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Endocrine-Disrupting Chemicals and Breastfeeding Duration: A Review

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Abstract

Purpose of review: The purpose of this review is to describe epidemiologic and toxicological literature investigating how endocrine-disrupting chemicals (EDCs) affect mammary gland development and function, thereby impacting lactation duration.

Recent findings: Per- and polyfluoroalkyl substances appear to reduce breastfeeding duration through impaired mammary gland development, lactogenesis, and suppressed endocrine signaling. Halogenated aromatic hydrocarbons have differing associations with lactation duration, likely due to the variety of signaling pathways that they affect, pointing to the importance of complex mixtures in epidemiologic studies. While epidemiologic literature suggests that pesticides and fungicides decrease or have no effect on lactation duration, toxicology literature suggests enhanced mammary gland development through estrogenic and/or antiandrogenic pathways. Toxicological studies suggest that phthalates may affect mammary gland development via estrogenic pathways, but no association with lactation duration has been observed. Bisphenol A was associated with decreased duration of breastfeeding, likely through direct and indirect action on estrogenic pathways.

Summary: EDCs play a role in mammary gland development, function, and lactogenesis, which can affect breastfeeding duration. Further research should explore direct mechanisms of EDCs on lactation, the significance of toxicant mixtures, and transgenerational effects of EDCs on lactation.

Keywords

Endocrine-disrupting chemicals; perfluoroalkyl substances; halogenated aromatic hydrocarbons; pesticides; phthalates; bisphenol-A; environmental toxicants; breastfeeding; lactation; mammary gland

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3.Conflicts of interest: None

Introduction:

Human milk is the optimal nutrition for infants (1). Breastfeeding confers long-term health benefits for children and mothers (2, 3), but global breastfeeding rates fall short of the recommended six months' exclusive breastfeeding and two years' any breastfeeding. Individuals stop breastfeeding for many reasons (1), and increasing evidence suggests that endocrine-disrupting chemicals (EDCs) may also influence lactation duration via interference with mammary gland development.

The mammary gland is highly dynamic throughout the life-course and develops over prenatal, peripubertal, pregnancy, and involution phases. Each phase is characterized by distinct morphological changes, regulated by endocrine-signaling pathways (4–9), that prepare the gland for lactation and represent sensitive windows of EDC exposure (5). Multiple reviews elucidate EDCs' effects on mammary gland development in the context of breast cancer (e.g., (5, 10–12)). Mechanisms of EDC action leading to breast cancer via impaired mammary gland development may likewise affect lactation, as proper mammary gland development is essential for lactation and optimal milk composition (13). Molecular targets of EDCs on mammary gland development offer insight into biological mechanisms underlying increasing epidemiologic evidence suggesting associations between maternal EDC exposure and lactation duration.

Review:

We summarize the epidemiological and toxicological literature investigating the influence of EDCs on mammary gland development and consequences for breastfeeding duration (Table 1). Generally, exclusive (no food or drink other than human milk) and any (human milk and other food or drink) breastfeeding are classified in accordance with World Health Organization definitions (14), but some studies allowed water within exclusive breastfeeding.

Per- and polyfluoroalkyl substances (PFAS):

PFAS are anthropogenic, degradation-resistant chemicals widely used in oil- and water-resistant consumer products, fire-fighting foam, and industrial surfactants (15). PFAS are present in air, soil, biota, and water worldwide (16), and humans have consistent exposure through ingestion of contaminated water and food (17, 18).

Epidemiologic evidence indicates that reduced breastfeeding duration may be among the adverse health effects attributed to PFAS exposure. Collectively, cohort studies from the Faroe Islands, Denmark, and Cincinnati, Ohio show that higher maternal serum PFAS (including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS)) in pregnancy are associated with shorter duration of exclusive and any breastfeeding (19–21), although the specific PFAS implicated differ across studies. Among Norwegian mothers, no association was found between maternal serum PFOA, PFOS, PFNA, PFHxS, or five other PFAS and duration of exclusive or any breastfeeding (22). However, analysis of PFAS mixtures

identified that PFOS and the perfluoroundecanoic acid:perfluorodecanoic acid ratio were associated with decreased duration of any breastfeeding, and that the PFHxS:PFOA ratio was associated with increased duration of any breastfeeding (22). Norwegian PFAS levels were lower than other cohorts, which may partially explain discrepant results across studies.

