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CLINICAL AND LABORATORY FINDINGS AMONG NAPHTHALENE BALLS MANUFACTURING WORKERS

By

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Abstract

Introduction: Exposure to naphthalene is associated with many toxic effects in humans and laboratory animals. **Aim of work:** To assess the clinical and laboratory changes among workers occupationally exposed to naphthalene during manufacturing of naphthalene balls. **Materials and Methods:** This study was conducted on fifty workers in naphthalene balls manufacturing factory. They were compared with fifty non-exposed individuals. Full history was taken and clinical examination was performed. Complete blood picture, reticulocyte count and G6PD activity, urinary naphthalene, albumin and α1 microglobulin in urine were measured in both groups. Environmental assessment of naphthalene in air at workplace was done. **Results:** The level of urinary (1- and 2-naphthol), urinary albumin and urinary α 1-microgloblin were significantly higher ($p< 0.001$) among the exposed group compared to the control one. Hemoglobin levels and hematocrit percentage were significantly decreased ($p< 0.001$) among the exposed group compared to the control. A statistically significant positive correlations among exposed workers were found between the level of urinary (1-and 2-napthanol) and each of duration of employment, urinary albumin and α 1-microgloblin . There were a statistically significant negative correlation between urinary (1 and 2-napthanol) and hemoglobin level. The geometric means of the measurement of naphthalene at workplace were 100 mg/m^3 which exceeded the occupational exposure limits according to Egyptian Environmental law (50 mg/m^3). **Conclusion:** Occupational exposure to naphthalene leads to increased risk of health hazards with possible renal and hematological impairment. Therefore environmental control measures and good work practices are recommended at the workplace.

Key words: Naphthalene exposure, Hemoglobin level, Urinary albumin, Urinary 1- and 2-napthanol and α 1-microgloblin

Introduction

Naphthalene is formed from either coal tar or petroleum. It is used in the production of a variety of industrial products as phthalic anhydride,1-naphthyl methyl carbamate insecticide, related products (tetralin and 1-naphthol), dispersant chemicals, moth repellent and synthetic tanning agents (HSDB, 2003). People are exposed to naphthalene by inhalation of outdoor and indoor air with naphthalene-containing moth-repellents, burning wood, and tobacco smoke. Exposure to naphthalene also occurs through contaminated water by landfills and underground discharges (Arey and Atkinson, 2003). High exposures occur among workers in industries where naphthalene is present at high concentrations, e.g., mothball manufacturing and creosote-impregnation facilities. Naphthalene is absorbed into the systemic circulation following inhalation, ingestion or dermal exposure resulting in systemic toxicity. Inhalation is considered to be the main route of exposure (ATSDR, 2005). Naphthalene is metabolized into a number of reactive epoxides, 1,2-naphthalene oxide, by cytochrome P450 oxidation. The epoxides can change to 1-naphthol or 2-naphthol, which can be conjugated to glucuronides and excreted in the urine (ATSDR, 2005). Naphthalene mothballs is a white solid compound. It is called white tar and tar camphor. It is sold commercially due to its freezing or solidification point. There is a relation between the freezing-point and the naphthalene content of the product. The relation depends on the type and relative amount of impurities that are present. The freezing point is changed appreciably by the presence of water and specifications using the suitable method (Mason, 1995). Exposure to naphthalene is associated with many toxic effects in humans and laboratory animals. Exposure to large amounts of naphthalene may damage or destroy red blood cells in the body resulting in a hemolytic anemia. Naphthalene undergoes oxidative hepatic metabolism, resulting in alpha naphthol and metabolites that produce oxidative stress. This results in oxidation and denaturation of hemoglobin, the production of Heinz bodies, and increased erythrocyte susceptibility to hemolysis (Sudakin et al., 2011). Individuals with glucose-6-

phosphate dehydrogenase deficiency are more susceptible to hemolysis by naphthalene. Inhalation of naphthalene causes gastrointestinal symptoms, such as nausea, vomiting, abdominal cramps and diarrhea; neurologic symptoms, such as confusion, excitement, and convulsions; renal problems; eye and skin irritation (ATSDR, 2005).

Aim of work

To assess the clinical and laboratory changes among workers occupationally exposed to naphthalene during manufacturing naphthalene balls (mothballs).

Material and Methods

Study design: This is a cross sectional comparative study.

Place and duration of the study: This study was carried out at a factory manufacturing mothballs in Helwan area, Southern Cairo, Egypt during the period from May to August in 2017.

