

## **Persistent Organic Pollutants**

### **Introduction**

Persistent organic pollutants (POPs) are a family of synthetic, carbon-based chemicals defined by their behavior. They are toxic, lipophilic, and resistant to degradation. Their structural durability means that POPs persist in the environment and can circulate globally – far from where they are produced, used, and discarded. Most POPs are semi-volatile, which means their transport is temperature dependent. They evaporate from warm regions and condense in cold regions and, hence, tend to drift toward the Poles and mountainous areas. Their ability to dissolve in lipids means that POPs bioaccumulate in the fatty tissues of living organisms. Many also biomagnify, which means that their concentration in fatty tissues increases by a factor of 10–100 with each rung of the trophic ladder ascended. Organisms at the top of the food chain thus bear the highest body burdens of POPs. Traces of POPs are found in the blood and body fat of all Americans, including newborns. Indigenous peoples in the Arctic, who are located at the receiving end of POPs transport and whose traditional diets are heavy in animal fat, have some of the highest recorded levels of POPs in the world.<sup>1</sup>

POPs serve many different functions. Most famously, POPs include a raft of chlorinated insecticides that were introduced into the U.S. economy after World War II: aldrin, chlordane, dichlorodiphenyl-trichloroethane (DDT), dieldrin, endrin, heptachlor, hexachlorobenzene (HCB), lindane, mirex, and toxaphene. POPs also include industrial compounds, such as polychlorinated biphenyls (PCBs), which were used as heat

exchange fluids, in electric transformers and capacitors, and as additives in paint, carbonless copy paper, sealants, and plastics. Polybrominated flame retardants (polybrominated diphenyl ethers/PBDEs) are another subgroup of POPs that offer fire protection to plastics, textiles, and furniture. The insecticide mirex has also been used as a fire retardant in plastics, rubber, and electrical products.<sup>2</sup>

Because of their toxicity, longevity, affiliation for fatty tissues, and tendency toward long-distance transport, many POPs have been banned for production and use in the United States. Consequently, body burdens for these POPs have been decreasing in recent decades among members of the general public. An exception is PBDEs, which are still used widely in the United States as flame retardants and for which human body burdens are increasing exponentially.<sup>3</sup> Another POP still in widespread use is perfluorooctanoic acid (PFOA, also known as C8), which is used in the manufacture of non-stick cookware and in stain-resistant, grease-resistant, and water-proof materials, such as food packaging and upholstery finishes.

Some POPs are of no commercial use but are generated as unintentional byproducts during other industrial processes, such as pesticide manufacturing, metal recycling, pulp and paper bleaching, or combustion. Unintentional POPs include dioxins and furans, and certain polycyclic aromatic hydrocarbons. Another unintentional POP is methylmercury, which is created, for example, when elemental mercury released during coal burning combines with carbon as a result of bacterial action in soils and sediments.<sup>1</sup>

Many, but not all, POPs are suspected carcinogens. One dioxin congener, for example, tetrachlorodibenzo-*p*-dioxin (TCDD) is classified as a known human carcinogen by the International Agency for Research on Cancer.<sup>4</sup> The agency classifies PCBs as a probable human carcinogen and considers chlordane, DDT, heptachlor, HCB, mirex, and toxaphene as possible human carcinogens.

Many POPs, including TCDD, are endocrine disruptors, and some behave like steroidal estrogens. This realization – together with the ubiquitous presence of POPs chemicals in breast milk and breast fat – has raised long-standing questions in the minds of both breast cancer activists and breast cancer researchers about the role of POPs in breast cancer etiology.<sup>5-7</sup> The strong evidence linking endogenous estrogens to breast cancer risk has lent biological plausibility to a causative role for POPs. Accordingly, considerable research has been directed toward illuminating the possible contribution of POPs to breast cancer. The results of these studies are summarized below.

