



# Feasibility of Biological Monitoring of Anatomy Laboratory Staff Exposed to Formaldehyde

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## Abstract

**Background:** Formaldehyde (FA) is a reactive carcinogenic compound and is used routinely in anatomy theatres. Recently, biological monitoring is introduced as a method of choice for monitoring of exposed workers to hazardous chemicals with systemic absorption.

**Objectives:** Considering the toxicity of formaldehyde and lack of a comprehensive method for its biological monitoring, the aim of this study was to explore a new and non-invasive method for biological monitoring of formaldehyde exposure in the staffs of anatomy theatre.

**Methods:** This study was a cross-sectional investigation and the population of this study was comprised of 20 exposed staffs in an anatomy theatre in Tehran, Iran. The personal monitoring of 20 staff was carried out during the early winter, according to a method from the National Institute of Occupational Safety and Health No. 2016. Biological monitoring was conducted by measuring FA in staff's exhaled breath after termination of the work shift. The data obtained were statistically analyzed using correlation analysis.

**Results:** The mean FA personal exposure and its concentration in the exhaled breath of anatomy's staffs were  $698 \pm 34$  and  $195 \pm 17$  as ppb, respectively. Correlation of staff's personal exposures to formaldehyde with the excreted formaldehyde in their exhaled breath was statistically significant ( $P < 0.001$ ).

**Conclusions:** The present study showed that the personal exposure of staffs to the FA was higher than the permissible exposure limit. Statistically significant positive correlation of staff exposure with the content of FA in their exhaled breath indicated the potential of biological monitoring of exposed group to FA through exhaled breath.

**Keywords:** Formaldehyde, Inhalation Exposure, Exhaled Breath, Biological Monitoring

## 1. Background

Clinical symptoms of inhalation exposure to formaldehyde (FA) include eye, nose, and upper-respiratory irritation, aggravate pre-existing asthma, and depressed lung function activities (1, 2). FA is a genotoxic chemical that can cause squamous cancer of the nasal passages and cancer of nasopharyngeal regions (3). International Agency for Research on Cancer (IARC) classified FA as 'human carcinogen' (group 1) (4). FA is also an endogenous compound produced in cells and excreted through exhaled breath (5).

The U.S. Occupational Safety Health Administration (OSHA) has established the permissible exposure limit (PEL) for airborne FA at a value of 0.75 parts per million (8 h time-weighted average (TWA)); the short-term (15 min) exposure limit (STEL) is 2 ppm. The National Institute of Occupational Safety and Health (NIOSH) has also presented PEL

of 0.016 ppm (8 h TWA) and 0.1 ppm (STEL). American regulating authorities require the individuals having higher exposure to use proper respirators (6).

Concerns have been raised regarding the health of employees and students exposed to FA in the anatomy laboratories due to the vapors emitted during the dissection of cadavers in producing complaints as: unpleasant odor (68%), cough (64%), sore throat and runny nose (56%), nasal irritation and itching (52%), and eye irritation (48%) (7). However, the effects of chronic exposure of FA could be more severe than respiratory symptoms and recently higher incidence of amyotrophic lateral sclerosis (ALS) was reported as the result of FA (8). Occupational monitoring of anatomy laboratory workers to FA in the various university anatomy theaters has been reported to be a health concern; more stringent evaluations and controls in the form of a lateral exhaust ventilation system for the dissection

tables and personal protective equipment were requested (9).

Generally, biological monitoring is an accurate evaluation of occupational exposure to volatile organic compounds (10). Due to the difficulties and disadvantages of blood and urine sampling, recent approaches for assessing occupational and environmental exposure to several chemicals as well as biological monitoring have focused on exhaled breath (11, 12). There is no commonly accepted method for biological monitoring for FA (13). Several factors, including the skin absorption, age-related differences in individual uptake, behaviors of workers, poor personnel work practice, the effectiveness of personal protective equipment (PPE), and the workload will probably influence personal sampling in workplaces. Biological monitoring has been traditionally recommended as the complementary method in the evaluation of the chemical exposures (14). However, this approach is changing and biological monitoring is recommended for hazardous chemicals as the method of choice for monitoring exposure and health risk assessment (15). There are several attempts for biological monitoring of FA such as: exploring DNA-protein cross-links in workers exposed to FA (16) and sister chromatid exchange rate in the personnel with exposure to FA in the range of 0.04 to 6.9 ppm (17). In clinical monitoring of cancer patients and cigarette smokers, FA was measured in their exhaled breath (12, 18).

