM, and 4.4 µM for 48 hours	Increases in DNA strand breaks at 4.4 nM and 4.4 µM (*p*-values not provided).	Ramos et al. (2019)
DNA strand breaks [Modified comet assay with Fpg enzyme]	Lymphocytes from PBMCs	0.001, 0.1, 2.5 mM for 1 hour	Increase in DNA strand breaks at 0.001 mM ($p < 0.001$), 0.1 mM ($p < 0.01$), and 2.5 mM ($p < 0.01$); no dose-response relationship observed.	Durovcova et al. (2018)
DNA strand breaks [Modified comet assays with Nth or hOGG1 enzymes]	PBMCs	0.001–10 µg/ml (4.3 nM–43 µM) for 4 or 48 hours	**Nth** (for detection of oxidized pyrimidines): statistically significant increases in DNA strand breaks at ≥ 0.1 µg/ml for 4 hours ($p < 0.05$), and ≥ 0.01 µg/ml for 48 hours ($p < 0.05$); positive dose-response relationships were observed. **hOGG1** (for detection of oxidized purines): statistically	Mokra et al. (2018)

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
			significant increases in DNA strand breaks at ≥ 0.01 µg/ml for 4 hours ($p < 0.05$), and ≥ 0.001 µg/ml for 48 hours ($p < 0.05$); positive dose-response relationships were observed.	
DNA strand breaks [Modified comet assay with Fpg enzyme]	Immortalized prostate epithelial RWPE-1 cells	45 µM for 24 hours	Increase in DNA strand breaks at 45 µM, $p < 0.001$.	Kose et al. (2020)
DNA strand breaks [Modified comet assay with Fpg enzyme]	Laryngeal carcinoma Hep-2 cells	0.44, 4.4 nM, 4.4 µM for 48 hours	No increase in DNA strand breaks with BPA treatment.	Ramos et al. (2019)
DNA damage [γ-H2AX]	Normal bronchial epithelial cells (BEAS-2B cell line)	12.5, 25, 50, 100, 200 µM for 24 hours	Increase in γ-H2AX at a cytotoxic concentration (200 µM, $p < 0.05$); cytotoxicity IC_{50} is approximately 100 µM.	George and Rupasinghe (2018)
DNA damage [γ-H2AX]	Normal fetal lung fibroblasts (WI-38, CCL-75)	0.01–100 µM for 24 hours	Increase in γ-H2AX at a noncytotoxic concentration (100 µM, $p < 0.05$). No data reported for BPA ≤ 100 µM.	Mahemuti et al. (2018)
DNA damage [γ-H2AX]	Immortalized lung IMR-90 fibroblasts	0.1, 1, 100 µM for 24 hours	Increase in γ-H2AX at 1 and 100 µM, $p < 0.05$, in the noncytotoxic concentration range, in a dose-dependent manner.	Hu et al. (2021)
DNA damage [γ-H2AX]	Immortalized NKNT-3 hepatocytes	1–100 µM for 24 or 48 hours	Increase in γ-H2AX (no *p*-values provided) at 2.5, 5, 10, and 100 µM for 24 hours, and at 5 and 10 µM for 48 hours. BPA > 10 µM caused cytotoxicity.	Kim et al. (2018)
DNA damage [γ-H2AX]	Normal breast epithelial HME1 cells	0.0043 nM for 2 months	Increase in γ-H2AX (*p*-values not provided)	Nair et al. (2020)
DNA damage [γ-H2AX]	Normal breast epithelial 184A1 cell line	10 nM for 12, 24, 48, and 72 hours; 10 or 100 nM for 24 hours	Increase in γ-H2AX at 10 nM for ≥ 12 hours (no *p*-values provided) and at 10 and 100 nM for 24 hours ($p < 0.0005$), in the noncytotoxic concentration range.	Pfeifer et al. (2015)
DNA damage [γ-H2AX]	MCF-10A cells	10 nM for 12, 24, 48, or 72 hours; 10 or 100 nM for 24 hours; 10 or 100 nM for 3 hours	Increase in γ-H2AX at 10 nM for ≥ 12 hours (no *p*-values provided), at 10 and 100 nM for 24 hours ($p < 0.0005$), and at 10 ($p < 0.01$) and 100 nM for 3 hours ($p = 0.01$), in the	Pfeifer et al. (2015)

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
			noncytotoxic concentration range.	
DNA damage [γ-H2AX]	Immortalized embryonic kidney HEK 293T cells	0.1, 1, 100 μM for 24 hours	Increase in γ-H2AX at 0.1 μM ($p < 0.05$), 1 and 100 μM ($p < 0.01$) in the noncytotoxic concentration range, in a dose-dependent manner.	Hu et al. (2021)
DNA damage [γ-H2AX]	PBMCs	50 nM for 24 or 48 hours	Increase in γ-H2AX at 50 nM for 24 hours, $p < 0.01$, at a noncytotoxic concentration. No increase at 48 hours compared to controls.	Di Pietro et al. (2020)
DNA damage [γ-H2AX]	CD3+ T cells [PHA stimulated PBMCs]	50 nM for 48 hours	Increase in γ-H2AX at a noncytotoxic concentration ($p < 0.01$).	Di Pietro et al. (2020)
DNA damage [γ-H2AX]	CD4+ T cells [PHA stimulated PBMCs]	50 nM for 48 hours	Increase in γ-H2AX at a noncytotoxic concentration ($p < 0.05$).	Di Pietro et al. (2020)
DNA damage [γ-H2AX]	CD8+ T or CD19+ B cells [PHA stimulated PBMCs]	50 nM for 48 hours	No significant difference in γ-H2AX with BPA treatment.	Di Pietro et al. (2020)
DNA damage [γ-H2AX]	Colorectal epithelial adenocarcinoma LS174T cells	1, 5, 10, 50 μM for 24 hours	No significant difference in γ-H2AX with BPA treatment.	Audebert et al. (2011)
DNA damage [γ-H2AX]	Colorectal carcinoma cell lines: HCT116 p53 wild-type (p53+/+) and HCT116 p53 null (p53−/−)	5 and 10 μM for 24 hours	Increases in γ-H2AX at both concentrations (no *p*-values provided) in the noncytotoxic concentration range, in a dose-dependent manner.	Kim et al. (2018)
DNA damage [γ-H2AX]	HepG2 cells	1, 5, 10, 50, 100 μM for 24 hours	No significant difference in γ-H2AX with BPA treatment.	Audebert et al. (2011)
DNA damage [γ-H2AX]	HepG2 cells	2.5, 5, 10, 20 μg/ml for 24 or 72 hours	Increase in γ-H2AX at 20 μg/ml [86 μM] for 72 hours ($p < 0.0001$), at a noncytotoxic concentration. No increase at 24 hours compared to controls.	Hercog et al. (2019)
DNA damage [γ-H2AX]	HepG2 cells	10 μg/ml (43 μM) for 72 hours	No significant difference in γ-H2AX with BPA treatment.	Hercog et al. (2020)
DNA damage [γ-H2AX]	HepG2 cells	0.1, 1, 100 μM for 24 hours	Increase in γ-H2AX at 0.1 μM, ($p < 0.01$), 1 μM ($p < 0.01$), and 100 μM ($p < 0.001$) in the noncytotoxic concentration range, in a dose-dependent manner.	Hu et al. (2021)
DNA damage [γ-H2AX]	HepG2 cells	0.5, 1, 5, 10 μM for 24 hours	Increases in γ-H2AX (no *p*-values provided) at 0.5, 1, 5, and 10 μM in the noncytotoxic concentration range, in a dose-dependent manner.	Kim et al. (2018)

Test endpoint	Cell type or tissue	Concentration/ duration	Results/comments	Reference
DNA damage [γ-H2AX]	HepG2 spheroids	100 nM for 24 hours	Increase in γ-H2AX (no *p*-value provided) at a noncytotoxic concentration.	Kim et al. (2018)
DNA damage [γ-H2AX]	HepaRG cells	40 and 60 μM for 24 hours	Increase in γ-H2AX at both doses ($p < 0.05$) in the noncytotoxic concentration range, in a dose-dependent manner.	Quesnot et al. (2016)
DNA damage [γ-H2AX]	MCF-7 cells	1 μM for 3 hours	Increase in γ-H2AX (no *p*-value provided) at a noncytotoxic concentration.	Iso et al. (2006)
DNA damage [γ-H2AX]	MCF-7 cells	10 nM for 12, 24, 48, and 72 hours; 10 or 100 nM for 24 hours	Increases in γ-H2AX at 10 nM for ≥ 12 hours (no *p*-values provided) and at 10 and 100 nM for 24 hours ($p < 0.0005$) in the noncytotoxic concentration range.	Pfeifer et al. (2015)
DNA damage [γ-H2AX]	MCF-7 cells	0.0043 nM for 2 months	Increase in γ-H2AX (*p*-values not provided)	Nair et al. (2020)
DNA damage [γ-H2AX]	MDA-MB-231 cells	10 nM for 12, 24, 48, and 72 hours; 10 or 100 nM for 24 hours	Increases in γ-H2AX at 10 nM for ≥ 12 hours (no *p*-values provided) and at 10 and 100 nM for 24 hours ($p < 0.0005$) in the noncytotoxic concentration range.	Pfeifer et al. (2015)
DNA damage [γ-H2AX]	Renal cell adenocarcinoma ACHN cells	1, 5, 10, 50, 100 μM for 24 hours	Increase in γ-H2AX at 10 μM (noncytotoxic concentration, $p < 0.05$), 50 μM (61% cell viability, $p < 0.01$), and 100 μM (32% cell viability, $p < 0.01$).	Audebert et al. (2011)
Unscheduled DNA synthesis (UDS)	Embryo-derived fibroblasts (RSa cells) [doubly infected with Simian virus 40 and Rous sarcoma virus]	0.001–10 μM without metabolic activation for 24 hours	Increase in UDS at the noncytotoxic concentration of 1 μM ($p < 0.05$) and decrease in UDS at 0.1 and 10 μM ($p < 0.05$).	Takahashi et al. (2001), also reported in Chapin et al. (2008)
DNA damage response [Western blot analysis for DNA damage markers]	Normal breast epithelial HME1 cells and MCF-7 cells	0.0043 nM for 2 months	HME1 and MCE-7 cells: Increased expression (no *p*-value provided) of p-Chk1, p-Chk2, and p-p53 proteins, at a noncytotoxic concentration.	Nair et al. (2020)
DNA damage response [gene expression]	HepG2 cells	10 μg/ml (43 μM) for 24 hours	No effect on DNA damage response (measured by expression of TP53, MDM2, CDKN1A, GDD45A, CHEK1, ERCC4).	Hercog et al. (2019)

CBMN, Cytokinesis blocked micronucleus; UDS, Unscheduled DNA synthesis; Fpg enzyme, formamidopyrimidine-DNA glycosylase; Nth, endonuclease III; hOGG1, human 8-oxoguanine DNA glycosylase; γ-H2AX, phosphorylated histone H2AX (Ser139); PHA, phytoemagglutinin; TP53, tumor protein P53; p-p53, phospho-p53 (Thr18); MDM2, MDM2 proto-oncogene; CDKN1A, cyclin-dependent

kinase inhibitor 1A; GDD45A, growth arrest and DNA damage inducible gene alpha; CHEK1, checkpoint kinase 1; p-Chk1, phospho-Chk1 (Ser345); p-Chk2, phospho-Chk2 (Thr68) [phosphorylated checkpoint kinase 2]; ERCC4, ERCC excision repair 4, endonuclease catalytic subunit.

Comet assay is also known as the single cell gel electrophoresis assay (SCGE). It is a measurement of the proportion of total DNA that is present in the tail (tail DNA%).
Alkaline comet assay, the technique applies lysis of the cells in alkaline (pH > 13) conditions.
Comet assay with neutral condition, the technique applies lysis of the cells in neutral (PH = 8) conditions.

Section F2 Genotoxicity studies of BPA – animal studies *in vivo*

Ten studies were reviewed by (Chapin et al. 2008) [See Appendix Table F2, *In vivo* genetic toxicity studies of bisphenol A, excerpted from CERHR (2008) Appendix II, Table 58 (*i.e.*, Chapin et al. (2008), page 226)]. More than 30 publications on this topic have published since 2008, and these studies are briefly discussed below.

Mutations

- A significant increase in dominant lethal mutation rate during the fourth (22–28 days post BPA exposure) ($p < 0.01$) and sixth (36–42 days post BPA exposure) ($p < 0.05$) week of mating intervals was observed in male Holtzman rats treated with 5 mg/kg-day BPA via gavage for 6 days (Tiwari and Vanage 2013).
- Administration of BPA to male SD rats via intraperitoneal injections (85 mg/kg-day for a total of five injections) did not cause dominant lethal mutations in germ cells (abstract only reported in Bond et al. (1980), also reported in Chapin et al. (2008), Haighton et al. (2002), and EU (2003)). Haighton et al. (2002) noted that 'The treatment dose of 85 mg/kg-day was reported to be the maximum tolerated dose'.
- Exposure to 10000 ppm BPA to *Drosophila melanogaster* via feeding did not induce mutations in the germ cells of offspring measured by the sex-linked recessive lethal (SLRL) test (Foureman et al. (1994), also reported in Chapin et al. (2008), Haighton et al. (2002), and EU (2003)). The SLRL test, a forward mutation assay, detects both point mutations and small deletions, in the germ line of the insect.

Chromosomal effects

<u>Micronuclei (MN)</u>

Rats

- A significant dose-dependent increase ($p < 0.05$) in MN was observed in the bone marrow cells of male and female Holtzman rats treated with noncytotoxic doses of BPA ranging from 0.01 – 50 mg/kg-day for 6 days via gavage (Tiwari et al. 2012).

- A dose-dependent increase (*p*-value was not provided) in MN formation was observed in the bone marrow cells of male Wistar albino rats chronically treated with noncytotoxic doses of BPA ranging from 50 – 1000 µg/kg-day for 90 days via the oral route (Srivastava and Gupta 2016).
- Exposure to 78 – 2500 mg/kg-day of BPA for three days via intraperitoneal *(i.p.*) injection did not increase MN formation in bone marrow cells of male Fischer 344 rats (NTP 1995).
- Administration of 200 mg/kg-day of BPA in drinking water to male SD rats for 10 days did not increase MN formation in bone marrow cells (De Flora et al. 2011).

Mice

- Significant increases ($p < 0.05$) in MN formation were observed in peripheral blood reticulocytes of Pzh:SFIS female mice treated with 10 or 20 mg/kg-day BPA daily in drinking water for 2 weeks (Gajowik et al. 2013).
- Administration of a single dose of BPA to ICR mice via gavage did not increase MN formation in bone marrow cells (500 – 2000 mg/kg BPA as reported in Gudi and Krsmanovic (1999), aka Shell Oil Co. (1999), also reported in Chapin et al. (2008), Haighton et al. (2002), and EU (2003)) or in peripheral blood cells (with 228 mg/kg as BPA reported in Masuda et al. (2005), also reported in Chapin et al. (2008)).
- Exposure to a single oral dose (10 – 100 mg/kg) or a repeat oral dose for five days (10 mg/kg) of BPA to Swiss albino mice did not increase MN formation in bone marrow cells (Naik and Vijayalaxmi 2009).

Other species

- A significant increase ($p < 0.05$) in MN formation was observed in the peripheral erythrocytes of turbot fish (*Scophthalmus maximus*) treated with 50 ppb BPA in aquarium water for three weeks (Bolognesi et al. (2006), also reported in Chapin et al. (2008)).
- A significant increase ($p < 0.001$, 10 mg/l BPA) and a positive dose-dependent relationship (1 – 10 mg/l BPA) in MN formation were observed in the embryonic cells of freshwater snails (*Physa acuta*) treated with BPA in water for one week (Sánchez-Argüello et al. 2012).

<u>Chromosome aberrations (CA)</u>

- A significant dose-dependent increase ($p < 0.05$) in the frequency of CA was observed in the bone marrow cells of male Holtzman rats treated with noncytotoxic doses of BPA ranging from 0.01 – 50 mg/kg-day for 6 days via gavage (Tiwari et al. 2012).

- Exposure to a single oral dose (10 – 100 mg/kg) or a repeat oral dose for five days (10 mg/kg) of BPA to Swiss albino mice did not increase the frequency of CA in bone marrow cells (Naik and Vijayalaxmi 2009).

Meiotic chromosome abnormalities, including congression failure, aneuploidy, hyperploidy, and meiotic delay

- Congression failure rates (one kind of meiotic aneuploidy) in oocytes were significantly increased in a dose-related manner ($p < 0.05$) in juvenile female mice (20 – 22 days old) orally exposed to 20, 40, and 100 µg/kg-day BPA for 6 – 8 days or 20 µg/kg-day for 7 days (Hunt et al. (2003), also reported in Chapin et al. (2008)). Hunt et al. (2003) concluded that BPA was a potential meiotic aneugen.
- An increase in chromosomal abnormalities including incomplete synapsis and end-to-end associations of sister chromatids in pachytene fetal oocytes was observed in pregnant C57Bl/6 mice on GD11.5 implanted with *s.c.* pellets to release BPA at 0.4 µg/day (20 µg/kg-day) for 7 days (Susiarjo et al. (2007), also reported in Chapin et al. (2008)). An increase in hyperploidy was also observed in 2-cell embryos or oocytes from 4–5-week-old female offspring of BPA-treated dams (Susiarjo et al. (2007), also reported in Chapin et al. (2008)).
- A significant dose-dependent increase ($p < 0.0001$) in meiotic chromosome abnormalities was observed in sperm of one-year-old CD1 male mice administered orally by pipette with 20 or 500 µg/kg-day BPA from PND1 – 12 (Vrooman et al. 2015).
- No induction of aneuploidy was observed in oocytes and zygotes of female C57Bl/6 mice orally treated with a single BPA dose (0.2 or 20 mg/kg), with 7 daily administrations of BPA (0.2 or 20 mg/kg-day) or exposed for 7 weeks to 0.4 mg/l BPA in drinking water (Pacchierotti et al. (2008), also reported in Chapin et al. (2008)).
- No delay of meiotic divisions and no induction of aneuploidy were observed in spermatocytes of (102/ElxC3H/El)F1 male mice orally treated with 0.002 – 0.2 mg/kg-day BPA for 6 days (Pacchierotti et al. (2008), also reported in Chapin et al. (2008)).

DNA damage

DNA adducts (details in section 5.3.1)

- DNA adducts were formed in the liver of BPA-treated male CD1 rats (Atkinson and Roy (1995b), also reported in Chapin et al. (2008)), and in the liver and mammary cells of BPA-treated female Swiss CD-1 albino mice (Izzotti et al. 2009).

Oxidative damage to DNA/RNA, measured by oxidized nucleotides (details in section 5.3.5 and Appendix H)

- Significant dose-dependent and time-dependent increases in 5-hydroxymethyl-2′-deoxyuridine and 8-hydroxy-2′-deoxyguanosine in female SD rats (Cho et al. 2009).
- Significant increases of urinary 8-oxoguanosine (8-oxoG, a marker for oxidative damage to RNA) in female SD rats (Li et al. 2019b).
- An increase (*p*-value not provided; statistical analysis not performed) in 8-OHdG was observed in the germinal epithelium of male Wistar rats exposed to BPA *in utero*, via lactation, and directly to 0.1 mg/l BPA in drinking water from PND21 to PND45 (Chianese et al. 2018).
- A significant increase in 8-OHdG was found in male and female Holtzman rats treated with 5 mg/kg-day BPA for six days by the oral route (Tiwari et al. 2012) and in common carp exposed to 2 mg/l BPA in water for 30 days (Gu et al. 2020).
- No significant increases of 8-OHdG were found in zebrafish or fathead minnow exposed to 0.64 to 5.12 mg/l BPA in water (Corrales et al. 2017).

DNA strand breaks, measured by alkaline comet assays

Rats

- A significant increase ($p < 0.05$) in DNA strand breaks was observed in pachytene spermatocytes of adult Wistar male rats treated with 200 µg/kg-day via gavage for 60 days (Liu et al. 2013). Liu et al. (2013) also reported BPA-induced DNA strand breaks in spermatocytes were inhibited by treatment with an estrogen receptor α (ERα) antagonist, ICI 182780. The authors suggest that ERα-mediated meiotic disruption may be a major contributor to BPA-related male reproductive disorders.
- A significant increase ($p < 0.05$) in DNA strand breaks was observed in peripheral blood cells of adult male Wistar albino rats treated with 250 mg/kg-day BPA orally for 4 weeks, but there was no increase in the 125 mg/kg BPA-treated group relative to the controls (Ulutas et al. 2011).
- A significant increase ($p < 0.001$) in DNA strand breaks was observed in isolated heart cells of adult Wistar rats treated with 30 mg/kg-day BPA via *s.c.* for 4 weeks (Amin 2019).
- A significant dose-dependent increase ($p < 0.05$) in DNA strand breaks was observed in the blood lymphocytes of male and female Holtzman rats treated with 0.01 – 50 mg/kg-day BPA orally for 6 days (Tiwari et al. 2012).

- A significant increase ($p < 0.001$) in DNA strand breaks was observed in sperm of male Holtzman rats treated with 5 mg/kg-day for 6 days via gavage (Tiwari and Vanage 2013).
- A significant increase ($p < 0.05$) in DNA strand breaks was observed in hepatic tissue of female rats treated with 10 mg/kg-day BPA via gavage for 30 days (Abdel-Rahman et al. 2018).
- A significant increase ($p < 0.01$) in DNA strand breaks was observed in spermatocytes of male SD rats treated with 200 mg/kg-day BPA via gavage for 10 days relative to the control groups (Wu et al. 2013a).
- Exposure to 200 mg/kg-day of BPA in drinking water for 10 days to adult SD male rats did not increase DNA strand breaks in peripheral blood lymphocytes (De Flora et al. 2011).

Mice

- Significant increases ($p < 0.05$, with all doses of BPA-treated) in DNA strand breaks were observed in sperm, lymphocytes and cells from spleen, kidneys, and lung of Pzh:SFIS male mice treated with 5 – 40 mg/kg-day BPA in drinking water for 2 weeks and cells collected 24 hours after the end of BPA exposure. However, not significant increase in 5 and 10 mg/kg dose groups in germ cells collected 5 weeks after the end of BPA exposure (Dobrzyńska and Radzikowska 2013).
- Significant increases ($p < 0.05$) in DNA strand breaks were observed in lung cells of Pzh:SFIS female mice treated with 5 or 10 mg/kg-day BPA daily in drinking water for 2 weeks (Gajowik et al. 2013).
- A significant increase ($p < 0.05$) in DNA strand breaks was observed in liver cells of male Swiss albino mice treated with 50 mg/kg-day BPA via gavage for 28 days (Elhamalawy et al. 2018).
- A significant dose-dependent increase ($p < 0.01$) in DNA strand breaks was observed in brain cells of juvenile KM male mice treated with 0.1 – 1000 µg/ml BPA (0.5 – 5000 µg/kg-day) via oral route by pipette (Zhou et al. 2017b).
- A significant increase ($p < 0.001$) in DNA strand breaks was observed in testicular cells of CD1 male mice treated with a total dose of 125 mg/kg BPA via gavage, but not in the 250 and 500 mg/kg BPA-treated animals (Sharma et al. 2018). No significant increases were observed in liver, kidney, urinary bladder, colon or lung of BPA-exposed animals (Sharma et al. 2018).

Other species

- Significant increases ($p < 0.05$) in DNA strand breaks were observed in freshwater crustaceans (*Daphnia magna*) treated with 3 or 30 µg/l BPA and in

aquatic midge (*Chironomus riparius*) treated with 50 or 500 µg/l BPA for 24 hours in water (Park and Choi 2009).
- Significant increases ($p < 0.001$) in DNA strand breaks were observed in the larvae of aquatic midge (*Chironomus riparius*) treated with 0.5 or 3 mg/l BPA for 24 or 96 hours in water (Martínez-Paz et al. 2013).
- Significant increases ($p < 0.05$) in DNA strand breaks (measured by % tail DNA and tail length) were observed in third instar larvae of wild type Oregon-R *Drosophila melanogaster* treated with food media containing 2.5 or 5.0 µg/ml BPA from the embryonic stage (egg) (Anet et al. 2019).

DNA strand breaks, measured by γ-H2AX

- An increase (*p*-value was not provided) in γ-H2AX was observed in spermatid of male Wistar rats exposed to BPA *in utero*, via lactation, and directly with 0.1 mg/l BPA in drinking water from PND21-PND45 (Chianese et al. 2018).
- Significant increases ($p < 0.05$) in γ-H2AX were observed in pachytene spermatocytes (germ cells) of adult Wistar male rats treated with 20 µg/kg-day BPA (Liu et al. 2014a) or 200 µg/kg-day BPA (Liu et al. 2013) via gavage for 60 days. Liu et al. (2013) also reported that the BPA-induced γ-H2AX in spermatocytes was inhibited by treatment with an ERα antagonist, ICI 182780.
- A significant increase ($p < 0.05$) in γ-H2AX was observed in hippocampal microglia of Wistar rats exposed to BPA *in utero*, via lactation, and directly with 0.1 mg/l BPA in drinking water from PND21–PND17 (Di Pietro et al. 2020).
- Significant increases ($p < 0.05$) in γ-H2AX were observed in the liver of juvenile SD male and female rats treated with 0.5 or 250 mg/kg-day BPA via gavage for 90 days, starting on PND9 (Kim et al. 2018).
- A significant increase ($p < 0.01$) in γ-H2AX was observed in rat spermatocytes of male SD rats treated with 200 mg/kg-day BPA via gavage for 10 days (Wu et al. 2013a).

Expression of poly(ADP-ribose) polymerase 1 (PARP-1, a marker of genotoxicity)

- Direct cutaneous exposure to 20 µg/ml BPA to adult earthworms (*Eisenia fetida*) for 48 hours significantly increased ($p < 0.05$) the expression of PARP-1 compared to controls. PARP-1 protein is involved in DNA repair processes, which work in the post-translational modification of other DNA repair proteins (Novo et al. 2018).

Table F2 *In vivo* genetic toxicity studies of bisphenol A, excerpted from CERHR (2008) Appendix II, Table 58 (i.e., Chapin et al. 2008, page 226)

Table 58
In Vivo Genetic Toxicity Studies of Bisphenol A

Species and sex	Dose (route)	Cells	Endpoint	Results	Reference
Male rat	85 mg/kg bw/day for 5 days (i.p.)	Germ	Dominant lethality	Negative	Bond et al. (1980)[a,b] (abstract only)
Male rat	200 mg/kg bw (i.p.) and 200 mg/kg bw for 4, 8, 12, or 16 days (oral)	DNA	Adduct formation	Positive	Atkinson and Roy (1995b)
Male and female mouse	500–2000 mg/kg bw (oral)	Bone marrow	Micronuclei	Negative	Gudi and Krsmanovic (1999)[a]; Shell Oil Co. (1999)[b]
Male mouse	1 mmol/kg bw **[228 mg/kg bw]** (oral)	Peripheral blood reticulocyte	Micronuclei	Negative	Masuda et al. (2005)
20–22-day-old female mouse	0.02–0.100 mg/kg bw/day (oral) for 6–8 days or 0.02 mg/kg bw for 3, 5, or 7 days	Oocyte	Congression failure	Positive at all doses; statistically significant with 7-day exposure	Hunt et al. (2003)
Pregnant mouse GD 11.5–18.5	0.4 μg/day s.c. pellet **[~20 μg/kg bw/day]**	Oocyte	Evaluation of pachytene fetal oocyte and of ploidy in oocytes and 2-cell embryos from adults that were exposed in utero	Incomplete synapsis, end-to-end association of sister chromatids, ↑hyperploidy	Susiarjo et al. (2007)
Female mouse	0.2 or 20 mg/kg bw acutely or daily for 7 days or 0.4 mg/L in drinking water for 7 weeks	Oocyte	Aneuploidy	Negative	Pacchierotti et al. (2007)
Male (102/ElxC3H/El) F_1 mouse	0.002–0.2 mg/kg bw for 6 days (oral)	Spermatocyte	Meiotic delay and aneuploidy	Negative	Pacchierotti et al. (2007)
Drosophila melanogaster	10,000 ppm (oral)	Offspring	Sex-linked recessive lethal test	Negative	Foureman et al. (1994)[a,b]
Turbot	50 ppb in aquarium water for 2 weeks	Erythrocyte	Micronuclei	Positive	Bolognesi et al. (2006)

[a]Reviewed by Haighton et al. (2002).
[b]Reviewed by European-Union (2003).

Table F3 *In vitro* genetic toxicity studies of bisphenol A, excerpted from CERHR (2008) Appendix II, Table 57 (i.e., Chapin et al. 2008, pp. 224 – 225).

Table 57
In Vitro Genetic Toxicity Studies of Bisphenol A

Concentration	Cell	Endpoint	Results	Reference
3.3–333.3 μg/plate, with and without metabolic activation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537	Mutagenicity	Negative	Haworth et al. (1983)[a,b]
50–500 μg/plate, with and without metabolic activation	*Salmonella typhimurium* strains TA97a, TA98, TA100, TA102	Mutagenicity	Negative	Schweikl et al. (1998)[a,b]
≤5000 μg/plate with and without metabolic activation	*Salmonella typhimurium* strains TA97, TA98, TA100, TA102	Mutagenicity	Negative	Takahata et al. (1990)[a,b]
≤1000 μg/mL, with and without metabolic activation	*Salmonella typhimurium* strain TA1538 and *Escherichia coli* strains WP2 and WP2uvrA	Mutagenicity	Negative	Dean and Brooks (1978)[a,b]
5–1250 μg/plate, with and without metabolic activation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA	Mutagenicity	Negative	JETOC (1996)[a,b]
1 mM **[228 mg/L]**, with and without metabolic activation	*Salmonella typhimurium* strains TA98 and TA100	Mutagenicity	Negative	Masuda et al. (2005)
0.1–0.2 mM **[23–46 mg/L]**, without metabolic activation	Chinese hamster V79 cells, hprt locus	Mutagenicity	Negative	Schweikl et al. (1998)[a,b]
5–60 mg/L without metabolic activation, 25–200 mg/L with metabolic activation, or 5–60 mg/L with and without metabolic activation[d]	Mouse lymphoma L5178Y cells, $tk^{+/-}$ locus	Mutagenicity	Negative (results questioned due to possible inability to count small colonies)	Myhr and Caspary (1991)[a,b]
Concentrations not specified, with and without metabolic activation	Mouse lymphoma L5178Y cells, $tk^{+/-}$ locus	Mutagenicity	Inconclusive without and negative with metabolic activation	Honma et al. (1999)[a,b]; Moore et al. (1999)[a,b]
25–200 μM **[5.7–46 mg/L]**, without metabolic activation	Syrian hamster embryo cells (Na+/K+ ATPase and hprt loci)	Mutagenicity	Negative	Tsutsui et al. (1998)[a,b]
10^{-8}–10^{-5} M **[0.002–2 mg/L]**, without metabolic activation	Human RSa cells	Mutagenicity	↑ at all doses	Takahashi et al. (2001)
≤500 mg/L, with and without metabolic activation	*Saccharomyces cerevisiae* strain JDI	Mutagenicity	Negative	Dean and Brooks (1978)[a,b]
10^{-8}–10^{-4} M **[0.002–23 mg/L]**, without metabolic activation	MCF-7 cells	DNA damage (assessed by comet assay)	↑ at ≥10^{-6} M **[0.2 mg/L]**	Iso et al. (2006)
10^{-4} M **[23 mg/L]**, without metabolic activation	MDA-MB-231 cells	DNA damage (assessed by comet assay)	↑	
20–40 mg/L, without metabolic activation and 30–50 mg/L with metabolic activation	Chinese hamster ovary (CHO) cells	Chromosomal aberration	Negative (inconsistent ↑ at high dose with metabolic activation)	Ivett et al. (1989)[a,b]; Tennant et al. (1986, 1987)[b]
350–450 μM **[80–103 mg/L]**, without metabolic activation and ≤250 μM **[57 mg/L]** with metabolic activation	CHO cells, clone WBL	Chromosomal aberration	Positive at ≥400 μM **[91.3 mg/L]** without metabolic activation[c]; negative with metabolic activation	Hilliard et al. (1998)[a]
400 and 450 μM **[91 and 103 mg/L]**, without metabolic activation	CHO cells, clone WBL	Chromosomal aberration	Positive[c]	Galloway et al. (1998)[a]
25–200 μM **[5.7–46 mg/L]**, without metabolic activation	Syrian hamster embryo cells	Chromosomal aberration	Negative	Tsutsui et al. (1998)[a,b]
10–30 mg/L	Epithelial-type rat liver cell line (RL1)	Chromosomal aberration	Negative	Dean and Brooks (1978)[b]
25–200 μM **[5.7–46 mg/L]**, without metabolic activation	Syrian hamster embryo cells	Aneuploidy/ polyploidy		Tsutsui et al. (1998)[a,b]

			Inconclusive (non-dose-related ↑ in aneuploidy at ≥50 μM **[11 mg/L]**)[e]; apparently positive[f]	
0.8–25 mg/L, without metabolic activation and 30–50 μg/mL, with metabolic activation	CHO cells	Sister chromatid exchange	Negative (one small ↑ was not reproducible)	Ivett et al. (1989)[a,b] Tennant et al. (1986)[b]
0.2–0.5 mM or nM[d] **[46–114 mg/L or μg/L]**	Rat hepatocytes	DNA strand breaks	Negative (↑ noted but scored as negative by study authors due to excessive cytotoxicity)	Storer et al. (1996)[a,b]
10^{-9}–10^{-5} M **[0.0002–2 mg/L]**, without metabolic activation	Human RSa cells	Unscheduled DNA synthesis	↑ at 10^{-6} M **[0.2 mg/L]** and ↓ at 10^{-7} **[0.02 mg/L]** and 10^{-5} M **[2 mg/L]**	Takahashi et al. (2001)
Not specified, but stated to cover range of cytotoxicity	A31-1-13 clone of BALB/c-3T3 cells	Transformation	Negative	Matthews et al. (1993)[a]
25–200 μM **[5.7–46 mg/L]**, without metabolic activation	Syrian hamster embryo cells	Transformation	Positive at ≥50 μM **[11.4 mg/L]** (non-dose-related ↑)[e]; equivocal[f]	Tsutsui et al. (1998, 2000)[a,b]
≤50 mg/L for 24 hr; ≤30 mg/L for 7 days, without metabolic activation	Syrian hamster embryo cells	Transformation	Negative	LeBoeuf et al. (1996)[a]
2–60 mg/L	Syrian hamster embryo cells	Transformation	Negative	Jones et al. (1988)[b]
50–200 μM **[11.5–46 mg/L],** without metabolic activation	Syrian hamster embryo cells	DNA adduct formation	Positive at ≥50 μM **[11 mg/L]** (dose-related ↑)	Tsutsui et al. (1998)[a,b]
1000 μg presence of peroxidase and hydrogen peroxide	Purified rat DNA	DNA adduct formation	Positive	Atkinson and Roy (1995a)
10–100 μM **[2.3–23 mg/L]**, metabolic activation unknown	Bovine brain microtubule protein	Inhibited microtubule polymerization	Positive	Metzler and Pfeiffer (1995)[a]
50–200 μM **[11.5–46 mg/L]**, no metabolic activation	Bovine brain microtubule protein	Inhibited microtubule polymerization	Positive (dose-related)	Pfeiffer et al. (1996)[b]
20–200 μM **[4.6–46 mg/L]**, metabolic activation unknown	Bovine brain microtubule protein	Inhibited microtubule polymerization	Positive (EC_{50} = 150 μM **[34 mg/L]**)	Pfeiffer et al. (1997)[a,b]
200 μM **[46 mg/L]**, without metabolic activation; 100 μM **[23 mg/L]** for metaphase arrest assay	Chinese hamster V79 cells	Aneuploidogenic potential as assessed by micronuclei formation, microtubule assay, and metaphase arrest	Positive	Pfeiffer et al. (1997)[a,b]
100–200 μM **[23–46 mg/L]**, without metabolic activation	Chinese hamster V79 cells	Aneuploidogenic potential as assessed by micronuclei formation	Positive	Ochi (1999)[a,b]
10 or 30 μM **[2.3 or 6.9 mg/L]**	Oocytes from Balb/c mice	Meiotic spindle formation	Centrosomes and spindles disorganized	Can et al. (2005)
0.05–0.4 mg/L	Oocytes from MF_1 mice	Aneuploidy	No hyper haploidy but ↑ diploid metaphase II oocytes at 0.2 mg/L	Pacchierotti et al. (2007)

[a]Reviewed by Haighton et al. (2002).
[b]Reviewed by European-Union (2003).
[c]According to the Haighton et al. (2002) review, positive results occurred at cytotoxic concentrations.
[d]Discrepancies noted between information presented by Haighton et al. (2002) and European-Union (2003).
[e]Conclusion by Haighton et al. (2002).
[f]Conclusion by European-Union (2003).
↑,↓ increase, decrease.

APPENDIX G. KC4, INDUCES EPIGENETIC ALTERATIONS

Table G1 Function of genes evaluated in the human studies reviewed in section 5.3.4

Gene Symbol	Gene Name	Gene Expression Product and Function
ADAM33	ADAM Metallopeptidase Domain 33	• ADAM family encodes transmembrane glycoproteins with a variety of functions, including cell adhesion and proteolysis (Yang et al. 2018). • ADAM33 expression may play role in development of gastric cancer and laryngeal carcinoma (Kim et al. 2009; Topal et al. 2012).
ARHGAP9	Rho GTPase Activating Protein 9	• Rho GTPases regulate cytoskeletal dynamics and affect many cellular processes (Han et al. 2021). Implicated in regulating adhesion hematopoietic cells to extracellular matrix (NCBI 2022). • Implicated in many hematopoietic cancers and other cancers (e.g., breast, liver) (GeneCards 2022; MalaCards 2022).
BAALC	Brain And Acute Leukemia Cytoplasmic Binder Of MAP3K1 And KLF4	• Gene identified by gene expression studies in AML patients. Tissues that express it develop from the neuroectoderm (GeneCards 2022). • Implicated in many cancers (MalaCards 2022), including breast (Birgersson et al. 2021), esophagus (Zhang et al. 2021a), and leukemia (Eisfeld et al. 2012; Hagag et al. 2018).
BDNF	Brain-derived neurotrophic factor	• Signaling molecule that activates signaling cascades downstream of NTRK2. Promotes survival and differentiation of neurons; participates in axonal grown; major regulator of synaptic transmission (UniProt 2022). • Implicated in brain cancers, neuroblastoma, breast cancer (MalaCards 2022).
CAPS2	Calcyphosine 2	• Encodes a calcium-binding protein. May participate in cAMP and calcium-phosphatidylinositol pathways (Wang et al. 2002). • Involved in several cancers, including lung, ovarian, endometrial (MalaCards 2022), colorectal cancer (Shao et al. 2016), esophageal (Li et al. 2017a).

Gene Symbol	Gene Name	Gene Expression Product and Function
ESR1	Estrogen receptor 1	• Encodes an estrogen receptor and ligand-activated transcription factor. Protein encoded by ESR1 regulates transcription of many estrogen-inducible genes that play a role in growth, metabolism, and other functions (NCBI 2022). • Involved in many cancers, including breast, endometrial, ovarian, and others (CIViC 2022).
FAM59B (now called GAREM2)	GRB2 Associated Regulator of MAPK1 Subtype 2	• Encodes an adaptor in the EGF signaling pathway (Taniguchi et al. 2013). Related to MAPK pathway in congenital thyroid cancer (GeneCards 2022). • Regulates tumor cell malignancy in cultured human NIH3T3 and HeLa cells (Tashiro et al. 2009). • Expressed in neuroblastoma cell lines (Taniguchi et al. 2013), multiple myeloma cells (Claudio et al. 2002), and human colorectal carcinoma cell lines (Frigola et al. 2002).
FBXO47	F-Box Protein 47	• Encodes a protein that acts as a ubiquitination inhibitor during meiosis and maintains telomere integrity. Potential role as a tumor suppressor (Simon-Kayser et al. 2005). • Associated with papillary renal cell carcinoma (Simon-Kayser et al. 2005), gastric cancer (Zhang et al. 2020a).
GRIN2B	Glutamate ionotropic receptor NMDA type subunit 2B	• Encodes a member of the N-methyl-D-aspartate (NMDA) receptor family, which mediate calcium permeability in the central nervous system (GeneCards 2022). • Mostly associated with neurodevelopmental disorders but altered methylation has been reported to be altered in some cancers (breast, ovarian, gastric, bladder, lung) (MalaCards 2022).
HDAC4	Histone deacetylase 4	• Encodes a protein that possesses histone deacetylase activity and represses transcription when tethered to a promoter (NCBI 2022). Histone deacetylation is a key factor in epigenetic regulation and plays an important role in transcriptional regulation, cell cycle progression, and development (GeneCards 2022).

