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Estimated Effects of Solvents and Mineral Oils on Cancer Incidence and Mortality in a Cohort of Aerospace Workers

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Background *A retrospective cohort study of workers employed at a California aerospace company between 1950 and 1993 was conducted; it examined cancer mortality from exposures to the rocket fuel hydrazine.*

Methods *In this study, we employed a job exposure matrix (JEM) to assess exposures to other known or suspected carcinogens—including trichloroethylene (TCE), polycyclic aromatic hydrocarbons (PAHs), mineral oils, and benzene—on cancer mortality (1960–2001) and incidence (1988–2000) in 6,107 male workers. We derived rate- (hazard-) ratios estimates from Cox proportional hazard models with time-dependent exposures.*

Results *High levels of TCE exposure were positively associated with cancer incidence of the bladder (rate ratio (RR): 1.98, 95% confidence interval (CI) 0.93–4.22) and kidney (4.90; 1.23–19.6). High levels of exposure to mineral oils increased mortality and incidence of lung cancer (1.56; 1.02–2.39 and 1.99; 1.03–3.85), and incidence of melanoma (3.32; 1.20–9.24). Mineral oil exposures also contributed to incidence and mortality of esophageal and stomach cancers and of non-Hodgkin's lymphoma and leukemia when adjusting for other chemical exposures. Lagging exposure measures by 20 years changed effect estimates only minimally. No associations were observed for benzene or PAH exposures in this cohort.*

Conclusions *Our findings suggest that these aerospace workers who were highly exposed to mineral oils experienced an increased risk of developing and/or dying from cancers of the lung, melanoma, and possibly from cancers of the esophagus and stomach and non-Hodgkin's lymphoma and leukemia. These results and the increases we observed for TCE and kidney cancers are consistent with findings of previous studies.* Am. J. Ind. Med. 48:249–258, 2005. © *2005 Wiley-Liss, Inc.*

KEY WORDS: cancer incidence; cancer mortality; occupational cohort; trichloroethylene; mineral oils; Cox model

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INTRODUCTION

The Rocketdyne Worker Study was initiated in the early 1990s in response to strong concerns voiced by area residents about the use of radioactive and toxic agents at a nuclear reactor and rocket-engine testing facility known as the Santa Susana Field Laboratory (SSFL), located in Southern California. We previously conducted a retrospective cohort

study of aerospace employees at the SSFL between 1950 and 1993, who engaged in rocket engine testing. That study focused exclusively on estimating cancer mortality from occupational exposures to hydrazines used at the SSFL in large quantities as rocket fuels in the 1950s and 1960s [Ritz et al., 1999; Morgenstern and Ritz, 2001].

Exposure of workers to known or suspected chemical carcinogens at this facility, however, was not limited to hydrazine rocket fuels. Thus, one aim of this new investigation was to determine whether these aerospace workers also developed cancers from exposures to other chemicals including trichloroethylene (TCE), polycyclic aromatic hydrocarbons (PAHs), mineral oils, and benzene. TCE and some PAHs have been classified as Group 2A carcinogens by the International Agency for Research on Cancer (IARC) based on limited evidence in humans and sufficient evidence of carcinogenicity in experimental animals [IARC, 1995, 1987a]. The carcinogenicity of mineral oils has been recognized by the National Institute for Occupational Safety and Health [NIOSH, 1998] and IARC [untreated and mildly treated oils were classified as Group 1; highly refined oils were classified as Group 3; IARC, 1987b]. Benzene, classified as a Group 1 human carcinogen by IARC can cause leukemia in highly exposed individuals [IARC, 1982; Savitz and Andrews, 1997].

We extended the mortality follow-up of this aerospace worker cohort for an additional 7 years (1994–2001) and, in addition, for the first time collected cancer-incidence information from the statewide California cancer registry (1988–2000) and eight other state cancer registries. This allowed us to evaluate cancer incidence for largely non-fatal cancers that are inadequately addressed in cancer mortality studies. Estimated hydrazine effects and results for prostate-cancer incidence in a combined cohort of both aerospace and radiation workers are presented elsewhere [Ritz et al, unpublished data; Krishnadasan et al., unpublished data].

METHODS

Subject Selection

The source population for this cohort consists of 55,000 workers employed between 1950 and 1993 at several Boeing North America (formerly Rockwell/Rocketdyne) facilities in Los Angeles. The cohort assembled included 6,107 male workers who had been employed before 1980 in the aerospace division of the SSFL. Subjects had to have worked at least 2 years at any Rockwell/Rocketdyne facility and never been monitored for radiation exposure, i.e., these employees had worked during the most active period of rocket engine testing but were never employed at the nuclear facilities also housed at the SSFL [Ritz et al., 1999; Morgenstern and Ritz, 2001].

Outcomes

Mortality information, including date of death and underlying and contributing causes of death, were obtained from multiple sources. Company records were initially used to identify deaths among workers with retirement benefits. All employee records were then matched against three different record systems: Social Security Administration beneficiary files (1935–1994), vital statistics files for California (1960–1994), and the U.S. National Death Index (NDI, 1979–2001). Whenever necessary, matches were verified by reviewing the information on death certificates obtained from state registries. Previously, a licensed nosologist coded the underlying and contributing cause of death information recorded on each death certificate using the 9th revision of the International Classification of Diseases (ICD-9). After 1994, NDI provided us with the underlying and contributing causes of death information; until 1998 these were coded according to ICD-9 and subsequently according to ICD-10. NDI was our sole source of mortality information between 1994 and 2001, since we found that for the period 1979–1994 the NDI search alone resulted in a nearly 100% complete vital-status search for our cohort [Ritz et al., 1999]. Analyses presented here are based on the underlying cause of death.

