CHAPTER 1

PERSISTENT ORGANIC POLLUTANTS: AN OVERVIEW

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1.1 WHAT ARE POPs?

Persistent organic pollutants (POPs) are a class of organic compounds that are characterized by their ability to resist degradation through environmental processes, remaining intact for long periods of time. They are semi-volatile and capable of traveling as vapor or being absorbed to particulate matter in environmental media, facilitating long-range transport. Their persistence and mobility have resulted in their ubiquitous presence in the environment, as well as biota, including humans. These chemicals are found even in the most remote areas of the world, such as deserts, open ocean, and the poles, where there is no human activity nor chemical sources, demonstrating their ability to travel such long distances. POPs also are mostly lipophilic, bioaccumulating in fat tissues, and subsequently amplifying in concentration in biota occupying the upper spectrum on the food chain.

Common types of POPs include polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins and furans (PCDD/Fs), and polybrominated diphenyl ethers (PBDEs), as well as organochlorine pesticides and fluorinated compounds. Many are still and/or were intentionally used as pesticides or manufactured for a variety of consumer or industrial applications, whereas others are byproducts of industrial activities. Some examples include DDT, which is still used to control mosquitoes carrying malaria in certain regions of the world, and PCBs, which were used as cooling insulating fluids for transformers and capacitors as well as paint and cement additives. These chemicals provided beneficial and economical solutions, and thus were applied in a
variety of mainstream commercial applications despite having an understanding of the unanticipated ubiquitous presence in the environment and effects on human health.

As a result of their chemical and physical properties, and their historic and widespread use, POPs have contaminated the globe appreciably in recent decades. Their eventual identification as contaminants soon after the industrial boom resulted in government regulation (banning or restricting use) of many of them. The first was the ban on the pesticide DDT (based on bird egg shell thinning) by the United States in 1972; many countries followed suit. An international POPs assessment was not initiated until the mid 1990s. In May of 1995, the United Nations Environment Programme (UNEP) Governing Council called for global action, after which the International Programme on Chemical Safety (IPCS) set out to assess the 12 worst offenders, called “the dirty dozen.” These legacy POPs included organochloride pesticides: DDT, endrin, dieldrin, aldrin, chlordane, toxaphene, heptachlor, hexachlorobenzene, and mirex; and industrial chemicals and byproducts: PCBs, dioxins, and furans. A total ban on production and use pertained to the 12 intentionally synthesized compounds, while the dioxins and furans were slated for virtual elimination.

In 2001, the text of the Stockholm Convention on Persistent Organic Pollutants was adopted. The global treaty aimed to restrict and eliminate the production and subsequent use, trade, release, and storage of the dirty dozen in order to globally protect human health and the environment. In 2010, the first set of chemical additions to the dirty dozen in the initial treaty were confirmed; chemicals currently controlled under the Stockholm Convention and their uses are listed in Table 1.1.

### 1.1.1 Exposure to POPs

Human exposure to POPs can occur through various pathways because of their current and/or past widespread use in an assortment of applications. The primary pathways for exposure to POPs are dietary exposures, occupational exposures, and environmental exposures (e.g., ingestion of contaminated dust and soils, inhalation of POPs in the air, etc.). Overwhelmingly, and certainly for legacy POPs, dietary exposures tend to dominate overall exposure to these compounds. The chemical and physical parameters lead to significant biomagnification in the food chain, which can reach up to 70,000-fold, resulting in relatively large exposures from the diet, particularly via fish and meat products.

Biomonitoring (the direct measurement of a chemical or its metabolite in the human body) is often used to evaluate human exposures to POPs and is considered the gold standard for estimation of exposure to dioxins. These compounds have been measured in populations worldwide for several decades. In the United States, the Centers for Disease Control and Prevention (CDC) conducts a large-scale, statistically based, biomonitoring effort, the National Health and Nutrition Survey (NHANES), in an effort to provide information
<table>
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<tr>
<th>Compound</th>
<th>CAS No.</th>
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<th>Industrial Chemical</th>
<th>By-Product</th>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>Elimination</td>
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<td>–</td>
<td></td>
<td></td>
<td>X</td>
<td>Restriction</td>
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on the health and nutritional status of the general noninstitutionalized and nonmilitary U.S. population, including quantifying chemicals and their metabolites in blood and urine. Levels of selected POPs as measured in the 2003/2004 survey (>2000 participants) are shown in Table 1.2, and generally represent levels in the U.S. population. Levels of different POPs vary across the globe, although the levels of many of the legacy POPs are similar in the United States to other developing countries, which tend to be higher than the less developed world. However, DDT and its metabolites are higher in countries in which it is still used in malarial control, and levels of PBDEs are higher in the United States because of higher usage of flame retardants than in other developed countries.5

1.1.2 Toxicity of POPs

POPs are linked to an array of health effects in humans and the environment, making them widespread, persistent, and toxic. Exposures can result in a wide range of adverse health effects in humans, including relatively acute effects, such as allergies, hypersensitivity, and dermatological rashes, as well as more severe effects, including endocrine disruption, reproductive and immune dysfunction, neurological disorders, and cancer. In this chapter, we review the toxicological impacts on humans and the environment of various categories of this notorious group of contaminants, the POPs.

1.2 PESTICIDES AS POPs

Many of the organochlorine pesticides, fungicides, or biocides currently listed as part of the Stockholm Convention are no longer used (e.g., aldrin, deildrin, chlordane, endrin, Mirex, hexachlorobenzene). However, because of their persistent and bioaccumulative properties, human exposure to these compounds—perhaps at very low levels—continues. Most of the pesticides classified as POPs bioaccumulate at higher levels in fatty animal tissues, and as a result, higher-fat foods, such as meat, fish, and dairy products, are primary sources of exposure in the general population. Notably, many of these chemicals (or their metabolites) cross the placenta and distribute into breast milk. However, biomagnification does not occur for some pesticides, such as endrin and lindane, because metabolism is rapid; thus, they are not typically detected unless there was a high level of exposure, or the exposure was very recent. The lipophilic nature of these compounds still results in some concentration in fatty tissues. The chemical structures for some of these chemicals are shown in Figure 1.1.

