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Review of Epidemiologic Evidence on Benzene and Lymphatic and Hematopoietic Cancers

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Exposure to benzene is generally accepted as a cause of acute myeloid leukemia (AML), but the association with other cell types of leukemia and other lymphatic and hematopoietic cancers is controversial. We compiled epidemiologic research on benzene and lymphatic and hematopoietic cancers in order to assess the pattern of associations. Eighteen relevant community-based and 16 industry-based studies were located. Four of seven studies of lymphatic and hematopoietic cancer in the aggregate identified relative risks of 1.8 or more, and eight of 14 total leukemia studies yielded relative risks in that range. The few available studies of specific histologic types of leukemia do not indicate larger or more consistent elevations in risk for AML compared to other leukemia cell types. Sporadic reports have linked benzene to non-Hodgkin's lymphoma and multiple myeloma, but most studies do not indicate a positive association. Limitations in study quality, particularly exposure assessment, pervade all of the studies reviewed, and the distinction between studies addressing benzene and those addressing jobs in industries that use benzene is somewhat arbitrary. Nonetheless, the epidemiologic evidence linking benzene to leukemia in the aggregate, as well as for subtypes other than AML, is no less persuasive than that for AML alone. Am. J. Ind. Med. 31:287–295, 1997. © *1997 Wiley-Liss, Inc.*

KEY WORDS: benzene; leukemia; lymphoma

INTRODUCTION

Benzene has been suspected as an occupational carcinogen since the 1920s [International Agency for Research on Cancer, 1982]. In 1981, the evidence that benzene is carcinogenic in experimental animals was characterized by the International Agency for Research on Cancer [1982] as ''limited,'' and the evidence that benzene is carcinogenic to humans was found to be ''sufficient.'' In part because the cancers of primary concern, lymphatic and hematopoietic neoplasms, are rare, case series documenting ''larger than expected'' numbers of such cancers among shoe workers in Italy [Vigliani & Saita, 1964] and Turkey [Aksoy et al., 1974] provided important early information regarding increased risk. Although such observations lend general support to the notion that more cases than expected have occurred, in the absence of information on the population at risk and disease rates in some comparison population, the magnitude of association between benzene exposure and lymphatic and hematopoietic cancers cannot be assessed.

Subsequent studies of benzene and cancer have attempted to measure exposure and disease risk directly in order to derive dose-response relations. Although controversy remains about the exact shape of the function relating benzene exposure to acute myeloid leukemia (AML) [Austin et al., 1980; Swaen and Meijers, 1989; Paustenbach et al., 1994], with particular uncertainty regarding risks in the low-dose range (around 10 ppm), it is generally accepted that benzene exposure in human populations is causally related to the development of AML.

Most of the epidemiologic studies include information on several types of leukemias and often on other types of cancers as well. In fact, many of the early studies found the

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strongest evidence linking benzene to total leukemia rather than AML [Aksoy et al., 1974; Girard and Revol, 1970; Thorpe, 1974]. In the rubber industry study, specific leukemia cell types other than AML were more strongly implicated [McMichael et al., 1976]. Lymphatic and hematopoietic cancers other than leukemias have also been associated with benzene exposure, including lymphoreticular sarcoma [Vianna & Polan, 1979] and multiple myeloma [Rinsky et al., 1987]. The possibility of a broader array of lymphatic and hematopoietic cancers resulting from benzene has been suggested by Goldstein, based largely on toxicologic data [Goldstein, 1988; Goldstein, 1990; Hricko, 1994].

Given a substantial number of epidemiologic studies addressing benzene and lymphatic and hematopoietic cancer, most of which include cancers other than AML, we undertook a systematic effort to identify and compile the results in order to evaluate the epidemiologic evidence linking benzene to a range of specific types of lymphatic and hematopoietic cancers.

