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 permissable, 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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Table 1. Descriptions of the hydrazine cohort (not monitored for radiation) and the asbsestos cohort (monitored for external radiation)

	Hydrazine Cohort	Asbestos Cohort
Number of subjects	6,107	4,563
Percent Male	100	94.0
Average follow-up time (years)	29.0	26.1
Average age (years) at start of follow-up	34.6	33.9
Number of person-years of follow-up	176,886	118,749
Number of total deaths	1,391	875
Number of cancer deaths	404	258
Total mortality rate (per 100,000/year)	786	737
Total cancer-mortality rate (per 100,000/year)	228	217
Pay type (percent of total)		
Salaried managerial/professional	45.1	33.6
Salaried technical/administrative	43.7	11.1
Hourly/union	11.3	50.7
Unknown	0.0	4.6

Table 2. Number of subjects, by category of presumptive hydrazine (HYD) exposure and asbestos (ASB) exposure* and by minimum duration (6 or 24 months) in selected jobs for defining exposure**

Exposure Variable	High	Medium	Low	Unexposed	Total
HYD-6	1,053	654	32	4,368	6,107
HYD-24	827	592	42	4,646	6,107
ASB-6	142	177	394	3,850	4,563

* For each exposure variable, a worker is classified in the category of his or her highest exposure level at the end of follow-up.

** Either 6 or 24 months of employment in selected jobs is required to be classified in the high-, medium-, or low-exposure categories. These categories reflect the relative probability of hydrazine exposure, rather than the amount of exposure.

Table 3. Adjusted rate ratios (RR; and 95% CIs)* for the effects of high and medium hydrazine exposure versus no exposure on **lung-cancer** mortality (ICD-9 162), by definition of hydrazine exposure (6- or 24-month criterion) and lag (in years) for measuring hydrazine exposure (N = 6,107; 146 cancer deaths)

		High Exposure			Medium Exposure		
Hydrazine Variable	Lag (Yrs)	No. Cancer Deaths	RR	95% CI	No. Cancer Deaths	RR	95% CI
HYD-6	0	44	1.68	(1.12, 2.52)	5	0.41	(0.17, 1.02)
	10	42	1.70	(1.13, 2.56)	4	0.36	(0.13, 0.98)
	15	41	1.93	(1.27, 2.93)	4	0.42	(0.15, 1.16)
HYD-24	0	36	1.70	(1.11, 2.59)	7	0.66	(0.31, 1.44)
	10	34	1.76	(1.15, 2.71)	6	0.65	(0.28, 1.49)
	15	34	2.10	(1.36, 3.25)	5	0.65	(0.26, 1.62)

* Estimated rate ratios are adjusted for age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to the SSFL (continuous).

Table 4. Adjusted rate ratios (RR; and 95% CIs)* for the effects of high and medium hydrazine exposure versus no exposure on **hemato- and lymphopoietic-cancer** mortality (ICD-9 200-208), by definition of hydrazine exposure (6- or 24-month criterion) and lag (in years) for measuring hydrazine exposure (N = 6,107; 41 cancer deaths)

		High Exposure			Medium Exposure		
Hydrazine Variable	Lag (Yrs)	No Cancer Deaths	RR	95% CI	No. Cancer Deaths	RR	95% CI
HYD-6	0	11	2.00	(0.88, 4.55)	7	1.80	(0.75, 4.28)
	10	11	2.26	(0.99, 5.16)	6	1.79	(0.71, 4.54)
	15	11	2.83	(1.22, 6.56)	5	1.79	(0.65, 4.94)
HYD-24	0	7	1.27	(0.51, 3.14)	6	1.51	(0.61, 3.72)
	10	7	1.49	(0.60, 3.69)	5	1.52	(0.57, 4.07)
	15	6	1.42	(0.54, 3.72)	4	1.32	(0.45, 3.90)

* Estimated rate ratios are adjusted for age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to the SSFL (continuous).

