Estimated Effects of Hydrazine Exposure on Cancer Incidence and Mortality in Aerospace Workers

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Background: Animal studies suggest that hydrazine is a lung carcinogen, but human studies have been rare, rather small, and limited to cancer mortality.

Methods: We examined cancer mortality and incidence in a cohort of aerospace workers with varying exposure to hydrazine contained in rocket fuels—extending previous mortality follow-up from 1994 to 2001 and investigating cancer incidence for the period 1988–2000 using population-registry data. We newly estimated hydrazine effects adjusting for occupational exposures to other carcinogens assessed through a job-exposure matrix. Rate-ratio estimates were derived from Cox proportional hazards and random-effects models using time-dependent exposure measures for hydrazine adjusting for trichloroethylene, polycyclic aromatic hydrocarbons, benzene, and mineral oil exposures.

Results: Exposure to hydrazine was positively associated with lung cancer incidence (estimated rate ratio for high vs low exposure with 20-year lag = 2.5; 95% confidence interval = 1.3–4.9) and with colorectal cancer incidence (2.2; 1.0–4.6). Dose–response associations were observed for both outcomes; similar associations were found for lung cancer mortality but not for colorectal cancer mortality. Effect estimates for cancers of the pancreas, blood and lymph system, and kidneys were based on small numbers rendering our analyses uninformative, and patterns considering exposure levels and lags were inconsistent. Use of random-effect models did not change our results.

Conclusions: The findings reported here are consistent with our previous results for lung cancer mortality; our new results suggest that exposure to hydrazine increases the risk of incident lung cancers. We also found, for the first time, an increased risk of colon cancers. Results for other cancer sites are inconclusive.

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We conducted a retrospective cohort study of aerospace workers who engaged in rocket engine testing operations at the Santa Susana Field Laboratory in Los Angeles County. These workers were employed between 1950 and 1993 at the Rocketdyne division of the Boeing Company (formerly Rockwell International). Examining cancer mortality in this cohort,[1,2] we previously found that presumed high exposures to hydrazines, including hydrazine, 1-methylhydrazine, and 1,1-dimethylhydrazine (hereafter referred to collectively as hydrazine), used in large quantities as a rocket fuel at the facility throughout the 1950s and 1960s, was positively associated with the risk of dying from lung cancer. Our earlier analyses also suggested possible increases in mortality from cancers of the lymphopoietic system and the bladder and kidney. Except for lung, previous associations for cancer mortality were imprecise and did not exhibit dose–response patterns.

In this article, we extend the mortality follow-up of this aerospace cohort from 1994 to 2001. In addition, data on cancer incidence were collected from the statewide California cancer registry (1988–2000) and 8 other state cancer registries for the period covered by the California registry. This incidence component allowed us to conduct more informative analyses of nonfatal cancers that are underreported on death certificates.

In addition to hydrazine, there was also widespread use of other known or suspected human carcinogens at the facility, including trichloroethylene (TCE) used in cleaning operations,[3] polycyclic aromatic hydrocarbons (PAHs) from the combustion of fuels,[4] mineral oils used mostly in machining operations,[5] and some limited exposure to benzene.[6] We newly developed a job-exposure matrix to assess the exposure potential to these carcinogens, allowing us to adjust our hydrazine estimates for potential confounding by these chemicals. Finally, we conducted a sensitivity analysis, including indicator variables, for 26 major job categories in a random-effects model to account for other unmeasured risk factors shared by workers employed in these jobs.

METHODS

Subject Selection

The source population for this study was 55,000 workers employed between 1950 and 1993 at several Rocketdyne facilities in Los Angeles. The cohort assembled to estimate the effects of hydrazine exposures consisted of 6107 male workers who had been employed before 1980 at the Santa Susana Field Laboratory, who had worked at least 2 years at

any Rockwell division, and who had never been monitored for radiation exposure.[1] These restrictions allowed us to assemble a cohort of aerospace employees who had worked at the Santa Susana Field Laboratory during the most active period of rocket engine testing between 1950 and 1980 and were never exposed to radiation at the nuclear facilities housed at the Santa Susana Field Laboratory. We excluded 63 (1%) of the 6107 workers from the mortality analyses because company records did not contain any job title or job code information. The incidence analyses included only those 5049 workers who were alive and at risk for being diagnosed with a first primary cancer on 1 January 1988 (see subsequently).

