2026 Update: Proposal for development of hazard identification materials on *p,p′*-bisphenol chemicals to support consideration for listing by the DARTIC in 2027

OVERVIEW

p,p′-Bisphenol chemicals consist of *p,p′*-bisphenols and their derivatives, including ethers and esters. There are currently two *p,p′*-bisphenols on the Proposition 65 list for reproductive toxicity, bisphenol A (BPA) and bisphenol S (BPS).

BPA was listed for the female reproductive endpoint in 2015 (OEHHA 2015) and the developmental endpoint in 2020 (Notice of listing developmental endpoint for BPA). BPS was listed for the female reproductive endpoint in 2023 (OEHHA 2023), and for the male reproductive (OEHHA 2024) and developmental (OEHHA 2025a) endpoints in 2025. In October 2025, OEHHA presented an initial proposal for the development of hazard identification materials on *p,p′*-bisphenol chemicals (OEHHA 2025b) to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for advice and consultation.

As discussed with the DARTIC at their meeting in 2025, a growing number of *p,p′*-bisphenol chemicals in addition to BPA and BPS have evidence suggesting concerns for reproductive toxicity. The scientific literature pertaining to the reproductive toxicity of *p,p′*-bisphenol chemicals is large, and growing. This poses a challenge in bringing additional *p,p′*-bisphenol chemicals to the DARTIC for listing consideration in a timely manner that cannot be met by developing hazard identification documents (HID) on individual *p,p′*-bisphenol chemicals, one at a time. This document discusses the Office of Environmental Health Hazard Assessment's (OEHHA) proposed approach to address this challenge.

PROPOSAL

This document provides an update on OEHHA's proposed approach discussed in October 2025 with the DARTIC for developing hazard identification materials on *p,p′*-bisphenol chemicals. OEHHA expects to bring these chemicals to the DARTIC in 2027 for consideration for listing.

This updated proposal provides information on the chemical identity of *p,p′*-bisphenols and their derivatives included in the review, the systematic literature search for studies that assessed DART effects of individual *p,p′*-bisphenol chemicals, consideration of reviews and other documents on a specific chemical as an efficient alternative to tabulating large numbers of individual studies, the selection of a subset of specific

outcomes for a given toxicity endpoint, and the presentation and level of detail to be included in study tabulations.

DARTIC INPUT ON THE PROPOSAL

OEHHA is seeking the DARTIC's advice and consultation on this updated proposal at the Committee's June 18, 2026 meeting. Specifically, advice and consultation is sought on:

1. The updated approach to the chemical identity of *p,p'*-bisphenols and their derivatives
2. The proposed consideration of reviews and other documents on specific chemicals that have a large evidence base, as an efficient alternative to tabulating large numbers of individual study findings
3. The proposed focus on a limited number of selected outcomes per endpoint

P,P'-BISPHENOL CHEMICALS

Chemical identity

p,p'-Bisphenol chemicals include p,p'-bisphenols and p,p'-bisphenol derivatives. As shown in Figure 1, p,p'-bisphenols have the basic structure of two phenol groups, with the hydroxyl groups at the para positions, that are joined by a single bridging atom frequently a carbon or sulfur atom). Any substituent(s) can be attached to the bridging atom.

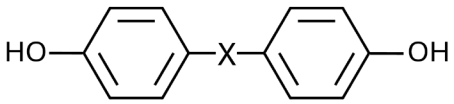

Figure 1. Representative structure of a *p,p'*-bisphenol.
X: represents a single atom (e.g., carbon or sulfur) linking two phenols and can have any substituent(s) attached to it.
Adapted from: *https://eur-lex.europa.eu/eli/reg/2024/3190/2026-02-23*

As shown in Figure 2, *p,p'*-bisphenol derivatives have one or more non-hydrogen substituents attached to either the six-carbon aromatic rings or the oxygens at the *para* positions.

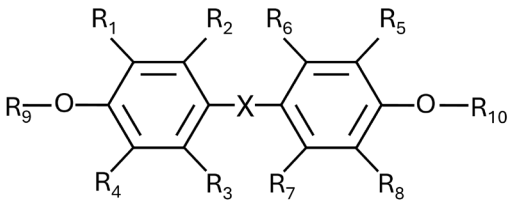

Figure 2. Representative structure of a *p,p′*-bisphenol derivative
X: represents a single atom linking two six-carbon aromatic rings and can have any substituent(s) attached to it.
$R_{1\text{-}10}$: represent substituents attached to the six-carbon aromatic rings and the oxygens at the *para* positions, at least one of which is not a hydrogen atom.
Adapted from: *https://eur-lex.europa.eu/eli/reg/2024/3190/2026-02-23*

Examples of *p,p′*-bisphenol derivatives include halogenated *p,p′*-bisphenols such as tetrabromobisphenol A (TBBPA) and *p,p′*-bisphenol ethers and esters.

An example of a *p,p′*-bisphenol ether is tetrabromobisphenol A bis(2,3-dibromopropyl) ether (TBBPA-DBPE), shown in Figure 3. An example of a *p,p′*-bisphenol ester is bisphenol A dimethacrylate (Bis-DMA), shown in Figure 4.

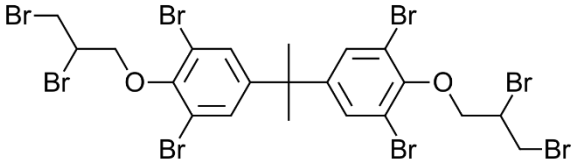

Figure 3. Structure of tetrabromobisphenol A bis(2,3-dibromopropyl) ether.

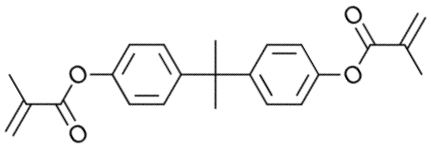

Figure 4. Structure of bisphenol A dimethacrylate.

