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Persistent Organic Pollutants (POPs): A Primer for Practicing Clinicians

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Abstract Persistent organic pollutants (POPs) are environmental chemicals that persist in the environment for long periods of time. The UN, under the Stockholm Convention, has regulated many of these POPs. However, because of their long half-lives, human exposure persists for decades even after production has been stopped. The health effects are varied and range from skin rashes to developmental delays to cancer, depending on the level of exposure. This review is meant as a primer for practicing clinicians to help identify acute exposure, to provide guidance to questioning patients, and be well-informed with regards to policy changes. It touches upon human exposure, current regulations, and health effect of the persistent organic pollutants, including: dioxin, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), and the endocrine disruptor bisphenol A (BPA).

Keywords Persistent organic pollutants · POPs · Dioxin · Polychlorinated biphenyl ethers · PCBs · Polybrominated diphenyl ethers · PBDEs · Hexabromocyclododecane · HBCD · Bisphenol A · BPA · Stockholm Convention

Introduction

Persistent organic pollutants (POPs) are well known environmental pollutants, of which the most well-known are dioxins, polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). Throughout recent history there have been multiple incidents where POPs have made it to the mainstream media. In 1962, Rachel Carson published *Silent Spring* about dichlorodiphenyltrichloroethane (DDT) and its impact on the environment, especially bird populations. Carson publicized that birds who ate DDT laid thinner shelled eggs, leading to their premature cracking/hatching and thus death [1, 2]. Her book ultimately led to the banning of DDTs in 1972. In 1968, over 1000 people ate PCB-contaminated rice oil in Yusho, Japan; PCB contaminated rice oil affected over 1000 people in the western part of Japan [3]; a similar incident occurred just over ten years later in Yucheng, Taiwan in 1979. Affected people showed pigmentation of their nails, acneiform eruptions, conjunctivitis, numbness and weakness [4]. More recently, in 2004, Ukrainian President Viktor Yushchenko was poisoned by 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) [5].

The Stockholm Convention, which controls many of these chemicals at a global level, is a treaty ratified by the global convention, organized by the United Nations Environment Program (UNEP). It was initially created in 2001 and signed in 2004 to eliminate, restrict or reduce the purposeful and unintentional production of the "dirty dozen," a group of persistent organic pollutants identified in 2001. The dirty dozen included aldrin, dieldrin, chlordane, DDT, endrin, heptachlor, mirex, toxaphene, PCBs, hexachlorobenzene (HCB), dibenzodioxins, and dibenzofurans [6]. Since then 11 new chemicals have been added. See Table 1 for a listing of all persistent organic pollutants included in the Stockholm Convention, their major health effects and their current regulatory status [7–23, 24•].

Many of these effects are related to how persistent organic pollutants interact with the environment. POPs are organic compounds that remain in the environment for extended periods of time. Once in the environment, they degrade very

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Table 1 Chemicals included in the Stockholm Convention – "The dirty dozen" and those subsequently added

