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Study of the Effect of Occupational Exposure to Volatile Organic Compounds (VOC's) on Male Reproductive Hormones

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Abstract: The furniture sector is dominated by small enterprises that operate with, labor- intensive methods and it is plagued by problems. Occupational exposure to solvents, is one of these problems and may lead to hazardous effects. There is a limited amount of literature on the effects of organic solvents on male reproductive functions, especially the exposure to a mixture of different volatile organic compounds (VOC'S). Studies on hormonal changes might be useful for detection of the reproductive dysfunction among the workers exposed. The study consists of 60 painting workers out of 1000 male workers in a furniture manufacturing plant. They worked in the painting and finishing processes and exposed directly or indirectly to a mixture of toluene, styrene and benzene at the work place (exposed group). Twenty seven, non -exposed male workers comprised the control group. VOC's were measured in the air samples from the workplace of the exposed workers. The reproductive male hormones (testosterone, FSH, LH) were estimated in the two examined groups. Participants stated that, they had some medical complaints. The most frequently mentioned complaints were musculoskeletal pain especially joint pain (53.3%), skin and mucous membrane irritation (56.6%). The testosterone was found to be significantly lowered, while, FSH and LH, were found to be significantly elevated in the exposed group in comparison to the control group. There was a significant negative correlation between the testosterone levels and the duration of exposure of workers and a significant positive correlation for the FSH while no significant correlation has been found for LH. Exposure to different levels of mixture of organic solvents (VOC'S), had toxic effects on male reproductive hormones through a direct testicular damage, especially in the prolonged exposure workers.

Key words: Solvents · Male reproductive hormones · Occupationally exposed · Furniture sector

INTRODUCTION

Furniture sector is dominated by small enterprises that operate with a labor- intensive method and employ almost exclusively male workers. The sector is plagued by problems such as long working hours, unprotected workers, physical and mental overload, exposure to paints, varnish, lacquer and glue and these materials contain volatile organic solvents (VOC's). Occupational exposure to solvents may lead to various injury and illness, through inhalation of the toxic vapors and /or absorption of irritants through the skin. The magnitude of hazards becomes more worsen in confined area. Various adverse effects for solvents intoxication such as cognitive impairment, behavioral, neuro-pathological, hepatotoxic and nephrotoxic effects have been reported in several studies [1-4]. Several organic solvents have been suggested to affect neurochemical mechanisms in the brain, which control gonadotropin release from the anterior pituitary [5-7]. There is a limited amount of literature on the direct effects of organic solvents on male reproductive functions. Testicular functions including testosterone secretion are very sensitive to chemical insult and they are relatively affected firstly among the

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body organs [8]. There are controversial reports on the effects of organic solvents on spermatogenesis and testicular histology [9-12]. Thus, there is inconclusive evidence for relations between exposure to solvents and male fertility. In addition, several studies have examined the reproductive toxicity of a single organic solvent. However, environmental and industrial solvent exposure usually involves exposure to a mixture of different organic solvents. Studies on hormonal changes might be useful for detection of reproductive dysfunction among workers exposed to a mixture of organic solvents. As, studies are mostly in animals and human studies in this regard are very limited, it merits more investigations.

The aim of this work is studying the impact of occupational exposure to a mixture of VOC's on the male reproductive hormones.

MATERIALS AND METHODS

The study consists of sixty furniture painting workers out of 1000 male workers in a furniture manufacturing plant. They had worked in the painting and finishing processes for more than 2 consecutive years. They were exposed group directly or indirectly to a mixture of toluene, styrene and benzene at the work place. Twenty seven non exposed male workers, who had worked outside the manufacturing building and, proved not exposed occupationally to VOC's were matched with the exposed workers for age, socioeconomic-status and designated as the control group. All subjects were selected with the following exclusion criteria.

