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POLICIKLIČNI AROMATIČNI UGLJOVODONICI, NJIHOVI URINARNI METABOLITI I ZDRAVLJE

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SAŽETAK

Svetska zdravstvena organizacija je kao jedan od zaključaka navela da je zagađenje vazduha vodeći ekološki rizik po zdravlje ljudi. Policiklični aromatični ugljovodonici (PAU) su dobro poznati kancerogeni agensi (preko pet stotina jedinjenja) koji uzrokuju rak pluća i kože, naročito kod profesionalno izloženih radnika. Značajnim smanjenjem emisije iz savremenih industrijskih postrojenja za sagorevanje, redukcijom emisije izduvnih gasova u saobraćaju i strogim zabranama pušenja na javnim mestama, može se smanjiti ekspozicija PAU. Izloženost PAU bi trebalo bolje istražiti, posebno u oblasti masovnog biomonitoringa koncentracija njihovih glavnih metabolita u urinu. Takav biomonitoring bi trebalo da integriše ekspoziciju hemijskim kancerogenima iz različitih izvora (vazduha, vode, hrane, potrošačkih proizvoda, profesionalnih postupaka, itd.), kao i izloženost hemijskim noksama preko respiratornog trakta (udisanjem), digestivnog trakta (gutanjem) ili preko kože. Analiza koncentracije glavnih metabolita PAU u urinu visoko sofisticiranom opremom je potrebna za dobijanje validne baze podataka. Tako dobijeni podaci neophodni su za procenu rizika i kreiranje zdravstvene politike, a sve u cilju smanjivanja izloženosti hemijskim karcinogenima.

Ključne reči: poličiklični aromatični ugljovodonici, hemijske nokse, zagađenje vazduha

Uvod

Prema podacima Svetske zdravstvene organizacije (SZO) zagađenje vazduha je među najvećim javno zdravstvenim problemima (1), što potvrđuje činjenica da preko 90% svetskog stanovništva živi u područjima gde je kvalitet vazduha ispod procenjenih normi SZO. Zagađenje vazduha ne potiče samo od čestica, nego i od toksičnih hemikalija (1). Upravo iz navednog razloga jako je važan biomonitoring, odnosno procena izloženosti ljudi hemikalijama (2). Od svih hemijskih zagađivača vazduha jedan od najvažnijih su policiklični aromatični ugljovodonici (engl. *Polycyclic Aromatic Hydrocarbons* - PAU) (Tabela 1), koji su imunotoksični, mogu da izazovu karcinome i aterosklerozu, a imaju i teratogena dejstva (1,3). Brojna istraživanja pokazuju da se PAU najviše dovode u vezu sa nastankom kancera pluća i kože (3,4). Procene su da će do 2025. godine zagađenje vazduha biti vodeći uzrok prevremenog umiranja (3,5). Voda se najčešće zagađuje izlivanjem industrijskih i komunalnih voda, koje takođe zagađuju zemljište. Zemljište se dodatno zagađuje čvrstim komunalnim otpadom, šumskim požarima, aktivnostima vulkana, odlaganjem industrijskog otpada itd. Cilj ovog rada je da analizira rasprostranjenost PAU u životnoj sredini, metabolizam nakon prodiranja u ljudski organizam i mogućnosti redukcije zagađenja ovim jedinjenjima i prevencije oboljevanja ljudi.

Rasprostranjenost policikličnih armatičnih ugljovodonika

PAU su perzistentna organska jedinjenja koja se sastoje od dva ili više kondenzovanih aromatičnih prstenova. Prisutni su u vodi, vazduhu i zemljištu. Nastaju nepotpunim sagorevanjem organske materije i postaju glavni izvor zagađenja atmosfere (6). PAU mogu nastati prirodnim ili antropogenim putem. Prirodnim putem, PAU u atmosferu dospevaju vulkanskim erupcijama i požarima. Međutim, antropogene aktivnosti koje dovode do nastanka PAU su najčešće gust saobraćaj, industrija, građevinski radovi, sagorevanja otpada na otvore-

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POLYCYCLIC AROMATIC HYDROCARBONS, THEIR URINARY METABOLITES AND HEALTH

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SUMMARY

The World Health Organization (WHO) stated as one of its conclusions that air pollution is a leading environmental health risk. Polycyclic aromatic hydrocarbons (PAHs) are well-known carcinogens (above five hundred compounds) that cause lung and skin cancer, especially in occupationally exposed workers. By significantly reducing emissions from modern combustion plants, traffic control, and strict smoking bans in public places, PAHs exposure can be reduced. PAH exposure ought to be better investigated, especially in the field of mass biomonitoring of the urinary concentrations of their major metabolites. Such biomonitoring ought to integrate exposures to chemical carcinogens from different sources (air, water, food, consumer products, professional procedures, etc.), as well as exposure to chemical noxae through the respiratory tract by (inhalation), digestive tract (ingestion), or through the skin. Analysis of the concentration of main PAHs metabolites in urine must be done with highly sophisticated equipment for a valid database to be obtained. The data thus obtained are necessary for risk assessment and health policymaking in order to reduce exposure to chemical carcinogens.