Literature search update

OEHHA conducted a comprehensive literature search of three databases, PubMed, Embase, SciFinder-n, using search terms for *p,p′*-bisphenol chemicals and DART outcomes (for DART search terms see Appendix A in recent HIDs (OEHHA 2023, 2024, 2025a e.g., Evidence on the Developmental Toxicity of Bisphenol S). As shown in the

flow diagram (Figure 5) for the literature search and screening process, the number of references identified for screening was 33,304.

The populations, exposures, comparators, and outcomes (PECO) criteria (Table 1) and descriptions of supplemental material (Table 2) were informed by inclusion criteria used in hazard identification documents for BPS (OEHHA 2023, 2024, 2025a) .

Table 1. Populations, exposures, comparators, and outcomes (PECO) criteria

PECO element	Evidence
Population	Human: Any population and life stage (occupational or general population, including children, pregnant people, and other sensitive populations). Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages) and non-mammalian animal species of any life stage (e.g., zebrafish, *C. elegans*, chicken, drosophila).
Exposures	Chemical Forms *p,p′*-Bisphenol chemicals, i.e., *p,p′*-bisphenols and *p,p′*-bisphenol derivatives. Human: Exposure to *p,p′*-bisphenol chemicals irrespective of exposure route. Exposure is defined by measurement in individual-level biospecimens (e.g., urine, blood, placenta, cord blood, etc.). Pharmaceutical exposure will be accepted and treated as direct dose of chemicals. Indirect measurements of individual chemical exposures (e.g., dietary questionnaire) are not considered. Animal: Exposure to *p,p′*-bisphenol chemicals, irrespective of administration route, with defined dose or concentration. Studies involving exposures to mixtures will be included only if the mixtures consist of only of *p,p′*-bisphenol chemicals. Measurement of internal levels of the administered *p,p′*-bisphenol chemical in the organism is not required.
Comparators	Human: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of *p,p*'-bisphenol chemicals. Case reports and case series will be tracked as “potentially relevant supplemental information.” Animal: A concurrent control group exposed to vehicle-only treatment, if a vehicle was used. Studies with historical control groups will be tracked as “potentially relevant supplemental information” and when a vehicle was used, studies lacking a vehicle control will be excluded.
Outcomes	Developmental and Reproductive Toxicity (DART): Female reproductive toxicity, male reproductive toxicity, and developmental toxicity.

Table 2: Major categories of 'potentially relevant supplemental material'

Category	Evidence
Mechanistic considerations and other data relevant to DART	*In vivo, in vitro*, *ex vivo*, and in silico studies reporting measurements related to DART outcomes that inform the biological or chemical events associated with phenotypic effects, in both mammalian and non-mammalian model systems. Other studies with relevant molecular data and/or inform mechanisms of action will also be included. Studies where the chemical is used as a laboratory reagent generally need not be tagged (e.g., chemical probe used to measure antibody response).
Toxicokinetic data (ADME)	Studies designed to capture information regarding absorption, distribution, metabolism, and excretion, including toxicokinetic and classical pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) model studies. Studies describing metabolism in bacteria or model systems not applicable to humans or animals should not be tagged.
Exposure characteristics	Studies that inform understanding of the production and uses of *p,p'*-bisphenol chemicals, exposure sources, environmental sampling, biomarkers of exposure, and measured concentrations in humans (e.g., biomonitoring data).
Mixture studies	Studies involving exposures to mixtures will be included if the exposure includes exposure to any combination of *p,p'*-bisphenol chemicals only. This categorization generally does not apply to epidemiological studies where exposures are myriad, often uncontrolled, and exposure sources might be unclear.
Case reports or case series	Case reports describing DART outcomes after exposure will be tracked as potentially relevant supplemental information.
Reviews or other records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.
Unnamed reports (other)	Other records identified that have no citation information (typically identified during gray literature searches).

Following a systematic review approach, the PECO criteria and descriptions of supplemental material shown in Tables 1 and 2 were used to screen the literature identified through the comprehensive literature search. Two independent reviewers conducted the title and abstract-level screening of the literature search results using SWIFT-Active Screener a software application that uses machine learning to predict relevance of studies based on manual screening decisions (Howard et al. 2016). Studies meeting the PECO criteria or the descriptions of supplemental material were then screened by two independent reviewers at the full-text level using DistillerSR. Studies meeting PECO criteria were tagged by DART endpoints and outcomes assessed, and studies with potentially relevant supplemental data were tagged by type of supplemental material.

