ADDENDUM REPORT

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Epidemiologic Study to Determine Possible Adverse Effects to Rocketdyne/Atomics International Workers from Exposure to Selected Chemicals

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SUMMARY

***Background and Objective*.** In the early 1990s, a worker health study was initiated in response to strong concerns voiced by area residents about the use of radioactive and toxic chemical substances at the Santa Susana Field Laboratory (SSFL) of Rocketdyne/Atomics International (AI), a division of Boeing North American (formerly Rockwell International). The effects of radiation exposures on cancer mortality were described in our previous report (dated May 1997 and released on September 11, 1997). In this addendum report, we describe the results of selected chemical effects on cancer mortality.

We determined that between 1955 and 1993, especially before 1980, many workers in the areas of rocket-engine testing were probably exposed to monomethyl hydrazine and other hydrazine compounds (referred to collectively as hydrazine throughout this report), kerosene fuels, trichloroethylene (TCE), asbestos, and other chemicals. Some radiation-monitored workers at the SSFL were exposed to asbestos, beryllium, and various solvents. Because we did not have enough information or resources to measure most of these chemical exposures, we restricted our attention to two chemicals--hydrazine and asbestos--for which proxy measures of exposure could be developed from available information. To examine the hypothesized effects of these exposures on cancer mortality, we conducted a retrospective cohort study in two separate groups employed at the SSFL. We examined whether workers presumptively exposed to hydrazine during rocket-engine testing experienced an increased rate of dying from lung cancer and other types of cancer that have been previously linked with toxic chemicals. In addition, we examined the possible effect of presumptive exposure to asbestos on lung-cancer mortality.

Methods. The hydrazine analyses included 6,107 men who were employed before 1980

at the SSFL, who worked at least two years at any Rockwell facility, and who were never monitored for radiation exposure at Rocketdyne/AI. The asbestos analyses included 4,563 men and women who were monitored for external radiation (the externally monitored cohort in our previous report). We used job-title and job-code information abstracted from personnel records to categorize the probability of exposure to hydrazine and asbestos. Workers were assigned to four categories of probable hydrazine exposure (high, medium, low, and unexposed), using two separate criteria for defining the three exposed categories--a minimum of 6 or 24 months in selected jobs. A similar method was used to measure asbestos exposure, but categorization was based on the 6-month criterion only.

All effects in this report were estimated by applying conditional logistic regression analysis to cancer deaths and their risk sets of survivors (as in the previous report). Hydrazine effects were estimated for several outcomes: death from lung cancer, all hemato- and lymphopoietic cancers, bladder and kidney cancers, upper-aerodigestive-tract cancers (oral cavity, pharynx, larynx, and esophagus), pancreatic cancer, and emphysema. Asbestos effects were estimated for lung-cancer mortality. Estimated effects were expressed as rate ratios (and 95% confidence intervals [CI]), comparing each exposed category with the unexposed group, and were adjusted for three potential confounders: age, pay type (a proxy for socioeconomic status), and time since hire or transfer to SSFL. Since the asbestos effect was estimated in the cohort monitored for radiation, we also adjusted this effect for cumulative doses of external and internal radiation. In addition, we examined the associations between smoking status and both exposure variables in subsets of subjects for whom smoking information was available. Chemical exposures were treated as time-dependent covariates and were lagged by zero, 10, and 15 years in the prediction models.

Results. The estimated rate ratio for lung-cancer mortality, comparing high versus no hydrazine exposure, ranged from 1.68 (95% CI = 1.12, 2.52) to 2.10 (95% CI = 1.36, 3.25), depending on the minimum criterion for defining exposure (6 or 24 months) and the lag for measuring exposure (0-15 years). No excess rates were observed for subjects in the medium- or low-exposure groups. The analysis of high exposure to hydrazine by decade suggested that this observed effect was limited primarily to exposure received during the 1960s. Similar results were obtained for hemato- and lymphopoietic-cancer mortality and for bladder- and kidney-cancer mortality, comparing high versus no hydrazine exposure, but these estimates are rather imprecise (all 95% CIs are wide and include one). No association was observed between hydrazine exposure and mortality from other smoking-related diseases or between hydrazine exposure and smoking in a subset of subjects. In addition, we found no association between asbestos exposure and lung-cancer mortality among radiation-monitored workers.

