ABSTRACT

Phthalates (Phthalic acid esters, PAEs) as a common industrial products, a growing body of scientific evidences indicate that exposure to PAEs in early life has a potential harmful effect on the growth and development of organisms in later life, among these hazards, exposure to PAEs widely may increase the risk of asthma in children, which has attracted more and more attention. This article introduced the reasons and effects of PAEs exposure in early life, the relationships between early-life PAEs exposure and childhood asthma from the perspectives of epidemiological and animal studies and the underlying mechanisms of action.

INTRODUCTION

According to the Global Initiative for Asthma (GINA) committee reported, asthma prevalence is still on the rise, especially in the developing countries and among young children and required the clinician to achieve current control of asthma and decrease the risk for future asthma exacerbation rather than merely evaluate the severity of asthma [1]. The findings of the national epidemiological survey on childhood asthma in 2010 revealed that the cumulative prevalence of asthma among children under 14 years old in major urban areas of China was 3.02%, nearly twice as much as 1.09% in the first survey in 1990. Asthma is a common chronic disease between children and adults [2], characterized by airway inflammation and increased mucus secretion. Its clinical manifestations are mainly dyspnea, chest pain, cough and Airway Hyper Reaction (AHR). It is a heterogeneous disease caused by the complex interaction between a variety of genetic and environmental factors [3,4].

The Developmental Origins of Health and Disease (DOHaD) theory suggests that early exposure to environmental chemicals can alter developmental pathways that lead to Disease and/or dysfunction later in life. Phthalic Acid Esters (PAEs) as a kind of environmental pollutants, have been shown associated with certain immune system and respiratory system disease [5–7], besides, more and more evidence has proved that exposure to PAEs in early life is associated with the occurrence of asthma in children.

Therefore, we summarized the research evidence of the association between PAEs exposure in early life and childhood asthma in the past five years, so as to provide ideas and theoretical data for asthma prevention and control.
The causes of exposure to PAEs in early life

PAEs are physically combined with consumer products rather than covalently combined, so PAEs is easily filtered out from products and expose to the human body through water, air, skin, food, etc. At the same time, recent concerns have been raised that food labels directly affixed to fruits and vegetables may also increase the risk of PAEs exposure [8].

The reasons why fetuses, infants and pregnant women are more sensitive to PAEs exposure than ordinary people are mainly as follows: Firstly, because of the sensitive stage, pregnant women respond more vulnerably to external damage, in addition, the placenta for PAEs doesn’t have very good blocking effect [9,10], mother during pregnancy exposing PAEs will cause fetal intrauterine exposure by vertical transmission, moreover, after birth, PAEs and related metabolites can also be transferred from the mother’s body to the baby’s body through breast milk. A Canadian study [11] found that the oxidized metabolites Mono-(2-Ethyl-5-Hydroxyhexyl) Phthalate (MEHHP) and Mono-(2-Ethyl-5-Oxohexyl) Phthalate (MEOHP) were detected in over 80% of breast milk samples, some correlation between maternal urine and breast milk for Mono-Ethyl phthalate (MEP), significantly positive correlations (r = 0.35–0.37) were observed between maternal urinary at <20 weeks gestation and infant meconium concentrations of MEHHP, MEOHP, and MEP, supporting the above hypothesis. Secondly, compared with adults, infants and children are more likely to be continuously exposed to PAEs because they are more likely to frequently touch floors and objects with residues of related toxins, and have higher respiratory rate per unit weight and hand to mouth activity frequency [12,13]. Third, enzymes related to biotransformation and metabolic detoxification have not been fully developed in neonates [14], so the toxic effect of PAEs on infants may be more obvious.

In addition, related studies have reported that maternal occupational exposure, relatively high level of modern household consumption, abnormal maternal BMI may directly or indirectly increase the risk of PAEs exposure in the early life of individuals [15–17].