Key words: polycyclic aromatic hydrocarbons, chemical noxae, pollution

Introduction

According to the World Health Organization (WHO), air pollution is one of the greatest public health problems (1), which is confirmed by the fact that more than 90% of the world's population lives in regions where air quality is below the norms estimated by the WHO. Air pollution is caused by particles, as well as by toxic chemicals (1). Due to the above-mentioned reason, biomonitoring is of great importance, that is, the assessment of human exposure to chemicals (2). One of the most important chemical air pollutants are polycyclic aromatic hydrocarbons (PAHs) (Table 1), they are immunotoxic, can cause cancers and atherosclerosis, and have teratogenic effects (1,3). Numerous studies have shown that PAHs are mostly associated with the appearance of skin and lung cancer (3,4). It is estimated that by 2025 air pollution will be the main cause of early deaths (3,5). Water is most frequently polluted by industrial and communal waters that also pollute the soil. The soil is additionally contaminated by solid communal waste, forest fires, volcanic activity, industrial waste disposal, etc. This review article aims to analyze the ubiquity of PAHs in the environment, metabolism after penetration into the human body, and the possibility of reducing pollution with these compounds and preventing human disease.

The ubiquity of polycyclic aromatic hydrocarbons

PAHs are persistent organic compounds that consist of two or more condensed aromatic rings. They are present in water, air, and soil. They originate from the incomplete combustion of organic matter and become the main source of atmospheric pollution (6). PAHs may originate from natural or anthropogenic activities. The natural ways for PAHs to reach the atmosphere are volcanic eruptions and forest fires. However, the most common anthropogenic activities that lead to the appearance of PAHs are dense traffic, industry, nom, grejanje domaćinstava fosilnim gorivima, spaljivanje bolničkog medicinskog otpada, duvanski dim, itd. (7,8).

U duvanskom dimu identifikovano je preko 500 različitih PAU, a najčešće su prisutni naftalen, fluoren i fenantren (9). Interesantno je da korišćenje dizel generatora za snabdevanje električnom energijom u Bejrutu, Bagdadu i Nju Delhiju doprinose da je kod nepušača srednja vrednosti 1-hidroksipirena (engl. *1-hydroxypyrene*) dva puta veća nego kod pušača u Sjedinjenim Američkim Državama, a 1,5 puta veća nego kod pušača u Italiji (10). Inače, 1-hidroksipiren je glavni urinarni metabolit PAU i najvažniji za njihov biomonitoring. Kina i Indija imaju najveću godišnju emisiju PAU usled sagorevanja fosilnih goriva, saobraćaja i sagorevanja duvana koja iznosi od 67.000 tona do 106.000 tona. Mnogo manja emisija je zabeležena u Sjedinjenim Američkim Državama, negde oko 8.500 tona PAU (11).

Takođe se smatra da je hrana potencijalno značajan izvor PAU, jer može da bude kontaminirana jedinjenjima PAU iz vode, vazduha i zemljišta (12,13). Dimljenje, grilovanje, pečenje i kuvanje hrane može još više da poveća sadržaj PAU (13). Kuvari koji više vremena provode u prženju hrane, u odnosu na one koji više kuvaju hranu, imaju veće vrednosti hidroksi-policikličnih aromatičnih ugljovodonika, ali ove razlike nisu bile statistički značajne (13). Takođe, isparenja tokom kuvanja ulja povećavaju koncentraciju 8-hidroksideoksiguanozina (engl. *8-hydroxydeoxyguanosine*) u urinu ljudi što ukazuje na oksidativno oštećenje DNK i lipidnu peroksidaciju koja favorizuje kancerogenezu (14). Mnoge osobe su svakodnevno izložene niskim vrednostima PAU, i zato kod njih postoji veliki rizik za nastanak malignoma (15). Istraživanja pokazuju da gojazne osobe imaju veći nivo PAU u odnosu na normalno uhranjene i pothranjene (8).