We re-examined cancer mortality in all workers included in the original cohort, following each subject from the start of employment or January 1, 1950, whichever date was later, to the date of death or December 31, 2001, whichever date was first.

We matched our cohort against the California cancer registry, which contained complete records for all incident cancers diagnosed in California between 1988 and 2000. In addition, we obtained data from eight other state cancer registries, i.e., Arizona (coverage period: 1981–2000), Arkansas (1996–2000), Florida (1981–2000), Nebraska (1993–2000), Nevada (1986–2000), Oregon (1996–2000), Texas (1995–2000), and Washington State (1992–2000), thereby identifying incident cancers that occurred in workers who had left California during follow-up. These states were selected because a search of all state cancer registries was not feasible. Thus, we focused on those states in which most of the deaths outside California had occurred for cohort members (percent of total deaths in our cohort between 1988 and 2000: Arizona 4.3%, Arkansas 0.7%, Florida 1.7%, Nebraska 0.4%, Nevada 3.4%, Oregon 2.9%, Texas 2.4%, Washington 2.1%; percent of deaths reported in all other non-California states: 11%). We included only incident cases diagnosed in these states between 1988 and 2000, i.e., the coverage period of the California cancer registry. We also searched the oldest cancer registry in California, the Los Angeles County Cancer Registry, which has collected cancer incidence information since 1972. This registry, however, provided coverage for no more than 38% of our cohort; thus, this information was only used to exclude cancer cases

diagnosed prior to 1988 from our denominator of cancer-free subjects at the start of follow-up in 1988.

The cancer-incidence cohort consists of 5,049 workers who were alive and at risk of being diagnosed with a first primary cancer on January 1, 1988, excluding deaths before 1988 and cancer incident cases ascertained prior to 1988 by one of the registries with earlier case ascertainment. Since follow-up for the incident cohort started in 1988, person-time for members of this cohort accrued only between 1988 and 2000, such that each cancer-free worker in 1988 was followed to date of diagnosis for a first primary cancer, death, or December 31, 2000, whichever date came first. Exposure information for cohort members was available for the complete length of employment at the facility prior to 1988.

The coding of cancer incidence was based on ICD-O, the International Classification of Diseases—Oncology [WHO, 1990], which is an extension of the neoplasm section of the ICD-10. ICD-O permits separate coding of topography and morphology in its Second Edition Codes (also referred to as ''site'' and ''tissue''). Non hemato- and lymphopoietic tumors were categorized on the basis of topography, while leukemia, lymphomas and other lymphopoietic malignancies were grouped on the basis of morphology codes. For all workers with more than one cancer diagnosis, we counted only the first primary cancer occurrence.

The cancer sites examined in this cohort were: esophagus and stomach, colon and rectum, lung, non-Hodgkin's lymphoma (NHL) and leukemia, kidney, bladder, brain, pancreas, and skin melanoma.

Exposure Measures

We conducted an extensive industrial hygiene review of the SSFL facility that included walk-through visits, interviews with managers and workers, and reviews of historical facility reports. We relied on job description manuals, combined with the information obtained in walk-through surveys, interviews with workers and managers, and company records to construct a job exposure matrix (JEM) for potentially carcinogenic exposures based on job titles and employment periods.

The personnel records contained job title information and the corresponding date of assignment to a particular job for each employee. Information on all job titles held at the company was extracted from these records. Detailed job description manuals for salaried and hourly workers are available from 1951 to 1993 (only 14 workers were still employed after 1993, and all of them held administrative positions). These manuals explain the basic functions of each job in an occupational summary and contain a description of the work performed, necessary licenses required for the work, typical materials, tools and equipment, knowledge and ability required for the work, and possible hazardous exposures, if applicable.

Relying on all resources mentioned above, job titles were rated according to exposures by an industrial hygienist (NK) and reviewed by two investigators (BR and AK), who are familiar with the facility operations and records and who conducted worker interviews independently. Discrepancies were discussed and resolved by consensus. All exposure assignments were made while blinded to cancer diagnoses. Each job title was assigned to one of four categories of presumptive exposure (high, medium, low, and none) for each chemical reflecting the relative intensity of that exposure over three different periods: (1) 1950s and 60s, (2) 1970s, and (3) 1980s and 90s. We were unable to link workers to locations at the facility such as specific rocket-engine test stands, because company records provided to us did not include this information. We were told by former employees, however, that many workers changed locations frequently with each new work assignment/project but most likely conducted similar tasks at each location and for each project.

Workers with job titles that indicated technical or mechanical work on rocket engines were presumed to have been exposed to hydrazine rocket fuels. High exposure to TCE also occurred at the rocket engine test stands that involved the cleaning (''flushing out'') of rocket engines. But TCE use was widespread at this facility beyond the rocket test stands since it was used as a general degreasing solvent to clean metal parts; thus, exposure was also likely to have occurred among other mechanics, maintenance and utility workers, and machinists. Benzene was present in hydrocarbon-based fuels such as gasoline and diesel and also had been used as a solvent and degreasing agent in the very early years of the facility's operations. Its use, however, was limited or banned in later years. Workers exposed to hydrocarbon fuel combustion products were considered exposed to PAHs. This group included operators of gasoline- and diesel-powered vehicles, workers in fleet service or warehousing, and jet and automotive engine mechanics and technicians. Mineral oils were used as a coolant and lubricant during machining operations. While machinists had the highest exposure potential, workers in areas where machining was performed were also considered potentially exposed.

