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Relationship of Benzene Exposure to Trans, Trans-Muconic Acid and Blood Profile of Shoe Workers in Romokalisari Surabaya, Indonesia

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Abstract

BACKGROUND: Benzene is a hazardous ingredient for health. Benzene is used as a latex glue solvent in the shoe industry.

AIM: The purpose of the study was to analyse the relationship between benzene exposure with trans, trans-muconic acid (t, t-MA) and the blood profile of shoe workers in Romokalisari Surabaya.

METHODS: The study was a cross-sectional design conducted in the shoe industry in Romokalisari Surabaya with some subjects of 20 shoe workers. Data collection was carried out by measuring benzene levels conducted at 8 measurement points in Surabaya Romokalisari, taking workers' blood, measuring body weight and conducting interviews with respondents. Data were analysed using correlation tests.

RESULTS: The results showed that there was no relationship between benzene levels with t, t-MA (p-value = 0.205), there was no relationship between benzene Risk Quotient (RQ) and t, t-MA (p-value = 0.271) and there was no relationship between the Excess Cancer Risk (ECR) and blood profile of workers in Romokalisari. However, there were some abnormal blood profile parameters due to exposure to benzene although it was small.

CONCLUSIONS: It seems another factors such as length of work, nutritional status, duration of exposure, weight, and frequency of exposure have a considerable contribution in the determination of intake of xenobiotic ingredients in the body to cause health effects especially blood profiles.

Introduction

The footwear home industry sector is one of the informal industrial sectors whose influence is strong on Indonesia's development with a total value of US $ 1.51 million which contributes 3% of the world's demand for footwear products [1], [2]. The process of making shoes in the informal shoe industry is always accompanied by factors that contain health and safety risks so that they are very vulnerable to biological hazards, chemical, physical and psychological hazards [1]. The hazardous substances present in the glue are volatile organic compounds (benzene, toluene, and xylene) which fall into the volatile VOC (Volatile Organic Compound) category [3].

Unfortunately, large and small industries use toluene and benzene as a mixture or reagent although it was hazardous material [3]. Benzene is a toxin with higher health risk and included in the category of carcinogens A1 (a confirmed human carcinogen) while toluene and xylene are included in the category A4 (not classifiable as a human carcinogen). This means that benzene is a carcinogen in humans whose termination of the bond is more difficult when compared to toluene and xylene [4].

Benzene is used as a latex glue solvent in the shoe industry [5], [6]. Benzene vapour in a low concentration could cause poisoning to humans if it were inhaled continuously. The negative effect of benzene such as bone marrow damage that occurs latently due to the metabolite reaction of benzene epoxide [7].

Benzene that enters the body will undergo phase I biotransformation with the cytochrome P450 2E1 (CYP 2E1) enzyme to become benzene epoxide, a compound that is unstable and will undergo oxidation to form trans, trans-muconaldehyde and then t, tMA) that will be released through urine. Relevant and sensitive indicators for measuring exposure and doses of benzene that enter the body, one of which is to use biological indicators (biomarkers), namely t, t-MA contained in the urine because it has a sufficient half-life that is 6 hours unlike benzene in the blood has a short half-life in the blood so the time taken for sampling is also very short [8].

The study conducted in Pakistan showed significant results from increasing the number of total leukocytes, lymphocytes, eosinophils, and monocytes as well as decreased platelet counts and neutrophil counts in shoemaking workers when compared to groups control [9]. Also, research conducted in Thailand about the workers exposed to benzene can alter haematological parameters with a significance of changes namely in decreasing haemoglobin, hematocrit and eosinophil count with trans, trans Muconic Acid (t, t- MA) in urine as a body biomarker [10].

Research in Indonesia, one of them shows that child labour in the Cibaduyut shoe industry in Bandung is threatened by various types of respiratory tract infections, bronchitis, liver and or kidney damage, even leukaemia [5]. Research in the same place conducted on showed that the results of tests carried out on the concentration of benzene exposure with blood profiles obtained several significant variables, namely haemoglobin level, erythrocyte levels, and eosinophil levels [11]. Other studies show that the working environment with adequate benzene vapor content (0.138-6.271 ppm) in the industrial gluing section of Tasikmalaya City sandals is able to provide a health effect that is strengthened by nearly 70 percent of workers experiencing respiratory problems and feeling dizzy due to long periods of steam [1]. Another study shows non-cancerous and cancerous effects due to benzene exposure for leather shoe industry workers in Pulogadung Small Industrial Center (PIK) [12].

The purpose of this study was to analyse the relationship between benzene exposure with trans, trans-muconic acid and the blood profile of shoe workers in Romokalisari Surabaya.

Material and Methods

This study was an observational study with a cross-sectional approach in Romokalisari Surabaya (home industry in Tambak Oso Wilangun Village) with seven home industry locations conducted during October-November 2016. The research subjects were all shoe craftsmen in Tambak Oso Wilangun Village with a total of 20 people with female and male workers who met the inclusion criteria, namely not menstruating, not pregnant, not taking certain drugs/anaesthesia and alcohol and in good health. The variables are toxicity score benzene, t, t-MA level, and blood profile.

Benzene measurements were carried out at 8 points in 7 work locations during the day (12.00-14.00 WIB) with the consideration this time is the peak time of work in using glue, the temperature is still quite high so that it can cause benzene in the glue to evaporate quickly so that the device can be caught air suction (vacuum pump) [12]. Benzene measurements are carried out by experts from the laboratories of the Surabaya City Health and Safety Technical Implementation Unit (UPTK3). Sampling of urine (samples of trans-trans Muconic-Acid) was carried out by asking the study subjects to accommodate 50 ml of urine in the urine pot that was provided and taken after the expiration period lasted about 7-8 hours while for measurement t, t-MA was carried out by the method Mass Spectra Liquid Chromatography by Prodia Surabaya laboratory. The method was NIOSH Methode 1501 with a sample taken by benzene vapour carried out by Gas Chromatography (GC)/FID & HC Analyzer. Set GC injector as 225°C, detector set in 225°C, the initial column in 50°C, hold time 3.0 minutes then 15°C/minutes to 200°C. Then, measured benzene levels will be compared to exposure limit standard of benzene according to REL NIOSH 2005 (normal if < 0.01 ppm) and Ministry of Manpower/Transmigration Indonesia No. 13 of 2011 (normal if < 0.5 ppm). Blood collection was done by taking 2-3 cc of venous blood from the workers and then examined using a Blood Cell Counter with blood cell examination performed using a haematology analyser.

Blood count is a measured hemoglobin level compared to the standard reference of male hemoglobin between 13.2-17.3 gr/dL = normal, and female hemoglobin levels between 11.7-15.5 gr/dl = normal, measurable hematocrit levels compared with references between 40-52% = normal, measured leukocyte levels were compared with reference values between 3,800-10,600 μ/L = normal and calculation of percentage results by referring to standards namely 50-70% neutrophils, 2-4% eosinophils, basophils 0-1%, lymphocytes 25-40%, and monocytes 2-8% [13].

Data collection was carried out by interviewing respondents using questionnaires and observations related to the characteristics of respondents and measurements of body weight and height. The analysis in this study was carried out by conducting correlation analysis using Spearman and Pearson (α = 0.05).

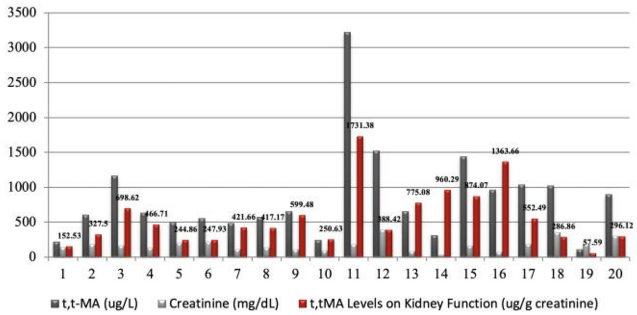

Figure 2: Trans Levels, Trans-Muconic Acid Workers in Romokalisari

Results

Measured Benzene Levels at Research Sites (ppm)

Based on Figure 1 shows that there are 2 locations where benzene exposure exceeds the benzene threshold value according to Ministry of Manpower and Transmigration Regulation No. 13 the year 2011 (> 0.05 ppm) which is the location V of 0.9129 ppm and location VI is 2.333 ppm [14]. Meanwhile, workers gender has the same percentage (50% female and 50% male).

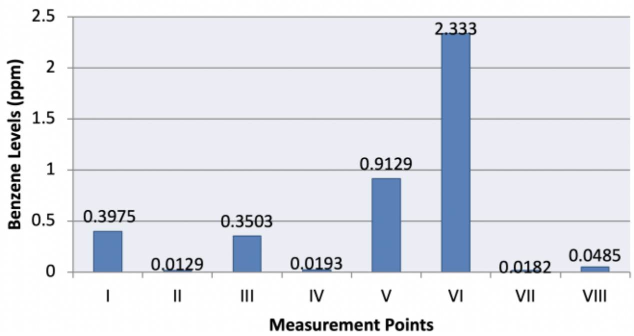

Figure 1: Measured Benzene Levels in the Study Area (ppm)

Trans, Trans Muconic Acid

Figure 2 shows the levels of trans, trans-muconic acid urine of the study subjects and correction of creatinine (μg/g creatinine) was carried out. The figure shows the highest t,t-MA level of 1,731.38 μg/g creatinine, which is the respondent at the 7th point of work location, while the lowest t,t-MA level is 57.59 μg/g creatinine, the respondent is at the 8th work point. From Figure 2 also shows that as many as 8 research subjects had levels of t, t-MA were not normal or outside the threshold/Biological Exposure Indices (BEI).

Blood Profile of Shoe Workers

Table 1 shows the levels of each blood profile parameter that is the subject of the study, namely the shoe craftsmen in Romokalisari Surabaya.

Of all subjects, the highest haemoglobin level was 16.4 g/dL, and the lowest was 9.6 g/dL, the highest hematocrit level was 46.5%, and the lowest was 27.7%, the highest leukocyte level was 15.430 μ/L, and the lowest level was 5,250 μ/L, the highest eosinophil level was 17% and the lowest was 0%, the highest neutrophil level was 93% and the lowest level was 37%, the highest basophil level was 1% and the lowest was 0%, the highest lymphocyte level was 46% and the lowest by 22% and the highest monocyte level by 11% and the lowest level by 3%.

Table 1: Blood Profile of Shoe Workers in Romokalisari

Sample (M/F)	Hemoglobin (g/dL)	Hematocrit (%)	Leukocyte (uL)	Eosinophil (%)	Basophil (%)	Neutrophil (%)	Limphocyte (%)	Monocyte (%)
1 (M)	15.8	45.9	7270	8	0	48	34	10
2 (M)	14.9	42.5	8370	3	0	64	27	6
3 (M)	15.8	46.5	5250	4	1	54	34	7
4 (M)	15.2	43.1	5320	5	0	58	28	9
5 (M)	14.9	42.9	7030	6	0	50	37	7
6 (F)	12.9	39.4	9050	3	0	45	46	6
7 (M)	15	44.5	11310	6	0	57	28	9
8 (F)	9.6	27.7	8700	4	0	64	26	6
9 (M)	16.4	46.5	9920	2	0	54	37	7
10 (F)	14.2	41.5	9130	7	0	61	26	6
11 (F)	12.8	38.1	8800	3	0	67	24	6
12 (F)	12.8	35.7	6690	2	0	61	29	8
13 (F)	13.3	39.6	8050	17	0	53	22	8
14 (M)	14.6	41.9	8720	4	0	60	26	10
15 (F)	13	37.6	15340	7	0	93	4	3
16 (F)	13.7	40.3	9620	4	0	65	24	7
17 (M)	14.2	40.3	8300	3	0	63	27	7
18 (M)	14.8	43.5	7510	7	1	37	45	10
19 (F)	15.1	42.9	15430	5	0	58	26	11
20 (F)	14	41.8	9830	4	0	53	37	6

Table 1 also shows the blood profile of the subjects in the normal category or not. Categorisation of grade values from each blood profile refers to the reference guidelines for standardised reference values by ISO 15189: 2012 regarding the specific requirements of medical laboratories used by the Surabaya Parahita Laboratory as partners in examining these blood profiles. Of the 20 research subjects, 19 respondents had normal haemoglobin levels, and only 1 respondent had a low haemoglobin level, as many as 19 respondents had normal hematocrit levels and as many as 1 respondents had low hematocytes, 17 respondents had normal leukocyte levels and 3 respondents had high leukocyte levels, as many as 11 respondents had normal eosinophil levels, as low as 1 respondent and as many as 8 respondents had high eosinophil levels, as many as 16 respondents had normal neutrophil levels, 3 respondents had low neutrophil levels, and as many as 1 respondents had high neutrophil levels, 20 respondents have normal basophil levels, as many as 14 respondents had normal lymphocyte levels, low as many as 4 respondents and as many as 2 respondents had high lymphocyte levels, and as many as 14 respondents had normal monocyte levels, and 6 respondents had high monocyte levels.

Relationship of Benzene Exposure to Trans, Trans-Muconic Acid

Table 2 shows that there is no correlation between benzene exposure and t,t-MA because the *p-value* > 0.05 (*p-value* = 0.205).

Table 2: Relationship of Benzene Exposure to Trans, Trans-Muconic Acid Shoe Workers in Romokalisari

Variable	*p-value*	*r*	N
Concentration of Benzene Trans, Trans-Muconic Acid	0.205	0.295	20

Intake of Benzene

The formula used to determine the intake of benzene toxin in the body is(14):

Intake of benzene = $\frac{\text{CxRxtExfExDt}}{\text{Wb x tavg}}$

Description:

C = benzene concentration (mg/m^3)

R = respiration rate (m^3/h)

tE = exposure time (hour/day)

fE = average exposure in a year (day/year)

Dt = exposure duration (years)

Wb = weight (kg)

Tavg = average of benzene exposure (non-carcinogen)

= 30 years x 365 days/year

Risk Quotient (RQ)

The formula used to find out the RQ is [15]:

RQ = $\frac{Intake}{RfDatauRfC}$

Risk characteristics for non-cancer effects can be known by sharing the value of Noncancer Intakes with RfC or RfC values with the assumption that:

1. If the RQ value ≤ 1 indicates an indication of the possibility of the risk of noncarcinogenic health effects, it must be maintained so that the numerical value of RQ does not exceed 1.

2. While RQ > 1 shows an indication of the possibility of risk of non-carcinogenic health effects and the need for control efforts [15].

The respondent's RQ value is as follows:

Table 3: Value of Risk Quotient Benzene in Romokalisari

Respondent	Intake Non-carcinogen	Risk Quotient
1	0.004084	0.480471
2	0.003391	0.398941
3	0.004022	0.473176
4	0.008403	0.988588
5	0.010251	1.206
6	0.003022	0.355529
7	0.004593	0.540353
8	0.000481	0.056588
9	0.009434	1.109882
10	0.006952	0.817882
11	0.228851	26.92365
12	0.0288	3.388235
13	0.155914	18.34282
14	0.171152	20.13553
15	0.078304	9.212235
16	0.112532	13.23906
17	0.120726	14.20306
18	0.175	20.58824
19	0.38811	45.66
20	0.181243	21.32271

Table 3 shows that most of the RQ shoe workers in Romokalisari are > 1 that is 12 respondents and 8 other respondents the RQ value is < 1.

RQ relationship with t, t-MA

Correlation test results show that there is no correlation between benzene RQ and t, t-MA workers in Romokalisari because the p-value is > 0.05 (0.271).

Table 4: Relationship between Risk Quotient Benzene and Trans, Trans-Muconic Acid Workers in Romokalisari

Variables	*p-value*	*r*	N
Trans, Trans-Muconic Acid RQ Benzene	0.271	0.258	20

Excess Cancer Risk (ECR) with a Blood Profile

When calculating cancer risk, lifelong exposure is needed. CSF (Cancer Slope Factor) value uses the value set by US-EPA of 0.055 mg/kg. Day. In calculating the health risk characteristics for the effect of cancer is the ECR which is used is the CSF value.

ECR values or risk characteristics for cancer effects can be obtained by multiplying the value of cancer intake by CSF values by the formula [15]:

ECR = Carcinogenic Intake (Ik) x CSF

Assuming the results of the ECR calculation are:

If the ECR is -4 10-4, then the concentration of benzene exposure to workers is not at risk of causing carcinogenic advisory effects.

If ECR > 10-4, the concentration of benzene exposure to workers can cause carcinogenic health effects.

The ECR value for the 20 respondents is as follows:

Table 5: ECR Value of Shoe Workers in Romokalisari

Respondent	Intake Carcinogen	ECR
1	0.00175	0.00009625
2	0.001453	0.000079915
3	0.001724	0.00009482
4	0.003601	0.000198055
5	0.004393	0.000241615
6	0.001295	0.000071225
7	0.001969	0.000108295
8	0.000206	0.00001133
9	0.004043	0.000222365
10	0.002979	0.000163845
11	0.098079	0.005394345
12	0.012343	0.000678865
13	0.06682	0.0036751
14	0.073351	0.004034305
15	0.033559	0.001845745
16	0.048228	0.00265254
17	0.05174	0.0028457
18	0.075	0.004125
19	0.166333	0.009148315
20	0.077675	0.004272125

Table 5 shows that the ECR value of all shoe workers in Romokalisari is > 10-4, which means that exposure to benzene at work sites can cause carcinogens in the worker's body.

ECR relationship with Blood Profile

Table 6: ECR relations with Blood Profile Workers in Romokalisari

Variables	*p-value*	*r*	N
Hemoglobin ECR	0.723	0.085	20
Hematocrit ECR	0.629	0.115	20
Leukocyte ECR	0.734	0.081	20
Eosinophil ECR	0.734	-0.081	20
Basophil ECR	0.644	0.110	20
Neutrophil ECR	0.697	-0.093	20
Limphocyte ECR	0.776	0.068	20
Monocyte ECR	0.254	0.268	20

Table 6 shows the results of the correlation analysis between the ECR and the blood profile of shoe workers in Romokalisari. Based on the results of the correlation test, it was found that there was no correlation between the ECR and the blood profile of shoe workers in Romokalisari.

Safe Duration of Exposure (Safe Dt)

In this study risk management was carried out in the form of reducing the duration of exposure to shoe workers in Romokalisari.

Safe Dt Non-Carcinogen

Calculation of safe DT non-carcinogen namely [15] :

$$\text{Safe Dt} = \frac{RfCxWbxtavg}{CxRxtExfE}$$

The safe Dt value of shoe workers in Romokalisari is as follows:

Table 7: Safe Value of Non-Carcinogen Workers in Romokalisari

Respondent	Safe Dt (Year)
1	70.8
2	50.1
3	33.8
4	40.5
5	29.9
6	47.8
7	55.5
8	53.0
9	22.5
10	29.3
11	1.6
12	2.4
13	2.3
14	1.1
15	2.2
16	2.0
17	2.2
18	1.2
19	0.4
20	0.7

From the data above shows the duration of safe exposure for each shoe worker in Romokalisari Surabaya, that is each worker is different. It can be seen that shoes workers 1 to 10 has a safe duration of exposure to get non-carcinogen effects from benzene exposure for decades. Unlike the 11th to 20th shoe workers who have a safe duration of exposure to get non-carcinogenic effects from benzene exposure very little time (< 3 years).

Safe Dt Carcinogen

Calculation of safe DT non-carcinogen namely(14):

$$\text{Safe Dt} = \frac{Wb\ x\ tavg\ x\ ECR}{C\ x\ R\ x\ tE\ x\ fE\ x\ CSF}$$

The safe Dt value of shoe workers in Romokalisari is as follows:

Table 7: Safe Value of Carcinogen Workers in Romokalisari

Respondent	Safe Dt (Year)
1	3.53
2	2.50
3	1.69
4	2.02
5	1.49
6	2.39
7	2.77
8	2.65
9	1.12
10	1.46
11	0.08
12	0.12
13	0.12
14	0.06
15	0.11
16	0.10
17	0.11
18	0.06
19	0.02
20	0.03

From the above data shows the duration of safe exposure to the carcinogen effect of benzene exposure for each shoe worker in Romokalisari Surabaya is that each worker is different. It is seen that shoe workers 1 to 10 has a safe duration of exposure to get carcinogen effects from benzene exposure < 4 years. In contrast to the 11th to 20th shoe workers who have a safe duration of exposure to get a carcinogen effect from benzene exposure very little time is < from 1 year.

Discussion

Benzene exposure measurement results in the study location showed several measurement points that benzene levels exceeded the threshold limit value (TLV) of benzene in the workplace according to the regulation of the minister of workforce No.13/MEN/X/2011, namely the normal limit of benzene levels of 0.5 ppm [14]. The measurement point for which the benzene TLV exceeds the standard NAV is at 2 measurement points, namely at points 5 and 6 which are 0.9129 ppm and 2.333 ppm respectively.

From the measurement results showed that there was a very large difference between the measurement points below and above the benzene TLV such as the difference in benzene levels between location 2 which had the lowest benzene levels and locations 5 and 6 with the highest benzene levels. This difference is influenced by several factors such as the number of shoes produced, the method/method of work done by workers, the type of raw material used in the production process and the presence of adequate ventilation.

The number of shoes produced by workers is proportional to the amount of glue used. The more shoes that are produced, the more glue is used. At the location of the highest NAV, shoes are 35-40 Kodi/week or around 700-800 pairs, while the location below the TLV produces 37 Kodishoes/week. At the highest location, TLV uses 9-10 kg of yellow glue and 6-7.5 kg of white glue to produce shoes, while at the location below the NAB, 8 kg of yellow glue and 5 kg of white glue is used.

The high level of benzene at the work site is due to a large amount of glue used during the production process. When the glueing process of the shoe occurs, the evaporation of glue in the air will be greater which can affect benzene levels in the air. Moreover, if the glue container is not closed again after use as is often the case at point 5 when observing. This is in line with another research shows a large amount of shoe production in line with the use of glue which is quite a lot is one of the causes of high levels of benzene in the leather shoe industry in PIK Pulogadung [5].

Based on observations in the field, almost all study locations lack air exchange or ventilation especially at locations 5 and 6. In locations 5 and 6 the condition of the window/ventilation is closed, the air exchange only relies on a fan. Also, in locations 5 and 6 the working conditions were not sufficient because of a large number of equipment and raw materials for making shoes that were not neatly arranged.

Biological monitoring (biomarker) is one of the monitoring conducted to evaluate the degree of exposure to workers that have been absorbed into the body of the worker [16]. Benzene in urine is one of the most important biomarkers for benzene and trans exposure, trans-muconic acid is the most sensitive and specific metabolite for benzene exposure because it can be detected in urine for benzene exposure with a concentration of < 1 ppm [8]. T-level, t-MA tolerated by the human body is < 500 µg/g creatinine [17].

Based on the results of the correlation test, it was shown that there was no correlation between benzene exposure and t level, t-MA shoe workers in Romokalisari. From the description of the levels of t, t-MA workers and benzene concentrations in the work environment showed that from 20 respondents, only 3 respondents were in benzene concentrations above the benzene threshold in the work environment and most of the workers had normal t, t-MA levels. In general, benzene that enters the body has 2 possibilities, namely metabolised in the body and then cause acute and chronic effects or excreted/excreted into urine metabolites, in this case, the metabolite t-MA [8].

A metabolite of t, t-MA urine is only used as a biological marker for people exposed to benzene. The manifestation of an individual exposed to benzene is seen from the metabolite. The level of t, t-MA in urine is the result of the metabolism of benzene, the more benzene inhaled, the greater the benzene that enters the body and is excreted [6]. The results of the correlation test analysis in this study indicate that there is no significant relationship between benzene RQ and t, t-MA. This research is not in line with the research which concludes that there is a relationship between RQ and t, t-MA in workers in Tambak Oso Wilangun, Surabaya. The results of the study did not show a significant relationship because workers with benzene RQ > 1 mostly had normal tt-MA levels [18].

In general, benzene that enters the body has 2 possibilities, namely metabolised in the body and then cause acute and chronic effects or excreted/excreted into urine metabolites, in this case, the metabolite t, t-MA [19]. Based on the results of a study that shows no correlation between RQ and t, t-MA means that benzene that enters the worker's body is mostly metabolized into the body. Also, out of the 20 shoe workers studied, only 3 workers working in the work environment whose benzene exposure exceeds the benzene threshold value, thus making the majority of t, t-MA normal workers. Worker nutrition can also influence the absence of a relationship between benzene RQ and t, t-MA levels. Some studies stated that there is a less form of t, t-MA metabolites in urine if the person has higher enzyme activity CYP 21. Also, the normal nutritional status of workers will cause the metabolic process in the body to run normally [20].

It can be seen that the results of the calculation of cancer risk level for each worker have a result of ECR > 10-4 calculation, the results explain that the exposure time is currently shoe workers in Romokalisari who have cancer health risks. There are several epidemiological and clinical studies that prove that long-term benzene exposure causes leukaemia, so it is classified as a carcinogenic substance in humans (Group 1) by the IARC [19]. Research conducted on crude oil mining workers found a decrease in leukocytes and platelets in workers, this is due to workers who are exposed to high benzene continuously 24 hours and long lasting which indicates a chronic haematological effect of their work [21].

The results showed no association between benzene concentrations with levels of t, t-MA urine, benzene RQ with t, t-MA and ECR with blood profile of research subjects, although there were abnormal levels of t, t-MA from the study subjects and there are also some abnormal blood profile parameters, but overall the levels of t, t-MA and blood profile of the study subjects were normal. This is due to hematologic disorders (pancytopenia, aplastic anaemia, thrombocytopenia, granulocytopenia, and lymphocytopenia) which are associated with benzene in the workplace occurring chronically [6].

In this study, there was no relationship between ECR and all blood profile parameters. This is indicated by only a small percentage (3 respondents) of the study subjects who were at the work location/measurement point with benzene levels above the benzene threshold with blood profile levels that were outside the normal values such as only in lymphocyte and blood monocyte levels. Also, most of the abnormalities of blood levels exist in the study subjects at the work site/measurement point with benzene levels below the threshold with blood profile levels outside of normal, i.e. haemoglobin levels, hematocrit, leukocytes, eosinophils, and neutrophils. From this, there are many factors that make no relationship between these variables, in other words, the variable benzene in the air is not a determining factor about blood profile abnormalities in the subjects of the shoe craftsmen in this study.

There are other factors such as length of work, nutritional status and others that can contribute to the absence of a relationship between ECR variables and blood profile. This is in line with the theory of Louvar and Louvar in determining exposure assessment regarding the amount of chemical intake received by individuals, where the factors of work duration, duration of exposure, weight, and frequency of exposure have a considerable contribution in determination of intake of xenobiotic ingredients in the body so that they can cause health effects [22]. In addition to this, the Agency for Toxic Substance and Disease Registry states that the presence of hematologic disorders (changes/abnormalities) in blood levels from the presence of benzene chemicals in the work environment occurs chronically, which requires a very long time to see the existence of the disorder [6].

The results of research conducted on petroleum industry conclude benzene levels in an inhaled work environment by employees (workers) (< 1 ppm) did not appear to be significantly at risk of causing haematological anaemia with a work period of 3-16 years [23]. In addition to the research conducted in a study of benzene exposure in the work environment in South Korea showed there was no significant relationship between haematological parameters and benzene air levels [24].

The concentration of benzene exposure to shoe workers in Romokalisari Surabaya is affected by the air condition at the location of the workers, and many of the materials are not in the form of shoe glue used for the production of shoes. From the calculation of the duration of safe exposure to get non-carcinogen and carcinogen effects it can be seen that some workers have a safe duration of exposure to get very large carcinogen and non-carcinogen effects that reach up to decades, but the parts again have a safe duration of exposure to get very small carcinogenic and non-carcinogenic effects that only reach < 1 year.

Like workers 19 and 20 have a safe duration of exposure to get non-carcinogenic effects only 0.4 and 0.7 years and have a safe duration of exposure to get the effect of carcinogens only 0.02 and 0.03 years. This is proportional to the RQ and ECR values of each worker. The 19^{th} and 20^{th} workers have a value of RQ > 1 and ECR > $10^{-4,}$ so it has a risk to get carcinogen and non-carcinogen effects faster than other workers. This is because the 19th and 20th workers are shoe workers who are at work locations with the highest benzene levels, namely locations 5 and 6 so that workers are exposed to more than other workers.

In conclusion, there is no correlation between benzene levels and t, t-MA, there is no relationship between RQ and t, t-MA and there is no relationship between the ECR and all the profile parameters of the blood workers in Romokalisari. Safe duration exposure of workers varies and is directly proportional to the RQ and ECR values of each worker. Although there is some effect found some abnormal blood profile parameters due to exposure to benzene. However it is so small. The caused for this difference with other studies such as length of work, nutritional status, duration of exposure, weight, and frequency of exposure have a considerable contribution in the determination of intake of xenobiotic ingredients in the body to cause health effects especially blood profiles.

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Data Availability

The manuscript data used to support the findings of this study have been deposited in the Relationship of Trans Kadar, Trans-Muconic Acid (Tt-Ma) In Urine with Hematological Profile In Coco Spbu WorkersPertamina Mor V with accessed on http://repository.unair.ac.id/45529/on Airlangga University.

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