



Airborne Persistent Organic Pollutants and Male Reproductive Health

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ABSTRACT

Persistent organic pollutants (POPs) are chemicals that persist in the environment, bioaccumulate through the food chain, and exhibit toxic effects that threaten the health of humans and animals alike. The potential influence of POP-related air pollution on male reproductive outcomes has attracted increasing interest in the scientific community and among policymakers and the public. Therefore, epidemiological studies on fertility should examine the impact of chronic exposure to POPs via inhalation. The objective of this review is to present and discuss the available evidence linking the exposure to airborne POPs to male reproductive health problems. This study focuses on the air concentrations, biomarkers, and potential effects on the male reproductive health of two classes of POPs: the industrial polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). Although the association between atmospheric pollutants and male reproductive health has been extensively investigated, particularly in relation to semen quality and endocrine outcomes, the molecular mechanisms of action, the adverse effects, and the dose-response relationships for many of these chemicals remain poorly understood. No systematic screening of common chemicals for negative endocrine effects is currently underway, and many questions remain regarding the impact on male reproductive health of exposures to these POPs. This review presents the air concentrations, biomarkers, and adverse male reproductive effects of PCBs and PBDEs pollutants. Given the dearth of information on this topic in the literature, studies are clearly needed to assess how pre- and post-natal exposure to airborne PCBs and PBDEs affects the male reproductive system. Future studies must also identify aerosols and airborne POPs that have a significant impact on male reproductive health and the pathways responsible for those effects.

Keywords: Air pollution; Persistent organic pollutants (POPs); Polychlorinated biphenyls (PCBs); Polybrominated diphenyl ethers (PBDEs); Male reproduction; Semen quality.

INTRODUCTION

Ambient air pollution has long been associated with various adverse health effects, ranging from subclinical

outcomes to fatalities (Kampa and Castanas, 2008; Ruckerl *et al.*, 2011). Nearly two decades ago, findings indicating declining sperm counts in regions of high pollution (Carlsen *et al.*, 1992; Auger *et al.*, 1995) have engendered the hypothesis that environmental pollutants may cause male infertility (Skakkebaek, 1993; Sharpe and Toppari *et al.*, 1996; Jurewicz *et al.*, 2009). More recently, the impact of air pollution on reproductive health has attracted increasing interest (Kampa and Castanas, 2008; Woodruff *et al.*, 2009; Hansen *et al.*, 2010; Ruckerl *et al.*, 2011), but thus far, few epidemiological studies have examined the potential link between air pollution and sperm quality. One follow-up longitudinal study on a sample of men from the polluted Teplice District of the Czech Republic revealed an association between abnormalities in sperm DNA chromatin and total episodic air pollution (i.e., a comparison of semen

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collected during periods of high versus low air pollution) (Rubes *et al.*, 2005). In a study from the United States, fine particulate matter (PM_{2.5}) was linked to decreased sperm motility and poor sperm morphology in clinical semen samples (Hammoud *et al.*, 2010). However, a third study found no association or only a weak association between air pollutants and sperm quality (Hansen *et al.*, 2010).

Persistent organic pollutants (POPs) are defined as chemicals that persist in the environment, bioaccumulate through the food chain, and exert toxic effects that harm humans and animals. The 1998 Protocol on POPs (Bull, 2003) was adopted by the Executive Body for the Convention on Long-range Transboundary Air Pollution on June 24, 1998 in Aarhus, Denmark. Sixteen substances and groups of substances were selected by a screening procedure, followed by discussions and negotiation. Consequently, there are now restrictions on the use of, for example, polychlorinated biphenyls (PCBs). However, human activities are the main sources of atmospheric PCBs, and PCBs are still being released into the environment through the disposal or accidental release of previously produced materials, through the volatilization of previously released materials, and through the creation of PCBs and dioxins during combustion (Breivik *et al.*, 2007; Yasuhara *et al.*, 2007). Atmospheric PCBs have been detected in the primary emissions from the vaporization or burning of products containing PCBs and in the secondary emissions coming from the volatilization of soil, vegetation, and water (Breivik *et al.*, 2002).

