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Narrative Review

Determination of Persistent Organic Pollutants in Human Breast Milk and Their Health Effects

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Abstract

Breast milk, the primary source of nutrition for infants, contains the ideal combination of carbohydrates, lipids, and proteins, and provides immunological and other health benefits that protect against infections. Persistent Organic Pollutants (POPs) are lipophilic organic compounds that accumulate in adipose tissues after being assimilated by the mother from the environment. Infants can be exposed to POP through breast milk, making breastfeeding a significant source of exposure. This review aims to provide a comprehensive overview of the numerous POPs that are contaminated in breast milk, the analytical techniques used to detect them in breast milk, and the potential health impacts of these pollutants on mothers through bioaccumulation and on infants through breastfeeding. Peer-reviewed articles published between 1989 and 2023 that covered several key features, including methodologies, health consequences, and other significant factors, were abstracted to assess the major results and research gaps. The majority of research investigated the relationship between POP concentrations in breast milk and socio-demographic variables. The studies revealed that several Organochlorine Pesticides (OCPs), Polychlorinated Biphenyls (PCBs), and their derivatives and industrial by-products, such as polyaromatic hydrocarbons (PAHs), could contaminate breast milk, posing potential health risks to infants exposed to POPs in many regions of the world.

Keywords: Breast milk; Breastfeeding; Bioaccumulation; Infant; Persistent Organic Pollutants

Introduction

The environment consists of vital biological components such as water, food, and air, all of which are fundamental substances that have the potential to enter the human body. When considering the mother-infant relationship, the mother's body serves as the environment for the offspring throughout the periods of pregnancy and lactation (1). Human milk stands as the ideal nutritional source for infants, providing the optimum combination of lipids, carbohydrates, and proteins for infant development. It is known to provide various benefits for growth, immunity, and development (2). Breastfeeding benefits have been established in the early neonatal period and continue throughout childhood into adulthood. It provides documented benefits in terms of immunological, nutritional and emotional well-being. Additionally, there are notable health advantages for the mother (3). There is compelling evidence demonstrating the accumulation of persistent organohalogens, particularly persistent organic pollutants

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(POPs), in breast milk. POPs are chemicals that exhibit significantly high concentrations in breast milk, posing a considerable hazard to human health (1).

Persistent Organic Pollutants

The protocol on persistent organic pollutants (POPs) has been developed under the guidance of the United Nations Economic Commission for Europe (UN-ECE) Convention on Long-Range Transboundary Air Pollution; POPs are defined as a group of chemical compounds that have highly toxic potential. They are persistent, plausible to bioaccumulate and have the potential for long-range atmospheric transport and deposition. These pollutants can have detrimental effects on humans and the environment whether the location is near or far from the sources (4). They can migrate through the air, water, soil, and sediments and ramp up to levels detrimental to wildlife and human health (5).

These compounds are extremely resistant to photolytic, biological, and/or chemical degradation (5). POPs can be divided into two groups: halogenated and non-halogenated. Most POPs are known to be halogenated chemicals. The majority of POPs are characterized by the presence of carbon-halogen (chlorine, fluorine, or bromine) bonds that are resistant to natural environmental degradation. Non-halogenated POPs are also persistent in the environment due to their stable chemical structure (6). POPs are heterogenous organic chemical groups that exist in the environment as, (i) Organochlorine Pesticides (OCPs) such as dieldrin, endrin, heptachlor, chlordane, dichlorodiphenyltrichloroethane (DDT), mirex, and toxaphene; (ii) Industrial pollutants including polychlorinated biphenyls (PCBs) like PCB-28; PCB-52; PCB-70; and PCB-77, polybrominated diphenyl ethers (PBDEs) like pentaBDE; decaBDE; heptaBDE and perfluorooctanesulfonate (PFOS), Perfluorooctanoic acid (PFOA); and (iii) unintentional by-products generated as a result of industrial activities such as dioxins (polychlorinated dibenzo-p-dioxins (PCDDs), polyaromatic hydrocarbons (PAHs), and furans (polychlorinated dibenzofurans (PCDFs) (6–8).

