ASSOCIATION BETWEEN BENZENE EXPOSURE AND CHILDHOOD LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS UPDATED TO JULY 2016

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Abstract

Benzene is one of the aromatic hydrocarbons which are classified in class 1 of carcinogenesis. Unlike adults, the risk of leukemia cancer in children caused by being exposed to benzene has not been proven. Hence in this study we tried to review systematically and meta-analyze the studies until July 2016 and update the results. For finding studies conducted in Iran and the world, the databases Pubmed, Scopus, Irandoc SID and ISI were used. In this study, 13 articles in all of which a similar methodology was used and they were done in period 1988 to 1997, were investigated. Because the heterogeneity of the studies was higher than 50%, the Random model was used ($I^2= 53.5\%$, $P$ value $< 0.05$). The mean of risk amount of studies was $RR = 1.76$ (1.28, 2.31), $P$ value $< 0.001$. The results of systematic review and meta-analysis of 13 studies showed that being exposed to benzene increases significantly the leukemia cancer risk by 72% ($P$ value $< 0.001$).

Keywords: Benzene, exposure, childhood, leukemia and systematic review.

1. Introduction

Benzene is one of the aromatic hydrocarbon combinations that are found in crude oil, fuel oil and other petroleum products. Also this combination at a high level is produced in the plastic resin factories etc. throughout the world [1]. Millions of people in the world are exposed to benzene through environment or occupation [2,3]. Based on initial
researches that showed a positive relationship between acute myeloid leukemia and being exposed to high concentration of benzene, the international cancer research agency (ICRA) has put the benzene in a primary carcinogenic class [4]. Environmental exposure with benzene is more than occupational one and in the range 1 to 10 PPB, which is mostly caused by emissions from vehicles and cigarettes [5]. Children may be exposed to benzene through air pollution, proximity to sources of benzene emissions (gas stations, car repair shops) or at home (the material that contains benzene) [6]. One of the main reasons of death of children is children cancer [7]. 30 percent of children's deaths are related to acute leukemia [8]. The relationship between being exposed to high concentrations of benzene in the workplace and leukemia in adults has been proved [4,9]; but there are no enough evidences of the relationship between benzene in workplace and leukemia cancer in children. The risk factors of leukemia cancer in children include the genetic disorders such as Down syndrome and Li-Fraumeni syndrome, radio therapy, chemotherapy and tobacco [8,10,11].

Children may mostly be exposed to low concentrations of benzene through anthropogenic resources [12,13] and road traffic [14]. Different combinations are caused in the air pollution by traffic source. Using the models that included wind speed, weather, traffic density, road width and the height of buildings, some studies have examined the relationship between childhood leukemia and traffic-related air pollution [14-17]. Some of these studies showed there is a positive relationship between being exposed to benzene and children's leukemia risk [2,18-21]. Although in many studies the relationship between being exposed to benzene and risk of childhood leukemia cancer has been examined, but the results are still confusing.

The cause of this difference in results may be caused by a difference in the study design, type of leukemia, the method of evaluating the being exposed to benzene. On the other hand, one other reason of the difference in the results is the low level of benzene exposure in children compared to adults in occupational situations that makes the intervention of other factors in the study [22]. Hence in this study we tried to update the relationship between benzene exposure and the risk of childhood leukemia cancer up to July 2016 by doing a systematical review and meta-analysis.

2. Materials and Methods

This study was a systematic review and meta-analysis of association between benzene exposure and childhood leukemia risk. To find the conducted studies in Iran and the world, SID, Irandoc, Scopus, Embase, PubMed and ISI were used.
2.1. Criteria of selection and evaluation of studies' quality

A list of titles and abstracts of all studies available in the mentioned databases was prepared by three researchers (Ya. F., Ha. K., Na. A.) to avoid bias. Related titles were evaluated independently, then searching was performed in the studies which had been published since 1986 to 2016. Searching was conducted for 2 weeks from 11/05/2016 to 25/05/2016, then related studies were entered into the study process using the blind method of initial evaluation independently. The main inclusion criterion of different articles to this study was colorectal cancer and DBPs drinking water.

The studies which were not included in the initial evaluations or were about clinical decision-making and unrelated evaluations to childhood leukemia were excluded from the study. In the second stage, abstracts of different selected studies were evaluated by a researcher using the STROBE check-list which is a standard check-list. This check-list includes 43 various aspects of methodology including sampling methods, measurements of the variables, statistical analysis and evaluates objectives of the study [23]. In this check-list, the minimum and maximum scores were considered as 40 and 45, respectively.

