upational and Environmental Medicine

Papers

Correspondence

Update of the Texaco mortality study 1947–93: part I. Analysis of overall patterns of mortality among refining, research, and petrochemical workers

Barbara J Divine, Christine M Hartman, Judy K Wendt

Abstract

Objective—To update information on the workers of the Texaco mortality study to determine if the patterns of mortality have changed with 16 additional years of follow up.

Subjects and ***methods—All*** workers were employed for ≥5 years at company refineries, petrochemical plants, and research laboratories from 1947–93. The cohort now consists of 28 480 employees with an average of ≥20 years of follow up.

Results—The overall mortality, and most cause specific mortalities were lower than or similar to those for the general population of the United States. For white men (86% of the cohort), there were 8873 observed deaths and 11 181 expected resulting in a significantly lower standardised mortality ratio (SMR) of 79. There were significant deficits for all the leading causes of death in the United States including all cancers, cancer of the lung, stroke, heart disease, respiratory disease, and accidents. Slightly increased mortality was found for cancer of the pancreas, cancer of the brain and central nervous system, leukaemia, and cancer of other lymphatic tissue. For cancer of the bone, the SMR was 162 (95% confidence interval (95% CI) 86 to 278), and for benign and unspecified neoplasms, it was 152 (95% CI 109 to 206). Overall mortality patterns for non-white men and women were similar to those for white men. Mortality patterns for white men were also examined by duration of employment, time first employed, location, and by job and process unit. There were significantly increased SMRs for brain cancer for those people employed as laboratory workers and on units with motor oil and for cancer of other lymphatic tissue for people employed on the fluid catalytic cracking unit.

Conclusions—The results of the updated study showed a favourable mortality experience for employees in the Texaco mortality study compared with the United States population. There were a few increases found consistently including, but not limited to, brain cancer and cancer of other lymphatic tissue. These increases led to additional analyses that will be discussed in the accompanying paper.

(Occup *Environ Med* 1999;56 167–173)

Keywords: petroleum; chemical industry; occupational cancer; mortality

Texaco, PO Box 1404, Houston, TX 77251, USA
B J Divine
C M Hartman

University of Texas, MD Anderson Cancer Center, 1100 Holcombe Boulevard, Pain Research Group, Box 221, HMB 15.556, Houston, TX 77030, USA
J K Wendt

Correspondence to:
Dr B J Divine, Texaco, PO Box 1404, Houston, TX 77251, USA.

Accepted 2 October 1998

Texaco published two epidemiological reports in 1985 and 1986 on the patterns of mortality at company refineries, petrochemical plants, and research laboratories.[1,2] The Texaco mortality study cohort consisted of over 21 000 workers whose mortality experience was followed up from 1947 to 1977. Results from these earlier analyses were generally favourable in that the overall mortality and most cause specific mortalities were lower than or similar to those for the general United States population.

White men experienced significant deficits for all causes of death combined, all malignant neoplasms, cancer of the lung, stroke, arteriosclerotic heart disease, respiratory disease, and accidents. Increased standardised mortality ratios (SMRs) were found for cancer of the pancreas, cancer of the brain, Hodgkin's disease, leukaemia, cancer of other lymphatic tissue, and benign and unspecified neoplasms, but none was significant. About half of the deaths in the benign and unspecified neoplasm category were from benign and unspecified neoplasms of the brain, and increased SMRs were found for brain tumours in people ever employed in the quality control and research laboratories.

This study expands and updates the earlier cohort by adding people who had met the cohort eligibility requirements since the earlier study end date of 31 December 1977, adding current and former employees of three former Getty Oil Company refineries acquired by Texaco as part of its purchase of Getty Oil, and extending vital status follow up to 31 December 1993. The large size of the cohort and the additional 16 years of follow up add substantial power to the original cohort to determine if the earlier observed patterns of mortality have continued. Information on complete work histories for all cohort members made it possible to examine mortality patterns in detail and to compare the results to other studies of refinery workers which have reported increased mortality from leukaemia, malignant melanoma, benign and unspecified neoplasms, kidney cancer, and mesothelioma.[3–8]

The cohort includes employees from 15 refineries (all but seven of which have now been sold or closed), two former packaging facilities, five chemical plants (all of which have been

sold or closed), and three research laboratories. The factories are in 11 states, began operations from 1903 to 1967, and range in size from 140 to 10 060 former and current employees.

Materials and methods

The original study cohort included all employees of Texaco who worked at selected refinery, petrochemical, and research establishments at least one day between 1 January 1947 and 31 December 1977; were employed at these for a cumulative total of ≥5 years; and were employed there on either their last day of employment or the original study end date.[1] Employees of other departments at these factories, employees who transferred to non-participating locations before the study end date, and employees at the former Jefferson Chemical Company who ended employment before 1955 were excluded. Because the duration of employment requirement was longer than usual for a cohort mortality study, information on people employed for ≥1 year was collected for the largest refinery in the study and for the three former Getty refineries. Comparisons of the patterns of mortality for the 1 year versus the 5 year cohorts showed no major differences.

Original study participants were identified from personnel separation rosters listing all employees who left the company between 1947 and 1978 and from computerised personnel files of workers employed in 1978. One hundred and seventeen men and eight women listed on the separation rosters for whom no work history could be found were included in the overall analyses, but not in the job specific analyses.

The current cohort consists of members of the original cohort as well as additional people employed at the Texaco mortality study factories who met the eligibility criteria by 31 December 1993. New cohort members were identified with computerised personnel information as well as by reviewing records of employees at the three Getty refineries that Texaco acquired in 1985. Data collected on each employee included name, social security number, race, sex, date of birth, and a complete history (if available) of all jobs held at any of the participating factories. Updated work history and employment status information on people employed in 1978 was obtained from the computerised personnel system as was information on new cohort members. Original records were requested if parts of the work history had not been computerised. People (1%) whose records lacked information about sex or race were assumed to be white men for the analysis.

Vital status information to 31 December 1993 for former employees was obtained from Texaco files where available, the National Death Index, the Social Security Administration master beneficiary record file, and the Health Care Financing Administration. People identified as alive by the Social Security Administration in 1985 were assumed to be alive if no matching death record was found by the National Death Index. Copies of death certificates were obtained from company files or from the health departments in the states where the deaths occurred. The deaths were coded by a trained nosologist to the eighth revision of the international classification of diseases (ICD-8) as the eighth revision is the one used by the analysis program.

Analyses of patterns of mortality were performed with the program developed by Monson.[9] The program uses the observed and expected numbers of deaths for specific causes to calculate SMRs, with the United States population as the comparison group. Ninety five per cent confidence intervals (95% CIs) were calculated assuming a Poisson distribution for the observed frequency in the numerator of the SMR. Person-years of observation were counted from the date the person attained 5 years of employment or the date the study began, whichever came last, until the study end date, the date of death, or the date lost to follow up, whichever came first. For subcohort analyses, person-years of observation were counted from the date the person attained the required duration of employment in that group or the date the study began, whichever came last.

Total mortality was examined by race and sex. Because of the few non-white women (0.8%), patterns of mortality for all women were examined with the mortalities for United States white women as the comparison. For white men, patterns of mortality were examined by duration of employment, by time first employed, by plant, by job and unit, and by grouped jobs and units (based on the potential for similar tasks and exposures) by duration of employment in the job or unit. For the analysis of mortality by date first employed, the year 1950 was chosen as a dividing date between the early years of the petroleum industry and the later years that tended to have more complex process units and increasing production. Also, about half of the cohort was first employed before 1950, and half after 1950. People who had numerous jobs could be counted in more than one job and unit analysis. See table 1 for a brief description of the potential exposures associated with some of the jobs and units examined.

Results

The study cohort included 28480 people (table 2) with 738 454 total person-years of observation. Over 92% of the cohort members were men, and of these, over 93% were white. Over 85% of the women were white. Because the cohort overwhelmingly consisted of white men (86.4%), the following descriptive statistics refer only to that group. Thirty six per cent of the cohort was dead, only 2.5% were lost to follow up, and death certificates were obtained for all but 1.9% of the deaths.

As of 31 December 1993, only 19% of the cohort was still employed, 44.6% had retired, and 2.5% had left because of a permanent disability. Thirty eight per cent were employed by the company at study locations for ≥30 years. Forty per cent of the cohort were born before 1920, and a quarter were first employed before 1940. Sixty seven per cent of the dead employ-

Table 1 *Texaco mortality study: potential exposures by job and process unit group*

Job or process unit	Description (potential for exposure)
Office, professional, and supervisor	Facility background exposure
Operators	Operate all process units in facility (potentially exposed to *all* chemicals present at facility)
Craft, maintenance	Provide maintenance support; potentially exposed to all chemicals present at facility (certain crafts have potential for exposure to asbestos)
Laboratory staff	Provide quality assurance checks, pilot plant operations, research activities; potentially exposed to all chemicals present at facility (no asbestos)
Fluid catalytic cracking unit (FCCU)	Uses mid-distillates as input, main product is gasoline; residual heavy ends give potential for exposure to polynuclear aromatics (PNAs) (no benzene)
Pipefitters and boilermakers	Could work in shop or any unit in factory; potentially exposed to all chemicals present at factory, including asbestos (under certain circumstances, potential for exposure is high)
Crude stills	Uses crude oil as input; produces gasoline, middle distillates, and heavy bottoms such as asphalt (potential for exposure to PNAs)
Motor oil units	Used to remove wax, solids, and PNAs from motor oils; potential exposure to removed materials, motor oils, and methyl ethyl ketone-toluene (no benzene exposure)
Delayed coking unit (DCU)	Potential for exposure to coke dust, PNAs, and heavy ends (no benzene or asbestos)
Receipt, pumping and storage (RPS)	Potential for high exposure to all factory streams and products (no asbestos)

ees were ≥65 years at the time of death with half of the deaths occurring since the end date of the previous study, 31 December 1977.

Table 3 shows the patterns of mortality for white and non-white men and for women. For white men, there were 8873 observed deaths and 11 181 expected giving a significantly lower all causes SMR of 79. Significant deficits were also found for the leading causes of death in the United States population: all cancers (SMR=81), digestive system cancers (SMR=77), lung cancer (SMR=67), arteriosclerotic heart disease (ASHD, SMR=82), stroke (SMR=86), non-malignant respiratory disease (SMR=65), and all external causes (SMR=62). The observed and expected numbers of deaths were similar for leukaemia, cancer of the pancreas, cancer of the brain and central nervous system, and cancer of other lymphatic tissue. Standardised mortality ratios >100 were found for benign and unspecified neoplasms (SMR=152), and bone cancer (SMR=162). Only the SMR for benign and unspecified neoplasms was significantly increased.

The increases for the causes of death from benign and unspecified neoplasms were examined further. Twenty one (51%) of the benign and unspecified neoplasms were benign (n=3) and unspecified brain tumours (n=18). Because many of the unspecified brain tumours could be malignant, it was decided to combine all the brain tumours together. If the deaths from benign and unspecified brain tumours were combined with the malignancies of the brain and central nervous system, there were 85 observed deaths and 75 expected, giving an SMR for brain tumours of 113, which is not significant.

An examination of the deaths from bone cancer showed that 10 of the 13 decedents died after 1978 when the ninth revision of the ICD codes (ICD-9) came into effect. In ICD-9, the coding rules were changed so that metastatic bone tumours were no longer classified with primary bone tumours. If the ICD-9 had been used to classify the underlying causes of death for the bone cancer death certificates instead of ICD-8, seven of the deaths would not have been coded to cancer of the bone. The SMR for bone cancer would then have been 75.

For non-white men, there were 437 observed deaths and 563 expected giving a significant all causes SMR of 78. Deficits were also found for many of the major causes of death—such as all cancers (SMR=81), cancer of the digestive system (SMR=90), lung cancer (SMR=82), prostate cancer (SMR=52), lymphohaematopoietic cancer (SMR=36), stroke (SMR=77), and non-malignant respiratory disease (SMR=55). The SMRs >100 were for cancer of the stomach (SMR=119), cancer of the pancreas (SMR=119), diabetes (SMR=137), and cancer of the brain and central nervous system (SMR=287). None of these were significant.

For women, there were 265 observed deaths and 325 expected giving a significant deficit for the all causes SMR=82. Deficits were also found for all the leading causes of death including all cancers (SMR=76), digestive system cancers (SMR=50), colon cancer (SMR=20), lung cancer (SMR=79), breast cancer (SMR=71), diabetes (SMR=38), ASHD (SMR=75), stroke (SMR=83), non-malignant respiratory disease (SMR=69), pneumonia (SMR=25), and all external causes (SMR=83). Standardised mortality ratios >100 were found for several cancer sites including cancer of the stomach (SMR=126), leukaemia (SMR=129), uterine cancer (SMR=143), and cancer of other lymphatic tissue (SMR=209). None of these was significant.

All further results apply only to the subcohort of white men and represent only a small subset of the total analyses. In general, the reported results are for the largest job unit groups studied or are for subgroups with results that differed from those expected and led to further cause specific analyses.

Table 4 shows the patterns of mortality by duration of employment. The patterns were similar for all of the groups, and all had significant deficits for all causes of death, all cancers, lung cancer, ASHD, respiratory disease, and all external causes of death. There were significantly increased SMRs for benign and unspecified neoplasms for those employed 230 years

Table 2 *Texaco mortality study: total cohort by vital status (n (%))*

Vital status on 31 December 1993	White men	Non-white men	Women	Total
Alive	15115 (61.4)	1303 (73.1)	1691 (80.8)	18109 (63.6)
Dead	8873 (36.1)	437 (24.5)	265 (12.7)	9575 (33.6)
Unknown	616 (2.5)	43 (2.4)	137 (6.5)	796 (2.8)
Total	24604 (86.4)	1783 (6.3)	2093 (7.3)	28480

Table 3 *Texaco mortality study: SMRs for selected causes of death, 1947–93*

Cause of death (ICDA-8)	White men n=24604, p-y=653857			Non-white men n=1783, p-y=36552			All Women n=2093, p-y=48045		
	Observed deaths	SMR[a]	95% CI	Observed deaths	SMR	95% CI	Observed deaths	SMR	95% CI
All causes	8873	79	78 to 81	437	78	71 to 85	265	82	72 to 92
All cancers (140-209)	1975	81	77 to 84	95	81	65 to 98	74	76	60 to 96
Cancer of digestive system (150-159)	505	77	70 to 84	31	90	61 to 128	11	50	25 to 90
Cancer of stomach (151)	88	80	64 to 98	9	119	54 to 226	3	126	25 to 367
Cancer of large intestine (153)	184	78	68 to 91	8	98	42 to 193	2	20	2 to 74
Cancer of pancreas (157)	132	105	88 to 125	7	119	48 to 244	4	91	24 to 232
Cancer of lung (162)	537	67	61 to 73	31	82	56 to 116	13	79	42 to 135
Cancer of bone (170)	13	162	86 to 278	1	296	4 to 1650	0	0	0 to 1503
Cancer of skin (172-173)	43	98	71 to 132	1	133	2 to 742	1	69	1 to 383
Cancer of breast (174)							15	71	40 to 118
Cancer of cervix (180)							1	30	0 to 167
Cancer of uterus (181)							4	143	39 to 367
Cancer of prostate (185)	218	99	87 to 114	7	52	21 to 107			
Cancer of bladder (188)	63	83	64 to 107	2	100	11 to 360	2	195	22 to 706
Cancer of kidney (189)	55	94	71 to 122	1	53	1 to 293	1	65	1 to 360
Cancer of brain and CNS (191-132)	64	108	83 to 137	4	287	77 to 735	1	40	1 to 221
Lymphatic and haematopoietic cancer (200-209)	226	99	87 to 113	3	36	7 to 106	11	131	65 to 234
Lymphosarcoma and reticulosarcoma (200)	26	75	49 to 110	0	0	0 to 417	0	0	0 to 309
Hodgkin's disease (201)	17	98	57 to 156	0	0	0 to 615	0	0	0 to 618
Leukaemia (204-207)	93	101	81 to 123	0	0	0 to 122	4	129	35 to 331
Other lymphatic tissue (202,203,208)	85	109	87 to 135	3	81	16 to 237	7	209	84 to 431
Benign and unspecified neoplasms (210-239)	41	152	109 to 206	2	150	17 to 543	0	0	0 to 267
Diabetes mellitus (250)	128	77	65 to 90	14	137	74 to 230	3	38	8 to 112
Arteriosclerotic heart disease (410-413)	3209	82	79 to 84	113	93	76 to 111	61	75	57 to 96
Vascular lesions of CNS (430-438)	645	86	79 to 92	35	77	54 to 107	22	83	52 to 125
Non-malignant respiratory disease (460-519)	549	65	60 to 71	19	55	33 to 87	14	69	38 to 116
Pneumonia (480-486)	226	74	65 to 85	9	52	24 to 98	2	25	3 to 89
Cirrhosis of liver (571)	101	47	38 to 57	2	14	2 to 50	5	81	26 to 188
All external causes (800-998)	457	62	56 to 68	61	91	70 to 117	14	83	45 to 139

p-y=Person-years.

(SMR=184) and for cancer of other lymphatic tissue for those employed **20–30** years (SMR=165). The SMR for cancer of other lymphatic tissue for those employed **≥30** years was not increased.

