Exhibit 239

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Mortality Study in an Italian Oil Refinery: Extension of the Follow-Up

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This article present the results of the extension of the follow-up of a cohort of workers employed in an Italian oil refinery. 1,583 workers employed in 1949–1982 in a northern Italy oil refinery plant were followed-up for mortality as of May 31, 1991. Environmental measurements documented potential exposure to benzene. Standardized mortality ratios (SMR) and their 95% confidence intervals (95% CI) were calculated using as references national (1949–1968) and regional mortality rates (1969–1991). Elevated mortality from lymphoma (seven deaths, SMR 190, 95% CI 76–391) and leukemia (eight deaths, SMR 225, 95% CI 97–443) was observed. No consistent trends by length of employment or time since first exposure were apparent. Nonetheless, the excess risk was particularly and significantly increased among workers with 15 or more years of employment, and 30 or more years since first employment. The findings of elevated mortality from leukemia and lymphoma are in agreement with those of other oil refinery studies. Chance, confounding, or other biases might have played a marginal, if any, role in determining the results. Exposure to benzene is a biologically plausible explanation. Am. J. Ind. Med. 35:287–294, 1999.

KEY WORDS: epidemiology; mortality; occupational cancer; oil refinery; benzene; leukemia; lymphoma

INTRODUCTION

The petroleum refinery industry employs hundreds of thousands of workers worldwide. Processing and maintenance workers may be exposed to a wide variety of agents, including known carcinogens such as benzene [IARC, 1989]. Many investigations have been conducted in several countries over the last years [Savitz and Moure, 1984; Harrington, 1987; Delzell et al., 1988; IARC, 1989; Wong and Raabe, 1989, 1990, 1995, 1997; Kriebel et al., 1990; Raabe and Wong, 1996], yet the entire pattern of the cancer risk possibly associated with working in this industry in different areas of the world has not been fully clarified, in particular the risk related to benzene exposure, a pollutant currently of major interest given its low-level, widespread environmental presence.

The mortality experience of workers employed in an oil refinery located near Milan, in northern Italy, was previously evaluated for the period 1949–1982 [Bertazzi et al., 1989]. That study uncovered a suggestive increase of cancer risk at different body sites, particularly for kidney (three deaths observed, 0.8 expected), brain (benign, malignant, unspecified tumors: 4/2.1), and leukemia (5/2.0). Lung cancer was elevated in some departments: Moving, most notably, Delivery, and Power Plant.

The follow-up of the cohort was extended as of May 31, 1991. This article presents the results for the entire period, 1949–1991.

MATERIALS AND METHODS

The study population comprised 1,583 male workers, ever employed between January 1, 1949, and December 31,

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TABLE I. Benzene Concentrations (mg/m³) in Production and Moving Departments in an Italian Oil Refinery, 1984–85

Department	No. samples	Min.	Median	Max.	% Samples ≥3.25 mg/m³ *
Production	18	0.10	0.4	24.7	28%
Moving	39	0.03	1.3	77.0	41%

*Current recommended permissible level in Europe, <3.25 mg/m³ (1 ppm).

TABLE II. Completeness of the Follow-Up of Workers in an Italian Oil Refinery, 1949–91

Vital status	Number of subjects	(%)
Alive	1,163	73.5
Deceased*	352	22.2
Not traced	58	3.7
Migrated abroad	10	0.6
Total	1,583	100.0

*13 deaths with unknown cause.

1982: after checking for errors, 12 subjects were excluded from the 1,595 subjects of the previous follow-up [Bertazzi et al., 1989].

Individual work histories inside the refinery were obtained from personnel files, which contained information on date of hire and leaving the plant, and on specific jobs held in different departments. Reconstruction of work processes and the results of industrial hygiene surveys performed in the period 1982–1985, in which levels of airborne contaminants were measured, led to the identification of the following work areas or departments: Production, Moving, Delivery, Power Plant, Laboratories, Maintenance, Clerical, plus the Other department category [Bertazzi et al., 1989]. Sixty-two percent of the subjects had worked in a single department during their career within the plant, 24% in two, and 14% in three or more departments; subjects were classified according to the longest job held. No update of occupational histories after 1982 was performed. The refinery ceased activity in 1993.

