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Non-Hodgkin lymphoma and benzene exposure: A systematic literature review

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Abstract

Epidemiological papers that address an association between benzene exposure and non-Hodgkin lymphoma (NHL) were identified and separated by study design. Eighteen studies contained 21 study groups—11 population-based case–control study groups, 3 nested occupation-based case–control study groups and 7 occupational benzene cohort study groups. Petroleum industry studies were not included. Only two of these 21 study groups showed statistically significant associations. However, these were among workers with multiple exposures across industries. Eleven of the 21 study groups presented ratios less than one, two equaled one, and eight were greater than one. Over all, about as many cases were observed (404) as expected (390.0) for an observed to expected ratio of 1.04 (0.94–1.14). After removal of the studies with multiple chemical exposures problems, the observed was 359 cases with 373.2 cases expected, yielding an odds ratio of 0.96 (0.86–1.06). Further assessment of an association with NHL should document the benzene exposure and separate out the contribution of non-benzene exposures.
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1. Introduction

A systematic review of the literature on benzene exposure and non-Hodgkin lymphoma (NHL) has been conducted. A search of the National Library of Medicine Pub-Med file has been regularly updated through April 15, 2005. Newly identified studies, and those in our previous review [1], were searched to find additional references. There is a large literature of petroleum industry studies that have previously received extensive analysis [2] and within which no increased risk of NHL has been observed. In order to more clearly evaluate the rest of the literature, the petroleum industry studies have not been included in this analysis. Care has been taken to include only those studies that specified benzene exposure rather than exposure to solvents including benzene. Eighteen studies with 21 study groups met this initial criterion for inclusion.

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Table 1
Study characteristics of population-based case–control studies of benzene exposure and non-Hodgkin lymphoma

Authors	Site	Population/ industry	Dates	Exposure source	Outcome ascertainment
Bernard et al. [3]	Yorkshire, United Kingdom	Population	1979–1981	Interviews	Registry, physician/lab surveillance
Blair et al. [4]	Iowa, Minnesota agriculture	Population (WM)	1980–1983	Interviews	Registry (IA), hospital surveillance
Fabbro-Peray et al. [5]	Languedoc-Roussillon, France	Population	1992–1996	Interviews	Hospital records
Gerin et al. [6], Fritschi and Siemiatycki [7]	Montreal, Canada	Population (Males)	1979–1986	Interviews	Hospital surveillance
Mao et al. [8]	Eight Provinces, Canada	Population	1994–1997	Mailed Questionnaires	Provincial cancer registries
Persson and Fredrikson [9]	Orebro and Linkoping, Sweden	Population	1964–1986, 1975–1984	Questionnaires	Hospital registry
Scherr et al. [10]	Metropolitan Boston	Population	1980–1982	Interviews	Hospital records
Schumacher and Delzell [11]	North Carolina	Population	1968–970, 1975–1977, 1980–1982	Death certificates	Death certificates

2. Population-based case–control studies

Table 1 shows the eight population-based case–control studies [3–11] by study characteristics and Table 2 shows them by study results. They contain odds ratios yielding a pooled odds ratio of 1.00 (95% confidence limits, 0.89–1.11) based on 325 cases observed and 326.1 cases expected. These odds ratios range between 0.5 and 2.0 with seven of the eleven being between 0.8 and 1.2. The set of 11 population-based study groups from the 8 studies did not show evidence of an associated with benzene exposure (Fig. 1).

Statistical significance is seen in only one association between benzene exposure and NHL [5], with an odds ratio = 2.0 and 95% confidence limits of 1.1–3.9. However, this association related to an aggregated benzene exposure group of workers in chemical or rubber production and of workers employed as printers, painters, and shoemakers. There is no analysis of

Table 2
Study results of population-based case–control studies of benzene exposure and non-Hodgkin lymphoma

