Retrospective cohort mortality study of workers at an aircraft maintenance facility. I Epidemiological results

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Abstract

A retrospective cohort study of 14 457 workers at an aircraft maintenance facility was undertaken to evaluate mortality associated with exposures in their workplace. The purpose was to determine whether working with solvents, particularly trichloroethylene, posed any excess risk of mortality. The study group consisted of all civilian employees who worked for at least one year at Hill Air Force Base, Utah, between 1 January 1952 and 31 December 1956. Work histories were obtained from records at the National Personnel Records Centre, St. Louis, Missouri, and the cohort was followed up for ascertainment of vital state until 31 December 1982. Observed deaths among white people were compared with the expected number of deaths, based on the Utah white population, and adjusted for age, sex, and calendar period. Significant deficits occurred for mortality from all causes (SMR 92, 95% confidence interval (95% CI) 90–95), all malignant neoplasms (SMR 90, 95% CI 83–97), ischaemic heart disease (SMR 93, 95% CI 88–98), nonmalignant respiratory disease (SMR 87, 95% CI 76–98), and accidents (SMR 61, 95% CI 52–70). Mortality was raised for multiple myeloma (MM) in white women (SMR 236, 95% CI 87–514), non-Hodgkin's lymphoma (NHL) in white women (SMR 212, 95% CI 102–390), and cancer of the biliary passages and liver in white men dying after 1980 (SMR 358, 95% CI 116–836). Detailed analysis of the 6929 employees occupationally exposed to trichloroethylene, the most widely used solvent at the base during the 1950s and 1960s, did not show any significant or persuasive association between several measures of exposure to trichloroethylene and any excess of cancer. Women employed in departments in which fabric cleaning and parachute repair operations were performed had more deaths than expected from MM and NHL. The inconsistent mortality patterns by sex, multiple and overlapping exposures, and small numbers made it difficult to ascribe these excesses to any particular substance. Hypothesis generating results are presented by a variety of exposures for causes of death not showing excesses in the overall cohort.

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Hill Air Force Base, Utah, is one of several facilities in the United States operated by the Air Force Logistics Command to maintain and overhaul aircraft and missiles. In the mid-1970s, workers at the base expressed concern over potential health effects from chemical exposures as a result of adverse health symptoms reported by around 120 persons who had worked in one particular building at the base. A congressional hearing produced preliminary evidence of a raised proportion of deaths from neoplasms of lymphatic and haematopoietic tissue, especially multiple myeloma.[1] After reviewing the problem in February 1980, the National Research Council's committee on toxicology suggested that a two phase epidemiological study be undertaken, a

retrospective cohort mortality study followed by a case-control study of any cause of death shown to be excessive in this population relative to an appropriately chosen comparison population. Of general concern to the workers were cancer, disorders of the neurological system, and dysfunction of the reproductive system[2] in relation to solvents used in aircraft maintenance operations. Particular concern was expressed regarding neoplasms of the lymphatic and haematopoietic system.

The United States National Cancer Institute, with financial support from the United States Air Force and technical support from the American Federation of Government Employees and the United States Air Force, undertook a retrospective cohort mortality study of workers at the base (1) to determine whether working at this aircraft maintenance facility was associated with an increased risk of death; (2) to evaluate in detail mortality risks associated with exposure to trichloroethylene; (3) to determine whether any raised risks for specific causes of death were associated with specific chemical exposures; and (4) to generate hypotheses for future research by evaluating the relation between various diseases and specific chemicals.

Methods

COHORT DEFINITION

The study group was composed of all civilian employees who worked for at least one year at Hill Air Force Base between 1 January 1952 and 31 December 1956. This cohort, numbering 14 457 persons, was assembled from individual earnings records (IERs) at the civilian branch of the National Personnel Records Center (NPRC), St Louis, Missouri. The IERs, which contain demographic and employment information, were used to establish eligibility of study subjects and to obtain identifying data for the cohort. From a feasibility study of a sample of records drawn from NPRC it was determined that a cohort, consisting of all persons who worked for at least one year at the base between 1952 and 1956, would provide adequate numbers of persons and adequate time since first exposure to study the effect of occupational exposure to trichloroethylene. The IERs for employment before 1952 were stored at NPRC in one alphabetical file (not separated by specific base). Official personnel folders (OPFs) were obtained for 99·8% of all subjects (14 425 out of 14 457) for the purpose of abstracting identifying information (name, date of birth, race, sex, etc) and complete work histories while employed at the base (job title, date started in that job, name of the department, and the corresponding department symbol for each job held at the base).

Vital state of cohort members was determined through a number of sources including the Social Security Administration (SSA), United States Office of Personnel Management files on civil servants, official personnel folders, veterans administration records, motor vehicle bureaux, national death index,[3] and interviews of base personnel. Of 14 066 white subjects (and persons of unknown race), 13 692 (97%) were successfully traced for vital state as of 31 December 1982. For persons who died during the study period, death certificates were obtained from state vital statistics offices. The underlying and contributory cause(s) of death were determined by a nosologist according to the rubrics of the International Classification of Diseases (ICD) in effect at the time of death. Causes of death were assigned ICDA-8 numerical codes for purposes of analysis.[4]

ASSESSMENT OF EXPOSURES

A detailed description of the procedures to assess exposures can be found in a companion paper.[5] Briefly, two industrial hygienists (DEM, JSL) conducted walkthrough surveys of the base, interviewed long term employees, and reviewed industrial hygiene files, position descriptions, and other historical documents from the base to obtain information on departments (called organisations by the air force), job titles and tasks, numbers of employees, operations, chemicals used, monitoring results, and engineering controls. From the personnel files of cohort members, over 150 000 job title and organisation combinations were abstracted and standardised for spelling and word order, reducing the job dictionary to roughly 43 000 job and organisation combinations.

Trichloroethylene (TCE) was of particular interest in this study because it was an important solvent used at the base by many workers (nearly 45 000 person-years of exposure). Special efforts were, therefore, made to evaluate exposures to TCE. Quantitative assessments of actual exposure levels could not be made. For each combination of job and organisation, an assessment was made as to whether it had frequent or infrequent peak exposures to TCE, or continuous, or intermittent low level exposures to TCE, or both. From these patterns of use, exposure indices were developed that reflected comparative differences in exposure. Many other solvents were used at the base and, where possible, they were qualitatively evaluated. As it was difficult to identify with confidence particular solvents used for some jobs, a category of "mixed solvents" was designated. Continuous or intermittent patterns of exposure to mixed solvents were identified and again exposure indices were developed that reflected comparative differences. The development of exposure indices for TCE and mixed solvents enabled analyses to be performed by cumulative and average exposures.

ANALYTICAL METHODS

Using the OCMAP[6] analysis program, standardised

mortality ratios (SMRs) and confidence intervals[7] were calculated for selected causes of death for the entire cohort and for subgroups with likely exposure to chemicals. The starting date for follow up was 1 January 1953 or one year after the start of employment, whichever was later. Person-years at risk were accumulated for the cohort by race, sex, and five year age and calendar era categories. Non-cancer rates for 1950–60 were obtained by using rates for 1960. The observed number of deaths was divided by the expected number of deaths and multiplied by 100 to give the SMR; SMRs are presented in table 3 when more than two observed, or two expected deaths, or both occurred. Confidence intervals (95%) around the SMRs were computed assuming that the observed numbers of deaths had a Poisson distribution.[7] Persons presumably deceased (based on vital state information from SSA and other sources) but lacking a death certificate were counted in the unknown cause of death category and included in the tabulation of "all causes of death." The χ^7 test for trend in SMRs across exposure categories was derived from the χ^2 test for linear trend of Breslow *et al.*[8]

A regrouping of lymphoreticular neoplasms was done to create two further categories with common histological characteristics: (1) non-Hodgkin's lymphoma (NHL) composed of lymphosarcoma and reticulosarcoma (ICD 200) and other neoplasms of lymphoid tissue (ICD 202) and (2) multiple myeloma (MM) (ICD 203). Utah death rates for NHL and MM were generated by the designers of OCMAP specifically for our use in this study.

