Cell-Type-Specific Leukemia Analyses in a Combined Cohort of More Than 208,000 Petroleum Workers in the United States and the United Kingdom, 1937–1989

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A large number of epidemiologic studies of workers in the petroleum industry have been conducted to investigate the carcinogenic and other health effects of exposure to petroleum products during manufacture and distribution. Of particular interest is the relationship between exposure to benzene or benzene-containing liquids in the petroleum industry and leukemia risk. However, few studies have investigated cell-type-specific leukemia risk. In the present investigation, all cohort studies of petroleum workers in the United States and the United Kingdom were combined into a single database for cell-type-specific leukemia analysis. The majority of these workers were petroleum refinery employees, but production, pipeline, and distribution workers in the petroleum industry were also included. The combined cohort consisted of 208,741 petroleum workers. Between 1935 and 1989, these workers contributed a total of 4,665,361 person-years of observation. More than 36 thousand deaths were reported among these workers during the 53 years of observation. Cell-type-specific leukemia risks were calculated using a meta-analysis procedure appropriate for combining occupational cohort studies. These risks were expressed in terms of cell-type-specific leukemia standardized mortality ratios (meta-SMRs). The meta-SMR for acute myelogenous leukemia was 0.96. The lack of an increase of acute myelogenous leukemia was attributed to the low levels of benzene exposure in the petroleum industry, particularly in comparison to benzene exposure levels in some previous studies of workers in other industries, who had been found to experience increased risk of acute myelogenous leukemia. Similarly, no increase in chronic myelogenous, acute lymphocytic, or chronic lymphocytic leukemias was found in petroleum workers (meta-SMRs of 0.89, 1.16, and 0.84, respectively). Meta-analyses restricted to refinery studies or to studies with at least 15 years of follow-up yielded similar results. The findings of the present investigation are consistent with those from several recent case-control studies.

INTRODUCTION

Workers in the petroleum industry are potentially exposed to hydrocarbons through inhalation of vapors from as well as dermal contact of crude oil, feed stocks, intermediate products during refining, and end products, such as gasoline (Runion, 1988; Raabe, 1993). Of special concern is benzene, which has been linked to an increased risk of leukemia, particularly acute myelogenous leukemia (AML). The first case report suggesting an association between exposure to benzene and leukemia appeared in 1928 (Delore and Borgomano, 1928). In the following years, additional case reports were published (Hunter, 1939; Vigliani and Saita, 1964; Browning, 1965; Gouguel *et al.*, 1967; Girard and Revol, 1970; Aksoy *et al.*, 1972). Most case reports were from England, Italy, France, and Turkey. Documentation, if any at all, of exposures to benzene or benzene-containing mixtures in these case reports was extremely poor. Furthermore, these reports lacked information concerning the size of population at risk, and, therefore, no risk estimates could be derived. Thus, case reports by themselves do not provide definitive evidence for causation but rather suggest potential areas for future epidemiologic research. One observation, however, emerged from these case reports: The predominant cell type of the reported leukemia cases was AML.

It was not until the 1970s that epidemiologic studies of individuals exposed to benzene were carried out. Judging by present day standards, some of the early studies were rather crude. For example, in the Thorpe (1974) study of leukemia incidence among employees at eight Esso petroleum affiliates in Europe, only active employees and annuitants, but not separated employees, were included. Furthermore, person-years of observation were estimated and not actually calculated. Similarly, in the Infante et al. (1977) study of rubber hydrochloride workers exposed to benzene at two Pliofilm manufacturing plants in Ohio, the cohort was incomplete (an unknown number of employment records were missing and no maintenance workers were included). Furthermore,

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mortality ascertainment in the Infante *et al.* (1977) study was only 75% complete. Likewise, employment histories were also incomplete. It appeared that some individuals included in the study had worked at the facilities for only a few days. and some might not have worked there at all (Wong *et al.*, 1983). Subsequent updates of the Infante *et al.* **(1977)** study by others (Rinsky *et al.*, 1981,1987) have improved mortality ascertainment. but the cohort incompleteness remained a major limitation of the study.

In a 1983 report. Wong discussed some of the unresolved issues regarding the relationship between benzene and leukemia. The same issues were iterated by a group of scientists convened by the International Agency for Research on Cancer (McMichael, 1988). One of the major issues raised by both Wong (1983) and McMichael (1988) is the relationship, if any. between benzene exposure and leukemia cell types other than AML.

In the past, leukemia was considered a single statistical category in most occupational epidemiologic studies, partly because of the historical nomenclature, unavailability of cell-type-specific rates for comparison and, most importantly, the paucity of cases by cell-type in individual studies (Wong, 1987a,b). Recently epidemiologic studies have demonstrated the importance of cell-type-specific analysis in studying leukemia. It has now been recognized that the diseases collectively known as leukemia are several distinct malignancies with different etiologic factors. Linet (1985) began her bcok on leukemia with the following: "Earlier epidemiologic reviews considered leukemia as a single disease with some minor differences in risk factors for each of the histopathologic types. In the last two decades, epidemiologic studies have provided evidence that diseases collectively identified as leukemia are several distinct malignancies characterized by varying age, sex, race, and ethnic group patterns. dissimilar secular trends, and different etiologic factors." Similarly, the diversity of different types of leukemia has long been recognized by hematologists, as indicated, for example. in the widely used textbook of hematology by Wintrobe *et al.* (1981): "Few authorities would disagree concerning the recognition of chronic myeloid leukemia (CML), acute myeloid leukemia (AML), polycythemia vera (PV), idiopathic myelofibrosis (IMF), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), Hodgkin's disease (HD), the non-Hodgkin's lymphomas (NHL), multiple myeloma (MM), and macroglobulinemia as distinct entities."

The question of whether all leukemia cell types can be affected by a common etiologic agent has also been examined at the cellular level, particularly with respect to hemopoietic stem cells. There are two types of stem cells: the pluripotential stem cells, which are responsible for the production of circulating elements, and their direct descendants, the committed precursor cells which are programmed to follow a single line of differentiation. Both *in vivo* and *in vitro* studies have indicated that th committed stem (precursor or progenitor) cells are capa ble of self-renewal and amplification. Previously a num ber of hypotheses have been proposed regarding the pos sible role of stem cells in benzene leukemogenesis. How ever. in most of these hypotheses little or no distinction was made between the pluripotential and the committed stem cells. Recent research has indicated that the com mitted stem cells or progenitor cells play an importa t part not only in the maintenance of normal. steady-st te hemopoiesis but also in the etiology of cell-type-specific leukemias.

Based on an investigation of immunoglobulin gene organization and expression in hemopoietic stem cell leukemia, Ford *et al.* (1983) have demonstrated that a clonal event leading to blast crisis can occur in a committed B cell precursor rather than in the pluripotential stem cell precursor. Similarly, based on human DNA analyses, Maher *et al.* (1993) concluded that CML and CLL do not arise from a common progenitor and that these malignancies arise from separate stem cells. Thus. recent advances in these areas confirm the epidemiologic observation that "leukemia" is a group of distinct malignancies. which should be analyzed separately.

