https://doi.org/10.31925/farmacia.2023.5.4 **ORIGINAL ARTICLE**

A PILOT STUDY ON FORMALDEHYDE EXPOSURE RISKS OF BAKERY WORKERS

ANA-MARIA VLĂSCEANU [1#], CAROLINA NEGREI [1]*, ANNE-MARIE CIOBANU [2#], ADRIAN COSMIN ROȘCA [3#], DANIELA GRĂDINARU [4], ANCA UNGURIANU [4], DANIELA BACONI [1]

[1]*Department of Toxicology, "Carol Davila" University of Medicine and Pharmacy, 37 Dionisie Lupu Street, 020021, Bucharest, Romania*
[2]*Department of Drug Control, "Carol Davila" University of Medicine and Pharmacy, 37 Dionisie Lupu Street, 020021, Bucharest, Romania*
[2]*Department of Drug Analysis, Biopharmacy and Biological Medicines, "Ovidius" University of Constanța, 6 Căp. Av. Al. Șerbănescu Street, 900470, Constanța, Romania*
[4]*Department of Biochemistry, "Carol Davila" University of Medicine and Pharmacy, 37 Dionisie Lupu Street, 020021, Bucharest, Romania*

**corresponding author: negrei.carolina@umfcd.ro*
#Authors with equal contribution.

Manuscript received: July 2023

Abstract

This study is intended to explore the impacts of formaldehyde (FA) on human health, the use and sources of FA exposure, and the regulations governing acceptable levels of FA in various products across various regions globally. The objective of this pilot study is to evaluate the risk of human FA exposure in traditional bakery units. The study group consisted of 46 subjects working in various areas: the production area (leavening, baking area, storage area), the area where bakery products are sold to customers and the delivery area to stores. The control group consists of 8 non-exposed, non-smokers subjects. Demographic, medical and anthropometric data were collected based on a questionary and the urinary levels of FA were evaluated as a biomarker of exposure. No statistically significant differences regarding the anthropometric and medical parameters of exposed workers and control group were obtained. The highest levels of FA were recorded in smokers working in the fermentation area. The results indicate statistically significant differences of FA levels between the workers in the processing areas and the control group. Likewise, the concentration of FA in the urine of the workers in the processing areas is significantly different compared to the workers in the administrative area. Overall, the measurements have substantiated the occurrence of FA emissions within bakeries, particularly at specific stages of the operational procedures, such as the leavening process.

Rezumat

Această cercetare explorează impactul formaldehidei (FA) asupra sănătății umane, utilizarea și sursele de expunere la FA, dar și reglementările care guvernează nivelurile acceptate de FA în diferite produse din diferite regiuni la nivel global. Obiectivul acestui studiu pilot este de a evalua riscul expunerii umane la FA în sectoarele de producție ale brutăriilor tradiționale. Grupul de studiu a fost format din 46 de subiecți care au lucrat în diverse domenii: zona de producție (zona de dospire, zona de coacere, zona de depozitare), zona în care produsele de panificație sunt vândute clienților și zona de livrare către magazine. Grupul de control este format din 8 subiecți neexpuși. Datele demografice, medicale și antropometrice au fost colectate pe baza unui chestionar, iar nivelurile urinare de formaldehidă au fost evaluate ca biomarker de expunere. Nu s-au obținut diferențe semnificative statistic în ceea ce privește parametrii antropometrici și medicali ai lucrătorilor expuși și ai grupului control. Cele mai ridicate niveluri de FA au fost înregistrate la afumătorii care lucrează în zona de dospire. Rezultatele indică diferențe semnificative statistic ale nivelurilor de FA între lucrătorii din zonele de prelucrare și grupul de control. De asemenea, concentrația de FA în urina lucrătorilor din zonele de prelucrare este semnificativ diferită față de lucrătorii din zona administrativă. În ansamblu, măsurătorile au fundamentat apariția emisiilor de FA în brutării, în special în etapele specifice ale procedurilor operaționale, cum ar fi procesul de dospire.

Keywords: formaldehyde, exposure, smokers, bakery workers, bakeries, health risks.

Introduction

Formaldehyde (FA) is a crucial molecule for the world economy, utilized in building, textiles, paper, plastics and chemical industries [17]. Recent data showed global FA output at 51.8 million metric tons, with China producing 40% of FA worldwide [17]. United States of America, Germany, India, Japan and Brazil are also other large-scale producers [39]. Environmental sources of FA are forest fires and volcanic activity [39].