Table **5** shows the patterns of mortality by time first employed, either before or after **1950.** The all causes **SMR** was **82** for the group first employed before **1950** and **64** for the group first employed after **1950.** The observed and expected numbers of deaths were similar for cancer of the pancreas, cancer of the **skin,** cancer of the brain and central nervous system, leukaemia, and cancer of other lymphatic tissue for the group first employed before **1950.** The SMR for benign and unspecified neoplasms was **146** and is of borderline significance. For the group first employed in **1950** and later, there were slightly increased **SMRs** for cancer of the pancreas and Hodgkin's disease, and the SMR for benign and unspecified neoplasms was **176.**

Almost all of the analyses by job and process unit showed deficits for all causes of death, all

Table 4 *Texaco mortality study: SMRs for selected causes of death, 1947–93, by duration of employment*

Cause of death (ICDA-8)	White men employed <10 y n=4017, p-y=138057			White men employed 10-19 y n=5372, p-y=187250			White men employed 20-29 y n=5759, p-y=157474			White men employed >30 y n=9456, p-y=171076		
	Observed deaths	SMR	95% CI	Observed deaths	SMR	95% CI	Observed deaths	SMR	95% CI	Observed deaths	SMR	95% CI
All causes	567	71	65 to 77	1263	80	76 to 85	2324	83	79 to 86	4719	79	76 to 81
All cancers (140–209)	119	73	60 to 87	267	84	74 to 95	514	84	76 to 91	1075	80	75 to 85
Cancer of digestive system (150–159)	29	71	48 to 102	68	80	62 to 102	132	79	66 to 94	276	76	67 to 85
Cancer of stomach (151)	6	88	32 to 192	10	66	32 to 122	28	96	64 to 139	44	74	54 to 100
Cancer of large intestine (153)	11	77	39 to 139	24	83	53 to 124	40	69	50 to 94	109	81	67 to 98
Cancer of pancreas (157)	5	64	21 to 150	19	117	71 to 183	40	125	89 to 170	68	98	76 to 124
Cancer of lung (162)	30	57	38 to 81	63	63	48 to 80	142	69	59 to 82	302	68	61 to 76
Cancer of bone (170)	0	0	0 to 524	1	71	1 to 397	4	182	49 to 465	8	215	93 to 425
Cancer of skin (172–173)	4	87	23 to 223	5	63	20 to 148	12	108	56 to 189	22	109	68 to 165
Cancer of prostate (185)	8	83	36 to 164	23	108	68 to 162	52	105	78 to 138	135	97	82 to 115
Cancer of bladder (188)	4	108	29 to 277	6	71	26 to 155	13	71	38 to 122	40	88	63 to 120
Cancer of kidney (189)	3	73	15 to 214	8	98	42 to 192	18	117	69 to 185	26	84	55 to 123
Cancer of brain and CNS (191–192)	8	125	54 to 246	14	125	68 to 210	16	100	57 to 162	26	100	66 to 147
Lymphatic and haematopoietic cancer (200–209)	18	95	56 to 150	39	114	81 to 156	70	124	97 to 157	99	84	68 to 102
Lymphosarcoma and reticulosarcoma (200)	3	107	22 to 313	8	136	58 to 267	10	109	52 to 200	5	30	10 to 70
Hodgkin's disease (201)	3	111	22 to 325	5	116	37 to 271	4	89	24 to 228	5	85	27 to 197
Leukaemia (204–207)	7	93	37 to 192	17	125	73 to 200	23	101	64 to 152	46	94	69 to 126
other lymphatic tissue (202,203,208)	5	91	29 to 212	8	80	34 to 158	31	165	112 to 234	41	94	68 to 128
Benign and unspecified neoplasms (210–239)	2	83	9 to 301	9	196	89 to 371	6	86	31 to 187	24	184	118 to 274
Diabetes mellitus (250)	2	18	2 to 64	13	58	31 to 98	32	79	54 to 112	81	91	72 to 113
Arteriosclerotic heart disease (410–413)	149	66	56 to 77	439	86	78 to 94	930	93	87 to 99	1691	77	73 to 81
Vascular lesions of CNS (430–438)	39	103	73 to 141	74	82	64 to 102	133	73	61 to 86	399	90	82 to 100
Non-malignant respiratory disease (460–519)	31	69	47 to 89	74	77	60 to 96	149	75	63 to 88	295	59	52 to 66
Pneumonia (480–486)	12	73	38 to 128	34	92	64 to 128	59	83	63 to 107	121	68	56 to 81
Cirrhosis of liver (571)	5	23	8 to 55	20	47	29 to 73	25	39	25 to 58	51	57	42 to 75
All external causes (800–998)	84	60	48 to 74	110	58	48 to 70	104	57	47 to 70	159	69	59 to 81

p-y=Person-years.

Table 5 Texaco mortality study: SMRs for selected causes of death by time first employed, 1947–93

Cause of death (ICDA)	White men employed before 1950 n=11649, p-y=383640			White men employed 1950 and after n=12955, p-y=270302		
	Observed deaths	SMR	95% CI	Observed deaths	SMR	95% CI
All causes	7644	82	81 to 84	1229	64	61 to 68
All cancers (140–209)	1655	84	80 to 88	320	68	61 to 76
Cancer of digestive system (150–159)	412	75	68 to 83	93	84	68 to 103
Cancer of stomach (151)	75	79	62 to 99	13	84	44 to 143
Cancer of large intestine (153)	152	78	66 to 92	32	80	54 to 112
Cancer of pancreas (157)	105	102	83 to 124	27	119	78 to 173
Cancer of lung (162)	449	72	65 to 78	88	50	40 to 62
Cancer of bone (170)	13	196	104 to 335	0	0	0 to 267
Cancer of skin (172–173)	32	105	72 to 148	11	82	41 to 147
Cancer of prostate (185)	195	100	86 to 115	23	98	62 to 147
Cancer of bladder (188)	55	83	62 to 108	8	88	38 to 173
Cancer of kidney (189)	43	94	68 to 126	12	94	49 to 164
Cancer of brain and CNS (191–192)	48	113	83 to 150	16	95	54 to 154
Lymphatic and haematopoietic cancer (200–209)	187	104	90 to 120	39	81	58 to 111
Lymphosarcoma and reticulosarcoma (200)	20	70	43 to 109	6	99	36 to 215
Hodgkin's disease (201)	12	93	48 to 163	5	111	36 to 258
Leukaemia (204–207)	84	113	90 to 140	9	50	23 to 94
Other lymphatic tissue (202,203,208)	67	113	87 to 143	18	98	58 to 155
Benign and unspecified neoplasms (210–239)	32	146	100 to 207	9	176	80 to 335
Diabetes mellitus (250)	116	86	71 to 103	12	42	22 to 73
Arteriosclerotic bean disease (410–413)	2833	84	81 to 87	376	66	60 to 73
Vascular lesions of CNS (430–438)	596	88	81 to 95	49	65	48 to 86
Non-malignant respiratory disease (460–519)	495	68	62 to 74	54	49	37 to 64
Pneumonia (480–486)	206	76	66 to 88	20	58	35 to 89
Cirrhosis of liver (571)	79	51	40 to 63	22	36	22 to 54
All external causes (800–998)	318	66	59 to 74	139	54	45 to 63

p-y=Person-years.

cancer, digestive system cancer, lung cancer, ASHD, stroke, and all external causes of death similar to those found for all white men. Therefore, the following table shows only the results for selected neoplasms for these job subgroups.

Table 6 shows the patterns of mortality for those employed in selected job and process groups mentioned below for at least 5 years. For those who were employed in office jobs, as managers and supervisors, or in professional jobs, there were non-significantly increased SMRs for cancer of the pancreas, bone cancer, skin cancer, prostate cancer, bladder cancer, and benign and unspecified neoplasms.

For those employed as operators and controlmen, the SMR for cancer of other lymphatic tissue were increased as was the SMR for benign and unspecified neoplasms for those ever employed in maintenance.

For those ever employed as laboratory staff, there were increased SMRs for skin cancer, cancer of the brain and central nervous system, and benign and unspecified neoplasms. For people employed on a fluid catalytic cracking unit, there was a significantly increased SMR for all lymphohaematopoietic cancer that partly resulted from a significantly increased SMR for cancer of other lymphatic tissue. Although the SMRs for the other lymphohaematopoietic cancers were also increased, they were not significant. The higher SMRs noted for skin cancer, kidney cancer, cancer of the brain and central nervous system, and benign and unspecified neoplasms were not significant.

For people employed as pipefitters or boilermakers, there were increased SMRs for bone cancer, kidney cancer, leukaemia, cancer of other lymphatic tissue, and benign and un-

Table 6 Texaco mortality study: SMRs for selected neoplasms, for selected jobs and process units, 1947–93

Cause of death (ICDA-8)	Office, professional, supervisor employed > 5 years white males n=7586, p-y=168489			Controlmen, operators employed > 5 y wgite men n=9542, p-y=247983			Craft, maintenance employed > 5y white men n=7910, p-y=220713		
	Observed deaths	SMR	95% CI	Observed deaths	SMR	95% CI	Obserwd deaths	SMR	95% CI
All cancers (140–209)	590	75	69 to 81	801	81	75 to 86	738	84	78 to 91
Cancer of digestive system (150–159)	166	78	67 to 91	203	75	65 to 86	193	82	70 to 94
Cancer of stomach (151)	19	54	32 to 84	41	89	64 to 120	36	90	63 to 125
Cancer of large intestine (153)	65	85	66 to 108	63	66	50 to 84	62	74	57 to 95
Cancer of pancreas (157)	53	131	98 to 171	52	101	75 to 133	56	124	94 to 161
Cancer of lung (162)	140	54	45 to 63	223	69	60 to 79	206	72	63 to 83
Cancer of bone (170)	5	208	67 to 486	3	91	18 to 264	4	139	37 to 357
Cancer of skin (172–173)	18	133	79 to 210	11	63	32 to 114	17	111	65 to 177
Cancer of prostate (185)	82	111	89 to 138	98	107	87 to 130	69	87	68 to 111
Cancer of bladder (188)	24	97	62 to 144	30	95	64 to 135	21	77	48 to 118
Cancer of kidney (189)	15	80	45 to 131	26	110	72 to 161	22	105	66 to 159
Cancer of brain and CNS (191–192)	15	84	47 to 138	20	85	52 to 132	22	105	66 to 160
Lymphatic and hematopoietic cancer (200–209)	54	75	57 to 98	93	101	82 to 124	71	88	69 to 111
Lymphosarcoma and reticulosarcoma (200)	8	77	33 to 152	10	70	34 to 129	5	40	13 to 94
Leukaemia (204–207)	23	79	50 to 118	37	98	69 to 135	25	76	49 to 112
Other lymphatic tissue (202,203,208)	21	82	51 to 126	40	129	92 to 175	30	109	74 to 156
Benign and unspecified neoplasms (210–239)	12	146	75 to 255	10	91	44 to 168	16	167	95 to 271

p-y=Person-years

specified neoplasms. Because of increases related to asbestos found in pipefitters in other similar studies, deaths from mesothelioma were reviewed in detail in a further paper. For people employed on the crude stills, the SMR for cancer of other lymphatic tissue is **172.** There were also non-significant increases for pancreas cancer and kidney cancer.

For people who were employed on the motor oil unit, one of the lube oil extraction units, the clay filter plant, or the paraffin plant, there were non-significantly increased SMRs for stomach cancer, pancreatic cancer, bladder cancer, lymphosarcoma, leukaemia, and benign and unspecified neoplasms. The SMR for cancer of the brain and central nervous system was **314 (95%** CI **115** to **684).**

Discussion

The patterns of mortality found in this **1993** update of the Texaco mortality study cohort are generally similar to earlier findings on this cohort.[2] As found in the **1977** study, mortality experience is more favourable for the cohort than the United States population. The cohort again experienced significantly fewer deaths from the leading causes of death in the United States, all causes combined, all cancers, heart disease, non-malignant respiratory disease, and all external causes. As in the earlier study, increased mortality was found for benign and unspecified neoplasms, and this result is now significant. The increased mortality from cancer of the bone, which was not found in the earlier study, resulted from an ICD revision coding artifact. Several of these tumours were carcinomas and not sarcomas or tumours of bone tissue origin. Coding rules for the ICD-9 were modified to prevent metastatic bone tumours from being coded as primary bone tumours. As stated in the results section, under these rules there was no excess of bone cancer. A similar result was found by Satin et *al.*[6]

The overall results of this analysis support the conclusions of the meta-analysis of petroleum industry workers by Wong and Raabe.[1] They found that the petroleum industry, in general, had a significantly low cancer mortality for all cancer sites combined and for cancers of the digestive system, stomach, and lung. These findings are confirmed by the current study. Wong and Raabe found mortality to be similar to that for the United States population for cancers of the skin, brain, pancreas, prostate, and kidney. These cancers show small increases in various subgroups in the current study, but the increases are not consistent, nor are they linked to increasing duration of employment in most of the job or unit specific subgroups.

The Wong and Raabe report did suggest that some of the refinery workers, especially those first employed before **1940,** might have an increased risk of leukaemia. However, a follow up meta-analysis that looked specifically at leukaemia cell types[11] showed no increased SMRs for acute myelogenous leukaemia or any of the other leukaemia cell types. The SMR for leukaemia for this cohort is as expected **(101)** and is only slightly increased **(113)** for those first employed before **1950.** None of the increases for total leukaemia in the current study is consistent among the subgroups studied, nor is any linked to increasing duration of employment in most of the job or unit specific subgroups.

The SMRs for brain cancer in laboratory workers have decreased compared with those found in the earlier mortality analysis for this cohort.[1] The earlier study showed SMRs of 210 and **221** for those employed as laboratory workers for ≥**1** year or ≥5 years, respectively. For the most recent update, the SMRs for the same groups have declined **to 164** and **169.** The original finding may reflect a chance cluster which has not continued. Even if the finding is not due to chance, there is no known exposure to chemical or physical agents for laboratory workers in the Texaco mortality study that has been causally associated with brain cancer. Also, laboratory practices have changed dramatically over the past **30** years, and exposure potentials have declined steadily through the automation of test procedures and advances in the design of laboratory ventilation.

Table **6** *Continued*

Laboratory staff employed > 5 y *white men n=2478, p-y=68286*			*FCCU process unu employed* > 5 y *white men n=1432, p-y=34975*			*Pipefitter, boilermaker employed* > 5 y *white men n=1974, p-y=53028*			*Crude & employed* > 5 y *white men n=1418, p-y=35270*			*Motor* oil units *employed* > 5 y white men *n=619, p-y=17782*		
Obsd deaths	*SMR*	*95% CI*	*Observed deaths*	*SMR*	*95% CI*	*Obsd deaths*	*SMR*	*95% CI*	*Observed deaths*	*SMR*	*95% CI*	*Observed deaths*	*SMR*	*95% CI*
171	67	57 to 78	141	93	78to 110	204	88	76 to 101	136	69	57 to 81	86	98	79 to 121
39	60	42to 81	38	95	67 to 130	48	75	56 to 100	37	65	46 to 90	24	99	63to 147
5	50	16 to 117	4	62	17 to 159	11	100	50 to 180	**5**	49	16to 114	6	142	52 to 309
25	104	67to 153	14	96	53 to 161	15	67	37to 110	7	35	14to 72	6	70	25 to 152
6	47	17 to 102	10	129	62 to 237	10	83	40 to 153	13	124	66 to 212	6	131	48 to 285
45	51	37to 68	32	63	43 to 90	**64**	85	66to 109	35	**58**	41 to 81	19	68	41to 107
0	0	0 to 504	0	0	0 to 801	2	259	29 to 935	0	0	0 to 525	1	336	4to 1869
7	149	60 to 307	5	191	62 to 446	4	102	27 to 260	1	33	Oto 184	1	72	1to 400
21	97	60to 148	13	94	50 to 161	21	97	60 to 149	19	89	53 to 138	10	117	56 to 215
5	69	22to 161	1	21	Oto 119	6	80	29 to 175	6	83	30 to 180	5	170	55 to 396
1	16	Oto 89	7	193	77 to 398	7	127	51 to261	7	154	62 to 317	2	98	11to 352
11	169	84 to 302	5	140	45 to327	3	56	11 to 165	2	51	6to 183	6	314	115 to 684
20	84	51 to 129	**25**	179	116 to 264	22	104	65 to 157	16	89	**51** to 144	7	88	35to 181
2	60	7 to 215	3	143	29 to 417	2	61	7 to 219	2	69	8 to 250	1	79	1 **to** 437
8	85	37to 167	8	142	61 to280	14	160	88 to 269	3	39	8to 114	4	121	33to 310
7	80	32 to 165	13	264	140 to 452	3	42	8 to 122	10	172	82 to 317	2	76	9to 274
5	182	59 to 425	3	186	37 to543	**6**	237	87 to 516	2	91	10 to 328	2	208	23to 750

Cancer of other lymphatic tissue is increased in several job unit specific analyses including workers employed on the fluid catalytic cracking units, the crude units, and as pipefitters. This cause of death category is composed of three different types of lymphohaematopoietic cancers including lymphoma, multiple myeloma, and polycythemia vera. The contribution of each of these causes of death to this result will be examined in the accompanying paper.

We have no explanation for the significant deficit for mortality from leukaemia for those first employed after 1950 (SMR=50). It is unlikely that insufficient latency is responsible. The SMR for leukaemia is much lower than those for many of the solid tumours that are often assumed to have a longer induction period than leukaemia.