The need to analyze leukemia data by cell type in relation to occupational exposures such as benzene has created some interesting challenges to epidemiologists. Workers in the petroleum industry represent one of the largest populations exposed to benzene. Numerous studies based on petroleum workers have been conducted in the United States and in the United Kingdom. Even though most of these studies consist of several thousanc workers who have been observed over several decades few individual studies offer adequate data for cell-type-specific analysis. The objective of the present investigation is to combine all the studies of petroleum workers in the United States and in the United Kingdom into a single large database, which can then be analyzed to evaluate cell-type-specific leukemia risks in these petroleum workers.

MATERIALS AND METHODS

Based on a consideration of both study design and data quality, only cohort studies were included in the analysis. Studies based on proportional mortality ratios (PMRs) were excluded from analysis because of the following limitations. In addition to the well-known methodological deficiencies of PMR studies (Wong and Decoufle, 1983; Wong *et al.*, 1985). some of the PMR studies of petroleum workers also suffered from incomplete ascertainment of deaths (Reeve *et al.*, 1982; Thomas *et al.*, 1980, 1982; Wong and Tabershaw, 1980). Furthermore, employment histories were not available in these PMR studies, and analyses were limited. Finally. the petroleum refineries included in these PMR studies have subsequently been studied more thoroughly with the cohort study design.

TABLE 1
Description of Epidemiologic Study Cohorts in the Petroleum Industry in the United States and the United Kingdom

	Cohort location	Number of workers	Observation period	Person-years	Total deaths	References
	10 retineries in US	10.763	1970–1986	125.241	1.405	Hornstra, 1990; Nelson, 1985
	El Segundo (CA) refinery	4,773	1950–1986	110.594	1.121	Dagg *et al.*. 1992: Wong *et al.*. 1986
	Richmond (CA) refinery	8.523	1950–1986	205.397	2,038	
	Port Arthur (TX) refinery	17,344	1937–1987	526,386	6,799	Satin *et al.*. 1994: Wen *et al.*, 1983
	Baton Rouge (LA) refinery	9.894	1970–1982	93.783	2.000	Shallenberger *et ai.*. 1992: Hanis *et al.*. 1982. 1985a.b
	Baytown (TX) refinery	8,722	1970–1982	80.684	1.374	
	Bayway (NJ) refinery	6.860	1970–1982	59.257	1,326	
	Beaumont (TX) refinery	7,119	1945–1987	166.427	2,194	Raabe *et al.*. 1994: Milcarek *et ai.*, 1994: Collingwood et al.. 1994; Morgan and Wong, 1984.1985a; Enterline and Henderson, 1985
	Paulsboro (NJ) refinery	4,855	1946–1987	120,718	1.681	
	Torrance (CA) refinery	1,991	1959–1987	33.331	408	
	2 California refineries	4,585	1973–1989	57,657	1.051	Tsai *et al.*, 1993; Marsh *et al.*, 1991: Honda *et al.*, 1995: Wongsrichanalai *et al.*, 1989: McCraw *et al.*, 1985: Joyner, 1983
	Deer Park (TX) refinery	6,831	1948–1983	181.782	1.180	
	Woodriver (IL) refinery	9,796	1940–1989	300,991	3.627	
	13 refineries in US	19,077	1947–1977	358,318	4,024	Divine *et al.*, 1985
	Production & pipeline in US	11,098	1946–1980	220,414	1,386	Divine and Barron. 1986, 1987
. Petroleum	Land-based terminals in US	9.026	1946–1989	239.125	2.066	Wong *et al.*, 1993; Wong and Trent, 1993
	Marine vessels in US	9.109	1946–1989	227,143	2,695	
Petroleum	8 refineries in UK	34,569	1951–1989	931,640	10,193	Rushton, 1993a,b,c; Rushton and Alderson, 1981,1983
	Distribution centers in UK	23.306	1951–1989	626.471	8,743	
	US and UK petroleum workers	208.741	1937–1989	4,665,361	56,411	

In addition to cohort and PMR studies, there were ... number of community-based case-control studies ...-type-specific leukemias, which included petro-... or petroleum-related occupations in the analyses. Most of these studies did not provide adequate information about the nature of exposure or details of employment. Methodological problems (such as control selection, recall of employment histories, adjustment of confounding factors) further complicated the interpretation. Therefore, case-control studies were not in-...ed in the quantitative analysis, but formed part of the basis of discussion.

A couple of reports based on linkage between tumor registry and census data have also been published (Olsen and Jensen, 1987; Jakobsson *et al.*, 1993). The Olsen and Jensen (1987) survey reported a deficit of acute leukemia in men employed at gasoline stations in Denmark, whereas the Jakobsson *et al.* (1993) survey reported an increased risk of acute myeloid leukemia in petrol station attendants in Finland. Both surveys were judged to be inadequate. Using occupational information derived from census data as a surrogate for exposure to specific chemicals can introduce substantial misclassification.

leukemia cases in certain industries based on census data involves a potentially substantial amount of inaccuracy. The problem of multiple comparisons based on the large number of cancer sites and industries or occupations examined further weakens the statistical findings from these surveys. As such, these reports are inadequate in assessing leukemia risk due to exposure to specific chemicals.

In the present investigation, a meta-analysis procedure was used in combining data from individual cohort studies of petroleum workers. The methodological details of the meta-analysis have been described elsewhere (Wong and Raabe, 1989). Data needed to carry out the meta-analysis included observed leukemia deaths by cell type and the distribution of age-specific person-years from each individual study. These data were usually not presented in published reports. Instead, such data were requested from the original investigators. For some studies, multiple reports on various portions of the cohort and/or updates were available. For the present analysis, data for the entire cohort based on the latest available update were used.

A specific analysis was carried out for each of the four major leukemia cell types (AML, CML. ALL, and CLL). The 8th Revision of the International Classification of Diseases was used in classifying deaths. The codes for AML, CML, ALL, and CLL are 304.0, 204.1, 205.0, and 205.1, respectively. For comparison in the US studies,

TABLE 2

Comparison of Leukemia Cell-Type Distribution between Petroleum Workers and the General Population

Cell type	Petroleum workers: n (%) US	UK	US and UK	% General population
Acute myelogenous leukemia	103 (46%)	45 (45%)	148 (46%)	43
Chronic myelogenous leukemia	43 (19%)	19 (19%)	62 (19%)	19
Acute lymphocytic leukemia	25 (11%)	9 (9%)	34 (10%)	11
Chronic lymphocytic leukemia	55 (24%)	28 (28%)	83 (25%)	28
Total	226 (100%)	101 (100%)	327 (100%)	100

Note. Goodness-of-fit test between the US–UK combined cohort of petroleum workers and the general population, $\chi^2_{3df} = 2.00$ ($P = 0.57$).

age-specific mortality rates for each of the four major leukemia cell types were derived from data provided by the National Center for Health Statistics (Selvin *et al.*, 1983). Although in general the accuracy of diagnosis of leukemia cell types based on death certificates was not as desirable as that based on pathological reports (particularly in the 1940s or 1950s), no potential bias was introduced in the present investigation, since diagnostic information in both petroleum workers and the comparison group (general population) was based on death certificates. Furthermore, the majority of leukemia deaths in petroleum workers occurred in or after the 1960s.

