Paternal-Specific Exposure and Child Health

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1 Introduction

5.9 million children (16,000 per day) died in 2015 of diseases which can be prevented and treated [1, 2]. We are still facing the challenges on how to reduce the child mortality rate [3]. This has led to increased demand for child health promotion. Many diseases are threatening the healthy growth of children. Some of them are preventable if effective measures can be taken early. In children, infectious diseases such as diarrhea and pneumonia account for the majority of childhood morbidity and mortality [4]. In addition to diarrhea and pneumonia, childhood illnesses also include respiratory symptom, respiratory infections, and asthma [5]. These diseases impose a heavy health and economic burden on society. According to the WHO European Region, although the child mortality rate is gradually declining, the rate of children dying from cancer is disappointingly increasing [6]. No matter which age group, leukemia is firmly the first cause of death of childhood cancer followed by brain cancer and non-Hodgkin's lymphoma.

It has been known to the public that the parents' healthy status and the environment which they contact most frequently can substantially impact children's health [7]. For example, more than 600,000 people die each year from secondhand smoke, 28% of whom are children. The source of secondhand smoke in the home is mostly from their parents [8]. In addition to smoke, several studies have reported that maternal and paternal exposures to POPs and radiation have an association with birth outcomes and childhood diseases [9–12]. The public is comparatively aware that maternal exposures to unhealthy lifestyle and toxic chemicals may have effects on childhood health. However, paternal exposure, which is anything the father of the baby is exposed to before or during his partner's pregnancy, has been omitted for a

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long time. Recently, researchers are beginning to recognize the significance of paternal exposure.

In this chapter, we summarize the paternal exposure effects of some common chemicals and physical agents on child health, especially POPs, radiation, and tobacco smoke. We have investigated the association and possible pathophysiological mechanisms of the exposed factors on adverse health outcomes in children.

2 Paternal Exposure to Persistent Organic Pollutants (POPs)

According to the U.S. Environmental Protection Agency (EPA), POPs are chemicals which exhibit toxic characteristics that can adversely affect human health and the environment around the world. They include intentionally produced chemicals currently or once used in agriculture, disease control, manufacturing, or industrial processes and unintentionally produced chemicals, such as dioxins [13, 14]. They have ability to biomagnify in the ecosystems and to bioaccumulate in humans and animals [14–16]. Because of the stable durability and potential for long-range transport of persistent organic pollutants, they are widely distributed in the world today, and they can be found even in places where they have not been used [15, 17, 18]. As a result, human exposure to POPs may occur via numerous ways. For example, exposure to POPs can occur through the environments such as food, drinking water, the outdoor and indoor air and at the work place (Fig. 1) [19]. They deserve global concern for their possibility of long-term existence in the environment, as well as their significant hazardous effects on human or animal health and the environment [19, 20].

Previous studies have suggested that potential exposure to POPs may have effects on child health, even at low-dose exposure level, such as metabolic health among children [16, 21]. Furthermore, several epidemiological studies have shown that maternal exposures to POPs have a contact with factors related to child development, such as birth weight and birth size [9, 22]. However, the health of an offspring is also linked to paternal exposure (Table 1). Few studies have shown that paternal occupational exposure to POP, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), may increase the body weight of the offspring [25]. More evidence has shown that paternal exposure to dioxin-contaminated chlorophenols was related to the development of certain birth defect in the offspring [26]. Limited results indicate that POP is likely to increase the risk of low birth weight or infant death due to paternal exposure [25, 28]. This does not mean that paternal exposure to POPs may not result in serious consequences for child health. Many previous researches which focused on paternal exposure to POPs and the outcomes of child health suffer from inaccurate exposure methods or no access to the needed information. More studies are necessary to be designed to explore the relationship between POP exposure and birth weight, birth size, congenital anomalies, or infant death. All of them play an important role on the