Company records provided us with job titles, job codes, and dates of employment for each worker, and this information was linked to our JEM to generate a time-dependent intensity score for each occupational chemical exposure and worker. The cumulative intensity score for each worker at a given time during follow-up sums across the product of all previous employment periods: exposure score for each job (0–3 scale for unexposed to highly exposed) $\times$ number of years in that job. For example, if a worker started his first job in 1963 with an intensity score of 2 (medium exposure) for TCE, changed his job in 1970 to another job code with an intensity score of 0 (unexposed), and retired in 1988, that worker's cumulative intensity score for TCE after retirement is $2 \times 7 + 0 \times 18 = 14$. We also conducted selected analyzes

with another set of exposure scores: unexposed 0, low 1, medium 5, and high 10. Since the results from these two sets of exposure scores were very similar, we only present results derived from the first set. For purposes of analysis, cumulative intensity scores during follow-up for each exposure were categorized into three groups: low (reference group), medium, and high and treated as time varying variables in our analyses. Relatively few workers were classified as having been exposed to high levels of benzene (2.6% with exposure score >12). We excluded 63 (1%) of 6,107 workers from our analyses for the mortality cohort because company records contained no job title or code information. Among the remaining 6,044 workers, 210 (3%) had a record that reported a single job title for which we were not able to find a job description. For these workers, we imputed an exposure score for each chemical, based on records of workers who had held the same job title without a job description and a similar job title for which we found a job description. We checked the sensitivity of our results to this imputation procedure by substituting the missing values also with several random numbers but found that our results were not influenced by these assignments.

Personnel record information of pay type was used to create a three-category measure for socioeconomic status: union employees paid on an hourly basis, salaried technical/administrative employees, and managerial/professional employees. Subjects who changed jobs during the follow-up period were categorized according to the jobs they held for the longest period. To control for the selective loss of less healthy workers during follow-up, we measured the time since first employment at SSFL and treated this variable in the analyses as a time-dependent continuous covariate [Flanders et al., 1993; Wilkinson and Morgenstern, 1995].

We were unable to control for race, since Rocketdyne did not systematically collect such data for its employees. According to the information on death certificates, however, 96% of all deceased workers were classified as white.

Information about tobacco smoking was systematically recorded for selected groups of workers who filled out routinely administered medical questionnaires between 1961 and 1969. However, since information about smoking status was not available for most subjects in our study population, we assessed the potential for confounding by examining the distribution of smoking and exposure status in this small

TABLE I. Distribution of Site-Specific Cancer Deaths in the Total Mortality Cohort (1950–2001), the Mortality Sub-Cohort (1988–2000), and the Cancer Incidence Cohort (1988–2000); Aerospace Workers

	Cancer deaths (1950–2001)	Cancer deaths (1988–2000)[k]	Cancer incidence (1988–2000)[l]
Esophagus and stomach cancers[a]	40 (6.7%)	23 (6.9%)	19 (2.8%)
Colon and rectum cancers[b]	62 (10.3%)	39 (11.6%)	90 (13.0%)
Lung cancers[c]	194 (32.3%)	100 (29.9%)	92 (13.3%)
Lymphoma and leukemia[d]	60 (10.0%)	27 (8.1%)	45 (6.35%)
Prostate cancers[e]	55 (9.2%)	35 (10.5%)	248 (35.9%)
Kidney cancers[f]	17 (2.8%)	9 (2.7%)	16 (2.2%)
Bladder cancers[g]	17 (2.8%)	10 (3.0%)	50 (7.3%)
Brain cancers[h]	18 (3.0%)	11 (3.3%)	10 (1.5%)
Pancreatic cancers[i]	39 (6.5%)	26 (7.8%)	21 (3.0%)
Skin cancers (melanoma)[j]	14 (2.3%)	8 (2.4%)	36 (5.2%)
All cancers	600 (100%)	335 (100%)	691 (100%)
Total no. of workers with available exposure measurement	6,044	5,149	5,049

[a]International Classification of Diseases (ICD)-9, 150–151; ICD-10, C15, C16; ICD-O 2, C15, C16.
[b]ICD-9, 153–154; ICD-10, C18–C21; ICD-O 2, C18–C21.
[c]ICD-9, 162; ICD-10, C33–C34; ICD-O 2, C33–C34.
[d]ICD-9, 200–208, exclude 2041; ICD-10, C81–C95, exclude C911; ICD-O 2, morphology code: 9590–9716 exclude 9650–9667, 9723, 9800–9980.
[e]ICD-9, 185; ICD-10, C61; ICD-O 2, C619.
[f]ICD-9, 189; ICD-10, C64–C66, C68; ICD-O 2, C64–C66, C68.
[g]ICD-9, 188; ICD-10, C67; ICD-O 2, C67.
[h]ICD-9, 191–192; ICD-10, C70–C72; ICD-O 2, C70–C72.
[i]ICD-9, 157; ICD-10, C25; ICD-O 2, C25.
[j]ICD-9, 172; ICD-10, C439; ICD-O 2, C44.
[k]Exclude workers died before 1988 and after 2000.
[l]Exclude workers died or diagnosed with cancer (from Los Angeles County Cancer Registry which started from 1972) before 1988.

subset of subjects for whom smoking information was available.

Statistical Methods

To estimate exposure effects on each type of cancer, we used proportional hazards modeling in calendar time with both fixed and time-dependent predictors. Results from the fitted models were used to derive estimated rate (hazard) ratios for each non-reference intensity category (medium and high) of each time-dependent cumulative exposure and their 95% confidence intervals (CI). To control for confounding, we included the following covariates in each model: pay type (two fixed binary variables), time since hire or transfer to SSFL (continuous time-dependent), and age (continuous time-dependent). The effect of each chemical exposure was estimated with and without adjustment for the other exposures including hydrazine.