For each US cohort, expected deaths by cell type were calculated by applying US specific rates to person-years. For the UK industrywide studies, cell-type-specific information has been published, and such information was taken directly from the publications (Rushton, 1993a,b,c). One Canadian cohort study (Schnatter *et al.*, 1992) and one Australian prospective survey (Christie *et al.*, 1991; Peach *et al.*, 1992) were not included in the analysis because cell-type-specific leukemia rates for Canada or Australia were not available.

The statistical procedure for meta-analysis consists of summing up the observed and expected deaths for a specific leukemia cell type from individual studies, and calculating the summary or meta-SMR. This simple procedure treats each individual cohort as a separate metastratum in data summarization, thus adjusting for individual studies while preserving the original adjustment using substrata specific to age, sex, race, and time period. In the present investigation, both cell-type-specific leukemia meta-SMRs and their corresponding 95% confidence intervals (95% CI) were calculated. Although other statistical procedures for meta-analysis are available, the meta-SMR procedure was used in this investigation because of its simplicity in computation and interpretation, its preservation of the adjustments in the individual studies, and its resemblance to the analyses in the original studies. Similar procedures have been used previously in analyzing data on asbestos and gastrointestinal cancer (Morgan *et al.*, 1985), artificial sweeteners and bladder cancer (Morgan and Wong, 1985b), formaldehyde and respiratory cancer (Nelson *et al.*, 1986), chemical dyes and bladder cancer (Matanoski and

low, a total of 19 individual cohorts have been included in the database, which means that there would be 76 (19 × 4) cell-type-specific SMRs. Approximately 4 statisti-

RESULTS

Included in the analysis were studies conducted or sponsored by seven major petroleum companies in the United States. Most of these studies consisted of refinery workers (Hornstra, 1990; Nelson, 1985; Dagg et a.

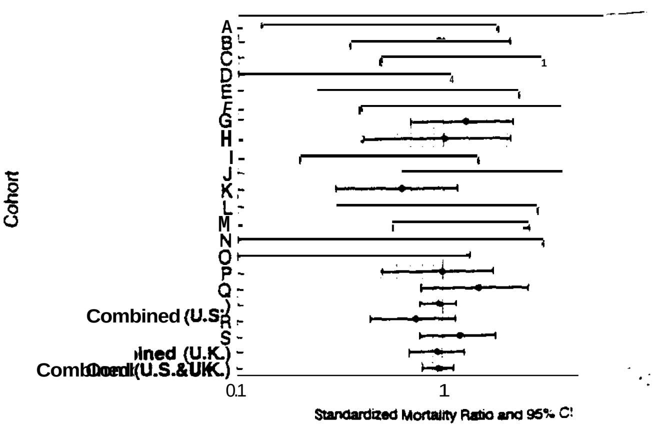

FIG. 1. Acute myelogenous leukemia among petroleum in the United States and the United Kingdom. 1937–1989 studies: R-S. UK studies.

TABLE 3
Meta-analysis of Acute Myelogenous Leukemia in Petroleum Workers in the United States and the United Kingdom, 1937–1989

Country	Cohort	Observed deaths	Expected deaths	SMR	95% CI
US	A	3	4.87	0.62	0.13–1.31
	B	6	6.33	0.95	0.35–2.07
	C	6	4.48	1.34	0.49–2.92
	D	0	3.37	0	0–1.09
	E	4	4.45	0.90	0.24–2.30
	F	4	2.80	1.43	0.39–3.66
	G	14	10.90	1.28	0.70–2.15
	H	[illegible]	6.91	1.01	0.41–2.08
	I	[illegible]	7.88	0.63	0.20–1.47
	J	6	3.56	1.69	0.62–3.68
	K	10	15.95	0.63	0.30–1.16
	L	4	3.65	1.10	0.30–2.82
	M	8	6.15	1.30	0.56–2.56
	N	0	1.23	0	0–3.00
	O	1	4.23	0.24	0.01–1.34
	P	12	12.11	0.99	0.51–1.73
	Q	13	8.81	1.48	0.79–2.53
US combined cohort		103	107.68	**0.96**	0.78–1.16
UK	R	20	26.60	0.75	0.45–1.15
	S	25	20.60	1.21	0.78–1.79
UK combined cohort		45	47.20	0.95	0.70–1.27
US–UK combined cohort		148	**154.88**	0.96	0.81–1.13

1992; Wong *et al.*, 1986: Satin *et al.*, 1994; Wen *et al.*, 1983; Shallenberger *et al.*, 1992; Hanis *et al.*, 1982, 1985a,b; Raabe *et al.*, 1994; Milcarek *et al.*, 1994: Collingwood *et al.*. 1994; Morgan and Wong, 1984, 1985a; Enterline and Henderson, 1983; Marsh *et al.*, 1991: Tsai *et al.*, 1993; Honda *et al.*, 1993: Wongsrichanalai *et al.*, 1989; McCraw *et al.*, 1983; Joyner, 1983; Divine *et al.*, 1985; Divine and Barron. 1986), except one which was based on workers in the production and pipeline division (Divine and Barron, 1987). A study, which was sponsored by the American Petroleum Institute and consisted of a cohort of land-based petroleum distribution workers and a cohort of marine petroleum distribution workers. was also included (Wong *et al.*, 1993: Wong and Trent, 1993). From the United Kingdom, two cohort studies of petroleum refinery and distribution workers sponsored by the Institute of Petroleum were included (Rushton. 1993a,b,c; Rushton and Alderson, 1981. 1983).

Previously Wong and Raabe (1989) provided a meta-analysis of leukemia (all cell types combined) based on studies of petroleum workers available at the time. The total leukemia meta-SMR was 1.12 (not significant) based on 279 deaths. Of the 14 US or UK studies reviewed by Wong and Raabe (1989), 3 refineries (Beaumont, Deer Park and Woodriver) showed a significant increase in total leukemia. Since the Wong and Raabe (1989) review, all but two studies in the United States and in the United Kingdom have been updated. In particular, based on the updated data, the total leukemia SMR for the Beaumont refinery has been reduced from 1.73 ($P < 0.05$) to 1.39 ($P > 0.05$), for the Deer Park refinery from 2.31 ($P < 0.05$) to 0.96 ($P > 0.05$), and for the Woodriver refinery from 2.12 ($P < 0.05$) to 1.23 ($P > 0.05$). Thus, all three significantly elevated leukemia SMRs reported in the 1989 review are no longer statistically significant. Furthermore, the updated Amoco study of 10 US refineries showed a significantly low total leukemia SMR of 0.39. Three new cohorts have been included in the present investigation, and the total leukemia SMRs for all three cohorts were less than 1.0 (Tsai *et al.*, 1993; Wong *et al.*, 1993; Wong and Trent, 1993). The updated total leukemia meta-SMR based on all petroleum cohorts in the United States and the United Kingdom has been recalculated to be 1.02 (498 observed deaths, 95% CI: 0.93–1.11).

