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URINARNI METABOLITI KAO INDIKATORI IZLOŽENOSTI LJUDI HEMIJSKIM KARCINOGENIMA

Vladan Radosavljević[1]
[1] Institut za epidemiologiju Vojnomedicinske akademije, Beograd, Republika Srbija

SAŽETAK

Izloženost stanovništva hemijskim karcinogenima iz životne sredine prestavlja sve veći javnozdravstveni problem. Kancerogene hemikalije mogu se klasifikovati u dve grupe: genotoksične i ne-genotoksične. Genotoksična hemikalija ima potencijal da indukuje nastanak karcinoma, bilo u direktnoj interakciji sa DNK ili sa ćelijskim strukturama odgovornim za očuvanje integriteta genoma. Negenotoksična hemikalija ima potencijal da indukuje rak na indirektan način ulazeći u procese etiopatogeneze karcinoma. Dosadašnja istraživanja ukazuju da se neorganska jedinjenja arsena mogu dovesti u vezu sa nizom malignih bolesti (rakom pluća, mokraćne bešike, kože, bubrega, jetre i prostate). Neorganski arsen pretežno se nalazi u mesu, mlečnim proizvodima i žitaricama, a organski arsen (arsenobetain) u morskim plodovima, voću i povrću. Metaboliti benzena dovode se u vezu sa različitim vrstama leukemija i limfomima, benzidin sa rakom mokraćne bešike, nikl sa rakom pluća, a jedinjenja hroma sa rakom pluća, rakom nosa i nazalnih sinusa. Najveća profesionalna izloženost benzenu je u industriji (kože, elektronskih uređaja, obuće, sportske opreme), a sa benzidinom osobe mogu doći u kontakt preko robe široke potrošnje (proizvodi od kože, odeća i igračke). Najviše koncentracije nikla izmerene su u pasulju, orasima i žitaricama. Kadmijum i kadmijumova jedinjenja uzrokuju rak pluća, a utiču i na pojavu raka bubrega i prostate. Rizik od hepatocelularnog karcinoma značajno je povišen kod ispitanika sa visokim koncentracijama urinarnih metabolita aflatoksina (adukti aflatoksin-N7-gvanina). Izomeri lindana nalaze se u mlečnim proizvodima, mesu, ribi, živini, baštenskom voću, uljima i mastima, lisnatom i korenovskom povrću i šećeru, a kod ljudi uzrokuju ne-Hodgkinov limfom. Postoji pozitivna veza između konzumiranja biljaka aristolohia i pojave urotelnih karcinoma. Ne postoje skrininzi za identifikaciju osoba koje su u velikom riziku da dobiju maligno oboljenje u narednih 10 ili 20 godina. U prevenciji nastanka malignih bolesti neophodno je staviti akcenat na pronalaženje adekvatnih metoda za određivanje koncentracija urinarnih metabolita za najtoksičnije hemijske karcinogene i definisati njihove rizične vrednosti.

Ključne reči: urinarni metaboliti, hemijski karcinogeni, maligne bolesti

Uvod

Tokom Rimskog carstva uvedena je nagrada za rimsko plemstvo ukoliko rano stupe u brak i steknu potomstvo. Razlog uvođenja ove nagrade je bio čest sterilitet kod rimskog plemstva usled premazivanja/izrađivanja kuhinjskog posuđa olovom. Bilo je neophodno gotovo dva milenijuma za razumevanje uzroka ovog steriliteta.

Izloženost stanovništva štetnim hemikalijama iz okoline prerasta u sve veću zabrinutost na globalnom nivou. Postojeći skrininzi prepoznaju bolesti u ranoj fazi svog razvoja (mamografija, Papanikolau test itd). S obzirom na veliki broj različitih malignih bolesti, broj takvih skringa je mali. Međutim, ne postoje skrininzi za osobe koje su u velikom riziku da u narednih 10 ili 20 godina dobiju maligno oboljenje. Određivanjem koncentracije urinarnih metabolita hemijskih karcinogena moglo bi da pomogne u identifikovanju najviše eksponiranih osoba ili grupa osoba. Znači, nedostatak skrininga za određivanje osoba u velikom riziku za nastanak malignih bolesti, sputava preventivnu onkologiju i povećava zdravstveni rizik. Mnoge regulatorne mere su u toku ili su već primenjene za opasne hemikalije, ali bi brz, jeftin, neinvazivan, pouzdan skrining, dostupan bilo gde i bilo kada velikom delu populacije, bio koristan u prevenciji izloženosti karcinogenim hemikalijama i smanjenju zdravstvenog rizika.

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URINARY METABOLITES AS INDICATORS OF HUMAN EXPOSURE TO CHEMICAL CARCINOGENS

Vladan Radosavljevic[1]

[1] Institute of Epidemiology, Military Medical Academy, Belgrade, Republic of Serbia

SUMMARY

Population exposure to environmental chemical carcinogens is a growing public health problem. Carcinogenic chemicals may be classified into two groups: genotoxic and non-genotoxic. A genotoxic chemical has a potential to induce the development of cancer, either in direct interaction with DNA or with cell structures, which are responsible for the maintenance of genome integrity. A non-genotoxic chemical has a potential to induce cancer indirectly by entering the processes of cancer etiopathogenesis. Previous research studies indicate that inorganic arsenic compounds may be associated with various malign diseases (lung cancer, urinary bladder cancer, skin, kidney, liver and prostate cancer). Inorganic arsenic is mainly present in meat, dairy products and grains, while organic arsenic (arsenobetaine) is present in seafood, fruit and vegetables. Benzene metabolites are associated with different types of leukemias and lymphomas, benzidine with bladder cancer, nickel with lung cancer, chromium compounds with lung cancer, nose and nasal sinus cancer. The greatest occupational exposure to benzene is in industry (leather, electronic device, shoes, sports equipment), while people may come into contact with benzidine through consumer goods (leather products, clothes, toys). The highest concentrations of nickel were measured in the beans, walnuts and grains. Cadmium and cadmium compounds cause lung cancer, and influence the occurrence of renal and prostate cancer. The risk of hepatocellular carcinoma is significantly increased in respondents with high concentrations of urinary metabolites of aflatoxin (aflatoxin N7-gvanine adducts). Lindane isomers are present in dairy products, meat, fish, poultry, garden fruit, oils and lipids, leaf and root vegetables and sugar, and they cause noon-Hodgkin lymphoma. There is a positive correlation between the consumption of aristolochia plants and the occurrence of urothelial carcinoma. There are no screening examinations for the identification of persons who are at great risk of developing malign disease in the next 10 or 20 years. As for the prevention of malign diseases, it is necessary to put an accent on finding the adequate methods for determining the concentrations of urinary metabolites for the most toxic chemical carcinogens and define their risk values.

Key words: urinary metabolites, chemical carcinogens, malign diseases

Introduction

In the Roman Empire, an award was introduced to encourage marriage and having children in Roman aristocracy. The reason for this award was frequent infertility in Roman aristocracy, which was caused by their pottery that was made using a lead glaze. Two millennia were necessary to realize the cause of this infertility.

Population exposure to harmful environmental chemicals is a growing concern globally. The existing screenings recognize early stage diseases (mammography, Papanicolaou test). Having in mind a great number of different malign diseases, the number of such screenings is small. However, there are no screenings for persons who are at a higher risk of developing certain malign diseases in the next 10 or 20 years. Determining the concentration of urinary metabolites of the most toxic chemical carcinogens could help in identifying the most exposed individuals or groups. Thus, the lack of screening to determine persons at a higher risk of malign diseases restrains preventive oncology and increases the health risk. Many regulations are ongoing or they have already been applied. However, a fast, cheap, non-invasive,

Kancerogene hemikalije mogu se klasifikovati u dve grupe: genotoksične i ne-genotoksične. Genotoksična hemikalija (GTkH) ima potencijal da indukuje nastanak karcinoma, bilo u direktnoj interakciji sa DNK ili sa ćelijskim strukturama odgovornim za očuvanje integriteta genoma (2). Negenotoksična hemikalija (NGTkH) ima potencijal da indukuje rak na indirektan način ulazeći u procese etiologije i patogeneze karcinoma (2).