Many of these compounds have demonstrated neurotoxicity in laboratory studies, and several have also demonstrated neurotoxicity in humans. In laboratory studies, these compounds tend to elicit hepatotoxicity (e.g., induction of phase I and II enzymes, tissue damage) and often liver tumors at higher doses. Neurotoxicity (e.g., tremors, seizures, altered levels of neurotransmitters)
<table>
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<tr>
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<th>75th</th>
<th>95th</th>
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<td>&lt;LOD</td>
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<td>&lt;LOD</td>
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<td>13.2</td>
<td>pg/g</td>
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<td>21.4</td>
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<td>&lt;LOD</td>
<td>ng/g</td>
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<td>21.2</td>
<td>30.0</td>
<td>54.6</td>
<td>μg/L</td>
</tr>
</tbody>
</table>

*a Measured as oxychlordane.
*b Measured as Heptachlor epoxide, a metabolite of heptachlor.
'pp′-Dichlorodiphenyltrichloroethane (DDT).
"2,2′,4,4′,5,5′-Hexabromobiphenyl (BB 153).
'e PFOS only, did not specify lipid adjusted.
/'As reported by Ferriby et al. on a WHO 1998 TEF/TEQ basis.
'* Not calculated; proportion of results below limit of detection was too high to provide a valid result.
have also been noted. Other reported effects include endocrine disruption, adverse effects on the immune system, teratogenic effects (e.g., skeletal deformations, cleft palate), reproductive toxicity, and carcinogenesis. Because of these documented toxicities, in combination with environmental persistence, the U.S. Food and Drug Administration continues to monitor food and water supplies for these compounds.

Although controversial, the use of DDT continues to the current day in selected applications (i.e., vector control). This lipophilic compound and its more persistent metabolites are highly bioaccumulative and have demonstrated toxicity in humans, laboratory animals, and wildlife. Several studies have indicated that DDT is directly genotoxic, and also has the potential to induce DNA damage via nongenotoxic mechanisms. Like many of the other organochlorine pesticides, DDT has also been associated with endocrine disruption, hepatotoxicity, developmental and reproductive toxicity, neurotoxicity, and carcinogenicity (e.g., leukemia, lymphoma, testicular cancer, breast cancer). Clearly, people living in areas where DDT is still used are exposed to a greater extent and have higher body burdens. Given the demonstrated toxicity to developing systems, the transfer of DDT (and its derivatives) are of particular concern in these sensitive populations.

1.3 DIOXINS, FURANS, AND PCBs

Dioxins are a group of planar tricyclic chemicals with similar structure and chemical properties. The term dioxin(s) is commonly used to refer to one or many of the polychlorinated dibenzo-p-dioxins (PCDDs) and/or polychlorinated dibenzofurans (PCDFs). Both chemical families contain many congeners, with variable numbers and positions of chlorine atoms (Fig. 1.2)—the configuration of which directly impacts toxicity. There are 75 PCDD congeners and 135 PCDF congeners, of which 7 of the dioxins and 10 of the furans are identified as toxic. Data demonstrate that congeners containing chlorine in the
2, 3, 7, and 8 positions are the most toxic. Notably, brominated and mixed brominated/chlorinated congeners also exist and may have similar toxicity to the chlorinated ones.

Dioxins are emitted from incineration or as accidental by-products of industrial activities, including incineration and combustion/processing of other chemicals, including trichlorophenol and the herbicide, 2,4,5-T. They are not produced intentionally and have no known commercial use except for scientific purposes, but are nearly ubiquitous. Unlike dioxins/furans, PCBs were intentionally and widely produced. They served as valuable insulating/heat exchange fluids in several industrial processes due to their desirable chemical stability, heat resistance, and nonflammability. They have also been used in paint and ceiling materials. PCB production peaked in the 1970s, and was eventually banned in the United States in 1979. According to the U.S. EPA, PCBs are the most widely studied environmental contaminants. Structurally, there are at least two types: coplanar and noncoplanar PCBs (also called nonortho-substituted and ortho-substituted, respectively). The coplanar congeners have two benzene rings in the same plane, structurally resembling dioxin. As such, these types of PCBs are also referred to as dioxin-like PCBs (DL-PCBs).

PCBs are inherently found in mixtures, always containing some level of DL-PCBs (Fig. 1.3). Noncoplanar PCBs will be discussed in more detail in a later section. Additionally, dioxins, furans, and PCBs are rarely found in the absence of one another, making it easier to study the chemicals as additive mixtures, despite the varying individual toxicities. For the purposes of this chapter, the term dioxin-like compound (DLC) will hereforth refer to any
mixture of the 7 PCDDs, 10 PCDFs, and 12 PCBs that are considered dioxin-like by the World Health Organization (WHO).  

1.3.1 DLCs

With the exception of occupational and accidental exposures, the large majority of DLC exposure occurs through the ingestion of food, with over 90% of dietary intake being from animal fats in meat, milk, eggs, and fish. Because of lipophilicity and persistence, dioxins accumulate at higher concentrations in fatty tissues and biomagnify, reaching higher levels in adipose tissues of larger, carnivorous animals. Due to increased awareness and preventative action, dioxin levels in the environment have been declining since the 1970s.

DLCs are easily absorbed in the gastrointestinal tract by chylomicrons and readily carried into the systemic circulation, where they partition into tissues and bind, accumulate, and/or are eliminated. Elimination of dioxins is controlled by three major parameters: the amount of body fat, the induction of a hepatic binding protein (which is dose dependent), and metabolism. Most DLCs are slowly metabolized. Elimination is more rapid at higher doses and in those with less body fat. These factors vary among species and also within species—in humans, kinetic parameters in children are different than adults. For example, the median observed half-life of TCDD among members of operation Ranch Hand sprayers of Agent Orange is 11.3 years, with a 95% confidence interval of 10.0–14.1 years, whereas Seveso, Italy children showed half-lives averaging 1.6 years.

There is a significant body of evidence indicating that essentially all toxic effects exhibited by dioxin and other DLCs are mediated through persistent activation of the aryl hydrocarbon receptor (AhR). Upon ligand binding, the AhR translocates to the nucleus, heterodimerizes with aryl hydrocarbon receptor nuclear translocator (Arnt), dissociates from the chaperone complex, and regulates the expression of a host of genes (the AhR gene battery) through binding with dioxin/xenobiotic response elements (DRE/XRE). The AhR gene battery includes drug-metabolizing phase I genes, including CYP1A1, CYP1A2, and CYP1B1; genes regulating phase II enzymes, including glutathione S-transferases (GST), uridine diphosphate glucuronosyltransferase (UDPGT), and aldehyde dehydrogenase (ALDH); and phase III genes, including several of the ABC transporters. The AhR also regulates many aspects of normal growth, development, and differentiation, as well as hypoxia, aging, and circadian rhythms. Recent studies indicate that the AhR is a key regulatory protein, as constitutive expression results in tumors, suggesting it may also be a tumor suppressor. Activation of the AhR can also lead to nonnuclear cell signaling processes, such as phosphorylation and calcium mobilization.