The Texaco mortality study update has several strengths, especially compared with other company studies of petroleum workers. The cohort is the largest in the petroleum industry including over 28 000 people from many places. More than half of the cohort was employed in the industry for >25 years, and its mortality experience has been studied for 47 years (1947–93). Vital status is unknown for <3% for the entire cohort, and the number of missing death certificates is <2%. Also, it is the only reported large study of refinery workers which includes information about the cohort members' complete work histories and the only one in which many analyses by both individual jobs and units as well as grouped jobs and units have been performed. In recent years, it has become common in the petroleum industry to use contract workers for maintenance activities and for the remaining workers to work on multiple crafts or units. However, this practice did not begin until the 1980s, and it is thus unlikely that it would have had an influence on the causes of death of interest which have ≥20 years of latency.

The study does have several limitations. As with other mortality studies, it has the problems associated with diagnoses from the death certificates for the cause of death—for example, diagnostic accuracy and specificity, and comparability of ICD codes over time. Although the cohort is one of the largest studied in the petroleum industry, many of the subgroups analysed are small in size, and for many of the causes of death, the number of deaths is small making the results inconclusive and difficult to interpret. Because of the numerous analyses done, some isolated increases in SMRs would be expected by chance alone.

Although the employee's complete work history was used, information about the specific chemicals associated with each of the job and unit combinations is not available nor is there any sampling data on industrial hygiene covering the first 30 years of the study. Jobs and units with similar responsibilities were grouped together for the analyses as a surrogate for exposures, but provide little information to link exposure to outcome.

Conclusion

This paper reports the overall results of the Texaco mortality study update. The results showed a favourable mortality experience for refinery, petrochemical, and research employees compared with the general United States population. Most causes of death showed either similar mortality or a significant deficit among the Texaco employees. There was a 21% deficit for all deaths for the total cohort which translates into an increased life expectancy of 2.9 years for Texaco refinery, petrochemical, and research workers compared with United States white men.[11]

Only a few increases were seen consistently in several of the analysis subgroups, which were significantly increased, or which have been found in other studies of petroleum industry workers. These include increases for cancer of other lymphatic tissue in workers employed on the fluid catalytic cracking unit and crude stills, and for benign and unspecified neoplasms and brain cancer in workers employed in the laboratories and on the units related to motor oil. Additional analyses of these results as well as results specific to leukaemia cell types and mortality from mesothelioma will be discussed in a later report.

1 Divine BJ, Barron V, Kaplan SD. Texaco mortality study I. Mortality among white male refinery, petrochemical, and research workers. *J Occup Med* 1985;27:445–7.

2 Divine BJ, Barron V. Texaco mortality study II. Patterns of mortality among white males by specific job groups. *Am J Ind Med* 1986;10:371–81.

3 Wong O, Raabe GK. Critical review of cancer epidemiology in petroleum industry employees, with a quantitative meta-analysis by cancer site. *Am J Ind Med* 1989;15:283–310.

4 McCraw DS, Joyner RE, Cole P. Excess leukemia in a refinery population. *J Occup Environ Med* 1985;27:220–2.

5 Nelson NA, Van Peenen PFD, Blanchard AG. Mortality in a recent oil refinery cohort. *J Occup Environ Med* 1987;29:610–2.

6 Satin KP, Wong O, *Yuan* LA, *et al*. A 50-year mortality follow-up of a large cohort of oil refinery workers in Turps. *J Occup Environ Med* 1996;38:492–506.

7 Shallenberger LG, Acquavella JF, Donaleski D. An updated mortality study of workers in three major United States refineries and chemical plants. *Br J Ind Med* 1992;49:345–4.

8 Tsai SP, Waddell LC, Gilstrap EL, *et al*. Mortality among maintenance employees potentially exposed to asbestos in a refinery and petrochemical plant. *Am J Ind Med* 1996;29:89–98.

9 Monson RR. Analysis of relative survival and proportionate mortality. *Computer Bwmed Res* 1974;7:325–32.

10 Wong O, Raabe GK. Cell-type specific leukemia analyses in a combined cohort of more than 208 000 petroleum workers in the United States and the United Kingdom. *Reg Toxicol Pharmacol* 1995;21:307–21.

11 Tsai SP, Hardy RJ, Wen CP. The standardized mortality ratio and life expectancy. *Am J Epidemiol* 1992;135:824–31.

Occup Environ Med 1999;56:174–180

Update of the Texaco mortality study 1947–93: part 11. Analyses of specific causes of death for white men employed in refining, research, and petrochemicals

Barbara J Divine, Christine M Hartman, Judy K Wendt

Abstract

Objective—To examine patterns of mortality for specific causes of death with increases in the Texaco mortality study to determine if the patterns are related to employment in the petroleum industry.

Methods--Mortality patterns by duration of employment in various job groups were examined for mesothelioma, non-Hodgkin's lymphoma, multiple myeloma, cell type specific leukaemia, and brain tumours.

Results—Mortality from mesothelioma was examined for the total cohort and for two maintenance groups with the greatest potential for exposure to asbestos. The insulator group had a standardised mortality ratio (SMR) of 3029, and a larger group consisting of insulators, carpenters, labourers, electricians, pipefitters, boilermakers, and welders had an SMR of 411. The mortalities from mesothelioma increased with increasing duration of employment. Mortality was lower for those first employed after 1950. An analysis of all brain tumours for the total cohort and some job and unit subgroups resulted in an SMR of 178 for those employed on the units related to motor oil and 166 for those employed as laboratory workers. Mortality from brain tumours in both of these job groups was higher for those employed ≥5 years in the group. An analysis of non-Hodgkin's lymphoma showed no consistent patterns among the various employment groups. Mortality from multiple myeloma was non-significantly increased among people employed on the crude (SMR=155) and fluid catalytic cracking units (SMR=198). Leukaemia mortality was not increased for the total cohort, and a cell type analysis of leukaemia mortality for the total cohort showed no significant increases for the major cell types. However, there were significant increases for acute unspecified leukaemia (SMR=276) and leukaemia of unknown cell type (SMR=231).

Conclusions—Analyses of specific causes of death by duration of employment in various job and process units did not show any patterns which suggest that, other than for mesothelioma, any of these increases in mortalities were likely to have resulted from workplace exposures or from employment at one of the places included in the Texaco mortality study.

(Occup Environ Med 1999;56:174–180)

Keywords: petroleum industry; mesothelioma; asbestos; non-Hodgkin's lymphoma; multiple myeloma; brain tumours

A recent report presented the 1947–93 patterns of mortality for the workers of the Texaco mortality study employed for ≥5 years at company refineries, petrochemical plants, and research laboratories.[1] The study cohort consisted of over 28 840 workers, and the results showed that the overall mortality and most cause specific mortalities were lower than those of the general United States population. The patterns of mortality for the job and process units were similar to those for the overall cohort. However, there were a few increases that were found consistently in several of the analysis subgroups, were significantly increased, or have been found in other studies of petroleum industry workers.

Significant increases for cancer of other lymphatic tissue, which includes both lymphoma and multiple myeloma, were reported in the earlier study of workers employed on the fluid catalytic cracking unit and on the crude stills. Non-significant increases were also found for several other job and unit combinations. Mortality from non-Hodgkin's lymphoma and multiple myeloma were examined separately to reflect more recent classifications of these diseases.

The total cohort of white men showed a significant excess for benign and unspecified neoplasms, and the excess was also noted in some of the job and unit analyses, especially for those ever employed in laboratories or on the motor oil units. Twenty one of the 41 deaths in the benign and unspecified neoplasm category were from benign and unspecified neoplasms of the brain. Brain cancer mortality was also increased for those ever employed in laboratories or on the motor oil units. Therefore, further analyses of all brain tumours (malignant, benign, and unspecified combined) by job and unit combinations were carried out.

A recent publication by Tsai et al[2] showed that a group of maintenance workers defined by their potential for exposure to asbestos had a significant excess of mesothelioma. Therefore, it was decided to examine mortality from

Texaco, PO Box 1404, Houston, TX 77251, USA
B J Divine
C M Hamnan

University of Texas, MD Anderson Cancer Center, 1100 Holcombe Boulevard, Pain Research Group — Box 221, HMB 15.556, Houston, TX 77030, USA
J K Wendt

Correspondence to:
Dr B J Divine, Texaco, PO Box 1404, Houston, TX 77251, USA.

Accepted 2 October 1998

mesothelioma for several job groups with the potential for exposure to asbestos.

An investigation of the mortality for leukaemias of specific cell types was also performed. Refinery workers have the potential to be exposed to benzene which has been associated with an increased risk of acute myelogenous leukaemia at high exposure levels.' Wong and Raabe' recently conducted a meta-analysis of leukaemia by cell type in petroleum industry cohorts but found no significantly increased risks for any cell type, including acute myelogenous leukaemia. Satin et al[5] found an excess of acute lymphocytic leukaemia in a recent cohort mortality study at a large refinery next to the largest factory included in the Texaco mortality study. However, there was no exposure-response relation, and the authors also found a large deficit for chronic lymphocytic leukaemia.

Methods

The expected numbers of deaths were obtained by multiplying the person-years for each subgroup analysed by the United States mortalities. Standardised mortality ratios (SMRs) were calculated as the ratio of the observed and expected numbers of deaths for specific causes multiplied by 100. The SMRs were tested for statistical significance with Poisson based 95% confidence intervals (95% CIs) assuming a two sided test. The SMRs were calculated for those people ever employed in the job and unit group of interest, and if there were sufficient numbers of deaths, for those people who were employed in the job and unit group for ≥5 years. The SMRs were also calculated by the period in which first employment occurred.

ANALYSIS OF DEATHS FROM MESOTHELIOMA

Mesothelioma does not have a specific code in the eighth revision of the international classification of diseases (ICD-8) that can be used to identify the deaths from this cause. Instead, depending on the phrasing of the death certificate, mesothelioma can be coded as a respiratory cancer (ICD-8 codes 162.1, 163, 163.0, or 163.9), a malignant neoplasm without mention of site (ICD-8 codes 199, 199.0, or 199.1), a benign respiratory disease (ICD-8 codes 212.3, 212.4, or 228), or a malignant neoplasm of the peritoneum (ICD-8 code 158). Death certificates for the Texaco mortality study cohort with any of these ICD-8 codes either as the underlying or as a contributory cause of death were reviewed. Those death certificates with any mention of mesothelioma were defined as a case.

Because mortalities for mesothelioma have not been published, the 1973–80, 1985–8, and 1988–91 surveillance, epidemiology, and end results programme of the National Cancer Institute mesothelioma incidences were used. As mesothelioma is almost always fatal, the incidences were assumed to be the same as the mortalities. It was assumed that the rates in the 1950s and 1960s were one quarter and one half, respectively, the rates for the 1970s. These assumptions were the same as those used for the recent report by Tsai et al[2] and are based on the pattern of incidences from the Connecticut tumour registry.[6]

Mortality from mesothelioma for the total cohort of white men was examined as well as the mortality in two job groups with the greatest potential for exposure to asbestos. The first job group consisted of people ever employed as insulators. The second group included people ever employed as insulators, pipefitters, welders, boilermakers, carpenters, electricians, and labourers, a grouping similar to that reported recently.* The mesothelioma patterns were examined for these groups by duration of employment and by time first employed in the job group.

ANALYSIS OF LYMPHOHAEMATOPOIETIC DEATHS

The combined categories of lymphohaematopoietic cancers in the published United States mortalities prevented analyses of these causes of death as separate entities. For example, lymphosarcoma and reticulum cell sarcoma comprise one category, whereas multiple myeloma, lymphoma, and polycythemia vera are grouped in another category. Haematologists recommend that lymphosarcoma and reticulum cell sarcoma should be grouped with lymphoma to make a non-Hodgkin's lymphoma category and that the other causes of lymphohaematopoietic cancers should be examined separately (Irons R, 1995; personal communication). Also, all of the leukaemias are grouped together in the published United States mortalities although the different cell types are different diseases and can have different aetiologies.

Mortalities for the period 1964–92 for multiple myeloma, leukaemia by cell type, and lymphoma were obtained from the mortality and population data system maintained by the University of Pittsburgh Department of Biostatistics.' The rates for the years before 1964 were assumed to be the same as those for 1965–9. The rates for unspecified leukaemia for the years 1980–92 were assumed to be the same as those for 1975–9. The rates for lymphosarcoma and reticulum cell sarcoma from Monson's program* were added to the lymphoma rates to give mortalities for non-Hodgkin's lymphoma. The mortalities for each of the causes of death of interest were then multiplied by the person-years for the subgroups to give the expected numbers of deaths for the specific cause of interest.

ANALYSIS OF DEATHS FROM BRAIN TUMOURS

Because several of the deaths from benign and unspecified neoplasms in the previous report on this cohort' were categorised as benign and unspecified brain tumours, United States mortalities for these two categories of death were also obtained from the University of Pittsburgh mortality and population data system. The rates were added together, and the rates for the years before 1964 were assumed to be the same as those for 1965–9. These rates were then multiplied by the person-years for the various groups of interest. Observed and expected numbers of deaths from brain tumours were added to those for cancer of the brain and

Table 1 Texaco mortality study: SMRs for mesothelioma and lung cancer, white men, 1947–93

	Mesothelioma			Lung cancer		
	Observed	SMR	95% CI	Observed	SMR	95% CI
Total cohort	44	297	216 to 399	537	67	61 to 73
Insulators (duration of employment):						
0 to 4 y	4	571	153 to 1462	31	77	52 to 110
5 to 19 y	1	714	9 to 3974	10	133	63 to 245
220 y	10	9916	447 to 18237	7	128	51 to 264
Before 1950	9	4586	2092 to 8706	18	159	94 to 251
1950 And after	2	1200	134 to 4335	5	61	20 to 141
Insulators, pipefitters, welders, labourers, boilermakers, electricians, carpenters (duration of employment):	29	411	275 to 590			
0 to 4 y	14	239	131 to 402	219	68	59 to 78
5 to 19 y	7	322	129 to 664	91	75	60 to 92
220 y	16	1053	601 to 1710	75	89	70 to 112
Before 1950	25	470	304 to 694	238	78	69 to 89
1950 And after	4	230	62 to 591	52	61	45 to 80

central nervous system to calculate an overall brain tumour SMR. The SMRs were calculated for the total cohort and for the job and unit groups where increased SMRs for either brain cancer or benign and unspecified neoplasms were found in the overall analysis.[1]

Results

MORTALITY ANALYSES OF MESOTHELIOMA

There were 44 deaths with any mention of mesothelioma on the death certificate. For all but one of these, mesothelioma was the underlying cause of death. All but eight of the decedents were first employed before 1 January 1950, and for all, at least 30 years had elapsed between the time they were first employed and the date of death. The mesothelioma SMR for the total cohort was 297 which was significant. There were 11 deaths from mesothelioma for those employed as insulators for ≥1 year (SMR=3029, 95% CI 1510 to 5420) and 29 deaths for those employed as insulators, pipefitters, welders, labourers, boilermakers, electricians, or carpenters for ≥1 year (SMR=411, 95% CI 275 to 590).

Table 1 shows the SMRs for mesothelioma for all white men and for the two exposure groups by duration of employment in the group and by time first employed. Almost all of the SMRs were significantly increased and corresponded with increasing duration of employment in each group. The highest SMRs are found among people employed as insulators for ≥20 years (SMR=9916). The SMRs were higher for people first employed in either of the job groups before 1950. Increased SMRs were also found for those people first employed after 1950 and were significant for the group of insulators.

Several of the deaths from mesothelioma were originally coded as primary lung cancer deaths (an ICDA-8 code of 162.9 for the underlying cause of death), and increased mortality from lung cancer has also been associated with exposure to asbestos.[9] Table 1 also shows the SMRs for lung cancer with the mesothelioma deaths with an ICDA-8 of 162.9 excluded for the two exposure groups defined by duration of employment. Only the subcohort of insulators had a mortality that increased slightly with duration of employment in the group. None of these SMRs was significant. For the larger exposure group, the SMRs increase with duration of employment, but all are <100. There was a non-significant increase for lung cancer for those first employed as insulators before 1950 (SMR=159) but a large deficit for those first employed in 1950 and after (SMR=60). No information on the smoking histories of the cohort was available.

Table 2 Texaco mortality study: SMRs for brain tumours, white men, 1947–93

	Observed	Expected	SMR	95% CI
Total cohort:				
Ever	85	75	113	90 to 140
Employed before 1950	62	54.8	113	86 to 145
Employed 1950 and after	23	20.2	113	72 to 170
Maintenance:				
Ever	61	55.1	110	84 to 142
Laboratory staff:				
Ever	19	11.4	166	99 to 259
Employed ≥5 y	15	8.1	185	103 to 305
Receiving, pumping, and storage:				
Ever	11	10.9	101	50 to 181
Pipefitter				
Ever	15	14.9	100	56 to 165
Motor oil unit:				
Ever	11	6.2	178	88 to 319
Employed ≥5 y	8	2.5	326	140 to 643

MORTALITY ANALYSES OF BRAIN TUMOURS

There were 21 observed deaths and 15.5 expected from benign and unspecified brain tumours, resulting in an SMR of 135 (not significant). There were 64 observed deaths and 59.5 expected from cancer of the brain and central nervous system. Combining all such tumours gave 85 observed deaths and 75 expected, for an SMR of 113 (table 2). Observed and expected deaths from brain tumours were compared for persons employed in maintenance (SMR=110); in receiving, pumping, and storage (SMR=101); as a pipefitter (SMR=100); as laboratory staff (SMR=166); and on the motor oil units (SMR=178). The total cohort SMRs for those first employed before 1950 and for those first employed in 1950 or later were the same (SMR=113). Mortality from brain tumours for people employed either in laboratory jobs or on the motor oil units for ≥5 years were higher than for people ever so employed, and the SMRs were significant (SMRs=185, and 326, respectively).