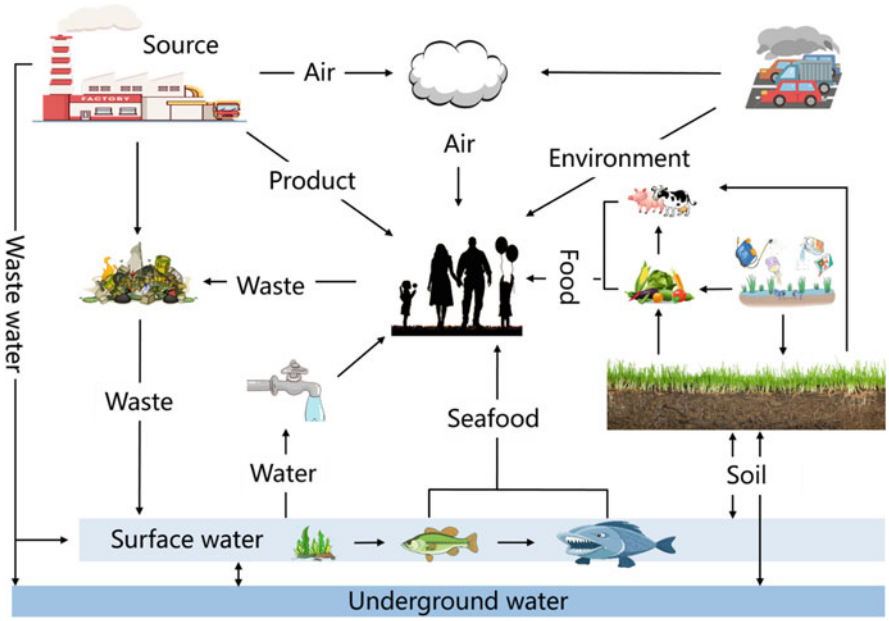

Fig. 1 The exposure pathways of POPs

Table 1 Paternal exposure of POPs and associations with child health

No. of participants	Exposure	Results	References
234 couples (from 2005 to 2009)	PBDEs(183,66,99)	PCB 195 and infant size: −6.94 (−102.96, 89.07)∗(girls); −148.39 (281.69, −15.08)∗ (boys)	[23]
	PCBs (167, 172,195)	*p,p´*-DDE and infant size: 0.12 (0.02, 0.22)∗(girls); 0.01 (−0.06, 0.07)∗(boys)	
	p,p´-DDE	Significant associations between parental concentrations of PCBs and birth size were more frequent among boys	
300 couples (from 1973 to 1974)	PCB	Combined parents' enrollment PBB exposure increased the odds of a male birth but did not reach statistical significance	[24]
1117 babies (from 1987 to 1988)	TCDD	Paternal exposure to TCDD yielded a nonstatistically significant increase in infant birth weight	[25]
9512 fathers and 19,675 births	Dioxincontaminated chlorophenols	Increased the risk of developing congenital anomalies of the eye and birth defects such as congenital anomalies of genital organs	[26]
398 fathers-infant	Organic solvents	Increased the risk of low birth weight children	[27]

∗*P* value <0.05 was considered the threshold for significance

development of child health. Researchers used a statistical model to estimate quantitative exposure measures on the data from Dutch Trade Union for Construction Workers, the Netherlands, 2001. They draw a conclusion that the paternal exposure to POP has been exposed to a positive corollary link with child congenital malformations [27]. A prospective pregnancy study with preconception enrollment of couples takes maternal and paternal serum concentrations into account and found that paternal serum concentrations of POPs, such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs), were significantly associated with birth size [23]. However, there is limited evidence of whether the associations were specific to paternal serum concentrations in other populations. Therefore, there is a need for more comprehensive investigations of the associations between paternal exposures and child development and growth when considering the correlation between parental exposures and child health.

Some experimental studies suggested that POPs, the potential endocrine-disrupting chemicals (EDCs), interact with steroid hormone levels which resulted in disturbing the hormone balance through binding to steroid receptor or disrupting the biosynthesis or metabolism of steroid [29, 30]. Thus, we speculate that the abnormal steroid hormone levels mediate the effects of paternal POP exposure on child health.

3 Paternal Exposure to Radiation

Radiation is energy that comes from a source and travels through space and may be able to penetrate various materials. There are many types of radiation. For example, shortwave radiation is widely used in wireless communications, radar observations, industrial manufacturing, and medical and other fields, which are closely related to our life [31]. Several studies suggested that short-term, low-level exposure of shortwave radiation has few adverse effects on human health [32]. More investigations are needed to focus on long-term, low- or high-level exposure of radiation. Attention should be focused on the people who are in radiation-related occupations, such as the workers in nuclear power plants or who live near a source of radiation.

Exposure to a high level of radiation to children is one of the known risk factors of childhood cancers [33], which has caught a great deal of attention in the public (Table 2). Gardner et al. have designed a case-control study to explore the relationship between paternal exposure to radiation and childhood tumors [10]. In the study, the children who were born near Sellafield nuclear plant and the children whose fathers were employed at the plant, particularly those exposed to high radiation dose before their child's conception, have a higher risk of developing tumors compared to the control. A study published in 2003 conducted analysis by using the data of 34,538 childhood cancer cases diagnosed in the UK between 1952 and 1986 [34]. The results of analysis supported the conclusion from Gardner et al. that there is a large connection between the risk of childhood cancer and paternal employment as a radiation worker. A follow-up study suggested an increased

Table 2 Paternal exposure to radiation and childhood cancer

The research methods	Country	Study population	Cancer	References
A case-control study	UK	People who live near Sellafield nuclear plant	Leukemia and non-Hodgkin's lymphoma	[10]
A case-control study	UK	Parents from National Registry for radiation workers	Malignant neoplasm or brain tumor	[34]
A case-control study	UK	Parents and children from the National Registry of Childhood Tumors	Leukemia and non-Hodgkin's lymphoma	[35]

morbidity of childhood leukemia and non-Hodgkin's lymphoma among the children of male parents who were exposed to radiation. However, the study did not reveal the correlation with radiation doses [35]. These observations in human populations suggested that different levels of exposure will lead to inconsistent incidence of childhood cancers. The possible mechanisms of the associations between paternal exposure to radiation and child cancers have been presented. The radiation can result in a germline mutation in the father or mother before conception or affect the developing fetus in utero directly [36]. More rigorous experimental designs are needed to provide more convincing evidence to persuade the public.