Prema Svetskoj zdravstvenoj organizaciji odnosno njenoj Međunarodnoj agenciji za istraživanje karcinoma, postoji 121 hemijsko jedinjenje svrstano u Grupu 1 (dokazani vrlo opasni kancerogeni). U Grupu 2A svrstano je 89 verovatnih hemijskih kancerogena, a u Grupu 2B, 318 mogućih kancerogenih (1). Kod nekih hemijskih karcinogena metabolizmom ne nastaju metaboliti koji se mogu detektovati u urinu (formaldehid, acetaldehid, etil alkohol). Izloženost ljudi najopasnijim hemijskim kancerogenima mogla bi se verovatno otkriti detektovanjem urinarnih metabolita odgovarajućim instrumentalnim metodama (indukovana kuplovana plazma, tečna hromatografija-masena spektrometrija).

Nekoliko supstanci iz Grupe 1 karcinogena su lekovi koji se trenutno koriste u kliničkoj praksi u terapiji karcinoma (ciklosporin, busulfan, tiotepa, ciklofosfamid, hlornafazin, azatioprin, etopozid u kombinaciji sa cisplatinom i bleomicinom, etopozid, hlorambucil, treosulfan, metoksalen (8-metoksipsoralen), melfalan, sredstva za alkilovanje, semustin), ali tu su i lekovi slični hormonima (estrogena terapija u postmenopauzi; estrogen-progestogena terapija menopauze (kombinovana), estrogen-progestogeni oralni kontraceptivi (kombinovani), dietilstilbestrol), i analgetičke smeše koje sadrže paracetamol (uzrok tzv. „fenacetinskih bubrega“).

Određeni industrijski procesi pri kojima se koriste ili nastaju supstance svrstane u Grupu 1 karcinogena mogu izrazito doprineti nastanku raka. Nepoznato je kako takvi procesi utiču na pojavu maligniteta (proizvodnja izopropil alkohola upotrebom jake kiseline, proizvodnja aluminijuma, proizvodnja auramina, livenje gvožđa i čelika, industrija gume, zavarivanje).

Postoje karcinogeni iz Grupe 1 koji metabolizmom ne daju jedinjenja koja mogu biti detektovana u urinu: pare jakih neorganskih kiselina (sumporne kiseline i hlorovodonične kiseline), bis (hlormetil) etar hlormetil metil etar, nitrati, nitriti i nitrozoamini. Za razliko od prethodno navedenih jedinjenja postoje i ona poput aristoholičnih kiselina, aflatoksina i nekih drugih karcinogena (u mnogo manjim razmerama) koja daju DNK adukte, koji se mogu smatrati vrstom urinarnih metabolita.

Karcinogeni entiteti navedeni kao „zagađenje vazduha na otvorenom“, „čađ“, „boje“, „emisije u zatvorenom prostoru usled sagorevanja u domaćinstvu“, „proizvodnja koksa“, „plinifikacija uglja“, „destilacija ugljenog katrana“ i „smola ugljenog katrana“ su prilično složeni procesi za analizu indikatora karcinogena u vidu urinarnih metabolita.

Metaboliti hemijskih karcinogena u urinu obično odražavaju nedavnu izloženost ljudskim kancerogenima i mogu dovesti u zabludu u slučaju povremene izloženosti (ako se meri koncentracija urinarnih metabolita neposredno ili ubrzo po zadesnoj izloženosti hemijskim karcinogenima). Zato je preporučljivo tri puta ponoviti merenje supstanci u urinu u normalnom fiziološkom stanju organizma. Izlučivanje urinarnih metabolita varira i zavisi od demografskih karakteristika, telesne težine i hidratacije organizma, pa je neophodno uzeti u obzir ove parametre pri određivanju urinarnih metabolita (3,4).

Metode

Pretraga literature je sprovedena u bazi podataka „PubMed advanced“ za period od 1. januara 2000. do 15. avgusta 2021. godine, kako bi se dobili potrebni podaci prema pretraživanim terminima. Vodeća pitanja u pregledu literature bila su izloženost ljudi hemijskim kancerogenima i mogućnost detekcije njihovih metabolita u urinu. Korišćeni su radovi koji su u celosti objavljeni u časopisima sa recenzijom, na engleskom jeziku, iz kategorija: „*Books and Documents*”, “*Clinical Trials*”, “*Meta-Analyses*”, “*Randomized Controlled Trials*”, “*Reviews*“ и „*Systematic Reviews*“. Kriterijumi za uključivanje ovih radova bile su sledeće ključne reči: hemijski kancerogeni, izloženost ljudi, prevencija raka, karcinogeni indikatori i metaboliti u urinu. Korišćena je strategija izbora članaka pretraživanje korak po korak. Prvi korak, termini u okviru za upit: hemijski kancerogeni I izloženost ljudi = 1760 referenci; Drugi korak, termini u okviru za upit: hemijski kancerogeni I izloženost ljudi I metaboliti u urinu = 29 referenci; Treći korak, termini u okviru za upit: hemijski kancerogeni I izloženost ljudi I metaboliti u urinu I kancerogeni indikatori = 6 referenci; Četvrti korak, termini u okviru za upit:

reliable screening, available to a great part of the population anywhere and anytime, would be useful in the prevention of exposure to carcinogenic chemicals and decrease of health risk.

Carcinogenic chemicals can be classified into two groups: genotoxic and non-genotoxic. A genotoxic chemical (GTcH) has a potential to induce cancer, either in a direct interaction with DNA or cell structures, which are responsible for the maintenance of genome integrity (2). A non-genotoxic chemical (NGTcH) has a potential to induce cancer indirectly by entering into processes of cancer etiology and pathogenesis (2).

According to the World Health Organization, that is, its International Agency for Cancer Research, there are 121 chemical compounds that are classified into Group 1 (proved as very dangerous carcinogens). There are 89 possible chemical carcinogens that are classified into Group 2A, while 318 possible carcinogens are in Group 2B (1). In some chemical carcinogens, metabolism does not produce metabolites that can be detected in urine (formaldehyde, acetaldehyde, ethyl alcohol). Human exposure to the most dangerous chemical carcinogens could possibly be found by detecting urinary metabolites with the help of appropriate instrumental methods (inductively coupled plasma, liquid chromatography - mass spectrometry).

Several substances from the Group 1 are currently used in the clinical practice for the treatment of cancer (cyclosporine, busulfan, thiotepa, cyclophosphamide, chlornaphazine, azathioprine, etoposide in combination with cisplatin and bleomycin, etoposide, chlorambucil, treosulfan, methoxsalen (8-methoxypsoralen), melphalan, alkylating agents, semustine), and there are also drugs which are similar to hormones (estrogen therapy in postmenopausa; estrogen-progesterone postmenopausal therapy (combined), estrogen-progesterone oral contraceptives (combined), diethylstilbestrol, and compound analgesic preparations containing paracetamol (cause of "phenacetin nephropathy").

Certain industrial processes, during which substances from Group 1 of carcinogens are used or produced, can contribute to cancer development. It is not known how these processes influence malignancy (the production of isopropyl alcohol with the help of strong acid, the production of aluminum, auramine, iron and steel casting, rubber products industry, welding). In some carcinogens from Group 1, metabolism does not produce compounds that can be detected in urine: strong inorganic acid mists (containing sulfuric acid and hydrochloric acid), bis (chloromethyl) ether, chloromethyl methyl ether, nitrates, nitrites, and nitrosamines. In contrast to previously mentioned compounds, some compounds, such as aristolochic acids, aflatoxin and other carcinogens (in smaller percentages) give DNA adducts, which can be considered as urinary metabolites.

Carcinogenic entities, which are marked as "outdoor air pollution", "carbon black dust", "paints", "indoor emissions from the household combustion", "fuel coke production", "gas production from coal", "distillation of coal tar" and "coal tar pitch", are very complex processes for the analysis of indicators of carcinogens in the form of urinary metabolites.