Table 1 provides a basic description of the individual US and UK cohort studies included in the present investigation. Although exposure patterns in each cohort might differ, all workers were potentially exposed to benzene-containing petroleum liquids as well as other hydrocarbons. It is quite likely that the "within-cohort" exposure variation is comparable to, if not greater than, the "between-cohort" exposure variation.

In the present investigation, a total of 19 individual cohorts were included in the meta-analyses. The combined cohort consisted of more than 308,000 petroleum workers, with approximately 150,000 from the United States and 58,000 from the United Kingdom. Over an observation period of 53 years (1937–1989), these work-

TABLE 4
Meta-analysis of Chronic Myelogenous Leukemia in Petroleum Workers in the United States and the United Kingdom, 1937–1989

Country	Cohort	Observed deaths	Expected deaths	SMR	95% CI
US	A	0	2.06	0	0–1.79
	B	2	8.85	0.70	0.08–2.53
	C	3	1.97	1.52	0.31–4.44
	D	2	1.55	1.29	0.16–4.66
	E	1	1.98	0.51	0.01–2.84
	F	0	1.26	0	0–2.93
	G	2	4.85	0.41	0.05–1.48
	H	3	3.08	0.97	0.20–2.83
	I	4	3.52	1.14	0.31–2.92
	J	1	1.60	0.62	0.02–3.45
	K	6	7.11	0.84	0.31–1.83
	L	4	1.58	2.53	0.69–6.46
	M	3	2.74	1.09	0.22–3.18
	N	2	0.54	3.68	0.54–13.28
	O	1	1.92	0.52	0.01–2.90
	P	8	5.40	1.48	0.64–2.92
	Q	1	3.95	0.25	0.01–1.39
US combined cohort		43	47.97	0.90	0.65–1.21
UK	R	11	12.30	0.89	0.44–1.59
	S	8	9.70	0.82	0.35–1.62
UK combined cohort		19	82.00	0.86	0.52–1.35
US–UK combined cohort		62	69.97	0.89	0.68–1.15

ers contributed more than 4.6 million person-years. More than 56 thousand deaths were reported in these studies. In particular, 498 deaths were ascribed to leukemia. Based on information available, 327 (66%) leukemia deaths among the petroleum workers were classifiable into one of the four major cell types: AML, CML, ALL, and CLL. Thus, 34% leukemia deaths in petroleum workers belonged to other or unspecified cell types. According to data provided by the National Center for Health Statistics (1990), the corresponding figure in the general population was similar (32–34%).

The distributions of leukemia deaths among the US and the UK petroleum workers by the four major cell-types were very similar (Table 2). The cell-type distribution for the US–UK combined cohort of petroleum workers was also similar to that in the general adult population (aged 13 or older), which was derived from Selvin *et al.* (1983). A formal goodness-of-fit test between the US–UK combined cohort of petroleum workers and the general population indicated that there was no significant difference between the two distributions (χ^2_{3df} = 2.00, P = 0.37).

Table 3 and Fig. 1 present the results of AML analysis for individual cohorts as well as for the combined cohorts. Because of the logarithmic scale, for SMRs less than 0.1, neither the point estimate nor the lower 95% confidence limit is presented in the figure. The number of observed AML deaths in each cohort ranged from 0 to 25. No significantly elevated AML SMR was detected for any cohort. For Cohort D, no AML deaths were observed, and, based on 3.37 expected, this deficit was almost statistically significant (SMR = 0, 95% CI: 0–1.09, P = 0.06). For the US combined cohort, 103 AML deaths were reported, compared to 107.68 expected. The corresponding AML meta-SMR for the US combined cohort was 0.96, with a 95% CI of 0.78–1.16. The UK combined cohort yielded similar results for AML (meta-SMR = 0.95, 95% CI: 0.70–1.27). For the US–UK combined cohort, there were 148 observed AML deaths, which were comparable to the 154.88 expected, and the meta-SMR for AML was 0.96 (95% CI: 0.81–1.13).

Results based on a similar analysis for CML are shown in Table 4 and in Fig. 5. In the United States, most cohorts contributed fewer than 5 CML deaths each, and the highest number of 8 observed CML deaths was reported in Cohort P. No significant CML SMR was found in any of the individual cohorts. For the US combined cohort, 43 observed deaths were ascribed to CML, whereas 47.97 CML deaths were expected. For the US combined cohort, the CML meta-SMR was 0.90, and the 95% CI was 0.65–1.21. For the UK combined cohort, the meta-SMR for CML was 0.86 (19 observed vs 23.00 expected, 95% CI: 0.52–1.35). For the US–UK combined cohort, a total of 62 CML deaths were observed, compared to 69.97 expected. The CML meta-SMR for all petroleum workers was 0.89 (95% CI: 0.68–1.15).

ALL accounted for only 10 to 11% of the 3 major cell types combined in both the petroleum workers and in the general population (Table 3). The number of ALL deaths in each individual study was extremely small. No

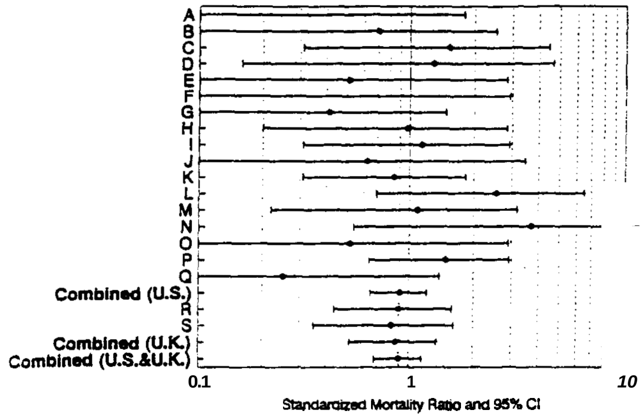

FIG. 2. Chronic myelogenous leukemia among petroleum workers in the United States and the United Kingdom. 1937–1989. **A–Q,** US studies; R–S, UK studies.

more than *2* ALL deaths were reported in most cohorts, and 6 cohorts reported no ALL deaths at all (Table 3 and Fig. 3). In Cohort K, however, 8 ALL deaths were observed, compared to 3.08 expected. The ALL SMR for Cohort K was 2.60 (95%CI: 1.12–5.11). No other cohort reported a significant ALL SMR. In the US combined cohort, 25 ALL deaths were reported, slightly higher than the 20.36 expected. The ALL meta-SMR for the US combined cohort was 1.23, which was not significant (95% CI: 0.79–1.81). The ALL meta-SMR for the UK combined cohort was slightly less (meta-SMR = 0.99, 95% CI: 0.45–1.88). In the overall combined cohort of both US and UK petroleum workers, the observed number of ALL deaths was **34,** whereas the expected number was '79.36: and the ALL meta-SMR was 1.16 (95% CI: 0.81–1.61).