This chapter is limited to a discussion of POPs for which the main route of exposure is dietary. Polycyclic aromatic hydrocarbons, an ingredient of air pollution, are described in Section I, Chapter B.1. on air pollutants. PBDEs, for which household dust appears to serve a second major vector of exposure and for which exposures are rising rather than falling, are considered in a companion chapter, which immediately follows this one. Organochlorine pesticides are considered here in this chapter as well as in the preceding chapter

on pesticides. This redundancy reflects that fact that some epidemiological studies have considered chlorinated pesticides in the context of POPs exposure, while others have examined their role in the context of exposure to pesticides of all kinds. Not intended to serve as a comprehensive review of the POPs literature, which is considerable, this chapter spotlights new discoveries and draws heavily on material contained in Brody et al.'s recent systematic critical review in *Cancer*, which represents an up-to-date assessment of the epidemiological studies of these and other pollutants.<sup>4</sup>

### Regulatory History of POPs

POPs enjoyed three decades of extensive use. Most were introduced after World War II and quickly insinuated themselves into the food chain. By 1950, produce free of pesticide residues was so scarce that the Beech-Nut Packing Company began allowing detectable levels of residue in baby food.<sup>8</sup> By 1951, DDT metabolites were discovered in human breast milk.<sup>9</sup> Thus, women of the baby boom generation were the first to be exposed to POPs in utero, in infancy, in childhood, and/or during puberty. This cohort is just entering the age of maximum breast cancer risk.

With the passage of the Toxics Substances Control Act in 1976, many POPs were phased out of domestic use, including PCBs and several chlorinated pesticides. However, this generalization obscures important waxings and wanings among individual chemicals. For example, DDT reached its peak usage in 1959, whereas toxaphene, which replaced DDT after its ban in 1972, did not peak until the early 1970s, when it quickly became the most heavily used

insecticide in the United States. Toxaphene was finally banned in 1990.<sup>10, 11</sup> While dieldrin was banned in 1975, aldrin, which converts to dieldrin in soil and in human tissue, was allowed as a termite poison until 1987.<sup>12</sup> Thus, even within the baby boom generation, different age cohorts were exposed to a changing kaleidoscope of different chemicals during different stages of early breast development.

POPs are currently being phased out globally in accordance with the United Nation's Stockholm Convention on Persistent Organic Pollutants. This treaty was adopted in Sweden in May 2001 and became international law in May 2004. Over 90 countries, including Canada, have joined as parties; the United States has not. The Convention has targeted 12 POPs for eventual worldwide elimination. It also provides a mechanism for adding additional chemicals to the list and compels member states to submit national implementation plans to the Stockholm Convention Secretariat. The original 12 POPs named in the treaty are aldrin, chlordane, DDT, dieldrin, dioxins, endrin, furans, heptachlor, hexachlorobenzene, mirex, PCBs, and toxaphene. There is variation in the manner in which different chemicals are treated under the treaty. For example, all production and use of endrin and toxaphene is banned outright, while DDT is restricted to controlling disease vectors, such as malarial mosquitoes. Under the treaty, governments are required to minimize the release of dioxins and furans as combustion byproducts with the goal of complete elimination where feasible.<sup>1</sup> The Convention gives governments until 2025 to phase out electrical equipment containing PCBs.

The nine pesticides regulated under the Stockholm Convention are no longer registered for sale or distribution in the United States. Uses were cancelled between 1969 (aldrin) and 1990 (toxaphene).<sup>13</sup> PCBs were banned domestically in 1978, although stocks still remain in electrical equipment.

By 2015, PFOA will be voluntarily phased out of consumer products but will still be allowed in manufacturing processes. The long residency times of POPs – which often exceed a human generation – ensure that POPs will be part of the ecological world long after their economic prohibition.

### **Routes of Exposure**

More than 90 percent of human exposure to POPs comes from diet, with freshwater fish the source of highest exposure. The primary source of exposure to PCBs is fish. The primary source of exposure to dioxins is dietary fat, particularly dairy products, fish, meat, and breast milk.<sup>4</sup> A major dietary source for young children is breast milk.<sup>14</sup> A breast-feeding mother transfers 20 percent or more of her body burden of POPs during the first six months of breast-feeding. This quantity leaves breast-fed children with higher body burden levels of POPs contaminants than their formula-fed counterparts. Nevertheless, breast milk serves to protect infants from the neurological and immunological risks posed by prenatal exposures to these same chemicals<sup>14</sup> and appears to counteract the adverse developmental effects of PCBs and dioxins.<sup>15</sup>