Binding and activation of the AhR is a key event in the mode of action (MOA) for DLCs (Fig. 1.4). Though the exact mechanistic processes associated with the multiple toxicities are not yet elucidated, key events in the MOA are relatively well defined. It is believed that dioxin acts through the AhR to
 invoke downstream events associated with either gene changes resulting from activation, or via nongenomic protein–protein interactions in the cell cytoplasm (actions independent of their actions with DNA).\textsuperscript{15} TCDD, the prototype DLC, is not directly mutagenic or genotoxic, but rather is classified as a potent hepatic tumor promoter, as well as inducing other cancers, in rodents.\textsuperscript{16} Several hypothesized MOAs have been discussed in the literature.

For example, the USEPA recently issued a draft MOA for site-specific carcinogenesis.

TCDD has been widely studied (more than 10,000 citations in PubMed), and continues to be at the forefront of public health and political debate. While extensive animal testing has been performed, there is also a large body of evidence from human data, and thus the findings from epidemiological and case studies will be the focus of discussion in this section. Dermatologic effects have been the most commonly reported conditions following high levels of exposure to DLCs in humans, though other effects reported include hepatomegaly, changes in hepatic enzyme levels (which can be indicative of cholestasis, liver regeneration or xenobiotic metabolism), liver cell damage caused from hepatic necrosis, skeletal or renal necrosis, and/or induction of hepatic microsomal activity.\textsuperscript{8} Some studies have reported changes in lipid and cholesterol levels, diabetes status, neurological effects, cancer, myocardial infarction, acute pancreatitis, reproductive effects, alternations to thyroid function, and cardiovascular health, though findings across cohorts are generally not consistent.\textsuperscript{17–19}

The effects that have been closely associated with exposure to high levels of dioxin and related chemicals are chloracne, a hyperproliferative and hyperkeratotic skin condition typified by large and widespread acne-like lesions, and prior to or instead of acne, erythema and sometimes brown skin discoloration that can persist for years. In mild cases, chloracne is reversible, though lesions can last for years once the external source of exposure is removed. Chloracne

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{TCDD’s hypothesized modes of action in site-specific carcinogenesis in rodents. See text for details. In each instance, the solid arrows depict pathways that are well established and are associated with low uncertainty. The dashed arrows represent connections that are less established and are associated with higher uncertainty. Adapted from reference [12].}
\end{figure}
has also been documented as occurring with and without other effects in workers exposed through accidental releases, in workers involved in daily production of dioxin-contaminated chemicals, and residents near large-scale accidental releases of contaminated chemicals.\(^8\) It has also been described following rice oil poisoning with PCBs, PCDFs, and other compounds\(^{20,21}\) Liver damage, as measured by specific markers of toxicity, is the other commonly observed acute effect associated with exposure to high levels of DLCs.

With respect to noncancer effects, studies on the Seveso, Italy cohort have evaluated an array of effects associated with a high-level acute exposure to DLCs (mainly TCDD) resulting from a chemical facility explosion, followed by ongoing chronic exposures due to the persistence of the compounds. Investigators have reported that these exposures during development are correlated with endocrine effects: altered thyroid status; neurobehavioral effects: altered hearing, psychomotor function, cognition, and dentition; and reproductive effects: disrupted development of reproductive organs, altered sex ratios, increased time to pregnancy, and male and female infertility effects, and other adverse health outcomes.\(^{22-27}\)

Many of the epidemiological studies evaluating carcinogenic effects have involved investigations in occupational cohorts (e.g., NIOSH, Ranch Hand), as well as the Seveso cohort. When the data are considered collectively, the body of evidence contains both null findings and positive findings.\(^{28}\) These data do not indicate a clear increase in any single type of cancer resulting from exposures to dioxins; however, the overall animal and epidemiological data have been considered sufficient to classify TCDD as a carcinogen in humans based on various studies and on the increased risk of all cancers combined.\(^{18,29}\) Reported cancers in humans include lung cancer, non-Hodgkin lymphoma, hepatocellular carcinoma, malignant melanoma, and several other malignant neoplasms.\(^{30}\) Many investigators often note the difficulties in evaluating exposures to DLCs given that in many of these cohorts, workers are exposed to many carcinogenic compounds. Notably, these effects are often correlated with dioxin exposures several orders of magnitude higher than the general population. As such, evaluating the risk of DLC exposures in the general population is a topic of great interest among scientists and policy makers.

Epidemiological observations in humans are supported by animal studies on cancer and noncancer end points. Long-term exposure to mice, rats, hamsters, and monkeys reported increased incidences of a large spectrum of tumors, including hepatocellular adenoma and carcinoma, thyroid follicular adenoma, histiocytic lymphoma, and cancer in the thyroid, liver, kidney, skin, lung, and leukemia.\(^{8,12}\) The liver has been identified as a primary target. Collectively, the data demonstrate that TCDD repeatedly administered at low doses via several routes of exposure have been shown to cause tumors at multiple sites in these animals.

Acute effects in animals also clearly demonstrate the wide range of sensitivities between species. For example, the \(LD_{50}\) values of TCDD range from
BROMINATED COMPOUNDS

0.6 μg/kg in the guinea pig to >5000 μg/kg in the Syrian golden hamster, and intraspecies differences in sensitivity to TCDD are reported to be up to 14-fold in mice alone. Reported acute toxic effects in most species include changes in liver metabolism and enzyme induction, effects on the nervous system and skin, thyroid hormone disruption, hypertrophy of hepatic, gastrointestinal, urogenital and cutaneous epithelia, subcutaneous edema, systemic hemorrhage, and changes in body and organ weights. Animal models have consistently demonstrated hepatotoxicity, endocrine disruption, immunotoxicity, cleft palate, developmental toxicity (e.g., malformations, growth retardation, fetal morality), reproductive toxicity (e.g., reduced testicular steroidogenesis, reduced plasma androgen concentrations, reduced reproductive organ weights, abnormal testis morphology, decreased spermatogenesis and reduced fertility, disruption of the estrous cycle, reduced litter size, and reduced fertility), and carcinogenesis associated with chronic exposures. Notably, many of these adverse effects in adult animals require toxic doses, though developing animals experience these effects at doses more than 100 times lower, demonstrating the increased susceptibility to dioxin in early-life exposures.