4 Paternal Exposure to Tobacco Smoking

In 1964, the U.S. General Surgeon released the first report to demonstrate the negative effects of tobacco use on health [37]. Thereafter, numerous investigations were conducted to identify the possible association between child health and maternal and paternal exposure to tobacco smoking. For example, a review published in 2017 aims to explore the role of tobacco smoke exposure in causing harm to children [38], including negative impact on fetal growth and birth outcomes [39], sudden infant death syndrome (SIDS) [40, 41], childhood obesity and related effects [42], and brain development and neurobehavioral disorders [11]. However, in those reviews, the child health outcomes were studied from maternal exposure to tobacco smoke and not from secondhand smoke. Secondhand smoke has been one of the established reasons for a variety of adverse health effects, such as children's cough, sputum [43], asthma [44], breathing difficulties, and lung function decline [45]. The source of secondhand smoke is not only from mothers but also from fathers. More studies focused on the association between paternal exposure to tobacco smoke and childhood diseases.

A birth cohort study was conducted between May 2009 and May 2010 in Nha Trang, Vietnam, by using the neonates' data of 1999 to explore the association between paternal tobacco smoking as a risk factor and infectious and non-infectious diseases among infants [46]. The epidemiological evidence indicated that paternal exposure to tobacco smoking independently increased the risk of lower respiratory tract infection. According to different studies, if we take actions to prohibit paternal tobacco smoking in the place where children are present, the lower respiratory tract infection-related hospitalizations will be reduced in this epidemiological setting.

Birth length, head circumference, and low birth weight are major parameters of fetal growth measurement [12]. A study published in 2013 using the nationwide Longitudinal Survey of Babies in the twenty-first Century in Japan, indicating the importance of birth length as a screening index of child health, reported that birth length had a relationship with the incidence of hospitalization due to all causes between 6 and 18 months of age, and the association was stronger than that with birth weight [47]. Maternal exposure to tobacco smoking has adverse effects on a series of birth outcomes, which has been widely accepted by the public [12]. Formerly, the child health effects of paternal exposure to smoking were examined as a passive risk factor during the period of fetus development in some studies [48–50]. These studies were unable to conclude the relationship between paternal smoking exposure and adverse birth outcomes in children. Inoue et al. conducted a follow-up hospital-based study from pregnancy to delivery of 1997–2010 with parents and newborn infants who delivered at a large hospital in Hamamatsu, Japan [12]. They suggested that the individual effects of paternal exposure to smoking are associated with short birth length and small head circumference. In addition to evaluating the independent effects, the study examined the interaction effect of parental smoking. This is an important detail in assessing the impact of parental exposure to tobacco smoking on children.

The animal models have also supported the association between paternal exposure to smoking and adverse child health outcomes including infertility, birth defects, and childhood cancers. The model of cigarette smoke condensate (CSC) exposure to paternal mice demonstrates testicular toxicity and developmental defects in the offspring. This study showed that CSC induced testicular DNA damage and cytotoxicity due to the accumulation of benzo(a)pyrene and cotinine [51]. More researches are needed to focus on exploring the mechanism of the genetic effects of parental exposure to tobacco smoking to provide convincing evidence. Then, we can develop more targeted prevention measures and methods.

5 Conclusion and Future Prospects

Exposures to unhealthy lifestyles and environmental risk factors during the period of fetal development can lead to adverse consequences for child health. The source of exposure is not only from the mother, but also from the father, or a combination of both parents. Many previous studies have reported the adverse effect of maternal

exposure to these risk factors on birth weight, fetal toxicity, fetal growth, etc. [25, 52]. In this chapter, we briefly describe the possible adverse effects of paternal exposure on the health of children. Epidemiological studies showed that the fathers with potentially high exposure to toxic and harmful chemicals, such as PCBs, TCDD, etc., physical agents, and high-risk behavior in the environment may have an increased risk of the congenital malformations, child cancer, or other adverse outcomes to their offspring compared to low or no exposure ones.

Limited results from functional studies imply the critical roles of paternal exposure effects on child health [53]. Paternal exposure, such as POPs, participate in the epigenetic biological process of the paternal germ line, involving DNA methylation, histone modifications or retention, etc. For example, pesticide dichlorodiphenyltrichloroethane (DDT) can induce intergenerational perturbation of sperm miRNAs [54, 55]. In the future, epidemiological and functional studies need to be performed to uncover the trans-generational mechanism of the paternal exposures and supply new insight into the pertinent intervention that can mitigate the effect of such exposures.

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