Table **6** and Fig. 4 present the results of the CLL analysis. In the United States, most individual cohorts reported 4 or fewer CLL deaths. Of the 17 US cohorts, 13 reported a lower than expected CLL mortality. In fact, Cohort K reported a significantly low CLL SMR of 0.30 (3 observed vs 10.04 expected, **95%** CI: 0.06–0.87). On the other hand, Cohort C reported a significantly high CLL SMR of 5.59 (9 observed **vs** 3.48 expected. 95% CI: 1.18–4.91). A total of 55 CLL deaths were observed in the US combined cohort, almost significantly less than the 69.19 expected (meta-SMR = 0.79, 95% CI: 0.59–1.03). There were 28 observed CLL deaths in the UK combined cohort, slightly less than the 29.70 expected (meca-SMR = 0.94, 95% CI: 0.63–1.36). In the US–UK combined cohort, 83 CLL deaths were observed, whereas 98.89 were expected; and the CLL meta-SMR was 0.84 (95% CI: 0.67–1.04).

The above meta-analyses were based on all 19 cohorts of petroleum workers, including refinery, production and pipeline, and distribution workers. If the meta-analyses were restricted to the 15 refinery cohorts (14 from the

TABLE 5
Meta-analysis **of** Acute Lymphocytic Leukemia in Petroleum Workers in the United States **and the** United Kingdom, 1937–1989

Country	Cohort	Observed deaths	Expected deaths	SMR	95% CI
US	A	0	0.84	0	0–4.39
	B	1	1.22	0.82	0.02–4.57
	C	1	0.89	1.12	0.03–6.24
	D	0	0.70	0	0–5.27
	E	1	0.83	1.20	0.03–6.68
	F	0	0.54	0	0–6.83
	G	3	2.02	1.49	0.31–4.36
	H	1	1.32	0.76	0.02–4.23
	I	1	1.47	0.68	0.02–3.79
	J	2	0.68	2.96	0.36–10.69
	K	8	3.08	2.60*	1.12–5.11
	L	0	0.69	0	0–5.35
	M	0	1.17	0	0–3.15
	N	0	0.23	0	0–16.04
	O	2	0.82	2.45	0.30–8.84
	P	3	2.14	1.40	0.29–4.09
	Q	2	1.62	1.23	0.15–4.44
US combined cohort		25	20.26	1.23	0.79–1.81
UK	R	4	5.30	0.75	0.20–1.92
	S	5	3.80	1.32	0.43–3.08
UK combined cohort		9	9.10	0.99	0.45–1.38
US–UK combined cohort		34	29.36	1.16	0.81–1.61

* $P < 0.05$.

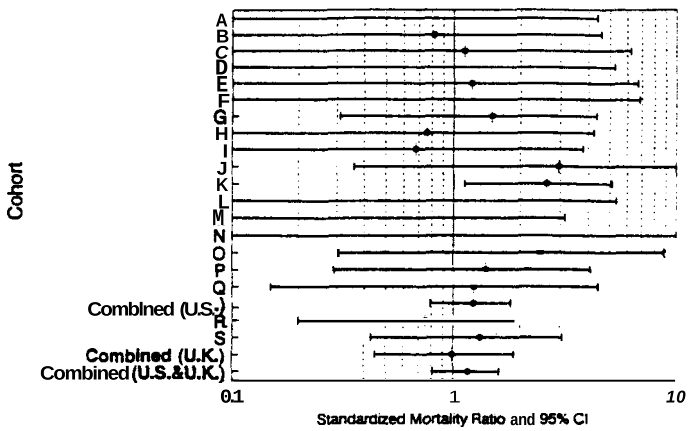

FIG. 3. Acute lymphocytic leukemia among petroleum workers in the United States and the United Kingdom, 1937–1989. A–Q. US studies; R–S. UK studies.

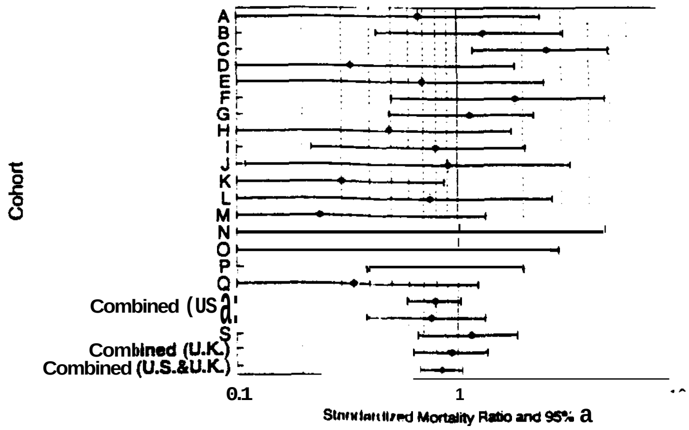

FIG. 4. Chronic lymphocytic leukemia among petroleum workers in the United States and United Kingdom, 1937–1989. A–Q. US studies: R–S, UK studies.

US and 1 from the UK), the cell-type-specific leukemia results remained essentially unchanged. The meta-SMRs for petroleum refinery workers in the United States and in the United Kingdom were 0.93, 0.94, 1.32, and 0.87 for AML, CML, ALL, and CLL, respectively (Table 7). None of the meta-SMRs for the US–UK combined cohort of petroleum refinery workers was statistically significant.

Among the 19 cohorts included in the analysis. length of follow-up ranged from 13 to 51 years. A separate analysis was carried out based on cohorts with at least 15 years of follow-up. Using this criterion, 3 cohorts were excluded. The results of this analysis based on cohorts with 15+ years of follow-up are presented in Table 8. The results for follow-up of 15+ years remained essentially the same.

DISCUSSION

The combined database in the meta-analysis represented one of the largest databases in epidemiologic

TABLE 6
Meta-analysis of Chronic Lymphocytic Leukemia in Petroleum Workers in the United States and the United Kingdom, 1937–1989

Country	Cohort	Observed deaths	Expected deaths	SMR
US	A	2	2.97	0.67
	B	3	3.79	1.32
	C	9	3.48	2.59*
	D	1	3.00	0.33
	E	2	2.92	0.69
	F	4	2.18	1.84
	G	8	6.99	1.14
	H	2	4.10	0.49
	I	4	4.99	0.80
	J	2	2.19	0.91
	K	3	10.04	0.30'
	L	2	2.67	0.75
	M	1	4.09	0.24
	N	0	0.79	0
	O	1	1.91	0.52
	P	[illegible]	7.22	0.97
	Q	2	5.87	0.34
US combined cohort		55	69.19	0.79
UK	R	12	15.80	0.76
	S	16	13.90	1.15
UK combined cohort		28	29.70	0.94
US–UK **combined cohort**		83	98.89	0.84

* $P < 0.05$.

