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Effects of Formaldehyde and Xylene Inhalations on Fatty Liver and Kidney in Adult and Developing Rats

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Abstract: The aim of this study was to investigate frequency of fatty liver and kidney of the developing and adult rats exposed to formaldehyde (HCHO) or xylene or a combination of these two agents. Ninety six female Sprague-Dawley rats were used in this study. At the beginning of the experiment, the rats were randomly divided into four groups with following ages. The animals were exposed to gases of technical xylene (300 ppm), HCHO (6 ppm) or technical xylene + HCHO (150 +3 ppm), 8 day^{-1} for 6 weeks. After the exposure period, the rats were anesthetized with xylazin-ketamine intraperitoneally. Animals were sacrificed by cervical dislocation. The weight of liver and kidney were measured. Left kidney and liver obtained from each rat. Sections were stained HδE, for the histopathologic investigation and sections stained by the Oilred O and Sudan Black stains for the demonstration of neutral triglycerides. At the end of the study period, the fat deposition observed in the liver and kidneys of the experimental groups was in the form of fine granular fats. This study showed that inhalation of HCHO, xylene or its combination (xylene + HCHO) lead to deposition of adipose tissue in the liver and kidneys.

Key words: Formaldehyde, xylene, fatty, liver, kidney, rat

INTRODUCTION

Formaldehyde (HCHO) is a colorless, flammable gas with a pungent, suffocating odour. It is soluble in water, acetone, benzene, diethyl ether, chloroform and ethanol. HCHO used to make plastics and resins for the production of intermediates and for other miscellaneous uses. HCHO also used as disinfectant in many human medicines and cosmetics, as an antiseptic in veterinary drugs and biological and in fungicides, textiles and embalming fluids (IARC, 1982). Exogenous HCHO is taken up into human body by ingestion, inhalation and dermal exposure. Inhaled HCHO appears to be readily absorbed by the upper respiratory tract but is not distributed throughout the body because of its rapid metabolism (Casanova *et al*., 1988; Heck *et al*., 1985).

HCHO may affect the systemic cellular immunity, as well as local immunity in bronchus (Balt: Bronchus Associated Lymphoid Tissue) (Sandikci *et al*., 2007a, b). However, chronic inhalation of HCHO causes hepatotoxicity (Kamata *et al*., 1997) and nephrotoxicity (Al Ghamdi *et al*., 2003). Xylene, an aromatic hydrocarbon widely used in industry such as toluene and methylalchol, as well as in medical technology as an organic solvent (Foy *et al*., 1996; Langman, 1994; Rana and Kumar, 1993). Xylene vapor absorbed rapidly from the lungs, while xylene liquid and vapor absorbed slowly through the skin.

Of the xylene absorbed, about 95% metabolized in the liver to Methylhippuric Acid (MHA) (Langman, 1994). Besides the 70-80% of metabolites excreted in the urine within 24 h that may play a role in the glomerular diseases (Askergren, 1981) and solvent-induced proximal tubuler cell injury (Al-Ghamdi *et al*., 2003) and progressive renal fibrosis, renal failure (Al-Ghamdi *et al*., 2004). Fatty liver, or steatosis, refers to a histopathological condition characterized by an excess accumulation of lipids, mainly Triacylglycerols (TAG), within hepatocytes (Burt *et al*., 1998). Fatty liver may classified as macrovesicular or microvesicular steatosis, depending on the size of the lipid vacuoles (Marceau *et al*., 1999; Van Steenbergen and Lanckmans, 1995). Hepatotoxicity characterized by Microvesicular Steatosis (MVS) and by an abnormal accumulation of many small cytoplasmic lipid droplets in hepatocytes. Fulminant or progressive cases of microvesicular steatosis may lead to liver failure and death

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(Jolly *et al*., 2004). Lipids or lipoids were demonstrated in the epithelium of the several parts of the tubules, the glomerular tufts, the walls of Bowman's capsules and the tubular lumens of the kidneys of the various species of domestic animals and humans. Toxic agents can cause to accumulation of lipid in the renal tubular epithelium (Jones *et al*., 1996).

The aim of this study was to investigate the frequency of fatty liver and kidney of the developing and adult rats exposed to HCHO or xylene or a combination of these two agents.

