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Review Article

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Effects of short and long-term exposure to benzene, toluene, ethylbenzene, and xylenes (BTEX) in indoor environment air on human health: A systematic review and meta-analysis

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ABSTRACT

Today, because of the increasing level of people's need to improve well-being in social and individual life, air pollutants have been released that have Pollution harms both human health and the environment. This research examined Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX) levels in indoor air across different global locations from 1963 to 2023. The investigation employed both; a systematic review and meta-analysis method. The health risks associated with long and short-terms exposure to benzene, toluene, ethylbenzene, and xylene were assessed. That average concentration benzene was 23.07 µg⁄m^3, toluene was 131.60, ethylbenzene was 28.91, and xylene was 63.87. Also, the health risk assessment based on a 95% confidence level showed that the pollutants in question play a role in causing diseases such as lung neoplasm, stomach neoplasm, colon neoplasm, liver neoplasm, headache, dizziness, nausea, insomnia, etc. Consequently, it is crucial to implement stringent measures aimed at lowering the levels of these contaminants in indoor spaces.

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Review

Today, to enhance the quality of life for people in terms of social, economic, and welfare aspects, there has been an increase in the release of various and undesirable pollutants for human health and the environment are interconnected. The most common and dangerous compounds caused by human activities is Volatile Organic Compounds (VOC), which include benzene, toluene, ethylbenzene, and xylene pollutants and are caused by industrial activities such as petrochemical processes, storage, paint distribution, solvent use, and combustion [1]. One of the ways of transmitting Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX) s in the air is the release of droplets resulting from exhalation, which remain suspended in the air for some time and increase the possibility of contaminating people in the environment [2, 3]. Analysis of related research suggests that both brief and prolonged contact with volatile substances can substantially impact human Health [1, 3-5]. including the risk of carcinogenesis (lung, liver, kidney), bladder, urothelium, leukemia, multiple myeloma, and nasopharynx Neoplasm, as well as respiratory irritation, sensitivity, or allergic reactions, skin rashes, dermatitis, eye, nose, and throat irritation, nausea, dizziness, headache, fatigue, asthma, weakness, loss of appetite, stress, lymph node damage, central nervous system disorder, anemia, According to research performed by Liu and collaborators. A 2022 study sought to examine the extent to which workers were exposed to BTEX compounds released in both indoor and outdoor environments of an electronic waste recycling facility. The research also aimed to assess the potential health impacts on individuals. The results showed that 95.2% of all workers exposed to BTEX have a higher probability of developing various types of cancer than others, and the cumulative risk of carcinogenesis through subsequent inhalation of benzene has a direct relationship with the concentration [6]. According to the reports of various organizations in the world, Annually, approximately 5 million individuals lose Many people experience health problems due to poor indoor air quality. The World Health Organization (WHO) has also Declared that the mortality rate due to internal pollutants is 2 million for developed countries and 4 million for developing countries [1]. Based on the International Agency for Research on Cancer (IARC), benzene has been classified as a Group 1 human Cancer-causing agent. Ethylbenzene has been placed in Group 2, while toluene and xylenes have been classified in Group 3 [3]. In addition to types of cancer, Partha et al.'s 2022 study on birth data from 175 countries shows that mothers who were exposed to BTEXs experienced premature birth with a ratio of one or higher, which puts both maternal and child health at risk [2]. So far, the system has suffered losses in the millions of dollars as a result of decreased employee productivity, material damage, and an increase in current costs. Beyond the wide range of indoor pollutants, the Cancer-causing agent of the presence of these contaminants is influenced by the air quality in the external environment surrounding the residence, the economic and social progress of the nation, the type of activity working conditions, environmental factors, and the season of year. In addition, the velocity of release and its concentration in the environment determine the degree of harm to human health. Furthermore, pollutant emissions from endogenous sources, including both permanent (construction materials, adhesives, paints, lacquers, etc.) and non-permanent (furniture, cleaning and disinfection products, kitchens, personal care items), With people spending more than 80% of their time indoors, the issues related to indoor air pollution have become more apparent. Among all the age groups, children will be exposed to more damage than adults due to the higher number of breaths per unit of time and the weaker respiratory system [3, 7]. Since the present studies, the evaluation of the risks caused by BTEX pollutants and their adverse

effects on humans health is less studied in the form of meta-analysis studies. Therefore, The goal of this structured review and meta-analysis is denotes evaluate the impacts of BTEX exposure on human health, both in the short and long term.