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. Records of all employees were also matched against 3 other 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 causes 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 coded in ICD-9 and subsequently in ICD-10). For the period 1979–1994, the NDI search alone resulted in a nearly 100% complete vital status search for our cohort[1]; thus, NDI was our sole source of mortality information from 1994 to 2001. The analyses presented here rely on underlying cause of death information only.

In summary, we reexamined cancer mortality in workers included in the original cohort, but followed each subject from the start of employment or 1 January 1950, whichever date was later, to the date of death or 31 December 2001, whichever date was first.

We obtained cancer incidence information from the California cancer registry from its statewide inception in 1988 until the end of 2000. Because a search of all possible state cancer registries for workers who had left the state of California during follow up was not feasible, we focused on states that reported the most deaths among cohort members outside of California (percent of total deaths in our cohort between 1988 and 2000: California 72%, Arizona 4%, Arkansas 1%, Florida 2%, Nebraska <1%, Nevada 3%, Oregon 3%, Texas 2%, Washington 2%; in all other U.S. states not searched: 11%). Thus, we identified incident cancers from 8 additional state cancer registries: 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). We used information from all registries with data recorded before 1988 (incidence cancer and death registries) to exclude ineligible subjects from our denominator; eg, the Los Angeles County Cancer Registry started data collection in 1972, but provided coverage for only 38% of our cohort. Our incidence cohort consists of 5049 workers who were still alive and at risk for being diagnosed with a first primary cancer on 1 January 1988, ie, follow up started (and person-time accrued) as of 1 January 1988 and ended at the date of diagnosis of a first primary cancer or death or 31 December 2000, whichever date came first.

The coding of cancer incidence was based on ICD-O, the International Classification of Diseases–Oncology (World Health Organization, 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"). Solid tumors were categorized on the basis of topography, whereas leukemias, lymphomas, and other lymphopoietic malignancies were grouped on the basis of morphology codes. For all workers with more than one cancer diagnosis during follow up, we counted only the first primary cancer occurrence.

We examined the influence of hydrazine on lung and colorectal cancer, non-Hodgkin lymphoma and leukemia, and cancers of the kidney, esophagus, stomach, and pancreas. We also report results for all smoking-related cancers except those of the lung and for 2 smoking-related sites, upper respiratory tract cancers and bladder, separately. The observed number of incident brain cancers was too small to be examined in multivariable models and prostate cancer results are reported elsewhere (Krishnadasan et al, unpublished data).

Exposure Assessment

We conducted an extensive industrial hygiene review of the Santa Susana Field Laboratory facility that included walkthrough visits, interviews with managers and workers, and review of historical facility reports. We relied on job description manuals combined with the information obtained in walkthrough surveys, interviews with workers and managers, and company records to construct a job-exposure matrix for carcinogen exposures based on job titles and employment periods.

Exposure assessments were conducted by our industrial hygienist and reviewed by 2 investigators (BR and AK) who were familiar with facility operations and records. Discrepancies were discussed and resolved by consensus. All exposure assignments were made without knowledge of cancer diagnoses. Each job title was assigned to one of 4 categories of presumptive exposure (high, medium, low, or unexposed) for each chemical reflecting the relative intensity of that exposure in each of 3 periods: the 1950–1960s, the 1970s, and the 1980–1990s. We were unable to link workers to a work location such as a specific rocket engine test stand because company records did not provide this information. However, former employees stated that many workers changed work locations frequently with new projects but most likely conducted similar tasks at each location and project.

Hydrazine was present primarily in rocket fuels. Therefore, any employee involved in working hands-on with rocket engines (repair work, testing, and cleaning of engines), or in fuel production and testing, was presumed to have been exposed to hydrazine. For example, rocket test stand mechanics were assigned to the highest hydrazine exposure intensi-

ties because they probably had the greatest contact with rocket engines and their fuels.