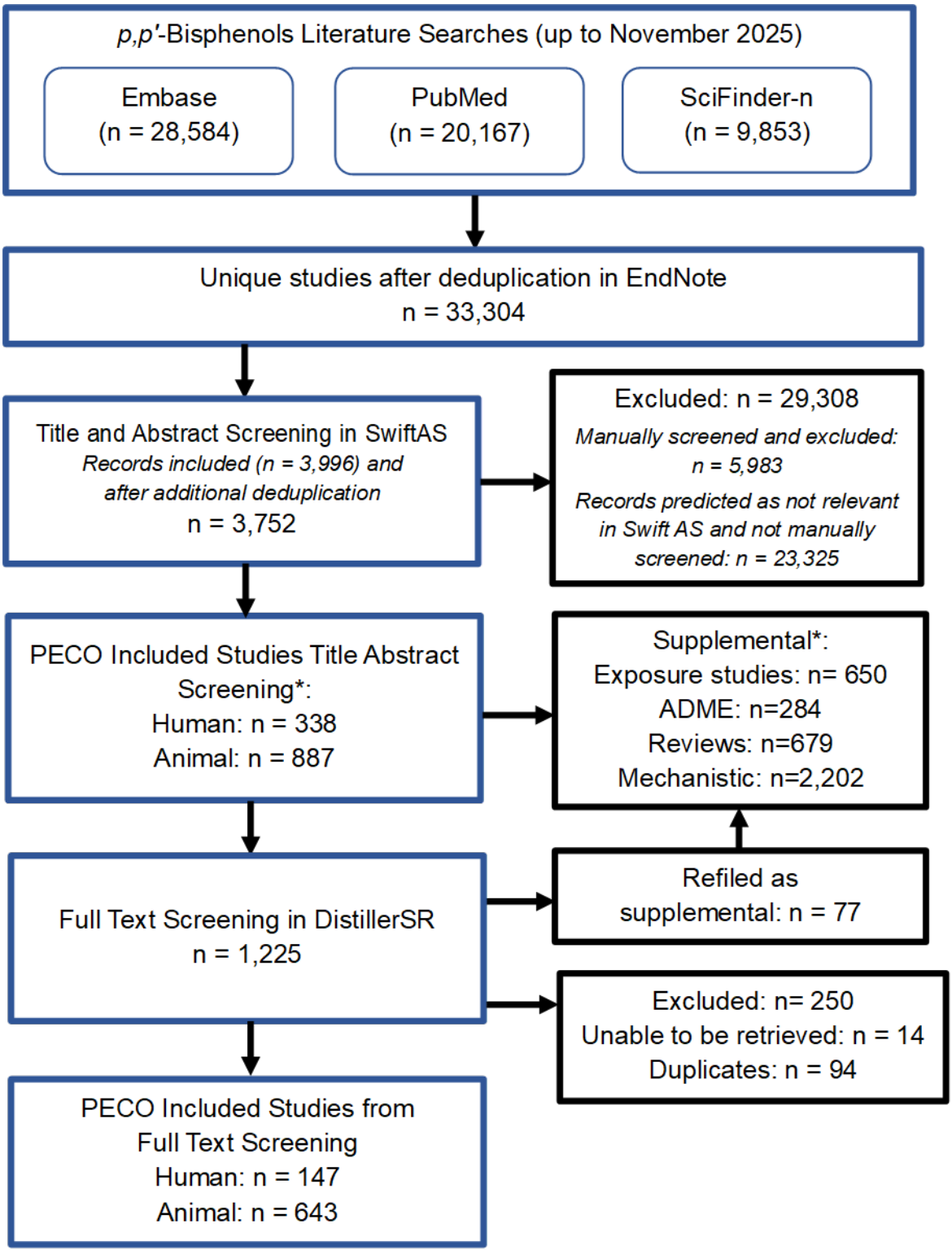

Figure 5. Literature search and screening flow diagram for p,p'-bisphenol chemicals and DART outcomes. *Not mutually exclusive between PECO and Supplemental.

Proposed scope and presentation of DART evidence

After completion of full text screening, 59 unique *p,p'*-bisphenol chemicals have been identified with information relevant to DART outcomes. Table 3 lists these *p,p'*-bisphenol chemicals and indicates how many studies meeting PECO criteria were identified for each, as well as how many were studies of exposed humans and how many were animal studies. As shown in Table 3, four *p,p'*-bisphenol chemicals have more than 100 studies relevant to DART outcomes, and forty-four have less than 10 studies.

For those chemicals with large numbers of studies (e.g., more than 50) relevant to DART outcomes, consideration will be given to the use of existing reviews and other documents, when available and appropriate, as an alternative to tabulating individual studies. These existing documents may include, for example, reports or reviews from government entities such as the US Environmental Protection Agency, the National Toxicology Program, the Agency for Toxic Substances and Disease Registry (ATSDR), and the European Chemicals Agency (ECHA). When applicable, OEHHA will provide the DARTIC with the source documents and referenced studies, as well as studies and reviews identified and included during full-text screening.

For example, in the case of methoxychlor, which has 177 studies that meet the PECO criteria (see Table 3), OEHHA proposes the following alternative to tabulating this large number of studies. Specifically, OEHHA proposes to rely on the ATSDR's Toxicological Profile on Methoxychlor (ATSDR 2002), and the "Proposal to List Methoxychlor in Annex A to the Stockholm Convention on Persistent Organic Pollutants (POPs)" (Stockholm Convention 2019) as an efficient way to summarize the large evidence base relevant to the female reproductive, male reproductive, and developmental toxicities of this chemical.

Table 3. *p,p'*-Bisphenol chemicals with information relevant to DART effects identified after completion of full-text screening. The number of studies (total, human, animal) meeting the PECO criteria are shown for each chemical, ordered from largest to smallest number of studies.

Chemical name	Abbreviation	CASRN*	Total Studies	Human Studies	Animal Studies
Bisphenol F	BPF	620-92-8	205	108	97
Methoxychlor	MXC	72-43-5	177	6	171
Tetrabromobisphenol A	TBBPA	79-94-7	138	11	127
Bisphenol AF	BPAF	1478-61-1	130	27	103
Bisphenol B	BPB	77-40-7	59	22	37
Benzophenone-2	BP-2	131-55-5	42	14	28
Tetrachlorobisphenol A	TCBPA or Cl4BPA	79-95-8	28	10	18
Bisphenol AP	BPAP	1571-75-1	26	15	11
Bisphenol Z	BPZ	843-55-0	22	12	10
Fluorene-9-bisphenol	BHPF or BPFL	3236-71-3	22	4	18
Cyclofenil	F-6066	2624-43-3	21	2	19
Bisphenol E	BPE	2081-08-5	17	2	15
Bisphenol C	BPC	79-97-0	14	3	11
Bisphenol A diglycidyl ether	BADGE or DGEBA	1675-54-3	13	1	12
Tetrabromobisphenol A bis(2,3-dibromopropyl ether)	TBBPA-DBPE or TBBPA-BDBPE	21850-44-2	12	0	12
Tetrabromobisphenol A bis(2-hydroxyethyl) ether	TBBPA-DHEE, -BHEE, or - OHEE	4162-45-2	9	0	9
Phenolphthalein	-	77-09-8	8	1	7
Tetramethyl bisphenol F	TMBPF	5384-21-4	7	0	7
Bisphenol A-glycidyl methacrylate	Bis-GMA	1565-94-2	6	0	6
Bisphenol G	BPG	127-54-8	6	2	4
Hydroxychlor	HPTE	2971-36-0	6	0	6
Tetrabromobisphenol S	TBBPS	39635-79-5	6	1	5

