Review

Banrida Wahlang*

Exposure to persistent organic pollutants: impact on women's health

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Abstract: This literature review focuses on the causal relationship between persistent organic pollutants (POPs) exposure and women's health disorders, particularly cancer, cardio-metabolic events and reproductive health. Progressive industrialization has resulted in the production of a multitude of chemicals that are released into the environment on a daily basis. Environmental chemicals or pollutants are not only hazardous to our ecosystem but also lead to various health problems that affect the human population worldwide irrespective of gender, race or age. However, most environmental health studies that have been conducted, until recently, were exclusively biased with regard to sex and gender, beginning with exposure studies that were reported mostly in male, occupational workers and animal studies being carried out mostly in male rodent models. Health-related issues pertaining to women of all age groups have not been studied thoroughly and rather disregarded in most aspects of basic health science research and it is therefore pertinent that we address these limitations in environmental health. The review also addresses studies looking at the associations between health outcomes and exposures to POPs, particularly, polychlorinated biphenyls (PCBs), dioxins and pesticides, reported in cohort studies while accounting for gender differences. Considering that current levels of POPs in women can also impact future generations, informative guidelines related to dietary patterns and exposure history are needed for women of reproductive age. Additionally, occupational cohorts of highly exposed women worldwide, such as women working in manufacturing plants and female pesticide applicators are required to gather more information on population susceptibility and disease pathology.

Keywords: breast cancer; cardiovascular; metabolic; POPs; women.

Background

Progressive industrialization and technological globalization have resulted in the production of a multitude of chemicals that are released into the environment on a daily basis. Environmental chemicals or pollutants are not only hazardous to our ecosystem and ecological equilibrium but also lead to various health issues affecting the human population worldwide. Numerous epidemiologic studies have demonstrated that occupational or accidental exposure to organic compounds and metals result in illnesses including cancer, cardiovascular events and pulmonary diseases. Moreover, an extensive amount of scientific research studies has confirmed the toxicological effects of these chemicals in both in vivo and in vitro models. Fundamentally, the health consequences of chemical/pollutant exposure in females are confounded and dictated by biological factors such as menarche, pregnancy, lactation and menopause which are absent when evaluating risk assessment and toxicological profiles simply considering male representatives. The tendency to develop disorders related to breast cancer, fibroids or reproduction is also unique to women's health. It is also important to keep in mind that the amount and type of exposure such as chronic versus acute and low dose versus high dose also play significant roles when elucidating exposure risks which is another crucial factor, considering that back in the day, women were not necessarily hired for industrial work but rather viewed as caretakers and homemakers. Given all these factors, it appears that health related issues pertaining to women of all age groups have not been extensively studied and rather disregarded in most aspects of basic health science research and it is therefore pertinent that we address these drawbacks and limitations especially in environmental health. So far, a number of organizations including the National Institutes of Health (NIH) and multiple research groups have recognized and acknowledged these discrepancies, especially with evidence of gender- and sex-differences in drug screening (1, 2), thereby stressing on the importance of using both male and female rodent models. This will facilitate risk assessment based on the identity of the subject (gender) and enable identification of biological sexual differences (sex) when investigating disease

*Corresponding author: Banrida Wahlang, PhD, Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Louisville School of Medicine, 505 S. Hancock Street, CTRB, Louisville, KY 40202-1617, USA, Phone: +502 852-3912, Fax: +502 852-8927, E-mail: banrida.wahlang@louisville.edu.
<http://orcid.org/0000-0002-4356-1743>

pathology and progression, drug and chemical toxicity and therapeutic/pharmacological interventions.

This review focuses on the effects of persistent organic pollutants (POPs) in women's health, with emphasis on cancer, cardio-metabolic events and reproductive health. The review also addresses studies that take gender into account while focusing on POPs, particularly PCBs (polychlorinated biphenyls), dioxins and pesticides. The publications described and cited in the current review were selected from a literature search using the following keywords – “persistent organic pollutant exposure in women”, “effects of persistent organic pollutant exposure on gender”, “persistent organic pollutant exposure and sex differences”, “persistent organic pollutants and transgenerational effects” and related terms. This review also identifies classes of pollutants in relation to health outcomes, because there is a myriad of environmental toxicants that affect human health. Moreover, it is important to review the health effects of not just a single chemical, but rather multiple classes of chemicals or cocktails of environmental pollutants to enable us to better predict their overall behavior as well as offer a more realistic representation of health outcomes from environmental chemical exposure.

Environmental pollutants of interest: POPs

POPs are poly-halogenated organic compounds that persist in the environment due to their resistance to biochemical and photolytic processes (3, 4). POPs comprise numerous artificial chemicals including polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), dioxins, brominated flame retardants (BFRs), perfluorinated compounds (PFCs) and polycyclic aromatic hydrocarbons such as benzo(*a*)pyrene found in coal and tar deposits. Due to their stability and lipophilic nature, POPs bioaccumulate in the adipose tissue of living organisms and climb up the food chain, biomagnify, and sequester in humans (5).

PCBs were manufactured from the 1930 to 1970s and commercially used as dielectric fluids due to their excellent thermodynamic stability. In light of their carcinogenic potency, PCB production has been banned for over three decades in the United States (US) (Toxic Substances Control Act, 1979) and worldwide when the Stockholm Convention on Persistent Organic Pollutants (POPs Treaty) was signed in 2001 and implemented in May 2004, when enough countries had ratified it (6–8).