Table 3 Texaco mortality study: SMRs for non-Hodgkin's lymphoma and multiple myeloma, white men, 1947–93

	Non-Hodgkin's lymphoma			Multiple myeloma		
	Observed	*SMR*	*95% CI*	*Observed*	*SMR*	*95% CI*
Total cohort:						
Ever	74	88	69 to 111	36	101	70 to 140
Employed before 1950	56	87	65 to 113	30	103	69 to 147
Employed 1950 and after	18	95	56 to 151	6	91	33 to 199
Maintenance:						
Ever	54	87	65 to 114	30	112	76 to 161
Operators:						
Ever	37	73	51 to 101	17	79	46 to 126
Fluid catalytic cracking unit:						
Ever	13	155	82 to 265	7	198	79 to 408
Employed 25 y	6	118	43 to 258	6	270	90 to 589
Receiving, pumping and storage:						
Ever	14	118	64 to 198	6	118	43 to 258
Pipefitters, boilermakers						
Ever	15	72	40 to 119	14	153	84 to 258
Delayed coking unit:						
Ever	6	86	31 to 188	6	196	71 to 427
Employed ≥ 5 y				1	156	2 to 873
Crude stills:						
Ever	16	122	70 to 199	9	155	70 to 294
Employed ≥ 5 y				5	172	55 to 401

MORTALITY ANALYSES OF NON-HODGKIN'S LYMPHOMA

Table 3 shows the results of the analysis of deaths from non-Hodgkin's lymphoma. Observed and expected deaths from lymphosarcoma, reticulum cell sarcoma, and lymphoma combined were similar for the total cohort (SMR=88) and for those employed in maintenance (SMR=87), in receiving, plumbing, and storage (SMR=118), on a process unit (SMR=73), on the delayed coking unit (SMR=86); on the crude unit (SMR=122); and as a pipefitter or boilermaker (SMR=72). The SMRs are similar for those first employed before 1950 (SMR=87) and first employed 1950 and after (SMR=95). For those ever employed on the fluid catalytic cracking unit, the SMR was 155, but it decreased to 118 for those employed on the fluid catalytic cracking unit ≥5 years. None of these SMRs was significant.

MORTALITY ANALYSES OF MULTIPLE MYELOMA

Table 3 also shows the results of the analysis of multiple myeloma. The observed and expected deaths were about the same for the total cohort (SMR=101); people employed in maintenance (SMR=112); employed in receiving, plumbing, and storage (SMR=118); and employed on a process unit (SMR=79). Similar results were seen for those first employed before 1950 (SMR=103) and first employed in 1950 and after (SMR=91). For those employed on the fluid catalytic cracking unit, the SMR was 198, and it rose to 270 for those employed on the fluid catalytic cracking unit ≥5 years. For those employed on the crude unit, the SMR was 155, increasing to 172 for those employed on the crude still ≥5 years. Four of the decedents were employed on both the fluid catalytic cracking unit and the crude unit. For those employed as a pipefitter or boilermaker, the SMR was 153; however, there were no deaths from multiple myeloma among people employed as pipefitters or boilermakers for ≥5 years. For those employed on the delayed coking unit the SMR was 196, but there was only one death among those employed on the delayed coking unit for ≥5 years. These SMRs for multiple myeloma were not significant.

Table 4 Texaco mortality study, SMRs for leukaemia by cell type, white men, 1947–93

	Observed	*Expected*	*SMR*	*95% CI*
Total cohort:				
Acute lymphocytic (ALL)	5	4.9	101	32 to 235
ALL, employed before 1950	5	3.8	133	42 to 311
Chronic lymphocytic (CLL)	15	18.6	80	45 to 133
CLL, employed before 1950	13	15.8	82	43 to 140
CLL, employed 1950 and after	2	2.8	72	8 to 262
Acute myelogenous (AML)	20	15.5	129	78 to 199
AML, employed before 1950	19	12.2	155	93 to 243
AML, employed 1950 and after	1	3.3	30	0 to 168
Chronic myelogenous (CML)	12	11.4	105	54 to 183
CML, employed before 1950	10	8.6	116	55 to 214
CML, employed 1950 and after	2	2.8	70	7 to 254
Acute unspecified (AUL)	15	5.4	276	154 to 455
AUL, employed before 1950	13	4.7	276	147 to 472
AUL, employed 1950 and after	2	0.7	273	30 to 986
Cell type unspecified (UL)	15	6.5	231	129 to 381
UL, employed before 1950	14	5.3	262	143 to 440
UL, employed 1950 and after	1	1.1	87	1 to 486

MORTALITY ANALYSES OF LEUKAEMIA BY CELL TYPE

The SMRs were calculated for the cell type specific leukaemias where there are at least four deaths (table 4) for the total cohort and for those first employed before and after 1950. All but one of the cell type groups showed deficits in the group first employed in 1950 and after. The mortality for acute lymphocytic leukaemia was the same as expected (SMR=101), and all of the acute lymphocytic leukaemia deaths occurred in people first employed before 1950 (SMR=133). There was a deficit for chronic lymphocytic leukaemia (SMR=80) with 13 of those deaths occurring in people first employed before 1950 (SMR=82) and two in those employed in 1950 and after (SMR=72).

The SMR for acute myelogenous leukaemia was 129. Nineteen of the 20 deaths occurred in people first employed before 1950 (SMR=155), and there was a deficit among people first employed in 1950 and after (SMR=30). Mortality from chronic myelogenous leukaemia was essentially the same as expected (SMR=105). Ten of the 12 deaths occurred in people first employed before 1950 (SMR=116), and there was a deficit of chronic

myelogenous leukaemia among people first employed in 1950 and after (SMR=70).

There were significant excesses for acute leukaemia, unspecified (SMR=276), and for leukaemia cell type unspecified (SMR=231). For acute leukaemia, unspecified, the SMR was essentially the same among people first employed before 1950 and those first employed in 1950 and after (SMRs=276 and 273 respectively). For leukaemia, cell type unspecified, the SMR was increased for those first employed before 1950 (SMR=262), but for those first employed in 1950 and after, there was a deficit (SMR=87).

Discussion

There was a significant increase in mortality from mesothelioma for the total cohort which was higher for people employed in maintenance subgroups based on their potential for exposure to asbestos. Although the increase was highest for people employed as insulators, mortality rose in all of the maintenance groups with increasing employment in that group. An examination of mortality by time first employed showed that the SMRs were highest for people first employed in any of the subgroups before 1950. Almost all of the cohort's increased mortality from mesothelioma was limited to the maintenance subgroups, especially insulators. There were only seven deaths from mesothelioma versus 5.3 expected (SMR=130) for those never employed in the maintenance subgroup and only two versus 3.9 (SMR=51) for those never employed in any maintenance job.

The finding of excess mortality from mesothelioma in this cohort was not unexpected. Materials containing asbestos were used in the past as thermal insulation for various vessels and pipes in refineries. There were no industrial hygiene sampling data about the levels of exposure to asbestos for the various crafts until the 1970s, and by that time work practices for asbestos handling had already been modified. However, insulators would have had the highest potential for exposure, followed by workers in other crafts who had to work with insulation to accomplish their tasks.

Several other petroleum industry studies have also shown increased mortalities for mesothelioma in refinery workers.[2-5] Other studies of refinery workers have not identified excess deaths from mesothelioma. Collingwood et *al*[13] found two deaths from mesothelioma versus 2.3 expected at the Mobil Paulsboro refinery, and Raabe et *al*[14] found one death from mesothelioma versus 3.2 expected at the Mobil Beaumont refinery.

Although mesothelioma is known to be associated with asbestos exposure in the shipbuilding industry," it is unlikely that much of the excess found in this cohort was associated with exposures in this industry during the second world war. No information on previous employment was available. However, even if all people who had the potential to be employed in shipbuilding during the second world war were excluded, the SMRs are still significantly increased.

Because of the lack of mortalities for mesothelioma and of a specific ICD code for this cause of death, the comparability of the mesothelioma SMRs among all these studies is unknown other than with the study by Tsai et *al*.[2] Our comparison mortalities were the same as those used in that study as was the definition of the maintenance subgroup. It is unknown why some of the refinery studies show lower than expected SMRs for mesotheliomas.

No increase in mortality from lung cancer was found in the larger maintenance subgroup. There was, however, a small increase in lung cancer mortality for those employed as insulators which rose with increasing duration of employment. The increases were small and not significant. There was a deficit of lung cancer mortality among those first employed in 1950 and after for both groups. No histories on smoking were available to indicate whether these increases were primarily found in smokers.

The SMR for all brain tumours for the total cohort (113) was similar to that reported for cancer of the brain and central nervous system (108) *in* the earlier report.' The highest SMRs for all brain tumours combined were 178 for people ever employed on any of the motor oil units and 326 for people employed on these units for ≥5 years. These results were similar to those for cancer of the brain and central nervous system where the SMRs were 164 and 314, respectively. An SMR for brain tumours of 166 was found for people ever employed in research or quality control laboratories and it was 185 for people employed as laboratory staff for ≥5 years. Again, these SMRs were similar to those for cancer of the brain and central nervous system where the SMRs were 142 and 169, respectively. Thus, other than increasing the number of deaths, combining all brain tumours together did not change the pattern of results found for the category of cancer of the brain and central nervous system alone.

There were no specific chemical exposures that might be common to the motor oil unit and the laboratory, and that have been associated with brain tumours. In any event, laboratory practices have changed dramatically over the past 30 years and exposure potentials have declined steadily through the automation of test procedures and advances in the design of laboratory ventilation. Similar decreases in exposure levels have also been achieved on operating units through the use of engineering controls and enhanced work practices.

With Texas death rates as the comparison, Satin et *al*[5] found an increase in benign and unspecified brain tumours at the Gulf/Chevron Port Arthur refinery. The SMR was much lower when United States death rates were used. A previous report on brain tumours in the Port Arthur refinery cohort[15] discussed the problems associated with diagnostic errors of brain tumours. Errors occur more often among inaccessible tumours—such as those occurring in the liver, brain, or pancreas. A potential for more accurate and complete reporting of brain tumours in occupational groups as a result of diagnostic sensitivity bias has also been dis-

cussed in several previous investigations.[16-18] Diagnostic sensitivity bias is one reasonable explanation for the increased SMR of 113 for brain tumours for the overall Texaco mortality study cohort.

The causes of malignant and benign brain tumours are still largely unknown.[19] Within the general population of the United States, the recorded cases of, and deaths from, cancers of the brain and central nervous system have been rising slightly since the 1970s.[20] Some or all of these increases are thought to result from the advent of computed tomography, magnetic resonance imaging, and other techniques that have led to improvements in the detection of previously undiagnosed or misdiagnosed cases of brain tumours.

The few established risk factors for brain tumours account for only a small proportion of cases. Genetics plays a part," and ionising radiation to the head is a strong, but rare, risk factor." [23] The only occupational exposure linked to increased risk of brain cancer is exposure to high concentrations of vinyl chloride,[24] which was not present at any of the Texaco mortality study locations. For dozens of occupational groups, slight, inconsistent excess risks of brain cancer have been reported by various investigators, but no convincing associations, certainly not specific causative agents, have been identified.[19]

The analysis of the SMRs for non-Hodgkin's lymphoma for the total cohort and for the job and process unit groups shows primarily deficits and slight increases. The only job group with a noticeable increase for non-Hodgkin's lymphoma is the fluid catalytic cracking unit (SMR=155), but the SMR decreases to 118 for those employed on the fluid catalytic cracking unit for ≥5 years. Thus, the increased SMRs found in the previous report' for cancer of other lymphatic tissue among people employed on the fluid catalytic cracking unit or the crude stills were not related to increased mortality from non-Hodgkin's lymphoma.

However, the *S M R* for multiple myeloma for people ever employed on the fluid catalytic cracking unit was 198, and it increased to 270 for those people with ≥5 years on this unit. For people ever employed on a crude unit, the SMR was 155, increasing to 172 for those people with ≥5 years on this unit. The increases for the groups employed for ≥5 years in the job are based on only six and five deaths, respectively, and some of these were employed on both units.

The SMR for multiple myeloma among those employed on the delayed coking unit for ≥5 years was lower than for the 1 year group, and there were no deaths from multiple myeloma in the group of pipefitters and boilermakers employed for ≥5 years. There were no specific exposures associated with employment on the fluid catalytic cracking unit or crude stills which have been associated with multiple myeloma. Also, there was no evidence that multiple myeloma was increased in petroleum workers overall. Wong and Raabe" carried out a rneta-analysis of multiple myeloma in a multinational cohort of over 250 000 petroleum workers. The SMR for multiple myeloma was 93, and there was no pattern by duration of observation.

The analysis of leukaemia by cell type showed a non-significantly increased SMR for acute myelogenous leukaemia for white men overall, which was limited to those people first employed before 1950. Because many of the deaths from leukaemia do not have a specific cell type mentioned on the death certificate, this resulted in significant excesses of both acute leukaemia and leukaemia, cell type unspecified. More detailed information about the specific cell type of leukaemia would reduce the increases in the unspecified categories, and increase the SMRs in some or all of the categories specific for cell type. However, although death certificates are considered to be highly accurate in their diagnosis of leukaemia,[26] the accuracy of the information specific to cell type is much lower. It would be better to have access to hospital and pathological information, but that is not possible in a study of this type. A meta-analysis of leukaemia by cell type in workers in the petroleum industry[4] did not show increased SMRs for acute myelogenous leukaemia or any of the other leukaemia cell types.

Although employees' complete work histories were used for these cause specific analyses, information about the specific chemicals associated with each of the job and unit combinations was not available, nor was there any industrial hygiene sampling data covering the first 30 years of the study. (For information about potential exposures associated with the jobs and units, see table 1 in the previous report'.) Jobs and units with similar responsibilities were grouped together for the analyses as a surrogate for exposures, but provided little information to link exposure and outcome.

Patterns of mortality were examined by time first employed to determine if the patterns had changed over time. Although many groups showed much lower SMRs for those more recently employed, in many cases the number of observed deaths was *so* small that the results were difficult to interpret.

Conclusion

Further analyses of specific causes of death by duration of employment in various job and process units did not show any patterns which would suggest that, other than for mesothelioma, any of these increases in mortalities were likely to result from either workplace exposures or employment at one of the locations included in the Texaco mortality study. The brain tumour rates in people employed in the motor oil units and the laboratories and the rates for multiple myeloma in those employed on the fluid catalytic cracking units rose with increasing duration of employment in these jobs. However, there was no known exposure common to these jobs which had been associated with brain cancer or multiple myeloma, nor has an increased risk of these causes of death been consistently found in other studies of petroleum workers. There was

only a slight and non-significant increase in the SMR for acute myelogenous leukaemia which is the only leukaemia cell type associated with benzene exposure. The increase in mesotheliomas has been found in other studies of refinery workers, and it rose steadily with duration of employment. The rate for mesothelioma was higher among those first employed >45 years ago and those employed in job groups with greater potential for exposure to asbestos.

1 Divine BJ, Hartman CM, Wendt JK. An updated report on the Texaco mortality study 1947–1993 Part I. Analysis of overall patterns of mortality. *Occup Environ Med* 1999;56:167–73.
2 Tsai SP, Waddell LC, Gilstrap EL, et *al*. Mortality among maintenance employees potentially *exposed* to asbestos in a refinery and petrochemical plant. *Am J Ind Med* 1996;29: 89–98.
3 Wong O. Risk of acute myeloid leukaemia and multiple myeloma in workers *exposed* to benzene. *Occup Environ Med* 1995;52:380–4.
4 Wong O, Raabe GK. Cell-type specific leukemia analyses in a combined cohort of more than 208,000 petroleum workers in the United States and the United Kingdom. Reg *Toxicol Pharmacol* 1995;21:307–21.
5 Satin KP, Wong O, Yuan LA, et *al*. A 50-year mortality follow-up of a large cohort of oil refinery workers in Texas. *J Occup Environ Med* 1996;38:492–506.
6 Fraumeni JF, Blot W. Lung and pleura. In: Schottenfeld D, Fraumeni JF, eds. *Cancer epidemiology and prevention*. Philadelphia: WB Saunders, 1982:564–82.
7 Marsh GM, Ehland J, Sefcik S. *Mortality and population data system (MPDS)*. Pittsburgh, PA University of Pittsburgh, Department of Biostatistics Technical Report, 1987
8 Monson RR. Analysis of relative survival and proportionate mortality. *Comput Biomed Res* 1974;7:325–32.
9 Doll R, Peto R *The causes of cancer*. New York: Oxford University Press, 1981:1243.
10 Schnatter AR, Theriault G, Katz AM, *et al*. A retrospective mortality study within operating segments of a petroleum company. *Am J Ind Med* 1992;22:209–29.
11 Kaplan SD. Update of a mortality study of workers in petroleum refineries. *J Occup Med* 1986;28:514–6.
12 Hornstra M. A mortality study of Whiting refinery employees. Chicago, IL: Report for Amoco Corporation, 1993.
13 Collingwood KW, Raabe GK, Wong O. An updated cohort mortality study of workers at a northeastern United States petroleum refinery. *Int Arch Occup Environ Hedrh* 1996;68: 277–88.
14 Raabe GK, Collingwood KW, Wong O. An updated mortality study of workers at a petroleum refinery in Beaumont, TX. *Am J Ind Med* 1998;33:61–81.
15 Wen CP, Tsai SP, Gibson RL. A report on brain tumors from a retrospective cohort study of refinery workers. *Ann NY Acad Sci* 1981;381:130–8.
16 Greenwald P, Friedlander BR, Lawrence CE, *et al*. Diagnostic sensitivity bias: an epidemiologic explanation for an apparent brain tumor excess. *J Occup Med* 1981;23: 690–4.
17 Wong O, Morgan RW, Bailey WJ, *et al*. An epidemiological study of petroleum refinery workers. *Br J Ind Med* 1986;43: 6–17.
18 Wong O, Whorton MD. Diagnostic bias in occupational epidemiologic studies: an example based on the vinyl chloride literature. *Am J Ind Med* 1993;24:251–6.
19 Inskip PD, Linet MS, Heineman EF. Etiology of brain tumors in adults. *Epidemiol Rev* 1995;15:382–414.
20 Ries LAG, Kosary CL, Hankey BF, et *al*, eds. SEER cancer statistics review 1973–94. Bethesda, MD: National Cancer Institute, 1997. (NIH publ no 97–2789).
21 Chung RY, Seizinger B R Molecular genetics of neurological tumors. *J Med Genet* 1992;29:361–7.
22 Ron E, Modan B, Boice JD Jr, et *al*. Tumors of the brain and central nervous system after radiotherapy in childhood. *N Engl J Med* 1988;319:1033–9.
23 Neglia JP, Meadows AT, Robison LL, et *al*. Second neoplasms after acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991;325:1330–6.
24 International Agency for Research on Cancer. *IARC Monographs of the evaluation of the carcinogenic risk of chemicals w humans. Overall evaluations of carcinogenicity: an updating of IARC monographs.* Vols 1-42, suppl 7. Lyon, France: International Agency for Research on Cancer, 1987.
25 Wong O, Raabe GK. Multiple myeloma and benzene exposure in a multinational cohort of more than 250,000 petroleum workers. *Reg Toxicol Pharmacol* 1997;26:188–99.
26 Percy C, Stanek III E, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* 1981;71:242–50.

