Chinese Medical Journal®

Polycyclic aromatic hydrocarbon: environmental sources, associations with altered lung function and potential mechanisms

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Polycyclic aromatic hydrocarbon (PAH) molecules are a large group of organic compounds with two or more fused benzene rings arranged in various configurations.[1] To date, hundreds of PAHs have been identified. PAHs are widespread environmental contaminants formed as a result of incomplete combustion of carbonaceous materials in both natural and anthropogenic process.[2] Compared to the natural sources, such as volcanic eruptions and wild fires, anthropogenic sources, such as industrial processes, cigarette smoke, vehicular exhaust, residential heating fuels and charcoal-grilled and flame-broiled food, make a larger contribution to the generation of atmospheric PAHs.[3] Through inhalation, ingestion and dermal contract, PAHs from all sources can easily be absorbed in the body and further metabolized and excreted in urine. The urinary monohydroxylated PAH (OH-PAH) has been widely considered as a biomarker to represent individual PAH exposure levels in many studies.[4-6]

The occurrence of PAHs has been of great concern for public health for several decades. In addition to its mutagenic and carcinogenic effects,[7,8] exposure to PAHs has been shown to be associated with respiratory diseases in recent years. In the present paper, we review the environmental sources of PAH exposures, the associations between exposure to PAHs and lung function alteration, and the potential mechanisms underlying such relationship.

Major emission sources of PAHs are from human activities in urban life. Traffic exhaust is thought to be a major outdoor source of PAHs. It was reported that about one-eighth of global environmental PAHs emission was attributed to vehicle exhaust in 2007.[9] Whereas in the indoor environment, exposure to PAHs is markedly increased by cigarette smoking. Currently, more than 500 different PAHs have been identified in cigarette smoke.[7] As the commission of the California Air Resources Board reported, the amount of PAHs generated by cigarette smoke was 1.5 to 4 times higher than those from other indoor combustion sources.[10] For non-smokers and non-occupational populations, the main source of PAHs exposure is through the diet. Some crops, such as rye, wheat, and lentils, may synthesize PAHs or absorb them via air, water, or soil.[11] More importantly, multiple processing and cooking methods at high temperatures, such as smoking, grilling, roasting, and broiling, could add considerable PAHs into the food.[12] PAHs in cooking fumes generated during high-temperature food processing may be absorbed into the human body with breathing.

Several studies investigated the associations between various environment sources of PAHs exposure and urinary metabolites in specific populations. One study from Poland mainly focused on the influence of environmental tobacco smoke exposure and residential characteristics on urinary OH-PAHs in 218 3-year-old children. They found higher levels of urinary 2-hydroxyfluorene (2-OHFlu), 9-hydroxyfluorene (9-OHFlu), and 1-hydroxypyrene (1-OHP) in children exposed to smoking at home compared to those without exposure. Gas-based appliances used for cooking were related to higher levels of urinary 2-OHFlu, 9-OHFlu, 1-hydroxyphenanthrene (1-OHPh), and 3-hydroxyphenanthrene (3-OHPh); and the use of coal, wood, or oil for heating was associated with elevated levels of urinary 1-OHP.[13] Another study among 1269 non-smoking housewives in Korea found that subjects living near a major road have significantly higher levels of urinary 2-OHFlu and 1-OHPh.[14] Hoseini et al[15] explored the effects of environmental and lifestyle factors on urinary OH-PAHs in 222 Iranian adults. Their results suggested that cigarette smoking, residency in high-traffic area, and exposure to insecticides or tar products were closely related to higher levels of urinary 1-hydroxynaphthalene (1-OHNa) and 2-hydroxynaphthalene (2-OHNa). Subjects exposed to candle burning had higher levels of urinary 2-OHNa and 9-OHFlu.[15]

Our research group analyzed the relationship between four major environment sources (cigarette smoking, traffic exposure, home-cooking, and dietary intake) and ten kinds of urinary OH-PAHs in 4092 urban participants from the Wuhan-Zhuhai Cohort in China. The findings indicated that

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000880

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Chinese Medical Journal 2020;133(13)

Received: 01-02-2020 **Edited by:** Li-Min Chen

tobacco smoking was significantly correlated to elevated levels of urinary 1-OHNa, 2-OHNa, and 2-OHFlu ($P < 0.0001$). Higher dietary PAH intake was associated with urinary 1-OHNa, 2-OHNa, and 9-OHFlu levels ($P < 0.05$). Individuals who spent more than 30 min in traffic showed increased levels of 9-OHFlu and 1-OHPh ($P < 0.05$) compared with those with no more than 30 min in traffic. Higher levels of urinary 1-OHP was closely related to home-cooking ($P = 0.0243$). What's more, our results suggested that good kitchen ventilation could decrease low-molecular-weight OH-PAHs levels ($P < 0.05$). We further investigated the combined effect of various exposure sources on urinary metabolites and found a stronger combined effect of cigarette smoking when co-exposure with any other sources occurred,[16] which confirmed the great contribution of cigarette smoking to PAH exposures.

In previous studies, exposure to PAHs has been reported to be associated with lung function decline in occupational populations. Wang et al[17] conducted a 4-year prospective investigation among 1243 coke oven workers and found that the baseline concentrations of urinary 1-OHNa, 2-OHNa, 2-OHFlu, 9-OHFlu, 1-OHPh, 2-hydroxyphenanthrene (2-OHPh), and the total urinary OH-PAHs ($\sum$OH-PAHs) were significantly negatively associated with the decline of forced expiratory volume in one second (FEV_1)/forced expiratory volume (FVC) ($P < 0.05$). Additionally, the baseline levels of urinary 1-OHNa, 1-OHPh, 2-OHPh, 9-hydroxyphenanthrene (9-OHPh), 1-OHP, and $\sum$OH-PAHs were related to forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) decline.