Table 1 Types of Persistent Organic Pollutants in the environment, their sources and human consumption methods

Type of POP	Source	Human consumption method	Reference
Organochlorine pesticides (OCP) (DDT, HCH)	Agricultural pesticides (Insecticides, Herbicides, and fungicides)	Direct exposure, contaminated fatty foods, cigarette	(6) (1)
Polychlorinated biphenyls (PCBs)	As coolants and hydraulic lubricants in transformers and capacitors, dielectric fluids in transformers and large capacitors, etc	Animal products-meat, fish, and dairy, mussels, oysters, water	(9) (6) (1)
Dioxin and Furan	Waste incineration and open-burning	Animal products-meat, fish, and dairy	(6) (1)
Polyaromatic hydrocarbons (PAHs) and Per- and Poly-fluoroalkyl Substances (PFASs)	Coal and wood, automobile emissions, and cigarette smoke	Dairy products, grain, flour, and bran rice, fruits, and vegetables	(6)

DDT – Dichlorodiphenyltrichloroethane, HCH – Hexachlorocyclohexane

POPs are lipophilic chemicals which combine with fat or lipids and are hydrophobic. POPs can be stored in the adipose tissues, bio-accumulated in the food chain, and biomagnified due to their stability and lipophilic characteristics (10). The bioaccumulation capability of POPs makes them extremely hazardous (11). DDTs, HCHs, and their derivatives are the dominant OCPs in human tissues, mostly adipose tissues. Breast milk included high amounts and quantities of *p,p'*-Dicholrodiphenyldicholroethylene (*p,p'*-DDE), and –HCH (12). High-fat foods like fish, pork, and dairy products are the primary sources of human exposure to dioxins and furans. Burning waste, particularly medical waste, is a major source of dioxins and furans in developing countries (6).

Polychlorinated biphenyls (PCBs) are a class of chlorinated hydrocarbons with 209 different constituents, of which about 120-140 are present in the environment. Due to their great persistence and mobility, PCBs have been discovered in practically every environmental unit (5). A higher concentration of PCB was recognized in the breast milk of European and North American women, than in the women in non-industrialized counties. According to a study conducted in 1981, 93% of human milk samples surpassed the standard set by the US Food and Drug Administration for neonatal PCB intake in mg/kg body weight (1).

Contamination of POPs in Breast Tissues

Human breast milk can serve as an indicator of the concentrations of organic pollutants present in the human body (13). When POPs are consumed via food or other routes such as inhalation or ingestion of airborne particles and indoor dust that are contaminated (14), they undergo bioconcentration in adipose tissues. Due to their prolonged half-life, they tend to accumulate in the body over time and with age. Throughout an individual's lifetime, these molecules persistently reside in fat tissues. POPs that circulate in serum can be excreted slowly through stool or quickly removed from the body via breastfeeding (1).

After giving birth, women produce colostrum while breastfeeding. This colostrum contains high levels of fat-soluble environmental pollutants, which can accumulate in the infant's body (15). In addition, lipophilic pollutant concentrations in breast milk have been found to remain stable throughout the lactating period after decreasing during the first month. These concentrations are close to the initial neonatal blood concentrations (13). Breast milk has been regarded as an optimal medium for analyzing POPs due to its high lipid content. Due to their lipophilic nature, POPs are concentrated in the lipid phases. It can provide information on the mother and infant's exposure and its non-invasive collection method (16).

Organochlorine exposure is highest during the embryonic and fetal stages. There are strong associations of organochlorines observed among maternal adipose tissues, cord blood, plasma and breast milk, indicating the transfer of those pollutants through the placenta and during lactation. The women who have breastfed one or more children have lower body accumulation of these compounds than the women who have not breastfed. This could be due to the fact that during breastfeeding, the maternal body eliminates a greater amount of these compounds (17). DDTs, HCHs, and their derivatives are the most common OCPs detected in human tissues, particularly adipose tissues (12).

PAHs and POPs are difficult to analyze due to their properties and are present in low concentrations in complex matrices. QuEChERS extraction methods are used to analyze a broad spectrum of analytes, such as multi-residue pesticide analysis, and several pollutants including antibiotics, mycotoxins, hormones, and persistent organic pollutants. These methods, including dispersive solid-phase extraction (d-SPE), are typically coupled with either gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-mass spectrometry (LC-MS) for analysis. Recently, GC and LC-tandem mass spectrometry have become popular with QuEChERS extraction due to their high selectivity, sensitivity, and specificity (18).