1.3.2 Nondioxin Like-PCBs

In comparison with DL-PCBs, nondioxin Like (NDL)-PCBs have been shown to elicit toxicity on some similar systems, but act through a different MOA (non-AhR mediated effects) and result in differential downstream impacts. Adverse effects reported in humans include hepatic, neurological, neuroendocrine, dermal, endocrine, immunological, and some carcinogenic effects. PCBs are not genotoxic, but are considered probable human carcinogens by IARC. Reported cancers in humans (mostly from occupational exposure cohorts) include cancers of the liver, GI tract, brain, and gallbladder. Perhaps the most well-studied end point associated with NDL-PCB exposures involves the myriad of effects related to developmental neurotoxicity. Examples of adverse findings have included altered psychomotor development, decreased birth weight, altered hormone levels (e.g., estrogen, thyroid), altered sperm morphology, and function. Laboratory studies have demonstrated similar effects, lending biological plausibility support to the observed effects in humans. Decreased cognitive effects have been reported in children that may persist for many years. Also similar to the DLCs, effects in humans are often difficult to evaluate in epidemiological studies due to confounding exposures with DLCs, and, in particular, other known neurotoxicants and POPs (such as DDT and mercury).

1.4 BROMINATED COMPOUNDS

In addition to the unintentional production of some brominated and mixed bromo-chloro dioxins and furans, several brominated POPs are now a part of the Stockholm Convention (or have been nominated for inclusion):
hexabromobiphenyl (HBB), a type of polybrominated biphenyl (PBB); several PBDEs; and hexabromocyclododecane (HBCD). Many of these compounds have been used in thousands of commercial products as flame retardants; brominated compounds are the most widely used flame retardant chemicals due to their efficacy and low cost.

1.4.1 PBBs

PBBs are the bromine analogs to PCBs. There are 209 possible congeners, and also like PCBs, they can be divided into planar and nonplanar compounds depending on the location of bromine substitutions (Fig. 1.5).

As such, the differences in structure translate into varying toxicities of certain PBB congeners. Like most of the brominated POPs, PBBs were used commonly as a flame retardant additive in several commercial products. HBBs, or HexaBBs, include 42 congeners: BB 128 through BB 169. HBBs are the most toxic of the PBBs, and have been targeted for elimination under the Stockholm Convention. They comprised the majority of technical mixtures of PBB flame retardants, FireMaster FF-1 and FireMaster BP-6. For this reason, the majority of data presented here evaluated the effects of these commercial mixtures.

Available data indicate that intestinal absorption of PBBs can be significant, and is estimated at around 90–95% in rats following various routes, doses and time periods of exposure to BB-153. The majority of administered dose accumulated in the adipose tissue, though smaller fractions were also seen in muscle, liver, and other organs. PBBs induce CYP450 enzymes in the liver, and some congeners have been shown to interact with the AhR. Metabolism and excretion is limited and/or slow, resulting in an estimated average half-life of HBBs in humans of 8–12 years.

PBBs are much like their PCB analogs with respect to toxicity. Information on the toxicological effects of PBBs in humans is derived primarily from an accident at the Michigan Chemical Company in St. Louis, Michigan in 1973. FireMaster BP-6 (250–500 kg) was inadvertently added to animal feed and distributed to several farms in the state, causing widespread contamination with PBBs. Reported effects in residents included changes in liver enzymes, nausea, pain, fatigue, skin disorders, hair loss—symptoms similar to DLC toxicity. In an early study after the accident, Landrigan et al. evaluated a cohort of 4545 residents and reported that serum PBB levels were not

![Figure 1.5. Chemical structure of polybrominated biphenyls (PBBs).](image)
associated with reported symptom prevalence rates, nor were they associated
with lymphocyte number or function. That same year, a study assessed the
neurological symptoms related to expected PBB exposure. The authors
reported that particularly among males, diminished performance on special
neurological tests was associated with the intake of contaminated foodstuffs,
but serum PBB levels were not associated with the strongest neurologic symp-
toms and were negatively associated with performance test scores, especially
in older males. No association was noted between PBBs and endometriosis
in the Michigan cohort, nor was an association between PBB or PCB serum
concentration and shorter time to menopause observed by Blanck et al. An
earlier examination of in utero exposure to PBBs (and PCBs) from mothers
and their infants in this cohort showed no associations between estimated
maternal PBB serum concentration at time of conception or enrollment PCB
levels and gestational age or birth weight in adjusted and unadjusted models.

Other studies have reported increased risk for developing breast cancer
(Henderson et al.,), though when other risk factors were taken into account,
odds ratios were unchanged. An increased risk for digestive system cancer and lymphoma risk has also been reported. Blanck et al. reported that girls
exposed to high levels of PBBs in utero and via breast milk experienced earlier
menstrual onset and pubic hair growth, suggesting an effect of PBBs on puberty.

Collectively, these evaluations present varied findings, including increased
odds of some cancers, endocrine and other hormone-disrupting effects, and
adverse reproductive and developmental effects. In general, the epidemi-
ological studies have failed to establish definitive associations between PBB
exposure and immunological status, cancer incidence, or reproductive and
developmental effects. PBBs are consistently negative in in vivo and in vitro
genotoxicity and mutagenicity assays. HBB has been shown to be carcino-
genic in animal models; hepatocarcinogenicity has been demonstrated in
multiple studies on mice and rats administered FireMaster FF-1, and caused
hepatocellular adenoma/carcinomas and cholangiocarcinomas in female
rats. The International Agency for Research on Cancer (IARC) concluded
that there was sufficient evidence to conclude that HBB is carcinogenic to
mice and rats, and possibly to humans.

1.4.2 PBDEs

PBDEs are organobromine compounds that are structurally similar to PCBs.
They are flame retardant chemicals and are used in a variety of commercial
products. Although there are a total of 209 possible PBDE congeners (Fig. 1.6),
commercial production resulted in three main mixtures: decabromodiphenyl
ether (decaBDE), octabromodiphenyl ether (octaBDE), or pentabromodiphe-
nyl ether (pentaBDE), based on the average degree of bromination.