Gene Symbol	Gene Name	Gene Expression Product and Function
		• Involved in many cancers, including breast cancer, multiple myeloma, hepatocellular carcinoma, and lung cancer (MalaCards 2022).
HKR1 (now called ZNF875)	Zinc Finger Protein 875	• Transcriptional repressor, predicted to be involved in negative regulation of transcription by RNA polymerase II (Alliance Genome 2022). • Possibly induced in lung cancer (Oguri et al. 1998).
HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	• Heterodimer anchored in the membrane that plays a central role in the immune system. Expressed in antigen presenting cells (NCBI 2022). • Involved in several lymphohematopoietic cancers, skin cancer, brain cancer, and others (MalaCards 2022).
HLA-DRB6	Major histocompatibility complex, class II, DR beta 6 (pseudogene)	• One of the major histocompatibility complex genes present in DR1, DR2, and DR10 haplotypes, found in about 26% of human HLA haplotypes (Wikigenes 2022). • Possibly involved in lung cancer (Dai et al. 2021).
HOXA10	Homeobox A10	• Encodes a DNA-binding transcription factor that may regulate gene expression, morphogenesis, and differentiation. Functions in fertility, embryonic development, and regulation of hematopoietic lineage commitment (NCBI 2022). • Involved in ovarian clear cell carcinoma, endometrial cancer, lymphohematopoietic cancers, gastric cancer, and others (MalaCards 2022).
IGF2R	Insulin like growth factor 2 receptor	• Involved in intracellular trafficking of lysosomal enzymes, activation of transforming growth factor beta, and degradation of insulin-like growth factor 2. Related to G protein-coupled receptor pathway and ERK signaling (GeneCards 2022). • Associated with hepatocellular carcinoma, breast cancer, colorectal cancer, pancreatic cancer, and others (MalaCards 2022).
IL-6ST	Interleukin 6 Cytokine Family Signal Transducer	• Encodes a signal transducer shared by many cytokines. Mediates signals that regulate immune response, hematopoiesis, bone metabolism, neuron survival, and other functions (GeneCards 2022).

Gene Symbol	Gene Name	Gene Expression Product and Function
		• Involved in breast cancer, leukemia, liver cancer, prostate cancer, and other cancers (MalaCards 2022).
MAPK1	Mitogen-activated protein kinase 1	• Encodes a member of the MAP kinase family, which act as an integration point for many biochemical signals and are involved in cellular processes such as proliferation, differentiation, transcription regulation, and development (GeneCards 2022). • Involved in lung, colorectal, ovarian, pancreatic, and several other cancers (MalaCards 2022).
MEST	Mesoderm specific transcript	• Plays a role in mesoderm development; loss of imprinting of this gene has been linked to some cancers (Wang et al. 2021g). Regulates pathway-mediated tumor metastasis (Kim et al. 2019b). • Associated with ovarian cancer, choriocarcinoma, breast cancer, lung cancer, and other cancers (MalaCards 2022).
NDN	Necdin, MAGE family member	• Encodes a growth suppressor that facilitates cell cycle arrest; binds to and represses activity of cell-cycle-promoting proteins; interacts with p53 to inhibit cell growth (UniProt 2022). • Downregulated in several cancers, including embryonal carcinoma, ovarian cancer, colorectal cancer, and other cancers (MalaCards 2022).
P2RX5	Purinergic receptor P2X 5	• Encodes a receptor for ATP that functions as a ligand-gated ion channel (GeneCards 2022). • Altered expression found in colorectal cancer, familial papillary thyroid cancer, glioblastoma, and other cancers (MalaCards 2022).
RAB40B	Member RAS oncogene family	• Encodes a component of E3 ubiquitin ligase complex, which mediates ubiquitination and proteasomal degradation of target proteins (GeneCards 2022). Involved in tumor-related process, including cell migration, invasion, proliferation, communication, and metastasis (Li et al. 2015; Zacharias et al. 2018). • Associated with gastric, breast, and lung cancer (MalaCards 2022).
RFX7	Regulatory factor X7	• Encodes a transcription factor; regulates multiple tumor suppressors, including p53 (Coronel et al. 2021).

Gene Symbol	Gene Name	Gene Expression Product and Function
		• Linked to several lymphohematopoietic cancers, breast cancer, and cervical cancer (MalaCards 2022).
STAT3	Signal transducer and activator of transcription 3	• Encodes a signal transducer and transcription activator, mediates expression of genes in response to cell stimuli and involved in cell cycle regulation, regulator of inflammatory response (GeneCards 2022). • Involved in many cancers, including lung, breast, colorectal, liver, prostate, ovarian and pancreas (MalaCards 2022).
SVIL	Supervillin	• Encodes a protein that is a high-affinity link between the actin cytoskeleton and the membrane. Contributes to myogenic membrane structure differentiation (GeneCards 2022). • SVIL isoforms have been implicated in stages of tumor development, including cell survival, migration, and metastasis (Zhao et al. 2020). • Involved in liver, lung, prostate, and other cancers (MalaCards 2022; Zhao et al. 2020).
TNFRSF25	TNF receptor superfamily member 25	• Encodes a receptor that stimulates NF-kappa B activity and regulates cell apoptosis; regulates lymphocyte homeostasis (NCBI 2022). • Hypermethylated in hepatocellular carcinoma, renal cell carcinoma, osteogenic sarcoma, salivary gland adenoma, and other cancers (MalaCards 2022).
TSP50 (aka PRSS50)	Testes-specific protease 50; serine protease 50	• Interacts with NF-kappa B (Lu et al. 2018). Novel member of cancer/testis antigens, expressed only in testes and various cancers (Cao et al. 2018a). Potential oncogene (Zhang et al. 2021c). • Involved in proliferation, apoptosis, migration and metastasis of various tumor types (Cao et al. 2018a). • Associated with breast, liver, gastric, testicular, lung, and other cancers (MalaCards 2022; NCBI 2022).

Table G2 Human observational studies on BPA and DNA methylation (ordered by life stage of exposure assessment and age at DNA methylation measurement)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Gene(s) affected	Results	Reference
USA, cross-sectional study, University of Washington Laboratory for the Study of Human Embryology fetal tissues bank. n = 50	Fetal liver tissue	Fetal liver tissue taken from voluntary 1st and 2nd trimester pregnancy terminations (GD74–120)	IL-6ST, STAT3	Hypomethylation of IL-6ST at specific CpG sites was associated with BPA levels but no association with average methylation of IL-6ST locus. Average percent DNA methylation of STAT3 increased when BPA was modeled as a continuous variable. No associations with site-specific methylation of STAT3.	Weinhouse et al. (2015)
USA, cross-sectional study, University of Washington Laboratory for the Study of Human Embryology fetal tissues bank n = 18	Fetal liver tissue	Fetal liver tissue taken from voluntary 1st and 2nd trimester pregnancy terminations (GD80–115)	Many genes	Pathway analysis of hypermethylated regions: strong enrichment of genes involved in regulation of nucleotide metabolic processes and genes predicted to be targeted by AhR in low BPA group compared to non-detects. Hypomethylated regions in the high BPA group vs low BPA group: regulation of metabolic processes. Both hypo- and hyper-: genes downregulated in response to estrogen (e.g., breast	Faulk et al. (2015)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Gene(s) affected	Results	Reference
				carcinoma amplified sequence 4 and breast cancer anti-estrogen resistance 3) in the high BPA group compared to non-detect and low groups and in the low BPA group compared to non-detects.	
China, cohort study, mother-child pairs. n = 146	Mothers' urine collected during 1st trimester of pregnancy, creatinine-adjusted	Placenta	HLA-DRB6, HLA-DRB1, HDAC4, FAM59B, ARHGAP9, RFX7, P2RX5	BPA exposure was associated with hypermethylation of CpG sites in: HLA-DRB6, HLA-DRB1, HDAC4, FAM59B, ARHGAP9, RFX7, P2RX5 and hypomethylation of 1 CpG site in HLA-DRB1.	Song et al. (2021b)
China, cohort study, mother-child pairs. n = 96	Mothers' urine collected during 1st trimester of pregnancy, creatinine-adjusted	Cord blood	CAPS2, TNFRSF25, HKR1	Levels of DNA methylation in promoter regions of HKR1, CAPS2, and TNFRSF25 were significantly higher in participants with BPA detected in maternal urine than those with BPA undetected. Significant positive linear associations observed and significantly different between highest tertile of BPA and undetected BPA.	Song et al. (2020b)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Gene(s) affected	Results	Reference
Germany, cohort study, mother-child pairs. Maternal BPA; DNA from cord blood. n = 472	Mothers' urine collected at 34th week of pregnancy, creatinine-adjusted	Cord blood	MEST, RAB40B	Two CpG sites were found to be significantly different between 1st and 4th quartiles of BPA exposure ($p < 0.001$, significant after Bonferroni correction). Specifically, hypomethylation of a CpG in the promoter region of MEST and of a CpG in an intron of RAB40B were each associated with high maternal BPA.	Junge et al. (2018)
US, cohort study, mother-child pairs. n = 116	Mothers' urine and plasma collected during 1st trimester of pregnancy	Cord blood leukocytes	PPARα, IGF2	BPA in maternal urine associated with a 1.22 (95% CI: -2.27, -0.16) percentage point decrease in methylation of PPARα and a 1.35 (95% CI: -2.69, -0.01) percentage point decrease in methylation of IGF2 in female infants, no significant associations in male infants.	Montrose et al. (2018)
Korea, prospective cohort study, children. n = 59	Mothers' urine collected during 2nd trimester of pregnancy, creatinine-adjusted	DNA from children's blood at ages 2 and 6 years.	IGF2R, SVIL	Methylation significantly increased at CpG site of IGF2R in high BPA exposure group compared to the low BPA exposure group at age 2 ($p = 0.00030$, FDR corrected $p < 0.10$) (not significant at age 6)	Choi et al. (2020c)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Gene(s) affected	Results	Reference
				Distribution of methylation of CpG site on SVIL gene significantly different by prenatal BPA exposure at ages 2 and 6 (p = 0.0012, FDR corrected p < 0.10).	
Sweden, cohort study, 7-year-old boys and girls. n = 317	Mothers' urine collected during 1st trimester of pregnancy, creatinine-adjusted	DNA from children's oral swabs	GRIN2B	Significant association between maternal BPA levels (BPA quartile treated as ordered categorical variable) and methylation level of the first CpG site of GRIN2B in girls. No associations in boys.	Alavian-Ghavanini et al. (2018)
Mexico, cohort study, 8–14-year-old boys and girls. n = 247	Mothers' urine collected during 3rd trimester of pregnancy	Blood	IGF2	Children in the second and third tertiles of *in utero* BPA exposure had hypermethylation of IGF2.	Goodrich et al. (2016)
Taiwan, cross-sectional study, 3-year-old children. n = 228	Urine, creatinine-adjusted	Blood, collected at the same time as the urine samples	MAPK1	BPA levels were negatively correlated with MAPK1 promoter methylation.	Yang et al. (2020)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Gene(s) affected	Results	Reference
Denmark, cross-sectional study, boys and girls through puberty. Examined every 6 months from 6–8 years-old up to 7 years later. n = 102	Urine	Blood, collected at the same time as the urine samples	BAALC, FBXO47, TAPBP, FAM83A, PNOC	Associated with same-day levels of BPA: BAALC, FBXO47, TAPBP Associated with mean yearly dichotomized levels of BPA: BAALC, FBXO47, TAPBP, FAM83A, PNOC.	Almstrup et al. (2020)
Spain, cohort study, adolescent boys. n = 118	Urine collected 9–11 years old, creatinine-adjusted	DNA (blood) collected 15–17 years old	BDNF	BPA concentrations were positively associated with BDNF DNA methylation at CpG6 and mean CpG methylation.	Mustieles et al. (2022)
Egypt, cross-sectional study, 10–13-year-old girls. n = 46	Urine, specific gravity-adjusted	Saliva, collected at the same time as the urine samples	NDN, HOXA10	One CpG site of NDN was significantly less methylated in BPA-high samples ($p < 0.02$). Comparing girls with non-detectable concentrations of BPA (n = 12) to those with BPA concentrations >4 ng/ml (n = 3), significantly less methylated in high samples at the HOXA10 gene.	Kim et al. (2013)
Lebanon, cross-sectional community-based study, adults (age >	Urine, creatinine-adjusted	Blood, collected at the same time as the	ESR1	No significant results when BPA levels and ESR1 promoter % methylation were analyzed as continuous variables in men or	Awada et al. (2019b)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Gene(s) affected	Results	Reference
18 years). n = 482		urine samples		women. In men, association between middle BPA tertile and lowest ESR1 promoter % methylation (OR: 2.63; 95% CI: 1.01–6.88).	
USA, cross-sectional study, women undergoing IVF at UCSF. n = 35	Serum	Blood, collected at the same time as the urine samples	TSP50	DNA methylation of TSP50_P137 site was higher among women in the lower BPA exposure group compared to higher exposure group (p = 0.005).	Hanna et al. (2012)
Taiwan, population-based case-control study, breast cancer patients. n = 44 cases; 125 controls	Urine, creatinine-adjusted	Blood, collected at the same time as the urine samples	ADAM33	No association of BPA with methylation of intron 1 of ADAM33 in cases or controls.	Yang et al. (2018)

Table G3 Human observational studies of BPA effects on global DNA methylation

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Results	Reference
USA, cross-sectional study, University of Washington Laboratory for the Study of	Fetal liver tissue	Fetal liver tissue taken from	BPA exposure associated with hypomethylation of regions of altered methylation in fetal liver DNA. BPA levels	Faulk et al. (2015)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Results	Reference
Human Embryology fetal tissues bank n = 18		voluntary 1st and 2nd trimester pregnancy terminations (GD80–115)	were positively associated with genome-wide DNA methylation in CGIs (CpG islands) and negatively associated with DNA methylation in CGI shores and shelves	
USA, cross-sectional study, University of Washington Laboratory for the Study of Human Embryology fetal tissues bank n = 18	Fetal liver tissue	Fetal liver tissue taken from voluntary 1st and 2nd trimester pregnancy terminations (GD80–115)	Significant hypomethylation of LINEs, LTRs, DNA elements, and satellite repeats were observed in the fetal liver DNA from the medium-BPA group compared to the low-BPA group. 1229 loci containing a transposon with significantly different DNA methylation were identified (medium vs. high). 29 (medium vs. low) and 0 (high vs. low) transposons with differential DNA methylation were identified	Faulk et al. (2016)
USA, cross-sectional study, University of Washington Laboratory for the Study of Human Embryology fetal tissue bank. n = 12	Placental and fetal liver and kidney tissues	Placenta and fetal liver and kidney tissue taken from voluntary 2nd trimester pregnancy terminations (GD91–115)	Free- or total-BPA levels (free- and conjugated-BPA) were positively associated with global methylation at LINE-1 CpG sites in the placenta ($p \leq 0.002$), but not significant in fetal liver or kidney tissues	Nahar et al. (2015)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Results	Reference
Spain, mother-child pairs. n = 318	Mothers' urine collected at week 20 of pregnancy and delivery, creatinine-adjusted	Cord blood	Maternal urinary BPA collected at 24th week of pregnancy was positively associated with LINE-1 methylation in cord blood in adjusted linear regression in all newborns (p = 0.001) and in males (p = 0.01). No associations between BPA and *Alu* methylation were observed. Non-monotonic relationship observed in girls (methylation of 3rd quartile maternal 24-week urinary BPA significantly increased compared to 1st). No associations between maternal urinary BPA collected at delivery with LINE-1 or Alu methylation.	Navarro-Lafuente et al. (2022)
US, mother-child pairs. n = 116	Maternal urine and plasma collected during 1st trimester	Cord blood leukocytes	No association with urine or plasma BPA with LINE-1 methylation overall or in infant girls. Borderline positive association in infant boys (a log unit increase in plasma BPA was associated with 0.55 (95% CI: -0.02, 1.11) percentage point increase in LINE-1 methylation and urine BPA with a 0.6 (95% CI: -0.04, 1.24) percentage point increase).	Montrose et al. (2018)
Mexico, mother-child pairs. n = 239	Maternal urine, creatinine-adjusted	Maternal blood and children/ adolescents	Urinary BPA tertiles were not significantly associated with LINE-1 methylation measured in blood leukocytes	Goodrich et al. (2016)

Study location, design, population, and sample size (n)	BPA exposure assessment	Tissues examined for DNA methylation	Results	Reference
		(aged 8-14) blood		
China, occupational study, male BPA-exposed and unexposed workers (ages 22–50 years) n = 149	Urine, creatinine-adjusted	Semen and blood	Urinary BPA significantly associated with LINE-1 hypomethylation in sperm DNA among all subjects (β, –0.011; $p < 0.001$) and in subjects without occupational BPA exposure (β, –0.012; $p < 0.026$). Urinary BPA not associated with LINE-1 methylation in peripheral blood	Miao et al. (2014)
China, occupational study, male BPA-exposed workers and unexposed community controls (ages 20–49 years) n = 56	Urine, creatinine-adjusted	Semen	BPA-exposed group exhibited significantly increased levels of global DNA hydroxymethylation in CpG islands among semen samples. Increased 5-hmc density in LINE-1, SINE, LTR (lone terminal repeats), satellite repeats were observed	Zheng et al. (2017)
China, occupational study, male BPA-exposed workers and unexposed community controls (ages 20–45 years) n = 158	Urine, creatinine-adjusted	Semen	Urinary BPA positively associated hydroxymethylation in LINE-1 among semen sample ($p < 0.05$)	Tian et al. (2018)

Table G4 Effects of BPA on methylation of individual genes in human cells *in vitro* (ordered by cell type, cell line, with primary cells first)

Cell type/system	BPA concentration (μM), duration	Results	Reference
Brain: SH-SY5Y neuroblastoma cells	0, 0.1, 1, or 10 μM for 48 or 96 hours	No significant changes in DNA methylation of p16, cyclin D2, and Rassf1 genes, with or without BPA treatment.	Senyildiz et al. (2017)
Breast: MCF-7 cells (ER-positive)	0, 0.01, 0.1, 1, 10, or 100 μM for 24 or 48 hours	CpG sites were similarly dysregulated in MCF-7 cells compared to ER+ tumor tissues from breast cancer patients in the Cancer Genome Atlas database (hypomethylated: RGS1, SERPINA6, HRG, ABCC2, SYP, ASAP1, PTTG1; hypermethylated: PHOX2B, MOS, ZNF514, GRIA1)	Awada et al. (2019a)
Breast: MCF-7 cells	0, 1, or 10 μM for 5 weeks	45 genes hypermethylated (including FOXK2, LKB1, LMX1A, CUGBP2); 32 genes hypomethylated (including (PTPRN2, TRIM27, BCAS3, ZNF423) in cells exposed to both concentrations.	Wang et al. (2018b)
Breast: MCF-7 cells	1.5×10^{-6} to 4.8×10^{-6} μM for 2 months	Hypermethylation of TIMP3, CHFR, ESR1, IGSF4 Hypomethylation of CASP8, RASSF1, GSTP1	Nair et al. (2020)
Breast: MCF-10F cells	0, 1, or 10 μM for 2 weeks	6 genes found to be hypermethylated and downregulated in cells treated with 1 and 10 μM BPA (PARD6G, BCL2L11 (or BIM), FOXP1, SFRS11, ELL2 and BTN3A2) 4 genes found to be hypomethylated and upregulated in cells treated 1 and 10 μM BPA (MLL, NUP98, BOLA3, CtIP) [many of these are related to cancer pathways]	Fernandez et al. (2012)
Breast: HME1 breast epithelial cells	1.5×10^{-6} to 4.8×10^{-6} μM for 2 months	Hypermethylation of CDH13, GSTP1	Nair et al. (2020)

Cell type/system	BPA concentration (μM), duration	Results	Reference
Breast: Human mammary epithelial cells (HMEC)	0, 0.01, or 0.1 μM for 1 week	Increased promoter hypermethylation of BRCA1, CCNA1, CDKN2A, THBS1, TNFRSF10C and TNFRSF10D; Decreased promoter hypermethylation of HIC1	Qin et al. (2012)
Embryonic stem cells: hESCs	0, 1 μM throughout differentiation	Hypomethylated: HOXA11, DNMT3B, HTR1A, GNAS, MYF5, GDNF, TBX1 Hypermethylated: PLXNB2, HYH14, GNG4, SMAD3, WNT5B, SMAD2, FGF19, TBX1, NRG1, ERα, IGF-1R, EDNRB, ACVR1, SOX5	Huang et al. (2017a)
Liver: HepG2 cells (hepatocellular carcinoma)	0, 0.1, 1, or 10 μM for 48 or 96 hours	No significant changes in DNA methylation of p16, cyclin D2, and Rassf1 genes	Senyildiz et al. (2016)
Placenta: BeWo cells (a cell line isolated from the placenta of a patient with choriocarcinoma)	0, 100 mM for 48 hours	Hypomethylation of CpG sites of ERα and Erβ promoters	Cao et al. (2022)
Prostate: PC-3 cells (prostate adenocarcinoma)	0, 0.1, 1, or 10 μM for 48 or 96 hours	Significant hypermethylation of p16 in cells exposed to 1 μM for 96 hours and 10 μM for 48 and 96 hours. No significant changes in CyclinD2 or Rassf1. Of 94 tumor suppressor genes analyzed, the promoter methylation status of 11 genes was significantly altered after 96 hours of 0.1, 1, or 10 μM BPA exposure (BCR, GSTP1, LOX, MGMT, NEUROG1, PDLIM4, PTGS2, PYCARD, TIMP3, TSC2, and ZMYDN10).	Fatma Karaman et al. (2019)

Table G5 Effects of BPA on methylation of individual genes in rodents *in vivo* (ordered by species, strain, and life stage of exposure)

Species and strain, sex, group size	Life stage, dosing regimen, duration, route	Results	Gene(s) affected	Reference
a/a wild-type mice (F1), female, 2–3 per group	*In utero* and lactation. 50 ng, 50 µg or 50 mg BPA/kg in diet during gestation and through lactation. Sacrificed at 10 months.	Enriched in significant differentially methylated regions in cancer-related pathways in genomic DNA isolated from the liver. Alterations (increases or decreases in different doses) in Jak, Rxr, Tmem, Rfxap	Jak, Rxr, Tmem, Rfxap	Anderson et al. (2017)
a/a wild-type mice (F1), male and female, 2–6 per group	*In utero* and lactation. 50 µg or 50 mg BPA/kg in diet during gestation and through lactation. Sacrificed PND22.	Enriched in significant differentially methylated regions in cancer-related pathways in genomic DNA isolated from the liver. Increased methylation of Myh7b, decreased methylation of Slc22a12	Myh7b, Slc22a12	Kim et al. (2014b)
BALB/c mice (F1), male and female, ≥ 4 per group	*In utero*. 5 µg/ml BPA via drinking water for one week pre-mating and during gestation. Sacrificed week 10	Significantly decreased methylation of MEST in fat tissue from BPA-treated mice.	Mest	Junge et al. (2018)
BALB/c mice, male and female	*In utero*. 20 µg/kg BPA via oral	Significantly increased CpG methylation in ESR1 in the prefrontal cortex in males (no changes in	Esr1	Kundakovic et al. (2013)

Species and strain, sex, group size	Life stage, dosing regimen, duration, route	Results	Gene(s) affected	Reference
offspring (F1), 6 per group	administration from GD0–19	females) and in the hypothalamus in females (no changes in males)		
C57BL/6J mice, wild-type females mated with Agouti A^{vy}/a males, F1 males and females, 9–31 per group	*In utero* and lactation. 0, 50 ng, 50 µg, or 50 mg/kg in diet during gestation and lactation. Sacrificed on PND22 or at 10 months	No changes in DNA methylation of Esr1 in mouse liver. Mice with hepatic tumors: Il-6st methylation decreased in 50 mg/kg diet group, marginally increased in 50 ng/kg diet group compared to controls. Stat3 methylation decreased in 50 µg/kg diet and 50 mg/kg diet groups compared to mice without tumors All mice: average methylation of Stat3 slightly higher in mice exposed to 50 µg/kg diet and 50 mg/kg diet compared to controls.	Esr1, Il-6st, Stat3	Weinhouse et al. (2015)
C57BL6 mice, female, 4 per group	Adult. 60 µg/kg-day BPA via gavage for 60 days	Hypermethylation of one CpG island near the Hand2 transcription start site, but no change in another CpG island in uteri.	Hand2 [mediator of antiproliferative effects of progesterone in uterus]	Neff et al. (2019)
CD-1 mice, male fetuses (F1), group size not specified	*In utero*. 0, 50, or 500 µg/kg-day BPA via gavage from GD11 to GD17	Significantly increased promoter CpG methylation of Esr1 exon 1A, Esr1 exon 1C, and Esr2 in fetal urogenital sinus mesenchyme	Esr1, Esr2	Bhandari et al. (2019)
CD-1 mice, female offspring (F1), group	*In utero*. 0 or 5 mg/kg BPA via i.p. injection from GD9 to GD16.	Significantly decreased CpG methylation of promoter and intron of Hoxa10 in uterine horns	Hoxa10	Bromer et al. (2010)

Species and strain, sex, group size	Life stage, dosing regimen, duration, route	Results	Gene(s) affected	Reference
size not specified	Female offspring sacrificed 2 weeks after birth			
CD-1 mice, female offspring (F1), 4 per group	*In utero*. 5 mg/kg-day BPA via peritoneal pump from GD9–PND14	Hypomethylation of ESR1 binding genes in uteri	Esr1	Jorgensen et al. (2016)
Kunming mice, male offspring (F1), 10 per group	*In utero*. 5 mg/kg-day BPA via gavage from GD0.5–17.5	Significantly increased methylation in promoter region of ESR1 and H19/Igf2 in testis	Esr1, H19/Igf2	Wei et al. (2020b)
Holtzman rats, male offspring (F1), 4–5 per group	Adult. 2.4 µg/30 µl BPA via s.c. injection from PND1–5. Sacrificed PND125.	Significantly increased methylation of CpG sites in the promoter regions of ESR1 and ESR2 in the adult testis	Esr1, Esr2	Doshi et al. (2011)
SD rats (F1), female, 11 per group	*In utero*. High butter fat diet + BPA (2.5, 25, 250, or 2500 µg/kg-day) in diet prenatally. Sacrificed PND140	Hypermethylation of CpG island of Car7 in mammary glands of BPA-exposed group. Reduced methylation in CpG island of Kcnv2 in 25 µg/kg-day group.	Car7 [*CA7*, carbonic anhydrase VII, associated with colorectal cancer] Kcnv2 [*KCNV2*, voltage-gated K+ channel subunit gene family V member 2]	Leung et al. (2017)
SD rats, male and female offspring	*In utero*, lactation. 0, 40 µg/kg-day BPA via gavage	Significantly increased CpG methylation in promoter region of ESR1 in the hippocampus	Esr1	Chang et al. (2016b)

Species and strain, sex, group size	Life stage, dosing regimen, duration, route	Results	Gene(s) affected	Reference
(F1), 6 per group	through gestation and lactation (44 days)			
SD rats, female, 5 per group	Lactation. 250 µg/kg BPA via gavage through lactation from PND2–PND20. Sacrificed PND100	Many genes hypo- and hypermethylated in mammary gland tissue. Several gene networks are related to cancer	Hypomethylated: Cdh1, Cyp19a1, Erbb2, Esr1, Foxo3, Gsk3b, Id1, Ncoa3, Pak1, PhF19, Prmt2, Pttg1, Rara, Snai1, Vegfa, Znf24, Fchsd2, Smarca4, Traf1 Hypermethylated: Asgr2, Ces1, Ehf, Elf2, Erbb2, Fgf9, Flot2, Homer2, Mapk4, Max, Mir-15, Mmp11, Myc, Pdha1, Pgr, Ptprk, Rhod, Sdpr, Tgfb1, Uck1	Jadhav et al. (2017)
SD rats, male, 22–32 per group	Postnatal. 0, 0.1, 1, 10, 100, 5000 µg/kg BW BPA via s.c. injection on PND1, 3, and 5. Sacrificed at 7 months.	Creb314, Tpd52 and Pitx3 were hypomethylated in prostate tissue compared to control at 0.1, 1, and/or 10 µg/kg. Paqr4 hypomethylated at all doses. Sox2 hypomethylated to greater extent with increasing doses.	Creb314, Tpd52, Pitx3, Paqr4, Sox2 [Tpd52, Creb3L4, and Sox2, are upregulated in prostate cancer; Pitx3 plays a role in development and stem cells; Paqr4 plays a role in cellular metabolism and abnormal expression has been associated with prostate cancer risk]	Prins et al. (2017)

Species and strain, sex, group size	Life stage, dosing regimen, duration, route	Results	Gene(s) affected	Reference
SD rats, male, 30–35 per group	Postnatal. 0 or 10 µg/kg BW via s.c. injection on PND1, 3, and 5. Sacrificed on day 10, 90, or 200.	Significantly hypomethylated Nsbp1 promoter in prostate at all time points. Hypermethylation of Hpcal1 promoter in prostate at days 10 and 90.	Nsbp1 [In family of HMGN proteins. NSBP1/HMGN5 may have oncogenic activities, demonstrated in glioma, bladder cancer, prostate cancer.]	Tang et al. (2012)
SD rats, male, ≥ 3 per group	Postnatal. 50 µg/kg BPA orally on PND1, 3, and 5. Prostate tissue samples taken on day 70	CpG island located close to promoter of Scgb2a1 was significantly hypomethylated in BPA-treated prostates compared control animals.	Scgb2a1	Wong et al. (2015)
SD rats, male, 20–30 per group	Adult. 0.1 µg/kg bw on postnatal days 1, 3, and 5 via s.c. injection. Sacrificed week 28.	No difference in DNA methylation of PDE4D4 in prostates at day 10. At days 90 and 200, CpGs 49-56 of BPA-treated rats were completely unmethylated, compared to oil-control prostates that were completely methylated. Loss of methylation inversely correlated with increased PDE4D4 gene expression.	Pde4d4 [phosphodiesterase type 4 variant 4, encodes an enzyme involved in cyclic AMP degradation; associated with preneoplastic prostatic lesions]	Ho et al. (2006)
Wistar rats, male offspring (F1), 10 per group	*In utero*, lactation. 50 µg/kg-day BPA via gavage *in utero* (GD0–GD21) or *in utero* and lactation (GD0–PND21) or lactation (PND0–PND21)	Significantly increased methylation of CpG site in the promoter region of ESR1 in testis	Esr1	El Henafy et al. (2020)

Table G6 Effects of BPA on methylation of individual genes in fish

Species	BPA concentration, duration	Observation	Reference
Zebrafish embryos	4.9-27.7 µM, up to 120 hours	Decrease in CpG methylation of promoter region of *vasa* (multiple CpG sites) and increase of *cyp19a2* (one CpG site)	Bouwmeester et al. (2016)
Male zebrafish (strain T)	500, 1000, or 1500 µg/l BPA for 21 days	Testes: hypomethylation of CpG sites in promoter regions of *cyp19a1a* Liver: hypomethylation of CpG sites of *esr1*	Zhao et al. (2017)
Rare minnow *Gobiocypris rarus*	15 µg/l for 7 or 14 days	Hypermethylation of CpG sites of *star* and *hsd11b2* at day 7; hypomethylation of a CpG site of *hsd3b* at day 14	Zhang et al. (2018a)

APPENDIX H. KC5, INDUCES OXIDATIVE STRESS

Table H1 Effects of BPA exposure on oxidative damage to DNA (urinary 8-OHdG) in human observational studies[1]

Study Design (Location)	Study population	Biological matrix for BPA	Association between BPA and urinary 8-OHdG	Reference
Cross-sectional (Jeddah, Saudi Arabia)	67 healthy participants (31 males and 35 females; aged 1–87 years old; median: 35 years old) with a total of 130 urine samples	Urine	BPA was significantly associated with increased 8-OHdG levels (r = 0.38, p < 0.0001).	Asimakopoulos et al. (2016)
Nested case-control (Massachusetts, USA)	461 pregnant women	Urine	An IQR (interquartile range) increase in BPA was associated with 9% increase in 8-OHdG (p < 0.01), adjusted for confounders such as maternal race, health insurance and BMI (Model 2).	Ferguson et al. (2016)
Case-control (Guangzhou, Guangdong Province, China)	465 6–12 years old children (215 children with attention-deficit hyperactivity disorder and 250 healthy children)	Urine	Significant positive association between BPA and 8-OHdG was found in all children (r = 0.257, p < 0.001)	Li et al. (2018d)

Study Design (Location)	Study population	Biological matrix for BPA	Association between BPA and urinary 8-OHdG	Reference
Cross-sectional (Singapore)	32 healthy participants (aged 22–37 years old)	Urine	BPA and 8-OHdG were positively correlated (r = 0.353, p < 0.05)	Liu et al. (2019)
Cross-sectional (Guangzhou, Guangdong Province, China)	96 children (aged 3–6 years old)	Urine	A significant positive association was found between BPA and 8-OHdG levels after log-transformation of data (r = 0.24, p = 0.016)	Lv et al. (2016)
Case-control (Dokki, Egypt)	49 children (average age: 6 years old) with autism spectrum disorders	Serum	Significant positive association between BPA and 8-OHdG was found in children with autism spectrum disorders (correlation coefficient, r = 0.39 and p = 0.013 for 40 boys; r = 0.735 and p = 0.024 for 9 girls).	Metwally et al. (2018)
Cross-sectional (from five geographic regions in Brazil)	300 children (urban residents, aged 6–14 years old)	Urine	Significant association between urinary 8-OHdG and BPA (r = 0.261, p < 0.01)	Rocha et al. (2018)

Study Design (Location)	Study population	Biological matrix for BPA	Association between BPA and urinary 8-OHdG	Reference
Cross-sectional (China)	11 healthy Chinese men (repeat urine measurements taken over 3 months)	Urine	Two-fold increase of BPA concentration was statistically significant associated with 3.8% (95% CI: 1.2%, 6.5%) increases in 8-OHdG ($p < 0.004$) in 512 spot urine samples	Wang et al. (2019f)
Cohort (Puerto Rico)	54 pregnant women with three urine samples during pregnancy (146 urine samples)	Urine	An IQR increase in BPA was associated with 21% higher 8-OHdG ($p = 0.001$)	Watkins et al. (2015)
Cross-sectional (Korea)	Participants of the "Biomarker Monitoring for Environmental Health" study with enrollment between April and December 2005. This study included 92 pre-menopausal and 134 postmenopausal women, and 259 men living in large cities.	Urine	BPA was positively associated with 8-OHdG (β = 0.103, $p = 0.008$ in Model 3, adjusted for age, BMI, cotinine, alcohol and exercise) in postmenopausal women, but not in men or premenopausal women.	Yang et al. (2009b)

Study Design (Location)	Study population	Biological matrix for BPA	Association between BPA and urinary 8-OHdG	Reference
Cross-sectional (residents near e-waste recycling region of Longtang Town, Qingyuan City, or in rural or urban reference areas, China)	116 residents (66 males and 50 females; aged 0.4–87 years old)	Urine	In the e-waste dismantling location, urinary BPA levels were positively correlated with urinary 8-OHdG levels (r = 0.413, p < 0.001). Similar positive correlations were also observed for the combined data from the two reference areas (not near e-waste recycling sites) (r = 0.465; p < 0.01).	Zhang et al. (2016)
Cross-sectional (Wuhan, China)	416 participants recruited from a hospital	Urine	Log-transformed urinary BPA was significantly associated with increased log-transformed urinary levels of 8-OHdG, adjusted for sex, age, smoking, drinking, and body mass index (β = 0.117; p < 0.001).	Zhong et al. (2022)[2]
Longitudinal cohort (East China)	275 children (aged 7–11 years old)	Urine	An interquartile range (IQR) increase in urinary BPA was significantly associated with 12.9% (95% CI: 6.1%, 19.6%) increase in 8-OHdG and 19.4% (95% CI: 11.7%, 27.1%) increase in 8-OHG, a marker for RNA damage	Zhou et al. (2019)

Study Design (Location)	Study population	Biological matrix for BPA	Association between BPA and urinary 8-OHdG	Reference
Cross-sectional (Taiwan)	186 pregnant women (Chang et al 2019); 202 pregnant women (aged 18–45 years old in Huang et al 2018)	Urine	No association between BPA and 8-OHdG was found (r = 0.02, p > 0.05) (Chang et al. 2019) No association between BPA measured at the third trimester and 8-OHdG (β = 0.59, p = 0.33) (Huang 2018)	Chang et al. (2019) Huang et al. (2018c) Huang et al. (2017b) (It appears that these three publications report on data from the same study population.)
Cross-sectional (Korea)	Participants of the "Biomarker Monitoring for Environmental Health" study with enrollment between April and December 2005. This study included 960 urban-residing adults (446 males and 514 females).	Urine	No association was found between 8-OHdG and BPA (β = 0.005; p = 0.823) after adjusting for age, sex, weight, smoking, and exercise. BPA was weakly positively associated with 8-OHdG in simple regression (β = 0.04; p = 0.011).	Hong et al. (2009)

Study Design (Location)	Study population	Biological matrix for BPA	Association between BPA and urinary 8-OHdG	Reference
Longitudinal cohort (US and Canada)	538 children and adolescents (median age: 11) with chronic kidney disease recruited from 2005–2015; serial urine samples were taken from 538 participants (at baseline) and reduced to 227 participants on the 5th visit due to loss to follow up over time (an average of 3-year follow up)	Urine	No association between BPA and 8-OHdG (β = 0.05, *p* = 0.06) in 2118 serial urine samples from 538 participants	Jacobson et al. (2020)[2]
Cross-sectional study (Shandong Province, China)	111 women (aged 20–40 years old) with unexplained recurrent spontaneous abortion	Urine	No association between BPA and 8-OHdG, adjusted for age, body mass index (BMI) and other confounders (β = 5.53; 95% CI: –2.51, 14.58; *p* = 0.176).	Liang et al. (2020)[2]
Cross-sectional (Seoul, Korea)	14 women (age: 24.4 ± 4 years old); Participants were asked to drink 100 ml wheat-sprouts juice every day for 14 days, and urine samples were taken on day 0, 3, 7, 10, and 14	Urine	No association between log-transformed BPA and 8-OHdG (β = 1.47, *p* = 0.18) [It is unclear if the urine samples were taken before wheat-sprout juice intake, or from a combination of samples taken before	Yi et al. (2011)

Study Design (Location)	Study population	Biological matrix for BPA	Association between BPA and urinary 8-OHdG	Reference
	after the first intake of wheat-sprouts juice		and after wheat-sprout juice intake (Figure 2).]	
Cross-sectional (Shenzhen, Guangdong Province, China)	100 white-collar workers without occupational exposure to BPA and disease symptoms	Serum	Significant negative correlation between BPA and 8-OHdG (r = –0.317; p < 0.001) without adjusting for confounding variables	Gao et al. (2021)[2]

[1] Studies in the table are sorted by the findings (positive, no significant, or negative association) and then alphabetically by author
[2] New studies not reviewed in Steffensen et al. 2020

Table H2 Effects of BPA exposure on oxidative damage to DNA in human and other mammalian cells *in vitro*

Test endpoint	Cell type	Concentration and duration	Results	Reference
8-OHdG	Human spermatozoa	300 µM for 20 hours	Statistically significant increases in the percentage of spermatozoa with 8-OHdG (p < 0.05)	Barbonetti et al. (2016)
Oxidative damage to DNA (measured by a modified Comet assay)	Human peripheral blood mononuclear cells (PBMC)	0.01, 0.1 or 1 µg/ml for 4 hours; or 0.001, 0.01, or 0.1 µg/ml for 48 hours	Oxidized pyrimidines: statistically significant concentration-dependent increases at ≥ 0.1 µg/ml for 4 hours (p < 0.05) and ≥ 0.01 µg/ml for 48 hours (p < 0.05). Oxidized purines: statistically significant concentration-dependent	Mokra et al. (2018)

Test endpoint	Cell type	Concentration and duration	Results	Reference
			increases at ≥ 0.01 µg/ml for 4 hours ($p < 0.05$) and ≥ 0.001 µg/ml for 48 hours ($p < 0.05$)	
Oxidative stress-induced DNA strand breaks (measured by a modified Comet assay)	Human lymphocytes from PBMC	0.001, 0.1 or 2.5 mM for 1 hour	Statistically significant increases in DNA strand breaks at 0.001 mM ($p < 0.001$), 0.1 mM ($p < 0.01$) and 2.5 mM ($p < 0.01$)	Durovcova et al. (2018)
Oxidative damage to DNA (measured by a modified Comet assay)	Human lung fibroblasts MRC-5 or human epithelia type 2 cells, Hep-2[1]	0.44 nM, 4.4 nM, or 4.4 µM for 48 hours	MCR-5: statistically significant increases at 4.4 nM and 4.4 µM compared to untreated control ($p < 0.01$). (No statistics were done for comparison with vehicle control, but the data shows that 4.4 nM and 4.4 µM BPA treated groups had higher oxidative DNA damage) Hep-2: Statistically significant decreases in two treated groups compared to untreated control ($p < 0.05$ at 0.44 nM, and $p < 0.01$ at 4.4 nM) (No statistics were done for comparison with vehicle control, but vehicle control had significantly decreased oxidative DNA damage, and it appears that there is no	Ramos et al. (2019)

Test endpoint	Cell type	Concentration and duration	Results	Reference
			difference between BPA treated groups and the vehicle control.)	
Oxidative damage to DNA (measured by a modified Comet assay)	Immortalized human prostate epithelial (RWPE-1) cells	45 µM for 24 hours	Increase in tail intensity (%) (statistics between Fpg and BPA treated with Fpg treated controls were not available, but the increase appears to be significant)	Kose et al. (2020)
8-OHdG	Primary rat hepatocytes	10 µM for 24 hours BPA or 1, 5 or 10 µM of BPAQ (BPA-3,4 quinone) for 24 hours	BPA: No increase in 8-OHdG; BPAQ: Statistically significant increases in 8-OHdG at 10 µM ($p < 0.05$)	Sakuma et al. (2010)
8-OHdG	Mouse embryonic fibroblast (NIH3T3) cells	2, 10 or 50 µM for 24 hours	Significantly increased 8-OHdG at 50 µM ($p < 0.01$)	Chen et al. (2016)
8-oxoGuanine (8-oxoGua), 5-hydroxycytosine (5-OH-Cyt), thymine glycol (ThyGly), 2,6-diamino-4-hydroxy-5-	Mouse embryonic fibroblast cells that are $Ku^{-/-}$	150 µM for 1 hour	No significant changes of 8-oxoGua, FapyGua or FapyAde; statistically significant increases of 5-OH-Cyt and ThyGly ($p < 0.05$)	Gassman et al. (2015)

Test endpoint	Cell type	Concentration and duration	Results	Reference
formamidopyrimidine (FapyGua), and 4,6-diamino-5-formamidopyrimidine (FapyAde)				

[1] There is some uncertainty regarding the tissue origin of Hep-2 cells. As stated by Gorphe (2019), "the Hep-2 cell line, first described in 1954 as laryngeal cancer cells, was reported as soon as in 1966 to be comprised of cervical adenocarcinoma cells derived via HeLa cell line contamination".