Company records provided us with job titles, job codes, and dates of employment for each worker. This information was linked to our job-exposure matrix that assigned 4 categories of presumptive exposure level during 3 periods to each job title to generate a time-dependent intensity score for each occupational chemical exposure and worker. A cumulative exposure score for each worker was calculated by summing across all employment periods before the index time (eg, diagnosis or death dates). Thus, each job held received an intensity score (0–3 from unexposed to highly exposed) that was multiplied by the number of years in the job. For example, if a worker held a job with an intensity score of 2 for hydrazine from 1964 through1970, then changed to another job with an intensity score of zero (unexposed), and retired in 1988, his cumulative exposure score for hydrazine at retirement is $(2 \times 7) + (0 \times 18) = 14$. We used the same job exposure matrix and scoring approach to assign exposure intensity for all chemicals assessed. Details about the job categories and types of exposures involved can be found in the article by Zhao et al.[7]

For hydrazine exposures, we also conducted selected analyses using alternate sets of intensity scores: unexposed = 0, low = 1, medium = 5, and high = 10. Because the results from these 2 sets of intensity scores were very similar, we only present results derived from the first set. To assess the impact of the greatest use of hydrazine rocket fuels in the 1960s, we alternatively used scores of 1 for low, 4 for medium, and 9 for high intensities for the 1960s while retaining the original scores for all other decades. Thus, we accounted for changes in hydrazine exposure intensity in 2 ways; first, we assigned exposure intensity scores per job title per decade, allowing a job to receive a different score (from 0–3) in each decade; and second, we changed the scoring weights to emphasize the high-exposure decade.

Among 6044 workers with job titles available, 210 (3%) records contained a single job title for which we did not obtain a job description. For these workers, we imputed an intensity score for each chemical based on records of workers who held the same job title and a similar job title with a job description. Alternatively, we substituted the missing values with random numbers; however, our results proved to not be sensitive to these various assignments.

Personnel record information of pay type was used to create a 3-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. We used "time since first employment at Santa Susana Field Laboratory" treated as a time-dependent continuous covariate to control for the selective loss of less healthy workers during follow up.[8]

We were unable to control for race, because 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, because 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 hydrazine exposure in this small subset of subjects for whom smoking information was available.

Statistical Methods

We used proportional hazards models based on calendar time with both fixed and time-dependent predictors to estimate exposure effects on cancers and derived estimated rate (hazard) ratios (RRs) and 95% confidence intervals (CIs) for each nonreference time-dependent cumulative exposure category (medium and high). Cumulative time-dependent exposure scores were categorized as high, medium, and low (the reference category) such that the lower cutoff value of 3 was close to the 25th percentile of the exposure distribution for hydrazine representing 1 year spent in the highest or 3 years in the lowest exposure intensity job category. We used different cutoff scores for the highest exposure (scores of 9, 12, and 15 representing 3, 4, and 5 years in a job with the highest exposure intensity rating) to examine associations at the high end of the exposure distribution, but we present only those for a score of 12. For each cancer type, we examined hydrazine associations with and without adjustment for other chemical exposures, including trichloroethylene, polycyclic aromatic hydrocarbons, mineral oils, and benzene. Benzene exposure was relatively rare in this cohort (see Table 1) and did not appear to confound the hydrazine associations. However, our results suggested the presence of mutual confounding for other chemicals (especially hydrazine, trichloroethylene, and mineral oils), ie, rate-ratio estimates differed appreciably when comparing single and multiple chemical models, suggesting that all chemical exposures except benzene needed to be retained in the models. Thus, we are presenting results from models adjusted for these chemicals.

We always included the following covariates in each model to control for confounding: pay type (2 binary variables), time since hire or transfer to the Santa Susana Field Laboratory (continuous time-dependent), and age (continuous time-dependent).

We computed median exposure scores based on the exposure experience of subjects throughout the entire follow up for each of the 3 categories and used these values in a test for monotonic trend. Finally, we allowed for varying periods of cancer induction/latency by lagging exposures 10 and 20 years before cancer occurrence or death.