Year Introduced to Stockholm Convention	Chemical Name	Original Use	Main Health Effects*	Regulation Status in the USA°
2004	Aldrin Dieldrin	Insecticide Insecticide	-Seizures -Anemia	1970: Production cancelled by US Department of Agriculture. 1972: Re-approved by EPA in 1972 to kill termites. 1987: Production voluntarily stopped by manufacturer.
	Chlordane	Pesticide	-Seizures -Bronchitis, sinusitis -Vomiting, diarrhea -Anemia -Immune dysfunction	1978: Cancelled by EPA for agricultural use over next 5 years. 1988: Cancelled for termite control.
	DDT	Pesticide	-Seizures -Premature labor -Endocrine disruption -Cancer	1972: Cancelled by EPA
	Endrin	Pesticide	-Seizures, degenerative neurological disease -Vomiting, diarrhea -Birth defects	1986: Cancelled
	Heptachlor	Pesticide	-Reproductive toxicity -Liver dysfunction	1988: Cancelled for use as pesticide in home and on crops Currently used for fire ant control in power transformers.
	Mirex	Pesticide; fire retardant	-Kidney dysfunction -Liver dysfunction -Reproductive toxicity	1977-1978: Cancelled by EPA
	Toxaphene	Pesticide	-Seizures -Immunodeficiency -Liver dysfunction -Renal failure -Thyroid cancer	1990: Cancelled by EPA
	PCBs	Insulating fluid; paint additive; lubricant	-Skin conditions -Depression -Anemia -Endocrine disruption -Liver Cancer	1977: Cancelled by EPA
	Hexachlorobenzene	Fungicide; additive to fireworks, ammunition & synthetic rubber	-Reproductive toxicity -Birth defects -Liver dysfunction	1965: Cancelled by EPA
	Dibenzodioxins Dibenzofurans	Byproduct of chlorine bleaching by paper mill; combustion; herbicide (Agent Orange)	-Chloracne -Cancer -Reproductive toxicity -Type II diabetes	Still produced as byproduct of combustion; emissions regulated by EPA
2009	Chlordecone	Insecticide	-Kidney dysfunction -Liver dysfunction -Reproductive toxicity	1978: Cancelled by EPA
	Lindane (gamma hexachlorocyclohexane)	Insecticide; use to treat lice & & scabies in humans	-Seizures -Anemia -Endocrine disruption	1976: Production stopped in USA Currently still imported for insecticide use.
	Hexabromobiphenyl	Flame retardant	-Skin conditions -Immunodeficiency -Liver dysfunction -Renal failure -Birth defects	1976: Cancelled by EPA
	Commercial pentaBDE Commercial octaBDE	Flame retardant	-Endocrine disruption -Reproductive toxicity	2004: Voluntarily phased out of production

Table 1 (continued)

Year Introduced to Stockholm Convention	Chemical Name	Original Use	Main Health Effects*	Regulation Status in the USA°
	Perfluorooctane sulfonic acid (PFOS) and its salts Perfluorooctane sulfonyl fluoride (PFOS-F)	Non-stick coating; protective coating on carpet and clothing	-Neurotoxicity -Endocrine disruption -Cancer -Immunodeficiency	Currently undergoing voluntary phase out: 3 M ceased production in 2002. Some production still exists from other companies.
	Alpha and beta hexachlorocyclohexane	Insecticide	-Seizures -Anemia -Endocrine disruption -Cancer	1976: Production stopped in USA
	Pentachlorobenzene	Pesticide byproduct	-Reproductive toxicity -Birth defects -Liver dysfunction	Produced as byproduct to benzene and carbon tetrachloride; not currently regulated in the USA but banned by the European Union since 2002.
2011	Endosulfan	Pesticide	-Seizures -Hyperactivity	Currently restricted to crops; scheduled to be cancelled for all uses in 2016.
2013	Hexabromocyclododecane	Flame retardant	-Endocrine disruptor -Cancer -Neurotoxicity	Still produced in the USA.

*More information on the health effects of the chemicals included in the Stockholm Convention can be found in the following references [7–23, 24•]

° More information on the regulation status of the chemicals included in the Stockholm Convention can be found in the following references [7–23, 24•]

slowly in air, water, and soil, contributed to by the fact that they are highly halogenated [25•]. Because they do not easily break down, they remain present in the environment despite the fact that many are currently regulated and have not been in production for decades. Classically they bioaccumulate and biomagnify as they move up the food chain [26]. Consumers higher on the food chain such as humans and other carnivores are exposed to higher concentrations than those at the bottom, which only eat vegetation. Human exposure begins prenatally as many POPs can cross the placenta. After birth exposure occurs through breast milk [27, 28] and also through inhalation, ingestion, and skin contact [28].