Chemical name	Abbreviation	CASRN*	Total Studies	Human Studies	Animal Studies
4,4'-Thiobis(6-tert-butyl-m-cresol)	TBBC	96-69-5	5	0	5
4-Hydroxyphenyl 4-isoprooxyphenylsulfone	BPSIP or d-8	95235-30-6	5	0	5
Bisphenol C2	BPC2 or BPC Cl	14868-03-2	5	0	5
4,4'-Butylidenebis (6-tert-butyl-m-cresol)	BBBC	85-60-9	4	0	4
4,4'-Dihydroxybenzophenone	DHBP	611-99-4	4	1	3
Bisphenol PH	BPPH or BPH	24038-68-4	4	1	3
Bisphenol TMC	BPTMC	129188-99-4	4	0	4
Bisphenol A bis(2,3-dihydroxypropyl) ether	BADGE-2H2O	5581-32-8	3	3	0
Bisphenol A bis(diphenyl phosphate)	BDP or BPA-BDPP	5945-33-5	3	1	2
Bisphenol BP	BPBP	1844-01-5	3	2	1
Dimethyl-bisphenol A	DMBPA	1568-83-8	3	0	3
Tetramethyl bisphenol A	TMBPA	5613-46-7	3	0	3
1,1,1-Tris(4-hydroxyphenyl)ethane	THPE	27955-94-8	2	0	2
2,4,4'-Trihydroxybenzophenone	THBP	1470-79-7	2	0	2
3,3'-Dichlorobisphenol A	3,3'-DiCLBPA	79-98-1	2	1	1
3-Chlorobisphenol A	3-CLBPA	74192-35-1	2	1	1
4,4'-(Octahydro-4,7-methano-5h-inden-5-ylidene)bisphenol	4,4'-OHBP	1943-97-1	2	0	2
4,4'-Thiodiphenol	TDP	2664-63-3	2	1	1
4-Benzyloxyphenyl 4-hydroxyphenyl sulfone	BPS-MPE	63134-33-8	2	0	2
Benzophenone-6	BP-6	131-54-4	2	0	2
Bisphenol A (2,3-dihydroxypropyl) glycidyl ether	BADGE-H2O	76002-91-0	2	2	0
Bisphenol A dimethacrylate	Bis-DMA	3253-39-2	2	0	2
Bisphenol S-monoallyl ether	BPS-MAE	97042-18-7	2	0	2
Phenol red or phenolsulfonphthalein	-	143-74-8	2	0	2
3,5'-Dichlorobisphenol A	3,5'-diClBPA	14151-65-6	1	1	0
4,4'-[1-[4-[1-(4-Hydroxyphenyl)-1-methylethyl]phenyl]ethylidene]bis[phenol]	TPPA	110726-28-8	1	0	1

Chemical name	Abbreviation	CASRN*	Total Studies	Human Studies	Animal Studies
4,4′-Sulfonylbis[2-(2-propen-1-yl)phenol]	TGSA	41481-66-7	1	0	1
4,4'-Oxydiphenol	4,4'-ODP	1965-09-9	1	0	1
Bis(4-hydroxyphenyl)[2-(phenoxysulfonyl)phenyl]methane	BHPMM	115481-73-7	1	0	1
2,2′,3,3′-Tetrabromo-4,4′,5, 5′-tetrahydroxydiphenylmethane	Bromophenol-5	-	1	0	1
3-Bromo-4-(2, 3-dibromo-4,5-dihydroxybenzyl)-5-methoxymethylpyrocatechol	Bromophenol-6	-	1	0	1
5,5’-Methylenebis(2-methoxy-4-methylphenol) or Lignin-derived bisphenol	LD-BP	-	1	0	1
Tetrabromobisphenol A dimethyl ether	TBBPA-DME	37853-61-5	1	0	1
Temephos	-	3383-96-8	1	0	1
Tetrabromobisphenol A bis(2,3-dibromo-2-methylpropyl) ether	TBBPA-DBMPE	97416-84-7	1	0	1
Tribromobisphenol A	Tri-BBPA	6386-73-8	1	0	1
Trichlorobisphenol A	Cl3BPA or triClBPA	40346-55-2	1	1	0

*Chemical Abstracts Service Registry Number (CASRN) from PubChem web page: PubChem.

The numbers of *p,p'*-bisphenol chemicals identified with information relevant to specific DART endpoints and outcomes, based on full-text screening, are presented in Table 4

Table 4. Numbers of p,p'-bisphenol chemicals with studies assessing individual DART endpoints and outcomes

DART endpoint and Outcome	Total Chemicals	Total Unique Chemicals
Male	41	1[a]
Sperm and Testicular Effects	37	0[b]
Reproductive Function	27	1[b]
Endocrine Effects	34	4[b]
Female	47	5[a]
Oocyte and ovarian effects	33	1[b]
Uterine effects	31	2[b]
Reproductive Function	30	1[b]
Endocrine Effects	38	6[b]
***Pregnancy Complications**	4	0[b]
Developmental	47	8[a]
Reproductive Effects	19	0[b]
Neurodevelopmental Effects	35	1[b]
Endocrine Effects	22	0[b]
Offspring Effects and Indices	40	2[b]
Early Development	37	1[b]
Gestational Age / Preterm Birth	9	0[b]

*Relevant to human epidemiology studies

a. Number of chemicals assessed only for the specified endpoint.

b. Number of chemicals assessed only for the specified outcome within each respective endpoint.