Mortality risks among white male and female workers were compared with the mortality experience for the white male and female populations living in the United States and the state of Utah. The larger United States population provides more stable rates, but the Utah population is more reflective of the lifestyle of the civilian workers in this cohort. Risks by estimated duration of exposure were assessed to evaluate exposure response relations for each of 25 categories of chemicals. Person-years of exposure were computed from date of first exposure, which could have been as early as 1939. All periods of employment at the base until 31 December 1982 were counted in determining person-years of exposure. All 25 categories of exposure were accounted for in exposure specific analyses. Person-years of follow up began one year from date of first exposure to a given chemical or on 1 January 1953, whichever was later. Analyses were also conducted by time since first exposure (latency).

For persons exposed to TCE and mixed solvents, SMRs were calculated by type of exposure (that is, frequent or infrequent peaks, continuous or intermittent low level exposures). Analyses by cumulative exposure were also performed, in which years of exposure were accumulated for each cohort member in the appropriate exposure category until the cumulative index exceeded the next higher cut off point. Each cohort member then remained in the highest attained category until leaving the study. Data were also analysed by time since first exposure, highest exposure, and average exposure.

Internal comparisons were made to reduce possible bias by socioeconomic or cultural differences between cohort members and the general population of Utah, and to determine whether raised SMRs were base wide or limited to specific exposure categories. This second method involved life table analyses with the procedure of Thomas and Gart,[9] which adjusted for age at entry into follow up (within five year categories) and competing causes of death. The Thomas-Gart (TG) method was used in place of the SMR because the unexposed subgroup in the cohort had small numbers; this violates the assumption made in using SMRs that no variation exists in death rates in the comparison group. Using this general linear multiple logistic model, white men and women exposed to a given chemical were compared with those of the same race and sex never exposed to any chemical while employed at the base. Chi square statistics and associated levels of significance (p values) were generated. Further TG analyses were also computed for groups with 20 or more years since first exposure to particular chemicals.

Results

DESCRIPTIVE STATISTICS

White men constituted 65% (9400/14 457) of the total cohort and 22% (3138) were white women. The numbers of non-white men (269) and women (122) were too small for analysis. Persons of unknown race (1061 men and 467 women) have been combined with white persons for purposes of statistical analysis. The combined group of white workers and persons of unknown race is called whites in this report. Because the overwhelming percentage of persons with known race were white (98% men and 96% women) and because information on race is available (from the death certificate) for essentially all known deaths, persons of unknown race consist almost entirely of those still alive or with unknown state. Roughly three quarters of the cohort were born after 1909. Fifty five per cent of the cohort were born in Utah. For the 1970 general Utah white population, 70% were born in Utah.[10]

A total of 9860 study subjects (68%) were known to be alive as of 31 December, 1982, 9182 (64%) were no longer working at the base, 678 (5%) were alive and working at the base, and 3832 (27%) persons were deceased. Follow up was highly successful, with vital state, as of 31 December 1982, known for over 97% of the cohort. Tracing was more successful for men (99%) than women (93%).

Table 1 Cause specific SMRs and 95% CIs adjusted for age, sex, and calendar period: white workers

Cause of death (ICDA 8th revision code)	*Obs*	*Exp†*	*SMR† (95% CI)*
All causes of death	3832	4146·0	92** (90–95)
Tuberculosis	11	9·1	121 (60–216)
All malignant neoplasms	641	712·3	90* (83–97)
Cancer of buccal cavity and pharynx	15	13·6	111 (62–183)
Cancer of digestive organs and peritoneum	174	197·2	88 (76–102)
Cancer of oesophagus	10	11·2	89 (43–164)
Cancer of stomach	39	41·9	93 (66–127)
Cancer of large intestine	56	65·8	85 (64–111)
Cancer of rectum	12	16·8	71 (37–125)
Cancer of biliary passages and liver	19	12·3	155 (93–242)
Biliary passages‡	15	8·7	172 (96–285)
Liver, primary‡	4	3·6	111 (30–284)
Cancer of pancreas	33	42·1	78 (54–110)
Cancer of all other digestive organs	5	7·5	67 (22–156)
Cancer of respiratory system	141	145·3	97 (82–115)
Cancer of larynx	4	5·9	68 (18–173)
Cancer of bronchus, trachea, lung	137	136·0	101 (85–119)
Cancer of all other respiratory tissues	0	3·3	0 (0–113)
Cancer of breast	30	41·4	73 (49–104)
All uterine cancers	14	14·2	99 (54–166)
Cancer of cervix uteri	9	6·5	139 (64–264)
Cancer of other female genital organs	14	13·9	101 (55–169)
Cancer of prostate	51	63·3	81 (60–106)
Cancer of testes and other male genital organs	4	3·6	112 (30–285)
Cancer of kidney and other urinary organs	13	15·6	83 (44–143)
Cancer of bladder	18	17·6	102 (61–162)
Malignant melanoma of skin	14	11·7	120 (66–201)
Cancer of eye	1	1·1	—
Cancer of central nervous system	16	23·7	68 (39–110)
Cancer of thyroid gland and other endocrine organs	1	4·1	25 (1–137)
Cancer of bone	4	2·8	143 (39–366)
Cancer of all lymphatic and haematopoietic tissue	87	85·4	102 (82–126)
Lymphosarcoma and reticulosarcoma	21	19·8	106 (66–162)
Hodgkin's disease	6	9·4	64 (24–140)
Leukaemia and aleukaemia	26	33·2	78 (51–115)
Cancer of all other lymphopoietic tissue	34	23·2	147* (102–205)
Multiple myeloma‡	20	11·7	170* (104–262)
Non-Hodgkin's lymphoma	32	23·9	134 (91–189)
All other malignant neoplasms	44	56·2	78 (57–105)
Benign neoplasms	15	11·2	134 (75–221)
Diabetes mellitus	78	79·1	99 (78–123)
Cerebrovascular disease	266	318·0	84** (74–94)
All heart diseases	1475	1590·6	93** (88–98)
Rheumatic heart disease	91	94·7	96 (77–118)
Ischaemic heart disease	1274	1368·1	93* (88–98)
Chronic disease of endocardium; other myocardial disease	10	22·0	46** (22–84)
Hypertension with heart disease	16	22·3	72 (41–117)
All other heart disease	84	111·1	76** (60–94)
Hypertension without heart disease	8	10·2	78 (34–154)
Non-malignant respiratory disease	249	287·5	87* (76–98)
Influenza and pneumonia	80	109·3	73** (58–91)
Bronchitis, emphysema, asthma	94	99·8	94 (76–115)
Bronchitis	14	18·9	74 (41–124)
Emphysema	68	75·4	90 (70–114)
Asthma	12	6·2	194* (100–339)
Other non-malignant respiratory diseases	75	83·9	89 (70–112)
Ulcer of stomach and duodenum	28	27·3	102 (68–148)
Cirrhosis of liver	69	77·3	89 (69–113)
Nephritis and nephrosis	25	22·1	113 (73–167)
All external causes of death	269	426·1	63** (56–71)
Accidents	181	297·7	61** (52–70)
Motor vehicle accidents	78	130·8	60** (47–74)
All other accidents	103	166·6	62** (51–75)
Suicides	72	88·9	81 (63–102)
Homicides and other external causes	16	20·3	79 (45–128)
All other causes of death	438	567·7	77** (70–85)
Unknown causes (999·9)	270		

*$p < 0·05$; **$p < 0·01$.
†Expected deaths include persons of unknown race. Utah state death rates were used as standard. SMRs and 95% CIs are presented only if number of observed or expected deaths > 2.
‡Special categories created for this study.

ANALYSIS OF TOTAL COHORT

Table 1 presents SMRs for white workers adjusted for age, sex, and calendar period, using Utah death rates as the standard. For 44 out of 65 causes of death the SMR was less than 100 indicating an overall favourable mortality experience for the cohort. Significant excesses only existed for cancer of all other lymphopoietic tissue (ICD codes 202–203, 208–209; SMR 147, 95% CI 102–205), multiple myeloma (MM) (ICD code 203; SMR 170, 95% CI 104–262), and for asthma (SMR 194, 95% CI 100–339).

