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BIOMAKERS OF TOLUENE AND THE IMPACT OF EXPOSURE TO TOLUENE IN INDOOR AIR ON PUBLIC HEALTH: LITERATURE REVIEW

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ABSTRACT

Biomakers of toluene and the Impact Of exposure to toluene in Indoor Air on Public Health: Literature Review. *Toluene is an organic solvent that is widely used in industry which is volatile and toxic to health. Based on data from the International Labor Organization in 2018, it is known that more than 1.8 million work-related deaths, one of which is due to toluene exposure, occur each year in Asia and the Pacific. Biomarker to determine the presence of toluene exposure in the human body, namely hippuric acid in the urine. This research is literature review. Database used in this study includes Science Direct and Google Scholar. There were several articles annotate that hippuric acid is a biomarker of toluene in human urine. Health problems due to exposure to toluene occur in humans who directly contact with glue and paint. Workers in gluing and coloring field had higher risk than workers in other field (P<0.01). Hippuric acid levels in the urine of workers exposed to toluene and xylene were 0.15 ± 0.04; 0.11 ± 0.01; and 0.19 ± 0.07 g g-1 creatinine, respectively. It is concluded that hippuric acid is a biomarker of toluene in human urine and the health effects due to exposure to toluene in indoor air include dizziness, vertigo, and eye irritation*

INTRODUCTION

Toluene is one of the most widely and frequently used organic solvents in paints and adhesives. Toluene is characterized by high volatility and toxicity [(1)]. Substances contained in adhesives are volatile organic compounds (VOCs), such as toluene, benzene, and xylene, which are classified as VOCs (Volatile Organic Compounds) [(2)]. In addition to being commonly found in adhesives, toluene is also present in gasoline, thinner, and paints. The health effects of VOC exposure in humans include respiratory disorders, eye irritation, sore throat, nausea, and vomiting [(3)]. Indoor VOC exposure levels have the potential to cause greater health disturbances compared to outdoor VOC exposure levels [(4)].

Toluene is commonly found in indoor environments such as home industries. A home industry is a small business unit or enterprise engaged in a specific industrial field in which one or two houses are used simultaneously as centers for production, administration, and marketing activities [(5)]. Factors that can influence health problems among workers in home industries include physical environmental conditions and production processes [(6)]. One type of home industry that extensively uses materials containing toluene is the footwear industry. The production process in the footwear industry may cause health problems due to exposure

to several hazardous materials used in shoe manufacturing, particularly shoe adhesives, if exposure occurs continuously and at high concentrations [7].

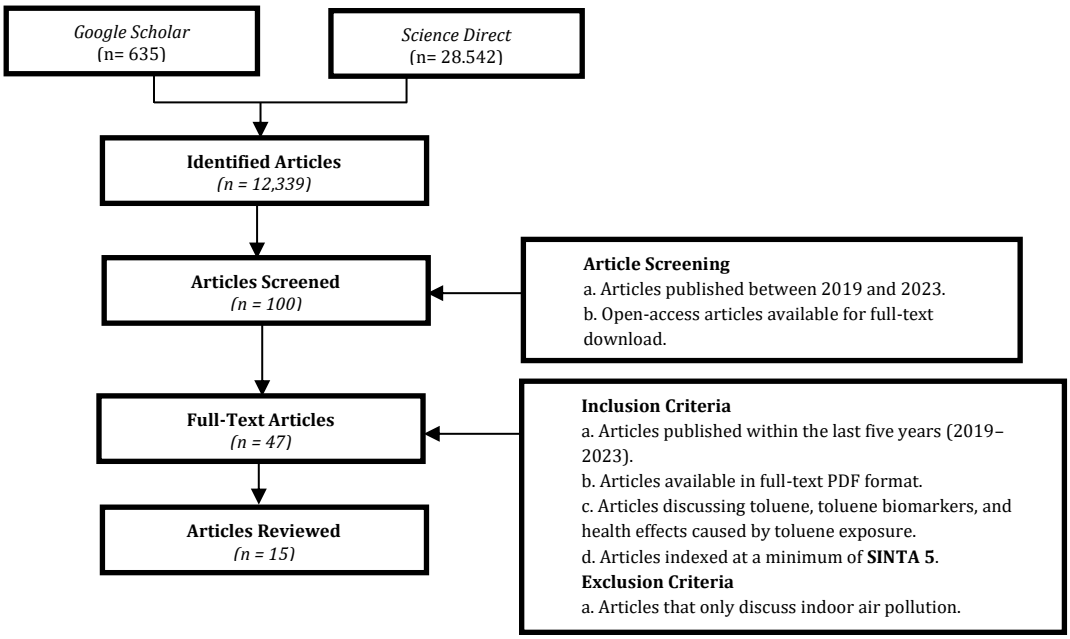
Toluene exposure at concentrations of 50 ppm to 200 ppm can cause acute central nervous system poisoning, characterized by headaches and drowsiness. Prolonged exposure to toluene exceeding the established Threshold Limit Value (TLV) may result in public health problems and occupational diseases [8]. Toluene has properties similar to benzene; it is a colorless liquid with a pleasant yet pungent odor and is highly volatile [9]. Toluene contained in adhesives easily evaporates, is readily inhaled, and enters the human respiratory tract. Various factors can influence the metabolism of toluene once it enters the human body, including age, sex, body composition, and individual health status [10]. Continuous exposure to toluene can cause health disorders such as dizziness, vertigo, eye irritation, skin irritation, respiratory disorders, impaired liver function, and central nervous system (CNS) disorders [11].