Table H3 Effects of BPA exposure on ROS or RNS generation in human cells *in vitro*, sorted by cell type

Cell type	BPA concentration and duration	Results	Reference
B lymphoblast cells (WiL2-NS)	100 µM for 24 hours	Increased ROS (not assessed via statistical test)	Jang et al. (2020)
Breast epithelial MCF10A cells	1 or 10 nM for 24 hours	No significant changes of ROS	Kang et al. (2013)
Breast cancer cells (MCF-7 and MDA-MB-231)	0.1 mM for 24 hours	Significantly increased intracellular ROS for both types of cells	Güzel et al. (2020)
Breast carcinoma cells (VM7Luc4E2)	1 µM for 72 hours	No significant changes of ROS	Lee et al. (2018a)
Colon cancer cell line (HCT116)	250 µM for 24 hours	Significantly increased both mitochondrial and intracellular ROS	Qu et al. (2018)
Colorectal adenocarcinoma cells (Caco-2)	120 µg/ml for 24 hours	No significant changes of ROS	Wang et al. (2020b)

Cell type	BPA concentration and duration	Results	Reference
Cortical neurons derived from human embryonic stem cells (hESCs)	0.1, 1, or 10 µM for 14 days	Significantly increased ROS (at all concentrations)	Wang et al. (2019b)
Neurons derived from hESCs, glutamatergic	0.1, 1, or 10 µM for 14 days	Significantly increased ROS (at all concentrations; concentration-dependent)	Wang et al. (2019a)
Dermal fibroblasts	50 µM for 3–60 minutes	Significantly increased ROS at 3 minutes	Lim et al. (2021)
Embryonic kidney HEK293A cells	0.01, 0.1, 1, 10, 50, 100, or 200 µM for 24 hours	Significantly decreased ROS at 10 µM or above	Chepelev et al. (2013)
Endometrial stromal cells	1000 pM for 30 minutes (ROS); 1000 pM BPA for 0, 24, 48, or 72 hours (NO).	Significantly increased ROS; No significant changes of NO	Cho et al. (2018b)
Erythrocytes	1) 10, 25, 100, 250, or 500 µg/ml for 1 hour; 2) 0.5, 5, 25, 100, or 250 µg/ml for 4 hours	Significantly increased ROS at 250 or 500 µg/ml for 1 hour or 25, 100, or 250 µg/ml for 4 hours	Maćczak et al. (2017)
Colonic goblet cells (LS174T)	150 µM for 24 hours	Significantly increased both mitochondrial and intracellular ROS	Zhao et al. (2019)
Liver, normal human liver cell (HL-7702)	0.16, 4, or 100 µmol/l for 24 hours	Significantly increased ROS	Liu et al. (2021c)
Liver, Chang liver cells (human hepatocyte derived cell line)	50 µM for 1–4 hours	Significantly increased intracellular ROS (at 4 hours) and NO	Oh and Lim (2008)
Liver, human hepatoma cells (HepG2)	0.000001, 0.001, 0.01, 0.1, 1, 10, or 100 µM for 24, 48, or 72 hours	Significantly increased both mitochondrial and cytosolic superoxide anion at all doses;	Huc et al. (2012)

Cell type	BPA concentration and duration	Results	Reference
		No significant changes of NO	
Liver, human hepatoma cells (HepG2)	30 or 60 μM for 24 hours	Significantly increased ROS at 60 μM; No significant changes of NO	Yarahalli Jayaram et al. (2020)
Liver, hepatoma cell line Hep3B	100 μM for 6 hours	Significantly increased nitrous oxide; No significant changes of ROS	Nakamura et al. (2018)
Lung, fetal lung fibroblasts	0.01, 1, 10, or 100 μM for 24 hours	Significantly increased ROS at 100 μM	Mahemuti et al. (2018)
Lung adenocarcinoma A549 cells	10 μM for 24 hours	Significantly increased ROS	Song et al. (2021a)
Lymphoblastoid cell lines	100 μM overnight	Significantly increased ROS in lymphoblasts from children with autism and unaffected siblings	Kaur et al. (2014)
Peripheral blood mononuclear cells (PBMCs)	0.06 – 250 μM for 1 hour	Significantly increased ROS at 0.3 μM or above	Michalowicz et al. (2015)
Placental choriocarcinoma JEG-3 cell line	5, 20, 50, 100, or 500 μM for 15, 30, 60, or 120 minutes	Significantly increased ROS at 50 μM (15 or 30 minutes, at 100 μM (15 or 30 minutes), and at 500 μM (all time points)	Perez-Albaladejo et al. (2017)
Neutrophils	0.03, 0.1, 0.3, 1, 3, 10, 20, or 100 μM for 2 hours	Significantly increased ROS at concentrations ≥ 1 μM (concentration-dependent)	Balistrieri et al. (2018)
Neutrophils, Polymorphonuclear	6.25, 11, or 25 ng/μl for 20 hours	Significantly increased NO at 6.25 and 25 ng/μl	Ratajczak-Wrona et al. (2019)

Cell type	BPA concentration and duration	Results	Reference
Neutrophils polymorphonuclear	16 nM or 1.6 μM for 2 hours	Significantly increased NO at both doses	Ratajczak-Wrona et al. (2021)
Ovary, KGN cells (granulosa like tumor cell line)	0.1, 1, 10, or 100 μM for 24 hours	Significantly increased intracellular ROS (at 1 μM or above (concentration-dependent)	Huang et al. (2020)
Ovary, KGN cells (granulosa like tumor cell line)	0.1, 1, 10, or 100 μM for 12 or 24 hours	Significantly increased intracellular ROS at 1 μM or above (concentration-dependent)	Huang et al. (2021)
Prostate stromal myofibroblast cells WPMY-1	Unspecified concentration for 24 hours	Significantly increased mitochondrial ROS	Hyun et al. (2021)
Prostate cancer cells, LAPC-4 (androgen-dependent) and PC-3 (androgen-independent)	0.001 μM for 15 minutes	Significantly increased ROS in LAPC-4; No significant changes of ROS in PC-3	Koong and Watson (2015)
Retinal pigment epithelium cells (ARPE-19)	10, 25, 50, or 100 μM for 24 hours	Significantly increased intracellular ROS at 100 μM	Chiang et al. (2021)
Neuroblastoma cell line (SH-SY5Y cells)	1 pM and 1 nM for 48 hours	Significantly increased NO at both doses	Ayazgok and Küçükkilinç (2018)
Umbilical vein endothelial cells	0.1 nM, 10 nM, or 1 μM for 6 hours	Significantly increased NO at 10 nM and 1 μM; No significant changes of ROS	Andersson and Brittebo (2012)

NO, nitric oxide

Table H4 Effects of BPA exposure on ROS or RNS generation in rodents *in vivo* studies (ordered by species, strain, and sex)

Species, sex and strain (group size)	BPA dose, duration, route	Results	Reference
Rat, female Wistar albino (n = 10)	25 mg/kg-day for 30 days, gavage	Significantly increased NO in the ovarian tissue	Avci et al. (2016)
Rat, female Wistar albino (n = 5)	25 mg/kg-day for 9 days, *i.p.* injection	Significantly increased ROS and NO in the ovarian granulosa cells	Banerjee et al. (2018)
Rat, female Wistar (n = 16)	40 mg/kg-day for 15 days, gavage	Significantly increased H_2O_2 (with calcium) in the thyroid; No significant change in H_2O_2 (without calcium)	Silva et al. (2018)
Rat, male Wistar albino (n = 7)	50 mg/kg-day for 70 days, gavage	Significantly increased NO in brain extracts	Abdou et al. (2021)
Rat, male Wistar albino (n = 10)	25 mg/kg-day, 5 days/week for 6 weeks, or 10 mg/kg-day, 5 days/week for 6 or 10 weeks, oral	Significantly decreased NO in the heart (25 mg/kg-day for 6 weeks, and 10 mg/kg-day for 10 weeks); No significant changes in NO (10 mg/kg-day for 6 weeks)	Aboul Ezz et al. (2015)
Rat, male Wistar albino (n = 8)	20 or 40 µg/kg-day from postnatal day (PND) 15 to 30, gavage	Significantly increased H_2O_2 and NO in the brain cerebrum and cerebellum at both doses (dose-dependent)	Ahmed et al. (2018)
Rat, male Wistar albino (n = 4)	0.2, 2, or 20 µg/kg-day for 30 days, oral	Significantly increased H_2O_2 in both the mitochondrial fraction and the microsome-rich fraction of the liver at all doses	Bindhumol et al. (2003)

Species, sex and strain (group size)	BPA dose, duration, route	Results	Reference
Rat, male Wistar albino (n = 10)	50 mg/kg-day for 30 days, gavage	Significantly increased NO in the serum	Faheem et al. (2021)
Rat, male Wistar albino (n = 10)	10 mg/kg-day, 5 days/week for 6 or 10 weeks, or 25 mg/kg-day, 5 days/week for 6 weeks, oral	Cerebral cortex: Significantly increased NO at 25 mg/kg-day for 6 weeks and not significant for the other two test conditions. Hippocampus: No significant change in NO for all three test conditions	Khadrawy et al. (2016)
Rat, male Wistar albino (n = 6)	150, 250, or 500 mg/kg-day for 14 days, oral	Significantly increased superoxide anion in the liver mitochondria at all doses (dose-dependent)	Khan et al. (2016)
Rat, male Wistar albino (n = 6)	50 µg/kg-day for 30 days, oral	No significant changes of ROS (in blood) or NO (in red blood cells)	Nagarajan et al. (2021)
Rat, male Wistar albino (n = 8)	5, 50, or 500 µg/kg-day for 8 weeks, oral	Significantly increased plasma NO (dose-dependent)	Ozaydin et al. (2018b)
Rat, male Wistar (n = 6)	50 µg/kg-day for 38 weeks, oral (drinking water)	Significantly increased liver H_2O_2	Azevedo et al. (2019)
Rat, male Wistar (n = 6)	0.2, 2, or 20 µg/kg-day for 45 day, oral	Significantly increased H_2O_2 in the epididymal sperm at all doses	Chitra et al. (2003)
Rat, male Wistar (n = 6)	0.005, 0.5, 50, or 500 µg/kg-day for 45 days, gavage	Significantly increased H_2O_2 in the testis at all doses (dose-dependent)	D'Cruz et al. (2012b)
Rat, male Wistar (n = 15)	250 mg/kg-day for 8 weeks, gavage	Significantly increased NO in the hippocampus	El Tabaa et al. (2017)

Species, sex and strain (group size)	BPA dose, duration, route	Results	Reference
Rat, male Wistar (n = 10)	100 µg/kg-day for 60 days, gavage	Significantly increased ROS (hydrogen peroxide; superoxide anion) and peroxynitrite in vascular cells isolated from the aorta; significantly decreased NO in vascular cells isolated from the aorta	Friques et al. (2020)
Rat, male Wistar (n = 8, F1)	40 µg/kg-day of pregnant rats (F0) from gestation day (GD) 0 to PND21, oral	Significantly increased ROS in male F1 in the liver at 15 or 26 weeks; No significant changes of ROS at 3 weeks	Jiang et al. (2014)
Rat, male Wistar (n = 4)	50, 100, or 150 mg/kg-day for 5 weeks (ROS) or 50 mg/kg-day (NO) of 5-week, *i.p.* injection	Significantly increased ROS (dose-dependent) in the kidney; Significantly increased NO in the kidney	Kobroob et al. (2018)
Rat, male Wistar (n = 16)	50 mg/kg-day for 12 weeks, gavage	Significantly increased ROS and NO in the kidney	Kobroob et al. (2021)
Rat, male Wistar (n = 15)	20 µg/kg-day for 30 days (PND36–66), gavage	No significant changes of superoxide anion in the caput/corpus or cauda epididymis	Ogo et al. (2018)
Rat, male Wistar (n = 10)	10 mg/kg-day for 45 days, gavage	Significantly increased H_2O_2 and NO in the testis	Olukole et al. (2020)
Rat, male Wistar (n = 10, F1)	25 or 250 µg/kg-day for 11 days in F_0 (GD10–21), gavage	Significantly increased H_2O_2 in the testis of male F1 at both doses	Olukole et al. (2019)

Species, sex and strain (group size)	BPA dose, duration, route	Results	Reference
Rat, male Wistar (n = 8)	250 mg/kg-day for 14 days, gavage	Significantly increased mitochondrial ROS	Shirani et al. (2019)
Rat, male Wistar (n = 8)	250 mg/kg-day for 14 days, gavage	Significantly increased mitochondrial ROS in the heart	Vanani et al. (2020)
Rat, male Sprague-Dawley (SD) (n = 6, F1)	1, 10, or 100 mg/kg-day for 7 days (GD14–21), gavage	No significant changes of superoxide anion in the testis of male F1	Quan et al. (2017)
Rat, female SD (n = 10)	0.05, 0.5, 5, or 50 mg/kg-day for 28 days, *i.p.* injection	Significantly increased ROS	Ijaz et al. (2020)
Rat, female SD (n = 7)	25 mg/kg-day on alternating days for 4 weeks, *i.p.* injection	Significantly increased ROS, nitrite, and H_2O_2 in the liver	Maryam et al. (2018)
Rat, male SD (n = 6)	200 mg/kg-day for 30 days, oral	Significantly increased H_2O_2 in the testis	Revathy et al. (2017)
Rat, male SD (n = 6)	200 mg/kg-day for 30 days, oral	Significantly increased H_2O_2 and ROS in the testis	Tamilselvan et al. (2014)
Rat, male SD (n = 7)	500 mg/kg-day for 2 weeks, gavage	Significantly increased ROS in the liver	Wang et al. (2021e)
Rat, male and female SD (n = 8)	0.1, 1, and 10 mg/kg-day for 16 days, subcutaneous injection	Significantly increased ROS in the brain at all doses	Ishtiaq et al. (2021)
Rat, male Swiss albino (n = 6, F0)	400 µg/kg for 6 weeks, *i.p.* injection to male F0 (twice per week)	Significantly increased NO in F0 and F1 in the testis	Al-Griw et al. (2021)
Rat, male albino	100 mg/kg-day for 30 days, oral	Significantly increased H_2O_2 in the liver	Ijaz et al. (2021)
Mice, male CD-1 (n = 40)	5 or 50 mg/kg-day for 6 weeks, gavage (F0)	Significant changes of intracellular ROS in the spermatozoa for F0 and F1; no changes for F2 and F3	Rahman et al. (2020)

Species, sex and strain (group size)	BPA dose, duration, route	Results	Reference
Mice, male CD-1 (n = 10)	50 µg/kg-day for 10 weeks, oral (via drinking water)	Significantly increased ROS, H_2O_2, and RNS in the serum, colon, and liver	Wang et al. (2019c)
Mice, male and female CD-1 (n = 10)	0.4 µM for 30 days, oral (via drinking water)	Significantly increased superoxide and 3-nitrotyrosine in the carotid artery rings	Saura et al. (2014)
Mice, male Swiss albino (n = 10)	0.5, 50, or 100 µg/kg-day for 60 days, *i.p.* injection	Significantly increased nitrite (an indicator of NO levels in tissue homogenate) in the testis at all doses	Chouhan et al. (2015)
Mice, male Balb/c (n = 6)	1 mg/kg-day for 8 weeks, gavage	Significantly increased ROS in the testis	Kaur et al. (2020)
Mice, male C57Bl/6J (n = 15)	50 µg/kg-day for 3 weeks, oral	Significantly increased ROS in the liver	Pirozzi et al. (2020)
Mice, female ICR (n not specified)	100 µg/kg-day for 7 days, oral	Significantly increased ROS in oocytes	Zhang et al. (2017b)

H_2O_2, hydrogen peroxide; NO, nitric oxide

Table H5 Effects of BPA exposure on ROS or RNS generation in rodent cells *in vitro* ordered by species and cell types

Species (strain, if reported), cell type	BPA concentration and duration	Results	Reference
Rat (SD), sperm	1, 10, or 100 µg/l for 2 hours	Significantly increased ROS at 100 µg/l	Ullah et al. (2019a)
Rat (SD), Sertoli cells	30, 50, or 70 µM for 24 hours	Significantly increased ROS at 50 and 70 µM (concentration-dependent)	Wang et al. (2017a)

Species (strain, if reported), cell type	BPA concentration and duration	Results	Reference
Rat (unspecified strain), TM3 (Leydig cells) and TM4 (Sertoli cells)	100 µM for 24 hours	Significantly increased ROS in both cell types	Ok et al. (2016)
Rat (SD), primary neurons from embryonic rat brain	50, 100, or 200 µM for 0-60 min	Significantly increased ROS at 200 µM, all durations tested	Cho et al. (2018a)
Rat (SD), primary hippocampal neurons	1 nM, 10 nM, 100 nM, 1 µM, 10 µM, or 100 µM for 6, 12, or 24 hours	Significantly increased ROS at 100 nm at 6 hours and 100 µM at 24 hours in neurons from female rats; Significantly increased ROS at 1 nM, 10 nM, 1 µM, and 100 µM at 24 hours in neurons from male rats	Meng et al. (2021)
Rat (Wistar), hippocampal neural stem cells from embryos	100 µM for 24 hours	Significantly increased ROS	Agarwal et al. (2016)
Rat (Wistar), kidney mitochondrial fraction	1, 5, 25, 50, 100, 125, 250, 500, and 1000 µM for 15 minutes	Significantly increased mitochondrial ROS at 125 µM and above (concentration-dependent)	Kobroob et al. (2018)
Rat, PC12 (derived from a transplantable rat pheochromocytoma)	50 µM for 72 hours	Increased ROS (not assessed by statistical test)	Zhang et al. (2021d)
Rat, follicular thyroid cell line PCCL3	10 nM for 24 hours	Significantly increased extracellular generation of H_2O_2	Silva et al. (2018)

Species (strain, if reported), cell type	BPA concentration and duration	Results	Reference
Mouse, osteocyte-like MLO-Y4 cells	100 or 200 μM for 12 hours	Significantly increased ROS at both concentrations (concentration-dependent)	Zhang et al. (2021e)
Mouse, hippocampal HT-22 cell line	1 nM, 10 nM, 100 nM, 1 μM, 10 μM, or 100 μM for 6 hours	Significantly increased ROS (at 1 nM, 100 nM, and 100 μM)	Pang et al. (2019)
Mouse, hippocampal HT-22 cell line	100, 200, and 400 μM for 3.5 hours	Significantly increased ROS at all concentrations (concentration-dependent)	Lee et al. (2008)
Mouse, colon carcinoma cell line (CT-26)	250 μM for 24 hours	Significantly increased ROS	Wang et al. (2021d)
Mouse, embryonic fibroblasts	Concentration not specified (within the range of 50 to 500 μM)	Significantly increased mitochondrial ROS	Hyun et al. (2021)
Mouse, renal cortical collecting duct cells (mpkCCD)	100 μM for 24 hours	Significantly increased ROS	Çiğ and Yildizhan (2020)
Mouse (ICR), primary lymphocytes	50 μM for 30 minutes	Significantly increased intracellular ROS	Lee and Lim (2010)
Mouse, macrophages from the peritoneal cavity	1, 10, 100, 1000, 10000, or 100000 nM for 48 hours	No changes in ROS	Yoshida et al. (2002)
Mouse, macrophage-like cells RAW264.7	3, 10, 30, or 50 μM for 24 hours	Significantly increased ROS at 10 μM or above (concentration-dependent)	Huang et al. (2018a)
Mouse, neuroblastoma N2a cell lines	0.01, 0.1, 1, 10, or 100 μM for 24 hours	Significantly increased non-peroxide-based	Lee et al. (2021)

Species (strain, if reported), cell type	BPA concentration and duration	Results	Reference
		intracellular ROS at 100 µM	
Mouse, hypothalamic neurons GT1-7	50 or 100 µM for 0 to 4 hours	Increased superoxides at 100 µM with 4 hours incubation; time- and concentration-dependent (no *p*-values provided)	Babu et al. (2013)
Mouse, multipotent neural progenitor cell line C17.2	100, 200, or 400 µM measured at 1, 2, 4, 6, 8, 10, and 720 minutes	Significantly increased ROS at 200 and 400 µM at all time points measured (concentration-dependent)	Kim et al. (2007)
Mouse, immortalized neuroblastoma Neuro2a and GC1 cells (immortalized cell line derived from testis)	50 µM (Neuro2a cells) or 100 µM (GC1 cells); 24 or 48 hours	Increased ROS; Generated highly reactive ROS such as hydoxy radical (·OH) and peroxynitrite ($ONOO^-$) at 48 hours	Ooe et al. (2005)
Mouse, oocytes	50 µg/ml for 14 hours	Significantly increased intracellular ROS	Li and Zhao (2019)
Mouse (CD-1), cultured neonatal ovaries	Neonatal ovaries were collected on postnatal day (PND) 0, and treated with 1 or 5 µg/ml BPA till PND2, 4 or 8	Significantly increased ROS at 5 µg/ml, PND8	Zhou et al. (2015)
Mouse (C57BL/6), pancreatic islet cells	100 µM for 12 hours	Significantly increased ROS	Chen et al. (2018a)

Species (strain, if reported), cell type	BPA concentration and duration	Results	Reference
Mouse, preadipocytes 3T3-L1	20 µM for 10 days (BPA treatment started before adipogenic inducers)	Significantly increased ROS	Choi et al. (2020b)
Mouse, differentiated adipocytes 3T3-L1	30 or 60 µM for 24 hours (BPA treatment started after 3T3-L1 differentiation)	Significantly increased NO at both doses	Yarahalli Jayaram et al. (2020)
Mouse, myoblast cell line (C2C12)	30 or 60 µM for 24 hours	Significantly increased NO at 60 µM	Yarahalli Jayaram et al. (2020)
Mouse, myoblasts cell line (C2C12)	150 µM for 6 hours	Significantly increased ROS	Liu et al. (2021d)
Mouse (ICR), spermatozoa	100 µM for 6 hours	Significantly increased ROS	Rahman et al. (2019)
Mouse, spermatocyte-derived GC-2 cells	20, 40, or 80 µM for 48 hours	Significantly increased ROS at all doses	Yin et al. (2017)
Mouse (NMRI), isolated testicular mitochondrial fractions	0.8 mM for 2 hours	Significantly increased mitochondrial ROS	Rezaee-Tazangi et al. (2020)
Mouse (NMRI), isolated testicular mitochondrial fractions	0.8 mM for 2 hours	Significantly increased mitochondrial ROS	Rafiee et al. (2021)
Mouse, an endothelial cell line originated from spleen (MSS31)	10^{-3} to 10^{3} µM for 16 hours	Significantly increased NO production (measured as nitrate and nitrite) at 1, 10, and 100 µM	Noguchi et al. (2002)

H_2O_2, hydrogen peroxide; NO, nitric oxide

APPENDIX I. KC6, INDUCES CHRONIC INFLAMMATION

Table I1 Additional animal studies examining BPA's effects on biomarkers of inflammation

Species, strain, and sex	Exposure Duration	Dose, Route	Site & changes in level of biomarkers observed	Reference
Studies that reported increases in inflammatory biomarkers or decreases of anti-inflammatory biomarkers				
Rat, Wistar, M	90 days	10 mg/kg-day; gavage	**Serum:** Significant increase in IL-1β ($p < 0.05$); **Adipose tissue**: significant increase in TNF-α expression ($p < 0.0001$)	Elgawish et al. (2020)
Rat, Wistar albino, M	70 days	50 mg/kg-day; oral	**Brain**: Significant increases in TNF-α and COX-2 mRNA expression levels	Abdou et al. (2021)
Rat, Wistar albino, M	8 weeks	50 mg/kg-day; gavage	**Serum**: Significant increase in IL-1β ($p < 0.001$); significant decrease in IL-10 (generally considered as an anti-inflammatory cytokine) ($p < 0.001$)	Elswefy et al. (2016)
Rat, Wistar, M	8 weeks	1 µg/ml; drinking water	**Serum**: Significant increases in TNF-α and IL-17	Lin et al. (2019)
Rat, Wistar albino, M	8 weeks	5, 50, or 500 µg/kg-day; oral	**Plasma:** Significant increases in TNF-α at all doses; significant increases in IL-4 and IL-6 at the two higher doses; no effect on IL-10	Ozaydin et al. (2018a)
Rat, Wistar albino, M	54 days	10 mg/kg-day; gavage	**Serum**: significant increases in IL-6 ($p < 0.01$) and TNF-α ($p < 0.05$)	Fadishei et al. (2021)
Rat, Wistar, M	5 weeks	50 mg/kg-day; oral	**Kidney**: Significant increases of mRNA expression and cytokine levels in TNF-α, IL-1β, IL-6, and IL-8 ($p < 0.05$ for each of the comparisons with control)	Jiang et al. (2020)

Species, strain, and sex	Exposure Duration	Dose, Route	Site & changes in level of biomarkers observed	Reference
Rat, Wistar albino, M	30 days	25 mg/kg-day; gavage	**Liver, brain, testis**: Significant ($p < 0.001$) increases in mRNA expression of IL-6, TNF-α, and IL-1β; significant decreases in mRNA expression of IL-10	Acaroz et al. (2019)
Rat, Wistar, M	4 weeks	500 mg/kg-day; oral	**Lung**: Significant increases of TNF-α and IL-6 (in unit "ng/mg tissue") ($p \leq 0.05$ reported for both cytokines)	Mansour et al. (2020)
Rat, Wistar albino, M	8 weeks	10 mg/kg-day; gavage	**Serum**: Significant increases in TNF-α and IL-6 ($p < 0.0001$ for both cytokines)	Mohsenzadeh et al. (2021)
Mouse, CD-1, M	24 weeks	0.5 mg/kg feed (the authors estimated that this was equivalent to 50 µg/kg-day; diet	**Serum**: Significant increases in serum levels of TNF-α, IL-6, IL-1β, and IL-18 ($p < 0.05$ for all four cytokines) **Liver**: Significant increases in mRNA expression of hepatic TNF-α, IL-6, IL-1β, and IL-18 ($p < 0.05$ for mRNA of all four cytokines)	Feng et al. (2020)
Mouse, C57/BL6, F	6 weeks	0.2 µg/ml; drinking water	**Kidney**: Significant increases in the protein expression of NF-κB at 0.2 µg/kg-day ($p < 0.05$)	Dong et al. (2020)
Studies that did not report increases in inflammatory biomarkers				
Mouse, CD-1, M	6 weeks	50 mg/kg-day; gavage	**Caput epididymis:** Significant decreases in IL-6, IL-10, and IFN-γ ($p < 0.05$ for all three cytokines) and decrease in IL-7 (p-value not available) **Cauda epididymis**: Significant decreases in IL-6 and IL-10 ($p < 0.05$ for both cytokines) **Epididymis:** Decreases in IL-7, and increases in CCL12, CRP, CFD, CCL7, CXCL16, IL-15, and more	Park et al. (2021)
Mouse, CD-1, F	*In utero*	BPA 5.0 mg/kg-day; via osmotic minipump infusion; female F1 were	**Mammary gland**: Significant decreases in mRNA expression of four chemokines (Cxcl2, Cxcl4, Cxcl14, and Ccl20) ($p < 0.05$ for each),	Fischer et al. (2016)

Species, strain, and sex	Exposure Duration	Dose, Route	Site & changes in level of biomarkers observed	Reference
	GD9–21; F1 observed at 8 weeks of age	ovariectomized at 6 weeks and tissues examined at 8 weeks	but not Ccl8, in mice exposed to BPA; significant decreases in mRNA expression of IL-1β, IL-1rn, and IL-7 ($p < 0.05$ for each)	

CCL, C-C motif ligand; CFD, complement factor D; CXCL, C-X-C motif ligand; COX-2, cyclooxygenase-2; CRP, c-reactive protein; GD, gestation day; IL, interleukin; IL-1rn, gene encoding IL-1RA (interleukin 1 receptor antagonist); *i.p.*, intraperitoneal; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor alpha.

APPENDIX J. KC8, MODULATES RECEPTOR-MEDIATED EFFECTS

Section J1 Estradiol (E2)

Table J1.1 Effects of BPA on estradiol (E2), estrone (E1), and estriol (E3) in human observational studies

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
Women with PCOS, girls with precocious puberty or premature thelarche, or pregnant women	PCOS. 86 PCOS women (age: 28.5 ± 5.1 years old) in Slovakia	Urine	Significant negative correlation of BPA with E2 in PCOS patients (R^2 = 0.513; p = 0.0001). No correlation with estrone [coefficient not reported].	Lazúrová et al. (2021)
Women with PCOS, girls with precocious puberty or premature thelarche, or pregnant women	PCOS and control. 30 women (16 with PCOS and 14 control) in Japan	Serum	No correlation of BPA with E2 (r = -0.019, p > 0.05).	Takeuchi and Tsutsumi (2002)
Women with PCOS, girls with precocious puberty or premature thelarche, or pregnant women	PCOS and control. 47 women with ovarian dysfunction (19 PCOS; 21 hypothalamic amenorrhea, 7 hyperprolactinemia) and 26 controls (women with normal	Serum	For all 73 women: no correlation of BPA with E2 (r = 0.162, p > 0.05).	Takeuchi et al. (2004)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	menstrual cycles) in Japan			
Women with PCOS, girls with precocious puberty or premature thelarche, or pregnant women	Precocious puberty and controls. 136 girls (6–9 years old) with precocious puberty and 136 healthy controls in China	Urine	No association of BPA with E2 in girls with precocious puberty (β = –0.135, p = 0.372).	Chen et al. (2018c)
Women with PCOS, girls with precocious puberty or premature thelarche, or pregnant women	Precocious puberty and controls. 35 girls with central precocious puberty, 26 girls with peripheral precocious puberty, and 21 controls in Korea	Urine	BPA was significantly positively correlated with E2 in girls with peripheral precocious puberty (p = 0.017). No correlation in controls (p = 0.062) and patients with central precocious puberty (p = 0.083).	Lee et al. (2014)
Women with PCOS, girls with precocious puberty or premature thelarche, or pregnant women	Girls with premature thelarche and controls. 50 girls (4–8 years old) with premature thelarche and healthy controls in Turkey	Urine	No association in girls with premature thelarche (r = 0.166, p = 0.37).	Durmaz et al. (2018)
Women with PCOS, girls with precocious puberty or premature	Pregnancy. 181 pregnant women in Puerto Rico	Urine	No association with E2 (% change per 2.80 ng/ml= 1.47%; 95% CI: –5.97, 8.91, p = 0.70), adjusted for maternal age, education, BMI.	Aker et al. (2016)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
thelarche, or pregnant women				
Women with PCOS, girls with precocious puberty or premature thelarche, or pregnant women	Pregnancy. 602 pregnant women in Puerto Rico	Urine	No association with E3 (% change per IQR= –2.18; 95% CI: –7.78, 3.78, $p = 0.17$), adjusted for specific gravity, study visit, BMI, maternal age, secondhand smoking, SES.	Aker et al. (2019)
Male partners in subfertile couples	Male partners in subfertile couples. 167 men from an infertility clinic in MA, USA	Urine	No association between BPA and E2 for all participants or for subgroups with more than 2 BPA measurements, adjusted for specific gravity, age, BMI, smoking, season, time of day of sample collection.	Meeker et al. (2010a)
Male partners in subfertile couples	Male partners in subfertile couples. 100 men from an andrology clinic in Egypt	Urine	Significant positive association between BPA and E2 ($r = 0.294$; $p < 0.001$).	Shokry et al. (2020)
Male partners in subfertile couples	Male partners in subfertile couples. 174 men in Czech Republic	Plasma and semen	BPA in plasma: Significant positive correlation with plasma E2 ($r = 0.363$, $p < 0.001$). No associations with plasma E1 or plasma E3. BPA in semen: Significant positive correlation with seminal E2 ($r = 0.318$, $p < 0.001$). Significant negative correlation with plasma E1 ($r = –0.257$, $p = 0.006$). No associations with plasma E2, plasma E3, seminal E1, or seminal E3.	Vitku et al. (2015)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
Female partners in subfertile couples	Female partners in subfertile couples. 511 women at a fertility clinic (25–39 years old) in Poland	Urine	No association of continuous measure or quartiles of BPA with E2. Continuous: r = 0.06; 95% CI: –0.02, 0.13; p = 0.14. Quartile 4: r = 0.04; 95% CI: –0.13, 0.21; p = 0.62.	Czubacka et al. (2021)
Women undergoing in vitro fertilization	Women. 58 women undergoing in vitro fertilization in the US	Serum	Bivariate associations: Suggestive inverse correlations for BPA with peak-E2 (r = −0.29, p = 0.06), and for BPA with peak-E2 per mature-sized follicle (r = −0.33, p = 0.03). Multivariable linear regression models: Non-statistically significant negative association of log-unit increase in BPA with decrease of −0.16 units in log peak-E2 (β = −0.16, 95% CI: −0.32, 0.01; p = 0.07). Statistically significant negative association of log-unit increase in BPA with decrease of –0.14 units in log peak-E2 per mature-sized follicle (β = –0.14, 95% CI: −0.24, −0.03; p = 0.01). Adjusted for race/ethnicity, smoking, baseline AFC.	Bloom et al. (2011)
Children with ADHD	Children with ADHD. 98 boys with ADHD and 42 control; 32 girls with ADHD and 26 control in Taiwan	Urine	Significant positive correlation between urinary BPA and E2 in girls (r = 0.370; p < 0.05). No correlation in boys (r = 0.005; p ≥ 0.05).	Tsai et al. (2020)
Children with autism	Children with autism and controls. 49 autistic children and 40 healthy controls in Egypt	Serum	No correlations between BPA and E2 in children with autism or healthy controls.	Metwally et al. (2020)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
Children and adolescents	Preadolescent girls. 48 preadolescent girls (7–8 years old) in Korea	Urine	Girls in highest tertile of BPA had higher E2 than girls in lowest tertile (p = 0.02) at the second time point (not significantly different at 1st time point, p = 0.05).	Lee et al. (2013a)
Children and adolescents	Boys. 117 boys (8–14 years old) in Mexico City	Urine	No association between urinary BPA and E2 (p > 0.05).	Ferguson et al. (2014)
Children and adolescents	Children and adolescents Participants (6+ years old) in two surveys (NHANES 2013–16 or Canadian study 2012–15)	Urine	Significant negative correlation of E2 detection frequency in Canadian boys ages 6-11 for 2nd (p = 0.008) and 4th (p = 0.019) quartiles vs 1st quartile of BPA (no association in NHANES), adjusted for age, BMI, creatinine, time of day, smoking, level of education, population group. Significant negative correlation of E2 geometric mean concentrations in NHANES adolescents, ages 12–19 for 2nd (p = 0.011) and 4th (p = 0.046) quartiles vs 1st quartile of BPA. No correlation in Canadian females ages 6-11 or 50-79.	Pollock et al. (2021)
Adolescents	Adolescents. 1317 12–19 years old from NHANES 2013-2016	Urine	Significant positive association of 3rd quartile of BPA with E2 in female adolescents. No associations in male adolescents.	Wang et al. (2021f)
BPA and estrogens measured in cord blood	Male newborns. 120 male newborns in Turkey.	Cord blood	Cord blood BPA was significantly positively correlated with E2 (r = 0.333; p = 0.001). BPA was positively associated with E2 levels in univariate analysis (β = 2.082; 95% CI: 0.493, 3.671; p = 0.011) and multivariate analysis adjusted for maternal	Sunman et al. (2019)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
			age, parity, BMI, DEHP, and MEHP (β = 1.842; 95% CI: 0.358, 3.326; p = 0.016).	
BPA and estrogens measured in cord blood	Newborns. 278 newborns in Japan	Cord blood	No significant association between fetal BPA in cord blood taken at delivery and E2 (β = 0.26, 95% CI: –0.11, 0.64), adjusted for sex, interaction of sex and BPA, days of mass screening test.	Minatoya et al. (2017)
BPA and estrogens measured in cord blood	Newborns. 60 maternal and child pairs in South Africa	Cord blood	Cord blood BPA positively correlated with cord blood E2 (r = 0.7, p = 0.002).	Gounden et al. (2021)
Maternal BPA exposure and association with estrogens in infants, children, or adult men	Newborns. 60 maternal and child pairs (3rd trimester and matching cord blood samples) in South Africa	Urine (maternal)	Maternal BPA correlated with cord blood E2 (r = 0.6, p = 0.02).	Gounden et al. (2021)
Maternal BPA exposure and association with estrogens in infants, children, or adult men	Male newborns. 137 male newborns in China	Urine (maternal)	Authors stated no significant association between BPA and E2 but results not reported.	Liu et al. (2016a)
Maternal BPA exposure and association with estrogens in infants, children, or adult men	Infants. 59 infants in Daishan, China	Urine	Urine samples were measured at birth, 14 days, 28 days, 42 days, 3 months, and 6 months and correlation analyses were conducted for different time periods and gender. Females: Significant positive correlation between urinary BPA and E2 at 14 days (r = 0.663, p < 0.001), 28 days (r = 0.452, p = 0.014), 42 days (r = 0.555, p = 0.003), and	Wang et al. (2017b)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
			3 months (r = 0.493, p = 0.008). Not significant at birth or 6 months. Males: Significant positive correlation between urinary BPA and E2 at 14 days (r = 0.550, p = 0.002), 28 days (r = 0.737, p < 0.001), 42 days (r = 0.601, p = 0.001). Not significant at birth, 3 months, or 6 months. All: Significant positive correlation between urinary BPA and E2 at 14 days (r = 0.525, p < 0.001), 28 days (r = 0.468, p < 0.001), 42 days (r = 0.580, p < 0.001), and 3 months (r = 0.269, p = 0.045). Not significant at birth or 6 months.	
Maternal BPA exposure and association with estrogens in infants, children, or adult men	Girls. 120 girls (8–13 years old; average: 10) in Mexico City	Urine (maternal)	No association of maternal urinary BPA in any trimester with E2 in girls, adjusted for child age, child BMI, urinary specific gravity.	Watkins et al. (2017)
Maternal BPA exposure and association with estrogens in infants, children, or adult men	Boys. 117 boys (8–14 years old) in Mexico City	Urine (maternal)	No association between maternal urinary BPA measured in 3rd trimester and E2 in boys 8–14 years old (p > 0.05).	Ferguson et al. (2014)
Maternal BPA exposure and association with estrogens in infants, children, or adult men	Children. 113 mother and child pairs in Mexico City	Urine (maternal and child)	No associations between maternal urinary BPA or peripubertal urinary BPA with E2 in children 8–13 years old.	Watkins et al. (2014)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
Maternal BPA exposure and association with estrogens in infants, children, or adult men	Men. 284 men (20–22 years old) in Australia	Serum (maternal)	No correlation between maternal BPA and E1 (r = –0.02) or E2 (r = –0.04) in male adult offspring [authors stated not statistically significant but no p-value reported].	Hart et al. (2018)
Occupationally exposed workers	Female workers. 106 women with occupational exposure and 250 unexposed	Urine and personal air sample monitoring (TWA8)	Women with higher time-weighted average (TWA8) had higher E2 levels than women with lower TWA8. No difference by urine BPA levels. No association between urine BPA and E2 in both models (adjusted for age, passive smoking, study center, or adjusted for age, passive smoking, study center, menstrual phase).	Miao et al. (2015)
Occupationally exposed workers	Female workers (26–41 years old). 51 women with at least one year direct occupational exposure to BPA and 104 unexposed	Not assessed	No association of occupational exposure to BPA with serum E2.	Hao et al. (2011) [article in Chinese]
Occupationally exposed workers	Male workers. 592 male workers (165 exposed to BPA and 427 non-exposed workers) in China	Urine	Significant positive association between urinary BPA and E2 (β = 0.0362, p < 0.001) among all 592 workers, but not the 427 workers without occupational BPA exposure.	Liu et al. (2015a)
Occupationally exposed workers	Male workers. 290 male workers (137 exposed to BPA and 153 non-exposed workers) in China	Serum	No association between BPA and E2 (β = 0.008; p = 0.659).	Zhou et al. (2013)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
Adults	Women. 143 healthy premenopausal women (18–44 years old) in Buffalo, NY	Urine	No association between urine BPA and E2 in model adjusted for creatinine only and model adjusted for creatinine, age, race, BMI.	Pollack et al. (2018)
Adults	Men. 308 young Danish men from the general population	Urine	Doubling of BPA associated with increased E2 (2.7%; 95% CI: 0.4%, 5.1%; p = 0.02) P trend across quartiles = 0.01 Adjusted for BMI, smoking, time of day of blood sampling.	Lassen et al. (2014)
Adults	Men. 81 (18–59 years old) male residents in Cameroon (44 in rural and 37 in urban area)	Urine	No associations between BPA and E2 among urban population, rural population, or all participants.	Manfo et al. (2019)
Adults	Men (fertile). 302 men with pregnant partners in four US cities	Urine	No correlations between BPA or creatinine-adjusted BPA and E2.	Mendiola et al. (2010)
Adults	Men. 215 healthy male university students (18–23 years old) in Southern Spain (Murcia Region)	Urine	No association of BPA with E2 in unadjusted model (β = 0.004; 95% CI: –0.005, 0.01) or model adjusted for BMI, smoking, creatinine, time to blood sampling (β = 0.004; 95% CI: –0.004, 0.01) models.	Adoamnei et al. (2018)
Adults	Men and women.	Urine	No association between BPA and E2 in men, premenopausal women, or postmenopausal women in	Galloway et al. (2010)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	715 adults (aged 20–74 years old) in Italy		models adjusted for age and study site or for age, study site, smoking, obesity, and creatinine.	
Adults	Men and women. 100 men and 100 women in Korea Biomonitoring Program of Hazardous Materials Survey	Urine	Women and men in the high BPA group had significantly higher E1 than those in the low BPA group (p = 0.04 for women; p = 0.0002 for men). Women and men in the high BPA group had significantly higher E2 than those in the low BPA group (p = 0.03 for women; $p = 8.2 \times 10^{-10}$ for men). No significant difference in E3 in men or women.	Kim et al. (2014a)
Adults	Men and women. 1116 middle-aged and elderly men and 1442 postmenopausal women (average age: 61.8 years old) in China	Urine	No association between BPA and E2 in men or postmenopausal women in all 3 models (unadjusted, adjusted for creatinine and age, or adjusted for creatinine, age, BMI, education, smoking, drinking, waist circumference, diabetes).	Li et al. (2014)
Adults	Men and women. 229 men and women (21–76 years old) in China	Serum	No association of BPA with E2 [r-value not reported].	Gao et al. (2021)