Statistically non-significant excesses (SMRs of at least 120) were found for cancers of the biliary passages and liver (SMR 155, 95% CI 93–242), uterine cervix (SMR 139, 95% CI 64–264), bone (SMR 143, 95% CI 39–366), malignant melanoma of the skin (SMR 120, 95% CI 66–201), non-Hodgkin's lymphoma (NHL) (SMR 134, 95% CI 91–189), and benign neoplasms (SMR 134, 95% CI 75–221). More than the expected numbers of deaths occurred for tuberculosis (SMR 121, 95% CI 60–216).

The significant deficits occurred for all causes of death (SMR 92, 95% CI 90–95), all malignant neoplasms (SMR 90, 95% CI 83–97), cerebrovascular disease (SMR 84, 95% CI 74–94), all heart diseases (SMR 93, 95% CI 88–98), ischaemic heart disease (SMR 93, 95% CI 88–98), chronic disease of the endocardium, and other myocardial insufficiency (SMR 46, 95% CI 22–84), all other heart diseases (SMR 76, 95% CI 60–94), non-malignant respiratory disease (SMR 87, 95% CI 76–98), influenza and pneumonia (SMR 80, 95% CI 58–91), all external causes of death (SMR 63, 95% CI 56–71), accidents (SMR 61, 95% CI 52–70), motor vehicle accidents (SMR 60, 95% CI 47–74), all other accidents (SMR 62, 95% CI 51–75), and all other causes of death (SMR 77, CI 95% 70–85). Many causes of death had non-significantly depressed SMRs.

Patterns of risk for NHL, MM, cancer of the biliary passages and liver, and asthma were not consistent by categories of latency or duration of employment among men or women. When the results of female SMRs for NHL and MM were considered together, the resulting χ^2 statistic (χ^2 3·85, p = 0·05) showed a significant positive trend with duration.

Because of the well known effect of solvents on the central nervous system,[11] a special effort was made to review deaths due to multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Since the only readily available rates for these specific diseases were aggregated for the entire United States for the 1968–78 period (unpublished data, National Cancer Institute), the SMRs could only be adjusted for age. Analysis of amyotrophic lateral sclerosis in white women produced the SMR of 321 (95% CI 87–821). Because death rates for ALS in women have been comparatively high in Davis and Weber counties (Utah)[12] where most of the people who work at the base reside, it is unlikely that the excess seen was due to chemical exposures at the base. No other neurological diseases showed an excess.

ANALYSIS BY EXPOSURE TO TRICHLOROETHYLENE

Tables 2–5 present data from the second aim of the study—namely, the evaluation of the association between exposure to TCE and specific causes of death. Tables 2 and 3 provide SMRs for selected causes of death for white men and women, ever exposed to TCE during their careers at Hill Air Force Base. Mortality from all causes combined was significantly depressed among men (SMR 92, 95% CI 87–96) and women (SMR 82, 95% CI 71–95), and several causes of death had significant deficits in SMRs. Although no significant excess risks occurred in either sex, non-significantly raised SMRs were found among men for cancers of the biliary passages and liver (SMR 196, 95% CI 85–386) and asthma (SMR 244, 95% CI 79–570), and among women for cancer of the cervix (SMR 224, 95% CI 61–574) and cancer of the lymphatic and haematopoietic system (SMR 143, 95% CI 58–295), particularly for NHL (SMR 286, 95% CI 78–731). Tables 4 and 5 present SMRs for selected causes of death for TCE exposed workers by estimated cumulative exposure categories. Significant upward trends by cumulative exposure were found among men for the categories "all causes of death" and "emphysema". Among women exposed to TCE, a significant negative trend by cumulative exposure was found for all cancers combined. Analysis by average exposure found a significant upward trend only among men for the all causes of death category (no table presented). Analyses by type of exposure to TCE (frequent *v* infrequent peak exposures, and continuous *v* intermittent low level) did not show any significant patterns.

ANALYSIS BY SPECIFIC DISEASES

Tables 6 and 7 consider the third aim of the study—namely, further analyses of the raised SMRs found in the overall cohort by total exposure to specific chemicals. Both tables display relative risks from exposure to 25 selected chemicals used on the base, plus the categories any chemical, any solvent, never exposed to any chemical, and total cohort. Exposure categories are not mutually exclusive because many workers had multiple exposures.

Multiple myeloma

Non-significantly raised SMRs for MM occurred among men and women exposed to the general category of any chemical, any solvent, or mixed solvents, and among women never exposed to any

Table 2 Cause specific SMRs and 95% CIs adjusted for age and calendar period: white men exposed to TCE

Cause of death (ICDA 8th revision code)	*Obs*	*Exp†*	*SMR (95% CI)*
All causes of death	1508	1647·8	92** (87–96)
Tuberculosis	0	3·7	0* (0–99)
All malignant neoplasms	248	268·5	92 (81–105)
Cancer of buccal cavity and pharynx	5	5·7	88 (29–206)
Cancer of digestive organs and peritoneum	74	74·7	99 (78–124)
Cancer of oesophagus	6	5·7	106 (39–230)
Cancer of stomach	14	16·0	88 (48–147)
Cancer of large intestine	27	23·3	112 (73–164)
Cancer of rectum	4	6·3	64 (17–163)
Cancer of biliary passages and liver	8	4·1	196 (85–386)
Biliary passages‡	6	2·5	238 (87–519)
Liver, primary‡	2	1·6	—
Cancer of pancreas	14	16·9	83 (45–139)
Cancer of all other digestive organs	2	2·8	72 (9–260)
Cancer of respiratory system	65	69·5	94 (72–119)
Cancer of larynx	1	2·9	34 (1–191)
Cancer of bronchus, trachea, lung	64	65·1	98 (76–126)
Cancer of all other respiratory tissues	0	1·4	—
Cancer of prostate	22	27·6	80 (50–121)
Cancer of testes and other male genital organs	1	2·0	—
Cancer of kidney and other urinary organs	8	6·7	120 (52–237)
Cancer of bladder	10	7·3	137 (65–251)
Malignant melanoma of skin	5	5·2	96 (31–224)
Cancer of eye	0	0·5	—
Cancer of central nervous system	9	10·1	89 (41–170)
Cancer of thyroid gland and other endocrine organs	1	1·5	—
Cancer of bone	3	1·1	263 (54–767)
Cancer of all lymphatic and haematopoietic tissue	30	34·6	87 (59–124)
Lymphosarcoma and reticulosarcoma	9	8·0	112 (51–213)
Hodgkin's disease	4	4·3	93 (25–237)
Leukaemia and aleukaemia	9	13·1	69 (31–130)
Cancer of all other lymphopoietic tissue	8	9·2	87 (38–172)
Multiple myeloma‡	5	4·5	111 (36–259)
Non-Hodgkin's lymphoma‡	10	9·8	103 (49–189)
All other malignant neoplasms	15	21·2	71 (40–117)
Benign neoplasms	5	4·3	117 (38–273)
Diabetes mellitus	26	27·6	94 (62–138)
Cerebrovascular disease	84	101·0	83 (66–103)
All heart diseases	618	640·6	97 (89–104)
Rheumatic heart disease	34	33·4	102 (71–142)
Ischaemic heart disease	551	561·7	98 (90–107)
Chronic disease of endocardium; other myocardial disease	3	8·0	37 (8–109)
Hypertension with heart disease	5	6·8	73 (24–171)
All other heart disease	25	43·0	58** (38–86)
Hypertension without heart disease	1	3·7	27 (1–149)
Non-malignant respiratory disease	104	118·3	88 (72–107)
Influenza and pneumonia	27	39·5	68* (45–100)
Bronchitis, emphysema, asthma	40	43·6	92 (66–125)
Bronchitis	7	8·4	84 (34–172)
Emphysema	28	33·6	83 (55–121)
Asthma	5	2·1	244 (79–570)
Other non-malignant respiratory diseases	37	36·9	100 (71–138)
Ulcer of stomach and duodenum	10	10·9	92 (44–169)
Cirrhosis of liver	25	36·3	69 (45–102)
Nephritis and nephrosis	8	8·6	93 (40–184)
All external causes of death	128	205·6	62** (52–74)
Accidents	79	141·1	56** (44–70)
Motor vehicle accidents	33	61·2	54** (37–76)
All other accidents	46	79·7	58** (42–77)
Suicides	41	45·5	90 (65–122)
Homicides and other external causes	8	10·0	80 (35–158)
All other causes of death	161	216·5	74** (63–87)
Unknown causes (999·9)	93		

*$p < 0·05$; **$p < 0·01$.
†Expected deaths include persons of unknown race. Utah state death rates were used as standard. SMRs and 95% CIs were presented only if number of observed or expected deaths > 2.
‡Special categories created for this study.