MATERIALS AND METHODS

We sought all published studies, primarily in the peer-reviewed literature, that generated a risk estimate relating benzene exposure to individual or grouped lymphatic and hematopoietic cancers. There was no minimum quality criterion for inclusion; instead, study quality was noted in the tabulations and interpretation of results. For both community-based and industry-based studies, an explicit effort to assess the role of benzene was required, omitting results from studies of industries in which benzene is known to be present (e.g., oil refineries, rubber manufacturing, shoe manufacturing) unless the researchers tried to isolate the subset of the population thought to have benzene exposure based on work locations or job titles. Similarly, we did not include studies of organic solvent exposure in the aggregate unless a subset of agents or workers was examined that directly addressed benzene. However, studies were not excluded for evaluating benzene as part of a relatively narrow subset of organic solvents. Although we began with the intention of conducting a quantitative meta-analysis, the disparities among studies in exposure assessment in particular made them of problematic comparability. The evaluation of the studies was therefore not based on formal quantitative criteria but rather on the patterns of results, emphasizing the magnitudes of relative risk estimates across studies.

A second criterion for inclusion was an explicit comparison of risk for persons thought to be exposed to benzene compared to those not thought to be exposed, usually generating a measure of relative risk (standardized mortality ratio, odds ratio, observed to expected ratio, etc.). We also sought to identify or calculate the number of exposed cases or precision of the risk estimate. This eliminated several case series reports that lacked an indication of the expected number of such cases [Vigliani and Saita, 1964] and one study that did not provide sufficient information to derive the number of exposed cases [Chinese Epidemiologic Study Group of Leukemia and Aplastic Anemia, 1992]. We attempted to include publications in languages other than English when the information was clearly relevant and not available elsewhere [Girard and Revol, 1970; Vai et al., 1989] but we are less confident that all relevant non-English-language publications were found.

When multiple publications were produced from the same study population, we tabulated results from the most complete or up-to-date version of the study [Rinsky et al., 1987; Paxton et al., 1994; Wong, 1995]. When reports differed by the amount of specific information available on benzene, we selected the most detailed report for inclusion in the tables. In one instance, the more recent study's results are not yet complete, so that we include parts of the earlier results [Yin et al., 1989], which are a subset of the later results [Travis et al., 1994].

The major division in the studies was between those that were conducted in a community population versus those that were based in a specific industry, such as oil refining or rubber manufacturing. Overall quality of exposure assessment was characterized as low, moderate, or high. For community studies, ''low'' meant that it was based on a job title or self-report with no evaluation by an industrial hygienist or similar expert, whereas ''high'' meant that the information was assessed by an expert familiar with the use of chemicals in the workplace. For industry-based studies, ''low'' meant that there was no explicit workplace evaluation, ''moderate'' meant that there was an evaluation to determine that benzene was present, and ''high'' meant that a systematic evaluation of job titles or environmental measurements was undertaken by an expert to determine probability of benzene exposure.

Some reports examined multiple groups defined by level of exposure, certainty of exposure, duration of exposure, or latency, which we included in the tabulations. When results were available with and without adjustment for potential confounders, we chose to present those which were adjusted. No distinction was made in the tables between incident and fatal cases. In some instances, we had to calculate odds ratios or observed to expected ratios from data provided in the study; 95% confidence intervals were calculated using appropriate methods [Rothman and Boice, 1982].

We used the codes from the Eighth Revision of International Classification of Diseases [US Department of Health and Human Services, 1980] to group cancers regardless of the original classification scheme used by investigators. We examined results for all lymphatic and hematopoietic cancers (ICD codes 200–209), non-Hodgkin's lymphoma (ICD codes 200 and 202), multiple myeloma (ICD code 203), leukemia and aleukemia (ICD codes 204–207), and leuke-

TABLE I. Description of Community-based Studies Reporting on Benzene and Lymphatic and Hematopoietic Cancers

