

## Can Formaldehyde Exposure Induce Histopathologic and Morphometric Changes on Rat Kidney?

### ¿La Exposición al Formaldehído Puede Inducir Cambios Histopatológicos y Morfométricos sobre el Riñón de Rata?

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**SUMMARY:** Formaldehyde is used traditionally for fixing the cadaver, and vaporized during dissection and practical studying on cadaver. This study was designed to determine the histopathologic and morphometric changes of rat kidney while all of the experiments were exposed to formaldehyde for 18 weeks. 28 male albino Wistar rats were divided into the following three experimental groups (E1: 2hrs/d, 2d/w; E2: 2hrs/d, 4d/w; E3: 4hrs/d, 4d/w) and one control group (C). when the exposure period was expired the animals were anaesthetized with chloroform. After cervical dislocation, the abdomen was dissected and the kidneys were taken. The kidney specimens were sectioned and stained with Haematoxylin and Eosin technique for histologic and morphometric study. Data were obtained from an Olympus light microscope and the analyzed with spss (version 11.5) and ANOVA test. In all histopathology sections of groups E1, E2 and E3, these similar changes were seen: mild glomerular congestion, focal congestion, and vacuolar degeneration of tubular cells. There were no evidences of inflammatory cells infiltration or fibrotic changes of interstitial tissue. Only mild, non-specific congestion was seen in cortical vessels. Also there were not any abnormalities in the staining of nucleus and cytoplasm. According to Morphometric study, Mean  $\pm$ SD of glomerulus's area in control, E1, E2 and E3 group were  $10802.66 \pm 1038.18$ ,  $10759.50 \pm 1971.88$ ,  $10434.73 \pm 1763.76$  and  $10077.64 \pm 2068.78$  micrometer, respectively. Mean  $\pm$ SD inner proximal tubule diameter in control, E1, E2 and E3 group were  $16.16 \pm 2.49$ ,  $16.92 \pm 2.90$ ,  $16.31 \pm 2.79$  and  $15.66 \pm 4.11$   $\mu$ m, respectively. Mean  $\pm$ SD of inner distal tubule diameter in control, E1, E2 and E3 group were  $15.96 \pm 4.47$ ,  $16.20 \pm 1.66$ ,  $16.96 \pm 1.63$  and  $17.45 \pm 3.26$   $\mu$ m, respectively. These differences were not significant between cases and control. This study showed that formaldehyde inhalation in 1.5 ppm can not make specific Histopathologic and Morphometric changes in rat kidney.

**KEY WORDS:** Formaldehyde; Exposure; Histology; Kidney; Rat; Morphometry.

## INTRODUCTION

Formaldehyde (CH<sub>2</sub>O) is a flammable, colorless reactive, readily polymerized gas at normal room temperature and pressure, with a relative molecular mass of 30.03, and a pungent odor. Formaldehyde is soluble in water, ethanol and diethyl ether. Also, it is used in polymerized form (Paraformaldehyde) (World Health Organization, 1989).

Under atmospheric conditions, formaldehyde is readily photo-oxidized by sunlight to carbon dioxide. In the absence of nitrogen dioxide, the half-life of formaldehyde is approximately 50 minutes during the daytime; while in the presence of nitrogen dioxide, these drops to 35 minutes (World Health Organization).

There are various sources of formaldehyde, but the major anthropogenic sources which affecting humans are in the indoor environments (ARB, 1999). Other anthropogenic sources include direct emissions; especially from the production and use of formaldehyde (World Health Organization).

Although formaldehyde has recently been classified by the IARC as "carcinogenic in humans" (class 1), it is still widely used in anatomy and pathology departments for the fixing and conservation of biological tissues. Its use therefore raises the question of occupational exposure (Perdelli *et al.*, 2006).