Discussion. We observed positive associations between our proxy measure of hydrazine exposure and the rates of dying from cancers of the lung, blood and lymph system, and bladder and kidney. The mortality rates for these cancers were approximately twice as great among workers classified in the high-exposure group as they were among workers classified in the unexposed group. Nevertheless, consistent effects were not observed for medium-exposure levels, except for cancer of the blood and lymph system. Although the lung-cancer results are consistent with those of animal studies, there are four methodologic problems that limit causal inference. First, effect estimation was relatively imprecise for most cancer outcomes, due to the small numbers of cancer deaths in the exposed categories. Thus, most of the 95% confidence intervals (around estimated rate ratios) were wide and included the null value (one) for all outcomes except lung cancer. Second, exposure classifications were based entirely on job titles,

not quantitative doses. Thus, there was certainly exposure misclassification, which could have biased the results. Since we have no reason to believe, however, that this misclassification was differential with respect to cancer outcome, we would expect the bias to be toward the null value. Such misclassification, therefore, might explain the negative findings for asbestos and lung cancer, but it implies that our hydrazine effects might be underestimated. Third, our effect estimates might be confounded by risk factors that were not included in the analyses, such as smoking and occupational exposures to other chemicals. We do not believe that confounding by smoking was appreciable because we observed little association between smoking status and hydrazine exposure in a subset of workers and because an effect of hydrazine was not observed for all smoking-related diseases. Nevertheless, we cannot rule out confounding by other chemical carcinogens, such as TCE, to which many subjects were likely exposed, including workers in the same jobs that were classified as probably involving exposure to hydrazine. Fourth, all outcome variables in this study were based on mortality, not cancer incidence. Thus, the findings reported here might not be an accurate reflection of risk-factor effects, especially for nonfatal cancers.

In conclusion, the results of this study suggest that occupational exposure to hydrazine and/or other chemicals associated with the same rocket-engine-testing jobs increased the risk of dying from lung cancer, and possibly other cancers, in this population of aerospace workers; however, causal inference is limited and our results need to be replicated in other populations. We recommend that the follow-up of our study cohorts be continued for the detection of both cancer mortality and incidence.

INTRODUCTION

In the early 1990s, a worker health study--discussed in this report--was initiated in response to strong concerns voiced by area residents about the use of radioactive and toxic chemical substances at the Santa Susana Field Laboratory (SSFL) of Rocketdyne/Atomics International (AI), a division of Boeing North America (formerly Rockwell International). The Atomics International division was involved in the development and testing of nuclear reactors and other nuclear projects in Area IV of the SSFL, while Rocketdyne was engaged in the development and testing of rocket engines and related technologies. In May 1997, we submitted a final report describing associations between external and internal radiation doses and cancer mortality among Rocketdyne/AI employees monitored for radiation exposures (Morgenstern et al., 1997). In those analyses, we found elevated cancer-mortality rates for workers exposed to higher, but permissible, cumulative doses of both types of radiation, and these observed effects were not limited to cancers of blood and lymph tissue.

This addendum report will focus on the possible effects of two chemicals on cancer mortality: hydrazine exposure associated with rocket-engine testing; and asbestos exposure associated with radiation-related activities. Although exposure to chemical carcinogens among rocket-engine-testing personnel was probably not limited to hydrazine, we did not have enough information or resources to measure exposures to other potential carcinogens in the workplace. To examine the hypothesized effects of these two exposures, we conducted a retrospective cohort study in two separate groups employed at the SSFL between 1950 and 1993.