The results of toxicokinetic studies indicated that inhaled FA absorption in humans occurs primarily at the site of entry. The site of absorption of FA from the respiratory tract depends on a number of factors, including airway anatomy, breathing pattern, and ventilation rate (19). According to some studies, the half-life of circulating FA in the bloodstream, upon the absorption in the respiratory tract is reported about 1 minute (20). Generally, it is reported that Inhaled FA rapidly biotransforms to formate (13, 21-23). Thus, FA, in exhaled breath has been reported in the range of a few parts per billion concentrations, however, the validity of measurement methods was reported questionable (21).

## 2. Objectives

Due to the toxicity of FA and the absence of any reliable biological monitoring for FA, the objective of this study was to explore the feasibility of biological monitoring of exposed anatomy staff through the analysis of unchanged FA in their exhaled breath.

## 3. Methods

This study was conducted at an anatomy theater of an Iranian medical school during early winter. The doors of

the theater were closed when the theater was not in use. The inclusion criteria for this study were: the healthy, non-smoking population with at least one year of work history. The participants of this study included 20 anatomy staff exposed to FA and 20 library staff for checking the residual concentration of FA in the exhaled breath of non-exposed working population. Upon approval of the proposal by the Shahid Beheshti University of Medical Sciences, written consent of all participants was received according to an ethics committee form. The authors of this study observed all safety precautions during their sampling and laboratory practices.

The anatomy theater was just equipped with a general ventilation system. There were also no local ventilation systems for dissection tables. The ventilation system of the theater was off the entire time during the winter. In this study, cadavers were placed on the tables. Dissection sessions usually last for two hours.

In order to investigate the relationship between the concentration of FA in the air with its concentration in exhaled breath, demographic data such as age, work hours, work experience, and health status as well as using personal protective equipment were investigated by face-to-face interview.

Personal exposure monitoring of participants who did not use any personal protective equipment was conducted according to the method presented by NIOSH method No. 2016 (24). The personal sampling was done with a flow rate of 0.1 lit/min for the period of 2 hours using sorbent tubes (SKC Inc., USA) (silica gel coated with 2, 4 Dinitrophenylhydrazine catalog No. 119-226). Absorbed FA on the coated silica gel was extracted with HPLC grade acetonitrile (Merck Co., Germany) and analyzed by Merck-Hitachi high-performance liquid chromatography (HPLC) model D-7000 equipped with ultraviolet (UV) detector set at 360 nm. The mobile phase consisted of 45% acetonitrile and 55% water, and an injection volume of 20  $\mu$ L, and stainless steel column packed with 5  $\mu$ m C-18 (Merck KGaA, Germany). A blank was collected for each set of sampling.

Before collecting the exhaled breath for biological monitoring, all of the subjects' lungs were washed via inhalation of clean ambient air with trace FA concentration below the detection limit (23  $\mu$ g/m<sup>3</sup>) for 10 minutes. Having completed the lung wash, exhaled breath was subsequently collected in prewashed 5 liters Tedlar bags while breathing clean air. Within 2 hours after exhaling breath sampling, four liters of exhaled breath was passed through silica gel sorbent tubes coated with dinitrophenylhydrazine (DNPH) via a pump with a flow rate of about 0.1 lit/min. Absorbed FA from exhaled breath on coated silica gel was extracted and analyzed the same as described earlier for personal samples.

The merits of the method for sampling and analysis

of FA in the breathing zone, including precision (inter-day and intra-day coefficient of variations), recovery, linear range concentrations, limit of detection (LoD) and limit of quantitation (LoQ) were examined according to the method described by Mitra (25).

For examining the association between inhalation and exhalation FA in anatomy's staff, the SPSS version 18.0 software (SPSS, Chicago, IL, USA) and Pearson correlation statistical test were used.