Toxicological studies have found evidence for PFAS-mediated disruption of mammary gland development and lactation. Specifically, mice exposed to PFOA during pregnancy displayed reduced mammary gland differentiation and delayed epithelial involution (23). PFOA-treated mice also did not have milk-filled alveoli just before birth, suggesting impaired lactogenesis (23). An inverse association between PFOA and mammary gland development also occurred in mice exposed to PFOA *in utero* and as juveniles (23–27). Transgenerational effects of prenatal PFOA exposure, including impacts on mammary gland development and lactation, persist into the F2 generation (24). PFOA is known to activate peroxisome proliferator-activated receptor-alpha (PPARa) (28, 29), which may impair lobularaveoli development within the mammary gland (30). PFOA may also interfere with lactation through suppression of prolactin and placental lactogen signaling (31), which stimulate mammary epithelial cell growth and differentiation and milk production (9, 32). Additionally, alterations in milk protein gene expression were observed during lactation among PFOA-exposed dams (23), which can affect both milk quantity and quality (33). Further research is needed to understand whether exposure timing and rodent strain-specificity (25, 27) influence these effects of PFAS exposure on mammary gland development.

Halogenated aromatic hydrocarbons:

Halogenated aromatic hydrocarbons encompass several classes of persistent and bioaccumulative compounds that contain aromatic rings as central components of their chemical structure, including polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (dioxins), polychlorinated dibenzofurans (PCDFs), and polybrominated biphenyl ethers (PBDEs) (34). Each class includes individual congeners that vary in chemical structure and biological reactivity. PCBs and PBDEs were previously manufactured for industrial applications and consumer products (34). Dioxins and PCDFs are produced as by-products of synthetic chemical production or incineration of chlorinated organic compounds (34). Ingestion of contaminated food, water, and dust is the most common, ongoing route of human exposure (34).

Epidemiologic studies have found modest or equivocal associations of maternal PCB exposure with breastfeeding duration (35–38). Studies of Michigan agricultural communities and anglers observed no association between commercial mixtures of PCBs (Aroclor 1254 and 1260) and duration of exclusive or any breastfeeding (36, 37). Exposure at delivery in both studies was modeled rather than measured, which may have misclassified true maternal pregnancy levels. A cohort of Mexican-American agricultural workers in California found that individual PCB congeners were associated with longer (PCB-49 and 52) or shorter (PCB-138, 153, and 180) duration of any breastfeeding, whereas PCB-44 and 118 showed no association with lactation duration (38). Collectively, these studies suggest that individual PCB congeners impact breastfeeding duration differently, perhaps based on their endocrine-

active characteristics, and point to the importance of accounting for chemical mixtures in epidemiologic research.

Other halogenated aromatic hydrocarbons such as dioxins, PCDFs, and PBDEs are less well studied. Among Michigan agricultural communities, no associations were found between maternal serum levels of 2,2',4,4',5,5'hexabromobiphenyl as a marker of total PBDEs and duration of exclusive or any breastfeeding (37). We found no other studies exploring the relation between other halogenated aromatic hydrocarbons and breastfeeding duration.

PCBs, dioxins, PCDFs, and PBDEs differ in the mechanisms by which they disrupt mammary gland development. Dioxins, PCDFs, and certain PCB congeners can bind and activate the aryl hydrocarbon receptor (AhR), which is involved with critical processes in numerous organs and cells (reviewed in (39, 40)). Notably, these exogenous ligands are associated with impaired development and function of mammary tissue via AhR-mediated mechanisms (e.g., (41–44)) and the development and tumor aggression of breast cancer (e.g., (29, 45, 46). The dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is the most potent and most widely studied AhR agonist. *In vivo* studies support a critical role for the AhR during *in utero*, puberty, and pregnancy/lactation phases of mammary gland development following activation by TCDD. Rodents exposed to TCDD across the life-course exhibited adverse effects on mammary gland development, including decreased cell proliferation, epithelial elongation, and branching; fewer and smaller terminal end buds; reduced overall mammary gland size; and reduced milk production (41, 42, 44, 47). Other dioxin-like compounds also activate the AhR at lower potencies (48), eliciting analogous effects. Some PCB congeners (e.g., PCB-138, 153, and 180) are used as indicators in epidemiologic literature but do not act through the AhR, and their effects on mammary gland development are less well understood.