In the 1960s, Rocketdyne was a very active participant in the national space program. The rocket engines were fueled by exotic fuels containing, for example, monomethyl hydrazine, hydrazine, and 1,1-dimethylhydrazine (referred to collectively as hydrazine throughout this

report). Hydrazines, especially monomethyl hydrazine, were used in large quantities at the facility from the mid 1950s to the early 1970s. (See Appendix A for a detailed description of chemicals used at the rocket-engine test stands at Rocketdyne.) This chemical substance has been classified by the U.S. Environmental Protection Agency (EPA, 1990) as an air toxin and a probable human (B2) carcinogen, i.e., there is sufficient evidence from animal studies to support carcinogenicity, but inadequate evidence from human studies (Shy, 1996). This lack of epidemiologic evidence is due to the absence of research, not to negative or inconsistent findings. As described in Appendix A, there is also evidence from genotoxic studies that suggest the biological plausibility of the carcinogenicity of hydrazine in humans. In addition, there is recent evidence from another aerospace facility that rocket-engine-testing personnel might have been exposed to nitrosamines produced by the oxidation of hydrazine (see Appendix A). Since these nitrosamines are potent carcinogens in laboratory animals and since they may be risk factors for human cancer, this evidence further supports the hypothesis of an increased cancer rate among rocket-engine-testing personnel at Rocketdyne.

The major objectives of this study were to estimate the possible effects of hydrazine and asbestos exposures on lung-cancer mortality. In addition, since little is known about the possible effects of hydrazine exposure in humans, we also examined the associations between hydrazine exposure and death from other diseases: hemato-and lymphopoietic cancers, bladder and kidney cancers, upper-aerodigestive-tract cancers (oral cavity and pharynx, larynx, and esophagus), pancreatic cancer, and emphysema.

METHODS

Study Design and Subject Selection

The source population for subjects in the retrospective cohort studies of radiation and chemicals was all workers employed at Rocketdyne/AI between 1950 and 1993--approximately 55,000 employees in the company's personnel files. Personnel records allowed us to define the study populations and to obtain employment information. Cause of death for deceased workers was obtained from death certificates that were retrieved from Rocketdyne/AI pension files and state vital statistics offices.

The hydrazine analyses included 6,107 men (the hydrazine cohort) who were employed before 1980 at the SSFL, who worked at least two years in any Rockwell division, and who were never monitored for radiation exposure, according to company records. Gender and employment restrictions were made to limit the size of the population for which funds were available to conduct an additional death-certificate search (following the follow-up of the radiation cohorts). These analyses were also restricted to unmonitored workers, because little apparent hydrazine exposure was measurable by our methods in radiation-monitored workers (though such exposure may have occurred), and because monitoring status may be associated with cancer mortality among workers with minimal doses of radiation (Wilkinson & Morgenstern, 1995).

In contrast, the asbestos analyses included 4,563 workers (the asbestos cohort; 94% male) who were monitored for external radiation at Rocketdyne/AI (the externally monitored cohort in our previous report; see Morgenstern et al., 1997). These analyses were restricted to monitored workers because little apparent asbestos exposure was measurable by our methods in unmonitored workers (though such exposure probably occurred).

The Rocketdyne/AI personnel office provided us with personnel records of all employees who had worked in that division. Cross-checking of personnel records against a transfer book

documenting the transfer of employees between divisions revealed that the personnel office lacked records for 1,690 of the listed employees. After an extensive record search involving all Rockwell divisions, we were able to obtain 1,063 (63%) of the missing records from other divisions. Only 248 of these retrieved records, however, belonged to workers who met our eligibility criteria for the hydrazine cohort. Thus, we estimate that records were missing for 146 eligible workers (2.3% of the eligible hydrazine cohort).

Death Certificates

If two independent company data sources identified an employee as active at the end of follow-up, we counted that person as alive. Vital status was determined to be alive for about 10% of the hydrazine cohort using this method. Employees not identified as alive or dead by company records were matched against three different record systems: the Social Security Administration (SSA) beneficiary-records files (cover period: 1935-1994), the vital-statistics files for the State of California (cover period: 1960-1994), and the U.S. National Death Index (NDI) (cover period: 1979-1994). Matches were verified by reviewing the information on death certificates.

From all sources combined, we identified 1,391 subjects in the hydrazine cohort who died between 1960 and 1994 and 875 subjects in the asbestos cohort who died between 1959 and 1994. We were able to obtain all but one death certificate for deceased workers in the hydrazine cohort and all but 30 death certificates for deceased workers in the asbestos cohort. All death-identification systems together guarantee a vital-status search complete enough to justify that a person is treated as alive at the end of follow-up if not identified as dead by at least one of the three computerized services or Rocketdyne/AI beneficiary records (see also Morgenstern et al.,

1997).