This review summarizes previously reported numerous POPs that are contaminated in breast milk, the analytical techniques used to detect them in breast milk, and the potential health impacts of these pollutants on mothers through bioaccumulation and infants through breastfeeding.

Methods

Peer-reviewed articles published between 1989 and 2023 were searched using relevant keywords in Google Scholar and PubMed databases. The searches were limited to English-written articles, and a comprehensive review was conducted to gather information on POP contamination in infants. Key features such as methodologies, health implications, and other vital factors were extracted to evaluate the major findings and research gaps. The results were summarized and discussed.

Results and Discussion

Analytical Techniques

Due to the critical characteristics of the POPs, developing an expeditious and highly sensitive analytical technique is crucial to identify and quantify POP residues in human colostrum at the initial level (19). QuEChERS extraction method is the most rapid, easy, cheap, effective robust, and safe method other than the less efficient classical extraction methods in multi-residue pesticide analysis. This approach has been widely used to identify POPs such as Dioxin, Polychlorinated biphenyls, Perfluoroalkyl compounds, and bromine-containing flame retardants in food, environmental, and biological matrices (18). This approach provides several advantages. To begin, samples pretreated with acetonitrile (MeCN-) can be injected into both GC and LC simultaneously utilizing the QuEChERS method. Additionally, MeCN is miscible with water (H2O), allowing it to extract target analytes from water-based matrices. Salts such as magnesium sulfate (MgSO4) or sodium chloride (NaCl) aid in the effective separation of the solvent from the aqueous media. Furthermore, tandem mass spectrometry (MS/MS) has gained prominence in the final stage of analyzing multiple persistent organic pollutants (POPs). This technique is acknowledged for its effectiveness in overcoming the difficulties associated with identifying target analytes in complex matrices that contain excessive amounts of interfering substances, such as the fat present in human milk (19). Various analytical techniques are mentioned in Table S1.

A study done in Santiago de Compostela (North-western Spain) (Table S1) describes that human milk samples contained the majority of the target contaminants, with median concentrations in the following order: PAHs (15 ng/g fat), Pyrethroids (PYRs) (12 ng/g fat), Organophosphate Pesticides (OPPs) (6.3 ng/g fat), Non-dioxin-like polychlorinated biphenyls (NDLPCBs) (2.89 ng/g fat), OCPs (2.85 ng/g fat), PBDEs (1.5 ng/g fat), and Dioxin-like polychlorinated biphenyls (DLPCBs) (0.52 ng/g fat). Maternal age, sample time point, and location of residency were found to be variables that may affect the levels of the majority of the discovered organic pollutants. There were important correlations found between place of residence and maternal age, particularly concerning certain pesticides such as dieldrin, fenthion and heptachlor. Additionally, significant interactions were observed between weight gain during pregnancy and smoking habits for PAHs and between owning pets and age for chlorpyrifos. Egg, mollusks, and vegetable oil consumption were also linked to increased levels of some of the targeted organic contaminants (20).

Whereas the study's Mirex detection; research is done in Canada, (21) frequency has increased in contrast to earlier research, and there has been a corresponding decrease in concentration over time (median 251 pg g^{-1} lipid/0.251 ng g^{-1} lipid; this study). Only 10 of the 298 samples had mirex concentrations of more than 1000 pg g^{-1} lipid, and less than 10% of the samples analyzed for Dodecachlorodimethanodibenzocyclooctane (DDC-CO) had concentrations greater than 50 pg g^{-1} lipid, which may explain why there was no correlation between participant parity and either mirex or DDC-CO concentrations in the current study.