While PBDEs share structural similarities to chlorinated aromatic compounds, they bind but do not activate the AhR (49). Nevertheless, female rats exposed to a PBDE mixture (DE-71) during gestation and lactation had reduced epithelial growth, lateral branches, and terminal end buds during puberty (50). However, exposure to environmentally-relevant levels of PBDEs during gestation and lactation has not been shown to affect mammary gland structure, milk synthesis protein biomarkers, or timing of weaning in lactating dams (51, 52). At these levels PBDEs perturbed β-catenin signaling (51) in a manner consistent with worse clinical breast cancer outcomes (53), suggesting that breast tissue is a target for PBDEs.

Organochlorine Pesticides (OCPs):

OCPs are persistent, bioaccumulative chlorinated hydrocarbons that have been used worldwide since the 1940s and include dichlorodiphenyltrichloroethane (DDT), methoxychlor, lindane, and hexachlorobenzene (HCB). DDT and other OCPs have been banned in many countries since the 1970s (54) but are still used in many parts of the world for agriculture and mosquito control related to malaria prevention (55–57).

Early studies of DDT and its breakdown product dichlorodiphenyldichloroethylene (DDE) indicated that maternal serum DDE was associated with shorter lactation duration among

cohorts in North Carolina (58), Mexico (59), and Michigan (36). However, among Mexican-American women in California, serum levels of p,p'-DDE, p,p'-DDT, and o,p'-DDT were associated with longer duration of any breastfeeding. The authors postulate that these results differ from previous studies because of unmeasured confounders associated with acculturation (38). The same study found that HCB was associated with shorter duration of any breastfeeding, and that the lindane breakdown product ß-hexachlorocyclohexane showed no association with breastfeeding duration (38).

More recent studies in South Africa, where DDT is used in malaria control, and Chiapas, Mexico where DDT is used for agriculture and malaria control identified no association between DDT and its metabolites and duration of breastfeeding (38, 60, 61). Methodologic differences may account for the discrepant findings across studies: among the South African cohort OCP concentrations were measured in breastmilk 14–487 days postpartum, and among the Chiapas cohort they were measured in maternal serum within 1 day of delivery. These approaches may not reflect an analogous etiologic window to pregnancy serum levels measured in other studies due to peripartum changes in maternal levels from cross-placental and breastmilk OCP transfer (62–64).

OCPs' effects on mammary gland development and function appear to occur through estrogenic and/or antiandrogenic pathways (reviewed in (65)). DDT, DDE, dichlorodiphenyldichloroethane, and other OCPs are highly biologically active as estrogen receptor (ER) agonists and androgen receptor (AR) antagonists (66). DDT enhances mammary gland development in pubertal rats, including increased cell proliferation (41). Structural analogs of DDT, such as methoxychlor, continue to show that these compounds increase mammary development (e.g., ductal and lobule growth) and gene expression (reviewed in (65)).

These toxicological findings are somewhat inconsistent with much of the epidemiologic literature, which largely finds DDE and DDT to be inversely or not associated with lactation duration. One study postulates that the inverse or lack of association between DDE and DDT and lactation duration found in epidemiologic literature is related to OCPs' effect on lactogenesis rather than sustained lactation, and women who are able to overcome this effect and initiate breastfeeding would not have difficulty continuing lactation (61). In fact, increased maternal serum DDE levels were associated with decreased breastfeeding initiation among first-time breastfeeding mothers in a sensitivity analysis among the Chiapas cohort (61) and among non-smokers in the Michigan anglers cohort (36).