Few environmental measurements of chemicals were available for some departments. Benzene concentrations in air were determined in the Production, where the majority of people operated, and Moving departments (Table I).

Of the workers enrolled in the study, 381 were still employed on May 31, 1991. Subjects who had left the plant before this date were followed up by contacting the Population Statistics Offices of the towns of subjects' last residence. Death certificates were obtained and coded according to standard rules following the International Classification of Diseases in use at the time of death, then converted to the VIII revision codes.

Workers contributed person-years from the beginning of employment in the plant until exit from the study (because of death, emigration, or loss to follow-up), or until the end of the study period. Calculation was performed using a FORTRAN computer program we developed [Zocchetti and Bertazzi, 1982], and successfully validated against other widely used programs [Monson, 1974; Marsh and Preininger, 1980].

As reference, we used the male mortality rates specific by age and calendar year of the entire country for the period 1949–1968 and rates of the Lombardy Region, in which the refinery was located, from the year of availability (1969) on. The majority of the cases (86%) and person-years (72%) occurred in the period 1969–1991; therefore, comparison of the cohort mortality was made with the regional population. This seemed appropriate, in that large geographical variations of mortality and cancer incidence are observed in Italy, for example, respiratory and lymphatic and hematopoietic cancers prevail in the northern regions, while digestive tract mortality rates are higher in the center–south [Cislaghi et al., 1986; Zanetti and Crosignani, 1992].

We calculated 95% confidence intervals (CI) of standardized mortality ratios (SMRs) using Byar's formula [Breslow and Day, 1987]. We performed analyses by length of employment (0–4, 5–14, 15+ years), time since first employment or "latency" (0–9, 10–19, 20–29, 30+ years), year of first employment (<1954, 1954–1962, 1962+, corresponding to dates of major changes in production technology), and department (longest job). Duration of employment was lagged 10 years to overcome the lack of occupational history information after 1982 [Checkoway et al., 1989]. Poisson regression modeling using internal reference was performed in the analysis of duration and latency.

RESULTS

Subjects contributed a total of 39,857 person-years. Vital status ascertainment was over 95% successful (Table II). We found 352 deaths and were able to obtain death certificates for 339 (96.3%); of the 13 missing causes of death, 12 were missing in the first follow-up period (1949–1982).

Overall mortality (Table III) was lower than expected, mainly because of a marked reduction of mortality from nonneoplastic cardiovascular, respiratory, and digestive diseases. All cancer mortality was similar to that expected, while digestive cancers were decreased (38 observed/48.1 expected). Rectum, lung, and kidney cancer mortality exhibited a marginal numerical increase of the SMR value. No deaths from mesothelioma were found. Mortality from melanoma (two cases), and brain cancers (five cases) was about twice the expected. Lymphatic and hematopoietic

TABLE III. Mortality From Selected Causes in an Italian Oil Refinery, 1949–91

Cause of death (ICD-8 codes)[a]	Observed deaths	Expected deaths	SMR[b]	95% CI[c]
All causes (000–999)	352	404.6	87	78–97
All cancer (140–209)	131	136.3	96	80–114
Digestive system (150–159)	38	48.1	79	56–108
Esophagus (150)	3	4.2	71	14–206
Stomach (151)	17	17.5	97	57–156
Colon (153)	5	6.6	75	24–176
Rectum (154)	4	3.5	114	31–291
Liver and gallbladder (155–156)	7	8.8	80	32–164
Pancreas (157)	2	5.0	40	4–143
Larynx (161)	3	5.9	51	10–150
Lung (162)	46	42.9	107	79–143
Melanoma (172)	2	0.9	229	26–825
Prostate (185)	4	5.0	79	21–203
Urinary bladder (189)	3	4.5	67	14–197
Kidney (189)	3	2.7	110	22–320
Brain (191)	5	2.4	208	67–485
Lymphatic and hematopoietic (200–209)	15	8.4	179	100–295
Lymphoma (200–202)	7	3.7	190	76–391
Hodgkin's disease (201)	2	1.3	151	17–544
Non-Hodgkin's lymphoma (200, 202)	5	2.4	212	68–495
Leukemia (204–207)	8	3.6	225	97–443
All circulatory diseases (390–458)	111	143.3	77	64–93
Ischemic heart diseases (410–419)	61	63.8	96	73–123
Cerebrovascular diseases (430–439)	18	36.7	49	29–78
Respiratory diseases (460–519)	13	24.2	54	29–92
Digestive diseases (520–577)	20	36.8	54	33–84
Cirrhosis (571)	12	26.4	45	23–79
External causes (800–999)	25	30.2	83	54–122