To test for a monotonic trend of cumulative exposures and derive a two-sided *P*-value for trend, we computed median intensity scores based on the exposure experience of subjects during the entire follow-up after dividing them into the three exposure categories. Furthermore, we allowed for varying periods of cancer induction/latency by lagging exposures 10 and 20 years prior to cancer incidence or mortality.

Only two cases of non-Hodgkin's lymphoma (NHL) and no cases for leukemia fell into the highest (exposure score >12) benzene exposures categories (rate ratio (RR) (95% CI) was 1.24 (0.30–6.91)). Benzene exposure was not associated with any of the cancers examined here, and did not appear to confound the estimated effects of other chemicals. Thus, mostly we are presenting results without adjustment for benzene. We also found no associations between presumed PAH exposures and cancers in this cohort and will not present these results. PAH exposure scores were retained in adjusted models for TCE and mineral oils, although they were strongly correlated with each other and hydrazine exposures ($r = 0.68$ and $r = 0.72$, respectively), but some analyzes suggested that there was mutual confounding between these chemicals.

RESULTS

In our mortality cohort containing 6,044 subjects, 2,117 (35%) workers had died by the end of 2001; 600 (28% of all deaths) had died of cancer, and lung cancer was the most

TABLE II. Descriptive Information for the Total Cancer Mortality (1950–2001) and Cancer Incidence Cohort (1988–2000); Aerospace Workers

	Mortality cohort (1950–2001) N = 6,044	Incidence cohort (1988–2000)[a] N = 5,049
Mean duration of employment (years)	15.9	16.0
Average age at first employment (years)	30.4	28.9
Average age in 1988 (years)	59.9	57.8
Average age at end of follow-up (years)	68.7	68.6
Trichloroethylene (TCE)		
Mean (median) exposure scores among exposed workers (score > 3)	10.2 (8.0)	10.1 (7.9)
Number of exposed workers (score > 3)	2,689 (44.5%)	2,227 (44.1%)
Polycyclic aromatic hydrocarbon (PAH)		
Mean (median) exposure scores among exposed workers (score > 3)	11.3 (8.6)	11.1 (8.4)
Number of exposed workers (score > 3)	2,648 (43.8%)	2,236 (44.3%)
Benzene		
Mean (median) exposure scores among exposed workers (score > 3)	9.5 (7.0)	9.2 (6.9)
Number of exposed workers (score > 3)	819 (13.6%)	686 (13.6%)
Mineral oils		
Mean (median) exposure scores among exposed workers (score > 3)	10.7 (8.0)	10.7 (7.8)
Number of exposed workers (score > 3)	1,499 (24.8%)	1,165 (23.1%)
Pay status		
Professional/salaried	2,702 (44.7%)	2,353 (46.6%)
Non-professional/salaried	2,656 (43.9%)	2,157 (42.7%)
Hourly	686 (11.4%)	539 (10.7%)

[a]Excludes workers who died or were diagnosed with a cancer (in the Los Angeles County Cancer Registry which started from 1972) before 1988.

common cause of cancer death (194 cases, 32% of cancer deaths). We identified 691 incident cases of cancer between 1988 and 2000 in the incidence cohort of 5,049 workers, and prostate cancer was the most commonly diagnosed cancer (248 cases, 36% of all incident cases) (Table I). Members of the mortality and incidence cohorts were similar in terms of average duration of employment, age at end of follow-up, pay status, and mean cumulative intensity scores for the four exposures among the exposed (score >3) at the end of follow-up (Table II). Employees in both cohorts were also comparable with respect to age at first employment and at start of our incidence cancer follow-up in 1988 (Table II).

TABLE III. Estimated Rate Ratios (RRs) and 95% Confidence Intervals (CIs) for the Effects of Cumulative TCE and Mineral Oil Exposure on Cancer Mortality and Incidence, by Category of Exposure Intensity, and Type of Cancer (Zero Exposure Lag)*