Phthalates and Bisphenol A (BPA):

Phthalates are non-persistent chemical plasticizers and excipients present in consumer products, including personal care products, medications, and dietary supplements (67, 68).

Epidemiologic research on phthalates and lactation is limited; one study in Cincinnati observed no association between nine maternal pregnancy urinary phthalate metabolites with duration of exclusive or any breastfeeding (69). BPA is a chemical used in the production of plastics, and its ability to interfere with endocrine signaling has been apparent since its creation as a synthetic estrogen in the 1930s (70). Limited epidemiologic evidence from a

cohort of Mexican women suggests an adverse effect on lactation duration with higher maternal urinary BPA (71). Other environmental phenols have not been examined in relation to breastfeeding outcomes in human studies, to our knowledge.

Collectively, toxicological research indicate that phthalates may impair mammary gland development, likely through estrogenic mechanisms (72). N-butyl benzyl phthalate increased the proliferative index and expression of genes related to mammary tissue cell proliferation following neonatal and pubertal exposures among rats (73, 74). Diethylhexyl phthalate (DEHP) exposure during pregnancy increased cell proliferation and number of alveolar buds in mice at concentrations relevant to human exposures (75). However, environmentally-relevant DEHP exposures during lactation were not associated with mammary gland endpoints in rats (76).

BPA and many of its analogues (e.g., bisphenol S (BPS)) interfere with nuclear receptor signaling as ER agonists (77, 78), allowing for both direct and indirect estrogen activity effects on mammary gland development and function. For example, i*n utero*, perinatal, and juvenile BPA exposure in rodents caused increased branching, duct development, number and volume of terminal end buds, and mammary epithelial cell proliferation, resulting in increased number of alveolar lobule cells (79–81), including at environmentally-relevant concentrations (82). Morphological changes persist into adulthood (80, 81). BPA exposure during gestation also impairs milk yield, lipid fraction, and protein synthesis (83, 84). Exposure to BPS also resulted in altered mammary gland development, including ERα and prolactin signaling in a manner suggestive of early involution and reduced nursing initiation in pups (85–87). Some studies have indicated potential non-monotonic dose-responses (88, 89), whereas others found no evidence of non-monotonicity (90). Timing of exposure during pregnancy is also likely important and an area of active research (87, 91). Collectively, these findings provide evidence that BPA and its analogues affect mammary gland development and lactation and provide additional support that these are outcomes susceptible to environmental EDCs, particularly those that are estrogenic.

Future Directions:

Toxicological and epidemiological research highlights the potential for modifiable environmental risk factors to influence human lactation. While the capacity for EDCs to impair mammary gland development is clear, the relationships between impaired mammary gland development reported in toxicological studies and altered lactation in humans are less well defined (11, 92). There is a need for further epidemiologic research exploring associations between EDCs and lactation outcomes, particularly with emerging highly fluorinated compounds, newer pesticides and fungicides, phthalates, and BPA analogues and other environmental phenols, which have scant evidence to date.

Consideration of additional exposure scenarios is likewise critical. Exposures to environmental contaminants rarely occur in isolation, and future research should evaluate joint exposures to complex environmental mixtures, particularly given toxicological evidence that EDCs may work through interrelated estrogenic, antiandrogenic, and antiestrogenic pathways to influence mammary gland development. Toxicological evidence of transgenerational effects of EDCs on lactation highlights the need for epidemiologic

research assessing EDC exposures during sensitive windows (e.g., pregnancy) and across generations, though such studies are logistically challenging to conduct.

Conclusions:

Toxicological and epidemiological research support that EDCs play a role in mammary gland development and function, which affect lactation duration. Further studies are needed to better understand the direct mechanism of EDCs on lactation, the significance of toxicant mixtures, and the transgenerational effects of EDCs on breastfeeding.

