

## Biochemical Changes among Medical Laboratories Staff Occupationally Exposed to Formaldehyde Vapors

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**Abstract: Background:** Increased levels of tumour markers: carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC -Ag), Alpha fetoprotein (AFP), and neuron-specific enolase (NSE) may indicate the onset of the carcinogenic process. The aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are the most commonly measured enzymes that detect hepatocellular injury. Formaldehyde has an important application as a disinfectant and preservative, reason why relevant workplace exposure may also occur in pathology and anatomy laboratories and in mortuaries. Urinary thioethers are excretion products resulting from a series of metabolic reactions which involve oxidation of lipophilic chemicals to water-soluble compounds **Objective:** The aim of the present study was to evaluate of the hazardous effects of occupational exposure to formaldehyde among lab technicians through measuring liver enzymes, hepatic tumor marker (AFP, CEA) and levels of urinary thioether as indicator of exposure to Carcinogenic compounds. **Method:** the study was conducted on thirty male workers employed in medical pathology and anatomy teaching laboratories. Thirty subjects were recruited as a control group matched for age, sex and socio-economic status. **Results:** the results revealed a high significant increase in the levels of urinary thioethers in exposed workers than those of control group and high significant elevation in the levels of tumors markers (CEA and AFP) in exposed workers in comparison with control group. Moreover, a significant increase in the levels of liver functions (AST and ALT) was observed in formaldehyde exposed workers. **Conclusion:** Present data indicate that formaldehyde exposed workers exhibit an increase in tumor markers levels and additionally increase in the levels of urinary thioethers. Safety Preventive measures should be applied for reduction of the formaldehyde vapors in these laboratories.

### INTRODUCTION

Liver injury has long been associated with occupational exposure to a wide variety of chemicals. Its susceptibility to chemical injury is a result of its unique position within the circulatory system, and also because it is the primary organ for the biotransformation of chemicals within the body, as liver is the main organ involved in

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the metabolism of toxins and medicinal agents.<sup>(1)</sup>

On the other hand, increased levels of tumour markers: e.g. carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC -Ag), Alpha foeto protein (AFP), and neuron-specific enolase (NSE) may indicate the onset of the carcinogenic process.<sup>(2)</sup>

Formaldehyde (FA) is a reactive, flammable and colourless gas with a strong and very characteristic pungent odour. Commercially, FA is manufactured as an aqueous solution called formalin, usually containing 37–40% by weight of dissolved FA.

Formaldehyde is commonly used in histopathology laboratories as a cytological fixative to preserve the integrity of cellular architecture for diagnosis, in anatomy laboratories as preservative and as disinfection.<sup>(3)</sup>

Exogenous formaldehyde can be absorbed following inhalation, or dermal contact and the extent of absorption being

dependent on the route of exposure. Formaldehyde (CH<sub>2</sub>O), the most simple and reactive of all aldehydes, is a colorless, reactive and readily polymerizing gas at room temperature. It has a pungent suffocating odor that is recognized by most human subjects at concentrations below 1 ppm.<sup>(4)</sup> In screening for possible effects of hepatotoxicants,

The aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are the most commonly measured enzymes that detect hepatocellular injury due to the toxicant's effect on all or part of the hepatocyte, including the cell membrane.<sup>(5)</sup>

Human studies have shown that chronic exposure to formaldehyde by inhalation is associated with eye, nose and throat irritation. Moreover, several studies report a carcinogenic effect in humans after chronic exposure to formaldehyde, in particular an increased risk for nasopharyngeal cancer. Since 2006,

International Agency for Research on Cancer (IARC) classified formaldehyde as carcinogenic to humans (Group 1), based on sufficient evidence in humans and in experimental animals. IARC also concluded that there is a "strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde".<sup>(6)</sup>

Environmental monitoring including FA of indoor workplace pollutants is carried out in many studies in order to correlate levels of pollutants with health effects.<sup>(7)</sup>

Concerning the health effects of FA. Little information is available regarding level between exposure to formaldehyde exposure, tumour markers, spirometric indices, as well as hematological and biochemical parameters.<sup>(7)</sup>

Urinary thioethers are excretion products resulting from a series of metabolic reactions which involve oxidation of lipophilic chemicals to water-soluble compounds.