TABLE 7
Meta-analysis of Cell-Type Specific Leukemias in Refinery Workers in the United States and the United Kingdom. 1937–1989

Cell type	Observed deaths	Expected deaths	Meta-SMR	95% confidence interval
...genous leukemia	78	84.08	0.93	0.73–1.16
...elogenous leukemia	35	37.42	0.94	0.65–1.31
...monocytic leukemia	21	15.85	1.32	0.81–2.01
...mphocytic leukemia	47	54.23	0.87	0.64–1.16

...n. Even though most of the individual cohorts were ...ely large, it is evident from Tables 3–6 that most ...cell-type-specific leukemia SMRs based on indi... cohorts were unstable, as most were based on ... numbers of deaths (particularly for ALL). One of ...ajor advantages of the meta-analyses carried out in ...present investigation is the stability of the combined ...

...h regard to cell-type-specific leukemia analyses, ...statistical power of the individual cohorts was lim... This was particularly true for the US cohorts, most ...ich were individual company or individual refinery ...es. The two UK studies were larger because they ... industrywide studies consisting of workers from ...eral companies. Based on the average of the 17 indi...al cohorts in the United States, the minimum SMR ...ectable at $a = 0.05$ and $3 = 0.20$ in an individual co... were 2.22, 3.02, 4.57, and 2.61 for AML, CML, XLL. ... CLL, respectively. All of these SMRs were higher ... twofold. The inadequacy of statistical power of in...ual studies was particularly evident for ALL.

...atistical power increased substantially by combin... the 17 US cohorts. Table 9 presents the minimum ...ectable SMRs at $a = 0.05$ and $\beta = 0.20$ for each of the ... major cell types. For AML, the US combined cohort ...vides sufficient statistical power (80% power at the ... level) to detect a risk ratio as small as **1.25**, if indeed ...there was an increased risk. Based on the US combined ...rt. the minimum detectable SMRs were 1.39 for ... and 1.32 for CLL, respectively. Even for XLL. the ... frequent cell type, the minimum detectable SMR ...ased on the US combined cohort was 1.63. All the min...um detectable SMRs based on the US combined cohort were less than twofold. The statistical power of the UK combined cohort was somewhat lower (Table 9). In the overall US–UK combined cohort of petroleum workers, the minimum detectable SMRs were 1.21, 1.32, 1.51, and 1.26 for AML, CML, ALL, and CLL, respectively. Thus, the absence of an increased risk of AML, CML, ALL, or CLL in petroleum workers in the United States or in the United Kingdom based on the meta-analyses in the present investigation could not be attributed to inadequate statistical power.

One may question why an increased risk of AML was not observed in petroleum workers, who were certainly exposed to some levels of benzene. The answer probably lies in the threshold of benzene exposure required to produce a significant increase of AML. To estimate the threshold, the data from the study of Pliofilm workers exposed to benzene (Rinsky *et al.*, 1987) updated through 1987 were analyzed specifically for AML. For the Pliofilm cohort as a whole, 6 deaths from AML were observed. compared to 1.19 expected (Table 10). The corresponding AML SMR of 5.03 was statistically significant. However, exposure–response analysis indicated that no increase of AML was detected for cumulative exposure below 200 ppm-years (SMR = 0.91). Furthermore. the exposure levels provided by Rinsky *et al.* (1987) were likely underestimated, and more realistic exposure estimates have been developed by others (Crump and Allen, 1984; Paustenbach *et al.*, 1992). Had the other exposure estimates been used, the observed AML threshold would have been much higher. Emerging evidence *in* the biologic search for a mechanism of benzene-induced AML suggests that benzene and its metabolites may induce AML via toxic disruption of regulatory

TABLE 8
Meta-analysis of Cell-Type-Specific Leukemias in Petroleum Workers in the United States and the United Kingdom. 1937–1989, Based on Cohorts with 15 or More Years of Follow-up

Cell type	Observed deaths	Expected deaths	Meta-SMR	95% contidence interval
...e myelogenous leukemia	138	143.38	0.96	0.81–1.14
...nic myelogenous leukemia	53	64.86	0.82	0.62–1.08
...e lymphocytic leukemia	33	27.08	1.22	0.83–1.71
...nic lymphocytic leukemia	71	89.74	0.79	0.62–1.00

TABLE 9
Minimum Detectable SMR (at $\alpha = 0.05$ and $\beta = 0.20$) by Leukemia Cell Type in Combined Cohorts of Petroleum Workers

Combined cohort	Cell type	Observed deaths	Expected deaths	Meta-SMR	95% confidence interval		P value	Minimum detectable SMR
					Lower limit	Upper limit		
US	AML	103	107.68	0.96	0.78	1.16	0.65	1.2[illegible]
	CML	43	47.97	0.90	0.65	1.21	0.47	1.3[illegible]
	ALL	25	20.26	1.23	0.79	1.81	0.29	1.6[illegible]
	CLL	33	69.19	0.79	0.59	1.03	0.08	1.3[illegible]
UK	AML	45	47.20	0.95	0.70	1.27	0.75	1.39
	CML	19	22.00	0.86	**0.52**	1.35	0.51	1.60
	ALL	9	9.10	0.99	0.45	1.88	0.97	1.99
	CML	28	29.70	0.94	0.63	1.36	*0.75*	1.51
US and UK	AML	148	154.88	0.96	0.81	1.13	0.58	1.21
	CML	62	69.97	0.89	0.68	1.15	0.34	1.32
	ALL	34	29.36	1.16	0.81	1.61	0.40	1.5[illegible]
	CLL	83	98.89	0.84	0.67	1.04	0.10	1.2[illegible]

mechanisms of cell growth and differentiation (Snyder and Kalf, 1994). If benzene-induced toxicity is a conditional step in benzene-related AML, this would lend biologic support to the observed threshold based on epidemiologic data (World Health Organization, 1993). Thus, the lack of an increased risk of AML in petroleum workers could have been due to the substantially lower benzene exposures in the petroleum industry than in the Pliofilm study, which included workers exposed to benzene levels as high as several hundred ppm.

Similarly, benzene exposure levels in case reports of AML in shoemakers from Istanbul, Turkey, were extremely high. These shoemakers, who used solvents containing up to 88% benzene. were exposed to air benzene levels up to 650 ppm (Aksoy, 1985). In addition, some of these shoemakers worked at their homes and were thus exposed all day and all week long.

In contrast, benzene exposure at refineries was substantially lower compared to levels at the Pliofilm plants or among Istanbul shoemakers. For example, for general plant operations at petroleum refineries, the mean benzene level of 14,824 samples from an industrywide survey was **0.22** ppm (Runion, 1988). For gauging content in the field (by production workers) or at refinery tank farms (by refinery workers), 60% of the industrial hygiene samples were <1 ppm, 22% were between 1 and [illegible] ppm, 8% were between **3** and 10 ppm, *7%* were between 10 and **25** ppm, and only 2% were between 25 and [illegible] ppm. Similarly, based on a comprehensive survey in the petroleum refining industry, Spears ***et*** *al.* (1987) reported that most measurements based on both 8-hr and 15-min time-weighted average benzene exposures were below 1 ppm.