Search strategy

This meta-analysis followed the PRISMA guidelines for systematic reviews and meta-analyses. PubMed, Scopus, and Web of Science databases were searched Up to 2023-10-28, using a combination of keywords related to the type of exposure and health outcomes. The search was based on a combination of MESH terms, as follows: ((Benzene) OR (Toluene) OR ("ethylbenzene dehydrogenase") OR (Xylenes)) OR (BTEX)) AND ((neoplasms) OR (cancer) OR (malignancy) OR (tumor) OR (Cardiovascular Diseases) OR (Heart Diseases) OR (Vascular Diseases) OR (asthma) OR (Sleepiness) OR (vertigo) OR (Vertigos) OR (Headache) OR (Headaches) OR (fatigue) OR (Central Nervous System Diseases) OR (Mutation) OR (Mutations) OR ("reduced fetal growth") OR ("Premature Birth") OR (sterility) OR (Infertility) OR ("Reproductive Sterility") OR (Anemia) OR ("Kidney Diseases") OR ("Liver Diseases") OR ("Liver Dysfunctions") OR ("Eye Diseases") OR ("Eye Disorders") OR ("Throat disease") OR (Conjunctivitis) OR ("Oral dysplasia") OR ("Liver Dysfunctions") OR ("Skin Diseases") OR (Dermatoses) OR (Dermatosis) OR (Nausea) OR (Coma) OR (Death) OR ("Bone marrow injury") OR ("Decreased memory") OR (Frailty) OR ("birth defect")) And (("Air Pollution, Indoor") OR ("Pollution, Indoor Air") OR ("Indoor Air Pollution") OR ("Air Quality, Indoor") OR (" Indoor Air Quality")).

Study selection

The studies were added to a document management system (Endnote, version X8, Thomson Scientific, Stamford, Connecticut, USA), and duplicates were removed. Two investigators (MF and SA) Independently reviewed the titles and abstracts of all remaining articles that met the eligibility criteria and excluded those that were not eligible. When the researchers disagreed, a third reviewer (Y M) was consulted to resolve the issue. The review included all studies, without restrictions based on publication date, language, participant age, gender, living area, or race.

Eligibility criteria

Inclusion criteria of studies: 1) Population: Studies were selected based on the general population of society regardless of race, age, and gender. 2) Contaminant exposure: short and long-terms exposure to the indoor BTEX pollutants. 3) Outcome: short and long-terms effects of exposure to BTEX. 4) Type of included studies: The review encompassed various types of observational research, including cohort studies, case-control studies, ecological studies, and cross-sectional studies.

Data extraction

Both researchers independently gathered the data. The extracted information for eligible studies was collected in a Microsoft Excel spreadsheet and included The Obtained information included the lead author's name, the year the study was published, the country where the research was conducted, the study design, and the specific pollutant investigated, type of outcome, effect size ((risk ratio (RR), odds ratio (OR), hazard ratio (HR)), 95% confidence interval, and sample size.

Quality evaluation

To minimize bias, the Newcastle-Ottawa Scale (NOS) was employed to assess Grade of the chosen research [8]. The NOS provides an checklist the important items for judging bias in studies. Studies were assigned a quality score from 0 to 9. Assessments with complete score of

7 or higher were considered high-quality, while those with a lower score were classified as low-quality.

Statistical analysis

All results were estimated at a 95% confidence level. The chi-square and I2 test Was utilized to check the heterogeneity. Data evaluation was carried out using Complete Meta-Analysis Program version 3. To combine the risk ratios of the included Research, random effects models were employed to assess the presence heterogeneity. The funnel plot was used for publication bias analysis.

Results

As illustrated in the Fig. 1, a total of 2,827 articles were identified in the initial search of databases until 2023-10-28 with 733, 283, and 1,811 related articles from PubMed, Web of Science, and Scopus, respectively. After eliminating duplicates, 2,202 articles were reviewed, and 58 articles met the inclusion criteria. No relevant studies were found by reviewing the reference lists of eligible articles. Finally, 57 studies were part of the meta-analysis.