		TCE				Mineral oils			
		Cancer mortality		Cancer incidence		Cancer mortality		Cancer incidence	
Cancer site	**Exposure categories**	**N**	**RR (95% CI)**	**N**	**RR (95% CI)**	**N**	**RR (95% CI)**	**N**	**RR (95% CI)**
Esophagus and stomach	Low (score $\leq$ 3)	18	1.00	9	1.00	22	1.00	11	1.00
	Medium (3<score $\leq$ 12)	15	1.40 (0.70, 2.82)	8	1.66 (0.62, 4.41)	11	1.97 (0.91, 4.27)	5	1.73 (0.56, 5.28)
	High (score > 12)	7	1.27 (0.52, 3.13)	2	0.82 (0.17, 3.95)	7	2.31 (0.65, 5.86)	3	1.99 (0.51, 7.81)
	P for trend**		0.535		0.974		0.060		0.284
Colon and rectum	Low (score $\leq$ 3)	36	1.00	49	1.00	48	1.00	67	1.00
	Medium (3 < score $\leq$ 12)	18	0.90 (0.51, 1.60)	28	0.93 (0.58, 1.50)	9	0.71 (0.34, 1.47)	15	0.89 (0.50, 1.60)
	High (score > 12)	8	0.76 (0.35, 1.68)	13	0.92 (0.49, 1.72)	6	0.65 (0.25, 1.70)	8	0.93 (0.43, 2.01)
	P for trend**		0.487		0.772		0.301		0.787
Lung	Low (score $\leq$ 3)	99	1.00	43	1.00	115	1.00	53	1.00
	Medium (3 < score $\leq$ 12)	62	1.05 (0.76, 1.44)	35	1.36 (0.86, 2.14)	47	1.41 (0.99, 2.01)	26	2.00 (1.21, 3.30)
	High (score > 12)	33	1.02 (0.68, 1.53)	14	1.11 (0.60, 2.06)	32	1.56 (1.02, 2.39)	13	1.99 (1.03, 3.85)
	P for trend**		0.910		0.601		0.026		0.017
Non-Hodgkin's lymphoma (NHL) and leukemia	Low (score $\leq$ 3)	27	1.00	28	1.00	41	1.00	39	1.00
	Medium (3 < score $\leq$ 15)	27	1.49 (0.86, 2.57)	16	0.88 (0.47, 1.65)	12	1.21 (0.61, 2.40)	2	0.19 (0.05, 0.81)
	High (score > 15)	6	1.30 (0.52, 3.23)	1	0.20 (0.03, 1.46)	7	2.88 (1.19, 7.00)	4	1.29 (0.44, 3.80)
	P for trend**		0.370		0.097		0.024		0.748
Kidney	Low (score $\leq$ 3)	7	1.00	6	1.00	10	1.00	12	1.00
	Medium (3 < score $\leq$ 15)	7	1.43 (0.49, 4.16)	6	1.87 (0.56, 6.20)	6	1.76 (0.59, 5.19)	2	0.58 (0.12, 2.73)
	High (score > 15)	3	2.03 (0.50, 8.32)	4	4.90 (1.23, 19.6)	1	1.01 (0.12, 8.44)	2	2.07 (0.42, 10.1)
	P for trend**		0.307		0.023		0.756		0.515
Bladder	Low (score $\leq$ 3)	8	1.00	20	1.00	10	1.00	32	1.00
	Medium (3 < score $\leq$ 12)	6	1.27 (0.43, 3.73)	19	1.54 (0.81, 2.92)	5	1.92 (0.61, 6.02)	13	1.75 (0.88, 3.49)
	High (score > 12)	3	1.15 (0.29, 4.51)	11	1.98 (0.93, 4.22)	2	1.28 (0.25, 6.44)	5	1.42 (0.52, 3.88)
	P for trend**		0.809		0.069		0.642		0.324
Pancreatic	Low (score $\leq$ 3)	22	1.00	13	1.00	33	1.00	17	1.00
	Medium (3 < score $\leq$ 12)	15	1.13 (0.58, 2.21)	7	0.85 (0.33, 2.17)	5	0.63 (0.24, 1.68)	3	0.72 (0.20, 2.59)
	High (score > 12)	2	0.35 (0.08, 1.50)	1	0.28 (0.04, 2.14)	1	0.26 (0.04, 2.00)	1	0.51 (0.06, 4.07)
	P for trend**		0.229		0.206		0.130		0.462
Brain	Low (score $\leq$ 3)	12	1.00	7	1.00	18	1.00	10	1.00
	Medium (3 < score $\leq$ 12)	3	0.42 (0.12, 1.50)	2	0.46 (0.09, 2.25)	0	NA	0	NA
	High (score > 12)	3	0.83 (0.23, 3.08)	1	0.47 (0.06, 3.95)	0	NA	0	NA
	P for trend**		0.613		0.382		NA		NA
Skin melanoma	Low (score $\leq$ 3)		NA	17	1.00		NA	21	1.00
	Medium (3 < score $\leq$ 12)		NA	15	1.44 (0.71, 2.92)		NA	9	2.15 (0.93, 4.98)
	High (score > 12)		NA	4	0.87 (0.29, 2.64)		NA	6	3.32 (1.20, 9.24)
	P for trend**		NA		0.987		NA		0.015

*Variables included in the model: time since first employment (continuous), socioeconomic status (categorical), age at event.
**Trend tests were performed by entering median exposure scores for each exposure category into the Cox model to obtain *P* value for trend.

Estimates for all cancer sites examined are presented for TCE and mineral oils without adjustment for exposure to other chemicals in Table III. Some estimates for single and multiple chemical models differed considerably and results adjusted for all exposures—hydrazine, TCE, PAHs, and mineral oils—are presented in Tables IV and V for relevant cancer sites.

TCE and Cancer Incidence and Mortality

High levels of TCE exposure (cumulative intensity score >15) were associated with an elevated incidence rate of kidney cancer (e.g., estimated RR at zero lag is 4.90 (1.23–19.6)); single pollutant models also suggested an increase in risk at medium exposure levels (Table III). While the size of the estimated effects generally increased when adjusting for additional chemical exposures, the 95% CI widened and included the null value due to the limited number of exposed cases in the high exposure groups. The association between TCE exposure and kidney-cancer mortality was weaker than for incidence in both single (RR for high exposure levels at zero lag: 2.03 (0.50–8.32)) and multi-chemical models (Tables III and IV).

TCE exposure was also associated with bladder-cancer incidence (RR for high exposure levels with zero lag: 1.98 (0.93–4.22)). Again effect estimates increased when we adjusted for exposure to other chemicals, did not change when exposures were lagged and a monotonic trend was suggested with increase in exposures for bladder cancer incidence. Results for bladder-cancer mortality were uninformative due to the much smaller number of deaths from this cause.

No associations were observed between TCE exposure and other cancers examined in this study.

Mineral Oil Exposure and Cancer Mortality and Incidence

Exposure to mineral oil was associated with lung-cancer mortality and incidence at both medium and high exposure levels (Table III); yet only models adjusted for other chemicals suggested a monotonic increase in risk across exposure levels (Table V). Strong associations with mineral-oil exposure were observed for lung-cancer incidence at the highest level of exposure after controlling for other chemicals in the model (RR: 4.02 (1.49–10.8)). Lagging of exposures did not influence the estimated effects much.

