Evaluation of the Exposure to Benzene and SpmA using the Urine of Workers in the Shoe Home Industry in Surabaya

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ABSTRACT

Introduction: Benzene is one of the pollutants in the shoe home industry that can cause cancer among the workers. The present research aimed to analyze the relationship between exposure to benzene and spmA (s-phenylmercapturic Acid) in the urine of shoe-making home industry workers in Surabaya. **Methods:** This was an observational study using an analytical research method where the total number of respondents in the sample was 10. The concentration of benzene was measured using Gas Chromatography-FID (Flame Ionization Detector). The data collection technique was descriptive analysis for each variable from among the worker's characteristics. The analysis of the relationship between the level of spmA in their urine and the worker's characteristics was performed using regression tests while the analysis of the relationship between the level of benzene in the air and the levels of workers' spmA was performed using the Spearman correlation test. **Results:** The benzene I levels in the work environment were found to be between 0.06 ppm - 53.8 ppm. The average spmA was 6.68 µg/g creatinine. The p value of the relationship between the variable levels of benzene and the levels of spmA was 0.879 with a Spearman correlation coefficient of 0.056. **Conclusion:** The mean concentration of benzene in the air at the 6 point uptake was over the threshold. Based on the results of the spmA examination, the mean value of spmA was below the threshold value. The test results on the level of benzene in the air and the spmA indicate a very weak relationship.

Keywords: benzene, spmA, shoe industry

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INTRODUCTION

Benzene is an aromatic organic solvent that is often used in industry (ATSDR, 2018). It is widely known as a good organic solvent for various industrial processes such as the rubber industry, shoes, paint solvents, as a component in motor fuel, as a component in detergent, in pesticides, and in pharmaceutical manufacturing (Wulandari, 2017). The National Institute of Occupational Safety and Health (NIOSH) reported that 9.8 million workers in the United States (US) and 400,000 workers in Denmark have been exposed to organic solvents. In Indonesia, organic solvents are widely used, especially in the industrial sector that uses chemical raw materials like the painting industry. One of the industrial sectors that is frequently exposed to benzene is car painting workshops (Rahayu, 2017).

The majority of industrial benzene values have been found to be above the limit. According to the findings of the study by Tualeka, A.R. *et al*. (2019), the benzene level in the printing sector in Surabaya is 70% higher than the 0.5 ppm threshold set by the Indonesian government. According to the findings of Sam Sam Ekabada's (2018) study on the effects of benzene on employees in the shoe-making home industry of Romokalisari Surabaya, the concentration of benzene was over the threshold of 90% in all home industrial locations.

The use of hazardous chemicals in the bonding process cannot be avoided during the manufacturing process as a whole. Exposure to organic solvent

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vapors also occurs during the glue process which can lead to occupational disorders including cancer.

Within 48 hours of exposure, benzene reaches the bloodstream, and the majority of the metabolites leave the body in the urine (Abadin *et al*., 2007). Human biomonitoring can reveal the level of benzene exposure in the worker's body. Biomarkers as markers of benzene exposure in the body can be used to conduct the human biomonitoring of benzene. SpmA is one indicator of benzene exposure in the body (spmA).

The association between benzene levels and spmA levels is consistent with the study conducted in Cibaduyut Bandung in the informal shoe-making industry. According to the findings of this study, there is a significant link between spmA levels and the occupational exposure to benzene, with p = 0.036 and p = 0.033, respectively, implying that the spmA levels in the employees reflect the workplace exposure to benzene. Another area of research in Bogor, West Java, is the shoe-making business. His findings revealed that when the benzene exposure was low, the content of spmA in the urine was equally low (Wulandari and Fauzia, 2019).

Based on the description above, the high solvent content in the glue during the shoe-making production process can pose a risk to worker health. Therefore, it is necessary to analyze the relationship of benzene exposure to the levels of spmA in the urine of the shoe-making home industry workers in Osowilangun Surabaya.

Trans-trans muconic acid (Tt-MA) and s-phenyl mercapturic acid are produced via benzene detoxification in the body using CYP2E1 enzymes, sulfation, and glutathione (spmA). According to the findings of Tualeka, Nirmawati and Adi (2017), consuming meals that are high in CYP2E1 enzymes and sulfation increases the benzene excretion according to the ttmA ratio by 980%. According to the findings of Tualeka, *et al*. (2019), a high intake of CYP2E1 and glutathione enzymes increases the spermA excretion among the shoe-making industry home workers.