[a]ICD-8, International Classification of Diseases, 8th revision.
[b]SMR, standardized mortality ratio.
[c]95% CI, 95% confidence interval (Byar's formula).

cancers were 80% increased (15/8.4): both lymphomas (7/3.7) and leukemias (8/3.6) showed an excess. On death certificates, the leukemia types were described as: one acute myeloid, one acute lymphatic, two chronic lymphatic, three acute, one not specified.

Cancer-specific mortality did not show any linear pattern with 10-year lagged length of employment in the refinery (Table IV). The two cases of melanoma occurred among workers employed 5–14 years. Kidney and brain

TABLE IV. Mortality From Selected Cancer Causes by Length of Employment Lagged 10 Years in an Italian Oil Refinery, 1949–91

	Length of employment (years)		
Cause of death	0–4	5–14	15+
All causes			
Obs/Exp	97/113.0	151/163.8	104/127.8
SMR[a]	86	92	81
95% CI[b]	70–105	78–108	66–99
All cancers			
Obs/Exp	29/31.0	59/54.6	43/50.7
SMR	94	108	85
95% CI	63–135	82–139	61–114
Digestive system			
Obs/Exp	8/10.9	17/19.2	13/18.0
SMR	73	89	72
95% CI	32–144	52–142	38–124
Stomach			
Obs/Exp	3/4.5	9/7.4	5/5.6
SMR	67	122	89
95% CI	13–195	56–232	29–207
Liver, gallbladder			
Obs/Exp	2/1.8	1/2.9	4/4.1
SMR	109	35	98
95% CI	12–395	0–193	26–251
Lung			
Obs/Exp	11/8.6	22/17.3	13/17.0
SMR	128	127	76
95% CI	64–228	80–193	41–131
Melanoma			
Obs/Exp	0/0.3	2/0.3	0/0.3
SMR	0	633	0
95% CI	0–1438	71–2285	0–1207
Kidney			
Obs/Exp	1/0.6	1/1.0	1/1.1
SMR	177	97	88
95% CI	2–985	1–538	1–489
Brain			
Obs/Exp	3/0.8	2/0.9	0/0.8
SMR	397	226	0
95% CI	80–1161	25–817	0–477
Lymphatic and hematopoietic			
Obs/Exp	4/2.8	4/3.0	7/2.6
SMR	142	134	271
95% CI	38–363	36–343	109–559
Lymphoma			
Obs/Exp	2/1.4	2/1.2	3/1.1
SMR	144	162	283
95% CI	16–521	18–583	57–827
Leukemia			
Obs/Exp	2/1.2	2/1.3	4/1.1
SMR	168	153	377
95% CI	19–606	17–551	101–965

[a]SMR, standardized mortality ratio.
[b]95% CI, 95% confidence interval (Byar's formula).

cancers were few and the SMR values decreased with length of employment. Lymphatic and hematopoietic tumors were significantly elevated among workers with 15+ years of employment; both lymphomas (3 deaths/1.1 expected) and leukemias (4/1.1) were in excess in this category. Tests for linear trend were not significant.

Lymphatic and hematopoietic malignancies were also associated with time since first employment (Table V): a significant excess was observed 30 or more years since first employment in the plant, based on four lymphoma and three leukemia deaths. Tests for linear trend were not significant.