First author (year)	Setting	Exposure data source	Exposure assignment	Quality of exposure assessment	Control for confounders
Girard (1970)	France	Interview	Self-report	Low	Age, sex
Ishimaru (1971)	Hiroshima & Nagasaki	Interview	Job title	Low	Age, sex, city, distance from A-bomb
Vianna (1979)	New York State	Death certificate	Job title	Low	None
Linos (1980)	Olmsted County, Minnesota	Medical records	Job title	Low	Age, sex, residence, duration of medical coverage
Flodin (1986)	Sweden	Interview	Self-report	High	None
Linet [CLL] (1987a)	Baltimore	Interview	Self-report	High	Age, sex, race
Linet [MM] (1987b)	Baltimore	Interview	Self-report	High	Age, sex, year, hospital
Schumacher (1988)	North Carolina	Death certificate	Job title	High	Age, race, year
Malone (1989)	US (multi-center)	Interview	Self-report	High	Age, sex, race, residence, education
Vai (1989)	Italy	Hospital record	Clinical evaluation	High	Age, sex, year
Crane (1989)	Houston	Interview	Self-report	High	None
Siemiatycki (1991)	Montreal	Interview	Job description	High	Age, income, smoking
Richardson (1992)	Paris	Interview	Job description	High	Age, sex, ethnicity, residence, hospital, prior cancer therapy
Scherr (1992)	Boston	Interview	Self-report	High	Age, sex, residence
Blair (1992)	Iowa & Minnesota	Interview	Job title	High	Age, sex, state, year, education, pesticides, family cancer history, hair dyes, direct/surrogate respondent
Crane[a] (1992)	Houston	Interview	Job title	Low	Age, sex, prior cancer therapy
Heineman (1992)	Denmark	Tax records	Job title	High	Age
Ciccone (1993)	Torino, Italy	Interview	Job title	High	Age, sex, smoking

[a]Some overlap with subjects in Crane et al. (1989).

mias divided by chronicity and cell type (acute and chronic, lymphocytic and myeloid).

RESULTS

Eighteen community-based (Table I) and 16 industry-based (Table II) studies provided data on benzene exposure and lymphatic and hematopoietic cancers. Community-based studies identified exposure from self-report of exposure or job title, with each having advantages and disadvantages (Table I). Only four studies integrated self-report, job title, and expert evaluation [Siemiatycki, 1991; Richardson et al., 1992; Heineman et al., 1992; Ciccone et al., 1993], which is optimal in such studies. The earliest studies generally did the poorest job of identifying exposure. Most, but not all, studies adjusted relative risks for age, and where appropriate for sex and race. Few studies included a broader array of potential confounders related to lifestyle and none attempted to incorporate information on other occupational workplace exposures.

Industry-based studies are concentrated in the chemical, oil, rubber, and shoe manufacturing sectors (Table II), all of which classified exposure based on industrial-hygienist judgments, sometimes combined with measurements. Most approaches to exposure assessment were considered to be of high quality. Consideration of confounding was largely limited to age and calendar time.

Four of seven studies of lymphatic and hematopoietic cancers in the aggregate showed two-fold or greater elevated risks associated with benzene exposure (Table III), with the Tsai et al. [1983] study largely uninformative due to small

TABLE II. Description of Industry-based Studies Reporting on Benzene and Lymphatic and Hematopoietic Cancers

First author (year)	Setting	Industry	Quality of exposure assessment	Control for confounders
Aksoy (1974)	Istanbul, Turkey	Shoe manufacturing	Low	None
Thorpe (1974)	Europe	Oil/petrochemical	High	Age
Rushton (1981)	United Kingdom	Oil/petrochemical	High	Age, duration of work, year hired
Tsai (1983)	Texas	Oil/petrochemical	High	Age, sex, year, race
Decouflé (1983)	US	Chemical	High	Age, year
Checkoway (1984)	US	Rubber	High	Age
Bond (1986)	Michigan	Chemical	High	Age, year
Austin (1986)	Illinois	Oil/petrochemical	High	Age
Wong (1987a, b)	US	Chemical	High	Age, year
Yin (1989)	China	All industries	High	Age
Ott (1989)	US	Chemical	Moderate	None
Hurley (1991)	United Kingdom	Coke and coal	Moderate	Age, year
AIPHS[a] (1992)	Australia	Oil/petrochemical	High	Age
Paxton (1994)	US	Pliofilm (rubber)	High	Age, year
Wong (1995)				
Greenland (1994)	Massachusetts	Transformer assembly	High	Age, year of hire, year of death
Travis (1994)	China	Multiple industries	High	Age, sex

[a]Abbreviation: AIPHS, Australian Institute of Petroleum Health Surveillance Program.