Metabolites of chemical carcinogens in urine usually reflect the recent exposure to human carcinogens and they can mislead us in case of periodical exposure (if the concentration of urinary metabolites is measured immediately after or soon after the accidental exposure to chemical carcinogens). Therefore, substances in urine in the normal physiological state of the body should be measured three times. The secretion of urinary metabolites varies and depends on demographic characteristics, body weight, and hydration, and therefore, all these parameters should be taken into account when urinary metabolites are determined (3,4).

Methods

The literature was searched in the data base "PubMed advanced" from 1 January 2000 to 15 August 2021, in order to get necessary data according to the searched terms. The leading questions during this search were human exposure to chemical carcinogens and the possibility of detection of their metabolites in urine. We used full-text articles that were published in the peer-reviewed scientific journals in the English language, from the categories: "Books and Documents", "Clinical Trials", "Meta-Analyses", "Randomized Controlled Trials", "Reviews" and "Systematic Reviews". Criteria for the inclusion of these studies were the following key words: chemical carcinogens, human exposure, prevention of

hemijski kancerogeni I izloženost ljudi I metaboliti u urinu I indikatori kancerogena I preventivna onkologija = 1 referenca.

Prva grupa članaka izostavljena je od daljeg razmatranja nakon uvida u naslove članaka. Nakon čitanja sažetaka članaka, druga i najbrojnija grupa članaka je izostavljena od daljeg razmatranja. Treća grupa članaka isključena je nakon uvida u metode i rezultate naučnih publikacija. Četvrta grupa članaka izostavljena je nakon analize celokupne publikacije. Konačno, peta grupa članaka nije uključena nakon upoređivanja sa ostalim člancima prema kriterijumima: naučna informativnost i naučna pouzdanost publikacija o najtoksičnijim predstavnicima hemijskih karcinogena i njihovih metabolita u urinu.

Arsen, organska jedinjenja arsena i neorganska jedinjenja arsena

Arsen i njegova neorganska jedinjenja svrstavaju se među najznačajnije hemijske karcinogene. Arsen je 20. najčešći element u zemljinoj kori i prisutan je u više od 200 mineralnih vrsta. Primarni put izlaganja arsenu za opštu populaciju je konzumiranje kontaminirane hrane ili vode. Dnevni unos arsena iz hrane i pića uglavnom se kreće u rasponu 20–300 µg/dan. Dnevni unos udisanjem može iznositi oko 20–200 ng u ruralnim područjima, 400–600 ng u gradovima bez značajne industrijske emisije arsena, oko 1 µg/dan kod nepušača, a u zagađenim područjima kod pušača i do približno 10 µg/dan (5,6). Neorganski arsen pretežno se nalazi u mesu, mlečnim proizvodima i žitaricama, a organski arsen (arsenobetain) u morskim plodovima, voću i povrću (5,6).

Metaboliti arsena u urinu, koji se koriste kao indikatori skore izloženosti, su: ukupni neorganski arsen, arsenobetain, monometilarsenska kiselina (MMAK) i dimetilarsenska kiselina (DMAK). Vlada Kanade pokrenula je 2007. godine nacionalno istraživanje na reprezentativnom uzorku opšte populacije, kod oko 30.000 stanovnika. Za ukupni neorganski arsen, MMAK i DMAK, određene su koncentracije u urinu od po 20 µgAs/L (95. percentil 15-26) (7).

Poznato je da neorganska jedinjenja arsena dovode u vezu sa rakom pluća, mokraćne bešike i kože. Takođe, primećena je povezanost između izloženosti arsenu i njegovim neorganskim jedinjenjima sa rakom bubrega, jetre i prostate.

Benzen

Benzen se uglavnom koristi za proizvodnju organskih hemikalija (stiren, fenol, cikloheksan, anilin, anhidrid maleinske kiseline, alkilbenzen i hlorobenzen), odnosno za proizvodnju lekova, boja, insekticida, deterdženata i plastike (8). Prirodno se javlja u naftnim proizvodima (sirova nafta i benzin), a dodaje se i bezolovnom benzinu. Koncentracija benzena u ovim gorivima je 1-2% (9).

Opšta populacija je najviše izložena benzenu putem duvanskog dima, vazduha u oblastima gde je gust saobraćaj, oko benzinskih pumpi, konzumiranjem zagađene vode i hrane iz područja kontaminiranih velikim količinama izduvnih gasova iz vozila ili toplana na tečna goriva (mazut). Najveća profesionalna izloženost je u industriji kože, industriji elektronskih uređaja, industriji obuće, industriji sportske opreme, pri radu s mašinama i sa kancelarijskim materijalom.

Metaboliti benzena imaju kancerogeni potencijal (10,11). Metaboliti benzena mogu uzrokovati akutnu mijeloidnu leukemiju i akutnu ne-limfocitnu leukemiju. Primećena je povezanost između izloženosti benzenu i akutne limfocitne leukemije, hronične limfocitne leukemije, multiplog mijeloma i ne-Hodgkinovog limfoma. Uobičajeni nivoi metabolita benzena u urinu su: 70–85% fenola, 5–10% hidrohinona, trans-mukonske kiseline i katehola i manje od 1% S-fenilmerkapturne kiseline (12,13).

Benzidin

Proizvodnja i upotreba benzidina u industriji boja zabeležena je u nekim zemljama u razvoju. Američka administracija za hranu i lekove ograničava sadržaj benzidina u bojama za hranu na 1 deo na milijardu (*parts per billion* - ppb) ili mg/kg. Iako se izlaganje benzidinu oralnim putem smatra malo verovatnim, ali nečistoće u sintetičkim sredstvima za bojenje mogu se metabolisati u benzidin nakon gutanja (14).

Opšta populacija može biti izložena benzidinu pri kontaktu sa robom široke potrošnje koja sadrži benzidin ili boje na bazi benzidina, poput proizvoda od kože, odeće i igračaka (15,16). Neke boje za hranu, u ograničenom broju proizvoda i na bezbednim nivoima, mogu sadržavati benzidin u tragovima (17). Benzidin uzrokuje rak mokraćne bešike, a indikatori karcinogena u urinu su benzidin i njegovi konjugati (monoacetilbenzidin).

cancer, carcinogenic indicators and metabolites in urine. Strategy step by step was used in order to choose the articles. The first step included terms in search lines: chemical carcinogens and human exposure = 1760 references; the second step included terms in search lines: chemical carcinogens and human exposure and metabolites in urine = 29 references; the third step included terms in search lines: chemical carcinogens and human exposure and metabolites in urine and carcinogenic indicators = 6 references; the fourth step included terms in search lines: chemical carcinogens and human exposure and metabolites in urine and indicators of carcinogens and preventive oncology = 1 reference.

The first group of articles was not left open for further consideration after reading the titles. After reading the abstracts, the second group, which was the most numerous group of articles, was not further considered. The third group of articles was excluded after the insight into the methods and results of scientific papers. The fourth group of articles was excluded after the analysis of the whole publication. Finally, the fifth group of articles was not included after the comparison with other articles according to the following criteria: scientific informativeness and scientific reliability of publications about the most toxic representatives of chemical carcinogens and their urinary metabolites.

Arsenic, organic and inorganic arsenic compounds

Arsenic and its inorganic compounds are classified as the most important chemical carcinogens. Arsenic is the twentieth element among the elements in the earth's crust and it is present in more than 200 mineral species. The primary path of exposure for the general population is the consumption of contaminated food or water. The daily intake of arsenic from food and beverages ranges from 20-300 µg/day. The daily intake due to inhalation can amount to 20-200 µg in rural regions, 400-600 µg in cities without significant industrial emissions of arsenic, around 1µg/day in non-smokers, and up to 10µg/day in polluted areas in smokers (5,6). Inorganic arsenic is mainly present in meat, dairy products, grains, while organic arsenic (arsenobetaine) is present in seafood, fruit and vegetables (5,6).

