Response to Commentary

Steinmaus and Smith Respond to “Proximity to Gasoline Stations and Childhood Leukemia”

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Benzene is an established cause of adult leukemia, but its role in childhood leukemia is less clear. In a recent meta-analysis, we identified associations of childhood leukemia with occupational and household product benzene exposure and traffic-related pollution. Residential proximity to gasoline stations or automobile repair facilities may be another source of benzene, and in 3 studies assessing these sources, we identified a summary relative risk of 1.59 (95% confidence interval: 0.70, 3.62). Although not statistically significant, this summary relative risk was of a magnitude similar to that of our other positive findings. In this issue of the Journal (Am J Epidemiol. 2017;185(1):5–7), Dr. Infante suggested that meta-analyses of studies on childhood leukemia and proximity to gasoline stations should involve some criteria that differ from those we used. These suggested criteria involved combining leukemia subtypes, excluding automobile repair facilities, and using nonleukemia cancers as control subjects. We reid our meta-analysis using these new criteria and obtained a summary relative risk of 2.42 (95% confidence interval: 1.51, 3.89). Overall, although this result should be interpreted in light of the relatively small sample size (3 studies) and its post-hoc nature, it provides additional new evidence for associations of childhood leukemia with both residential proximity to gasoline stations and exposure to benzene.

Millions of people are exposed to benzene worldwide in either occupational or environmental settings. Although benzene is an established cause of leukemia in adults (1), its relationship with childhood leukemia is less clear. In a recent meta-analysis of epidemiologic data on benzene and childhood leukemia published in this Journal (2), we identified statistically significant associations between benzene and childhood leukemia based on studies in which investigators assessed occupational sources and household products (summary relative risk (sRR) = 1.96, 95% confidence interval (CI): 1.53, 2.52; n = 20 studies) and studies in which they assessed traffic-related pollution (sRR = 1.48, 95% CI: 1.10, 1.99; n = 12 studies). Gasoline stations or automobile repair facilities may also be a source of benzene exposure, and we identified 3 studies in which the authors examined associations between residential proximity to these sources and childhood leukemia (3–5). All 3 studies had relative risk estimates greater than 1.0 (although one was only 1.1), and the summary relative risk for the meta-analysis of these 3 studies was 1.59 (95% CI: 0.70, 3.62). Notably, this summary relative risk is not only above 1.0, it is also of a magnitude similar to that of most of our positive findings from the examination of other benzene sources.

Almost all of the studies used in our meta-analysis provided a number of results based on examinations of different leukemia subtypes (acute myeloid leukemia (AML) vs. acute lymphocytic leukemia (ALL) vs. all subtypes combined), different exposure metrics (e.g., residential proximity to gasoline stations alone vs. residential proximity to gasoline stations or automobile repair facilities), or differences in several other exposure or study design factors. In order to meet the assumption of independence for the statistical approaches we used, we established a set of criteria a priori for selecting a single result from each study for inclusion in our final meta-analysis calculations. For example, when a study presented separate results for AML and ALL, we selected the result for AML because this subtype is the one most strongly linked to benzene in adults (1, 6, 7). When a study presented one result for residential proximity to gasoline stations, another result for residential proximity to automobile repair facilities, and a separate result for residential proximity to one or the other, we chose the latter because products containing benzene are used at both types of facilities (8).
In his recent commentary in this *Journal* (9), Dr. Infante suggested 3 criteria for selecting study results that differed from those we used. First, he suggested that priority should be given to results that combine AML and ALL. The advantage of this approach is that if benzene is related to both subtypes of leukemia, this approach could increase the statistical power of both the study result and the meta-analysis that uses it. In fact, in both of our meta-analyses of occupational and household product benzene use and our meta-analysis of traffic-related pollution, elevated summary relative risks were seen for both AML and ALL, although they were higher in the former for both occupational household product exposures (for AML, sRR = 2.34, 95% CI: 1.72, 3.18; for ALL, sRR = 1.57, 95% CI: 1.21, 2.05) and traffic-related pollution (for AML, sRR = 2.07, 95% CI: 1.34, 3.20; for ALL, sRR = 1.49, 95% CI: 1.07, 2.08).