A licensed nosologist coded the cause-of-death information recorded on each death certificate using the 9th revision of the International Classification of Diseases (ICD-9) (U.S. DHHS, 1989; 1991). Both the underlying and associated (contributing) causes were coded, but the analyses presented in this paper are based on underlying causes only. The coding was checked for accuracy, and discrepancies were discussed and reconciled by two members of the study team.

Chemical Exposures

With the help of walk-through visits, interviews of managers and workers, and historical facility reports, we conducted an extensive industrial-hygiene review of the SSFL facility (see Appendix A). Chemical inventories were obtained for the years 1955-94 for hydrazine and some solvents, documenting the amounts bought by the facility. Using these sources, we determined that the principal chemicals used at rocket-engine test stands were hydrazines, kerosene fuels (RP-1), chlorine, fluorine, hydrogen peroxide, isopropyl alcohol, nitric acid, nitrogen tetroxide (NTO), trichloroethylene (TCE), and 1,1,1-trichloroethane (TCA). To some extent, workers could also have been exposed to beryllium, asbestos, and other chemicals.

Because we were not able to obtain air-monitoring data for any chemicals used at Rocketdyne/AI before 1985, we focused on two chemicals--hydrazine and asbestos--for which proxy measures of exposure could be developed from available information. The information gathered during the industrial-hygiene review helped us to identify jobs, periods, and work locations with a high probability of appreciable exposure to hydrazine and asbestos at the SSFL; but we were unable to do the same for other chemicals.

We originally planned to develop a job-exposure matrix for hydrazine, based on the three major components: work location, job title, and period. It soon became clear, however, that our ability to link workers with job locations was extremely limited, since location codes on personnel records do not actually identify the work locations of most employees. In general, we could only crudely link individual workers to one of the major Rocketdyne/AI areas, but rarely to a specific room, building, or rocket-engine test stand. Although hydrazines were used at only three of the 12 test stands, workers assigned to these jobs tended to rotate among the test stands in operation.

Consequently, we had to rely on a rather crude method for measuring hydrazine exposure for personnel working at rocket-engine test stands. Workers were assigned to 4 categories of presumptive exposure (high, medium, low, and unexposed) on the basis of job titles, job codes, and employment periods alone, using information from worker and manager interviews and company-record reviews. These categories reflect the relative probability of hydrazine exposure, rather than the amount of exposure. All exposure classification was done blind to survival status and cause of death. Assignment to the three exposed groups (high, medium, and low) was based on at least 6 or 24 months in selected jobs; i.e., we developed two hydrazine measures, called HYD-6 and HYD-24. The high-exposure group includes workers employed as propulsion/test mechanics or propulsion/test technicians. Employees holding these job titles might have been responsible for pumping hydrazine into test-stand fuel tanks and into rocket engines and fuel tanks. Such fuel-loading procedures officially involved "closed systems" to avoid exposure, but leakage of fuel from the system was allegedly a common occurrence. The medium-exposure group includes employees who, according to their job titles, were present during engine-test firings potentially involving hydrazine use, but they did not necessarily have direct contact with

hydrazine through fueling procedures. Such job titles include propulsion/test inspector, test engineer, research engineer, and instrumentation mechanic. The low-exposure group includes workers with job titles who may or may not have been present at engine-test firings (e.g., flight-line mechanics and engineers). At any time during follow-up, a worker was assigned to the highest category for which he qualified. The unexposed group includes all workers who did not qualify for any of the exposed categories (given the 6- or 24-month criterion). Refer to Appendix B for an abridged list of job titles assigned to each exposed category.

For several years during the 1960s, workers at one test stand experimented with powdered beryllium for use in rocket propellants. To minimize exposure to workers, this beryllium work was conducted in a closed system, and workers were supposed to wear respirators. Although we were unable to obtain monitoring data from this period, it is likely that some beryllium exposure occurred (see Appendix A). We believe, however, that such exposure was probably limited to no more than a few dozen workers, yet we were unable to identify these workers.