The relationship between the level of benzene and the level of spmA is in line with the research conducted in the informal shoe-making industry in Cibaduyut Bandung. Based on the results of the study, it showed there to be a significant relationship with the level of spmA with p=0.036 and p=0.033, respectively, which means that the level of spmA in the workers indicates exposure to benzene at work (Wulandari, 2017). Another supporting research is the shoe-making industry in Bogor, West Java. His research results show that where there is a low benzene exposure, the concentration of spmA in the urine is also low (Wulandari, 2019).

The home shoe-making industry is one area of work that needs attention because the number engaged in the industry continues to grow while the risk of disease due to said work is inevitable. Exposure to high levels of benzene can occur in workers who work in the home shoe-making industry as it uses benzene. The level of benzene exposure in the worker's body can be seen through human biomonitoring. The human biomonitoring of benzene can be done by measuring biomarkers as the markers of benzene exposure in the body. One of the markers of benzene exposure in the body is spmA. Benzene metabolism can occur in almost all body tissues but the most important storage site for benzene metabolites is in the liver. Benzene oxide can react further with glutathione which is excreted in the urine as spmA (Purwanto, 2014).

Research on benzene detoxification in the workplace has been carried out in various industries. Other industries, such as the car painting industry where workers are also exposed to benzene, have not yet been carried out.

In the production process, the use of hazardous chemicals in the bonding process cannot be avoided. In the gluing process, exposure to organic solvent vapors occurs and allows for the occurrence of occupational diseases such as cancer.

Within 48 hours of exposure, benzene reaches the bloodstream and the majority of the metabolites leave the body in the urine (Abadin *et al*., 2007). Human biomonitoring can reveal the level of benzene exposure in the worker's body. Biomarkers as markers of benzene exposure in the body can be used to conduct the human biomonitoring of benzene. spmA is a marker of benzene exposure in the body.

The relationship between benzene levels and spmA levels is consistent with the research on the informal shoe-making industry in Cibaduyut Bandung. Based on the results of this study, there is a significant relationship with the level of spmA with p = 0.036 and p = 0.033, respectively, which means that the level of spmA in workers indicates exposure to benzene in the workplace (Wulandari *et al*., 2017). Another supporting research is in the shoe-making industry in Bogor, West Java. The results of his research showed that where there was a low benzene exposure, the concentration of spmA

in the urine was equally low (Wulandari and Fauzia, 2019).

Based on the description above, the high solvent content in the glue during the shoe-making production process can pose a risk to worker health. Therefore, it is necessary to analyze the relationship of benzene exposure to the levels of spmA in the urine of the shoe-making home industry workers in Osowilangun Surabaya.

METHODS

This was an observational study because the data was obtained without a direct intervention. The population in this study was the total population of all workers in the shoe-making home industry, at a total of 20 workers. Sample inclusion criteria:1. Respondents who are no more than 50 years old; 2. Respondents have worked for more than 20 years.

According to the inclusion criteria above, the eligible population was 11 respondents. And total samples 10 respondents. Workers have individual characteristics.

The number of samples was determined using the following form:

$$n = \frac{Z^2_{1-\alpha/2}\, p\,(1-p)\, N}{d^2(N-1) + Z^2_{1-\alpha/2}\, p\,(1-p)}$$

Description:

n = 10 samples

α = degree of confidence = 0.05

p = proportion of respondents who consume foods rich in CYP2E1 enzymes and glutathione = 0.5

q = 1-p proportion of respondents who consume foods rich in CYP2E1 and the enzyme glutathione = 0.5

d = limit of error or absolute precision

Set =0.05 or Z1- /2 = 1.96

Materials and Equipment

Measurement of benzene

Benzene concentration was measured using a Gas Chromatography tool, specifically an FID (Flame Ionization Detector).

SpmA Measurement

Chemical Material

The chemicals needed included standard spmA, aquabides, distilled water, solid NaOH, ethyl acetate (p.a), HPLC grade methanol, perchloric acid (p.a), creatinine standard aquabides, saturated picric acid, concentrated HCl, and urine samples.

