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Progress in the Induction of Gestational Diabetes Mellitus by Environmental Exposure to the Novel Flame Retardant Triphenyl Phosphate during Pregnancy

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Abstract: *Introduction*: Triphenyl phosphates, or TPhPs, are a family of newly discovered pollutants that contaminate the environment, endanger ecological safety, and cause health problems for people when they linger in the surrounding environment for extended periods of time. *Methods*: This study reviewed the state of the research on the environmental distribution of TPhP, the amount of TPhP exposure during pregnancy, the relationship between TPhP exposure and gestational diabetes mellitus, the possible mechanism by which TPhP exposure during pregnancy causes gestational diabetes mellitus, and the risk of gestational diabetes mellitus in the offspring as a result of TPhP exposure during pregnancy. *Results*: During pregnancy, if pregnant women come into contact with TPhP, which is widely used in various industrial products, it is highly likely to disrupt the body's metabolic balance, have a significant impact on the induction of gestational diabetes mellitus, and increase the health risks for both the mother and the baby. *Discussion*: These findings provide critical insights for risk assessment and prevention strategies targeting gestational TPhP exposure. *Significance:* What is already known about this subject? TPhP is a pollutant that is harmful to people's health. When pregnant women are exposed to TPhP for a long time, their chances of developing gestational diabetes increase. What does this study add? This paper systematically summarizes the effects and mechanisms of TPhP on pregnant women, and provides theoretical support and factual basis for the research on TPhP and gestational diabetes.

Keywords: Organophosphorus flame retardants; Triphenyl phosphate; Pregnancy exposure; Gestational diabetes mellitus

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1. Introduction

As the most widely used organophosphorus flame retardant (OPFR), triphenyl phosphate (TPhP) is extensively added to plastics, textiles, and consumer products as both a flame retardant and plasticizer [1]. OPFRs, as persistent pollutants,

enter the environment via abrasion and volatilization, posing risks to ecosystems and human health [2–5]. Human exposure to these pollutants can occur through multiple pathways, including skin contact, ingestion of dust, and inhalation [6]. Human urine, placenta, and blood are examples of biological samples that include OPFRs or their metabolites [7]. Studies have shown that TPhP is a common endocrine disruptor, and long-term exposure is closely related to insulin resistance and glucose metabolism disorders [8]. Many epidemiologic studies show that pregnant women are exposed to OPFRs on a wide scale [3–7]. Therefore, to offer a scientific foundation for elucidating the health risks of TPhP to pregnant women, safeguarding the health of mothers and newborns, and preventing TPhP exposure, this study analyzes the effects of TPhP exposure during pregnancy on the induction of gestational diabetes mellitus. Given the widespread environmental presence of TPhP, it is critical to first characterize its distribution across different media to understand potential exposure pathways during pregnancy.

2. Grouping of TPhP environmental presence levels and OPFRs

This paper focuses on triphenyl phosphate (TPhP), one of the most commonly used organophosphate flame retardants. As a phosphate ester flame retardant, TPhP serves as a primary alternative to polybrominated diphenyl ethers (PBDEs) in resin and PVC materials [1,9–11]. TPhP can be physically added to materials, and it persists in the environment due to its extreme volatility and lack of chemical bonding [12]. TPhP and its metabolites are frequently detected in human biological samples (e.g., urine, placenta), highlighting direct exposure risks [13–16], especially the potential threat to the health of mothers and infants in pregnant women.

The most commonly used OPFR, TPhP, is commonly found in hydraulic fluids, construction materials, polymers, and electrical equipment [17]. Due to the release of materials from indoor furniture, decorations, and electrical appliances, OPFRs are in dust from almost all indoor environments. The concentration and compositional characteristics of OPFRs in indoor dust vary greatly between countries and regions. The concentration of TPhP in indoor dust is generally higher in developed countries. The predominant OPFRs in indoor dust include TPhP and its structural analogues [6]. These regional disparities in OPFR concentrations likely reflect differences in regulatory frameworks and industrial practices, emphasizing the role of policy in shaping exposure patterns. Developed regions exhibit significantly higher TPhP concentrations in indoor dust than developing countries [18]. This suggests that electronic equipment continually releases TPhP into the indoor air. Pregnant women and other special populations have occupational exposure to TPhP in these unique indoor situations that is significantly higher than the general population's daily exposure.

