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Commentary

Residential Proximity to Gasoline Stations and Risk of Childhood Leukemia

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Significant elevations in the risk of childhood leukemia have been associated with environmental exposure to gasoline; aromatic hydrocarbons from refinery pollution, petroleum waste sites, and mobile sources (automobile exhaust); paints, paint products, and thinners; and secondary cigarette smoke in the home. These higher risks have also been associated with parental exposure to benzene, gasoline, motor vehicle–related jobs, painting, and rubber solvents. These exposures and jobs have 1 common chemical exposure—benzene, a recognized cause of acute leukemia in adults—and raise the question of whether children represent a subpopulation in which a higher risk of leukemia is associated with very low level exposure to environmental benzene.

benzene; childhood leukemia; gasoline stations; gasoline; residential exposure

Abbreviations: ALL, acute lymphatic leukemia; AML, acute myelogenous leukemia; CI, confidence interval; CL, childhood leukemia.

Editor's Note: *A response to this commentary appears on page 5.*

Over the past decades, the average benzene content of gasoline has been approximately 1%–3% (and up to 5%) in the United States (1, 2) and 3%–5% in European countries (3, 4). Because benzene is known to be associated with adult leukemia and lymphomas (5–14), a number of investigators have evaluated the risk of childhood leukemia (CL) in relation to several potential sources of benzene exposure, including parental occupational sources (15–26), maternal environmental sources (27–29), household products (e.g., painting products) (16, 21, 30–36), traffic density (37–43), and air pollution from the release of toxic chemicals into the environment (44, 45).

Most recently, in their meta-analysis, Carlos-Wallace et al. (46) brought together this important literature. Parental occupational exposures, household product exposures, traffic density, and related air pollution measures were significantly associated with CLs. The authors concluded that several metrics of benzene exposure were associated with CL; yet, they did not find an association between residential proximity to gasoline service stations and CL. Carlos-Wallace et al. selected 3 case-control studies for use in a meta-evaluation of this association (47–49) and concluded that the relative risks for CL using data from these 3 studies of residential proximity to gasoline stations were all above 1.0 but were not statistically significant overall (46). The lack of an observed association between residential proximity to gasoline stations and CL, however, may have been a reflection of the methodology used for the selection of results from these 3 studies. I suggest that the authors consider modifying their analysis based on these studies by including the data related to residential proximity to gasoline stations only and all types of CL.

Two of the 3 studies cited provided data separately for residential proximity to gasoline stations and risk of CL (47, 48), and the third provided data for proximity to gasoline stations and automotive repair garages combined (49). With regard to residential proximity to gasoline stations only, Brosselin et al. (47) showed that for total CL (acute lymphatic leukemia (ALL) and acute myelogenous leukemia (AML) combined), the odds ratio was 2.1 (95% confidence interval (CI): 1.1, 4.0; based on 19 cases). This overall odds ratio for CL was a reflection of the ALL odds ratio being 2.0 (95% CI: 1.0, 4.0; based on 16 cases) and the AML odds ratio being 2.5 (95% CI: 0.7, 8.8; based on

3 cases). Thus, the study demonstrated a significant 2-fold risk for total CL, as well as for ALL separately. Although the results for AML were not statistically significant, the odds ratio was slightly greater than the odds ratio for ALL; however, it was based on only 3 cases and included a 95% confidence interval that ranged from 0.7 to 8.8. In their meta-analysis, Carlos-Wallace et al. (46) selected the results for AML from only the study by Brosselin et al. (47). They then combined data for residential proximity to gasoline stations with the data for residential proximity to automotive repair garages. As a result, in Table 2 of their meta-analysis, they listed an odds ratio of 1.1 for AML in relation to CL under the subheading "Studies of Residential Proximity to Gas Stations." Contrary to this, they did not include the much larger data set for ALL and did not present data analysis for residential proximity to gasoline stations only. To be consistent with the types of exposures and risk indicated in their Table 2, I suggest that they include the results for total CL (and perhaps for ALL and AML separately if they choose) as related to gasoline stations only.

Combining data for residential proximity to gasoline stations with data for proximity to automotive repair garages in an analysis of CL risk seems reasonable because emissions from gasoline vapor potentially occur in both situations. Exposures to gasoline vapors would seem to be lower in the vicinity of automotive repair garages as compared with gasoline stations, although I have not been able to locate literature on this subject. Such an environmental exposure differential, however, is consistent with the findings of Brosselin et al. (47), who found that the odds ratio for the association of CL and residential proximity to gasoline stations only was 2.1 (95% CI: 1.1, 4.0) as compared with an odds ratio of 1.4 (95% CI: 0.9, 2.1) for the association with residential proximity to repair garages only. Hence, combining data for these exposures dilutes the findings related to CL risk associated with residential proximity to gasoline stations.