Equipment

The equipment needed included an analytical balance, refrigerator, micro pipette, pH meter, polyethylene bottle, syringe, centrifuge, degasser, vortex, High Performance Liquid Chromatography with a UV detector and reverse phase C18 column (4 x 4 mm ID., particle size) 5µm), a UV-Visible Spectrophotometer, 10 ml brown glass bottle, 100 ml brown glass bottle, 100 ml clear glass bottle, basin, 100 - 1000 L micro pipette, 3000 rpm centrifuge, balance, pH meter, and a vacuum pump. The analytical equipment used was a set consisting of a High Performance Liquid Chromatography (HPLC) UV detector and a UV-Visible Spectrophotometer.

Procedure

Creatinine Analysis

Creatinine analysis was performed using the de Jaffe method. Creatinine analysis was performed based on the color change of the creatinine-picrate complex. A normal creatinine level based on the standards of the WHO regulation is 0.3-3.0 g/L.

Creatinine Standard Solution Preparation

Dissolve 0.3 mg of creatinine with 0.1 M HCl in a 25 mL volumetric flask. Furthermore, variations in the concentration of 0.12 were made; 0.48 ;1.2; 2,4; and 4.8 g/L were measured using a UV-Visible spectrophotometer at a wavelength of 485 nm.

• *Urine Creatinine Analysis*

The number of g of s-phenyl mercapturic acid per gram of creatinine was used to calculate the amount of creatinine. To remove the sediment from the urine sample, it was centrifuged first. In a 25 mL volumetric flask, 0.5 mL saturated picric acid

(solid picric acid diluted in 30 mL distilled water until saturated) and 1.00 mL 1 M NaOH were added. This was combined with the mixture, then 0.1 mL of centrifuged urine sample was added and allowed to stand for 10 minutes before being diluted with 0.1 N HCl to determine the limit. At a wavelength of 485 nm, the measurements were taken with a UV-Visible spectrophotometer. The blanks were subjected to the same process.

• *Analysis of spmA (spmA)*

The spmA analysis was carried out based on the method used by Prapin Tharnpoopasiam et. al (2004) (14). Verification was carried out to support the results of the study adjusted to the experimental conditions. Verification included a repeatability test, the determination of LOD and LOQ, the determination of optimum conditions, and recovery.

• *Preparation of spmA Standard Stock Solution*

The spmA standard solution was prepared by dissolving 1 mg in 10 mL of methanol. The spmA standard solutions were diluted with aquabides to 1000 ppm and stored at temperatures below 0°C.

• *Verification of the spmA Analysis Method*

Prior to the analysis of the spmA in urine, optimization was carried out to determine the optimum separation conditions adapted to the conditions of the equipment and the surrounding environment, including the determination of optimum conditions, the repeatability test, the limit of detection test (LOD), and the limit of quantification (LOQ) and the optimization of recovery percentages.

Determination of the Optimum Conditions

The optimum conditions were obtained by optimizing retention by varying the ratio of the mobile phase to separate the spmA chromatogram from the urine matrix.

Manufacturing of the Mobile Phase Variations

The mobile phase variation was carried out by making 3 compositions with a ratio of methanol – 0.01N perchloric acid to 0.0012 N (40%:60%; 35%:65%;30%:60%), then the three mobile phases were filtered through a membrane.

Optimum condition measurement

The measurement of the optimum conditions was carried out by comparing the peak area of the urine chromatogram. The standard was added to the prepared urine by varying the 3 element ratio compositions (ratio of methanol:perchloric acid 0.0012 N = 40:60, 35:65, 30:70). (70): Average American weight (as the standard weight average used in the formula).

Testing of the Limit of Detection (LOD) and Limit of Quantification (LOQ)

The LOD and LOQ values were calculated statistically using linear regression and the standard calibration curve was the closest to being undetectable.

Repeatability Test

The spmA standard solutions with 3 concentration variations were injected into the HPLC column (High Performance Liquid Chromatography) 6 times for each concentration.

Recovery Test

The spmA standard solution, urine, and spmA standard were added to the prepared urine and 20 L was injected into the column and eluted with the optimum eluent ratio. The difference in peak chromatogram results between the urine and the spmA standard in the same urine sample were compared with the peak area of the spmA standard with the same concentration to obtain the percentage of recovery.