It is simpler to ignore OPFR contamination in water bodies, substrates, and soils than it is in the atmosphere and dust. Although precipitation and runoff into the water bodies, etc., all of which make the environmental water bodies, substrates, and soils important collection points for OPFRs, there are numerous ways for OPFRs to enter water bodies, substrates, and soils. These methods include industrial wastewater and domestic sewage discharges from flame retardant manufacturers, as well as OPFR residuals in the environmental media. Soil samples from urban areas show significant TPhP contamination via atmospheric deposition [19]. With the help of atmospheric movement, they can travel great distances before being deposited in their surroundings. he global dispersion of TPhP underscores the urgency to evaluate its toxicological impacts, particularly on vulnerable populations such as pregnant women.

3. Environmental toxicity study of TPhP exposure

Emerging evidence highlights TPhP's role as a metabolic disruptor, with studies linking its exposure to insulin resistance and glucose homeostasis impairment [20,21]. TPhP can accumulate in living things and may potentially harm human health at the highest trophic level through the food chain because it is primarily employed as an additive rather than being bonded by reaction with components. Since TPhP is widely dispersed throughout the environment, it is critical and essential to conduct a thorough toxicity study. The foundation for assessing TPhP's environmental risk is its toxicity data. epidemiological investigations have discovered that TPhP has an endocrine-disrupting effect that can cause metabolic disorders and other diseases [22]. According to cytotoxicity tests, TPhP disrupts the metabolism of cellular hormones [23–25]. Translating these toxicological findings to human health requires understanding real-world exposure levels, which have been increasingly documented in pregnant populations. Levels of TPhP exposure during pregnancy in domestic and international women.

Global studies confirm widespread OPFR exposure in pregnant populations [3–7,26,27]. Women in mid- and late-pregnancy had their urine examined by Kosarac *et al.*, who discovered that the majority of the OPFR metabolites in the urine were DPHP, a TPhP metabolite with an average concentration of 4.71 ng/mL and a detection rate of 97% [28]. The assays were comparable [29]. This information was gathered from nested case-control research. DPHP was found in the urine of mid-pregnant women by Feng *et al.* (100% detection rate, geometric mean 1.1 ng/mL) [30]. Multiple studies have demonstrated that the detection rate of DPHP, a TPhP metabolite, is detected in 79–100% of maternal urine samples [26,27,31]. While these toxic effects are concerning, their relevance to human health depends on the extent of real-world exposure, which has been increasingly documented in pregnant populations. The widespread detection of TPhP metabolites in pregnant women underscores the need to investigate its potential role in disrupting glucose metabolism during pregnancy.

4. Exposure to TPhP raises risk of glycemic disorders and insulin resistance

TPhP exposure has emerged as a novel risk factor for glucose metabolic disorders, independent of traditional contributors like obesity [8]. Among environmental pollutants, organophosphate flame retardants such as TPhP have emerged as potential diabetogens. Chinese cohort studies reveal widespread OPFR exposure due to industrial production, correlating with metabolic dysfunction [8,18]. People who are exposed to OPFRs may be more likely to develop type 2 diabetes, citing a previous study. According to earlier research, people who are exposed to OPFRs may have a higher chance of acquiring type 2 diabetes [18]. Ding *et al.* demonstrated that combined exposure to multiple OPFRs disrupts glucose homeostasis, with TPhP and DPHP being the primary contributors [8].