Authors	*N*	*n*	Expected	OR	95% Confidence limits
Bernard et al. [3]	158			0.49	0.21–2.00
Blair et al. [4]	662	153	139.1	1.1	0.9–1.4
Fabbro-Peray et al. [5]	445	22	11	2	1.1–3.9
Gerin et al. [6],	215	9 (M/H)	11.3 (M/H)	0.8 (M/H)	0.4–1.6 (M/H)
Fritschi and Siemiatycki [7]		19 (L)	31.7 (L)	0.6 (L)	0.4–1.0 (L)
		187 (none)	187 (none)	1.0 (none)	
Mao et al. [8]	764 (M)	36 (M)	30 (M)	1.2 (M)	0.8–1.9 (M)
	705 (F)	5 (F)	6.3 (F)	0.8 (F)	0.2–1.8 (F)
Persson and Fredrikson [9]	199	3	3.8	0.8	0.1–3.8
Scherr et al. [10]	303	12	10	1.2	0.5–2.6
Schumacher and Delzell [11]	433 (W)	56 (W)	72.3 (W)	0.77 (W)	0.56–1.07 (W)
	68 (B)	10 (B)	10.6 (B)	0.94 (B)	0.58–2.30 (B)
Sum		325	326.1	1.00	0.89–1.11
Excluding Fabbro-Peray [5]		303	315.1	0.96	0.85–1.07

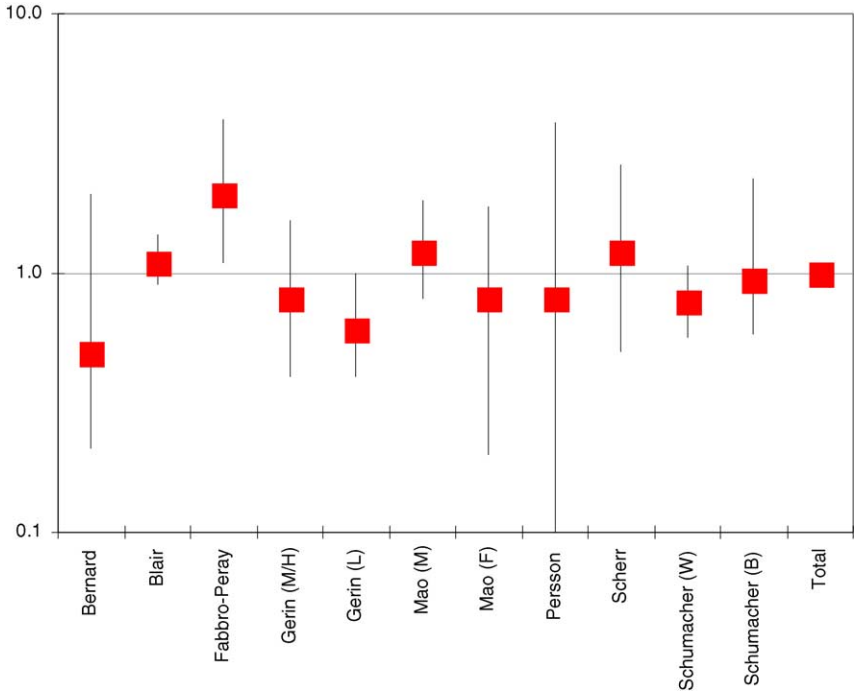

Fig. 1. Population-based case–control studies odds ratios of non-Hodgkin lymphoma for benzene exposure (OR and 95% confidence limits; individually and pooled).

whether the risks are similar in the various industrial groups or whether they cluster. This study contributed only 7% of the observed cases and had little effect on the over-all risk estimate. The pooled odd ratio with its exclusion was 0.96 with 95% confidence limits of 0.85–1.07. Many studies that do not show an association with benzene had identified other significant occupational or non-occupational exposure factors.

3. Occupation-based case–control studies

None of three nested occupation-based case–control studies (Table 3) have a significant odds ratio with benzene exposure (Table 4). The Greenland et al. [12,13] and Ott et al. [14] studies find as many exposed cases as expected. The Wilcosky et al. [15] study of rubber workers found significant associations for lymphosarcoma with carbon tetrachloride, carbon disulfide, hexane and xylenes but not for benzene, a common co-exposure in solvent mixtures. These confounding exposures lend difficulty to attributing the observations to benzene exposure.

