

Review

Polychlorinated Biphenyls (PCBs) in the Environment: Occupational and Exposure Events, Effects on Human Health and Fertility

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Abstract: In the last decade or so, polychlorinated biphenyls (PCBs) garnered renewed attention in the scientific community due to new evidence pointing at their continued presence in the environment and workplaces and the potential human risks related to their presence. PCBs move from the environment to humans through different routes; the dominant pathway is the ingestion of contaminated foods (fish, seafood and dairy products), followed by inhalation (both indoor and outdoor air), and, to a lesser extent, dust ingestion and dermal contact. Numerous studies reported the environmental and occupational exposure to these pollutants, deriving from building materials (flame-retardants, plasticizers, paints, caulking compounds, sealants, fluorescent light ballasts, etc.) and electrical equipment. The highest PCBs contaminations were detected in e-waste recycling sites, suggesting the need for the implementation of remediation strategies of such polluted areas to safeguard the health of workers and local populations. Furthermore, a significant correlation between PCB exposure and increased blood PCB concentrations was observed in people working in PCB-contaminated workplaces. Several epidemiological studies suggest that environmental and occupational exposure to high concentrations of PCBs is associated with different health outcomes, such as neuropsychological and neurobehavioral deficits, dementia, immune system dysfunctions, cardiovascular diseases and cancer. In addition, recent studies indicate that PCBs bioaccumulation can reduce fertility, with harmful effects on the reproductive system that can be passed to offspring. In the near future, further studies are needed to assess the real effects of PCBs exposure at low concentrations for prolonged exposure in workplaces and specific indoor environments.

Keywords: persistent organic pollutants; polychlorinated biphenyls; environment; occupational exposure; human exposure; health effects; fertility

1. Introduction

Chemicals detected in the environment, with the peculiarity of having long half-lives in soils (generally years), sediments, air (several days) or biota are defined as persistent organic pollutants (POPs). In recent years, studies on chemistry and effects of POPs are increasing and this topic became a fascinating scientific research area [1–4]. Several POPs are listed under the Stockholm Convention on Persistent Organic Pollutants, including chlorinated (and brominated) aromatics, such as polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans, polychlorinated dibenzo-p-dioxins and polybrominated diphenyl ethers, as well as several organochlorine pesticides (e.g., dichloro-diphenyl-trichloroethane and its metabolites, chlordane, toxaphene, etc.) [5]. Moreover, these POPs can be easily absorbed by microplastics, which become vectors of these organic contaminants, facilitating their dispersion in different environmental compartments [6–8].

Polychlorinated biphenyls are persistent organic pollutants that have a negative impact on the ecosystem and all living beings and continue to represent a serious risk to human health [9]. Large-scale production of PCBs started in 1945. Thanks to their chemical characteristics and thermal stability, they were used as dielectric fluids (in transformers and electric capacitors) and as additives for pesticides, flame retardants, insulators, paints, glues and printing inks [10,11]. PCBs are obtained from oil and tar, from which benzene is extracted, and then transformed into biphenyl, which is subsequently chlorinated to polychlorinated biphenyl. The chemical structure is characterized by the presence of two aromatic rings on which there are 1 to 10 chlorine atoms (Figure 1).

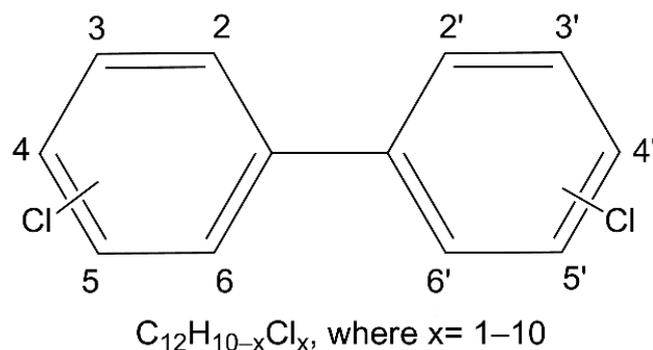


Figure 1. General structure and formula of PCBs. Chlorine atoms can replace hydrogens in different positions of the aromatic rings.