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Its potential to act as an electrophile and act with macromolecules such as DNA, RNA and protein to form reversible adducts or irreversible cross-links (Gichner, 1995) makes it as a conventional tissue fixative (particularly in cadaver's fixation). Acute formaldehyde exposure produces mainly mucosal irritation of the eye and upper respiratory tract in humans (Zwart *et al.*, 1988) and a long-term exposure leads to the production of Histopathologic changes, even nasal tumors in rodents (Monticello *et al.*, 1996).

Formaldehyde also causes pulmonary function impairment (Berbstein *et al.*, 1984), asthmatics reactions in sensitized individuals (Burge *et al.*, 1985; Gorski & Krakowiak, 1991) and histopathologic and morphometric alterations in testis and spleen (Golalipour *et al.*, 2007; 2008).

Cadavers for gross anatomy laboratories are usually prepared by using embalming fluid which contains formaldehyde as a principal component. During the process of dissection, formaldehyde vapors are emitted from the cadavers, resulting in the exposure of medical students and their instructors to elevated levels of formaldehyde in the laboratory.

The American Conference of Governmental Industrial Hygienists (ACGIH) has set a ceiling limit for FA at 0.3 ppm. In Japan, the Ministry of Health, Labor and Welfare has set an air quality guideline defining two limit values for environmental exposure to formaldehyde: 0.08 ppm as an average for general workplaces and 0.25 ppm for specific workplaces such as a formaldehyde factory (Ohmichi *et al.*, 2006). Although there are many reports on indoor formaldehyde concentrations in gross anatomy laboratories, only a few reports have described personal formaldehyde exposure levels.

In the dissection lab, and during cadaver's dissection, instructors of anatomy and medical students are exposed to formaldehyde vapor derived from fixed cadavers (Ohmichi *et al.*).

This study was designed to determine the morphohistologic changes of rat kidney tissue while all of the experiments were exposed to formaldehyde in the dissection lab and determining its relationship with the duration of exposure for 18 weeks.

## MATERIAL AND METHOD

The study was performed in 2004 in the Faculty of Medicine, Gorgan University of Medical Science on 28 al-

bino Wistar rats aged 6–7 postnatal weeks provided by the Iranian Pasteur Institute.

28 male Albino Wistar rats randomly divided into three equal case groups based on the differences between exposure periods:

-E1 -2h/day, for 2days/week for 18 weeks (2h/day, 2days/week).

-E2 -2h/day, for 4days/week for 18 weeks (2h/day, 4days/week).

-E3 -4h/day, for 4days/week for 18 weeks (4h/day, 4days/week).

-Control. There was a control group without any exposure that did not undergo any exposure.

Using a digital scale, the mean weights for each group were 252g (E3), 209g (E2), 222g (E1) and 195g (control group).

Approval for this study was gained from the Animal Care and Ethics Committee of the Gorgan University of Medical Sciences. The concentration of formaldehyde vapor was measured at the beginning, during and at the end of the study by means of Detector Tube and Dragger Pump (model 31, Dragger Company, made in Germany) after the covers of the cadavers were removed. The mean vapor concentration of dissection room was 1.5 ppm. The temperature of dissection room was 20-26 °C and the air pressure was 760-763 atm.

At non-exposure times, all groups were kept in laboratory animal house, which was far from the place of exposure with no formaldehyde detection. The animal house was ventilated and its temperature was kept around 21°C with air conditioner system and adequate light was prepared. All groups were fed with a standard similar diet (provided by Iranian Pastor Institute) two times a day (morning and afternoon); but water was available *Ad libitum*. The cages of the case groups were placed at a height the same as cadaver's height with a distance of 15cm apart from them for 18 weeks, corresponding to time protocols mentioned above. During each period of exposure, the control group was kept in the animal house.

When the exposure period was finished, the whole experiments and control groups were anaesthetized with chloroform. After cervical delocalization, in each case, the abdomen was dissected and whole of the left kidney was extracted. Then specimens with 4 mm thickness were taken from the middle of each kidney. These specimens were fixed in "Formaldehyde buffer solution" for 48 hours.

