Phthalates are a kind of synthetic plasticizers, which are extensively used as plastic productions to improve their plasticity and flexibility. However, exposure to phthalates has been proved an increased risk of respiratory disease, because by they affect the development and functions of the lung and immune system. Here, we attempt to review respiratory health of phthalate exposure. Firstly, we describe the relationship between phthalates and lung function and airway inflammation. Then, the role of phthalates in asthma, lung cancer, rhinitis, and respiratory tract infections and the possible mechanisms of action are discussed. Finally, possible effective measures to reduce exposure to phthalates are proposed, and health care workers are called upon to provide educational resources and advocate for informed public health policies.

Overall, the evidence for association between phthalate exposure and respiratory disease is weak and inconsistent. Therefore, thorough implementation in large populations is needed to produce more consistent and robust results and to enhance the overall understanding of the potential respiratory health risks of phthalate in long-term exposure.

Keywords: inflammation; interventions; lung function; phthalates; respiratory health.

Introduction

Phthalates are chemical plasticizers used extensively in food processing and storage, cosmetics, and other vinyl products. Since phthalate plasticizers are not chemically (but only physically) connected to the polymer system, slight changes in the environment, such as pH, temperature and pressure, irradiation or contact with lipid, would accelerate the leaching or migrating or vaporizing out of phthalate from the plastic embodiment into the surrounding environments, ultimately posing a burden on human health [1].

The physicochemical properties of phthalates determine their industrial applications, environmental dynamics, and consequently the dominant human exposure routes. Whereas both dermal absorption and inhalation may be important pathways for low molecular weight (LMW) phthalates [2]; ingestion (including food, tap and bottled water, soil, and dust) is likely most important for high molecular weight (HMW) phthalates [3]. To be sure, it is not independent of each pathway and could be comprehensively cross-exposed through a variety of pathways. Its impact on the top consumers in the ecosystem (humans) is increasing at a proportionate rate, although its toxicity was noted by Hocking in 1967 (e.g., dimethyl phthalate (DMP) as a repellents and attractants) [4].

Decades of research have linked exposure to phthalates to endocrine disorders, respiratory symptoms, and effects on reproduction and neurodevelopment [5]. Phthalate exposure in early life may have long-term adverse effects on respiratory health due to immaturity of the lungs, immune system, and developmental physiology. In a growing number of epidemiological studies, phthalates have been linked to asthma, airway inflammation, and reduced lung function, and early studies on phthalate exposure and respiratory conditions date back to the 1970s [6]. Phthalate exposure and respiratory diseases, particularly asthma, have been of increasing concern in recent years [7]. Although the mechanisms behind the development of respiratory disease are not fully understood, environmental exposure through the airway and airway is suspected to contribute to the development and progression of the disease.

In this review, we seek to summarize current knowledge about the effects of phthalates on respiratory health at
Multiple levels. This review elucidates the effects of phthalate exposure on airway inflammation and lung function, and integrates the results of epidemiological studies and plausible mechanisms of phthalate exposure on the respiratory system. Then, the need for primary prevention and effective interventions were raised. Finally, conclusions are drawn on current evidence of a link between phthalate exposure and respiratory disease.

**Literature search process**

This review was completed by exploring literature retrieved on PubMed. The papers published in the past 15 years were mainly considered for the study. The main keywords used to search articles included “phthalate”, “lung disease”, “airway inflammation”, “lung function” and “prevention”. We also used the terms “OR” and “AND” to search for two or more keywords at the same time, so that no relevant literature was omitted. The papers were checked manually and then filtered based on title, abstract and the paper contents. Endnote software was used to store the bibliography data and add citations. We reviewed a total of 78 articles on phthalate and lung disease, and selected 15 articles with clear, detailed and conclusive data and information on the effects of phthalate on airway inflammation marker Fractional exhaled nitric oxide (FeNO) and lung function, and 24 articles related to phthalate and asthma, rhinitis, lung infection, and lung cancer, and 7 articles on the impact of preventive measures on phthalate exposure.