Analysis by year of hire showed a mortality excess of lymphatic and hematopoietic neoplasms in all periods, except for lymphoma, for which no deaths were observed among workers employed after 1962 (Table VI). The analyses failed to isolate any specific department where the risk of lymphatic and hematopoietic malignancies was confined; five of the eight leukemia deaths occurred in Production (3 observed/1.1 expected) and Maintenance (2/0.6); lymphoma deaths were more distributed across departments.

Lung cancer mortality was elevated only in the Moving (7 observed/4.0 expected, SMR 176, 95% CI 71–363), Delivery (3/1.7, SMR 177, 95% CI 36–517), and Power Plant (4/2.1, SMR 191, 95% CI 51–490) departments, as in the previous follow-up.

DISCUSSION

The main finding of this study of an Italian cohort of male oil refinery workers examined within a 42-year span was the excess mortality from leukemia and lymphoma. Despite the absence of an increasing linear trend of risk, the excesses for both causes of death were observed in the highest category of length of employment and time since first employment. Other mortality excesses were based on few cases (melanoma) or with risk patterns not compatible with an occupational etiology (brain cancer). Lung cancer was slightly above expectation in some departments. Kidney cancer was not elevated; however, the power of the study may have been too low to detect a possible modest increase of risk. Mortality from nonneoplastic diseases was markedly reduced.

Selection bias was unlikely, given the high percentage of traced workers. We had information that one of the subjects with missing cause of death had leukemia, but were not able to confirm this through official records (he had been working in the Power Plant department from 1954 to 1967, when he died at the age of 39 years).

Possible misclassification of disease, if present at all, was probably of the nondifferential type. Cause of death certification by area physicians was probably not influenced by the knowledge of the subject's occupation, and coding of the underlying cause of death was made following standard

TABLE V. Mortality From Selected Cancer Causes by Time Since First Employment in an Italian Oil Refinery, 1949–91

	Time since first employment (years)			
Cause of death	**0–9**	**10–19**	**20–29**	**30+**
All causes				
Obs/Exp	34/44 6	90/88.0	122/145.5	106/126.5
SMR[a]	76	102	84	84
95% CI[b]	53–107	82–126	70–100	69–101
All cancers				
Obs/Exp	11/9.5	34/27 5	48/51.9	38/47.3
SMR	115	124	92	80
95% CI	58–207	86–173	68–123	57–110
Digestive system				
Obs/Exp	2/3.4	12/9.5	12/17.8	12/17.4
SMR	60	126	67	69
95% CI	7–215	65–221	35–118	36–120
Stomach				
Obs/Exp	1/1.6	7/4.1	5/6.6	4/5.3
SMR	64	171	76	76
95% CI	1–357	68–352	25–178	20–195
Liver, gallbladder				
Obs/Exp	0/0.5	1/1.2	1/2.9	5/4.2
SMR	0	81	35	120
95% CI	0–674	1–448	0–195	39–281
Lung				
Obs/Exp	3/2.1	12/8.4	19/17 3	12/15 0
SMR	140	143	110	80
95% CI	28–410	74–250	66–171	41–139
Melanoma				
Obs/Exp	0/01	0/0.2	2/0.3	0/0.3
SMR	0	0	653	0
95% CI	0–3743	0–1789	73–2358	0–1199
Kidney				
Obs/Exp	0/0.2	1/0.5	2/1.0	0/1.1
SMR	0	210	196	0
95% CI	0–2382	3–1166	22–709	0–337
Brain				
Obs/Exp	3/0.3	2/0.6	0/0 9	0/0.6
SMR	960	341	0	0
95% CI	193–2804	38–1231	0–401	0–618
Lymphatic and hematopoietic				
Obs/Exp	2/1.3	4/1.9	2/2.6	7/2 5
SMR	149	207	76	282
95% CI	17–536	56–530	9–275	113–581
Lymphoma				
Obs/Exp	1/0.7	1/0.9	1/1.1	4/1.0
SMR	141	108	95	402
95% CI	2–785	1–602	1–527	108–1028
Leukemia				
Obs/Exp	1/0.6	3/0.8	1/1.1	3/1.0
SMR	177	367	88	289
95% CI	2–984	74–1071	1–488	58–845

[a]SMR, standardized mortality ratio.
[b]95% CI, 95% confidence interval (Byar's formula).