Mortality patterns among workers exposed to acrylamide: 1994 follow up

Gary M Marsh, Lorraine J Lucas, Ada O Youk, Laura C Schall

Abstract

Objective—To update the mortality experience of a cohort of 8508 workers with potential exposure to acrylamide at three plants in the United States from 1984–94.

Methods—Analyses of standardised mortality ratios (SMR) with national and local rates and relative risk (RR) regression modelling were performed to assess site specific cancer risks by demographic and work history factors, and exposure indicators for acrylarnide and muriatic acid.

Results—For the 1925–94 study period, excess and deficit overall mortality risks were found for cancer sites of interest: brain and other central nervous system (CNS) (SMR 0.65, 95% confidence interval (95% CI) 0.36 to 1.09), thyroid gland (SMR 2.11, 95% CI 0.44 to 6.17), testis and other male genital organs (SMR 0.28, 95% CI 0.01 to 1.59), and cancer of the respiratory system (SMR 1.10, 95% CI 0.99 to 1.22); however, none was significant or associated with exposure to acrylamide. A previously reported excess mortality risk of cancer of the respiratory system at one plant remained increased among workers with potential exposure to muriatic acid (RR 1.50, 95% CI 0.86 to 2-59), but was only slightly increased among workers exposed or unexposed to acrylamide. In an exploratory exposure-response analysis of rectal, oesophageal, pancreatic, and kidney cancer, we found increased SMRs for some categories of exposure to acrylamide, but little evidence of an exposure-response relation. A significant 2.26-fold risk (95% CI 1.03 to 4.29) was found for pancreatic cancer among workers with cumulative exposure to acrylamide >0.30 mg/m³.years; however, no consistent exposure-response relations were detected with the exposure measures considered when RR regression models were adjusted €or time since first exposure to acrylamide.

Conclusion—The contribution of 1115 additional deaths and nearly 60 000 person-years over the 11 year follow up period corroborate the original cohort study findings of little evidence for a causal relation between exposure to acrylamide and mortality from any cancer sites, including those of initial interest. This is the most definitive study of the human carcinogenic potential of exposure to acrylamide conducted to date.

(*Occup Environ* Med 1999;56:181–190)

Keywords: acrylamide; muriatic acid; cohort mortality study

Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, PA, USA
G M Marsh
A O Youk
L C Schall

22 Brier Road, Whitehouse Station, NJ 08889, USA
L J Lucas

Correspondence to:
Dr G M Marsh, A-410 Crabtree Hall, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, USA.
email: grnarsh+@pitt.edu

Accepted 17 September 1998

In 1989, Collins et *al*[1] reported the mortality experience of 8854 workers with potential exposure to acrylamide, a substance widely used in the manufacture of water soluble polymers used for water treating, paper mining, and sugar processing, at four Cytec Industries (formerly the chemical division of American Cyanamid Company), in three United States plants (Fortier, LA; Kalamazoo, MI; and Warners, NJ), and a plant in Botlek, The Netherlands. The original acrylamide study was prompted by animal studies that suggested acrylamide's carcinogenic potential based on an increased incidence of cancers of the brain and central nervous system (CNS), thyroid gland, other endocrine glands, and reproductive organs,'[3] and by limited epidemiological data. Sobel et *al*[4] in a small cohort mortality study of 371 workers exposed to acrylamide, reported 11 observed cancer deaths versus 7.9 expected due to excess cancers of the digestive tract and respiratory system among workers exposed to organic dyes. Among workers not exposed to organic dyes, four cancer deaths were observed versus 6.5 expected.

The original acrylamide study found no significant excesses in total or cause specific mortality between 1925 and 1983 in the four plants. An exposure-response analysis of 2293 workers with exposure to acrylamide showed no trend of increased risk of mortality from several cancer sites. A significant excess in respiratory cancer (SMR 1.31, $p < 0.05$) was found at the Warners factory, which was largely confined to two groups: men who worked in the muriatic acid operations (n=11 deaths) between 1925 to 1956, and men hired between 1940 to 1949 who had worked less than 1 year in various departments (n=52 deaths). The investigators, including two of the current authors (GMM and LJL) concluded that the results did not support the hypothesis that acrylamide is a human carcinogen.'

An extended and updated investigation was undertaken to examine the acrylamide cohort mortality experience from malignant neoplasms relative to exposure to acrylamide, and to investigate the apparent cluster of respiratory cancers at the Warners factory with emphasis on exposure to muriatic acid. We report here the results of an 11 year follow up (1984–94) of the original acrylamide cohort.

Methods

STUDY POPULATION

The original acrylamide cohort included 8854 male employees with full time work experience

Table 1 Characteristics of study plants and popularion used in 1994 update

Characteristics	*Fortier*	*Kalamazoo*	*Warm*	*AU plants*
Plant start up date	1951	1930	1917	—
AMD production dates	1966 present	1967 present	1954-85	—
Total subjects:	1295	60	7153	8508
White men	1172	57	6013	7242
Non-white men	123	3	1140	I266
Year of birth:				
< 1900	1	5	633	639
1900-19	197	15	2602	2814
1920-39	724	17	2908	3649
≥ 1940	373	23	1010	1406
Year of hire (entry into study):				
1925-39	0	5	1584	1589
1940-49	0	12	2471	2483
1950-59	730	17	1566	2313
1960-73	565	26	1532	2123
Duration of employment (y):				
< 1	230	6	3932	4168
1-4.9	285	12	1537	1834
5-9.9	133	3	434	570
10-19.9	248	8	453	709
Z20	399	31	797	1227
Person-years (1925-94):				
Total	40592	1884	245255	287731
Unexposed to AMD	21320	726	201781	223827
Exposed to AMD*	19272	1158	43474	63904
0.001-0.029 (mg/m³.y)	6710	328	6274	13312
0.03-0.29	11850	632	12296	24778
≥0.30	712	198	24904	25814
Person-years (1950-94):				
Total	40592	1778	214615	256985
Unexposed to AMD	21320	644	174467	196431
Exposed to AMD*	19272	1134	40148	60554
0.001-0.029 (mg/m³.y)	6710	328	6248	13286
0.03-0.29	11850	608	11991	24449
Z0.30	712	198	21909	22819
Tobacco smoking:				
Never smoker	196	4	421	621
Ever smoker	550	25	1558	2133
unknown	549	31	5174	5754

***Person-years refer to follow up time not exposure time. Person-years among unexposed workers includes follow up time of workers before their first exposure to AMD (started employment in an unexposed job).**

Table 2 Vital status of study population by plant: follow up to the end of 1994

Vital status	*Fortier*	*Kalamazoo*	*Warners*	*AB plants*
Alive:	987	36	3777	4800
Assumed	582	19	2861	3462
Confirmed	405	17	916	1338
Dead:	288	24	2970	3282
Death certificate (%)	280 (97)	24 (100)	2807 (95)	3111 (95)
No death certificate	8	0	163	171
Unknown (%)	20 (2)	0 (0)	406 (6)	426 (5)

at any of the four study plants between 1 January 1925 and 31 January 1973. In the current update, we did not include the 346 workers from the Botlek plant because the follow up was incomplete at the time of analysis. For the United States plants, company records were reviewed to update the work histories and the exposures to acrylamide and muriatic acid of study members actively employed at the end of 1983. The United States study cohort includes 8508 workers.

Table 1 shows selected characteristics of the United States study population by plant. The Warners factory is the oldest and largest plant in the study contributing 84% of the total study members and person-years. About half of the cohort was hired before 1950 and employed at the Warners or Kalamazoo plants, and about half were short term workers (defined as <1 year of employment). Most of the cohort members in each plant are white. Because of incomplete data, tobacco smoking history had limited use as a covariable in the original exposure-response analysis and now.

COHORT TRACING

The vital status of the United States study members was determined as of 31 December 1994 with Cytec personnel and pension files and based on a two stage tracing protocol that uses several conventional tracing sources, including the Social Security Administration and the National Death Index.[5] Consistent with our protocol, all people who died after the 1994 follow up period or who were traced and not identified as deceased during the study period were assumed to be alive as of the study end date. Those with unknown vital status were untraceable due to missing Social Security numbers, a methodological limitation of the original study due mostly to Warners employees who started work before the establishment of Social Security. Death certificates were obtained from the corresponding state health department, and to conform with the original study, were coded by a nosologist to the underlying cause of death with the 8th revision rules of the international classification of diseases (ICD-8).

Table 2 shows the plant specific vital status of the United States study population at the end of 1994. A total of 3282 deaths as identified through 1994, an increase of 1115 deaths from the original 1983 follow up of the United States plants. People lost to follow up decreased from 513 (6%) in the original study to 426 (5%). Death certificates were obtained for 3111 (95%) of all deaths.

EXPOSURE ESTIMATES

Acrylamide

The general methods of the quantitative estimates of exposure to acrylamide detailed by Collins et al[1] considered a worker as exposed to acrylamide if his cumulative exposure value is >0.001 mg/m³.years, the approximate equivalent exposure of a 1 day average concentration to the current permissible exposure limit of 0.3 mg/m³. From the individual worker job histories and the job and time specific exposure estimates, three time dependent summary measures of exposure to acrylamide, were computed for each worker:

- Duration of exposure=the sum of the days spent in jobs with non-zero exposure to acrylamide (y)
- Cumulative exposure=the product of the number of days in each job and the estimated average daily exposure to acrylamide, summed across all jobs (mg/m³.y)
- Average intensity of exposure=the ratio of cumulative to duration (mg/m³)

Exposure estimates for the 1984–94 period were assigned with the 1983 exposures to acrylamide developed in the original study. Few employees in the follow up period would have potential exposure to acrylamide, as the Warners plant stopped acrylamide operations in 1985 and any extrapolation error would be small with minimal impact on our findings. This conservative operating assumption was also supported by a review of industrial hygiene monitoring data and by plant personnel, including one coauthor (LJL), knowledgeable

Table 3 Summary statistics for exposure measures to AMD and muriatic acid by plant, all workers, 1925-94

*Exposure indicator**	*Fortier*	*Kalamazoo*	Warners	*AU plants*
Acrylamide:				
Duration of exposure (y):				
Minimum	0	0	0	0
25th percentile	0	0	0	0
Median	0	2.62	0	0
75 th percentile	5.40	15.58	0	0
Maximum	34.62	41.67	40.99	41.67
Mean	4.16	7.62	1.20	1.69
SD	7.25	9.68	4.79	5.42
Coefficient of variation	174.3	127.1	400.5	319.9
Average intensity of exposure (mg/m^3):				
Minimum	0	0	0	0
25 th percentile	0	0	0	0
Median	0	0.003	0	0
75 th percentile	0.010	0.008	0	0
Maximum	0.055	0.124	2.200	2.200
Mean	0.007	0.009	0.115	0.098
SD	0.011	0.019	0.364	0.336
Coefficient of variation	157.2	201.8	315.8	342.7
Cumulative exposure ($mg/m^3.y$)				
Minimum	0	0	0	0
25 th percentile	0	0	0	0
Median	0	0.02	0	0
75 th percentile	0.06	0.08	0	0
Maximum	0.81	0.72	32.31	32.31
Mean	0.04	0.08	0.29	0.25
SD	0.08	0.15	1.34	1.23
Coefficient of variation	190.7	180.8	458.3	487.6
Muriatic acid;				
Duration of exposure (y):				
Minimum			0	
25 th percentile			0	
Median			0	
75 th percentile			0	
Maximum			26.53	
Mean			0.08	
SD			1.02	
Coefficient of variation			1256.4	

**Computed from date of hire to earliest of date of ending work, death, or 31 December 1994.*

of acrylamide processes during the follow up period.

Muriatic *acid*

Muriatic acid production operated only at the Warners plant between **1422** and **1937;** between **1937** and **1956** muriatic acid exposure was restricted to trans-shipment and repackaging. Duration of exposure was the only muriatic acid exposure measure computed as only a qualitative estimate was assessed (presence or absence of potential exposure for each job).

Table **3** shows selected summary statistics for the three measures of exposure to acrylamide computed for all workers in the **1994** acrylamide cohort and for duration of exposure to muratic acid at Warners. For all workers combined, **60 554 (24%)** of the total person-years are associated with exposure to acrylamide (table **1).** The values of each exposure measure are generally small, consistent with the observation in table **1** that nearly half of the study members were short term workers. For example, at Warners, the mean intensity of exposure to acrylamide was **0.115** and the mean duration of exposure to muratic acid was only **0.08** years.

Exposure to acrylamide varied, as each of the domestic plants produced or used acrylamide differently. Acrylamide is produced in **two** forms, wet acrylamide in aqueous solution, and dry acrylamide that can be in either a powder or a solid pellet. The Warners plant produced both forms of acrylamide. The Fortier factory manufactured wet acrylamide monomer. Both plants used wet and dry acrylamide in the formulation of other products. Kalamazoo used only wet acrylamide. Potential exposure may have occurred during monomer and polymer production from inhalation of dry powder, acrylamide monomer, or aerosols of acrylamide solution and dermal absorption of the acrylamide monomer and solutions.

STATISTICAL ANALYSES

Descriptive analysis of SMRs

We examined the total and cause specific mortality experiences of the United States acrylamide cohort from **1** January **1925** to **31** December **1994.** Cohort analyses were performed with a modified life table procedure from the occupational cohort mortality programme (OCMAP).[6-8] Person-years at risk contributed by each study member were jointly classified by plant, race, age group, calendar time, duration **of** employment (DOE), and the time since first employment (TSFE). Person-year counts began at the date of hire and continued until date of death or the end of the **1994** study period. For workers lost to follow up, person-year counts stopped at the last date of known vital status, which was always the date of the end of employment.

We computed expected numbers of deaths by multiplying average annual race, age, and time specific standard population death rates by the person-years at risk in the corresponding race age time intervals. To coincide with update periods, **1980–4** rates were applied to **1980–3** person-years and **1985–9** rates were applied to **1984–9** person-years. *As* in the original study, expected numbers of deaths for the United States plants were computed with the total United States male population as the standard population. United States male death rates covering the **1925–89** observation period were obtained from the cohort analysis software developed by Monson.[9] For the **1990-4** period, corresponding United States rates were obtained for comparable categories from the mortality and population data system (MPDS) maintained at the University of Pittsburgh."

As an enhancement to the original study, we computed expected numbers of deaths based on MPDS rates for the male populations of the counties surrounding the factory (for Warners-Middlesex and Union Counties, NJ) or the local county in which the subcohort largely resides (for Fortier-Jefferson Parish, LA; for Kalamazoo-Kalamazoo County, MI). Due to limitations of the MPDS data, expected numbers of cancer deaths were limited to the period **1950-94;** non-cancer deaths were limited to **1960-94** (with **1962-4** rates applied to **1960–4** person-years). MPDS rates were used only for those cause of death categories defined by identical or nearly identical ICD codes in the Monson and MPDS rate files. Because local death rates usually provide the most valid external mortality comparisons (as they help to adjust for the social, cultural, and economic factors related to disease), all but the aggregate analysis were based exclusively on local rates. Moreover, because the counties involved repre-

sent large population areas, the local rates are measured with good precision.

Mortality excesses and deficits were expressed as standardised mortality ratios (SMRs) along with their 95% confidence intervals (95% CIs). The SMRs were computed for subgroups of the cohort defined by plant, race, follow up period, calendar period, year of hire, duration of employment, and the time since first employment. The SMRs were also computed for selected causes of death for the measures of exposure categories of acrylamide and muriatic acid with and without exposure lagging.[11] Here, person-year counts in the unexposed baseline categories include the observation time of workers before their first exposure. The significance of SMRs was assessed with Poisson probabilities. All tests were done at the 0.05 significance level and no adjustment was made for multiple comparisons.