4. Occupation-based cohort studies

Five of the seven occupational benzene cohorts (Table 3) have standardized mortality ratios (SMR) of 0.89–1.06 (Table 4), one [20] has no exposed case and the seventh [27] (the Chinese benzene cohort) has an SMR of 4.5 (1.3–8.4). Controversy exists about the variety and levels of exposures in that cohort as well as underascertainment of NHL cases in the comparison group [28]. Unlike various studies of rubber workers, most of the Chinese benzene cohort exposures have not been reported with examinations of co-exposures and other exposures. In the Chinese benzene cohort, the industrial sectors with the greatest number of cases [29] were chemical, other/mixed exposure and coatings (painters and other coating application workers). Analysis assessing similarity of risk across industrial groups has not been done. Until the contribution of benzene exposure, or the risk to persons with significant exposure only to benzene, is separately reported, the import of these data for the assessment of risk from benzene exposure cannot be determined. Fur-

Table 3
Study characteristics of occupation-based case–control and cohort studies of benzene exposure and non-Hodgkin lymphoma

Authors	Site	Population/industry	Dates	Exposure source	Outcome source[a]
Occupation-based case–control studies					
Greenland et al. [12], Greenland [13]	Pittsfield, Massachusetts	Transformer assembly plant (WM)	1969–1984	Plant manager interviews, work history records	Compensation records, DCs
Ott et al. [14]	Union Carbide	Chemical Plant Research and Development	1940–1978	Work history records	DCs
Wilcosky et al. [15]	Akron, Ohio	Rubber manufacturing plant	1964–1973	Work history records	DCs
Occupational cohort studies					
Bloemen et al. [16], Bond et al. [17], Ott et al. [18]	Dow Chemical Michigan	R&D, chemical manufacturing plants (WM)	1940–1996	Work history records	DCs
Collins et al. [19]	Monsanto Sauget, Illinois	Chemical plant	1940–1997	Work history records	DCs
Decouffle et al. [20]	Conoco plant	Chemical manufacturing	1950–1977	Hire-fire work records	DCs
Rinsky et al. [21], Paxton et al. [22]	Goodyear plants, OH, USA	Pliofilm manufacture	1940–1996	Work history records	DCs
Seniori Costantini et al. [23,24], Fu et al. [25]	Florence, Italy	Shoemakers	1950–1999	Work history records	DCs
Sorahan et al. [26]	UK	Benzene factories	1968–2002	Inspectory of factories registry	Office of national statistics
Yin et al. [27]	China	Benzene industries	1972–1987	Salary and administrative records	Employee medical record, DCs

[a] DC, death certificate.

ther, the reported dose–response curves for benzene in units of either ppm or ppm-yrs are U-shaped, not monotonically increasing, which also needs an explanation. The data from the Chinese study is further aberrant, since its mortality data for malignant lymphoma includes both NHL and Hodgkin lymphoma. In contrast, the UK study [26] has clearly distinguished the two. Our analysis of their NHL cases by industrial group (personal communication) indicates similar risks across the various industrial groups without clustering in certain industries or among the industries where most measured plants had the highest exposures (i.e., $\geq$25 ppm).

5. Discussion

Most studies of benzene exposure and NHL found no association. Occasional study groups (2 of 21) exhibit an association between benzene and NHL, but these present analyses of association with benzene without considering concurrent solvent exposures and were in populations with mixed chemical exposures. Across all study designs, we found that investigators observed a total of 404 cases with 390.0 cases expected for a pooled odd ratio of 1.04 (0.94–1.14) (Table 5). The observed/expected ratio is 1.04 with 95% confidence limits of 0.93–1.14. Exclusion of the multi-exposure study groups yield a set of 17 study groups with 359 cases with an expected of 373.2 cases, for a pooled odds ratio of 0.96 (0.86–1.07). In toto, the studies do not demonstrate an increased risk of NHL from benzene exposure. Clarification of the contribution of non-benzene exposures to the risk estimates are necessary before a causal inference can be considered. Refined analysis of any association between benzene exposure and NHL will require validation of the benzene exposure and careful assessment of alternative and concurrent exposures before a different judgment can be rendered. Studies from the rubber industry in the 1980s had initially pointed out an association between benzene and chronic lymphocytic leukemia. However,