Workers in a given job category (such as mechanics, machinists, administrators, and engineers) may share similar unmeasured occupational or lifestyle factors affecting cancer risk such as exposure to unmeasured work-related carcinogens or diet, physical activity, and smoking habits. For example, jobs that involve routine handling of highly flammable materials may attract more light or nonsmoking employees due to workplace restrictions on smoking. Thus, we applied the discrete time hazard model technique to approximate the continuous time process[9] and estimated random

TABLE 1. Characteristics of the Aerospace Worker Cohort

	Mortality Cohort (1950–2001) (n = 6044)	Incidence Cohort (1988–2000)¶¶ (n = 5049)
Mean duration of employment (years)	15.9	16.0
Mean age at first employment (years)	30.4	28.9
Mean age at end of follow up (years)	68.7	68.6
Mean age in 1988 (years)	59.9	57.8
Pay status; %		
Professional/salaried	45	47
Nonprofessional/salaried	44	43
Hourly	11	11
Number of cancer cases	600	691
Esophagus cancers*	20	11
Stomach cancers†	20	8
Colon and rectum cancers‡	62	90
Lung cancers§	194	92
Non-Hodgkin lymphomas (NHL)‖	43	29
Leukemias¶	17	16
Prostate cancers#	55	248
Kidney cancers**	17	16
Bladder cancers††	17	50
Brain cancers‡‡	18	10
Pancreatic cancers§§	39	21
Melanoma skin cancers‖‖	14	36
Hydrazine exposure		
Mean (median) exposure in workers with an intensity score >3	14.2 (9.4)	14.0 (9.2)

*ICD-9: 150; ICD-10: C15; ICD-O 2: C15.
†ICD-9: 151; ICD-10: C16; ICD-O 2: C16.
‡ICD-9: 153–154; ICD-10: C18–C21; ICD-O 2: C18–C21.
§ICD-9: 162; ICD-10: C33–C34; ICD-O 2: C33–C34.
‖ICD-9: 200–203, 208; ICD-10: C81–C90, C95; ICD-O 2: morphology code: 9590–9716, 9723, excluding 9650–9667.
¶ICD-9: 204–207, excluding 2041; ICD-10: C91–C94, excluding C911; ICD-O 2: morphology code: 9800–9980.
#ICD-9: 185; ICD-10: C61; ICD-O 2: C619.
**ICD-9: 189; ICD-10: C64–C66, C68; ICD-O 2: C64–C66, C68.
††ICD-9: 188; ICD-10: C67; ICD-O 2: C67.
‡‡ICD-9: 191–192; ICD-10: C70–C72; ICD-O 2: C70–C72.
§§ICD-9: 157; ICD-10: C25; ICD-O 2: C25.
‖‖ICD-9: 172; ICD-10: C439; ICD-O 2: C44.
¶¶Excludes workers who died or were diagnosed with cancer before 1988, (from Los Angeles County Cancer Registry which started from 1972, and other registries, see text).

effects for 26 major job categories assigning each worker to a category corresponding to his longest held job.

RESULTS

In our mortality cohort, 2117 (35%) workers had died by the end of 2001. The underlying cause of death was reported as cancer in 600 workers (28% of all deaths), lung cancer being the most common cause (194 cases, 32% of all cancer deaths). From 1988 through 2000, we identified 691 incident cancers among 5049 workers at risk. The mortality and incidence cohorts were similar in terms of average duration of employment, pay status, cumulative chemical exposure scores and age at end of follow up, age at first employment, and age at start of follow up for the incidence cohort in 1988 (Table 1). Using random-effects models that included a total of 26 major job categories did not change our effect estimates or conclusions; thus, in the following, we report only the results from proportional hazards models.

High-level hydrazine exposure was associated with both mortality and incidence of lung cancer, and dose–response trends were suggested when exposures were lagged by 20 years (Table 2). With weights that emphasize the suspected greater exposure potentials during the 1960s, associations for lung cancer mortality were stronger in the highest hydrazine exposure categories (at zero lag for score >45, RR = 1.8; 95% CI = 1.0–3.1; P for trend = 0.02).

Hydrazine exposures increased the incidence rate of colorectal cancers at moderate (1.5; 0.8–2.9; zero lag) and high exposure levels (2.3; 1.1–5.0, zero lag), and a trend was suggested. Lagging exposures by 20 years did not change estimates much. In contrast to our incidence results, we observed little or no association for colorectal cancer mortality.

We saw somewhat increased rates but no dose–response pattern for non-Hodgkin lymphoma and leukemia mortality (20-year lag for >3 vs ≤3 exposure score RR = 1.8; 0.82–4.2), and no associations were observed for incidence of these cancers. For kidney cancers, an increase in incidence was suggested at medium but not high hydrazine exposure levels. We also observed increased mortality rates for kidney cancers in both exposure categories (zero year lag for >3 vs ≤3 exposure score, RR = 2.3; 0.67–8.24), but no associations were apparent when lagging exposures by 20 years (Table 2).