Relative risk regression analysis

Relative risk regression modelling was used to investigate the dependence of the internal cohort rates (modelled as time to death) for selected cancer sites on combinations of the categorical acrylamide or muriatic acid exposure measures, with adjustment for potential confounding factors. Study data from the entire 1925–94 period were modelled. For each cancer site examined, risk sets were explicitly constructed from the cohort data file with age as the primary time dimension, with the RISKSET program module in OCMAP-PLUS.[8] To adjust for year of birth (cohort) effects, risk sets were caliper matched on year of birth. The time dependent exposures were evaluated for each person at each event time they were at risk.

Multiplicative relative risk (RR) models of the form $\lambda(t) = \lambda_0(t) \exp\{x(t)\beta\}$ were fitted to the internal cohort rates. Mathematical details of the models are given elsewhere.[12–14] The conditional logistic regression program in EGRET[15] was used to estimate β from the explicitly constructed risk sets. Categorised forms of the covariates were considered to parallel the descriptive SMR analysis of mortality relative to exposure. The demographic and exposure variables were first considered univariately as categorical variables to identify patterns of univariate associations with the outcome and sparse data problems. Possible exposure-disease associations were then evaluated with a forward stepwise approach to adjust for possible confounders. Effect modification was assessed as far as possible.

The significance of each main effect (expressed as a global p value) and interaction was assessed with a likelihood ratio statistic. For the quantitative exposure variables that had a monotonic pattern in the parameter estimates, a test for linear trend was conducted (expressed as a trend p value). All tests were done at the 0.05 significance level with no adjustment made for multiple comparisons.

Results

GENERAL MORTALITY BY STUDY PERIOD

Table 4 presents SMRs by cause and study period for the combined 1994 United States acrylamide cohort (some findings for the 1925–83 period differ slightly from those

Table 4 Observed deaths and SMRs for selected causes by follow up period, all workers, national comparisons

	1925–83			1984–94			1925–94		
Cause of death (ICDA–8)†	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All causes (000–999):	2167	0.91**	0.87 to 0.95	1115	0.76**	0.72 to 0.81	3282	0.85**	0.82 to 0.88
All malignant neoplasms (140–209)	496	1.06	0.96 to 1.15	357	0.89*	0.80 to 0.99	853	0.98	0.92 to 1.05
Buccal cavity and pharynx (140–149)	13	0.83	0.44 to 1.42	8	0.96	0.41 to 1.89	21	0.88	0.54 to 1.34
Digestive organs and peritoneum (150–159)	141	1.07	0.90 to 1.26	85	0.89	0.71 to 1.10	226	0.99	0.87 to 1.13
Oesophagus (150)	16	1.15	0.66 to 1.87	15	1.30	0.73 to 2.14	31	1.22	0.83 to 1.73
Stomach (151)	35	1.34	0.94 to 1.87	12	0.95	0.49 to 1.66	47	1.22	0.89 to 1.62
Large intestine (153)	38	0.94	0.67 to 1.29	28	0.78	0.52 to 1.13	66	0.87	0.67 to 1.10
Rectum (154)	16	1.20	0.69 to 1.95	8	1.26	0.55 to 2.49	24	1.22	0.78 to 1.82
Liver (155, 156)	5	0.51	0.16 to 1.20	5	0.58	0.19 to 1.35	10	0.55	0.26 to 1.00
Pancreas (157)	27	1.09	0.72 to 1.59	17	0.91	0.53 to 1.46	44	1.01	0.74 to 1.36
Respiratory system (160–163)	202	1.25**	1.08 to 1.44	139	0.94	0.79 to 1.11	341	1.10	0.99 to 1.22
Larynx (161)	8	1.10	0.48 to 2.18	6	1.25	0.46 to 2.71	14	1.16	0.63 to 1.95
Lung (162, 163)	194	1.27**	1.10 to 1.46	133	0.94	0.78 to 1.11	327	1.11	0.99t01.24
Bone (170)	2	0.88	0.11 to3.18	0	—	0.00 to 6.19	2	0.70	0.08 m 2.52
Skin (172, 173)	4	0.48	0.13 to 1.23	6	0.89	0.33 to 1.93	10	0.66	0.31 to 1.22
Prostate (185)	29	0.96	0.64 to 1.38	38	0.82	0.58 to 1.13	67	0.88	0.68 to 1.11
Testis and other male genital organs (186,187)	0	—	0.00 to 1.23	1	1.92	0.05 to 10.70	1	0.28	0.01 to 1.59
Bladder (188)	13	1.06	0.56 to 1.81	14	1.38	0.75 to 2.31	27	1.20	0.79 to 1.75
Kidney (189)	12	1.06	0.55 to 1.86	10	1.11	0.53 to 2.04	22	1.08	0.68 to 1.64
Brain and other cenual nervous system (191,192)	5	0.36*	0.12 to 0.85	9	1.15	0.53 to 2.19	14	0.65	0.36 to 1.09
Thyroid gland (193)	2	2.32	0.28 to 8.37	1	1.80	0.04 to 10.01	3	2.11	0.44 to6.17
All lymphopoietic tissue (200-209)	39	0.88	0.62 to 1.20	21	0.60'	0.37 to 0.92	60	0.76*	0.58 to 0.97
Lymphosarcoma and retidosarcoma (200)	6	0.70	0.26 to 1.53	0	—	0.00 to 2.35	6	0.59	0.22 to 1.29
Hodgkin's disease (201)	8	1.39	0.60 to 2.74	0	—	0.00 to 4.04	8	1.20	0.52 to 2.37
Leukaemia and aleukaemia (204–207)	14	0.78	0.43 to 1.31	9	0.68	0.31 to 1.29	23	0.74	0.47 to 1.10
Other lymphatic tissue (202,203,208)	11	0.92	0.46 to 1.66	11	0.65	0.32 to 1.16	22	0.76	0.48 to 1.16
Benign neoplasms (210–239)	8	1.24	0.54 to 2.44	2	0.60	0.07 to 2.15	10	1.02	0.49 to 1.87
Diabetes mellitus (250)	26	0.77	0.50 to 1.12	15	0.53**	0.30 to 0.87	41	0.66**	0.47 to 0.89
Diseases of the circulatory system (390–458)	1019	0.90**	0.85 to 0.96	434	0.61**	0.56 to 0.67	1453	0.79**	0.75 to 0.83
Non-malignant respiratory disease (460-519)	105	0.75**	0.62 to 0.91	74	0.53**	0.42 to 0.67	179	0.64**	0.55 to 0.74
Cirrhosis of the liver (571)	68	1.08	0.84 to 1.37	12	0.54*	0.28 to 0.94	80	0.94	0.74 to 1.17
All external causes of death (800–998)	199	0.70**	0.61 to 0.81	43	0.65**	0.47 to 0.87	242	0.69**	0.61 to 0.79
Unknown causes (999.9)	101			70			171		
People (n)	8508			5942			8508		
Person-years	228816			58916			287731		

*p<0.05; ** p<0.01.
†Monson life table programme ICD–8 categories, labels, and codes for US plants for 1925–89; corresponding MPDS rates for 1990–4.

Table 5 Observed deaths and SMRs for selected cancer sites by plant, US workers, 1950–94, local county comparison

Cause of death (ICDA–8)†	Fortier			Kalamazoo			Warnm		
	Obs	SMR	95%CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All malignant neoplasms (140–209)	99	0.93	0.76 to 1.14	6	1.03	0.38 to 2.24	736	0.91**	0.84 to 0.97
Buccal cavity and pharynx (140–149)	4	1.32	0.36 to 3.39	0	—	0.00 to 24.72	17	0.75	0.44 to 1.20
Digestive organs and peritoneum (150–159)	23	1.04	0.66 to 1.56	0	—	0.00 to 2.49	198	0.83**	0.72 to 0.96
Oesophagus (150)	4	1.41	0.38 to 3.61	0	—	0.00 to 33.01	27	1.00	0.66 to 1.45
Stomach (151)	4	1.37	0.37 to 3.56	0	—	0.00 to 11.91	40	0.89	0.63 to 1.21
Large intestine (153)	8	1.01	0.44 to 1.99	0	—	0.00 to 8.11	58	0.69**	0.52 to 0.89
Rectum (154)	1	0.58	0.01 to 3.22	0	—	0.00 to 20.91	21	0.93	0.58 to 1.42
Pancreas (157)	6	1.36	0.50 to 2.96	0	—	0.00 to 12.58	38	0.94	0.66 to 1.28
Respiratory system (160–163)	36	0.78	0.55 to 1.08	4	1.95	0.53 to 4.99	298	1.11	0.98 to 1.24
Bronchus, trachea, lung (162)‡	34	0.77	0.54 to 1.08	4	2.02	0.55 to 5.16	284	1.11	0.99 to 1.25
Prostate (185)	3	0.52	0.11 to 1.52	1	1.86	0.04 to 10.34	63	0.85	0.66 to 1.09
Testis and other male genital organs (172.5, 173.5, 186, 187)‡	0	—	0.00 to 10.88	0	—	0.00 to 129.95	2	0.81	0.10 to 2.91
Bladder and other Urinary organs (188, 189.9)‡	2	1.08	0.13 to3.89	0	—	0.00 to 19.71	25	1.02	0.66 to 1.50
Kidney (189.0, 189.1,189.2)‡	3	0.98	0.20 to 2.87	1	6.95	0.17 to 38.70	18	0.89	0.53 to 1.41
Central nervous system (191,192)	5	1.80	0.59 to4.21	0	—	0.00 to 22.57	9	0.49*	0.22 to 0.93
Thyroid gland and other endocrine glands (193, 194)‡	1	3.93	0.10t021.91	0	—	0.00 to 291.70	5	2.17	0.71 to 5.07
All lymphatic and haematopoietic tissue (200–209)	11	1.30	0.65 to 2.32	0	—	0.00 to 5.96	46	0.66**	0.48 to 0.88
Leukaemia and aleukaemia (204–207)	2	0.63	0.08 to 2.27	0	—	0.00 to 17.75	21	0.80	0.50 to 1.23
Other lymphopoietic tissue (202,203,208, 209)‡	8	2.31	0.99 to4.54	0	—	0.00 to 13.68	14	0.50*	0.28 to 0.85

*p<0.05; **p<0.01.
†MPDS ICD–8 Categories, labels and codes for US plants.
‡MPDS ICD codes differ from corresponding Monson codes.

reported by Collins et al[1] due to the cohort data revisions noted above). During the 1984–94 update period there were 1115 deaths, yielding a significant (p<0.01) 24% overall deficit in total mortality compared with the general United States population. For the overall 1925–94 study period, there was a significant (p<0.01) 15% deficit in total mortality based on 3282 observed deaths and 287 731 person-years.

The SMRs for all malignant neoplasms combined and for many cancer site specific categories also decreased in the 1984–94 update period. In particular, cancer of the respiratory system decreased from a significant (p<0.01) 25% excess in mortality for the 1925–83 period to a 6% deficit (based on 139 cancer of the respiratory system deaths), resulting in a non-significant 10% excess for the combined 1925–94 study period. Most of the deaths from cancer of the respiratory system were due to lung cancer.

For the other cancer sites of initial interest in the combined study period (table 4), we found deficits in deaths for cancer of the brain and other parts of the CNS (SMR 0.65, 95% CI 0.36 to 1.09) and cancer of the testis and other male genital organs (SMR 0.28, 95% CI 0.01 to 1.59). A non-significant excess in cancer of the thyroid gland was based on three deaths (SMR 2.11, 95% CI 0.44 to 6.17). The SMR for thyroid cancer decreased to 1.80 in the 1984–94 update period. Most of the non-malignant cause of death categories shown in table 4 showed deficits in deaths for the update and combined study periods and many deficits were significant (p<0.05). The SMRs for some cancer site specific categories increased in the update period; however, none of the resulting excesses in the update or combined study periods was significant.

Although not shown here, SMR analyses by race, period, year of employment and duration of employment were essentially unremarkable for the initial cancer sites and the other cause of death categories examined in table 4.

GENERAL MORTALITY BY PLANT

Table 5 shows the 1950–94 cancer mortality experience of workers from each United States plant compared with the local male populations. Restricting the observation period excluded only 12 cancer deaths, all from the Warners plant. Shown are the cancer site categories of initial interest (brain and other parts of the CNS, thyroid and other endocrine glands, and testis and other male genital organs) or sites with at least 20 observed deaths across the three plants. For certain categories (thyroid and other endocrine glands), the observed number of deaths differs between tables 4 and 5 due to the slight variations in the ICD codes used in the MPDS and Monson rates.

Table 5 shows that 736 (88%) of the observed cancer deaths occurred at Warners (SMR 0.91, 95% CI 0.84–.97), whereas only six occurred at Kalamazoo (SMR 1.03, 95% CI 0.38 to 2.24). None of the plants show significant excess in mortality at any specific cancer site. Among the initial sites, non-significant excesses in deaths occurred at Fortier for brain and other parts of the CNS (SMR 1.80, 95% CI 0.59 to 4.21) and thyroid and other endocrine glands at Fortier (SMR 3.93, 95% CI 0.10 to 21.91), and at Warners (SMR 2.17, 95% CI 0.71 to 5.07). The two deaths from cancer of the testis and other male genital organs occurred at Warners resulting in a 19% deficit (SMR 0.81, 95% CI 0.10 to 2.91).

CANCER MORTALITY BY EXPOSURE TO ACRYLAMIDE

Table 6 depicts the 1950–94 cancer mortality experience of all United States workers compared with those with exposure to acrylamide for the selected cancer sites examined in table 5. Consistent with original study results, we found deficits compared with local county

Table 6 Observed deaths and SMRs for selected cancer sites by exposure to acrylamide, US workers, 1950–94, local county comparison

Cause of death (ICDA–8)†	Unexposed (<0.001 mg/m³.y)			Exposed (≥0.001 mg/m³.y)		
	Obs	SMR	95% CI	Obs	SMR	95% CI
All malignant neoplasms (140–209)	681	0.89**	0.83 to 0.96	160	0.98	0.83 to 1.14
Buccal cavity and pharynx (140–149)	18	0.85	0.50 to 1.34	3	0.65	0.13 to 1.89
Digestive organs and peritoneum (150–159)	177	0.81**	0.70 to 0.94	44	1.03	0.75 to 1.38
Oesophagus (150)	24	0.96	0.61 to 1.42	7	1.41	0.57 to 2.90
Stomach (151)	39	0.95	0.68 to 1.30	5	0.69	0.22 to 1.60
Large intestine (153)	55	0.72*	0.54 to 0.93	11	0.71	0.36 to 1.28
Rectum (154)	17	0.82	0.48 to 1.32	5	1.33	0.43 to 3.09
Pancreas (157)	30	0.80	0.54 to 1.14	14	1.79	0.98 to 3.01
Respiratory system (160 to 163)	276	1.07	0.95 to 1.20	62	1.04	0.79 to 1.33
Bronchus, trachea, lung (162)	260	1.07	0.94 to 1.20	62	1.09	0.84 to 1.40
Prostate (185)	60	0.88	0.67 to 1.14	7	0.58	0.23 to 1.19
Testis and other male genital organs (172.5, 173.5, 186, 187)	2	0.86	0.10 to 3.10	0	—	0.00 to 7.09
Bladder and urinary organs (188, 189.9)	22	0.98	0.61 to 1.48	5	1.19	0.39 to 2.77
Kidney (189.0, 189.1,189.2)	16	0.84	0.48 to 1.37	6	1.36	0.50 to 2.96
Central nervous system (191,192)	11	0.64	0.32 to 1.14	3	0.74	0.15 to 2.15
Thyroid gland and other endocrine glands (193, 194)	4	1.91	0.52 to 4.88	2	4.27	0.52 to 15.42
All lymphatic and haernatopoietic tissue (200–209)	43	0.67**	0.48 to 0.90	14	0.98	0.54 to 1.64
Leukaemia and alaeukaemia (204–207)	17	0.70	0.41 to 1.12	6	1.15	0.42 to 2.51
Other lymphopoietic tissue (202,203,208,209)	16	0.63	0.36 to 1.02	6	1.00	0.37 to 2.18
People (n)	7532			2004		
Person–years	202409			54576		

*p<0.05; **p<0.01.
†MPDS ICD–8, labels, and codes for US plants.

cancer mortality among both exposed and unexposed workers for all cancers combined and many specific cancer sites, including brain and other parts of the CNS, and testis and other male genital organs. Although the original study reported a significant (p<0.05) 31% excess for cancer of the respiratory system among unexposed workers (and 14% among those exposed), we now found that up to the end of 1994 only slight non-significant 7% and 4% excesses for cancer of the respiratory system among the unexposed and exposed groups, respectively. These decreased SMRs follow from the overall reduction in mortality from cancer of the respiratory system during the 1984–94 follow up period noted in table 4. For the initial site, cancer of thyroid and other endocrine glands, a non-significant increased mortality risk was found among both unexposed (SMR 1.91, 95% CI 0.52 to 4.88) and exposed (SMR 4.27, 95% CI 0.52 to 15.42) workers.