MATERIALS AND METHODS

Animal groups and experimental design: In the present study, 96 female Sprague-Dawley rats, which were bred since seven years as a closed colony at the Experimental Animal Resources and Research Unite of Veterinary Physiology were used. At the beginning of the experiment the rats were randomly divided into four groups with following ages: the embryonic day 1 (beginning of the embryonic period) (Group 1), 1 day old infantile rats (Group 2), 4 week old rats (Group 3) and adult rats (Group 4), each containing 24 animals. Group 1 established as follows: female rats were housed overnight with adult males (one male to three females) from the same strain and supplier. The day that vaginal smears were found to be sperm positive was considered day 1 of the embryonic day. Newborn rats were kept together in the same cage with their mothers. As well as 1 day old infantile rats (Group 2) were kept with their mothers. All studies with animals described herein were reviewed and approved by University of Adnan Menderes Institutional Animal Ethics Committee.

Exposure design: Inhalation exposure procedures have been described by Valentine and Kennedy (2001). The whole body of rats exposed to the solvents. Each cage had a separate supply of test solvents. To acclimatize the rats were housed in close chamber fitted 4 rat cages, made of glass and stainless steel, as a set of 6 animals per cage under standard laboratory conditions (light period 6:00-20:00 h, 24±1°C, tap water and standard pellet diets were given ad libitum) for 2 weeks. These chambers were operated dynamically with filtered air at an air flow rate providing the necessary amount of gases to the animals the test gases of technical xylene (300 ppm), (Li *et al*., 1986), HCHO (6 ppm) (Monticello *et al*., 1989) or a combination of technical xylene and HCHO (150 +3 ppm) for 8 h day^{-1} (between 9:00-17:00 h) during 6 weeks. The position of the cages within the chamber was systematically changed a week basis. Fresh air was provided at a constant temperature. Control animals were placed in an identical chamber without the addition of these two agents. Levels of xylene and HCHO in cages were monitored by gas detection pumps by the methods of Norback *et al*. (1995) (Technical xylene; (Sigma CAS No: 1330-20-7) and HCHO (Sigma CAS No: 50-00-0): Sigma Chemical Co., St., Louis, Missouri, USA. Accuro® Gas Detection Pump, Arta-F001-6400.00; for xylene: 10/a Batch-ARSD-0632-6733161, for formaldehyde: 2/a Batch-ARTA-0351-8101751).

Sample collection, preparation: After the exposure period, the rats were anesthetized with xylazin-ketamine intraperitoneally. Animals were sacrificed by cervical dislocation. The weight of liver and kidney were measured. Left kidney and liver obtained from each rat. The half of tissue samples was fixed in solution of formol calcium at +4°C and in a dark place for 16 h. And than 10 μm frozen sections obtain from with cryostat. For the demonstration of neutral triglycerides sectioned tissues were stained by the Oil red O and Sudan Black stains. The other tissue samples were fixed 10% Neutral Buffer Formalin (NBF) solution and then embedded in paraffin for histopathology investigation. About 6 μm thickness paraffin sections were stained HδE.

It was determined frequency of fatty kidney and liver of the growing and adult rats exposed to HCHO or xylene or a combination of these two agents (Gregson *et al*., 1979). Photographs of the tissues were taken, when seemed necessary with a Leica DC-200 camera.

Statistical analysis: To determine liver and kidney weight on control and experiment groups, ANOVA test was employed. Determination of the group source of the difference was done with the Duncan's test. SPSS 10.0 for Windows® statistic package program was used.

RESULTS AND DISCUSSION

The liver and kidney weighs of adult and developing rats exposed to xylene and HCHO were shown in Table 1. A decrease in liver and kidney weight was observed in the groups I and II subjects compared to their controls (Table 1). In the adult (group IV) rats no statistical significant difference was found between the experimental and control groups. In the group III an increase in the weight of both the liver and kidneys was observed compared to the controls (Table 1).