Polybrominated diphenyl ethers (PBDEs) have been extensively used as flame retardants in commercial products such as furnishing foam, plastics, synthetic textiles, construction materials, and electronic devices (de Wit, 2002), although they may leak into the environment (Renner, 2000). PBDEs are generated during combustion under similar conditions as polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs); semi-volatile organic PCDD/Fs and the highly brominated PBDEs are released into the atmosphere in urban areas by sources of combustion such as motor vehicles (Wang *et al.*, 2010; 2011). PCBs, PCDDs, organochlorine pesticides, and PBDEs, except deca-BDE (BDE-209), represent four classes of halogenated compounds that have recently been listed in the Stockholm Convention on POPs (UNEP, 2011). To date, only a few epidemiological studies have examined the association between POP pollution in the air and male reproductive problems. In this article, we review two chemical classes of POPs: PCBs and PBDEs. We summarize the data available on the concentrations of PCBs and PBDEs in the air, describe the effects of inhaling these POPs, and discuss their potential influence on male reproductive health.

AIR CONCENTRATIONS, BIOMARKERS, AND POTENTIAL MALE REPRODUCTIVE HEALTH EFFECTS

Polychlorinated Biphenyls

PCB concentrations in the air are generally higher in urban areas than in rural or remote areas (Motelay-Massei

et al., 2005; Shen *et al.*, 2006; Jamshidi *et al.*, 2007). The concentration of PCBs can be at least an order of magnitude higher indoors than outdoors (Wallace *et al.*, 1996; Vorhees *et al.*, 1997), although not all PCB sources are known. Ambient PCB concentrations were reported to have declined slowly from the 1980s to the 1990 by one study (Vorhees, 2001), but another study has suggested no significant decline in PCBs between 1997 and 2005 (Harrad *et al.*, 2006). In Southern Taiwan, the average dry deposition fluxes of total PCBs in the ambient air at four sites was found to be 289–1010 pg/m²/day (0.540–1.94 pg WHO-TEQ/m²/day), with the velocity of individual PCBs increasing with the number of chlorinated substitutions (Mi *et al.*, 2012).

Occupational exposure to atmospheric PCBs, which accounts for a significant part of human exposure to PCBs, occurs mainly through inhalation (Wolff, 1985). Under certain circumstances, inhalation may be one of the major routes of PCB intake by humans: (Currado and Harrad, 1998) reported that inhalation accounts for 6%–64% (mean 25%) of overall human PCB exposure, and Xing *et al.* (2011) estimated the mean exposure to total airborne PCBs through the gaseous/particulate phase to be 162 ng/day for e-waste workers in Taizhou, China.

Hydroxylated PCBs have been found in human blood, in the abiotic environment, and even in soil (Safe *et al.*, 1995; Ueno *et al.*, 2007). A clinical study detected high PCB levels in the blood of participants exposed to high PCB concentrations in their environmental air and dust (Rudel *et al.*, 2008). This case study suggests that, at least in certain situations, PCB residues in homes may be more significant contributors to overall exposure levels than sources such as a diet.

Evidence regarding the effects of inhaled atmospheric PCBs on male reproductive health remains limited. Table 1 presents some epidemiological studies on the link between PCBs and semen quality or sex hormone levels including a set of studies from Taiwan. In an unfortunate incident between 1978 and 1979, over 2,000 Taiwanese people unknowingly consumed rice oil contaminated with PCBs and pyrolytic products of PCBs, mainly PCDFs. This event was referred to as *Yucheng* (or “oil-disease” in Chinese), and many subsequent studies have investigated health outcomes among the *Yucheng* cohort (Hsu *et al.*, 1985). Children born to mothers who had ingested the contaminated rice oil suffered from growth retardation, dysmorphic physical features, delayed cognitive development, behavioral problems, and middle-ear disease (Guo *et al.*, 1995; Chao *et al.*, 1997; Yu *et al.*, 1998). Males exposed prenatally to PCBs from the rice oil had a high proportion of sperm with abnormal morphology and showed a reduction in the percentages of motile and rapidly motile sperm and in indicators of human sperm-hamster oocyte penetration or binding capability. In addition, serum testosterone (TT) and the square root of TT/estradiol (E₂) levels were lower, and the serum follicle-stimulating hormone (FSH) and the square root of E₂/FSH levels had increased among *Yucheng* boys aged > 13 years compared to boys unexposed to PCBs (Guo *et al.*, 2000; Hsu *et al.*, 2005). PCBs may interfere with the hypothalamus–pituitary–gonadal axis by disrupting normal endocrine

Table 1. Epidemiologic studies addressing effects of PCBs and PBDEs on semen quality and hormone outcomes.