Study sample

The study was conducted on two groups: an exposed and a control group. The first group included 50 male workers on the production line in the factory. The total number of workers in production line was 120. Simple randomization enrolled 60 workers, however, only 55 workers from the 3 shifts within the factory who accepted to participate in this study, and 5 were excluded from the study according to exclusion criteria. Inclusion criteria for exposed workers included being employed in the factory for at least 5 years.

A 50 control subjects were chosen from security personnel and administrative workers, who had never been exposed to naphthalene dust.

Exclusion criteria for both the exposed and control groups included any history of chronic illness as diabetes, renal diseases, autoimmune diseases, malignancy or receiving drugs as chemotherapy and /or radiotherapy the last 6 months.

Study methods:

- A questionnaire consisted of socio-demographic status, present, past, family and occupational histories (onset and duration of employment), and special habits as smoking in details. The study was conducted using face-to-

face interviews in the local language of the country.

- Clinical examination was done for both the studied groups.

- Worker safety was assessed by observing the use of self-protective equipments like gloves, masks as a safety personal protection.

-Evaluation of work place included assessment of general maintenance and chemical handling, presence of proper exhaust ventilation and over all conditions of walls, ceiling and floor, and air circulation in the work place.

-Laboratory Investigations:

Blood and urine samples were collected at the end of the work shift in the workplace. Five milliliters of blood were drawn and were divided into two tubes: one is plain for serum separation, the other tube contained EDTA-anticoagulant. Urine samples were collected in polyethylene tubes and were frozen at –18°C until analysis. Tubes were transported to the laboratory (on dry ice) as early as possible for analysis.

1- Analysis of hematological parameters:

Complete blood count parameters were estimated by Sismex xs, 800i, Japan. G6PDH activity was measured by kinetic method (Cat No: G6P12205, BioMed Diagnostics) using Spectrophotometer 5010 v5, Berlin (Normal: 6.4-18.7 U/gHb). Blood films were prepared and stained with brilliant cresyl blue supravital stain to count reticulocytes under microscope (Normal: 0.5-2.5 %). The blood parameters used in this study included hemoglobin (Normal: 14-17 g/dL), Packed cell Volume (Hematocrit %: 38-50), WBCs (Normal: 4-11x103/Cmm), Platelet counts (PLTs,) (Normal: 150-450 x 103/Cmm).

2- Assessment of renal function:

Quantitative analyses of proteins in urine were performed using a Behring BN IProSpec nephelometer (Siemens Healthcare, GmbH, Germany) (Schotters et al., 1988). Glomerular renal function was assessed by determining albumin in urine, while tubular renal function was assessed by determining α1-microglobulin in urine. The protein concentrations in urine were expressed per gram of creatinine. Urinary creatinine was determined

photometrically by kinetic Jaffe´ method using Hitachi 917 automated biochemical analyzer (Roche) (Taussky, 1954).

3- Determination of naphthalene metabolites (1-and 2-naphthol) in urine:

At time of analysis frozen urine samples were thawed and mixed to homogenize them thoroughly. Two ml of urine were mixed with 4 ml of Na acetate buffer solution (0.1 mol/l, pH 5.0) and 25 μl β-glucuronidase and incubated overnight at 37°C. Each sample was centrifuged for 10 min at 1500 g. A total of 1.4 ml of the supernatant was transferred into 1.8 ml glass sample vials. Samples were extracted using solid phase extraction (C18, 1 mL, 100 mg) using methanol (2 ml) and water (2 ml) then washed with water (1 ml) and 30% acetonitrile (1 ml), and eluted with 200 μL methanol. Then 350 μl were injected into three dimensional high performance lipid chromatography/fluoresce detection (3D-HPLC-FLD) (excitation 227nm, emission 430 nm) (Agilent 110 LC system) for quantitative analysis of 1- and 2-naphthol according to the method of Preuss and Angerer (2004). Urinary naphthalene metabolites were adjusted by urinary creatinine. The lowest limit of detection was estimated to be 1.5 μg/L for 1-naphthol and 0.5 μg/L for 2-naphthol.

-Environmental assessment:

Workplace air samples for naphthalene were taken by the industrial hygienist of the factory. Samples were collected during shift time from different places during mothballs manufacturing.