PentaBDE is composed mostly of tetrabrominated (BDE 47) and penta-
brominated (BDEs 99 and 100) congeners. OctaBDE’s main components are
largely heptabrominated (BDE 183) and octabrominated (BDEs 196, 197 and
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203) congeners. DecaBDE consists primarily of the fully brominated congener (BDE 209) (with 10 bromines). In 1999, decaBDE, octaBDE, and pentaBDE comprised approximately 80, 6, and 14% of worldwide production of PBDEs, respectively. Although the United States ceased production of pentaBDE and octaBDE in 2004, there are still many products that contain high levels of these PBDE mixtures, and they are both highly persistent in the environment. As most other POPs, PBDEs are lipophilic, therefore bioaccumulate in fatty tissues and biomagnify through the food chain.

Studies characterizing potential effects of PBDEs in humans have been relatively limited until recently. As public health interest increases, additional epidemiological investigations are being conducted and published. These studies generally focus on three main outcomes: endocrine disruption, neurotoxicity, and reproductive toxicity. The latter two outcomes may be related to endocrine disrupting effects, lending mechanistic support to the observed toxicities in both humans and in experimental studies. The available epidemiological studies tend to be focused around these key toxicological effects, and have been based on findings from laboratory studies, as well as knowledge about compounds with similar structure, such as polychlorinated biphenyls (PCBs).

The majority of laboratory studies on PBDEs published to date have focused on the commercial mixture, pentaBDE, or the individual congeners contained in pentaBDE (primarily BDEs 47 and 99); however, a number of studies are available reporting on exposures to other commercial mixtures, decaBDE and octaBDE. Similarly, epidemiological studies have also primarily focused on effects associated with exposure to BDEs 47 and 99, or sum concentrations of PBDEs. However, an increasing number of studies have reported on BDEs 100, 153, 154, and 183. It is important to note that because the chemical kinetics associated with BDE 209 may be different than the lower-brominated other congeners, it is addressed separately and is excluded from the generalizations and trends discussed in this section.

Data in laboratory studies demonstrate altered levels of thyroid hormones following exposures to PBDEs in rodents. Studies in animals have also indicated the potential for hydroxylated PBDEs to interfere with thyroid hormones. This is partially due to the similarity in structure between PBDEs and thyroid hormones triidothyronine (T3) and thyroxin (T4), and thus the potential for PBDEs to mimic and disrupt homeostatic conditions. Based on these findings, a similar mechanism of action has been evaluated in humans.

Figure 1.6. Chemical structure of polybrominated diphenyl ethers (PBDEs).
In fact, the majority of studies in human populations have evaluated the disruption of the endocrine system, and much of the focus has been on disruption of thyroid hormones. Key findings include:

- Negative association between thyroid-stimulating hormone (TSH) and BDE 47 in men who consumed fatty fish from the Baltic Sea.\(^{51}\)
- Lack of correlations between concentrations of PBDEs and thyroid hormones (T3 and T4; total and free) in a small group of paired maternal and fetal samples.\(^{52}\)
- Lack of significant correlations between PBDE concentrations and T3, T4, or TSH; in a small-scale study of recycling workers; authors also noted that all of the levels were within normal physiological ranges.\(^{53}\)
- Significantly higher concentrations of TSH in serum from e-waste dismantlers with PBDE concentrations approximately double a control group.\(^{54}\)
- PBDE exposure at levels observed in the general U.S. population was associated with increased thyroglobulin antibodies and increased T4 in adult males.\(^{55}\)
- Umbilical cord levels of PBDEs were not associated with higher TSH or FT4.\(^{56}\)
- PBDE exposures were associated with lower maternal TSH during pregnancy.\(^{57}\)
- e-Waste recycling workers with elevated PBDE serum levels had significantly lower TSH compared with control groups.\(^{58}\)

Given the range of findings in the literature, it is hard to draw definitive conclusions about the effects of PBDEs on thyroid homeostasis. Many different populations have been studied worldwide, including both occupationally exposed cohorts as well as sensitive cohorts (e.g., pregnant women and infants).\(^{59,60}\) The difficulties in finding consistencies may be due to the fact that many of the studies did not evaluate the same congeners, nor did they conduct congener-specific analyses, but rather depended on analyses based on the sum of PBDEs measured (which was also not consistent among studies). Concurrent exposure to PCBs (known endocrine disruptors) is also a factor that was not considered in many studies. Further, measurement of thyroid hormones is often subject to a large amount of analytical sensitivity and variability. Despite these limitations, the evidence suggests that serum concentrations of PBDEs, and some congeners in particular, are associated with altered levels of thyroid hormones.

Neurotoxicity has also been a primary end point of concern since the publication of a series of rodent studies by Eriksson and Viberg. This group of investigators has evaluated developmental neurotoxic potential of many BDE congeners (as well as other BFRs, PCBs, etc.) in a mouse model. These studies have collectively spurred many other investigators to evaluate the neurotoxicity of PBDE congeners reviewed by Costa and Talsness.\(^{61,62}\) Further, several
studies have cited potential neurotoxic potential due to structural similarity to PCBs, also known neurotoxicants. A handful of studies have been published recently addressing neurotoxicity outcomes in human populations and potential associations with PBDE exposures. In one study, PBDEs were associated primarily with positive neuropsychological function, although some negative effects were observed. Herbstam et al. observed that negative associations were observed between PBDE serum concentrations and neurobehavioral parameters. Several investigators have reported on underlying mechanisms of neurotoxicity based on research using in vitro models in both animal and human cell lines. Recent studies are highlighted by findings from studies using human neuroblastoma cell lines, demonstrating apoptosis, DNA degradation, increased release of intracellular calcium, release of cytochrome c, and other markers of cell damage following exposures to DE-71 and BDE 47. When considered collectively, this body of literature supports an association between exposure to PBDEs and neurodevelopment. However, data gaps and limitations to available data still exist, highlighting the need for additional research to understand potential adverse effects in human, particularly considering a number of the confounders that limit the interpretation of the data currently available. Future investigations will aid in more fully characterizing the type and severity of effects in humans, as well as underlying mechanisms.

Several studies have evaluated the downstream impact of endocrine disruption, genetic disturbance, and other potential adverse effects on reproductive toxicity. Harley et al. reported decreased fecundability odds ratios, as measured by time to pregnancy, for BDE 100, 153, and the sum of PBDEs; no effects were noted for the other congeners measured individually. Several years earlier, Main et al. reported an association with cryptorchidism, which was supported by findings from a pilot study of sperm quality on 10 Japanese men in which a significant inverse relationship between both end points for BDE 153 were observed.