Exclusion Criteria:

- Suffering from any chronic diseases, or any hormonal troubles which may induce sterility
- Receiving treatment with chemotherapeutic drugs, radio-therapy or exposure to radiation.
- Had done any of the following operations: bladder neck, hydrocele, hypospadias, undescended testicle, spermatocele, varicocelectomy, vasectomy, inguinal hernia repair and prostatectomy
- Had a high fever in the last 6 months
- Had prostatitis, epididymitis, testicular torsion or trauma
- Had any of the following infections: chlamydia, gonorrhea, herpes, HIV and syphilis.
- Taking any dietary supplements for muscle building or any narcotic drugs

An interview questionnaire especially designed, covering present and past occupational histories as well as inquiries about manifestations suggestive of chronic solvents intoxications was done for both exposed and control groups. All subjects included in this work were clinically assessed. Five milliliters of blood were collected from all the subjects. The sera were separated by centrifugation and stored at -20°C, for measurement of:

- Serum testosterone, which was determined using an ELISA kit purchased from Callbioteck inc, USA according to the method of Chen *et al*. [13].
- Serum follicular stimulating hormone (FSH), which was measured using ELISA kit purchased from Callbioteckinc, USA according to the method of Rose [14] and Qiu *et al*. [15].
- Serum Lutinizing Hormone (LH) was determined using ELISA kit purchased from Callbioteckinc, USA according to the method of Morimoto and Inouye [16].

Statistical Analysis: Statistical analysis was done using SPSS version 16. Independent t-test and analysis of variance (ANOVA) with the least significant difference (LSD) were used for comparison of the quantitative results. Correlation coefficient was also used to study the relationships between the quantitative variables. The level of significant was at less than 0.05.

RESULTS

Table 1 and Fig. 1 shows the results of environmental study. It can be noticed that the concentrations of VOC's in air of the work place are below the threshold value for these VOC's. The demographic and other characteristics of the exposed group are described in Table 2. All of the participants were male, 84% were married and all of them had children except 2 workers (1%), who are recently married. The mean age for the exposure and control groups was 39.2±9.9 years and 41.3±15.1years, respectively. The mean age difference between the two groups was non-significant. The average period of exposure of the exposure group was 13.741±8.01 years when the protective measures were investigated, only 5% of the exposed workers are always using the protective masks or gloves at work and the rest of them (95%) are rarely using or not using at all the protective masks or gloves at work. Almost all participants stated that, they had some medical complaints. The most

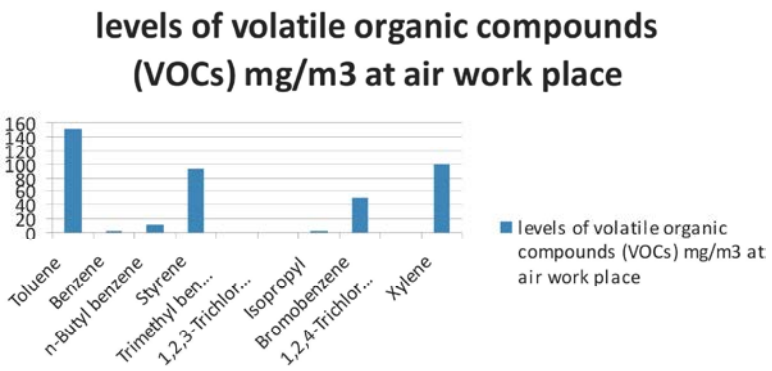

Fig. 1: Concentration of different volatile organic compounds (VOCs) mg/m^3 at air work place

Table 1: International maximum allowable air levels for different solvents at work place