According to the study conducted in Lebanon, in breast milk samples, only DDE was detected out of the screened persistent organic pollutants (POPs), such as hexachlorobenzene, PCBs, lindane, β-BHC, heptachlor, DDE, dieldrin, endrin, Dichlorodiphenyldichloroethane (DDD), DDT plus. The presence of DDE contamination in breast milk (17.9% of samples) exhibited a significant correlation with maternal age ($\rho = 0.34$, $p = 0.0143$) pre-pregnancy Body Mass Index (BMI) ($\rho = 0.41$, $p = 0.0155$), with a mean (SD) concentration of 11.6 (5.0) μg/L and a range varying from 5.7 to 21.4 μg/L. POPs tend to accumulate in adipose tissues, and individuals with greater BMI are often related to increased body fat. Consequently, some POPs transfer into breast milk because breastfeeding women utilize fat reserves when secreting milk. In comparison to mothers who consumed cereal less frequently, those who consumed cereal at least twice a week exhibited detectable levels of DDE contamination in their breast milk ($p = 0.015$). A significant association between DDE contamination and consuming potatoes, dry beans, or canned beans at least once a week ($p = 0.026$, 0.036, and 0.002, respectively) was also discovered. (22).

The study discovered that HCB residue in human milk in Jinhua, China was more common than DDE and β -HCH, according to the detection rate. This is possibly due to the greater contamination source of HCB compared to DDE and β -HCH in China; including Jinhua. According to the study OPPs and PYRs were not discovered in human milk in Jinhua. Among the organochlorine pesticides (OCPs) detected in human milk, the detection rate was highest for hexachlorobenzene (HCB) (83.6%), followed by *p,p′*-DDE (58.2%), and β-hexachlorocyclohexane (β-HCH) (36.4%). Regarding mean levels *p,p′*-DDE (85.2 ± 105.1 ng/g lipid) had the highest concentration, followed by β-HCH (32.0 ± 59.0 ng/g lipid) and HCB (29.4 ± 30.0 ng/g lipid). A positive correlation was observed between the presence of *p,p′*-DDE residues in human milk and age ($r = 0.279$, $p = 0.027$, $n = 55$). The Kruskal-Wallis H test indicated that the older mothers (age ≥ 34) had considerably larger amounts of *p,p′*-DDE in their human milk than the younger mothers (age ≤ 29). Social demographic factors such as BMI, parity, eating habits, environment, living style, etc. were not correlated to pesticide amounts in human milk (23).

A study conducted in Poland (24) discovered a statistically significant difference of $p < 0.1$ between milk samples from urban and rural mothers in 2,3,7,8-tetrachloro-dibenzo-p-dioxin (2,3,7,8-TCDD) (P50, 0.985 vs. 0.313 pg Toxicant Equivalent Quotient (TEQ)/g fat); 1,2,37,8,9 - HxCDD (P50, 0.133 vs. 0.061 pg TEQ/g fat); and 2,3,4,6,7-HxCDF (P50, 0.138 vs. 0.068 pg TEQ/g fat). No significant differences were observed for the remaining 14 PCDD/F and 12 dl-PCB congeners. The approach described in this study is appropriate for detecting low levels of PCDD/Fs and dl-PCBs in the biological sample.

A study conducted at Insular Materno-Infantil University Hospital in Spain, (19) analyzed of both colostrum and mature milk samples and revealed the presence of nine OCP residues. However, the levels of other OCPs were either undetectable or significantly lower level, well below the detection limits of the applied method. The analysis of the samples revealed that both hexachlorobenzene and *p,p′*-DDE were detected in 100% of the samples. The median concentrations of hexachlorobenzene and *p,p′*-DDE were found to be 0.75 μg/L and 8.84 μg/L in colostrum, and 0.76 μg/L and 9.14 μg/L in milk, respectively. The highly chlorinated marker-PCBs, namely nos. 138 and 180 were the most frequently detected congeners, present in 100% of both sample types. In both milk and colostrum samples, the study detected the presence of several PAH compounds, namely fluorene, phenanthrene, naphthalene, fluoranthene, pyrene, chrysene, and benzo[a]anthracene.