Several studies have directly evaluated cytotoxic and genotoxic effects in immortalized human cell lines exposed to BDE congeners, as well as hydroxylated and methoxylated derivatives, or commercial mixtures, demonstrating release of intracellular calcium, apoptosis, DNA damage (often measured by formation of reaction oxygen species—ROS), morphological changes, or disruption/activation of cell signaling involved in toxicity. Genotoxicity has also been evaluated in a study of Chinese workers from an e-waste dismantling site; Yuan et al. reported that the frequency of micronucleated cells was 5% in the exposed group and 0% in the control group, thus suggesting an association between exposures to e-waste and DNA damage. (Notably, the authors concluded that exposures to other compounds, such as PAHs or metals, may have also been responsible for the observed genotoxic effects).

Data characterizing potential effects associated with exposures to PBDEs in humans are becoming increasingly available. When the data are considered collectively, it appears that human populations may be at risk of health effects, primarily endocrine disrupting effects that may manifest as neurotoxic or
reproductive outcomes. Additional research is needed to more fully understand the mechanistic aspects of toxicity following exposures, as well as to more fully understand the quantitative relationships between exposure and response. Further, these data collectively suggest that some BDE congeners are more potent or operate via different mechanisms than others. Many mechanistic studies have been published in the last decade describing responses to PBDEs in human cells or human cell lines. Findings from in vitro studies generally provide biological plausibility for the observed effects in vivo and in human studies. Mechanistic studies also indicate that BDE congeners may induce differential effects via different mechanisms (similar to DLCs), resulting in different potencies, though some data suggest a potential for common mechanistic action—at least on a qualitative basis. There is increasing interest in understanding the underlying mechanisms and structure activity relationships of BDE congeners, as well as hydroxylated and methoxylated derivatives.

DecaBDE, or BDE 209, has been evaluated less often than the other compounds. Toxicity findings are inconsistent and controversial, and a number of data gaps remain with respect to identifying critical effects (in animals and humans), quantitatively extrapolating toxicity to observed exposure levels, and confidently assessing risk in humans. The potential association between BDE 209 and neurotoxicity is one of the most prominent toxicological issues in the field of BFR research. Many studies, commentaries, and reviews followed the initial publication by Viberg et al.72 demonstrating alterations in behavior, habituation, and memory in mice exposed to BDE 209 on PND3. More recent findings include:

- Dose-related reduction of serum thyroxine levels, delayed development of the palpebral reflex in neonatal mice, disruption of normal sex- and age-specific characteristics of spontaneous locomotion in adults.73
- Impairment in performing behavioral tasks was observed in aging mice following neonatal exposure to decaBDE.74
- Changes in spontaneous behavior, as well as changes in cholinergic susceptibility in male NMRI neonatally exposed to BDE 209.75
- Adverse affects on several proteins important to normal brain growth and development in mice following oral exposure.76
- Impaired synaptic plasticity in adult rats following developmental exposures.77
- A lack of treatment-related effects in a GLP, guideline-based (OECD 426) developmental neurotoxicity study resulting in a no-observed adverse effect level (NOAEL) of 1000 mg/kg/d (the highest dose tested).78
- Adverse effects on reproductive parameters, thyroid hormone levels, and neuronal development associated with gestational exposures and/or postnatal exposures in rats.79–81
- Inhibition of testosterone and estradiol secretion in porcine ovarian follicular cells.82
There are many uncertainties associated with evaluating the toxicity of BDE 209, many of which were discussed by Alcock et al. There are also many inconsistencies in the reported findings as addressed by Williams and DeSesso, including nonlinearities in dose, with low dose effects not being seen at high doses. Further, although there is potential for endocrine disruption in laboratory settings, several of the authors indicate that additional studies at environmentally relevant doses are required to more adequately characterize observed effects.

Studies focusing on BDE 209 in humans are sparse, which may be partially due to analytical challenges in accurately measuring the congener. Data are highlighted by findings recently reported by Van den Berg et al. In this study, serum levels of BDE 209 were measured and analyzed for potential relationships with lifestyle and diet. The country of residence was the only significantly relevant variable that explained the observed serum levels. No consistent relationships were measured for diet, household, clothes, number and/or duration of use of electronics, or occupational activities. The authors further interpreted the impact of BDE 209 levels in serum by estimating the margin of exposure (MOE) with the most sensitive end points in animal studies. The resulting MOE was at least two orders of magnitude for average exposure levels in Europe, though may be less for women with the highest levels of BDE 209. Blood and milk levels of BDE 209 are frequently not reported in studies of PBDE levels in humans. This is partly due analytical challenges (e.g., the background presence of BDE 209 in analytic laboratories). In addition, modification of capillary column length is indicated in the GC-MS procedure for measurement of this BDE. Estimating levels of BDE 209 by reporting a fraction of the level of detection when it is not detected can produce erroneously high reported levels of this congener. A short half-life of elimination can be another challenge to determination of BDE exposure. Stapleton and Webster discuss older and newer flame retardants in some depth.

1.4.3 HBCD

HBCD is a nonaromatic, brominated cyclic alkane that is primarily used as a flame retardant. HBCD encompasses 16 potential stereoisomers; commercial HBCD mixtures are composed primarily of three diastereomers, α-, β-, and γ-HBCD, and the isomeric composition varies in technical grade HBCD, although γ-HBCD predominates (Fig. 1.7). HBCD is lipophilic and strongly bioaccumulates and biomagnifies, leading to an ubiquitous presence in the environment and biota. Despite the widespread, high-volume use of HBCD, there are relatively few studies available characterizing its toxicity. Even fewer studies fully characterized the compound with respect to stereoisomer composition, which may be of particular importance with respect to both exposure and toxicity. The chapter by Szabo on HBCD describes these compounds in some detail.
Currently, there is no human in vivo data on HBCD toxicity, with the exception of one early study examining skin sensitization, reporting negative findings. The limited human data stem from in vitro assays on human cell lines. These data indicate activation of the thyroid receptor, as well as activation (or antagonism) of the AhR, androgen receptor (AR), progesterone receptor (PR), and estrogen receptor (ER) by HBCD.\textsuperscript{88,89} Adverse effects resulting from HBCD exposure to natural killer (NK) cells have also been reported in human cells. HBCD did not cause significant increases in structural or chromosome aberrations in an in vitro mammalian cytogenetic test on human lymphocytes.\textsuperscript{90} HBCD exposures did not impact DNA methylation in human HepG2 cells nor primary hepatocytes, though it did cause a lack of promoter demethylation in specific regions in primary hepatocytes.\textsuperscript{91} A handful of in vitro studies in human cell lines have reported on the cytotoxicity associated with HBCD exposures. These studies underscore the importance of evaluating specific stereoisomers as there are clearly differences in toxicokinetic profiles\textsuperscript{92,93} and toxicity. For example, using the human HepG2 hepatoma cell line, Zhang et al.\textsuperscript{94} evaluated the cytotoxicity of six $\alpha$-, $\beta$-, and $\gamma$- HBCD (+/−) isomers. Various assays were used to evaluate cytotoxicity following exposures to HBCD in these HepG2 cells, observing a potency of $\gamma > \beta > \alpha$. The authors further noted that Hep G2 cells exposed to (+) enantiomers expressed significantly lower cell viability than those exposed to (−) enantiomers. Additional assays revealed a positive correlation between LDH release and ROS formation, leading the authors to propose that HBCD toxicity may be mediated via oxidative damage.