Table 3 Cause specific SMRs and 95% CIs adjusted for age and calendar period: white women exposed to TCE

Cause of death (ICDA 8th revision code)	*Obs*	*Exp†*	*SMR (95% CI)*
All causes of death	186	227·2	82** (71–95)
Tuberculosis	0	0·2	—
All malignant neoplasms	33	49·4	67* (46–94)
Cancer of buccal cavity and pharynx	0	0·6	—
Cancer of digestive organs and peritoneum	7	13·0	54 (22–111)
Cancer of oesophagus	0	0·2	—
Cancer of stomach	0	2·0	—
Cancer of large intestine	2	5·5	37 (4–132)
Cancer of rectum	1	1·1	—
Cancer of biliary passages and liver	2	1·2	—
Biliary passages‡	2	1·1	—
Liver, primary‡	0	0·2	—
Cancer of pancreas	2	2·5	81 (10–291)
Cancer of all other digestive organs	0	0·5	—
Cancer of respiratory system	0	3·1	0 (0–121)
Cancer of larynx	0	0·1	—
Cancer of bronchus, trachea, lung	0	2·8	0 (0–131)
Cancer of all other respiratory tissues	0	0·2	—
Cancer of breast	9	11·5	79 (36–149)
All uterine cancers	4	4·1	98 (27–251)
Cancer of cervix uteri	4	1·8	224 (61–574)
Cancer of other female genital organs	4	4·0	100 (27–255)
Cancer of kidney and other urinary organs	0	0·8	—
Cancer of bladder	1	0·6	—
Malignant melanoma of skin	1	0·6	—
Cancer of eye	0	0·1	—
Cancer of central nervous system	0	1·4	—
Cancer of thyroid gland and other endocrine organs	0	0·4	—
Cancer of bone	0	0·1	—
Cancer of all lymphatic and haematopoietic tissues	7	4·9	143 (58–295)
Lymphosarcoma and reticulosarcoma	3	1·2	261 (54–761)
Hodgkin's disease	0	0·3	—
Leukaemia and aleukaemia	2	1·9	—
Cancer of all other lymphopoietic tissue	2	1·5	—
Multiple myeloma‡	1	0·8	—
Non-Hodgkin's lymphoma‡	4	1·4	286 (78–731)
All other malignant neoplasms	0	4·2	0* (0–86)
Benign neoplasms	2	0·8	—
Diabetes mellitus	6	6·8	88 (32–191)
Cerebrovascular disease	22	26·6	83 (52–125)
All heart diseases	70	78·7	89 (69–112)
Rheumatic heart disease	8	8·6	93 (40–184)
Ischaemic heart disease	54	60·2	90 (67–117)
Chronic disease of endocardium; other myocardial disease	1	1·5	—
Hypertension with heart disease	1	2·0	—
All other heart disease	6	7·4	82 (30–178)
Hypertension without heart disease	0	0·7	—
Non-malignant respiratory disease	4	10·6	38* (10–97)
Influenza and pneumonia	0	6·3	0** (0–59)
Bronchitis, emphysema, asthma	2	2·1	95 (12–343)
Bronchitis	0	0·5	—
Emphysema	2	1·0	—
Asthma	0	0·5	—
Other non-malignant respiratory diseases	2	2·5	80 (10–287)
Ulcer of stomach and duodenum	0	1·1	—
Cirrhosis of liver	3	3·4	88 (18–257)
Nephritis and nephrosis	1	1·3	—
All external causes of death	9	13·0	69 (32–131)
Accidents	7	9·8	71 (29–147)
Motor vehicle accidents	5	4·7	106 (34–247)
All other accidents	2	5·2	39 (5–140)
Suicides	2	2·0	99 (12–357)
Homicides and other external causes	0	0·7	—
All other causes of death	17	34·2	50** (29–80)
Unknown causes (999·9)	20		

*$p < 0·05$; **$p < 0·01$.
†Expected deaths include persons of unknown race. Utah state death rates were used as standard. SMRs and 95% CIs are presented only if number of observed or expected deaths > 2.
‡Special categories created for this study.

Table 4 SMRs (Obs/Exp) for selected causes of death among white men by cumulative exposure to TCE

Cause	Cumulative exposure < 5	5–25	> 25	Total exposure	χ for trend†
All causes	87** (562/649·2)	88* (341/386·3)	99 (605/612·3)	92* (1508/1647·8)	2·48*
All cancers	94 (99/105·6)	87 (56/64·1)	94 (93/98·8)	92 (248/268·5)	0·12
Buccal/pharynx	89 (2/2·3)	— (0/1·3)	144 (3/2·1)	88 (5/5·7)	0·64
Biliary passages‡	200 (2/1·0)	500* (3/0·6)	106 (1/0·9)	236 (6/2·5)	−0·67
Primary liver cancer‡	324 (2/0·6)	— (0/0·4)	— (0/0·6)	127 (2/1·6)	§
Pancreas	90 (6/6·7)	75 (3/4·0)	81 (5/6·2)	83 (14/16·9)	−0·18
Lung	96 (25/26·0)	88 (14/15·9)	107 (25/23·3)	98 (64/65·1)	0·42
Prostate	68 (7/10·3)	48 (3/6·2)	109 (12/11·1)	80 (22/27·6)	1·12
Testes	119 (1/0·8)	— (0/0·5)	— (0/0·7)	50 (1/2·0)	—
Kidney	191 (5/2·6)	— (0/1·6)	124 (3/2·4)	120 (8/6·7)	−0·57
Bladder	142 (4/2·8)	177 (3/1·7)	107 (3/2·8)	136 (10/7·3)	−0·38
CNS	73 (3/4·1)	163 (4/2·5)	57 (2/3·5)	89 (9/10·1)	−0·19
All lymphatic and haematopoietic tissue	73 (10/13·8)	61 (5/8·3)	119 (15/12·6)	87 (30/34·6)	1·26
Leukaemia	58 (3/5·2)	— (0/3·2)	124 (6/4·8)	69 (9/13·1)	1·34
Multiple myeloma‡	114 (2/1·8)	95 (1/1·1)	119 (2/1·7)	111 (5/4·5)	0·03
Non-Hodgkin's lymphoma‡	128 (5/3·9)	129 (3/2·3)	57 (2/3·5)	103 (10/9·8)	−0·91
Ischaemic heart disease	94 (207/219·5)	94 (123/131·2)	105 (221/211·1)	98 (551/561·7)	1·12
Emphysema	31** (4/12·8)	90 (7/7·8)	131 (17/12·9)	83 (28/33·6)	2·82*
Asthma	129 (1/0·8)	423 (2/0·5)	250 (2/0·8)	244 (5/2·1)	0·33
Cirrhosis of liver	47* (7/14·9)	55 (5/9·1)	105 (13/12·3)	69 (25/36·3)	1·82
Nephritis	58 (2/3·4)	102 (2/2·0)	126 (4/3·2)	93 (8/8·6)	0·88

*$p < 0·05$; **$p < 0·01$.
Cumulative exposure categories were derived by cumulatively multiplying the exposure index assigned to each job by time exposed at that level (see Stewart *et al*[5] for a detailed explanation of the derivation).
†Derived from χ^2 test for linear trend.[8]
‡Special categories created for this study.
§χ not computed if number of observed deaths < 5.