Table J1.2 Effects of BPA on estradiol (E2) in human studies *in vitro* (ordered by tissue type [alphabetical, with primary cells listed first])

Cell type/system	BPA concentration, duration	Results	Reference
Adrenal: adrenocortical carcinoma H295R cells	30 to 3000 ng/ml [0.13 to 13 µM] for 24 hours	Significantly increased E2 levels at 3000 ng/ml	Zhang et al. (2011)
Adrenal: adrenocortical carcinoma H295R cells	0.1, 1, 10, 30, 50, 70 µM for 48 hours	No differences in E2 levels	Feng et al. (2016)
Breast: mammary fibroblast 3A HMF3A cells, breast cancer MCF-7 cells, or breast cancer ZR-75-1 cells	1 µM for 3 days	Significantly increased E2 levels in all cell types	Williams and Darbre (2019)
Lung. primary fetal lung fibroblasts	0.01 to 100 µM for 24 hours	Significantly increased E2 levels at 100 µM	Mahemuti et al. (2018)
Ovary: cumulus granulosa cells from IVF patients	100 µM for 48 hours	Significantly decreased E2 levels	Pogrmic-Majkic et al. (2019)
Ovary: luteinized granulosa cells from IVF patients	0.02, 0.2, 2, 20 µg/ml [0.087, 0.87, 8.7, 87. µM] for 48 hours	Significantly increased E2 levels at 20 µg/ml	Mansur et al. (2016)
Ovary: ovarian granulosa cells from non-PCOS and PCOS patients	0.01 to 1 µM for 24 hours	Significantly decreased E2 levels at 1 µM in granulosa cells from PCOS patients, no significant differences in E2 levels from non-PCOS patients	Wang et al. (2017c)
Ovary: ovarian granulosa KGN cells	0.5, 5, 50, or 500 µg/l [0.002, 0.022, 0.22, 2.2 µM] for 6 hours	Significantly decreased E2 levels at 0.5 [0.002 µM] and 5 µg/l [0.022 µM], no differences at 50 or 500 µg/l [0.22 or 2.2 µM]	Shi et al. (2021)
Ovary: ovarian granulosa KGN cells	10 pM [0.01 µM] for 24 hours	Significantly increased E2 levels	Liu et al. (2021b)
Placenta: choriocarcinoma JEG-3 cells Choriocarcinoma JEG-3 cells transducted with CYP19A1-shRNA (knockout)	0.1 to 50 µM for 24, 48, and 72 hours Transducted studies: 10 µM for 12 hours	Significantly and dose-dependently decreased E2 levels at 10 and 50 µM at 24 hours, 1–50 µM at 48 hours, and 0.1-50 µM at 72 hours Significantly decreased E2 levels after CYP19A1 knockout	Xu et al. (2019a)

Cell type/system	BPA concentration, duration	Results	Reference
Choriocarcinoma JEG-3 cells transducted with CYP19A1-pLVXhygro (overexpression)		Significantly increased E2 levels after CYP19A1 overexpression	
Placenta: choriocarcinoma BeWo cells	100 mM [100000 µM] for 48 hours	Significantly increased E2 levels	Cao et al. (2022)

Table J1.3 Effects of BPA on estradiol (E2) in non-human mammalian studies *in vivo* (ordered by species, strain, and life stage)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Gerbil, Mongolian, female, 5 per group	*In utero*. 0 or 50 µg/kg-day [0.05 mg/kg-day] F0 maternal exposure from GD8 to end of lactation (46 days total) via gavage; F1 sacrificed at PND180	No significant differences in serum E2 levels in female offspring	Leonel et al. (2020b)
Mouse, C57BL/6, male and female, 3 pooled samples per group (each pooled sample is from 5 or 6 animals)	*In utero*. 0 or 20 µg/kg-day [0.02 mg/kg-day] F0 maternal exposure from GD13 to GD16 via gavage, F1 sacrificed at GD17 or PND1	Significantly increased E2 levels in urogenital sinus in males and females at PND1, no differences at GD17	Arase et al. (2011)
Mouse, C57BL/6J, female, 10–21 per group	*In utero*, lactation. 0, 0.05, or 5 mg/kg-day F0 maternal exposure from GD15 to PND21; F1 sacrificed at 8 weeks old	Significantly increased serum E2 levels at 0.05 mg/kg bw dose group	Naule et al. (2014)
Mouse, C57BL/6, female, 16 per group	Juvenile, adult. 0, 5, 50, or 500 µg/kg-day [0.005, 0.05, or 0.5 mg/kg-day] for 28 days via gavage	Significantly decreased serum E2 levels in 5 and 500 µg/kg-day dose groups, no differences at 50 µg/kg-day	Cao et al. (2018b)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Mouse, CD-1, male, 6 per group	*In utero*. 0, 0.5, or 50 µg/kg-day [0.0005 or 0.05 mg/kg-day] F0 maternal exposure from GD7 to PND0 via oral administration; F1 mated to generate F2, F2 mated to generate F3, F3 sacrificed at PND60	No significant differences in serum E2 levels in F3 males	Shi et al. (2019b)
Mouse, CD-1, female, 4–5 per group	*In utero*. 0, 0.5 or 50 µg/kg-day [0.0005 or 0.05 mg/kg-day] F0 maternal exposure from GD7 to PND0 via oral administration (pipet feeding); F1 mated to generate F2, F2 mated to generate F3, F3 sacrificed at 3, 6 or 9 months old	Significantly increased serum E2 levels in F3 female offspring at 6 months old at 0.5 µg/kg-day, but not 50 µg/kg-day, no significant differences at 3 or 9 months old	Shi et al. (2019a)
Mouse, CD-1, females, 5-10 per group	*In utero*. 0, 0.5, 5, 50 mg/kg-day from F0 maternal exposure from GD10 to GD17 via gavage twice daily; F1 sacrificed at PND20, 28, 35, or 56	No significant differences in serum E2 levels at PND20, 28, 35, or 56	Tucker et al. (2018)
Mouse, CD-1, male, 9–13 per group	*In utero*, postnatal. 0 or 20 µg/kg-day [0.02 mg/kg-day] F0 maternal exposure from GD11 to GD17 followed by F1 exposure from PND1 to PND15 via oral administration; F1 sacrificed at 4 months old	No differences in serum E2 levels	Taylor et al. (2020)
Mouse, CD-1, male and female, 5 per group	*In utero*, lactation, juvenile or postnatal, juvenile. 0, 12, 25, 50 mg/kg-day F0 maternal exposure from gestation to	*In utero*, lactation, juvenile exposed: significantly increased serum E2 levels in female offspring at all dose groups, no significant differences in serum E2 levels in male offspring	Xi et al. (2011)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	weaning then F1 exposure postweaning to 5 weeks old or F1 postweaning to 5 weeks old via gavage	Postnatal, juvenile exposed: no differences in serum E2 levels	
Mouse, CD-1, male, 3–4 per group	*In utero*, lactation, postnatal. 0 or 10 µg/ml F0 maternal exposure from GD10 to PND31 via drinking water; F1 sacrificed at PND78	Significantly increased testicular E2 levels, no significant differences in white abdominal or perigonadal epithelial white adipose tissue E2 levels	Chioccarelli et al. (2021)
Mouse, CD-1, male and female, 6 per group	Postnatal, juvenile, adult. 0, 50 µg/kg-day [0.05 mg/kg-day], 10 mg/kg-day from PND0 to PND60 via *s.c.* injection every 3 days	Significantly increased serum E2 levels in males at 10 mg/kg, significantly increased serum E2 levels in females at both dose groups	Shi et al. (2017a)
Mouse, CF-1 mice, female, 7–10 per group	Adult. Exp. 1: 0, 0.0005, 0.0045, 0.05, 0.125, 1.125, 3.375, 6.75, or 10.125 mg/day to pregnant females (F0) on GD1 to GD4 via *s.c.* injection, F0 assessed on GD2 to GD5 Exp. 2: 0, 6.75, or 10.125 mg/day single *s.c.* injection to pregnant females (F0) on GD0, 1, or 2; F0 assessed on GD2 to GD5	No differences in urinary E2 levels at any dose in either treatment designs	Berger et al. (2008)
Mouse, FVB, male and female, 3-5 per group	*In utero*. 0, 0.5, 20, or 50 µg/kg-day [0.0005, 0.02, or 0.05 mg/kg-day] F0 maternal exposure from GD11 until PND0 via oral dosing; F1 assessed at 3-months-old, mated to generate F2, F2 assessed at 12 months old	Significantly decreased serum E2 levels in F1 offspring at 3 months old at 20 µg/kg-day; no significant differences in serum E2 levels in F2 offspring at 12 months old	Mahalingam et al. (2017)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Mouse, ICR, female, 5 per group	Adult. 0, 2, 20, or 200 mg/kg-day F0 exposed from GD13 to GD16 via oral administration; sacrificed at GD17	Significantly increased blood E2 levels in pregnant mice at 20 and 200 mg/kg (authors stated serum in material and methods, but plasma in legends for figure 1)	Tan et al. (2013)
Mouse, ICR, female, 8 per group	Adult. 0 or 50 µg/kg-day [0.05 mg/kg-day] for 60 days via gavage	Significantly decreased serum E2 levels	Tang et al. (2020)
Mouse, ICR, female, 8 per group	Adult. 0, 0.04, 0.4, 4, 40 mg/kg-day for 12 weeks via gavage	No significant differences in serum or brain E2 levels	Xu et al. (2015b)
Mouse, Kunming, male, 10 per group	*In utero*. 0, 2.5, 5, 10, 20, 40 mg/kg-day from GD0.5 to 17.5 via gavage; F1 sacrificed at PND21 or PND56	Significantly decreased serum E2 levels at PND21 and PND56 at all doses	Wei et al. (2019b)
Mouse, Kunming, male and female, 20 per group	*In utero*. 0 or 500 mg/kg-day F0 maternal exposure from GD8 to GD14 via gavage; F1 sacrificed at 8 weeks old	Significantly increased serum E2 levels in offspring	Ma et al. (2018)
Mouse, Kunming, male, 6 per group	Juvenile, adult. 0 or 20 mg/kg-day for 4 weeks via gavage	Significantly decreased E2 levels	Cao et al. (2020) [article in Chinese]
Mouse, unspecified, female, 15 per group	*In utero*. 0 or 5 mg/kg-day F0 maternal exposure from GD1 to GD18 via gavage; F1 sacrificed at PND21 or 56	Significantly decreased serum E2 levels at PND21 and 56	Han et al. (2020)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, ovariectomized F344, female, 12–15 per group	Adult. Rats received a single *s.c.* injection of 2000 mg/kg bw of N-*bis*(2-hydroxypropyl) nitrosamine (DHPN) and followed by 1000 ppm sulfadimethoxine (SDM) for 8 weeks via drinking water, followed by 0 or 10000 ppm [10000 µg/g] BPA for 27 weeks via diet	No differences in serum E2 levels	Takagi et al. (2001)
Rat, Long-Evans, male, 6 per group	*In utero*. 0, 2.5, or 25 µg/kg-day [0.0025 or 0.025 mg/kg-day] F0 maternal exposure from GD12 to GD21 via gavage; F1 sacrificed at PND21, 35, and 90	No significant differences in serum E2 levels in male offspring at PND21, 35, or 90. Significantly increased testicular explant E2 production at both dose groups at PND90, no significant differences in isolated Leydig cell E2 production.	Abdel-Maksoud et al. (2015)
Rat, Long-Evans, male, 6 per group	Juvenile. 0 or 5 µg/l [0.005 µg/ml] for 14 days starting at PND21 or PND35 via drinking water	No differences in serum or testicular E2 levels, significantly increased E2 production in basal Leydig cells	Jeminiwa et al. (2021)
Rat, Long-Evans, male and female, 10–12 per group	Juvenile. 0, 2.4, 10 µg/kg-day [0.0024 or 0.01 mg/kg-day], 100 or 200 mg/kg-day from PND21 to 35 via gavage	Significantly decreased serum E2 levels at 2.4 and 10 µg/kg-day and 100 mg/kg-day dose groups	Akingbemi et al. (2004)
Rat, SD, male, 8-10 per group	*In utero*. 0, 25, or 250 µg/kg-day [0.025 or 0.25 mg/kg-day] F0 maternal exposure from GD10 to GD21 via gavage; F1 sacrificed at PND21 or PND180	No differences in serum E2 levels in offspring at PND21 or PND180	Brandt et al. (2014)
Rat, SD, male, 8 per group	*In utero*.	Significantly increased plasma E2 levels at 50 µg/l dose group	Ullah et al. (2019b)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	0, 5, 25, or 50 µg/l [0.005, 0.025 or 0.05 µg/ml] F0 maternal exposure from GD1 to GD21 via drinking water; F1 sacrificed at PND80		
Rat, SD, male and female, 9-16 per group	*In utero*. 0 or 40 µg/kg-day [0.04 mg/kg-day] F0 maternal exposure from GD1 to PND0 via oral administration; F1 sacrificed at 22-weeks old	Increased plasma E2 levels in female offspring, but not male offspring (statistical significance not reported)	Aloisi et al. (2002)
Rat, SD, male, 6 per group	*In utero*, lactation. 0 or 50 mg/kg-day F0 maternal exposure from GD6 to GD21 and lactation via gavage; F1 sacrificed at 12-weeks-old	No difference in plasma E2 levels in offspring	Balci et al. (2022)
Rat, SD, male, 5 per group	*In utero*, lactation. 0, 50, 100, or 200 mg/kg-day F0 maternal exposure from GD0 to PND20 via gavage; F1 sacrificed at PND20	Significantly increased serum E2 levels at 100 and 200 mg/kg	Lü and Zhan (2010)
Rat, SD, male and female, 3 per group	*In utero*, lactation. 0, 50 µg/kg-day [0.05 mg/kg-day] or 50 mg/kg-day F0 maternal exposure from GD7 to PND21 via gavage; F1 sacrificed PND15, 30, 45, or 60	Significantly increased serum E2 levels at PND30	Lee et al. (2013b)
Rat, SD, male and female, 9–16 per group	Lactation. 0 or 40 µg/kg-day [0.04 mg/kg-day] F0 maternal exposure from PND1 to PND21 via oral administration; F1 sacrificed at 22 weeks old	Increased plasma E2 levels in females and males (statistical significance not reported)	Aloisi et al. (2002)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, SD (NCTR), male and female, 10–17 per group	*In utero*, postnatal. 0, 2.5, or 25 µg/kg-day [0.0025 or 0.025 mg/kg-day] F0 maternal exposure from GD6 to GD21 followed by F1 exposure from PND1 to PND21 via gavage; F1 sacrificed at PND21	No differences in serum E2 levels in male or female offspring	Ferguson et al. (2011)
Rat, SD, male and female, 8 per group	*In utero*, lactation, juvenile. 0, 1, or 10 µg/ml F0 maternal exposure from GD6 to PND21, followed by F1 exposure from PND21 to PND56 via drinking water; F1 sacrificed at PND56	Significantly increased serum E2 levels in female offspring at both dose groups, significantly increased in male offspring at 10 µg/ml dose group only	Wu et al. (2020a)
Rat, SD (NCTR), female, 18–21 per group	*In utero*, postnatal, juvenile, adult. 0, 2.5–2700 µg/kg-day, 100000 or 300000 µg/kg-day [0.0025–2.7, 100, or 300 mg/kg-day] F0 maternal exposure from GD6 to PND0, followed by F1 exposure from PND1 to PND80 via gavage; F1 assessed at PND80	Significantly increased serum E2 levels in female offspring at 100000 and 300000 µg/kg-day	Delclos et al. (2014)
Rat, SD (NCTR), female, 8–10 per group	*In utero*, postnatal, juvenile, adult. 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day [0.0025, 0.025, 0.25, 2.5, or 25 mg/kg-day] Continuous dose: F0 maternal exposure from GD6 to PND0, then F1 exposure from PND1 to sacrifice via gavage; F1 sacrificed at PND1, PND21, PND90, 6 months old, or 1 year old	Significantly decreased serum E2 levels at 2500 and 25000 µg/kg-day continuously dosed for 1 year, no differences at PND21, PND90, or 6 month old animals in continuous dose or stop dose groups, no differences in 1 year stop dose group	Patel et al. (2017)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	Stop dose: F0 maternal exposure from GD6 to PND0 then F1 exposure from PND1 to PND21 via gavage, F1 sacrificed at PND90, 6 months old or 1 year old		
Rat, SD, male, 8 per group	Postnatal, juvenile. 0 or 50 µg/kg-day [0.05 mg/kg-day] from PND15 to PND30 via *s.c.* injection	No difference in plasma E2 levels	Brouard et al. (2016)
Rat, SD, male and female, 7 per group	Juvenile. 0 or 40 µg/kg-day [0.04 mg/kg-day] from PND23 to PND30 via oral administration; sacrificed at PND37 or PND90	No differences in serum E2 levels in males or females at PND37 or PND90	Ceccarelli et al. (2007)
Rat, SD, male, 7 per group	Juvenile, adult. 0, 5, 25, 50 µg/l [0.005, 0.025. 0.05 µg/ml] for 48 weeks via drinking water	Significantly increased plasma E2 levels at 50 µg/l dose group	Ullah et al. (2018b)
Rat, SD, female, 6 per group	Juvenile, adult. 0 or 50 mg/kg-day for 6 weeks via oral administration	Significantly decreased serum E2 levels	Zhou et al. (2014a)
Rat, SD, female, 8 per group	Juvenile, adult. 0 or 10 mg/kg-day for 6 weeks via gavage	No differences in serum E2 levels	Zaid et al. (2018)
Rat, SD, female, 5 per group	Juvenile, adult or adult. 0 or 330 mg/kg-day starting at 1-month-old (young) or 3-month-old (adult) for 12 weeks via oral administration	Significantly increased serum E2 levels in young female rats after 10 or 12 weeks of exposure, significantly decreased serum E2 levels in female adults at 10 or 12 weeks of exposure.	Hamdy et al. (2018)
Rat, SD, male, 10 per group	Adult.	No differences in serum E2 levels	Wu et al. (2016)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	0, 10, 30, or 90 µg/kg-day [0.01, 0.03, or 0.09 mg/kg-day] for 4 weeks via gavage		
Rat, SD, male, 10 per group	Adult. 0, 10, 30, 90, or 270 µg/kg-day [0.01, 0.03, 0.09 or 0.27 mg/kg-day] for 4 weeks via gavage	Significantly increased serum E2 levels in 30 µg/kg dose group	Wu et al. (2020b)
Rat, SD, female, 10 per group	Adult. 0, 0.05, 0.5, 5, or 50 mg/kg-day for 28 days via *i.p*. injection	Significantly decreased plasma E2 levels at 50 mg/kg	Ijaz et al. (2020)
Rat, SD, female, 12 per group	Adult. 0, 0.001, 0.1 mg/kg-day for 90 days via gavage	Significantly decreased serum E2 levels in both dose groups	Lee et al. (2013c)
Rat, SD albino, female, 5 per group	Adult. 0, 0.02, 20, or 200 mg/kg bw 3 times/week for 6 weeks via gavage	Significantly increased serum E2 levels in all doses	Osman et al. (2021)
Rat, SD, female, 5 per group	Adult. 0 or 200 mg/kg-day for 4 days (either days 1–4 or days 5–8) of pseudopregnancy via *s.c.* injection	No differences in serum E2 levels in pseudopregnant rats at either dosing regime	Spencer et al. (2002)
Rat, SD, female, 6 per group	Adult. 0, 10, 50, or 100 µg/kg-day [0.01, 0.05, or 0.1 mg/kg-day] for 12 weeks via gavage	Significantly decreased serum E2 levels at 10 µg/kg-day, no significant differences at 50 or 100 µg/kg-day	Thilagavathi et al. (2018)
Rat, SD, male and female, 10 per group	Adult (female); Juvenile, adult (male). 0 or 200 mg/kg-day for 14 days via gavage	Significantly increased serum E2 levels in females, no significant differences in males	Quignot et al. (2012)
Rat, Wistar, female, 8–10 per group	*In utero*. 0, 25, or 250 µg/kg-day [0.025 or 0.25 mg/kg-day] F0 maternal	No differences in serum E2 levels in female offspring at PND50 or 110	Durando et al. (2011)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	exposure from GD8 to GD23, F1 sacrificed at PND50 or PND110		
Rat, Wistar, female, 5 per group	*In utero*, lactation. 0, 0.05, or 20 mg/kg-day F0 maternal exposure from GD6 to PND21 via drinking water; F1 mated at 3 months and sacrificed at GD1, 3, 6, or 7	Significantly decreased serum E2 levels in F1 females at GD3 at 0.05 mg/kg-day	Martínez-Pena et al. (2017)
Rat, Wistar, male and female, 9–12 per group	*In utero*, lactation. 0, 10, or 50 µg/kg-day [0.01 or 0.05 mg/kg-day] F0 maternal exposure from gestation to PND21 via gavage; F1 sacrificed at PND21 or PND180	Dams at PND21: No differences in plasma E2 levels Males at PND21: Significantly increased plasma E2 levels at 10 µg/kg Females at PND21: Significantly increased plasma E2 levels at 10 µg/kg Males at PND180: Significantly decreased plasma E2 levels at 10 µg/kg Females at PND180: No differences in plasma E2 levels	Silva et al. (2019)
Rat, Wistar, male, 6 per group	*In utero*, postnatal. 0, 2.4, or 10 µg/kg-day [0.0024 or 0.01 mg/kg-day] F0 maternal exposure from GD12 to PND0 via *s.c.* injection; followed by F1 exposure from PND1 to PND21; F1 sacrificed at PND21	Significantly increased plasma E2 levels at 10 µg/kg-day dose group	Castro et al. (2018a)
Rat, Wistar, female, 5 per group	Postnatal. 0, 0.05, or 20 mg/kg every 48 hours from PND1 to PND7 via *s.c.* injection	No differences in serum E2 levels	Monje et al. (2007)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, Wistar, female, 7 per group	Postnatal. 0, 0.05, or 20 mg/kg-day single *s.c.* injection on PND1, 3, 5, or 7; raised to adult, mated, and sacrificed at GD5	No differences in serum E2 levels in pregnant rats on GD5	Varayoud et al. (2011)
Rat, Wistar, male, 6 per group	Juvenile, adult. 0 or 50 mg/kg-day for 30 days via oral administration	Significantly decreased serum E2 levels	Alboghobeish et al. (2019)
Rat, Wistar albino, male and female, 6 per group	Juvenile, adult. 0, 1, 5, or 10 ppm [1, 5, 10 µg/ml] for 6 months via drinking water	Significantly decreased serum E2 levels in males fed a normal or anemic diet at 10 ppm, significantly increased serum E2 levels in females fed a normal or anemic diet at 10 ppm	Rashid et al. (2018)
Rat, Wistar, male, 8 per group	Adult. 0, 25, 50, 300, or 600 µg/kg-day [0.025, 0.05, 0.3, or 0.6 mg/kg-day] for 4 days via *s.c.* injection	Significantly increased plasma E2 levels at all doses	Castro et al. (2013)
Rat, Wistar, male, 10 per group	Adult. 0 or 10 mg/kg-day for 14 days via gavage	Significantly increased serum E2 levels	Olukole et al. (2018)
Rat, Wistar albino, female, 5 per group	Adult. 0 or 25 mg/kg-day for 9 days via *i.p.* injection	Significantly decreased serum E2 levels	Banerjee et al. (2018)
Rat, Wistar, female, 8 per group	Adult. 0 or 10 mg/kg-day for 8 weeks via oral administration	Significantly decreased serum E2 levels	Behmanesh et al. (2018)
Rat, Wistar albino, female, 7 per group	Adult. 0 or 20 mg/kg-day for 15 days via gavage	Significantly decreased serum E2 levels	Fouad et al. (2021)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, Wistar, female, 10 per group	Adult. 0, 5, 50, 300, 600, or 800 mg/kg-week for 3 months via oral administration	Significantly and dose-dependently decreased serum E2 levels at 50 mg/kg-week and above, no significant differences in serum E2 levels in cesarean phase females at 45 days or 90 days or full-term females at 5 mg/kg-week	Srivastava and Dhagga (2019)
Rat, unspecified albino, female, 5 per group	*In utero*, lactation, juvenile, adult. 0, 50, or 200 mg/kg-day F0 maternal exposure from GD0 to PND21, followed by F1 exposure for 3 months via oral administration	Significantly and dose-dependently increased serum E2 levels in dams and female offspring at both dose groups	Moustafa and Ahmed (2016)
Rat, unspecified, female, 15 per group	Postnatal. 0, 0.5, 5, or 50 mg/kg-day from PND1 to PND10 via *s.c.* injection	Significantly increased plasma E2 levels at 50 mg/kg	Ahsan et al. (2018)
Rat, unspecified albino, male, 10 per group	Adult. 0 or 5 mg/kg-day for 3 weeks via *i.p.* injection	Significantly increased serum E2 levels	Eshak and Osman (2014)
Rat, unspecified, female, 6 per group	Adult. 0 or 250 mg/kg-day for 30 days via gavage	Significantly increased serum E2 levels (authors noted significant increase in text, but also noted $p > 0.05$)	Raheem et al. (2020)
Rat, unspecified albino, female, 12 per group	Adult. 0 or 150 mg/kg-day F0 exposure from GD0 to 20 via stomach gavage; F0 assessed at GD4, 10, and 20	Significantly decreased serum E2 levels in pregnant rats at GD20, but not GD4 or GD10	Saadeldin et al. (2018)
Sheep, female, 9-18 per group	Postnatal. 0, 0.5 or 50 µg/kg-day [0.0005 or 0.05 mg/kg-day] from PND1 to PND14 via *s.c.* injection; sacrificed at PND30	No differences in serum E2 levels at PND30	Rivera et al. (2015)

Table J1.4 Effects of BPA on estradiol (E2) in non-human mammalian studies *in vitro* (ordered by species, cell type, cell line)

Cell type/system	BPA concentration, duration	Results	Reference
Immature boar testes	10 nM for 48 hours (pretreated with G-protein coupled estrogen receptor antagonist (G-15) for 2 hours)	Significantly decreased E2 levels	Pawlicki et al. (2019)
Mouse antral follicles from FVB mice	4.4, 44, or 440 µM for 120 hours	Significantly decreased E2 levels at 44 and 440 µM	Peretz et al. (2011)
Mouse ovarian antral follicles from C57BL/6 mice	0.004 to 438 µM for 96 hours	Significantly decreased E2 levels at 43.8 µM and above	Ziv-Gal et al. (2013)
Mouse (Kunming) preantral follicles	4.5 and 45 µM for 4, 8, or 10 days	Significantly decreased E2 levels at 8th and 10th day of preantral follicle culture at 45 µM (based on comparison with untreated control, although there does not appear to be any significant difference between the untreated control and the vehicle control, the latter of which received 1 µl/ml DMSO)	Wang et al. (2018a) [article in Chinese]
Pig primary granulosa cells	10 µM for 24 hours	Significantly increased E2 levels	Song et al. (2019)
Pig primary granulosa cells	10 µM for 24 or 48 hours	Significantly increased E2 levels at 24 and 48 hours	Wu et al. (2018)
Pig primary granulosa cells	0.1, 1, or 10 µM for 48 hours	Significantly increased E2 levels at 0.1 µM, but decreased levels at 1 and 10 µM	Grasselli et al. (2010)
Pig ovarian granulosa cells	10 nM to 100 µM for 72 hours	Significantly decreased FSH-stimulated E2 levels between 1 to 100 µM	Mlynarcikovic et al. (2005)
Pig granulosa cells and theca interna cells from follicles on days 10–12 co-culture	20 ng/ml [0.087 µM] for 24 hours	Significantly increased E2 levels	Rak et al. (2017)

Cell type/system	BPA concentration, duration	Results	Reference
Rat primary granulosa cells	10 μM for 24 hours	Significantly decreased E2 levels	Lee et al. (2019a)
Rat primary granulosa cells	0.01 to 100 μM for 48 hours	Significantly decreased E2 levels at 10 and 100 μM	Chen et al. (2017a) [article in Chinese]
Rat primary granulosa cells	0.1 to 100 μM for 72 hours	Significantly and concentration-dependently decreased E2 levels between 1 and 100 μM	Zhou et al. (2008)
Sheep primary granulosa cells	1 nM to 200 μM for 48 hours	Significantly increased E2 levels at 10 μM and above	Teteau et al. (2020)

Section J2 Progesterone and progesterone receptor

Table J2.1 Effects of BPA on progesterone (P4) in human studies *in vitro* (ordered by tissue type [alphabetical, with primary cells listed first])

Cell type/system	BPA concentration, duration	Results	Reference
Adrenal: adenocarcinoma H295R cells	0.3, 3, 30, 300, or 3000 ng/ml for 24 hours	Significantly increased P4 levels at 3000 ng/ml, no differences at lower concentrations	Zhang et al. (2011)
Adrenal: adenocarcinoma H295R cells	0.1 to 70 µM for 48 hours	Significantly decreased P4 levels at 30, 50, and 70 µM	Feng et al. (2016)
Ovary: human cumulus granulosa cells from IVF patients	100 µM for 48 hours	Significantly increased P4 levels	Pogrmic-Majkic et al. (2019)
Ovary: luteinized granulosa cells from IVF patients	0.02, 0.2, 2, or 20 µg/ml for 48 hours	Significantly decreased P4 levels at 2 and 20 µg/ml	Mansur et al. (2016)
Ovary: ovarian granulosa KGN cells	0.5, 5, 50, or 500 µg/l for 6 hours	Significantly decreased P4 levels at 5 and 50 µg/l	Shi et al. (2021)

Table J2.2 Effects of BPA on progesterone (P4) in non-human mammalian studies *in vivo* (ordered by species, strain, life stage)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Mouse, CD-1, female, 5–10 per group	*In utero*. 0, 0.5, 5, 50 mg/kg twice daily F0 maternal exposure from GD10 to GD17 via gavage, F1	No significant differences in serum P4 levels at PND20, 28, 35, or 56	Tucker et al. (2018)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	sacrificed at PND20, 28, 35, or 56		
Mouse, CD-1, male and female, 5 per group	*In utero*, lactation, juvenile, or juvenile only. 0, 12, 25, 50, mg/kg-day F0 maternal exposure from gestation to weaning then F1 exposure postweaning to 5 weeks old, or F1 postweaning to 5 weeks old via gavage	No differences in serum P4 levels in animals exposed *in utero* to 5 weeks old, or postweaning to 5 weeks old, at any dose	Xi et al. (2011)
Mouse, CF-1 mice, female, 7–10 per group	Adult. Exp. 1: 0, 0.0005, 0.0045, 0.05, 0.125, 1.125, 3.375, 6.75, or 10.125 mg/day to pregnant females (F0) on GD1 to GD4 via *s.c.* injection, F0 assessed on GD2 to GD5 Exp. 2: 0, 6.75, or 10.125 mg/day single *s.c*. injection to pregnant females (F0) on GD0, 1, or 2; F0 assessed on GD2 to GD5	Exp. 1: Significantly decreased urinary P4 levels in F0 females on GD2, 3, 4, and 5 at 10.125 mg/day Exp. 2: No significant differences in urinary P4 levels in F0 females at any dose group administered on any day (GD0, 1, or 2) or assessed at any day (GD2, 3, 4, or 5)	Berger et al. (2008)
Mouse, FVB, male and female, 3–5 per group	*In utero*. 0, 0.5, 20, or 50 µg/kg-day F0 maternal exposure from GD11 until PND0 via oral dosing; F1 assessed at 3-months-old,	No significant differences in P4 levels in F1 or F2 offspring at any dose	Mahalingam et al. (2017)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	mated to generate F2, F2 assessed at 12 months old		
Mouse, ICR, female, 8 per group	Adult. 0 or 50 µg/kg-day for 60 days via gavage	Significantly decreased serum P4 levels	Tang et al. (2020)
Mouse, Kunming, female, 20 per group	*In utero*. 0, 2.5, 5, 10, 20, or 40 mg/kg-day F0 maternal exposure from GD0.5 to GD17.5 via gavage, F1 sacrificed at PND56	Significantly decreased P4 levels at PND56 at all doses	Wei et al. (2019a) [article in Chinese]
Mouse, Kunming, female, 10 per group	*In utero*. 0, 2.5, 5, 10, 20, or 40 mg/kg-day F0 maternal exposure from GD0.5 to GD17.5 via gavage, F1 sacrificed at PND21 or PND56	Significantly decreased serum P4 levels at all doses in animals at PND21 and PND56	Wei et al. (2020a)
Mouse, unspecified, female, 15 per group	*In utero*. 0 or 5 mg/kg-day F0 maternal exposure from GD1 to GD18 via gavage; F1 sacrificed at PND21 or PND56	Significantly decreased serum P4 levels at PND21 and PND56	Han et al. (2020)
Rat, SD (NCTR), female, 18–21 per group	*In utero*, postnatal, juvenile, adult. 0, 2.5, 8, 25, 80, 260, 840, 2700, 100000, or 300000 µg/kg-day F0 maternal exposure from GD6 to PND0, then F1 exposure from PND1 to	Significantly decreased serum P4 levels at 300000 µg/kg-day, no differences at lower doses	Delclos et al. (2014)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	PND80 via gavage; F1 sacrificed at PND80		
Rat, SD (NCTR), female, 8–10 per group	*In utero*, postnatal, juvenile, adult. 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day Continuous dose: F0 maternal exposure from GD6 to PND0, then F1 exposure from PND1 to sacrifice via gavage; F1 sacrificed at PND1, PND21, PND90, 6 months old, or 1 year old Stop dose: F0 maternal exposure from GD6 to PND0 then F1 exposure from PND1 to PND21 via gavage, F1 sacrificed at PND90, 6 months old or 1 year old	No differences in serum P4 levels in continuous or stop dose animals at any age	Patel et al. (2017)
Rat, SD, female, 5 per group	Juvenile, adult. 0 or 330 mg/kg bw starting at 1-month-old (young) or 3-months-old (adult) for 12 weeks via oral administration; assessed every 2 weeks	Significantly decreased serum P4 levels in adult rats after 4 weeks of exposure, no differences in serum P4 levels after 2, 6, 8, 10, or 12 weeks of exposure or in juvenile rats	Hamdy et al. (2018)
Rat, SD, female, 8 per group	Juvenile, adult. 0 or 10 mg/kg-day for 6 weeks via gavage	Significantly decreased serum P4 levels	Zaid et al. (2018)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, SD, female, 10 per group	Adult. 0, 50 µg, 500 µg, 5 mg, or 50 mg/kg for 28 days via *i.p*. injection	Significantly decreased plasma P4 levels at 5 and 50 mg/kg	Ijaz et al. (2020)
Rat, SD albino, female, 5 per group	Adult. 0, 20 µg, 20 mg, or 200 mg/kg bw 3 times/week for 6 weeks via gavage	Significantly increased serum P4 levels in all dose groups	Osman et al. (2021)
Rat, SD, female, 5 per group	Adult. 0 or 200 mg/kg for 4 days (either days 1-4 or days 5-8) via *s.c.* injection, sacrificed 1 day after last treatment	Significantly decreased serum P4 levels when treated from days 5 through 8 of pseudopregnancy, no differences in serum P4 when treated from days 1 through 4 of pseudopregnancy	Spencer et al. (2002)
Rat, SD, female, 6 per group	Adult. 0, 10, 50, or 100 µg/kg-day for 12 weeks via gavage	Significantly decreased serum P4 levels at 10 µg/kg-day, no significant differences at 50 or 100 µg/kg-day	Thilagavathi et al. (2018)
Rat, Wistar, female, 8–10 per group	*In utero*. 0, 25, or 250 µg/kg-day F0 maternal exposure from GD8 to GD23 via osmotic pump, F1 sacrificed at PND50 or PND110	Significantly decreased serum P4 levels at PND50 at both doses, no differences at PND110	Durando et al. (2011)
Rat, Wistar, female, 5 per group	*In utero*, lactation. 0, 0.05, or 20 mg/kg-day F0 maternal exposure from GD6 to PND21 via drinking water; F1 mated at 3 months and sacrificed at GD1, 3, 6, or 7	Significantly decreased serum P4 levels in F1 females at GD1 exposed to 20 mg/kg-day and at GD6 at 0.05 mg/kg-day, no differences were observed in animals at GD3 or GD7	Martínez-Pena et al. (2017)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, Wistar, male and female, 9–12 per group	*In utero*, lactation. 0, 10, or 50 µg/kg-day F0 maternal exposure from gestation to PND21 via gavage; F1 sacrificed at PND21 or PND180	Mothers at PND21: no differences in plasma P4 levels Males at PND21: significantly increased plasma P4 levels at 10 µg/kg-day Males at PND180: significantly decreased plasma P4 levels at both doses Females at PND21: significantly increased plasma P4 levels at 10 µg/kg-day Females at PND180: no differences in plasma P4 levels	Silva et al. (2019)
Rat, Wistar albino, male and female, 6 per group	Juvenile, adult, 0, 1, 5, or 10 ppm for 6 months via drinking water	Males: significantly increased serum P4 levels in animals at 5 and 10 ppm fed a normal diet, increased in animals at 10 ppm fed an anemic diet Females: significantly decreased serum P4 levels in animals at 5 and 10 ppm fed a normal or anemic diet	Rashid et al. (2018)
Rat, Wistar albino, female, 5 per group	Adult. 0 or 25 mg/kg-day for 9 days via *i.p.* injection	Significantly decreased serum P4 levels	Banerjee et al. (2018)
Rat, Wistar, female, 8 per group	Adult. 0 or 10 mg/kg-day for 8 weeks via oral administration	No differences in serum P4 levels	Behmanesh et al. (2018)
Rat, Wistar albino, female, 7 per group	Adult. 0 or 20 mg/kg-day for 15 days via gavage	Significantly decreased serum P4 levels	Fouad et al. (2021)
Rat, Wistar, female, 10 per group	Adult.	Significantly and dose-dependently decreased serum P4 levels at 50 mg/kg-week and above, no significant differences serum P4 levels in cesarean phase	Srivastava and Dhagga (2019)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	0, 5, 50, 300, 600, or 800 mg/kg-week for 3 months via oral administration	females at 45 days or 90 days or in full-term females at 5 mg/kg-week	
Rat, unspecified, female, 8 per group	Postnatal. 0, 0.5, 5, or 50 mg/kg from PND1 to PND10 via *s.c.* injection; sacrificed at PND75	Significantly decreased plasma P4 levels at 50 mg/kg dose, no significant differences at other doses	Ahsan et al. (2018)
Rat, unspecified albino, female, 12 per group	Adult. 0 or 150 mg/kg-day to pregnant females (F0) from GD0 to 20 via stomach gavage; F0 assessed at GD4, 10, and 20	Significantly decreased serum P4 levels in F0 pregnant females at GD10 and GD20, no differences at GD4	Saadeldin et al. (2018)