Once in the body, POPs preferentially partition in tissues with high lipid content such as adipose tissue and the liver, due to their lipophilic nature via uptake by adipocytes, and are then stored within lipid droplets. However, in the long term, this accumulation can lead to larger body burdens, which are then slowly released into the blood stream. When there is large mobilization of adipose tissue, such as during periods of weight loss, pregnancy, after pregnancy and during breastfeeding, the POPs may be released at a faster rate from adipose tissue into the blood stream [29]. Several studies have shown that after large weight losses, like after bariatric surgery, there are higher serum levels of POPs [30•, 31].

Some of POPs health effects are likely mediated by their interaction with the adipose and other tissues in which they are stored. POPs may induce obesogenic effects and also induce a pro-inflammatory state that can lead to the metabolic syndrome and diabetes [29, 32, 33]. These effects may also be age/period of development specific [34]. There have been recent studies that hypothesize exposure to persistent organic pollutants with the increasing prevalence of cardiovascular disease (CVD) [32, 35–37]; little evidence can link POPs with increasing incidence of cardiovascular disease and the metabolic syndrome given a dearth of prospective studies [38]. The lipophilic nature of the persistent organic pollutants may induce CVD by making lipophilic membranes more permeable to toxic hydrophilic chemicals [32], which in turn results in an inflammatory response. The exposure of lipophilic and hydrophilic compounds at the same time or sequentially may be more toxic than individually [32].

This article reviews some of the persistent organic pollutants that exist in significant concentrations in the environment such that the general population may have significant exposure. The review covers dioxins, polychlorinated biphenyl ethers, polybrominated diphenyl ethers, and hexabromocyclododecane. See Fig. 1 for the chemical structures of each pollutant covered. The review includes bisphenol A which, while not itself a persistent

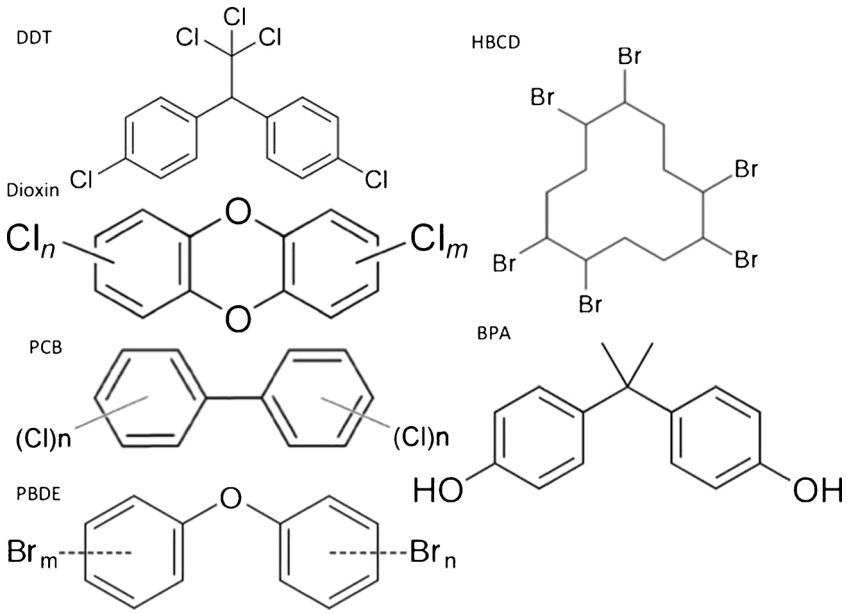

Fig. 1 Chemical structure of selected persistent organic pollutants. DDT, dioxin, PCB, PBDE, BPA, and HBCD

organic pollutant, does act like a POP and is often grouped with POPs when environmental pollutants are discussed.