In fact, 12 POPs, known as the “Dirty Dozen”, including PCBs, were banned from global production and use by the POPs treaty. Table 1A shows all the POPs listed for elimination since 2004. Between 2009 and 2017, the Stockholm Convention added additional chemicals to their list for elimination or restriction including more pesticides, and industrial chemicals comprising agents categorized as BFRs and PFCs (Table 1B) (9–11). Unlike PCBs, polychlorinated dibenzo-*p*-dioxins (PCDDs) or simply dioxins are by-products of organochloride manufacturing or incineration of chlorine-containing substances (12). The most toxic member of the dioxin family, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), also inaccurately referred to as “the dioxin” is a known contaminant of Agent Orange, an herbicide used by the US military during the Vietnam War from 1961 to 1971. On the other hand, BFRs are organo-bromine compounds, incorporated into industrial products to reduce their flammability, and such compounds can leak from consumer products leading to human exposure and health risks (13). Experimental studies have shown that conventional BFRs such as polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane and tetrabromobisphenol A can induce endocrine, reproductive and behavioral abnormalities with some human epidemiologic studies confirming these laboratory observations (14, 15). Most PBDEs have been banned while specific exemptions on production and usage have been imposed on other BFRs. Other emerging POPs such as polybrominated dibenzo-*p*-dioxin and dibenzofuran (PBDDs and PBDFs) occur as trace contaminants in flame retardants (16). Similar to BFRs, PFCs are also hazardous industrial chemicals, and act as fluorosurfactants which are ubiquitously used in Teflon products, water resistant textiles and fire-fighting foam; examples of PFCs include perfluorosulfonic acids and related derivatives (17, 18).

The health implications associated with exposure to POPs can be classified as either acute or chronic, depending on the dose, duration and types of chemicals or mixtures. Historically, human exposures to POPs occurred primarily through occupational or accidental exposures which were generally at high doses over shorter periods of time and viewed as acute exposures. Incidences of mass PCB poisonings were reported where people consumed rice bran oil that was previously contaminated with PCBs and PCDFs during production resulting in accidental exposures, namely, “Yusho disease” or “oil disease” in 1968 that affected 14,000 people in Japan, and “Yu-cheng disease” in 1979 that affected approximately 2000 people in Taiwan (19–22). These cohorts suffered from multiple disorders including chloracne, ocular lesions and carcinogenesis. Such health effects were also observed

Table 1: Types of persistent organic pollutants (POPs) under the Stockholm Convention list.

Chemical class/name	Type	Action taken
A. Stockholm Convention (2004)		
Polychlorinated biphenyls (PCBs)	Industrial chemicals/dielectric fluids	Elimination (Annex A) Reduction of releases from unintentional production (Annex C)
Polychlorinated dibenzo- <i>p</i> -dioxins (PCDDs)	Industrial by-products	Reduction of releases from unintentional production (Annex C)
Polychlorinated dibenzofurans (PCDFs)	Industrial by-products	Reduction of releases from unintentional production (Annex C)
Aldrin, dieldrin, endrin, chlordane, heptachlor, hexachlorobenzene, Mirex, toxaphene	Organochlorine pesticides (OCPs)	Elimination (Annex A)
Dichlorodiphenyl-trichloroethane (DDT)	Organochlorine pesticide	Restriction of use (Annex B)
B. Additional chemicals added to the list (2009–2017)		
Polybrominated diphenyl ethers (tetra- and penta-, hexa- and hepta-) (PBDEs), hexabromocyclododecane (HBCD) and hexabromobiphenyl	Industrial chemicals/brominated flame retardants	Elimination (Annex A)
Perfluorooctanesulfonic acid (PFOS), its salts and perfluorooctanesulfonyl fluoride (POSF)	Industrial chemicals/fluorosurfactants	Restriction of use (Annex B)
Chlorinated naphthalenes (di- to octa-)	Industrial chemicals/electrical insulation	Elimination (Annex A) Reduction of releases from unintentional production (Annex C)
Hexachlorobutadiene	Industrial chemical/solvent	Elimination (Annex A) Reduction of releases from unintentional production (Annex C)
Chlordecone, α -, β - and γ -hexachlorocyclohexane (Lindane), Endosulfan and its related isomers	Organochlorine pesticides	Elimination (Annex A)
Pentachlorobenzene	Organochlorine pesticide	Elimination (Annex A) Reduction of releases from unintentional production (Annex C)
Pentachlorophenol and its salts and esters	Organochlorine pesticides	Elimination (Annex A)
Short-chained, chlorinated paraffins	Industrial chemicals/plasticizers	Elimination (Annex A)

in occupational populations that worked at electrical manufacturing plants or dealt with PCB-containing equipment (23–26). A number of industrial accidents and emissions have resulted in dioxin contamination and exposure. The “Seveso disaster” that took place in Italy in 1976 was an industrial accident that led to the highest exposures of TCDD ever known in residential populations while the use of Agent Orange left major health impacts in the Vietnamese population (27, 28). On the contrary, chronic exposures are normally at lower concentrations and transpire over the person’s lifetime. Chronic exposure to POPs occur predominantly through dietary sources such as consumption of POPs-contaminated sea food (29, 30). Other exposure routes include inhalation, in utero exposures through the mother, and to a lesser extent, through breastfeeding (31, 32). Moreover, serum levels of POPs in humans tend to be higher in women than men despite notions that childbirth and breastfeeding are means of POPs clearance (5, 33). Exposure to POPs can damage the nervous, hormonal, reproductive, and immune systems

with very high exposures resulting in mortality (34–37). While acute exposures to POPs are often associated with birth defects and cancer (22, 23), chronic and background exposures are more frequently associated with metabolic and cardiovascular diseases (38, 39).

Mechanism(s) of action of POPs

Cellular and molecular mechanisms associated with toxicity mediated by exposure to POPs appear to involve multiple receptor pathways (Table 2). In vivo and in vitro studies have demonstrated toxicological effects of POPs in different organ systems and illustrated the various mechanistic facets that eventually influence disease outcomes. The most commonly studied mechanistic pathway of POPs toxicity is the aryl hydrocarbon receptor (AhR) activation pathway, which in due course activates the AhR target gene battery, resulting in undesirable

Table 2: General protein-chemical interactions that mediate toxicity.