**Phthalates and inflammation**

Previous studies have shown that exposure to phthalates can adversely affect the respiratory and immune systems, thus contributing to a dramatic epidemic of allergic respiratory diseases [8, 9]. Epidemiological studies have reported a positive association between phthalate exposure and airway inflammation [10]. FeNO, a marker of airway inflammation, is responsive to environmental pollutants that contribute to respiratory health problems. It offers a method to test for associations between phthalate exposure and subclinical changes in airway inflammation [11]. As early as in 2012, a positive association between phthalate biomarkers and FeNO was first reported [12]. A study conducted among 56 children with asthma in the Seoul Metropolitan Area in Korea also reported that the increase in metabolites of Di (2-ethylhexyl)phthalate (DEHP) in urine was associated with increased FeNO [13]. Exposure to total airborne and gas-phase phthalates was found to be associated with increase in FeNO [14], implying active respiratory inflammation when exposed to higher indoor airborne PAEs. A recent study also found that a doubling increase in indoor airborne PAEs (DEHP, DMPP, DPP, DEP) was associated with the increase in FeNO, which may affect cardiorespiratory health as reflected by changes in airway inflammation [15].

Although there is no direct evidence of phthalates' inflammatory activity, oxidative stress may play a mediating role, predisposing the immune system to Th2 and Th17 responses (Figure 1). Oxidative stress is the result of imbalances of antioxidants and ROS in the body and plays a vital role in the pathogenesis of various types of pulmonary inflammation [16]. Pulmonary toxicological studies have shown that DBP increased the level of oxidative stress and promoted the recruitment and activation of neutrophil in the lung, which contribute to inflammatory lung diseases [17]. Nrf2, as a key transcription factor of oxidative stress, was proved to be an upstream regulatory protein of TSLP in pulmonary epithelial cells [18]. TSLP is an essential cytokine of epithelial cells and regulate naïve CD4+ T cells toward a Th2 phenotype [19]. It’s worth noting that DBP had found to inactivate Nrf2 and up-regulated the expression of TSLP, thus activation of mast cells and airway inflammation [17, 18]. In addition, DEHP caused down-regulation of E-cadherin in airway epithelial cells and upregulation of costimulatory molecules/pro-inflammatory cytokines in DCs, which responsible for conversion of airway inflammation with eosinophilic predominance to a mixed granulocytic airway inflammation with Th2/Th17 [20].

**Figure 1:** The promoting effect of phthalate exposure on airway inflammation. TSLP, thymic stromal lymphopoietin; Th2, T helper 2 cell; Th17, T helper 17 cell.
Importantly, maternal DINP exposure could promote OVA-induced allergic airway response in pups in part by upregulation of PI3K/Akt pathway [21]. Studies have shown that the increased airway inflammation in offspring induced by phthalate may be related to the DNA hypermethylation in CD4^+ T cells [22].

**Phthalates and lung function**

Phthalates can leach into indoor and outdoor airborne particulate matter and dust, which then be ingested or absorbed and induce lung injury (Table 1). Phthalates on forehead skin wipes has been reported to have an inversely associated with decreases in lung function tests in residential area near a petrochemical complex [23]. In addition, Urinary metabolites of phthalates are inversely associated with pulmonary function test values in the general population [24], children [25], adolescents [26] and older adults [13]. Several epidemiological study reported an association of prenatal exposure to LMW-phthalates with poorer lung function [27, 28] and postnatal exposure to DEHP and di-isononyl phthalate (DINP) metabolites are associated with a lower lung function in childhood [29], indicating prenatal and postnatal exposure to phthalates may be a risk factor for respiratory disease in children.