Other than PBDEs, the most prevalent POPs found in human tissues are DDE (the major metabolite of DDT) and PCBs. Levels in human tissues rise with

age and are consistently higher in African Americans than in Caucasians.<sup>5</sup>

Since the discontinuation of the use of chlorinated pesticides and PCBs in the 1970s, levels of these POPs detected in food and human tissues have declined in western nations, including the United States.<sup>5</sup>

## Critical Review of the Literature

### In vitro Studies

The ability of many POPs to act as endocrine disruptors was first appreciated by Rachel Carson in her 1962 book *Silent Spring*. Her observations were based on animal and human studies. They have since been corroborated by in vitro studies. Many POPs are weakly estrogenic in experimental models. The pesticides endosulfan, toxaphene, and dieldrin, for example, have estrogenic effects on human estrogen-sensitive cells.<sup>16</sup> The ability to use estrogen-sensitive cell lines to screen POPs for endocrine disruption was perfected with the development of the E-SCREEN assay by Soto and others in 1995.<sup>17</sup>

Most illuminating are the bioassays that attempt to replicate the real-life mixtures of POPs to which human populations are exposed. For example, a mixture of POPs, including DDT and HCH, acted together to create proliferative effects on MCF-7 cells, even when each mixture component was present at levels below its no-observed-effect concentration. Combined effects were both additive and synergistic.<sup>18</sup>

In vitro studies have demonstrated that, while DDT itself is estrogenic, its persistent metabolite, DDE,

does not bind with estrogen receptors and instead acts an anti-androgen. While some PCB congeners are estrogenic, the most persistent forms are actually anti-estrogens.<sup>19</sup> Thus, the hypothesis that guided much early epidemiological research – that PCB and DDT/DDE exposure may raise breast cancer risk via increased estrogenicity – is based on a false presumption.

### In vivo Studies

Animal studies point to the importance of early life exposures, that is, exposures that take place at the time of birth or around puberty.<sup>20</sup> Compounds that retard development of the mammary gland are associated with increased risk of breast cancer.<sup>21</sup>

Mammary gland development is guided by cells at the blind ends of the ducts called terminal end buds. These are the branching and dividing points in the ductal tissue that blaze the trails for new networks of epithelial ducts in the growing mammary gland.<sup>21</sup> With each menstrual cycle before a full-term pregnancy, estrogen directs the elongation and branching of the duct system.<sup>22</sup> Terminal end buds are especially vulnerable to carcinogenic damage. Rodent studies indicate that the number of terminal end buds exposed to the carcinogen is related to the risk of tumor formation. The sooner the terminal end bud differentiates into adult structures, the more protected the animal is against mammary carcinogenesis.<sup>21</sup> POPs known to delay mammary gland development in laboratory animals following early-life exposure include dieldrin, TCDD dioxin, organochlorine mixtures, PCBs, and PFOA.<sup>21</sup> PFOA has been identified as a mammary gland carcinogen in animal studies.<sup>23</sup>

Exposure to PFOA in mice is associated with stunted mammary gland development. Female mice exposed during pregnancy exhibited diminished epithelial branching of mammary glands that disrupted the ability to lactate. Exposed female offspring also displayed stunted mammary growth and branching patterns.<sup>24</sup> This finding is significant, in that delayed mammary development is associated with increased susceptibility to carcinogenesis.<sup>21</sup> In rats, prenatal exposure to dioxins can increase the susceptibility of the mammary gland to subsequent carcinogenic insults.<sup>20</sup>

## **Human Studies**

A large number of epidemiological studies have investigated the role of PCB body burden in breast cancer etiology. Overall, the vast majority of these studies have not provided strong evidence for an association between PCBs and breast cancer. However, the evidence to date generally supports an association between breast cancer and PCB exposure for subpopulations of women who have inherited polymorphisms in cytochrome P450 genes.<sup>4</sup> More specifically, women with a variant of the CYP1A1 gene called m2 are at greater risk for breast cancer when they are exposed to PCBs. Cytochrome P4501A1 (CYP1A1), which is involved in the metabolism of steroid hormones and polycyclic aromatic hydrocarbons in humans, is induced by PCBs. About 10–15 percent of U.S. white women possess the variant genotype. Another CYP1A1 polymorphism with presumed similar function is present in an even larger proportion of African American women. Women with high PCB body burden and the CYP1A1 variant genotype have a two- to three-fold

increased risk of breast cancer, compared to women with lower levels and without this genetic trait. This risk elevation is higher than the excess risk reported for many established breast cancer risk factors.<sup>4,25</sup>