The information presented in Table 4 is consistent with an initial assessment of the literature regarding the range of outcomes assessed for *p,p'*-bisphenol chemicals (OEHHA 2025b). We therefore propose to limit the scope and type of information presented in the HID to focus primarily on the following subset of outcomes:

1. Male reproductive toxicity: sperm and testicular effects, and endocrine effects.

2. Female reproductive toxicity: oocyte and ovarian effects, uterine effects, and endocrine effects.

3. Developmental toxicity endpoint: we will start by considering effects on offspring reproductive toxicity and time permitting, other effects such as fetal and birth size, gestational length, growth, and neurodevelopmental effects may also be considered.

The DARTIC may, however, consider all DART outcomes assessed in the literature, since all the studies (and associated PDFs) presented in Table 4 will be provided to the Committee.

Here we provide examples of tabulations of study data in the HID. Tables of human studies and tables of animal studies will be prepared for each of the three DART endpoints.

Female reproductive toxicity

Studies in Humans

Table 5. Epidemiologic studies of female reproductive toxicity

Reference; study location, period, design, sample	Exposure Matrix and *p,p'*-Bisphenol chemical(s)	LOD, ng/mL	Detection Rate	Median Concentration ng/mL	Outcome	Results	Covariates	Sources of bias to note: Information, Selection, Confounding
Huang et al. 2022 China 2015-2018 Cohort n = 446	Urine Spot BPB BPF TBBPA	 0.232 0.507 0.454	 90% 64% 65%	 0.23 0.61 0.47	**Endocrine** Serum thyroid hormone levels: T3, T4, FT3, FT4, TSH	**Endocrine** **BPB** associated with lower FT4 Trimester 1: per unit increase: **-10.5, 95% CI: -17.5, -2.8** Associated with higher FT4 Trimester 2: med vs. low: **9.8 95% CI: 1.7, 18.6** high vs. low: 7.4 95% CI: -0.4, 15.8 associated with lower T4 Trimester 1: per unit decrease: **-10.9, 95% CI: -19.1, -1.8** **BPF** associated with higher TSH Trimester 1: per unit increase: **70.8, 95% CI: 0.2, 191.1** med vs. low: 10.5, 95% CI: -36.9, 93.3 high vs. low: **97.4, 95% CI: 16.3, 235.2** associated with lower TSH Trimester 2: per unit decrease: **-29.7 95% CI: -49.4, -2.4** associated with higher T4 Trimester 2: per unit increase: **6.3 95% CI: 0.4, 12.6** Associated with higher FT4 Trimester 2: med vs. low: **8.6, 95% CI: 0.5, 17.3** high vs. low: 2.5 95% CI: -5.1, 10.8	Maternal age, pre-pregnancy BMI, drinking before pregnancy, passive smoking during pregnancy, gravidity, parity, and fetus sex	Information Bias: Imputation of levels below LOD (over 20%) could impact findings for BPF and TBBPA. Selection Bias: Participants were chosen for "Zhuang" ancestry.

Reference; study location, period, design, sample	Exposure Matrix and *p,p'*-Bisphenol chemical(s)	LOD, ng/mL	Detection Rate	Median Concentration ng/mL	Outcome	Results	Covariates	Sources of bias to note: Information, Selection, Confounding
						TBBPA associated with lower T3 Trimester 1: med vs. low: **-8.3, 95% CI: -15.8, -0.01** high vs. low: -3.1, 95% CI: -10.7, 5.1 Associated with higher T4 Trimester 2: med vs. low: -3.2 95% CI: -9.1, 3.2 high vs. low: **6.9 95% CI: 0.5, 13.7** Associated with higher FT4 Trimester 2: med vs. low: 0.8 95% CI: -6.7, 8.8 high vs. low: **9.4 95% CI: 1.46, 17.9**		

Studies in Animals

Table 6. Evidence on female reproductive toxicity in animal models

Study Design	*p,p'*-Bisphenol chemical(s)	Treatment period	Outcomes assessed	Major Findings
Zhu et al. 2025 **Pregnant female SD rats**, 11-weeks-old n = 6 dams per treatment group	**BPAF** Purity: ≥ 97% 50 or 100 mg/kg-day Vehicle control: corn oil **Internal concentrations:** **Plasma post-birth** 50 mg/kg-d: 6 hr C_{max}: 653.54 ng/mL 168 hr C_{last}: 71.30 ng/mL 100 mg/kg-d: 6 hr C_{max}: 825.29 ng/mL 168 hr C_{last}: 77.75 ng/mL **Ovaries at PND 21** Control: <LOD 50 mg/kg-d: 3.66 ng/mg 100 mg/kg-d: 15.67 ng/mg	**Route:** Oral (gavage) **Duration:** GD 3 to GD 21; daily **Assessment:** PND 21	**Oocyte/ovary** 100 mg/kg-d: Gonad weights Gonad histopathology **Endocrine** Plasma levels (E2, Testosterone, FSH, LH)	**Oocyte/ovary** Increased vacuolization in follicular antrum and decreased number of follicles. No effect on relative ovary weight **Endocrine** Increased E2 and LH at 100 mg/kg-day, and No effects on testosterone or FSH
Huang et al. 2017 **Marine medaka** (*Oryzias melastigma*) 15 fish, n = 3 replicates for each treatment group	**TBBPA** Purity: Not stated 0.05 or 0.2 mg/L Vehicle control: 0.2% DMSO **Internal concentration: N/A**	**Route**: Water **Duration**: Hatching to 4 months, exposure solution renewed every two days **Assessment**: Adult	**Oocyte/ovary** Oogenesis Gonadosomatic index (GSI) **Endocrine** Whole body homogenate (E2 level)	**Oocyte/ovary:** No effects. **Endocrine:** No effects
Huang et al. 2017 **Marine medaka** (*Oryzias melastigma*) 15 fish, n = 3 replicates for each treatment group	**TCBPA** Purity: Not stated. 0.05 or 0.2 mg/L Vehicle control: 0.2% DMSO **Internal concentration: N/A**	**Route**: Water. **Duration**: Hatching to 4 months, exposure solution renewed every two days. **Assessment**: Adult	**Oocyte/ovary** Oogenesis Gonadosomatic index (GSI) **Endocrine** Whole body homogenate (E2 level)	**Oocyte/ovary** GSI: Decreased at 0.2 mg/L **Endocrine:** No effects