Ligands	Receptor/protein	Response
Dioxins (PCDDs), coplanar PCBs, PCDFs, OCPs, e.g. DDT	Arylhydrocarbon receptor (AhR)	Activation (agonist)
Non-coplanar PCBs, dioxins, PBDEs, PFCs, OCPs	Constitutive androstane and pregnane-xenobiotic receptors (CAR and PXR)	Activation (agonist)
Coplanar PCBs, PBDEs, PBDFs/PFCs	Peroxisome proliferator activated receptors (PPARs)	Repression (antagonist)/activation (agonist)
Mixtures of POPs, e.g. TCDD and Endosulfan, PFCs, OCPs, e.g. Chlordecone/PCDFs	Farnesoid-X-receptor (FXR)	Activation (agonist)/repression (antagonist)
PCBs, OCPs, e.g. atrazine, chlordane	Epidermal factor growth receptor (EGFR) signaling	Inhibition (antagonist)
PCBs, Hydroxyl PCBs, non-coplanar PBDEs	Ryanodine receptor (RyR)	Activation (agonistic)
PCBs, PBDEs	Thyroid function (TH)	Direct or indirect activation (agonistic)
PCBs, hydroxyl PCBs, PBDEs, OCPs, e.g. DDT, toxaphene, dioxins	Estrogen receptor (ER)	Activation or inhibition (agonist or antagonist or indirectly through receptor cross-talk)
Hydroxyl PCBs	Progesterone receptor (PR)	Inhibition (antagonist)
PCBs, PBDEs	Androgen receptor (AR)	Suppression and inhibition (antagonist)

effects (40). The AhR is a ligand-activated transcription factor predominantly expressed in the liver but also found in extra-hepatic tissues; its activation leads to induction of xenobiotic genes such as cytochrome P450 enzymes, CYP1A1 and CYP1A2 (41). Dioxins are potent AhR ligands with TCDD being considered the most toxic, therefore, terms such as “toxic equivalency factor” (TEF) and “toxic equivalency quotient” (TEQ) are used to express the toxicity of dioxins, furans and coplanar or “dioxin-like” PCBs relative to TCDD whose TEF is 1. Apart from xenobiotic metabolism, AhR activation plays a crucial role in developmental pathways such as hematopoiesis and differentiation, hence its activation is also linked to cell cycle pathways, cell proliferation and carcinogenesis (42). Moreover, AhR can cross-talk with the estrogen receptor (ER), nuclear factor kappa B (NF- κ B) and nuclear factor (erythroid-derived 2)-like 2-related factor (Nrf2) activation pathways, resulting in anti-estrogenic activities, as well as upregulation of inflammatory cytokines such as interleukins, formation of reactive oxygen species (ROS), and induction of anti-oxidant enzymes which all precede oxidative stress and tissue damage (41, 43–45).

Other hepatic, xenobiotic receptors namely the pregnane-xenobiotic receptor (PXR) and the constitutive androstane receptor (CAR) are also targets of POPs such as non-coplanar PCBs that are “phenobarbital-like” (46, 47). Endobiotic receptors such as the peroxisome proliferator-activated receptors (PPARs) and the farnesoid-X-receptor (FXR) are also targeted by POPs (48–51). Activation or inhibition of these hepatic nuclear receptors are associated with metabolic outcomes such as steatosis, dysregulated and altered energy metabolism and obesity; hence such

POPs that are capable of influencing energy metabolism have been described the new emerging term “metabolism disrupting chemicals” (52). Multiple POPs have the ability to interfere with production or mimic activity of hormones in the human endocrine system, thereby disrupting thyroid hormone (TH) and endocrine homeostasis. Some POPs, particularly dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), dioxins, PCBs and BFRs are popularly known as “endocrine disrupting chemicals” (EDCs), or xenoestrogens, or environmental hormones (53–55). Notably, other investigated mechanisms of POPs toxicity include epigenetic modifications, microRNA alterations, interference with epidermal growth factor receptor (EGFR) signaling, agonistic effects on the ryanodine receptor (RyR), and direct effects on pancreas and vascular endothelium (56–66). Because exposure to POPs consist of a cocktail of chemicals that can interact with more than one biological target, outcomes of POPs exposure therefore result in cancer, endocrine and cardio-metabolic disorders. Furthermore, given their biological targets, women, infants, children, and the elderly appear to be especially vulnerable to certain effects of POPs; for example thyroid diseases are more prevalent in women and the elderly population is more susceptible to dementia (67, 68).

Effects of POPs on cancer

Various studies looking at POPs exposure in women have focused primarily on breast cancer given that it is the

most common cancer in females especially in the Western world. Indeed, a number of reports published in more recent years have shown positive associations between risk for developing breast cancer and exposure to pollutants including PCBs, PFCs and dioxin-like chemicals. Although the scientific evidence available up to date contains conflicting results regarding the association of POPs with breast cancer, with some studies stating that there are no significant effects (69–71); the availability of more diverse cohorts and larger population size with varying exposure levels has however confirmed the role of POPs in breast cancer development.