TABLE III. Results of Studies Reporting on Benzene and Total Lymphatic and Hematopoietic Cancers

First author (year)	Study setting	Exposed cases	Relative risk	95% CI
Vai (1989)	Community	15	13.3	8.0–22.2
Tsai (1983)	Industry	0	0.0	0.0–3.3
Decouflé (1983)	Industry	4	3.8	1.1–10.2
Bond (1986)	Industry	7	1.3	0.5–2.8
Wong (1987a)	Industry	30[a]	1.3	0.9–1.8
		8[b]	1.0	0.5–2.1
AIPHS (1992)	Industry	10[c]	1.9	0.7–4.6
		7[d]	2.3	0.8–6.5
Travis (1994)	Industry	82	3.4	1.9–6.1

[a]Continuous benzene exposure.
[b]Intermittent benzene exposure.
[c]Medium versus low benzene exposure.
[d]High versus low benzene exposure.

TABLE IV. Results of Studies Reporting on Benzene and Total Leukemia

First author (year)	Study setting	Exposed cases	Relative risk	95% CI
Girard (1970)[a]	Community	30	2.9	1.1–7.4
Ishimaru (1971)[b]	Community	24	1.8	0.9–3.7
Linos (1980)	Community	4	3.3	0.6–27.6
Thorpe (1974)	Industry	8	1.2	0.5–2.4
Rushton (1981)	Industry	18	2.3	1.0–5.0
Tsai (1983)	Industry	0	0.0	0.0–8.7
Decouflé (1983)	Industry	3	6.8	1.4–19.9
Bond (1986)	Industry	4	1.9	0.5–4.9
Austin (1986)	Industry	15	NA	NA
Wong (1987a)	Industry	6[c]	1.4	0.5–3.0
		1[d]	0.7	0.0–3.7
Yin (1989)	Industry	25	5.7	4.0–8.0[e]
Hurley (1991)	Industry	5	0.4	0.1–1.0
Paxton (1994)	Industry	14	3.6	2.0–6.0
Greenland (1994)	Industry	NA[f]	0.9	0.3–3.1
		NA[g]	1.4	0.6–3.2

[a]Acute, CLL, myeloid combined.
[b]Welders and radiologists excluded to exclude presumed x-ray rather than benzene exposure.
[c]Continuous exposure.
[d]Intermittent exposure.
[e]From Wu (1988).
[f]Any versus no exposure.
[g]Over 97.5 percentile versus no exposure.

numbers. Although the comparison between benzene-exposed workers and the general population in Wong's [1987a] study provided evidence against an association with lymphatic and hematopoietic cancers, internal comparisons to the unexposed cohort and, particularly, analyses of risk in relation to cumulative benzene exposure [Wong, 1987b]

TABLE V. Results of Studies Reporting on Benzene and Specific Histologic Types of Leukemia

First author (year)	Study setting	Exposed cases	Relative risk	95% CI
Lymphocytic				
Checkoway (1984)	Industry	4	2.5	NA
Ott (1989)	Industry	2	1.5	NA
Chronic Lymphocytic				
Girard (1970)	Community	9	3.7	1.2–10.7
Linet (1987a)	Community	60[a]	1.4	0.9–2.2
		43[b]	1.5	0.9–2.5
		31[c]	0.9	0.5–1.5
Malone (1989)	Community	NA	1.1	0.6–2.0
Myeloid				
Ciccone (1993)	Community	9	1.7	0.6–5.5
Bond (1986)	Industry	4	4.4	1.2–11.4
Austin (1986)	Industry	15	NA	NA
Ott (1989)	Industry	5	1.0	NA
Acute				
Girard (1970)	Community	17	3.0	1.1–8.1
Richardson (1992)	Community	22[d]	1.3	0.8–2.3
		15[e]	2.8	1.3–5.9
Aksoy (1974)	Industry	26	2.2	1.4–3.2
Acute Myeloid				
Flodin (1986)	Community	0	0.0	—
Crane (1989)	Community	6	1.1	0.3–3.8
Crane (1992)	Community	4	3.3	0.5–22.3
Wong (1995)	Industry	6	5.0	1.8–11.0

[a]Calculated from Table 4 based on self-reported exposure.
[b]Based on Hoar et al. (1980) job-exposure matrix.
[c]Based on National Occupational Hazards Survey (Sieber et al., 1991) job-exposure matrix.
[d]Any exposure.
[e]Medium or high exposure.