Compounds	Subjects/area	Main findings	References
PCBs/PCDFs (contaminated oil)	Young Yucheng men prenatally exposed to PCBs and PCDF/Taiwan	↓ (normal morphology, motility, and oocyte penetration capacity)	Guo <i>et al.</i> , 2000
PCBs/PCDFs (contaminated oil)	Young Yucheng men prenatally exposed to PCBs and PCDF/Taiwan	↓ (serum testosterone and the square root of TT/ E ₂ levels) ↑ (serum FSH and the square root of E ₂ /FSH levels)	Hsu <i>et al.</i> , 2005
PCBs/PCDFs (contaminated oil)	Adult Yucheng men postnatally exposed to PCBs and PCDF/Taiwan	↓ (oocyte penetration capacity) ↑ (oligospermia rate)	Hsu <i>et al.</i> , 2003
PCBs (serum)	Adult Native American population/US	↓ (serum TT)	Goncharov <i>et al.</i> , 2009
PCB 153 (serum)	Young men undergoing a conscript examination for military service/Sweden	↓ (sperm motility)	Richthoff <i>et al.</i> , 2003
PCBs (blood)	Men with normal semen quality/The Netherlands	↓ (sperm concentration and motility)	Dallinga <i>et al.</i> , 2002
PCB 138 (serum)	Male partners of subfertile couples visiting an infertility clinic/US	↓ (sperm motility and normal morphology)	Hsu <i>et al.</i> , 2003
BDE-153 (serum)	Young males recruited from a university Department of Andrology/Japan	↓ (sperm concentration and testis size)	Akutsu <i>et al.</i> , 2008
PBDEs (dust)	Men recruited from an andrology lab/US	↓ (serum LH and FSH) ↑ (serum SHBG)	Meeker <i>et al.</i> , 2009
BDE-47, BDE-100 and total BDE (plasma)	Men recruited in a fertility clinic/Canada	↓ (sperm motility)	Abdelouahab <i>et al.</i> , 2011

↓: significant decrease; ↑: significant increase; E₂: estradiol; FSH: follicle-stimulating hormone; PCBs: polychlorinated biphenyls; PCB 153: 2,2',4,4',5,5'-hexachlorobiphenyl; PCDFs: polychlorinated dibenzofurans; TT: testosterone; BDE-153: 2,2',4,4',5,5'-hexabromodiphenyl ether; LH: luteinizing hormone; SHBG: sex hormone binding globulin; BDE-47: 2,2',4,4'-tetrabromodiphenyl ether; BDE-100: 2,2',4,4',6-pentabromodiphenyl ether.

signaling by FSH and luteinizing hormone (LH). FSH stimulates the aromatization and metabolism of TT in the Sertoli cell, and the increased levels of FSH in the *Yucheng* boys might have resulted from the effects of the feedback regulatory system between FSH and TT. Another study found increased oligospermia rates among *Yucheng* adult men exposed postnatally to PCBs/PCDFs and a reduction in the capability of their sperm to penetrate oocytes (Hsu *et al.*, 2003).

In studies conducted elsewhere, Goncharov *et al.* (2009) demonstrated that an elevation in serum PCB levels was associated with a lower concentration of serum TT in Native American men. In Sweden, Richthoff *et al.* (2003)

studied 305 male conscripts aged 18 to 21 years and found a robust inverse association between serum PCB 153, a biomarker of total PCB exposure, and the percentage of motile sperm. A negative association between PCB metabolites in blood and sperm count was also found in a subgroup of men with normal semen quality in the Netherlands (Dallinga *et al.*, 2002). In the United States, Hauser *et al.* (2003) investigated 212 males from subfertile couples visiting a fertility clinic and found a clear dose-response relationship between serum PCB 138 levels and sperm motility and morphology scores below the World Health Organization (WHO) reference level. Thus, although the impact of airborne PCB concentrations on adult male

reproductive health is poorly understood, these findings offer indirect evidence of the potential hazards that airborne PCBs pose to male reproductive health.