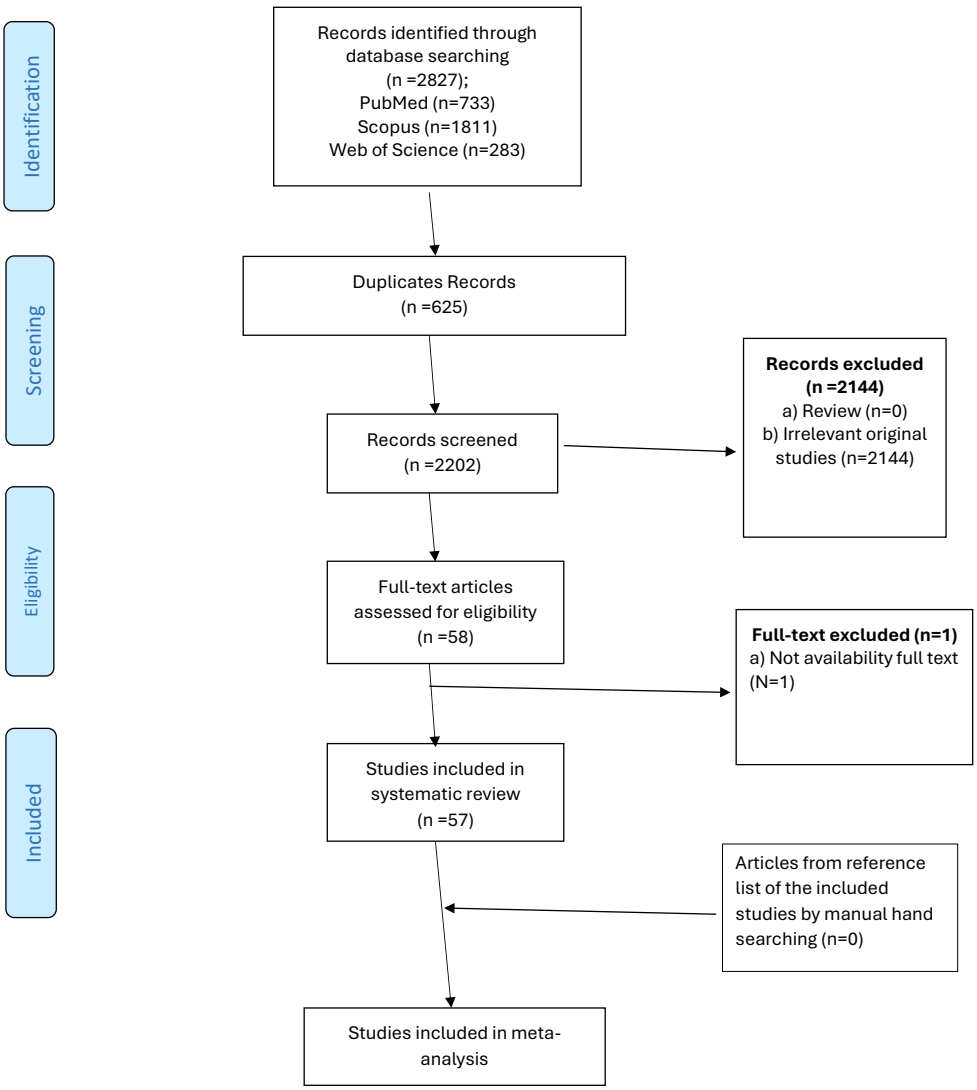

Fig. 1.The PRISMA flowchart of the literature search and identification

Study characteristics

As illustrated in the Table 1 The overall sample size was 106,064. The largest number of articles were conducted in American countries (18.8 %). The publication year of included articles ranged from 1996 to 2023. The design of the articles was in the form of observational studies, mostly Cross-Sectional studies (54.6%). Most of the studies investigated association with air pollutant exposure and non-cancerous health outcomes.

Meta-analysis

As illustrated in the Fig. 2, we conducted on three studies. In the study of Lamplugh (2018) which Examined the link between benzene exposure and leukemia risk, with a relative risk of 1.75 and a 95% confidence interval of 1.39 to 2.32.", The results show that study of Yin 1996 the exposure to benzene and leukemia cancer with a relative risk of 2.6 and a 95% confidence interval (0.7, 16.9) and study of Bloemen 2004 the exposure to benzene and leukemia cancer with a relative risk of 1.2 and a 95% confidence interval (0.2, 4).The meta-analysis the results indicated a statistically significant relationship between the exposure to benzene and leukemia cancer with a relative risk of 1.72 and a 95% confidence interval (1.27, 2.17) I^2=0.0 % (p=0.84).

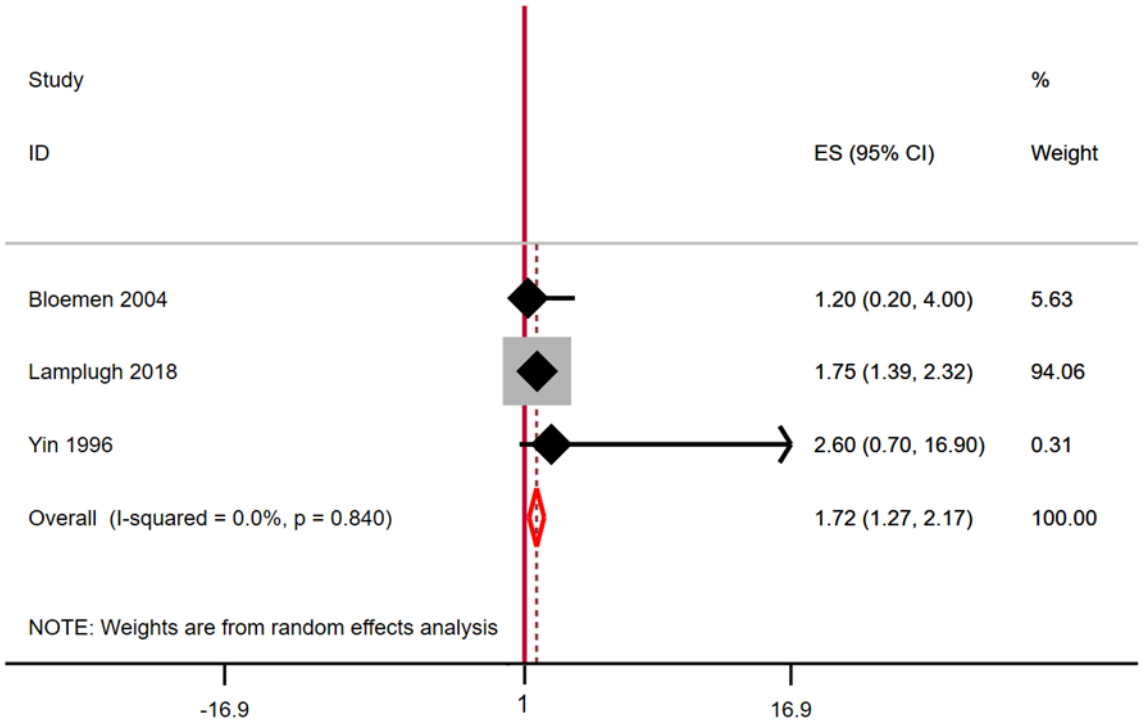

Fig. 2. The meta-analysis in terms of exposure to benzene and leukemia cancer

Table 1. The characteristics of the studies included in the systematic review [9-30]

