COMMENTS TO CALIFORNIA OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Request for Relevant Information on the Reproductive Toxicity of p,p'-Bisphenol Chemicals

Submitted: November 20, 2025

RE: DARTIC Review for Possible Listing Under Proposition 65 as Causing Reproductive Toxicity

INTRODUCTION

These comments are submitted in response to the Office of Environmental Health Hazard Assessment's (OEHHA) October 21, 2025 request for relevant information regarding the reproductive toxicity of p,p'-bisphenol chemicals for review by the Developmental and Reproductive Toxicant Identification Committee (DARTIC). We strongly support the listing of p,p'-bisphenol chemicals under Proposition 65 as causing reproductive toxicity based on substantial scientific evidence demonstrating these chemicals' profound effects on reproductive health, particularly through impacts on mammary gland development and breast cancer risk.

SUMMARY OF KEY POINTS

Bisphenol chemicals, including BPA and its substitutes BPS and BPF, are endocrine-disrupting chemicals that mimic estrogen and interfere with normal reproductive system development and function [1, 2].

Critical windows of vulnerability exist during prenatal development, infancy, and puberty when bisphenol exposure can cause permanent alterations to reproductive tissues, particularly mammary glands [14, 15].

Prenatal bisphenol exposure crosses the placental barrier and induces epigenetic changes that persist throughout life, increasing breast cancer susceptibility decades after exposure ends [14, 16, 18].

Bisphenol exposure negatively impacts lactation and breastfeeding outcomes, which are fundamental reproductive functions [11, 12].

BPA substitutes (BPS and BPF) demonstrate similar reproductive toxicity profiles as BPA, supporting concerns about the entire class of p,p'-bisphenol chemicals [6, 7].

Population exposure is virtually universal (over 90% of people), making this a significant public health concern requiring precautionary regulatory action [1].

REPRODUCTIVE TOXICITY EVIDENCE: BREAST DEVELOPMENT AND CANCER

Mammary Gland Development as a Reproductive Endpoint

The mammary gland is a reproductive organ whose development is inextricably linked to female reproductive function. Disruption of normal mammary gland development represents reproductive toxicity with profound implications for lactation, breastfeeding capacity, and long-term breast cancer risk.

Prenatal and Early-Life Exposure: Critical Windows of Vulnerability

The timing of bisphenol exposure is crucial in determining reproductive harm. Prenatal and early developmental periods represent windows of heightened vulnerability when even low-dose exposures can cause permanent alterations to reproductive tissues [14, 15].

Fetal exposure to BPA crosses the placental barrier and alters mammary gland development at the cellular and molecular levels [14, 16]. Animal studies demonstrate that prenatal BPA exposure at environmentally relevant doses increases the number of terminal end buds—structures considered targets for malignant transformation—alters ductal architecture, and enhances sensitivity to estrogen [14]. These changes are equivalent to established human breast cancer risk factors.

Critically, research demonstrates that prenatal BPA exposure shifts the window of susceptibility for chemically-induced mammary tumors [15, 17]. Exposed offspring show increased cancer susceptibility at postnatal day 100 but not at day 50, indicating that BPA alters the developmental trajectory of mammary tissue in ways that increase cancer risk at specific life stages [15]. This delayed effect illustrates how prenatal reproductive toxicity may not manifest for years or decades, underscoring the need for precautionary protection of developing fetuses.

The developing fetus and newborns have low or absent activity of enzymes needed to metabolize BPA, making them particularly vulnerable to its effects [1]. This metabolic vulnerability, combined with the critical nature of prenatal mammary gland programming, establishes fetal exposure as a major reproductive health concern.

Epigenetic Mechanisms and Transgenerational Effects

Prenatal BPA exposure induces epigenetic changes and alters expression of key genes involved in breast development and tumor suppression [16, 18]. These effects persist long after the exposure ends, representing permanent alterations to reproductive tissue function. The ability of bisphenol chemicals to induce lasting epigenetic modifications that alter mammary gland biology across the lifespan provides a mechanistic basis for their classification as reproductive toxicants.

Studies show that prenatal exposure to BPA induces preneoplastic lesions in the mammary gland, demonstrating direct reproductive organ toxicity that predisposes to cancer development [16]. These alterations occur through estrogen receptor-dependent mechanisms and include DNA methylation changes that affect genes critical for normal mammary development and function [6, 18].

IMPACTS ON LACTATION: DIRECT REPRODUCTIVE HARM

Lactation represents a fundamental reproductive function in mammals, and interference with this function constitutes clear reproductive toxicity. Multiple lines of evidence demonstrate that bisphenol exposure negatively impacts lactation capacity and breastfeeding outcomes.