One of the initial studies published in 1999 reported a link between OCPs and breast cancer risk using a human breast cancer screening model to study toxaphene, also known as Camphechlor which was a replacement for DDT, and two of its congeners (72). Toxaphene was used heavily as an agricultural insecticide in the US and its concentrations is abnormally high in regions of the northern hemisphere such as the Canadian Arctic and the Great Lakes (73). Initially, toxaphene was reported to have a weak estrogenic activity and Stelzer et al. (72) confirmed this OCP's estrogenic response in MCF7-E3 estrogen sensitive breast cancer cells, suggesting that exposure to mixtures of estrogenic pollutants may account for increases in occurrence of breast cancer with higher incidences in North America (74, 75). A study on the Greenlandic Inuit women population published in 2011 demonstrated a correlation between serum levels of PFCs including perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) with risk for breast cancer (76, 77). Additionally, women with breast cancer also had significantly higher levels of PCBs in the highest quartile. Another study published recently on the Inuit women population where measurements of pollutant levels were carried out during two time periods (2000–2003 and 2011–2014) reported that significant positive associations were reported between breast cancer risk with PCBs and perfluoroalkyl acids (78). The study also reported that the majority of measured compounds including PCBs, DDE, and PFOS declined significantly during the 10-year period, however an increase was observed for the perfluorinated carboxylic acids (PFCAs). The Arctic Inuit population has been a cohort of interest for studying POPs exposure for decades, as this population exhibited the highest body burdens for legacy POPs such as PCBs and hormone-disrupting chemicals, contributed by the traditional Greenlandic marine diet of consuming whale, seal, seabirds and polar bear (79). Additionally, the Inuit population also appear to have a higher frequency of mutation of the tumor suppressor gene (*BRCA1* founder

mutation) which contributes synergistically to risk for breast cancer (80, 81).

A study carried out with women in India reported an association between breast cancer and OCPs obtained from food consumption. Notably, it was seen that the pesticide levels were higher in younger women compared to older women (82), despite the expectation that POPs clearance occurs through childbirth and lactation (33). Another case-control study in the Alaskan Native population revealed that women with ER- or progesterone receptor (PR)-tumor types tended to have higher concentrations of persistent pesticides (83). A recent study from Spain looking at POPs in serum and adipose tissue of breast cancer patients reported that certain POPs depending on their localization can contribute to breast cancer aggressiveness (84). For example, PCB138 levels in the serum was positively associated with ER and PR expression whereas PCB180 adipose tissue level was positively associated with gene expression of the oncogene, human epidermal growth factor receptor 2 (*HER2*). Furthermore, a research group studying OCP contamination and risk for breast cancer in a rural Victorian population in Australia confirmed a positive dose-response relationship for heptachlor epoxide while another study in Mexican women indicated a correlation between concentrations of OCPs including hexachlorobenzene and DDT in breast adipose tissue with benign breast tumors (85, 86).

A study in Japanese women demonstrated that elevated serum levels of OCPs and some PCBs were associated with global hypomethylation of leukocyte deoxyribonucleic acid (DNA), which is in alignment with a another study reported in the Greenlandic Inuit population where high serum POP levels were inversely associated with global DNA methylation, indicating that POPs can mediate epigenetics thereby influencing carcinogenesis (87, 88). Also, preliminary findings by Hoyer et al. in a Danish cohort demonstrated that p53 mutations may have a modifying effect on breast cancer risk associated with exposures to OCPs further implicating the possibility of gene-environment interactions for breast cancer (89). To reiterate these findings, a research group identifying patterns for hospitalization of women with breast cancer concluded that residential proximity to waste sites for hazardous chemicals including POPs and volatile organic compounds was a significant contributor to breast cancer hospitalization (90).

Apart from breast cancer, serum total PCB concentration and consumption of sport fish in the Great Lakes area, enriched in PCBs and DDE, have been positively associated with the occurrence of fibroids (91). Fibroids, also known as uterine leiomyomas, are benign tumors

that develop from the smooth muscular tissue of the uterus in premenopausal women. Furthermore, women with fibroids also displayed higher mean concentrations of PCBs, PBDEs, DDE and other OCPs in subcutaneous fat, and a number of POPs and their metabolites were detected in the endometrium of premenopausal women who were undergoing hysterectomies for fibroids, implying that POPs body burden may contribute to the pathological development of such hormone-related disorders (91, 92). An exploratory study by Trabert et al. reported positive associations between serum DDE, and six PCB congeners [99, 138, 146, 153, 196, and 206] and the odds for a fibroid diagnosis (93). Studies in Mexico where OCP residues were analyzed in rural Maya women postulated a positive association between OCP residues with the high rates of cervical uterine cancer and breast cancer mortality in the area and also identified higher levels of OCPs like dieldrin and DDE in blood samples of women suffering from cancer of the uterine cervix (94, 95). With regard to endometrial and ovarian cancer, there is a lack of studies to provide evidence for associations, although a study on organochlorine compounds such as DDT provided no significant associations with endometrial cancer risk (96). However, a study carried out in the US on southeast Asian immigrant women looking at DDT and its metabolite DDE, suggested that DDE does affect ovarian function in women eventually altering other endpoints such as fertility, pregnancy and reproductive cancers (97). In addition, another study recently published provided significant associations between adipose tissue levels of POPs such as PCBs and OCPs such as dieldrin and hexachlorobenzene with deep infiltrating endometriosis (98). Interestingly, a study on a Swedish cohort looking at middle-aged and elderly women established no significant risk between dietary PCB exposures and incidences of breast, endometrial or ovarian cancer (99), indicating the importance of type and time of exposure as factors for predicting diseases risks.

The number of studies investigating effects of POPs on other types of cancer other than breast cancer, specifically in women, is extremely scarce with reports of cancer incidences evaluated mostly for pesticide exposures. The Seveso Women's Health Study reported that high dioxin exposures can lead to multi-site cancers (100). Also, the Norwegian Women and Cancer Study elucidated the risk of fish liver consumption, which is a popular food type in Norway, with incidences of total cancer and cancer of the breast, uterus and colon in women but the results from this randomly selected population-based study sample reported no significant dose-effects (101). In fact, the research group reported that fish liver consumption was correlated with decreased risk for total cancer. Another

study in California residents looking at OCP exposure and risk for hepatocellular carcinoma found that pesticide exposures were associated with a higher risk of developing liver cancer in males rather than females (102).