Compounds that are metabolized via

electrophilic intermediates can be considered as potentially genotoxic substances<sup>(6)</sup>. There has been growing interest in the determination of specific thioethers or mercapturic acids in urine as markers of exposure to these potentially toxic reactive electrophilic compound.<sup>(8)</sup>

The aim of the present study was to evaluate of the hazardous effects of occupational exposure to formaldehyde among lab technicians through measuring liver enzymes (AFP,CEA) and levels of urinary thioether.

## **SUBJECT AND METHODS**

The present study included 30 lab technicians occupationally exposed to formaldehyde in teaching laboratories for more than 5 years (workers group), and 30 subjects selected from administrative departments never occupationally exposed to formaldehyde (control group). Detailed personal, occupational and medical questionnaire was completed with each worker through personal interview. Verbal

consent, approval of the Ethical committee was obtained. All participants signed individual consents prior to the study. Subjects with history of viral hepatitis, bilharziasis, blood transfusion, or hospitalization for surgery were excluded from the study.

**Collection and Assay:** Random blood samples were collected from all subjects by sterile disposable syringes. Samples were left to clot then centrifuged. The separated serum was used for estimation of biochemical parameters and tumor markers analysis. Serum aminotransferases (ALT and AST) were estimated by the method of Bergmeyer *et al*<sup>(9)</sup>. Enzymatic immunoassay for the determination of Alpha fetoprotein (AFP) while Carcinoembryonic antigen (CEA) in human serum was estimated according to Chierigatti *et al*<sup>(10)</sup>. Spot urine samples were collected from all subjects for analysis of thioether levels in urine. Urinary thioethers were determined after alkaline hydrolysis as described by Vainio *et al*<sup>(11)</sup> Environmental monitoring of formaldehyde in air was carried out by using

direct reading instrument applying infrared analyzer principal<sup>(12)</sup>

**Statistical Analysis:** The collected data and the laboratory results were computerized. Statistical analysis was done through SPSS version 17.0. The quantitative results were expressed as means  $\pm$  standard deviation (SD), and Independent t-test and Pearson's correlation coefficient were used in the analysis of the results. P value  $\leq$  0.01 was considered significant.

## RESULTS AND DISCUSSION

Formaldehyde in air was evaluated in the selected laboratories and the mean levels was 1.3 ug/m<sup>3</sup>  $\pm$  1.5 which exceeds the local standard levels of 0.37 ug/m<sup>3</sup> and also the international standards of Occupational Safety and Health Administration (OSHA) which is 0.75 ppm.<sup>(13)</sup> The characterization of the population studied is summarized in Table 1. Controls and exposed workers did not differ significantly in age, gender distribution and in smoking habits..

**Table 1: Characterization of the population studied**

	Control	Exposed	P-Value
Gender			NS
Females	16(53.3%)	18(60%)	
Males	14(46.7)	12(40%)	
Age(years)	36.3±4.1	37.5±0.49	NS
Duration of Exposure(years)	-	7.5±3.6	
Cigarettes Smoke			NS
Non-Smokers	22(73.3%)	23(76.7%)	
Smokers	8(26.7%)	7(23.3%)	

NS: Not Significant

Table 1 represent Characterization of the population studied where no significant difference in the levels of age and cigarettes smoke

**Table 2: Liver enzymes, AFP, CEA and Urinary Thioethers among subjects of the two examined groups**

	Control	Exposed	Independent t-test	
	N=30	N=30	t	P
	Mean±SD	Mean±SD		
ALT(U/L)	29.5±8.6	66.3±21.9	8.54	P<0.001
AST(U/L)	28.6±9.5	64.7±16.7	10.2	P<0.001
AFP(ng/ml)	3.06±1.12	13.09±3.2	15.8	P<0.001
CEA(ug/ml)	0.27±0.14	8.03±2.8	15.6	P<0.001
Urinary Thioether (umol/mmol creatinine)	38±4.88	83±6.7	29.2	P<0.001

Table (2) & Figure (1) show mean values of the liver enzymes (ALT and AST) tumor markers (APF and CEA) and urinary thioethers of the laboratories staff were significantly higher among exposed technicians compared to their controls.

Although the link between toxic hepatitis and exposure to formaldehyde is relatively well documented, there is no specific laboratory or histological diagnostic tests for chemically-induced hepatitis. In general for detection of liver cellular injury, occupational medical surveillance programs have relied on measurement of the conventional liver enzymes.<sup>(14)</sup>

For routine screening of chemicals that are

known or suspected to cause hepatocellular injury, the ALT is considered to be the aminotransferase most specific for the liver.. Abnormal ALT can sound as an alarm to alert medical staff to the possibility of some kinds of liver problem, which require further medical workup.