The second data set used in the meta-analysis (46) was from a study by Harrison et al. (48). They compared the incidence of childhood solid tumors with that of CL. The results of this analysis indicated that for persons who resided within 100 meters of a gasoline station, the odds ratio for CL was 1.99 (95% CI: 0.73, 5.43; based on 8 cases); no separation of cell types was presented in the report. Concerned that solid tumors may be related to gasoline exposures, the authors (48) conducted a second analysis using incidence data for the population area from which the cases of CL were selected in order to estimate the number of expected CL cases. The results from the incidence rate analysis indicated there were 8 cases observed versus the 5.4 that were expected (incidence rate = 1.48, 95% CI: 0.65, 2.93). Of these 2 analyses, the authors (48) preferred the results based on the solid tumor comparison, because the age distribution estimated for the general population incidence analysis was inferred and standardization for age and sex could not be accomplished. The authors (48) also preferred the solid tumor comparison analysis because the fugitive emissions being evaluated had been associated only with lung cancer, which is rare in the age group of children being studied (0–15 years). Hence, the solid tumor control group seemed to be adequate for comparison. Harrison et al. (48) further justified their preference for results from the solid tumor analysis portion of their study by noting that their incidence analysis indicated there was no increase in the risk of childhood solid tumors in the area. Carlos-Wallace et al. (46) included only the results of the study by Harrison et al. (48) that were based on the general population incidence rate for CL. I suggest that the analysis based on solid tumors be given preference in their meta-analysis because it seems there is more justification for doing so.

In the third study used in the meta-analysis, Steffen et al. (49) evaluated the risk of CL using combined data for residential proximity to gasoline stations and automotive repair shops. They did not separate their data for these 2 exposures situations in their study. The authors found an odds ratio of 3.6 (95% CI: 1.3, 9.9) for ALL based on 13 cases and an odds ratio of 7.7 (95% CI: 1.7, 34.3) for AML

Table 1. Residential Proximity to Gasoline Stations and Risk of Childhood Leukemia

First Author, Year (Reference No.)	RR	95% CI	Type of Leukemia	No.	Recommendation
Brosselin, 2009 (47)					
Data from Carlos Wallace (46[a])	1.1	0.5, 2.5	AML	7	Excluding data for proximity to auto repair shops and to include residential proximity to gasoline stations for all CL
Replacement data	2.1	1.1, 4.0	CL	19	
Harrison, 1999 (48)					
Data from Carlos Wallace (46[a])	1.48	0.65, 2.93	CL	8	Case-control study results based on solid tumors as controls to replace general population incidence analysis
Replacement data	1.99	0.73, 5.43	CL	8	
Steffen, 2004 (49)					
Data from Carlos Wallace (46[a])	7.7	1.7, 34.3	AML	4	Adding results for acute lymphatic leukemia
Replacement data	4.0	1.5, 10.3	CL	17	

Abbreviations: AML, acute myelogenous leukemia; CI, confidence interval; CL, childhood leukemia.
[a] Data obtained from Table 2 of this study.

based on 4 cases. With their data for ALL and AML combined, the odds ratio for CL was 4.0 (95% CI: 1.5, 10.3). Furthermore, based on the 17 total cases of CL evaluated in the study (49), the authors demonstrated a significant dose-response relationship between residential proximity to a gasoline station or automotive repair garage and the risk of CL. For those with 1–35 months of residential proximity, the corresponding odds ratio for CL was 3.4; for those with 36 months or more, it was 4.7 (P for trend < 0.05). The identification of a significant dose-response relationship in an epidemiologic study is usually a strong indication of causality (11). Carlos-Wallace et al. (46) used only the AML portion of these study results in their meta-analysis. I suggest that they include the data for ALL and AML combined from the study by Steffen et al. (49). The selection of only childhood AML results for inclusion in the analysis presented in Table 2 of their article (46) is again confusing because the table title indicated that the results were for "childhood leukemia."

As shown in Table 1, based on the recommended revisions to the data entry for residential proximity to gasoline stations (indicated as "replacement data"), the risk of CL ranges from essentially 2-fold in the studies by Brosselin et al. (47) and Harrison et al. (48) to 4-fold in the study by Steffen et al. (49). From the 3 studies included in their meta-analysis, it seems fairly clear that there is a significant association between CL and residential proximity to gasoline stations.

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