Our analyses also suggested an association between mineral-oil exposure and mortality and incidence from cancer of the esophagus and stomach at both exposure levels but these estimates were rather imprecise. When we compared any exposure (score >3) to the reference group, the RR was 2.08 (1.04–4.16) for mortality, and 1.81 (0.67–4.90) for incidence in single chemical models. Models adjusted for all

TABLE IV. Estimated RRs and 95% CIs for the Effects of Cumulative TCE Exposure on Cancer Mortality/Incidence, by Category of Exposure Intensity, Type of Cancer, and Exposure Lag (0 and 20 Years)

			Zero exposure lag[a]			20 years exposure lag[a]		
Cancer outcome	Cancer site (total N of cases)	Exposure categories	No. of case	RR	95% CI	No. of case	RR	95% CI
Mortality	Kidney (17)	Low (score $\leq$ 3)	7	1.00		10	1.00	
		Medium (3 < score $\leq$ 15)	7	0.85	0.15, 4.93	6	1.69	0.29, 9.70
		High (score > 15)	3	0.96	0.09, 9.91	1	1.82	0.09, 38.6
		P for trend*		0.933			0.635	
	Bladder (17)	Low (score $\leq$ 3)	8	1.00		8	1.00	
		Medium (3 < score $\leq$ 12)	6	0.63	0.10, 3.97	7	0.95	0.15, 6.02
		High (score > 12)	3	1.58	0.13, 18.8	2	1.85	0.12, 27.7
		P for trend*		0.572			0.533	
Incidence	Kidney (16)	Low (score $\leq$ 3)	6	1.00		6	1.00	
		Medium (3 < score $\leq$ 15)	6	1.26	0.26, 6.14	7	1.19	0.22, 6.40
		High (score > 15)	4	7.71	0.65, 91.4	3	7.40	0.47, 116
		P for trend*		0.103			0.120	
	Bladder (50)	Low (score $\leq$ 3)	20	1.00		20	1.00	
		Medium (3 < score $\leq$ 12)	19	1.79	0.62, 5.17	20	1.76	0.61, 5.10
		High (score > 12)	11	3.80	0.97, 14.8	10	3.68	0.87, 15.5
		P for trend*		0.048			0.064	

*Trend tests were performed by entering median exposure scores for each exposure category into the Cox model to obtain *P* value for trend.

[a]Variables included in the model: time since first employment (continuous), socioeconomic status (categorical), age at event, and all other carcinogens, including hydrazine (for all other carcinogens we used the same exposure cutpoints as for TCE).

chemicals suggested a dose response and a stronger effect at the highest exposure level for both mortality and incidence, but the magnitude of the effect estimates diminished for mortality but not for incidence when exposure was lagged by 20 years.

High exposure to mineral oil was positively associated with NHL and leukemia mortality in single chemical models and for both outcomes in multiple chemical models and increased when we lagged exposures by 20 years. Finally, mineral-oil exposure was strongly and monotonically associated with melanoma incidence in both single and multiple chemical models and lagging exposures reduced the effect estimates only slightly. We found little or no associations between mineral-oil exposure and other cancer sites, including colorectal and pancreatic cancers.

DISCUSSION

In our aerospace cohort, we found higher rates of bladder-cancer and kidney-cancer incidence in workers occupationally exposed to TCE, and we observed higher rates of lung-cancer mortality and incidence, and melanoma incidence in both single and multiple chemical models. Multi-chemical adjusted models also suggested increased

TABLE V. Estimated RRs and 95% CIs for the Effects of Cumulative Mineral Oil Exposures on Cancer Mortality/Incidence, by Category of Exposure Intensity, Type of Cancer, and Exposure Lag (0 and 20 Years)

			Zero exposure lag[a]			20 years exposure lag[a]		
Cancer outcome	**Cancer site (total N of cases)**	**Exposure categories**	**No. of case**	**RR**	**95% CI**	**No. of case**	**RR**	**95% CI**
Mortality	Esophagus and stomach (40)	Low (score $\leq$ 3)	22	1.00		27	1.00	
		Medium (3 $<$ score $\leq$ 12)	11	2.54	0.88, 7.28	10	1.59	0.55, 4.62
		High (score $>$ 12)	7	4.17	1.00, 17.4	3	1.70	0.33, 8.71
		P value for trend*		0.076			0.432	
	Lung (194)	Low (score $\leq$ 3)	115	1.00		134	1.00	
		Medium (3 $<$ score $\leq$ 12)	47	2.12	1.28, 3.52	44	2.01	1.19, 3.41
		High (score $>$ 12)	32	3.31	1.69, 6.49	16	2.11	0.96, 4.68
		P value for trend*		0.001			0.040	
	Lymphoma and leukemia (60)[b]	Low (score $\leq$ 3)	41	1.00		48	1.00	
		Medium (3 $<$ score $\leq$ 15)	12	1.42	0.57, 3.56	8	0.91	0.33, 2.57
		High (score $>$ 15)	7	5.27	1.50, 18.6	4	7.53	1.82, 31.1
		P value for trend*		0.031			0.062	
Incidence	Esophagus and stomach (19)	Low (score $\leq$ 3)	11	1.00		11	1.00	
		Medium (3 $<$ score $\leq$ 12)	5	2.34	0.51, 10.7	5	2.19	0.49, 9.90
		High (score $>$ 12)	3	7.53	0.96, 59.3	3	6.95	0.95, 51.0
		P value for trend*		0.066			0.068	
	Lung (92)	Low (score $\leq$ 3)	53	1.00		53	1.00	
		Medium (3 $<$ score $\leq$ 12)	26	2.37	1.15, 4.91	29	2.50	1.22, 5.10
		High (score $>$ 12)	13	4.02	1.49, 10.8	10	3.10	1.09, 8.79
		P value for trend*		0.002			0.011	
	Lymphoma and leukemia (45)[b]	Low (score $\leq$ 3)	39	1.00		39	1.00	
		Medium (3 $<$ score $\leq$ 15)	2	0.20	0.04, 1.01	2	0.24	0.05, 1.19
		High (score $>$ 15)	4	4.38	1.02, 18.9	4	5.15	1.20, 22.2
		P value for trend*		0.262			0.227	
	Skin melanoma (36)	Low (score $\leq$ 3)	21	1.00		22	1.00	
		Medium (3 $<$ score $\leq$ 12)	9	3.09	0.98, 9.74	9	2.95	0.94, 9.27
		High (score $>$ 12)	6	11.6	2.58, 52.5	5	8.58	1.75, 42.1
		P value for trend*		0.002			0.010	