TABLE VI. Mortality From Lymphoma and Leukemia by Year of First Employment and Department in an Italian Oil Refinery, 1949–91

	Lymphoma	Leukemia
Year of first employment		
<1954		
Obs/Exp	4/2.3	4/2.2
SMR[a]	177	178
95% CI[b]	48–454	48–455
1954–1962		
Obs/Exp	3/0.7	1/0.7
SMR	419	146
95% CI	84–1223	2–811
>1962		
Obs/Exp	0/0.7	3/0.6
SMR	0	478
95% CI	0–515	96–1397
Department		
Production		
Obs/Exp	1/1.2	3/1.1
SMR	86	280
95% CI	1–476	56–817
Delivery		
Obs/Exp	1/0.1	0/0.1
SMR	784	0
95% CI	10–4383	0–2934
Moving		
Obs/Exp	0/0.3	1/0.3
SMR	0	307
95% CI	0–1069	4–1710
Maintenance		
Obs/Exp	0/0.6	2/0.6
SMR	0	315
95% CI	0–572	35–1139
Power plant		
Obs/Exp	1/0.2	0/0.2
SMR	555	0
95% CI	7–3091	0–2061
Laboratories		
Obs/Exp	1/0.1	0/0.1
SMR	673	0
95% CI	9–3746	0–2737
Clerical		
Obs/Exp	1/0.5	1/0.6
SMR	182	174
95% CI	2–1015	2–968
Others		
Obs/Exp	2/0.4	1/0.4
SMR	469	230
95% CI	53–1695	3–1282

[a]SMR, standardized mortality ratio.
[b]95% CI, 95% confidence interval.

rules, so that information on the cohort can be considered comparable to that of the reference populations. Concordance of the information on cause of death and hospital record is sufficiently good for many neoplastic diseases in occupational epidemiology studies, and we had the opportunity to quantitatively verify this in the Lombardy Region [Pesatori et al., 1990].

Occupational, environmental, life-style, and socioeconomic factors have been suggested as risk factors for leukemia and other lymphatic and hematopoietic tumors [Schottenfeld and Fraumeni, 1996]. It is improbable that any of them played an important role in this study. First, for most of them the force of the association with lymphatic and hematopoietic tumors is not very strong, so that very large differences in risk factor distribution between the cohort and the referent population would be needed to produce important confounding effects. These differences are unlikely, since we used the regional population for comparison. Still, it could be argued that socioeconomic factors could be distributed differently among the cohort (lower socioeconomic status) and the general population, albeit local. However, the possible resulting bias would be towards obscuring any association, since a low socioeconomic status is associated with low mortality from lymphatic and hematopoietic tumors. We also conducted internal analyses using Poisson regression, admittedly, with very low precision due to small numbers, which did not contradict the SMR analysis results (see below). Similar considerations apply to smoking, for which additional indirect arguments against a strong confounding effect can be put forward: data on smoking habits in the plant showed that the proportion of smokers was substantially similar across departments [Bertazzi et al., 1989]; in addition, lower mortality from nonneoplastic smoking-related diseases was observed.

There are several potential time-related confounders in occupational cohort studies, usually synthesized in the concept of the healthy worker effect (HWE). HWE is usually stronger (but by no means confined to) for nonneoplastic diseases, and varies with age, length of employment, time since, and age at first exposure [Checkoway et al., 1989]. In this study, the lower mortality from circulatory, respiratory, and digestive diseases (50–80% of expected) indicates the presence of a strong HWE.