Male reproductive toxicity

Studies in Humans

Table 7. Epidemiologic studies of male reproductive toxicity

Reference; study location, period, design, sample	Exposure Matrix and *p,p'*-Bisphenol chemical(s)	LOD, ng/mL	Detection Rate	Median Concentration ng/mL	Outcome	Results	Covariates	Sources of bias to note: Information, Selection, Confounding
Jeseta et al. 2024 Czech Republic, 2019-2021 Cross-sectional n = 349	Seminal plasma BPF BPAF	 0.001 0.0002	 14.3 23.9	 0.00071 0.00049	**Sperm** Ejaculate volume (mL) Sperm concentration (mil/mL) Progressive motility (%) Sperm morphology (%) Total sperm count (mil) DNA fragmentation index % = (fragmented spermatozoa + degenerated spermatozoa/total spermatozoa counted) x 100	**Sperm** Per 10-fold increase in continuous BP: **BPF** **DNA integrity β=-0.1 (p=0.01)*** *The BPF detection rate was low and the significant association with DNA integrity was not observed when analyzing a categorical (above vs. below limit of quantification) BPF exposure variable, so authors caution that it might be a "false-positive result affected by censored values imputation" **BPAF** no associations	Age, BMI, ejaculation abstinence, smoking, reactive oxygen species (ROS)	Information Bias: Low detection rates could impact findings as mentioned. Selection Bias: Sample of participants from a single care center. Confounding Bias: Models adjusted for ROS, which may be on the casual pathway from bisphenols to semen quality.

Studies in Animals

Table 8. Evidence on male reproductive toxicity in animal models

Study Design	*p,p'*-Bisphenol Chemical(s)	Treatment period	Outcomes assessed	Major Findings
Zhu et al. 2025 **Pregnant female SD rats**, 11-weeks-old n = 6 dams per treatment group	**BPAF.** Purity: ≥ 97% 50 or 100 mg/kg-day Vehicle control: Corn oil **Internal concentrations:** **Plasma post-birth** 50 mg/kg-d: 6 hr C_{max}: 653.54 ng/mL 168 hr C_{last}: 71.30 ng/mL 100 mg/kg-d: 6 hr C_{max}: 825.29 ng/mL 168 hr C_{last}: 77.75 ng/mL **Testes at PND 21** Control: <LOD 50 mg/kg-d: 6.98 ng/mg 100 mg/kg-d: 9.05 ng/mg	**Route**: Oral (gavage) **Duration**: GD 3 to GD 21; daily **Assessment**: PND 21	**Sperm/testis** 100 mg/kg-d: Gonad weights. Gonad histopathology **Endocrine** Plasma levels (E2, Testosterone, FSH, LH) Anogenital distance (AGD)	**Sperm/testis** Decreased relative testis weight and Dissolution of interstitial cells and decreased primary spermatocytes at both doses **Endocrine** Decreased testosterone at both doses, Increased LH at 100 mg/kg-day, and No effect on E2 or FSH Decreased AGD at both doses
Yang et al. 2017 **Zebrafish,** wildtype AB strain, four-months-old	**BPF** Purity: ≥ 98%. 0.001, 0.01, 0.1, or 1 mg/L Vehicle control: 0.01% DMSO **Internal concentration:** N/A	**Route**: Water. **Duration**: 21 days; daily **Assessment**: Adult	**Sperm/testis** Germline cell distribution (0.1 and 1 mg/L) Gonadosomatic index (GSI) Testis structure **Endocrine** Whole body homogenate levels (E2, Testosterone, Testosterone/E2 ratio)	**Sperm/testis** Decreased spermatogonia and spermatocytes Increased spermatids Decreased GSI at 1 mg/L Increased testis interstitial space at 1 mg/L **Endocrine** Decreased testosterone at ≥ 0.01 mg/L, Increased E2 at ≥ 0.1 mg/L, and Decreased testosterone/E2 ratio at all concentrations

Study Design	*p,p'*-Bisphenol Chemical(s)	Treatment period	Outcomes assessed	Major Findings
Huang et al. 2017 **Marine medaka** (*Oryzias melastigma*) 15 fish, n = 3 replicates for each treatment group	**TBBPA** Purity: Not stated 0.05 or 0.2 mg/L Vehicle control: 0.2% DMSO **Internal concentration:** N/A	**Route**: Water. **Duration**: Hatching to 4 months; solution refreshed every two days **Assessment**: Adult	**Sperm/testis** Testicular histopathology. Gonadosomatic index (GSI) **Endocrine** Whole body homogenate (Testosterone level)	**Sperm/testis:** No effects **Endocrine:** No effects
Huang et al. 2017 **Marine medaka** (*Oryzias melastigma*) 15 fish, n = 3 replicates for each treatment group	**TCBPA** Purity: Not stated. 0.05 or 0.2 mg/L. Vehicle control: 0.2% DMSO. **Internal concentration:** N/A.	**Route**: Water. **Duration**: Hatching to 4 months; solution refreshed every two days. **Assessment**: Adult.	**Sperm/testis** Testicular histopathology. Gonadosomatic index (GSI). **Endocrine** Whole body homogenate (Testosterone level)	**Sperm/testis:** No effects. **Endocrine:** Decreased testosterone at 0.2 mg/L