Finally, top papers which had earned the minimum score of (40) given to the check-list questions, were entered into the study and their data were extracted for meta-analysis. Funnel plot and Egger's test were used to determine Publication Bias [24].

2.2. Data extraction

In this study, 13 articles which the used methodology was almost the same in all of them and were conducted from 1988 to 2016, were evaluated. The important data required for data analysis including related data to the subject, title, time and location of study, number of cases, exposure assessment, range age childhood were collected.

3.2. Meta-analysis of studies

The meta-analysis was done by comprehensive meta-analysis V. 2.2.064 software. Higgins $I^2$ was used to calculate the heterogeneity of the studies. At meta-analysis stage, Random effect was used for the studies where $I^2$ was greater than 50% and fixed effect was used for the studies in which $I^2$ was smaller than 50%. In this study, the significance level was P-value < 0.05.

3. Results

1.3. Identifying the related studies
As shown in Figure 1, the related studies were identified. By searching in the databases SID, Ovid, Scopus, Embase, Irandoc, PubMed and ISI, in general 253 articles were obtained. Based on the title and abstract and some other reasons 98 articles were set aside in Eligibility stage. Of the remaining 155 articles, 142 articles were set aside for some reasons such as reported correlation, hazard risk, Letter comments, or correspondence. Finally 13 articles remained for meta-analyzing.

2.3. Characteristics of studies

The general characteristics of the studies including the first author, year of publication, place, risk ratio, the number of cases, the time domain, the age range of children and evaluating the exposure (Table1). The domain of publication years of articles was 1988 to 2016. 5 studies in the United States and 8 other studies were conducted in other countries and the children age range was 1 to 15 years.

Table-1. General characteristics of the 13 studies included in the final analysis.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Effect size</th>
<th>No. Case</th>
<th>Location</th>
<th>Study Years</th>
<th>Children’s range Ages, years</th>
<th>Exposure Assessment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feingold et al</td>
<td>1992</td>
<td>1.6</td>
<td>0.5</td>
<td>United States</td>
<td>1976–1983</td>
<td>0–14</td>
<td>Benzene, based on occupations and expert evaluation</td>
<td>[25]</td>
</tr>
<tr>
<td>Buckley et al</td>
<td>1989</td>
<td>2</td>
<td>1.2</td>
<td>United States and Canada</td>
<td>1980–1984</td>
<td>0–18</td>
<td>Solvents, based on lifetime occupational history; 52 agents in 9 categories</td>
<td>[26]</td>
</tr>
<tr>
<td>Infante-Rivard et al</td>
<td>1991</td>
<td>0.62</td>
<td>0.2</td>
<td>Spain</td>
<td>1983–1985</td>
<td>0–15</td>
<td>Solvents, based on occupation, specific</td>
<td>[27]</td>
</tr>
</tbody>
</table>