Dioxins and Polychlorinated Biphenyl Ethers (PCBs)

Dioxin is also a well-known persistent organic pollutant secondary to its use in Agent Orange during the Vietnam War. Agent Orange itself refers to all herbicides that were used during the Vietnam War, but its legacy refers to its contamination with 2, 3, 7, 8-tetrachlor-dibenzo-para-dioxin (TCDD) [39]. Dioxin itself is a generic term that refers to a group of 210 different compounds, 75 polychlorinated dibenzo-p-dioxins (PCDDs) and 135 polychlorinated dibenzofurans (PCDFs) [25•]. Their toxicity varies dependent on the position of chlorine within the congener. Dioxin itself is not produced intentionally except for research purposes, but rather is a byproduct from incineration or secondary to the processing of other chemicals, including herbicides. Polychlorinated biphenyls, some of which act similarly to dioxins, were on the other hand, intentionally created for their heat resistant and insulating properties. PCBs were frequently used as heat exchange fluids in industrial processes and in paints and ceiling tiles. PCB production was banned in the USA by the EPA in 1979. Because of their persistence, PCBs are still seen in measurable levels/levels high enough to affect health today, though these levels have declined at a slow rate since their ban. Current exposure to dioxins and other dioxin-like compounds through eating contaminated foodstuffs is thought to constitute 90 % of exposure [40, 41]; dairy and animal products more so than produce [42], although inhalation and ingestion of dust also contribute [43, 44].

Initially proposed by the Canadian Ministry of the Environment and then later adopted by the US Environmental Protection Agency (EPA) and the World Health Organization (WHO), dioxins and dioxin-like compounds are measured in terms of Toxic Equivalency Factors (TEFs) [45]. TEFs are important given the varying toxicities of the many different dioxin-like compounds, which include certain PCBs. Because they are usually not found in pure form but instead in mixtures, the individual TEFs are summed to form the Total Toxicity Equivalence of the substance [45], which expresses the mixtures' toxicity as if it were pure TCDD [46]. Over the years, these TEFs are updated according to new research and added to for new compounds that are found to have dioxin-like activity [47, 48]. The TEF assignment is based on the biological activity of each compound with the aryl hydrocarbon receptor (AhR), also known as the dioxin receptor. However, not all compounds that bind the Ah-receptor are considered dioxin-like. Compounds that are considered dioxin-like and are given TEFs, must meet the following 4 criteria

- Be structurally similar to TCDD,
- Bind to the aryl-hydrocarbon receptor,
- Produce a response on binding to the Ah-R,
- Be persistent and bioaccumulate and biomagnify up the food chain [47].

When dioxin-like compounds bind the Ah-receptor, the receptor translocates to the nucleus, eventually regulating gene expression through binding with the dioxin response elements. This mechanism controls many reactions necessary for human life, such as drug metabolizing phase I, II, and III genes, including CYP1A1, glutathione S-transferases, and aldehyde dehydrogenase. It also regulates aspects of human

growth and development, and may act as a tumor suppressor [25•]. Most frequently reported human cancers associated with dioxin and dioxin-like compounds include lung cancer, hepatocellular carcinoma, non-Hodgkin's lymphoma, and malignant melanoma [10].

Polybrominated Diphenyl Ethers (PBDEs) and Hexabromocyclododecane (HBCD)

Brominated flame-retardants, including PBDEs and HBCD, have been widely used as flame-retardants in carpeting, furniture cushions, and electrical appliances since the 1970s when the adverse health effects of PCBs were discovered. The bromines, as the chloride atoms did for PCBs, are capable of quenching free radical production from fires, and thus preventing further fire spread [49•]. There are 209 theoretical PBDE congeners based on the positions of the bromines around the diphenyl ether rings. There are three main commercial products named for the number of bromines present on the most prevalent congener in the mixture: pentaBDE, octaBDE, and decaBDE. Certain PBDEs were initially phased out in the USA in 2004 with penta and octaBDE preparations. Commercial production of decaBDE mixtures was stopped in the USA by the end of 2013.