TABLE VI. Results of Studies Reporting on Benzene and Non-Hodgkin's Lymphoma

First author (year)	Study setting	Disease group[a]	Exposed cases	Relative risk	95% CI
Girard (1970)	Community	LS/RS	1	0.8	0.1–7.4
Vianna (1979)	Community	LS	499	2.0	1.8–2.1
Schumacher (1988)	Community	LS/RS, Other LC	56[b]	0.8	0.5–1.1
			10[c]	0.9	0.4–2.1
Siemiatycki (1991)	Community	All NHL	26[d]	0.7	0.5–1.1
			6[e]	0.8	0.3–1.9
Scherr (1992)	Community	All NHL	NA	1.2	0.5–2.6
Blair (1992)	Community	All NHL	153	1.1	0.9–1.4
Checkoway (1984)	Industry	LS	6	3.0	NA
Bond (1986)	Industry	LS/RS	2	1.8	0.2–6.6
Wong (1987a)	Industry	LS/RS	3[f]	1.1	0.2–3.3
			1[g]	1.2	0.0–6.4
Ott (1989)	Industry	All NHL	5	1.0	NA
Greenland (1994)	Industry	All NHL	NA	1.0	0.2–4.5

[a]LS, lymphosarcoma; RS, reticulsarcoma; LC, lymphatic cancer; NHL, non-Hodgkin's lymphoma.
[b]Whites, 95% CI estimated based on 90% CI.
[c]Blacks, 95% CI estimated based on 90% CI.
[d]Any exposure, 95% CI estimated based on 90% CI.
[e]Substantial exposure, 95% CI estimated based on 90% CI.
[f]Continuous exposure.
[g]Intermittent exposure.

support a positive association with relative risks in the range of 2–5 in the most highly exposed groups. Overall, given the diversity of methods and likely bias toward the null from nondifferential exposure misclassification, the replicated evidence of increased risk is notable across a series of relatively high-quality industry-based studies.

Leukemia in the aggregate provides stronger evidence for an increased risk, with relative risks above 2 in two community-based studies [Girard and Revol, 1970; Linos et al., 1980] and four industry-based studies [Rushton and Alderson, 1981; Decouflé et al., 1983; Yin et al., 1989; Paxton et al., 1994] (Table IV). Two studies yielded relative risk estimates of 1.5 to 2.0 [Ishimaru et al., 1971; Bond et al., 1986], but several studies generated relative risk estimates near or below 1.0. The comparison of benzene-exposed workers to the general population yielded the relative risk estimates reported for Wong [1987a] in Table IV, with internal cohort comparisons not calculable due to an absence of cases in the unexposed cohort, but dose-response analyses showing a concentration of risk in the most highly exposed group [Wong, 1987b]. For example, in the group with over 720 ppm-months of occupational benzene exposure, the SMR was 2.8 (95% confidence interval 0.6–8.1), based on three observed cases.

Analysis of specific cell types of leukemia provides the most direct suggestion of a general rather than specific association of benzene with leukemia (Table V). Studies grouped leukemias in different ways, e.g., aggregating all lymphatic or all acute leukemias, so that the number of reports for individual cell types is limited. Also, imprecision is more problematic for specific histologic types of leukemia than for leukemia in the aggregate. Both studies examining lymphocytic leukemia and two of three studies addressing chronic lymphocytic leukemia generated relative risks of 1.5 or more. Two of four studies of myeloid leukemia and acute myeloid leukemia met this criterion, whereas all three studies generated relative risks of 2 or more for acute

TABLE VII. Results of Studies Reporting on Benzene and Multiple Myeloma

Reference (year)	Study setting	Exposed cases	Relative risk	95% CI
Linet (1987b)	Community	NA	1.2	0.4–3.6
Heineman (1992)	Community	137[a]	1.3	1.0–1.6
		52[b]	0.8	0.6–1.1
Ott (1989)	Industry	5	1.4	NA
Wong (1995)	Industry	4	2.9	0.8–7.5

[a]Possible exposure.
[b]Probable exposure.

leukemia. The quality of studies is quite mixed, limited particularly for the community studies which contribute over half of the relative risk estimates, perhaps because it is difficult to accrue a sufficient number of cases in industry-based studies to examine specific histologic types of leukemia. The overall pattern does not indicate an association limited to AML, with the evidence for lymphocytic leukemia similar to that for myeloid leukemia.