Table 5 SMRs (Obs/Exp) for selected causes of death among white women by cumulative exposure to trichloroethylene

Cause	Cumulative exposure < 5	5–25	> 25	Total exposure	χ for trend†
All causes	78 (35/44·7)	60* (18/29·9)	87 (133/152·5)	82* (186/227·2)	0·90
All cancer	88 (10/11·4)	43 (3/7·0)	64* (20/31·1)	67* (33/49·4)	−2·94*
Buccal/pharynx	— (0/0·1)	— (0/0·1)	— (0/0·4)	— (0/0·6)	—
Biliary passages‡	435 (1/0·2)	— (0/0·1)	143 (1/0·7)	189 (2/1·1)	—
Primary liver cancer‡	— (0/0·0)	— (0/0·0)	— 0/0·1)	— (0/0·2)	—
Pancreas	— (0/0·5)	— (0/0·3)	125 (2/1·6)	81 (2/2·5)	—
Lung	— (0/0·7)	— (0/0·4)	— (0/1·7)	— (0/2·8)	—
Breast	107 (3/2·8)	119 (2/1·7)	57 (4/7·0)	79 (9/11·5)	−0·89
Kidney	— (0/0·2)	— (0/0·1)	— (0/0·5)	— (0/0·8)	—
Bladder	— (0/0·1)	— (0/0·1)	265 (1/0·4)	183 (1/0·6)	—
CNS	— (0/0·4)	— (0/0·2)	— (0/0·8)	— (0/1·4)	—
All lymphatic and haematopoietic tissue	277 (3/1·1)	— (0/0·7)	128 (4/3·1)	143 (7/4·9)	−0·93
Leukaemia	240 (1/0·4)	— (0/0·3)	82 (1/1·2)	106 (2/1·9)	—
Multiple myeloma‡	602 (1/0·2)	— (0/0·1)	— (0/0·5)	130 (1/0·8)	—
Non-Hodgkin's lymphoma‡	328 (1/0·3)	— (0/0·2)	330 (3/0·9)	286 (4/1·4)	0·2
Ischaemic heart disease	107 (11/10·3)	13** (1/7·5)	99 (42/42·4)	90 (54/60·2)	0·43
Emphysema	— (0/0·2)	— (0/0·1)	314 (2/0·6)	198 (2/1·0)	—
Asthma	— (0/0·1)	— (0/0·1)	— (0/0·3)	— (0/0·5)	—
Cirrhosis of liver	326 (3/0·9)	— (0/0·5)	— (0/2·0)	88 (3/3·4)	—
Nephritis	— (0/0·3)	— (0/0·2)	114 (1/0·9)	76 (1/1·3)	—

*$p < 0·05$; **$p < 0·01$.
Cumulative exposure categories were derived by cumulatively multiplying the exposure index assigned to each job by time exposed at that level (see Stewart *et al*[5] for a detailed explanation of the derivation).
†Derived from χ^2 test for linear trend.[8]
‡Special categories created for this study.
§χ not computed if number of observed deaths < 5.

Table 6 SMRs and 95% CIs for MM among white workers by exposure to selected groups of chemicals

	Men			*Women*		
Exposure category	*Obs*	*Person-years*	*SMR (95% CI)*	*Obs*	*Person-years*	*SMR (95% CI)*
Any chemical	12	222426	164 (85–286)	3	45359	218 (45–636)
Any solvent	11	215076	156 (78–280)	3	44566	220 (45–642)
Mixed solvents	11	214723	157 (78–281)	3	43960	223 (46–653)
Trichloroethylene	5	152111	111 (36–259)	1	23634	130 (3–722)
Stoddard solvent	5	146274	117 (38–272)	1	31960	114 (3–633)
Carbon tetrachloride	7	142266	176 (71–363)	2	35290	200 (25–721)
Other chemicals	4	93724	118 (32–304)	3	20463	386 (80–1129)
JP4/High octane aviation gasoline	2	81265	106 (13–382)	0	13278	—
Freon	3	53193	209 (43–612)	0	5088	—
Solder flux	2	51555	162 (20–585)	0	4548	—
Isopropyl alcohol	2	49915	165 (20–596)	0	5314	—
Zinc chromate	0	44250	—	2	12886	681 (82–2459)
1,1,1-Trichloroethane	0	27223	—	2	1215	5660 (685–20445)
Acetone	1	43719	81 (2–452)	2	8885	648 (78–2342)
Toluene	2	32903	186 (22–670)	3	13373	835 (172–2440)
Methyl ethyl ketone	1	32212	96 (2–536)	2	10042	904 (109–3267)
Methylene chloride	4	22770	574 (156–1469)	0	3091	—
Metal fumes/dust	0	25667	—	0	1512	—
Ortho-dichlorobenzene	0	20829	—	0	2117	—
Perchloroethylene	0	13281	—	2	2446	1705 (206–6159)
Known or suspected carcinogens	1	15996	129 (3–717)	0	2291	—
Other alcohols	1	14785	221 (6–1231)	0	1712	—
Chloroform	0	2951	—	0	250	—
Styrene	0	2812	—	0	937	—
Nitroglycerine	0	1910	—	0	7	—
Silica	0	2113	—	0	121	—
Xylene	0	1837	—	0	444	—
Never any chemical	2	47307	105 (13–380)	3	54039	258 (53–753)
Total cohort	14	269733	152 (83–255)	6	99398	236 (87–514)

Obs = No of observed deaths due to multiple myeloma.
Person-years of follow up since 1 January 1953 or one year from first exposure to given chemical, whichever is later.

Table 7 SMRs and 95% CIs for NHL among white workers by exposure to selected groups of chemicals

	Men			*Women*		
Exposure category	*Obs*	*Person-years*	*SMR (95% CI)*	*Obs*	*Person-years*	*SMR (95% CI)*
Any chemical	19	222426	123 (74–192)	7	45359	279 (112–575)
Any solvent	18	215076	121 (72–192)	7	44566	282 (113–581)
Mixed solvents	18	214723	122 (72–192)	7	43960	286 (115–560)
Trichloroethylene	10	152111	103 (49–189)	4	23634	286 (78–731)
Stoddard solvent	9	146274	97 (44–184)	3	31960	185 (38–540)
Carbon tetrachloride	9	142266	103 (47–195)	6	35290	325 (119–708)
Other chemicals	8	93724	118 (50–228)	4	20463	283 (77–723)
JP4/High octane aviation gasoline	5	81265	114 (37–227)	1	13278	184 (5–1022)
Freon	3	53193	95 (20–279)	0	5008	—
Solder flux	4	51555	143 (39–367)	0	4548	—
Isopropyl alcohol	3	49915	110 (23–322)	0	5314	—
Zinc chromate	4	44250	135 (37–346)	2	12886	377 (46–1363)
1,1,1-Trichloroethane	4	27223	188 (51–482)	0	1215	—
Acetone	3	43719	114 (24–334)	1	8885	183 (5–1018)
Toluene	3	32903	129 (27–378)	2	13373	307 (37–1108)
Methyl ethyl ketone	3	32212	134 (28–393)	1	10042	251 (6–1400)
Methylene chloride	2	22770	134 (16–484)	0	3091	—
Metal fumes/dust	0	25667	—	0	1512	—
Ortho-dichlorobenzene	1	20829	70 (2–388)	1	2117	1008 (25–5616)
Perchloroethylene	2	13781	190 (23–685)	2	2446	968 (117–3496)
Known or suspected carcinogens	1	15996	66 (2–366)	0	2291	—
Other alcohols	2	14785	203 (25–734)	0	1712	—
Chloroform	0	2951	—	0	250	—
Styrene	0	2812	—	0	937	—
Nitroglycerine	0	1910	—	0	7	—
Silica	0	2113	—	0	121	—
Xylene	0	1837	—	0	444	—
Never any chemical	3	47307	79 (16–231)	3	54039	136 (28–398)
Total cohort	22	269733	114 (72–173)	10	99398	212 (102–390)

Obs = No of observed deaths due to non-Hodgkin's lymphoma.
Person-years of follow up since 1 January 1953 or one year from first exposure to given chemical, whichever is later.

chemical (table 6). The SMRs for several specific chemicals were raised, but they were based on small numbers and were usually not statistically significant. Significantly raised SMRs occurred among men exposed to methylene chloride (SMR 574, 95% CI 156–1469), but no deaths from MM occurred among the 129 women ever exposed to this agent (only 0·09 would have been expected). Significantly raised SMRs were found among women exposed to 1,1,1-trichloroethane (SMR 5660, 95% CI 685–20 445), toluene (SMR = 835, CI = 172–2440), methyl ethyl ketone (MEK) (SMR 904, 95% CI 109–3267), and perchloroethylene (tetrachloroethylene) (SMR 1705, 95% CI 206–6159), but not among men.