Table 5. Adjusted rate ratios (RR; and 95% CI)* for the effects of high hydrazine exposure (HYD-6) versus no exposure on lung-cancer mortality and hemato/lymphopoietic-cancer mortality, by decade of exposure (zero lag)

Decade of Exposure	Lung Cancer		Hemato/Lymphopoietic Cancer	
	RR	95% CI	RR	95% CI
1950-59	0.88	(0.54, 1.44)	0.86	(0.32, 2.28)
1960-69	2.01	(1.21, 3.33)	2.45	(0.91, 6.58)
1970-79	1.45	(0.70, 3.01)	0.00	(0.00, **)
1980-89	0.46	(0.06, 3.64)	0.89	(0.00, **)

* Estimated rate ratios are adjusted for age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to the SSFL (continuous).

** Upper limits cannot be estimated because of small numbers of outcome events in the high-exposure category.

Table 6. Adjusted rate ratios (RR; and 95% CIs)* for the effects of high and medium hydrazine exposure versus no exposure on **bladder- and kidney-cancer** mortality (ICD-9 188, 189), by definition of hydrazine exposure (6- or 24-month criterion) and lag (in years) for measuring hydrazine exposure (N = 6,107; 22 cancer deaths)

		High Exposure			Medium Exposure		
Hydrazine Variable	Lag (Yrs)	No. Cancer Deaths	RR	95% CI	No. Cancer Deaths	RR	95% CI
HYD-6	0	8	1.83	(0.68, 4.92)	0	---	---
	10	7	1.50	(0.55, 4.12)	0	---	---
	15	7	1.65	(0.59, 4.56)	0	---	---
HYD-24	0	8	2.55	(0.94, 6.86)	0	---	---
	10	7	2.12	(0.77,.5.83)	0	---	---
	15	6	1.80	(0.63, 5.12)	0	---	---

* Estimated rate ratios are adjusted for age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to the SSFL (continuous).

Table 7. Adjusted rate ratios (RR; and 95% CIs)* for the effects of high and medium hydrazine exposure versus no exposure on **upper-aerodigestive-tract-cancer** mortality (ICD-9 140-150, 161), by definition of hydrazine exposure (6- or 24-month criterion) and lag (in years) for measuring hydrazine exposure (N = 6,107; 25 cancer deaths)

		High Exposure			Medium Exposure		
Hydrazine Variable	Lag (Yrs)	No. Cancer Deaths	RR	95% CI	No. Cancer Deaths	RR	95% CI
HYD-6	0	3	0.51	(0.14, 1.82)	3	1.20	(0.35, 4.17)
	10	3	0.56	(0.15, 2.03)	3	1.35	(0.39, 4.73)
	15	3	0.69	(0.19, 2.53)	3	1.69	(0.47, 6.06)
HYD-24	0	2	0.41	(0.09, 1.86)	2	0.83	(0.19, 3.63)
	10	2	0.46	(0.10, 2.09)	2	0.96	(0.22, 4.23)
	15	2	0.57	(0.13, 2.61)	2	1.18	(0.26, 5.27)

* Estimated rate ratios are adjusted for age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to the SSFL (continuous).

Table 8. Adjusted rate ratios (RR; and 95% CIs)* for the effects of high and medium hydrazine exposure versus no exposure on **pancreatic-cancer** mortality (ICD-9 157), by definition of hydrazine exposure (6- or 24-month criterion) and lag (in years) for measuring hydrazine exposure (N = 6,107; 23 cancer deaths)

		High Exposure			Medium Exposure		
Hydrazine Variable	Lag (Yrs)	No. Cancer Deaths	RR	95% CI	No. Cancer Deaths	RR	95% CI
HYD-6	0	2	0.37	(0.08, 1.69)	4	1.52	(0.50, 4.62)
	10	2	0.43	(0.09, 1.98)	4	1.77	(0.57, 5.49)
	15	2	0.48	(0.10, 2.25)	4	1.95	(0.62, 6.12)
HYD-24	0	1	0.24	(0.03, 1.85)	4	1.72	(0.56, 5.22)
	10	1	0.28	(0.04, 2.21)	4	2.04	(0.66, 6.31)
	15	1	0.32	(0.04, 2.51)	4	2.26	(0.72, 7.09)

* Estimated rate ratios are adjusted for age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to the SSFL (continuous).