Table 4
Study results of occupation-based case–control and cohort studies of benzene exposure and non-Hodgkin lymphoma

Authors	Cases	Observed	Expected	OR	95% Confidence limits
Occupation-based case–control studies					
Greenland et al. [12], Greenland [13]	15 LS and RCS	6	6	1.00	0.22–4.53
Ott et al. [14]	52 NHL deaths among 29,139 male employees	5	5.0	1.0	0.2–2.3
Wilcosky et al. [15]	9 NHL in WMs of 6678 total employees 1964–1973	6	2.0	3.0	ns
Sum		17	13	1.31	0.76–2.09
Excluding Wilcosky [15]		11	11	1.00	0.50–1.79
Occupational cohort studies					
Bloemen et al. [16], Bond et al. [17], Ott et al. [18]	2266 employees > 1 month in benzene	10	9.4	1.06	0.51–1.79
Collins et al. [19]	4417 employees hired 1940–1977	11	12.4	0.89	0.44–1.59
Decouffle et al. [20]	259 men in plant 1947–1960	0	0.36	0	
Rinsky et al. [21], Paxton et al. [22]	1845 employees in plants, 1936–1996	5	5.19	0.96	0.31–2.25
Seniori Costantini et al. [23,24], Fu et al. [25]	2008 employees after 1938 and during 1950–1999	4	3.84	1.04	0.28–2.67
Sorahan et al. [26]	5514 workers exposed 1966–1967 or earlier	15	15.9	0.94	0.53–1.56
Yin et al. [27]	74,828 employees, 1972–1987	17[a]	3.78	4.5	1.3–28.4
Sum		62	50.9	1.22	0.93–1.56
Excluding Yin [27]		45	47.1	0.96	0.70–1.28

[a] Includes Hodgkin lymphoma.

when the work histories were developed to show the exposures to each of a wide range of solvents, significant associations were found for carbon tetrachloride and carbon disulfide, but not for benzene [30]. Similar analyses should be conducted for other studies in which an association between benzene exposure and NHL is suggested.

A particular powerful observation is found in the report by Rinsky et al. (2002), which is the latest follow-up report of the Ohio Pliofilm cohort study. This study has been the primary basis for most quantitative risk analyses of the carcinogenic potency for benzene. It has had the most intensive examination and re-examination of its exposure database and is the study for which most

Table 5
Pooled summary analysis of case–control and cohort studies of benzene exposure and non-Hodgkin lymphoma across study designs, with and without multi-exposure exclusions

Source	Design	Observed	Expected	OR	95% Confidence limits
All studies					
Population-based	Case–control	325	326.1	1.00	0.89–1.11
Occupation-based	Case–control	17	13	1.31	0.76–2.09
Occupation-based	Cohort	62	50.89	1.22	0.94–1.56
	Sum	404	390.0	1.04	0.94–1.14
With exclusions					
Population-based	Case–control	303	315.1	0.96	0.85–1.07
Occupation-based	Case–control	11	11	1.00	0.50–1.79
Occupation-based	Cohort	45	47.1	0.96	0.70–1.29
	Sum	359	373.2	0.96	0.86–1.06

observers accept that benzene was the only significant solvent exposure. While there is considerable disagreement as to how best to handle the exposure and population assumptions, there is little disagreement about the outcome data in this study. By the time of this report, all living cohort members had had at least 20 years of follow-up. The observation period has now been sufficient for the expectation of more than five NHL deaths, and five have been observed.

In isolation, this study [21] yields a risk estimate of 0.96 (0.31–2.25) and the UK study [26] yields a risk estimate of 0.94 (0.53–1.56). When the results of the 18 study groups without known multi-exposure/diagnostic issues are brought into the analysis, the pooled odds ratio is 0.96 (0.86–1.06). Pooling of the results from all 18 of these study groups has not changed the point estimate but has yielded a marked narrowing of the confidence limits of that point estimate from 0.31–2.25 to 0.86–1.06. This procedure demonstrates that the inclusion of the data from the additional relevant study groups has greatly reduced the range of uncertainty in the risk estimate assessing the association hypothesis.

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