Preparation and Measurement of the spmA Standard Solution

Standard calibration was carried out by varying the concentration of 5 spmA standards (100;200;400;600;800;1000 mg/L and 1;2;4;6;8;10 g/L) which were then measured using HPLC at 205 nm.

Urine Sample spmA Analysis

The respondents were observed to consume foods containing salmon and fish oil as well as glutathione from asparagus, avocado, tomatoes, grapes, and oranges for 7 (seven) days. After that, the spmA concentration in their urine was measured.

The workers were examined according to their individual characteristics such as age, gender, length of work, BMI, smoking behavior, alcohol consumption, and level of exercise. The concentration of benzene was measured using Gas Chromatography-FID (Flame Ionization Detector) using a UPTK3 laboratory. The concentration of spmA in the worker's urine was measured using liquid chromatography via the Prodia Laboratory.

The research was conducted in the shoe-making industry in Osowilangun Village, Benowo District, Surabaya. The research was conducted in December 2019. The data collection was carried out after the respondents had filled in the informed consent form. The data collection technique was in the form of a descriptive analysis of each variable for the worker's characteristics. The relationship between the level of spmA in the urine and the characteristics of the workers was examined using regression tests. The analysis of the relationship between the level of benzene in the air and the level of worker spmA was carried out using the Spearman correlation test.

RESULTS

Characteristics of the Respondents

Based on Table 1 showing the characteristics of the respondents, this study was dominated by male workers by 70%. The age of the workers in this study was dominated by workers in an age range of 31 - 40 years (50%). Years of service were dominated by workers with a length of service of 20-24 years by 30%. The smoking habit of the workers was dominated by non-smokers at 90%. For the variable on the consumption of foods rich in CYP2E1 and glutathione enzymes, 50% of workers had a habit of consuming foods rich in CYP2E1 and glutathione enzymes.

Table 1. Frequency Distribution

Variable	Category	N	%
Gender	Men	7	70
	Women	3	30
Age	<30 year	1	10
	31-40 year	5	50
	41-50 year	3	30
	51-60 year	1	10
Years of service	10 – 14 years	2	20
	15 – 19 years	1	10
	20 -24 years	3	30
	25 - 29 years	2	20
	30-34 years	2	20
Smoking habit	Active smoker	1	10
	Non-active smoker	9	90
Consume Foods rich enzyme CYP2E1 and Glutathione	Yes	5	50
	No	5	50

Concentration of Benzene in the Air in the Workplace

The findings indicate that the mean concentration of benzene was 11.43 ppm, the maximum concentration of benzene was 53.8 ppm, and the minimum concentration of benzene was 0.06 ppm. The threshold limit value of benzene according to the Regulation of the Minister of Manpower of the Republic of Indonesia Number 5 of 2018 was lower than the average concentration of benzene in the workplaces sampled.

Concentration of SpmA in Urine

The concentration of benzene spmA metabolite in urine was measured through the means of laboratory tests. The threshold value (TLV) issued by the ACGIH in 2018 is 25 μg/g of creatinine.

Table 2. Distribution of the respondents based on the exposed level of benzene in the air of the shoe-making home industry in Osowilangun Surabaya in 2019

Respondent	Benzene level (ppm)	Benzene level (mg/m3)
Respondent 1	0.06	0.1912898
Respondent 2	0.20	0.63763265
Respondent 3	0.20	0.63763265
Respondent 4	19.40	61.8503673
Respondent 5	19.40	61.8503673
Respondent 6	8.50	27.0993878
Respondent 7	0.20	0.63763265
Respondent 8	0.06	0.1912898
Respondent 9	12.50	39.8520408
Respondent 10	53.80	171.523184
Minimum	0.06	0.19
Maximum	53.8	171.52
Mean	11.43	36.44
Median	4.35	13.86
Standard deviation	16.89	53.86

Based on the results of the testing for spmA in the sampled urine carried out in the laboratory from the 10 shoe-making home industry workers, the average value of spmA was 6.68 µg/g of creatinine. This value is below the safe limit.

Relationship between Benzene and SpmA Exposure in Urine

The Spearman correlation from Table 4 between the variable levels of benzene and the levels of spmA have a p value of 0.879. This value is greater than α = 5% and has a Spearman correlation coefficient value of 0.056.