Available in vivo laboratory data characterize a number of end points following exposure to HBCD in laboratory animals, including acute toxicity, hepatic and thyroid toxicity, neurotoxicity, reproductive toxicity, and genotoxicity. This research has been conducted in a number of species, including rats, mice, and rabbits, and ranges from very short to chronic 90-day high-dose exposures. These studies generally indicate the liver and thyroid are target
tissues. Repeated dose studies in rats have resulted in increased relative liver weights, increased thyroid weights, increased levels in hepatic enzymes (both phase I and II), altered lipid metabolism, and changes in thyroid hormone levels.\textsuperscript{95–99} Multi- and single-generation studies have documented reproductive toxicity, including adverse impacts on end points, such as decreased fertility index, decreased testis weight, number of primordial follicles, altered thyroid hormone levels, and decreased trabecular bone mineral density.\textsuperscript{100–103} Neurodevelopmental effects include indications of impaired brain development.\textsuperscript{100,104–106} Moreover, \textit{in vitro} assays in rat cell lines have demonstrated that HBCD blocks dopamine uptake in brain synaptosomes\textsuperscript{106} and inhibits depolarization-evoked calcium import and neurotransmitter release.\textsuperscript{107} A single, 28-day study failed to observe significant immunotoxicity following a 28-day dietary HBCD exposure and subsequent respiratory syncytial virus (RSV) infection in mice.\textsuperscript{108}

Standard mutagenicity testing showed that HBCD does not have substantial mutagenic potential in several strains of \textit{Salmonella typhimurium}.\textsuperscript{109} Additionally, an \textit{in vivo} micronucleus test in mice showed no clastogenic activity (no breaking or disrupting of chromosomes).\textsuperscript{110} Collectively, these data indicate that HBCD lacks significant genotoxic potential \textit{in vitro} as well as \textit{in vivo}. In regard to carcinogenicity, one chronic feeding study in mice is available, and evaluated the effects of up to 1300 mg/kg/d HBCD after 18 months.\textsuperscript{111} While various types of tumors were observed in several organs, incidences were sporadic and the authors did not consider them to be substance related.

1.5 \textbf{PERFLUORINATED COMPOUNDS}

Polyfluorinated alkylated substances (PFAS) are a group of organic compounds consisting of a hydrophobic alkyl chain of varying length and a hydrophilic end group. The carbon chain can be partially or fully fluorinated; fully fluorinated PFAS are called PFCs. These chemicals are of special concern in environmental toxicology because of the strength of the C-F covalent bond and consequent persistence in the environment. PFCs with negatively charged end groups, including sulfonates, carboxylates, and phosphates, are called anionic perfluorinated acids, and include the most studied (and most largely manufactured in the United States) perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) (Fig. 1.8). PFOA is used to make

![Figure 1.8. Chemical structure of PFOA (left) and PFOS (right).](image-url)
fluoropolymers like Teflon, and PFOS is used commonly in the semiconductor industry, as well in the past in 3M’s Scotchgard carpet treatment. Treatment with these PFCs makes the products resistant to stains, oil, and water, making them particularly useful in a variety of applications, such as in nonstick cookware, grease-resistant food packaging, carpet treatments, Teflon, Gor-Tex, and personal care products.

Some other PFAS are perfluorobutanesulfonic acid (PFBS), used to replace PFOS in Scotchgard, perfluorooctanesulfonamide (PFOSA), formerly a component of Scotchgard, and perfluorooctanesulfonyl fluoride (POSF), which is used to make PFOS-based chemicals. Currently PFOS, its salts, and POSF are included as restricted industrial chemicals in the Stockholm Convention. Although PFOS had been produced and used extensively in the chemical industry since the 1950s, the U.S. EPA became aware of its potential for extreme persistence, bioaccumulation, and toxicity in the late 1990s when low levels of PFOS were found widespread in sera of the nonoccupationally exposed, general U.S. population. Its major manufacturer, 3M, shortly thereafter ceased production of PFOS-related chemicals in 2000. PFOA is still produced, but a major manufacturer, DuPont, has voluntarily agreed to cease production in 2013. Other manufacturers around the world still produce these compounds and similar chemicals that are believed to break down into PFOS or PFOA after release into the environment. Currently, PFOS and PFOA are the focus of research, though investigations are ongoing both on shorter and longer chain PFCS as well as for other fluorinated compounds. Structural analysis of the larger group of PFAS reveals that studies performed on PFOS and PFOA may be applicable to many other fluorinated chemicals, suggesting a cause for concern regarding far more fluorinated compounds than initially expected.

Animal studies on the toxicokinetics of PFOS and PFOA suggest that they are readily absorbed following oral administration, not metabolized, poorly eliminated via the urine or feces (the degree to which route prevails is species dependent), and undergo extensive enterohepatic circulation. PFAS structurally resemble fatty acids, and are believed to behave like such within the body. Perfluorinated compounds, unlike most other POPs, are lipophobic and therefore do not accumulate in fatty tissues. Instead, they bind to proteins and accumulate in the liver, kidney, and blood. A study on in utero exposure in mice also indicated that breast milk could be a substantial exposure route for PFOA. Reported half-lives of PFOA and PFOS in human blood serum are believed to be between 3.8 and 5.4 years, respectively, in adults. Based on kinetic modeling, the disposition of PFAS has been shown to depend largely on the expression of two transport proteins in the rat kidney, OATP1 and OAT3. Additionally, there was recently shown to be a dose-dependent uptake of PFOA into the liver, as well as a dose-dependent association of the compound with subcellular liver fractions. Considerable variability has been demonstrated with respect to elimination rates for PFOA across species, which is postulated to be a result of differences in the expression of organic anion
transporters (OATs) and renal tubular resorption. Further, renal clearance and liver accumulation largely depends on chain length (shorter compounds have faster elimination rates), gender, and species. Though the half-life for these chemicals is quite long, the toxicokinetic profiles and mechanisms for such persistence are not completely understood.