Our data suggested some association between hydrazine exposure and both mortality and incidence of pancreatic cancer, although small numbers of exposed cases resulted in

TABLE 2. Prevalence of Chemical Exposures in the Aerospace Cohort

Exposure	Mortality Cohort (1950–2001) (n = 6044) No. (%)	Incidence Cohort (1988–2000) (n = 5049) No. (%)
Hydrazine		
None/low exposure (score ≤3)	3401 (56)	2800 (56)
Medium exposure (score 3 to ≤12)	1593 (26)	1394 (28)
High exposure (score >12)	1050 (17)	850 (17)
Trichloroethylene (score >3)	2689 (45)	2227 (44)
Polycyclic aromatic hydrocarbons (score >3)	2648 (44)	2236 (44)
Benzene (score >3)	819 (14)	686 (14)
Mineral oil (score >3)	1499 (25)	1165 (23)

low precision and power for our test of trend. To address this limitation, we treated cumulative hydrazine exposure as a continuous variable. The estimated rate ratio for pancreatic cancer mortality per 10 units increase in exposure score was 1.5 (1.1–2.0; zero lag) and was more pronounced for incidence (1.7; 1.3–2.4; zero lag).

We observed little association between smoking status and chemical exposures in a subset of 200 subjects for whom smoking status was known for the 1960s; among workers with an intensity score >3 for hydrazine exposure, 54% were smokers in the 1960s compared with 58% of the unexposed (score ≤3); mean exposure scores also did not differ between smokers and nonsmokers. Hydrazine exposures were also not found to be related to most other smoking-related cancers, including bladder cancers, upper respiratory tract cancers, and all other smoking-related cancers, except lung, taken together (Table 3).

DISCUSSION

We confirmed our previously published results that aerospace workers exposed to hydrazine are at increased risk for lung cancer mortality.[1] Furthermore, we observed an increased colon and rectum cancer incidence in hydrazine-exposed workers. Our previous and current results for leukemia and lymphomas, kidney cancers, and pancreatic cancers are inconclusive, primarily due to small numbers of exposed cases. However, there was some evidence for a dose–response association with pancreatic cancer.

Hydrazine has been classified by the U.S. Environmental Protection Agency as group B2 (probable human carcinogen),[10] and both hydrazine and 1,1-dimethylhydrazine have been classified as a group 2B possible human carcinogen by the International Agency for Research on Cancer[11] based on sufficient evidence in animals—oral or inhalation exposures producing lung tumors in rats and mice and liver, nasal and some colon tumors in rats—but inadequate evidence in humans.

Epidemiologic evidence linking hydrazine exposure to cancer risk in humans is scarce. A British study of hydrazine production workers found no associations between hydrazine exposure and cancer mortality but was too small to be conclusive (427 workers; 25 cancer deaths, 8 from lung cancer).[12] An Italian study of thermoelectric power plant employees exposed to hydrazine and other chemicals reported an excess mortality rate from all cancers for those employed 10 or more years at the facility (12 cancers deaths; 4.35 expected).[13]

We previously reported that aerospace workers highest exposed to hydrazine during rocket engine testing operations experienced greater lung cancer mortality (RR = 1.7; 1.1–2.5), and rate increases were more pronounced for 1960s-era exposures when hydrazine rocket fuel use was most prevalent at the facility.[1] We not only confirmed our previous conclusions for lung cancer mortality, showing associations with hydrazine exposures after 7 additional years of follow up, but found a trend with dose when we lagged exposures by 20 years. Importantly, the hydrazine results persisted when we controlled for exposures to other chemical carcinogens used at this facility. Our new lung cancer incidence data further strengthened our results and suggested a dose–response pattern. This observation may be due to higher diagnostic accuracy for cancer registry data compared with death certificate data. Cancers at other sites can metastasize to the lungs, which can lead to lung cancer being incorrectly listed as underlying cause of death. We again found some indication that the contributions of exposures during the time of greatest hydrazine use were important.