In multiple uses, FA is used directly in an aqueous solution (*formalin*) as a disinfectant and preservative. As a natural byproduct of metabolism, FA can be found in many different foods that are naturally

occurring, such as fruits, vegetables, meats, fish, crustaceans and dry mushrooms [34]. However, it can also be added to some food products as a preservative [18]. FA can appear in several sources other than food materials. Some sources include building materials such as plywood, particleboard and MDF, household products, such as cleaning agents, disinfectants and air fresheners or some essential oils from aromatic plants with antimicrobial activity [7, 21]. FA can also be released when cosmetic items such as nail polish and hair straightening products contain FA-releasing ingredients. Another source of FA is tobacco smoke, as in its composition there is a vast array of around 4700 distinct chemical components and within this category are aldehydes, specifically formaldehyde, propionaldehyde, butyraldehyde, acetaldehyde, acrolein and crotonaldehyde [14, 39]. In comparison to individuals who do not smoke, the act of smoking of a single cigarette result in a 3.5-fold elevation in the concentration of aldehydes in the saliva. Following the consumption of at least ten cigarettes per day, a notable twofold elevation in the concentration of these chemicals was seen in the saliva [14]. In addition, the aerosol produced by e-cigarettes, much like that of traditional cigarettes, also contains reactive aldehydes such as acrolein, acetaldehyde and formaldehyde.

FA can be also produced in food while cooking, as many foods undergo the Maillard reaction. Cooking temperature, time and food moisture affect the Maillard reaction and FA levels in food increase with cooking temperature and time [31]. Therefore, FA can occur when bread is baked [23]. Significant effects on FA release are exerted on the production of flavouring substances in bakery depending on the type of flour, cereals used, processing phases and preparation method. During the investigation of a case of nasopharyngeal cancer in a subject who had always worked in a bakery in Tuscany (Italy), a previously unknown exposure was discovered: the release of FA during the fermentation and baking of bread [3]. In one research, a dependable and precise testing methodology was introduced for the purpose of monitoring FA levels in dairy products. The primary rationale behind employing this testing methodology stems from the significant toxicological impacts of FA on human health when ingested through food consumption [12]. Another method for detection of FA in foods is HPTLC (high performance thin layer chromatography). This method is used to efficiently and economically determine the levels of FA in milk samples [11]. The HPTLC method possesses significant advantages in terms of cost-effectiveness and flexibility. It necessitates very small quantities of solvents, resulting in minimum environmental damage [33, 35].

FA can cause skin irritation, sensitization, allergic responses and respiratory issues. FA is banned in some countries and limited in others to reduce risk [23]. According to the harmonized classification and labelling approved by the European Union, FA is toxic if swallowed, is toxic in skin contact, causes severe skin burns and eye damage, is toxic if inhaled, may cause cancer, is suspected of causing genetic defects, and may cause allergic skin reactions [13].

FA's frequent use raises health concerns as this molecule has an important sensitizing effect based on its ability to interact with proteins. Asthma is one of the problems associated with the sensitizing potential [17, 23]. Long-term FA exposure, particularly at work, has been linked to degenerative diseases, upper and lower airway irritation, cough, wheezing, body sores, chest problems, abdominal issues and appetite loss [17]. Long-term occupational FA exposure can result in pharyngeal congestion, chronic pharyngitis, chronic rhinitis, loss of olfactory function, lacrimation and corneal problems, heartburn, tremor, lethargy and other symptoms [10]. A variety of illnesses could be brought on by FA's ability to alter micro-RNA and gene expression patterns [12].

Neurasthenia symptoms from FA exposure include headaches, dizziness, insomnia and memory loss. According to research, exposure to FA increased headache and dizziness by 30% to 60% [29].

Exposure to FA was shown to increase lung damage, minor airway anomalies and pulmonary ventilation resistance [18].

Some studies indicate that FA exposure can cause a gradual decline of WBC (white blood cells), platelets and Hb counts [15, 21].

The DNA and chromosomes of human peripheral blood cells can be harmed by FA resulting in geno-toxicity, particularly once biotransformation capability is reached [4, 38]. According to Health Canada and WHO (World Health Organization), FA is only mildly genotoxic, with most effects manifesting *in vivo* in cells from tissues or organs following initial contact [1].