#### 4. Results

The mean ( $\pm$  SD) of age and work history of anatomy staff was  $41.5 \pm 0.46$ ,  $15 \pm 0.36$  years, respectively.

Linear range concentration of FA analysis in breathing zone was  $300 \mu\text{g}/\text{m}^3 - 8 \text{ mg}/\text{m}^3$  ( $r^2 = 0.998$ ). The inter-day CV for FA samples ranged from 1.65% to 6.51% and intra-day CV ranged from 0.84% to 4.31%. The recovery from FA samples ranged from  $100 \pm 0.87\%$  to  $100 \pm 7\%$ . LoD and LoQ for the analytical method were 23 and 77.5 as  $\mu\text{g}/\text{m}^3$ , respectively.

The average of FA exposure and the average FA concentration in the exhaled breath of the anatomy's staff were  $698 \pm 34$  and  $195 \pm 17$  as ppb, respectively (Figure 1). The average residual FA in the exhaled breath of non-exposed librarian was 52 ppb. The positive Pearson statistical significant correlation of occupational exposure of the anatomy's staff with concentrations of FA in their exhaled breath was demonstrated (R square = 0.478 and  $P < 0.001$ ) (Figure 2).

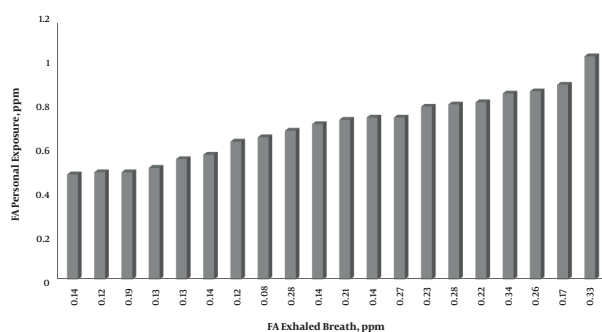


Figure 1. Personal exposure and exhaled FA in anatomy staff

#### 5. Discussion

According to the results of this study, exposure of 35% of the anatomy personnel was higher than OSHA's PEL (PEL-TWA = 750 ppb) (22). Generally, anatomy's staff exposures in this study were almost identical to their colleagues in other countries such as Japan and Portugal (26, 27).

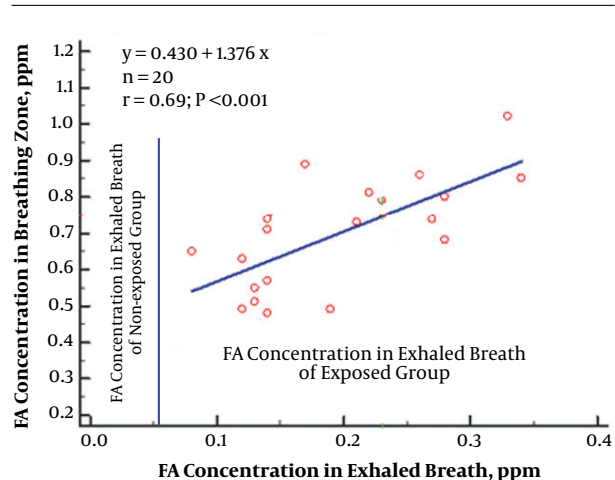


Figure 2. Correlation of subject's exposure to FA and its concentration in their exhaled breath

Some authors have expressed doubts in measuring appreciable amounts of FA in exhaled breath (23). However, in studies have reported residual FA in the exhaled breath, which was in agreement with the concentration of FA in the exhaled breath of healthy unexposed librarians in this study (11, 28). Generally, FA in exhaled breath might be due to diet, indoor air pollutants, and FA emitted from wood products (28, 29). Ebelera et al. in their study also demonstrated high concentration of FA in the cancer patient and healthy subjects in the range of 0.42 - 1.2 and 0.3 - 0.6 as ppm, respectively (30). However, other authors reported a lesser amount of FA in the exhaled breath of healthy subjects than the prior study (18, 28).