Table J2.3 Effects of BPA on progesterone (P4) in non-human mammalian studies *in vitro* (ordered by species, tissue type [alphabetical, with primary cells listed first])

Cell type/system	BPA concentration, duration	Results	Reference
Mouse Leydig TM3 and TM4 cells	100 µM for 24 hours	Significantly decreased P4 production in both cell lines	Ok et al. (2017)
Mouse antral follicles from FVB mice	4.4, 44, or 440 µM for 120 hours	Significantly decreased P4 levels at 44 and 440 µM	Peretz et al. (2011)
Pig ovarian granulosa cells	10 nM to 100 µM for 72 hours	Significantly increased P4 levels at 10 µM, significantly decreased P4 levels at 100 µM	Mlynarcikovic et al. (2005)
Pig primary granulosa cells	0.1, 1, or 10 µM for 48 hours	Significantly decreased P4 levels at all concentrations	Grasselli et al. (2010)
Rat ovarian granulosa cells from immature female Wistar rats	0.1 to 100 µM for 24 hours	Significantly decreased P4 production at 100 µM	Samardzija et al. (2018)
Rat ovarian granulosa cell from mature SD rats	0.1 to 100 µM for 48 hours	Significantly increased P4 production at 0.1, 1, and 10 µM, significantly decreased P4 production at 100 µM	Zhou et al. (2008)
Rat primary granulosa cells	0.1 to 100 µM for 48 hours	Significantly decreased P4 levels at 10 and 100 µM	Chen et al. (2017a) [article in Chinese]
Sheep primary granulosa cells	1 nM to 200 µM for 48 hours	Significantly decreased P4 levels at 100 and 200 µM	Teteau et al. (2020)

Table J2.4 Effects of BPA on progesterone receptor (PR) in human studies *in vitro* (ordered by tissue type [alphabetical, with primary cells listed first], followed by transfected cells from other species, and cell-free systems)

Cell type/system	BPA concentration, duration	Results	Reference
Breast: breast cancer MCF-7 cells	1 μM for 5 days	No significant difference in PR mRNA expression	Diel et al. (2002)
Breast: breast cancer MCF-7 cells	1 to 100 nM for 6 days	Significantly increased PR protein levels at 25, 50, and 100 nM	Krishnan et al. (1993)
Breast: MCF-7 cells and MCF-7 mammospheres	Cells: 10 nM for 24 hours Mammospheres: 10 nM for 10 days	No differences in PR mRNA expression in cells or mammospheres	Lillo et al. (2017)
Breast: breast cancer MCF-7 cells	1 μM for 72 hours	Significantly increased PR protein expression	Samuelsen et al. (2001)
Breast: breast cancer MCF-7 cells	10 μM for 6 or 24 hours	Non-statistically significantly increased PR mRNA expression after 6 and 24 hours	Tarnow et al. (2013)
Breast: breast cancer MCF-7 cells	10 μM for 48 hours	Increased gene expression of PR (211-fold increase)	(Tilghman et al. 2012)
Uterus: human endometrial stromal fibroblasts from patients undergoing hysterectomy for fibroids or pelvic organ prolapse	5, 25, 50 or 100 μM for 48 hours	No differences in PRA or PRB mRNA expression	Aghajanova and Giudice (2011)
Uterus: endometrial stromal cells from healthy human endometrium	1 pM, 1 nM, or 1 μM for 24 hours	Significantly increased PR protein expression at 1 μM and total PR (PRA and PRB) mRNA expression at 1 μM, PRB mRNA expression alone was not significantly different	Mannelli et al. (2015)

Cell type/system	BPA concentration, duration	Results	Reference
Uterus: human endometrial ECC-1 cells	0.1 μM for 1 to 5 days	Significantly increased PR mRNA expression after 1, 2, or 3 days, increased PR protein expression after 5 days	Bergeron et al. (1999)
Uterus: Ishikawa endometrial adenocarcinoma cells	1 μM for 24 hours	Significantly increased total PR and PR-B mRNA expression	Aldad et al. (2011)
Uterus: Ishikawa endometrial adenocarcinoma cells	0.01 to 1 μM for 24 hours	Increased PR mRNA expression (calculated EC_{50}: 0.1272 and 0.4709 μM), induced PR protein expression at 1 μM [statistical significance not reported]	Schaefer et al. (2010)
Breast: PR-TM-Luc (derived from mammary gland adenoma T47-D) cells	up to 40 μM for 48 hours	Antagonized P4-induced PR activity (IC_{50} 18.5 μM)	Doan et al. (2020)
Breast: TM-Luc (derived from mammary gland adenoma T47-D) cells	0.001 to 1 mM for 24 or 48 hours	No antagonistic effects on PR activity	Simon et al. (2016)
Cervix: HELN PR (derived from HeLa cells and stably expressing chimeric PR with ERα DBD)	0.1 to 10 μM for 16 hours	BPA was not active for PR activity	Grimaldi et al. (2019)
Yeast stably transfected with human PR gene and progesterone response element	[concentration range not specified] for 60 min	Did not exhibit agonistic or antagonistic effects on PR	Li et al. (2010)
Cell free recombinant human PR competitive binding assay	0.5 to 250 μM [duration not reported]	Bound to PR with IC_{50} of 45 μM and relative binding affinity of 0.1%	Scippo et al. (2004)
Cell free competitive binding assay	up to 10 μM [duration not reported]	Did not bind PR up to 10 μM	Takayanagi et al. (2006)

Table J2.5 Effects of BPA on progesterone receptor (PR) in non-human mammalian studies *in vivo* (ordered by species, strain, life stage)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Gerbil, Mongolian, female, 5 per group	*In utero*, lactation. 0 or 50 µg/kg F0 maternal exposure from GD8 to end of lactation via gavage; F1 sacrificed at PND180	Significantly increased percent of positive cells for PR in mammary gland epithelium (as measured by immunohistochemistry), no differences in mammary gland PR protein levels (as measured by Western Blot)	Leonel et al. (2020b)
Gerbil, Mongolian, female, 5 per group	Adult. 0, 50, or 5000 µg/kg-to pregnant females (F0) from GD8 to end of lactation (39 days total) via gavage, F0 sacrificed at 18 months old	F0: Significantly decreased percentage of PR positive cells in normal alveoli of mammary glands and in hyperplastic mammary glands at both dose groups. In carcinoma tissue, percentages of PR positive cells were the lower than in hyperplastic tissues of BPA treated groups. No comparison was made with controls, due to lack of carcinoma in control.	Ruiz et al. (2021)
Monkey, ovariectomized African green, female, 1–3 per group	Adult. 0 or 50 µg/kg-day for 4 weeks via osmotic pump	No effects on PR mRNA expression in endometrial glands or stroma cells	Aldad et al. (2011)
Mouse, CD-1, female, 6–10 per group	*In utero*. 0, 25, or 250 ng/kg-day F0 maternal exposure from GD9 to PND4 via osmotic pump; F1 sacrificed at PND30	Significantly increased percent of cells expressing PR in epithelial compartment of mammary glands at both doses	Munoz-de-Toro et al. (2005)
Mouse, CD-1, female, 5–6 per group	*In utero*, lactation. 0, 25, or 250 ng/kg-day F0 maternal exposure from GD9 to	Significantly increased PR expression in luminal epithelial cells of the uterus at both doses	Markey et al. (2005)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	PND4 via osmotic pump, F1 sacrificed at 3 months old		
Mouse, CF-1, female, 8 per group	Adult. 0, 3.375, 6.75, or 10.125 mg/animal-day to pregnant females (F0) from GD1 to GD4 via *s.c.* injection; F0 sacrificed on GD6	Increased uterine PR-B protein expression at 3.375 mg/animal-day and decreased at 10.125 mg/animal-day relative to controls, but not statistically significant	Berger et al. (2010)
Mouse, ICR, female, [group size not reported]	*In utero*. 0 or 2 µg/kg-day F0 maternal exposure from GD6.5 to GD17.5 via oral administration, F0 sacrificed at GD18.5	Increased PR mRNA expression in placentae with male embryos, decreased PR mRNA expression in placentae with female embryos	Imanishi et al. (2003)
Mouse, Kunming, female, 20 per group	*In utero*. 0, 2.5, 5, 10, 20, or 40 mg/kg-day F0 maternal exposure from GD0.5 to GD17.5 via gavage, F1 sacrificed at PND56	Significantly decreased PR mRNA expression in ovaries at PND56 at all doses	Wei et al. (2019a)[article in Chinese]
Mouse, Kunming, female, 10 per group	*In utero*. 0, 2.5, 5, 10, 20, or 40 mg/kg-day F0 maternal exposure from GD0.5 to GD17.5 via gavage, F1 sacrificed at PND21 or PND56	Significantly increased PR expression in the ovaries at all doses in offspring at PND21, significantly decreased PR expression at all doses in offspring at PND56	Wei et al. (2020a)
Mouse, unspecified, female, 15 per group	*In utero*. 0 or 5 mg/kg-day F0 maternal exposure from GD1 to GD18	Significantly increased PR mRNA levels in ovary at PND21, significantly decreased PR mRNA levels in ovary at PND56	Han et al. (2020)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	via gavage; F1 sacrificed at PND21 or PND56		
Mouse, unspecified, female, 4–5 per group	Juvenile, adult. 0, 0.1, or 1% BPA for 5 months via diet	No differences in PR mRNA expression in uterus	Toda et al. (2002)
Rat, ovariectomized DA/Han, female, 6 per group	Juvenile. 0 or 200 mg/kg bw for 3 days via gastric tube	Significantly decreased PR mRNA expression in uterus	Diel et al. (2000)
Rat, SD, female, 10–11 per group	*In utero*. 0, 10 or 50 µg/kg-day F0 maternal exposure from GD14 to GD22 via oral administration; F1 sacrificed at PND1	Significantly increased PR immunoreactivity in medial preoptic nucleus at 10 µg/kg-day dose, but not 50 µg/kg-day	Fahrenkopf and Wagner (2020)
Rat, SD CD, female, 8 per group	*In utero*. 0 or 250 µg/kg-day F0 maternal exposure from GD2 to GD20 via gavage; F1 sacrificed at PND50	Significantly increased PR-A protein expression in mammary glands, increased PR-B protein levels but not significantly significant	Jenkins et al. (2009)
Rat, SD, male, 9 per group	Juvenile. 0 or 285.4 ppm for 90 days via diet	Significantly increased PR mRNA expression in hypothalamus	Zhang et al. (2013)
Rat, Wistar, female, 8–10 per group	*In utero*. 0, 25, or 250 µg/kg-day F0 maternal exposure from GD8 to GD23 via osmotic pump, F1	No differences in PR protein expression in mammary gland at PND50 or PND110	Durando et al. (2011)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	sacrificed at PND50 or PND110		
Rat, Wistar, female, 7 per group	Postnatal. 0, 0.05, or 20 mg/kg-day single *s.c.* injection on PND1, 3, 5, or 7, raised to adulthood, mated, F0 assessed at GD5	Significantly decreased PR mRNA levels in the uterus at both doses	Varayoud et al. (2011)
Rat, Wistar (Alpk:APfSD), 5 per group	Postnatal, juvenile. 0, 0.002. 0.02. 0.2, 2, 20, 200, 400, or 800 mg/kg-day single dose via gavage; sacrificed 4, 8, or 24 hours later or given 3 daily doses and sacrificed 24 hours later	Significantly increased PR mRNA expression in the uterus 4 hours after single dose treatment of 200, 400, or 800 mg/kg, or 8 hours after single dose treatment of 800 mg/kg, no differences in PR expression in animals given one or three daily doses and assessed 24 hours later, PRA and PRB protein expression was increased (1.4- to 11.2-fold) 4, 8, and 24 hours after one dose at 800 mg/kg and 24 hours after three daily doses at 800 mg/kg	Ashby and Odum (2004)
Rat, ovariectomized Wistar, female, 5–6 per group	Adult. 0 or 10 mg single *s.c.* injection, sacrificed 24 hours later	Significantly increased PR mRNA levels in preoptic area and anterior pituitary, no differences in mediobasal hypothalamus	Funabashi et al. (2001)
Rat, ovariectomized Wistar, female, 3–5 per group	Adult. 0, 10 µg, 100 µg, 1000 µg, or 10 mg single *s.c.* injection, sacrificed 24 hours later	Significantly increased PR protein levels (measured as number of PR immunoreactive cells) in preoptic area and ventromedial hypothalamic nucleus at 100 µg, 1000 µg, and 10 mg doses	Funabashi et al. (2003)
Rat, ovariectomized Wistar, female, 5–6 per group	Adult. 0 or 10 mg single *s.c.* injection, sacrificed 6, 12, or 24 hours later	Significantly increased PR mRNA levels in frontal cortex, significantly decreased PR mRNA levels in temporal cortex, no effects in parietal cortex levels after 6, 12, and 24 hours	Funabashi et al. (2004)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, ovariectomized Wistar, female, 6 per group	Adult. 0 or 10 mg single *s.c.* injection, sacrificed 24 hours later	Significantly increased PR mRNA expression in anterior pituitary	Furuta et al. (2006)
Sheep, female, 5–8 per group	*In utero*. 0 or 0.5 mg/kg-day from GD30 to GD90 via *s.c.* injection; placenta assessed at GD65 or GD90	Increased PR mRNA in placentomes at GD65 (statistical significance not reached), no differences at GD90	Song et al. (2020a)

Table J2.6 Effects of BPA on progesterone receptor (PR) in non-human mammalian studies *in vitro* (ordered by species, tissue type [alphabetical, with primary cells listed first])

Cell type/system	BPA concentration, duration	Results	Reference
Mouse embryonic stem cells (mESCs)	0.1 μM for 10 days	Significantly increased PR mRNA and protein levels	Lee et al. (2019c)
Mouse mammary organoids from virgin female C57BL/6	1 nM or 1 μM for 72 hours	Significantly increased total PR mRNA expression, significantly increased PR-B mRNA expression at 1 nM but not 1 μM, no significant differences in PR-A mRNA expression	Altamirano et al. (2020)
Rat pituitary tumor GH3 cells	0.1, 1, or 10 μM for 24 hours	Significantly and dose-dependently increased PR mRNA and protein levels at all concentrations	Kim et al. (2012)
Rat pituitary tumor GH3 cells	0.1, 1, or 10 μM for 24 hours	Significantly increased PR mRNA and protein levels at all concentrations	Vo et al. (2012)
Sheep primary granulosa cells	1 nM to 200 μM for 48 hours	No effects on PR mRNA expression between 1 to 100 μM	Teteau et al. (2020)

Section J3 Androgen receptor

Table J3.1 Effects of BPA on AR in human studies *in vitro* (ordered by tissue type [alphabetical, with primary cells listed first], followed by transfected cells from other species, and cell-free systems)

Cell type/system	BPA concentration, duration	Result	Reference
Blood: TK6 human lymphoblast cells	10, 10^3, or 10^5 nM for 24, 48, or 72 hours	Significantly increased AR expression at 10^3 nM at 72 hours and at 48 and 72 hours at 10^5 nM and 10^3 nM	Chen et al. (2021)
Bone: recombinant human U2OS cells expressing human AR	0.01 nM to 100 µM [duration not specified]	AR nuclear translocation observed at 12.5 µM, with no functional nuclear foci formation at any concentration. High concentration BPA displaced the synthetic androgen R1881 from AR and inhibited formation of nuclear foci.	Teng et al. (2013)
Bone: human osteosarcoma U2OS cells with AR CALUX	0.01 nM to 10 µM for 24 hours	Antagonized DHT-induced AR activity (IC_{50}: 1.5 µM)	Wang et al. (2014b)
Breast: MCF-7 human breast cancer cells	1 µM for 7 days	No effect on AR mRNA expression	Diel et al. (2002)
Breast: MCF-7 transfected with AR-T877A, a mutant AR found in hormone-refractory prostate cancers	1 nM for 16 hours	Activated AR-T877A mediated luciferase activity	Wetherill et al. (2002)
Breast: MDA-kb2 (MDA-MB-453 derived breast carcinoma transfected with MMTV luciferase reporter)	1 or 10 µM for 24 hours	Antagonized DHT-induced AR activity (Kolšek et al. indicated both concentrations were tested for luciferase activities in Table 1, but only one value is shown in Figure 3)	Kolšek et al. (2015)
Breast: MDA-kb2 cells	1.17 nM to 150 µM for 28 hours	Antagonized DHT-induced AR activity (IC_{01}: 0.408 µM)	Orton et al. (2014)

Cell type/system	BPA concentration, duration	Result	Reference
Breast: MDA-kb2 cells	3 nM to 10 μM for 18 hours	Antagonized T-induced AR activity, with maximum inhibition 98.8% (IC_{50}: 0.51 μM)	Pelch et al. (2019)
Breast: TARM-Luc (human mammary gland T47-D cells with AR luciferase expression vector)	Up to 40 μM for 48 hours	Antagonized dihydrotestosterone (DHT)-induced AR activity (IC_{50}: 4.3 μM)	Doan et al. (2020)
Breast: TARM-Luc	0.001 to 1 mM for 24 or 48 hours	Did not show antagonist activity for AR	Simon et al. (2016)
Cervix: HELN AR (Stable expression of AR with ERα DBD in HeLa ERE-luciferase cells)	1 nM to 10 μM for 16 hours	Antagonized R1881-induced AR activity (IC_{50}: 4.32 μM)	Grimaldi et al. (2019)
Liver: human hepatoma HepG2 cells transiently transfected with pGL3-PSA-Luc and AR expression plasmid	0.01 to 10 μM for 24 hours	Antagonized T-induced AR activity (IC_{50}: 318 nM)	Lee et al. (2003)
Liver: human hepatoma HepG2 cells transfected with AR expression plasmid and C3-Luc	0.1, 1, or 10 μM for 24 hours	Did not show agonistic or antagonistic activity for AR	Gaido et al. (2000)
Kidney and Prostate: HEK293T (human embryonic kidney 293T) and human prostate cancer DU145 cells transfected with pGL2/ARETATA reporter and hAR expression vector	1, 10, or 100 nM for 24 hours	BPA increased AR-mediated transcriptional activity of pGL2/AREIII-TATA at all concentration levels in both cell types (authors did not report statistical significance)	Wu et al. (2013b)

Cell type/system	BPA concentration, duration	Result	Reference
Prostate: human primary prostate epithelial cells (HPEpiC)	1 nM for 72 hours	Significantly increased AR mRNA expression	Wang et al. (2021c)
Prostate: human prostate fibroblasts (HPrF)	1 nM for 72 hours	Significantly decreased AR mRNA expression	Wang et al. (2021c)
Prostate: 22Rv1/MMTV and 22Rv1/MMTV-GRKO (glucocorticoid receptor knockout) human prostate epithelial carcinoma	0.01 nM to 10 μM for 24 hours	Antagonized DHT-induced AR activity in both cell lines (IC_{50}: 3.83 μM in 22Rv1/MMTV and 9.09 μM in 22Rv1 MMTV-GRKO)	Lee et al. (2019b)
Prostate: human androgen-dependent prostate cancer cell lines LNCaP (expressing mutant AR-T877A) and LAPC-4 (expressing wild type AR), and androgen-independent prostate cancer cell line 22Rv-1 (expressing mutant AR-H874Y), transfected with ARR2-LUC (probasin reporter) or CMV-B-galactosidase	0.01 to 10 μM for 48 hours	BPA by itself weakly induced luciferase activity at the probasin reporter in the three cell lines. BPA enhanced DHT-induced AR-T877A activation in LNCaP cells and AR-H874Y activation in 22Rv-1 cells, as shown by increased luciferase activity at the probasin reporter (although the most significant enhancement was observed at the lowest dose of BPA). This induced luciferase activity by DHT and BPA was blocked by the AR antagonist Casodex, indicating AR specific effect. BPA had no enhancement effect on DHT induced wild type AR activation in LAPC-4 cells.	Wetherill et al. (2005)
Prostate: PALM human prostate cancer cells	Up to 22 μM for 24 hours	Antagonized R1881-induced AR activity (EC_{50}: 8.1 μM)	Cavanagh et al. (2018)

Cell type/system	BPA concentration, duration	Result	Reference
Prostate: PALM (PC3 human bone metastasis of prostate cancer cells co-transfected with androgen responsive gene, MMTV-Luc, and AR expressing plasmid)	0.01–10 μM for 40 hours	Weak agonistic activity towards AR (statistically significant at 10 μM) and strong antagonistic activity towards AR in the presence of R1881 (IC_{50}: 0.92 μM)	Molina-Molina et al. (2013)
Testes: human Sertoli cells (HseC)	20 μM for 6 or 48 hours	Significantly decreased AR protein expression after 6 and 48 hours	de Freitas et al. (2016)
Chinese hamster ovary (CHO-K1) cells stably transfected with plasmid containing human AR cDNA and plasmid with AR response element fused to luciferase gene	0.01 to 100 μM for 24 hours	Antagonized DHT-induced AR activity (IC_{50}: 2.06 μM)	Araki et al. (2005)
CHO-K1 transiently transfected with human AR expression plasmid pSVAR0 and MMTV-Luc reporter	0.15, 0.3, 1.3, 2.5, 5, 10, 20, and 40 μM [duration not reported]	Antagonized R1881-induced AR activity to 90% of control at 20 μM. Lowest effect concentration (LOEC): 0.6 μM Maximum effect concentration (MOEC): 20 μM	Bonefeld-Jorgensen et al. (2007)
CHO-K1 transiently transfected with human pSG5-hAR, pMMTV-luc, and pRL-TK	Activity: 1 nM to 10 μM [duration not reported] Translocation: 1 nM to 10 μM BPA pretreatment for 30 min followed by co-treatment with DHT for 60 min	Antagonized DHT-induced AR activity (significant at all concentrations tested). Inhibited DHT-induced AR stabilization (significant between 0.1 and 10 μM) Reduced DHT-induced AR nuclear translocation	Huang et al. (2019)

Cell type/system	BPA concentration, duration	Result	Reference
CHO-K1 transiently transfected with human AR expression plasmid pSVAR0 and MMTV-Luc reporter	0.1 nM to 100 µM [duration not reported]	Antagonized R1881-induced AR activity (IC_{50}: 3.2 µM)	Kruger et al. (2008)
CHO-K1 cells transfected with human AR	0.1 to 50 µM for 24 hours	Antagonized R1881-induced AR activity (IC_{50}: 19.6 µM)	Roy et al. (2004)
CV-1 cells (derived from African green monkey kidney) transiently transfected with pMMTV-CAT and human AR/pcDNA3.1	0.1 to 10 µM for 24 hours	Antagonized DHT-induced AR activity (IC_{50}: 2.14 µM); BPA alone had no agonistic activity	Sun et al. (2006)
CV-1 cells transiently transfected with human pSG5-AR and MMTV-Luc, Renilla-Luc	10 nM to 100 µM for 24 hours	Antagonized R1881-induced AR activity (IC_{50}: 2.34 µM); did not activate AR transcriptional activity	Teng et al. (2013)
CV-1 cells transfected with human wild-type AR or AR-T877A	1 nM for 16 hours	Activated AR-T877A mediated luciferase activity, no effect on wild type AR	Wetherill et al. (2002)
CV-1 cells transiently transfected with pMMTV-CAT and human AR/pcDNA3.1	0.1 to 10 µM for 24 hours	Antagonized DHT-induced AR activity (calculated IC_{50}: 0.746 µM); BPA alone had no agonistic activity	Xu et al. (2005)
Vero (African green monkey kidney) cells transfected with human AR/pcDNA3.1 and pMMTV-Luc	0.001 to 1 mg/l for 24 hours	Significantly antagonized testosterone-induced AR activity at 1 mg/l	Sun et al. (2012)
Mouse NIH3T3 transiently transfected with $p(ARE)_2$-	0.1 to 10 µM for 24 hours	Antagonized DHT-induced AR activity (IC_{50}: 4.3 µM)	Kitamura et al. (2005)

Cell type/system	BPA concentration, duration	Result	Reference
luc, human pSG5-hAR, phRL-CMV			
Mouse Sertoli 15p-1 cells transiently transfected with human AR expression plasmid and reporter ($pARE_2$-TATA-Luc)	0.01 to 10 µM for 24 hours	Antagonized T-induced AR activity (IC_{50}: 80 nM)	Lee et al. (2003)
Yeast transformed with human AR gene	1 nM to 100 µM for 2 hours	No agonistic activity on AR; Antagonized DHT-induced AR activity	Li et al. (2010)
Cell-free binding assay with human AR	0.1 nM to 10 µM [duration not specified]	Did not bind to AR	Takayanagi et al. (2006)

R1881, methyltrienolone (a synthetic androgen)

Table J3.2 Effects of BPA on AR in non-human mammalian studies *in vivo* (ordered by species, strain, life stage)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Gerbil, Mongolian, male and female, 10 per group	*In utero*. 0 or 40 µg/kg-day F0 maternal exposure from GD17 to 24 via oral gavage; F1 sacrificed at PND1 or 90	[The gerbil female prostate is similar to the human female Skene's gland.] PND1 female F1: significantly decreased frequency of AR-positive cells in prostate epithelial buds and the periurethral mesenchyme, with no effect in the paraurethral mesenchyme or the smooth muscle layer PND90 female F1: significantly increased frequency of AR-positive cells in prostate epithelium and stroma PND1 male F1: significantly decreased AR-positive cells in periurethral	Rodríguez et al. (2016)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
		mesenchyme and smooth muscle layer, with no effect in the epithelial buds or ventral mesenchymal pad PND90 male F1: no effect on frequency of AR-positive cells in prostate epithelium or stroma	
Gerbil, intact or orchiectomized Mongolian, male, 5 per group	Juvenile. Single 50 mg/kg s.c. injection at 45 days old; sacrificed at 52 or 120 days old	Intact, 52 days old: No differences in AR-positive prostatic epithelial or stromal cells Intact, 120 days old: Significantly decreased frequency of AR-positive prostatic epithelial cells, no difference in stromal cells Castrated, 52 days old: Significantly decreased frequency of prostatic stromal cells, no difference in epithelial cells Castrated, 120 days old: No differences in AR-positive prostatic epithelial or stromal cells	Colleta et al. (2017)
Gerbil, male, 6 per group	Adult. 0 or 50 µg/kg-day for 6 months via drinking water	Significantly increased frequency of AR positive cells in dorsolateral and ventral prostate lobes	Facina et al. (2018)
Gerbil, male, 7 per group	Adult. 0 or 50 µg/kg-day for 29 weeks via drinking water	Significantly increased frequency of AR positive cells in both the dorsolateral and ventral prostate lobes	Facina et al. (2021)
Gerbil, Mongolian, females, 5 per group	Adult. 0, 50, or 5000 µg/kg-day to pregnant females (F0) from GD8 to end of lactation (39	F0: Significantly increased percentage of AR positive cells in normal alveoli of mammary glands at 5000 µg/kg and significantly increased percentage of	Ruiz et al. (2021)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	days total) via gavage; F0 sacrificed at 18 months old	AR positive cells in hyperplastic mammary glands in both dose groups. The percentages of AR positive cells were the highest in carcinoma tissues compared to hyperplastic tissues of BPA-treated groups. No comparison was made with controls, due to lack of carcinoma in control.	
Mouse, C57BL/6J, male, 4 per group	Adult. 0, 50 µg/kg-day, or 5 mg/kg-day for 4 weeks via oral gavage	Significantly increased AR protein expression in medial preoptic area after exposure to 50 mg/kg-day; no significant differences in AR expression in medial amygdala or bed nucleus of the stria terminalis (in forebrain)	Picot et al. (2014)
Mouse, CD-1, male, 5 per group	*In utero*. 0 or 50 µg/kg-day F0 maternal exposure from GD16 to 18 via diet; F1 sacrificed at PND3, 21, or 60	Significantly increased binding activity of prostate AR to Mibolerone (an AR agonist) in PND21 and 60 mice	Gupta (2000)
Mouse, CD-1, female, 10–13 per group	*In utero*. 0, 0.5, 5, 50 mg/kg twice daily F0 maternal exposure from GD10 to 17 via oral gavage; F1 sacrificed at 8 or 14 months	Significantly decreased mammary gland AR mRNA expression in 8-month-old female offspring exposed to 5 mg/kg BPA, no significant changes in AR expression in 14-month-old female offspring or other dose levels	Tucker et al. (2018)
Mouse, CD-1, male, 8–12 per group	*In utero*, lactation, juvenile. 0 or 10 µg/ml F0 maternal exposure from GD10 to PND21 via drinking water, F1 post-weaning (PND22) to PND31 via	Decrease in testicular AR mRNA expression in male offspring (not statistically significant)	Chioccarelli et al. (2021)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	drinking water; F1 sacrificed at PND78		
Mouse, ICR, male, 6 per group	Juvenile. 0, 0.04, 0.4, or 4 mg/kg-day for 18 days via gavage; sacrificed at 13 weeks old	Significantly decreased AR protein levels in amygdala and bed nucleus of the stria terminalis at 0.4 and 4 mg/kg-day and in the lateral septum at 0.04, 0.4, and 4 mg/kg-day	Wang et al. (2021b)
Mouse, Kunming, male, 6 per group	Juvenile, adult. 0, 20 mg/kg-day via intra gastric administration for 4 weeks	Significant decreased serum AR compared to non-treated control; the decrease was not significant in comparison with the vehicle control	Cao et al. (2020) [article in Chinese]
Rabbit, New Zealand, male, 5 per group	*In utero*. 0 or 50 mg/kg-day F0 maternal exposure from GD15 to GD31 via oral administration; F1 assessed at GD17, 21, 26, 27, 28, 29, 30, 31, or PND3	GD27: Significantly decreased AR mRNA expression in fetal testes PND3: Significantly increased AR mRNA expression in testes No differences at GD17, 21, 26, 28, 29, 30, or 31	Ortega-García et al. (2021)
Rat, ovariectomized DA/Han, female, 6 per group	Juvenile. 0, or 200 mg/kg bw for 3 days via gastric tube	Significantly decreased uteri AR mRNA expression in 200 mg/kg bw group	Diel et al. (2000)
Rat, Holtzman, male, 8–10 per group	Postnatal. 0 or 300 µg/kg bw from PND1 to 5 via *s.c.* injection; sacrificed at PND15, 30, 45, or 90	Significantly decreased testicular AR mRNA expression at PND30, 45, and 90, but not PND15; significantly decreased testicular AR protein expression at PND30 and 90	Salian-Mehta et al. (2014)
Rat, Long-Evans, male, 10–11 per group	*In utero*. 0, 2.5, or 25 µg/kg bw F0 maternal exposure from gestation day (GD) 12 to 21 via	Significantly increased caput epididymis AR protein expression in male offspring on PND35; no significant differences at PND21 or 90	Abdel-Maksoud et al. (2018)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	oral gavage; F1 sacrificed at postnatal day (PND) 21, 35, or 90		
Rat, SD, male, 10 per group	*In utero*. 0, 25, or 250 µg/kg-day F0 maternal exposure from GD10 to GD21 via gavage; F1 sacrificed at PND21	Significantly increased ventral prostate AR protein expression of male offspring in both dose groups	Bernardo et al. (2015)
Rat, SD, male, 2–3 per group	*In utero*. 0, 25, or 250 µg/kg-day F0 maternal exposure from GD10 to 21 via gavage; F1 sacrificed at PND21 or 180	Increase in ventral prostate AR protein levels in male offspring at PND21 or 180 (not statistically significant)	Brandt et al. (2014)
Rat, SD, male, 9 per group	Juvenile, adult. 0 or 285.4 ppm for 90 days via diet (diet was soy and alfalfa free)	Significantly increased hypothalamic AR mRNA expression	Zhang et al. (2013)
Rat, SD, male, 10 per group	Adult. 0 or 2 µg/kg-day for 14 days via oral gavage	No effect on testicular AR mRNA expression	Jin et al. (2013)
Rat, SD, male, 10 per group	Adult. 0, 10, 30, 90, or 270 µg/kg via gavage for 4 weeks	Significantly increased AR protein expression in ventral prostate of rats administered 30 or 90 µg/kg BPA, no significant differences in dorsolateral prostate AR	Wu et al. (2020b)
Rat, SD, male, 5 per group	Adult. 0, 0.0005, 0.5, or 5 mg/kg bw via oral gavage for 8 weeks	Dose-dependently decreased testicular AR protein expression, with significant decreases in the 0.5 and 5 mg/kg bw dose groups	Qiu et al. (2013)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, Wistar, male, 7–9 per group	*In utero*. 0, 25, or 250 µg/kg-day F0 maternal exposure from GD8 to GD23 via s.c. osmotic pump; F1 sacrificed at PND15, 30, or 120	Significantly decreased percentage of AR positive periductal stromal cells in the ventral prostate at PND30 in both dose groups, no significant differences at PND15 or 120	Ramos et al. (2003)
Rat, Wistar, male, 4 per group	*In utero*. 0, 25, or 250 µg/kg-day F0 maternal exposure from GD8 to GD23 via *s.c.* osmotic pump; F1 sacrificed at PND30	Significantly decreased percentage of AR positive periductal stromal cells in the ventral prostate in both dose groups, no significant differences in epithelial cells or interductal stromal cells	Ramos et al. (2001)
Rat, Wistar, male and female, 10 per group	*In utero*. 0, 25, or 250 µg/kg-day F0 maternal exposure from GD9 to GD23 via *s.c.* osmotic pump; F1 sacrificed at PND30	Significantly decreased mammary gland AR protein expression in male offspring exposed to 250 µg/kg-day BPA, no significant differences in female offspring	Kass et al. (2015)
Rat, Wistar, male, 10 per group	*In utero*, lactation. 0, 0.5, or 5 mg/kg bw F0 maternal exposure from GD18 through PND5 via *s.c.* administration; F1 sacrificed at PND90	Significantly decreased testicular AR mRNA expression in male rats exposed to 5 mg/kg bw	Campos et al. (2019)
Rat, Wistar, male, 6 per group	*In utero*, lactation. 0, 0.5, or 5 mg/kg F0 maternal exposure from GD18 to PND5 via *s.c.* injection; F1 sacrificed at PND90	Significantly increased pituitary AR mRNA expression in male offspring exposed to 0.5 mg/kg, no significant differences in the hypothalamus AR mRNA expression at either dose	Oliveira et al. (2017)
Rat, Wistar, female, 10 per group	*In utero*, lactation. 0, 0.5, or 50 µg/kg-day F0 maternal exposure from GD9 to	Significantly increased AR protein expression at 0.5 µg/kg bw in the primordial follicles; significantly	Santamaría et al. (2016)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	PND21 via drinking water; F1 sacrificed at PND90	decreased AR protein expression in the primary follicles at 0.5 µg/kg bw, and in the primary, preantral, and antral follicles at 50 µg/kg bw	
Rat, Wistar, male and female, 10 per group	*In utero*, lactation. 0 or 64 µg/kg-day F0 maternal exposure from GD9 to PND21 via drinking water; F1 sacrificed at PND30	Significantly decreased mammary gland AR protein expression in male offspring, no significant differences in female offspring	Kass et al. (2015)
Rat, Wistar (EGFP-GnIH), male, 6 per group	Postnatal. 0 or 50 µg/kg from PND1 to 3 via *s.c.* injection; sacrificed at PND3	No effect on mRNA expression of medial amygdala AR or AR target genes	Ubuka et al. (2018)
Rat, Wistar, male 6 per group	Postnatal. 0 or 0.5 mg from PND2 to PND12 via injection; sacrificed at PND18	Increased AR protein expression in stroma and epithelium of seminal vesicles (the authors used a – to +++ categorical scoring system for immunostaining intensity, and BPA scored +++ for both stroma and epithelium AR)	Williams et al. (2001)
Rat, Wistar, male and female, 6 per group	Postnatal, juvenile. 0, 25, or 50 mg/kg from PND19 to PND68 via oral gavage; sacrificed at PND120	No effect on hypothalamic or pituitary AR mRNA expression	Kadir et al. (2021)
Rat, orchiectomized Wistar, male, 13 per group	Juvenile. 0, 3, 50, 200, 500 mg/kg-day for 7 days via oral administration	Significantly increased AR protein expression in prostate in 3, 50, and 200 mg/kg-day treated rats relative to control group	Nishino et al. (2006)
Rat, unspecified albino, male, 10 per group	Juvenile/adult (130–150 g). 0 or 5 mg/kg bw for 3 weeks via *i.p.* injection	Significantly decreased testicular AR mRNA expression (authors defined statistically significant as $p \leq 0.05$)	Eshak and Osman (2014)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Sheep, female, 5–8 per group	*In utero*. 0 or 0.5 mg/kg-day from GD30 to 90 via *s.c.* injection; placenta assessed at GD65 or 90	No significant difference in placentome AR mRNA expression on either GD65 or 90	Song et al. (2020a)

Table J3.3 Effects of BPA exposure on AR in mammalian cells *in vitro* (including human cells transfected with mouse AR) and cell-free systems (ordered by species, cell type, cell line, with cell-free systems last)