According to worker and manager interviews, solvents were used throughout the facility and during most operations. For example, TCE was used in large quantities at the test stands to clean engines fueled by liquid oxygen and kerosene and to remove combustible deposits and vapors. Nevertheless, due to the pervasiveness of solvent use and the lack of exposure-monitoring and worker-location data, it was impossible to identify specific workers or job titles with a high probability of solvent use.

Although certain rocket-engine-testing personnel were probably exposed to asbestos, we were not able to identify which workers were most likely exposed. On the other hand, the most extensive asbestos exposure that we documented at Rockedyne/AI was associated with radiation

work; thus, our assessment of asbestos effects was conducted in those workers externally monitored for radiation (see Morgenstern et al., 1997). We identified two Area IV location codes from personnel records that were associated with asbestos exposure for nuclear and liquid-metal mechanics, engineers, and machinists. Asbestos exposure was found to occur primarily in building 006 (sodium laboratory) and building 143 (sodium reactor experiment) of the SSFL before 1980. Thus, employees working between 1950 and 1980 in these buildings were likely to have been exposed to airborne asbestos. Tasks most likely associated with high exposure levels involved cutting through and patching up asbestos insulation. Workers mixed bags of dry asbestos with water in a 5-gallon bucket until the mixture became mud-like. Interviews also revealed that workers did not wear respirators while performing such tasks before the early 1980s.

We created a 4-category variable (ASB-6) to measure asbestos exposure that was similar to our hydrazine measure. Workers were assigned to high, medium, or low exposure categories, based on at least 6 months in selected jobs during certain periods. The high-exposure group includes any type of mechanic, machinist, or technician who worked for at least 6 months in building 006 or 143 before 1980. The medium-exposed group includes any type of engineer who worked for at least 6 months in building 006 or 143 before 1980. The low-exposure group includes subjects with other job titles who worked for at least 6 months before 1980 in building 006 or 143 and any type of mechanic, machinist, or technician who did not work in buildings 006 or 143. The unexposed group includes all other subjects.

Personnel and Medical Records

Personnel records were used to create a three-category measure of pay type as a proxy for

socioeconomic (SES) 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 those jobs held longest at Rocketdyne/AI. Evidence for the construct validity of this SES measure comes from our analyses of education level obtained from death certificates for deceased workers in the radiation-monitored cohort: We found a strong consistent association between mean years of education and pay-type category.

Since Rocketdyne/AI did not systematically collect data on the race of its employees before 1972, we were unable to control for this factor in our analyses. According to the information on death certificates, however, 96% of all deceased workers were white.

Information about tobacco smoking was systematically recorded for two groups of workers in routinely administered medical questionnaires from different periods. Between 1961 and 1969, questionnaires completed by selected workers indicated current smoking status (smoker or nonsmoker); after 1980, questionnaires completed by selected workers indicated smoking history (current or former smoker or never smoker). Since smoking information was not available for most subjects in our two study populations, we assessed potential confounding of chemical effects by examining the associations between smoking status and each exposure variable in subsets of subjects for whom smoking information was available (i.e., 295 in the hydrazine cohort and 1,080 in the asbestos cohort).

Statistical Methods

Given the methods described above for selecting workers for the hydrazine analyses, follow-up for this cohort began at the latest of three dates: 1) the start of work at the SSFL; 2)

the start of work at any Rockwell division plus two years; or 3) January 1, 1950. For the asbestos analyses, follow-up began at the start of external-radiation monitoring or on January 1, 1950, whichever date came later (Morgenstern et al., 1997). In both sets of analyses, follow-up ended on the date of death or on December 31, 1994, whichever date came earlier.

Since hydrazine exposure is known to cause lung cancer in animals (U.S. EPA, 1990) and since asbestos is known to be a risk factor for lung cancer in humans (Monson, 1996), lung-cancer mortality (ICD-9 162) was the major outcome of interest in both sets of analyses. In addition, since very little is known about hydrazine effects in humans (Shy, 1996), we also examined its possible effects on death from hemato- and lymphopoietic cancers (including leukemias, lymphomas, lymphosarcomas, reticulosarcomas, myelomas, and Hodgkin's disease; ICD-9 200-208), bladder and kidney cancers (exit organs; ICD-9 188-189), upper-aerodigestive-tract cancers (oral cavity and pharynx, larynx, and esophagus; ICD-9 140-150, 161), pancreatic cancer (ICD-9 157), and emphysema (ICD-9 492). In addition to the exploratory objective of these analyses, there was also a methodologic objective: Because we did not have sufficient smoking data to control for this variable in the analysis, we wanted to assess associations between hydrazine exposure and several smoking-related diseases, aside from lung cancer.