The various combinations determined by the number and position of the chlorine atoms result in 209 different compounds called congeners. The IUPAC (International Union of Pure and Applied Chemistry) nomenclature assigns each congener a number between 1 and 209 [12]. The chemical and physical characteristics of PCBs differ considerably among congeners leading to a high structural variability, which has direct consequences on persistence and bioaccumulation. Based on the number of chlorine atoms, PCB congeners can be divided into low-chlorine PCBs if they contain four or fewer chlorine substituents, and high-chlorine PCBs if they have more than four chlorine atoms [13]. These differences determine their environmental availability and their routes of exposure. High-chlorine PCBs are relatively non-volatiles, mainly present in food and more persistent than low-chlorine PCBs, thanks to their resistance to metabolic degradation. Conversely, low-chlorine PCBs, often referred to as transient or episodic forms due to their relatively short half-lives, are semi-volatiles and are rapidly metabolized [14–16]. Low-chlorine PCBs are the main PCBs found in indoor [17] and outdoor [18–20] air, especially in large cities and urban industrial areas, e.g., in the air of major cities [16,21–24].

Among all 209 compounds classified as PCBs, 12 (i.e., PCB 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169 and 189) have physio-chemical and toxicological properties comparable to those of dioxins and furans and are, therefore, called dioxin-like PCBs. Being all coplanar, they can bind to the aryl hydrocarbon receptor (AhR), which is the canonical receptor

for 2,3,7,8-tetrachlorodibenzo-p-dioxin [25]. Importantly, non-dioxin-like PCBs account for a significantly high proportion of PCBs found in human serum, adipose tissue and breast milk [26]. Moreover, PCBs could be also divided into “legacy” and “non-legacy” or “contemporary” [27]. The latter are formed as inadvertent by-products during the production of currently sold paints, inks and dyes, so are released into the environment unintentionally [28–31].

Although their use was banned in the 1970s, their resistance to chemical and thermal degradation results in bioaccumulation in marine organisms and humans. Thus PCBs continue to be an environmental and human health concern [13,32]. The occurrence of several chronic diseases, such as endocrine dysfunction, type 2 diabetes, cardiovascular disease, obesity, liver disorders, and neurological deficits, have been associated with exposure to PCBs [33]. Moreover, they affect the immune, reproductive, nervous and endocrine systems and are carcinogenic [34–36].

Considering the growing interest in this research field, the present review aims to discuss the accumulation of the different PCBs based on their chemical-physical and toxicological characteristics, routes for human exposure (both environmental and occupational) and subsequent effects on human health.

2. Methodology

Based on the recent scientific literature related to PCBs occurrence in the environment, this review had three main objectives: (1) describe the different routes for human exposure to PCBs; (2) highlight the importance of PCBs level of contamination in workplaces for occupational exposure; (3) discuss the effects on human health due to exposure and bioaccumulation of PCBs. The keywords “persistent organic pollutants”, “polychlorinated biphenyls”, “environment”, “occupational exposure”, “human exposure”, “health effects” and “fertility” were selected individually or jointly to search for relevant information on the Web of Science, Scopus and Google Scholar. The literature search covered articles published between 1990 and 2022.

3. Human Exposure and Bioaccumulation of PCB

3.1. Routes for Human Exposure

PCBs can be generated from thermal processes, mainly waste incineration, but also steel smelting and domestic and industrial combustion of coal and wood (Figure 2). However, it must be considered that PCB congeners combined emissions generally contribute only a few percent to total air POPs emissions from domestic coal and wood combustion, which are mainly made of polycyclic aromatic hydrocarbons and particulate matter [37,38]. The main PCBs emission sources are electricity production (principally due to the consumption of coal as fuel), steel production and incineration, including that of waste. In addition to point sources, PCBs can be transported for long distances via deposition and resuspension processes (i.e., dry fallout and vapor deposition) that can be described as the grasshopper effect [39,40]. Human exposure to PCBs can derive from different sources, such as dietary intake, inhalation, ingestion of dust and dermal contact [41]. In Figure 2 are shown the main routes for the release of PCBs into the environment and relative human exposure routes.

The main exposure route to PCBs for humans is the consumption of contaminated food, mainly fish, seafood and dairy products [42,43]. In fact, numerous studies have shown that animal products containing fats are the most contaminated food sources, so their intake represents one of the principal routes of exposure to these POPs. Due to frequent health recommendations regarding fish consumption, determining the contribution to dietary intake of chemical contaminants, such as PCBs, is a matter of particular concern. Indeed, it was concluded that population groups that frequently consume large quantities of dietary items rich in fats could experience significantly higher health risks from exposure to PCBs and POPs in general [44–46]. Epidemiological studies have shown a correlation between the consumption of contaminated fish and the increase in the serum concentrations of

PCBs [45]. Very recently, the association between dietary intake and PCBs serum levels was examined, revealing that body mass index can modify this association with a stronger connection among normal/underweight individuals [47].