EXPLORATORY EXPOSURE-RESPONSE ANALYSIS OF SMRS

Four cancer sites—rectum, oesophagus, pancreas, and kidney—were selected for more detailed exploratory exposure-response analyses based on a ≥20% excesses in mortality in exposed workers and deficits in unexposed workers (table 6); none of these excesses was significant. Table 7 shows observed deaths and SMRs based on local rates (1950–94) for the four cancer sites by duration of employment, the time since first employment, and the three exposure measures, duration of exposure to acrylamide, intensity of exposure to acrylamide, and cumulative exposure to acrylamide. The exposure categories for cumulative expo-

Table 7 Observed deaths and SMRs for selected cancer sites by duration of employment, time since first employment, and measures of exposure to acrylamide, all US workers, 1950–94, local county comparisons

	Oesophagus			Rectum			Pancreas			Kidney		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
Duration of employment (y):												
< 1	12	0.84	0.43 to 1.46	5	0.51	0.16 to 1.18	17	0.87	0.51 to 1.39	8	0.79	0.34 to 1.55
1–14	9	0.95	0.43 to 1.80	12	1.37	0.71 to 2.39	15	0.95	0.53 to 1.57	7	0.86	0.35 to 1.78
≥ 15	10	1.60	0.77 to 2.94	5	0.86	0.28 to 2.02	12	1.19	0.61 to 2.08	7	1.36	0.55 to 2.79
Time since first employment (y):												
< 20	3	0.69	0.14 to 2.01	3	0.71	0.15 to 2.07	4	0.66	0.18 to 1.68	2	0.58	0.01 to 2.09
20–9	6	0.80	0.29 to 1.73	5	0.85	0.28 to 1.98	11	1.08	0.54 to 1.92	3	0.54	0.11 to 1.58
230	22	1.21	0.76 to 1.83	14	0.98	0.53 to 1.64	29	1.00	0.67 to 1.44	17	1.18	0.69 to 1.89
Duration of exposure (y):												
Unexposed	24	0.96	0.61 to 1.42	17	0.82	0.48 to 1.32	30	0.80	0.54 to 1.14	16	0.84	0.48 to 1.37
0.001–4.999	4	1.63	0.45 to 4.18	3	1.92	0.40 to 5.61	5	1.46	0.47 to 3.41	2	0.99	0.12 to 3.59
5–19	3	1.80	0.37 to 5.26	1	0.71	0.02 to 3.96	5	1.79	0.58 to 4.17	3	1.88	0.39 to 5.48
≥20	0	—	0.00 to 4.10	1	1.20	0.03 to 6.70	4	2.42	0.66 to 6.19	1	1.18	0.03 to 6.56
Cumulative exposure (mg/m³.y):												
<.001	24	0.96	0.61 to 1.42	17	0.82	0.48 to 1.32	30	0.80	0.54 to 1.14	16	0.84	0.48 to 1.37
0.001–0.029	2	2.58	0.31 to 9.30	1	2.31	0.06 to 12.88	3	2.77	0.57 to 8.09	1	1.45	0.04 to 8.08
0.03–0.29	3	1.70	0.35 to 4.97	2	1.73	0.21 to 6.23	2	0.73	0.09 to 2.64	2	1.17	0.14 to 4.23
20.30	2	0.82	0.10 to 2.98	2	0.92	0.11 to 3.31	9	2.26*	1.03 to 4.29	3	1.49	0.31 to 4.35
Mean intensity of exposure (mg/m³):												
Unexposed	24	0.96	0.61 to 1.42	17	0.82	0.48 to 1.32	30	0.80	0.54 to 1.14	16	0.84	0.48 to 1.37
0.001–0.019	2	1.37	0.17 to 4.95	2	2.12	0.26 to 7.65	4	1.69	0.46 to 4.32	1	0.66	0.02 to 3.66
0.02–0.29	3	1.53	0.32 to 4.47	0	—	0.00 to 2.03	5	1.50	0.49 to 3.49	3	1.71	0.35 to 5.01
20.30	2	1.26	0.15 to 4.53	3	2.89	0.60 to 8.43	5	2.31	0.75 to 5.40	2	1.68	0.20 to 6.08

*p<0.05.

sure to acrylamide are those used in the original study.' To help discern trends in SMRs, categories for the other variables were chosen to most evenly distribute the numbers of observed deaths simultaneously across the cancer sites examined.

For duration of exposure and time since first exposure to acrylamide, SMRs are generally smallest in the lowest categories. The SMRs for oesophageal cancer increased monotonically with increasing values of both duration of exposure and time since first exposure to acrylamide. Table 7 shows no consistent evidence of an increased risk for cancer mortality associated with exposure to acrylamide, except for pancreatic cancer, where we found a significant ($p<0.05$) 2.26-fold risk (95% CI 1.03 to 4.29) in mortality among workers with a cumulative exposure to acrylamide of 20.30 mg/m^3.years. Although a monotonically increasing risk with duration of exposure to acrylamide was found, none was found with cumulative exposure to acrylamide. An increased, non-significant 2.77-fold risk (95% CI 0.51 to 8.09) among workers was detected in the lowest cumulative exposure category. Lagged cumulative exposure to acrylamide (not shown) for periods of 5, 10, and 20 years produced a similar pattern of findings as noted in table 7.

RISK OF CANCER OF THE RESPIRATORY SYSTEM RELATIVE TO EXPOSURE TO ACRYLAMIDE AND MURIATIC ACID

We fitted RR regression models for cancer of the respiratory system with the subset of the cohort that had potential exposure to muriatic acid (Warners plant workers hired before 1957). All models were based on 276 cases of cancer of the respiratory system (16 exposed to muriatic acid) and 5923 controls, and were adjusted for age and calendar time. In the univariate models, only smoking (characterised as: never, ever, unknown) was a significant predictor of cancer of the respiratory system risk with RRs of 1.00, 8.72, 7.34, respectively. None of the variables considered, including the categorical muriatic acid or exposure to acrylamides, was a significant predictor of risk of cancer of the respiratory system. Workers exposed to muriatic acid had a non-significant 1.50-fold (95% CI 0.86 to 2.59) risk of cancer of the respiratory system compared with workers unexposed to muriatic acid. Models that included an exposure variable representing the joint effects of muriatic acid and exposure to acrylamide had no significant RRs or heterogeneity in risks of cancer of the respiratory system across the joint effects considered (results not shown).

Table 8 Summary of *relative risk* regression analysis *for* cancer of *the* pancreas, US *plants, 1925–94*

			US plants (44 cases, 10261 non-cases)			
Variable	*Category*	*Deaths*	*Risk ratio*	*95% CI*	*Global test (df)*	*Test for trend* (df)*
Univariate models†						
Race	White	39	1.00			
	Non-white	5	0.86	0.34 to 2.20	0.105 (1) p=0.746	—
Year of hire	1925–39	10	1.00			
	1940–49	18	1.09	0.48 to 2.49		
	1950–59	12	1.10	0.44 to 2.78		
	1960–73	4	1.59	0.40 to 6.36	0.405 (3) **p=0.939**	—
Duration of employment (y)	<1	17	1.00			
	1–14	15	1.11	0.55 to 2.24		
	≥15	12	1.39	0.66 to 2.96	0.738 (2) **p=0.692**	—
Time since first employment (y)	<20	4	1.00			
	20–29	11	1.48	0.38 to 5.73		
	≥30	29	1.28	0.32 to 5.15	0.378 (2) **p=0.828**	—
Smoking‡	Never	0	1.00			
	Ever	12	4.96	0.82 to infinity		
	unknown	32	3.59	0.64 to infinity	3.79 (2) p=0.145	—
Time since first exposure (y)	<20	34	1.00			
	20–29	5	2.19	0.84 to 5.73		
	≥30	5	2.54	0.95 to 6.80	4.58 (2) p=0.101	4.22 (1) p=0.040
Duration of exposure (y)	<0.001	30	1.00			
	0.001–<5	5	1.73	0.64 to 4.60		
	5–19	5	2.01	0.78 to 5.23		
	≥20	4	2.37	0.82 to 6.82	4.161 (3) p=0.245	3.91 (1) p=0.048
Cumulative exposure (mg/m^3.y)	<0.001	30	1.00			
	0.001–<0.03	3	3.14	0.92 to 10.71		
	0.03–<0.30	2	0.77	0.18 to 3.26		
	30.30	9	2.63'	1.23 to 5.60	7.69 (3) p=0.053	—
Mean intensity of exposure (mg/m^3)	<0.001	30	1.00			
	0.001–0.02	4	1.77	0.61 to 5.12		
	0.02–<0.30	5	1.67	0.64 to 4.34		
	30.30	5	2.86'	1.08 to 7.56	4.74 (3) p=0.192	—
Bivariable models:¶						
Cumulative exposure (mg/m^3.y)	<0.001	30	1.00			
	0.001–<0.03	3	2.51	0.63 to 9.92		
	0.03–<0.30	2	0.57	0.11 to 2.99		
	30.30	9	1.75	0.48 to 6.39	3.77 (3) p=0.287	—
Mean intensity of exposure (mg/m^3)	<0.001	30	1.00			
	0.001–<0.02	4	1.27	0.34 to 4.78		
	0.02–<0.30	5	1.05	0.26 to 4.18		
	20.30	5	1.94	0.52 to 7.22	1.18 (3) p=0.759	—

*p <.05. †Trend tests performed only on exposure variables exhibiting a monotonic increase or decrease in parameter estimates. ‡Risk sets matched on exact age and year of birth, §LogXact used to model smoking due to sparse data problems. ¶Risk sets matched on exact age and year of birth, models adjusted for time since first exposure to acrylamide.

EXPLORATORY RR REGRESSION ANALYSIS

Table 8 shows the RR regression models relating internal cohort rates for pancreatic cancer to the potential confounding variables of interest and the categorical measures of exposure to acrylamide. The number of deaths observed, the estimated RR (95% CI), and the global test (of main effect) p value and a trend test p value, if warranted (monotonic increasing or decreasing pattern of exposure estimates) are shown for each category of the variables considered. The category used as baseline always has an RR value of 1.0; individual RRs are significant if their 95% CIs do not contain 1.0. All models are based on 44 cases and 10 261 controls and adjusted for age and calendar time.

The top section of table 8 shows that none of the potential confounding variables considered is a significant predictor of risk of pancreatic cancer. Smoking history and time since first exposure to acrylamide had relatively low global test p values (0.145 and 0.101, respectively) and RRs >2.0 in the non-baseline categories. Due to sparse data, the model for smoking history was fitted with the exact conditional (stratified) logistic regression program LogXact.[16] Time since first exposure to acrylamide had a significant (p=0.040) positive monotonic trend in the parameter estimates.

The univariate models of the three measures of exposure to acrylamide show a pattern of RRs qualitatively similar to the pattern of SMRs in table 7. The RRs are generally larger than the corresponding SMRs, due to the 20% deficit in risk of pancreatic cancer among workers in the lowest exposure categories (table 7) that serves as the baseline for the RR models. Table 8 shows that duration of exposure to acrylamide has a significant (p=0.048) monotonic increase in the parameter estimates with increasing duration of exposure to acrylamide. Table 8 also shows that cumulative exposure to acrylamide is a predictor of pancreatic cancer risk of borderline significance (p=0.053), although the increase in RRs with increasing exposure to acrylamide is not monotonic. The RRs for the highest exposure categories of both cumulative exposure to acrylamide and intensity of exposure to acrylamide are significant (p<0.05).

The bottom of table 8 shows models for cumulative exposure to acrylamide and intensity of exposure to acrylamide, adjusted for the time since first exposure to acrylamide. Because of the sparse data for smoking history (zero non-smoking cases), models adjusted for smoking history would not converge. The adjusted models show a pattern of RRs qualitatively similar to their univariate counterparts; however, RRs are uniformly lower, suggesting positive confounding by time since first exposure to acrylamide. Cumulative exposure to acrylamide is no longer a significant predictor of pancreatic cancer in the adjusted models, and the RRs for the highest exposure categories of both cumulative exposure to acrylamide and intensity of exposure to acrylamide are no longer significant. Lagged analyses (5, 10, and 20 years) with other categories of cumulative exposure to acrylamide produced a pattern of RRs for cumulative exposure to acrylamide qualitatively similar to those shown in table 8.

Discussion and conclusions

The overall mortality patterns found in the 11 year follow up period indicated a significant reduced mortality risk from all causes combined and all cancer sites combined. A similar pattern was noted for the entire 1925–94 study period. This favourable mortality pattern is probably influenced in part by the healthy worker effect, a relative absence of deleterious health risks relative to employment, and the effects of continuing employment with its many benefits—such as improved health care and quality of life.

For the 1925–94 study period, we found no significant overall risk or plant specific risk for the cancer sites of initial interest: cancer of the brain and other parts of the CNS, thyroid and other endocrine glands, testis and other male genital organs, and cancer of the respiratory system. However, among the workers exposed to acrylamide, except for cancer of the respiratory system, the few observed deaths for the sites of initial interest resulted in low statistical power to detect important excesses and precluded a detailed examination of exposure-response.

Although not significant, we found increased SMRs for cancer of the thyroid gland (and the larger category, thyroid gland and other endocrine glands) among several cohort subgroups, including a fourfold risk among workers exposed to acrylamide and a twofold risk among unexposed workers. This pattern, based on six cases, with a decreasing SMR across the update periods does not support a causal association between exposure to acrylamide and cancer of the thyroid and suggests that other unmeasured occupational or non-occupational factors may be involved with these excesses. Additional cohort follow up will help to elucidate these possibilities.

An examination of the cluster of suspected cases of cancer of the respiratory system among Warners employees' identified an additional five cases of cancer of the respiratory system among workers with potential exposure to muriatic acid before 1957. Although there is some suggestion that employees with exposure to muriatic acid with and without exposure to acrylamide are at increased risk of cancer of the respiratory system, the limited number of observed deaths (n=16) and incomplete data on smoking history preclude definitive conclusions. Our modelling of cancer of the respiratory system risk showed no evidence of a joint effect of muriatic acid and exposure to acrylamide.

In an exploratory exposure-responseanalysis of SMRs, we found a non-significant monotonically increased risk of pancreatic cancer relative to duration of exposure to acrylamide. No increased risk pattern was found for either cumulative exposure or intensity of exposure to acrylamide, although a significant 2.26-fold risk was found among workers in the highest

category of cumulative exposure to acrylamide. (20.30 mg/m³.years). All 14 cases of pancreatic cancer exposed to acrylamide were born before 1939 and hired before 1966. No consistent pattern was readily apparent when individual work history records were examined. A non-significantly increased risk of pancreatic cancer was found in the original study among workers exposed to acrylamide, but there was no trend with increasing exposure.'

Modelling results showed a pattern of RRs qualitatively similar to those found in the SMR analysis and suggested potential confounding with time since first exposure to acrylamide and with a history of smoking. Smoking is the most consistent risk factor for pancreatic cancer, associated with a greater than twofold increased risk.'' In models adjusted for time since first exposure to acrylamide, we found less evidence of an exposure-response relation for cumulative exposure and intensity of exposure to acrylamide; RRs for these measures decreased to non-significant levels suggesting that this variable acted as a positive confounding factor. Although our inclusion of time since first exposure to acrylamide as a co-factor in models with cumulative exposure to acrylamide and intensity of exposure to acrylamide is statistically appropriate and biologically relevant, some bias may have resulted in the models for cumulative exposure to acrylamide due to the collinearity between the two time dependent factors.

Given the absence of a significant absolute risk, the weak evidence for an exposure-response relation and the inability to consider smoking adequately, as a potential confounding factor, our findings for cancer of the pancreas should be interpreted with caution, in the context of an exploratory analysis to generate hypotheses. This is supported by a recent review by Anderson et *al* who concluded that an occupational aetiology was probably unimportant, given the breadth of workplace experiences examined with few positive findings.'' Additional follow up may elucidate whether the association is spurious or warrants further examination. Among the other cancer sites examined in the exploratory analysis (oesophagus, rectum, and kidney), we found increased SMRs for some categories of exposure to acrylamide, but little evidence of an exposure-response relation.

Nearly half of the cohort were short term workers, a characteristic not presented in the original study findings. About 50% of the acrylamide cohort worked >1 year and only 1936 (23%) worked ≥ 10 years. Consequently, most of the cohort had minimal potential for exposure to acrylamide or were exposed to low levels. Contrary to many other occupational cohort studies, short term workers did not show a differential mortality pattern often associated with increased mortality for both malignant and non-malignant diseases. The long duration of follow up in this study may have mitigated the mortality influence of short term workers.

The limitations of our acrylamide study—namely a large proportion of short term workers—skewed distribution of person-years with respect to duration of exposure, low exposures, and incomplete smoking data, are found in many occupational cohort studies. As such, many studies restrict cohort entry to long term employees. Had short term employees been excluded in the 1994 update, valuable data would have been lost—for example, the cancer of the respiratory system cluster. Potential selection bias from workers lost to follow up may be operating, but the effects would be minimal due to the small percentage of workers involved. Because we did not adjust p values for multiple comparisons, some of our significant SMRs and RRs may be simply chance occurrences.

Our study also has low statistical power to detect excess risks for many cancer sites of initial interest, especially in the subgroup analyses. For example, for the combined 1925–94 study period, our study has the following power to detect twofold or greater risks in mortality (at the 5% one sided significance level): cancer of the brain and other parts of the CNS (0.25), thyroid gland (0.18), and testis and other male genital organs (0.41). On the other hand, the corresponding power to detect cancer of the respiratory system of 0.87 is excellent. Although power is not relevant for the excess of pancreatic cancer identified in the exploratory analysis, a future study of this size would have a power of nearly 100% to detect a twofold or greater excess.