Second, Dr. Infante suggested that meta-analyses of benzene and childhood leukemia should focus on gasoline stations and not combine data for gasoline stations with those for automobile repair facilities (9). As noted in his commentary, data concerning the relative levels of benzene at automobile repair facilities and gasoline stations are scarce. However, given the much larger volume of gasoline used at gasoline stations compared with automobile repair facilities, Dr. Infante’s argument that exposures near gasoline stations are likely to be higher than those near automobile repair facilities is reasonable. Dr. Infante’s final suggestion involved the 2 different control groups used in the study by Harrison et al. (4). In 1 group, a case-control analysis was done using children with solid tumors as the controls. In the other, incidence ratios were calculated using estimated population distributions from the source population. Based on the concern that benzene or a correlated exposure might impact the risks of other cancers, we a priori selected the incidence ratio result. However, given that Harrison et al. examined the relationship between residential proximity to gasoline stations and solid tumors and found no evidence of an association, selecting the case-control odds ratio, as suggested by Dr. Infante, seems a valid alternative that is unlikely to introduce substantial bias.

Using the statistical methods presented in our original paper (2), we investigated how our results would change if we incorporated Dr. Infante’s suggestions (9), that is, if we preferentially selected data on all leukemia types combined (rather than just AML), used results from just gasoline stations (when available), and used the case-control data from Harrison et al. rather than the incidence study data. Using our original criteria, we reported a summary relative risk of 1.59 (95% CI: 0.70, 3.62; $\chi^2$ heterogeneity statistic = 5.08; $P$ for heterogeneity = 0.08). However, using the new criteria suggested by Dr. Infante, the summary relative risk increased to 2.42 (95% CI: 1.51, 3.89; $\chi^2$ heterogeneity statistic = 1.38; $P$ for heterogeneity = 0.50). The 2 sets of data used in each analysis are shown in Table 1, and the meta-analysis results are shown in Table 2. Overall, as with our original result, this new finding is consistent with an association between residential proximity to gasoline stations and a higher risk of childhood leukemia. Importantly though, this new result should be interpreted in light of the post-hoc manner in which it was generated and the relatively small increase in statistical power.

### Table 1. Study Data Used in the Original and New Meta-Analyses of Residential Proximity to Gasoline Stations and the Risks of Childhood Leukemia

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Location</th>
<th>Years</th>
<th>Leukemia Type</th>
<th>Exposure</th>
<th>Study Design</th>
<th>No. of Cases</th>
<th>Weight, %</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlos-Wallace et al., 2016 (2)</td>
<td>France</td>
<td>2003-2004</td>
<td>AML</td>
<td>Repair garage or gasoline station</td>
<td>Case-control</td>
<td>7</td>
<td>41.2</td>
<td>1.1</td>
<td>0.5, 2.5</td>
</tr>
<tr>
<td>Harrison et al., 1999 (4)</td>
<td>United Kingdom</td>
<td>1990-1994</td>
<td>All leukemias</td>
<td>Gasoline station only</td>
<td>Case-control</td>
<td>8</td>
<td>47.0</td>
<td>1.48</td>
<td>0.65, 2.93</td>
</tr>
<tr>
<td>Steffen et al., 2004 (5)</td>
<td>France</td>
<td>1995-1999</td>
<td>AML</td>
<td>Repair garage or gasoline station</td>
<td>Case-control</td>
<td>4</td>
<td>11.8</td>
<td>7.7</td>
<td>1.7, 34.3</td>
</tr>
<tr>
<td>Harrison et al., 2009 (3)</td>
<td>France</td>
<td>2003-2004</td>
<td>ALL and AML</td>
<td>Repair garage or gasoline station</td>
<td>Case-control</td>
<td>19</td>
<td>53.7</td>
<td>2.1</td>
<td>1.1, 4.0</td>
</tr>
<tr>
<td>Steffen et al., 2004 (5)</td>
<td>France</td>
<td>1995-1999</td>
<td>ALL and AML</td>
<td>Gasoline station only</td>
<td>Case-control</td>
<td>8</td>
<td>22.2</td>
<td>1.99</td>
<td>0.73, 5.43</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CI, confidence interval; RR, relative risk estimate.

*Infante suggests that his new result should be interpreted in light of the post-hoc manner in which it was generated and the relatively small increase in statistical power.*
small number of studies on which it is based. Further research on childhood leukemia and residential proximity to gasoline stations that involves larger sample sizes and more detailed residential and exposure histories could add new insights into this important issue.

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Conflict of interest: M.T.S. has received consulting and expert testimony fees from law firms representing both plaintiffs and defendants in cases involving exposure to benzene. Other author reports no conflicts.

REFERENCES