Epidemiological evidence of the association

This paper reviewed the population epidemiological data on the relationship between early life exposure to PAEs and the incidence of childhood asthma in recent five years (Table 1) and summarized from the following points;

PAEs exposure is correlated with asthma outcome: Overall population epidemiological evidences suggest PAEs exposure early life may be associated with the occurrence of childhood asthma, but still there were some discrepancies between the results. In three cohort studies, A.A.M, et al. [18] found that higher exposure levels to low–molecular weight PAEs in early life compared to high–molecular weight PAEs may increase the risk of childhood asthma (aOR:1.03;95% CI (0.86, 1.23)), besides, their results revealed that high–molecular weight PAEs such as DEHP may be a positive

Table 1: Epidemiological studies of the association between early life phthalates exposure and children asthma.

<table>
<thead>
<tr>
<th>Author</th>
<th>Participant</th>
<th>Research type</th>
<th>Sample</th>
<th>Exposure time</th>
<th>Outcome time</th>
<th>Outcome classification</th>
<th>Primary results</th>
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<tbody>
<tr>
<td>[18]</td>
<td>Population one: 987 pairs for women in late pregnancy of 26.7 ± 5.5 years old and children of 4.4 ± 0.5 years old; Population two: 494 pairs for women in late pregnancy of 31.6 ± 5.3 years old and children of 4.5 ± 0.3 years old.</td>
<td>Cohort study</td>
<td>Levels of high-molecular weight (eight kinds) and low-molecular weight (three kids) PAEs metabolites in maternal urine.</td>
<td>third trimester</td>
<td>4-6 years old</td>
<td>According to the ISAAC* questionnaire: 1. current wheeze, 2. current asthma, 3. ever asthma.</td>
<td>1. Low-molecular weight PAEs metabolites are mainly associated with increased risk of asthma in children; 2. Higher levels of DEHP metabolites in the third trimester may be related to the reduced risk of childhood asthma; 3. Gender and maternal asthma history interact with PAEs level on the asthma outcomes in children.</td>
</tr>
<tr>
<td>[19]</td>
<td>136 for women in late-stages of pregnancy; 99 for children aged 2; 110 for children aged 5; 171 for children aged 8.</td>
<td></td>
<td>Levels of four PAEs monoester metabolites (MEP, MBP*, MBzP, MEHP) in the urine of mothers and children aged 2 and 5 and serum IgE levels in children aged 8 years.</td>
<td>third trimester, aged 2 and 5 years old</td>
<td>8 years old</td>
<td>According to the ISAAC Chinese version: 1. asthma, 2. a history of wheezing.</td>
<td>1. In boys, higher MEHP levels at ages 2 and 5 increased the risk of asthma at age 8; 2. In boys, mothers exposed to high levels of MBzP increased the risk of wheezing in their offspring; 3. In children with asthma, higher levels of MEHP at age 5 and MBzP at age 2 were associated with higher serum total IgE levels at age 8.</td>
</tr>
<tr>
<td>[17]</td>
<td>552 pairs for mother and child (the average age and gestation of the mothers was 31 years old and 28 weeks respectively).</td>
<td></td>
<td>Levels of 12 phthalate metabolites including DEHP and DINP* in maternal urine.</td>
<td>third trimester</td>
<td>5 years old</td>
<td>According to Danish modified version of ISAAC: 1. wheeze within the last 2 years, 2. self-reported asthma, 3. doctor diagnosed asthma, 4. use of medicine to treat asthma/cold within the last 12 months.</td>
<td>1. Mothers with high BMI and children with low birth weight have a higher incidence of asthma in children; 2. Mothers with abnormal BMI had higher urine PAEs levels during late pregnancy; 3. Asthma rates are higher in children with a family history of asthma.</td>
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</table>

*: ISAAC International Study of Asthma and Allergies in Childhood; MBP: Mono-Butyl Phthalate; DINP: Diisononyl Phthalate
Some factors may have certain interaction effect: A growing body of evidence suggests that there are interactions between a child's gender, family history of asthma and the level of PAEs for the asthma outcomes. Studies found that exposure to PAEs in early life was associated with a higher risk of childhood asthma in boys compared to girls, female gender may be a protective factor for asthma. Ku HY, et al. [19] found that among boys, high levels of exposure to PAEs in early life was associated with a higher prevalence of asthma, suggesting that the related physical fitness of pregnant mothers may indirectly affect the occurrence of childhood asthma by influencing the exposure level of PAEs.