Animal Research also have showed that lung alveolar development was inhibited after both oral and iv high dose DEHP, and the increase of fat particle size in DEHP lipid emulsion may cause pulmonary granuloma [30]. The perinatal DEHP exposure led to decreased gas-exchange space as evidenced by increased lung interstitial tissue proportion in newborn rats, VEGF gene expression was altered and might be involved as one of the possible molecular mechanisms [31, 32].

**Phthalates and respiratory disease**

**Asthma and plausible mechanism**

As early as in 2014, a Columbia Center for Children’s Environmental Health Cohort study had reported that prenatal exposure to BBzP and di-n-butylphthalate (DnBP) was associated with asthma-like symptoms in children aged 5 and 11-year-old [37]. Researchers discovered

<table>
<thead>
<tr>
<th>Years</th>
<th>Population</th>
<th>Age, years</th>
<th>Sample type</th>
<th>Sampling frequency</th>
<th>Phthalate</th>
<th>Lung function test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>100 (males)</td>
<td>20–60</td>
<td>Urinary</td>
<td>–</td>
<td>MBP</td>
<td>FVC, FEV1, PEF</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td>140 (females)</td>
<td>20–60</td>
<td>Urinary</td>
<td>–</td>
<td>MBP</td>
<td>FVC, FEV1, PEF</td>
<td>NS</td>
</tr>
<tr>
<td>2014</td>
<td>30</td>
<td>34.6–56.6</td>
<td>Urinary</td>
<td>–</td>
<td>MEHP, MINP</td>
<td>PEF % of PV, FEV1/FVC</td>
<td>Increases</td>
</tr>
<tr>
<td>2014</td>
<td>3,147</td>
<td>20.7 ± 13.3</td>
<td>Urinary</td>
<td>–</td>
<td>MnBP, MBZP, MCPP, DEHP</td>
<td>FEV1, FVC, FEV1/FVC</td>
<td>Decreases</td>
</tr>
<tr>
<td>2018</td>
<td>132</td>
<td>2</td>
<td>Urinary</td>
<td>–</td>
<td>MEP</td>
<td>FEV1, FVC</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>147</td>
<td>5</td>
<td>Urinary</td>
<td>–</td>
<td>MEP</td>
<td>FEV1, FVC</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td>191</td>
<td>9</td>
<td>Urinary</td>
<td>–</td>
<td>MEP</td>
<td>FEV1, FVC</td>
<td>Decreases</td>
</tr>
<tr>
<td>2018</td>
<td>537</td>
<td>≥60</td>
<td>Urinary</td>
<td>–</td>
<td>MEHHP, MEOHP, MnBP, ∑DEHP</td>
<td>MEH</td>
<td>Decreases</td>
</tr>
<tr>
<td>2018</td>
<td>392 (kids)</td>
<td>≥18</td>
<td>Prenatal urine</td>
<td>Two time points</td>
<td>DEHP, DINP</td>
<td>FEV25–75% (their age seven children)</td>
<td>Decreases</td>
</tr>
<tr>
<td>2019</td>
<td>1,033</td>
<td>8.1</td>
<td>Outdoor and indoor Prenatal urine</td>
<td>Once</td>
<td>DEHP, DINP</td>
<td>FEV1</td>
<td>Decreases</td>
</tr>
<tr>
<td>2020</td>
<td>319 (kids)</td>
<td>≥18</td>
<td>Prenatal urine</td>
<td>Two time points</td>
<td>MCOP</td>
<td>FEV1 (their age seven children)</td>
<td>Decreases</td>
</tr>
<tr>
<td>2020</td>
<td>397</td>
<td>47.1 ± 12.4</td>
<td>Forehead surface</td>
<td>Three times</td>
<td>DnBP, BBzP, DEHP, DINP</td>
<td>FEV1, FVC</td>
<td>Decreases</td>
</tr>
<tr>
<td>2020</td>
<td>237</td>
<td>41.4 ± 6.6</td>
<td>Forehead surface</td>
<td>Three times</td>
<td>DEP</td>
<td>FEV1, FVC</td>
<td>Decreases</td>
</tr>
<tr>
<td>2022</td>
<td>714 (boys)</td>
<td>14 ± 3</td>
<td>Urinary</td>
<td>–</td>
<td>MCNP, MnBP, MIBP, MEOH, MBzP</td>
<td>FEV1, FVC</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>675 (girls)</td>
<td>14 ± 2.9</td>
<td>Urinary</td>
<td>–</td>
<td>MCNP, MnBP, MIBP, MEOH, MBzP</td>
<td>FEV1, FVC</td>
<td>Decreases</td>
</tr>
</tbody>
</table>