*Trend tests were performed by entering median exposure scores for each exposure category into the Cox model to obtain *P* value for trend.

[a]Variables included in the model: time since first employment (continuous), socioeconomic status (categorical), age at event, and all other carcinogens, including hydrazine (for all other carcinogens we used the same exposure cutoffs points as for mineral oil).

[b]For NHL and leukemia, benzene exposure (lower cutoff, 3; upper cutoff, 9) was included in the model.

risks for esophageal and stomach cancer and NHL and leukemia incidence and mortality in workers exposed to mineral oil. No other consistent associations were found for these two exposures and the cancer sites examined here, nor were associations observed for benzene or PAH exposures when adjusting for potential confounders.

A recent review of over 80 published papers assessing cancer risk from TCE exposures gave the greatest weight of evidence to occupational cohort studies [Wartenberg et al., 2000]. Those occupational cohort studies that employed the most rigorous exposure assessment found evidence of excess cancer incidence with TCE exposure for kidney, prostate, and liver cancers, and they suggested increased risks for some lymphopoietic cancers including non-Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma. However, the reviewers cautioned that few studies were able to isolate the effects of TCE exposure from the effects of other occupational exposures; thus, many previous results may have been confounded. In the present study, we observed too few liver cancers (only six deaths and six incident cases) to allow meaningful multivariable regression analyzes. Furthermore, few cases of hemato- and lymphopoietic cancers were classified as highly exposed to TCE (Table III), and we did not observe associations between TCE and these cancers. We saw some evidence, however, for a possible TCE effect on kidney cancer incidence although our effect estimates from multi-chemical adjusted models were imprecise. Moreover, these results also suggest effects of TCE exposure on bladder-cancer incidence and a trend with increasing dose, while previous studies did not consistently report TCE effects on mortality or incidence from bladder cancers.

In accordance with a recent NIOSH [1998] report, we found mineral oil exposures to be associated with esophageal- and stomach-cancer mortality, lung-cancer mortality, NHL and leukemia incidence, and importantly, melanoma incidence in our cohort. Specifically, NIOSH concluded that substantial evidence exists for increased cancer risks of the larynx, rectum, pancreas, skin, scrotum, and bladder among workers exposed to mineral oil, and that evidence is equivocal for cancers at several other sites, including stomach, esophagus, lung, prostate, brain, colon, and the hematopoietic system. Our study did not have enough cases to allow us to examine laryngeal cancers, and we did not observe increased risks for bladder or colon and rectum cancer incidence in our cohort. We found no evidence in our study for increased risk of workers dying from pancreatic or brain cancers when exposed to mineral oils.

Another recent review of occupational and environmental PAH exposures listed epidemiologic evidence that high occupational exposure to PAHs entails a substantial risk of developing lung cancers in several industries [Boffetta et al., 1997], e.g., the transport industry where workers were heavily exposed to diesel engine exhaust. Bladder cancers were found to be associated mostly with exposures to coal tar and pitch, and skin cancers followed high dermal exposure in those same industries. We believe that the most likely reasons why we did not observe PAH-cancer associations in our study are that (1) inhalation was the most likely primary exposure route and (2) PAH exposures from hydrocarbon (mostly diesel) combustion in our cohort are lower than in other worker groups studied previously. Relatively few workers in our cohort were exposed to benzene, and we found no indication that at the levels of exposure experience in this cohort, benzene may have caused leukemia.

Our exposure classification was based on a JEM derived from job titles and job codes. The main limitations of a JEM are exposure misclassification and decreased study power, since it is an inherently ecologic exposure measure and assumes that exposures are homogeneous within specified groups, e.g., job titles. Because exposure misclassification would be expected to be non-differential with respect to cancer outcome, bias most likely would result in underestimation of effects. Although we do not have information on jobs held by subjects before or after employment at

TABLE VI. Carcinogen Exposure Score Distributions by Smoking Status for a Subgroup of Rocketdyne Workers for Whom This Information Was Available for 1960–1969

	Smoking status	No. of workers	No. of exposed (percent)	Test of percent difference (*P*-value)*	Mean (standard deviation)[a]	Test of mean value difference (*P*-value)**
TCE	Non-smoker	87	37 (42.5)	0.796	12.3 (7.7)	0.769
	Smoker	113	46 (40.7)		11.8 (7.6)	
PAHs	Non-smoker	87	40 (46.0)	0.705	11.6 (7.6)	0.950
	Smoker	113	55 (48.7)		11.5 (7.6)	
Mineral oils	Non-smoker	87	14 (16.1)	0.217	13.2 (6.1)	0.363
	Smoker	113	26 (23.0)		11.3 (6.1)	

*Two sided test of proportional difference was performed to test whether percents of workers exposed to each carcinogen were different between non-smoker and smoker groups. Exposed was defined as exposure score >3 and unexposed was defined as exposure score ≤ 3.