FA has been identified as a human carcinogen, and its correlation with nasopharyngeal cancer and leukaemia has been documented in numerous epidemiological investigations [28, 30, 32]. In 2004, International Agency for Research on Cancer (IARC) has classified formaldehyde as group I carcinogen with sufficient evidence for nasopharyngeal carcinoma [9, 17, 20, 27]. A funeral industry case-control research connected FA to myeloid leukaemia mortality [39].

Recent evidence indicate that genetic factors could be involved in the toxicity of FA. Nowadays it is recognized that aldehyde dehydrogenase 2 (ALDH2) metabolizes reactive aldehydes reducing their toxicity. The presence of the genetic variant ALDH2*2 significantly reduces the ability to detoxify reactive aldehydes in humans [31]. Therefore, an increased health risk for diseases such as cancer or cardio-vascular disease could exist with frequent exposure to aldehydes, in case of inefficient aldehyde metabolism.

The analysis of a limited number of pollutants is conducted in relation to a specific phenotype, employing a hypothesis-driven approach to comprehend the connections between exposure and disease [24].

The negative health impact of FA exposure is becoming an increasing health issue, necessitating further research and mitigation as the FA industry expands globally to support economic growth and it affects millions of people [29].

The present study aims to evaluate the FA exposure in traditional occupational sectors such as bakeries and to compare the risk of FA exposure depending on the specific stages of the operational procedures. The influence of smoking habit of the exposed subjects was also evaluated.

Materials and Methods

Subjects

The study group consists of 46 subjects working in bakeries, in various areas: production area (leavening area, baking area, storage area) and administrative areas such as the area where bakery products are sold to customers, the delivery area to stores. Bakeries were from three Romanian areas, and samples were collected over the period April - May 2023. The control group consisted of 8 non-smoking subjects.

All individuals who agreed to participate in the study were fully informed about the study and each subject signed an informed consent form prior to the study. The study was conducted in accordance with the Declaration of Helsinki.

Sample collection

The urine samples were collected in sterile poly-ethylene containers (50 mL) and frozen at -20°C until analysis.

Demographic, medical and anthropometric data

Simultaneously with the collection of urine samples, demographic, medical and anthropometric data were recorded from participants using a pre-designed questionnaire, including the following items: sex, age, BMI, weight, height, the presence of allergies, general medical history, prescription usage, smoking and dietary habits. Systolic blood pressure (BP), diastolic BP, hearth rate, blood oxygen saturation were measured for each subject.

Determination of FA concentrations in urine samples

The analysis was performed with Formaldehyde assay kit (catalogue number MAK131, Sigma-Aldrich), where formaldehyde is derivatized with aceto-acetanilide in the presence of ammonia resulting in a fluorescent ($\lambda ex = 370$, $\lambda em = 470$ nm) product, proportional to the FA present in samples.

Statistical analysis

We used the Statistical Package for Social Sciences software (SPSS, version 15, 115 Chicago, IL, USA). Results are presented as mean ± standard deviation (SD). Comparison between groups was performed using Student's unpaired t-test. The level of significance was set at 0.05.

Results and Discussion

Two distinctive groups of subjects were established according to the working place: bakery workers (n = 24) and administrative or managerial workers (n = 22). Non-smoker and smoker categories were revealed both the group within the group of bakery and administrative workers, while the control group consists of non-smoker subjects.

The studied sample population was homogenous as regards the age or BMI (Table I). Following the analysis of the cardiovascular parameters, it was observed that the highest values of hearth rate were recorded among smokers and workers in the administrative area. At the same time, the BP values tend to be at the limit of the high levels for the administrative workers. Regarding the blood oxygen saturation level, the lowest values were observed among smokers and administrative workers.