Developmental toxicity

Studies in Humans

Table 9. Epidemiologic studies of developmental toxicity

Reference; study location, period, design, sample	**Exposure Matrix and *p,p'*-Bisphenol chemical(s)**	**LOD, ng/mL**	**Detection Rate**	**Median Concentration ng/mL**	**Outcome**	**Results**	**Covariates**	**Sources of bias to note: Information, Selection, Confounding**
Zhu et al. 2023 Northern China 2010–2016 Case-control study (population based) n = 122 cases, n = 164 controls	Placental samples BPZ BPF BPB BPAF BPAP TBBPA CL3BPA CL4BPA BHPF	(ng/g) 0.047 0.013 0.008 0.004 0.007 0.229 0.038 0.003 0.004	Not reported	Cases, controls (ng/g) 3.91, 3.52 2.16, 1.93 1.06, 1.08 2.65, 2.65 1.90, 1.94 1.67, 2.01 1.96, 2.34 1.21, 1.19 1.72, 1.72	**Neurodevelopment** Neural tube defects (NTD)s and subtypes spina bifida and anencephaly	**Neurodevelopment** Bisphenols, high vs. low (median cutoff): Risk of NTDs: **BPZ - OR: 3.11 (95% CI: 1.20, 8.09)** For female infants: **BPZ - OR: 6.60 (95% CI: 1.23, 35.40)** For no folic acid use: **BPZ - OR: 3.38 (95% CI: 1.06, 10.77)** Risk of Spina bifida: **BPZ - OR: 3.80 (95% CI: 1.23, 11.74)** **Associations for BPZ and Overall NTDs and spina bifida seen between lowest and highest tertiles (Supplemental Tables S5/S6). P for trend statistically significant for overall NTDs (*p* = 0.002) and spina bifida (*p* = <0.001)** No association with NTDs (or subtypes): BPF, BPB, BPAF, BPAP, TBBPA, CL3BPA, CL4BPA, BHPF Weighted quantiles sum mixture was associated with higher odds of NTDs [**OR: 4.34 (95% CI: 1.69, 11.20)**] Contributions for overall NTDs in were: BPZ: 28.99%; CL4BPA 10.33%. Mixture was also associated with higher odds spina bifida [**OR: 3.76 (95% CI: 1.24, 11.76**)] Contributions were: BPZ: 36.06%; BHPF 7.87%	Maternal age, pre-pregnancy BMI, gestation weeks at delivery, periconceptional use of folic acid, smoking during pregnancy, and history of birth defect	Information Bias: Detection rates not given in manuscript, unable to evaluate, if any, imputation. Selection Bias: Limited information on how controls were matched besides infants "without congenital malformations. Confounding Bias: Fetal sex was not included in original models, but used for stratified analyses

Studies in Animals

Table 10. Evidence on developmental toxicity in animal models

Study Design	*p,p'*-Bisphenol chemical(s)	Treatment period	Outcomes assessed	Major Findings
Abdallah et al. 2023 **Pregnant NMRI mice**, two- to four-months-old	**BADGE** Purity: ≥ 99.8%. 10 µM, estimated 500 µg/kg-day. Vehicle control: 0.1% EtOH **Internal concentration:** Not quantified due to technical limitations	**Route**: Oral (drinking water). **Duration**: GD 10.5 to GD 18.5 **Assessment**: GD18.5, PND 8, and 3 months	**F1 Oocyte/ovary development** Meiotic phase distribution Chromosome segregation Follicle stages and count	**F1 Oocyte/ovary development** Altered meiotic phase stage distribution Altered chromosome segregation Increased reciprocal chromosomal exchanges in prophase I at GD 18.5, Increased missegregation in meiotic metaphase I, and Aneuploid oocytes in meiotic metaphase II at 3 months Increased multi-oocyte follicles at PND 8 and 3 months
Abdallah et al. 2023 **Pregnant NMRI mice**, two- to four-months-old	**BPAF** Purity: ≥ 99.8%. 10 µM, estimated 500 µg/kg-day Vehicle control: 0.1% EtOH **Internal concentration:** GD 18.5 maternal plasma: 5.96 µg/L	**Route**: Oral (drinking water). **Duration**: GD 10.5 to GD 18.5. **Assessment**: GD 18.5, PND 8, and 3 months	**F1 Oocyte/ovary development** Meiotic phase distribution Chromosome segregation Follicle stages and count	**F1 Oocyte/ovary development** Altered meiotic phase stage distribution Altered chromosome segregation Increased reciprocal chromosomal exchanges in prophase I at GD 18.5, Increased missegregation in meiotic metaphase I, and Aneuploid oocytes in meiotic metaphase II at 3 months Increased multi-oocyte follicles at PND 8 and 3 months