Given the paucity of focus on other types of cancer in women with regards to POPs, it is indeterminant to conclude if exposure to POPs appears to be the biggest risk for breast cancer in women because women are less susceptible to other forms of cancers compared to their male counterparts, or if they are simply more susceptible to hormone-related cancers, or if it is due to the estrogenic and endocrine-disrupting nature of said chemicals. Nonetheless, the insufficiency of studies on the incidences of other cancer types correlated with exposure to POPs that have been established in males such as cancer of the liver, is a prerequisite for investigating other cancer types in POPs cohort studies considering that women may also have varying exposure levels compared to men as well as different receptor potency and target gene battery which can influence toxicological outcomes.

Effects of POPs on cardiovascular diseases

Cardiovascular diseases comprise disorders related to the heart and blood vessels and include coronary artery diseases such as atherosclerosis and myocardial infarction, hypertensive disorders, stroke, cardiomyopathy and thromboembolism. Traditionally, men were thought to be at higher risks for developing heart diseases such as atherosclerosis than women, specifically due to the different effects of sex hormones on metabolism. Men also tend to develop heart diseases at least 10 years earlier than women, or during mid-life, which is popularly considered as the "male disadvantage". However, there is a common misperception that women are "protected" from heart disorders, given that cardiovascular diseases are a common cause of death for women who were 65 years and older (103). A study evaluating data from the National Health and Nutrition Examination Surveys (NHANES) taken during 1988–1994 and 1999–2004, reported an increased prevalence of myocardial infarction in women from the 1958–1994 cohort (0.7%) over the 1999–2004 cohort (1.0%), which was the opposite in men; and that although mid-life men still had a higher risk for developing cardiovascular events compared to mid-life women, this age gap has been narrowing in recent years (104). A plausible explanation for the shift in traditional paradigms regarding gender-specific trends in cardiovascular diseases could be due

to multiple factors pertaining to dietary habits, lifestyle patterns and environmental exposures.

Epidemiologic studies have documented positive associations between serum concentrations of POPs such as PCBs and DDE with cases of hypertension in many cohorts such as the Anniston population in Alabama, who resided near the Monsanto PCB plant and who have high concentrations of both dioxin-like and non-dioxin-like PCBs (105, 106). The Greenlandic Inuit population also showed increased risk of hypertension with dioxin-like PCB exposure in the younger population while the NHANES 1999–2002 participants showed risk for hypertension with some PCBs [74, 99, 118, 126, 138/158, 170 and 187] (107, 108). Furthermore, Lind et al. reported that circulating levels of DDE were related to prevalent hypertension in the elderly population (109). Again, most of these studies did not address gender specific differences until recently. Nonetheless, the literature available so far, strongly suggest that effects on cardiovascular events impact both men and women, with women being more prone to POPs cardiovascular toxicity in some cases. For example, women from a population of the Seveso cohort in Italy displayed higher risks of mortality related to hypertensive diseases compared to men, indicating that the high accidental exposures to TCDD in the Seveso women 15 years ago resulted in cardiovascular events (110). Ha et al. performed a gender-based study on the NHANES 1999–2002 population and found that both PCDDs and PCDFs were strongly associated with prevalence of newly diagnosed hypertension cases among women, while they showed weaker positive trends of associations in men (111). On the other hand, dioxin-like and non-dioxin-like PCBs, were positively associated with hypertension only in men and tended to be inversely correlated with hypertension in women, while OCPs showed no clear correlation for either gender. It is well known that most AhR agonists that are dioxin-like have anti-estrogenic effects that may have played a role in susceptibility (112). Of interest, however, was the fact that dioxins and dioxin-like compounds with lower TEFs displayed clearer positive trends of associations than dioxins and dioxin-like compounds with higher TEFs (111), suggesting that POPs may mediate their toxic effects in the vasculature through pathways that may be exclusive of AhR binding.

A cross-sectional study in the elderly population in Uppsala, Sweden, by Lind et al. observed that the long-chain perfluoroalkyl substances, especially perfluoroundecanoic acid, were related to the presence of overt carotid artery atherosclerosis in women compared to men (113). Moreover, the long-chain PFCs showed positive relationships for echogenicity of the intima-media complex,

indicative of increased collagen tissue in the arterial wall in women, suggesting susceptibility to atherosclerotic plaque formation and future cardiovascular events. In addition, Lin et al. reported that higher serum concentrations of PFOS were associated with an increase of carotid intima-media thickness in a cohort of adolescents and young adults, and this effect was more pronounced in women (114).

These epidemiologic data strongly support the argument that POPs can predispose women to cardiovascular diseases. Additionally, the effects seen in women are different from their male counterparts, because certain POPs have the ability to alter sex hormone activity, eventually affecting metabolic parameters such as cholesterol breakdown.

Effects of POPs on metabolic/hepatic events

Interferences in metabolic processes that regulate normal body homeostasis can lead to metabolic disorders, resulting in people suffering from metabolic conditions such as the metabolic syndrome, obesity, diabetes and insulin resistance, dyslipidemia and hepatic malfunctions leading to steatosis and steatohepatitis. The term ‘metabolic syndrome’ was formally coined in 1998 to describe a constellation of risk factors namely abdominal adiposity, hypertension, glucose intolerance/hyperglycemia, hypertriglyceridemia and low high-density lipoprotein levels, therefore leading to diabetes mellitus and cardiovascular morbidity (115). Women are thought to be at greater risk for developing cardiovascular disorders as a consequence of symptoms of the metabolic syndrome as opposed to men (116). Varying situations in the biological life of women such as pregnancy, lactation, menopause and use of hormonal contraception therapy play a role in predicting risks and consequences of such metabolic disorders.