VOCs	MAC[1]	OSHA PEL- TWA	NIOSH REL-TWA	ACGIH TLV- TWA	Levels of (VOCs) mg/m^3 at air work place
Toluene	188 mg/m^3	760 mg/m^3	375 mg/m^3	192 mg/m^3	151.4 mg/m^3
Benzene	1.6 mg/m^3	3.19 mg/m^3	3.19 mg/m^3	1.6 mg/m^3	1.3 mg/m^3
n-Butyl benzene	70.5 mg/m^3	NA	NA	NA	10.28 mg/m^3
Styrene	126.5 mg/m^3	420 mg/m^3	215 mg/m^3	85 mg/m^3	91.4 mg/m^3
Trimethyl benzene	NA	NA	125 mg/m^3	NA	0.2 mg/m^3
1,2,3-Trichlorobenzene	0.1 mg/m^3	NA	NA	NA	0.02 mg/m^3
Isopropyl	NA	980 mg/m^3	980 mg/m^3	400 mg/m^3	1.7 mg/m^3
Bromobenzene	NA	NA	NA	NA	49.14 mg/m^3
1,2,4-Trichlorobenzene	NA	NA	NA	NA	0.085 mg/m^3
Xylene	100	435mg/m^3	435mg/m^3	435 mg/m^3	100 mg/m^3

NA: not available

MAC: Maximum allowable concentrations according to Egyptian Environmental Law 4 *(EEAA, 1994).*

ACGIH: American Conference of Industrial Hygienists, TLV: Threshold Limit Value, TWA: Time Weighted Average for 8 hours shift, OSHA: Occupational Safety and Health Administration of the US, PEL: Permissible exposure limits by US laws, NIOSH: National Institute of Occupational Safety and Health, REL: Recommended exposure limits, EU: European Union, OEL: Occupational exposure limits. http://www.cdc.gov.

Table 2: Characteristics of the studied groups

Parameters	Exposed n=60	Controls n=27	P-value of the independent t-test
Age(years)			
Range (min-max)	19 - 58	20 - 70	0.458*
Mean ±S.D	39.2±9.9	41.3±15.1	
Duration of employment (years)			
Range (min – max)	2 - 29	--	--
Mean ±S.D	13.741±8.012	--	--
Marital status			
Married (number- %)	50- (84%)	18 – (66%)	0.06*
Single (number- %)	10- (16%)	9 – (34%)	
Smoking			
Non -smoker (number- %)	29-(47%)	20- (74%)	0.01**
Smoker (number- %)	32-(53%)	7- (26%)	
Using Personal Protective Equipment (PPE)			
No (number- %)	39(65%)	--	--
Yes (number- %)	21(35%)	--	--
Always (number- %)	3(14.29%)	--	--
Rarely (number- %)	18(85.71%)	--	--

P value > 0.05 not significant

** P value < 0.05 significant

Table 3: Statistical comparison of male reproductive hormones among the studied groups

Parameter	Groups	N	Mean	SD	P-value of the independent t-test
FSH (mlU/ml)	Control	27	7.41	2.88	P< 0.0001
	Exposed	60	12.84	3.11	
LH (mlU/ml)	Control	27	4.51	1.53	P < 0.001
	Exposed	60	5.71	2.35	
Testosterone (ng/ml)	Control	27	4.91	2.09	P < 0.001
	Exposed	60	3.77	1.13	

* P value < 0.05 significant

Table 4: Analytical comparison of the male reproductive hormones between the four groups

	Controls (27)		< 10 yrs (22)		11-20 yrs (20)		> 20 yrs (18)		
	G1		G2		G3		G4		
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P-value
FSH	7.4	2.91	9.68	1.86	14.3	1.67	15.5	2.68	P< 0.0001
	(G2,3,4)		(G1,3,4)		(G1.2)		(G1.2)		
LH	4.5	1.54	6.3	2.72	5.3	1.94	5.2	1.58	P< 0.05
	(G2)		(G1)		(--)		(--)		
TESTOSTERONE	4.9	2.11	4.2	1.26	3.5	.88	3.5	1.13	P< 0.01
	(G3,4)		(--)		(G1)		(G1)		

Group 1: The control group

Exposed group was divided to three groups according to duration of exposure into:

Group 2 :< 10 years of exposure

Group 3: 11-20 years of exposure

Group 4: > 20 years of exposure

Table 5: Correlation coefficient between duration of exposure and reproductive hormones among the male workers