Reduced Breastfeeding Duration and Success

Research demonstrates that mothers in the highest BPA exposure tertile were significantly less likely to be breastfeeding at one month postpartum (89.9%) compared to those in the lowest tertile (97.2%) [11]. Higher prenatal BPA exposure has been associated with perceived insufficient milk supply and shorter breastfeeding duration [11, 12].

The mechanism underlying these effects likely involves BPA's estrogen-like properties. High estrogen levels are known to inhibit lactation, and BPA's ability to mimic estrogen can interfere with the hormonal cascade necessary for successful milk production and breastfeeding establishment [11]. This represents direct toxicity to a core reproductive function.

BPA Transfer Through Breast Milk and Infant Exposure

BPA has been detected in human breast milk in 75-93% of samples, with typical concentrations ranging from 0.4 to 3.4 ng/mL [9, 10]. This demonstrates not only that lactating women are exposed to BPA, but that this exposure is transferred to nursing infants during a critical developmental window.

According to the World Health Organization, exclusively breastfed infants consume on average 0.3 ?g/kg body weight of BPA daily through breast milk [9]. A Chinese study found that breast milk BPA concentrations were negatively correlated with infant weight and length gain rates [13], suggesting that bisphenol exposure during this vulnerable period may impact infant growth and development.

The presence of BPA in breast milk and its effects on infant development highlight another dimension of reproductive toxicity: the potential for bisphenol chemicals to cause harm not only to the exposed mother's reproductive system but also to the developing reproductive organs of nursing infants [9, 10].

MECHANISTIC EVIDENCE OF REPRODUCTIVE TOXICITY

Estrogen Receptor-Dependent Mechanisms

BPA functions as an endocrine-disrupting chemical by mimicking estrogen and binding to estrogen receptors [1, 2]. Laboratory studies demonstrate that BPA promotes proliferation, migration, and invasion of breast cancer cells through estrogen receptor-dependent mechanisms [2]. This hormonal mimicry disrupts normal reproductive tissue development and function.

The reproductive system is exquisitely sensitive to hormonal signals during critical developmental windows. Inappropriate estrogenic signaling from BPA exposure during these periods can permanently alter reproductive organ structure and function, including mammary gland architecture, sensitivity to hormones, and cancer susceptibility [14, 16].

Low-Dose Effects Below "Safe" Levels

Importantly, preclinical studies demonstrate that BPA exposure at doses below FDA-considered safe levels can increase breast cancer risk [2]. This finding is particularly concerning because it suggests that current regulatory standards may not adequately protect reproductive health. The ability of low-dose BPA to cause reproductive harm supports the need for conservative safe harbor levels under Proposition 65.

Interference with Cancer Treatment

BPA can interfere with the effectiveness of breast cancer treatments including tamoxifen and chemotherapy, potentially worsening outcomes for those already diagnosed [1]. This interference with medical treatment of reproductive system cancers provides additional evidence of BPA's reproductive toxicity and its serious health implications.

EVIDENCE ON BPA SUBSTITUTES: CLASS-WIDE CONCERNS

Studies indicate that BPA substitutes like BPS and BPF have similar risk profiles as BPA for increasing breast cancer development and progression in laboratory studies [6, 7]. BPF shows comparable estrogenic activity to BPA, while BPS is approximately 10 times less potent but still demonstrates significant estrogenic effects [6, 7].

The similar reproductive toxicity profiles of BPA substitutes support the Committee's approach of reviewing p,p'-bisphenol chemicals as a class rather than individual compounds. This class-based approach is scientifically sound and prevents "regrettable substitutions" where harmful chemicals are simply replaced with structurally similar compounds with comparable toxicity [7].

California's recent listing of BPS for both female and male reproductive toxicity (effective December 29, 2023 for female reproductive toxicity and expanded to include male reproductive toxicity in January 2025) demonstrates regulatory recognition of the reproductive hazards posed by this chemical class.

HUMAN EPIDEMIOLOGICAL EVIDENCE

While laboratory and animal evidence provides strong mechanistic support for bisphenol reproductive toxicity, human epidemiological data adds important context. A case-control study found significantly higher BPA concentrations in both urine and breast adipose tissue of breast cancer patients compared to non-cancerous individuals [3], suggesting a relationship between BPA exposure and breast disease in humans.

Several studies found associations between BPA levels and breast cancer risk factors such as increased mammographic breast density [1]. While some large epidemiological studies have not found consistent associations between BPA exposure and breast cancer risk [4, 5], this does not negate the substantial mechanistic and animal evidence of reproductive harm.