Table I

Demographic, anthropometric, behavioral and clinical characteristics, recorded in study subjects selected from bakery and administrative workers *vs.* control group

Variable	Control group (n = 8)	Smokers (n = 33)	Non-smokers (n = 13)	Bakery workers (n = 24)	Administrative workers (n = 22)
Age, years	43.63 ± 7.52	46.6 ± 9.48	45.04 ± 9.48	47.12 ± 5.69	46.95 ± 9.39
Weight, kg	68.5 ± 15.24	71.86 ± 8.72	67.61 ± 14.08	69.12 ± 11.89	71.09 ± 9.46
Height, cm	161.09 ± 6.86	166 ± 6.28	163.66 ± 7.54	166.12 ± 6.58	165.45 ± 7.01
BMI, kg/m^2	28 ± 10.32	26 ± 2.76	26 ± 7.47	25 ± 3.81	26 ± 3.12
Systolic BP, mmHg	133.4 ± 11.8	130.4 ± 21.14	129.22 ± 13.11	121.37 ± 16.7	137.27 ± 17.63
Diastolic BP, mmHg	73.3 ± 6.1	79.86 ± 5.91	76.11 ± 5.91	77.91 ± 10.19	80.63 ± 10.92
Heart rate	72.54 ± 4.65	79.86 ± 12.52	69.11 ± 5.07	70.62 ± 10.12	77.59 ± 13
Blood Oxygen saturation	96.9 ± 4.65	95.7 ± 1.7	97.11 ± 1.02	97 ± 1.02	95.4 ± 1.99
Allergy	4/8	6/33	4/13	3/24	6/22

Data are presented as means ± SD (standard deviations); n = number of subjects

The concentration of FA ranged from 16.01 μg/L to 46.13 μg/L, indicating a significant interindividual variations.

Table II presents the descriptive data on the level of urinary FA across various categories. The highest

values (means ± SD) among the analysed groups were recorded among smokers and bakery workers.
The difference of urinary FA level was significantly greater ($p < 0.001$) in the smokers (33.2 ± 8.24 μg /L), than in the control group (19.38 ± 2.94 μg /L). Also, statistically significant differences were also recorded in the case of non-smokers bakery workers (27.57 ± 10.05 μg /L), compared to the control group (19.38 ± 2.94 μg /L). The urinary concentration of FA was similar in smokers and non-smokers bakery workers, and both were significantly different form control group. These results indicate an exposure to FA, both among smokers and among non-smoking bakery workers. The results suggests that there are no significant differences between smokers and non-smokers bakery workers, regarding the levels of FA in urine while both differ significant from the control group.

Table II

Urinary FA levels, recorded in study subjects selected from bakery workers, administrative workers *vs*. control group

Variable	Control group (n = 8)	Smokers (n = 33)	Non-smokers (n = 13)	Bakery workers (n = 24)	Administrative workers (n = 22)	All subjects (n = 54)
Urinary formaldehyde level, μg /L	19.38 ± 2.94	33.2 ± 8.24$^{*\#}$	27.57 ± 10.05*	37.78 ± 7.49*§	27.84 ± 6.49*§	30.39 ± 9.49

Data are presented as means ± SD (standard deviations); n = number of subjects; * $p < 0.001$ *vs*. Control Group $^{\#}$ $p < 0.05$ (smokers *vs*. non-smokers); § $p < 0.001$ (bakery workers *vs*. administrative workers)