According to the findings of the research conducted in Yucatan, Mexico, the municipality of Kanasin, which is close to the state capital and is part of the metropolitan region, had the highest concentration of OCP. The highest levels were identified in heptachlor epoxide (18.43 mg/kg), aldrin (0.122 mg/kg), dieldrin (0.121 mg/kg), endrin (1.92 mg/kg), endrin aldehyde (0.112 mg/kg), endosulfan II (0.157 mg/kg), and 4, 4′-DDD (0.235 mg/kg). Based on the analysis conducted, it can be concluded OCP contamination in breast milk, which is caused by the use of banned and restricted pesticides in agricultural and animal operations, impacts and encourages the bioaccumulation of residues in Maya women's breast milk and the presence of identified and quantified OCP residues may increase the risk of breast cancer in women and neurodevelopmental abnormalities in their offspring (25).

A study conducted in France, (26) showed that French women had significantly lower absolute PCB exposure levels than Danish and Finnish women while having lower proportions of PCDDs and greater proportions of PCBs (both dl- and ndl-PCBs). The opposite pattern, including a smaller percentage of ortho-PCBs, was seen in Finnish women.

According to the study conducted in Flanders, Belgium, (27) 84 individual samples were collected from newborn mothers between 2 and 8 weeks after delivery. The analytical procedure is summarized in Table S1. PCB congeners PCB 118, PCB 138, PCB 153, PCB 170, and PCB 180 were detectable in all 84 individual samples and the pooled sample, as were pesticides HCB, *p,p'*-DDE, oxychlordane, and β-HCH, dl-PCBs, and PCDD/Fs. PCB congeners PCB 31, PCB 52, PCB 95, and PCB 149, as well as the insecticides α-chlordane, ɤ-chlordane, and α-HCH, were all found to be below the Limit of Quantitation (LOQ) in all individual samples. This study discovered pollutants such as metabolites of the pesticide DDT, trans-nonachlor, and the brominated flame retardant HBCD in higher concentrations. Most pollutant concentrations in this investigation were lower or comparable to those identified in the combined Belgian sample from the 2006 WHO human milk study. The exceptions were the pesticides dichlorodiphenyltrichloroethane (DDT) and its metabolites (which increased by 25%), trans-nonachlor (which increased by 94%), and the brominated flame retardant hexachlorocyclododecane (HBCD), which increased by 153%. Even though these pesticides were restricted in Belgium more than 30 years ago, the concentrations of DDT and its metabolites and trans-nonachlor in the pooled sample from this investigation were 25% and 94% higher, respectively, than the results of the WHO study conducted four years earlier. Perfluorinated compounds, PFOS and PFOA, were traceable in all 40 samples. However, PFNA and PFHxS were only quantifiable in 42.5% and 20% of the samples, respectively. These chemicals were discovered for the first time in human milk samples from Belgium.

A study conducted in Hong Kong, (28) identified compounds, including HCB (range: 17.0–29.6 ng g^{-1} fat), trans-nonachlor (4.1–18 ng g^{-1} fat), cis-heptachlor-epoxide ((<0.5–1.0 ng g^{-1}fat), oxy-chlordane (2.4–9.4 ng g^{-1} fat), alpha-HCH (<0.5–1.0 ng g^{-1} fat), beta-HCH (288–1380 ng g^{-1} fat), and BDE 47 (0.9–4.6 ng g^{-1} fat), BDE 153 (0.6–1.4 ng g^{-1} fat). Dieldrin, with concentrations ranging from less than 0.5 to 2 ng per gram of fat, was present in eight pools. However, it was not detected in Pools 6 and 7, which included mothers from mainland China. In some pools, Parlar 26, Parlar 50, BDE 28, BDE 99, and BDE 100 were detected at levels below or extremely close to the LOQ levels. According to the social demographic factors associated with the measured POP concentrations, levels of beta-HCH, cis-heptachlor-epoxide, sum-chlordane, and trans-nonachlor were lower in milk pools from mothers who had mostly lived in mainland China, but no geographic-specific features were revealed for HCB and PBDE. A substantial positive association between the mother's age (17 – 42) and beta-HCH ($r = 0.855$, $p = 0.002$) and sum-chlordane ($r = 0.894$, $p < 0.0005$) concentrations revealed that body load for these pesticides was age dependent, but no age relationship could be seen for other pesticides.