The dose–response association observed for hydrazine and colorectal cancer incidence is a new finding. This is the first time that incidence data were available to us. Colorectal cancer mortality was not related to hydrazine exposures previously, nor is it in our extended follow up. The difference between our incidence and mortality findings might suggest differential fatality of colorectal cancer cases by hydrazine exposure. For example, case fatality might be lower in exposed workers if they undergo more cancer screening, detection, and early treatment.

Our previous mortality study tentatively suggested associations between hydrazine exposure and death from cancers of the hemato- and lymphopoietic system, bladder and kidney, and pancreas.[1] For combined lymphoma and leukemia mortality, our previous study suggested increased rates for highly exposed workers (2.8; 1.2–6.6; 15-year lag) and moderately exposed workers (1.7; 0.59–4.76; 15-year lag) when exposed for more than 6 months. However, these associations vanished when we required a minimum of 2 years of high exposure. Although our present analyses again supported a small increase in mortality for workers exposed for at least 1 year at any level, there was no dose–response. More importantly, our new data for non-Hodgkin lymphoma and leukemia incidence does not support the mortality results. As a caveat, if lymphomas and leukemias have shorter induction periods than solid tumors, we would have missed incident cancers caused by 1960s hydrazine exposures occurring before 1988. Our mortality results show stronger associations with a 20-year lag, but one might argue that the period between the start of cancer induction and death is longer than the period between induction and first diagnosis.

We found some suggestion for an increased risk of developing and dying from kidney cancer in hydrazine-exposed workers at any level, although the dose pattern was inconsistent and lagging exposures by more than 10 years removed most associations. In our previous study, the small number of exposed deaths required that we estimated mortality rate ratios for bladder and kidney cancers combined. Here, we examined the 2 sites separately and did not find positive associations with bladder cancer incidence or mortality.

Finally, in our extended follow-up study, we are seeing increased rates for pancreatic cancer mortality and incidence, especially among the highest-exposed workers. Although the small number of exposed cases rendered the categorical results inconclusive, estimates relying on a continuous exposure measure suggested a rate increase with increasing hydrazine exposure score.

Our exposure assessment was based on a job-exposure matrix. The main limitation of this approach is its potential for exposure misclassification, because it is an inherently

TABLE 3. Association of Cumulative Hydrazine Exposure With Selected Cancer Mortality and Incidence, by Type of Cancer, Category of Exposure, and Exposure Lag

		Zero Lag*				20-Yr Lag*			
		Cancer Mortality		Cancer Incidence		Cancer Mortality		Cancer Incidence	
Cancer Site	Exposure Categories	No. Cases	RR (95% CI)	No. Cases	RR (95% CI)	No. Cases	RR (95% CI)	No. Cases	RR (95% CI)
Colon and rectum	Low (score ≤3)†	37	1.00	43	1.00	40	1.00	43	1.00
	Medium (3 < score ≤12)	14	0.90 (0.41–2.01)	26	1.64 (0.86–3.11)	12	0.83 (0.35–1.95)	28	1.75 (0.93–3.30)
	High (score >12)	11	1.02 (0.47–3.07)	21	2.09 (1.02–4.31)	10	1.55 (0.61–3.90)	19	2.16 (1.02–4.59)
	P for trend‡		0.973		0.043		0.481		0.041
Lung	Low (score ≤3)†	100	1.00	44	1.00	121	1.00	44	1.00
	Medium (3 < score ≤12)	46	1.46 (0.96–2.22)	21	1.15 (0.60–2.20)	37	1.24 (0.78–1.96)	22	1.18 (0.62–2.24)
	High (score >12)	48	1.49 (0.94–2.35)	27	2.31 (1.21–4.43)	36	1.67 (0.99–2.83)	26	2.49 (1.28–4.86)
	P for trend‡		0.065		0.007		0.031		0.003
NHL and leukemia§	Low (score ≤3)†	28	1.00	27	1.00	35	1.00	27	1.00
	Medium (3 < score ≤12)	20	1.74 (0.78–3.89)	13	0.98 (0.37–2.60)	18	2.04 (0.86–4.83)	15	1.34 (0.53–3.42)
	High (score >12)	12	1.80 (0.68–4.78)	5	1.29 (0.40–4.12)	7	2.48 (0.81–7.54)	3	1.15 (0.28–4.65)
	P for trend‡		0.259		0.856		0.130		0.885
Kidney	Low (score ≤3)†	6	1.00	5	1.00	10	1.00	6	1.00
	Medium (3 < score ≤12)	5	2.04 (0.49–8.42)	8	2.97 (0.79–11.3)	4	0.89 (0.19–4.28)	8	1.92 (0.50–7.39)
	High (score >12)	6	2.34 (0.49–11.2)	3	0.72 (0.12–4.50)	3	1.24 (0.19–7.98)	2	0.46 (0.06–3.59)
	P for trend‡		0.221		0.647		0.778		0.384
Pancreas	Low (score ≤3)†	20	1.00	11	1.00	22	1.00	11	1.00
	Medium (3 < score ≤12)	13	1.15 (0.42–3.12)	7	1.63 (0.47–5.65)	13	1.58 (0.57–4.42)	7	1.71 (0.49–5.99)
	High (score >12)	6	2.08 (0.65–6.62)	3	1.99 (0.41–9.57)	4	2.02 (0.53–7.61)	3	2.38 (0.48–11.9)
	P for trend‡		0.285		0.424		0.347		0.329