The effects of POPs on diabetes appear controversial yet intriguing, with studies demonstrating a positive correlations between diabetes and dioxins/PCBs, while other studies reported no such correlation with high exposure to POPs and yet other studies reporting associations between PCBs and type 1 diabetes among pregnant women (117, 118). Nonetheless, in terms of diabetes, men did not appear to be as vulnerable as women, per studies in the Seveso cohort where the mortality rate from diabetes was doubled in women living around the accidental exposure area as compared to women residing in the

reference area but the same relationship was not observed in men (119). Researchers performing a 24-year follow up study on the Yu-cheng cohort who were victims of a mass PCB and PCDF poisoning in Taiwan, found that diabetes was twice as prevalent in the Yu-cheng women as compared to the reference women population (120); but there was no significant increase in diabetes risk for men in this cohort. Furthermore, a follow-up study on PCB-exposed farmers in Michigan reported that women experienced twice the incidence of self-reported type 2 diabetes when total PCBs exceeded 5 parts per billion; however, there was no such increased diabetic risk for PCB-exposed men (121). In addition, women with high PCBs levels in early pregnancy appeared to have a higher risk for gestational diabetes mellitus, and both PCBs and PBDEs were considered potential modifying risk factors for gestational diabetes (122–124).

Other than dioxins and PCBs, exposure to DDE was also confirmed as a risk factor for type 2 diabetes in a case-control study performed in southern Sweden in a well-defined population of women who were within the age range of 51–59 (125). Furthermore, DDE, hexachlorobenzene and PCBs (138, 153, 180) were all considered modifiable risk factors for type 2 diabetes and insulin resistance in a cohort of Spanish women with a history of gestational diabetes mellitus (126). Using plasma concentrations and mechanistic modeling, these pollutants were also associated with the prevalence of type 2 diabetes in a cohort of Norwegian women. Also, plasma concentrations of hexachlorobenzene and PCBs were also associated with incidences of type 2 diabetes in a Nurses' Health Study conducted in Massachusetts (127, 128).

From a mechanistic standpoint, it has been proposed that women may be more susceptible to diabetes than men due to their higher estrogen levels (120). POPs can induce cytochrome P450s such as CYP1A1/CYP1B1 which could catalyze the hydroxylation of the estradiol A ring, resulting in the generation of free radicals and reactive oxygen species. Reactive free radicals eventually induce oxidative stress which is often associated with pathologies such as diabetes and liver injury. It has also been hypothesized that dioxin-like POPs may act through the estrogen-dependent PPAR pathway to upregulate insulin-like growth factor binding protein-1 which counters the effects of insulin and aggravate diabetes (129). In addition, it appears that POPs, especially dioxins and PCBs, directly target the pancreas and affect pancreatic beta cell function thereby hampering insulin secretion, consequently leading to glucose intolerance and hyperglycemia (52). Therefore, looking at pancreatic vulnerability in women

could be another important aspect to further explore the effects of POPs on diabetes.

In terms of obesogenic effects, a study conducted in Belgium in an adult population of both men and women demonstrated that high serum levels of hexachlorocyclohexane were positively correlated with increased body mass index and abdominal adiposity while serum PCB levels showed an inversed correlation with body mass index (130). Moreover, as observed in an elderly population in Uppsala, the lower chlorinated PCBs were associated with the existence or development of abdominal adiposity while the high molecular weight congeners that are heavily chlorinated appeared to have the opposite effect (131). Importantly, this observation suggests that the lower molecular weight PCB congeners that are broadly dioxin-like elicit an effect that is different from the heavily chlorinated congeners that are mostly non-dioxin like. Interestingly, the same study also reported that low-dose exposures to DDE and dioxins were also associated with abdominal adiposity. A cross-sectional study in postmenopausal, non-diabetic, obese women showed that women with higher plasma concentrations of POPs appeared to have decreased insulin sensitivity while obese women with better cardio-metabolic profiles had lower plasma POPs concentrations, implicating the ability of POPs to disrupt energy homeostasis in women (132). Effects of POPs on obesity appeared to be gender-based as evident from a children cohort study in the Faroes Island where girls tended to be more obese with prenatal PCB exposures compared to boys (133).

Epidemiologic studies shown strong associations between POPs especially dioxins and PCBs with liver diseases, including elevated liver enzymes and non-alcoholic fatty liver diseases encompassing steatosis and steatohepatitis (52, 134). However, hepato-toxicology is yet another area where gender or sex-based differences have not been widely acknowledged. Only a handful of studies are available for POPs and women's hepatic health, including one cross-sectional study investigating sex-based associations for POPs (BDEs, OCPs and PCBs) and non-alcoholic fatty liver disease in patients who had undergone bariatric surgery that reported adverse associations between POPs and liver enzymes only among women (135). The liver is a sexually dimorphic organ, and it has been established that the cytochrome P450 genes are expressed in the liver in a sexually-biased pattern (136, 137). Because men and women may exhibit major differences in terms of POPs metabolism, as well as responses to lipid carbohydrate and bile acid metabolism, it is clear that more gender-based studies are needed, including in-depth women's cohort studies that address the effects of pollutants on the

liver, which not only regulates energy metabolism but also xenobiotic detoxification.⁶