Comparing research findings from various regions worldwide, DDE, HCB, and PCB were commonly identified. DDE was found to be the main persistent organic pollutant (POP) in research done in Lebanon; in 17.9% of the samples, the mean concentration was 11.6 (5.0) µg/L. Similarly, research in Jinhua revealed that *p,p'*-DDE had the highest mean concentration (85.2 ± 105.1 ng/g lipid), particularly in breast milk from mothers who were 34 years of age or older. In Spain's Insular Materno-Infantil University Hospital, DDE was detected in colostrum (8.84 µg/L) and milk (9.14 µg/L), along with HCB at 0.75 µg/L in colostrum and 0.76 µg/L in milk. However, in Flanders, Belgium, both HCB and *p,p'*-DDE were below the Limit of Quantitation (LOQ), and HCB (range: 17.0–29.6 ng g^{-1} fat) was also identified in Hong Kong.

When considering PCBs, A Polish investigation found no statistically significant variations for the remaining 12 dl-PCB congeners. In France, PCB exposure levels were higher than in Danish and Finnish women, with lower proportions of PCDDs and higher proportions of PCBs (both dl- and ndl-PCBs). Therefore, in Flanders, Belgium, PCB congeners 31, 52, 95, and 149 were below the Limit of Quantitation (LOQ), but PCB congeners 118, 138, 153, 170, and 180 were detected in all 84 individual samples and the pooled sample.

In general, diverse analytical methods were employed to detect persistent organic pollutants in human breast milk. In all trials, extraction and purification processes were conducted. Given the relatively high-fat content in human milk, especially in colostrum, a cleanup step was considered essential to remove lipids that might diminish signals or potentially damage the chromatography column (19). Analyzing PAHs and POPs is tough due to their properties and low concentrations in complex samples. The QuEChERS method, initially designed for monitoring pesticides, proves effective for this purpose. The QuEChERS method, involving dispersive solid-phase extraction (d-SPE), is commonly paired with gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-mass spectrometry (LC-MS) for analysis. Recently, there's been a trend toward using GC and LC-tandem mass spectrometry for its high selectivity and sensitivity. This flexibility allows for the modification of extraction methods for target analytes by choosing different extraction solvents, salt formulations, and buffers for salting-out partitioning. Additionally, various d-SPE and solid-phase extraction (SPE) sorbents can be selected for the cleanup process. Traditional extraction methods involve multiple steps because analytical instruments like gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry (GC-MS and LC-MS) exhibit limited selectivity compared to the more commonly used GC and LC-tandem mass spectrometry (GC-MS/MS and LC-MS/MS) with the QuEChERS method (18).

Health Effects

Infancy is the period during which an infant undergoes rapid body development, and during this stage, the immune system, reproductive system, and neurological systems are functionally immature (1). Breast milk is considered an essential complete food for an infant since it provides almost all the important nutrients and promotes infant growth and development. As well as it is crucial for the prevention of infections and cognitive improvement. POPs particularly highly lipophilic, tend to accumulate in breast milk. However epidemiological studies discovered that POPs can be transferred to infants through breastfeeding and have potential health risks in infants (12). POP levels in breast milk were directly associated with infant gut microbial function, early childhood behavioral problems (HBCD), developmental abnormalities (4), increased blood pressure (Dioxins/furans/OCPs) (6), and delayed infant growth. Recently, several POPs have been associated with reducing immunity in infants and children, neurobehavioral impairment (PCB/OCPs), and cancer induction or promotion (OCPs and PCBs) (6, (12).

Children's estimated blood POP levels were greater during the first months of postnatal life than those measured during their prenatal lives on average; As a result of breastfeeding, levels increased during the first three to four months of life and then started to reduce from the fourth to fifth month; in Spain, this corresponds to the time that most mothers go back to work and either cease breastfeeding or start combining it with other types of food. Breastfeeding leads to increased levels of persistent organic pollutants (POPs) in children's blood after birth (29).