Study Design	*p,p'*-Bisphenol chemical(s)	Treatment period	Outcomes assessed	Major Findings
Zhu et al. 2025 **Pregnant female SD rats**, 11-weeks-old n = 6 dams per treatment group	**BPAF** Purity: ≥ 97% 50 or 100 mg/kg-day Vehicle control: corn oil **Internal concentrations:** **Plasma post-birth** 50 mg/kg-d: 6 hr C_{max}: 653.54 ng/mL. 168 hr C_{last}: 71.30 ng/mL 100 mg/kg-d: 6 hr C_{max}: 825.29 ng/mL 168 hr C_{last}: 77.75 ng/mL **Ovaries at PND 21** Control: <LOD 50 mg/kg-d: 3.66 ng/mg 100 mg/kg-d: 15.67 ng/mg **Testes at PND 21** Control: <LOD 50 mg/kg-d: 6.98 ng/mg 100 mg/kg-d: 9.05 ng/mg	**Route:** Oral (gavage) **Duration:** GD 3 to GD 21; daily **Assessment:** PND 21	**F1 reproductive toxicity and endocrine effects** **Female:** **Oocyte/ovary** 100 mg/kg-d: Gonad weights Gonad histopathology **Endocrine** Plasma levels (E2, Testosterone, FSH, LH) **Male:** **Sperm/testis** 100 mg/kg-d: Gonad weights Gonad histopathology **Endocrine** Plasma levels (E2, Testosterone, FSH, LH) Anogenital distance (AGD)	**F1 reproductive toxicity and endocrine effects** **Female:** **Oocyte/ovary** Increased vacuolization in follicular antrum and decreased number of follicles No effect on relative ovary weight **Endocrine** Increased E2 and LH at 100 mg/kg-day, and No effects on testosterone or FSH **Male:** **Sperm/testis** Decreased relative testis weight and Dissolution of interstitial cells and decreased primary spermatocytes at both doses **Endocrine** Decreased testosterone at both doses, Increased LH at 100 mg/kg-day, and No effect on E2 or FSH Decreased AGD at both doses
Kaiglová et al. 2025 ***C. elegans*,** strain not specified Sample sizes not reported	**BPAF** Purity: 99% 0.5, 1, or 5 µM Vehicle control: Unspecified, 100 µM stock solution prepared in 10% EtOH	**Route:** Cultured on Nematode Growth Medium **Duration:** Four hours from embryo stage **Assessment:** 18 and 48 hours post-exposure	**Growth** Body length at 18 hours post exposure **Neurodevelopment** Anterior touch– habituation (non-associative learning), at 48 hours post exposure	**Growth** Decreased body length at 1 and 5 µM BPAF **Neurodevelopment** Increased number of touches required for habituation at all concentrations

Study Design	*p,p'*-Bisphenol chemical(s)	Treatment period	Outcomes assessed	Major Findings
Kaiglová et al. 2025 ***C. elegans*,** strain not specified Sample sizes not reported	**BPF** Purity: 98% 0.5, 1, or 5 µM Vehicle control: Unspecified, 100 µM stock solution prepared in 10% EtOH	**Route:** Cultured on Nematode Growth Medium **Duration:** Four hours from embryo stage **Assessment:** 18 and 48 hours post-exposure	**Growth** Body length (18 hours) **Neurodevelopment** Anterior touch habituation (non-associative learning, 48 hours)	**Growth** No effects **Neurodevelopment** Increased number of touches required for habituation at all concentrations

REFERENCES

Abdallah S, Jampy A, Moison D, Wieckowski M, Messiaen S, Martini E, et al. 2023. Foetal exposure to the bisphenols badge and BPAF impairs meiosis through DNA oxidation in mouse ovaries. Environ Pollut 317:120791.

ATSDR. 2002. Toxicological profile for methoxychlor.

Howard BE, Phillips J, Miller K, Tandon A, Mav D, Shah MR, et al. 2016. Swift-review: A text-mining workbench for systematic review. Syst Rev 5:87.

Huang H, Liang J, Tang P, Yu C, Fan H, Liao Q, et al. 2022. Associations of bisphenol exposure with thyroid hormones in pregnant women: A prospective birth cohort study in China. Environ Sci Pollut Res Int 29:87170-87183.

Huang Q, Chen Y, Lin L, Liu Y, Chi Y, Lin Y, et al. 2017. Different effects of bisphenol a and its halogenated derivatives on the reproduction and development of oryzias melastigma under environmentally relevant doses. Sci Total Environ 595:752-758.

Jeseta M, Kalina J, Franzova K, Fialkova S, Hosek J, Mekinova L, et al. 2024. Cross sectional study on exposure to BPA and its analogues and semen parameters in Czech men. Environ Pollut 345:123445.

Kaiglová A, Bárdyová Z, Hockicková P, Zvolenská A, Melnikov K, Kucharíková S. 2025. Caenorhabditis elegans as a model to assess the potential risk to human health associated with the use of Bisphenol A and its substitutes. Int J Mol Sci 26.

OEHHA. 2015. Hazard identification materials for consideration of the female reproductive toxicity of Bisphenol A. Reproductive and Cancer Hazard Assessment Branch. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency.

OEHHA. 2023. Evidence on the female reproductive toxicity of Bisphenol S. Reproductive and Cancer Hazard Assessment Branch. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency.

OEHHA. 2024. Evidence on the male reproductive toxicity of Bisphenol S. Reproductive and Cancer Hazard Assessment Branch. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency.

OEHHA. 2025a. Evidence on the developmental toxicity of Bisphenol S. Reproductive and Cancer Hazard Assessment Branch. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency.

OEHHA. 2025b. Proposal for development of hazard identification materials on p,p'-bisphenol chemicals, to support consideration for listing by the DARTIC in 2026.

Stockholm Convention. 2019. Stockholm convention on persistent organic pollutants. Proposal to list methoxychlor in annex a to the stockholm convention on persistent organic pollutants. Rome, 1–4 October 2019.

Yang Q, Yang X, Liu J, Ren W, Chen Y, Shen S. 2017. Effects of BPF on steroid hormone homeostasis and gene expression in the hypothalamic-pituitary-gonadal axis of zebrafish. Environ Sci Pollut Res Int 24:21311-21322.

Zhu H, Cheng Q, Liu J, Jin L, Li Z, Ren A, et al. 2023. Associations among bisphenol A, its analogs, and chlorinated derivatives in placenta and risk for neural tube defects: A case-control study. Sci Total Environ 900:165586.

Zhu Y, Liu X, Liu X, Shi Y, Li H, Ru S, et al. 2025. Toxicokinetics and reproductive toxicity of maternal bisphenol AF exposure during gestation in offspring of Sprague Dawley rats. Chem Biol Interact 409:111424.