At the end of the study period, the fat deposition observed in the liver and kidneys of the animals was in the form of fine granular fats. For those exposed to HCHO and xylene + HCHO inhalation, fat was found among the experimental group (Fig. 1). The frequency of liver steatosis among the control groups and those exposed to

Table 1: The liver and kidney weight in different aged rats exposed to HCHO, xylene or mixture of the two

	Control		HCHO		Xylene		Xylene + HCHO		
Groups	Liver	Kidney	Liver	Kidney	Liver	Kidney	Liver	Kidney	p-value
I	0.98±0.04^{a}	0.18±0.03$^{\wedge}$	0.70±0.05^{b}	0.15±0.01^{B}	0.77±0.08^{b}	0.15±0.01^{B}	0.65±0.03^{b}	0.14±0.05^{B}	Liver** Kidney*
II	2.50±0.07^{a}	0.35±0.01$^{\wedge}$	2.07±0.08^{b}	0.34±0.08$^{\wedge}$	2.11±0.07^{b}	0.30±0.01^{B}	2.64±0.08^{a}	0.35±0.01$^{\wedge}$	Liver*** Kidney*
III	3.24±0.10^{c}	0.45±0.01^{B}	3.82±0.21^{ac}	0.60±0.02$^{\wedge}$	4.71±0.15^{a}	0.71±0.02$^{\wedge}$	4.25±0.53^{ab}	0.61±0.05$^{\wedge}$	Liver** Kidney***
IV	4.60±0.22	0.71±0.05	4.71±0.23	0.75±0.06	4.41±0.22	0.71±0.05	4.91±0.24	0.78±0.03	NS

$^{a-c}$Means within a line with no common superscript differ significantly-(Liver weight), $^{\wedge-B}$Means within a line with no common superscript differ significantly-(Kidney weight), *p<0.05, **p<0.01, ***p<0.001, NS: Not-Significant, HCHO: Formaldehyde

Table 2: Frequency of fatty on liver and kidney in different aged rats exposed to HCHO, xylene or mixture of the two

	Control		HCHO		Xylene		Xylene + HCHO	
Groups	Liver	Kidney	Liver	Kidney	Liver	Kidney	Liver	Kidney
I	-	-	+	+	+	+	++	++
II	-	-	+	+	+	+	++	++
III	-	-	+	+	+	+	+	++
IV	-	-	+	+	+	+	+	++

HCHO: Formaldehyde. (-): Negative, (+): Few, (++): Moderate *p<0.05, **p<0.01, ***p<0.001, NS: Not-Significant, HCHO: Formaldehyde

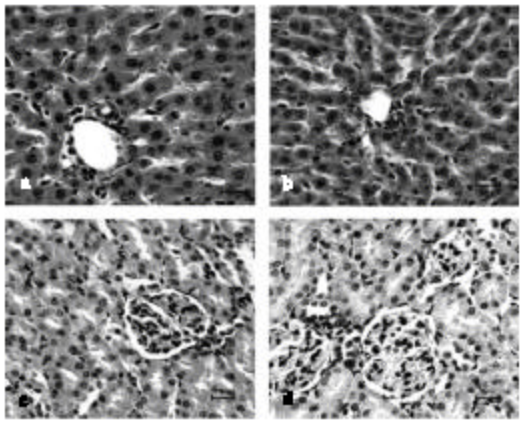

Fig. 1: a) Microscobic appearance of the liver in the xylene + HCHO group, HδE stain. Bar: 20 μm, b) Microscobic appearance of the liver in the control group, HdE stain. Bar: 20 μm, c) Microscobic appearance of the kidney in the xylene + HCHO group, HδE stain. Bar: 20 μm and d) Microscobic appearance of the kidney in the control group, HδE stain. Bar: 20 μm

HCHO, xylene or xylene +HCHO inhalation was shown in Table 2. Fat deposition in kidney was found among animals from the experimental group exposed to HCHO and xylene +HCHO inhalation (Fig. 2). The frequency of fat deposition among the control groups and those exposed to HCHO, xylene or xylene +HCHO inhalation was shown in Table 2. Beall and Ulsamer (1984) reported an increase in the liver size and weight, when HCHO was given at high concentrations and was attributed in part to passive congestion due to inflammation in hepatocytes and perhaps to hepatic burn, hyperemia and edema. However, Kamata *et al*. (1997) reported a decrease in the triglyceride levels and liver mass, hyperplasia in epithelial cells, hyperkeratosis and squamous metaplasia in rats exposed to 15 ppm HCHO inhalation for 6 h a day 5 days a week for a period of 28 months. Also, Rusch *et al*. (1983) observed that exposure to 2.95 ppm HCHO inhalation for 26 weeks led to a decrease in the liver mass in monkeys and rats. The loss in hepatic mass was attributed to necrosis and loss of parenchyma (Beall and Ulsamer, 1984).