Polybrominated Diphenyl Ethers

PBDEs such as tetra-, penta-, hexa-, and hepta-BDEs have recently been added to the POP list of the Stockholm Convention (UNEP, 2011). PBDEs are sold as three commercial mixtures: penta-BDE, octa-BDE, and deca-BDE (Allen et al., 2007). PBDEs are lipophilic POPs detected worldwide in environmental and human samples (Law et al., 2008), which can be absorbed by humans from the air or foodstuffs and then accumulated in fatty tissues. The concentrations of PBDEs appear to be increasing, and both human and non-human trends indicate that this increase may be rapid.

Air concentrations of PBDEs are generally higher indoors than outdoors (Hazrati and Harrad, 2006). Indoor air is regarded as the primary source of PBDE exposure for the general population (Harrad et al., 2006; Allen et al., 2007), and PBDE concentrations in offices are higher than in homes (Harrad et al., 2006; Saito et al., 2007). In Taiwan, higher atmospheric concentrations of PBDE are found in urban locales than in rural and industrial areas, suggesting regional differences in the usage of products contaminated with PBDE-related molecules (Lin et al., 2012). Fromme et al. (2009) identified a significant positive correlation between air and dust PBDE levels. Exposure pathways for PBDEs presently remain unclear, but may include food, air, and dust.

PBDEs have been detected in samples collected from humans including fat, blood, breast milk, and semen (Antignac et al., 2009; Zhao et al., 2010; Liu et al., 2012; Shy et al., 2012). Based on studies in animals, PBDEs and their metabolites have been speculated to mimic thyroid hormones and disrupt thyroid homeostasis (Zhou et al., 2002; Tseng et al., 2008). Because thyroid hormones and sex hormones regulate the proliferation and differentiation of Sertoli cells and sperm production, PBDEs might affect male reproductive health by interfering with thyroid- and sex-hormone functions. Kuriyama et al. (2005) reported that exposure during development to a single low dose (60 µg/kg body weight) of 2,2',4,4',5-pentabromodiphenyl ether (BDE-99) can reduce sperm count in rats, and Tseng et al. (2006) reported that neonatal exposure to BDE-209 reduces the mitochondrial membrane potential in epididymal sperm and the amplitude of lateral sperm head displacement, and induces hydrogen peroxide production in the sperm of sexually mature mice. Exposure to BDE-209 during development may also induce sperm-head abnormality, oxidative stress, chromatin DNA damage, and histopathological changes in the testes of mouse offspring (Tseng et al., 2013).

Only a few previous studies have examined the potential relationships between the concentration of PBDEs in dust and internal PBDE levels in humans, sperm quality, and sex hormone levels. A summary of published epidemiological investigations into the effects of PBDEs on semen quality or sex hormones is listed in Table 1. In a pilot study on 45 young Japanese males, a simple linear regression model was used to

show a strong inverse correlation between the concentration of 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153) in sperm and total sperm concentration ($r = -0.841$, $p = .002$) and testis size ($r = -0.764$, $p = .01$) (Akutsu et al., 2008). A cross-sectional study on American men reported a robust inverse relationship between PBDE levels in house dust and serum concentrations of luteinizing hormone (LH) and FSH, and a positive association between PBDEs and sex hormone-binding globulin (SHBG) (Meeker et al., 2009). Similarly, in a Canadian study, semen mobility was negatively correlated to serum levels of BDE-47, BDE-100, and total PBDEs in adult men recruited during their first physician visit to investigate fertility problems (Abdelouahab et al., 2011). However, evidence of clinical symptoms in male reproductive system resulting from high PBDE exposure remains controversial.

CONCLUSION

This brief review presented the air concentrations, the biomarkers, and the adverse effects of PCB and PBDE pollutants on male reproductive health. Given the scarcity of published information on this topic, future studies assessing the influence of pre- and post-natal exposure to air PCBs and PBDEs on male reproductive system functions are clearly required.

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