**Two sided *t*-test was performed to test the difference between means of exposure distribution between smokers and non-smoker.

[a]Mean and standard deviation statistics were derived from the exposure distribution by excluding those unexposed (exposure score ≤ 3).

Rocketdyne, these workers on average were employed for extended periods (16 years) at this facility. The proportion of missing job titles was very small, and we do not expect the missing information to have affected our results.

Our results were not sensitive to the choice of scores for exposure categories (i.e., 0–3 as presented in this paper vs. scores of 0, 1, 5, and 10; see ''Methods''). We hypothesized that jobs may have resulted in higher exposures in earlier decades and conducted selected analyses in which exposure categories were scored higher for the 1950s and 1960s (0, 3, 6, and 9) than more recent decades (0, 1, 2, and 3). However, both sets of analyses produced similar results for the estimated effects of cumulative exposures.

Another potential source of bias in our study is confounding by unmeasured risk factors, especially smoking for all smoking-related cancers. We observed only weak associations between smoking status (proportion of smokers and mean cigarettes per day) and exposures to TCE, PAHs, and mineral oils in a subset of 200 subjects for whom we had information on smoking status for the 1960s (Table VI). Therefore, we believe that the estimated exposure effects reported in this paper were not appreciably confounded by smoking.

Using cancer registries to ascertain cancer outcome information has a number of advantages over the use of death certificates. First, cancer registry data are often more accurate than death certificates because greater care is taken to ensure that the registered diagnosis is correct and more information including histology is used to derive the diagnoses in turn reducing misclassification. Second, for predominantly non-fatal cancers, many more cases are identified during follow-up. A comparison of mortality and incidence data suggests that the occurrences of colon and rectum cancer, NHL, leukemia, kidney and bladder cancer, and skin melanoma were considerably under-reported on death certificates. Most likely because these cancer sites have relatively high 5-year survival rates according to the Surveillance Epidemiology and End Results (SEER) program: based on SEER 1995–2001 data, the 5-year survival for colon and rectum cancer is 64.1%, for NHL it is 60.2%, for leukemia 47.6%, for kidney cancer 64.6%, for bladder cancer 81.8%, and for skin melanoma: 91.6% [SEER Cancer Statistics Review, 2005]. Mortality data seemed to adequately represent the occurrence of more fatal cancers such as those of the esophagus, stomach, lung, brain, and pancreas in our cohort. For these cancers we observed more cases in our mortality cohort possibly because: (1) we estimated that our incidence cohort missed 11% of all incident cases between 1988 and 2000; (2) some workers were diagnosed with cancers before 1988 but died after 1988 and, thus, while counted in the mortality cohort were not captured in our incidence cohort.

One major limitation of our cancer incidence study is that we missed information on cases diagnosed before 1988. Since we began our follow-up in 1988, our results may not accurately reflect the effects of carcinogenic exposures that resulted in non-fatal cancers before 1988.

In conclusion, the results of our extended mortality follow-up and new incidence study suggest that Rocketdyne workers exposed to high levels of TCE exposure were probably at increased risk of kidney and bladder cancers. Our results also suggest that workers exposed to mineral oil were probably at increased risks of esophageal, stomach, and lung cancers and melanoma.

REFERENCES

Boffetta P, Jourenkova N, Gustavsson P. 1997. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. Cancer Causes Control 8(3):444–472.

Flanders DW, Cardenas VM, Austin H. 1993. Confounding by time since hire in internal comparisons of cumulative exposure in occupational cohort studies. Epidemiology 4:336–341.

International Agency for Research on Cancer. 1982. Some industrial chemicals and dyestuffs, chemical, environmental and experimental data. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals in Humans.

International Agency for Research on Cancer. 1987a. Overall evaluations of carcinogenicity: An updating of IARC monographs, Volumes 1–42, Supplement 7.

International Agency for Research on Cancer. 1987b. Mineral oils. IARC monographs on carcinogenicity of chemicals to man, Supplement 7.

International Agency for Research on Cancer. 1995. Dry cleaning, some chlorinated solvents and other industrial chemicals. IARC monographs on the evaluation of carcinogenic risks to humans.

Morgenstern H, Ritz B. 2001. Effects of radiation and chemical exposures on cancer mortality among rocketdyne workers: A review of three cohort studies. Occup Med 16:219–237.

SEER Cancer Statistics Review. 2005. 1975–2002, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER data submission, posted to the SEER web site 2005.

National Institute for Occupational Safety and Health. 1998. Criteria for a recommended standard—Occupational exposure to metalworking fluid, DHHS (NIOSH) Pub. No. 98-102. Cincinnati, OH: NIOSH.

Ritz B, Morgenstern H, Froines J, Moncau J. 1999. Chemical exposures of rocket-engine test-stand personnel and cancer mortality in a cohort of aerospace workers. J Occup Environ Med 41:903–910.

Savitz DA, Andrews KW. 1997. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. Am J Ind Med 31(3):287–295.

Wartenberg D, Reyner D, Scott CS. 2000. Trichloroethylene and cancer: Epidemiology evidence. Environ Health Perspect 108(Suppl 2):161–176.

WHO (World Health Organization). 1990. International classification of diseases for oncology (ICD-O), 2nd ed. In: Perey C, Van Holten V, Muir C, editors. Geneva: World Health Organization.

Wilkinson GS, Morgenstern H. 1995. Internal comparisons do not always control for the healthy worker effect (abstract # 230). Am J Epidemiol 141(Suppl):S58.