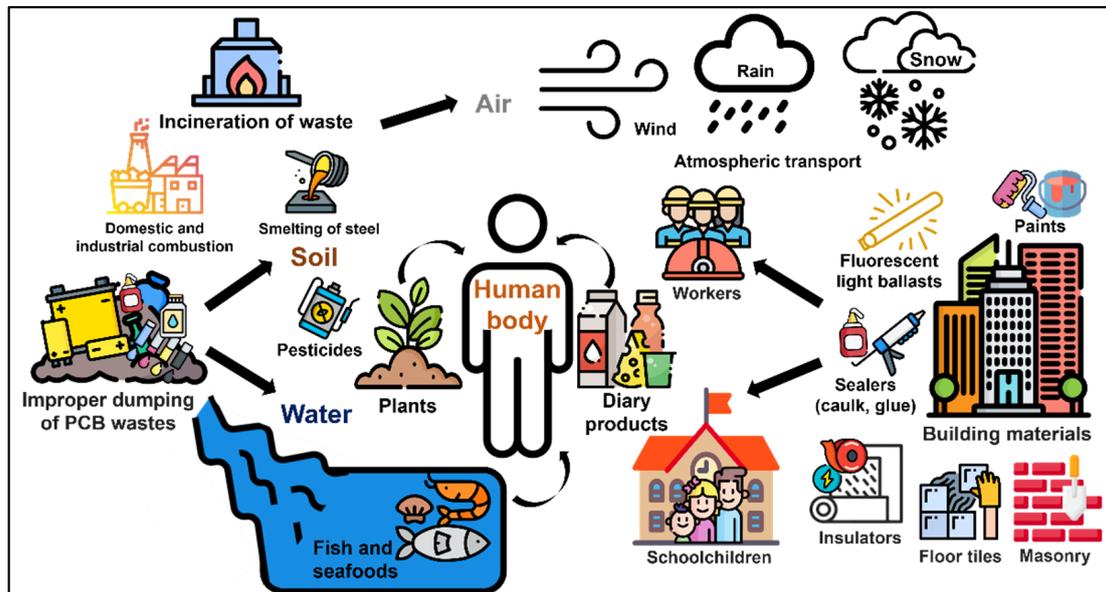


Figure 2. PCB sources and routes for human exposure.

Studies that investigated PCBs human intake through food consumption are mainly focused on fish, followed by meats (beef, pork, and poultry), dairy products and chicken eggs. Recently, it was found that salmon is the food item that contains the highest amount of POPs including PCBs, followed by canned tuna, beef steak, butter and fried chicken [48]. However, a reduction in PCB concentration in food was observed over the last 20 years, indicating a decrease in dietary exposure over time [48]. Furthermore, it has to be underlined that different human populations may differ in their exposure susceptibility to PCBs because of their differences in terms of lifestyle, living environment and dietary habits [49].

A second route for PCB exposure, albeit often overlooked, is inhalation, mainly indoors and to a lesser extent outdoors. This applies particularly to densely populated industrial areas and homes and buildings that have been constructed using PCBs in sealants and other building materials [24,50,51]. In fact, the highest concentrations of PCBs are found in the indoor and outdoor air of industrialized and densely populated urban areas in the cities of Chicago, Milwaukee, Toronto, Philadelphia and New York [23,52–57]. Since the volatilization of airborne PCBs is temperature dependent, this phenomenon can lead to their release from environmental or reservoirs, such as rivers, lakes, landfills or contaminated building materials [24,26,58]. Airborne PCBs also include most of the recently discovered non-legacy PCBs. Non-legacy PCBs are present in both indoor and outdoor environments and they can ultimately accumulate in the bodies of exposed populations. Many studies have reported the presence of non-legacy PCBs in air samples around the world. Volatilization from commonly used paints is the most likely source of these contaminants [28,59,60]. In 2010, over 50 non-legacy PCBs were detected in pigments employed in household paint [29]. Several studies have analyzed the effect of indoor air on PCB contamination. This is due to the fact that levels in indoor air may be several orders of magnitude greater compared to outdoor air and that people spend much more time indoors than outdoors. In order to get more information about potential health hazards due to indoor air PCBs in the literature, some studies investigated the PCB indoor concentration in schools, as well as the blood levels. In different schools the blood analyses indicated an increase in teachers from a school with heavy contamination of low chlorinated PCB [61–64].

Among all the exposure pathways, the dietary intake of PCBs continues to be the major one, despite having observed a recent increase in contributions from indoor air inhalation.

The other possible exposure routes (dermal contact and ingestion of dust) do not contribute significantly to the overall PCB exposure [41]. If the decrease in PCB concentrations in food observed in the last years continues, PCB inhalation could become comparable to dietary exposure in the near future [48]. This trend is related to the fact that legacy high-chlorine PCBs can be metabolized and eliminated from the food chain, whereas non-legacy PCBs are still inadvertently produced in modern paints and consumer items [13,29,65].