Analysis was performed by HPLC according to U.S. National Institute for Occupational Safety and Health, OSHA Method ORG-35 (OSHA, 1982). The geometric means of the measurement of naphthalene were 100 mg/m3; ranged from 50–150 mg/m3. The measurements exceeded the occupational exposure limits according to Egyptian Environmental law (50 mg/m3) (EEAA, 1994) and occupational safety and health administration (50 mg/m3) (NIOSH, 2005)

Consent

A consent to participate in the study and an agreement to give blood and urine samples from each individual

were obtained after explaining to them the objectives and the importance of this study. All participants were treated according to the Helsinki Declaration of biomedical ethics.

Ethical approval

The study was approved by the ethical committee of the Department of Occupational and Environmental Medicine, Cairo University, Egypt. An approval from the factory authority to perform this study was obtained.

Data management

The data were coded and entered using the statistical package SPSS 15.0 for windows. The mean values, standard deviation (SD) median and ranges were estimated for quantitative variables, as for the qualitative variables, data were represented as frequencies and percentages. Comparisons between the exposed and non-exposed groups using two-tailed Student's t-test and Chi-squared tests for normally distributed variables and nonparametric Mann–Whitney test for quantitative variables, which were not normally distributed. Spearman coefficient correlation test was used to test the correlation between variables among the exposed groups. P-value of less than 0.05 was considered statistically significant.

Results

Table (1): Demographic characteristics of the studied groups.

	Exposed (No=50)	Non-exposed (No=50)	Test	p value
Age in years Mean ± SD Median -range	49.4± 7.07 50(29-60)	47.47± 6.70 48.5(29-59)	1.63 #	0.976
Smoking habit **No (%)** Smoker 33 (%) Non-smoker 67(%)	18(54.5%) 32(47.8%)	15(45.5%) 35(52.2%)	0.407###	0.523
£Smoking index Median -range	289(45-1034)	233(35-655)	0.72 ##	0.654
Work duration (years) Mean ± SD Median -range	28.7 ± 9.27 17(4-35)	----------	--------	-------
Using of PPE€ **No (%)** **Yes** **NO**	18(36%) 32(64%)	---------	-------	-------

#Independent sample t test (mean ± SD) ###Chi-square (x2)

##Mann-Whitney test (median-range)

£ Smoking index: number of cig./day x duration of smoking in years

€ PPE: Using personal protective equipment among exposed workers

Table (1) showed that there was no statistically significant difference regarding age, smoking index and number of smokers between exposed and non-exposed groups. There was only 36% of workers use PPP.

Table (2): The prevalence of clinical symptoms among the studied groups.

	Exposed (No=50) No (%)	Non-exposed (No=50) N0 (%)	X^2	p value
Cough	18(36%)	5(10%)	9.55	**0.002***
Expectoration	17(34%)	3(6%)	8.13	**0.004***
Rhinitis	11(22%)	2(4%)	7.16	**0.015***
Conjunctivitis	11(22%)	3(6%)	5.31	**0.041***
Contact dermatitis	18(36%)	4(8%)	11.42	**0.001****

*: Statistically significant * *: Highly statistically significant

Table (2) showed that all studied clinical symptoms were statistically significantly higher among the exposed workers when compared to non-exposed.

Table (3): Hematological and renal function parameters among the studied groups.

	Exposed (No =50)	Non-exposed (No =50)	Test	p value
Hb level g/dl (Median –range)	13.1(10-17)	15(13-17)	-4.207#	**< 0.001****
	No (%)	No (%)		
Decreased Hb (No =31) **Normal Hb (No =69)**	28(90.3%) 22(31.9%)	3(9.7%) 47(68.1%)	29.21##	**< 0.001****
	Median -range	Median -range		
Hematocrit %	39.7(28.2-49.1)	50(40.2-54)	-6.310#	**< 0.001****
WBCs 10^3/Cm	6.2(3.9-13.1)	6.3(4.6-8.8)	-0.283#	.777
Platelets 10^3/Cm	214(155-371)	201(158-344)	-0.637#	.524
Reticulocytes %	0.5 (0.1-0.8)	0.3(0.1-0.7)	-1.188#	.235
G6PD activity	7.8(4-18.2)	6.2(3-16.2)	-.598#	0.55
1-naphthol μg/l **2-naphthol μg/l**	55(8.4-180.6) 40.3(5.6-170)	12 (2.4-35.4) 10 (2.1-33.4)	7.59# 6.78#	**< 0.001**** **< 0.001****
Albumin in urine gm/creatinine	1.2(0.2-1.8)	0.2 (0.1-0.3)	5.89#	**< 0.001****
α 1-microglobulin gm/creatinine	1.4 (0.3-1.7)	0.6 (0.1-0.4)	8.21#	**< 0.001****

#: Mann-Whitney test (median-range) ##:Chi-square (x^2)

* *: Highly statistically significant

Table (3) showed that there were statistically significant decrease levels of hemoglobin, hematocrit %, while there were increased levels of urinary1-naphthol, 2-naphthol, albumin and α 1-microgloblin among exposed group compared to non-exposed. There were no statistically significant difference regarding WBCs, platelets, reticulocytes and G6PD activity among exposed subjects.