Row	1st author	Country	Exposure	Study design	Effect	Adjusted	Outcome	Sample size	Quality
1	ARI AKIF 2020	IstanbulOLANKARA	benzene toluene	Cross-sectional	Odds Ratio	Adjusted	lung cance Noncancer	60	*********
2	Bloch j 2022	European	benzene	Ecological study	Odds Ratio	Adjusted	Upper airway disorders	115	*******
3	Blanc lapierre 2018	canada	benzene toluene xylene	case–control study	Odds Ratio	Adjusted	prostate cancer	3908	*********
4	Bloemen li 2004	united states	benzene	cohort	Rate Ratio	Adjusted	Lymphatic leukemia death	2266	********
5	Cipolla m 2016	korea	xlyene	case–control study	Odds Ratio	Adjusted	Sore throat cough a cold	74	********
6	Ge´rin michel 1998	canada	Benzene Toluen Xlyene	case–control study	Odds Ratio	Adjusted	Esophagus cancer Colon cancer Stomach Rectum cancer Pancreas cancer lung cancer prostate cancer Bladder cancer Kidney cancer Melanoma Lymph nodes cancer	533	*******
7	Hulin m 2010	China	benzene ethly toluene xlyene	case–control study	Odds Ratio	Adjusted	asthma	63	*******
8	Jung Dayoung 2022	Korea	case–control study	Benzene toluene Ethly benzene xlyene	Odds Ratio	Adjusted	Ophthalmitis Headache Carcinogen non Carcinogen	328	*********

Table 1.Continued

Row	1st author	Country	Exposure	Study design	Effect	Adjusted	Outcome	Sample size	Quality
9	Kotzias DI 2009	European- Italy	Ecological study	benzene	Odds Ratio	Adjusted	lung cancer leukemia Chronic obstructive pulmonary disease inflammation Pneumonia and acute lower respiratory infections (ALRI)	112	*******
10	Kponee, K. Z. 2018	Nigeria	Cross-sectional	benzene xlyene	Odds Ratio	Adjusted	Eye Irritation Neurologic Symptoms Skin Irritation Throat Irritation Aplastic Anemia Gastrointestinal Symptoms	20	*****
11	Kumar am 2014	Delhi	Cross-sectional	benzene toluene ethly benzene xlyene	Rate Ratio	Adjusted	cancer Non cancer	170	******
12	Lee wei Chia 2006	Tainan	Cross-sectional	benzene toluene ethly benzene xlyene	Hazard Ratio	Adjusted	cancer asthme non cancer risks	12	*******
13	Lerner Jorge Esteban Colman 2018	Argentina	Cross-sectional	benzene	Odds Ratio	Adjusted	cancer	34	********
14	Moslem ali reza 2020	China	Iran	benzene toluene ethly benzene xlyene	Odds Ratio	Adjusted	cancer Non cancer	16	******
15	nayek Sukanta 2019	india	Cross-sectional	benzene toluene xlyene	Odds Ratio	Adjusted	carcinogenic non carcinogenic	84	*******

Table 1.Continued

Row	1st author	Country	Exposure	Study design	Effect	Adjusted	Outcome	Sample size	Quality
16	Norbäck Dan 2017	Malaysia Johor Bahru,	Cross-sectional	ethly benzene	Rate Ratio	Adjusted	Sore throat fatigue headache dermal symptoms	32	*******
17	Petralia SA 1999	Surabaya, Indonesia	Cross-sectional	toluene	Odds Ratio	Adjusted	Children's respiratory allergy	80	*******
18	Siwarom Sirinapa 2017	Bangkok	Cross-sectional	benzene	Odds Ratio	Adjusted	Cough sneezing breath	436	******
19	Sakellaris Ioannis 2021	Portugal, Spain, Italy, Greece, France, Hungary, Holland and Finland	Ecological study	benzene toluene xlyene ethly benzene	Odds Ratio	Adjusted	Eye irritation Dysfunction of breathing (respiratory phlegm and wheezing) Sick building syndrome(SBS) general Heart dysfunction	148	******
20	Tunsaringkarn Tanasorn 2014	Bangkok city in Thailand	Cross-sectional	benzene toluene ethylbenzene	Odds Ratio	Adjusted	cancer Dizziness Headache	434	*****
21	Song-Nian Yin 1996	China	cohort	benzene	Odds Ratio	Adjusted	mortality malignant lymphoma leukemia lung cancer Lymphocyte malignancy chronic leukemia chronic malignant lymphoma Urinary tract Pregnancy Nasopharynx Brain tumor‘ Colon, rectal cancer Stomach dysfunction Esophagealdysfunction Liver and gallbladder cancer	75	******