Effects of POPs on reproductive health

POPs affect sexual function and fertility in adults, as well as developmental toxicity in offspring. Exposure to POPs affect fertility and reproductive health in both men and women; however, this section will address reproductive toxicity observed in women only. Preliminary studies investigating the effects of POPs in the context of female reproductive health began about two decades ago when exposure assessments were carried out in pregnant women (138, 139). Importantly dioxins, PCBs, some OCPs, PFCs and BDEs are all categorized as EDCs because of their interference on hormonal activities. Being EDCs, these POPs can dictate the onset of menarche and menopause in women, hence influencing the quality of life including reproductive development, duration of fertility period, risk for osteoporosis and cardiovascular diseases. A cross-sectional analysis employing the NHANES data from 1999 to 2008 demonstrated a clinically relevant association between levels of persistent EDCs comprising of PCBs [74, 99, 105, 118, 138, 153, 156, 170, 183], pesticides (DDE, hexachlorocyclohexane, Mirex), phthalates and a furan with early age at menopause in a large representative sample of women in the US (140). Evidence from the study suggested that increasing exposures to these chemicals adversely affected ovarian function especially as PCBs can bio-accumulate in the ovarian follicular wall, therefore, slowly damaging the follicular pool leading to early menopause. A setback of menopause is the reduction in estrogen levels, making women more vulnerable to osteoporosis, and some dioxin-like PCBs have been found to exacerbate bone weakness in postmenopausal women (141). In terms of menarche, a study analyzing multi-chemical exposure in Akwesasne Mohawk girls suggested that estrogenic PCB congeners affected the odds of reaching menarche and additional cohort studies performed in North Carolina and Chukotka (Russia), implicated that increased PCB levels among girls were associated with younger ages of attaining menarche and early sexual maturation (142–144). Furthermore, in Greenlandic women, age at menarche has diminished by 3 years as compared to a 100 years ago, which is an important factor to consider given that early menarche increases the risk for breast cancer (77). Interestingly, a study assessing in utero and postnatal exposure to

polybrominated biphenyls also associated increased exposures with early age at menarche (145). However, when investigating the historical Seveso women cohort, there was no clear evidence that TCDD affected ovarian function in this population (146), while Han women from Northern China showed an association between PCBs, DDE and PAHs with polycystic ovary syndrome (147). Besides, multiple animal studies have shown many POPs that are EDCs affecting ovarian structure and function, and therefore environmental pollutant exposures should be considered important determinants when making fertility assessments (148).

Exposure to POPs is also unfavorable to fetal growth and development bearing in mind the inept metabolism, organ development and rapid growth during this stage (149, 150). Outcomes from in utero and prenatal exposures to POPs have been of interest since the 1980s with the notion that these exposures impact both intermediate birth outcomes and future life events and adult health. Several studies reported impaired fetal growth, reduced birth weight and lower head circumference with low levels of PCBs in mothers while other studies found inconsistent findings (151–154). Because PCB congeners can be estrogenic or anti-estrogenic in nature which can influence birth outcomes, and because time of exposure can also affect developmental growth, these conflicting findings may be a reflection of differences in PCB congener composition and time of exposure (155). Another argument proposed was that certain study populations consumed high amounts of fish and high intakes of fish oil could improve placental blood flow which could result in heavier birth weights (156). Maternal serum and cord blood levels of DDT and DDE have also been linked to preterm birth, reduced birth weight, smaller head circumference at birth and incidences of spontaneous abortions (154, 157–159). Similar observations related to reduced birth weight were seen with maternal serum and cord blood for PFOA and PFOS (160–162) and PBDEs (163, 164); while conflicting findings were found for hexachlorobenzene (165–167). Some studies suggested that the reduced birth weight could be due to increase in maternal gestation weight gain, although the relationship is more complex (150). Low birth weight of Vietnamese infants have also been related to high levels of TCDD and dioxin congeners in the mothers while maternal blood levels of PCDDs, PCDFs and PCBs were associated with lower birth weight in the Yusho cohort (168, 169). Also, the Yu-cheng women who were accidentally exposed to PCBs and PCDFs were reported to have higher rates of delivering a stillborn baby compared to the reference control population (170).

Differences in gender ratio at birth were not observed in this cohort although Yu-cheng men were found to have fewer male offspring compared to the reference control (171, 172). However, exposure to POPs can alter maternal hormone levels, which could potentially regulate the offspring sex. For example, trans-chlordane, DDT, DDE, PCB138 and PCB158 were speculated to behave as testosterone triggers which led to more baby boys, while PCB180 and hexachlorohexane have the opposite effect (31). Pregnant women who consumed maternal diets rich in dioxin-like compounds such as dioxin-like PCBs were reported to deliver babies with lower birth weight while increased fatty fish consumption during pregnancy have been associated with fetal growth retardation, raising concerns on necessary dietary guidelines for women of reproductive age (173–175). Background exposures to POPs have also been implicated in disrupting TH balance among pregnant women in Korean and Norwegian women; and altered maternal thyroid homeostasis could consequently affect fetal development (176, 177). Serum concentrations of POPs have also been associated with risk of developing pre-eclampsia, another pregnancy complication while ongoing exposures to POPs can also hamper the success of in vitro fertilization (178, 179).

There is a growing area of interest to investigate sex-based differences and birth outcomes such as fetal length and ponderal index from prenatal exposures to POPs. Some studies have shown that reduced fetal growth associated with prenatal exposures to mixtures of PCBs, PBDEs and DDT or PCBs and DDE were more pronounced in girls while the opposite effect was seen for hexachlorobenzene (180–182). However, another study looking at only PCBs reported that maternal-mediated PCB exposure was detrimental to fetal growth significantly in boys, but not in girls (152). These differences in findings reiterate the significance of looking at behaviors of mixtures rather than a single class of compounds. Additionally, data from an international general population study demonstrated that in utero exposure to dioxin-like compounds led to a shorter gestational age, particularly for boys (183) while a recent study from a prospective birth cohort in Japan concluded that prenatal exposures to OCPs disrupted reproductive hormones of the fetus in utero significantly for boys (184).