HWE increases with length of employment: many cohort studies found spurious negative association of mortality with length of employment even in the absence of any exposure effect (this aspect of the HWE is sometimes called healthy worker "survivor" effect, HWSE) [Checkoway et al., 1989; Steenland and Stayner, 1991]. This is the result of unbalanced distribution of employment status: "active" and "inactive" person-years are differently distributed in the different categories of duration of employment; in particular, higher proportions of inactive person-years (and, hence, higher mortality rates) occur in categories with low duration

of employment [Steenland and Stayner, 1991]. In other words, length of employment (and other related indices which incorporate it) could be confounded by employment status. Different options, alone or combined, are available for dealing with HWSE: two simple methods are lagging of exposures and direct adjustment for employment status; other complex methods may be necessary in some situations, however [Pearce, 1992; Steenland et al., 1996]. In this study, this effect was evident for several neoplastic and many nonneoplastic causes of death: the largest mortality decrease for causes was observed in the highest category of length of employment, notwithstanding the lagging. We found elevated mortality from leukemia and lymphoma in the highest category of length of employment; in light of the above arguments, the excess could have been even more pronounced in the absence of the HWSE.

HWE decreases with length of follow-up or time since first employment, so spuriously positive association of mortality with latency may be found [Checkoway et al., 1989]. We did not observe such a pattern for nonneoplastic diseases, however. Hence, the increased mortality from lymphatic and hematopoietic tumors in the upper category of latency is hardly attributable to HWE.

A further source of bias could stem from the use of SMR: different SMRs are in principle not comparable, because they are not mutually standardized [Miettinen, 1972]. When data are sparse, however, other theoretically preferable techniques ("direct" standardization, Mantel-Haenszel stratification, Poisson regression) can become unreliable, and this is the main reason for the popularity of SMR [Breslow and Day, 1987]. We performed internal analyses using Poisson modeling; the pattern of risks by length of employment and latency were in agreement with those obtained through standardization. The results (not shown) confirmed the elevated risks in the highest category of length of employment and latency; adjustment for employment status produced negligible changes. However, the validity of this analysis is questionable: given the sparseness of the data, the relative risk estimates were highly unstable (very large confidence intervals). Moreover, for the same reason only a coarse categorization of age (three categories: <54, 55–69, 70+), and calendar year (two categories: 1949–1982, 1983+) was feasible; therefore, residual confounding was likely.

In summary, it seems that the excess of mortality from leukemia and lymphoma noted in this cohort of refinery workers cannot be attributed to uncontrolled confounding or bias or chance alone, but appears to be related to working conditions in the plant. However, it is difficult to associate this excess to specific chemicals inside the plant on the basis of the limited exposure information available; moreover, the risk excess was not concentrated in any particular department. Infante [1993] argued that benzene, the only ubiquitous leukemogen agent found in refineries, is the most plausible explanation for the observed elevated risks of leukemias in the refinery industry. Some authors found in a U.S. oil refinery cohort, among workers hired before 1940, an elevated risk of lymphatic leukemia, but not for myelocytic leukemia, the type most strongly associated with benzene exposure. After 1940, both types of leukemia were in excess; they interpreted this finding as evidence that chemicals other than benzene may play a role [Wongsrichanalai et al., 1989]. Other investigations failed to find associations between leukemia and benzene in refineries [McCraw et al., 1985; Austin et al., 1986]. Benzene exposure has also been linked with other lymphatic and hematopoietic tumors (lymphoma, multiple myeloma), and chromosomal damage to lymphocytes has been documented [Rinsky et al., 1987; Infante, 1993; Blair et al., 1993; Yin et al., 1996; Hayes et al., 1997].

In this study, the possible role of benzene exposure could not be formally analyzed because the quantitative data available concerned a small number of area samples collected in one particular time period in only two departments. These limited data indicate that a substantial fraction of the workforce had probably been exposed to benzene levels that are currently regarded as hazardous: in Production and Moving, it comprised 15,890 person-years (46.8% of the total observation time accrued by the cohort). In relatively recent years, 30–40% of the samples showed airborne levels of benzene exceeding 1 ppm, the recommended European occupational exposure limits [European Commission, 1994]. Levels had certainly been higher in the past. In spite of the lack of actual measurements in this plant, Maintenance and Laboratory workers in the refinery industry are known to be exposed to benzene during their activities.

Occupational exposures in petroleum refining have been classified by the International Agency for Research on Cancer (IARC) in group 2A ("probably carcinogenic to humans"), on the basis of limited epidemiologic evidence regarding skin cancer and leukemia, and on sufficient experimental evidence (induction of skin tumors in rodents) [IARC, 1989].