For all exposure categories in table 6, the TG procedure[9] was used to assess the significance of mortality differences among persons exposed to specific chemicals and persons in the cohort never exposed to any chemical while working at the base. In general, the results from the TG analyses for persons dying of multiple myeloma were consistent with the results from table 6. The significant associations held among men exposed to methylene chloride ($n = 4$, $\chi^2 = 6{\cdot}8$, $p = 0{\cdot}009$) and women exposed to 1,1,1-trichloroethane ($n = 2$, $\chi^2 = 11{\cdot}5$, $p = 0{\cdot}001$) or perchloroethylene ($n = 2$, $\chi^2 = 5{\cdot}6$, $p = 0{\cdot}018$). The associations were not significant among women for multiple myeloma and exposures to toluene ($n = 3$, $\chi^2 = 3{\cdot}6$, $p = 0{\cdot}058$) or MEK ($n = 2$, $\chi^2 = 1{\cdot}6$, $p = 0{\cdot}204$). When the analysis was restricted to 20 years or more after first exposure, the association was statistically significant for multiple myeloma among men exposed to methylene chloride ($n = 2$, $\chi^2 = 4{\cdot}1$, $p = 0{\cdot}043$) and among women exposed to perchloroethylene ($n = 2$, $\chi^2 = 4{\cdot}6$, $p = 0{\cdot}034$), but not among women exposed to toluene ($n = 3$, $\chi^2 = 3{\cdot}2$, $p = 0{\cdot}077$).

NON-HODGKIN'S LYMPHOMA

For NHL, SMRs were greater than 100 for many chemicals and tended to be higher among women (table 7). For men, none of these excesses was statistically significant. For women, statistically significant associations were found among the total cohort (SMR 212, 95% CI 102–390), persons ever exposed to any chemical (SMR 279, 95% CI 112–575), any solvent (SMR 282, 95% CI 113–581), mixed solvents (SMR 286, 95% CI 115–560), carbon tetrachloride (SMR 325, 95% CI 119–708), and perchloroethylene (SMR 968, 95% CI 117–3496). The association between perchloroethylene and NHL among white women was statistically significant in the TG analyses ($n = 2$, $\chi^2 = 5{\cdot}2$, $p = 0{\cdot}022$). As well as the two perchloroethylene exposed cases, one other female case (reported in table 6 as "never exposed to any chemical") worked in a dry cleaning shop during non-Hill employment, where exposure to perchloroethylene may have occurred. When results for perchloroethylene-exposed men and women were combined, the overall SMR for NHL was 315 (95% CI 86–609).

A review of work histories of persons dying from MM or NHL suggested that an unusual proportion of women developing these diseases may have worked in either or both of two fabric handling departments where "dope" (a substance used in fabric treatment) and solvents were used. Multiple myeloma was significantly raised among women employed in parachute repair (SMR 1717, 95% CI 354–5018), and among those in fabric cleaning (SMR 1155, 95% CI 140–4174), but no deaths were found from either cause among men employed in these shops. Non-Hodgkin's lymphoma was not significantly raised among men or women employed in these areas.

Cancer of the biliary passages and liver

For cancers of the biliary passages and liver, no significant associations occurred with exposure to any specific chemical (table not shown), although many of the SMRs were raised. Separate SMRs for cancer of the biliary passages and for liver cancer generally showed no significant excess risks. The TG analyses for liver cancer found no significant associations; the TG analyses for cancer of the biliary passages, however, showed significant associations for women exposed to zinc chromate ($n = 2$, $\chi^2 = 3{\cdot}96$, $p = 0{\cdot}04$). This association persisted when latency was taken into consideration ($n = 2$, $\chi^2 = 12{\cdot}56$, $p < 0{\cdot}001$).

Asthma

In the total cohort, the SMR for asthma among men was 205 (95% CI 94–389). All of the male cases had been exposed to some chemical while employed at Hill Air Force Base. The SMRs among men were raised for several of the exposures, especially for Stoddard solvent (SMR 301, 95% CI 110–655), carbon tetrachloride (SMR 328, 95% CI 120–714), and methylene chloride (SMR 932, 95% CI 192–2723). For male asthma cases, the TG analyses showed a significant association only with exposure to methylene chloride ($n = 3$, $\chi^2 = 8{\cdot}43$, $p = 0{\cdot}004$). All three of these cases had at least five years of exposure to methylene chloride. Data to evaluate risk when latency (at least 20 years since first exposed or first employed) was considered were inadequate ($n = 1$). Among women the SMR for asthma was 168 (95% CI 35–490), but none of the three cases had exposure to any chemical.

ANALYSIS OF SPECIFIC CHEMICALS

Mixed solvents

We evaluated the SMRs for selected causes of death among white men and women, by cumulative exposure to mixed solvents. The SMRs were sig-

nificantly raised for asthma among men (SMR 240, 95% CI 104–473), and for NHL among women (SMR 286, 95% CI 115–560) (table 7). Significant deficits were found among men for all causes of death (SMR 94, 95% CI 90–98) and, among women, for all causes of death (SMR 90, 95% CI 80–99), and all cancer (SMR 75, 95% CI 58–96). Among men, significant upward trends occurred across cumulative exposure categories for pancreatic cancer, particularly 20 years after first exposure ($n = 17$, $\chi^2 = 2{\cdot}47$), and for emphysema ($n = 44$, $\chi^2 = 2{\cdot}29$). Insufficient numbers of cases existed among women in most subcategories to allow analysis by cumulative exposure, although all three cases of MM had more than five years of exposure.

Other selected chemicals

We further examined individual causes of death by chemical exposure and found many significant deficits for various causes of death for exposures to specific chemicals. Significantly raised SMRs occurred for men exposed to xylene (cancer of the central nervous system, SMR 1436, 95% CI 174–5184); and for women exposed to JP4/high octane aviation gasoline (cancer of buccal cavity and pharynx, SMR 853, 95% CI 103–3079), freon (breast cancer, SMR 309, 95% CI 124–637), solder flux (breast cancer, SMR 310, 95% CI 113–675), and isopropyl alcohol (breast cancer, SMR 312, 95% CI 125–643). The excesses of breast cancer among women exposed to freon, solder flux, and isopropyl alcohol were not independent: six out of seven of these cases had exposure to all three chemicals.

The TG analyses of breast cancer showed highly significant associations with exposures to isopropyl alcohol ($n = 7$, $\chi^2 = 17{\cdot}37$, $p < 0{\cdot}001$), freon ($n = 7$, $\chi^2 = 15{\cdot}37$, $p < 0{\cdot}001$), solder flux ($n = 6$, $\chi^2 = 15{\cdot}14$, $p < 0{\cdot}001$), and other alcohols ($n = 2$, $\chi^2 = 10{\cdot}24$, $p = 0{\cdot}001$). Also, breast cancer was significantly raised among women exposed to methylene chloride ($n = 3$, $\chi^2 = 6{\cdot}12$, $p = 0{\cdot}01$).