Table (4): Urinary1-naphthol and 2-naphthol among smokers and non-smokers of the studied groups (®).

	Exposed (No =50)		**Non-exposed (No =50)**		**Z test ®**	**p value**
	Smokers No =18 Median -range	**Nonsmokers No =32** Median -range	**Smokers No =15** Median -range	**Nonsmokers No =35** Median -range		
1-naphthol *μ*g/l	60.4(7.4-189.4)	15(2.4-73.5)	10(2.6-54.3)	4.9(1.5-25.4)	10.48¥ 9.12@ 7.24† 2.14‡	**<0.001**** **<0.001**** **0.008*** **0.03***
	60.4(7.4-189.4)	15(2.4-73.5)	10(2.6-54.3)	4.9(1.5-25.4)		
2-naphthol *μ*g/l	45.3(6.8-180.3)	10.8(2.2-36.2)	9(2.1-46.3)	3.2(0.5-20.6)	7.34¥ 6.56@ 5.68† 2.05‡	**<0.001**** **<0.001**** **0.005*** **0.02***
	45.3(6.8-180.3)	10.8(2.2-36.2)	9(2.1-46.3)	3.2(0.5-20.6)		

®: Z value obtained by Mann-Whitney test. Data presented by median (range)

¥: (comparison between smokers of the exposed group and non-exposed group)

@: (comparison between nonsmokers of the exposed group and non-exposed group)

†: (comparison between smokers and nonsmokers among exposed group)

‡: (comparison between smokers and nonsmokers among non-exposed group).

*: Statistically significant **: Highly statistically significant

Table (4) showed that there were statistically significant differences between smokers of the exposed and non-exposed group ; nonsmokers of the exposed and non-exposed group ; smokers and nonsmokers among the exposed group ; smokers and nonsmokers among the non-exposed groups , regarding increased values of urinary1-naphthol and 2-naphthol.

Table (5): Correlation coefficient between different variables among the exposed group.

Exposed group (No =50)	Hb level gm/l	α 1-microgloblin gm/creatinine	Albumin in urine gm/ creatinine	1-naphthol μg/l	2-naphthol μg/l
Duration of Employment	r= - 0.53 **p=0.002***	r= 0.37 **p =0.01***	r=0.45 **p = 0.02***	r= 0.81 **p <0.001****	r=0.74 **p <0.001****
Smoking Index	r =0.15 p =0.391	r =0.13 p =0.302	r =0.07 p =0.563	r= 0.85 **p <0.001****	r=0.76 **p <0.001****
1-naphthol μg/l	r= -0.63 **p <0.001****	r= 0.41 **p =0.005***	r =0.57 **p = 0.004***	--------	r=0.71 **p <0.001****
2-naphthol μg/l	r= -0.76 **p <0.001****	r= 0.51 **p = 0.02***	r =0.43 **p = 0.03***	r= 0.75 **p <0.001****	------

*: Statistically significant **: Highly statistically significant

Table 5 showed statistically significant positive correlations between each of urinary1-naphthol and 2-naphthol and each of duration of employment, smoking index; α1-microgloblin and albumin in urine. Hemoglobin levels were inversely correlated with each of duration of employment, urinary1-naphthol and 2-naphthol.

Discussion

Although there are limited human data considering chronic exposure to naphthalene, experimental studies (Van Winkle et al., 1995 and Fanucchi et al., 1997) reported damage to ciliated and Clara cells of the bronchiolar epithelium in mice. The current study found higher prevalence of cough, expectoration, rhinitis, conjunctivitis and contact dermatitis among exposed workers compared to non-exposed (Table 2). This is similar to the findings of NTP, 2000 who found an increased incidence of alveolar and bronchiolar adenomas, olfactory epithelium metaplasia among

female mice due to naphthalene exposure. Our study was concomitant with the study done by ATSDR, 2005 that dermal exposure to naphthalene causes skin irritation. Individuals who are sensitive to naphthalene and dermal contact may give rise to severe dermatitis. In their experimental studies Xu et al., 1992 and Lou et al. 1996 detected that ocular exposure to naphthalene resulted in eye irritation, corneal damage, lens opacities and the formation of cataract.