After tissue processing and paraffin embedding, 10 sections from each specimen were cut at 4mm and stained with Hematoxylin & Eosin (H&E) staining was used. All of the sections were studied by OLYMPUS light microscope with multiple magnifications (40x, 100x, 400x).

Also Morphometric study including glomerulus's area, Glomerulus's diameter, outer and inner Proximal and distal tubule diameter was done by using Olisa software. The data were analyzed with SPSS (version 11.5) and compared by ANOVA ( $p < 0.05$ ).

## RESULTS

Among all experimental groups (E1, E2 and E3) these non-specific changes were seen: mild congestion in the glomeroli, focal congestion and vacuolar (hydropic) degeneration of tubular cells of all experimental groups. Interstitial hyperemia was seen in the parenchyma without

any inflammation or fibrosis in the interstitial tissue. (Figs.1-4) Mild congestion of cortical blood vessels was detected which was not specific. No remarkable abnormality in the cytoplasm and nuclei of renal parenchymal cells were observed. No histopathologic changes were seen among control group.

The Morphometric findings are depicted in Tables I and II. Mean  $\pm$ SD of glomerulus's area in control, E3, E2 and E1 group were  $10802.66 \pm 1038.18$ ,  $10759.50 \pm 1971.8$ ,  $10434.73 \pm 1763.76$  and  $10077.64 \pm 2068.788$  micrometer respectively. Mean  $\pm$ SD inner proximal tubule diameter in control, E3, E2 and E1 group were  $16.16 \pm 2.49$ ,  $16.92 \pm 2.90$ ,  $16.31 \pm 2.79$  and  $15.66 \pm 4.11$  micrometer respectively. Mean  $\pm$ SD of and inner distal tubule diameter in control, E3, E2 and E1 group were  $15.96 \pm 4.47$ ,  $16.20 \pm 1.66$ ,  $16.96 \pm 1.63$  and  $17.45 \pm 3.26$  micrometer respectively. According to morphometric Indices such as glomerulus's area, Glomerulus's diameter, proximal tubule diameter and outer distal tubule diameter there were not any difference between cases and control groups.