Figure1. Flow chart for identification of relevant studies
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Year</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Country</th>
<th>Time Frame</th>
<th>Pub Year</th>
<th>Location</th>
<th>Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKinney et al</td>
<td>1991</td>
<td>4</td>
<td>0.3</td>
<td>118</td>
<td>United Kingdom</td>
<td>1974–1988</td>
<td>0–14</td>
<td>Benzene, based on occupations and specific questions about benzene</td>
<td>[28]</td>
</tr>
<tr>
<td>Cocco et al</td>
<td>1996</td>
<td>1.5</td>
<td>0.3</td>
<td>8</td>
<td>Italy</td>
<td>1980–1989</td>
<td>Unknown</td>
<td>Solvents, based on occupations, JEM, and expert evaluation</td>
<td>[29]</td>
</tr>
<tr>
<td>McKinney et al</td>
<td>2008</td>
<td>2</td>
<td>0.7</td>
<td>5.8</td>
<td>United Kingdom</td>
<td>1991–1996</td>
<td>0–14</td>
<td>Solvents, based on occupations and expert evaluation</td>
<td>[30]</td>
</tr>
<tr>
<td>Perez-Saldivar et al</td>
<td>2008</td>
<td>2.81</td>
<td>0.48</td>
<td>16.43</td>
<td>Mexico</td>
<td>1999–2000</td>
<td>0–15</td>
<td>Work as a mechanic, based on occupational history before conception</td>
<td>[31]</td>
</tr>
<tr>
<td>Reid et al</td>
<td>2011</td>
<td>0.93</td>
<td>0.42</td>
<td>2.09</td>
<td>Australia</td>
<td>2003–2006</td>
<td>0–14</td>
<td>Benzene, based on occupations and expert evaluations</td>
<td>[32]</td>
</tr>
<tr>
<td>Shu et al</td>
<td>1988</td>
<td>4</td>
<td>1.8</td>
<td>9.3</td>
<td>China</td>
<td>1974–1986</td>
<td>0–15</td>
<td>Benzene, based on occupations and specific exposures</td>
<td>[33]</td>
</tr>
<tr>
<td>Shu et al</td>
<td>1999</td>
<td>0.7</td>
<td>0.3</td>
<td>1.6</td>
<td>United States</td>
<td>1989–1993</td>
<td>0–15</td>
<td>Benzene, based on occupations and specific exposures</td>
<td>[34]</td>
</tr>
<tr>
<td>Smulevich et al</td>
<td>1999</td>
<td>3.1</td>
<td>1.5</td>
<td>6.3</td>
<td>Russia</td>
<td>1986–1988</td>
<td>0–14</td>
<td>Solvents, based on occupations and job categories</td>
<td>[35]</td>
</tr>
<tr>
<td>Kishi et al</td>
<td>1993</td>
<td>2.73</td>
<td>1.21</td>
<td>6.31</td>
<td>Japan</td>
<td>1980–1990</td>
<td>0–15</td>
<td>Benzene, based on home exposures</td>
<td>[36]</td>
</tr>
<tr>
<td>Slater et al</td>
<td>2011</td>
<td>2.33</td>
<td>1.3</td>
<td>4.18</td>
<td>United States and Canada</td>
<td>1996–2006</td>
<td>0–1</td>
<td>Petroleum products, based on personal interview about household exposures 1 month before and during pregnancy</td>
<td>[20]</td>
</tr>
<tr>
<td>Symanski et al</td>
<td>2016</td>
<td>1.29</td>
<td>1.08</td>
<td>1.52</td>
<td>United States</td>
<td>1995–2011</td>
<td>0–14</td>
<td>Benzene Ambient Air Levels, National-Scale</td>
<td>[37]</td>
</tr>
</tbody>
</table>
3.3. Estimating the risk and meta-analysis

The highest and lowest amount of risk was related to the studies of Shu et al RR=4 (1.76, 9.09) and Infante-Rivard et al RR = 0.62 (0.2, 1.92). The highest and lowest percentage of weight of the studies was related to Symanski et al (17.57%) and Perez-Saldivar et al (2.41%).

Since the heterogeneity of the studies was higher than 50%, the Random model was used ($I^2 = 53.5\%, P = I^2$ value < 0.05). The mean amount of risk of studies was $RR = 1.76$ (1.28, 2.31), $P$ value < 0.001 (Figure 2).

![Figure 2. Forest plot of meta-analysis on benzene exposure and childhood leukemia.](image)

Reversibility of funnel chart as well as the Eggers’ test (Intercept = 0.97, $P$ value = 0.12) showed there is not any considerable publication error in studies (Figure 3).

![Figure 3. Funnel plot of the studies included in the meta-analysis.](image)
4. Discussion

The systematic review and meta-analysis showed that being exposed to benzene increases the risk of leukemia significantly (p value < 0.001). Lamm et al. study risk assessment according to cohort studies performed by NIOSH (including 9 cases of leukemia), and compared their results with other studies [38]. Results show that leukemia induce to exceeding benzene exposure, meaning a high benzene exposure more than 20 ppm or an estimated cumulative benzene exposure more than 250 ppm-years. Results this study show consistent across the reviewed studies besides in the chinese study by Wong et al [39]. This first review reported no consistent witness for leukemia with benzene exposure. In the Savitz et al. study on lymphatic and hematopoietic cancers [40]. They recognized 14 studies, 3 environmental and 11 occupational, on benzene and total leukemia and 16 studies, 9 environmental and 7 occupational, on benzene and specific histologic types of leukemia [41]. But, they did not perform any meta-analysis. They concluded that associated benzene exposure to leukemia, also acute and chronic lymphocytic and myeloid leukemia, is no less persuasive than that for AML alone”, but did not propose any quantitative estimates. In the most new systematic review published in 2005, Schnatter et al evaluated 22 occupational cohort and case-control studies [42]. A high AML risk was reported study, especially in more highly exposed workers of rubber, shoe, and paint industry. The outcomes on CLL were controversial with an increased risk in case-control studies, however with no increase in cohort studies. Information for ALL and CML were inconclusive [42]. The results of our systematic review and meta-analysis both strengthen the evidence of the effect of benzene exposure with leukemia risk, and provide quantitative estimates of effect size. These estimates indicated an increased risk to substantially lower dose than that suggested by Lamm et al. Constantly with the previous reports In 1989, Lamm et al. published a risk assessment according to cohort study performed by NIOSH (including 9 cases of leukemia), and compared their results with those of the other studies. They concluded that AML induced to benzene exposure, meaning a max benzene exposure more than 20 ppm or an estimated cumulative benzene exposure more than 250 ppm-years [38]. Mechanistic studies support this outcomes. The higher summary RR for maternal versus exposure benzene and higher RR for gestational exposure are consistent with a more relationship in the fetal period. For childhood leukemia, shown that the disease is usually initiated in utero: The leukemic translocations and other genetic changes have been shown to be present in blood spots collected at birth [43, 44].