Since then, several cohort studies have been published; some are extensions of follow-up or expansions of cohorts previously considered in the IARC monograph [Wongsrichanalai et al., 1989; Dagg et al., 1992; Shallenberger et al., 1992; Rushton, 1993a,b; Satin et al., 1996]. An increased risk of leukemia has been reported in some of these studies, in the whole cohort or in subgroups [Wongsrichanalai et al., 1989; Shallenberger et al., 1992; Rushton, 1993a,b]. Increased risks were observed for different cell-specific types of leukemia. Positive relationships between leukemia risk and length of employment and/or latency have been reported. In general, risk excesses were observed among workers with more than 20–30 years of employment and/or after 20–30 years since first employment [Dagg et al., 1992; Shallenberger et al., 1992; Satin et al., 1996]. A study

showed elevated mortality for men with 10 years or more of employment and for workers with 10 to 39 of latency [Wongsrichanalai et al., 1989]. Elevated risks for other lymphatic and hematopoietic cancers have also been reported. Lympho-reticulosarcomas were found in excess after 30 years of employment and latency in one study [Dagg et al., 1992]. A study found an increased risk of Hodgkin's disease among workers hired before 1940 [Satin et al., 1996].

Other industrial cohorts not included in the IARC monograph have recently been examined (for a few of them there is some overlap with previously investigated cohorts) [Christie et al., 1991a,b; Marsh et al., 1991 (later expanded by Tsai et al., 1996); Schnatter et al., 1992; Tsai et al., 1993, 1997; Milcarek et al., 1994; Collingwood et al., 1996; Huebner et al., 1997; Järvholm et al., 1997; Pukkala, 1998; Raabe et al., 1998]. The risk of leukemia (mortality or incidence) was elevated in some studies [Christie et al., 1991a,b; Järvholm et al., 1997; Raabe et al., 1998]. In one of them (an expansion of a previously nonpublished study) leukemia mortality increased with increasing length of employment and time since first employment: in particular, risks were elevated among workers employed for 30 or more years and among workers with 20 or more years of latency [Raabe et al., 1998]. Mortality excesses regarding other lymphatic and hematopoietic cancers (lymphoma, myeloma, other lymphatic tissue cancer) were also reported [Christie et al., 1991a,b; Collingwood et al., 1996; Tsai et al., 1996; Pukkala, 1998; Raabe et al., 1998]. For these causes of death, elevated risks after 30 years of length of employment and/or latency were found in some studies [Collingwood et al., 1996; Tsai et al., 1996].

A few studies reported an increased mortality from lung cancer in refineries [IARC, 1989; Bertazzi et al., 1989; Rushton, 1993a]. In this study, lung cancer mortality was elevated among workers in departments where exposure to polynuclear aromatic hydrocarbons (PAH) was probable, i.e., in the Power Plant, Moving, and Delivery departments. In Moving and Delivery, in particular, sources of PAH exposure were a filling platform, loading of bitumen, and a parking area where truck engines were often on for long periods of time.

The finding on melanoma was based on a very small number of deaths. Increased mortality or incidence of skin cancers, including melanoma, were reported in some studies [IARC, 1989; Christie et al., 1991b; Schnatter et al., 1992; Rushton, 1993a; Pukkala, 1998].

We recorded two deaths from aortic aneurysms (expected was not calculated). Elevated mortality from this cause was observed in some studies [Schnatter et al., 1992; Rushton, 1993a].

We observed no cases of mesothelioma, which was reported in excess in another oil refinery in Genoa, northern Italy [Gennaro et al., 1994, 1995; Wong, 1995].

In conclusion, among workers in this Italian oil refinery, lymphoma and leukemia exhibited an elevated mortality in the whole cohort and a positive (albeit not monotonic) association with length of employment and time since first employment. These findings are in agreement with those of other studies on oil refinery workers performed in different countries. The association is biologically plausible, since workers in oil refineries are exposed to a number of known or suspected carcinogenic substances, including benzene.

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