Metabolites of arsenic in urine, which are used as indicators of recent exposure, are the following: total inorganic arsenic, arsenobetaine, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). The government of Canada launched the study on the representative sample of general population in 2009, which included around 30000 inhabitants. Concentrations of urine of 20 µgAs/L were determined for the total inorganic arsenic, MMA and DMA (95th percentiles 15-26) (7).

It is known that inorganic arsenic compounds are associated with lung cancer, urinary bladder cancer and skin cancer. Also, the relation between the exposure to arsenic and its inorganic compounds and kidney cancer, liver cancer and prostate cancer was noticed.

Benzene

Benzene is mainly used for the production of organic chemicals (styrene, phenol, cyclohexane, aniline, anhydride of maleic acid, alkylbenzene and chlorobenzene), that is, for the production of drugs, paints, insecticides, detergents and plastic (8). In nature, it appears in petroleum products (crude oil and petrol), and it is added to unleaded fuel. The concentration of benzene in these fuels is 1-2% (9).

The general population is most exposed to benzene through tobacco smoke, air in areas with heavy traffic, around petrol stations, the consumption of polluted water and food from regions, which are contaminated by high amounts of exhaust gases from vehicles or power plants that use liquid fuels (mazut fuel oil). The greatest occupational exposure is in leather industry, industry of electronic devices, shoe industry, sporting equipment industry, when working with machines and office supplies.

Benzene metabolites have a carcinogenic potential (10,11). Metabolites of benzene cause acute myeloid leukemia and acute non-lymphocyte leukemia. The connectedness between the exposure to benzene and acute lymphocyte leukemia, chronic lymphocyte leukemia, multiple myeloma, and non-Hodgkin lymphoma was noticed. The usual levels of metabolites of benzene in urine are: 70-85% of phenol, 5-10% of hydroquinone, trans, trans-muconic acid and catechol and less than 1% of S-phenylmercapturic acid (12,13).

Polihlorobifenili (*PCB*)

U zavisnosti od položaja i broja atoma hlora, postoji 209 pojedinačnih kongenera *PCB*-a (srodnih jedinjenja). Grupu „dioksinu sličnih (DS)“ čini dvanaest *PCB*-a. *PCB* se nikada nisu koristili kao pojedinačna jedinjenja, već kao složene smeše. *Frame* i koautori i *Johnson* i koautori navode oko 130 od 209 *PCB*-a u komercijalnim proizvodima. U takvim komercijalnim proizvodima koncentracije PCB-a bile su iznad 0,05% (18,19).

Prehrambeni proizvodi se redovno analiziraju na *PCB*-e u nacionalnim (Skandinavija, Finska) i međunarodnim programima za nadzor kvaliteta hrane (Evropska agencija za bezbednost hrane – EFSA) (20,21), s fokusom analize na *PCB*-a, koji se analiziraju zajedno sa dioksinima i furanima. Jaja se obično analiziraju na PCB, s fokusom na žumance (22,23). Voće i povrće se analizira ređe od prehrambenih proizvoda koji su bogati lipidima. *PCB* se koriste i u vojne svrhe. *PCB* se uglavnom primenjuju u dielektričnim tečnostima u kondenzatorima i transformatorima. Takođe se koriste kao zaptivači, plamenotporni premazi, u mastilima, lepkovima, mikrokapsulacijama boja za kopiranje papira bez ugljenika, transportnim trakama, gumenim proizvodima, bojama, punilima pesticida, plastifikatorima, poliolefinskim nosačima katalizatora, uljima za mikroskope, površinskim premazima, izolatorima od žice i metalnim premazima (24,25). Nepravilno rukovanje elektronskim otpadom identifikovano je kao izvor zagađenja životne sredine *PCB*-ima, posebno za staru opremu (26).

PCB se mogu naći širom sveta u merljivim koncentracijama u svim komponentama životne sredine (zemljište i sedimenti, voda, vazduh), u divljim životinjama i telu svakog čoveka. Izloženost ljudi *PCB*-ima uglavnom se javlja konzumiranjem kontaminirane hrane, ali i udisanjem i dermalnom apsorpcijom. *PCB* se apsorbuje putem organskog ugljenika u zemljište, a kad se jednom upije, relativno je postojan (27). Hrana je glavni put za konzumiranje *PCB*-a .

PCB su decenijama dospevali u vazduh iz industrijskih objekata, vojnih lokacija, deponija opasnog otpada, elektrolučnih peći, spaljivanja i drugih oblika sagorevanja, mulja iz kanalizacije, građevinskog materijala, boja, zaptivača, zaptivnih masa za pod, lepkova i plastifikatora kod starijih zgrada (28,29). *PCB* iz tla, sedimenata, vazduha i vode ulazili u lanac ishrane bioakumulacijom u biljkama i životinjskim mastima. *PCB* se akumuluraju u masnim tkivima svih životinja, u svim mlečnim proizvodima koji sadrže masti i u jajima (23,30). Koncentracije *PCB*-a su obično najviše kod mesožderskih riba koje dolaze iz zagađenih voda (31). Opšta populacija je decenijama bila izložena višestrukim izvorima *PCB*-a, retko jednom komercijalnom proizvodu. Izloženost opšte populacije *PCB*-ma je verovatno moguća kod slabo razvijenih i slabo kontrolisanih afričkih i azijskih zemalja ili zadesno u drugim delovima planete.

Sagorevanjem uglavnom starog otpada i drugim procesima na visokim temperaturama nastaju *PCB*. Biljno lišće (kupus i salata) bioakumulira organske zagađivače i može služiti za biomonitoring pomoću vrlo osetljivih instrumentalnih metoda za procenu zagađenja *PCB*-om (32-34). Tokom višedecenijskog perioda neograničene primene PCB-ova upijali su se u okolne materijale, poput betona ili drveta, i kontaminirali naročito vazduh u zatvorenom prostoru (29).

Dospevanje *PCB*-a u vodu se uglavnom odigrava putem ispuštanja kućne kanalizacije, industrijskih otpadnih voda, ulične kišne kanalizacije, procednih voda sa deponija čvrstog otpada, atmosferskog taloženja i oticanja vode sa njiva i voćnjaka uglavnom obsolentnih pesticida ili njihovih jedinjenja (35,36). Tokom ranih 1990-ih, hrana je identifikovana kao glavni put čovekove izloženosti lipofilnim i postojanim *PCB*-ima (20,37,38). U evropskoj opštoj populaciji više od 90% izloženosti PCB-ima bilo je putem hrane, (mleko i mlečni proizvodi za gotovo sve grupe novorođenčadi i mališana), proizvodi od ribe i morskih plodova za većinu adolescenata, odraslih i starijih (19,39-43). Područje Baltičkog mora bilo je veoma kontaminirano *PCB*-ima, što je bilo jasno potvrđeno uzorcima masne ribe sa istočne obale Švedske (44). Jetra je glavni organ za metabolizam *PCB*-a, a zatim intestinum. PCB se dovodi u vezu sa nastankom malignog melanoma, ne-Hodžkinovog limfoma i karcinoma dojke. Visoko hlorisani PCB opstaju u telu, sa poluživotom u od 8 do 15 godina, dok manje hlorisani PCB imaju kraći poluživot (45).

Nikl i jedinjenja nikla

Nikl je široko rasprostranjen u prirodi i nalazi se u životinjama, biljkama i zemljištu. To je 24. element po zastupljenosti, koji čini oko 0,008% zemljine kore (46). Zbog otpornosti na koroziju i

Benzidine

The production and usage of benzidine in dye industry was noted in some developing countries. The Food and Drug Administration of the United States of America limited the contents of benzidine in color additives to 1 part per billion (ppb). Although exposure to benzidine via ingestion is considered highly unlikely, impurities in synthetic coloring agents may be metabolized to benzidine after ingestion (14).

The general population can be exposed to benzidine in contact with consumer goods containing benzidine or benzidine-based dyes, such as leather products, clothes and toys (15,16). Some food colorants, in the limited number of products and at safe levels, can contain trace amounts of benzidine (17). Benzidine causes urinary bladder cancer, while benzidine and its conjugates (monoacetylbenzidine) are indicators of urinary carcinogens.