The occupational exposure to FA occurs in a variety of different sectors, such as healthcare sector, the wood processing industry and other industry sectors. A recent study confirmed the release of aldehydes (FA and acetaldehyde) in bakeries and pastry industries, especially in some phases of the work process, such as leavening [26].
The current pilot study is the first that evaluate the FA exposure in the traditional production sectors of bakeries in Romania.
For some of the analysed parameters such as age, weight, height, body mass index, BP, the analysed groups did not register statistically significant differences.
In other studies, on smoking, it was revealed that smoking has an impact on the heart rate of young individuals who smoke, leading to an elevation in resting heart rate [25] or the effect of smoking involves an elevation in both systolic and diastolic BP, as well as an increase in heart rate and peripheral vascular resistance [11, 26].
More than half of the subjects included in the study do not suffer from allergies, a few cases were registered to be allergic to some medicines such as acetylsalicylic acid, iodine and antibiotics from the cephalosporin class.
The subject included in the study suffer from chronic diseases such as hypertension, the presence of kidney stones, hypercholesterolemia, depressive syndrome).
Most of the subjects included in the study live in a rural area, and their dietary habits consist of consuming food products obtained in their own household.
The peculiarity of the work shifts is that, for the people who work in the production area, it was imposed to work on 3 shifts, including during the night.
The presence of carbon monoxide in smoke diminishes the blood's ability to transport oxygen, hence contributing to increased strain on the heart. It is worth noting that the aforementioned risks are heightened in the presence of diabetes, hypertension, high cholesterol and glucose intolerance [25].
In case of bakery workers, the level of FA exposure can be influenced by many variables: ventilation, the size of the production rooms, the floor space, the flour type and yeast used, the temperature setting throughout the leavening process [10, 22].
The published data on the FA levels in urine as a marker for exposure to formaldehyde are limited. Some attempts were made to use the formic acid in urine as a biomarker for exposure to low levels of FA, but the conclusion was that biological monitoring of FA exposure (*via* formic acid shifts) at these low levels was not a feasible technique [16]. In contrast, a significant increase of formic acid level in FA-exposed workers compared to controls ($p < 0.05$) was shown in a study that evaluate the occupational exposure to FA of anatomy-pathology laboratory workers [20]. In other study, urinary formic acid concentrations were found to correlate strongly with occupational exposure to FA [26]. However, the use of formic acid as a biomarker of FA exposure is still considered questionable, given the poor understanding of the normal variation of formiate concentration in the urine [19].
Therefore, it is suggested that the urine FA levels could be also used as a biomarker of exposure to FA in various occupational settings. The results of our study indicate that the urine FA concentrations of bakery workers is significantly increased compared to control. No effect of smoking habits was found, in agreement with other recent studies [20].
Although the urine FA levels are limited use to evaluate the exposure to FA, recent studies indicate that urine FA levels are involved in various pathology. Therefore, Alzheimer's disease progression was correlated with urine FA levels [19], a correlation was found between urine FA and cognitive abilities in the clinical spectrum of Alzheimer's disease [36, 38], and urine

FA level was shown to be inversely correlated to mental state examination scores in senile dementia [37].

Conclusions

The results of this pilot study provided new information on the occupational exposure of bakery workers to FA and revealed no effect of smoking habits in this setting. The levels of urinary FA were increased in bakery workers compared to administrative workers and they were significantly different from the control group suggesting a significant occupational exposure to FA in traditional bakery production sectors. This exposure may have some pathogenetic significance as FA is a highly toxic compound and it is recognized as a human carcinogen. Therefore, safety issues and appropriate measures should be indicated to protect workers. The need to inform workers, the measures to reduce pollution at workplace during bread production, mainly in the leavening phase are important to reduce the exposure and to protect the worker's health.

Acknowledgement

This research was funded by Project POCU/993/6/13/154722 „Net4Science: The applied doctoral and postdoctoral research network in the fields of smart specialization Health and Bioeconomy".

Conflict of interest

The authors declare no conflict of interest.