For land-based gasoline distribution workers, the highest exposures were received by drivers of tank trucks using the splashing method for loading during 1950–1964 (Smith ***et*** *al.*, 1993); and their full-shift exposure level for total hydrocarbons was estimated to be 220 ppm, which was equivalent to approximately 3.5 ppm of benzene (International Agency for Research on Cancer, 1989). For marine distribution workers, the highest exposures occurred among deck personnel during loading with open-hatch venting (Smith ***et*** *al.*, 1993); and their full-shift exposure level for total hydrocarbons was estimated to be 250 ppm, or approximately 4 ppm of benzene. These exposure data indicated that petroleum workers, even including those who worked in the industry decades ago, would not have accumulated sufficient

TABLE 10
Acute Myelogenous Leukemia by Cumulative Benzene Exposure

Cumulative exposure in ppm-years	Observed deaths	Expected deaths	Standardized mortality ratio	95% confidence interval
<40	1 } 1	0.84 } 1.09	1.19 } 0.91	0.03–6.63 } 0.0[illegible]
40–200	0	0.25	0	0–14.75
200–400	2	0.07	27.21**	3.29–98.24
400+	3	0.03	98.37**	20.28–287.65
Total	6	1.19	5.03**	1.84–10.97

** $P < 0.01$.

benzene exposure in excess of the estimated AML threshold derived from the Pliofilm study.

Distribution of leukemia cases by cell type in the petroleum workers was similar to that in the general adult population (Table 2). In particular, of the four major cell types AML accounted for 46% in the petroleum workers and 43% in the general adult population. In contrast, [illegible] all the leukemia patients with benzene exposure in Istanbul (the majority being shoemakers) had acute nonlymphocytic leukemia or ANLL (Aksoy *et al.*, 1976; Linet, 1985).

Because of the generally low benzene exposures among petroleum workers, the lack of an increased risk of AML is not surprising. Of the 19 individual cohorts examined, none showed a statistically significant AML SMR. In a previous analysis based on Cohort G, AML was significantly elevated; SMR = 2.19 and 95% CI: [illegible]–3.32 (Wongsrichanalai *et al.*, 1989). A nested case-control study within Cohort G has been conducted to determine the cause of the increase (Austin *et al.*, 1986). The investigation did not identify any specific job or department responsible for the increase, and comparison of the benzene exposure levels of cases and controls did not indicate any association with benzene exposure at the refinery. The authors offered several possible reasons for the increase: (i) unidentified exposures other than benzene at the refinery, (ii) exposures at work sites other than the refinery, (iii) unidentified nonoccupational exposures, or (iv) chance. Based on the present meta-analysis, it was unlikely that some yet unidentified exposures other than benzene were responsible for the AML increase reported in the previous analysis of Cohort G, unless these unidentified exposures were unique [illegible] that particular refinery. More likely, the AML increase in Cohort G was due to one or more of the other three reasons offered by the investigators of the original study. For example, cigarette smoking and other nonoccupational lifestyle risk factors have been linked to an increased risk of AML in some recent studies (Severson [illegible], 1990; Friedman, 1993; Sander *et al.*, 1993; Linet, [illegible]). In **any** event, the analysis based on the latest up-[illegible] Cohort G indicated that AML was no longer significantly elevated (SMR = 1.28, 95% CI: 0.70–2.15).

For CML, no significant increase or deficit was observed in the individual cohorts of petroleum workers. [illegible] meta-analyses based on the combined cohorts showed that There was no increase of CML. This finding [illegible] increased CML risk was further supported by two [illegible]-control studies of CML. In a case-control study of [illegible] in Sweden, no association (P = 0.91) was found [illegible] the disease and occupational exposures to petroleum products (Brandt *et al.*, 1978). Thus, the authors [illegible]: "unlike the patients with ANLL, occupational exposures to petrol products was not unduly common among rhe patients with CML." In another case-control study of CML conducted by investigators at the [illegible] of Leeds and the University of Edinburgh ([illegible] *et al.*, 1990), exposure histories of 122 CML cases and 241 controls were examined. This study did not find any association between CML and exposures to benzene or solvents ($P = 0.41$). The authors concluded: "This case-control study failed to reveal any risks for solvent or chemical exposure." Thus, there is no increased CML risk associated with chronic exposures to benzene or other aromatic hydrocarbons. This conclusion is consistent with the view expressed in the ***Cecil's Textbook of Medicine*** (19th ed.): "Benzene exposure increases the risk of acute myelogenous leukemia (AML) but not of CML" (Wyngaarden *et al.*, 1992).

For ALL, only Cohort K showed a significant increase (SMR = 2.60, 95% CI: 1.12–5.11). A review of the available employment histories of the ALL cases by the authors of the original cohort did not shed any additional light on a possible explanation for the excess. Moreover, it is interesting to note that there was a significant deficit of CLL (**3** observed vs 10.04 expected) in the same cohort. Five of the eight ALL cases in Cohort K were diagnosed in a small county in the South and, therefore, the ALL excesscoupled with a CLL deficit could have been the result of misclassification due to local diagnostic practice. Even if only one case had been misclassified, the ALL SMR for Cohort K would not have been statistically significant.

No other individual cohorts showed a significant increase of XLL. In fact, no ALL deaths were reported in six individual cohorts. For the US–UK combined cohort, the observed number of ALL deaths was not significantly different from the expected (**34** observed vs 29.36 expected, $P = 0.40$). Because of the rarity of ALL, few population-based case-control studies of ALL have addressed the issue of ALL in petroleum workers. In a case-control study based on 5147 leukemia deaths from 16 states in the United States, Loomis and Savitz (1991) reported that not a single ALL case had worked in the petroleum refining industry (odds ratio = 0). Although the number of ALL in the study was not reported, it can **be** estimated that approximately 10% of the total number or 500 were ALL. The finding from the Loomis and Savitz (1991) study that none of the ALL cases worked in the petroleum industry supported the results of the ALL meta-analysis in the present investigation. In a review on environmental factors of leukemia, Brandt (1985) also concluded "Unlike ANLL there seems to be little evidence at present that the development of ALL is related to exposure to some chemicals."