Toluene absorbed by the body is metabolized and excreted in urine as its dominant metabolite. Approximately ±20% of inhaled toluene is eliminated unchanged through exhaled air, while the remaining ±80% is metabolized into benzoic acid, which subsequently conjugates with glycine in the liver to form hippuric acid and is then excreted through urine [9]. The purpose of this study is to identify biomarkers of toluene exposure in the human body and to examine the health impacts resulting from toluene exposure.

MATERIALS AND RESEARCH METHODS

This study is a literature review. A literature review is a systematic, reproducible, and explicit method used to identify, evaluate, and synthesize research findings as well as scholarly ideas from researchers and practitioners, which are generally published in the form of journal articles. The databases used in this study were Google Scholar and ScienceDirect, with the keywords "Toluene, Hippuric Acid, Health Effects."

The selected articles were required to meet specific inclusion and exclusion criteria. The inclusion criteria were: articles published within the last five years (2019–2023), articles available in full-text PDF format, articles discussing toluene, toluene biomarkers, and health effects caused by toluene exposure, and articles indexed at a minimum of SINTA 5. The exclusion criterion was articles that focused solely on indoor air pollution.



Gambar 1. Literature Review Process

RESEARCH RESULTS AND DISCUSSION

Based on the results of the database search, a total of 12,339 articles were identified. The articles were then screened based on open-access availability and full-text accessibility published between 2019 and 2023, resulting in 100 articles. Further screening was conducted according to the predefined inclusion and exclusion criteria, yielding 47 articles. The final screening was performed by removing duplicate articles, resulting in 15 articles selected for review. The description of the reviewed articles is presented in Table 1.

Table 1. Results of the Review of 15 Articles on Toluene Biomarkers and the Health Effects of Toluene Exposure Following the Screening Process