NS means no significant. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow.
that exposure to mixtures heavily weighted by LMW compounds (monoethyl phthalate [MEP], mono-butyl phthalate [MBP], and monoisobutyl phthalate [MiBP]) are associated with increased odds of childhood asthma and wheeze in boys and in children born to women without a history of asthma [38], suggesting effect modification by child sex and maternal asthma in associations between prenatal phthalate mixtures and child asthma. In addition, a Shanghai, Children, Home, Health study by Zhang et al. reported that high concentrations of HMW-phthalates were significantly associated with childhood diagnosed asthma, and exposure to phthalates is associated with a higher risk of asthma in girls than in boys [39]. DEHP has been reported to be more associated with wheezing, respiratory infections, and asthma in girls than in boys, but these differences were not statistically significant [40]. However, a Japanese cross-sectional study came up with different results that mixed phthalates exposure in urine samples of children was not significantly associated with asthma [41]. Most of the above studies used cross-sectional or case-control design or assessment of phthalate esters in PVC materials/dust as a marker of phthalate exposure, that limiting the inference of the conclusion. According to the current research, the results of the study on the relationship between phthalate exposure and asthma are inconsistent, which need to be confirmed by further research. Therefore, it is particularly urgent to conduct a further prospective cohort study on prenatal and postnatal phthalate exposure metabolites and asthma, to determine the susceptibility period of exposure.

Experimental studies in vivo and vitro have shown that phthalate enhanced the immune response to T cell, macrophage and dendritic cells through the multiple signaling pathways, leading to an aggravation of the atopic march, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinase P38, phosphatidylinositol 3-kinase (PI3K)/Akt and peroxisome proliferator-activated receptor α signaling pathways [42–44]. In addition, maternal phthalate exposure, in the one hand, may upregulated PI3K/Akt pathway and downstream NF-κB translocation, in the other hand, upregulated the thymic stromal lymphopoietin (TSLP)/TSLPR/IL-7R pathway, which promoting the expression of Th2 cytokines and increasing incidence of allergic diseases in offspring [21, 45]. Recently, epigenetic markers are of great concern, especially DNA methylation. Researchers found phthalate exposure decreased the DNA methylation of TSLP and increased the DNA hyper-methylation in CD4+ T cells and the hypo-methylation of the IGF2R in dendritic cells, further, enhancing allergic lung inflammation [22, 46, 47] (Figure 2).

**Lung cancer and plausible mechanism**

Unlike in asthma and bronchitis, no much information (clinical evidences) is seen in literature for implicating link of phthalates to cancer incidence in humans. Nevertheless, it is thought increasingly that there exists a link between lung cancer and EDC like phthalates, because high expression of ERα in non-small cell lung cancer (NSCLC) [48], which bound to DEHP to mimic natural hormones and exert carcinogenesis [49]. In 1983, phthalates was found to have a possible deleterious effect in
promoting lung cancer in women in a case-referent study of lung cancer mortality in acetylene and phthalic anhydride plants [50]. Data from animal showed dibutyl phthalate (DBP) may enhance the adverse clinical effects caused by ozone, such as lung cancer and oviduct cancer [51].