3.2. Occupation and Exposure Events in Workplaces

The potential health risks posed by pollutants, such as PCBs in the indoor environment are of great concern [66–70]. People generally spend more than 90% of their time indoors, between their home and their workplace. For many years there has been a large use of PCBs in the production of materials and/or objects typically found in indoor environments, such as building, sealing and caulking and materials, fluorescent lighting fixtures, electrical equipment, plasticizers, surface coatings, paints and ink [71,72]. Therefore, they could still be released in the indoor environment, absorbed as indoor dust and bio accumulated by people via non-dietary ingestion and inhalation pathways.

Indoor PCBs inhalation is a cause for concern in schools and other buildings (e.g., offices) constructed and refurbished especially from the 1950s to the late 1970s, as demonstrated by several studies investigating indoor PCB exposure in the United States and Europe [17,61,73–79]. During this period, caulking compounds (waterproofing technique), sealants and other building materials (e.g., fluorescent light ballasts) contained high levels of PCBs, and affected buildings still represent a major problem for chronic inhalation. The most relevant data concerning PCB air pollution in indoor environment are reported in Table 1.

Table 1. Concentration of PCB in indoor environments around the world.

Continent	Country	Location	Type of Site	Concentration	Reference	
Asia	Taiwan	Tainan	Urban	4.730 ng·m ⁻² day ⁻¹	[80]	
			Urban/industrial/rural	0.57–0.65 ng·m ⁻² day ⁻¹	[81]	
	South Korea	Pohang	Industrial	2.1 ng·m ⁻² day ⁻¹	[82]	
	Japan	Hong Kong	Office	52.5–589 ng·g ⁻¹	[83]	
			Electronic factory	47–249 ng·g ⁻¹		
			Manufacturing plant	709 ng·g ⁻¹		
			Electronic factory, commercial office, hospital, school and shopping store	107–233 ng·g ⁻¹		
	China	Taizhou	-	Nonferrous Metallurgical Facilities	0.0155–0.770 ng·m ⁻³	[84]
			E-waste recycling site	37.75–65.83 ng·m ⁻³	[85]	
			Urban	5.28–21.48 ng·m ⁻³		
	China	Quingyuan and Guangzhou	E-waste recycling site	568–11,500 ng·g ⁻¹	[86]	
			Rural	55.3–658 ng·g ⁻¹		
			Urban	38.6–226 ng·g ⁻¹		
	Vietnam	-	Industrial	0.94–1665 ng·g ⁻¹	[87]	
	Singapore	Singapore	Home	11–1900 ng·g ⁻¹	[88]	
India	Chennai	E-waste recycling site	3.6–53 ng·g ⁻¹	[89]		
		suburban industrial roadsides	1.6 ng·g ⁻¹			

Table 1. Cont.

Continent	Country	Location	Type of Site	Concentration	Reference
America	Canada	Toronto	Home	56–820 ng·g ⁻¹	[90]
			Home air	0.11–5.11 ng·m ⁻³	[17]
			Home dust	<LOD–521 ng·g ⁻¹	
	United States	Chicago	Urban	4500 ng·m ⁻² day ⁻¹	[91]
			Resident	190 ng·m ⁻² day ⁻¹	[92]
			Urban-industrial	0.075–5.5 ng·m ⁻³	[23]
		New Jersey	Urban	10–40 ng·m ⁻² day ⁻¹	[93]
			Suburban	0.9–3 ng·m ⁻² day ⁻¹	
			Background	0.8–2 ng·m ⁻² day ⁻¹	
			Texas	Home	
	Illinois	Dwelling and church	199–43,540 ng·g ⁻¹	[94]	
	Iowa	School	39.2–1.24 ng·m ⁻³	[95]	
Indiana and Iowa	School	0.5–194 ng·m ⁻³	[79]		
Europe	United Kingdom	Birmingham	Home	57–860 ng·g ⁻¹	[90]
	France	Thau lagoon	Rural	0.715 ng·m ⁻² day ⁻¹	[96]
	Germany	Stuttgart	School	3643–13,561 ng·m ⁻³	[61]
		North-Rhine Westphalia	E-waste recycling site	8000–330,000 ng·g ⁻¹	[97]
	Czech Republic	Brno	Home air	0.14–4.23 ng·m ⁻³	[17]
Home dust	11.4–358 ng·g ⁻¹				
Africa	Nigeria	Abraka and Warri	Office	96.6–3949 ng·g ⁻¹	[98]
		Lagos	Power Station office	0.02–2.20 ng·m ⁻² day ⁻¹	[99]
	South Africa	Durban	E-waste recycling site	50–490 ng·g ⁻¹	[100]
			Office	923–1040 ng·g ⁻¹	
Computer laboratory	360–1880 ng·g ⁻¹				
Oceania	New Zealand	Wellington	Home	46 ng·g ⁻¹	[90]
-	Turkey	Izmir	Industrial	409 ng·m ⁻² day ⁻¹	[101]