Growth and Reproductive Problems

Conflicting evidence exists regarding breastfeeding exposure and weight gain in infancy. However, preliminary findings suggest that in-utero PCB exposure may contribute to low birth weight (1). A relationship exists between increasing maternal serum HCB and PCB levels and reduced birth weight. Also, decreased gestation length, head circumference, crown-heel length, and birth length have been associated with increased maternal or cord serum HCB levels. In the multivariate models, there was a negative association between birth weight and increasing levels of PCBs ($\beta = -174.1$ g; 95% CI: -332.4, -15.9) as well as HCB ($\beta = -161.1$ g; 95% CI: -296.6, -25.7) . After additional adjustment for gestational weight gain, these estimates were slightly reduced ($\beta = -154.3$ g; 95% CI: -300.8, -7.9 for HCB and $\beta =$

−135.7 g; 95% CI: −315.4, 43.9 for PCBs) A significant decrease in head circumference was observed with higher HCB levels. Additionally, smaller head circumferences were observed in association with DDE, total PCBs and non-dioxin-like PCBs (30).

Reproductive issues and diseases are caused by malfunctions in the male and female reproductive systems. POP exposure directly influences the reproductive system: reduced sperm quality and quantity influence the sex ratio and early puberty (11). In animal studies, PCBs and dioxins have been firmly associated with decreased sperm count and fertility, as well as endometriosis, and changes in sexual development and behavior (1).

Endocrine Disruption

The endocrine system assumes responsibility for various functions such as growth, development, and regulation via various glands such as the pituitary, and pancreas; which secrete different hormones (11). Previous studies reported that the binding of dioxin, furan, and dioxin-like PCBs with aryl hydrocarbon receptor and their interaction with hormone receptors, directly influenced the transcription factors activation, thereby disrupting the normal function of hormones (6). POPs interfere with the endocrine process of lactation, as evidenced by the association between elevated levels of PCBs and DDE in breast milk and reduced duration of breastfeeding (1). Women with higher DDE levels breastfed for shorter periods, decreasing from 7.5 to 3.0 months as DDE levels ranged from 0-2.5 to ≥12.5 ppm (31).

Epidemiological investigations have documented that POPs are influenced by thyroid disruption due to certain POPs having chemical structures that are similar to thyroid hormones (THs) (32). There is a correlation between increased dioxins and PCB levels and considerably lower plasma concentrations of total thyroxine and total triiodothyronine in the mother, as well as elevated plasma concentration of TSH has been found in infants during the second and third months after birth, according to research on 105 maternal-infant pairs by Nickerson (2006) (1). There was a tendency for a reduction in maternal plasma thyroid hormone (TT_4) levels during the final month of pregnancy in association with elevated planar-PCB Toxicant Equivalent Quotient (TEQ) levels ($r = -0.27$, $p < 0.05$). The breastfed group with high dioxin exposure demonstrated a significantly elevated TSH level (8.5 ± 6.0 compared to 11.6 ± 8.0 μIU/mL, $p < 0.05$, and 1.6 ± 0.6 compared to 2.3 ± 1.0 μIU/mL, $p < 0.0004$). When categorizing infants into low and high total PCB-dioxin TEQ-exposed breastfed groups (median = 72.43 pg TEQ/g fat), the high-exposed group exhibited a significantly lower mean plasma FT_4 level in the second week after birth (24.6 ± 3.5 compared to 23.0 ± 3.3 pmol/L, $p < 0.05$) (33). The research conducted in the LUPE cohort (2015–2016, Bavaria, Germany); reported that PBDEs had the highest thyroid-disrupting potencies among the POP studied (32).

The impact of *p,p'*-DDE was observed to primarily disrupt gene expression by inhibiting the progesterone receptor (PR) at DDT, potentially interacting with estrogen receptor (ERα) and PR at a concentration of 1.0×10^{-8} mol/L. Notably, comparable findings were identified with *p,p'*-DDT, suggesting potential interactions with ER_{α} and PR at a concentration of 10^{-5} mol/L, leading to significant estrogenic and anti-progesterone activities (34).