Polychlorobiphenyls (PCBs)

Depending on the position and number of chlorine atoms, there are 209 congeners of PCBs (similar compounds). A group of dioxine-like (DS) PCBs is made of twelve PCBs. PCBs have never been used as separate compounds, but as complex mixtures. Frame et al. and Johnson et al. state that around 130 of 209 PCBs are in commercial products. In such commercial products, concentrations of PCBs are above 0.05% (18,19).

Food products are analyzed regularly for PCBs (Scandinavia, Finland) and international programs for the supervision of food quality (European Food Safety Agency) (20,21), while this analysis is focused on dioxine-like PCBs, which are analyzed together with dioxins and furans. Eggs are usually analyzed for PCBs, especially yolks (22,23). Fruit and vegetables are analyzed more rarely than food products that are rich in lipids. PCBs are used for military purposes, as well. Also, they are used as sealants, fire retardants, in caulks, adhesives, carbonless copy paper, transport systems, rubber products, paints, pesticide extenders, plasticizers, wire coatings and metal coatings (24,25). The improper handling of electric waste has been identified as a source of pollution with PCBs, especially for older devices (26).

PCBs can be found across the world in concentrations that can be measured in all components of the environment (soil and sediments, water, air), in wild animals and human bodies. The human exposure to PCBs mainly happens via the consumption of contaminated food, as well as via inhalation and dermal absorption. PCBs are absorbed via organic carbon in the soil, and once they are absorbed, they remain relatively stable (27). Food is the main path of ingestion of PCBs.

For decades, PCBs have reached air from industrial facilities, military locations, hazardous waste landfills, electric arc furnace, burning and other forms of combustion, mud from sewage, construction materials, dyes, sealants, sealing floor masses, adhesives, plasticizers in older buildings (28,29). PCBs from soil, sediments, air and water entered the food chain by bioaccumulation in plants and animal fats. PCBs are accumulated in adipose tissues of all animals, in all dairy products containing fats, and eggs (23,30). Concentrations of PCBs are usually the highest in carnivorous fish, which come from polluted waters (31). The general population has been exposed to the multiple sources of PCBs for decades, rarely via one commercial product. The exposure of general population to PCBs is likely in less developed and weakly controlled African and Asian countries or accidentally in other parts of the world.

PCBs appear during the combustion of mainly old waste and other processes at high temperatures. Leaves of plants (cabbage and salad) bioaccumulate organic pollutants and may be used for biomonitoring with the help of very sensitive instrumental methods for the assessment of pollution with PCB (32,34). During the unlimited application of PCBs over decades, they have been absorbed by materials, such as concrete or wood, and they have particularly contaminated the indoor air (29).

PCBs get into water via drainage systems, industrial waste waters, rainwater drains, processed water from solid waste landfills, atmospheric sedimentation, and water discharge from agricultural fields and fruit gardens with obsolete pesticides or their compounds (35,36). During the early 1990s, food was identified as the main source of human exposure to lypophilic and stable PCBs (20,37,38). In the European general population, more than 90% of exposure to PCBs was via food (milk and dairy products for almost all groups of newborns and children), fish products

na toplotu, tvrdoće i čvrstoće, nikl je deo mnogih legura, a koristi se za galvanizaciju, keramiku, pigmente i međuprodukte (katalizatori, stvaranje drugih jedinjenja nikla). Feronikal se koristi za pripremu čelika, a nerđajući čelici sadrže čak 25–30% nikla. Sagorevanje fosilnih goriva je najviše doprinelo da se nikl nađe u atmosferi, čineći 62% antropogenih emisija tokom 1980-ih (47,48). Konzumiranje nikla putem hrane i u manjoj meri pijaće vode, primarni su načini ekspozicije niklu opšte populacije (nepušači).

Najviše koncentracije nikla izmerene su u pasulju, orasima i žitaricama. Iako se koncentracije nikla razlikuju u zavisnosti od vrste hrane, prosečne vrednosti su uglavnom u opsegu od 0,01 do 0,1 µg/g. Jedinjenja nikla i metal nikl uzrokuju rak pluća, nosne šupljine i paranazalnih sinusa. Rastvorljiva jedinjenja nikla se brzo apsorbuju kroz pluća i izlučuju se urinom kao nikl. Dovode se u vezu sa karcinomom pluća, nosne šupljine i paranazalnih sinusa.

Šestovalentni hrom (Cr6+) i jedinjenja šestovalentnog hroma

Hrom (Cr6+) se retko javlja u prirodi. Do 2013. godine njegova jedinjenja su se široko koristila kao: pigment za tekstilne boje, kao i za boje uopšte, za mastila i plastiku, antikorozivna sredstva, sredstva za zaštitu drveta, za završnu obradu metala i hromiranje, za štavljenje kože, u pesticidima i kao nečistoća u cementu (49). Jedinjenja šestovalentnog hroma izazivaju rak pluća, a utiču i na pojavu karcinoma nosa i nazalnih sinusa. Njihov urinarni metabolit je hrom.

Kadmijum i jedinjenja kadmijuma

Zemljina kora u proseku sadrži 0,1–0,2 mg/kg kadmijuma, veće koncentracije se nalaze u rudama cinka, olova i bakra. Prirodni nivoi kadmijuma u okeanskoj vodi su uglavnom do 5 ng/l, pa čak i do 110 ng/l (50-52). Kadmijum se koristi za pigmente, staklo, glazure, keramiku, gumu, emajle, umetničke boje, vatromete, premaze i oplate (gvožđe, čelik, aluminijum i obojeni metali), stabilizatore za plastiku, legure obojenih metala (bakar, cink, olovo, kalaj, srebro i drugi plemeniti metali), poluprovodnike i fotonaponske uređaje, automobilske sisteme, vojnu opremu i morske/priobalne instalacije (51). Nikl-kadmijumske baterije se široko primenjuju u železničkoj i avionskoj industriji, za bežične električne alate, mobilne telefone, prenosne računare, kućne aparate i igračke (51). Kadmijum je takođe prisutan kao nečistoća u fosilnim gorivima (ugalj, nafta, gas, drvo), cementu i fosfatnim đubrivima.

Dnevni unos kadmijuma za američku populaciju putem hrane se procenjuje na 18,9 µg/dan po osobi (52). Prosečne procene nedeljnog unosa putem hrane u Evropskoj uniji 2,3 µg/kg telesne težine. Bilo kakav unos kadmijuma u organizam je neprihvatljiv, jer je izuzetno karcinogen. Kadmijum i kadmijumova jedinjenja uzrokuju rak pluća, a utiču i na pojavu raka bubrega i prostate. Urinarni metaboliti su beta 2-mikroglobulin i N-acetil-β-D-glukozaminidaza.

1,3-butadien

1,3-butadien nastaje isključivo antropogeno. Široko se koristio u proizvodnji sintetičke gume i polimera, kao važne komponente automobila, građevinskog materijala, delova računara, telekomunikacione opreme, odeće, zaštitne odeće, ambalaže i predmeta za domaćinstvo. Takođe se koristio kao međuprodukt u proizvodnji osnovnih petrohemikalija (53). Butadien je sveprisutni zagađivač životne sredine koji uglavnom potiče od proizvoda sagorevanja (emisije motornih vozila i duvanskog dima). Postoji uzročna veza između izloženosti 1,3-butadienu i nastanku leukemije, kao i ne-Hodgkinovog limfoma (54). Njegovi urinarni metaboliti su: 1,2-dihidroksibutil merkapturna kiselina i monohidroksi-3-butenil merkapturna kiselina. Ovi urinarni metaboliti su važni kao pokazatelji izloženosti 1,3-butadienu, vrlo opasnom karcinogenu.