Cell type/system	BPA concentration, duration	Results	Reference
Human HeLa cells transiently transfected with mouse AR pcDNA3.mAR	0.005 to 5 µM for 2 hours	Partially inhibited DHT binding to AR, up to 40% at 50 nM	Lee et al. (2003)
Human HeLa cells transiently transfected with mouse AR pcDNA3.mAR fused with green fluorescent protein (GFP)	10 µM for 60 min	BPA interfered with testosterone-induced AR nuclear translocation (author reported no statistics)	Lee et al. (2003)
Mouse preadipocytes (3T3-L1 cells)	80 µM from day 0 to 2 of differentiation	No effect on AR mRNA expression (data not shown)	Phrakonkham et al. (2008)
Mouse prostate urogenital sinus mesenchyme cells	0.01 pM to 100 µM for 4 days	Significantly increased AR mRNA expression at 1 nM BPA and above	Richter et al. (2007)
Mouse spermatocyte GC-2 cell line	0.1 or 10 pM for 24, 48, or 72 hours	No effect on AR mRNA expression	Sidorkiewicz et al. (2018)
Rat Sertoli cells	200 µM for 30 mins to 24 hours	No significant difference in AR protein expression (data not shown)	Izumi et al. (2011)
cell free recombinant rat AR binding assay	10 to 1000 µM for 24 hours	Weak binding affinity for recombinant rat AR	Kim et al. (2010b)

Section J4 Testosterone

Table J4.1 Effects of BPA on serum testosterone levels in human observational studies, sorted by gender and medical condition

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
Women or girls with polycystic ovary syndrome (PCOS), girls with precocious puberty, or pregnant women	PCOS and control. 112 girls with PCOS and 61 controls (aged 13–19 years old) in Japan	Serum	Significant correlation between increased serum BPA and increased total testosterone (T) (correlation coefficient, r = 0.52; $p < 0.001$) or free T (r = 0.44; p = 0.009) in univariate analysis. In multivariate model, BPA was significantly associated with serum total T, adjusted for other confounders (regression coefficient, β = 0.005; $p < 0.001$).	Akin et al. (2015)
	PCOS and control. 171 women (71 with PCOS and 100 controls)	Serum	Significant positive association between serum BPA and T (r = 0.192; $p < 0.05$) in all participants	Kandaraki et al. (2011)
	PCOS and control. 49 women with PCOS and 39 healthy controls in India	Serum	Increased serum BPA was significantly correlated with increased T (r = 0.443; p = 0.001)	Kawa et al. (2019)
	PCOS 106 women with PCOS (18–40 years old) in Poland	Serum	In women with PCOS, increased serum BPA was significantly correlated with increased T (r = 0.285; p = 0.004) and free androgen index (FAI) (r = 0.196; p = 0.049)	Konieczna et al. (2018)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	PCOS. 86 PCOS women (age: 28.5 ± 5.1 years old)	Urine	Significant negative association between urinary BPA and total T (β = –0.07125; p = 0.0078) or free T (β = –0.2197, p = 0.0094)	Lazúrová et al. (2021)
	PCOS and control. 357 women (119 PCOS cases and 238 controls) in China	Serum	Higher BPA exposure (> 75th percentile) had higher T compared with ≤ 75th percentile BPA exposure (p = 0.03)	Luo et al. (2020)
	PCOS and control . 30 women (16 with PCOS and 14 control) in Japan	Serum	Women: BPA significant positively correlated with total T (r = 0.559, p < 0.01) and free T (r = 0.598, p < 0.001).	Takeuchi and Tsutsumi (2002)
	PCOS and control. 47 women with ovarian dysfunction (19 PCOS; 21 hypothalamic amenorrhea, 7 hyperprolactinemia) and 26 controls (women with normal menstrual cycles) in Japan	Serum	For all 73 women: Increased serum BPA was significantly correlated with increased total T (r = 0.391, p < 0.001) and free T (r = 0.504, p < 0.001). For 26 controls: Increased BPA and increased free T were also significantly correlated (r = 0.478, p < 0.05)	Takeuchi et al. (2004)
	PCOS and control. 40 premenopausal women with PCOS	Serum	In women with high serum BPA levels (above 95th% of the BPA levels measured in the controls), significantly higher FAI was observed compared to those with lower BPA (p = 0.037).	Tarantino et al. (2013)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	and 20 healthy controls in Italy		In the multivariate analysis, increased BPA was significantly associated with increased FAI (β = 0.343, *p* = 0.014), adjusted for BMI and other confounding factors.	
	Precocious puberty and control. 35 girls with central precocious puberty, 26 girls with peripheral precocious puberty, and 21 controls in Korea	Urine	BPA was significantly positively correlated with T in controls (*p* = 0.009), patients with central precocious puberty (*p* = 0.001), and patients with peripheral precocious puberty (*p* = 0.003).	Lee et al. (2014)
	Pregnancy. 602 pregnant women in Puerto Rico	Urine	In simple correlation, BPA was significantly associated with decreased T at 24–28 weeks gestation (–17.37%; 95% CI: –26.7%, –6.87%). Non-significant negative association between BPA and T in linear mixed models adjusted for BMI, maternal age and other confounders (–4.19%; 95% CI: –9.64%, 1.59%).	Aker et al. (2019)
Male partners in subfertile couples	Cases were male partners in subfertile couples. Controls were male partners of couples with a documented or suspected female cause of infertility, or sperm donors. 163 men recruited through four fertility	Urine	Increased BPA was significantly correlated with reduced T levels; 50% increase in urinary BPA was associated with 2.6% reduction of T (*p* = 0.04) in all participants.	Den Hond et al. (2015)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	clinics for a case control study in Belgium (40 cases, 86 controls and 43 excluded from the study due to incomplete samples)			
	Male partners in subfertile couples. 167 men from an infertility clinic in MA, USA	Urine	No association between BPA and total or free T for all participants or for subgroups with more than two BPA measurements, adjusted for confounders. Significant positive association between BPA and FAI among those with more than two BPA measurements (β = 0.89, p = 0.02).	Meeker et al. (2010a)
	Male partners in subfertile couples. 100 men from an andrology clinic Egypt	Urine	Significant negative association between urinary BPA and total T (r = –0.265; p = 0.001).	Shokry et al. (2020)
	Male partners in subfertile couples. 191 men from an infertility clinic in Czech	Plasma	No correlation between plasma BPA and total T (r = –0.06; p = 0.442), free T (r = –0.048; p = 0.553), or FAI (r = –0.04; p = 0.621)	Vitku et al. (2016)
Children with ADHD	Children with ADHD and control. 98 boys with ADHD and 42 control; 32 girls with ADHD	Urine	No correlation between urinary BPA and total T or free T in boys (r = 0.018 and 0.034, respectively; $p \geq 0.05$) or girls (r = –0.085 and 0.263, respectively; $p \geq 0.05$)	Tsai et al. (2020)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	and 26 control in Taiwan			
Children and adolescents	Boys. 117 boys (8–14 years old) in Mexico City	Urine	No association between urinary BPA and total or free T (p > 0.05)	Ferguson et al. (2014)
	Preadolescent girls. 48 preadolescent girls (7–8 years old) in Korea	Urine	No correlation between serum T and urinary BPA with any BPA exposure groups (Tertile 1, 2, 3 by BPA levels) measured at two time points (one year apart; all p > 0.05)	Lee et al. (2013a)
	Preadolescent boys. 172 boys (9–11 years old) in Canada	Urine	Urinary BPA was significantly positively correlated with total T, adjusted for BMI, maternal education and other confounders: 1. BPA by tertile: For the top exposure group (T3), β = 1.49 (95% CI: 1.03, 2.15); p = 0.02; p_{trend} = 0.03 2. BPA as a continuous variable: β = 1.19 (95% CI: 1.03, 1.44); p = 0.02	Mustieles et al. (2018)
	Children and adolescents. Participants (6+ years old) in two surveys (NHANES 2013–2016 or Canadian study 2012–2015)	Urine	No association between urinary BPA and T in any subpopulation stratified by gender or age (6–11 years old vs. 12+ years old); all p > 0.05	Pollock et al. (2021)
	Children and adolescents.	Urine	Female adolescents (12–19 years old): BPA was significantly associated with increased T in the highest BPA	Scinicariello and Buser (2016)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	276 children and 318 adolescents from NHANES 2011–2012		exposure group (Q4) (53.73%, 95% CI: 12.75%, 109.59%), compared with Q1; $p_{trend} < 0.01$ Male adolescents (12–19 years old): BPA was significantly associated with decreased T in Q2 (–50.84%, 95% CI: –71.92, –13.93) and Q4 (–52.29%, 95% CI: –71.35%, –20.55%), compared with Q1; no changes in Q3; $p_{trend} = 0.02$ Children (6–11 years old): No association between urinary BPA and T in children of either sex aged 6–11	
	Children and adolescents. 1317 6–19 years old from NHANES 2013–2016	Urine	No association between BPA and T in male or female children or adolescents, adjusted for age, race and other confounders. Significant negative association between BPA and FAI in female adolescents (β = –0.104; 95% CI: –0.202, –0.007), adjusted for potential confounders	Wang et al. (2021f)
Maternal BPA exposure and association with T in infants, children, or adult men	Newborns. 60 maternal and child pairs (3rd trimester and matching cord blood samples) in South Africa	Serum	All participants: Cord blood T was correlated negatively with cord serum BPA ($r = –0.6$; $p = 0.02$) and maternal BPA levels ($r = –0.52$; $p = 0.05$). Cord blood T was negatively correlated with maternal BPA-G and cord serum BPA-G ($p = 0.009$ for both) Male infants: Maternal BPA-G was significantly negatively correlated with cord blood total T in male infants ($r = –0.5$; $p = 0.02$).	Gounden et al. (2021)
	Male newborns. 137 male newborns in China	Urine (maternal)	For all subjects, increased log_2-transformed maternal urinary BPA in the 3rd trimester was significantly associated with decreased T in cord blood, after adjusting for confounders (β = –31.09; 95% CI: –53.07, –9.11). The highest quartile of BPA also showed a significant negative association (β = –180; 95% CI: –333.5, –26; $p = 0.022$; $p_{trend} = 0.004$)	Liu et al. (2016a)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	Newborns. 278 newborns in Japan	Cord blood	No significant positive association between fetal BPA in cord blood taken at delivery and T (r = 0.25, 95% CI: –0.16, 0.66), adjusted for confounders.	Minatoya et al. (2017)
	Infants. 59 infants in Daishan, China	Urine	Urine samples were measured at birth, 14 days, 28 days, 42 days, 3 months, and 6 months and correlation analyses were conducted for different time periods and genders. Female: Significant positive correlation between urinary BPA and T at 3 months (r = 0.527, p = 0.004); no significant correlation for other time periods. Male: No significant correlation for any time period. All: Significant positive correlation between urinary BPA and T at 3 months (r = 0.375, p = 0.004); not significant for other time periods.	Wang et al. (2017b)
	Girls. 120 girls (8–13 years old; average: 10) in Mexico City	Urine (maternal)	An increase in maternal urinary BPA interquartile range (IQR) measured in the second trimester was significantly associated with higher serum T in girls, adjusted for child age, child BMI z-score, and urinary specific gravity (33.2%, 95% CI: 0.3%, 77%; p < 0.05). No association with maternal BPA measured in the 1st or 3rd trimester or geometric mean of prenatal BPA in all three trimesters using the same model: 1st trimester: 3.2%, 95% CI: –27%, 47%; 3rd trimester: 3.2%, 95% CI: –28.1%, 37,3%; all combined: 11.5%, 95% CI: –13.5%, 44.4%	Watkins et al. (2017)
	Boys.	Urine (maternal)	No association between maternal urinary BPA measured in the 3rd trimester and total or free Tin boys 8 – 14 years old (p > 0.05)	Ferguson et al. (2014)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	117 boys (8–14 years old) in Mexico City			
	Men. 284 men (20–22 years old) in Australia	Serum (maternal)	No correlation between serum T and maternal serum BPA (r = 0.06; the authors stated not statistically significant without providing a p-value)	Hart et al. (2018)
Occupationally exposed male workers	Male workers. 592 male workers (165 exposed to BPA and 427 non-exposed) in China	Urine	No association between urinary BPA and total or free T for all 592 workers, or the 427 workers without occupational BPA exposure. Significant negative association between urinary BPA and FAI (β = –0.0234, p = 0.021) among all 592 workers, but not the 427 workers without occupational BPA exposure.	Liu et al. (2015a)
	Male workers. 290 male workers (137 exposed to BPA and 153 non-exposed workers) in China	Serum	Increased BPA was significantly associated with decreased free T by linear regression (β = –0.049; p = 0.007) and with decreased FAI (β = –0.073; p = 0.007) No association between BPA and total T (β = –0.009, p = 0.456)	Zhou et al. (2013)
	Male workers. 281 male workers in epoxy resin factories in Guangdong, China	Serum	No association between serum BPA and T, either in univariate (r = 0.22, 95% CI: –0.09, 0.32) or multivariate (β = 0.19, 95% CI: –0.05, 0.31) models adjusted for age, marital status, educational level, smoking, and alcohol consumption.	Zhuang et al. (2015)
Adults	Men. 308 young Danish men from the general population	Urine	After adjusting for confounders, a doubling of BPA was significantly associated with increased 1) total T: 0.7 (95% CI: 0.2, 1.1); p =0.002; p_{trend} across quartiles = 0.003	Lassen et al. (2014)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
			2) free T: 2.7% (95% CI: 0.08%, 5.3%); $p = 0.04$; p_{trend} across quartiles = 0.02	
	Men. 81 (18–59 years old) male residents in Cameroon (44 in rural and 37 in urban area)	Urine	With the simple regression model, increased BPA was significantly correlated with reduced total T ($r = –0.433$; $p < 0.05$), reduced free T ($r = –0.402$, $p < 0.05$), and reduced bioavailable T ($r = –0.402$, $p < 0.05$) for urban residents; significant with bioavailable T only for all participants ($r = –0.299$; $p < 0.001$) With the multivariate regression model, increased BPA was significantly associated with reduced free T (β = –0.017; $p = 0.031$) and reduced bioavailable T (β = –0.397; $p = 0.032$), adjusted for age, cigarette/coffee/tea consumption and other confounders.	Manfo et al. (2019)
	11 healthy men and 30 women (16 with PCOS and 14 without PCOS) in Japan	Serum	Men: No significant correlation, per authors (correlation coefficient or *p*-value not reported). All participants: BPA was significant positively correlated with total T ($r = 0.595$, $p < 0.001$) and free T ($r = 0.609$; $p < 0.001$).	Takeuchi and Tsutsumi (2002)
	Men. 560 men (18–55 years old) in China	Urine	No association between BPA and T for all participants, or within participants stratified by smoking status or BMI, except that for those with BMI ≥ 25. BMI ≥ 25: Increased BPA associated with significantly decreased T with crude relative risk (RR) = 0.49 (95% CI: 0.24, 0.98). After adjusting for age, BMI and other confounders, the RR was no longer significant (RR = 0.52, 95% CI: 0.26, 1.05).	Liang et al. (2017)
	Men (fertile).	Urine	No correlation between urinary BPA (creatinine-adjusted) and total or free T, either by simple correlation or multivariate models adjusted for confounders	Mendiola et al. (2010)

Population (general)	Population (detailed)	Biological Matrix for BPA	Results	Reference
	302 men with pregnant partners in four US cities		Significant negative correlation between urinary BPA (creatinine-adjusted) and FAI (r = –0.11; p = 0.04)	
	Young men. 215 healthy male university students (18–23 years old) in Southern Spain (Murcia Region)	Urine	No association between urinary BPA and T either in an unadjusted model (β = 0.09; 95% CI: –0.11, 0.3) or an adjusted model (β = 0.03; 95% CI: –0.18, 0.23)	Adoamnei et al. (2018)
	Adults. 1116 middle-aged and elderly men and 1442 postmenopausal women (average age: 61.8 years old) in China	Urine	No association between BPA and T in all 3 models tested (unadjusted, adjusted for creatinine and age, or adjusted for more confounders) for all participants.	Li et al. (2014)
	Adults. 715 adults (aged 20–74 years old) in Italy	Urine	Men: Higher urinary BPA was associated with higher total T, in models adjusted for age and study site (β = 0.0237; p = 0.044), and in models additionally adjusted for smoking, measures of obesity, and urinary creatinine concentrations (β = 0.046; p = 0.004). Women: No associations between BPA and T in the two models performed.	Galloway et al. (2010)

Table J4.2 Effects of BPA on testosterone in human studies *in vitro* (ordered by tissue type [alphabetical, with primary cells listed first])

Model	Concentration and duration	Results	Reference
Adrenal: H295R adrenocortical carcinoma cells	0.1, 1, 10, 30, 50, 70 μM for 48 hours	Significantly and dose-dependently decreased T levels at 1 μM and above, not significantly decreased at 0.1 μM	Feng et al. (2016)
Adrenal: H295R adrenocortical carcinoma cells	0.03 to 30 μM for 48 hours	Significantly and dose-dependently decreased T levels at 0.1 μM and above, not significantly different at 0.03 μM	Wang et al. (2014b)
Adrenal: H295R adrenocortical carcinoma cells	0.3 to 3000 ng/ml for 24 hours	Significantly and dose-dependently decreased T levels at 30 ng/ml and above, not significantly decreased between 0.3 to 10 ng/ml	Zhang et al. (2011)
Ovary: human ovarian granulosa KGN cells	0.5, 5, 50, or 500 μg/l for 6 hours	No differences in T levels	Shi et al. (2021)
Testes: human fetal testes collected between 7 to 12 gestational weeks (GW)	10 nM to 10 μM for 72 hours	Significantly decreased T levels at 10 nM and 10 μM, no significant differences at 0.1 or 1 μM	Ben Maamar et al. (2015)
Testes: human fetal testes collected between GW6.3–11.1	0.001nM to 10 μM for 24, 48, or 72 hours	Significantly decreased T levels at 100 nM and above after 24 hours and at 10 nM and above after 48 or 72 hours, not significantly different at 0.001 nM after 48 hours	Eladak et al. (2015)
Testes: human fetal testes collected between GW6 to 11	1 pM to 10 μM for 24, 48, or 72 hours	Significantly decreased T levels after 24, 48, or 72 hours at 0.0.01 and 10 μM, significantly decreased T levels after 48 and 72 hours at 0.1 μM, no significant differences at 1 pM	N'Tumba-Byn et al. (2012)
Testes: adult testes from prostate cancer patients	1 nM to 10 μM for 24 or 48 hours	Significantly decreased T levels after 24 or 48 hours at 10 μM, no significant difference at lower concentrations	Desdoits-Lethimonier et al. (2017)

Table J4.3 Effects of BPA on testosterone (T) in non-human mammalian studies *in vivo*

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Gerbil, male, 7 per group	Adult. 0 or 50 µg/kg-day for 6 months via drinking water	No significant difference in serum T levels	Facina et al. (2021)
Mouse, C57BL/6J, male, 3 per group	*In utero.* 0, 5, or 50 µg/ml F0 maternal exposure from GD1 to GD21 via drinking water; F1 sacrificed at PND14 or 35	Significantly decreased serum T levels in male offspring at PND14 in both dose groups, significantly decreased serum T levels at 50 µg/ml dose group at PND35	Yang et al. (2019b)
Mouse, C57BL/6, male, 7 per group	*In utero*, lactation. 0, 0.2, or 2 µg/ml F0 maternal exposure from GD6 to PND21 via drinking water; F1 sacrificed at PND49	Significantly decreased serum T levels in 2 µg/ml dose group in male offspring	Meng et al. (2018)
Mouse, C57BL/6, male, 7 per group	Juvenile, adult. 0, 0.5, or 50 µg/ml for 4 or 8 weeks via drinking water	Dose-dependently decreased plasma free T levels, but only statistically significant at 50 µg/ml after 8 weeks (the authors used $p < 0.02$ as the threshold for statistical significance).	Takao et al. (1999)
Mouse, C57BL/6, male, 5 per group	Adult. 0 or 20 mg/kg-day for 7 days via *i.p.* injection collected 48 or 56 hours after last injection	Significantly decreased serum T levels collected at 48 and 56 hours after last injection	Li et al. (2021a)
Mouse, CD-1, female 4–5 per group	*In utero.* 0, 0.5 or 50 µg/kg-day F0 maternal exposure from GD7 to GD20 via oral administration; F3 sacrificed at 3-, 6-, or 9-months-old to assess transgenerational effects	No significant differences in serum T levels in F3 females at 3, 6, or 9 months of age	Shi et al. (2019b)
Mouse, CD-1, female, 6–10 per group	*In utero*.	Significantly decreased serum T levels in female offspring at PND35 exposed	Tucker et al. (2018)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
	0, 0.5, 5, 50 mg/kg F0 maternal exposure from GD10 to GD17 via gavage twice daily; F1 sacrificed at PND20, 28, 35, or 56	to 5 mg/kg BPA, significantly increased serum T levels in female offspring at PND56 exposed to 50 mg/kg BPA; no significant differences at PND20 or 28	
Mouse, CD-1, male, 3–4 per group	*In utero*, lactation. 0 or 10 µg/ml F0 maternal exposure from GD10 to PND31 via drinking water; F1 sacrificed at PND78	Significantly decreased testicular T levels, no significant differences in T levels in white abdominal or epididymal adipose tissue in PND78 male offspring	Chioccarelli et al. (2021)
Mouse, CD-1, male and female, 5 per group	*In utero*, lactation, juvenile, or juvenile. 0, 12, 25, 50, mg/kg-day F0 maternal exposure from GD1 to PND20 and gavage to F1 mice from PND21 to 49, or exposure beginning from PND20 to 49 via gavage; F1 males sacrificed at PND50 and females during proestrus phase at approximately PND50	For both exposure scenarios: Significantly decreased serum T levels in male offspring at 25 and 50 mg/kg-day, no differences in female serum T levels	Xi et al. (2011)
Mouse, CD-1, male and female, 6 per group	Postnatal, juvenile. 0, 50 µg/kg bw, or 10 mg/kg bw every 3 days from PND1 to 60 via *s.c.* injection	No significant differences in serum T levels in male or female mice at PND60	Shi et al. (2017a)
Mouse, FVB, female, 3–5 per group	*In utero.* 0, 0.5, 20, 50 µg/kg-day F0 maternal exposure from GD11 to PND0 via oral dosing; F1 sacrificed at 3-months-old, F2 sacrificed at 12-months-old	No differences in serum T levels in F1 mice at 3 months of age; Significantly decreased serum T levels in F2 mice at 12 months from F0 dams exposed to 20 µg/kg-day	Mahalingam et al. (2017)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Mouse, ICR, male, 10 per group	*In utero.* 0 or 20 µg/kg-day F0 maternal exposure from GD1 to GD5 via oral administration; F1 sacrificed at PND10, 20, 24, 35, or 50	Significantly decreased serum and testicular T levels in male offspring at PND24, 35, and 50	Hong et al. (2016)
Mouse, ICR, male, 5 per group	Postnatal. 0 or 125 mg/kg single *i.p.* injection at PND18	Increased T levels by two-fold one hour after injection [statistical significance not reported]	Song et al. (2002)
Mouse, ICR, male, 6 per group	Juvenile. 0, 0.004, 0.04, 0.4, or 4 mg/kg-day for 18 days via gavage	Significantly decreased T levels in the brain at 0.04, 0.4, and 4 mg/kg-day	Wang et al. (2021b)
Mouse, castrated or sham operation, ICR, male, 8 per group	Adult. 0, 0.4 or 4 mg/kg-day for 45 days via *s.c.* injection	Significantly decreased T levels in serum and brain of intact, sham operated mice, no significant differences in castrated mice	Fang et al. (2017)
Mouse, ICR, male, 7 per group	Adult. 0 or 10 mg/kg via *i.p.* injection for 12 weeks	Significantly decreased serum T levels	Park et al. (2018)
Mouse, ICR, male and females, 8 per group	Adult. 0, 0.04, 0.4, 4, 40 mg/kg-day for 12 weeks via gavage	Decreased serum T levels at 0.4 mg/kg-day and above, significantly decreased at 0.4 mg/kg-day only; significantly decreased T levels in brain of male mice at and above 0.4 mg/kg-day	Xu et al. (2015b)
Mouse, Kunming, male, 10 per group	*In utero.* 0, 2.5, 5, 10, 20, or 40 mg/kg-day F0 maternal exposure from GD0.5 to GD17.5 via gavage; F1 sacrificed at PND21 or PND56	Significantly and dose-dependently decreased serum T levels in male offspring at PND21 and PND56	Wei et al. (2019b)
Mouse, Kunming, male and female, 20 per group	*In utero.* 0 or 500 mg/kg-day F0 maternal exposure from GD8	Significantly decreased serum T levels in offspring (both sexes combined)	Ma et al. (2018)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
	to GD14 via gavage; F1 sacrificed at 8-weeks-old		
Mouse, Kunming, male and female, 30 per group	*In utero.* 0, 2, 20, or 200 mg/kg F0 maternal exposure from GD9 to birth via gavage; F1 sacrificed at PND26	No significant differences in serum T levels in male or female offspring	Zou et al. (2020)
Mouse, Kunming, male, 6 per group	Juvenile, adult. 0, 20 mg/kg-day via gavage for 4 weeks	Significantly decreased serum T levels compared to untreated control	Cao et al. (2020) [article in Chinese]
Mouse, Kunming, male, 7 per group	Adult. 0 or 120 mg/kg-day for 2 weeks via gavage	Significantly decreased serum T levels	Wang et al. (2019e)
Mouse, NMRI, male, 9 per group	Adult. 0 or 100 µg/kg-day for 4 weeks via *s.c.* injection	Significantly decreased serum T levels	Veissi et al. (2018)
Mouse, Swiss albino, male, 10 per group	Adult. 0, 0.5, 50, or 100 µg/kg-day for 60 days via *i.p* injection	Significantly decreased serum T levels in all groups (0.5 µg/kg-day exposure group had the lowest T levels)	Chouhan et al. (2015)
Mouse, Swiss albino, male, 10 per group	Adult. 0, 80, 120, or 240 mg/kg-day for 45 days via gavage	Significantly and dose-dependently decreased serum T levels	Samova et al. (2018)
Mouse, Webster albino, male, 10 per group	Adult. 0, 300 or 600 mg/kg bw for 4 weeks via gavage	Significantly and dose-dependently decreased serum T levels	Nawaz et al. (2021)
Mouse, unspecified albino, male, 10 per group	Adult. 0. 20, or 40 mg/kg-day for 30 days via *i.p.* injection	Significantly and dose-dependently decreased serum T levels	Abed et al. (2019)
Rabbit, New Zealand, male and female, 5 per group	*In utero.* 0 or 50 mg/kg-day F0 maternal exposure from GD15 to 31 via oral administration (dissolved in ethanol); F1 sacrificed at	Significantly increased serum T levels in offspring at PND3, no significant differences in offspring at other ages	Ortega-García et al. (2021)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
	GD17, 21, 27, 28, PND1, 2, or 3		
Rabbit, New Zealand White, male, 6 per group	Adult. 0, 10, 20, or 100 mg/kg-day for 9 weeks via gavage	Significantly decreased serum T levels at all doses with a significant trend	Karabulut and Gulay (2020)
Rat, F344/DuCrj, males, 8 per group	Juvenile. 0, 235, 466, 950 mg/kg-day for 44 days via diet	No significant differences in serum free T levels	Takahashi and Oishi (2001)
Rat, IGS, male, 4–6 per group	*In utero,* lactation. 0, 4, 40, 400 mg/kg bw F0 maternal exposure from GD6 to PND20 via gavage; F1 sacrificed at 9- or 36-weeks old	Significantly increased plasma T levels in 9-week-old male offspring at 4 and 40 ng/ml dose groups, non-statistically significant increase in plasma T levels in 36-week-old male offspring at all dose groups; non-statistically significant increase in testes T levels at both 9- and 36-week-old male offspring at all dose groups	Watanabe et al. (2003)
Rat, Long-Evans, male, 10–12 per group	*In utero*, lactation or juvenile, adult. 0 or 2.4 µg/kg-day F0 maternal exposure from GD12 to PND21 or from PND21 to 90 via gavage; F1 sacrificed at PND90	No significant differences in serum T levels for either exposure scenario. Significantly decreased LH-stimulated T production in Leydig cells *ex vivo* for both exposure scenarios.	Akingbemi et al. (2004)
Rat, Long-Evans, male, 10–12 per group	Juvenile. 0, 2.4, 10 µg/kg-day, 100 or 200 mg/kg-day from PND21 to 35 via gavage	Significantly decreased serum T levels at 2.4 µg/kg-day dose, no significant differences at higher doses	Akingbemi et al. (2004)
Rat, Long-Evans, male, 6 per group	Juvenile: prepubertal or pubertal. 0 or 5 µg/l for 14 days via drinking water starting at PND21 or PND35	Significantly decreased serum T levels and basal testicular explant T production with prepubertal or pubertal exposure. Significantly decreased LH-stimulated testicular explant T production with prepubertal exposure	Jeminiwa et al. (2021)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Rat, SD, male, 8 per group	*In utero.* 0, 25, or 250 µg/kg-day F0 maternal exposure from GD10 to GD21 via gavage; F1 sacrificed at PND180	No significant differences in serum T levels in male offspring at PND180	Brandt et al. (2014)
Rat, SD, male, 8 per group	*In utero.* 0, 5, 25, or 50 µg/l F0 maternal exposure from GD1 to GD21 via drinking water; F1 sacrificed PND80	Significantly decreased plasma T levels at 50 µg/l dose group in male offspring at PND80	Ullah et al. (2019b)
Rat, SD, male, 10 per group	*In utero*, lactation. 0 or 2 µg/kg-day F0 maternal exposure from GD10 to PND7 via *s.c.* injection; F1 sacrificed PND30, 50, or 90	Significantly decreased T levels at PND30 and 50, but not at PND90, in male F1 rats	Bai et al. (2011)
Rat, SD, male, 6 per group	*In utero,* lactation. 0 or 50 mg/kg-day F0 maternal exposure from GD6 to PND21 via gavage [reported as 'intragastric lavage' in publication]; F1 sacrificed at 12-weeks-old	No significant differences in plasma T levels in male offspring	Balci et al. (2022)
Rat, SD, male, 5 per group	*In utero,* lactation. 0, 50, 100, or 200 mg/kg F0 maternal exposure from GD0 to PND20 via gavage; F1 sacrificed at PND20	Significantly decreased serum T levels in male offspring at PND20 [data not shown]	Lü and Zhan (2010)
Rat, SD, male and female, 7–13 per group	*In utero* or lactation. 0 or 40 µg/kg-day F0 maternal exposure from GD1 to GD21 or PND1 to PND21 via oral administration; F1 sacrificed at 22-weeks-old	No significant differences in plasma T levels in offspring exposed from GD1 to GD21 or from PND1 to PND21	Aloisi et al. (2002)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Rat, SD, male and female, 10–14 per group	*In utero*, lactation. 0 or 2 µg/kg F0 maternal exposure from GD10 to PND7 via *s.c.* injection; F1 sacrificed PND80	Significantly decreased serum T levels in male offspring, but not female offspring	Chen et al. (2014)
Rat, SD, male and female, 14 per group	*In utero,* lactation. 0, 50 µg/kg-day, or 50 mg/kg-day F0 maternal exposure from GD7 to PND21 via gavage; F1 sacrificed at PND15, 30, 45, or 60	No significant differences in serum T levels in male or female offspring at PND15, 30, 45, or 60	Lee et al. (2013b)
Rat, SD (NCTR), male and female, 10–17 per group	*In utero*, postnatal. 0, 2.5, or 25 µg/kg-day F0 maternal exposure from GD6 to GD21, then F1 exposure from PND1 to PND21 via gavage	The authors reported no significant differences in serum T levels in male or female offspring. However, only 6 of the 15 males in the low dose group had T levels above the detection limit of 4.0 ng/dl. [For statistical analyses the authors state that the detection limit of 4.0 ng/dl was imputed for cases where the measured value was below the limit of detection.]	Ferguson et al. (2011)
Rat, SD, male, 8 per group	Postnatal. 0 or 50 µg/kg-day from PND15 to 30 via *s.c.* injection	No significant differences in plasma T levels	Brouard et al. (2016)
Rat, SD, female, 13 per group	Postnatal. 0 or 50 µg/kg-day from PND1 to PND16 via *s.c.* injection; sacrificed at 6 months old	Significantly increased serum T levels	Yang et al. (2019c)
Rat, SD, male and female, 7 per group	Juvenile. 0 or 40 µg/kg from PND23 to 30 via oral administration; sacrificed at PND37 or 90	Significantly decreased serum T levels in males at PND37; no significant differences in males or females at PND90	Ceccarelli et al. (2007)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Rat, SD (pretreated with 75 mg/kg bw ethane dimethane sulfonate to eliminate Leydig cells and stimulate regeneration by Leydig stem cells), males, 6 per group	Juvenile. 0, 100, or 1000 pmol/testis via intratesticular injection for 21 days	Significantly increased serum T levels at 1000 pmol/testis, but not 100 pmol/testis	Chen et al. (2018b)
Rat, SD, male, 5 per group	Juvenile. 0 or 25 mg/kg bw once a week for one month via *i.p.* injection	Significantly decreased serum T levels	Ok et al. (2017)
Rat, castrated SD, male, 10 per group	Juvenile, adult. Treated with 1 mg/kg-day T via *s.c.* injection, then treated with 0, 10, 30, 90 µg/kg-day for 4 weeks via gavage	Significantly decreased serum T levels at 90 µg/kg relative to model control (T and vehicle treated). No effect on serum DHT.	Wu et al. (2011)
Rat, SD, male, 5 per group	Adult. 0 or 50 mg/kg for 52 days via gavage	Significantly decreased plasma T levels	Jahan et al. (2016)
Rat, SD, male, 6 per group	Adult. 0 or 200 mg/kg-day for 42 days via gavage	Significantly decreased serum T levels	Jiang et al. (2016)
Rat, SD, male, 10 per group	Adult. 0 or 2 µg/kg-day for 14 days via gavage	Significantly decreased serum T levels and testicular T levels	Jin et al. (2013)
Rat, SD albino, male, 5 per group	Adult. 0, 0.02, 20, or 200 mg/kg bw, 3 times/week for 6 weeks via gavage	Significantly decreased serum total and free T levels at all dose levels	Osman et al. (2021)
Rat, SD, male, 6 per group	Adult. 0 or 50 mg/kg bw, 3 times/week for 3 or 6 weeks via gavage	Significantly decreased plasma T levels at 3- and 6-week exposure durations	Othman et al. (2016a)
Rat, SD, male, 14 per group	Adult. 0, 0.0005, 0.5, and 5 mg/kg bw via gavage for 8 weeks	Dose-dependent increase in intra-testicular T levels, only statistically significantly increased at 5 mg/kg bw	Qiu et al. (2013)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Rat, SD, male, 7 per group	Adult. 0, 5, 25, or 50 mg/kg for 28 days via oral administration	Significantly decreased plasma T levels at all doses, significantly decreased intra-testicular T at 25 and 50 mg/kg	Ullah et al. (2018a)
Rat, SD, male, 5 per group	Adult. 0 or 200 mg/kg for 4 weeks via gavage	Significantly decreased serum T levels	Wang et al. (2016a)
Rat, SD, male, 10 per group	Adult. 0, 10, 30, 90 µg/kg for 4 weeks via gavage	No significant differences in serum T levels	Wu et al. (2016)
Rat, SD, male, 10 per group	Adult. 0, 10, 30, 90, 270 µg/kg-day for 4 weeks via gavage	Non-statistically significant dose-dependent decrease in serum T levels	Wu et al. (2020b)
Rat, SD, female, 10 per group	Adult. 0, 50 µg/kg, 500 µg/kg, 5 mg/kg, or 50 mg/kg for 28 days via *i.p.* injection	Significantly increased plasma T levels at 5 and 50 mg/kg	Ijaz et al. (2020)
Rat, SD, female, 12 per group	Adult. 0, 0.001, 0.1 mg/kg bw for 90 days via gavage	Significantly and dose-dependently decreased serum T levels	Lee et al. (2013c)
Rat, Wistar, male, 6–8 per group	*In utero.* 0, 25, or 250 µg/kg-day F0 maternal exposure from GD8 to GD23 via osmotic pump; F1 sacrificed at PND15, 30, or 120	Significantly increased serum T levels in offspring at PND15 at both doses in F1 rats, no significant differences at PND30 or PND120.	Ramos et al. (2003)
Rat, Wistar, male, 10 per group	*In utero,* lactation. 0, 0.5, or 5 mg/kg-day F0 maternal exposure from GD18 to PND5 via *s.c.* administration; F1 sacrificed at PND90	Significantly increased serum T levels in male offspring at 5 mg/kg-day on PND90	Campos et al. (2019)
Rat, Wistar, male, 10 per group	*In utero,* lactation. 0 or 2.5 mg/kg-day from F0 maternal exposure from GD1	Significantly decreased serum T levels in male offspring on PND35	Cardoso et al. (2010)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
	to PND21 via drinking water; F1 sacrificed PND35		
Rat, Wistar, male, 6 per group	*In utero*, lactation. 0, 0.5, or 5 mg/kg F0 maternal exposure from GD18 to PND5 via *s.c.* injection; F1 sacrificed at PND90	Increased serum T levels in male offspring in 5 mg/kg group on PND90 [data not shown]	Oliveira et al. (2017)
Rat, Wistar, male and female, 9–12 per group	*In utero,* lactation. 0, 10, 50 µg/kg-day F0 maternal exposure from GD1 to PND21 via gavage; F1 sacrificed at PND21 or 180	Significantly increased plasma T levels in male and female offspring at PND21 exposed to 10 µg/kg-day; significantly decreased plasma T levels in PND180 males at both doses; no significant differences in plasma T levels in exposed F0 dams at PND21	Silva et al. (2019)
Rat, Wistar, male, 6 per group	*In utero*, postnatal. 0, 2.4, or 10 µg/kg-day F0 maternal exposure from GD12 to PND0, then F1 exposure from PND1 to 21 via s.c. injection; F1 sacrificed PND21	Significantly and dose-dependently decreased plasma T and DHT levels in F1 male rats at PND21	Castro et al. (2018a)
Rat, Wistar albino, male, 10 per group	*In utero* or *in utero*, lactation, or lactation. 0 or 50 µg/kg-day F0 maternal exposure from GD0 to GD21, or GD0 to PND21, or PND1 to PND21 via gavage; F1 sacrificed at PND60	Significantly decreased serum T levels in male offspring exposed from GD0 to PND21 or PND1 to PND21, non-statistically significant decrease in GD0 to GD21 group	El Henafy et al. (2020)
Rat, Wistar, male, 8 per group	Lactation. 0, 50 µg/kg-day, or 5 mg/kg-day F0 maternal exposure from PND3 to 15 via *s.c.* injection; F1 sacrificed at PND15 or 21	Significantly increased serum T levels in male offspring at PND15 at 5 mg/kg-day, no significant differences at PND21	Santos-Silva et al. (2018)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Rat, Wistar, male, 3–6 per group	Postnatal. 0 or 0.5 mg daily from PND2 to 12 via s.c. injection; sacrificed on PND18, 25, 35, or 90	Non-statistically significant increase in plasma T levels at PND18, but not at PND35 or PND90	Sharpe et al. (2003)
Rat, Wistar, female, 6 per group	Postnatal, juvenile. 0, 25, or 50 mg/kg from PND19 to PND68 via gavage; sacrificed at PND120	Significantly increased plasma T levels in both dose groups at PND120	Kadir et al. (2021)
Rat, Wistar, male, 6 per group	Juvenile. 0 or 50 mg/kg for 30 days via oral administration	Significantly decreased serum T levels	Alboghobeish et al. (2019)
Rat, Wistar, male, 11 per group	Juvenile. 0 or 3 mg/kg bw for 2 or 5 weeks via *s.c.* injection	Significantly decreased plasma T levels after 5 weeks, but not 2 weeks	Herath et al. (2004)
Rat, Wistar, male, 15 per group	Juvenile. 0, 20, or 200 µg/kg on PND36 to 66 via gavage	No significant differences in plasma T levels at PND66	Ogo et al. (2017)
Rat, Wistar albino, male, 6 per group	Juvenile, adult. 0, 125, or 250 mg/kg-day for 90 days via gavage	Significantly and dose-dependently decreased plasma T levels	Ahbab et al. (2017)
Rat, Wistar albino, male, 8 per group	Juvenile, adult. 0 or 25 mg/kg-day for 4 weeks via oral administration	Decreased serum T levels [statistical significance not reported]	Munir et al. (2017)
Rat, Wistar albino, normal or anemic, male and female, 6 per group	Juvenile, adult. 0, 1, 5, or 10 ppm for 6 months via drinking water	Dose-dependent decrease in serum T levels of normal and anemic male rats, statistically significant at two higher doses. Significant and dose-dependent increase in serum T levels in female normal and anemic rats	Rashid et al. (2018)
Rat, Wistar, male, 6 per group	Not specified (likely juvenile, adult, based on starting body weight of 150–200 g). 0 or 25 mg/kg-day for 28 days via gavage	Non-statistically significant decrease in serum T levels	Baralić et al. (2020)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Rat, Wistar albino, male, 10 per group	Adult. 0 or 50 mg/kg bw for 14 days via oral administration	Significantly decreased serum T levels	Akintunde et al. (2019)
Rat, Wistar, male, 5 per group	Adult. 0, 1, or 10 mg/kg bw for 30 days via gavage	Significantly and dose-dependently decreased plasma T levels	Asma et al. (2020)
Rat, Wistar, male, 8 per dose	Adult. 0, 25, 50, 300, or 600 µg/kg-day for 4 days via *s.c.* injection	Significantly and dose-dependently decreased plasma T levels	Castro et al. (2013)
Rat, Wistar, male, 6 per group	Adult. 0, 0.005, 0.5, 50 or 500 µg/kg-day for 45 days via gavage	Significant and dose-dependent decrease in plasma T levels	D'Cruz et al. (2012a)
Rat, Wistar, male, 7 per group	Adult. 0 or 100 mg/kg bw for 4 weeks via oral administration	Significantly decreased serum T levels	Grami et al. (2020)
Rat, Wistar albino, male, 7 per group	Adult. 0 or 50 mg/kg-day 14 days via gavage	Significantly decreased serum T levels	Gules et al. (2019)
Rat, Wistar, male, 10 per group	Adult. 0, 5, 25, or 125 µg/kg for 35 days via gavage	Significantly and dose-dependently decreased serum T levels	Kazemi et al. (2016)
Rat, Wistar, male, 10 per group	Adult. 0 or 10 mg/kg-day for 14 days via gavage	Significantly decreased serum T levels	Olukole et al. (2018)
Rat, Wistar albino, male, 6 per group	Not specified. 0 or 200 mg/kg for 21 days via oral administration	Significantly decreased serum T levels	Bahariv et al. (2016)
Rat, unspecified, female 8 per group	Postnatal. 0, 0.5, 5, or 50 mg/kg from PND1 to PND10 via *s.c.* injection; assessed at PND75	Significantly increased plasma T levels at 50 mg/kg	Ahsan et al. (2018)
Rat, unspecified albino, male, 10 per group	Adult. 0 or 150 mg/kg bw for 8 weeks via stomach tube	Significantly decreased serum T levels	Abdel-Halim et al. (2016)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Rat, unspecified albino, male, 8 per group	Not specified (likely juvenile, adult, based on starting body weight of 140–160 g). 0 or 10 mg/kg bw for 14 days via oral administration	Significantly decreased serum T levels	El-Beshbishy et al. (2013)
Rat, unspecified albino, male, 10 per group	Not specified (likely juvenile, adult, based on starting body weight of 130 –150 g). 0 or 5 mg/kg for 3 weeks via *i.p*. injection	Significantly decreased serum T levels	Eshak and Osman (2014)
Rat, unspecified albino, male, 10 per group	Adult. 0 or 1.2 mg/kg for 3 weeks (6 days/week) via gavage	Significantly decreased serum T levels	Mahmoud et al. (2019)
Rat, unspecified albino, male, 8 per group	Adult. 0 or 50 mg/kg-day for 8 weeks (6 days/week) via gavage	Significantly decreased serum T levels	Mohamed and Arafa (2013)
Rat, unspecified albino, male, 8 per group	Adult. 0 or 50 mg/kg-day for 8 weeks (6 days/week) followed by 4 weeks recovery via gavage	Significantly increased serum T levels	Mohamed and Arafa (2013)
Rat, unspecified albino, female 12 per group	Adult (pregnant) 0 or 150 mg/kg-day F0 maternal exposure from GD0 to GD20 via gavage; F0 assessed at GD4, 10, and 20	Significantly decreased serum T levels in pregnant rats at GD20, no significant differences at GD4 or GD10	Saadeldin et al. (2018)
Rat, unspecified albino, male, 12 per group	Adult. 0, 50, 100, 200 mg/kg for 14 or 28 days via oral administration	Significantly and dose-dependently decreased serum T levels at all dose groups exposed for both 14 and 28 days	Sencar et al. (2021)
Rat, unspecified albino, male, 5 per group	Adult. 0 or 100 mg/kg bw for 15 days via gavage	Significantly decreased serum T levels	Yousaf et al. (2016)