High concentrations of low-chlorine PCB congeners were detected in the indoor air of polluted schools in Germany [61]. Furthermore, there was a significant correlation between PCB exposure and increased blood PCB concentrations in teachers who had worked in these contaminated school buildings.

In a school in the town of Columbus Junction (Iowa) different PCB concentrations were found based on construction year, which in turn relates to different use of PCB-containing building materials during the time [95]. The highest concentrations were detected in the rooms in the oldest wing of the building (e.g., 39.2 ng·m⁻³ in the math room PCBs constructed before 1920), while the lower values were measured in rooms built more recently (e.g., 1.24 ng·m⁻³ in the practice gym completed in 2012).

In the literature, a different distribution of PCBs was reported for workplaces. Manufacturing plants showed high concentrations (709 ng·g⁻¹), and similar PCB values (range 107–233 ng·g⁻¹) were observed in schools, offices, electronic factories, hospitals and shopping malls [83]. PCBs were also detected in the air of paper industries, at a concentration up to 2300 ng·m⁻³ [102]. Many studies investigated PCB concentrations in the settled dust around the world. For example, PCBs values ranged from 11 to 1900 ng·g⁻¹ in northern

Vietnam [87], while higher concentrations of total PCBs (199–43,540 ng·g⁻¹) were detected in dwellings and churches in Illinois, USA [94].

Regarding e-waste recycling sites, higher concentrations were discovered in North-Rhine Westphalia, Germany (from 38,000 to 330,000 ng·g⁻¹) [97] compared to those in indoor dust from Quingyuan, southern China (568–11,500 ng·g⁻¹) [86] and in Durban, South Africa (50–490 ng·g⁻¹) [100]. A recent study reported information on the distribution and composition of PCBs in electronic repair workshop dust in Nigeria. The results indicated concentrations of PCBs from 96.6 to 3949 ng·g⁻¹ with a mean value of 1234 ng·g⁻¹ with hexa-PCBs being the most prevalent PCB homologs, which have a high estimated hazard index and cancer risk values associated with human exposure [98]. The regulation of the e-waste problem requires more attention and many efforts, such as source control, limitation of illegal importation of domestic e-waste collection, transportation and process control.

Environmental remediation measures of such polluted areas should be implemented to control the health risks facing the workers and local population.

3.3. Presence of PCB in Human Fluids and Bioaccumulation

Considering the above-mentioned pathways for human exposure to PCBs and their resistance to chemical and thermal degradation, the bioaccumulation of these compounds must be taken into account.

The bioaccumulation of toxic substances can take place either directly from the environment in which the organism lives (bioconcentration) or through ingestion along the trophic chains (biomagnification or biological magnification) or in both ways. Biomagnification is a process in which a chemical compound accumulates through the food chain from lower concentrations in prey species to higher concentrations in predatory species. In the case of bioconcentration, the amount of substance in the body's tissues becomes progressively higher than those present in the environment from which it was absorbed. Since PCBs are found in the organic part of the soil and marine and lake sediments, they can be absorbed by plants and ingested by aquatic organisms. Due to their poor degradability, this phenomenon leads to biomagnification along the trophic levels of the food chain. PCBs bioaccumulate in the adipose tissue of living organisms, so their concentration increases along the trophic web, together with their toxicity for both animals and humans. High-chlorine PCBs have a greater potential for bioaccumulation and biomagnification along the food chain [103–105].

The biomonitoring approach in blood and non-invasive biological matrices, such as urine, was used to assess worker exposure to PCBs [106]. For instance, concentrations of PCB metabolites up to 174 µg·L⁻¹ have been detected in human urine from former PCB-exposed workers of a transformer recycling company in Germany [107]. The highest concentrations were observed for low-chlorine PCBs, to which workers are easily exposed through inhalation. Several studies have shown that detection of PCBs in blood is still a serious cause for concern [108–114]. PCB concentrations up to 0.442 µg·L⁻¹ were detected in the plasma of a group working in a building with documented PCB contamination (total indoor air PCB concentration in the range 70–1500 ng·m⁻³) [115]. Furthermore, data from the last decade demonstrate widespread human exposure to non-legacy PCB congeners that were not present in commercial PCB blends [13]. Non-legacy PCBs were also detected. In particular, PCB 11, one of the most frequently detected PCBs [116], was found at a concentration from 0.005 to 1.717 µg·L⁻¹ in the plasma of pregnant women. Along with it, different dioxin-like PCBs inadvertently formed as by-products in chemical processes, have also been found at high concentrations. Despite the evidence of the widespread presence of non-legacy PCBs in the environment and consumer products, the metabolism of PCBs and the physiological fate of individual metabolites remain poorly understood.