On the other hand, we also found that the above studies have some limitations, which may affect the credibility of its conclusions. First, in real life, all kinds of PAEs, PAEs and other environmental toxicants are often exposed to the human body in combination, and there may be certain correlations between all kinds of PAEs. The study of Johnk C, et al. [17] did not conduct further statistical analysis on the relationship between combined exposure to PAEs and asthma outcome. In contrast, the study of A.A.M, et al. [18] used Weighted Quantile Sum (WQS) method [17-19,22], considering the association between PAEs and the association between combined exposure to PAEs and asthma outcomes. Second, Ku HY, et al. [19] observed certain correlations between children's PAEs exposure levels at 2 and 5 years old and asthma outcome at age eight, however, the three cohort studies mentioned above did not take into account the possible influence of postnatal self-exposure to PAEs on the association of PAEs exposure levels of mothers in late pregnancy and outcome of childhood asthma. Third, in the above three studies, the outcome information of asthma was obtained by questionnaire survey, which is subjective to some extent, and may not be as accurate as the diagnosis results of professional doctors, so the information may have a certain selection bias. Finally, due to the short half-life of PAEs in urine and the high time variability of some PAEs, it may not be accurate to represent the exposure level of PAEs in the early life only through the PAEs level in the urine of the mother in the late pregnancy.

Therefore, by nearly five years of population epidemiological data, we can conclude that early life exposure levels of PAEs can impact on children with asthma, but more profound people studies is still needed to confirm and explore the relationship, besides, in the process of further researches, PAEs combined exposure, children's self-exposure of PAEs, and so on should be taken into consideration, in addition, the extrapolation of relevant conclusions should also take the differences of geographical and population characteristics into account.

Potential mechanisms of childhood asthma induced by early life exposure to PAEs

There are relatively a few population evidences on the potential mechanism of childhood asthma induced by PAEs exposure in early life, and they are mainly case-control studies. We reviewed the population study data in the
Table 2: Epidemiological studies of the potential mechanism of the children asthma induced by phthalates exposure in early life.

<table>
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<tr>
<th>Author</th>
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<th>[21]</th>
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<tr>
<td>Participant</td>
<td>126 for children with asthma and 327 for control children aged three</td>
<td>Population one: 256 for children from CEAS* aged three; Population two: 54 for children who came to the hospital for treatment after eating food contaminated with DEHP; Population three: 2701 children aged eight from the IOW* birth cohort.</td>
</tr>
<tr>
<td>Research type</td>
<td>Case control study</td>
<td></td>
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<tr>
<td>Sample</td>
<td>Urine levels of four PAE metabolites (MEP, MBP, MBzP, MEHHP) and genetic polymorphism of the genes related to oxidative stress (The GSTM1, GSTP1 (rs1695), SOD2 (rs5746136), SOD2 (rs4880), CAT (rs769218), MPO (rs2071409), EPHX1 (rs1051740) and EPHX1 (rs2740171)* by oral mucosa cell samples</td>
<td>Urine levels of PAEs metabolites (SOH-MeHP, MEP, MBP, and MBzP) and methylation levels of 21 candidate genes including AR, TNF-a and IL-4 etc.</td>
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<tr>
<td>Primary results</td>
<td>1. Urine levels of MEHHP was significantly associated with asthma (OR = 1.33, 95% CI (1.11 - 1.60)); 2. The risk of asthma in children with SOD2 (rs5746136) TT genotype was higher than CC genotype; 3. The level of MEHHP in urine was higher in children with SOD2 TT genotype; 4. The OR value of the interaction of MEHHP and SOD, gene polymorphism (TT) on the occurrence of asthma was about 3.04.</td>
<td>1. Urine levels of SOH-MEHP was negatively correlated with TNF methylation in population one and two; 2. High urine levels of SOH-MEHP was a risk factor for asthma in population one (OR = 2.17, 95% CI (1.03-4.56)); 3. In population two and three, the hypomethylation of TNF-a 5' CGI was positively associated with the prevalence of asthma. 4. Approximately 20% of the effect of SOH-MEHP on asthma was mediated by TNF-a 5' CGI hypomethylation.</td>
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As shown in Table 2, past five years (Table 2) and concluded that the potential mechanisms may include the following points:

**Oxidative stress response:** More and more population studies have shown that oxidative stress plays an important role in the pathogenesis of asthma, and the oxidative stress level is mainly reflected in the levels of various antioxidant enzymes [23–25].

I-Jen W, et al. [20] found that individuals with Superoxide Dismutase 2 (SOD2) (rs5746136) TT genotype had higher risk of asthma and higher level of MEHHP in vivo than those with CC genotype. The interactive effect of SOD2 TT with the residual of MEHHP on the asthma was estimated (OR: 3.04; 95%CI (1.61-5.73)).

Compared with population studies, more animal experiments have found that oxidative stress reaction plays an important role in the relationship between PAEs exposure and allergic asthma. Wei Q, et al. [26] found that the oxidative stress level of the mice in the PAEs exposure group was increased, and the immune responses of TH2 and TH17 were aggravated, besides, after the blocking of oxidative stress with vitamin E, the TH2 immune response of the mice was suppressed, and the asthma symptoms were also alleviated, which was consistent with the effect obtained by MESRI AN, et al. [27], using melatonin to block oxidative stress, these results suggest that PAEs may aggravate TH2 type allergic asthma by aggravating oxidative stress. You H, et al. [28] found that after the injection of anti-Thymic Stromal Lymphopoietin (TSLP) antibody in the exposed DEHP sensitized mice to neutralize the effect of TSLP, the antibodies and immunoglobulin related to TH2 immune response in vivo decreased, and the mucus secretion in the respiratory tract decreased, TSLP plays an important role in mediating allergen and lung allergic reaction, and is mainly produced by damaged epithelial cells, can be caused by bacterial, viral infections, oxidative stress [29], therefore, the experiment suggested that oxidative stress plays a role in the pathogenesis of asthma, and TSLP may be an effective target to inhibit the “adjuvant” effect of DEHP on asthma.

In addition, the first controlled human exposure study [30] observed that exposure to Dibutyl Phthalate (DBP) can affect the levels of airway immune mediator and airway responsiveness, so, the changes in immune levels may be an intermediate or progressive process.

**Tumor necrosis factor-α (TNF-α):** Wang I, et al. [21] observed that the methylation of the 5’ CGI region of the TNF-α gene was correlated with individual levels of 5OH-MEHP (DEHP metabolite marker) and MBzP, as well as the occurrence of asthma in the population, the mediation analyses estimated that 20% of the total effect of 5OH-MEHP on asthma is mediated by TNF-α 5’ CGI, besides, the evidence suggested that the epigenetic mechanism may play a role in the occurrence of related diseases. At the same time, there are increasing evidences that there are significant differences in serum TNF-α levels in children with asthma with different degrees of airway obstruction and severity of asthma, and the TNF-α levels in children with asthma are higher than those in the control group [31–33]. Therefore, clinical detection of TNF-α level may be help to predict the occurrence and severity of asthma, and contribute to the prevention and treatment of asthma disease.

It can be concluded from the above evidences that the potential mechanisms of childhood asthma induced by early life PAEs exposure are mainly related to oxidative stress, gene polymorphism, changes in TNF-α level and epigenetic variation, but there is relatively a little evidence on the mechanism of population studies from early life PAEs exposure to childhood asthma completely, so more and more in-depth population studies are needed to explore the underlying mechanisms.

**DISCUSSION**

With the development of industrialization, people
References