Metabolizam policikličnih aromatičnih ugljovodonika

U organizmu ljudi metabolizmom PAU nastaje 1-hidroksipiren (Tabela 1), koji reakcijama prelazi u1-hidroksipiren-glukuronid i 1-hidroksipiren-sulfat i kao takva jedinjenja se izlučuje urinom (3). Jedinjenje 1-hidroksipiren predstavlja najznačajniji metabolit pirena u ljudskom urinu (3,16,17). Vreme poluraspada metabolita PAU u urinu ljudi kreće se od 5 sati do 17 dana (3). Njihove vrednosti u urinu ljudi mogu biti veće usled prisustva zagađivača u vazduhu i vodi, načina ishrane i genetskih polimorfizama metaboličkih enzima (1).

Putem urina izlučuju se PAU manje molekulske mase (npr. fenantren, fluoren, antracen i naftalen), a fecesom veće molekulske mase (benzo[a]piren, koranulen, ovalen, koronen) (18,19). Urinarni metaboliti fenantrena i naftalena ukazuju na izloženost PAU iz vazduha (20-22), a 1-hidroksipiren na izloženost PAU ne samo iz vazduha, nego i na njihovo unošenje putem kože (20-22).

Usled izloženosti populacije velikom broju hemikalija, kao i sagledavanjem značaja PAU za nastanak brojnih oboljenja, započeto je sa inicijativom da se koordinira i unapredi humani biomonitoring u Evropi (23-25). Benzo[a]piren-diol-epoksid-N2deoksiguanozin je najviše proučavan produkt nastao iz PAU, konkretno iz benzo[a]pirena (26-29). Postoje interakcije između izloženosti kadmijuma, hroma i nikla i izloženosti PAU, koje utiču na povećanje oksidativnih markera u urinu (30).

Nakon prodiranja u organizam PAU se neravnomerno raspoređuju. U krvi, PAU imaju vreme poluraspada od 5 časova, u nemasnom tkivu od 22 časa, a u masnom tkivu od 400 časova (3). Vrednost 1-hidroksipirena u urinu može se posmatrati kao biomarker za trenutnu izloženost PAU i oslobađanje PAU iz masnog i nemasnog tkiva, kao i iz drugih delova tela.

Tabela 1. Policiklični aromatični ugljovodonici (PAU), njihovi intermedijarni i urinarni metaboliti

Glavni policiklični aromatični ugljovodonik (PAU)	Intermedijarni metabolit PAU	Urinarni metabolii PAU
Benzopiren	Epoksidi →Fenoli→Kinoni Benzopiren-7,8-Epoksid → → Benzopiren-7,8-diol → →Benzopiren-7,8-diol-9,10-epoksid	1-Hidroksipirenglukuronid i 1-Hidroksipirensulfat Benzopiren-7,8-diol-9,10-epoksid deoksiguanozin

construction sites, open waste burning, domestic heating with fossil fuels, hospital incineration, tobacco smoke, etc. (7,8).

More than 500 different PAHs have been identified in tobacco smoke, while the most common ones are naphthalene, fluorene, and phenanthrene (9). It is interesting that diesel generators that are used for electric supply systems in Beirut, Baghdad, and New Delhi contribute to the fact that the median levels of 1-hydroxypyrene in non-smokers are two times higher in comparison to smokers in the United States of America, and 1.5 higher in comparison to smokers in Italy (10). In addition, 1-hydroxypyrene is the main urinary metabolite of PAHs and the most important for their biomonitoring. China and India have the highest annual emission of PAHs due to the combustion of fossil fuels, traffic, and tobacco smoke, and it ranges from 67.000 tons to 106.000 tons. Lower emissions were recorded in the United States of America, around 8.500 tons of PAHs (11).

Also, food is thought to be a significant source of PAHs because it can be contaminated with PAHs from the air, soil, and water (12,13). Smoking, grilling, roasting, and boiling may increase the contents of PAHs (13). Cooks, who spent more time frying food, had higher levels of hydroxyl-polycyclic aromatic hydrocarbons than those who boiled food, but this difference was not statistically significant (13). Also, oil fumes increase the concentration of 8-hydroxydeoxyguanosine in human urine, indicating oxidative DNA damage and lipid peroxidation that favors carcinogenesis (14). Many people are exposed to low levels of PAHs every day, and therefore, they have a high risk of malignant disease occurrence (15). Research has shown that obese persons have higher PAHs levels than those who have normal weight or are underweight (8).

The metabolism of polycyclic aromatic hydrocarbons

In the human organism, PAHs metabolism produces 1-hydroxypyrene (Table 1), which becomes 1-hydroxypyrene-glucuronide and 1-hydroxypyrene-sulfate through chemical reactions and is excreted through urine in those forms (3). 1-hydroxypyrene conjugate is the most important pyrene metabolite in human urine (3,16,17). Half-lives of PAHs metabolites in urine range from 5 hours to 17 days (3). Their levels in human urine may be higher due to the higher presence of air and water pollutants, diet, and genetic polymorphisms in metabolizing enzymes (1).