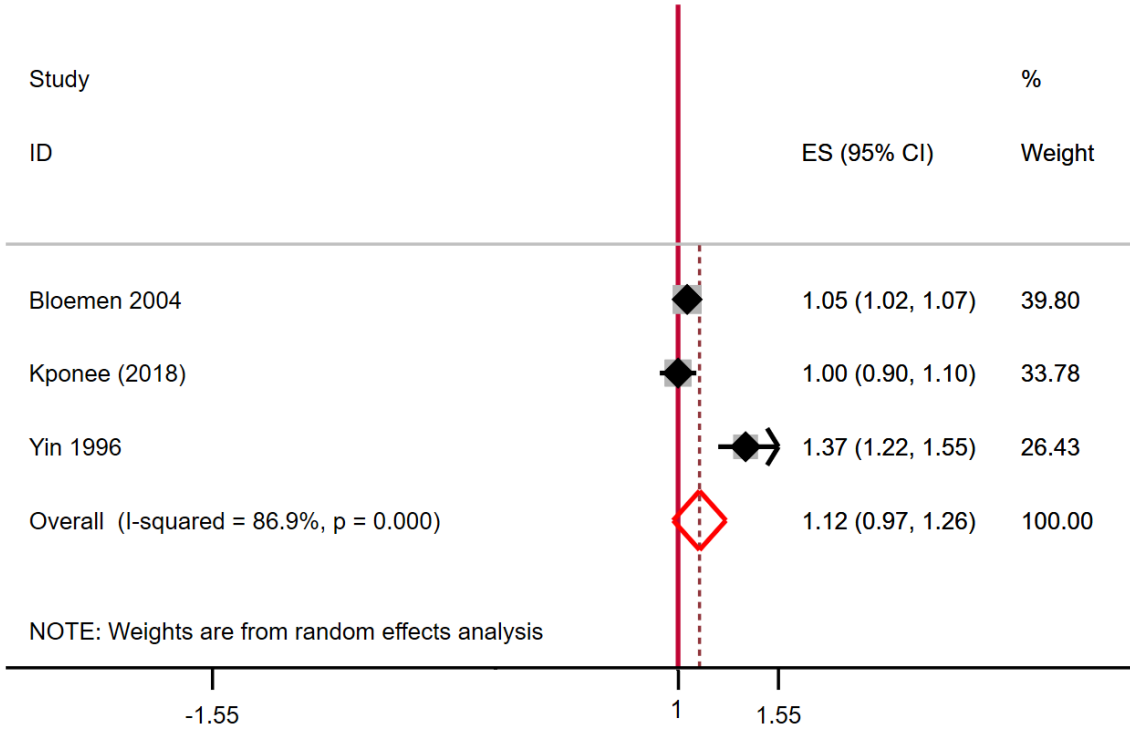

Fig. 3. The meta-analysis in terms of exposure to xylene and sore throat

As illustrated in the Fig. 3, we conducted on three studies. In the study of Kponee (2018) which investigated the exposure to xylene and Sore throat with a odds ratio of 1 and a 95% confidence interval (0.9, 1.1), study of Yin 1996 the exposure to xylene and Sore throat with a odds ratio of 1.37 and a 95% confidence interval (1.22, 1.55) and study of Bloemen 2004 the exposure to Xylene and Sore throat with a odds ratio of 1.05 and a 95% confidence interval (1.02, 1.07). The meta-analysis results showed that a non-significant relationship between the exposure to Xylene and Sore throat with an OR of 1.12 and a 95% confidence interval (0.97, 1.26) I^2=87 % (p=0.0).

As illustrated in the Fig. 4 we conducted on three studies. In the study of Moslem 2020 which investigated the exposure to benzene and cancer risk with a OR of 7.11 and a 95% confidence interval (6.81, 7.41), study of Lerner 2018 the exposure to benzene and cancer risk with a OR of 1 and a 95% confidence interval (0.5, 1.5) and study of Tunsaringkarn 2014 the exposure to benzene and cancer risk with a OR of 1.12 and a 95% confidence interval (1.03, 1.79). The meta-analysis results showed high heterogeneity between Inquiries into the impact of benzene exposure on cancer risk were part of the meta-analysis. Due to the significant heterogeneity, a pooled effect size was not calculated with a OR of 3.08 and a 95% confidence interval (-1.28, 7.44) I^2=99.7 % (p=0.0).

As illustrated in the Fig. 5, we conducted on three studies. In the study of Ari 2020 which investigated the exposure to toluene and noncancer risk with a OR of 1.4 and a 95% confidence interval (1.1, 3.4), study of Moslem 2020 the exposure to toluene and noncancer risk with a OR of 5.02 and a 95% confidence interval (4.89, 5.15) and study of Tunsaringkarn 2014 the exposure to toluene and noncancer risk with a odds ratio of 1.27 and a 95% confidence interval (0.99, 1.68). The meta-analysis showed high heterogeneity for the link between toluene exposure and noncancer risk with a OR of 2.58 and a 95% confidence interval (-0.41, 5.58) I^2=99.5 % (p=0.0).