To estimate effects, we employed the risk-set approach for follow-up data described by Breslow and Day (1987). In this approach, conditional logistic regression is used to compare individuals who have died from the index disease with individuals still at risk of dying (the risk set of "survivors"). Risk sets for all analyses presented in this report were based on post-matching survivors to index deaths on calendar time. As an alternative approach in certain analyses, we post-matched survivors to index deaths on age, but this approach yielded approximately the same estimates for hydrazine and asbestos effects.

Three time-dependent indicator variables representing high, medium, and low exposure to hydrazine or asbestos at the time of the index death were included as predictors in the logistic-regression models. Since there were very few subjects in the low-exposure hydrazine group, however, effect estimates for this category are not reported (see Table 2). To allow for varying periods of induction/latency between exposure and death and to deal with possible selection bias, exposure measurements were lagged by zero, 10, and 15 years (see Arrighi and Hertz-Picciotto, 1994). Lagging was achieved by ignoring exposure for each subject in a risk set within zero, 10, or 15 years of the index death. In addition, the number of years spent in high-exposure hydrazine jobs was treated as a time-dependent continuous predictor in separate models. Since the potential for hydrazine exposure within jobs probably changed over time, we also modeled the effect of high exposure (for at least 6 months) by decade of exposure (1950-89). This was done by including in the model a binary variable for high exposure in each of four decades.

Rate ratios and 95% confidence intervals (CI) for exposures were derived from the estimated logistic parameters and standard errors. To control for confounding, we included the following covariates in each model: age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to SSFL at death (continuous). Time since hire or transfer was included to control for the selective loss of less healthy workers (Flanders et al., 1993). Since the asbestos effect was estimated in the cohort monitored for radiation, we also adjusted this effect for cumulative doses of external and internal radiation.

RESULTS

The unmonitored hydrazine cohort and the radiation-monitored asbestos cohort are described in Table 1. Both study populations are characterized by a long average follow-up time

(29 and 26 years, respectively) and a high percentage of salaried employees (89% and 45%, respectively). There were 1,391 total deaths in the hydrazine cohort (23% of the total), of which 404 (29%) were from cancer as the underlying cause, yielding a total cancer-mortality rate of 228 per 100,000/year. There were 875 total deaths in the asbestos cohort (19% of the total), of which 258 (29%) were from cancer as the underlying cause, yielding a total cancer-mortality rate of 217 per 100,000/year. During the follow-up period, about 28% of the men in the unmonitored cohort were classified as presumptively exposed to hydrazine using the 6-month criterion for defining exposed jobs (HYD-6), and about 24% were exposed using the 24-month criterion (HYD-24); most of these exposed subjects were categorized in the high-exposure group (Table 2). Sixteen (16) percent of subjects in the monitored cohort were classified as presumptively exposed to asbestos using the 6-month criterion for defining exposed jobs (ASB-6).

The estimated effects of high and medium hydrazine exposure on lung-cancer mortality are shown in Table 3. The estimated rate ratio (RR) for the high-exposure group, relative to the unexposed group, ranged from 1.68 (95% confidence interval [CI] = 1.12, 2.52) to 2.10 (95% CI = 1.36, 3.25), depending on the minimum criterion for defining exposure (6 or 24 months) and the lag for measuring exposure (0-15 years). We observed a slight increase in the rate ratio with increasing lag. No excess rates were observed for subjects in the medium-exposure group (RR < 1). By modeling years of work in high-exposure jobs as a continuous time-dependent predictor with zero lag, the estimated rate ratio per 10-year increment of high exposure was 1.65 (95% CI = 1.18, 2.32); i.e., each 10-year increase in the number of years spent in high-exposure jobs is associated with a 65% increase in the rate of lung-cancer mortality.