Exposure to TPhP has been shown to drastically decrease metabolic function in rodents, according to an animal investigation. Prenatal TPhP exposure in mice induced metabolic dysfunction in offspring, including insulin resistance [28]. PPARγ-independent pathways may mediate TPhP-induced lipid accumulation. This suggests that PPARγ is not the only pathway through which TPhP-induced adipogenesis is mediated [29]. An additional investigation on adult mice verified that exposure to TPhP led to increased levels of glucose and the HOMA-IR index [8]. To address this knowledge gap, emerging studies have begun to unravel the molecular pathways through which TPhP interferes with endocrine and metabolic functions in pregnancy.

5. Potential mechanisms by which exposure to TPhP during pregnancy causes endocrine disruption and gestational diabetes mellitus

The term "gestational diabetes mellitus" (GDM) describes the various degrees of problems in glucose metabolism found during pregnancy. In 2014, the prevalence of GDM in China reached a high of 18.9% [30]. Negative outcomes for mothers and babies (shoulder dystocia, cesarean delivery, suprapregnancy, preterm labor, and severe newborn abnormalities) are more likely in cases of GDM [32]. Research has demonstrated that the release of anti-insulin chemicals by the placenta during pregnancy causes aberrant glucose tolerance, which in turn causes a partial or total lack of insulin during pregnancy. A normal blood glucose level is maintained by compensating with an increase in insulin secretion, but an abnormal glucose tolerance occurs when there is a malfunctioning of the pancreatic β-cells in the secretion of insulin. As pregnancy goes on, the secretion of anti-insulin hormones such as placental prolactin, progesterone, and adrenocorticotropic hormone gradually increases, and the anti-insulin effect gradually strengthens. Numerous OPFRs, including TPhP, have been demonstrated in recent in vitro experiments to exhibit binding-speak activity with the pregnane X receptor and to exhibit some endocrine-disrupting effects [32] .

Fatty acid transport in placental trophoblast cells is regulated by PPARγ-induced fatty acid transport protein (FATP), fatty acid binding protein (FABP), and cluster of differentiation 36 (CD36), according to *in vitro* mechanistic research [33]. To encourage trophoblast uptake of fatty acids, the PPARγ agonist rosiglitazone works on placental trophoblast cells FATP and FABP [34]. It was discovered that rosiglitazone and TPhP target genes differently and activate PPARγ phosphorylation sites inconsistently [35]. Studies on PPARγ and its controlled lipid metabolism-related gene levels have confirmed in the literature that TPhP exposure significantly increases the quantity of CD36 protein in cells [36]. CD36, a transmembrane glycoprotein critical for fatty acid transport, is upregulated by TPhP exposure [36,37]. CD36 facilitates fatty acid uptake and esterification across cell types [37]. In the meantime, CD36 is a crucial membrane receptor for the cytosolic route, which allows cells to absorb low-density lipoprotein (LDL), a lipoprotein high in cholesterol [38]. The literature has shown that TPhP increases progesterone levels *in vitro* models, demonstrating TPhP-induced progesterone synthesis via PPARγ [39]. Steroid hormone synthesis and TPhP-induced fat deposition may be mediated by the PPARγ downstream target gene CD36. It has been established that TPhP is an endocrine disruptor. It can build up in the placenta, deposit lipids in the placental cell membrane. While these mechanistic insights are critical, bridging experimental evidence to clinical prevention strategies remains a challenge, necessitating focused research on TPhP-induced gestational diabetes.

Placental endocrine disruption by TPhP exacerbates insulin resistance, a core feature of GDM [8,32]. TPhP disrupts diabetes-related pathways by altering key receptors (e.g., insulin receptor and glucose transporters) and downstream signaling [8]. However, there have been no studies on the mechanism by which it induces gestational diabetes mellitus. Furthermore, many metabolites, like DPHP, a common metabolite of TPhP, other TPhP metabolites may have non-specific effects [40]. Future research should prioritize longitudinal cohorts to track TPhP exposure across trimesters, combined with multi-omics approaches to identify biomarkers linking placental dysfunction to GDM pathogenesis.

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