4. Effects of PCBs on Human Health

The International Agency for Research on Cancer (IARC) has classified PCBs as probable human carcinogens (Group 2A) [117]. PCBs target several human systems, including the nervous system, the endocrine systems (thyroid, thymus, pancreas and gonads), the reproductive system, the cardiovascular system and the immune system (Figure 3). This review will focus in particular on neurological and reproductive health outcomes.

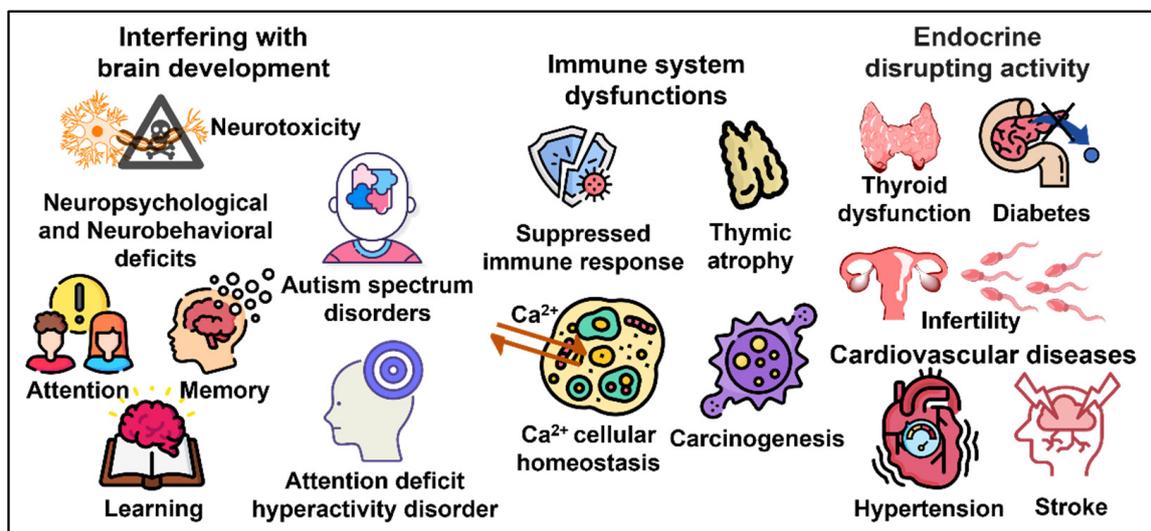


Figure 3. Representation of the main targets of PCBs with related disorders in humans.

4.1. Nervous System Disorders and Other Dysfunctions

The developing brain was identified as a vulnerable target for PCBs by different scientific studies on both humans and animals [118]. Numerous reviews of the epidemiological literature have inferred that exposure to PCBs during nervous system development enhances the risks of neuropsychological deficits in children, as demonstrated by impaired cognitive and psychomotor function, as well as attention, learning and memory deficits [119–122]. Moreover, recent studies suggest that prenatal exposure to PCBs may increase the risk of autism spectrum disorders [120,123–127] and attention deficit hyperactivity disorder [128–131]. Prenatal exposure to PCBs is also associated with an increased risk of low birth weight, defined as <2500 g at birth, [132–136] and lower development for gestational age [137–139]. Experimental studies on animals confirm that PCB exposures cause neurobehavioral effects similar to those observed in humans [140–143]. Recent studies suggested that PCB 11 is able to alter the dendritic and axonal growth of neurons by interfering with brain development [144]. However, the 209 PCB congeners that are capable of producing neurotoxic effects and the mechanisms by which PCBs interfere with nervous system development still remain to be determined. In addition, new questions are emerging about the potential neurotoxicity of low-chlorine PCBs, not only those released from PCB-containing equipment and materials manufactured before the production ban, but also the non-legacy PCBs that represent a significant proportion of contemporary human PCB exposures. Recent epidemiological studies suggest that non-dioxin-like PCBs and low-chlorine PCBs are primarily responsible for PCB-associated neurotoxicity [118]. On the other hand, dioxin-like PCBs are associated with diseases that affect various organs; in particular, the skin, liver and immune system [145–147] are also carcinogenic [148–156].