Table 4 shows the adjusted effects of hydrazine exposure on hemato- and lymphopoietic-cancer mortality. The estimated rate ratio for high exposure ranged from 1.27 (95% CI = 0.51,

3.14) to 2.83 (95% CI = 1.22, 6.56). The observed effect was noticeably stronger for HYD-6 than for HYD-24, and it increased slightly with increasing lag; nevertheless, all of these estimates were imprecise (i.e., all 95% CIs were relatively wide and all but one included the null value). The rate ratios for medium exposure showed a similar pattern, but they tended to be smaller and even less precisely estimated. Separate analyses for leukemia and lymphoma mortality were not informative enough to distinguish which cancer outcome was associated with hydrazine exposure.

The estimated effects of hydrazine (HYD-6) on lung-cancer mortality and hemato- and lymphopoietic-cancer mortality by decade of exposure are shown in Table 5. For both cancer outcomes, the effect of hydrazine exposure seems to be limited primarily to exposure received during the 1960s. The estimated rate ratio for high exposure versus unexposed was 2.01 (95% CI = 1.21, 3.33) for lung cancer and 2.45 (95% CI = 0.91, 6.58) for hemato- and lymphopoietic cancer.

The effects of hydrazine on bladder- and kidney-cancer mortality are also imprecisely estimated (Table 6). The estimated rate ratio for high exposure ranged from 1.50 (95% CI = 0.55, 4.12) to 2.55 (0.94, 6.86), and there were no deaths in the medium-exposure groups. The observed effect was a little stronger for HYD-24 than for HYD-6 (the opposite pattern observed for hemato- and lymphopoietic cancers), and it did not vary systematically with the lag. Separate analyses for bladder- and kidney-cancer mortality were not informative enough to distinguish which cancer outcome was associated with hydrazine exposure.

The estimated effects of hydrazine exposure on mortality from other smoking-related diseases are shown in Tables 7-10. High exposure was not associated with an excess mortality rate of upper-aerodigestive-tract cancers (Table 7), pancreatic cancer (Table 8), or emphysema

(Table 9). The estimated rate ratios for medium exposure, however, tended to be greater than one, and they increased somewhat with increasing lag; nevertheless, these estimates were very imprecise. When deaths from all smoking-related cancers, except lung, were combined into a single outcome, there was no apparent effect of either high or medium hydrazine exposure (Table 10).

In the cohort of subjects monitored for external radiation, there was little association between asbestos exposure (ASB-6) and lung-cancer mortality. The estimated rate ratio for high exposure, compared with no exposure, was 1.10 (95% CI = 0.39, 3.07) using a zero lag and 1.26 (95% CI = 0.47, 3.36) using a 15-year lag.

DISCUSSION

We observed positive associations between our proxy measure of hydrazine exposure and the rates of dying from cancers of the lung, blood and lymph system, and bladder and kidney. Nevertheless, consistent effects were not observed for medium-exposure levels, except for hemato- and lymphopoietic cancers; and effect estimation was relatively imprecise, except for high exposure and lung cancer, due to the small numbers of cancer deaths in the exposed categories. On the other hand, the estimated rate ratio for lung-cancer mortality tended to increase with increasing lag, which is consistent with the long induction/latency for this cancer, and it was consistent across two operational definitions of exposure (HYD-6 and HYD-24). In addition, we were able to control for the potentially confounding effects of age, socioeconomic status (pay type), time since hire or transfer to SSFL (by statistical adjustment), calendar time (by post-matching), and radiation exposure (by selection of the cohort).

Although hydrazine is known to be carcinogenic in animals and although there is

genotoxic evidence supporting the biological plausibility of carcinogenicity in humans (see Appendix A), there is no clear epidemiologic evidence linking hydrazine exposure with cancer risk. In a British study of hydrazine production-workers, Morris et al. (1995) found no effect of hydrazine exposure on cancer mortality, but this was a very small study of only 427 workers (25 cancer deaths; 8 from lung cancer). In an Italian study of workers at a thermoelectric power plant, Cammarano et al. (1984) reported an excess mortality rate for all cancers among workers with 10 or more years of employment (12 cancers deaths; 4.35 expected). These investigators, however, were not able to link the excess cancer mortality to hydrazine exposure, because several carcinogens were present in the workplace and they did not measure exposures to hydrazine or those other chemicals.