Since the genotoxic action of benzene metabolites induces genetic abnormalities, it seems probable that benzene exposure can initiate leukemia in utero by causing the chromosomal rearrangements and mutations that are on the
causal pathway to these malignancies in fetal hematopoietic stem cells. This hypothesis is supported by human and animal studies that show the following: 1) benzene and its metabolites cross the placenta into the fetuses of exposed humans and mice [45, 46]; 2) low levels of benzene exposure alter the growth of myeloid and erythroid progenitor cells in fetal tissue in mice [45] and decrease CD4 and CD8 T-cell counts in neonatal beef calves [47]; 3) in utero benzene exposure increases the frequency of micronuclei and DNA recombination events in hematopoietic tissue of fetal and postnatal mice [48, 49]; and 4) benzene exposure induce oxidative stress and disrupts hematopoietic cell signaling pathways in the fetal blood progenitor cells of exposed mice [50].

Taken together, these data strongly propose that benzene can initiate childhood leukemia in utero and that early life exposures can induce the leukemic clone to proliferate further. Most of the studies used here were adjusted or matched for age and sex. Over adjustment related to socioeconomic status is possible, however the summary RR changed minimally when only studies adjusted for socioeconomic status were examined. Other factors, such as radiation, genetics, and viral infections, have also been associated to childhood leukemia [51].

Benzene exposure can be highly associated with other toxic agents, including other solvents or common air pollutants [52]. Hence, this results cannot represent the effects of benzene and could be due to these other factors. For example, air pollution can contain a number of carcinogenic agents, including diesel exhaust and polycyclic aromatic hydrocarbons. Less research has been done on these other agents than on benzene, so the possibility that some other agent is accountable for some or all of the associations we recognized cannot be ruled out. However, benzene seems the most plausible agent because it, and not these other agents, has been clearly associated to leukemia in exposed adults [2].

The strong association between benzene and leukemia in adults, the data on biologic plausibility presented in previous studies, and the fact that we identified elevated summary RR for a variety of different potential benzene exposure metrics combine to support the hypothesis that benzene is responsible for the associations identified here. Most of the occupational studies used self-reports of job histories and expert evaluations or self-reports of specific exposures. Self-reported show that to correlate reasonably well with company, pension, or union records [53, 54].

Results of some studies shown fairly good agreement between self-reported exposures and industrial hygiene measurements, employer reports, and expert evaluations, although results varied widely across studies [55]. Raaschou-Nielsen et al study show a correlation of 0.55 for the association between traffic density and weekly average benzene air concentrations, which rose to 0.68 when more complex models that included street configuration.
and meteorological data were, used [56]. Also results in the our study RR of 1.76 (95% CI:1.28, 2.31), agree with those from some previous meta-analyses [6, 57, 58]. For example, in a meta-analysis of 8 studies of traffic density published up to July 2011, Boothe et al showeda summary OR for leukemia of 1.53 (95% CI: 1.12, 2.10) for postnatal exposures. This is similar to the summary RR of 1.46 (95% CI: 1.03, 2.08) that we reported for a collection of studies that included studies of traffic density, studies of more complex traffic pollution models, 4 studies published since 2011, and findings by leukemia subtype. In a meta-analysis, Zhou et al showed a pooled OR for ALL and solvents of 1.25 (95% CI: 1.09, 1.45), but they did not evaluate AML or specific data on benzene. There were some limitations in this study that include: not separating the cohort and case-control studies into two subgroups, the language limitation (except for English and English), setting aside the studies that have used the method of blinding, lack of the similar classification in concentration of benzene.

5. Conclusion

The result of systematic review and meta-analysis of 13 studies showed that being exposed to benzene increases significantly by 72% the leukemia cancer risk (P value < 0.001). The results of this study support the increase in risk of leukemia cancer resulting from confronting the benzene. Therefore, it is recommended being exposed to this dangerous combination is reduced as possible.

6. References


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