Parameter		Duration of exposure (Years)
FSH (mlU/ml)	Pearson correlation	0.7
	Sig. (2-tailed)	P< 0.0001*
LH (mlU/ml)	Pearson correlation	-0.2
	Sig. (2-tailed)	NS
Testosterone (ng/ml)	Pearson correlation	-0.3
	Sig. (2-tailed)	P< 0.01*

* P value < 0.05 significant

frequently mentioned problems were musculoskeletal pain especially joint pain 53.3%, skin and mucous membrane irritation of the workers 56.6%. The male reproductive hormones revealed significant changes between the two studied groups (Table 3). The testosterone was found to be significantly lowered in the exposed group in comparison to the control one. While, FSH and LH were found to be significantly elevated in the exposed group in comparison to the control one.

Table 4 shows an analytical comparative for the different concentration of the male reproductive hormones of the control group (G1) and the exposed group, the later was divided into three groups according to the duration of exposure of its workers into: Group II (G2) included 22 males exposed workers to less than 10 years of exposure to mixture of organic solvents. Group III (G3) included 18 males exposed between 10-20 years to the same mixture. Group IV (G4) included 20 males exposed workers to more than 20 years of exposure to a mixture of organic solvents. The results obtained from Table 4 showed that, the mean concentration of testosterone in G2, 3, 4 is decreasing and this decrease is significant only in prolonged exposure (G3, 4) when compared to G1. While the mean concentration of FSH in G2, 3, 4 is increasing and this increase is highly significant in the three exposed groups (G2, 3, 4), when compared to the control one. The mean concentration of LH is increasing only in prolonged exposure (G3, 4) but this increase was not significant. Table 5 shows a significant negative correlation between the testosterone levels and the duration of exposure of the exposed group and a significant positive correlation between the FSH and the duration of exposure, while no significant correlation has been found for LH.

DISCUSSION

Several epidemiologic studies have suggested that organic solvents affect male reproductive functions [5, 9, 10, 17-19]. In addition, Mandiracioglu *et al*. [20] mentioned that the average blood toluene and benzene were 6.95 times and 1.64 times respectively higher in groups of furniture workers that are engaged in painting and varnishing than those performing other tasks. In the present study, environmental assessment of the VOC's levels was within the concentrations of standard as mentioned in OSHA, NIOSH and ACGIH. The highest compound was toluene, xylene, styrene and bromobenzene. Several organic solvents have been investigated under the aspect of impairment or disruption of the neurochemical mechanisms in the brain which control hypo-physeal gonadotropin release [The hypothalamus pituitary axis]. And literature on the direct effects of organic solvents on the male reproductive function was limited, especially in the occupational sector.