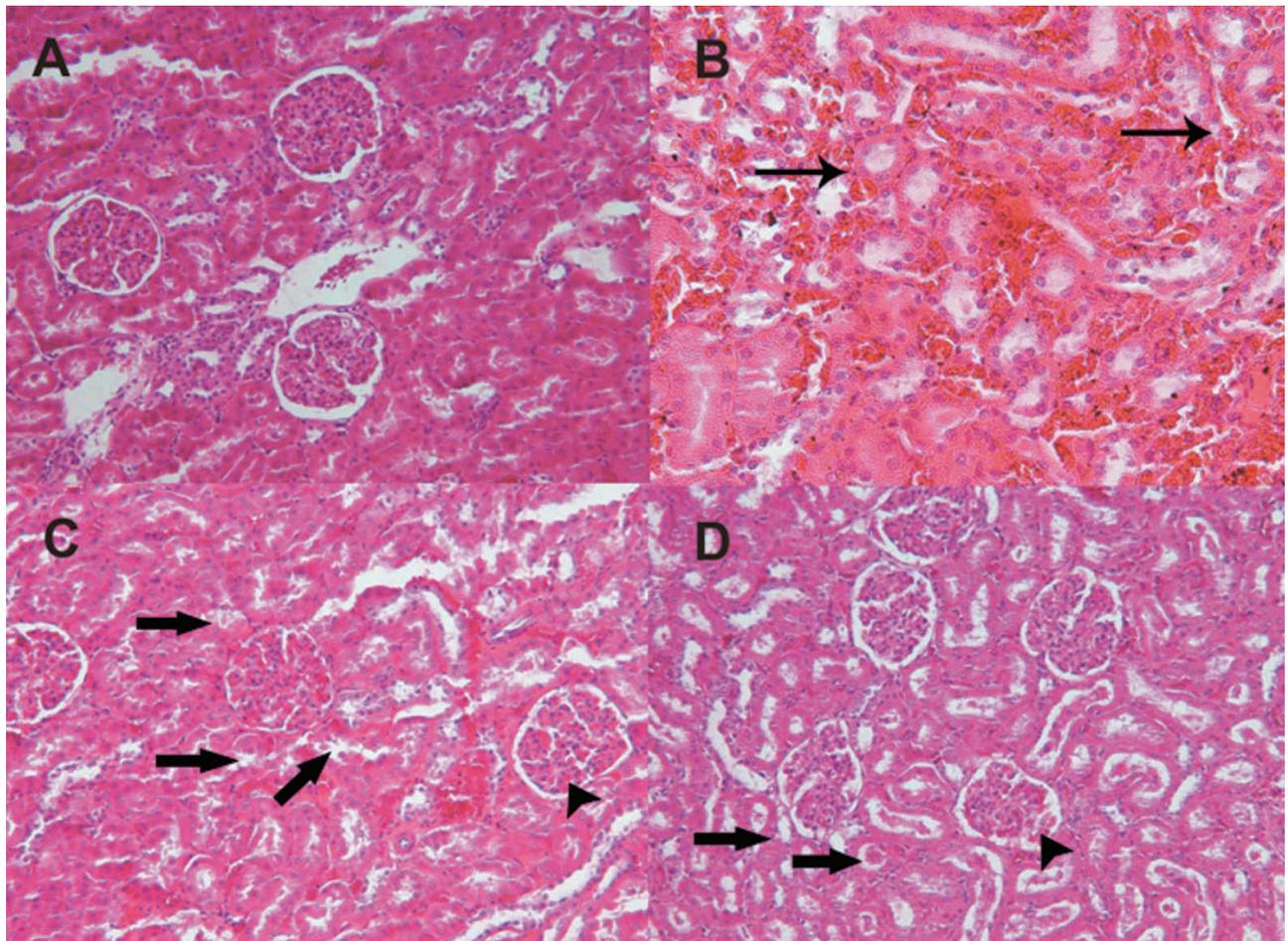


Fig 1. A. Control group: no histopathologic change has been shown. B. E1 group: Shows interstitial bleeding (†) C, D. E2 and E3 group: Vacuolar degeneration of tubular cells (U) and glomerular congestion (ä). (H&E staining, X400).

Table I. Mean  $\pm$ SD of glomerulus area and glomerulus diameter in rats of treatment and control group.

Groups (n=7)	M $\pm$ SD Glomerulus diameter ( $\mu$ m)	M $\pm$ SD glomerulus area ( $\mu$ m <sup>2</sup> )
Control	414.53 $\pm$ 21.68	10802.66 $\pm$ 1038.18
E1 (2h/d,2d/w)	403.64 $\pm$ 35.47	10759.50 $\pm$ 1971.88
E2 (2h/d,4h/w)	398.81 $\pm$ 54.25	10434.73 $\pm$ 1763.76
E3 (4h/d, 4d/w)	392.53 $\pm$ 35.85	10077.64 $\pm$ 2068.78

Table II. Mean  $\pm$ SD outer and inner Proximal tubule diameter, Outer distal tubule diameter and inner distal tubule diameter in rats of treatment and control group (micrometer).

