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HEMATOLOGICAL TOXICITIES ASSOCIATED WITH LONG TERM EXPOSURE TO BENZENE IN SAUDI ARABIA

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Abstract: -

Background *:- the danger of benzene when in contact with the skin or ingestion, but little is known about this substance's danger in the long term by inhalation. This study aims to measure the risk of long-term exposure to benzene among people exposed to it permanently, such as station workers, and to spread sufficient awareness to society in the Kingdom of Saudi Arabia.* ***Materials and Methods:-****A 110 Workers size They were divided into four patient groups according to the chronic exposure rate to benzene, one control group, and three other groups of exposures. patient groups 1 (controlled group), patient groups 2 (exposed less than 1y), patient groups 3 (exposed 1-5 y), patient groups 4 (more than 5). Each group is compared with blood sample parameters (ALT, WBC, MCV, Neutrophils, Eosinophils, Lymphocyte, Monocyte, PLT, Basophils, HB, HEMATOCRIT, MCH, MCHC, AST). Blood samples were drawn from the participants, and statistical tests were performed. Significant change ($p \leq 0.05$) was examined compared to the control group. Workers' exposure to benzene led to a significant change in hematological, hormonal, and hepatic factors compared to the control group.* ***Results:-*** *there is a significant correlation between years of exposure and, WBC, MCV, Neutrophils, Eosinophils, Lymphocyte, Monocyte, while there is no significance observed with other values.* ***Conclusion:-*** *We conclude that blood and liver are affected by chronic doses of benzene through inhalation, after our study was on the group most exposed to benzene, which are gas station workers.*

Keywords: - *Hematological toxicities , benzene, station workers.*

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INTRODUCTION:

The word "benzene", when looking for the origin of the word, we will find that it is derived from "benzene gum" (benzoin resin), It is a well-known perfume among people who worked in the profession of perfumery in Europe in the early sixteenth century as a product from Southeast Asia. Michael Faraday isolated and identified benzene for the first time in 1825. **[1]** In 1833, it was produced by Ellard Mitchlich by distilling benzoic acid (from a gum called benzo) and lime. Then after that they dumped it with gasoline . In 1836, there was a French chemist, Auguste Laurent, who named the substance "Fin". **[2]**This word became the origin of the English word "phenol", which is benzene hydroxyl, and "phenyl", which is the root formed by extracting the hydrogen atom (free radical H •) from benzene. **[3]** Benzene is used as a base material for the manufacture of other substances, such as ethylbenzene, cumene, cyclohexane, nitrobenzene, and alkylbenzene. **[4]**

According to the Agency for Toxic Substances and Disease Registry (ATSDR) (2007), gasoline is produced from reactions that come from volcanoes, such as forest fires, synthetic fibers, and lubricants, but is primarily an industrial substance. The main sources of exposure to gasoline are tobacco smoke, petrol stations, and industrial emissions from factories and companies. However, benzene can be swallowed and absorbed through the skin and contact with contaminated food or water. Benzene is collected through activated charcoal tubes to measure its level in air and water, and then it is analyzed using gas chromatography. As for the human being, the level of benzene is measured through urine, blood and respiratory tests.

There are several tests available to measure exposure to benzene in humans. Where we can measure the presence of the same substance by breathing, blood or urine, but because of the biological transformation or exhalation and the rapid exit of these substances from the human body, these tests are often performed within the first 24 hours after exposure to the patient.

In previous studies, it was found that benzene has almost complete absorption when taken orally in a study conducted by laboratory animals . Parke and Williams (1953) **[5]**

There are several important experimental studies regarding respiratory absorption of benzene (Nomiyama and Nomiyama,) (1950) The study was conducted on 23 people who were exposed to concentrations of benzene, from 47 to 100 parts per million (150 to 320 mg / m3) for two to three hours. At first, in the first 5 minutes, absorption was at its highest level (70-80%). After that, it began to decrease rapidly. 15 minutes later, it became between 20 and 60%, then after one hour between 20 and 50%. Significant variation was observed between individuals.

The absorption of benzene through the skin is by liquid and vapor. Absorption ratio By skin, it has been studied more often in experimental animals than in humans. Benzene absorption through the Skin has been studied in humans (Franz, 1984) as well as in laboratory animals (Maibach and Anjo, 1981) .Of course, the absorption rate of benzene through the skin is less than by inhalation or by mouth. The main reason for this is the rapid volatilization of benzene from the skin. When excreted, A large amount of benzene is excreted through the lungs, and thus experiments that only measure excretion in feces and urine are considered imprecise and may significantly reduce the true absorption value.

References, studies, and reports that include poisoning with benzene and excreting it from the body after oral exposure is limited to experimental animals. For example, in one of the reports examining the toxicity of the metabolism and excretion of biological radioactive foreign substances, Park and Williams (1953) recovered a large proportion of the administered dose on Respiration as a non-metabolized product (43%). This amount compared to 33% of the urinary excretion, where it was divided into components such as hydroquinone by 4.8% and also phenols associated with (23% of the dose), catechol (2.2%) and others. The remaining amounts remain deposited in the internal tissues of the body or excreted in the stool.

An important report from the studies of inhaled benzene excretion, Nomiyama (1974) showed that some benzene absorbed by the body could be excreted in the urine in the form of phenols attached to sulfates, glucuronides, or MAs.In the concentrations of benzene used (52-62 ppm) (166-198 mg / m3), the respiratory absorption absorption was 47%, and for excretion by the respiratory system about 17%. These values were very clearly consistent with those obtained in a previous study by Srbova et al. (1950), who stated that the retention of benzene in the respiratory system ranged between 16.4 and 41.6% during a 7-hour exposure period.

Only limited data have been found on benzene excretion following cutaneous exposure in humans.

Franz (1984) reported that four volunteers were exposed to 14 C-benzene (0.0024 mg / cm2 on the skin, trace amounts of the patch are excreted in urine over a period of 36 hours, indicating the ability of the compound to penetrate the cutaneous barrier.

MATERIALS AND METHODS:

Cross sectional study, the purpose is to measure the extent of some of the possible hematological toxicities associated with long term exposure to benzene in Saudi Arabia. The study was approved by the Clinical Research Ethics Committee at the Ministry of Health, Kingdom of Saudi Arabia, and written informed consent It was obtained from all patients prior to experimental entry . A number of 110 from 200 workers were approved, as the reason for the rejection was the workers 'fear during the Corona pandemic. The study period It was from early February 2020 to April 2021 And The analyzes were repeated 3 times to ensure the correctness of the results.

The study was conducted on a preliminary sample of male workers. They are professionally exposed on a daily basis to urban pollutants, the most important of which is gasoline in stations. All subjects in the primary sample were randomly selected . The professionally exposed workers are males from Taif. Their average working hours were calculated for at least 80% of their working time (at least 8 hours per day , 6 days a week). Bearing in mind that these workers are not provided with tools or spares to protect from fumes and gases.

We obtained a blood sample from the participants and conducted laboratory tests on it for 110 workers. Lab analyzes included: ALT, AST, WBC, RBC, Hemoglobin, Hematocrit, PLT, MCV, MCH, MCHC, Neutrophils, Eosinophils, Basophils, lymphocytes, Monocytes.

The samples were divided into 4 patient groups according to the rate of exposure to benzene during the previous years : patient groups 1 (controlled group) , patient groups 2 (exposed less than 1y) , patient groups 3 (exposed 1-5 y) , patient groups 4 (more than 5) Each group is compared with all the above-mentioned parameters, and the division was done randomly. The sampling was done inside Al-Khadra Medical Laboratory in Taif , Samples were withdrawn inside the laboratory in sterile rooms after the groups divided each group on a separate day and at different times.
The workers participating in the research are all workers at petrol stations inside the city of Taif, working an average of 8 hours a day for 6 days a week. Workers who work in other workplaces, workers with chronic diseases, and females were excluded. The groups divided the benzene exposure group into 4 groups based on the duration of the benzene exposure, several variables were used in the comparison, including age and occupational history.

The t-test was used to assess the significance of the differences between the mean values of the measured parameters in the respective test groups, compared to the corresponding control group. A significant difference was accepted at $P < 0.05$.

RESULTS:

One hundred and ten male gasoline station workers were included in this study. They were divided into 3 patient groups: **group 2** (exposed less than 1y), **group 3** (exposed 1-5 y) and **group 4** (more than 5). In addition, 20 healthy males with average ages to the patients and without occupational exposure to gasoline were selected as control group **(group 1).**

The station workers were selected in this study because of their excessive and continuous exposure to benzene, with an average of 8 hours per day, six days per week. Workers were gathered from various petrol stations in Taif city, and informed consent was obtained before starting.

This study's mean age is 34 years, and the average years of exposure to benzene are ten years. Blood samples were obtained inside the Green Laboratory in Taif to measure: ALT, AST, HB, HEMATOCRIT, MCV, MCH, MCHC, WBC, Basophils, Neutrophils, Eosinophils, Lymphocyte, Monocyte.

Table 1: Descriptive analysis of ages and years of exposure of the workers involved in the study (N=130)

		No	%	Mean
Age	20 -30 y	56	43	34.3
	30 - 40 y	38	29.2	
	40- 50 y	10	7.6	
	more than 50	6	4.6	
	Control group	20	15.3	33.2
Year of Exposure	less than1 y	12	10.9	10.7
	1-5 y	18	16.3	
	more than 5y	80	72.7	

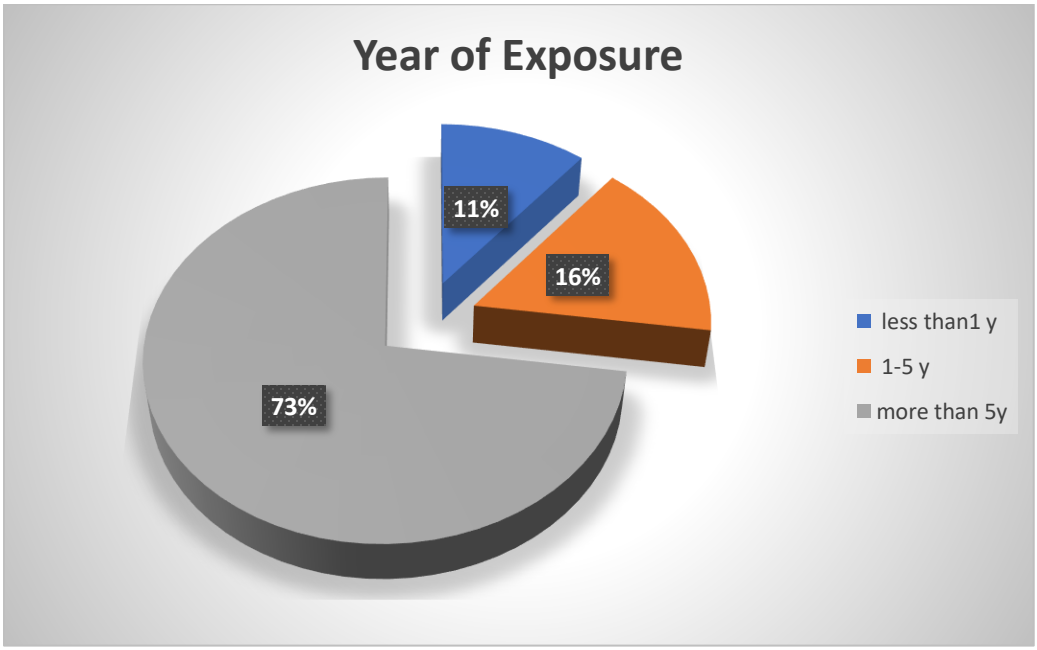

Figure 1; Years of exposure of the workers involved in the study to gasoline.

Table 2: Descriptive analysis of hematological, hormonal, and ALT and AST serum levels of the workers involved in the study (N=110)

		No	%	Mean	Reference range
WBC	below 4000	14	12.7	5894.5 mm	4000-10000 mm
	normal range (between 4000-10000)	90	81.8		
	above 10,000	6	5.4		
RBC	below 4.5 m/mm	0	0	5.8 milion /mm	4.5-5.5 milion /mm
	normal range	82	74.5		
	above 5.5 m/mm	28	25.4		
HB	Below 13 g/dl	24	21.8	14.8 g/dl	13-17 g/dl
	normal range	86	78.1		
HEMATO CRIT	below 40 %	6	5.4	45.7%	40-50%
	Normal range(40-50%)	94	85.4		
	above 50%	10	9		
PLT	below 150,000	2	1.8	248677.4 mm	150000-400000/mm
	normal range	108	98.1		
	above 400,000	0	0		
MCV	below 80	78	70.9	78.8 fl	83-101 fl
	normal range	32	29		
	above 100	0	0		
MCH	below 27	94	85.4	25.5 pg	27-32pg
	normal range	16	14.5		
	above 32	0	0		
MCHC	below 31.5	36	32.7	32.4 %	31.5-34.5%
	normal	74	67.2		
	above 34.5	0	0		
Neutrophils	below 36%	2	1.8	57.6 %	36-66%
	normal range	72	65.4		
	above 66%	36	32.7		
Eosinophils	in normal range	60	54.5	0.34 %	00-03%
	in abnormal range	50	45.4		
Basophils	in normal range	110	100	0.11 %	00-01%
	in abnormal range	0	0		
Lymphocyte	below 24%	6	5.4	39.3 %	24-44%
	normal	72	65.4		
	above 44	32	29		
Monocyte	in normal range	96	87.2	2.63 %	00-04%
	in abnormal range	14	12.7		
AST	in normal range (Up to 37 U/l	110	100	23.6 U/I	Up to 37 U/l
	in abnormal range	0	0		
ALT	in normal range Up to 42 U/l	80	72.7	29.5 U/I	Up to 42 U/l
	in abnormal range	30	27.2		
	in abnormal range	70	63.6		

Table 3: Hematological effects of gasoline vapors in fuel station workers (less than 1 year, from 1-5 years & more than 5 years) (N=110) when compared to control (N=20).

	Groups	mean	Standard deviation	P value
WBC	Group 1 (controlled group)	8765	27.354	
	Group 2 (exposed less than 1y)	7615	2536.1	
	Group 3 (exposed 1-5 y)	5942	1760.9	.003*
	Group 4 (more than 5)	5617.7	1552.8	
RBC	Group 1 (controlled group)	4.8	0.31	
	Group 2 (exposed less than 1y)	5.97	0.36	
	Group 3 (exposed 1-5 y)	5.86	0.67	.153
	Group 4 (more than 5)	5.76	0.42	
HB	Group 1 (controlled group)	15.3	0.579	
	Group 2 (exposed less than 1y)	14.85	0.054	
	Group 3 (exposed 1-5 y)	14.46	0.797	.442
	Group 4 (more than 5)	14.89	1.04	
HEMATOCRIT	Group 1 (controlled group)	43.3	1.34	
	Group 2 (exposed less than 1y)	46.46	1.57	
	Group 3 (exposed 1-5 y)	44.16	2.57	.698
	Group 4 (more than 5)	45.97	3.80	
PLT	Group 1 (controlled group)	287354	15641	
	Group 2 (exposed less than 1y)	225000	16431	.000*
	Group 3 (exposed 1-5 y)	247225	88278	
	Group 4 (more than 5)	252692	41569	
MCV	Group 1 (controlled group)	83.3	1.99	
	Group 2 (exposed less than 1y)	77.9	2.08	
	Group 3 (exposed 1-5 y)	75.9	8.31	.803
	Group 4 (more than 5)	79.7	5.28	
MCH	Group 1 (controlled group)	29.4	1.13	

	Group 2 (exposed less than 1y)	24.9	1.42	
	Group 3 (exposed 1-5 y)	24.95	2.67	.650
	Group 4 (more than 5)	25.83	1.81	
MCHC	Group 1 (controlled group)	33.7	0.765	
	Group 2 (exposed less than 1y)	32	0.985	
	Group 3 (exposed 1-5 y)	32.79	0.260	.100
	Group 4 (more than 5)	32.42	0.826	
Neutrophils	Group 1 (controlled group)	64.6	6.78	
	Group 2 (exposed less than 1y)	68.05	5.53	
	Group 3 (exposed 1-5 y)	55.37	11.5	.000*
	Group 4 (more than 5)	56.58	7.66	
Eosinophil	Group 1 (controlled group)	0.43	0.45	
	Group 2 (exposed less than 1y)	0.53	0.53	
	Group 3 (exposed 1-5 y)	0.119	0.27	.004*
	Group 4 (more than 5)	0.369	0.65	
Basophils	Group 1 (controlled group)	0.9	0.21	
	Group 2 (exposed less than 1y)	0.285	0.30	.876
	Group 3 (exposed 1-5 y)	0.011	0.005	
	Group 4 (more than 5)	0.11	0.243	
Lymphocyte	Group 1 (controlled group)	36.4	7.32	
	Group 2 (exposed less than 1y)	28.65	6.07	
	Group 3 (exposed 1-5 y)	41.01	10.3	.000*
	Group 4 (more than 5)	40.52	7.49	
Monocyte	Group 1 (controlled group)	1.9	1.32	
	Group 2 (exposed less than 1y)	2.48	1.38	
	Group 3 (exposed 1-5 y)	3.46	0.98	.018*
	Group 4 (more than 5)	2.44	1.037	

*. The Chi-square statistic is significant at the .05 level.as we show in table 3

Table 3 shows that there is a significant correlation between years of exposure and, WBC, MCV, Neutrophils, Eosinophils, Lymphocyte, Monocyte, while there is no significance observed with other values.

DISCUSSION:

This study aims to measure the risk of long-term occupational exposure to gasoline and measure the possible associated endocrinal, hematological, and hepatic enzymes toxicities in Saudi Arabia and to spread awareness among workers and society about the dangers of long-term exposure to gasoline and its components.

One hundred and ten male gasoline station workers were included in this study. They were divided into 3 patient groups: group 2 (exposed less than 1y - 12 cases), group 3 (exposed 1-5 y - 18 cases) and group 4 (more than 5 – 80 cases). In addition, 20 healthy males with average ages to the patients and without occupational exposure to gasoline were selected as control group (group 1).

The station workers were selected in this study because of their excessive and continuous exposure to gasoline (with an average of 8 hours per day and six days per week). Workers were gathered from various petrol stations in Taif city, and informed consent was obtained from each patient before starting.

All cases were subjected to complete medical and occupational history including age, marital status, respiratory and chronic diseases, and history of operation, drug intake, and duration of employment, location and use of protective equipment. Any individual with history of diabetes, renal or hepatic disease or allergy was excluded. Blood samples were obtained inside the Green Laboratory in Taif to measure and the sera were subjected to estimation of the following parameters: ALT, AST, HB, HEMATOCRIT, MCV, MCH, MCHC, WBC, Basophils, Neutrophils, Eosinophils, Lymphocyte, Monocyte.

This study's mean age is 34 years, and the average years of exposure to benzene are ten years while the mean age of the control is 33 years.

In the present study, patient groups 2, 3, and 4 who were exposed to benzene were compared to the control group concerning hematological effects. The parameters showed a significant coloration between years of exposure and WBC, MCV, Neutrophils, Eosinophils, Lymphocyte, and Monocyte (p when 0. 05) compared to the control group. At the same time, there is no significance with other values (Basophils, HB, HEMATOCRIT, MCH, MCHC, PLT, RBC).

Patient Group 2, WBC (7615mm + 2536.1) RBC (5.97 million\mm + 0.36) and HB (14.85g\dl + 0.054) HEMATOCRIT (46,46% + 1,57) PLT (225000 mm + 16431) MCV (77.9 fl + 2.08) MCH (24.9 pg + 1.42) And MCHC (32% + 0.985) Neutrophils (68.05 % +5.53) Eosinophils (0.53 % +0.53)Basophils (0 .285 % + 0.30) LYMPHOCYTE (28.65 % + 6.07) MONOCYTE (2.48 % + 1.38).

Patient Group 3, WBC (5942 mm + 1760. 9) RBC (5.86 million\mm + 0.67) and HB (14.46g\ dl + 0.797) HEMATOCRIT(44.16 % + 2.57) PLT (247225 mm+88278) MCV(75.9 fl+ 8.31) MCH (24.95 pg + 2.67) And MCHC (32.79 % + 0.260)Neutrophils (55.37 % +11.5)Eosinophils (0 .119 % +0.27) Basophils (0.011% + 0.005)LYMPHOCYTE (41.01 % +10.3) MONOCYTE (3.46%+0.98).

Patient Group 4 ,WBC (5617.7 mm + 1552.8) RBC (5.76 million\mm + 0.42) and HB (14.89 g\dl + 1.04) HEMATOCRIT(45,97 % + 3,80) PLT (252692 mm+ 41569) MCV (79.7 fl+5.28)MCH(25.83 pg+1.81) And MCHC (32.42%+0.826)Neutrophils (56.58 % +7.66) Eosinophils (0.369 % + 0.65) Basophils (0.11 % + 0.243) LYMPHOCYTE (40.52 % +7.49) MONOCYTE (2.44%+1.037).

Long-term exposure to benzene causes apparent haematological effects, such as a significant decrease in the number of white blood cells, which is consistent with Lan et al. (2004), Robert Schnatter et al. (2010), and others and D'Andrea (2017). **[7] [8]**The study also proved that an increase in the rate of exposure to gasoline might lead to neutropenia.

Regarding to the HB, HEMATOCRIT, MCH, MCHC, Basophils, the current study showed that there is no correlation between years of exposure to gasoline among workers and between the effect on these factors; this is inconsistent with what was mentioned by Aksoy et al. and Bogadi-Sare regarding to MCH, MCHC and consistent with D'Andrea, M.A(2017) **[9] [10]** regarding to HB and HEMATOCRIT.

Besides, the study also showed that long-term exposure might cause Lymphocytosis in groups exposed to gasoline. This may differ from what was previously reported by Bogadi-Sare et al. (2000) reported in immunotoxicity research results when factory workers were exposed to benzene in the form

of reductive B lymphocytes, also inconsistent with what was mentioned by Le Noir (1897). **[11]**

CONCLUSION AND RECOMMENDATION:

We conclude that blood and liver are affected by chronic doses of benzene through inhalation, after our study was on the group most exposed to benzene, which are gas station workers.

We recommend the continuous examination of workers exposed to gasoline and the expansion of their medical insurance to cover the costs of analyzes and treatment for those who have already been affected by the previous periods of chronic exposure to gasoline, as well as intensifying studies related to this field due to the abundance of vulnerable groups and their high risk over time.

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