References

1. Alvarado LMA, Richer A, Vrekoussis M, Hilboll A, Hedegaard ABK, Schneising O, Burrows JP, Unexpected long-range transport of glyoxal and formaldehyde observed from the Copernicus Sentinel-5 Precursor satellite during the 2018 Canadian wildfires. *Atm Chem Physics*, 2020; 20: 2057-2072.
2. Aprea MC, Scancarello G, Banchi B, Bozzi N, Poli C, Bartoli D, Enza Iaia T, Arena L, Farina GA, Della Libera S, Exposure to flour dust and aldehydes during bread production: Preliminary data. In Proceedings of the Atti del 32 Congresso Nazionale A.I.D.I., 24–26 June 2015; p.79 (in Italian).
3. Barbosa E, Dos Santos ALA, Peteffi GP, Schneider A, Müller D, Rovaris D, Bau CHD, Linden R, Antunes MV, Charão MF, Increase of global DNA methylation patterns in beauty salon workers exposed to low levels of formaldehyde. *Env Sci Poll Res.*, 2019; 26: 1304-1314.
4. Blejan EI, Popa DE, Costea T, Cioaca A, Olariu L, Ghica M, Gerogescu M, Stancov G, Arsene AL, The *in vitro* antimicrobial activity of some essential oils from aromatic plants. *Farmacia*, 2021; 69(2): 290-298.
5. Boeniger MF, Formate in urine as a biological indicator of formaldehyde exposure. *a review. Am Ind Hyg Assoc J.*, 1987; 48(11): 900-908.
6. Cammalleri V, Pocino RN, Marotta D, Protano C, Sinibaldi F, Simonazzi S, Petyx M, Iavicoli S, Vitali M, Occupational scenarios and exposure assessment to formaldehyde: A systematic review. Indoor Air., 2022; 32(1): e12949.
7. Chang PT, Hung PC, Tsai SW, Occupational exposures of flour dust and airborne chemicals at bakeries in Taiwan. J *Occup Environ Hyg.*, 2018; 15(8): 580-587.
8. Chen F, Wang N, Tian X, Qin Y, Su J, He R, He X, The potential diagnostic accuracy of urine formaldehyde levels in Alzheimer's disease: A systematic review and meta-analysis. *Front Aging Neurosci.*, 2022; 14: 1057059.
9. Costa S, Costa C, Madureira J, Valdiglesias V, Teixeira-Gomes A, Guedes de Pinho P, Laffon B, Teixeira JP, Occupational exposure to formaldehyde and early biomarkers of cancer risk, immunotoxicity and susceptibility. *Env Res.*, 2019, 179: 108740.
10. Delikhoon M, Fazlzadeh M, Sorooshian A, Baghani AN, Golaki M, Ashournejad Q, Barkhordari A, Characteristics and health effects of formaldehyde and acetaldehyde in an urban area in Iran. *Environ Pollut.*, 2018; 242: 938–951.
11. Drain CB, Cigarette smoking--its effects on anesthesia. *AANA J.*, 1974; 42(4): 323-325.
12. Dugheri S, Bonari A, Pompilio I, Colpo M, Mucci N, Arcangeli G, An integrated air monitoring approach for assessment of formaldehyde in the workplace. *Saf Health Work.*, 2018; 9(4): 479-485.
13. ECHA, https://echa.europa.eu/it/substance-information/-/substanceinfo/100.000.002)
14. Eschner MS, Selmani I, Groger TM, Zimmermann R, Online comprehensive two- dimensional characterization of puff-by-puff resolved cigarette smoke by hyphenation of fast gas chromatography to single-photon ionization time-of-flight mass spectrometry: quantification of hazardous volatile organic compounds. *Anal Chem.*, 2011; 83(17): 6619-6627.
15. Ge J, Yang H, Lu X, Wang S, Zhao Y, Huang J, Xi Z, Zhang L, Li R, Combined exposure to formaldehyde and PM2.5: Hematopoietic toxicity and molecular mechanism in mice. *Env Int.*, 2020; 144: 106050.
16. Gottschling LM, Beaulieu HJ, Melvin WW, Monitoring Of Formic Acid In Urine Of Humans Exposed To Low Levels Of Formaldehyde. *Am Ind Hyg Assoc J.*, 2010; 45: 19-23.
17. Guan Y, Xie C, Guo H, Yarkony DR, Neural network based quasi-diabatic representation for S0 and S1 states of formaldehyde. *J Phys Chem A.*, 2020; 124(49): 10132-10142.
18. Jinadasa BKKK, Elliott C, Jayasinghe TM, A review of the presence of formaldehyde in fish and seafood. *Food Control*, 2022; 136(6): 108882.
19. Karjalainen A, Leppänen M, Ruokolainen J, Hyttinen M, Miettinen M, Säämänen A, Pasanen P, Controlling flour dust exposure by an intervention focused on working methods in Finnish bakeries: a case study in two bakeries. *Int J Occup Saf Ergon.*, 2022; 28(3): 1948-1957
20. Liang X, Zhang J, Song W, Wang K, Zhang B, Formaldehyde exposure in indoor air from public places and its associated health risks in Kunshan City, China. *Asia Pac J Public Health.*, 2018; 30(6): 551-560.
21. Miligi L, Piro S, Airoldi C, Di Rico R, Ricci R, Paredes Alpaca RI, De Pasquale F, Veraldi A,

Ranucci A, Massari S, Marinaccio A, Stoppa G, Cenni A, Trane C, Peruzzi A, Aprea MC, Formaldehyde and Acetaldehyde Exposure in "Non-Traditional" Occupational Sectors: Bakeries and Pastry Producers. *Int J Environ Res Public Health*, 2023; 20(3):1983.