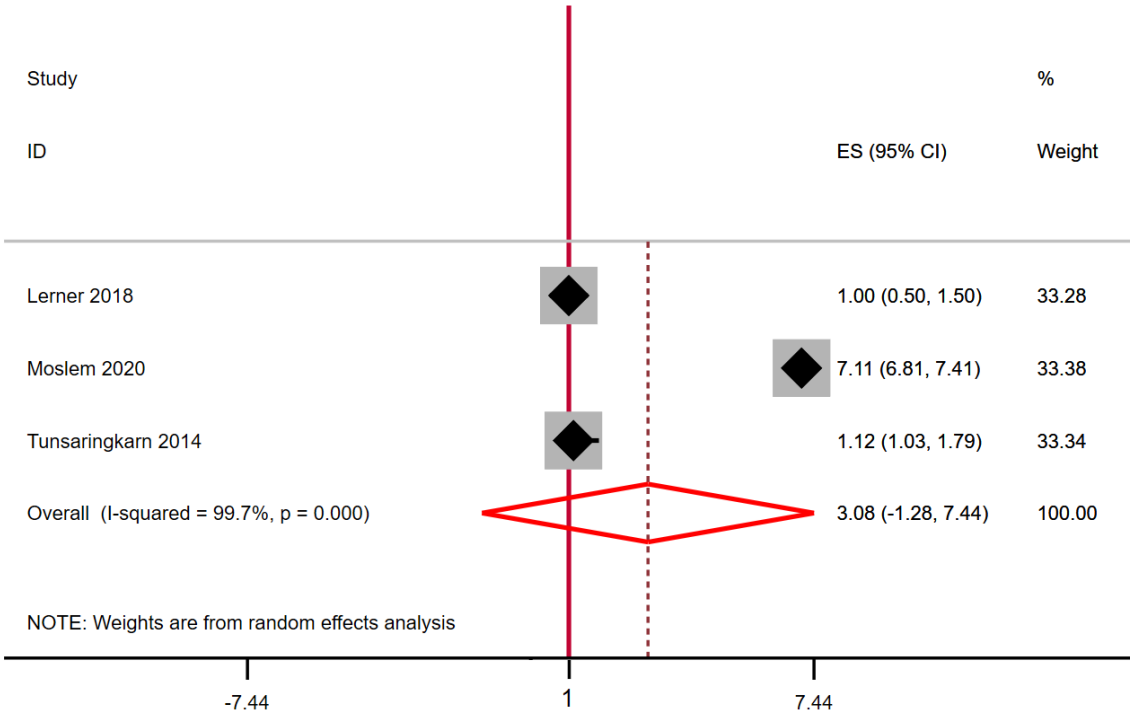

Fig. 4. The meta-analysis in terms of exposure to benzene and cancer risk

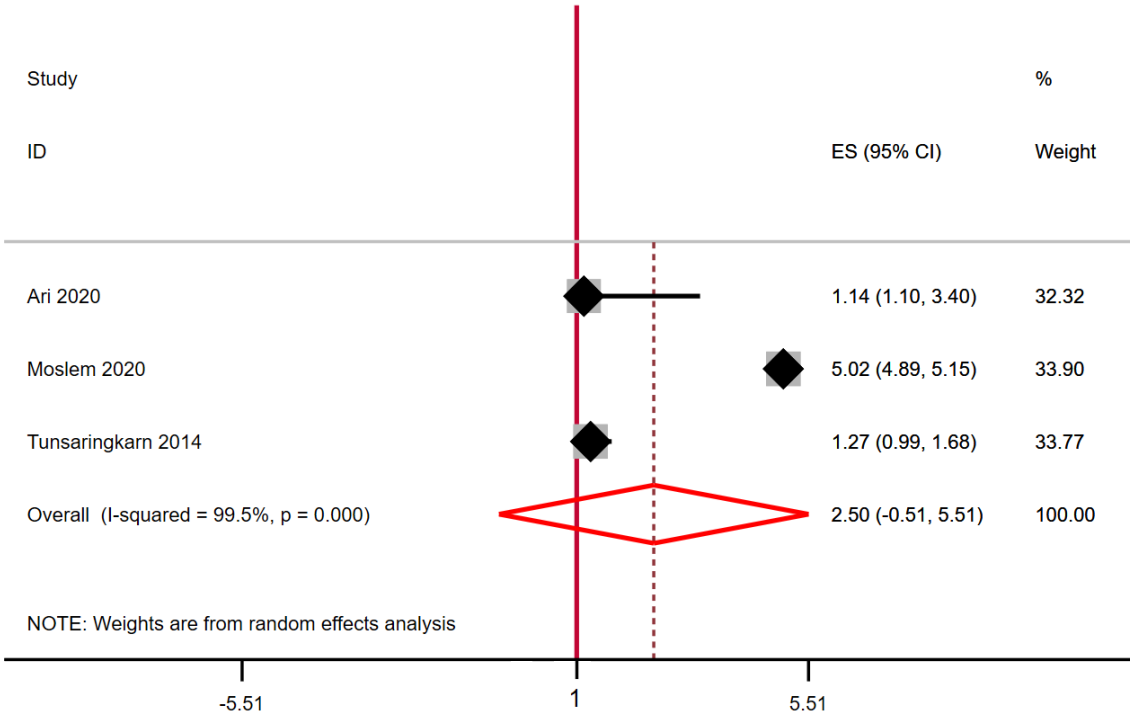

Fig. 5. The meta-analysis in terms of exposure to toluene and non-cancer risk

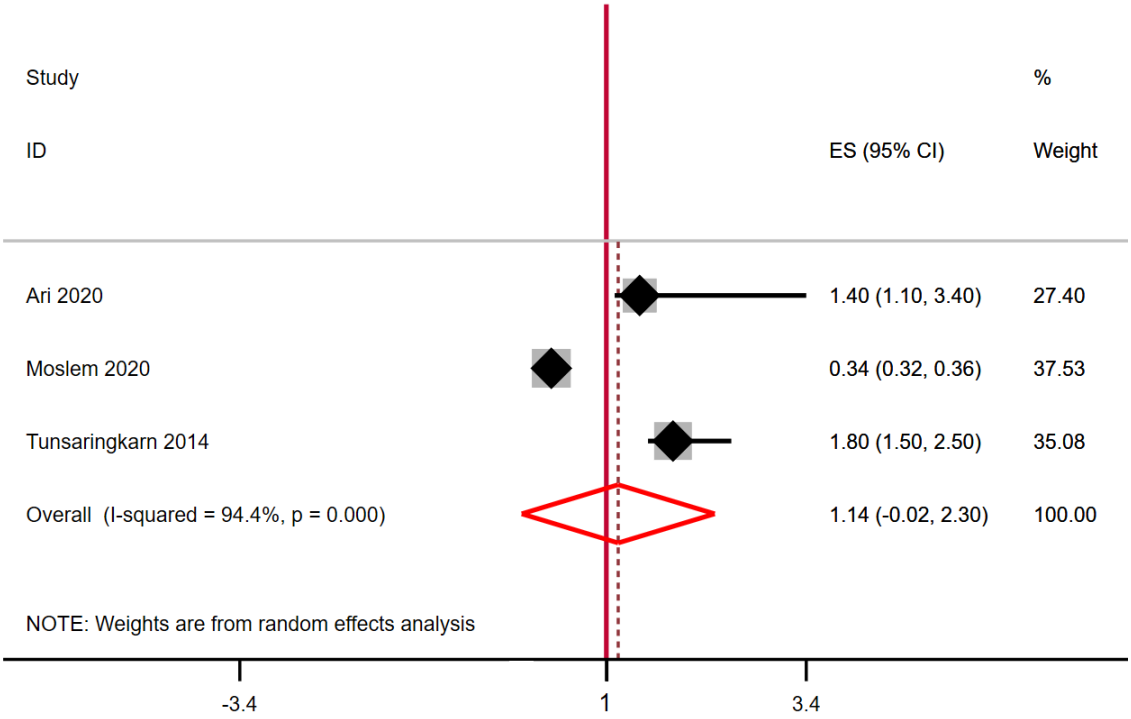

Fig. 6. The meta-analysis in terms of exposure to xylene and non cancer risk

As illustrated in the Fig. 6, we conducted on three studies. In the study of Tunsaringkarn 2014 which investigated the exposure to xylene and noncancer risk with a OR of 1.8 and a 95% confidence interval (1.5, 2.5), study of Ari 2020 the exposure to xylene and noncancer risk with a odds ratio of 1.4 and a 95% confidence interval (1.1, 3.4) and study of Moslem 2020 the exposure to xylene and noncancer risk with a OR of 0.34 and a 95% confidence interval (0.32, 0.36). The result of the meta-analysis showed there is a non-significant relationship between the exposure to xylene and noncancer risk The meta-analysis showed high heterogeneity for the link between xylene exposure and noncancer risk with a OR of 1.14 and a 95% confidence interval (-0.02, 2.30) I^2=94.4 % (p=0.0).

Discussion

This research consists of comprehensive systematic review and meta-analysis, designed to examine the negative health impacts resulting from both brief and prolonged exposure to BTEX pollutants found in indoor air environments. The results showed that across studies conducted from 1963 to 2023, average concentrations of the BTEX pollutants in indoor air environments were reported as follows: benzene 23.07 µg/m^3, toluene 131.60 µg/m^3, ethylbenzene 28.91 µg/m^3, and xylene 63.87 µg/m^3. The places investigated for these pollutants were divided into two groups: industrial environments (including printing factories, plastic factories, chemical production industries, painting workshops, houses and schools in industrial towns, sculpture industries, vehicle assembly plants, etc.) and non-industrial environments (including restaurants, beauty salons, hotels, urban and rural houses, schools in residential areas, kindergartens, hospitals, etc.). The sources producing these pollutants include Liquefied Petroleum Gas (LPG), oil, Petrol, coal, tobacco smoke, charcoal, spraying, cosmetics and various paints and solvents such as thinner, cement, wood paint cleaners, glue, furniture, new or refurbished