Despite all diverse results presented by the authors in this study regarding the concentration range of FA in exhaled breath, the authors of this study believe that the reason behind the conflicting results might be due to the hardship of its sampling and analysis of FA. Therefore, considering the task of validation processes of the NIOSH method No. 2016 locally in this study and statistically significant positive correlation between FA concentrations in breathing zone and FA concentrations in exhaled breath of healthy exposed subjects, measurement of FA in the exhaled breath as biomarker of exposure in healthy and non-smokers workers seemed feasible in this study. Generally, established biomarkers of exposure of FA through measuring DNA adducts and sister chromatid exchange rate in blood samples, are more complex than measuring FA through exhaled breath samples (16, 17). The method presented in this study does not require invasive sampling and elaborate analysis. However, due to the limited number of exposed in this study, a more comprehensive study is proposed.

Occupational exposure to FA could endanger the health of anatomy's staff. A new method proposed for biological monitoring of exposed population through exhaled breath could provide an alternative monitoring. However, for definite and credible results, a more thorough study with a larger population with stringent measures for limiting confounding factors is recommended.

## References

- Tang X, Bai Y, Duong A, Smith MT, Li L, Zhang L. Formaldehyde in China: Production, consumption, exposure levels, and health effects. *Environ Int.* 2009;**35**(8):1210-24. doi: [10.1016/j.envint.2009.06.002](https://doi.org/10.1016/j.envint.2009.06.002). [PubMed: [19589601](https://pubmed.ncbi.nlm.nih.gov/19589601/)].
- Vandenplas O, Fievez P, Delwiche JP, Boulanger J, Thimont J. Persistent asthma following accidental exposure to formaldehyde. *Allergy.* 2004;**59**(1):115-6. [PubMed: [14674947](https://pubmed.ncbi.nlm.nih.gov/14674947/)].
- Noisel N, Bouchard M, Carrier G. Evaluation of the health impact of lowering the formaldehyde occupational exposure limit for Quebec workers. *Regul Toxicol Pharmacol.* 2007;**48**(2):118-27. doi: [10.1016/j.yrtph.2007.02.001](https://doi.org/10.1016/j.yrtph.2007.02.001). [PubMed: [17408825](https://pubmed.ncbi.nlm.nih.gov/17408825/)].
- Jafari MJ, Rahimi A, Omidi L, Behzadi MH, Rajabi MH. Occupational exposure and health impairments of formaldehyde on employees of a wood industry. *Health Promot Perspect.* 2015;**5**(4):296-303. doi: [10.15171/hpp.2015.035](https://doi.org/10.15171/hpp.2015.035). [PubMed: [26933649](https://pubmed.ncbi.nlm.nih.gov/26933649/)]. [PubMed Central: [PMC4772800](https://pubmed.ncbi.nlm.nih.gov/PMC4772800/)].
- Krilaviciute A, Heiss JA, Leja M, Kupcinskis J, Haick H, Brenner H. Detection of cancer through exhaled breath: A systematic review. *Oncotarget.* 2015;**6**(36):38643-57. doi: [10.18632/oncotarget.5938](https://doi.org/10.18632/oncotarget.5938). [PubMed: [26440312](https://pubmed.ncbi.nlm.nih.gov/26440312/)]. [PubMed Central: [PMC4770726](https://pubmed.ncbi.nlm.nih.gov/PMC4770726/)].
- Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: A new meta-analysis and potential mechanisms. *Mutat Res.* 2009;**681**(2-3):150-68. doi: [10.1016/j.mrrev.2008.07.002](https://doi.org/10.1016/j.mrrev.2008.07.002). [PubMed: [18674636](https://pubmed.ncbi.nlm.nih.gov/18674636/)].