Despite the findings of this study linking our measure of hydrazine exposure to cancer mortality, there are several methodologic problems that limit causal inference. Aside from the low precision in estimating effects (rate ratios), our exposure classifications were based entirely on job titles, not quantitative doses. Thus, there was certainly exposure misclassification, which could have biased the results. Not only was it impossible to determine from job titles which workers were actually assigned to specific buildings or rocket test stands involving the use of hydrazines, but also exposure to hydrazine at any test stand typically resulted from accidental and unpredictable occurrences. Since we have no reason to believe, however, that this exposure misclassification was differential with respect to cancer outcome, we would expect the bias to be toward the null value. Such misclassification, therefore, implies that our hydrazine effects might be underestimated. Furthermore, the frequency of test firings and the amount of hydrazine used at Rocketdyne was greatest between the 1950s and the early 1970s, which is roughly consistent with our results: We found that the effects of hydrazine exposure on lung-cancer mortality and

hemato- and lymphopoietic-cancer mortality were limited primarily to exposure received during the 1960s.

Nondifferential misclassification of asbestos exposure, leading to bias toward the null, might explain the negative findings for asbestos and lung cancer. Indeed, there is some indirect evidence for exposure misclassification from our secondary analysis of mesothelioma deaths, which we can assume had been exposed to asbestos (though not necessarily at Rocketdyne/AI). Of the 4 mesothelioma deaths detected in the radiation-monitored cohort, only one was classified in the high-exposure category; the other three were classified as unexposed. Alternatively, the negative findings for asbestos might be due to insufficient exposure of Rocketdyne/AI workers to airborne asbestos, but this explanation does not seem too plausible for the earlier part of our follow-up period before the widespread use of protection equipment in the early 1980s.

Another potential source of bias in our study is confounding by risk factors that were not included in the analyses, such as smoking and occupational exposures to other chemicals. We do not believe that confounding by smoking was appreciable in the hydrazine cohort, however, because we observed little association between smoking status and hydrazine exposure in a subset of 295 subjects (Table 11). In addition, an effect of hydrazine was not observed for smoking-related diseases other than lung, bladder, and kidney cancers (Tables 7-10). Nevertheless, potential confounding from other chemical exposures is more problematic. Workers assigned to test stands, for example, were probably exposed to TCE that was used in cleaning ("flushing") the rocket engines after test firings. There is some evidence that TCE may be a risk factor for cancers of the liver, biliary passages, kidney, and non-Hodgkin's lymphomas (though not lung cancer) (IARC, 1995; Weiss, 1996; Morgan et al., 1998). Thus, TCE exposure might have confounded the estimated effects of hydrazine exposure on these cancers if workers

in the same jobs were exposed to both hydrazine and TCE. Indeed, this scenario is very likely. As noted in the Introduction, it is also possible that workers exposed to hydrazine were also exposed to nitrosamines, another probable carcinogen, which may have been produced by the oxidation of hydrazine. Unfortunately, we had no way to observe the associations between hyrdazine exposure and other chemical risk factors for cancer.

Another methodologic problem is that all outcome variables in this study were based on mortality, not cancer incidence. Since several cancers, such as bladder cancer, are not highly fatal, incident cases would not have been counted as outcome events if they were still alive at the end of the follow-up period. Furthermore, even if such cases died during follow-up, they might not be listed as the underlying cause of death on death certificates, or they might not be listed at all. Thus, the findings reported for these cancers in our study might not be an accurate reflection of risk-factor effects. Empirical evidence for this problem comes from another occupational study by Demers et al. (1992), who found that estimated effects on bladder and colon cancers differed for incidence and mortality data in the same population.

In conclusion, the results of this study suggest that occupational exposure to hydrazine and/or other chemicals associated with the same rocket-engine-testing jobs increased the risk of dying from lung cancer, and possibly other cancers, in this population of aerospace workers; however, causal inference is limited and our results need to be replicated in other populations. We recommend that the follow-up of our study cohorts be continued for the detection of both cancer mortality and incidence.

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