Regarding dioxins and breast cancer, evidence is sparse but suggestive. Occupational cohort studies of dioxin-exposed female workers and studies of Russian women living near a dioxin-contaminated chemical plant yielded positive findings, but these studies involved women exposed to many chemicals. Moreover, some of the studies were not controlled for confounding by established risk factors.<sup>4</sup> Much of our knowledge about dioxin and breast cancer comes from a cohort of women exposed by a 1976 industrial accident in Seveso, Italy. Early studies with limited follow-up time showed no links between dioxin exposure and breast cancer incidence.<sup>26,27</sup> But by 2002, researchers had found a statistically significant, dose-response-increased risk for breast cancer incidence with individual serum dioxin level among women in the Seveso Women's Health Study. More specifically, a 10-fold increase in dioxin level – as measured shortly after the accident – was associated with a two-fold increase in breast cancer incidence.<sup>28</sup> This study highlights the significance of long latency periods and the importance of having knowledge of chemical exposures decades before diagnosis. Breast cancer incidence may continue to increase in this cohort of 981 women and further follow-up is warranted. Many members in the cohort, who, at the time of the explosion ranged from infancy through 40 years old, are just now old enough to be at risk for breast cancer.<sup>4</sup>

More than 50 investigations have been published that ask whether women with breast cancer have elevated body burdens of organochlorine chemicals. The results are conflicting and unpersuasive. Many of these studies focused on PCBs or DDT and its metabolites. While early, small-scale studies found higher levels of, for example, DDE in cases than in controls, newer, larger, better-designed studies, by and large, have not replicated these results. Meta-analysis of prospective studies, as well as pooling of retrospective studies, has failed to yield odds ratios above unity. In other words, women with breast cancer, as a group, do not have higher body burdens of particular POPs contaminants than women without breast cancer.<sup>4-6, 29</sup> While some earlier studies seemed to suggest that high body burdens of organochlorines may increase risk in African American women, results from a recent case-control study of nearly 700 African American women did not confirm these results.<sup>30</sup>

Researchers are divided on the significance of these negative findings. Some believe these results reassuring.<sup>5</sup> Others argue that the putative role for endocrine-disrupting POPs should not be dismissed prematurely, because most epidemiological studies have so far not considered timing of exposure and genetic polymorphisms relevant in the biological pathways by which certain POPs might influence breast cancer risk. Further, recent evidence from in vitro models demonstrates that estrogenic pollutants – POPs and non-POPs alike – can act together at low levels to influence cancer risk.<sup>6</sup> Moreover, as one researcher points out, the demonstration that hormone replacement therapy contributes to breast cancer risk required an investigation of more than 150,000 women. By

contrast, the pooled analysis of prospective studies, which relied on only 1857 women with breast cancer, has limited statistical power. From this point of view, the jury is still out on POPs and breast cancer.<sup>6</sup>

Epidemiological studies of POPs and breast cancer are limited due to three important methodological shortcomings. One is the presumption that contemporary measures adequately reflect past exposures.<sup>5</sup> However, as indicated above, the PCB congeners that are estrogenic are short-lived and more difficult to measure in biological samples. Hence, existing studies may not be able to assess the importance of POPs that are most quickly metabolized.<sup>5</sup> One Danish study that examined a bank of blood samples drawn many years prior to the development of breast cancer found higher levels of dieldrin in women who went on to develop breast cancer. Women with the highest levels of dieldrin had more than double the risk of breast cancer compared to women with the lowest levels.<sup>19</sup> However, this study also measured other POPs with similar biological activity and observed no excess risk associated with these chemicals. It is therefore possible that the excess risk associated with dieldrin could be due to chance alone.

The second limitation of epidemiological studies of POPs and breast cancer is that many studies have not considered combined effects of environmental estrogens.<sup>6</sup> Some researchers have therefore called for studies that measure the total effective xenoestrogen burden. One recent Spanish study measured levels of 16 organochlorine pesticides in the adipose tissue of 198 breast cancer patients at the time of diagnosis and compared them to 260 women without breast cancer matched on age.