In general, PFOS and other perfluorinated compounds have been reported to cause a wide range of toxic effects in animals and humans via multiple routes of exposure. Effects are generally related to one hypothesized MOA, which involves induction of peroxisome proliferators, notably activation of peroxisome proliferator-activated receptor-α (PPARα). PPARα, a member of the nuclear receptor superfamily, affects expression of target genes involved in cell proliferation and differentiation, and immune and inflammation responses. Its endogenous ligands include free fatty acids and eicosanoids. PFOS and PFOA are also relatively weak ligands for mouse, rat, and human PPARα. Studies on the varying sensitivities of PPARα to agonists have shown that guinea pigs, primates, and humans are less sensitive, whereas hamsters, rats, and mice are more so. Another mechanism in which PFAs may potentially cause peroxisome proliferation is through disrupting lipid metabolism and transport. Luebker et al. demonstrated in vitro that several fluorinated compounds impede fatty acid binding to L-FABP, suggesting antagonism as a potential mechanism of peroxisome proliferation. However, additional studies in laboratory animals have suggested CAR-mediated mechanisms, as well as others, are likely involved given that tumors and other adverse effects are noted in PPARα knockout mice.

The majority of epidemiological data stem from several studies on the effects of chronic occupational exposure to high concentrations of PFOA or PFOS. More recently, epidemiological studies have focused on examining associations between PFOS/PFAS exposure and reproductive or developmental effects. Some studies on occupationally exposed cohorts have shown a positive association between serum FOA/PFOS concentration and sex hormone concentrations, as well as levels of cholesterol and triglycerides whereas other examinations did not show this same relationship. The very few epidemiological data available from the nonoccupationally exposed population do not indicate a significant risk of reduced birth weight or gestational age. One of these studies was a large, longitudinal, population-based study that concluded that maternal cord blood PFOS concentration was not associated with birth weight, gestational age, birth length, head circumference, abdominal circumference, placental weight, or ponderal index, though the authors did report a negative association between PFOA and birth weight. Conversely, Washino et al. reported PFOS was statistically significant with birth weight, but PFOA was not. In a study on Ohio residents, researchers did not find an association between serum PFOS/PFOA and self-reported effects: miscarriage or preterm birth. PFOS and PFOA exposures above the median serum level were weakly associated with.
PFOS was related to an increased risk for low birth weight, whereas PFAS was weakly associated with birth defects.

Many data will result from the C8 Health Project, which evaluates potential effects associated with consumption of PFOA-contaminated drinking water in West Virginia. For example, initial observations include an increase between PFOA and PFOS and elevated total cholesterol and LDL-C levels and a higher prevalence of hyperuricemia, though C8 investigators caveat that additional assessments are required given the limitations of their cross-sectional data set.

Collectively, findings from epidemiological studies are conflicting or are associated with limitations, underscoring the need for further investigations to more fully characterize potential effects in humans. However, data from laboratory studies may aid in understanding potential effects in humans, though adverse health effects observed in these studies are generally associated with exposures that result in serum concentrations much higher than human serum concentrations in the general population.

In studies on PFOS/PFOA in animals, regardless of route of exposure, the liver appears to be a major target organ. Other sensitive effects include changes in thyroid hormones and sex hormones, high-density lipoprotein (HDL) levels, immunotoxicity, hepatotoxicity and liver tumors (via a nongenotoxic MOA), and mortality. Neither PFOS nor PFOA has been shown to be mutagenic in a variety of assays. A 2-year bioassay in rats showed that a high dose of 20 ppm PFOS in the diet resulted in an increase in hepatocellular adenomas, and a group fed the same diet for only 1 year and then monitored for the second developed thyroid follicular cell adenomas. PFOA has also been shown to induce hepatocellular adenomas, Leydig cell tumors, and pancreatic acinar cell tumors in male rats.

Exposure during development (especially via breast milk) has resulted in significant health effects in laboratory animals. Gestational PFOA exposure in mice lead to delayed mammary gland development and/or lactational differentiation in three generations. Additionally, drinking water exposure, at concentrations approximating those reported in human drinking water, altered mammary gland development in mice. Studies of PFAS in rat, mouse, and rabbit collectively show that overt teratogenic effects are generally not significant at doses below those that cause maternal toxicity, though subtle effects are observed. At the highest doses tested, fetal weight reduction, cleft palate, delayed ossification, and cardiac abnormalities are the most frequent effects noted. Dose-dependent effects were seen in newborns when dams were allowed to give birth, including pale color and inactivity leading to death. In mice, the same effects were noted, although a higher dose was required.

Lau et al. and Luebker et al. demonstrated that in utero PFOS exposure affects rat pup development characterized by delayed weight gain, eye opening, pinna unfolding, surface righting, and air righting, often continuing past weaning. Thyroid hormone homeostasis was also abnormal, though levels
of TSH were not affected. Additionally, in the two-generational developmental study, the effects previously noted in the F1 generation were not seen in the F2 generation.\textsuperscript{150} One chapter in this volume is exclusively devoted to PFCs.\textsuperscript{151}

### 1.6 CONCLUSIONS

POPs are organic chemicals that are resistant to environmental degradation. These compounds are capable of long-range transport, and typically bioaccumulate in animal and human tissues. Many of these compounds also have the potential to result in significant effects on human health and wildlife. Some POPs have been evaluated in epidemiological studies, though a large part of our understanding of the health effects of POPs is based on data generated in laboratory studies and limited data reporting adverse effects in domestic animals and wildlife. Collectively, data on this group of chemicals contribute to a wide variety of toxicities, including, but not limited to cancer, endocrine effects, and reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and a variety of skin conditions. Biomonitoring studies indicate that generally, levels of certain of the legacy POPs in humans continue to decline, while some newer or emerging POPs, for example, PBDEs, are increasing. However, additional research is needed to more fully understand the health effects associated with chronic, low-level exposures to these persistent compounds.

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