- Azari MR, Asadi P, Jafari MJ, Soori H, Hosseini V. Occupational exposure of a medical school staff to formaldehyde in Tehran. *Tanaffos.* 2012;**11**(3):36-41. [PubMed: [25191427](https://pubmed.ncbi.nlm.nih.gov/25191427/)]. [PubMed Central: [PMC4153202](https://pubmed.ncbi.nlm.nih.gov/PMC4153202/)].
- Roberts AL, Johnson NJ, Cudkovic ME, Eum KD, Weisskopf MG. Job-related formaldehyde exposure and ALS mortality in the USA. *J Neurol Neurosurg Psychiatry.* 2016;**87**(7):786-8. doi: [10.1136/jnnp-2015-310750](https://doi.org/10.1136/jnnp-2015-310750). [PubMed: [26169306](https://pubmed.ncbi.nlm.nih.gov/26169306/)]. [PubMed Central: [PMC4738165](https://pubmed.ncbi.nlm.nih.gov/PMC4738165/)].
- Gurbuz N, Coskun ZK, Liman FA, Anil A, Turgut HB. The evaluation of formaldehyde exposure in the anatomy laboratories and the preventive measures. *Gazi Med J.* 2016;**27**(2).
- Rezazadeh Azari M, Naghavi Konjin Z, Zayeri F, Salehpour S, Seyedi MD. Occupational exposure of petroleum depot workers to BTEX compounds. *Int J Occup Environ Med.* 2012;**3**(1):39-44. [PubMed: [23022850](https://pubmed.ncbi.nlm.nih.gov/23022850/)].
- Moser B, Bodrogi F, Eibl G, Lechner M, Rieder J, Lirk P. Mass spectrometric profile of exhaled breath-field study by PTR-MS. *Respir Physiol Neurobiol.* 2005;**145**(2-3):295-300. doi: [10.1016/j.resp.2004.02.002](https://doi.org/10.1016/j.resp.2004.02.002). [PubMed: [15705543](https://pubmed.ncbi.nlm.nih.gov/15705543/)].
- Spanel P, Smith D. Quantification of trace levels of the potential cancer biomarkers formaldehyde, acetaldehyde and propanol in breath by SIFT-MS. *J Breath Res.* 2008;**2**(4):46003. doi: [10.1088/1752-7155/2/4/046003](https://doi.org/10.1088/1752-7155/2/4/046003). [PubMed: [21386190](https://pubmed.ncbi.nlm.nih.gov/21386190/)].
- Takeuchi A, Takigawa T, Abe M, Kawai T, Endo Y, Yasugi T, et al. Determination of formaldehyde in urine by headspace gas chromatography. *Bull Environ Contam Toxicol.* 2007;**79**(1):1-4. doi: [10.1007/s00128-007-9172-0](https://doi.org/10.1007/s00128-007-9172-0). [PubMed: [17618393](https://pubmed.ncbi.nlm.nih.gov/17618393/)].
- Jakubowski M, Trzcinka-Ochocka M. Biological monitoring of exposure: Trends and key developments. *J Occup Health.* 2005;**47**(1):22-48. [PubMed: [15703450](https://pubmed.ncbi.nlm.nih.gov/15703450/)].
- Jakubowski M. Biological monitoring versus air monitoring strategies in assessing environmental-occupational exposure. *J Environ Monit.* 2012;**14**(2):348-52. doi: [10.1039/c1em10706b](https://doi.org/10.1039/c1em10706b). [PubMed: [22130625](https://pubmed.ncbi.nlm.nih.gov/22130625/)].
- Shaham J, Bomstein Y, Gurvich R, Rashkovsky M, Kaufman Z. DNA-protein crosslinks and p53 protein expression in relation to occupational exposure to formaldehyde. *Occup Environ Med.* 2003;**60**(6):403-9. [PubMed: [12771391](https://pubmed.ncbi.nlm.nih.gov/12771391/)]. [PubMed Central: [PMC1740563](https://pubmed.ncbi.nlm.nih.gov/PMC1740563/)].
- Shaham J, Gurvich R, Kaufman Z. Sister chromatid exchange in pathology staff occupationally exposed to formaldehyde. *Mutat Res.* 2002;**514**(1-2):115-23. [PubMed: [11815250](https://pubmed.ncbi.nlm.nih.gov/11815250/)].