Non-Hodgkin's lymphoma was generally not associated with an overall elevated relative risk (Table VI), with only three studies providing support for such an association [Vianna and Polan, 1979; Checkoway et al., 1984; Bond et al., 1986] and a number of well-designed, large studies failing to report increased risks [Schumacher and Delzell, 1988; Siemiatycki, 1991; Blair et al., 1992].

Multiple myeloma, first linked to benzene in the report of two cases by DeCouflé et al. [1983] was strongly associated with benzene exposure in the study of Pliofilm workers [Rinsky et al., 1987; Wong, 1995], in which four cases were observed versus 1.37 expected (Table VII). Other studies [Linet et al., 1987; Ott et al., 1989; Heineman et al., 1992] found only very weak associations (relative risks under 1.5).

DISCUSSION

The pattern of epidemiologic study results across broad and narrow groups of lymphatic and hematopoietic cancers does not lead to a conclusion that benzene is a cause of AML alone. Considering the strength and precision of associations, the data are most supportive of a rather broad effect on lymphatic and hematopoietic cancers or leukemia in general. Since these diseases are subsets of one another, extremely strong associations for AML would have to influence the total leukemia results, which would, in turn, influence the results for all lymphatic and hematopoietic cancers. However, the diseases are not quantitatively dominant subsets, with AML making up approximately 24% of all leukemias, and leukemias making up 41% of all lymphatic and hematopoietic cancers [Young et al., 1981]. Thus, although these findings reflect overlapping groups, they do not simply indicate an association with a single subset of cases. Wong [1995] recently highlighted the strong association between benzene exposure and AML in the Pliofilm cohort (six observed, 1.19 expected, relative risk of 5.03), yet by subtraction from the observed and expected numbers of total leukemias [Paxton et al., 1994], the residual of leukemias other than AML are also associated with benzene exposure (eight observed, 2.70 expected, relative risk of 2.96) [Savitz and Andrews, 1996]. The perception that the association between benzene and AML dominates the overall pattern of epidemiologic study results is not supported by our review.

Restricting our analyses to epidemiologic studies excludes a number of lines of evidence. Extensive laboratory research [Goldstein, 1988] was not considered, even though such studies provide an important component of the overall assessment of the health effects of benzene. Case series on benzene and leukemia provide evidence both for specific associations with AML as well as other cell types of leukemia [International Agency for Research on Cancer, 1982], but were not included in the tabulations unless explicit comparison was made of risk among exposed and unexposed individuals. Even epidemiologic studies of industries in which benzene is known to have been used were excluded unless benzene was examined explicitly. The extensive data from the petroleum industry [Delzell et al., 1988; Savitz and Moure, 1984] and rubber industry [McMichael et al., 1976] are potentially relevant to assessing the health risks associated with benzene, but without some restriction to the subsets of workers with benzene exposure the data are difficult to apply.

We did not exclude any studies for failure to meet minimum quality criteria. Exposure assessment, particularly in community-based studies, is subject to substantial error and may well reach a point at which the authors' assertions that benzene is under investigation can be challenged. Inferences based on aggregations of job titles, without careful review by industrial hygienists [Vianna & Polan, 1979] or other corroboration of inferences regarding benzene exposure, are subject to a great deal of uncertainty. Self-reported exposure of cases and controls [Girard and Revol, 1970; Malone et al., 1989] may be superior to assessment by job title if the study subjects have sufficient understanding of their work environment. The optimal approach in community-based studies is the synthesis of self-report with expert evaluation [Siemiatycki, 1991] or specialized questionnaires designed to elicit essential information for assessment of exposure [Stewart and Stewart, 1994]. Few community-based studies attained that level of quality. Where cases and controls contribute subjective information, there is the potential for biased reporting (over-reporting of exposure by cases) and falsely elevated associations. Otherwise, for inferences based on job titles or

other more objective data, the errors are likely to be similar for cases and controls and the resulting bias toward failing to identify associations that are truly present.

Industry-based studies have used more objective exposure assessment methods, relying on blinded coding by experts or inferring exposure based on job characteristics. Some involvement with exposure assessment experts was almost always involved, ensuring a higher minimum quality. Nonetheless, even with certainty that benzene is present in the work environment and that some individuals are exposed, there is often substantial uncertainty regarding which individual jobs involved exposure to benzene and the magnitude of that exposure. Quantitative inferences relating levels of benzene exposure to risk of cancer is impossible in all but a few of the epidemiologic studies reviewed [Paustenbach et al., 1994]. Given the diversity of approaches to exposure assessment and their varying quality, the potential for the intensity and accuracy of exposure assessment to produce notably different risk estimates should be noted.