The present data show the effects of VOC's exposure upon male reproductive hormones, which revealed significant changes in the levels of FSH, LH and testosterone as compared to controls. This might indicate an increased risk of sub fertility, as mentioned in the studies of Luderer *et al*. [19] and that of Welch *et al*. [21], as higher levels of FSH and LH and lower levels of testosterone than control is an indicative of reproductive dysfunction. Welch *et al*. [21, 22] reported in his two studies an increased risk of sub-fertility, due to lowered of the total sperm count for painter workers without a concurrent change in serum FSH, LH and testosterone. The present study demonstrates inhibitory effects for the exposure to the solvents mixture in exposed workers on the testosterone levels. These findings have been demonstrated by Yilmaz *et al*. [18], who found that serum and testicular testosterone levels are reduced in adult rats after inhalation of 1500 ppm or 3000 ppm of paint thinner that contains 66% toluene. Hanaa *et al*. [7] have confirmed this finding through the use of three inhalants. She has proved that, each one of the three inhalants used in her study (Gasoline, per-chloroethelene and toluene) has decreased the testosterone levels in the exposed rats. Also, Tsukahara *et al*. [23] showed the same findings not only in prepubertal and adult male rats but also in fetal male rats. Hashem *et al*. [17] and Yilmaz *et al*. [18] reported that toluene inhalation affects testosterone synthesis and secretion via a direct action on the Leyding cells. The results of our study are within the same findings of those two studies and through the hormone- hormone feed-back mechanism, the lowered level of serum testosterone due to solvents exposure will stimulate the secretion of gonadotrophic hormones (FSH, LH) from the anterior pituitary, as our results revealed rise in the levels of FSH, LH of the exposed group compared to the control one. Increased secretion of gonadotrophic hormones (FSH, LH) are often observed in the setting of primary testicular damage, due to reduced negative feed-back from the sertoli cells in exposed worker groups of Luderer *et al*. [19]. Also, Hashem *et al*. [17] found the same results on rats that inhale the volatile substance toluene. The inhibition of testosterone secretion through the inhibitory toxic effect of solvents on gonadotropin releasing hormone (GnRH) or through its inhibitory effect on pituitary responsiveness to GnRH as proved by Yilmaz *et al*. [5] on male rats, has not been proven yet in our study and the anti-gonadotropic effects, which in-turn lead to reproductive dysfunction in humans, needs long standing exposure as explained by Tsukahara *et al*., [23] in their study on fetal and adult rats and that of Hashem *et al*. [17]. The last study found a direct proportionality between the histopathlogical and biochemical changes observed in the testis of rats exposed to toluene inhalation and its direct toxic effects on spermatogenic cells, Sertoli cells and Leyding cells and these toxic effects were significantly correlated with blood toluene of rats and length of exposure duration.

In the present study, the duration of exposure to a mixture of solvents was negatively correlated with testosterone concentrations, where the mean concentration of testosterone of G3,4 [the groups of longer duration of exposure] were decreased, as that of G2, but their decrease were significant. Yilmaz *et al*. [18] suggested that inhalation of paint thinner for 30 days inhibits testosterone synthesis and secretion, by direct action on the Leyding cells. Thus this negative correlation observed in the study may represent a direct effect due to testicular damage caused by solvent exposure. This association has been found by Svenson *et al*. [11] in printing workers exposed to toluene. Also, Hashem *et al*. [17] on albino rats, found a direct proportionality between the length of toluene inhalation (blood toluene) and its direct toxic effects on testosterone and gonadotropin hormones. However, Luderer *et al*. [19] found no significant association for solvent exposure with testosterone levels in groups of workers exposed to different types of solvents. In the exposed group under study, we found a significant positive association

between the duration of exposure to a mixture of solvents and the FSH concentrations. This finding became more obvious in Table 3, where the mean concentration of FSH were increased in all exposed groups (G2, 3, 4) and these increase were highly significant. The increased FSH concentrations are often observed in the setting of primary testicular damage, due to reduced negative feed-back mechanism. This association has been proved by Svenson *et al*. [10] in printing workers exposed to toluene and also by Hashem *et al*. [17] and Luderer *et al*. [19].

Abnormalities in reproductive hormone concentrations have been inconsistently associated with occupational solvent exposure in men [19]. Reduced LH, FSH and testosterone were associated with recent toluene exposure in printer workers [24]. In contrast, chronic toluene exposure was associated with increased FSH and unchanged LH and testosterone concentrations [24]. In our study there was a significant reduction in levels of testosterone and significant increase in the FSH and LH levels in exposed group compared to the control one and there were associations between the testosterone and FSH and the duration of solvent exposure. While, there was no apparent correlation between LH and the duration of solvent exposure. This could be explained by the fluctuations in the mean of LH concentration for the three groups of exposure (Table 3). These findings are in line with those obtained by Morck *et al*. [24] and that of Luderer *et al*. [19], who found no association between LH and any of solvent exposure indices of her study, but there was a tendency for LH to decrease with increasing aromatic solvent exposure. Likewise the testosterone, while the FSH showed a tendency to increase with all solvent exposure indices. Thus FSH tend to increase by 1.3 fold and 1.2 fold for every 10 fold increase in the chlorinated solvent exposure index and increase in total solvents or thinners, degreasers, varnishes an adhesives, respectively [19].

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