Since PCB serum levels have been linked to chronic diseases, their possible association with the incidence of all-cause dementia and Parkinson's disease was also assessed using a population-based prospective cohort study in a north Italian highly polluted area [157]. A positive association between the onset of dementia not mediated by hypertension and total PCB serum levels was observed, whereas the unstable risk estimates for Parkinson's disease did not permit to conclude a possible association. PCBs have been suspected for some

time of having adverse effects on neuropsychological functioning in humans and there are studies that have found associations between serum PCB levels and neurobehavioral deficits in older adults; while there is evidence of slowing of cognitive function in children associated with exposure to PCBs, the evidence of comparable effects on adults is far less well understood [158–160].

The results of different epidemiological studies indicate that exposure to PCBs is also associated with immune system dysfunctions, including thymic atrophy and suppressed immune responses, [161–163] and cardiovascular diseases, such as stroke and hypertension [164–169]. In addition, several studies have shown that non-dioxine-like PCBs alter the cellular homeostasis of calcium, increasing the levels of intracellular Ca^{2+} ions and/or the activation of different cellular processes mediated by the same Ca^{2+} ions. In fact, they operate by altering the structure and function of ryanodine receptors, channels that allow the release of calcium from the sarcoplasmic reticulum of muscle cells and from the endoplasmic reticulum, which is found in other cells [170,171]. Furthermore, the mechanism of PCB toxicity comprises the inhibition of antioxidant defense enzymes, including superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione transferase [172–177].

4.2. Endocrine Disrupting Activity and Effects on Reproductive Organs

PCBs have been considered endocrine disruptors because their exposure was associated with diabetes [46,178], cardiovascular diseases—mainly hypertension [166] and the functionality of the endocrine system, particularly the thyroid and reproductive organs (the primary targets of most endocrine disruptors) [3,179,180]. Several studies have shown that PCBs can interfere with endocrine processes and persistent exposure to them can considerably decrease animal and human fertility and reproductive quality [181]. In fact, the reproductive toxicity of PCBs was proved in both animal and human studies [182,183]. However, their role and mechanism of action are still poorly understood and current evidence is still inconclusive. A study conducted in northern Italy revealed no association between PCB exposure and prevalence of endocrine and metabolic diseases and hypertension [35].

PCBs have been found in follicular and amniotic fluid, uterine muscle, ovarian tissue, placenta, fetal cord blood and breast milk [184,185]. PCBs accumulate over time in human follicular fluid, as observed for the accumulation in serum [186]. Moreover, high PCB concentrations in the follicular fluids are found in women experiencing assisted reproductive technology, which can contribute to in vitro fertilization failure [187]. Women's exposure to PCBs can damage ovarian function, leading to reproductive problems, such as abnormal hormone levels, premature ovarian failure and finally infertility [188]. Other adverse effects in women, associated with PCB exposure, are the earlier onset of menopause, altered menstrual function, the increase in miscarriage risk and of time taken to get pregnant [189–192]. In contrast to this evidence, a recent study examined the link between the level of PCBs in serum and various female reproductive health outcomes, finding no correlation between serum PCB levels and infertility, but only an association between the reduction in the number of pregnancies and PCB concentration [193]. Moreover, the majority of the studies that found an association between PCB exposure during pregnancy and reduced cognitive functions among children have not taken into consideration some confounding factors, such as the co-exposure to other toxic compounds (i.e., Hg, Pb and iodine).

Male exposure to endocrine disruptors, such as PCBs and their consequent bioaccumulation, has been associated with the reduction in semen quality, fertility and anogenital distance [34,194–199]. In particular, environmental exposure to PCBs influences circulating reproductive hormone levels, sperm concentration, motility, morphology and quantity and quality of gametes, and it alters the redox state of the seminal plasma and other sperm factors (e.g., sperm DNA integrity) [34,194,195,200,201]. A correlation between increasing serum PCB levels and lower concentration of serum testosterone in some American males was noticed [202]. Furthermore, significant associations between low environmental

levels of serum dioxin-like PCBs in male partners of subfertile couples and pregnancy outcomes of in vitro fertilization, such as implantation, clinical pregnancy and live births were observed [203]. PCBs may have direct effects on spermatogenesis as they easily penetrate the blood–testis barrier [204], and their accumulation is also associated with testicular cancer [205]. A constant decline in the quality of human semen was observed in many industrialized countries [206]. This probably arises from continuous, repeated and prolonged exposure to POPs that are still today widely used in the production chains of food and consumer products [207–210].