Table 3. Frequency Distribution of the SpmA Concentration in the Urine of the Shoe-making Home Industry Workers in Osowilangun Surabaya in 2019

Respondent	Examination Type	SPMA results (µg/g creatinine)	Hippuric Acid Yield (µg/g creatinine)
Respondent 1	spmA	1.95	54.87
Respondent 2	spmA	4.57	13.12
Respondent 3	spmA	0.99	33.47
Respondent 4	spmA	7.58	96.43
Respondent 5	spmA	25.2	863.96
Respondent 6	spmA	6.02	11.19
Respondent 7	spmA	6.72	960.18
Respondent 8	spmA	9.13	274.16
Respondent 9	spmA	3.43	306.41
Respondent 10	spmA	1.25	57.09
Minimum		0.99	
Maximum		25.20	
Mean		6.68	
Median		5.29	
Standard deviation		7.07	
Skewness		2.31	

Table 4. Relationship between Benzene Exposure and spmA Levels in Urine

spmA level in Urine	Concentration of Benzene		Total	Sig.
	<0.5 ppm	>0.5 ppm		
<25 µg/g creatinine	5	4	9	0.879
>25 µg/g creatinine	0	1	1	

Relationship between Years of Service and the Level of SpmA in Urine

The results of the analysis using the multiple linear regression test method had a p value of 0.971. This value indicates that there is no effect between years of service and the level of spmA in the worker's urine. In Table 5 regarding the cross-tabulation between years of service and the level of spmA in the urine, one person with a work duration of 22 years had a level of spmA in their urine showing more than 25 µg/g creatinine present.

Relationship between Smoking Behavior and SpmA Levels in Urine

The results of the analysis using the multiple linear regression tests resulted in a p value of 0.834. This value indicates that there is no effect between smoking behavior and the level of spmA in the urine of workers. In Table 6, the cross-tabulation between smoking behavior and the spmA level in the worker's urine indicated that only one worker had a urine spmA level of more than 25 µg/g creatinine with non-smoking behavior.

DISCUSSION

Concentration of Benzene in the Working Environment

The lowest benzene concentration in the work environment (0.19 mg/m^3) and the highest (53.80

Table 5. Relationship between years of service and the level of SpmA in urine

spmA level in Urine	Years of Service (in years)						Total	Sig.
	10	15	20	22	25	30		
<25 µg/g creatinine	2	1	1	1	2	2	9	0.971
>25 µg/g creatinine	0	0	0	1	0	0	1	

Table 6. Relationship between Smoking Behaviorand spmA Levels in Urine

spmA level in Urine	Smoking Behavior		Total	Sig.
	Yes	No		
<25 µg/g creatinine	1	8	9	0.879
>25 µg/g creatinine	0	1	1	

mg/m3) were found in the six samples taken, with an average benzene concentration in the work environment of 11.43 ppm or 36.44 mg/m^3. Benzene is classified in group A1 (a chemical that has been proven to be a carcinogen for humans) with a TLV of 0.5 ppm and a PSD (Permitted Brief Exposure) of 2.5 ppm according to the Regulation of the Minister of Manpower of the Republic of Indonesia Number 5 of 2018 concerning Occupational Safety and Health. The average concentration of benzene in the shoe manufacturing business exceeded the Threshold Value. The TLV for benzene, according to the ACGIH, is 10 ppm (Zuliyawan,2010). This shows that benzene vapor was present in the workplace and that it has the potential to enter the worker's body (Tualeka *et al*., 2019).

Concentration of SpmA in Urine

The level of spmA in the urine of respondents was below the threshold value set by the ACGIH of 25 g/g creatinine (Worksafe, 2018). Based on the results of the spmA examination of all shoe-making industry workers totaling 10 respondents, the lowest spmA level was 0.99 g/g and the highest spmA level was 25.2 g/g. The average spmA was 6.68 g/g of creatinine. The average value obtained indicates that the level of spmA was below the threshold value.

Concentration of Benzene and the Level of SpmA in the Shoe-making Home Industry at Osowilangun, Surabaya

The ventilation in the work area is a general ventilation system that relies on a natural air exchange using parts of the building such as the windows and doors that are left open. The smaller the vent size, the less air that enters, meaning that it cannot replace the contaminated air.