22. Mundt KA, Gallangher AE, Dell LD, Natelson E, Boffetta P, Gentry PR, Formaldehyde, hematotoxicity, and chromosomal changes. *Cancer Epidemiol Biomarkers Prev.*, 2018; 27(1): 119.
23. Naddafi K, Nabizadeh R, Rostami R, Ghaffari HR, Fazlzadeh M, Formaldehyde and acetaldehyde in the indoor air of waterpipe cafés: measuring exposures and assessing health effects. *Building and Environment*, 2019; 165: 106392.
24. Negrei C, Vlasceanu AM, Baconi DL, Exposome research: definition, scope and the need for multidisplinary research. *Farmacia*, 2023; 71(4): 655-669.
25. Papathanasiou G, Georgakopoulos D, Papageorgiou E, Zerva E, Michalis L, Kalfakakou V, Evangelou A, Effects of smoking on heart rate at rest and during exercise, and on heart rate recovery, in young adults. *Hellenic J Cardiol.*, 2013; 54(3): 168-177.
26. Parmar MP, Kaur M, Bhavanam S, Mulaka GSR, Ishfaq L, Vempati R, C MF, Kandepi HV, Er R, Sahu S, Davalgi S, A Systematic Review of the Effects of Smoking on the Cardiovascular System and General Health. *Cureus*, 2023; 15(4): e38073.
27. Peteffi GP, da Silva LB, Antunes MV, Wilhelm C, Valandro ET, Glaeser J, Kaefer D, Linden R, Evaluation of genotoxicity in workers exposed to low levels of formaldehyde in a furniture manufacturing facility. *Toxicol Ind Health*, 2016; 32(10): 1763-1773.
28. Protano C, Buomprisco G, Cammalleri V, Pocino RN, Marotta D, Simonazzi S, Cardoni F, Petyx M, Iavicoli S, Vitali M, The carcinogenic effects of formaldehyde occupational exposure: a systematic review. *Cancers*, 2021; 14(1): 165.
29. Rani R, Srivastava MM, Development and validation of HPTLC Method for the estimation of formaldehyde in milk. *Natl Acad Sci Lett.*, 2016; 39(1): 29-24.
30. Reingruber H, Pontel LB, Formaldehyde metabolism and its impact on human health. *Curr Op Tox.*, 2018; 9: 28-34.
31. Rodrigo C, The effects of cigarette smoking on anesthesia. *Anesth Prog.*, 2000; 47(4): 143-150.
32. Scarselli A, Corfiati M, Marzio DD, Iavicoli S, National Estimates of Exposure to formaldehyde in Italian Workplaces. *Ann Work Expo Health.*, 2017; 1: 33-43.
33. Sebaei AS, Gomaa AM, El-Zwahry AA, Emara EA. Determination of Formaldehyde by HPLC with Stable Precolumn Derivatization in Egyptian Dairy Products. *Int J Anal Chem.*, 2018; 2018: 2757941018.
34. Sinharoy P, McAllister SL, Vasu M, Gross ER, Environmental Aldehyde Sources and the Health Implications of Exposure. *Adv Exp Med Biol.*, 2019; 1193: 35-52.
35. Stan M, Burcea-Dragomiroiu GTA, Vasiliu A, Ginghina O, Nitescu GV, Vlasceanu AM, Ciobanu AM, Baconi DL, Screening method for the detection of dextromethorphan abuse by HPTLC; *Farmacia*, 2022; 70 (6): 1123-1131.
36. Subasi NT, Formaldehyde advantages and disadvantages: Usage areas and harmful effects on human beings. biochemical toxicology-heavy metals and nanomaterials, 2020; IntechOpen.
37. Tong Z, Zhang J, Luo W, Wang W, Li F, Li H, Luo H, Lu J, Zhou J, Wan Y, He R, Urine formaldehyde level is inversely correlated to mini mental state examination scores in senile dementia. *Neurobiol Aging.*, 2011; 32(1): 31-41.
38. Wang Y, Pan F, Xie F, He R, Guo Q, Correlation Between Urine Formaldehyde and Cognitive Abilities in the Clinical Spectrum of Alzheimer's Disease. *Front Aging Neurosci.*, 2022; 14: 820385.
39. Zhang L, Formaldehyde: exposure, toxicity and health effects. Royal Society of Chemistry, (2018a), CPI Group Ltd, UK.
40. Zhang ZF, Zhang X, Zhang XM, Liu LY, Li YF, Sun W, Indoor occurrence and health risk of formaldehyde, toluene, xylene and total volatile organic compounds derived from an extensive monitoring campaign in Harbin, a megacity of China. *Chemosphere*, 2020; 250: 126324.