Finally for CLL, as remarked above, Cohort K exhibited a significant deficit. On the other hand, Cohort C showed a significant excess of CLL (SMR = 2.59, 95% CI: 1.18–4.91). As discussed earlier, approximately **4** statistically significant SMRs could be expected to occur by chance, given that there were 76 SMRs tested at the α = 0.05 level. Indeed, there were **3** statistically significant SMRs in Tables **3–6.** For the US combined cohort, the CLL SMR was 0.79 (95% CI: 0.59–1.03), almost significantly low at the 0.05 level. For the US–UK combined cohort, the CLL meta-SMR was 0.84, indicating that there was no increased CLL risk among petroleum workers in the United States or the United Kingdom. This finding was supported by a recent case-control study of chronic lymphocytic leukemia and chemical exposures conducted by epidemiologists at the University of Washington (Malone *et al.*, 1989). This study found that the risk ratio for CLL associated with exposure to aromatic hydrocarbons (including benzene) was **1.1**. Similarly, in a case-control studies of 342 CLL cases in the Baltimore area, benzene was found to be unrelated to any increased risk of CLL (Linet *et al.*, 1987). In the case-control study conducted by Loomis and Savitz (1991) discussed above. no significant increase in CLL among petroleum refining workers was found. Similarly. in the Swedish case-control study conducted by Brandt *et al.* (1978) discussed earlier, no association between exposure to petroleum products and CLL was detected ($P = 0.70$).

In addition, the relationship between lymphocytic leukemia and solvent exposures in rubber industry workers has been examined previously. In a nested case-control study of lymphocytic leukemia, risks associated with exposure to **24** solvents used in the rubber industry were investigated (Checkoway *et al.*, 1984). Unfortunately, the analysis was not further specified into the two main subgroups. CLL or ALL. However, the ratio of CLL to ALL is approximately $2\frac{1}{2}$ to 1 in the general adult population, and. therefore, the analysis was weighted more heavily with CLL than with ALL. A number of solvents (e.g., carbon disulfide, carbon tetrachloride), but not benzene, were observed to be significantly associated with lymphocytic leukemia in rubber industry workers.

In addition to the overall meta-analyses based on all cohort studies of petroleum workers in the United States and the United Kingdom, we also conducted meta-analyses restricted to studies of refinery workers only (Table 7). The results based on refinery studies were similar to those based on all petroleum studies. Furthermore, we also performed meta-analyses based on studies with at least 15 years of follow-up (Table 8). The results remained unchanged, after stratification by length of follow-up.

As discussed previously (Wong and Raabe, 1989, 1990), data are not available from individual studies for a meta-analysis by level of exposure to petroleum products. A few individual studies have presented exposure–response analyses by leukemia cell type. A review of these analyses will shed additional light on the interpretation of the meta-analyses in the present investigation. For refinery workers. in the case-control study of Cohort G. detailed analyses of AML by benzene exposure categories were carried out (Austin *et al.*, 1986). The controls were found to have a higher cumulative benzene exposure than the AML cases. Other cumulative measures of benzene exposure were obtained using differenr weighting schemes, and for each of these measures the controls consistently scored higher than the cases. Thus. the AML increase reported in the previous analysis of Cohort G could not be attributed to benzene exposure. Furthermore, the increase was substantially reduced and no longer statistically significant in the latest update of Cohort G.

Among petroleum distribution workers, drivers of tank trucks have the highest potential for exposure to hydrocarbons including benzene. In the UK distribution study, Rushton (1993c) provided cell-type-specific analysis for drivers. The AML SMR for drivers was 1.[illegible] (95% CI: 0.82–2.65). Unfortunately, no analysis by exposure to either total hydrocarbons or benzene was carried out. Analysis by hire date indicated that an increased leukemia risk (all cell types) was observed in workers who started work before 1940, but it was not clear whether this result holds true for AML as well. In the US study of distribution workers, no increased risk for either leukemia (all cell types combined) or AML was found for drivers. Furthermore, exposure–response analyses were carried out for both leukemia (all cell types combined) and AML in the US study (Wong *et al.*, 1993; Wong and Trent. 1993). Analyses using logistic regression models based on length of exposure, cumulative exposure, and frequency of peak exposure did not find any increased risk or exposure–response relationship between these exposure indices and leukemia (all cell types combined) or AML (Wong and Trent. 1993). Thus, these detailed analyses from individual studies supported the results of the meta-analyses based on the combined cohorts in the present investigation.

The meta-analyses by leukemia cell type in the present investigation underscore the importance of taking cell-type specificity into consideration. Moreover. recently the concept of even more specific diagnostic categories ("sub-cell types") has been gaining increasing use in epidemiologic analyses. For example, AML as a single disease category may not be as homogenous as once thought to be. especially for etiologic investigation:. Recent research suggests that, at the molecular or cytogenetic levels. AML may be considered a heterogenous disease (Smith *et al.*, 1992). In a recent epidemiologic study using *ras* mutation-positive (*ras*-positive) AML as a molecular subtype, Taylor *et al.* (1992) reported that *ras*-positive AML was associated with occupational exposures but not *ras*-negative AML. In another case-control study of ANLL, a distinction between normal and abnormal karyotypes was made (Crane *et al.*, 1989). In the cytogenetically defined subset of ANLL with abnormal karyotype. the odds ratios were *5.3* (95% CI: 1.[illegible]–21.9) for smoking more than *2* packs of cigarettes per day, and 5.9 (95% CI: 1.4–25.6) for consuming more than *2* oz. of alcohol daily. For benzene exposure (level unspecified), on the other hand. the odds ratio was 1.[illegible] (95% CI: 0.3–3.8). Thus. in the future, cytogenetic information will likely further increase the specificity of disease classification, which in turn will improve epidemiologic analyses.

CONCLUSION

In conclusion, epidemiologic data have demonstrated that, given high enough exposure level over an extended

... of time, benzene can increase the risk of acute ...genous leukemia. Furthermore, where quantita... exposure estimates are available, epidemiologic data ... indicated that the observed threshold needed to in...ase the risk of acute myelogenous leukemia has been ...imated to be at least 200 ppm-years of benzene ...re, and most likely substantially higher based on ...ealistic exposure estimates (in the range of 400– ...pm-years). The meta-analysis on acute myeloge... leukemia in the present investigation based on a ...bined cohort of more than 208,000 US and UK pe...leum workers has demonstrated that these workers ...ere not at an increased risk of acute myelogenous leu...emia because benzene exposure levels in the petroleum ...ndustry have been substantially lower than needed to ...the observed threshold.

...thermore, in assessing the relationship between ...ne exposure and leukemia, a distinction must be ...made with respect to histological cell types of leukemia. The meta-analyses on chronic myelogenous leukemia, acute lymphocytic leukemia, and chronic lymphocytic leukemia have demonstrated that there is no increased risk for any of these cell-type-specific leukemias among petroleum (refinery, production, pipeline, and distribu... workers in the United States or in the United K...gdom. Meta-analyses restricted to refinery studies or ...studies with at least 15 years of follow-up yielded similar results. The conclusion of the present investigation ... supported by case-control studies on cell-type-specific leukemias conducted in the United States, the United Kingdom, and other countries.

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...e thank all the investigators of the original studies included in our ...alysis. A partial list of these investigators can be found in Table 1. W...thout their participation and willingness to share their data with ...s, this meta-analysis would have never been possible.

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