Carcinogenic Effects

POP concentrations in low-density lipoproteins are associated with a variety of cancers. High levels of these POPs are associated with an increased risk of breast cancer due to POPs accumulating in adipose tissues. Perfluorooctane sulfonate (PFOS), and perfluorooctanoic acid (PFOA) have been associated with a higher risk of breast cancer in women (11). The consumption of chlordecone-contaminated food in the French West Indies has been associated with an increased risk of cancer. In breast cancer patients, higher amounts of OCP residues were detected than in normal females, regardless of age, diet, and geographical distribution. OCP has been associated with an increased risk of breast cancer. According to the International Agency for Research on Cancer (IARC) benzo[k]fluoranthene, benzo[b]fluoranthene, benzo[j]fluoranthene, and indeno[1,2,3-c,d]pyrene are classified as possible human carcinogens, while several PAHs, such as benzo[a]anthracene and benzo[a]pyrene, are categorized as probable human carcinogens. Individuals exposed to TCDD at doses 10–1000 times higher than the normal population had increased chances of all cancers, according to studies (6).

More chlorine substitutions in PCBs meant a higher presence of lipoproteins compared to plasma. The correlation between chlorine substitutions and distribution in low/very low-density lipoproteins (LDL/VLDL) and high-density lipoproteins (HDL) was 0.64 ($p < 0.001$) and 0.61 ($p < 0001$), respectively. Analyzing multiple factors, it was discovered that having high levels of POPs in HDL is more connected to cardiovascular disease (CVD), while increased POP concentrations in LDL/VLDL are more linked to cancer (35).

Immunological Effects

People who have been exposed to low-level environmental concentrations of POPs have also shown immune-modulating effects (5). Researchers investigated the impact of PCB levels during the perinatal and postnatal, on the occurrence of infectious diseases. After vaccination, researchers evaluated humoral immunity by assessing antibodies and immunologic markers in children at the age of 42 months. The study suggests that prenatal PCB exposure is linked to decreased levels of antibodies for measles and mumps after vaccination. Significant changes in T-cell markers were also observed, indicating an increased vulnerability to infectious diseases (1). In the Canadian study, Inuit women had an average PCB level of 111.3 µg/L in breast milk, much higher than the 28.4 µg/L found in Caucasian women ($p = 0.05$). The concentrations of PCB in milk fat were 3.60 mg/kg for Inuit women and 0.77 mg/kg for Caucasian women, respectively (36). In Canadian Inuit babies exposed to high levels of organochlorines, there was a higher chance of acute otitis and difficulties with vaccinations, as many failed to generate antibody responses to standard vaccines (5).

Dutch infants' pre- and post-natal exposure to PCBs and PCDDs was associated with certain immunological abnormalities. Although their study did not discover any more diseases among the children as a result of these aberrations, it is still possible that they persisted and presaged later difficulties including immune suppression, allergies, and autoimmune diseases. The Swedish study suggests a potential direct link between the dietary consumption of PCDD/F and PCBs and a reduction in the number of cells involved in immune defense against viruses and tumors (5).

Gaps in the current research and areas for future studies

The primary focus of our review was to identify the types of POPs contaminated in breast milk in various countries, analytical techniques used to detect POP levels in human breast milk, and their health consequences on the mother and the newborn. POP accumulation in adipose tissues and transmission through breastfeeding pose possible health hazards to the infant, including growth and reproductive disorders, endocrine disruption, and immunological abnormalities, as well as the development of breast cancer in mothers. However, monitoring and determining the level of POPs in breast milk is important for reducing the risk to infants.

Comparative studies on groups of children who were breastfed versus those who were given formula in environments with similar conditions can provide valuable insights into the transfer of persistent organic pollutants (POPs) via breast milk. Further research is required to comprehend the process of how POPs enter adipose cells. Improved technique and experimental parameters can lower the method's detection limit, which helps identify low-level contaminants in samples of breast milk. It is crucial to conduct further research to understand the impact of persistent organic pollutants (POPs) on newborns' health.

Conclusion

Based on the referenced research articles, it can be concluded that POPs have the potential to accumulate in human breast tissues, transfer through breastfeeding to infants, and pose health risks for both mothers and infants. Furthermore, the analytical methodologies for determining POPs in breast milk were comparable among investigations. Among referred articles except for HBCD isomer separation, which was generally detected using Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), all POPs in breast milk were detected by gas chromatography-mass spectrometry (GC-MS). The methodological variations that were most obvious were the clean-up techniques used and the organic solvents chosen for extraction. Finally, this area of research should improve with the current knowledge and suggest that encouraging long-term monitoring of POPs in human milk is necessary to ensure the health of infants.

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