Recent studies indicated that  $\gamma$ -glutamyl transpeptidase (GGT) in addition to ALT and AST are used as sensitive biomarkers for possible hepatocellular damage due to exposure to organic solvents.<sup>(15)</sup>

In the current study, the absolute values of liver enzymes (ALT, AST) of all exposed workers were found to be highly elevated compared to their controls, The liver enzymes of all the control subjects were within the normal levels.

Statistically the mean values of liver enzymes of the exposed subjects showed an abnormal significant elevation compared to the control.

In Agreement with the present results, several studies showed that liver enzymes

were significantly elevated in workers exposed to organic solvents compared to controls.<sup>(16)</sup>e.g. the first study presented similar results in shoe repairers who work in supermarkets, and use the glues which contain mixtures of organic solvents, the workers had higher levels of ALT and AST compared to their controls. <sup>(16)</sup>

In the second study cumulative exposure to a mixture of organic solvents was found to cause a significant increase in liver enzymes (AST, ALT, and GGT) in male shipyard workers. In third study car painters exposed to organic solvents, revealed a significant increase in their AST level in the exposed workers compared with their control.

However, controversial data were observed in relation to hepatotoxicity of organic solvents which might be explained as a consequence of the low levels of exposures or to the insensitive tests used for evaluating liver function which are able to detected mild changes of early stages.<sup>(17)</sup>

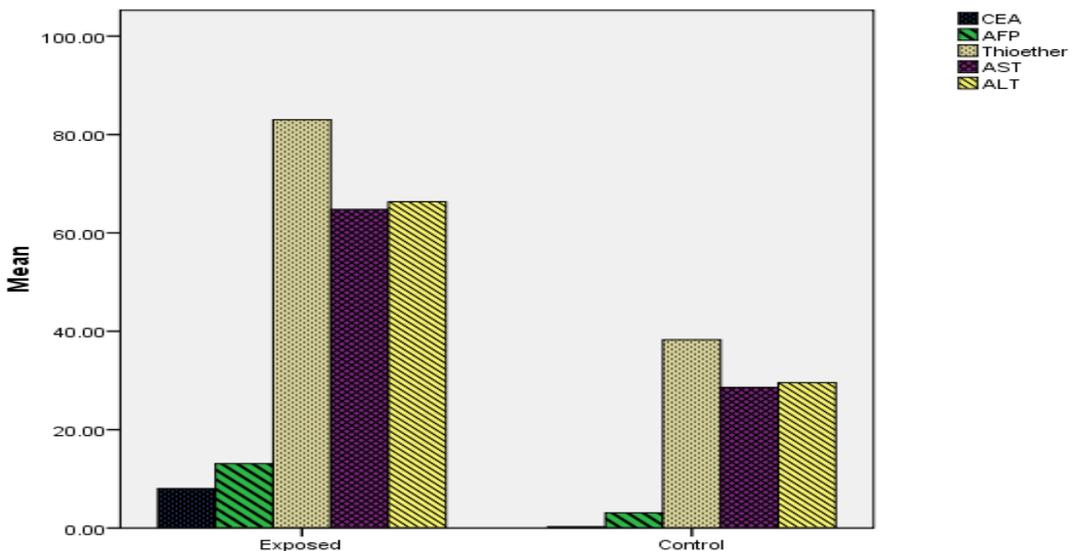
Concerning AFP and CEA (table 2, Figure 2),

many recent studies mentioned that serum concentrations of AFP and CEA were found to be elevated during liver injury, and have been suggested to be of prognostic importance in acute liver failure. So, the significant elevation in the levels of AFP in the present study could denote the magnitude of liver injury in the workers, and that monitoring of AFP and CEA might be used as screening marker for prediction of acute liver failure in workers exposed to formaldehyde vapors.<sup>(18)</sup>