PAHs of lower molecular weight are excreted via urine (e.g., phenanthrene, fluorene, anthracene, and naphthalene), while PAHs of higher molecular weight are excreted via feces (benzo[a]pyrene, corannulene, ovalene, coronene) (18,19). Urinary metabolites of phenanthrene and naphthalene indicate exposure to PAHs from the air (20-22), while 1-hydroxypyrene indicates exposure to PAHs not only through inhalation but also through dermal intake (20-22).

Due to the exposure of the population to a wide range of chemicals and the realization that PAHs are significant for the occurrence of numerous diseases, an initiative was started to coordinate and advance human biomonitoring in Europe (23-25). Benzo[a]pyrene diol epoxide N2 deoxyguanosine is the most studied PAH-derived adduct formed by Benzo[a]pyrene (26-29). There are interactions between Cd, Cr, Ni exposure, and PAHs exposure that have an effect on the urinary increase of oxidative markers (30).

After penetrating the body, PAHs are unevenly distributed. In the blood, PAHs have half-lives of 5 hours, 22 hours in the lean tissue, and 400 hours in the adipose tissue (3). The value of 1-hydroxypyrene

Table 1. Polycyclic aromatic hydrocarbons (PAHs), their intermediate metabolites and their final urinary metabolites

The main Polycyclic aromatic hydrocarbon (PAH)	Intermediate metabolites of the PAHs	Final urinary metabolites of the PAHs
Benzo[a]pyrene	Epoxides → Phenols → Quinones	1-Hydroxypyrene Glucuronides and Sulfates
	Benzo[a]pyrene-7,8-Epoxide → → Benzo[a]pyrene-7,8-diol) → → Benzo[a]pyrene-7,8- diol-9,10-epoxide)	Benzo[a]pyrene-7,8- diol-9,10-epoxide deoxyguanosine

Rezultati populacionih studija urinarnih metabolita PAU

U Nemačkoj, između 2014. i 2017. godine, sprovedeno je istraživanje na 2.294 dece i adolescenata uzrasta 3-17 godina. Rezultati istraživanja su pokazali da su ispitanici koji su koristili fosilno gorivo za grejanje ili gas za kuvanje, imali veće koncentracije urinarnih metabolita PAU (31).

U studiji sprovedenoj u Kanadi uočeno je da su koncentracije metabolita PAU u urinu u vezi sa promenama vrednosti kreatinina (32). Zapaženo je da su pušenje, godine starosti i pol značajno povezani sa koncentracijama 1-hidroksipirena u urinu.

Takođe, ishrana predstavlja najverovatniji uzrok neobjašnjene varijacije u vrednostima urinarnih metabolita PAU (33-35).

Studija sprovedana u Flandriji obuhvatila je tinejdžere uzrasta 14-15 godina sa područja gde je bila razvijena industrija i to fabrika čelika (n=197; od januara 2010. do novembra 2010.) i fabrika sekača i drobilica (n=199; od maja 2010. do februara 2011.) (15). Urinarni biomarkeri za PAU su u značajnoj meri bili povezani sa višim koncentracijama 8-hidroksideoksiguanozina (8-OhdG) u urinu. To znači da eksponiranost višim koncentracijama PAU dovodi i do oštećenja DNK, što može da se potvrdi prisustvom 8-OhdG u urinu.

Na Tajvanu je 61 vojni kuvar (koji su prosečno dnevno provodili 6,3 sati kuvajući) i 37 muškaraca kontrolne grupe (koji nisu bili kuvari i nisu bili izloženi isparenjima tokom kuvanja ulja) dali uzorke urina prvog (pre smene) i petog radnog dana (posle smene) (14). Uočeno je da su srednje vrednosti 1-hidroksipirena pre smene i posle smene bile statistički značajno veće kod vojnih kuvara. Brojne studije su ukazale da izlaganje isparenjima tokom kuvanja ulja vodi oksidativnom oštećenju DNK (36,37).

U studiji sprovedenoj u Južnoj Koreji u periodu od 2009. do 2017. analizirano je 15.125 uzoraka urina (3). Visoke vrednosti PAU otkrivene su po prvi put kod građevinaca (putara, radnika koji su pokrivali krovove), rudara i dostavljača (uličnih prodavaca, prevoznika, radnika u ribarnicama). Ukupna prosečna vrednost 1-hidroksipirena u urinu je bila manja od 1 μg/L za analiziranih 15.125 uzoraka (3). Kod neizloženih urinarna koncentracija 1-hidroksipirena bila je 0,5 μg/L.