The adverse health effects found in this study could be attributed to the increased levels of naphthalene vapour in the workplace during naphthalene balls manufacturing together with poor ventilation. Moreover, the minority of the workers (36%) were wearing personal protective equipment during work (Table1).

In the current study there were statistically significant decreased levels of Hb and HCT % (Table 3) among exposed workers compared to non-exposed. Moreover, hemoglobin levels were inversely correlated with each of duration of employment, urinary1-naphthol and 2-naphthol (Table 5). On the contrary, Sudakin et al. (2013) in their study, using the National Health and Nutrition Examination Survey data (2003-2004), found that there was a positive association between naphthalene and Hb and HCT.

Lim et al. (2009) found higher rates of hemolysis in children with gluclose-6-phosphate dehydrogenase deficiency in African Americans naphthalene mothballs usage. In the present study, although environmental monitoring of naphthalene exceeded permissible limits, there were no evidence of hemolysis; there is no statistically significant difference between exposed and non-exposed groups as regards reticulocytes percent and G6PD activity and both of them are within normal ranges (Table 3). This may be due to chronic exposure of the workers in this study to naphthalene while, in Lim et al. study, exposure to naphthalene was acute.

There are limited studies about naphthalene exposure and renal functions. In the present study there is statistically significant increase in urine albumin and α1-microgloblin among exposed group compared to non-

exposed (Table 3). Kundra et al. (2015) reported a case of naphthalene poisoning following ingestion of mothballs, presented with prolonged hemolytic anemia and methaemoglobinaemia. Renal injury as a complication of naphthalene induced hemolysis and hemoglobinuria has been reported by Qian et al. (2010); hemoglobin liberates into plasma, is filtered in the glomerulus and then incorporated into proximal tubules. The increased intracellular level of heme is potentially cytotoxic and causes acute renal injury through different mechanisms: decreased renal perfusion, direct cytotoxicity and intratubular casts formed from heme proteins. Recently Ekambaram et al. (2017) reported a case of a child with naphthalene-induced acute severe hemolytic anemia and acute renal injury from accidental ingestion.

The current study showed an increased level of urinary 1, 2 naphthol among workers occupationally exposed to naphthalene (Table 3). This is in accordance with (li et al., 2006; Petropoulou et al., 2006; Klotz et al., 2011 and Sudakin et al., 2013) who used 1,2 naphthol as biomarkers for the determination of the internal dose of naphthalene in general population as well as among workers occupationally exposed to naphthalene.

Tobacco smoking is known to contribute to polycyclic aromatic hydrocarbon uptake in general and to naphthalene uptake in particular (Serdar et al., 2003). Although there was no statistically significant difference between exposed workers and control group as regards smoking habit and the smoking index (Table1), the current study found statistically significant increase in naphthalene among smokers compared to non-smokers in both groups. Levels of naphthalene among exposed smokers were higher 3 times than exposed non-smokers (Table 4). In addition, there were statistically significant positive correlations between the smoking index and naphthalene (Table 5). This is in agreement with Preuss et al. (2005) who found positive correlation between urinary 1-naphthol and 2-naphthol in all 277 urine samples of smokers occupationally exposed to polycyclic aromatic hydrocarbon. Also, Sudakin et al. (2013) found higher levels of urinary

naphthalene metabolites among current smokers.

From what mentioned above, naphthalene concentrations in urine reflect the sum of all possible pathways of naphthalene uptake; tobacco smoking, inhalation of workplace naphthalene, dermal and/or oral uptake. All these contributors may be of different significance and they can superpose each other.

Exposure time is an important determinant of increased body burden of many toxicants (Kamel et al., 2011). In the current study positive correlations were found between the duration of employment and each of 1-naphthol and 2-naphthol, α1-microgloblin and albumin in urine (Table 5). Therefore, risk of exposure among workers in mothballs manufacturing is likely to increase when they spend long periods of time at work, especially in the absence of protective equipments and under poor hygienic conditions.

Conclusion and recommendations: The detection of higher urinary levels of naphthalene among occupational exposed workers leads to high risk for their health. Therefore, applying proper and suitable environmental control measures at workplace and good work practices presented by wearing personal protective equipments are highly recommended.

Conflict of interests

The authors declare that there is no conflict of interest exists in this research.

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