Species and strain, sex, group size	Route, duration, dosing regime	Results	Reference
Field voles (*Microtus agrestis*), male and female, 11–15 per group	Adult. 0, 10, 50, or 250 mg/kg-day for 4 days via *s.c.* injection	Significantly increased plasma T levels in males and females at 250 mg/kg-day	Nieminen et al. (2002)

Table J4.4 Effects of BPA on testosterone (T) in non-human mammalian studies *in vitro*

Model	Concentration and duration	Results	Reference
Mouse fetal testes explants from PND12.5 mice	10, 100 nM, 1, or 10 µM for 24, 48, or 72 hours	Significantly decreased T levels at 1 and 10 µM after 48 and 72 hours, and at 10 µM after 24 hours, no significant differences at 10 or 100 nM after 24, 48, or 72 hours	Eladak et al. (2015)
Mouse fetal testes explants from PND12.5 NMRI and C57BL/6 mice	10 pM, 0.01, 0.1, or 10 µM for 24, 48, or 72 hours	Significantly decreased T levels after 24, 48, or 72 hours at 10 µM, no significant differences at 1 pM, 0.01, or 0.1 µM after 24, 48, or 72 hours	N'Tumba-Byn et al. (2012)
Mouse primary Leydig cells from CBA/Lac and C57BL/6j mice	10 µM for 17 hours	Non-statistically significant increases in T levels in Leydig cells from both mice strains	Savchuk et al. (2013)
Mouse primary antral follicles from CD-1 mice	1, 10, and 100 µg/ml for 20, 24, 48, 72, or 96 hours	Significantly decreased T levels at 10 and 100 µg/ml after 72 and 96 hours. T levels were increased at 1 µg/ml after 72 and 96 hours, but was not statistically significant, no differences were observed after 24 or 48 hours	Peretz and Flaws (2013)
Mouse primary antral follicles from CD-1 mice	1 or 10 µg/ml for 20 hours, then placed in DMSO media for 4, 28, 52, or 76 more hours	Non-statistically significant increases in T levels after 96 hours of total exposure, no significant differences after 24, 48, or 72 hours of total exposure	Peretz and Flaws (2013)
Mouse primary antral follicles from FVB mice	4.4, 44, and 440 µM for 120 hours	Significantly decreased T levels at 44 and 440 µM, no significant differences at 4.4 µM	Peretz et al. (2011)

Model	Concentration and duration	Results	Reference
Mouse TM3 Leydig cells	1, 10, or 100 µM for 48 hours	Significantly decreased T levels at all concentrations [significant decreases in cell viability were observed at 100 µM]	Goncalves et al. (2018)
Mouse TM3 Leydig cells	0.04 to 50 µg/ml for 24 hours	Significantly decreased T levels at 10 µg/ml and above [significant decreases in cell viability were observed at 10 µg/ml and above], T levels at concentrations between 0.04 and 5 µg/ml were slightly increased but not significant	Jambor et al. (2019)
Mouse TM3 Leydig cells	10 µM for 24 or 48 hours	Significantly decreased T levels at 24 and 48 hours	Li et al. (2021a)
Mouse TM3 Leydig cells and TM4 Sertoli cells	100 µM for 24 hours	Significantly decreased T levels	Ok et al. (2017)
Mouse TM3 Leydig cells	5 µM 48 hours	Significantly decreased T levels	Xu et al. (2020)
Mouse MA-10 Leydig tumor cells	0.1 to 30 µM for 24 hours	Significantly increased T levels at 0.1, 10, and 30 µM, no significant differences at 0.3, 1, or 3 µM	Dankers et al. (2013)
Rat fetal testes explants from SD and Wistar rats	1 nM to 100 µM for 24, 48, or 72 hours	Significantly decreased T levels at 10 µM after 24, 48, or 72 hours, and at 0.1 µM after 72 hours, no significant differences were observed at other concentrations or durations	Ben Maamar et al. (2015)
Rat fetal testes explants from Wistar rats	1 pM, 0.01, 0.1, or 10 µM for 24, 48, or 72 hours	Significantly decreased T levels at 10 µM after 24, 48, or 72 hours, no significant differences at 1 pM, 0.01, or 0.1 µM	N'Tumba-Byn et al. (2012)
Rat testes explants from SD rats	1, 10, 100 ng/ml for 2 hours	Non-statistically significant decreases in T levels (in ng/g testis tissue)	Ullah et al. (2018a)
Rat primary Leydig cells from SD rats	1 to 1000 nM BPA for 24 hours	No significant differences in T levels [data not shown]	Murono et al. (2001)

Model	Concentration and duration	Results	Reference
Rat R2C Leydig tumor cells	0.1, 1, and 10 nM for 24 hours	Significantly and dose-dependently decreased T levels at all concentrations	Kim et al. (2010a)
Rat seminiferous tubule explants from SD rat, 7 days after treatment with ethane dimethane sulfonate to eliminate Leydig cells and stimulate regeneration by Leydig stem cells	1, 10, 100, 1000 nmol/l for one week, then placed in luteinizing hormone-containing medium to stimulate Leydig cell differentiation for two weeks	Significantly increased T levels at 1000 nmol/l, no significant differences at 1, 10, or 100 nmol/l	Chen et al. (2018b)
Rat ovarian theca-interstitial cells from SD rats	0.1 to 100 μM for 72 hours	Significantly increased T levels at all concentrations	Zhou et al. (2008)

Section J5 Thyroid hormone and thyroid hormone receptors

Table J5.1 Effects of BPA on serum levels of thyroid hormones in human observational studies (ordered by participant characteristics)

Population (general)	Population (detailed)	BPA measurement	Results	Reference
Children and adolescents with thyroid dysfunction	Children and adolescents with thyroid dysfunction and control. 57 cases (30 hyperthyroidism, 6 hypothyroidism, 21 other) and 288 hospital-based controls in China	Serum	Decrease in thyroid stimulating hormone (TSH) in healthy controls (R^2 = 0.477, p < 0.001). Increase in TSH in hyperthyroid cases (R^2 = 0.753, p = 0.033).	Guo et al. (2021)

Population (general)	Population (detailed)	BPA measurement	Results	Reference
Women with thyroid nodules (diameter greater than 3 mm)	Women with thyroid nodules and control. 106 women with thyroid nodules and 106 population controls (≥34 years old) in Cyprus and Romania	Urine	Increase in TSH (β = 0.121; 95% CI: 0.008, 0.234; *p* = 0.037), adjusted for age, body mass index (BMI), study site, disease status, and creatinine for all participants. No association with free thyroxine (FT4).	Andrianou et al. (2016)
Pregnant women	Pregnancy. 181 pregnant women in Puerto Rico	Urine	Increase in FT4 (% change per IQR (2.80 ng/ml) = 4.11%; 95% CI: 0.12, 8.10), adjusted for maternal age, education, and BMI. No association with TSH or FT3.	Aker et al. (2016)
Pregnant women	Pregnancy. 602 pregnant women in Puerto Rico	Urine	Increase in total triiodothyronine (TT3) (% change per IQR = 2.10; 95% CI: 0.22, 3.99), adjusted for specific gravity, study visit, BMI, maternal age, secondhand smoking, socioeconomic status. No association with TSH, FT4, total thyroxine (TT4) or T3/T4 ratio.	Aker et al. (2019)
Pregnant women	Pregnancy. 439 pregnant women (116 preterm birth cases and 332 control) in MA, US	Urine	Decrease in TSH (% change per IQR = –8.21; 95% CI: –14.2, –1.83). Increase in FT4 (% change per IQR = 4.79; 95% CI: 0.82, 8.92). No association with TT3 or TT4. Adjusted for specific gravity, gestational age, maternal age, health insurance provider, BMI.	Aung et al. (2017)
Pregnant women	Pregnancy.	Urine	Borderline decrease in maternal TT4 with closest measurement of BPA (β = -0.13; 95% CI: -0.25, 0.00), adjusted for age, education, country of birth, poverty, alcohol and drug use during pregnancy,	Chevrier et al. (2013)

Population (general)	Population (detailed)	BPA measurement	Results	Reference
	335 pregnant women in the Salinas Valley, CA, US (CHAMACOS cohort)		iodine intake, hexachlorobenzene and polychlorinated biphenyls (PCB) serum concentrations. No associations with maternal FT4, maternal TSH, neonatal TSH.	
Pregnant women	Pregnancy. 1996 pregnant women in Sweden	Urine	Decrease in FT4/FT3 ratio (β = –0.02; SE = 0.01; p = 0.03). Decrease in TT4/TT3 ratio (β = –0.73; SE = 0.27; p = 0.008). Nonmonotonic (U-shape) association with TT4 (p = 0.03). No association with TSH, FT4, FT3, TT3. Adjusted for age, thyroid peroxidase antibodies, thyroglobulin antibodies, human chorionic gonadotropin, urinary creatinine, smoking status, BMI, education, ethnicity, parity.	Derakhshan et al. (2019)
Pregnant women	Pregnancy. 555 pregnant women in China	Urine	Thyroid hormones measured in pregnancy: Decrease in TSH per unit increase in BPA (β = –0.10; 95% CI: –0.20, –0.005) in women with pre-pregnancy BMI ≥ 23 kg/m^2. No associations with FT4 or in those with BMI < 23 kg/m^2. Adjusted for creatinine, age, education, gestational diabetes mellitus, husband smoking, parity, gestational age when hormones measured. Thyroid hormones measured in cord serum: No associations with FT3, FT4, TSH.	Wang et al. (2020c)

Population (general)	Population (detailed)	BPA measurement	Results	Reference
Male partners in subfertile couples	Male partners in subfertile couples. 167 men at an infertility clinic (18–55 years old) in the US	Urine	Borderline increase in TSH using the geometric mean BPA from all participants (β = 0.88; 95% CI: 0.76, 1.00; p = 0.046), adjusted for specific gravity, age, BMI, smoking, season, time of day of sample collection. No associations with FT4 or TT3.	Meeker et al. (2010a)
Maternal BPA exposure and association with thyroid hormones in infants, children, or adult men	Newborns. 53 newborn boys in France	Cord blood	Decrease [not significant] in TSH in cord blood (r = –0.25; p = 0.077).	Brucker-Davis et al. (2011)
Maternal BPA exposure and association with thyroid hormones in infants, children, or adult men	Newborns. 348 newborns in China	Maternal urine	Thyroid hormones measured in cord blood: Decrease in TT3 (β = –0.05; 95% CI: –0.10, –0.01) Decrease in FT3 (β = –0.11; 95% CI: –0.21, –0.01) Decrease in TSH (β = –1.91; 95% CI: –3.32, –0.50) No associations with TT4, FT4. Adjusted for maternal age, education, gravidity, passive smoking, vitamin supplementation, child's gender.	Li et al. (2020a)
Maternal BPA exposure and association with thyroid	Newborns. 278 newborns in Japan	Cord blood	No associations with TSH or FT4 in newborn blood spots, adjusted for sex, interaction of sex and BPA, and days of mass screening test.	Minatoya et al. (2017)

Population (general)	Population (detailed)	BPA measurement	Results	Reference
hormones in infants, children, or adult men				
Maternal BPA exposure and association with thyroid hormones in infants, children, or adult men	Newborns. 249 newborns in OH, US	Maternal urine (samples taken at 16 or 26 weeks of gestation)	Decrease in TSH measured in cord blood in newborn girls for average BPA (% change, –36.0; 95% CI: –58.4, –1.7) and 26-week BPA (% change, –42.9; 95% CI: –59.9, –18.5), adjusted for maternal age, race, education, alcohol, cotinine, parity, prenatal vitamin use, PCB 153, C-section delivery, gestational week at delivery and newborn sex. No associations with TSH, TT4, TT3, FT4, FT3 in all newborns combined or in male newborns.	Romano et al. (2015)
Maternal BPA exposure and association with thyroid hormones in infants, children, or adult men	Newborns and children. 1,267 mothers, 853 newborns, 882 5-year-old children in the Netherlands	Maternal urine (samples taken at early, mid and late pregnancy)	Maternal thyroid hormones: No associations with TSH, FT4, or TT4. Cord blood thyroid hormones: Maternal BPA measured in late pregnancy was associated with increase in TSH (β = 0.04, 95% CI: 0.007, 0.07), adjusted for fetal sex, fetal distress, method of delivery, parity, ethnicity, maternal education, BMI, smoking status, creatinine. No association with FT4. Childhood thyroid hormones: Maternal BPA measured in late pregnancy was associated with decrease in FT4 (β = –0.11; 95% CI: –0.21, –0.01), adjusted for age, BMI, ethnicity, sex, maternal education, smoking status,	Derakhshan et al. (2021)

Population (general)	Population (detailed)	BPA measurement	Results	Reference
			creatinine. No association with TSH.	
Maternal BPA exposure and association with thyroid hormones in infants, children, or adult men	Children. 574 6-year-old children in South Korea	Maternal urine (2nd trimester)	No associations with TT3, TSH, FT4 for all children, adjusted for age (months), sex, body mass index, mother's age, mother's education, monthly household income, secondhand smoke, urinary creatinine level. Stratified by gender: significant decrease in TT3 in boys (β = –0.02; p = 0.035); significant increase in TT3 in girls (β = 0.02; p = 0.037).	Jang et al. (2021)
Occupationally exposed workers	Male workers. 90 male workers at a plastic processing factory (21-54 years old) in Egypt	Serum	Increase in TT3 (r = 0.237; p = 0.02). No associations with TT4, TSH.	Metwally et al. (2019)
Occupationally exposed workers	Male and female workers. 21 male and 7 female workers in epoxy resin plants (22–62 years old) in China	Urine	Increase in FT3 (r = 0.57, p = 0.002). Weak, non-significant increase in FT4 (r = 0.33, p = 0.096). No associations with TSH, TT3, TT4.	Wang et al. (2012a)
Adolescents and adults	Adolescents and adults. 329 adolescents (12–19 years old) and 1346 adults (≥ 20 years old) in NHANES in the US	Urine	Decrease in TT4 (β = –0.095; 95% CI: –0.19, –0.00063) in adults when unweighted for sampling strategy (not significant when weighted). No associations with TT3, FT3, FT4, TSH, thyroglobulin in adults or adolescents or with TT4 in adolescents.	Meeker and Ferguson (2011)

Population (general)	Population (detailed)	BPA measurement	Results	Reference
Adolescents and adults	Adolescents and adults. 1829 adolescents and adults (≥ 12 years old) in NHANES in the US	Urine	Decrease in TT4 (β = –0.087; 95% CI: –0.17, –0.0014), adjusted for sex, age, race/ethnicity, creatinine, cotinine, BMI. No associations with TSH, FT3, FT4, TT3.	Kim et al. (2017)
Adults	Women. 180 women (18–40 years old) in Poland	Serum and urine	Decrease in FT4 with serum BPA (r = –0.151; *p* = 0.045). No associations with serum BPA and TSH or urinary BPA and TSH or FT4.	Milczarek-Banach et al. (2020)
Adults	Adults. 1254 adults (≥ 19 years old) in South Korea	Urine	Increase in TT4 (β = 0.014; 95% CI: 0.002, 0.026). Decrease in TT3 (β = –0.012; 95% CI: –0.020, –0.003). Both adjusted for age, sex, BMI, smoking, income. No association with FT4, FT3, TSH, thyroxine binding globulin (TBG).	Choi et al. (2020a)
Adults	Adults. 151 obese/overweight adults and 43 lean adults in Belgium	Urine	Increase in TSH in lean men and women combined (β = 0.35; 95% CI: 0.05, 0.66), adjusted for age, weight loss. No associations with FT4 in lean adults or when stratified by sex. No associations with TSH or FT4 in obese/overweight adults.	Geens et al. (2015)
Adults	Adults. 5108 adults (≥ 19 years old) in South Korea	Urine	Decrease in TT3 in all subjects (β = –0.627; 95% CI: –1.131, –0.123). Decrease in TT4 in all subjects (β = –0.060; 95% CI: –0.099, –0.020). When stratified by BMI, decrease in TT4 in adults with BMI ≥ 25 kg/m^2 (β = –0.098; 95% CI: –0.161, –0.035)	Kwon et al. (2020)

Population (general)	Population (detailed)	BPA measurement	Results	Reference
			No association with TSH. Adjusted for age, education, income, smoking, alcohol, exercise, survey year, other phthalates.	
Adults	Adults. 2340 adults (≥ 18 years old) in Thailand	Serum	Decrease in FT4 in males (β = –105; p = 0.001). No association in females.	Sriphrapradang et al. (2013)
Adults	Adults. 1354 men and 2040 women (≥ 40 years old) in China	Urine	Men [for each quartile increase in BPA]: Increase in FT3: 0.068 pmol/l (95% CI: 0.065, 0.071) Decrease in FT4: –0.027 pmol/l (95% CI: –0.030, –0.024) Decrease in TSH: –0.084 µIU/ml (95% CI: –0.099, –0.069) Women [for each quartile increase in BPA]: Increase in FT3: 0.10 pmol/l (95% CI: 0.09, 0.11) Increase in FT4: 0.006 pmol/l (95% CI: 0.003, 0.008) Decrease in TSH: –0.13 µIU/ml (95% CI: –0.14, –0.11) Adjusted for age, creatinine, BMI, education, occupation, smoking, alcohol consumption, cholesterol, thyroglobulin antibody, thyroid peroxidase antibodies.	Wang et al. (2013c)

Table J5.2 Effects of BPA on thyroid hormone receptors in human studies *in vitro* (ordered by tissue type, followed by transfected cells from other species)

Cell type/system	BPA concentration, duration	Results	Reference
Breast: human MCF-7 Tet-off cells stably transfected with chimeric molecule of green fluorescent protein, glucocorticoid receptor, and thyroid hormone receptor β (GFP-GR-TRβ)	25, 50 or 100 μM for 3 hours	Significantly induced nuclear translocation of GFP-GR-TRβ chimeric receptor at all concentrations tested, indicating BPA interacts with TRβ.	Stavreva et al. (2016)
Kidney: human TSA201 (derived from HEK293 cells) transiently transfected with human TRα1 or human TRβ	10 nM to 100 μM [duration not specified]	Antagonized T3-induced luciferase activity of TRα1 and TRβ between 1–100 μM, 10 μM suppressed TR-mediated transcription.	Moriyama et al. (2002)
Liver: human hepatoma HepG2 cells transfected with thyroid response element (TRE) and human TRβ1	0.01 nM to 10 μM for 24 hours	Lowest observed effect concentration: 1 μM. Activated reporter gene and induced activity by 1.6x, decreased T3-induced activity by 0.8x in competition assay.	Hofmann et al. (2009)
Liver: human hepatoma HepG2 transfected with human TRβ1	12.5, 25, or 50 μM for 24 hours	Antagonized T3-induced TR activity at 25 and 50 μM; did not exhibit thyroid hormone activity.	Sun et al. (2008)
Ovary: human granulosa COV434 cells	1 nM, 0.1 μM, or 10 μM for 24 or 48 hours	No differences in TRα mRNA expression at 24 or 48 hours.	Mlynarcikova and Scsukova (2020)
CV-1 (derived from African green monkey kidney) cells	1 to 100 nM for 24 hours	Significantly decreased T3-induced TR-β1 luciferase activity.	Sheng et al. (2012)

Cell type/system	BPA concentration, duration	Results	Reference
transfected with TR-β1 and TH response elements			
CV-1 cells transfected with human TRβ	1 μM to $10^{-4.5}$ M (~31.6 μM) for 24 hours	Significantly inhibited T3-induced luciferase activity at 10 μM and higher (IC_{50}: 16.4 μM), BPA did not exhibit thyroid hormone activity.	Sun et al. (2009)
Vero (derived from African green monkey kidney) cells transfected with thyroid hormone receptor β	0.001, 0.01, 0.1, and 1 mg/l	Significantly decreased T3-induced luciferase activity at 1 mg/l, did not exhibit agonist activity.	Sun et al. (2012)

Table J5.3 Effects of BPA on thyroid hormones in non-human mammalian studies *in vivo* (ordered by species, strain, and life stage)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Mouse, C57BL/6J, male, 8 per group	Juvenile, adult. 0, 250 μg/kg, or 250 mg/kg for 5 weeks via diet	Significantly decreased serum total T4 levels in 66-week-old mice at 250 μg/kg dose group, non-significant decrease in total T4 in 250 mg/kg dose group. No differences in serum T4 at 10 weeks of age.	Yang et al. (2021a)
Rat, ovariectomized F344, female, 12–15 per group	Adult. Rats received a single *s.c.* injection of 2000 mg/kg bw of N-bis(2-hydroxypropyl) nitrosamine (DHPN) (used to establish thyroid carcinoma) and followed by 1000 ppm sulfadimethoxine (SDM) for 8 weeks via drinking water, followed by 0 or	Significantly increased serum T3 and T4 levels; no differences in serum TSH levels.	Takagi et al. (2001)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	10000 ppm BPA for 27 weeks via diet		
Rat, ovariectomized F344, female, 12 per group	Juvenile, adult. Rats received a single *s.c.* injection of 2000 mg/kg DHPN followed by 0 or 10000 ppm BPA for 20 weeks via diet	Significantly increased serum T4 levels, no differences in serum T3 or TSH levels.	Takagi et al. (2002)
Rat, F344, female, 8–10 per group	Juvenile, adult. Non-injected or DHPN injected followed by 0, 250, or 1000 µg/kg for 64 weeks via gavage	Non-injected: Significantly increased serum free T4 levels in 1000 µg/kg dose group; no differences in serum T3 or TSH levels. DHPN injected: No differences in serum T3, free T4, or TSH levels.	Zhang et al. (2017a)
Rat, Crj:CD (SD) IGS, male and female, 1–9 per dose	*In utero,* lactation. 0, 4, or 40 mg/kg-day F0 maternal exposure from GD6 to PND20 via oral gavage; F1 sacrificed at 1, 3, or 9 weeks old	No difference in plasma T4 levels in male or female offspring at 1, 3, or 9 weeks old.	Kobayashi et al. (2005)
Rat, Long-Evans, male and female, 6–10 per group	*In utero*, postnatal. 0, 4, 40, or 400 µg/kg-day F0 maternal exposure from GD0 to PND0 via diet, then F1 exposure from PND1 to 9 via oral administration; F1 sacrificed at PND21	No differences in serum T4 or TSH levels in male or female offspring.	Sadowski et al. (2014)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, SD, male and female, 8–9 per group	*In utero,* lactation. 0, 0.1, or 50 mg/l F0 maternal exposure from GD11 to PND21 via drinking water; F1 sacrificed at PND7 or PND21	Dams at PND0: Significantly decreased serum free T4 levels at 0.1 mg/l, no effects at 50 mg/l. Dams at PND7: Significantly decreased serum free T4 at 0.1 mg/l, no effects at 50 mg/l. Dams at PND21: No differences in serum free T4 levels. Males at PND0: No differences in serum free T4 levels. Males at PND7: Significantly increased serum T4 levels at 0.1 mg/l, no effects at 50 mg/l. Males at PND21: Significantly decreased serum free T4 levels at 50 mg/l . Females at PND0, PND7, or PND21: No differences in serum free T4 levels.	Xu et al. (2007)
Rat, SD, male, 10 per group	*In utero*, lactation. 0 or 0.1 mg/l BPA F0 maternal exposure from GD11 to PND21 via drinking water; F1 sacrificed at PND21 or PND90	Dams at GD21: Significantly decreased serum total and free T4 levels , no differences in total or free T3 levels. Males at PND21: Significantly decreased serum total and free T3 and T4 levels, no differences in T3 or T4 levels in prefrontal cortex or hippocampus. Males at PND90: Significantly decreased T3 levels in prefrontal cortex and hippocampus, no differences in serum total or free T3 or T4 levels.	Xu et al. (2019b)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, SD, male and female, 7–9 per group	*In utero*, lactation. 0, 1, 10, or 50 mg/kg F0 maternal exposure from GD6 to sacrifice via diet; sacrificed at PND4, 8, 15, or 35	Significantly increased serum total T4 levels in offspring on PND15 at all dose groups; no differences at PND4, 8 or 35; no differences in serum TSH in male offspring at PND15.	Zoeller et al. (2005)
Rat, SD, male and female, 8 per group	*In utero,* postnatal. 0, 2.5, 25, 250, 2500, or 25000 µg/kg-day F0 maternal exposure from GD6 to PND0, then F1 exposure from PND1 to PND15 via gavage; F1 sacrificed on PND15	No differences in serum total T4 levels in male or female offspring.	Bansal and Zoeller (2019)
Rat SD, male and female, 19–23 per group	*In utero,* postnatal. 0, 2.5, or 25 µg/kg-day from F0 maternal exposure from GD6 to GD21, then F1 exposure from PND1 to PND21 via gavage; F1 sacrificed at PND21	No differences in serum T3 or T4 levels in male or female offspring.	Ferguson et al. (2011)
Rat, SD, female, 10 per group	Postnatal. 0, 5, 50, or 500 µg/50 µl from PND1 to PND10 via *s.c.* injection; sacrificed at PND13 or between PND90-120	PND13: No differences in serum TSH levels. PND90-120: Significantly decreased serum T4 levels in 5 µg/50 µl and 500 µg/50 µl dose groups, significantly increased serum TSH levels in 50 µg/50 µl dose group, no differences in serum T3 levels, no differences in Tshb or Trhr expression in pituitary, or Trh expression in hypothalamus.	Fernandez et al. (2018)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, SD, female, 7 per group	Juvenile. 0, 20, or 100 mg/kg-day from PND28 to PND70 via gavage	Significantly decreased serum total T4 levels in both dose groups; no differences in total or free T3 levels, free T4 levels, or TSH levels.	Zhang et al. (2020b)
Rat, SD, male and female, 10 per group	Juvenile. 0, 2, 6, or 18 mg/kg-day for 28 days (5 days/week) from PND23 to PND60 via oral gavage	Males: Significantly increased serum TSH levels in 6 and 18 mg/kg-day dose groups, no differences in serum T4 levels. Females: Significantly increased serum T4 levels in 18 mg/kg-day dose group, significantly increased serum TSH levels in 2 mg/kg-day dose group.	Tassinari et al. (2020)
Rat, SD albino, female, 5 per group	Adult. 0, 20 µg/kg bw, 20, or 200 mg/kg bw, 3 times/week for 6 weeks via oral gavage	Significantly and dose-dependently increased serum TSH levels.	Osman et al. (2021)
Rat, Swiss, male and female, 8 per group	Lactation. 0 or 250 mg/kg bw F0 maternal exposure during lactation via intramuscular injection; F1 sacrificed during suckling phase	Significantly decreased plasma free T3 and T4 levels and significantly increased plasma TSH levels in offspring.	Mahmoudi et al. (2018)
Rat, Wistar albino, male and female, 6 per group	*In utero.* 0, 20, or 40 µg/kg-day F0 maternal exposure from GD1 to GD20 via gastric intubation; F1 sacrificed at GD20	Significantly and dose-dependently decreased serum T3 and T4 levels in dams and fetuses; significantly and dose-dependently increased serum TSH levels in dams and fetuses.	Ahmed (2016)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, Wistar, male and female, 9–12 per group	*In utero,* lactation. 0, 10, 50 µg/kg-day F0 maternal exposure from GD1 to PND21 via gavage; F1 sacrificed at PND21 or PND180	Dams at PND21: No differences in plasma T3 or T4 levels. Males at PND21: Significantly decreased plasma T3 levels at 10 µg/kg-day. Males at PND180: Significantly decreased plasma T4 levels in 10 µg/kg-day. Females at PND21: No differences in plasma T3 or T4 levels. Females at PND180: Significantly decreased plasma T4 levels at 10 µg/kg-day.	Silva et al. (2019)
Rat, Wistar albino, male, 6 per group	Postnatal. 0, 20, or 40 µg/kg from PND15 to PND30 via gastric intubation; sacrificed at PND30	Significantly and dose-dependently decreased serum T3 and T4 levels; significantly and dose-dependently increased serum TSH levels.	Ahmed et al. (2018)
Rat, Wistar, male and female, 8 per group	Lactation. 0, 50 µg/kg-day, or 5 mg/kg-day F0 maternal exposure from PND3 to PND15 via *s.c.* injection; F1 sacrificed at PND15, PND21, or PND180	Dams at PND21: No differences in serum T3 or T4 levels. Males at PND15: Significantly decreased serum T4 levels at 50 µg/kg, no differences at 5 mg/kg-day. Males at PND21: No differences in serum T3 or T4 levels. Males at PND180: No differences in serum T3 or T4 levels. Females at PND15 or PND21: No differences in serum T3 or T4 levels.	Santos-Silva et al. (2018)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
		Females at PND180: Significantly increased serum T4 levels at 5 mg/kg-day.	
Rat, Wistar, male, 6 per group	Not specified (likely juvenile or adult based on starting weight of 150-200 grams). 0 or 25 mg/kg-day for 28 days via oral gavage	Significantly decreased serum T4 levels, no differences in serum T3 levels.	Baralić et al. (2020)
Rat, Wistar albino, male and female, 6 per group	Juvenile. 0, 1, 5, or 10 ppm for 6 months via drinking water	Significantly increased serum TSH levels in 10 ppm dose group male and female rats fed an anemic diet; no significant difference in rats fed a normal diet.	Rashid et al. (2018)
Rat, Wistar albino, male, 6 per group	Juvenile, adult. 0, 125, or 250 mg/kg-day for 90 days via gavage	No differences in plasma T3 or T4 levels.	Ahbab et al. (2017)
Rat, Wistar, males, 8 per group	Adult. 0 or 40 mg/kg-day for 15 days via gavage	Significantly increased serum total T4 levels; no differences in serum total T3 levels.	da Silva et al. (2019)
Rat, Wistar, male, 7 per group	Adult. 0 or 10 mg/kg bw for 90 days via oral gavage	Significantly decreased serum free T3 levels, no differences in serum free T4 levels.	Elgawish et al. (2020)
Rat, ovariectomized	Adult. 0, 33, or 333 µg/kg-day for 12 weeks via diet	No differences in serum T3, T4, or TSH levels.	Seidlova-Wuttke et al. (2005)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
SD, female, 12 per group			
Rat, unspecified albino, male, 8 per group	Adult. 0 or 50 mg/kg bw for 30 days via oral administration	Significantly decreased serum T3 and T4 levels; significantly increased serum TSH levels.	Mohamed and Rateb (2019)
Rat, unspecified albino, male, 20 per group	Not specified (likely juvenile or adult based on starting weight of 200 grams). 0 or 200 mg/kg-day for 35 days via oral gavage	Significantly decreased serum T3 and T4 levels, significantly increased serum TSH levels.	Mohammed et al. (2020)
Sheep, Lacaune, male and female, 6–12 per group	*In utero*. 0 or 5 mg/kg-day F0 maternal exposure from GD28 until end of pregnancy (GD145) via s.c. injection; F0 assessed weekly during pregnancy, F1 assessed at delivery and 2 months old	Mothers during pregnancy: Consistently decreased serum total T4 levels relative to vehicle controls, mean total T4 significantly decreased. Serum free T4 levels were decreased at the beginning half of pregnancy, but similar to controls during the last half. Mothers at delivery: No differences in serum total or free T4 or total T3. Newborn lamb cord blood: Significantly decreased serum total T4 levels, no differences in free T4 or total T3 levels. Newborn lamb at birth: Significantly decreased serum total and free T4 levels, no differences in total T3. Lamb at two months old: No differences in serum total or free T4 or total T3.	Viguié et al. (2013)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Field vole (*Microtus agrestis*), male and female, 11–15 per group	Adult. 0, 10, 50 or 250 mg/kg-day for 4 days via s.c. injection	Significantly increased plasma T4 levels in males at 250 mg/kg-day, no difference in females; no differences in plasma TSH levels.	Nieminen et al. (2002)

Table J5.4 Effects of BPA on thyroid hormones in non-human mammalian studies *in vitro* (ordered by species, cell type, cell line, with cell-free systems last)

Cell type/system	BPA concentration, duration	Results	Reference
Rat and mouse isolated cerebellar granule cells from 6- to 9-day old SD rats or 6 day old C56BL/6 mice	0.1 nM for 6 hours	Significantly increased TRα and TRβ mRNA expression in mouse cells but not in rat cells	Jocsak et al. (2019)
Rat isolated cerebellar cells from SD rats	0.1 nM for 6 or 18 hours	Significantly decreased TRα and TRβ mRNA expression and increased protein expression relative to non-treated controls in both Glia+ and Glia- cultures	Somogyi et al. (2016)
Rat pituitary GH3 tumor cells stably transfected with thyroid response element TRE-Luc (GH3.TRE-Luc cells)	0.01 to 500 μM for 24 hours	BPA increased luciferase activity up to 1 μM, and decreased activity at higher concentrations. [cytotoxicity occurred above 100 μM]	Freitas et al. (2011)
Rat pituitary tumor GH3 cells	0.01 nM to 100 μM for 48 hours	Significantly inhibited T3 binding to TR between 1 and 50 μM in a non-competitive manner	Jung et al. (2007)
Rat pituitary tumor GH3 cells	0.01, 0.1, 1 or 10 mg/l for 48 hours	Significantly decreased Trα and Trβ gene expression at 10 mg/l, no differences at lower concentrations or for dio1 gene expression	Lee et al. (2017c)
Rat pituitary tumor GH3 cells	1 nM to 1 μM for 48 or 96 hours	Significantly decreased Trα and Trβ gene expression at 1 μM	Lee et al. (2018c)

Cell type/system	BPA concentration, duration	Results	Reference
Rat pituitary tumor GH3 cells transfected with TRE	0.1 to 50 μM	Significantly increased TR-mediated luciferase transcription at 5, 10, and 50 μM without T3, and only 50 μM with T3	Zhang et al. (2018b)
Cell free competitive binding assay with nuclear TR from SD rat liver	1 μM to 1 mM overnight incubation at 4C	Exhibited weak binding to rat TR, displaced T3 from endogenous TR with inhibition constant of 200 μM	Moriyama et al. (2002)
Cell free competitive binding assay with thyroid hormone receptor from nuclear extract of rat pituitary MtT/E-2 cells	10 to 100 μM for 40 mins	Exhibited weak binding activity to rat TR	Kitamura et al. (2002)

Section J6 Prolactin

Table J6.1 Effects of BPA on prolactin (PRL) in rats *in vivo* (order by strain and life stage)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
Rat, F344, female, 10 per group	Juvenile, adult. 0, 50, 200, or 400 mg/kg-day for 6 or 12 weeks via oral administration	Significantly increased serum PRL levels in all dose groups after 6 and 12 weeks	Hao et al. (2011)
Rat, ovariectomized F344 grafted with pituitary MtT/E2 cells, female, 5–6/ dose	Juvenile, adult. 0, 0.5, 5, or 50 mg/ml 3 times/ week for 7 weeks via *i.p*. injection	No differences in serum PRL levels.	Maruyama et al. (1999)
Rat, ovariectomized F344 and SD, female, 8–12 per group	Adult. 0 or 40-45 µg/day via Silastic capsule for 3 days	Significantly increased serum PRL levels in F344 rats but not SD rats	Steinmetz et al. (1997)
Rat, SD (NCTR), male and female, 18–23 per group	*In utero*, postnatal, juvenile, adult. 0, 2.5, 8, 25, 80, 260, 840, 2700, 100000, or 300000 µg/kg-day F0 maternal exposure from GD6 to PND0, then F1	Significantly decreased serum PRL levels in females at 300000 µg/kg-day, no differences in females at lower doses, no differences in males at any dose	Delclos et al. (2014)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	exposure from PND1 to PND80 via oral gavage; F1 sacrificed at PND80		
Rat, SD, male, 5 per group	*In utero*, lactation. 0, 50, 100, or 200 ml/kg-day F0 maternal exposure from GD0 to PND20 via oral gavage; F1 sacrificed at PND20	Significantly increased serum PRL levels in male offspring at PND20 at 200 mg/kg dose, significantly increased PRL levels in dams at 200 mg/kg	Lü and Zhan (2010)
Rat, SD albino, female, 5 per group	Adult. 0, 20 µg, 20 mg, or 200 mg/kg bw 3 times/week for 6 weeks via oral gavage	Significantly increased serum PRL levels at all doses	Osman et al. (2021)
Rat, ovariectomized Wistar, female, 6 per group	Adult. 0 or 10 mg single *s.c.* injection, sacrificed 24 hours later	No differences in serum PRL levels	Furuta et al. (2006)
Rat, ovariectomized Wistar, female, 6 per group	Adult. 0, 11, 78, 128, or 250 mg/kg-day for 7 days via *s.c.* injection	Significantly increased serum PRL levels at 128 and 250 mg/kg-day doses	Goloubkova et al. (2000)
Rat, Wistar, female, 10 per group	Adult. 0, 5, 50, 300, 600, or 800 mg/kg-week for 3	Significantly and dose-dependently decreased serum PRL levels at 50 mg/kg-week and above, no significant differences in cesarean phase females at	Srivastava and Dhagga (2019)

Species, strain, sex, group size	Life stage, dose, duration, and regime	Results	Reference
	months via oral administration	45 days or 90 days or full-term females at 5 mg/kg-week	
Rat, unspecified albino, male, 10 per group	Adult. 0 or 1.2 mg/kg 6 days/week for 3 weeks via oral gavage	Significantly increased serum PRL levels	Mahmoud et al. (2019)

Section J7 Other nuclear receptors

Table J7.1 Effects of BPA exposure on PPARα in human cells *in vitro*

Cell type/system	BPA concentration (μM), duration	Results	Reference
Liver: human hepatoma Huh-7-PPRE-Luc cells	0, 0.1, 1, 10, or 100 μM for 24 hours	10 and 100 μM BPA induced a significant increase of PPRE-luciferase activity[a]	Wang et al. (2010)

[a] PPRE is an indicator of PPARα, PPARβ/δ, or PPARγ activation. PPRE results are reported for each of the three PPAR subtypes.