The challenges of human epidemiological studies in this context are significant: the latency period between exposure (particularly prenatal exposure) and cancer development may span decades [16]; exposure is virtually universal, making unexposed control groups difficult to identify [1]; and measuring prenatal exposures retrospectively in adults is methodologically challenging. The absence of definitive human epidemiological proof should not preclude preventive regulatory action given the strength of mechanistic evidence, the ubiquity of exposure, and the serious nature of reproductive harm [7, 20].

PUBLIC HEALTH IMPLICATIONS AND THE PRECAUTIONARY PRINCIPLE

Universal Exposure Creates Widespread Risk

BPA has been detected in over 90% of human biological samples, indicating virtually universal exposure across the population [1]. This widespread exposure, combined with evidence of reproductive toxicity, creates a significant public health burden affecting millions of Californians during vulnerable life stages.

Vulnerable Populations Require Special Protection

Fetuses, infants, pregnant women, and lactating women represent populations with heightened susceptibility to bisphenol reproductive toxicity [1, 14, 15]. Protecting these vulnerable groups during critical windows of development aligns with Proposition 65's purpose of informing the public about exposures to chemicals that cause reproductive harm.

Traditional Cancer Risk Factors Explain Only Half of Cases

Traditional cancer risk factors explain only approximately half of breast cancer cases, suggesting that environmental factors like BPA may play a significant unrecognized role in the remaining cases [20]. Given that breast cancer risk is closely tied to reproductive factors (age at menarche, age at first birth, breastfeeding duration, etc.), environmental chemicals that disrupt reproductive development and function may contribute substantially to breast cancer burden.

Latency Period Necessitates Precautionary Action

The latency period between bisphenol exposure (particularly during prenatal or early-life windows) and manifestation of reproductive harm may span decades [16]. This long latency makes definitive human studies exceptionally challenging and means that by the time adverse effects become apparent in exposed populations, irreversible harm has already occurred. This temporal disconnect between exposure and outcome necessitates precautionary regulatory action based on mechanistic and animal evidence rather than waiting for human epidemiological proof [7, 20].

REGULATORY PRECEDENT AND INTERNATIONAL ACTIONS

The European Union's decision to lower acceptable BPA exposure limits by 20,000-fold reflects growing international recognition of bisphenol reproductive toxicity based on accumulating evidence of harm [7]. California has already recognized the reproductive toxicity of BPA (listed in 2015 for female reproductive toxicity) and BPS (listed in 2023 for female reproductive toxicity, expanded in 2025 to include male reproductive toxicity).

The Institute of Medicine has declared BPA a potential risk factor for breast cancer [1], providing authoritative support for regulatory action. These precedents demonstrate scientific and regulatory consensus that bisphenol chemicals pose reproductive hazards warranting public health interventions.

RECOMMENDATIONS

Based on the substantial evidence of reproductive toxicity, we strongly recommend that DARTIC:

List p,p'-bisphenol chemicals under Proposition 65 as causing reproductive toxicity, with particular attention to female reproductive toxicity given the extensive evidence regarding mammary gland development, lactation impacts, and breast cancer risk.

Consider male reproductive toxicity as well, following the precedent set with BPS listing expansion, as endocrine disruption affects both male and female reproductive systems.

Adopt a class-based listing approach that includes p,p'-bisphenols and their ethers and esters, preventing regrettable substitutions with structurally similar compounds.

Establish conservative Maximum Allowable Dose Levels (MADLs) that protect vulnerable populations during critical windows of development, particularly prenatal, infant, and pubertal exposures.

Consider the full spectrum of reproductive harm, including impacts on mammary gland development (a reproductive organ), lactation and breastfeeding (fundamental reproductive functions), and long-term cancer risk in reproductive tissues.

Recognize that reproductive toxicity includes effects that may not manifest until decades after exposure, particularly when exposures occur during critical developmental windows.

CONCLUSION

The scientific evidence overwhelmingly supports listing p,p'-bisphenol chemicals under Proposition 65 as causing reproductive toxicity. These chemicals disrupt normal reproductive organ development, interfere with lactation, induce epigenetic changes that persist across the lifespan, and increase breast cancer risk—particularly when exposures occur during critical windows of prenatal and early-life development [1, 2, 14, 15, 16, 18].

Given the universal nature of bisphenol exposure [1], the vulnerability of fetuses and infants [14, 15], the serious nature of reproductive harm including cancer [2, 16], and the long latency between exposure and adverse outcomes [16], precautionary regulatory action is warranted [7, 20]. Proposition 65 listing will provide essential public health protection by informing Californians about exposures to these reproductive toxicants, particularly during vulnerable life stages.

We urge DARTIC to expeditiously list p,p'-bisphenol chemicals as reproductive toxicants under Proposition 65 to protect the reproductive health of current and future generations of Californians.

Respectfully submitted,

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BIBLIOGRAPHY