household appliances, frying and cooking oils, biomass fuels with cow dung, various heating devices such as fireplaces, and smoking. Furthermore, the release of that pollutantion of the mentioned sources has increased the concentration exposure per cubic meter of air Within interior environments, which has heightened the possibility of suffering from various long and short-terms adverse health outcomes. The type of fuel used, employee smoking habits, and lack of proper and sufficient ventilation have also exacerbated these adverse health effects. After assessing the health risk based on the 95% confidence level, the findings revealed a significant association between benzene concentration and leukemia cancer risk, which was in line with similar studies. At the same time, Based on the Integrated Risk Information System)IRIS(standard CASRN 71-43-2, the carcinogenicity of benzene is registered in carcinogenicity category A [31]. Furthermore, these outcomes align with the conclusions drawn by Yusoff and colleagues.'s study that investigated the effect of leukemia from occupational benzene exposure in fetuses in pregnant mothers' wombs [32]. Also, the concentration of toluene was lower than the IRIS 108-88-3 standard, which has no significant relationship with non-carcinogenic effects caused by exposure [33]. Considering that the concentration of xylene was lower than the concentration reported in the IRIS 1330-20-7 standard, according to the present study, the short-term effects are not consistent with the xylene concentration [34]. Also, these outcomes of Kamani et al.'s study on BTEX concentrations in indoor air in Zahedan showed that the increased pollutant concentrations compared to the standards confirmed the pathogenicity of toluene alone but not xylene alone. This is because xylene, unlike toluene, cannot cause disease on its own and should be considered together with other contaminants. Our study's outcomes corroborate these findings [35]. Also, these results of Janjani et al.'s Analysis of the concentration BTEX in the air inside hairdressing salons showed Beauty salons exhibit the highest levels of toluene, with peak concentrations reaching 219.4 (μg/m^3) units. The mean concentration of benzene exposure was more than for female employees (1.04 x 10^-5) μg/m^3 than for men (4.05 x 10^-6) μg/m^3. Additionally, the concentration of ethylbenzene exposure for employees was 2.08 x 10^-6 μg/m^3 for men and 3.8 x 10^-6 μg/m^3 for women, which has been associated with possible carcinogenic risks. The above findings for benzene contaminant are consistent with our study findings, while they are not In accordance with these results of the ethylbenzene contaminant [36]. In a study conducted by Norouzian Baghani et al., A study was conducted to examine the indoor air quality of 50 beauty salons. Ten-liter air samples were collected from each salon and analyzed for BTEX levels using GC-FID. The results of this resarch showed that the average concentration of benzene (32.40 ± 26.38) μg/m^3 was more than the levels Advised with Health Canada, ANSES, and HKSAR. Among BTEX compounds, ethylbenzene (62.38±32.37) μg/m^3 had the highest concentration in the halls. Next, the cancer risk values across various birth age groups were of <6, 6 to <21, and 21 to <81 were calculated for benzene (1.83 × 10^-3, 2.76 × 10^-4, and 1.50 × 10^-4, respectively) μg/m^3 and ethylbenzene (4.9 × 10^-4, 7.30 × 10^-5, and 3.52 × 10^-5, respectively) μg/m^3, which were significantly above the recommended levels for long-term exposure. The results demonstrated a significant relationship between benzene concentration and the structural and operational characteristics, such as The study revealed that benzene concentration was significantly affected by factors such as the ventilation system, the size of the halls, the number of people inside, the number of services provided, and whether bridal makeup was being performed. The results of the reseach for the quantity of the benzene pollutant are consistent with the current study, but these results contradict the findings for the ethylbenzene pollutant [37]. Research carried out by Alsbou and colleagues. On the subject of BTEX pollutants from heaters in indoor air during winter, the results showed that the oil heater was the most polluted based on the measurement of BTEX, with the amount of 290 μg/m^3, respectively from the more than to the lowest level of pollutant production. The heater

with diesel fuel had the amount of 120 µg/m^3, the wood fuel heater Maintained a concentration of 31 µg/m^3, and the electric heater had a concentration of 16 µg/m^3. Toluene was the most prevalent compound in all air samples. Additionally, a risk assessment was performed to identify where the cancer risks associated with benzene and ethylbenzene exceeded acceptable levels. Since the compounds are non-carcinogenic, the Hazard Quotient (HQ) was less than one, so they are unlikely to cause health problems, This result is in agreement with the current study's findings [38].

In an analysis conducted by L. Hinwood et al. on the impact of woodworking arts and crafts in indoor environments, concentrations of ethylbenzene and xylene pollutants increased. The presence of heaters and smokers in this environment was also found to have a direct relationship with the elevated concentrations of these pollutants [39] . Also, considering that among all the available articles, at least three were homogenously related to the research did not include ethylbenzene, an indoor air contaminant, in its systematic meta-analysis, despite this pollutant's known negative impacts on health. In this study, all the above-mentioned cases were addressed in studies conducted over 70 years. However, due to the heterogeneous treatment of each environmental development depending on a disease and the lack of a sufficient number of articles in this field, we invite researchers and thinkers interested in this field to conduct further studies.

Conclusion

The obtained of study revealed that the more pollutants, in indoor air were toluene, while ethylbenzene had the lowest pollutant concentration compared to toluene, xylene, and benzene. Considering the adverse effects of long and short-terms exposure to each of these pollutants differs, it is necessary after prolonged contact in an indoor environment to evaluate the health of occupationally exposed people after improving ventilation. Assessing people's health on a periodic basis, implementing rules prohibiting smoking in the indoor environment, and reducing the contact of pathogenic agents with people as much as possible.

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Competing interests

The authors have no conflicts of interest to disclose.

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Ethics considerations

"Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely ob-served by the authors."

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