Data in vitro studies shed some light on the mechanism of the induction of lung cancer by phthalates (Figure 3). It has reported that DEHP stimulated NSCLC migration and invasion via NF-kB mediated up regulation of IL-6 [52]. Moreover, DEHP and mono (2-ethylhexyl) phthalate (MEHP) exposure have been demonstrated to be associated with enhanced migration and changes in cellular structure in A549 cells [53]. Subsequently, Kim had presented evidence that DEHP stimulates the proliferation of NSCLC and induces inflammation and EMT by activating MAPK and Wnt/β-catenin signaling pathways [54]. Binder et al. investigated the effect of DBP inhalation exposure on A549 by establishing air–liquid interface exposure conditions in vitro identical to potential occupational diastolic exposure, and found DBP induced genotoxicity at DNA and chromosome level in sub-cytotoxic conditions. Since genomic instability was accompanied by increased generation of the lipid peroxidation marker MAD, oxidative stress might play an important role in phthalate-induced genotoxicity [55].

Others

Some investigations have found that phthalate exposure is associated with respiratory tract infection and rhinitis. Previous reports have indicated that higher concentration of BBP in dust was found in families with the children rhinitis cases [56], which was consistent with a study in Shanghai about rhinitis [57]. Exposure to high concentrations of DBP, DEHP, and HMW-phthalates in house settled dust was a risk factor for rhinitis for children, especially for boys [57]. In addition, prenatal exposure to phthalates was associated with childhood rhinitis [58]. What is noteworthy is that prenatal exposure to BPA and HMW-phthalates might increase the risk of respiratory tract infections throughout childhood, thus, inducing a variety of diseases [40]. Parallelly, a SELMA study in Swedish showed maternal phthalate exposure during early pregnancy may be a risk factor for wheeze in early childhood [59].

Possible effective measures

Typically, manufactured chemicals, such as phthalates, are not required to conduct comprehensive studies on the long-term health effects of exposure before they can be used in industrial processes and consumer products. It usually takes years of observation and experimentation to identify chemicals as potentially harmful to human health, and by then it is difficult to identify and remove significant sources of exposure because of the ubiquity of environmental exposures. However, the solution is often to replace potentially harmful chemicals with chemicals that are structurally similar and have unknown long-term health effects. Currently, bis(2-ethylhexyl) terephthalate (DEHTP) and diisononyl ester (DINCH) have become substitutes for DEHP widely used in everyday products. However, recent animal studies have shed light on the possible health risks of this phthalate replacement [60, 61]. Therefore, we should take certain measures to minimize the use of phthalates to protect health.

Owing to the short half-life of phthalates, dietary and behavioral interventions, even for a short period, can reduce the exposure to these chemicals (Table 2). A school for girls in Taiwan reported reduction in urine phthalate