Groups (n=7)	Inner distal tubule diameter	Outer distal tubule diameter	Inner Proximal tubule diameter	Outer Proximal tubule diameter
Control	15.96 $\pm$ 4.47	27.20 $\pm$ 7.58	16.16 $\pm$ 2.49	44.31 $\pm$ 4.65
E1 (2h/d,2d/w)	16.20 $\pm$ 1.66	27.03 $\pm$ 3.18	16.92 $\pm$ 2.90	42.43 $\pm$ 4.74
E2 (2h/d,4h/w)	16.96 $\pm$ 1.63	26.97 $\pm$ 5.82	16.31 $\pm$ 2.79	41.87 $\pm$ 4.61
E3 (4h/d, 4d/w)	17.45 $\pm$ 3.26	26.46 $\pm$ 4.17	15.66 $\pm$ 4.11	42.83 $\pm$ 5.00

## DISCUSSION

This study showed that exposure to formaldehyde vapor in the concentration of 1.5 ppm, can not affect kidney except causing non-specific histopathologic changes such as: Mild congestion in the glomerules and blood vessels, vacuolar degeneration of tubular cells and interstitial hyperemia in the parenchyma. Our findings are in agreement with similar pervious studies were done by other researchers (AIHA, 1983; Dubreuil *et al.*, 1976; Rusch *et al.*, 1983; Wilmer *et al.*, 1987).

In a study done by American Industrial Hygiene Association (AIHA) in 1983, rats were exposed to 3ppm formaldehyde vapor for 6 hour/day, 5 day/week for 4 weeks which revealed no histopathologic changes in the kidney (AIHA).

Dubreuil *et al.* study on rats after 22 hour/day exposure to 1.6 ppm formaldehyde vapor for 90 days showed no histopathologic changes in the kidney. Rusch *et al.* found no histopathologic changes in the kidney tissue of rats exposed to 1ppm formaldehyde vapor for 22 hour/day, 7 day/week for 26 weeks.

The data obtained in the research on rats showed no histopathologic changes in the kidney while two groups of experiments were exposed to 10 and 20 ppm formaldehyde vapor for 8hour/day, 5 day/week during 4 weeks (Wilmer *et al.*, 1989).

Exposure of rats to formaldehyde concentrations of 0, 1, 10 and 20 ppm in a 6 hour/day, 5 day/week protocol for 13 weeks in Woutersen *et al.* study revealed histopathologic changes just in 10 and 20 ppm exposed groups, which this concentration was more than the concentration used in our study (Woutersen *et al.*, 1987).

Wilmer *et al.* designed a 13-week experiment on rats which were exposed to 0, 1 and 2 ppm formaldehyde vapor for 8 hour/day, 5 day/week; Data revealed no histopathologic changes just in the kidney. Also, they designed another 13 week study in which rats were exposed to 2 and 4 ppm formaldehyde vapor intermittently (30 minutes exposure followed by 30 minutes non-exposure period) for 4 hour/day. Their comparison between two studies showed that the most important factor which determine the severity of histopathologic changes is the Vapor's concentration other than accumulative dose (dose exposure duration) (Wilmer *et al.*, 1987, 1989).

The morphometric results of this study did not any differences between cases and control groups, with regarding to these findings, morphometric results is adapted with histopathologic findings.

Considering to detailed study of formaldehyde kinetic in the human body and focus on it's fast metabolism (less

than 1.5 minute) in the blood, it could be assumed that formaldehyde cytotoxicity could be due to its main metabolite "Formic acid" (Dart, 2004).

Formic acid is degraded mainly by metabolization in the liver and excretion from kidney. Saturable first-order kinetics of formic acid, also primary and systemic metabolic acidosis associated with lactic acidosis due to cytochrome oxidase in the kidney are two leading mechanisms which could be assumed responsible for decrement of both formaldehyde metabolism in the liver and excretion in the kidney. Consequently, formic acid concentration can reach to its serum cytotoxic level (Dart).

Also, other possible mechanism of lack of toxic effect of formaldehyde on kidneys has explained by previous studies. These researches reported that formaldehyde may be detoxified principally via action of formaldehyde dehydrogenase (FDH), a specific enzyme that catalyzes the conversion of formaldehyde, glutathione and NAD<sup>+</sup> to S-formylglutathione and NADH (Pourmotabbed & Creighton, 1986; Uotila & Mannervik, 1979).