Researchers found an increased risk for breast cancer in leaner, post-menopausal women that was related to the total body burden of all estrogenic chemicals, excluding natural hormones. The pesticides aldrin and lindane were also individually associated with risk.<sup>31</sup>

A third problem is that many studies do not consider the timing of exposure. The results of animal studies suggest that future epidemiological studies need to focus on exposures that occur when the mammary gland is most sensitive to hormones in order to capture time-specific responses.<sup>20, 32</sup> A new study that used banked blood samples gathered from young women from 1959–1967 in Oakland, California did find an association between exposure to DDT before age 14 and breast cancer risk before age 50. By contrast, women who were not exposed to DDT before age 14 showed no association between DDT levels and breast cancer.<sup>33</sup> In other words, girls' and younger adolescents' DDT exposure during the years of peak DDT usage in the U.S. was linked to breast cancer risk, while DDT exposure at older ages was not. As the authors note, many baby boom women heavily exposed to DDT in childhood have not yet reached age 50. The significance of early-life exposure to DDT for breast cancer risk may not yet be fully understood and may be quite large.<sup>33</sup>

Two others areas of research are noteworthy. The first examines the effect of POPs exposure on breast cancer survival or relapse. A few studies have found a significant association between high PCB levels and the risk of death among women with estrogen-positive breast cancer. Another found that higher levels of PCBs were associated with more aggressive breast cancer.<sup>4</sup> Dieldrin has

also been linked to higher breast cancer mortality,<sup>34</sup> and organochlorine exposure has been linked to higher rates of breast cancer recurrence.<sup>35</sup> In light of the higher POPs body burden in African American women and their higher mortality rate from breast cancer, this line of inquiry seems worth pursuing.

The second examines the effects of POPs exposure on lactation. A small body of evidence suggests that some POPs contaminants interfere with human milk production, possibly by inhibiting prolactin. In studies conducted in both North Carolina and Mexico, women with the highest levels of DDT in their breast milk had poorer lactational performance and consequently weaned their infants sooner than mothers whose pesticide levels were lower. Similar studies come from the Netherlands, where mothers with high levels of PCBs and dioxins in their breast milk had significantly lower volumes of milk and lower fat content.<sup>15, 36-38</sup> These studies support animal studies, described above, that indicate that POPs can interfere with the ability to lactate. Such studies indirectly affect breast cancer risk, as breast-feeding has a protective effect against breast cancer.<sup>39</sup>

## **Conclusions and Future Directions**

POPs exposures are pervasive and, indeed, universal. The absence of an unexposed population and the long latency period between exposure and onset of disease make epidemiological study challenging. In vitro studies indicate the importance of considering mixtures of chemicals that share pathways of endocrine disruption. In vivo studies indicate that early-life exposures to POPs can alter the development of the mammary gland in ways that make the breast more

susceptible to later carcinogenic assaults. Human studies that measure exposure at the time of a breast cancer diagnosis are not helpful in explicating the role that POPs may play in breast cancer etiology. Epidemiologists, chemists, and toxicologists should work together to develop methods to study the associations between complex mixtures of POPs and breast cancer, as well as other health outcomes.

- Do POPs exposures make breast cancer more lethal? And do the higher POPs body burdens in African American women explain their higher rates of breast cancer mortality?
- Finally, which are the most relevant POPs to study? As pointed out above, many studies have focused on the role PCBs and DDE may play in breast cancer development, yet resources may be better directed at other compounds in light of the fact that neither DDE nor most PCBs are estrogenic or mammary carcinogens.

Outstanding questions include:

- Do POPs contribute to a cocktail of estrogenic chemicals that act in concert to raise the risk of breast cancer? Or, in practical terms, does the blood sera of women with breast cancer exhibit increased mitogenicity?
- Can bioassays such as the E-SCREEN test provide a measure of internal exposure to estrogen-like chemicals?
- Does exposure to POPs interfere with the ability to lactate? (Longer duration of breast-feeding affords increased protection against breast cancer.)
- How do POPs exposures during crucial periods in early life – especially prenatal and pubertal – alter mammary gland development in girls?

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