*Variables included in the model: time since first employment (continuous), pay type (categorical), age at event (continuous), and all other carcinogens (trichloroethylene, polycyclic aromatic hydrocarbons, and mineral oils using the same exposure cutoffs points as for hydrazine).

†Reference category.

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

§For NHL and leukemia, benzene exposure (lower cutoff: 3; upper cutoff: 9) was included in the model in addition to trichloroethylene, polycyclic aromatic hydrocarbons, and mineral oils.

TABLE 4. Associations of Cumulative Hydrazine Exposure With Smoking-Related (except lung) Cancer Mortality and Incidence (zero lag)*

		Mortality		Incidence	
Cancer Site	**Exposure Categories**	**No. Cases**	**RR (95% CI)**	**No. Cases**	**RR (95% CI)**
Upper respiratory tract	Low (score ≤3)†	29	1.00	20	1.00
	Medium (3 < score ≤12)	13	1.08 (0.48–2.44)	13	1.73 (0.71–4.22)
	High (score >12)	8	0.61 (0.23–1.66)	5	1.02 (0.30–3.46)
	P for trend‡		0.43		0.91
Bladder	Low (score ≤3)†	10	1.00	26	1.00
	Medium (3 < score ≤12)	5	1.23 (0.33–4.62)	13	0.67 (0.28–1.61)
	High (score >12)	2	0.30 (0.04–2.05)	11	0.62 (0.23–1.68)
	P for trend‡		0.25		0.35
Smoking-related (except lung)§	Low (score ≤3)†	61	1.00	58	1.00
	Medium (3 < score ≤12)	30	1.13 (0.64–2.00)	39	1.30 (0.76–2.22)
	High (score >12)	20	1.15 (0.58–2.27)	20	0.87 (0.43–1.75)
	P for trend‡		0.63		0.67

*Estimates are adjusted for: time since first employment (continuous), pay type (categorical, age at event, and all other carcinogens (trichloroethylene, polycyclic aromatic hydrocarbons, and mineral oils using the same exposure cutoff points as for hydrazine).
†Reference category.
‡Trend tests were performed by entering median exposure scores for each exposure category into the Cox model to obtain *P* value for trend.
§CD-9: 140–150 (excluding 142, 147), 188–189, 157, 161; ICD-10: C00–C15 (excluding C079–C089), C11, C64–C68, C25, C32.

ecologic measure and we assume that exposures apply homogeneously to all workers holding a job title during a specified period. However, because we blinded our raters to case status while they assigned exposures to job categories, misclassification of exposure would be nondifferential and most likely result in attenuation of estimated effects.

We did not have information about jobs held before or after Rocketdyne/Rockwell employment, but our subjects were mostly long-term workers with an average of 16 years' employment at this company. Furthermore, although we expect these highly skilled and well-trained employees to have had similar jobs at other companies, hydrazine fuels may have been a rather unique exposure limited to this rocket engine testing facility. Although some job title information was missing from facility records, missing job titles accounted for only 3% of the total; thus, we do not expect this missing information to have affected our results.