No	Authors	Title	Research Results	Key Findings
1	Oginawati K, Anka AAH, Susetyo SH, Febriana SA, Tanziha I, Prakoeswa CRS (2021)	*Urinary hippuric acid level as a biological indicator of toluene exposure on batik workers*	Workers employed for more than two years had Odds Ratios (ORs) of 6.43, 6.75, and 9.00 for higher urinary hippuric acid levels compared to unexposed workers. Exposed workers experienced health symptoms.	Mean urinary hippuric acid concentrations were higher among workers continuously exposed to toluene.
2	Anggraini DCP, Tualeka AR, Jalaludin J, Ahsan (2022)	*Relationship between airborne toluene exposure and kidney function disorders among automotive painting workers in Surabaya*	The relationship between toluene exposure and creatinine and BUN levels was weak but positive (r = 0.244 and 0.042).	Long-term exposure to toluene above threshold limits may lead to kidney function impairment.
3	Nauli M, Ashar T, Lubis R (2019)	*Toluene exposure and urinary hippuric acid levels among printing workers in Medan*	Mean ambient toluene concentration was 6.97 ppm, below the threshold limit (50 ppm). Mean urinary hippuric acid was 143.5 mg/g creatinine.	Gender was associated with urinary hippuric acid levels; no association was found between ambient toluene concentration and urinary hippuric acid.
4	Prayogi ARY et al. (2020)	*Determination of safe non-carcinogenic toluene concentration in Surabaya printing industry*	73% of workers had exposure levels above normal, while 27% were below normal.	Toluene concentration in Surabaya printing industries exceeded normal levels (0.2 ppm).
5	Ayu PS et al. (2020)	*Relationship between toluene concentration, malondialdehyde (MDA), and health complaints in printing workers*	Mean toluene concentration was 1.2311 ppm and mean MDA level was 8.323 MU; a relationship between toluene and MDA was observed.	Health complaints included coughing (74%), headaches (63%), and shortness of breath (26%).
6	Hormozi M et al. (2019)	*Quantification of urinary metabolites of toluene and xylene as biological indices of exposure*	Urinary hippuric acid levels ranged from 0.11–0.19 g g^{-1} creatinine; significant correlations were found between exposure and biomarkers.	Chronic exposure to toluene and xylene increased urinary metabolites and may cause brain disorders, dermatitis, and cancer.
7	Ramadhini BK, Sulistyorini L (2021)	*Correlation between worker characteristics and health complaints due to organic solvent exposure*	No association was found between age or smoking habits and health complaints; work duration was significantly associated.	Long-term exposure (up to 21 years) to organic solvents including toluene caused nervous system complaints.

No	Authors	Title	Research Results	Key Findings
8	Huang L et al. (2021)	*Exposure and health effects of benzene, toluene, and naphthalene among Chinese chefs*	Indoor kitchen toluene concentrations exceeded standards; higher levels were found in frying kitchens.	Continuous exposure during frying and grilling increased health risk; urinary S-BMA was higher in frying cooks.
9	Tualeka AR et al. (2022)	*Relationship between toluene concentration, risk quotient, and neurotoxicity*	Forty-eight workers experienced neurotoxic effects; exposed workers had a 1.38-fold higher risk.	Majority of workers (65%) had unsafe RQ values; toluene RQ was a key determinant of neurotoxicity.
10	Pan L et al. (2023)	*Effects of low-level indoor toluene exposure on neural network alterations*	Frontal theta DTF at 70 ppb was significantly higher than at 0, 17.5, and 55 ppb.	Indoor toluene exposure adversely affected cognition and neural network function.
11	Balkhyour MA et al. (2023)	*Environmental and biological monitoring of toluene exposure in paint industry*	Airborne toluene ranged from 0.2–414 ppm; urinary hippuric acid ranged from 217.2–4045.5 mg/g creatinine.	Hippuric acid was confirmed as a biological indicator of occupational toluene exposure.
12	Wang TS et al. (2021)	*Occupational health risk assessment of BTX in Shanghai*	Health risk from benzene and toluene was significantly high ($P < 0.001$).	Workers in gluing and painting tasks had the highest exposure risk; sources were adhesives and paints.
13	Zhan C et al. (2023)	*Alterations in brain functional connectivity due to low-level indoor toluene*	At 70 ppb exposure, DTF theta values were significantly higher than lower concentrations.	Indoor toluene altered brain functional connectivity without affecting behavior.
14	Zhang ZF et al. (2020)	*Indoor occurrence and health risks of VOCs in Harbin*	Highest toluene concentration was found in study rooms (0.10 mg m^{-3}).	Indoor carcinogenic risk was higher than outdoor risk due to prolonged indoor exposure.
15	Zhang Z et al. (2021)	*BTEX concentrations in newly decorated rooms*	Mean indoor toluene concentration exceeded standards (0.20 mg/m^3).	Newly decorated or painted rooms posed inhalation health risks.