Zaključak

Zabrana pušenja na javnim mestima i smanjenje emisije iz industrijskih postrojenja za sagorevanje fosilnih goriva i ostalih organskih materija mogu doprineti smanjenoj emisiji a samim tim i izloženosti PAU. Izloženost PAU bi trebalo i dalje istraživati, posebno u oblasti biomonitoringa koncentracije 1-hidroksipirena u urinu. Podaci biomonitoringa reflektuju aktuelni unos i/ili metabolizam praćenih hemikalija. Trenutno se koriste slučajni uzorci urina (eng. spot urine sample) da bi se odredile koncentracije PAU hidroksi metabolita. Buduće studije bi trebalo da sadrže podatke o personalnoj izloženosti PAU iz različitih izvora, čiji je unos omogućen na različite načine (udisanjem, preko kože ili ingestijom). Visoko sofisticirana oprema i instrumenti kao i neinvazivno uzorkovanje (recimo uzorkovanje urina) su neophodni za formiranje baze podataka radi procene izloženosti PAU. Biomonitoring PAU na velikom broju uzoraka u cilju validne procene eksponiranosti PAU bi omogućio bolji uvid u štetan uticaj ovih hemijskih agenasa i preduzimanje preventivnih mera za smanjenje ili eliminaciju izloženosti njima.

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in urine may be observed as a biomarker for the current exposure to PAHs and release of PAHs from the adipose and lean tissue, as well as from other body parts.

The results of studies on polycyclic aromatic hydrocarbons

In Germany, a study was conducted between 2014 and 2017, and it included 2294 children and adolescents aged 3 to 17. The results of the study showed that examinees, who used domestic fuel for heating or gas for cooking, had higher concentrations of urinary metabolites of PAHs (31).

In a study conducted in Canada, it was noticed that concentrations of PAHs metabolites in urine were connected with the changed creatinine levels (32). It was reported that tobacco smoking, age, and sex were significantly connected with the urinary concentrations of 1-hydroxypyrene.

Also, diet was the most likely cause of the unexplained variation of levels of urinary PAHs metabolites (33-35).

A study that was conducted in Flanders included teenagers aged 14-15 from the area with developed industry, that is, a stainless steel factory (n=199; from January 2010 to November 2010), and a shredder factory (n=199; from May 2010 to February 2011) (15). Urinary biomarkers for PAHs were significantly correlated with higher concentrations of 8-hydoxydeoxyguanozine (8-OhdG) in urine. This means that exposure to higher concentrations of PAHs leads to DNA damage, which can be confirmed by the presence of 8-OhdG in urine.

In Taiwan, sixty-one military cooks (daily average time spent cooking was 6.3 hours) and 37 men from the control group (who were not cooks and were not exposed to cooking oil fumes) gave urine samples on the first weekday (pre-shift) and the fifth workday (post-shift) (14). It was found that the mean value of 1-hydroxypyrene before the shift and after the shift was significantly higher in military cooks. Numerous studies have shown that exposure to cooking oil fumes leads to oxidative DNA damage (36,37).

In one study conducted in South Korea, 15125 urine samples were analyzed from 2009 to 2017 (3). High values of PAHs were found for the first time among construction workers (road pavers, roofers), miners, and deliverers (street vendors, transporters, fishery workers). The overall average value of 1-hydroxypyrene in urine was lower than 1 µg/L for the 15125 analyzed samples (3). In workers who were not exposed, the urinary concentration of 1-hydroxypyree was 0.5 µg/L.

Conclusion

The prohibition of smoking in public places and the reduction of emissions from modern plants for the combustion of fossil fuels and other organic material may contribute to the decreased emission of and exposure to PAHs. Exposure to PAHs should be investigated further, especially monitoring the observed increase in concentrations of 1-hydroxypyrene in urine. Biomonitoring data reflect the actual intake and/or metabolism of the monitored chemicals. Currently, single spot urine samples are used to determine the concentrations of PAHs hydroxyl metabolites. Future studies should provide data on the personal PAH exposure from different sources whose intake was enabled via different routes (inhalation, skin contact, and ingestion). Highly sophisticated equipment and instruments and non-invasive sampling (for example, urine sampling) are necessary for forming a database to estimate PAH exposure. Large-scale biomonitoring of PAHs for the purpose of valid assessment of PAH exposure would provide better insight into the harmful effects of these chemical agents and taking preventive measures to reduce or eliminate exposure to them.

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