Table J7.2 Effects of BPA exposure on PPARα in rodent studies *in vivo* (ordered by species, strain, and life stage)

Species and strain, sex, group size	Life stage of exposure, dosing regimen, duration, route	Results	Reference
C57BL/6J mice (F1), male, 15–22 per group	*In utero*. 0 or 1 µg/kg-day F0 maternal exposure from embryonic day 7.5–16.5 via oral gavage; F1 sacrificed at 14 weeks	Significant decrease in PPARα mRNA levels in livers of male offspring	Long et al. (2021)
Swiss albino mice, male, 6 per group	Adult. 0, 4, 8, or 16 mg/kg BPA for 14 days via intraperitoneal (i.p.) injection	Liver: significant increase in PPARα mRNA and protein levels in all treated groups. Testes: significant increase in PPARα mRNA levels in all treated groups [non-monotonic], with significant increases in PPARα protein levels in 4 and 8 mg/kg dose groups and a significant decrease in 16 mg/kg dose group.	Sharma et al. (2019)
Albino rats, female, 6 per group	Juvenile (7 weeks of age) to adult. 150 mg/kg-day BPA in corn oil for 4 weeks via i.p. injection	Significant decrease in PPARα protein levels in liver	Thabet et al. (2020)
SD rats (F1), female, 9–10 per group)	*In utero*, lactation. 0 or 1 mg/l F0 maternal exposure from GD6 through lactation (PND21) via drinking water; F1 sacrificed PND21	No change in PPARα mRNA levels in livers of female offspring	Somm et al. (2009)

Species and strain, sex, group size	Life stage of exposure, dosing regimen, duration, route	Results	Reference
SD rats (F1), male, 8 per group	*In utero*, lactation. 0 or 50 µg/kg-day F0 maternal exposure during pregnancy and lactation; F1 sacrificed at 16 weeks	Significant decrease in PPARα mRNA levels in kidneys of male offspring	Hsu et al. (2019)

Table J7.3 Effects of BPA exposure on PPARα in non-human mammalian studies *in vitro*

Species/Cell line	BPA concentration, duration	Observation	Reference
Mouse, Leydig tumor cells, MA-10	1 nM for 24 hours	Significantly increased PPARα protein levels	Gorowska-Wojtowicz et al. (2019)
Rat, hepatoma cells, FaO	0.001, 0.01, 0.1, or 1 µM for 24 hours	Significantly decreased PPARα mRNA levels at 1 µM	Grasselli et al. (2013)

Table J7.4 Effects of BPA exposure on PPARγ in human cells *in vitro*[16] (ordered by tissue type [alphabetical, with primary cells listed first], followed by transfected animal cells)

Cell type/system	BPA concentration (μM), duration	Results	Reference
Adipose: primary human preadipocytes	25, 50 μM [reported as 4 days in text, 6 days in figure legend]	50 μM significantly increased PPARγ mRNA expression	Boucher et al. (2014)
Adipose: omental adipose tissue explants, obtained from biopsies of children undergoing abdominal surgery	0.01, 1, 80 μM for 24 hours	Significantly increased mRNA expression of PPARγ at all concentrations	Wang et al. (2013a)
Adipose: human adipose stromal/stem cells (ASCs)	1 μM for 7, 14, or 21 days	Significantly increased mRNA expression of PPARγ at 7 days; no induction at 14 or 21 days	Ohlstein et al. (2014)
Adipose: human ASCs (authors defined ASC as adipose-derived mesenchymal stem cells)	0.0001, 0.01 μM for 14 days	Significantly increased mRNA expression of PPARγ (0.001 μM at 1 or 3 days; 0.01 μM at 6 days)	Salehpour et al. (2020)
Adipose: human visceral preadipocytes (HPA-v)	0.01, 1, 80 μM for 24 hours starting at day 0 or for 14 days of differentiation	Significantly increased mRNA expression of PPARγ at all concentrations	Wang et al. (2013a)
Bone: PPARγ$_2$-CALUX cell line (human osteosarcoma (U2OS) cells transfected with an expression vector for PPARγ2)	0.3–250 μM for 24 hours	No PPARγ agonist activity with or without the addition of S9. Weak PPARγ antagonist activity with and without S9	Dusserre et al. (2018)

[16] One study, Chamorro-Garcia et al. (2012), used African green monkey kidney fibroblast-like cells transfected with human PPARγ

Cell type/system	BPA concentration (μM), duration	Results	Reference
Bone: PPARγ CALUX cell line (U2OS cells transfected with human PPARγ)	1, 3, 10, 50 μM for 24 hours	Weak but statistically significant activation of PPARγ in 1, 10, and 50 μM dose groups	(Pereira-Fernandes et al. 2013)
Bone: U2OS cells transfected with human PPARγ2	1, 10, 100, 1000 μM for 24 or 48 hours	Weak (relative increase was >10% but < 50%) activation of PPARγ. No PPARγ antagonistic activity	(Simon et al. 2016)
Bone marrow: human bone marrow-derived mesenchymal stromal stem cells (hMSCs)	0.1 μM for 14 days	No change in PPARγ mRNA levels	Chamorro-Garci-a et al. (2012)
Kidney: human embryonic kidney 293H cells transfected with PPARγ-UAS-bla	1 – 100 μM for 24 hours	BPA inhibited PPARγ activation induced by rosiglitazone	Schaffert et al. (2021)
Kidney: human embryonic kidney HEK293T cells transfected with a PPAR response element (PPRE) X3-TK-luc	1, 10, 100 μM for 12 hours	100 μM BPA caused a significant increase of PPRE-luciferase activity[a]	Gao et al. (2020b)
Liver: L02 cells (normal human liver cells) transfected with a control plasmid	1, 10 μM for 48 hours	Significantly induced mRNA expression of PPARγ. Protein expression of PPARγ was increased but not quantified.	Long et al. (2021)
Liver: human hepatoma HepG2 cells transfected with Gal4 reporter DNA binding domain (DBD) linked to the ligand binding domain (LBD) of PPARγ	5 μM for 24 hours	Slight, non-significant induction of reporter activity	Sui et al. (2012)

Cell type/system	BPA concentration (μM), duration	Results	Reference
Liver: human hepatoma Huh-7-PPRE-Luc cells	0, 0.1, 1, 10, or 100 μM for 24 hours	10 and 100 μM BPA induced a significant increase of PPRE-luciferase activity[a]	Wang et al. (2010)
Macrophages: THP-1 macrophages transfected with PPRE X3-TK-luc	1, 10, 100 μM for 12 hours	100 μM BPA induced a significant increase of PPRE-luciferase activity[a]	Gao et al. (2020b)
Monocytes: wild-type (WT, i.e., PPARγ+/+) human monocyte-like THP-1 cells	100 μM for 12 hours	Significantly induced PPARγ mRNA expression in WT cells (based on visual inspection of Figure 2D by OEHHA)	Gao et al. (2020b)
Ovary: human ovarian serous carcinoma cell line OVCAR-3	0.01 μM for 24 hours	No alterations in PPARγ mRNA expression	Hoffmann et al. (2017)
Ovary: human ovarian cumulus granulosa cells (hCGC)	100 μM for 6 or 48 hours	Significantly induced PPARγ mRNA expression after 6 and 48 hours of exposure	Pogrmic-Majkic et al. (2019)
Uterus: cultured human endometrial stromal fibroblasts from 8 hysterectomy specimens	5, 25 μM for 48 hours	No effect on PPARγ expression (data not shown by authors)	Aghajanova and Giudice (2011)
Animal cells transfected with human PPAR: COS-7 cells (African green monkey kidney fibroblast-like cells) transiently transfected with human PPARγ	0.0001–10 μM for 24 hours	No activation or antagonism of PPARγ	Chamorro-Garci-a et al. (2012)

Table J7.5 Effects of BPA exposure on PPARγ in rodents *in vivo* (ordered by species, strain, and life stage)

Species and strain, sex, group size	Life stage of exposure, route, duration, dosing regimen	Results	Reference
C57BL/6J mice (F1), male and female, 15–22 per group	*In utero*. 0 or 1 µg/kg-day F0 maternal exposure from embryonic day 7.5–16.5 via oral gavage; F1 sacrificed at 14 weeks	Significant increase in PPARγ mRNA and protein expression in livers of male and female offspring	Long et al. (2021)
C57Bl/6J mice (F1), male, 16–19 per group	*In utero*, lactation, postweaning to adult. 0, 0.5, 5, 50, or 500 µg/kg-day via oral gavage. F0 maternal exposure from 2nd week of pregnancy through lactation; F1 exposure from 21 days old until sacrifice at 140 days	Significant increase in PPARγ mRNA levels in livers of male offspring in 0.5 and 5 µg/kg-day dose groups. Slight, non-significant increase in PPARγ mRNA levels in epididymal fat.	Biasiotto et al. (2016)
C57BL/6 mice, female, 6 per group	Juvenile (5 weeks of age) to adult. 0, 50, or 5000 µg/kg-day for 10 weeks via drinking water	Increase [not statistically significant] in PPARγ mRNA levels in liver. Significant increases in the mRNA expression of two PPARγ target genes, FABP4 and LXRα.	Gao et al. (2020b)
ICR (CD-1) mice, female, 10 per group	Adult. 0 or 100 mg/kg single *i.p*. injection on day 1; sacrificed on day 13	Significantly increased PPARγ mRNA levels in liver. Relative mRNA expression level in the BPA-treated group was increased 3.8-fold when normalized to ribosomal protein S29mRNA levels and 6-fold when normalized to β-actin mRNA levels.	Arroyo-Salgado et al. (2018)
Swiss albino mice, male, 6 per group	Adult.	Significant increase in PPARγ mRNA and protein levels in livers in all treated groups. Significant increase in PPARγ	Sharma et al. (2019)

Species and strain, sex, group size	Life stage of exposure, route, duration, dosing regimen	Results	Reference
	0, 4, 8, or 16 mg/kg BPA for 14 days by intraperitoneal (i.p.) injection	mRNA levels in testes in all treated groups. Significant increase in PPARγ protein levels in testes in 4 and 8 mg/kg dose groups; significant decrease in 16 mg/kg dose group.	
Sprague-Dawley (SD) rats (F1), female, 9–10 per group)	*In utero*, lactation. 0 or 1 mg/l F0 maternal exposure from GD6 through lactation (PND21) via drinking water; F1 sacrificed PND21	Significantly increased PPARγ mRNA levels in parametrial white adipose tissue in female offspring	Somm et al. (2009)
SD rats (F1), female, 4 per group	*In utero*, lactation. 0, 1, or 10 µg/ml F0 maternal exposure from GD6 through lactation via drinking water; F1 sacrificed PND50	Significant dose-dependent decrease in PPARγ mRNA and protein levels in perigonadal and perirenal adipose tissue in female offspring	Zhang et al. (2014)
SD rats, female, 6–8 per group	Adult. 0 or 2.5 µg/kg-day for 30 days before pregnancy and first 20 days of pregnancy via drinking water; sacrificed GD20	Significantly decreased PPARγ mRNA levels in uterine arteries of pregnant rats	Barberio et al. (2021)
Wistar rats, male, 5 per group	Adult. 0 or 406 mg/kg-day for 28 days via oral gavage	Significantly increased PPARγ mRNA in pancreatic islets	Rahmani et al. (2020)

Table J7.6 Effects of BPA exposure on PPARγ in non-human mammalian studies *in vitro* (ordered by species, cell type, cell line)

Species, cell type, cell line	BPA concentration, duration	Observation	Reference
Mouse, bone marrow, mesenchymal stromal stem cells (mMSCs)	100 nM for 14 days differentiation	No significant effect on PPARγ2 mRNA levels	Chamorro-Garci-a et al. (2012)
Mouse, fibroblasts, NIH3T3	1 nM for 8 days before induction of adipogenesis and during differentiation (16 days total)	Significantly increased PPARγ mRNA levels throughout differentiation (on day 0, 2, 4, and 8)	Longo et al. (2020)
Mouse, hepatoma cells, H1L7.5c1 (derived from hepa1c1c7 cells)	0.001 to 1 mM for 24 hours	Activated PPARγ in luciferase reporter gene assay	Simon et al. (2016)
Mouse, hypothalamic neurons, mHypoA-POMC/GFP-2 and mHypoE-43/5 cell lines	100 μM for 4 hours	Significantly increased PPARγ mRNA levels in both cell lines	Salehi et al. (2019)
Mouse, Leydig tumor cells, MA-10	1 nM for 24 hours	Significantly decreased PPARγ protein levels	Gorowska-Wojtowicz et al. (2019)
Mouse, preadipocytes, 3T3-L1	0.01 to 25 μM for up to 6 days	Significantly increased PPARγ mRNA at 25 μM at day 2 and 6	Ahmed and Atlas (2016)
Mouse, preadipocytes, 3T3-L1	1 nM for 3 weeks (2 weeks before adipogenesis and throughout differentiation)	Significantly increased PPARγ mRNA at day 8 of adipogenesis and protein levels at day 4 and 8 of adipogenesis (PPARγ expression data only available for day 4 and 8)	Ariemma et al. (2016)

Species, cell type, cell line	BPA concentration, duration	Observation	Reference
Mouse, preadipocytes, 3T3-L1	0.1, 1, 10 nM for 24 or 48 hours	No significant effect on PPARγ mRNA levels after 24 or 48 hours	Atlas et al. (2014)
Mouse, preadipocytes, 3T3-L1	1pM, 1nM for 10 days after differentiation	Significantly increased PPARγ2 mRNA levels at 1 pM, but not 1 nM	Héliès-Toussaint et al. (2014)
Mouse, preadipocytes, 3T3-L1	1 nM for 8 days before induction of adipogenesis and during differentiation (16 days total)	Significantly increased PPARγ mRNA levels at day 4 during clonal expansion and terminal differentiation, but not at day 2 or 8	Longo et al. (2020)
Mouse, preadipocytes, 3T3-L1	80 µM for 3 or 8 days	Significantly increased PPARγ2 mRNA levels on day 8, but not day 3.	Phrakonkham et al. (2008)
Mouse, preadipocytes, 3T3-L1	10^{-15} M [duration not reported]	Significantly increased PPARγ mRNA expression	Zhou et al. (2017a) [article in Chinese, see Fig. 6B]
Mouse, preadipocytes, 3T3-L1, transfected with PPRE-tK-luc	0, 10, 50, 80 µM for 48 hours	Significantly increased PPRE-luciferase activity at 80 µM[a]	Biasiotto et al. (2016)
Mouse, preadipocytes, 3T3-L1, transfected with PPARγ-Luc	1 µM for 24 hours	Did not significantly increase PPRE-luciferase activity[a]	Sargis et al. (2010)
Rat, hepatoma cells, FaO	300 ng/ml for 24 hours	Significantly decreased PPARγ mRNA levels	Grasselli et al. (2013)
African green monkey, kidney fibroblast-like cells, COS-7, transfected with polar bear PPARγ	Up to 2.5×10^{-5} M for agonist assay or 5×10^{-5} M for antagonist assay	Significant antagonistic activity towards PPARγ; IC50 value of 4.61×10^{-5} M. No agonist activity	Routti et al. (2016)
African green monkey, kidney fibroblast-like	0.1–50 µM for 24 hours	Significantly increased PPRE luciferase activity at 25 and 50 µM[a]	Ahmed and Atlas (2016)

Species, cell type, cell line	BPA concentration, duration	Observation	Reference
cells, COS-7, transfected with mouse PPARγ, mouse RXR, and PPRE-luc			

[a] PPRE is an indicator of PPARα, PPARβ/δ, or PPARγ activation. PPRE results are reported for each of the three PPAR subtypes.

Table J7.7 Effects of BPA exposure on AhR in human cells *in vitro* (ordered by tissue type, with primary cells listed first)

Cell type/system	BPA concentration, duration	Results	Reference
Liver: primary human hepatocytes from 3 donors: LH50, LH51, and LH52	10, 100 μM for 24 hours (mRNA) or 48 hours (protein)	10 μM BPA slightly increased AhR mRNA levels above vehicle control in LH51 and decreased levels in LH50 and LH52. 100 μM BPA decreased AhR mRNA in LH50 and had no change in the other 2 donors. 10 and 100 μM BPA for 48 hours increased AhR protein levels compared to vehicle controls in LH51. [statistical significance not reported]	Vrzal et al. (2015)
Liver: human hepatoma HepG2-Luc cells (HepG2 cells stably transfected with the ptKLuc vector harboring four dioxin-responsive elements upstream of the thymidine kinase promoter and the luciferase gene)	Up to 40 μM for 24 hours	No activation of AhR	Doan et al. (2020)

Cell type/system	BPA concentration, duration	Results	Reference
Liver: human HepG2 cells transfected with AhR (AZ-AhR)	10, 25, 50, 75, 100 µM for 24 hours	Significantly induced AhR-mediated luciferase activity with a dose-dependent trend [cell viability was significantly decreased at 100 µM]	Vrzal et al. (2015)
Liver: human HepG2 cells	0.001, 0.01, 0.1 µM for 48 hours	Dose-dependent increased transcription and protein expression of AhR (statistically significant increases of mRNA at 0.01 an 0.1 µM; statistically significant increases of protein at all concentrations)	Yu et al. (2021)
Mammary gland: T47-D-Luc cells (T47-D cells stably transfected with the ptKLuc vector harboring four dioxin-responsive elements upstream of the thymidine kinase promoter and the luciferase gene)	Up to 40 µM for 24 hours	No activation of AhR	Doan et al. (2020)

Table J7.8 Effects of BPA exposure on AhR in rodents *in vivo* (ordered by species, strain, and life stage)

Species and strain, sex, group size	Life stage of exposure, route, duration, dosing regimen	Results	Reference
C57BL/6 mice, male, 7 per group	*In utero*, lactation. 0, 0.2, or 2 µg/ml F0 maternal exposure from gestation day (GD) 6 through lactation via drinking water; F1 sacrificed postnatal day (PND) 49	Significantly increased AhR protein levels in testis of male offspring at 2 µg/ml	Meng et al. (2018)

Species and strain, sex, group size	Life stage of exposure, route, duration, dosing regimen	Results	Reference
C57BL/6 mice, male, 10 per group	*In utero*, lactation, ± postweaning to adult. 0, 0.2, or 2 µg/ml perinatal exposure from GD6 to PND21, with or without 0.2 µg/ml postweaning exposure until PND51 via drinking water	Significant dose-dependent increase in AhR protein expression in spleens of male offspring exposed only perinatally or exposed both perinatally and post-weaning	Gao et al. (2020a)
CD-1 mice, female, 5 per group	*In utero*. 0, 0.5, or 50 mg/kg-day bw F0 maternal exposure from GD1 to GD11 via gavage; sacrificed GD12	Non-statistically significantly decreased AhR mRNA expression at 0.5 mg/kg-day and increased at 50 mg/kg-day in placenta	Tait et al. (2015)
ICR mouse embryos, male and female, 12 per group	*In utero*. 0, 0.02, 2, 200 or 20000 µg/kg-day F0 maternal exposure from GD6.5 to GD13 or GD17.5 via oral gavage	Significantly increased AhR mRNA expression in cerebra and cerebella in GD14.5 and GD18.5 male and female embryos at 0.02, 200, or 20000 µg/kg [no effect in cerebra of GD14.5 females at 200 µg/kg]; increased AhR mRNA levels in testes and ovaries at 0.02 and 20000 µg/kg at GD14.5 and 0.02, 2, or 200 µg/kg at GD18.5	Nishizawa et al. (2005)
SD rats, male, 8 per group	*In utero*, lactation. 0 or 50 µg/kg-day F0 maternal exposure during pregnancy and lactation via oral administration; male F1 rats sacrificed at age 16 weeks	Significantly increased AhR protein levels in kidneys of male offspring	Hsu et al. (2019)

Table J7.9 Effects of BPA exposure on AhR in non-human mammalian studies *in vitro* (ordered by species, cell type, cell line)

Cell type/system	BPA concentration, duration	Observation	Reference
Mouse, hepatoma cells, Hepa1.12cR, transfected with AhR-luciferase reporter gene	10^{-8} to 10^{-4} M for 24 hours	Inhibited *AhR*-luciferase reporter gene activity at Lowest effect concentration (LOEC): 5.0×10^{-5} M Maximal effect concentration (MOEC): 1.0×10^{-4} M	Bonefeld-Jorgensen et al. (2007)
Mouse, hepatoma cells, Hepa1.12cR, transfected with AhR-luciferase reporter gene	10^{-4} to 10^{-5} M	Borderline AhR agonism at 10^{-5} M, antagonized 60 pM TCDD-induced AhR activity to 44% relative to controls	Kruger et al. (2008)
Mouse, hepatoma cells, H1L7.5c1 (derived from hepa1c1c7 cells)	0.001 to 1 mM for 24 hours	No effect on *AhR* luciferase reporter gene assay	Simon et al. (2016)
Rat, hepatoma cells, H4IIE, transfected with dioxin response elements (DREs) upstream of Cyp1a1 gene	1 to 40 µM for 24 hours	No response at concentrations tested	Doan et al. (2020)

Table J7.10 Effects of BPA exposure on PXR in human cells *in vitro* (ordered by tissue type, with primary cells listed first and transfected animal cells last)

Cell type/system	BPA concentration, duration	Results	Reference
Bone: human osteoblast cells (hFOB and MG-63 cell lines) transfected with a plasmid	0.1, 1, 10 µM [duration not specified]	Significantly increased PXR transcriptional activity in both cell lines	Miki et al. (2016)

Cell type/system	BPA concentration, duration	Results	Reference
containing CYP3A4 promoter (XRE) cDNA (referred to as SXR by study authors)			
Kidney: human embryonic kidney HEK293T cells transfected with PXR	0.1, 1, 10, 25 μM for 24 hours	Significantly induced PXR-mediated luciferase activity at 10 and 25 μM	Vrzal et al. (2015)
Liver: primary human hepatocytes from 3 donors: LH50, LH51, and LH52	10, 100 μM for 24 hours	10 μM BPA increased PXR mRNA levels above vehicle control in LH51 and LH52, decreased in LH50; 100 μM BPA decreased PXR mRNA levels in LH50, slight decrease in LH52, no change in LH51. 10 and 100 μM BPA increased PXR protein levels in LH51. 100 μM BPA increased PXR target CYP3A4 mRNA in all 3 donors, and CYP3A4 protein in LH51. [statistical significance not reported].	Vrzal et al. (2015)
Liver: human hepatoma cells transfected with hPXR and CYP3A4 promoter (DPX2 cells)	10, 25, 50 μM for 24 hours	Activation of PXR demonstrated through induction of luciferase activity driven by the CYP3A4 promoter	Kuzbari et al. (2013)
Liver: human hepatoma (HepG2) cells transfected with hPXR	1, 5, 10, 20 μM for 24 hours	Significantly induced PXR activity at concentrations ≥ 5 μM	Sui et al. (2012)
Liver: human HepG2 cells transfected with hPXR (referred to as SXR by study authors)	0.1, 1, 10 μM for 24 hours	Stimulated PXR-mediated transcription on CYP3A4 promoter at 10 μM	Takeshita et al. (2001)

Cell type/system	BPA concentration, duration	Results	Reference
Liver: human HepG2 cells	0.001, 0.01, 0.1 μM for 48 hours	Significantly increased mRNA levels of PXR and its target CYP3A4 at all 3 concentrations; significantly increased PXR protein levels at 0.001 μM and CYP3A4 levels at all 3 concentrations	Yu et al. (2021)
Uterus: human cervical HeLa cells transfected with human PXR (HG5LN-hPXR cell line)	A range of concentrations for 16 hours [concentrations not reported]	PXR reporter gene luciferase activity was increased up to 37% of the activity induced by the positive control (PXR agonist SR12813 at 3 μM). This maximum increase was reached at 10 μM	Creusot et al. (2010)
Uterus: HG5LN cells expressing GAL4(DBD)-PXR(LBD)	0.001–10 μM for 16 hours	Activated PXR up to 28% of that induced by 3 μM SR12813 (calculated EC50: 93.7 μM)	Grimaldi et al. (2019)
Uterus: HG5LN-hPXR cell line	0.001–10 μM for 16 hours	10 μM BPA statistically significantly increased activation of PXR compared to vehicle control; activation was approximately 40% of that induced by 3 μM SR12813	Molina-Molina et al. (2013)
Uterus: human endometrial adenocarcinoma (HEC-1) cells	1 μM for 36 hours	Induced expression of PXR mRNA and protein and activated PXR-mediated transcription	Masuyama et al. (2005)
Animal cells transfected with human PXR: COS-7 cells (African green monkey kidney fibroblast-like cells) transfected with human CMVs-PXR	0.1 and 10 μM for 24 hours	Significantly increased PXR luciferase activity at 10 μM	DeKeyser et al. (2011)

Table J7.11 Effects of BPA exposure on PXR in non-human mammalian studies *in vitro*

Cell type/system	BPA concentration, duration	Results	Reference
African green monkey, kidney fibroblast-like cells, COS-7, transfected with CYP3A1 reporter gene with PXR expression plasmid	10 pM to 10 μM for 36 hours	Did not affect PXR-mediated transcription of *Cyp3a1* reporter gene	Masuyama et al. (2000)
Rat, hepatoma cells, FAO rPXR, expressing rat PXR and CYP3A1 promoter	1 to 50 μM for 24 hours	Did not increase luciferase activity of rat PXR	Kuzbari et al. (2013)

Table J7.12 Effects of BPA exposure on CAR, GR, LXR, PPARβ/δ, RAR, and RXR, in human cells *in vitro* (ordered by receptor, tissue type, with primary cells listed first and transfected animal cells last)

Nuclear receptor	Cell type/system	BPA concentration, duration	Results	Reference
CAR	Liver: primary human hepatocytes from 3 donors: LH50, LH51, and LH52	10, 100 μM for 24 hours	10 μM BPA increased CAR mRNA levels in LH51 and LH52 and decreased levels in LH50; 100 μM BPA decreased CAR mRNA levels in LH50 and LH51 and increased levels in LH52 [statistical significance not reported]	Vrzal et al. (2015)
CAR	Liver: human HepG2 cells	0.001, 0.01, 0.1 μM for 48 hours	No change in CAR transcription levels; significantly decreased CAR protein levels	Yu et al. (2021)

Nuclear receptor	Cell type/system	BPA concentration, duration	Results	Reference
CAR (CAR1, CAR2, and CAR3	Animal cells transfected with human CAR: COS-1 cells (African green monkey kidney fibroblast-like cells) transfected with human CMV2-CAR1, CMV2-CAR2, or CMV2-CAR3	0.1 or 10 μM for 24 hours	Increased CAR1 luciferase activity at 0.1 and 10 μM in the presence of ANDRO (a mouse CAR inverse agonist, used to decrease activity of constitutively expressed CAR1); no activity in CAR2; increased CAR3 luciferase activity at 10 μM	DeKeyser et al. (2011)
GR	Breast: human breast carcinoma MDA-kb2 cells	1, 10 μM for 24 hours	No agonistic or antagonistic activity towards GR	Kolšek et al. (2015)
GR	Breast: TGRM-Luc cells derived from human breast carcinoma T47-D cell line	1, 10, 100, 1000 μM for 24 or 48 hours	No agonistic or antagonistic activity towards GR	Simon et al. (2016)
GR	Liver: primary human hepatocytes from 3 donors: LH50 LH51, and LH52	10, 100 μM for 24 hours	10 μM BPA decreased GR mRNA levels in LH50 and LH52 and increased levels in LH51, 100 μM BPA decreased GR mRNA levels in LH50 and LH51 and increased levels in LH52 [statistical significance not reported]	Vrzal et al. (2015)
LXRα, RARα, RXR	Liver: human HepG2 cells transfected with RARα, RXR, LXRα, or	5 μM for 24 hours	No induction of activity for any receptors	Sui et al. (2012)
PPARβ/δ	Kidney: human HEK293 cells	0.1, 1, 10, 25, 50 μM for 24 hours	25 and 50 μM activated PPARβ/δ	Li et al. (2021b)

Nuclear receptor	Cell type/system	BPA concentration, duration	Results	Reference
PPARβ/δ	Ovary: human COV434 cells (derived from granulosa cell tumor)	0.001, 0.1, 10 μM for 24 or 48 hours	No effect on mRNA expression of PPARβ/δ	Mlynarcikova and Scsukova (2020)
PPARβ/δ	Liver: human hepatoma Huh-7-PPRE-Luc cells	0, 0.1, 1, 10, or 100 μM for 24 hours	10 and 100 μM BPA induced a significant increase of PPRE-luciferase activity[a]	Wang et al. (2010)
RXRα	Ovary: human COV434 cells (derived from granulosa cell tumor)	0.001, 0.1, 10 μM for 24 or 48 hours	No effect on mRNA expression of RXRα	Mlynarcikova and Scsukova (2020)
RXRα	Animal cells transfected with human PXR: COS-7 cells (African green monkey kidney fibroblast-like cells) transfected with human RXRα	0.001–10 μM [duration not specified]	No activation or antagonism	Chamorro-Garci-a et al. (2012)

[a] PPRE is an indicator of PPARα, PPARβ/δ, or PPARγ activation. PPRE results are reported for each of the three PPAR subtypes.

Table J7.13 Effects of BPA exposure on LXR, PPARβ, RAR, RoR, and RXR in rodents *in vivo* (ordered by receptor, species, strain, and life stage)

Nuclear receptor	Species and strain, sex, group size	Route, duration, dosing regimen	Results	Reference
LXR	C57BL/6 mice, male, 12 per group	Juvenile (6 weeks of age) to adult. 0, 1, 10, 50, or 250 μg/kg for 35 days via gavage	Significantly increased LXR mRNA levels in liver at 10 μg/kg (increases were higher at 50 and 250 μg/kg doses but not reported as significant by the authors)	Ji et al. (2020)

Nuclear receptor	Species and strain, sex, group size	Route, duration, dosing regimen	Results	Reference
LXRα	C57BL/6 mice, female, 6 per group	Juvenile (5 weeks of age) to adult. 0, 50, or 5000 µg/kg-day for 10 weeks via drinking water	Significantly increased LXRα mRNA levels in liver at both doses	Gao et al. (2020b)
LXRα	ICR mice, female, group sizes not reported	*In utero*. 2 µg/kg-day F0 maternal exposure from GD6.5 to GD17.5; sacrificed GD18.5	Increased mRNA levels of LXRα in placentae with male embryos, not detected in placentae with female embryos	Imanishi et al. (2003)
PPARβ	Swiss albino mice, male, 6 per group	Adult. 0, 4, 8, or 16 mg/kg BPA for 14 days by intraperitoneal (i.p.) injection	Significant increase in PPARβ mRNA and protein levels in livers in all treated groups. Significant increase in PPARβ mRNA levels in testes in all treated groups. Significant increase in PPARγ protein levels in testes in 4 and 8 mg/kg dose groups; significant decrease in 16 mg/kg dose group.	Sharma et al. (2019)
RARα	ICR mice embryos, male and female, 12 per group	*In utero*. 2 µg/kg-day F0 maternal exposure from GD6.5 to GD11.5, 13.5, 15.5, or 17.5 via oral administration	Increased RARα mRNA levels in male and female embryo cerebella at GD12.5, decreased mRNA levels in male and female cerebra at GD14.5, and decreased mRNA levels in testes of male embryos at GD14.5 and GD18.5	Nishizawa et al. (2003)
RARα	ICR mice embryos, male and female, 12 per group	*In utero*. 0, 0.02, 2, 200 or 20000 µg/kg-day F0 maternal exposure from GD6.5 to GD13 or 17.5 via oral administration	Significantly increased RARα mRNA expression in cerebra at GD14.5 and GD18.5 in male and female embryos at 200 or 20000 µg/kg; increased levels in cerebella in GD14.5 embryos at 0.02 µg/kg, GD18.5 embryos at 0.02, 200, or 20000 µg/kg; increased mRNA levels in ovaries in GD14.5 female embryos at	Nishizawa et al. (2005)

Nuclear receptor	Species and strain, sex, group size	Route, duration, dosing regimen	Results	Reference
			0.02, 200, or 20000 µg/kg, in testes in GD18.5 male embryos at 20000 µg/kg, and in ovarian tissues in female embryos at 20000 µg/kg	
Retinoic acid receptor-related orphan receptor γ (RoRγ)	ICR mice, female, group sizes not reported	*In utero*. 2 µg/kg-day F0 maternal exposure from GD6.5 to GD17.5; sacrificed GD18.5	Decreased levels of RoRγ mRNA in placentae with female embryos, not detected in placentae with male embryos	Imanishi et al. (2003)
RXRα	ICR mice embryos, male and female, 12 per group	*In utero*. 0, 0.02, 2, 200 or 20000 µg/kg-day F0 maternal exposure from GD6.5 to GD13 or 17.5 via oral administration	Significantly increased RXRα levels in cerebra and cerebella in GD14.5 male and female embryos at 0.02, 200, or 20000 µg/kg, and in cerebra in GD18.5 male and female embryos at 200 or 20000 µg/kg; increased levels in gonads in GD14.5 embryos at 20000 µg/kg and in GD18.5 embryos at 200 µg/kg	Nishizawa et al. (2005)
RXRα	ICR mice embryos, male and female, 12 per group	*In utero*. 2 µg/kg-day F0 maternal exposure from GD6.5 to GD11.5, 13.5, 15.5, or 17.5 via oral administration	Decreased RXRα mRNA levels in male cerebra and cerebella at GD12.5, decreased levels in female cerebella at GD12.5, 14.5, and 18.5, decreased levels in testes in male embryos and ovaries in female embryos at GD14.5.	Nishizawa et al. (2003)

Table J7.14 Effects of BPA exposure on GR, LXR, and PPARβ/δ in non-human mammalian studies *in vitro* (ordered by receptor, species, cell type, cell line)

Nuclear receptor	Cell type/system	Concentration, duration	Results	Reference
GR	Mouse, fibroblasts, NIH3T3, transfected with three glucocorticoid responsive elements: a synthetic glucocorticoid response element (3X-GRE), mouse mammary tumor virus (MMTV) promoter, or non-GRE containing glucocorticoid responsive C/EBPα promoter	1–1000 nM for 16 hours	Did not directly activate GR (as reflected by a lack of activity at these promoters)	Atlas et al. (2014)
GR	Mouse (C57BL/6), mammary organoids	1 nM or 1 μM for 72 hours	Did not significantly alter GR mRNA levels	Altamirano et al. (2020)
GR	Mouse, preadipocytes, 3T3-L1, transfected with GR-Luc (containing GRE)	1 μM for 24 hours	Significantly increased GR-luc activity	Sargis et al. (2010)
LXR (LXRα and LXRβ)	Mouse, macrophages, J774A.1	1 or 10 nM for 18 hours	Significantly increased LXRα mRNA and protein expression at 10 nM; No effect on LXRβ mRNA	Ampem et al. (2019)
PPARβ	Mouse, Leydig tumor cells, MA-10	1 nM for 24 hours	Significantly decreased PPARβ protein levels	Gorowska-Wojtowicz et al. (2019)
PPARδ	Rat, hepatoma cells, FaO	300 ng/ml for 24 hours	Significantly decreased PPARδ mRNA levels	Grasselli et al. (2013)

Table J7.15 Effects of BPA exposure on nuclear receptors in fish and other species *in vivo/ex vivo* (ordered by appearance in main text)

Receptor	Species	Concentration, duration	Results	Reference
PPARγ, PPARβ/δ, RXR	Gilthead sea bream *(Sparus aurata)* juveniles	5 or 50 mg/kg bw in feed for 21 days	Increased mRNA expression in the liver of PPARα (50 mg/kg bw), PPARγ and PPARβ (5 and 50 mg/kg bw), and RXR (5 mg/kg bw)	Maradonna et al. (2015)
AhR	Female zebrafish	15, 150, or 1500 µg/l for 28 days, then 0, 14, or 28 days in clean water	Dose-dependent increases in AhR1 mRNA expression in liver	Duan et al. (2013b)
PXR	Rare minnow *(Gobiocypris rarus)*	5, 15, 50 µg/l for 14 or 35 days	Females: significantly increased PXR mRNA levels at all concentrations after 14 days, significant increases at 5 or 50 µg/l after 35 days. Males: increased at 5 µg/l, decreased at 15 or 50 µg/l at 14 days; decreased at 5 or 15 µg/l after 35 days	Gao et al. (2014)
RXRγ	*Xenopus* tail culture	10^{-7}, 10^{-6}, 10^{-5} M for 5 days	Slight decrease in RXRγ mRNA levels [statistical significance not reported]	Iwamuro et al. (2006)
RXR	Freshwater snail (*Physa acuta)*	100 or 500 µg/l for up to 96 hours	Decreased RXR mRNA levels at 100 or 500 µg/l at 48 and 24 hours, respectively. Increased RXR mRNA levels at 500 µg/l after 96 hours	Morales et al. (2018)
GR	Rainbow trout (*Oncorhynchus mykiss*)	Oocytes exposed to 0.3, 3, or 30 µg/ml for 3 hours, then fertilized and larvae collected at 42- or 65-days post fertilization (dpf)	Significant increase in whole body GR protein levels in 65 dpf larvae of 30 µg/ml exposed oocytes	Birceanu et al. (2015)
Growth hormone receptor (GHR)	Black seabream (*Acanthopagrus schlegeli*) hepatocytes	1, 10, 100 nM or 1 µM	Decreased GHR1 mRNA levels between 1 nM to 1 µM and *ghr2* at 10 nM	Jiao and Cheng (2010)

APPENDIX K. KC10, ALTERS CELL PROLIFERATION, CELL DEATH OR NUTRIENT SUPPLY

List of studies not included in the review by Chapin et al. (2008) showing BPA-induced MCF-7 cell proliferation:

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Hess-Wilson JK, Boldison J, Weaver KE, Knudsen KE. 2006. Xenoestrogen action in breast cancer: impact on ER-dependent transcription and mitogenesis. Breast Cancer Res Treat 96:279-292.

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Lloyd V, Morse M, Purakal B, Parker J, Benard P, Crone M, et al. 2019. Hormone-Like Effects of Bisphenol A on p53 and Estrogen Receptor Alpha in Breast Cancer Cells. Biores Open Access 8:169-184.

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Molina-Molina JM, Amaya E, Grimaldi M, Sáenz JM, Real M, Fernández MF, et al. 2013. In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. Toxicol Appl Pharmacol 272:127-136.

Nakagawa Y, Suzuki T. 2001. Metabolism of bisphenol A in isolated rat hepatocytes and oestrogenic activity of a hydroxylated metabolite in MCF-7 human breast cancer cells. Xenobiotica 31:113-123.

Nakaya M, Onda H, Sasaki K, Yukiyoshi A, Tachibana H, Yamada K. 2007. Effect of royal jelly on bisphenol A-induced proliferation of human breast cancer cells. Biosci Biotechnol Biochem 71:253-255.

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