Failure to isolate benzene from closely associated agents that may themselves cause lymphatic and hematopoietic cancers could introduce confounding. In the rubber industry, for example, associations between benzene and lymphocytic leukemia were reported [Checkoway et al., 1984], yet other solvents were as or more strongly associated with lymphocytic leukemia, making isolation of the etiologic agent difficult. Environments associated with the petrochemical industry, shoe manufacturing, and painting contain a wide array of organic solvents and other potentially carcinogenic chemicals which were not fully addressed in the published reports. In fact, no matter how carefully job titles and work settings are examined, the ability to isolate benzene from concomitant exposures will be limited.

Diagnostic quality of lymphatic and hematopoietic cancers can be problematic, especially in past time periods and for deaths rather than incident cases. Diagnoses would generally be superior in community-based studies in which incident cases are identified through hospital records or tumor registries. Although death certificates, typically used in industry-based studies, are accurate for broad groupings like leukemia, they are subject to substantial error in making inferences about specific histologic types of leukemia [Percy et al., 1981]. Such misclassification across histologic types would tend to dilute associations that occur only within a specific subtype of leukemia, and reduce precision if many cases are relegated to the ''unspecified'' category.

The methods for identifying all relevant research to be included in this review are vulnerable to bias as well. The decision of the authors to publish articles and include selected results may be affected by the pattern of those results. Evaluations of benzene and cancer that did not produce positive associations may have been less likely to be published given the general knowledge that benzene is carcinogenic. Even in studies that were published, the decision to provide results specifically for benzene among an array of agents of interest may have been influenced by whether an association was found. One might expect such bias to be strongest for AML, in which failure to find associations is seen as aberrant.

In light of the research findings reviewed here, sufficient uncertainty remains to encourage additional study with refined exposure assessment. Clarification of the pattern of benzene associations with specific leukemia and lymphoma cell types requires extremely large studies, so that cohort studies with sufficient statistical precision are required. If based on mortality as the endpoint, such studies may be lacking in sufficient diagnostic precision to address this issue. Community-based case-control studies, which have the potential for attaining adequate study size and accurate diagnoses, are severely limited in their ability to assess exposure across diverse industries. Although a number of agents have been effectively reconstructed by experts [Gerin et al., 1984], benzene poses particular challenges: It was rarely used in pure form, but as one among several solvents; it is no longer used as a commercial solvent, so that present-day measurements provide no information relevant to past exposures; and the benzene levels of concern are relatively low. In spite of limitations, mortality follow-up of historically exposed cohorts should continue, with attention to identifying diagnostic subtypes of these cancers, as well as refined exposure assessment in community-based studies. Even where exposure has terminated, continued follow-up is warranted to fully understand the long-term consequences of benzene exposure.

A recently completed study in China may provide the clearest evidence to date regarding benzene and lymphatic and hematopoietic cancers [Yin et al., 1994; Dosemeci et al., 1994]. Methods, but not detailed results, from this large cohort and nested case-control study of multiple factories have been described, and it promises to provide refined exposure and cancer data on a cohort of nearly 80,000 exposed men and women, as well as 36,000 unexposed workers [Yin et al., 1994]. Differences in leukemia cell type distributions between Caucasian and Chinese populations, however, may affect the generalizability of their results, at least in regard to the types of leukemia affected by benzene exposure.

CONCLUSION

The epidemiologic evidence linking benzene to leukemia in the aggregate, as well as acute and chronic lymphocytic and myeloid leukemia, is no less persuasive than that for AML alone. Specificity of association was once cited as a hallmark of causality [Hill, 1965], yet with expansion of knowledge regarding agents such as tobacco, ionizing radiation, and asbestos, the criterion of specificity has little

value. By analogy with other known carcinogens, it would be surprising if benzene's only carcinogenic effect was on AML. Limitations in the literature, particularly in regard to exposure assessment and the ability to isolate benzene from concomitant workplace exposures, preclude more definitive conclusions.

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