Another potential source of bias is confounding by unmeasured risk factors, especially smoking. However, we believe that confounding by smoking was not appreciable in this cohort because we observed little association between smoking status and chemical exposures in a subset of 200 subjects for whom we had information on smoking status for the 1960s. Furthermore, if the increased lung cancer mortality was in fact due to confounding such that highly exposed workers were more likely to have been smokers, we would expect other known smoking-related cancers to also be associated with hydrazine exposures. We did not, however, observe positive associations between hydrazine exposures and most other smoking-related cancers, including bladder cancers and all other smoking-related cancers (except lung) taken together.

Using population-based cancer registries to ascertain incident cases has several advantages over death certificates. First, cancer registry diagnoses are expected to be more accurate than death certificates because more information (such as pathology/histology reports) is available to ensure that the registered diagnoses are correct, thereby preventing some disease misclassification. Second, death certificates will miss many nonfatal cancers not mentioned as the underlying cause. However, a limitation of our incidence analyses is that it only includes cancer cases diagnosed 1988–2000. Thus, our incidence findings do not capture any effects of exposures that resulted in nonfatal cancers before 1988, a limitation that may be important for cancers with relatively short induction/latent periods such as leukemias.

We performed some sensitivity analyses to assess the possible bias introduced by incomplete coverage of our cohort by cancer registries from 1988 through 2000; we estimated that we missed 11% of all incident cancers. Because we also expected 184 workers to have been diagnosed with a cancer but not been reported to a cancer registry before 1988, we first randomly excluded 184 subjects from our incidence cohort of 5049 workers. Then we randomly assigned 82 of the remaining 4174 cancer-free workers to a cancer type and diagnosis date based on the distribution observed in our data. Results from 500 such simulated datasets were very similar to those presented here for incidence of cancers.

Our extended mortality study and the new cancer incidence component both support our previous findings that hydrazine exposures increased lung cancer and potentially pancreatic cancer risk in this aerospace worker cohort. The fact that incidence for colon and rectum cancers was increased while mortality was not underscores the importance

of not relying solely on mortality data to assess the impact of exposures on nonfatal cancers in occupational cohort studies. Due to the relatively limited number of exposed cases, our current data do not lend support to conclusions concerning hydrazine exposures and leukemias and lymphoma, and kidney cancers.

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REFERENCES

1. Ritz B, Morgenstern H, Froines J, et al. Chemical exposures of rocket-engine test-stand personnel and cancer mortality in a cohort of aerospace workers. *J Occup Environ Med*. 1999;41:903–910.
2. Morgenstern H, Ritz B. Effects of radiation and chemical exposures on cancer mortality among Rocketdyne workers: a review of three cohort studies. *Occup Med*. 2001;16:219–237.
3. International Agency for Research on Cancer. Dry cleaning, some chlorinated solvents and other industrial chemicals. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, vol 63; 1995.
4. International Agency for Research on Cancer. *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs*, vols 1–42; Suppl 7; 1987.
5. International Agency for Research on Cancer. Mineral oils. *IARC Monographs on Carcinogenicity of Chemicals to Man*. Suppl 7; 1987.
6. International Agency for Research on Cancer. Some industrial chemicals and dyestuffs, chemical, environmental and experimental data. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals in Humans*; 1982.
7. Zhao Y, Krishnadasan A, Kennedy N, et al. Estimated effects for solvents and mineral oils and Cancer Mortality and Incidence. *Am J Ind Med*. 2005;48:249–258.
8. Flanders DW, Cardenas VM, Austin H. Confounding by time since hire in internal comparisons of cumulative exposure in occupational cohort studies. *Epidemiology*. 1993;4:336–341.
9. Hosmer DL, Lemeshow S. *Applied Logistic Regression*, 2nd ed. Wiley-Interscience; 2000.
10. US Environmental Protection Agency. *Integrated Risk Information system (IRIS) on Hydrazine/hydrazine Sulfate*. Washington, DC: National Center for Environmental Assessment, Office of Research and Development; 1999.
11. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*, vol 71.
12. Morris J, Densem JW, Wald NJ, et al. Occupational exposure to hydrazine and subsequent risk of cancer. *Occup Environ Med*. 1995;52:43–45.
13. Cammarano G, Crosignani P, Berrino F, et al. Cancer mortality among workers in a thermoelectric power plant. *Scand J Work Environ Health*. 1984;10:259–261.