In the present study, a decrease in liver and kidney weight was observed in the groups I and II subjects compared to their controls (Table 1). In the adult group, however, no statistical significant difference was found between the experimental and control groups. In the group III, an increase in the weight of both the liver and kidneys was observed compared to the controls (Table 1). The groups I and II liver and kidneys were affected adversely by the effect of dose and duration of inhalation. The increase in weight observed in group III thought to be directly related to their ages. The lack of a significant difference between the experimental and controls in group IV was thought to be the result of shorter exposure times and smaller doses.

Kum *et al*. (2007a) in their study observed that exposures to xylene, HCHO and mixture of them are toxic to liver tissue. Woutersen *et al*. (1987) reported that while 6 h a day of 10 ppm of HCHO exposure for 5 days a week for 13 weeks did not induce any hepatotoxic effect, increasing the dose to 20 ppm induced mild effects. Exposure to HCHO at concentrations of 3 ppm and below for up to 6 months was reported to have had no effect on the liver (Beall and Ulsamer, 1984). In this study, similarly no hepatotoxic effect was observed among the

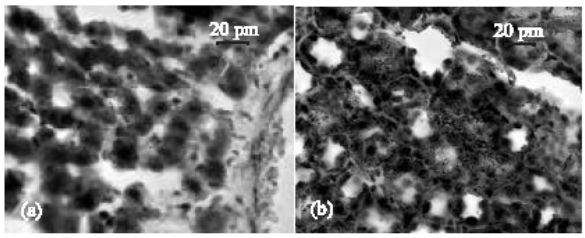

Fig. 2: (a) Microscobic appearance of the liver in the xylene + HCHO inhalation, Oil red O stain. Bar: 20 µm and (b) Microscobic appearance of the kidney in the xylene + HCHO inhalation, Oil red O stain. Bar: 20 µm

groups following HCHO inhalation. Simmons *et al.* (1991) in their studies, reported the absence of hepatotoxic effect attributable to acute (6 h of single dose) and short exposure periods (3 days, 6 h day^{-1}) of 1600 ppm p-xylene in 2-month-old male rats. Neghab and Stacey (1997) reported remarkable increases in the serum bile acid concentrations with exposure to organic solvents like toluene and xylene. Elovaara *et al.* (1980) described serious hepatic injury upon inhalation of 300 ppm xylene levels together with alcohol intake for 18 weeks. Porru *et al.* (2001) described long term exposure to organic solvents like toluene and xylene as a risk factor for liver cancer. In the study, xylene inhalation was not associated with any hepatotoxic effects.

Long term exposure to organic solvents also leads to negative effects on the kidneys. Al-Ghamdi *et al.* (2004) reported apoptosis and progressive renal fibrosis in the proximal renal tubules with long term exposure to toluene and xylene. Ehrenreich (1977) reported the development of glomerulonephritis and membranous nephropathy with chronic organic solvent inhalation. Also, Lauwerys *et al.* (1985) described several nephrotoxic effects of solvents that affect the tubules and glomeruli including epithelial enlargement, ballooning and hydrophilic necrosis. Kum *et al.* (2007b) reported that exposure to gases 8 h day^{-1} for 6 weeks did not cause renal toxicity. In this study, no nephrotoxic effect was observed among the groups with exposure to xylene inhalation for 6 weeks at 300 ppm dosing.

Dossing *et al.* (1983) reported that patients exposed organic solvents for prolonged periods caused marked steatosis in 11 of 156 patients, focal necrosis in 6 of 156 patients, while other 6 of 156 patients had fibrosis and enlargement of the portal canals. Lundqvist *et al.* (1999) suggested that exposure to organic solvents play a role in enhancing steatosis in the liver. Chung *et al.* (2005) described steatosis in the liver of rats exposed chronically to carbon tetrachloride (CCl_4). Again, Chang *et al.* (2005) demonstrated that exposure of mice to a twice daily dose of 0, 2.5, 25 and 125 ng of Tetrachlorodibenzo p-Dioxin (TCDD) for 20 weeks resulted in fatty infiltrations in their livers. In this study, rats from both group I and group II exposed to inhalation of HCHO, xylene or xylene + HCHO combination were observed to have more fat deposition in their liver parenchyme and kidneys (Table 2) than their controls.

CONCLUSION

The inhalation of HCHO, xylene or its combination (xylene + HCHO) lead to deposition of adipose tissue in the liver and kidneys. However, it is necessary to conduct studies with varying periods and dose schedules for the establishment of detailed results.

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