Transgenerational exposures to POPs

Adverse health effects that develop in children as a result of prior chemical exposures by previous generations

including their parents and grandparents are deemed transgenerational effects, and such exposures are considered transgenerational exposures. Transgenerational effects are commonly understood to be due to transmission of information from the parent to the child that affects the child's traits or phenotype without altering the primary DNA structure or nucleotide sequence; in other words, epigenetic inheritance. Implications of transgenerational exposures reviewed in this section are associated with maternal exposures and hence, are impactful to the said mother and such effects can also be broadly categorized as consequences of maternal exposures.

Serial studies conducted on the offspring of Yu-cheng women reported that the children of highly-exposed PCBs/PCDFs mothers showed signs of cognitive deficits and impaired neonatal dental developmental, apart from retarded growth at birth (185, 186). These Yu-cheng children, born between 1978 and 1992, underwent extensive neurological examinations and displayed delayed cognitive processing as well as attention deficits and behavioral problems (186). Furthermore, Yu-cheng children suffered from hyperpigmentation, nail deformities, acne scars, hair loss and were more susceptible to inflammatory diseases (185, 187, 188). Susceptibility to infections and immunomodulation was also reported in Inuit infants while a long-term Dutch cohort study demonstrated that prenatal exposures to PCBs and dioxins induced immunologic changes that persisted into adulthood (189, 190).

Other birth cohort studies in Europe have demonstrated negative associations between prenatal PCB and dioxin exposures and psychomotor and neurologic development in children (191, 192). In contrast, a large, multi-center study conducted in the US observed variable results when studying associations between low levels of prenatal PCB exposure and cognitive/motor development of 8-month-old infants while 4-year-old children whose mothers consumed sports fish from the Great Lakes and therefore have higher levels of PCBs, exhibited poor neurological development, suggesting that such effects may be subjected to dose and duration of exposure (193, 194). A study conducted in a Spanish birth cohort found positive associations between concentrations of PBDEs in breast milk and impaired neuropsychological development in infants 12–18 months of age (195). Also, in utero exposure to DDT and DDE was associated with delayed neurodevelopment in Mexican-American children (196). While some studies projected that these neuropsychological and cognitive effects of POPs may not impact adulthood as observed in a long-term study

that followed-up beyond childhood (197); other studies have suggested that in utero exposure to POPs like PCBs can have long-term impact on intellectual function (198). Nonetheless, it is pertinent to say that exposures to POPs such as PCBs, dioxins and DDT at levels that are higher than the average exposure levels of the general population may possibly have long-term impact on cognitive function in children (199, 200). Likewise, effects of POPs in children appeared to be associated with chronic obstructive lung diseases that persisted way into adulthood (201). A compelling observation was that Yu-cheng boys also exhibited alterations in sex hormones such as higher serum estradiol and lower testosterone levels when mothers had higher levels of PCBs/PCDFs while a follow-up analysis on boys who participated in the North Carolina Infant Study demonstrated that higher prenatal exposures to DDE was associated with increased height and weight gain at puberty (202, 203). These gender-based effects in children may be attributed to the estrogenic and anti-androgenic of some of these POPs such as DDE which can greatly sway endocrine physiology and homeostasis (204).

Other diseases

Other disease types that can result from exposures to POPs include cognitive impairment, neurological disorders, nephrotoxicity, respiratory problems and thyroid disorders among others. With regard to women's health, acute and accidental exposures to POPs have been much more extensively studied; however, disorders arising from chronic exposures have been more male-oriented. In fact the literature is scarce in the context of subtle disorders associated with chronic and low-dose exposure to environmental chemicals in women with only a handful of studies published to date (68, 205, 206). This apparent gap in knowledge necessitates investigations for such disorders employing epidemiologic and animal studies to accurately address sex-based differences associated with chronic exposures. Nonetheless, the amount of evidence available so far clearly portrays the causal effects of POPs in disorders exclusive to women's health such as breast cancer and heavily impact other health disorders that may not necessarily be gender-based. A schematic diagram demonstrating main biological receptors and proteins that are targeted by POPs described in this review and the health consequences that arise from various chemical-receptor interactions is shown in Figure 1.

Figure 1: A schematic presentation of the main biological receptors activated by POPs and some of the consequent pathological responses and diseases reported in women. Illustrations of organs (liver and reproductive system) were obtained from <https://reactome.org> (207).

Conclusion

The current review addressed certain health impacts of environmental chemical exposures in women based on available epidemiologic findings and stressed on the importance of acknowledging gene-environment interactions in women's health. It also noted the insufficiency of studies pertaining to gender-based exposure research (based on gender identity of the subject) and studies on sex-related differences and similarities (based on biological sex differences), albeit incredibly progressive findings and research advancement in the field of environmental health. The review also highlighted the need for more guidelines on dietary patterns and information on exposure history for women of reproductive age and pregnant women alike, considering that current levels of POPs in women can also affect future generations. Moreover, although women population studies such as the Greenlandic Inuit, Yusho, Yu-cheng and Seveso cohorts have been acknowledged and are still undergoing research investigations, occupational cohorts of highly exposed women world-wide including women working in electrical-manufacturing plants and female pesticide applicators are in dire need to further investigate disease susceptibility and progression. Additionally, existence of sex-gene interactions has already been established, especially for vital organs such as the liver, and these interactions are of significance when exploring pathological

mechanisms and designing drug therapy. Therefore, emphasis on sex–gene interactions in environmental health can also provide valuable data to further understand how environmental exposures can result in certain outcomes such as the observable feminization of male organs (208). Furthermore, research studies on genotype–environment and environment–environment interactions have garnered a much bigger audience in the past decade or so with increased communal environmental awareness and public health consciousness. To conclude, assessing gender-sensitive and sex-based differences in POPs exposures can provide a distinct socio-cultural perspective to environmental pollutant exposure studies, otherwise restricted to health outcomes only; and can be of paramount value in environmental health as this will allow researchers to better identify and ascertain the affected or vulnerable populations.

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