Toluene is a hydrocarbon chemical also known as methylbenzene. Toluene is easily and commonly found in adhesives and paints [12]. Activities that may cause health problems due to toluene exposure include individuals who work or live in environments with high levels of toluene exposure, such as those employed in the footwear industry, wall paint industry, and even individuals living in houses that have recently undergone renovation and redecorating [13]. Long-term and continuous exposure to toluene can lead to various health problems. Health effects associated with toluene exposure include dizziness, vertigo, and eye irritation [14]. In addition, toluene exposure also affects brain functional connectivity [15]. Prolonged exposure to toluene at levels exceeding the threshold limit value may result in health disorders such as decreased kidney function [8]. Other studies have reported that hazardous indoor pollutants, including toluene, have detrimental effects on cognition and neural network function [16].

It is known that health complaints experienced by workers exposed to toluene include coughing (74%), headaches (63%), and shortness of breath (26%) [17]. Health impacts resulting from toluene exposure in the workplace are categorized as Occupational Diseases.

Based on data from the International Labour Organization in 2018, more than 1.8 million work-related deaths occur annually in the Asia and Pacific region [18].

Serious health problems caused by toluene primarily affect the nervous system (brain and nerves). Nervous system effects may be temporary, such as headaches, dizziness, and loss of consciousness. However, effects such as incoordination, cognitive impairment, and loss of vision and hearing may become permanent following repeated or continuous exposure to high concentrations of toluene, particularly due to intentional solvent abuse. During pregnancy, high-level toluene exposure may cause developmental disorders, including intellectual disability and growth retardation in children. Other effects of toluene exposure on the human body include reproductive disorders, liver and kidney impairment, and reduced immune function [19].

Several factors may contribute to health problems due to toluene exposure, including length of employment and toluene concentrations exceeding the permissible exposure limit. It is known that prolonged duration of work in a particular industry may lead to health complaints among workers [20]. Recent findings indicate that toluene exposure concentrations in printing industries in Surabaya exceeded normal levels, reaching 0.2 ppm, and were classified as abnormal [21]. Workers involved in gluing and coloring tasks have a significantly higher health risk compared to workers in other job categories ($P < 0.01$) [12].

Toluene enters the human body primarily through inhalation and is subsequently metabolized [13]. The health impacts of toluene exposure in the human body can be detected through biomarkers. A key biomarker of toluene exposure is the concentration of hippuric acid in human urine. The primary metabolic pathway of toluene in the human body involves side-chain oxidation through the sequential action of cytochrome P-450, alcohol dehydrogenase, and aldehyde dehydrogenase, resulting in benzoic acid, which subsequently conjugates with glycine to form hippuric acid, the main urinary metabolite of toluene [22].

It has been reported that urinary hippuric acid levels among workers exposed to toluene and xylene were 0.15 ± 0.04, 0.11 ± 0.01, and 0.19 ± 0.07 g g^{-1} creatinine. A significant association was found between toluene and xylene exposure and urinary hippuric acid levels [23]. Consistent with other studies, workers with employment duration of more than two years had Odds Ratios (ORs) of 6.43, 6.75, and 9.00 and showed higher urinary hippuric acid concentrations compared to unexposed workers [24]. Based on urinary analysis of kitchen workers, S-benzylmercapturic acid (S-BMA) levels were higher among cooks working in frying kitchens compared to those working in steaming kitchens. Cooks who were continuously exposed through frying and grilling activities exhibited a higher potential health risk [25].

CONCLUSIONS AND RECOMMENDATIONS

The conclusions drawn from the review of several articles indicate that continuous exposure to toluene, whether at low or high levels, can cause adverse health effects, such as dizziness, vertigo, and eye irritation. Toluene exposure may also affect brain functional connectivity. The health effects resulting from toluene exposure in the human body can be identified or detected through biomarkers. Hippuric acid has been proven to be a biomarker of toluene exposure.

Given the numerous health impacts associated with airborne toluene exposure, the general public—particularly workers who experience continuous exposure to toluene—are advised to use appropriate personal protective equipment (PPE) during work activities and to reduce the duration of time spent in environments with high levels of toluene exposure.

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