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Key Points:

- EDCs appear to affect breastfeeding duration by impacting mammary gland development and function and associated lactogenesis signaling.
- PFAS reduce breastfeeding duration through impaired mammary gland development, lactogenesis, and suppressed endocrine signaling.
- Individual halogenated aromatic hydrocarbons differ in their impact on lactation duration, likely due to the variety of signaling pathways they affect.
- While epidemiologic literature suggests that pesticides and fungicides decrease or have no effect on lactation duration, toxicological literature suggests that these chemicals enhance mammary gland development through estrogenic and/or antiandrgogenic pathways.
- More research is needed to explore the relation between EDCs and lactation, identify mechanisms by which EDCs influence lactation, account for the significance of toxicant mixtures, and explore transgenerational effects of EDCs on lactation.

Table 1 (Original):

Mechanisms of action from the toxicological literature and findings from the epidemiological literature supporting effects of endocrine-disrupting chemicals on breastfeeding

Group	Example / Subgroup	Potential Mechanism of Toxicity in Relation to Mammary Gland Development and Lactation	Overview of Epidemiologic Evidence of Association with Breastfeeding
Per - & polyfluoroalkyl substances (PFAS)	PFOA	• PPARα activation (28, 29) • Impaired mammary gland differentiation, lobular alveoli development, epithelial involution (23–27, 30) • Suppression of prolactin and placental lactogen signaling (31) • Alterations in milk protein gene expression (23) • Transgenerational impacts on mammary gland development (24)	• Epidemiologic studies generally support an association of greater PFAS with shorter duration of breastfeeding (19–21) • One study suggests that low level exposures to specific, less well-studied PFAS, may increase breastfeeding duration (22)
Halogenated aromatic hydrocarbons	TCDD	• AhR activation (48) • Reduced mammary gland size, epithelial elongation, branching, terminal end bud development, and milk production (41, 42, 44, 47)	• To our knowledge, the influence of dioxins and dibenzofurans on breastfeeding have not been characterized in the epidemiologic literature. • Associations of PCBs with breastfeeding duration are mixed (35–38) • One study observed no association of PBDEs with either initiation of duration of any or exclusive breastfeeding (37)
	PCDFs	• AhR activation (48)	
	PCBs	• Dioxin-like PCBs activate the AhR (48)	
	PBDEs	• Bind, but do not activate, the AhR (49) • Disrupt mammary gland development, including β-catenin signaling (50, 51)	
Organochlorine Pesticides (OCPs)	DDT	• ER agonist and AR antagonist (66) • Enhanced mammary gland development in pubertal rats (41)	• DDT exposure is generally associated with shorter duration of breastfeeding (36, 58, 59) • Some studies observe longer duration of breastfeeding (38) or no association (60, 61) with exposure to DDT or its breakdown products
Phthalates and Bisphenols	BBP, DEHP	• Impaired mammary gland (72) • BBP increases the proliferative index and expression of cell proliferation genes in mammary tissue (73, 74) • DEHP increases cell proliferation and number of alveolar buds (75) • Mammary gland effects are not observed at environmentally-relevant concentrations (76)	• Epidemiologic investigations of the influences of phthalates or BPA and its substitutes on breastfeeding are sparse • Limited epidemiologic evidence suggests no association of phthalates with breastfeeding duration (69) and shorter duration of any breastfeeding with greater BPA exposure (71)
	BPA, BPS	• ER agonist (77, 78) • Accelerated mammary gland development (e.g., branching, duct development, mammary epithelial cell proliferation) (79–82) • Reduced mammary gland differentiation, milk yield, lipid fraction, and protein synthesis (83, 84) • Altered ERα and prolactin signaling (85–87)	

Table Abbreviations: AhR = Aryl hydrocarbon receptor; AR = Androgen receptor, BBP= N-butyl benzyl phthalate, DDT = Dichlorodiphenyltrichloroethane, DEHP = Diethylhexyl phthalate, ER = Estrogen receptor, PBDEs = Polybrominated diphenyl ethers, PCBs = Polychlorinated biphenyls, PCDFs = Polychlorinated dibenzofurans, PFOA= Perfluorooctanoic acid, PPARα = Peroxisome proliferator-activated receptor-alpha, TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin