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Relationship of Benzene Concentration, ECR Benzene, Malondialdehyde, Glutathione, and DNA Degeneration in Shoe Industrial Workers in Osowilangun, Indonesia

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Abstract

In the shoes industry, benzene constitute as one of the source of chemical hazard especially used in the gluing section. This compound is metabolized by the liver, forming free radicals in the body which can ultimately reduce the concentration of glutathione and increased malondialdehyde causing DNA degeneration. The purpose of this study was to determine the relationship between benzene concentration, excess cancer risk (ECR), malondialdehyde, glutathione, and DNA degeneration among workers in shoes industry in Osowilangun, Surabaya. This is an observational study with a cross-sectional design. The number of research samples was 25 respondents. The average concentration of benzene in workers was above the threshold (10.31 ppm). There were 15 (60%) respondents with ECR >0.0001 who experienced DNA degeneration. There was no relationship between benzene concentration, malondialdehyde, glutathione, and DNA degeneration. However, there was a relationship between benzene ECR, malondialdehyde, glutathione, and DNA degeneration in the shoe industry workers in Osowilangun.

Keywords

benzene, malondialdehyde, glutathione, DNA degeneration

Introduction

Indonesia is a country with many small, medium, and large industries. The rapid development of the industries increases labor exposure that is translated into increased health risks. Health risks due to work can be caused by work accidents, direct and indirect exposure to hazardous chemicals, and risky behavior for workers and working environment conditions that do not meet the requirements. One of the industries with the risk of exposure to hazardous chemicals is the shoe industry. The gluing process in this industry causes workers to be

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exposed to hazardous chemicals. According to Laelasari et al,[1] exposure to hazardous chemicals from the use of ineligible glue is one of the risk factors that is not anticipated by workers, thus increasing the risk of disease to workers. According to Lu,[2] the use of glue can cause exposure to organic solvent vapor and is very likely to cause health effects if inhaled continuously for a long time. Hazardous organic solvents that are widely used in the shoe industry are BTX (Benzene, Toluene, and Xilene). Almost all organic solvents are toxic when inhaled or ingested in large quantities and exceeding the threshold. Benzene is classified into group 1 chemicals which are carcinogenic.[3]

Benzene can enter the body in the form of gas, solid, or liquid form. Benzene that enters the body is metabolized into benzene epoxide. In the liver, benzene epoxide is an unstable compound which is converted into phenols so that it can be excreted through urine.[4] When inhaled, benzene can cause aplastic anemia and leukemia. Some research work conducted in Europe, America, and Mexico have shown a significant relationship between increased levels of benzene in the air and increased cases of cancer and leukemia of the local population. Studies in the United States found that inhalation of benzene, although within a certain threshold, has been shown to cause chromosomal abnormalities in sperm cells.[1] The occurrence of health problems due to benzene exposure in shoe industry workers was also reported in China. This study stated that workers exposed to benzene were at risk of death from leukemia with a relative risk of 2.3 higher than those who are not exposed to benzene.[5] With regard to the exposure concentration of chemicals and their impact on workers' health, the Indonesia Government has sought to regulate the threshold value of occupational exposure in 2011 through Permenakertrans No.13/MEN/X/2011, concerning the threshold value of physical factors and chemical factors in the workplace. This regulation set the threshold value for benzene exposure in the workplace at 0.5 ppm (Ministry of Manpower and Transmigration, 2011).[6]

Damages due to free radicals, one of which is exposure to benzene in the body, can be overcome with antioxidants. Antioxidants are needed to prevent oxidative stress. Oxidative stress is a condition of imbalance between the amount of free radicals that exist with the amount of antioxidants in the body. Free radicals are compounds that contain one or more unpaired electrons in their orbitals, so they are highly reactive and are able to oxidize surrounding molecules such as lipids, proteins, DNA, and carbohydrates.[7] Antioxidants are defined as substances that can delay, prevent, or eliminate oxidative damage to target molecules, namely proteins, lipids, and DNA.[8] The body can naturally produce antioxidants that are able to overcome the effects of free radicals, yet the increase in supply of free radicals leads to the need of supply of antioxidants from outside. One of the antioxidants produced by the body is glutathione.

Glutathione levels in the body become an important aspect that must be considered because disruption of glutathione synthesis and metabolism results in impaired glutathione function as an antioxidant which in turn causes various diseases.[9] Antioxidant activity is measured through levels of malondialdehyde (MDA) as a result of lipid peroxidation. Malondialdehyde is a reactive molecule with the molecular formula $C_3H_4O_2$.[10] According to research conducted by Odewabi in Nigeria in 2014, exposure to free radicals, especially benzene among gas station workers, can increase MDA levels in workers. Research by Suparno et al[11] also stated that high levels of plasma MDA as a marker of oxidative stress can result in DNA disorders. Therefore, this study aims to look at the relationship between concentration and excess cancer risk (ECR) benzene, MDA, glutathione, and DNA degeneration in shoe industry workers in Osowilangon, Surabaya.

Methodology

This is an observational study with cross-sectional design. The study was conducted in the Osowilangun shoe industry in Surabaya in September 2019. The study population was 25 workers in the Osowilangun shoe industry with a sample size equal to that of the population.

The research variables consisted of independent variables in the form of benzene concentration and ECR benzene and the dependent variables in the form of MDA, glutathione, and DNA degeneration. Data were obtained from the results of laboratory tests and using questionnaires. Measurement of MDA levels in the urine was performed using a spectrophotometer, glutathione levels were measured using the enzyme linked immunosorbent assay method, and DNA degeneration was measured using acrylamide electrophoresis with silver staining. To determine DNA degeneration, the real-time polymerase chain reaction method is used. In the statistical analysis, the data are tested using cross tabulation to determine the relationship between variables in the categorical data. Numerical data were tested using Pearson for the relationship test.

Result

Respondents were examined through several characteristics including age, sex, last education, and body mass index (BMI). Below is a distribution table of the characteristics of the respondents studied.

As shown in Table 1, most of the respondents were between 46 and 65 years old (32% in the 46-55 years old category and 32% in the 56-65 years old category, respectively). There were 13 (52%) men and 12 (48%) women. Most of the respondents highest education level were high school (44%) and most respondents (52%) had a normal BMI.

Benzene ECR Calculation

Characteristics of health risks can be expressed by the ECR for carcinogenic or cancer effects. The ECR was calculated by multiplying the cancer intake value by the cancer slope factor (CSF) value. The ECR value is declared safe if $\leq 10^{-4}$. The ECR formula used is as follows:

Table 1. Distribution of Respondent Characteristics.

Characteristics of Respondents	Frequency	Percentage
Age		
16-25	2	8
26-35	0	0
36-45	7	28
46-55	8	32
56-65	8	32
Gender		
Male	13	52
Female	12	48
Education level		
Primary	10	40
Junior high	4	16
Senior high	11	44
BMI		
Underweight	2	8
Normal	13	52
Overweight	10	40

Abbreviation: BMI, body mass index.

$$\text{ECR} = \text{Carcinogenic intake}\,(I_k) \times \text{CSF}.$$

Excess cancer risk calculation results can indicate the level of carcinogenic risk in workers due to exposure to chemicals—one of which is benzene. If the ECR value is $\leq 10^{-4}$, workers exposed to benzene are not considered to be at risk of carcinogenic as it is within safe limits. Conversely, if the ECR value $>10^{-4}$, workers exposed to benzene have a risk of carcinogenic effects. Based on the ECR calculation results in Table 2, almost all workers have an ECR value $>10^{-4}$, whereas only 1 worker had an ECR value of $\leq 10^{-4}$. In sum, almost all workers were at risk of carcinogenic effects.

Based on Table 3, of the 25 respondents, there were 15 (60%) respondents with benzene concentrations below the threshold value ($\leq$0.5 ppm) and 10 (40%) respondents with benzene concentrations exceeding the threshold limit value (>0.5 ppm). An ECR value or benzene carcinogenic risk of >0.0001 was indicated by 24 (96%) respondents. This means they had a carcinogenic risk and only 1 (4%) of the respondents indicated an ECR value of 0.0001.

Based on Table 4, 10 (40%) respondents who were exposed to benzene concentrations exceeding the threshold value (0.5 ppm) had a carcinogenic risk with an ECR value >0.0001. Of the 15 (60%) respondents who were exposed to benzene concentrations within the safe limit there were 14 (56%) respondents who had a carcinogenic risk with an ECR value >0.0001 and only 1 (4%) respondents who had a carcinogenic risk with an ECR value of 0.0001. Most respondents had carcinogenic risks with ECR values >0.0001, but exposure to benzene concentrations was still within safe limits.

Table 5 shows that there is no relationship between benzene concentration and MDA levels as the P value was >.25 ($P = .393$). Meanwhile, from the characteristics of carcinogenic risk (ECR) in benzene, there is a relationship between benzene ECR and MDA levels because the P value <.25 ($P = .142$). As such,

Table 2. Calculation of Benzene Carcinogenic (ECR) Risk Characteristics in Shoe Industry Workers in Osowilangun.

No	Carcinogenic intake (Ik), mg/kg/d	Cancer Slope Factor (CSF), mg/kg/d	Excess Cancer Risk (ECR)
1	0.028009301	0.029	0.00081227
2	0.014476156	0.029	0.000419809
3	0.004389141	0.029	0.000127285
4	0.023055386	0.029	0.000668606
5	0.020845665	0.029	0.000604524
6	2.051100087	0.029	0.059481903
7	2.835162856	0.029	0.082219723
8	0.851117973	0.029	0.024682421
9	0.029462408	0.029	0.00085441
10	0.004958649	0.029	0.000143801
11	1.890469185	0.029	0.054823606
12	1.20605121	0.029	0.034975485
13	0.015197621	0.029	0.000440731
14	0.025133332	0.029	0.000728867
15	0.050500021	0.029	0.001464501
16	0.319923046	0.029	0.009277768
17	0.028809567	0.029	0.000835477
18	0.015788537	0.029	0.000457868
19	0.020896729	0.029	0.000606005
20	0.152694918	0.029	0.004428153
21	1.993950529	0.029	0.057824565
22	0.821133899	0.029	0.023812883
23	0.637067458	0.029	0.018474956
24	0.000785664	0.029	2.27843E-05
25	0.063154147	0.029	0.00183147

Table 3. Distribution of Benzene Concentrations and ECR.

Variable	Frequency	Percentage
Benzene concentration		
1. $\leq$0.5 ppm	15	60
2. >0.5 ppm	10	40
Benzena ECR		
1. ECR $\leq$ 0.0001	1	4
2. ECR > 0.0001	24	96

Abbreviation: ECR, excess cancer risk.

Table 4. Results of Cross-Tabulation Test Between Benzene Concentration and Benzene ECR.

	Benzene ECR		
Benzene Threshold	>0.0001	$\leq$0.0001	Total
>0.5 ppm	10	0	10
	40%	0%	40%
$\leq$0.5 ppm	14	1	15
	56%	4%	60%
Total	24	1	25
	96%	4%	100%

Abbreviation: ECR, excess cancer risk.

Table 5. Relationship of Benzene Concentration and ECR and Malondialdehyde.

Variable	Mean	SD	*P* Value (0.25)	N
Benzene concentration	10.31	17.66	.393	25
Malondialdehyde	7.85	2.63		
Benzene ECR	0.015	0.024	.142	
Malondialdehyde	7.85	2.63		

Abbreviations: ECR, excess cancer risk; SD, standard deviation.

Table 6. Relationship of Benzene Concentration and ECR With Glutathione.

Variable	Mean	SD	*P* Value (0.25)	N
Benzene concentration	10.31	17.66	.45	25
Glutathione	35.65	10.5		
ECR Benzena	0.015	0.024	.184	
Glutathione	35.65	10.5		

Abbreviations: ECR, excess cancer risk; SD, standard deviation.

benzene ECR affects the presence of MDA levels in the body rather than benzene concentration. The benzene concentration has an average of 10.31 ppm, while the benzene ECR has an average of 0.015 ppm with an average MDA level of 7.85.

Based on Table 6, there is no relationship between benzene concentration and glutathione levels with *P* value >.25 ($P = .45$). The characteristics of carcinogenic risk (ECR) in benzene show an association between benzene ECR and glutathione levels, with a *P* value <.25 ($P = .184$). This showed the potential of benzene ECR in reducing the glutathione levels in the body where the average concentration of benzene was 10.31 ppm, whereas the average ECR of benzene was 0.015 ppm with the average glutathione level being 35.65.

In Table 7, of 10 (40%) respondents who were exposed to benzene concentrations exceeding the threshold value (0.5 ppm), there were 6 (24%) respondents who experienced DNA degeneration. Of the 15 (60%) respondents exposed to benzene concentrations within the safe limit, there were 9 (36%) respondents who experienced DNA degeneration. It can be seen that the majority of respondents experienced DNA degeneration with benzene exposure were below the threshold value.

Table 8 shows that of the 24 (96%) respondents who had a benzene ECR value >0.0001 there were 15 (60%) respondents who experienced DNA degeneration and 9 (36%) respondents did not experience DNA degeneration. Respondents with benzene ECR values ≤0.0001 did not undergo DNA degeneration. It was clear that most respondents experienced DNA degeneration with benzene ECR values >0.0001. Respondents who experience DNA degeneration were expected to have a higher risk of carcinogenicity.

Table 7. Results of Cross-Tabulation Tests Between Benzene Concentration and DNA Degeneration.

	DNA Degeneration		
Benzene Threshold	Degeneration	Normal	Total
>0.5 ppm	6	4	10
	24%	16%	40%
≤0.5 ppm	9	6	15
	36%	24%	60%
Total	15	10	25
	60%	40%	100%

Table 8. Results of Cross-Tabulation Tests Between Benzene ECR and DNA Degeneration.

	DNA Degeneration		
Benzene ECR	Degeneration	Normal	Total
>0.0001	15	9	24
	60%	36%	96%
≤0.0001	0	1	1
	0%	4%	4%
Total	15	10	25
	60%	40%	100%

Abbreviation: ECR, excess cancer risk.

Discussion

Of the characteristics of respondents in the shoe industry workers in Osowilangun, Surabaya, of the 25 respondents mostly aged 46 to 65 years, 52% were male with a high school education (44%) and the BMI was mostly normal. After the measurements were made, there were 10 (40%) respondents who were exposed to benzene exceeding normal levels above the threshold (0.5 ppm). The average concentration of benzene is 10.31 ppm. These results indicate that the benzene concentration is quite high beyond the normal threshold value set by the government (0.5 ppm). This was consistent with Astuti's research[12] which states that the results of the measurement of benzene in the mechanical work environment of the AHASS workshop in Patrang subdistrict and Sumbersari subdistrict, Jember district had an average value exceeding the threshold value (3.5118 ppm). However, this result is different from that of by Haen and Oginawati[13] that the average concentration of benzene in the breathing zone of respondents (sol workers) was still within safe limits below the threshold (0.238 ppm). Febriantika et al[14] also showed that the average concentration of benzene inhaled by workers in the printing industry X in Semarang was 0.13 ppm.

Excess cancer risk is a risk for the effects of cancer that can be determined by multiplying the value of cancer intake with CSF. If ECR ≤0.0001, then the concentration of benzene exposure in workers has not caused carcinogenic health effects. However, if the ECR >0.0001, then the concentration of benzene exposure in workers can cause carcinogenic health effects.[15] According to Indriyani et al,[16] exposure to chemicals carcinogenic risk if the ECR calculation results were more than 0.0001. From the results of the ECR calculation, the benzene

ECR value of most respondents was above 0.0001 where there was only 1 respondent who had a benzene ECR value below 0.0001. This means that almost all respondents have a risk of being carcinogenic or cancer affected. Of the 24 respondents who were at risk of causing carcinogenic effects, 12 (40%) of them were exposed to benzene exceeding the normal limit value (>0.5 ppm). This was consistent with research conducted by Febrian et al[17] that in the lifetime carcinogenic effect there was a risk of cancer with an ECR value of 4.95×10^{-4}, that is, ECR $>10^{-4}$. In addition, according to the results of a research by Febriantika et al,[14] the average value of benzene ECR on real-time exposure is 2.8×10^{-4} to 1.2×10^{-3} and 10^{-3} to 4.3×10^{-3} on lifetime exposure. A concentration of benzene ECR $>10^{-4}$ indicates excess risk of cancer. This was different from the research conducted by Handoyo and Wispriyono[18] that the ECR of benzene on tollgate officers at Kebun Jeruk tollgate was 2.5E-06, while the benzene ECR on administrative officers at Kebun Jeruk tollgate was 4.4E-07. Both ECR values had a safe risk level with ECR values $<10^{-4}$ (0.0001).

The results of this study indicate that there was no relationship between benzene concentration and MDA levels. However, there was a relationship between benzene ECR and MDA levels. The results of the statistical test of benzene concentration and MDA levels were $P = .393$ ($P > .25$), while the benzene ECR with MDA levels was $P = .142$ ($P < .25$). This indicates that most of the shoe industry workers in Osowilangun had high level of carcinogens corresponding to the MDA level in their body. This was consistent with research conducted by Tualeka et al[19] which found that there was no relationship between benzene concentration and MDA levels ($P = 1.000$; $r = 0.000$). Subandrate[20] stated that the average MDA level of gas station employees was 0.731 nmol/mL which was higher than the average MDA control. This can be caused by oxidant compounds especially benzene in the gas station environment which is metabolized in the body to free radicals which in turn oxidize lipids and form MDA.

In this study, there was no relationship between benzene concentration and glutathione levels but there was a relationship between benzene ECR and glutathione levels. Statistical test results between benzene concentration and glutathione levels were $P = .45$ ($P > .25$), while the benzene ECR and glutathione levels were $P = .184$ ($P < .25$). This was consistent with research conducted by Tualeka et al[19] which states that there was no relationship between benzene concentration and glutathione levels ($P = 1.000$; $r = 0.000$). This was probably due to availability of various other antioxidants (glutathione peroxidase, superoxide dismutase, and catalase) that play a role in reducing free radicals not studied here. However, benzene ECR can reduce levels of glutathione in the body than benzene concentration.

The cross-tabulation tests in Tables 7 and 8 show that there was no relationship between benzene concentration and the incidence of DNA degeneration. A total of 9 (36%) respondents experienced DNA degeneration with benzene exposure below the threshold value. There was a relationship between benzene ECR and DNA degeneration. A total of 15 (60%) of respondents experienced DNA degeneration with benzene ECR values >0.0001. Respondents who experience DNA degeneration have a higher risk of carcinogenicity. According to Nikmah et al,[21] the disruption of DNA synthesis can be caused by the reaction of benzene oxide metabolites that bind to nucleic acids. Hiraku and Kawanishi[22] stated that the mechanism of DNA damage can be induced by the major benzene benzoquinone and hydroquinone metabolites investigated in relation to apoptosis and carcinogenesis. Benzene metabolites can cause DNA damage through the generation of H_2O_2 in cells before internucleosomal DNA fragmentation leads to apoptosis. Reactive benzene metabolites have been identified including benzene oxide, phenol, hydroquinone, catechol, and benzoquinone which can produce various types of DNA lesions.[23] Benzene hydroquinone and benzoquinone metabolites can form DNA additives in vitro. In addition, DNA addition was also observed in vivo by Bauer et al with 32P method post labeling in rabbit liver cells treated subcutaneously with benzene.[24] According to Kolachana et al,[25] a combination of phenol, catechol, and hydroquinone can produce a significant increase in oxidative DNA damage in the rat bone marrow. Benzenetriol can also increase oxidative DNA damage significantly. The conversion of benzene to phenolic metabolites and subsequently producing oxidative DNA damage can play a role in genotoxicity, myelotoxicity, and benzene-induced leukemia. A study conducted by Ren et al[26] provided evidence that benzene exposure could induce hypomethylation of Long Interspersed Element-1 (LINE-1) and hypermethylation" of DNA repair genes.

Conclusion

Most respondents experienced DNA degeneration with an ECR value >0.0001. This means that respondents who experience DNA degeneration have a higher risk of carcinogenicity. There was no relationship between benzene concentration and MDA, glutathione, and DNA degeneration. However, there was a relationship between benzene ECR and MDA, glutathione, and DNA degeneration in shoe industry workers in Osowilangun. The ECR value of benzene in workers needs to be routinely determined so as to prevent the carcinogenic effects due to exposure to chemicals that exceed the threshold. Among prevention should be the use of personal protective equipment such as respirator or chemical masks so that exposure to chemicals, especially benzene, via inhalation are significantly minimized.

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