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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 redid 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; χ^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; χ^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

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

First Author, Year (Reference No.)	Location	Years	Leukemia Type	Exposure	Study Design	No. of Cases	Weight, %	RR	95% CI
Carlos-Wallace et al., 2016 (2)									
Brosselin et al., 2009 (3)	France	2003–2004	AML	Repair garage or gasoline station	Case-control	7	41.2	1.1	0.5, 2.5
Harrison et al., 1999 (4)	United Kingdom	1990–1994	All leukemias	Gasoline station only	Incidence study	8	47.0	1.48	0.65, 2.93
Steffen et al., 2004 (5)	France	1995–1999	AML	Repair garage or gasoline station	Case-control	4	11.8	7.7	1.7, 34.3
Using Infante's Suggestions (9)									
Brosselin et al., 2009 (3)	France	2003–2004	ALL and AML[a]	Gasoline station only[a]	Case-control	19	53.7	2.1	1.1, 4.0
Harrison et al., 1999 (4)	United Kingdom	1990–1994	All leukemias	Gasoline station only	Case-control[a]	8	22.2	1.99	0.73, 5.43
Steffen et al., 2004 (5)	France	1995–1999	ALL and AML[a]	Repair garage or gasoline station	Case-control	17	24.1	4.0	1.5, 10.3

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CI, confidence interval; RR, relative risk estimate.
[a] Infante suggestions that differ from those in the meta-analysis by Carlos-Wallace et al.

Table 2. Meta-Analysis Results in the Original and New Analyses of Residential Proximity to Gasoline Stations and the Risks of Childhood Leukemia

First Author, Year (Reference No.)	No.	Summary RR[a]	95% CI	Heterogeneity χ^2	*P* for Heterogeneity
Carlos-Wallace, 2016 (2)	19	1.59	0.70, 3.62	5.08	0.08
Infante, 2016 (9)	44	2.42	1.51, 3.89	1.38	0.50

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Summary relative risks were calculated using the fixed effects method with adjustments of the 95% confidence interval in the presence of heterogeneity (10).

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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