By comparison, our acrylamide study has many methodological strengths that include: large cohort size; long observation period; good death certificate ascertainment for the United States plants; sufficient statistical power to detect meaningful excesses for many categories of cause of death; ample duration of exposure (many years of acrylamide production); quantitative measures of exposure to acrylamide and the use of local county comparison rates and robust modelling of internal cohort rates, a methodological improvement on the original 1989 report.

In summary, this study has many strengths and is the most definitive study of the human carcinogenic potential of exposure to acrylamide conducted to date. The contribution of 1115 additional deaths and nearly 60 000 person-years over the 11 year follow up corroborate the original cohort study findings—namely, little evidence of a causal relation between exposure to acrylamide and mortality from any cancer sites, including those of initial interest. An increased risk of mortality from cancer of the respiratory system, noted in the original study, decreased considerably in the update period and remains only slightly increased among workers exposed and unexposed to acrylamide. Additional follow up of the cohort may elucidate whether the excess of thyroid cancer and the association found between exposure to acrylamide and pancreatic cancer in an exploratory analysis are spurious or warrant further examination.

This work was supported by Cytec Indusmes. We acknowledge Steve Sefcik, Consultant and Al Johnson of Cytec Industries who provided computer programming support.

1 Collins JJ, Swaen GH, Marsh GM, *et al.* Mortality patterns among workers exposed to acrylamide. *J Occup Med* 1989;31:614–17.
2 Johnson KA, Gorzinski SJ, Bodner KM, *et al.* Chronic toxicity and oncogenicity study of acrylamide incorporated in the drinking water of Fischer 344 rats. *Toxicol Appl Pharmacol* 1986;85:154–68.
3 Bull RJ, Robinson M, Laurie RD, *et al.* Carcinogenic effects of acrylamide in Sencar and A/J mice. *Cancer Res* 1984;44: 107–11.
4 Sobel W, Bond GG, Parson TW, *et al.* Acrylamide cohort mortality study. *Br J Ind Med* 1986;43:785–8.
5 Schall LS, Marsh GM, Henderson VL. A two-stage protocol for verifying vital status in large historical cohort studies. *J Occup Environ Med* 1997;39:1097–102. 6Marsh GM, Preininger ME. OCMAP: a user-oriented occupational cohort mortality analysis program. *American Statistician* 1980;34: 245–6.
7 Marsh GM, Ehland J, Paik M, *et al.* OCMAP/PC: a user-oriented cohort mortality analysis program for the IBM PC. *American Statistician* 1986;40:308–9.
8 Marsh GM, Youk AO, Sefcik SS, *et al.* OCMAP-PLUS: a program for the comprehensive analysis of occupational cohort data. 3*Occup Environ Med* 1998;40:351–62.
9 Monson RR. Analysis of relative survival and proportional mortality. *Computers and Biomedical Research* 1974;7:325.
10 Marsh GM, Ehland J, *Sefcik* SS. *Mortality and population data system* [technical report]. Pittsburgh, PA University of Pittsburgh, Department of Biostatistics, 1997.
11 Caplan RJ, Marsh GM, Enterline PE. A generalized effective exposure modeling program for assessing dose-response in epidemiologic investigations. *Computers and Biomedical Research* 1984;16:587–96.
12 Breslow NE, Day NE. *The design and analysis of cohort studies. Statistical methods in cancer research.* Vol II. Lyon: International Agency for Research on Cancer, Oxford University Press, 1987.(IARC Sci Publ No 82.)
13 Cox DR. Regression models and life tables [with discussion]. *Journal of the Royal Statistical Society* 1972;34:187–220.
14 Cox DR. Partial likelihood. *Biometrika* 1975;62:269–76.
15 *EGRET, Version 1.02.09.* Seattle, WA: Statistics and Epidemiology Research Corporation, 1991.
16 Cytel Software. *LogXact turbo: software for exact conditional logistic regression.* Cambridge, MA: Cytel Software, 1993.
17 Anderson KE, Poter JD, Mack TM. Pancreatic cancer (chapter 35). In: Schonenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention,* 2nd *ed.* New York: Oxford University Press,1996.

Correspondence and editorials

Occupational and *Environmental Medicine* welcomes correspondence relating to any of the material appearing in the journal. Results from preliminary or small scale studies may also be published in the correspondence column if this seems appropriate. Letters should be not more than 500 words in length and contain a minimum of references. Tables and figures should be kept to an absolute minimum. Letters are accepted on the understanding that they be subject to editorial revision and shortening.

The journal also publishes editorials which are normally specially commissioned. The Editor welcomes suggestions regarding suitable topics; those wishing to submit an editorial, however, should do so only after discussion with the Editor.

CORRESPONDENCE

Mortality of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base

EDITOR—Tomenson *et al*[1] reported results from a cohort study of men exposed to methylene chloride in the manufacture of cellulose triacetate film base. One of the findings in the study was four observed deaths from brain and other central nervous system (CNS) tumours compared with 2.8 expected cases based on national mortality rates. This is an interesting finding, as Heineman *et al*[2] previously reported an association between exposure to methylene chloride and astrocytic brain cancer in a case-control study of men from southern Louisiana and northern New Jersey who had died. However, Tomenson et *al* dismissed the finding as two of their cases "had minimal exposure to methylene chloride". They furthermore argued that "no support for an association between methylene chloride and brain cancer was provided by the other three retrospective cohort studies".[3-5] However, only one of the three studies that Tomenson et *al* referred to reported data on brain cancer. Hearne et *al*[3] found two observed deaths from brain cancer compared with **1.7** expected based on reference rates from New York State, excluding New York City, and 2.0 expected based on interval rates from Kodak, Rochester. Brain cancer data were not reported in the studies by Lanes et *al*[4] and Gibbs et *al*.[5] The four other available cohort studies[6-9] that included workers exposed to methylene chloride also did not report data on brain cancer.

It would have been prudent for Tomenson et al to bring to the attention of the reader the lack of data on the association between methylene chloride and brain cancer. Not supported is different from not reported!

ELSEBETH LYNGE
Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen, Denmark

1 Tomenson JA, Bonner SM, Heijne CG, *et al*. Mortality of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base. *Occup Environ Med* 1997;54:470–6.
2 Heineman EF, Cocco P, Gomez MR, *et al*. Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. Am *J Ind Med* 1994;26:155–69.
3 Hearne FT, Pifer JW, Grose F. Absence of adverse mortality effects in workers exposed to methylene chloride: an update. *J Occup Med* 1990;32:234–40.
4 Lanes SF, Rothman KJ, Dreyer NA, *et al*. Mortality update of cellulose fiber production workers. *Scand J Work Environ Hedrh* 1993;19: 426–8.
5 Gibbs GW, Amsel J, Soden K. A cohort mortality study of cellulose triacetate-fiber workers exposed to methylene chloride. *J Occup Environ Med* 1996;38:693–7.
6 Sinks T, Lushniak B, Haussler BJ, *et al*. Renal cell cancer among paperboard printing workers. *Epidemiology* 1992;3:483–9.
7 Cragle DL, Wells SM, Tankersley WG. An occupational morbidity study of a population potentially exposed to epoxy resins, hardeners and solvents. *Appl Occup Environ Hyg* 1992;7: 826–34.
8 Shannon HS, Haines T, Bernholz C, *et al*. Cancer morbidity in lamp manufacturing workers. *Am J Ind Med* 1988;14:281–90.
9 Ott MG, Carlo GL, Steinberg S, *et al*. Mortality among employees engaged in chemical manufacturing and related activities. Am *J Epidemiol* 1985;122:311–22.

Authors' reply—Lynge is correct to point out that Gibbs et *al*[1] and Lanes et *al*[2] did not report brain cancer mortality in two cohorts of United States cellulose triacetate fibre workers in Cumberland, Maryland, and Rock Hill, South Carolina. At the time of writing our paper,' the paper by Gibbs et *al*[1] had not been published. However, we had access to a more detailed report' of the mortality experience of workers at the Cumberland facility. For comparison purposes, Gibbs' also reports some mortality findings for workers at the Rock Hill factory. When the paper of Gibbs et *al*[1] was published, we removed the reference to the unpublished report.' Unfortunately we overlooked the fact that the published paper did not include the brain cancer findings which we now give.

Gibbs et *al*[1] and Gibbs' reported mortality results for workers in two groups exposed to methylene chloride. Among workers in the high exposed group (**350-700** ppm) there was one death from cancer of the central nervous system (CNS) (**2.01** expected) and three deaths from cancer of the CNS (**2.54** expected) in the low exposure group (50–100 ppm).' Exposure levels of workers in the Rock Hill cohort studied by Lanes et *al*[2] were similar to those of workers in the Cumberland cohort, but it was not possible to separate them into exposure categories. There was one death from cancer of the CNS (1.52 expected) in the Rock Hill workers.' Hence these studies do not provide support for an association between methylene chloride and brain cancer. However, we apologise for not ensuring that readers had access to the relevant data.

When discussing the supporting evidence for an association between brain cancer and exposure to methylene chloride, we focused on the information provided by the four cohorts of workers producing cellulose triacetate fibres or film base.[1-3 5] These workers had high and well characterised exposure to methylene chloride compared with workers in the four other cohort studies cited by Lynge,[6-9] which did not report brain cancer mortality, but they have limited relevance to an assessment of the human health effects of exposure to methylene chloride.

JOHN A TOMENSON
SUSAN M BONNER
ICI Epidemiology Unit, Northwich, Cheshire, CW8 4DJ, UK

COLIN G HEIJNE
DAVID G FARRAR
ICI Chemicals and Polymers, Runcorn, Cheshire, WA7 4QF, UK

TREVOR F CUMMINGS
ICI Chemicals and Polymers, Middlesborough, Cleveland, TS90 8JA, UK

1 Gibbs GW, Amsel J, Soden K. A cohort mortality study of cellulose triacetate-fiber workers exposed to methylene chloride. *J Occup Environ Med* 1996;38:693–7.
2 Lanes SF, Rothman KJ, Dreyer NA, *et al*. Mortality update of cellulose fiber production workers. *Scand J Work Environ Health* 1993;19: 426–8.
3 Tomenson JA, Bonner SM, Heijne CG, *et al*. Mortality of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base. *Occup Environ Med* 1997;54:470–6.
4 Gibbs GW. The mortality of workers employed at a cellulose acetate and triacetate fibers plant in Cumberland, Maryland: a 1970 cohort followed 1970–89. A Final Report to the Hoechst Celanese Corporation, May 1992.
5 Hearne FT, Pifer JW, Grose F. Absence of adverse mortality effects in workers exposed to methylene chloride: an updare. J *Occup Med* 1990;32:234–40.
6 Sinks T, Lushniak B, Haussler BJ, *et al*. Renal cell cancer among paperboard printing workers. *Epidemiology* 1992;3:483–9.
7 Cragle DL, Wells SM, Tankersley WG. An occupational morbidity study of a population potentially exposed to epoxy resins, hardeners and solvents. *Appl Occup Environ Hyg* 1992;7: 826–34.
8 Shannon HS, Haines T, Bernholz C, *et al*. Cancer morbidity in lamp manufacturing workers. *Am J Ind Med* 1988;14:281–90.
9 Ott MG, Carlo GL, Steinberg S, *et al*. Mortality among employees engaged in chemical manufacturing and related activities. *Am J Epidemiol* 1985;122:311–22.

Inhalation of ammonium nitrate fuel oil explosive: and possible concomitant exposure

Author's reply—Sostrand' has suggested that the nitrogen dioxide component of diesel engine exhaust fumes may have caused the symptoms detailed in the case of ammonium nitrate fuel oil explosive (ANFO) inhalation that I reported recently?

This is unlikely for the following reasons:

- Symptom onset after inhalation of the ANFO plume was immediate
- At the time of the *ANFO* inhalation the miner was charging a face at ground level and the diesel powered platform truck had been switched off for about **15** minutes
- There were no other diesel units operating in the area
- Three other miners in the same area who were not exposed to the ANFO plume were unaffected
- The affected miner had regularly worked in very similar conditions for *9* years without symptoms.

Sostrand has correctly indicated that diesel fuel is commonly used in ANFO. As I indicated in my previous report either the hydrocarbon solvent fuel oil, or the ammonium nitrate, or possibly both of these components of ANFO, may have caused the symptoms described.'

A MICHAEL DONOGHUE
The Medical Centre, Mount Isa Mines Limited, Mount Isa, Queensland 4825, Australia

1 Sostrand P. Inhalation of ammonium nitrate fuel oil explosive (ANFO): and possible concomitant exposure. *Occup Environ Med* 1998;55:647.
2 Donoghue AM. Inhalation of ammonium nitrate fuel oil explosive (ANFO). *Occup Environ Med* 1998;55:144.

CORRECTION

Risk of pulmonary tuberculosis relative to silicosis and exposure to silica dust in South African gold miners by E HNIZDO, J MURRAY (1998;55:496–502).

The cumulative dust exposure measurements given in this paper were in units of ghm^{-3} and not in mg/m^3-y as incorrectly stated. The cumulative dust exposure in ghm^{-3} units was calculated as a sum of products between the number of shifts spent in an occupational category, the average number of hours spent underground in the occupational category, and the average respirable dust concentration (mg/m^3) for the occupational category. To convert the cumulative dust from ghm^{-3} into mg/m^3-y one needs to multiply the average

exposure of 14.3 given in the paper by 1000 and divide by (270x8) to obtain 6.6 mg/m³-y.

We are grateful to Professor HJ Woitowitz from the Institute of Work and Social Medicine in Giessen, Germany, for pointing out this error.

NOTICES

International Course of Molecular Epidemiology. 19-24 **April** 1999. **Villa Gualino, Torino, Italy.**

The Institute for Scientific Interchange Foundation, the International Agency for research on cancer, the University of Torino, the Centre for Oncologic Prevention, and the Italian Molecular Epidemiology Group are running this course.

Keynote lectures
- Current perspectives in cancer research and prevention
- The aetiology of common diseases and their pathogenetic pathways

Session 1—molecular dosimetry: techniques and methods
- DNA adducts and protein adducts
- From adduction to DNA damage

Session 2—genetic susceptibility
- high and low penetrance cancer genes
- metabolic polymorphisms
- DNA repair

Session 3—epidemiological methods
- Study design: transitional and formal studies
- Case-control, cohort studies
- Bias, confounding, and effect modification

Session 4—DAN damage
- Acquired mutations and mutational spectra
- Cytogenetic damage

Session 5—statistical analysis
- Exploratory data analysis
- Univariate analysis
- Multivariate analysis

Session 6—issues in molecular epidemiology
- Ethical aspects
- Combined evidence, meta-analysis
- Causality assessment

Course directors: P Vineis **(Torino),** P Boffetta (Lyon). Faculty (provisional list): N Rothman (Bethesda), M Berwick (New York), D Phillips (Sutton), M Ingelman-Sundberg (Stockholm), F Real (Barcelona), P Hainaut (Lyon), R Montesano (Lyon)
Keynote speakers: P Kleihues (Lyon), F Perera (New York)

No registration fee is required. The ISI Foundation has reserved single rooms for participants from April 18 to 24 at Vila Gualino. The full board package is ITL. 780.000. Deadline for registration: 28, February 1999

For information contact: ISI Secretariat, Villa Gualino, Viale Semmio Severo **65,** Torino, Italy. Tel 0039 11 6603090, **fax** 0039 11 6600049; email: **isi@isi36a.isi.it** - www.isi.it

EPICOH 14th International Conference on Epidemiology in Occupational Health. Herzlia, Israel. 10–14 October 1999.

The ICOH together with the Occupational Health and Rehabilitation Institute in Israel is organising the EPICOH 14th International Conference on Epidemiology in Occupational Health.

The main topics of the conference are:
- Occupational work related diseases
- Occupational cancer
- Occupational epidemiology
- Molecular epidemiology
- Biological markers
- Value of pre-employment examinations
- Exposure assessment
- Reproductive health studies
- Communicable diseases

For information contact: **Dr** Judith Shaham, Occupational Health and Rehabilitation **Institute,** PO Box 3, Ra'anana, Israel. Tel 00 972 9 771 0092; fax 00 972 9 771 2212; email judiths@trendline.co.il

International Conference on The Combined Effects of Environmental Factors ICCEF 2000. 26–29 August 2000, Savonlinna, Finland.

The 9th international conference on the combined effects of environmental factors will take place in Savonlinna, in the beautiful eastern lake area of Finland. The conference is organised under the auspices of the International Society of Complex Environmental Studies (ISCES) in cooperation with national and international research institutes and universities.

The ICCEF 2000 invites all scientists who are interested in basic or applied studies related to complex interactions and combined effects of physical, chemical, psychosocial, and biological environmental factors on human health and wellbeing, or on biological systems. Contributions cover the following main subject areas ***Complex Environmental Studies, Combination Epidemiology, Combination Toxicology, Combined Mutagens, Genotoxins, Carcinogens and Teratogens, Combined Environmental and Psychosocial Factors, Psychophysiological Studies on Combined Environmental Factors, Methodological Issues and Computer Simulation as well as Modelling.*** The programme will include introductory lectures, oral and poster presentations. The working language of the Conference is English.

Further details from: Dr Olavi Manninen, The International ISCES Society, c/o Labour Protection Depzrtment, PO Box 272, FIN-33101 Tampere, Finland. Tel 00358 3 260 8820; fax 00358 3 2608899; email: **Olavi.Manninen@tsp.stm.vn.fi**