- Fuchs P, Loeseken C, Schubert JK, Miekisch W. Breath gas aldehydes as biomarkers of lung cancer. *Int J Cancer.* 2010;**126**(11):2663-70. doi: [10.1002/ijc.24970](https://doi.org/10.1002/ijc.24970). [PubMed: [19839051](https://pubmed.ncbi.nlm.nih.gov/19839051/)].
- National Research Council. *Review of the environmental protection agency's draft IRIS assessment of formaldehyde*. Washington, DC: The National Academies Press; 2011. doi: [10.17226/13142](https://doi.org/10.17226/13142).
- Nielsen GD, Larsen ST, Wolkoff P. Recent trend in risk assessment of formaldehyde exposures from indoor air. *Arch Toxicol.* 2013;**87**(1):73-98. doi: [10.1007/s00204-012-0975-3](https://doi.org/10.1007/s00204-012-0975-3). [PubMed: [23179754](https://pubmed.ncbi.nlm.nih.gov/23179754/)]. [PubMed Central: [PMC3618407](https://pubmed.ncbi.nlm.nih.gov/PMC3618407/)].
- Nelson DL, Cox MM. Standard amino acid. *Lehninger Principles of Biochemistry.* 2004.
- Ovrebo S, Haugen A, Skaug V. Biotransformation of formaldehyde in cultured human bronchus. *Environ Res.* 2002;**89**(1):38-42. doi: [10.1006/enrs.2002.4347](https://doi.org/10.1006/enrs.2002.4347). [PubMed: [12051783](https://pubmed.ncbi.nlm.nih.gov/12051783/)].
- National Research Council. *Review of the formaldehyde assessment in the National Toxicology Program 12th report on Carcinogens*. Washington, DC: The National Academies Press; 2014. doi: [10.17226/18948](https://doi.org/10.17226/18948).
- U.S. Department of Health and Human Services; Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health (NIOSH). *Formaldehyde: Method 2016. NIOSH manual of analytical methods (NMAM).* 2003;(2).
- Mitra S, Winefordner JD, editor. *Sample preparation techniques in analytical chemistry*. Hoboken, New Jersey: John Wiley & Sons; 2003. p. 12-20. doi: [10.1002/0471457817](https://doi.org/10.1002/0471457817).
- Kurose T, Koderia H, Aoyama H, Kawamata S. Formaldehyde concentration in the air and in cadavers at the gross anatomy laboratory in Hiroshima University. *Hiroshima J Med Sci.* 2004;**53**(3-4):33-7. [PubMed: [15726890](https://pubmed.ncbi.nlm.nih.gov/15726890/)].
- Costa S, Pina C, Coelho P, Costa C, Silva S, Porto B, et al. Occupational exposure to formaldehyde: Genotoxic risk evaluation by comet assay and micronucleus test using human peripheral lymphocytes. *J Toxicol Environ Health A.* 2011;**74**(15-6):1040-51. doi: [10.1080/15287394.2011.582293](https://doi.org/10.1080/15287394.2011.582293). [PubMed: [21707428](https://pubmed.ncbi.nlm.nih.gov/21707428/)].
- Riess U, Tegtbur U, Fauck C, Fuhrmann F, Markewitz D, Salthammer T. Experimental setup and analytical methods for the non-invasive determination of volatile organic compounds, formaldehyde and NOx in exhaled human breath. *Anal Chim Acta.* 2010;**669**(1-2):53-62. doi: [10.1016/j.aca.2010.04.049](https://doi.org/10.1016/j.aca.2010.04.049). [PubMed: [20510903](https://pubmed.ncbi.nlm.nih.gov/20510903/)].
- Taskinen HK, Kyyronen P, Sallmen M, Virtanen SV, Liukkonen TA, Huida O, et al. Reduced fertility among female wood workers exposed to formaldehyde. *Am J Ind Med.* 1999;**36**(1):206-12. [PubMed: [10361608](https://pubmed.ncbi.nlm.nih.gov/10361608/)].
- Ebeler SE, Clifford AJ, Shibamoto T. Quantitative analysis by gas chromatography of volatile carbonyl compounds in expired air from mice and human. *J Chromatogr B Biomed Sci Appl.* 1997;**702**(1-2):211-5. [PubMed: [9449573](https://pubmed.ncbi.nlm.nih.gov/9449573/)].