4,4'-metilenbis (2-hloroanilin)

4,4'-metilenbis (2-hloroanilin) je veštački proizvod. Čist 4,4'-metilenbis (2-hloroanilin) se ne koristi komercijalno, osim za laboratorijske radove (55), ali 4,4'-metilenbis (2-hloroanilin) čini do 90–92% proizvedenih komercijalnih hemikalija (anilinske boje) za premaze i livene poliuretane. Opšta populacija može biti izložena anilinskim bojama ako živi na području kontaminiranom ovim jedinjenjima. Anilinske boje uzrokuju karcinom mokraćne bešike kod izloženih osoba (56). Urinarni metaboliti za 4,4'-metilenbis (2-hloroanilin) su anilini i njihovi konjugati.

and seafood for the majority of adolescents and older people (19, 39-43). The region of the Baltic Sea was very contaminated by PCBs, which was clearly confirmed by the samples of fatty fish from the Swedish east coast (44). Liver is the main organ for the metabolism of PCBs, and then intestinum. PCBs are associated with the occurrence of malign melanoma, non-Hodgkin lymphoma and breast cancer. Highly chlorinated PCBs remain in the body, with the half-life of 8 to 15 years, while less chlorinated PCBs have shorter half-life (45).

Nickel and nickel compounds

Nickel is widely present in nature, in animals, plants and soil. It is the 24th most abundant element, which makes up about 0.008% of the earth's crust (46). Due to its resistance to corrosion and heat, due to its hardness, nickel is part of many alloys, and it is used for galvanization, ceramics, pigments and intermediates (catalyzers, creation of other nickel compounds). Ferronickel is used for the preparation of steel, while stainless steel contains 20-25% of nickel. The combustion of fossil fuels contributed most to atmospheric nickel concentrations, making 62% of anthropogenic emissions in 1980s (47,48). The consumption of nickel via food, and to the lesser extent, via drinking water, is the primary way of exposure of the general population to nickel (non-smokers).

The highest concentrations of nickel have been measured in beans, walnuts and grains. Although nickel concentrations depend on the type of food, average values mainly range from 0.01 to 0.1 µg/g. Nickel compounds and metal nickel cause lung cancer, nose and paranasal sinus cancer. Soluble nickel compounds are quickly absorbed through lungs and excreted via urine as nickel. They are associated with lung cancer, nose cancer and paranasal sinus cancer.

Hexavalent chromium (Cr+) and hexavalent chromium compounds

Chromium (Cr+) rarely appears in nature. Until 2013, its compounds have been widely used as: the pigment for textile colors, as well as colors in general, for inks and plastics, anti-corrosive agents, wood preservatives, metal finishers and chromium plating, for tanning, in pesticides, and as impurities in cement (49). The hexavalent chromium compounds cause lung cancer, nose and nasal sinus cancer. Chromium is its urinary metabolite.

Cadmium and cadmium compounds

The earth's crust contains 0.1-0.2 mg/kg of cadmium on average, while higher concentrations are in the ores of zinc, lead and copper. The natural level of cadmium in the oceans ranges from 5 ŋg/L to even 110 ŋg/L (50-52). Cadmium is used for pigments, glass, glaze, ceramics, rubber, stainless products, artistic colors, fireworks, coatings and plating (iron, steel, aluminum, and colored metals), stabilizers for plastics, alloys of colored metals (copper, zinc, lead, tin, silver and other precious metals), semiconductors and photovoltaic devices, vehicle systems, art equipment and sea/coastal installations (51). Nickel-cadmium batteries are widely used in rail industry and aviation, for wireless electric tools, mobile phones, laptops, home appliances and toys (51). Cadmium is also present in impurities in fossil fuels (coal, petroleum, gas, wood), cement and phosphate fertilizers.

The daily intake of cadmium for the American population via food is estimated at 18.9 µg/day per person (52). The average weekly intake in the European Union is 2.3 µg/kg/body weight. Any intake of cadmium into the organism is not tolerable, because it is highly carcinogenic. Cadmium and cadmium compounds cause lung cancer, and it influences kidney cancer and prostate cancer. Urinary metabolites are beta 2-microglobulin and N-acetyl-ß-D-glucosaminidase.

1,3-Butadiene

1,3-butadiene is released from the anthropogenic sources. It has been widely used in the production of synthetic rubber and polymers, as important components of cars, construction materials, computer parts, telecommunication equipment, clothes, protective clothes, packaging and household utensils. Also, it has been used as an intermediate in the production of basic petrochemicals (53). Butadiene is the omnipresent environmental pollutant, which mainly originates from combustion products (emissions from vehicles and tobacco smoke). There is a causal relationship between the exposure to 1,3-butadiene and occurrence of leukemia and non-Hodgkin lymphoma (54). Its urinary

2,3,7,8-tetrahlorodibenzo-para-dioksin (2,3,7,8-*TCDD*)

2,3,7,8-tetrahlorodibenzo-para-dioksin (2,3,7,8-*TCDD*) nema komercijalne primene, ali se zbog svoje izuzetno velike karcinogenosti razmatra u onkologiji. Izvori ispuštanja 2,3,7,8-*TCDD*-a u životnu sredinu su: mesta spaljivanja (komunalni otpad, bolnički otpad, opasni otpad), izvori sagorevanja (cementne peći, drva za gorivo, dizel vozila, peći na ugalj), industrijski izvori (fabrike celuloze i papira, hemijska industrija, metalna industrija) i drugi izvori (kanalizacijski mulj, biohemijski procesi, fotolitički procesi, šumski požari, slučajna ispuštanja) (57). 2,3,7,8-*TCDD* je postojan u životnoj sredini i akumulira se u životinjskoj masti (mesu, mleku, jajima, ribi). Dioksin je potpuni karcinogen, može da podstiče pojavu bilo kog karcinoma kod ljudi, ali su dokazi najjači za nastanak raka pluća.

Polihlorovani dibenzofurani (*PCDF*)

Najznačajniji polihlorovani dibenzofuran (*PCDF*) je pentahlorodibenzofuran (*PeCDF*). *PeCDF* se može oslobađati tokom nekontrolisanog sagorevanja. Ranije se oslobađao i tokom rafiniranja i obrade metala; hemijske proizvodnje hlorofenola, *PCDF*-a, vinil-hlorida i beljenja pulpe (58,59). *PCDF* se mogu akumulirati u masnom tkivu životinja, pa su se tokom ranijih decenija najveće koncentracije *PCDF* nalazile u ribi, mesu, jajima i mlečnim proizvodima (60,61). Urinarni metaboliti za 2,3,4,7,8-pentahlorodibenzofuran su metoksi-pentahlorodibenzo furan i dimetoksi-pentahloro-bifenil.

Bis (hlorometil) etar (*BCME*) i hlorometil metil etar (*CAMEO*)

BCME se koristi u proizvodnji plastike, jonoizmenjivačkih smola i polimera (62). *BCME* se koristi kao industrijski rastvarač, vodoodbojni sastojak, sastojak jonoizmenjivačke smole i polimera (62). Izloženost ljudi *BCME* i *CAMEO* je putem udisanja i dermalnog kontakta, jer se *BCME* i *CAMEO* oslobađuju tokom proizvodnje u vazduh (63). *BCME* i *CAMEO* uzrokuju rak pluća. U biološkim tečnostima ove supstance se brzo hidrolizuju na hlorovodoničnu kiselinu, metanol i formaldehid (64), zato ne postoje njihovi pouzdani urinarni metaboliti.

1,2-dihloropropan

1,2-dihloropropan je isključivo sintetički proizvod. Koristio se u proizvodnji propilena, tetrahloridnog ugljenika i tetrahloretilena, kao i u proizvodnji sredstava za uklanjanje mrlja na tekstilu, zatim ekstrakata ulja i parafina, jedinjenja za ribanje, sredstava za čišćenje metala, odmašćivača na bazi rastvarača, lepkova i insekticida (65,66). Glavni put unosa u ljudski organizam je kroz respiratorni trakt. Koncentracije u urinu koreliraju sa koncentracijama u udahnutom vazduhu. 1,2-dihloropropan izaziva rak bilijarnog trakta (holangiokarcinom). 1,2-dihloropropan se nepromenjen izlučuje urinom.