The general population is exposed through ingestion of foods; PBDEs having bioaccumulated in animals higher on the food chain [50], or in produce exposed to pesticides. In recent years, ingestion and inhalation of dust has become an increasing source of exposure, either on par or surpassing exposure through foodstuffs [51–53]. There has been some evidence to suggest that PBDE sera concentrations are slowly decreasing over time, but this trend has not been shown to be statistically significant in a recent paper using National Health and Nutrition Examination Survey (NHANES). As more time passes from when commercial penta- and octa-BDE congeners were phased out in 2004, concentrations will likely slowly decrease. Unlike with the lower brominated congeners, the more recent phase out of deca-BDE, and it's main component, BDE-209 is thought to have less of an impact on serum levels given its shorter half-life of weeks rather than years [54•]. Additionally BDE-209 exposure at baseline is already lower, with detection in 12 % of samples from NHANES 2005–2006 and 11 % in 2007–2008 [54•].

The major health effects in humans are divided into three main categories: endocrine disruption, reproductive and developmental toxicity, and neurotoxicity [25•]. In terms of endocrine disruption, alterations in thyroid function are prominent. Studies have shown that this is likely due to the similarities in structure between PBDEs and the thyroid hormones T3 and T4. Most animal studies show that increasing PBDE concentrations lead to decreased free and/or total T4 in a dose dependent fashion [55–57]. Certain human studies on the other hand note that higher PBDE levels are associated with higher levels of T4 and decreased TSH concentrations [57–60]. It is not entirely clear if PBDEs' effect on reproductive function is mediated by their effect on thyroid function or independently. It is well known that thyroid hormones can influence ovulation, menstruation, and ultimately fertility. Within animal studies, PBDEs can have both pro-estrogen and anti-estrogen effects [61, 62]. PBDEs have also been associated with delayed onset of puberty. Elevated PBDE concentrations have been associated with increased time to pregnancy [63]. This has significant impact given widespread exposure to certain PBDE congeners in the USA [54•] and the high cost of fertility treatments that parents and society may have to pay to have children.

Higher concentrations of PBDE levels in maternal serum have been correlated with lower scores in offspring's intelligence and attention [64, 65]. One potential hypothesis is related to the role that maternal thyroid hormones have in fetal brain development [66]. Mice studies demonstrate that the neurotoxicity may occur in a dose dependent fashion [49•, 67–69]. Exposure can lead to alterations in mice locomotion, rearing, and total activity levels [67]. These neurobehavioral affects appear to be most prominent when exposure occurs within early neurodevelopment in mice, within the first two weeks post-natally [70]; this time period corresponds to the last trimester and early childhood in humans [49•]. The neurotoxicity may not be limited to behavioral effects but also expands to synaptic plasticity; elevated levels of BDE-209 in the hippocampus corresponding to decreased plasticity in rats [49•].

Hexabromocyclododecane (HBCD), while a brominated flame retardant like PBDEs, is actually composed of a non-aromatic, brominated cyclic alkane. Sixteen potential stereoisomers exist with commercial mixtures largely comprised of γ-diastereomers with smaller amounts of α- and β-diastereomers [25•]. However when exposed to high temperatures, as can occur during processing or production, the stereoisomers rearrange into a specific composition on 78 % α, 13 % β, and 9 % γ-HBCD [71]. Like PBDEs, it is also lipophilic, and both biomagnifies and bioaccumulates within the environment. HBCD enters the environment during production or by leaching out of commercial products. It then binds tightly to soil and sewage particulates given their strongly hydrophobic character [71]. Because HBCD biomagnifies, it is found in increasing levels in fish, birds, and humans, both within blood and breast milk [71]. It is unknown if the major exposure to humans is from the diet or from dust exposure as is becoming the case for PBDEs [72]. Compared to PBDEs, research into HBCD is limited. HBCDs are known to induce drug-metabolizing enzymes in rats, induce cancer, and disrupt thyroid homeostasis [71, 73]. Rats with neonatal exposures also have developmental neurotoxic effects such as alterations in learning and memory [71].