In addition to the effects on the people directly exposed, PCBs might influence the epigenetic modification process since their harmful effects on the reproductive system can be passed to offspring. In fact, PCBs can be transferred from mother to fetus via the placenta [211], resulting in transgenerational effects [212,213], such as heritable epimutations in sperm and brain [214]. Prenatal exposure to PCBs affects gestational length and birth weight [215,216] and causes the reduction in intelligence quotient and fecundity in the offspring [217–219]. Moreover, in-utero exposure to PCBs results in children having sperm with abnormal morphology, reduced motility and capacity to penetrate hamster oocytes [220], a reduction in male reproductive function that is transferred on to the next three generations [221]. Not least, high maternal blood concentrations of PCBs at the end of pregnancy are linked to the reduction in anogenital distance in male neonates, a parameter considered as a promising marker of male reproductive health [222].

Although PCBs are indeed declining, as also demonstrated by Raffetti et al. [223], being persistent they are not currently completely absent in various biological fluids. After all, PCBs, used in various types of industrial products, are persistent organochlorine pollutants, considered a potential endocrine disrupting compound, and exposure to these toxins has a negative impact on the chromatin integrity of spermatozoa [224]. Therefore, it cannot be ruled out that these pollutants could have a synergistic action with other pollutants, such as some heavy metals, that have been found in the sperm of subjects residing in areas of high environmental impact. In fact, there are numerous reports demonstrating the correlation between heavy metals with oxidative damage to DNA. In particular, it has been shown that some heavy metals have the potential to alter the properties of the sperm nuclear basic proteins (SNBP) in individuals residing in high environmental impact areas. In these subjects, surprisingly, the SNBP, instead of having their canonical role of protecting DNA, are involved in oxidative DNA damage [225]. In addition, seminal antioxidant activity has also been shown to be lower in these subjects living in areas of high environmental impact [226]. Environmental pollution also has a significant bearing on the susceptibility of a given population to various diseases, and semen quality has been found to be a potential indicator of susceptibility to viral insults in those highly polluted areas, capable of helping to predict the risk of harmful effects of viral outbreaks [227,228]. Very recently it has also been demonstrated that kallikrein-related serine peptidase 3 appears to be an early biomarker of environmental exposure in young women [229]. For these reasons, biosensors have been developed for environmental pollution along with new technologies, especially because altered environmental conditions, together with the direct and indirect short- and long-term effects of viral infection, have the potential to produce a deterioration in sperm quality with significant implications for male fertility, particularly in those areas with a greater environmental impact [230]. Pollutants, such as heavy metals, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, dioxins, pesticides and ultrafine particles, produced by human activities pose real threats to the body's entire defense system. Trials from preclinical and clinical research studies indicate that compromised male fertility and gonadal development, as well as cancers of the reproductive system, resulting from the exposure to organic and inorganic pollutants can be contrasted by flavonoids [231].

It should be emphasized that the majority of the studies are carried out on adult subjects to verify the possible association of the effects on fertility with ongoing exposures in adult males. However, the exposure of a developing organism may have more pronounced and persistent negative effects. Collectively, these data indicate the need for biological

monitoring studies on PCBs taking into account not only the substances widely used, but also paying attention to the potential biomarkers indicative of long-term effects (e.g., sperm DNA damage) and the co-exposure to other toxic compounds.

5. Conclusions

In this review, we considered recent scientific studies related to the presence of PCBs in the environment. In particular, we discussed the potential routes for their release into the environment and consequent human exposure, occupational exposure events, and related effects on human health. Dietary intake was the main exposure pathway, even if the contribution from indoor air inhalation could become comparable to dietary exposure in the next years. On the other hand, we have underlined how several literature studies have detected high PCB concentrations in indoor environments (both air and dust) derived from building material (furniture, paints, caulking compounds and sealants) with the consequent transport to the human web. Furthermore, e-waste recycling sites resulted to be the most PCB-contaminated workplaces (concentration up to 330,000 ng·g⁻¹). These phenomena are of particular concern considering the occupational exposure of workers, indicating the need for better remediation strategies of such polluted workplaces in order to prevent health problems of workers and local populations. Negative effects on human health (neuropsychological and neurobehavioral deficits in children, dementia, immune system dysfunctions, cardiovascular diseases and cancer) were reported to occur at higher PCB concentrations compared to human exposure, demonstrating a hazard for human health. Although PCBs exposure does not necessarily entail clinically relevant consequences in the short term, recent studies suggest that their bioaccumulation can reduce fertility with transgenerational effects. Further studies must be performed to assess the real consequences of PCBs contamination at concentrations in the range of human exposure.

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