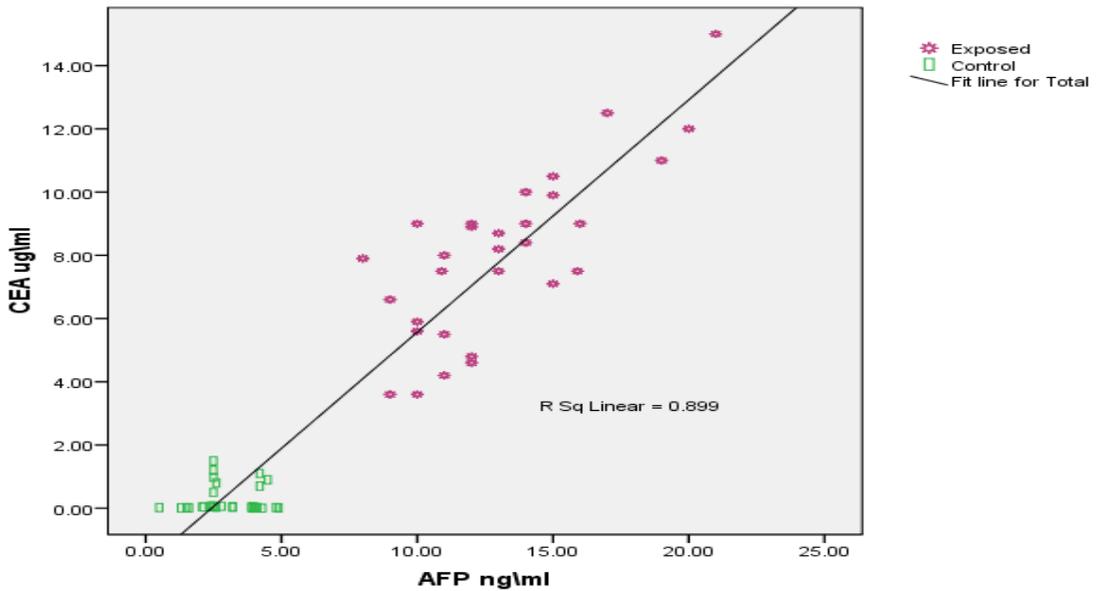
Inhalation of the chemical (FA) together

with the product fumes that occurred during formaldehyde exposures can result in increased urinary thioether excretion. The values of tumour markers higher than the upper limits of normal ranges may reflect the potential risk of some disturbances due to chronic exposure to Formaldehyde vapors.

Our findings concerning the effect of smoking are also consistent with several other studies that have shown that global thioethers excretion was higher in smokers than non-smokers.<sup>(19)</sup>



**Figure 1: The mean levels of biochemical parameters in the examined two groups. The high levels of biochemical changes were significantly higher than those of control subjects**



**Figure 2: The mean levels of tumor markers(AFP and CEA) in exposed and control groups where direct positive association were found in exposed subjects in comparison with control group**

**Table 3: Correlation Coefficient of air formaldehyde and biochemical parameters**

		Air Formaldehyde(HCHO)
ALT(U/L)	r =	0.43
	Significant,(2-tailed)	P<0.01
AST(U/L)	r =	0.189
	Significant,(2-tailed)	NS*
AFP(ng/ml)	r =	0.49
	Significant,(2-tailed)	P<0.01
CEA(ug/ml)	r =	0.48
	Significant,(2-tailed)	P<0.01
Urinary Thioether(umol/mmol creatinine)	r =	0.42
	Significant,(2-tailed)	P<0.01

\*NS: Not significant

Table (3) & Figure (2) shows a significant formaldehyde vapors and the level of AFT, positive correlation between air level of CEA level, ALT, AST and level of urinary

thioethers. The only insignificant correlation were in the level of AST and formaldehyde in air. Prolonged or concentrated exposure to the formaldehyde vapors can generate a wide damage to the liver cells as indicated by different biochemical functions.<sup>(20)</sup>

Our findings came in accordance with pervious studies that linked occupational exposure in metals and organic solvents industry where exposure to FA was present with the development of tumors.<sup>(21)</sup> In chronic exposure to FA, the values of tumor markers were found to be higher of normal ranges, potential risk of carcinogenicity is expected.<sup>(22-24)</sup>

Moreover, higher incidence of cancer is suspected in exposed subjects showing high levels of tumors markers and higher levels of urinary thioethers.

## CONCLUSION

In conclusion, our study points to the necessity of evaluating health status of workers occupationally exposed to

formaldehyde especially staff in histopathology and anatomy laboratories. The revealed association between formaldehyde exposure, biochemical indices, and the levels of tumor markers should be further studied in larger groups of workers.

This results indicate the need for strict preventive measures for those these results, actions for those exposed to FA vapors including those working in macroscopic examination of specimens.

In general, reduction of exposure to formaldehyde vapors among occupationally exposed workers may be may be achieved through adequate local exhaust ventilation and by keeping the biological specimen containers closed during the macroscopic examination.

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