Bisphenol A (BPA)

Bisphenol A was first synthesized in 1891, and has since become one of the most commonly produced chemicals worldwide [74]. While not technically a persistent organic pollutant because of its short half-life, BPA is often grouped together with other POPs given its ubiquitous presence in the environment. Despite BPA's short half-life, it is found in urine at relatively constant levels like a chemical with much longer half-life would. It is also found in blood, breast milk, saliva and amniotic fluid [74]. The concentrations in amniotic fluid are up to five times higher than those in corresponding maternal serum, demonstrating a significant prenatal exposure [75]. Within the environment, BPA is present in soil, dust, water, and air samples.

Bisphenol A is currently used as an additive in polycarbonate plastics and epoxy resins in the lining of metal food cans, in paints, office equipment, and dental adhesives to name a few [74]. BPA is also used in carbonless thermal receipt paper as a color developer. Food, especially through canned items, is thought to be the predominant source of exposure [76]; BPA monomers can migrate out of polycarbonate linings in cans into the food products they house during storage or during processing [77]. In younger children with more hand to mouth contact, dust may be a significant pathway to exposure [78, 79]. In adults, BPA quickly undergoes first-pass metabolism in the liver, and sometimes gut, to BPA-glucuronide, which is then renally excreted [80]. However, in infants, liver enzyme activity is lower, leading to decreased glucuronidation of BPA in infants and potentially greater exposure in an already at-risk population.

Thermal receipt paper may also be a significant means of exposure given the paper's ubiquitous presence in twenty-first century life; this exposure may be due to unwashed hand to mouth behavior or through direct dermal contact. It has even been reported that cashiers have higher urinary levels of BPA than the general public [81].

The toxicity of bisphenol A stems from its nature as an endocrine disruptor. Endocrine disruptors as defined by the WHO are "exogenous substance of mixture that alters the function of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny or its subpopulation" [82]. As an endocrine disruptor, BPA interacts with both nuclear estrogen receptors and estrogen receptors on the cell membrane; at higher doses, BPA can also interact with androgen and thyroid hormone receptors [83]. Given that the endocrine system is highly regulated and hormones vary widely with age and stage of development, it is understandable that human sensitivity to BPA varies widely with age and maturity, leading to susceptible developmental windows. This complicates the study of BPA with regards to when the exposure occurs and the latency period to the many different health effects associated with BPA, ranging from infertility to cardiovascular disease to impairments in neurodevelopmental outcomes. Though the evidence is mixed, early exposure has been associated with neurodevelopmental, specifically autism spectrum disorders and attention deficit hyperactivity disorder [84]. When pregnant mice were exposed to BPA, there was increased insulin resistance during pregnancy with corresponding decreased glucose tolerance. These mice also had higher levels of insulin resistance post-partum than their controls; their offspring also had increased insulin resistance [85]. These findings correlate with human epidemiology studies that demonstrate an association between BPA exposure and type 2 diabetes and heart disease [86]. Adult exposure of BPA to rats showed an increase in hematological malignancies, testicular interstitial cell tumors in male rats, and an increase in fibroadenomas in female rats [87].

Conclusions

Persistent organic pollutants constitute a significant environmental exposure and despite increasing regulations at the national and global level, the general population continues to be exposed at levels that may cause lasting health effects. Dioxins and PCBs have been well studied but the newer persistent organic pollutants like PBDEs and perfluorinated compounds, not explored here, require more research to further elucidate their health effects, especially given that much of what is known of POPs health effects is extrapolated from animal studies. Additionally, many of the human studies are occupational assessments where exposures are at much higher levels than those of the general population, and are retrospective or cross-sectional in nature. Even less is known about the exposure to vulnerable populations like infants, children, and pregnant women. As stewards of their patients' health, it behooves clinicians to become familiar with the different environmental exposures their patients may face.

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Compliance with Ethics Guidelines

Conflict of Interest Darrah Haffner declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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