![Figure 3: Plausible molecular signaling mechanism elicited by phthalates in lung cancer. MAPK, mitogen-activated protein kinase; IκBα, nF-κB, nuclear factor kappa B; ROS, reactive oxygen species.](image-url)
<table>
<thead>
<tr>
<th>Year</th>
<th>Participants</th>
<th>Research design</th>
<th>Recommended intervention items</th>
<th>Intervention period</th>
<th>Analytes</th>
<th>Reference</th>
</tr>
</thead>
</table>
| 2021     | 35 pregnant women | Pre-, mid-, and postintervention, one group | **Nutrition and diet:** Replace fast food, puffer food, canned food, and microwaved food with healthier food  
**Lifestyle habit:** Restricted use of phthalate-containing household products such as hair colorants, shampoos, perfumes, wrapping food in plastic containers; avoid touching plastic floors and decorating materials; proper exercise  
**Environment:** Faraway second-hand smoking; limited transport with car | Until ninth month | MEHP, MEHHP, MECPP, MEP, MnBP, MMP, MIBP, ΣLPAEs, ΣDEHP, Σ10PAEs | [64]      |
| 2021     | 51 mothers with infants (26 experimental/25 control) | Pre- and post-intervention, randomized controlled trial | **Web-based behavioral intervention:** avoiding foods containing high levels of fat and dairy products such as cheese and ice cream; using stainless steel and glassware for cooking; avoiding using new furniture and cars and refrain from using PCPs and cosmetics with strong fragrances and colors; exercising and washing hands frequently. | 4 weeks | MEHP, MEOHP, MEHHP, BPA, TCS, parabens | [63]      |
| 2020     | 288 infants (143 experimental/145 control) | Pre- and post-intervention, randomized controlled trial | **Residential intervention:** Removal of lead hazards in paint, dust, water, and soil in and around the home, extensive cleaning, and removal of dust  
Repairing any deteriorating or water-damaged wall material, removing loose or peeling paint, reapplying paint | NA | MEHHP, MEOHP, MEHP, MECPP, MEP, BzP, MCOP, MCNP, MIBP, MnBP | [66]      |
| 2020     | 26 participants from 9 households | Pre- and post-intervention, one group | **Residential intervention** introduction of recommended lifestyle changes to lower exposure to selected endocrine disruptors in the indoor home environment | 6 months | BPA, BPS, 4-NP, DEP, DiBP, DEHP | [67]      |
| 2016     | 100 girls | Pre- and post-intervention, one group | **Personal care products intervention:** Restricted use of phthalate-containing household products such as hair colorants, shampoos, perfumes, | 3 days | Phthalate, parabens, TCS, BP-3 | [68]      |
| 2015     | 30 girls | Pre- and post-intervention, one group | **Nutrition supplements and medication and diet:** Replace fast food, puffer food, canned food, and microwaved food with healthier food  
**Lifestyle habit:** Restricted use of phthalate-containing household products and food contained in a plastic bag or plastic wrapping, avoid touching plastic floors and decorating materials; proper exercise | 7 days | MMP, MEP, MBP, MBzP, MEHP, MEHHP, MEOHP, MECPP | [62]      |
| 2015     | 10 pregnant women | Pre-, mid-, and postintervention, one group | **Dietary intervention:** balanced diet intended to minimize dietary phthalate exposure | 3 days | MEHHP, MEOHP, MEHP, MECPP, MBP, MEP, MIBP, MBzP, MCOP, MCNP | [69]      |
metabolites through hand washing, not eat food in plastic packaging, and reducing use of personal care products [62]. A Web-based behavioral intervention study in Korean also showed the urinary concentration of MEHP, mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) was reduced in mothers with young children [63]. Moreover, it is reported phthalate metabolites were significantly lowered after the diet of participants was restricted to eat fast foods and encouraged to consume healthy foods [64]. Undoubtedly, reducing exposure to phthalate in the environment is also an effective intervention, such as denying second-hand smoke [65].

Relying on one-period interventions to prevent phthalate exposure throughout life is burdensome and unachievable, despite their proven effectiveness. Therefore, it is necessary to develop a comprehensive programme to reduce exposure to environmental hazards at every stage of life.

Conclusions

Currently, we found inadequate evidence of association (lack of consistency) between phthalate exposure and respiratory diseases. Asthma is the focus of research on respiratory diseases caused by phthalate exposure. The possible factors for lack of consistency to the fact: small population samples, which are not representative of the general population; the study population is of different ages, such as infants and young adults; the time and frequency of sampling, which affect the concentration of phthalate metabolites because it metabolizes quickly. Future studies, need to improve the accuracy of associations between phthalate exposure and these health effects by using larger sample sizes and longitudinal surveys across multiple stages of life to produce more consistent and robust results. On the other hand, we should also take steps to protect our own health by reducing phthalate exposure, in which health care professionals pay an indispensable role in preventing phthalate exposure by providing resources to patients concerned and advocating for informed public health policies.

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Informed consent: Not applicable.

Ethical consent: Not applicable.

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