Lindan

Komisija za ekološku saradnju (67,68) predstavila je podatke da je lindan zabranjen za upotrebu u 52 zemlje, a u 33 zemlje je ograničena ili strogo ograničena upotreba, a u 10 zemalja nije registrovan. Lindan proizvodi nekoliko proizvođača širom sveta, uglavnom u Indiji i Kini (69). Ljudi su izloženi lindanu koji se nalazi u prašini domaćinstva. U studiji sprovedenoj širom SAD lindan je izmeren u prašini domaćinstava u količini 5,85 ppm (69). U Singapuru, uzorci prašine u zatvorenom prostoru iz 31 doma sadržali su lindan u rasponu od 2,23 ng/g do 2,9 ng/g (70). Izomeri lindana nalaze se u mlečnim proizvodima, mesu, ribi, živini, baštenskom voću, uljima i mastima, lisnatom i korenovskom povrću i šećeru. Kod ljudi lindan uzrokuje ne-Hodgkinov limfom. Hlorfenoli su urinarni metaboliti lindana.

Aflatoksini

Postoji najmanje 13 različitih vrsta prirodnih aflatoksina. Aflatoksin B1 se smatra najčešćim i najmoćnijim aflatoksinom, a proizvode ga gljivice Aspergilus Flavus i Aspergilus parasiticus (71). Aspergilus Flavus je posebno zastupljen u tropskim predelima, a glavni domaćini su mu: kukuruz, kikiriki i seme pamuka, dok su orašasti plodovi ređe kontaminirani. Pojedini začini mogu ponekad sadržavati aflatoksine. Zbog trgovine poljoprivrednim proizvodima širom sveta, nijedan region sveta nije bezbedan od aflatoksina (71). Aflatoksini B1, B2, G1 i G2 mogu se sakupljati u prašini u pogonima za preradu hrane (kakao, kafa i začini) (72). Rizik od hepatocelularnog karcinoma značajno je povišen kod ispitanika sa visokim koncentracijama

metabolites are the following: 1,2-dihydroxybutyl mercapturic acid and monohydroxy-3-butenyl mercapturic acid. These urinary metabolites are important indicators of exposure to 1,3-butadiene, which is a very dangerous carcinogen.

4,4'-methylenebis (2-chloroaniline)

4,4'-methylenebis (2-chloroaniline) is a synthetic product. Pure 4,4'-methylenebis (2-chloroaniline) is not used commercially, except for laboratory work (55), but 4,4'-methylenebis (2-chloroaniline) makes 90-92% of produced commercial chemicals (aniline colors) for dyes and cast polyurethanes. The general population may be exposed to aniline colors if people live in the regions contaminated by these compounds. Aniline colors cause cancer of urinary bladder in exposed persons (56). Urinary metabolites for 4,4'-methylenebis (2-chloroaniline) are anilines and their conjugates.

2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD)

2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) has no commercial application, but due to its high carcinogenicity, it is examined in oncology. The sources of release of TCDD into the environment are: locations of combustion (municipal waste, hospital waste, hazardous waste), sources of combustion (cement furnace, wood for fuel, diesel vehicles, coal furnace), industrial sources (paper and cellulose factories, chemical industry, metal industry) and other sources (sewage mud, biochemical processes, photolytic processes, forest fires, accidental release) (57). TCDD is constant in the environment and it is accumulated in animal fats (meat, milk, eggs, fish). Dioxin is a complete carcinogen, and it can cause any cancer in humans, but the strongest proofs are for the development of lung cancer.

Polychlorinated dibenzofurans (PCDFs)

The most common polychlorinated dibenzofuran (PCDF) is pentachlorodibenzofuran (PeCDF). PeCDF can be released during the uncontrolled combustion. Previously it was released during refining and processing of metals, chemical production of chlorophenol, PCDB, vinyl chloride and bleaching of pulp (58,59). PCDF can be accumulated in the adipose tissue of animals, and therefore, during the previous decades, the highest concentrations have been in fish, meat, eggs and dairy products (60,61). Urinary metabolites for 2,3,4,7,8-pentachlorodibenzofuran are methoxy-pentachlorodibenzofuran and dimethoxy-pentachloro-biphenyl.

Bis (chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME)

BCME is used in the production of plastics, ion-exchange resins and polymers (62). CMME is used as an industrial solvent, water repellent, component of the ion-exchange resin, and polymers (62). The human exposure to BCME and CMME is via inhalation and dermal contact, because BCME and CMME are released during the production into the air (63). BCME and BCME cause lung cancer. In biological fluids, these substances are quickly hydrolyzed to hydrochloric acid, methanol and formaldehyde (64), and therefore, there are no reliable urinary metabolites.

1,2-dichloropropane

1,2-dichloropropane is a synthetic product. It has been used for the production of propylene, carbon tetrachloride and tetrachloroethylene, as well as in the production of agents used for the removal of stains on textile, then in the oil and paraffin extraction, compounds used for cleaning, agents used for cleaning of metal, degreasers based on solvents, adhesives and insecticides (65,66). It is inhaled via respiratory tract mainly. Concentrations in urine correlate with the concentrations in the inhaled air. 1,2-dichloropropane causes cancer of biliary tract (holangiocancer). 1,2-dichloropropane is excreted via urine in the unchanged form.

Lindane (hexachlorocyclohexane, γ-HCH)

The Commission for Environmental Cooperation (67,68) presented data that lindane is prohibited in 52 countries, while its usage is limited or strictly limited in 33 countries and not registered in 10 countries. Lindane is produced by a few manufacturers, mainly in India and China (69). Humans are exposed to lindane which is present in household dust. In a study conducted in the USA, lindane was measured in household dust in concentrations 5.85 ppb (ppb – parts per billion) (69). In Singapore, samples of indoor dust from 31 households contained γ-HCH and ß-HCH that

urinarnih metabolita aflatoksina (adukti aflatoksin-N7-gvanina) (73-75).

2-naftilamin

Opšta populacija može biti izložena 2-naftilaminu iz: duvanskog dima, različitih isparenja koja sadrže 2-naftilamin, nekih boja i boja za kosu kontaminiranih 2-naftilaminom i izduvnih gasova dizel goriva. 2-naftilamin izaziva rak mokraćne bešike kod ljudi. Njegovi urinarni metaboliti su: 2-naftilamin, N- (2-naftil) -hidroksilamin, bis- (2-amino1-naftil) fosfat, 2-aminobifenil i 4-aminobifenil.

4-aminobifenil

4-aminobifenil se formira tokom sagorevanja duvana (glavni izvor izloženosti za opštu populaciju). Ostali potencijalni izvori su: kozmetički aditivi u boji, boje za kosu, fungicidi koji se koriste za jabuke, isparenja od ulja i rafinirane svinjsknj masti (76). Život u blizini mesta zagađenih benzidinom može rezultirati izlaganjem 4-aminobifenilu, jer određene bakterije mogu razgraditi benzedin na 4-aminobifenil (77). Verovatno postoje i drugi izvori izlaganja iz okoline, jer su biomarkeri izvedeni iz aromatičnih amina (adukti hemoglobina, urinarni metaboliti) identifikovani kod nepušača koji nisu profesionalno izloženi ovim hemikalijama. 4-aminobifenil uzrokuje rak mokraćne bešike (56). Njegovi urinarni metaboliti su: N-hidroksi-4-aminobifenil, N-glukuronidi i 4-aminobifenil - DNK adukti.

Aristolohična kiselina

Aristolohična kiselina I i II su alkaloidne komponente iz brojnih vrsta porodice Aristolochiaceae (Aristolochia, Asarum) (71). Koristile su se u tabletama za mršavljenje i u razvijenim zemljama su zabranjene. Ali, biljke su sveprisutne u svetu i uzrokuju fibrozu i otkazivanje bubrega (hronična bolest) sa fatalnim ishodima (nefropatija kineskog bilja). Postoji pozitivan odnos između konzumiranja biljaka aristolohia i pojave urotelnih karcinoma. U uzorcima urotela kod svih pacijenata sa urotelijskim karcinomom pronađeni su DNK adukti aristolohične kiseline (71). Njihovi urinarni metaboliti su urinarni DNK adukti aristolohične kiseline (71).