Differing from high levels of PAH exposure in an occupational environment, exposure to low levels of PAHs was observed in general populations. In our studies, we investigated the association between the concentrations of PAHs in ambient particle matter and urine, and lung function decline. We studied 2747 Chinese adults in an urban Wuhan cohort and observed significant associations between increased levels of urinary OH-PAHs and reduced lung function. Specifically, each 1-unit increase in log-transformed levels of urinary 2-OHNa, 2-OHFlu, 9-OHFlu, 1-OHPh, 2-OHPh, 3-OHPh, 4-hydroxyphenanthrene (4-OHPh), 9-OHPh, 1-OHP, and $\sum$OH-PAHs was associated with −23.79, −41.76, −19.36, −39.53, −34.35, −27.37, −36.87, −33.47, −25.03, and −37.13 mL change in FEV_1, respectively (all $P < 0.05$). Each 1-unit increase in log-transformed levels of urinary 2-OHNa, 2-OHFlu, 1-OHPh, 2-OHPh, 4-OHPh, and $\sum$OH-PAHs was associated with a −24.39, −33.90, −28.56, −27.46, −27.15, and −27.99 mL change in FVC (all $P < 0.05$).[18]

To quantify the associations of 16 fine particulate matter ($PM_{2.5}$)-bound PAHs with lung function levels, we studied 224 Chinese participants who enrolled in two study periods (2014–2015 and 2017–2018) of the Wuhan-Zhuhai cohort. Each one interquartile-range increase of naphthalene, acenaphthene, fluoranthene, and pyrene was associated with 26.82, 60.99, 45.25, and 23.37 mL decline in FVC, respectively; fluoranthene and pyrene were associated with 27.43 and 15.49 mL decline in FEV_1. Compared with the persistently low-exposure level groups, persistently long-term high levels of three high-molecular-weight PAHs exposure (benzo[a]anthracene, dibenzo[a,h]anthracene, and benzo[ghi]perylene) were associated with a −214.54, −226.13, and −265.00 mL change in FVC in 3 years.[19] Our findings verified that both external and internal exposure of PAHs affect lung function.

Epidemiological and experimental studies have supported the hypothesis that exposure to noxious environment pollutants, such as PAHs, induce oxidative damage by activating the cytochrome P450 family of enzymes. These could increase reactive oxygen species, attack biological macromolecules (such as proteins, lipids, and DNA), and lead to impairment of lung epithelium or tissue.[20-22] We used urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG), the predominant metabolite of oxidative DNA lesions, and 8-isoprostane (8-*iso*-PGF2α), the terminal product of cell membrane lipid peroxidation, as markers of oxidative damage. Significant associations between PAH exposure and oxidative damage (elevated levels of urinary 8-OHdG) and decrease of FVC were observed leading to the concept that 8-OHdG may play a mediating role in the association between total high-molecular-weight OH-PAHs ($\sum$HMW OH-PAHs) and a decrease of FVC.

Persistent inflammation might be another mechanism for lung function decline. *In vivo* and *in vitro* studies have reported that PAH exposure may induce continuing lung inflammation.[23] Airway inflammation involving cytokines and growth factors, such as tumor necrosis factor-α, interleukin (IL)-4, and IL-6, which are secreted by inflammatory cells may be responsible for the development of airway hyper-responsiveness and structural change in the airway wall. The cell apoptosis and remodeling[24,25] might play an important role in lung function decline. In support of this, epidemiological studies have shown that exposure to PAHs is linked to increased levels of C-reactive protein, IL-1β, and immune cells[26-28]; increase in these inflammatory factors is correlated with a decline in lung function.[29]

As a protective biomarker of lung epithelium integrity, club cell secretory protein-16 (CC16) is produced in abundance by non-ciliated bronchiolar club cells under physiological conditions. Once oxidative stress and inflammation appears, a large amount of CC16 can be secreted to protect the respiratory tract.[30] Lower levels of CC16 have been linked to lung function decline and development of respiratory diseases.[31] Our previous study found that plasma CC16 accounted for 22.13% of the association between $\sum$HMW OH-PAHs and FVC among individuals with higher $\sum$HMW OH-PAHs (>0.67 μg/mmol creatinine). After 3 years of follow-up, individuals with low level of plasma CC16 had a significant decline of FVC when exposed to high level of $\sum$HMW OH-PAHs.[32]

In conclusion, PAHs are a group of environmental contaminants from multiple sources, often associated with incomplete combustion. Environmental sources and life-styles affect the types and levels of urinary OH-PAHs. Both parent PAH in the atmosphere and its metabolites in urine are significantly associated with a decrease in lung function. Evidence indicates that oxidative damage, inflammatory response, and the reduction of CC16 may be involved in the pathological process of lung function decline induced by PAHs exposure. Understanding the influence of environmental PAHs exposure on urinary metabolites could help

control the emission of PAHs and reduce their harmful health effects.

Funding

This work was supported by grants from the Key Program of the National Natural Science Foundation of China (No. 91543207) and the National Key Research and Development Program of China (No. 2016YFC1303903).

Conflicts of interest

None.

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How to cite this article: Cao LM, Mu G, Chen WH. Polycyclic aromatic hydrocarbon: environmental sources, associations with altered lung function and potential mechanisms. Chin Med J 2020;133:1603–1605. doi: 10.1097/CM9.0000000000000880