Discussion

Over the years many chemicals have been used at this base in the repair and maintenance of aircraft. These include chlorinated hydrocarbons (trichloroethylene, perchloroethylene, chloroform, 1,1,1-trichloroethane, methylene chloride, ortho-dichlorobenzene, and freon), aromatic hydrocarbons (toluene, xylene), aliphatics (isopropyl alcohol, and other alcohols), and other compounds such as carbon tetrachloride, solder flux, zinc chromate, silica, and high octane fuels. Exposure of man to these chemicals is of concern because several cause cancer in animals (chloroform, methylene chloride, isopropyl alcohol, silica, perchloroethylene, and trichloroethylene).[13] Data, however, are lacking or insufficient to draw definite conclusions about their effects in man.[13] This study of 14 457 civilian workers at an air force aircraft maintenance facility was initiated because this population provided the opportunity to obtain important epidemiological information on trichloroethylene and other chemicals widely used in industry, and because of preliminary evidence indicating that these workers might be experiencing a high proportion of deaths due to MM.[1] Experimental studies of TCE provided limited evidence for carcinogenicity in animals.[13]

Compared with other epidemiological studies of cohorts exposed to solvents, the study is large and is one of the few to present results for both sexes. Several limitations need to be considered, however, in interpreting the results. Many SMRs were computed because the cohort had potential exposure to a large number of chemicals. Subgroup analyses were done by sex, by specific chemical, by latency, and by duration of exposure or level of exposure. Few deaths occurred from most diseases showing raised SMRs. Although subgroup analysis is an important step in establishing new links between diseases and specific exposures, it also introduces chance results due to the increase in the number of comparisons and a decrease in the size of the subgroups being analysed. Due to the multiple statistical comparisons, some of the significantly high and low SMRs probably reflect chance observations.[14] Also, overlap of chemical use among defined exposure groups was considerable, with most workers exposed to more than one chemical. This makes it difficult to relate excess risks to specific chemical exposures. Many of the solvents were used interchangeably and some may have been contaminated with other chemicals. Clustering of disease excesses also occurred for certain exposure categories—for example, men exposed to methylene chloride had excess risks for MM and cancer of the biliary passage, bladder cancer, and asthma. Furthermore, some chemicals under study are metabolised into other chemicals.

Smoking histories were not available. For smoking to confound associations, however, not only must it have been a risk factor for the disease of interest, but the proportion who smoked must differ between the exposed and unexposed members of the cohort. Evidence to date does not indicate a direct relation between smoking and multiple myeloma, non-Hodgkin's lymphoma, or cancer of the biliary passages and liver.[15] Other investigators have seldom found that the proportion of smokers differed substantially between exposed and unexposed subjects,[16 17] and we have no reason to suspect a difference in the current study. The study also lacked information on other factors of lifestyle, such as religion and consumption of alcohol.

Statistical results were generally consistent whether based on SMRs or the life table TG

procedure.[9] Both methods adjust for differences in age and calendar year, but the second procedure is based on comparisons within the cohort of workers. The first method is more easily interpreted, however, as it provides estimates of relative risk.

Persons living in Utah have lower death rates than the United States population,[18] largely attributable to differences in lifestyle due to the influence of the Church of Jesus Christ of Latter Day Saints (Mormons).[19] Therefore, we used death rates from the state of Utah to generate expected numbers of deaths in computations of SMRs. Comparison with Utah death rates provided a comparison that was culturally closer to the cohort than use of United States population death rates, with only a slight loss of stability. Additional analyses (not presented), with the United States population as the standard, produced slightly lower SMRs, but were consistent with the results shown in this paper. Use of national or state death rates as the standard is generally thought to underestimate the true underlying relative risks in occupational mortality studies because of the healthy worker effect.[20]

To rule out cultural and behavioural differences between the workers in the cohort and the population of Utah, within cohort analyses (TG method) provided a closer possible cultural group for comparison by utilising an employed population as the comparison group. Because of few cohort members in the never exposed group, however, this last analysis suffered from problems of stability. Also, the proportion of never exposed workers who were in salaried rather than wage grade jobs was 61% compared with less than 1% of exposed workers, indicating that the TG analyses did not compare groups of exactly similar socioeconomic state.

These limitations do not invalidate results from this study. On the contrary, it possessed strengths that provided unique opportunities to evaluate mortality risks associated with exposures found in this facility. With over 14 000 study subjects followed up for over 25 years, this was a large occupational cohort. The study included an exposure assessment component that was more detailed than typically found in epidemiological studies. Although misclassification of exposures to specific substances undoubtedly occurred, the degree of misclassification associated with this approach is likely to be substantially less than that from analyses based only on occupational titles. Consistency of findings using national, state, and unexposed worker populations as comparison groups decreases the likelihood that results are due to chance.

DISEASES

When compared with the general mortality experience of the Utah population, mortality in the study cohort was significantly raised for MM and NHL among white women and for asthma and cancer of the biliary passages and liver among white men. The MM excess was of particular interest as a preliminary investigation of 67 cancer deaths, identified by workers and air force officials, had shown a raised number (four) of multiple myelomas. Significant deficits occurred for several causes. More detailed evaluation of mortality patterns by specific chemical exposures uncovered a number of associations. Small numbers for most chemicals and overlapping exposures, however, complicate interpretation.

Significantly raised SMRs for MM occurred among women exposed to perchloroethylene, 1,1,1-trichloroethane, toluene, and MEK, and among men exposed to methylene chloride, all based on fewer than five deaths. Non-significant increases, however, were associated with exposures to some other chemicals and were also seen among women never exposed to chemicals. All three cases of MM among women exposed to chemicals worked in fabric handling operations (two worked specifically on parachute repair), where they may have had contact with carbon tetrachloride, perchloroethylene, trichloroethylene, and possibly toluene, Stoddard solvent, "dope" (a stiffening agent for cloth), or nitrocellulose paint. Specific identification of the chemicals used in these products could not be made. Two of these cases had also been exposed to 1,1,1-trichloroethane, toluene, methyl ethyl ketone, and zinc chromate in other work areas. One of the women classified as having no exposure to chemicals had worked in a dry cleaning shop before coming to work at the base.

A carcinogenesis bioassay study found significant increases in mammary tumours in rats and lung and liver tumours in mice given methylene chloride by inhalation.[21] The excess of MM among white men exposed to methylene chloride has not been found in other epidemiological studies. A survey of workers exposed to methylene chloride in the production of photographic chemicals noted an excess for pancreatic cancer (eight observed deaths *v* 3·2 expected) but not for MM.[22 23] No such excess for pancreatic cancer was noted for exposures to methylene chloride in the current study, although a significant trend in SMRs was found across cumulative exposure categories for men exposed to mixed solvents. Ott *et al*[24 25] studied synthetic fibre production workers exposed to methylene chloride in South Carolina. Based on a total of 54 deaths, no excess mortality was seen for any cause of death.

An excess of NHL was seen among women exposed to perchloroethylene, based on two deaths (one in the parachute repair section at the base and the other, who may have also been exposed to perchloroethylene as a laundry and dry cleaning worker outside of the base, as an aircraft mechanic). A recent inhalation carcinogenesis bioassay showed

increases in hepatocellular carcinomas in mice and mononuclear cell leukaemia in male rats after exposure to perchloroethylene.[26] Epidemiological evaluations are, however, inconsistent. Studies of dry cleaners exposed to various solvents including perchloroethylene, Stoddard solvent, and carbon tetrachloride have shown significant excesses for the various cancers—namely, liver among women only[26a]; cervix uteri and oesophagus, with slight excesses for cancers of the bladder and the lymphatic and haematopoietic system[27]; urinary tract[28]; kidney, and genital sites with non-significant increases for lymphosarcoma and bladder cancer[29]; lung and kidney[30]; and leukaemia and lymphoma in men exposed to 1,1,2,2-tetrachloroethane and dry cleaning solvents.[31]

Other studies have reported associations with NHL among chemists[32 33] and farmers.[34–37] In Sweden, Hardell *et al*[38] related malignant lymphoma (Hodgkin's disease and NHL) to phenoxy acids, chlorophenols, and organic solvents (especially benzene, trichloroethylene, perchloroethylene, and styrene), and Persson *et al*[39] found an association between NHL and solvents, phenoxy acids, and creosote.

Excess risk of liver cancer among women, but not among men, has been associated with exposure to solvent, using data from the Finnish Cancer Registry.[40 41] Other studies have found excesses of liver cancer for broadly defined occupational groups such as metal workers,[42] coast guard marine inspectors,[43] and agricultural workers.[44] Krain[45] noted an excess of bile duct cancers among workers in the aircraft and other industries. We were unable to relate the excess mortality from cancer of biliary passages and liver to any particular chemical exposure. In laboratory animals, liver tumours may be produced by exposures to trichloroethylene,[46 47] perchloroethylene,[26] or chloroform.[48 49] It was difficult to evaluate liver cancer, however, because there were few cases and because it is difficult to distinguish metastatic cancers from primary cancers using only information from death certificates. Percy *et al*[50] found that the proportion of hospital diagnoses of liver cancer also noted on the death certificate was around 50%, and about three quarters of death certificates with a mention of liver cancer could be confirmed by hospital records. For comparison, these proportions for MM were 97% and 98% respectively.