Etilen oksid

Etilen oksid se koristi kao osnovna supstanca za proizvodnju važnih derivata kao što su: di-, tri- i poli- (etilen) glikoli, celuloza i poli- (propilen) glikol, etri etilen glikola, etanol-amini, alkoholi i masni amini, alkil fenoli. Veoma malo etilen oksid se koristi direktno u gasovitom obliku kao sredstvo za sterilizaciju, fumigant i insekticid (sam ili u smeši sa azotom, ugljen-dioksidom ili dihlorofluorometanom). On se koristi za sterilizaciju lekova, bolničke opreme, medicinskih predmeta za višekratnu upotrebu, ambalažnog materijala, hrane, knjiga, muzejskih predmeta, naučne opreme, odeće, krzna, vagona, aviona i košnica. Postoji uzročno-posledična veza između izloženosti etilen oksidu i pojave limfnog i hematopoetskog karcinoma (ne-Hodgkinov limfom, multipli mijelom i hronična limfocitna leukemija) i raka dojke kod ljudi (54). Njegovi urinarni metaboliti su: S-(2-hidroksietil) glutation i N-acetil-S-(2-hidroksietil)-L-cistein [hidroksietil merkapturna kiselina (HEMA)] - konjugati sa glutationom, kao i etilen glikol (54).

Zaključak

Većina ljudi ne zna koliki broj kancerogenih hemikalija i u kojoj meri dospeva svakodnevno u organizam čoveka. Karcinomi su uglavnom multikauzalne bolesti, ali kod postojanja intenzivne izloženosti prethodno pomenutim hemijskim karcinogenima, vrlo verovatno da su upravo te hemikalije i glavni etiološki faktori. Nažalost, mnogi od ovih karcinogena imaju kumulativni efekat. Nije moguće eliminisati kancerogene materije iz našeg života, ali možemo unaprediti njihovo otkrivanje u organizmu ljudi i na taj način redukovati ili eliminisati njihovo prisustvo u životnom okruženju. To je zadatak preventivne onkologije.

Savremene metode poput tečne hromatografije visokih performansi mogu otkriti oko nekoliko hiljada različitih jedinjenja u ljudskom urinu. Ali ova i slične metode zahtevaju posebne laboratorijske uslove, toksikološke laboratorije, obučeno osoblje, specijaliste toksikološke hemije i izuzetno su skupe. Urinarni metaboliti karcinogena mogu se otkriti kvalitativnim i kvantitativnim analizama, koje bi trebale biti razvijene tako da sa sigurnošću predstavljaju biomarkere ekspozicije hemijskim karcinogenima.

ranged from 2.23 ηg/g to 2.9 ηg/g (70). LIndane isomers are present in dairy products, meat, fish, poultry, fruit, oils and fats, leaf and root vegetables and sugar. In humans, lindane causes non-Hodgkin lymphoma. Chlorophenols are urinary metabolites of lindane.

Aflatoxins

There are at least 13 different species of natural aflatoxins. Aflatoxin B1 is deemed to be the most common and most powerful aflatoxin. It is produced by the fungus Aspergillus Flavus and Aspergillus Parasiticus (71). Aspergillus Flavus is present in tropical regions, while its main hosts are: corn, peanuts, and cotton seeds, while nuts are more rarely contaminated. Certain spices may contain aflatoxins. Due to the agricultural products trade around the world, there is no region in the world which is safe (71). Aflatoxins B1, B2, G1 and G2 can be present in the dust in food processing industry (cacao, coffee, spices) (72). The risk of hepatocellular carcinoma is significantly higher in respondents with high concentrations of urinary metabolites of aflatoxin (aflatoxin-N7-gvanine adducts) (73,75).

2-Naphthylamine (2-NA)

The general population may be exposed to 2-NA from: tobacco smoke, steams that contain 2-NA, some colors and hair dyes contaminated by 2-NA, and exhaust gas of diesel fuels. 2-Naphthylamine causes urinary bladder cancer in humans. Its urinary metabolites are: 2-Naphthylamine, N-(2-naphthyl)-hydroxilamine, bis- (2-aminol-naphthyl) phosphate, 2-aminobiphenyl, and 4-aminobiphenil.

4-aminobiphenyl

4-aminobiphenyl is formed during the combustion of tobacco (the main source of exposure for the general population). Other potential sources are: cosmetic additives in colors, hair dyes, fungicides that are used for apples, steams from oils and refined lard (76). Living near the place, which is contaminated by benzidine, may result in the exposure to 4-aminobiphenyl, because certain bacteria can dissolve benzedine to 4-aminobiphenyl (77). Probably there are other sources of environmental exposure, because biomarkers that are derived from aromatic amines (hemoglobin adducts, urinary metabolites) have been identified in non-smokers, who have not been exposed to these chemicals professionally. 4-aminobiphenyl causes urinary bladder cancer (56). Its urinary metabolites are the following: N-hydroxy-4-aminobiphenyl, N-glucuronides and 4-aminobiphenyl-DNA adducts.

Aristolochic acid

Aristolochic acids I and II are alkaloid components from numerous species from the family Aristolochiaceae (Aristolochia, Asarum) (71). They were used in weight loss pills and they were prohibited in developed countries. However, these plants are omnipresent in the world and they cause fibrosis, and kidney failure (chronic disease) with fatal outcomes (Chinese herbs nephropathy). There is a positive relationship between the consumption of aristolochia plants and the development of urothelial carcinoma. In the samples of urothelia in all patients with urothelial carcinoma, DNA adducts of aristolochic acid were found (71). Their urinary metabolites are urinary DNA adducts of aristolochic acid (71).

Etylene oxide

Etylene oxide is used as the main substance for the production of important derivatives, such as di-, tri- and poly- (ethylene) glycols, ethers of ethylene glycol, ethanol amines, alcohol and fatty amines, alkyl phenols. Ethylene oxide is barely used directly in the gaseous state as an agent for sterilization, fumigant and insecticide (alone or in mixture with nitrogen, carbon dioxide or dichloromethane). It is used for the sterilization of drugs, hospital equipment, reusable medical devices, scientific equipment, clothes, fur, railroad cars, planes and beehives. There is a causal relationship between the exposure to ethylene oxide and the development of lymphoma and hematopoietic carcinoma (non-Hodgkin lymphoma, multiple myeloma, chronic lymphocyte leukemia) and breast cancer (54). Its urinary metabolites are: S-(2-hydroxyethyl) glutation and N-acetyl-S-(2-hydroxyethyl)-L-cysteine [hydroxyethyl mercapturic acid (HEMA)] – conjugates with glutation, as well as ethyl glycol (54).

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Conclusion

The majority of people does not know how many carcinogenic chemicals, and to what extent, enter the human organism every day. Cancers are mainly multicausal diseases, but in case of intense exposure to the previously mentioned chemical carcinogens, it is very likely that these chemicals are the main etiological factors. Unfortunately, many of these carcinogens have a cumulative effect. It is not possible to eliminate carcinogenic substances from our lives, but we can improve their detection in the human organism and thus, reduce or eliminate their presence in the environment. This is a task of preventive oncology.

Contemporary methods such as high performance liquid chromatography can detect a few thousands of different compounds in human urine. However, this and similar methods demand special laboratory conditions, toxicology laboratories, trained personnel, toxicology specialists and they are very expensive. Urinary metabolites of carcinogens may be detected with the help of qualitative and quantitative analyses, which should be developed to represent biomarkers of exposure to chemical carcinogens.

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Autor za korespondenciju: Dr Vladan Radosavljević, Institut za epidemiologiju Vojnomedicinske akademije, Crnotravska 17, 11000 Beograd, Republika Srbija; e-mail: vladanr4@gmail.com

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Corresponding author: Dr Vladan Radosavljević, Institute of Epidemiology Military Medical Academy, Crnotravska 17, 11000 Belgrade, Republic of Serbia; e-mail: vladanr4@gmail.co