Benzene in the shoe-making home industry appears in the form of vapor which is present in the glue. Steam is heavier than air, therefore steam tends to be in the lower part of the room. With an inadequate ventilation system, benzene vapor in the work area may be left behind. It is also possible that there is steam that is left behind, which can possibly be inhaled by the workers.

The pathways for benzene exposure in the body include the respiratory system, digestive tract, and skin. The respiratory tract is the dominant route of exposure. The benzene vapor in a room gets heavier if it is supported by poor ventilation. Health risks that can occur include shortness of breath, respiratory problems, central nervous system depression, and heart failure. Benzene that enters through the digestive tract is very rare. This is because any benzene that is ingested accidentally can cause symptoms such as vomiting, staggering, and a loss of consciousness. Benzene that enters the body through the skin can occur when the skin comes into direct contact with substances containing benzene (Abadin *et al*., 2007).

Benzene in the form of vapor enters the body through inhalation and it is primarily absorbed through the lungs. About 40-60% of the amount of benzene that people are exposed to is inhaled (Wijaya and Suyono, 1995). If inhaled, benzene is not excreted by expiration and the benzene will be absorbed into the blood. Benzene that has entered the body through the blood network will circulate throughout the body. Benzene is then converted into metabolites in the liver and bone marrow. Most of the metabolic products will be excreted through urine. Other pathways of benzene oxide metabolism include a reaction with glutathione (GSH) to form spmA and the conversion of ring openings with iron to trans, trans-muconic acid which is trans-reactive, as a transmuclonaldehyde intermediate (Abadin *et al*., 2007).

The test results indicated a p value of 0.879 which is greater than 5%. This demonstrates a Spearman correlation coefficient value of +0.056 between the level of benzene in the air and the results of the spmA testing. This demonstrates a lack of link between the benzene levels and spmA levels. Furthermore, the correlation coefficient is positive, showing that the value of spmA tends to rise in tandem with the benzene level. Another study conducted on junior high school children in Bandung found that benzene, which is still present in low average quantities, causes an average concentration of spmA in the students that does not surpass the threshold value (Putra, Wispriyono, and Kusnoputranto, 2019). There is no environmental data on the benzene range in previous investigations. Internal metabolites such as spmA demonstrate this. SpmA is an excellent metabolite of a complex mixed pollutant that causes nucleic acid oxidative damage (Andreolia *et al*., 2015). Another study in Cibaduyut, Bandung indicated that informal shoe manufacturing revealed a considerable level of spmA among the workers, indicating a working exposure to benzene (Wulandari *et al*., 2017). Even at low concentrations, toluene in the working air environment can impede spmA metabolism, resulting in low spmA levels

as well as actual benzene exposure (Carrieri *et al*., 2018). Genetics and enzyme induction are two of the elements that influence toxin metabolism in the body.

The Relationship between Smoking Behavior and SpmA Levels in Urine

The findings of this study highlight that there was found to be no correlation between smoking behavior and the level of spmA in the workers' urine. According to the findings of Abadin *et al* (2007), Wulandari *et al* (2017), and Tualeka *et al* (2019), there was found to be no link between smoking behavior and spmA level. A relationship between toxin and effect, such as the relationship between smoking behavior and spmA, cannot be determined based on the limited sample size of this study.

Relationship between Years of Service and SpmA Level in Urine

According to the regression test results, the variable length of time spent working with spmA had a p value of 0.971. Each independent variable had no effect on the level of spmA in the urine if the p value is greater than 0.05. Other variables outside the regression model that can affect benzene exposure, according to other studies, include smoking behavior, the use of personal protective equipment, medical history, drug consumption, diet / intake, and alcohol consumption (Kusuma, Setiani and Joko, 2015). Additional studies have found that other factors such as the length of employment, nutritional status, the duration of exposure, body weight, and the frequency of exposure play a significant role in influencing xenobiotic drug intake.

CONCLUSION

The concentration of benzene in the air at the 6 points of intake indicates that the mean value was over the threshold. Based on the results of the spmA examination, the mean value of spmA was below the threshold value. The test results show there to be a very weak relationship between the level of benzene in the air and the test results for spmA.

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