The statistically significant SMR for asthma among men exposed to methylene chloride in this study was also unexpected. Methylene chloride is metabolised to carbon monoxide, which results in increased carboxyhaemoglobin concentrations in man.[51] As the three deaths from asthma occurred many years after last exposure, however, it is unlikely that methylene chloride was causally related to this excess. Occupational asthma has been described among men employed as spray painters, presumably due to exposure to isocyanate,[52] but there was no suggestion of exposure to isocyanate among those asthma cases in our study.

We found significant SMRs for breast cancer among women exposed to freon, solder flux, and isopropyl alcohol. These chemicals were also significantly associated with breast cancer in the TG analysis, as were methylene chloride and other alcohols. Several recent studies have reported a raised risk of breast cancer among women who drank alcoholic beverages,[53–58] although a causal association remains uncertain and may be confounded by other risk factors.[59] Alcoholic beverages contain ethyl alcohol, which is close in chemical structure to some of the alcohols used by the cohort. Teta *et al*[60] have reported an excess risk of breast cancer among cosmetologists. The excess of breast cancer in women exposed to methylene chloride is intriguing, given the ability of this agent to produce mammary tumours in rats.[21] Breast cancer is influenced by factors of lifestyle and socioeconomic state,[61] so that it is more appropriate to use the TG analysis, which is based on the mortality experience of other women employed at the base as the standard for comparison. It is interesting that SMRs for bladder cancer among men in the current study were raised, though not significantly, after exposure to the same chemicals.

Recent studies of incidence of testicular cancer among United States navy personnel have implied an excess risk among aircraft repair workers.[62 63] It was suggested that dimethylformamide (DMF) may be the causal agent. There was no use of DMF at the base; nor was there any excess mortality from testicular cancer.

EXPOSURES

The solvents used at the base were primarily chlorinated hydrocarbons (chloroform, ortho-dichlorobenzene, freon, methylene chloride, perchloroethylene, 1,1,1-trichloroethane, trichloroethylene), aromatic hydrocarbons (toluene, xylene), alcohols (isopropyl alcohol, other alcohols), and carbon tetrachloride. Perchloroethylene is similar to trichloroethylene in chemical structure, and is metabolised to trichloroethylene.[64] Several of the solvents under question are fat soluble and are stored in fatty tissue.[65] As well as concerns raised by bioassay studies of carcinogenesis, a major toxic effect of these solvents has been depression of the central nervous system.[66 67] A raised SMR for cancer of the central nervous system among men exposed to xylene, which has acute toxic effects on the system, has not, to our knowledge, been previously reported.

Several approaches were adopted to evaluate mortality risks associated with exposure to TCE. No overall association was found between exposure to

TCE and any cause of death within this study. This is consistent with other cohort studies of TCE exposed workers.[68 69] Although an overall deficit of deaths from emphysema among men exposed to TCE was found (SMR 83, 95% CI 55–121), we cannot explain the significant upward trend of the SMRs by cumulative exposure to TCE seen in table 4. Two other epidemiological studies on case series of liver cancers[70 71] found no association with TCE exposed jobs. Experimental studies of TCE provide limited evidence for carcinogenicity in animals.[13] Methyl chloroform (1,1,1-trichloroethane), which largely replaced TCE in the 1970s as the primary solvent used at the base, is generally not considered to be carcinogenic.[72 73]

A considerable effort was put into estimating potential exposures from inhalation in this study, particularly to TCE and mixed solvents. It was not possible to evaluate potential dermal exposures, which could have led to misclassification of study subjects. Also, most of the cohort who had exposure to TCE were exposed to comparatively low concentrations of this chemical. For other chemicals, estimates of exposure levels, either from inhalation or dermal absorption, could not be made. Although we think that the sensitivity was high for assigning chemical exposure to jobs, we are less certain regarding the specificity of this approach—that is, it seems likely that some jobs with certain chemical exposures were not recognised. When exposure to solvents seemed likely, but uncertainty existed in assigning the specific solvents used, the project industrial hygienists (JSL, DEM) assigned the category of mixed solvents. Thus some persons classified as non-exposed to a particular substance may have actually had such an exposure. Such misclassification of exposure would moderate exposure response gradients.[74]

Conclusions

Although this is the largest study to date of workers exposed to TCE, no significant or persuasive relations were found between various measures of exposure to TCE and the risk of any specific malignancy. These results are consistent with other epidemiological studies of workers exposed to TCE. Because of the few deaths for many types of cancer and the low levels of exposure to TCE, it is only possible to suggest, at this time, that occupational exposure to TCE probably does not pose a strong carcinogenic risk for man.

Given the original concern regarding excess deaths from MM among workers at the base we were not surprised to find raised SMRs for MM and NHL. These SMRs were associated with various chemical exposures and could not be specifically ascribed to any particular substance. The most consistent associations were seen for two specific work areas; statistically significant SMRs for MM among women (SMR 1717, 95% CI 354–5020) and non-significant raised SMRs for NHL in both sexes were seen for workers in departments concerned with fabric cleaning and repair of parachutes. Exposures in these departments included various solvents as well as a "dope" of unknown formulation used as a stiffening agent for fabric. With regard to specific exposures and the risks of MM, statistically significant SMRs were seen among women exposed to perchloroethylene (SMR 1705, 95% CI 206–6159), toluene (SMR 835, 95% CI 172–2440), methyl ethyl ketone (SMR 904, 95% CI 109–3267), and 1,1,1-trichloroethane (SMR 5660, 95% CI 685–20 445). For NHL, no statistically significant associations were noted for men, whereas among women, significant associations occurred with exposure to any chemical (SMR 279, 95% CI 112–575), any solvent (SMR 282, 95% CI 113–581), mixed solvents (SMR 286, 95% CI 115–560), carbon tetrachloride (SMR 325, 95% CI 119–708), and perchloroethylene (SMR 968, 95% CI 117–3496). The few cases, multiple and overlapping exposures, differences in SMRs between the sexes, and multiple non-significant associations with many other chemicals complicate any attempt to relate the mortality excesses for MM and NHL to specific exposures. Further complicating interpretations are the raised SMRs for both of these tumours among women never exposed to chemicals at the base. None the less, the associations between these tumours and chemicals such as carbon tetrachloride and perchloroethylene that cause cancer in laboratory animals, plus similarities to other epidemiological investigations that have noted associations between various solvent exposures and risks of lymphatic and haematopoietic neoplasms, provide a biological plausibility which, we believe, does not allow these findings to be clearly dismissed as chance occurrences.

Exposure assessment in this cohort also allowed exposure specific assessment of risks of cancer sites that were not in excess in the total cohort. Here, even more than in the case of MM and NHL, caution is needed to avoid overinterpretation of what may be chance observations. Perhaps the most provocative finding, however, was the series of associations with excess breast cancer, a cancer site not usually associated with occupational exposures. Included were significantly raised SMRs among women exposed to isopropyl alcohol (SMR 312, 95% CI 125–642), freon (SMR 309, 95% CI 124–638), solder flux (SMR 310, 95% 114–674), and non-significant associations with methylene chloride (SMR 204, 95% CI 42–597) and other alcohols (SMR 271, 95% CI 33–980). Increasing employment of women in blue collar jobs indicates the need for further evaluation of these associations in studies that will allow assessment as to whether they are related to job

exposures or to factors of lifestyle associated with women employed in these jobs.

The conclusions, recommendations, or other views expressed herein are those of the authors and do not necessarily reflect the official views of the United States Air Force, Department of Defence, or the American Federation of Government Employees. We thank our colleagues at the National Cancer Institute for their thoughtful criticisms of this report.

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Accepted 7 January 1991

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