In kidney, prominent deposits of FDH reaction product are present throughout the renal cortex, being

especially strong in epithelial cells lining proximal convoluted tubules. Glomeruli, distal tubules and collecting ducts have little or no FDH activity (Keller *et al.*, 1990).

The results obtain in our study are in agreement with those obtained by other researchers (AIHA; Dubreuil *et al.*; Rusch *et al.*; Wilmer *et al.*, 1987, 1989; Woutersen *et al.*). Consequently it seems that Formaldehyde vapor exposure in the concentrations similar to our study can not make Histopathologic changes in rat kidney which could be detectable by light microscope. Also, there is no direct relationship between the duration of exposure to formaldehyde vapor and the intensity of Histopathologic changes in the kidney.

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**GOLALIPOUR, M. J.; AZARHOUSH, R.; GHAFARI, S.; DAVARIAN, A. & FAZELI, H. S. A.** ¿La exposición al formaldehído puede inducir cambios histopatológicos y morfométricos sobre el riñón de rata? *Int. J. Morphol.*, 27(4):1195-1200, 2009.

**RESUMEN:** El formaldehído se utiliza tradicionalmente para la fijación de cadáveres y vaporiza durante la disección y los estudios prácticos en el cadáver. Este estudio fue diseñado para determinar los cambios histopatológicos y morfométricos de riñones de ratas expuestas al formaldehído, durante 18 semanas. 28 ratas albinas Wistar se dividieron en tres grupos experimentales (E1: 2 h/d, 2d/s, E2: 2 h/d, 4d/s; E3: 4 h/d, 4d/s) y un grupo control (C). Cuando el período de exposición se cumplió los animales fueron anestesiados con cloroformo. Después de la dislocación cervical, el abdomen fue disecado y se obtuvieron los riñones. Los especímenes de riñón fueron seccionados y teñidos con técnica hematoxilina y eosina para el estudio histológico y morfométrico. Los datos fueron obtenidos con un microscopio óptico Olympus, el análisis con el software SPSS (versión 11.5) y la prueba de ANOVA. En todas las secciones histopatológicas de los grupos E1, E2 y E3, se observaron cambios similares: congestión glomerular leve, congestión focal y degeneración vacuolar de las células tubulares. No hubo evidencias de la infiltración de células inflamatorias o cambios de tejido fibrótico intersticial. Sólo una leve congestión no específica fue observada en vasos corticales. Además no hubo anomalía en la tinción del núcleo y el citoplasma. De acuerdo al estudio morfométrico, la Media  $\pm$  DS del área glomerular en los grupos control, E1, E2 y E3 fue 10802,66 $\pm$ 1038,18, 10759,50 $\pm$ 1971,88, 10434,73 $\pm$ 1763,76 y 10077,64 $\pm$ 2068,78  $\mu$ m, respectivamente. La Media  $\pm$ DS del diámetro interno del túbulo proximal en los grupos control, E1, E2 y E3 fueron 16,16 $\pm$ 2,49, 16,92 $\pm$ 2,90, 16,31 $\pm$ 2,79 y 15,66 $\pm$ 4,11  $\mu$ m, respectivamente. La Media  $\pm$ SD del diámetro interno de los túbulos distales en los grupos control, E1, E2 y E3 fueron 15,96 $\pm$ 4,47, 16,20 $\pm$ 1,66, 16,96 $\pm$ 1,63 y 17,45 $\pm$ 3,26  $\mu$ m, respectivamente. Estas diferencias no fueron significativas entre los casos y el control. Este estudio mostró que la inhalación de formaldehído en 1,5 ppm no produce cambios histopatológicos y morfométricos específicos en el riñón de la rata.

**PALABRAS CLAVE:** Formaldehído; Exposición; Histología; Riñón; Rata; Morfometría.

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