Table 9. Adjusted rate ratios (RR; and 95% CIs)* for the effects of high and medium hydrazine exposure versus no exposure on **emphysema** mortality (ICD-9 492), by definition of hydrazine exposure (6- or 24-month criterion) and lag (in years) for measuring hydrazine exposure (N = 6,107; 27 cancer deaths)

		High Exposure			Medium Exposure		
Hydrazine Variable	Lag (Yrs)	No. Deaths	RR	95% CI	No. Deaths	RR	95% CI
HYD-6	0	3	0.46	(0.13, 1.63)	4	1.83	(0.61, 5.47)
	10	3	0.49	(0.14, 1.75)	4	2.01	(0.67, 6.07)
	15	3	0.54	(0.15, 1.93)	4	2.18	(0.72, 6.62)
HYD-24	0	3	0.62	(0.17, 2.21)	3	1.77	(0.51, 6.19)
	10	3	0.68	(0.19, 2.43)	3	2.02	(0.57, 7.10)
	15	3	0.74	(0.21, 2.65)	3	2.26	(0.64, 8.02)

* Estimated rate ratios are adjusted for age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to the SSFL (continuous).

Table 10. Adjusted rate ratios (RR; and 95% CIs) for the effects of high and medium hydrazine exposure versus no exposure on all **smoking-related cancer** mortality, excluding lung cancer (ICD-9 140-150, 157, 161, 188, 189), by definition of hydrazine exposure (6- or 24-month criterion) and lag (in years) for measuring hydrazine exposure (N = 6,107; 70 cancer deaths)

		High Exposure			Medium Exposure		
Hydrazine Variable	Lag (Yrs)	No. Cancer Deaths	RR	95% CI	No. Cancer Deaths	RR	95% CI
HYD-6	0	13	0.82	(0.43, 1.59)	7	0.97	(0.43, 2.17)
	10	12	0.81	(0.41, 1.60)	7	1.06	(0.47, 2.38)
	15	12	0.94	(0.47, 1.86)	7	1.22	(0.54, 2.76)
HYD-24	0	11	0.90	(0.45, 1.80)	6	0.93	(0.40, 2.20)
	10	10	0.89	(0.43,.1.83)	6	1.04	(0.44, 2.46)
	15	9	0.90	(0.42, 1.92)	6	1.17	(0.49, 2.79)

* Estimated rate ratios are adjusted for age at death (continuous), pay type (two fixed binary variables), and time since hire or transfer to the SSFL (continuous).

Table 11. Number (and percent) of current and former smokers among subsets of subjects in the hydrazine and asbestos cohorts who were included in three medical surveys at the SSFL, by exposure category and period

	1961-69		1983-92		
Exposure Category	No. (%) Curr. Smokers	Total Subjects	No. (%) Curr. Smokers	No. (%) Exsmokers	Total Subjects
			Hydrazine (HYD-6)		
High	14 (58.3)	24	8 (23.5)	19 (55.9)	34
Medium	14 (63.6)	22	1 (11.1)	6 (66.7)	9
Low/Unexp.	88 (57.1)	154	12 (23.0)	24 (46.2)	52
Total	116 (58.0)	200	21 (22.1)	49 (51.6)	95
			Asbestos (ASB-6)		
High	27 (84.4)	32	8 (30.8)	12 (46.2)	26
Medium	15 (57.7)	26	5 (29.4)	7 (41.2)	17
Low	43 (62.3)	69	2 (12.5)	8 (50.0)	16
Unexposed	389 (67.8)	619	95 (34.5)	91 (33.1)	275
Total	474 (63.5)	746	110 (33.0)	118 (35.3)	334

APPENDIX A: Use and Toxicology of Chemicals at Rocket-Engine Test Stands

The principal chemicals used at the rocket test stands were hydrazines (i.e., hydrazine, 1-methylhydrazine [MMH], 1,1-dimethylhydrazine [UDMH]), kerosene fuels (RP-1), asbestos, beryllium, chlorine, fluorine, hydrogen peroxide, isopropyl alcohol, nitric acid, nitrogen tetroxide (NTO), trichloroethylene (TCE), and 1,1,1-trichloroethane (TCA). There were other chemicals used at the test stands in considerably smaller quantities, and they are discussed in the UCLA industrial hygiene survey. Information on chemical use derives from industrial hygiene surveys conducted by UCLA students in July and August 1994, materials supplied by Boeing, and information collected from other sites where rocket engines were tested.

The purpose of the UCLA industrial hygiene survey was to identify current and past operations and processes conducted at the site. The secondary goal was to identify chemical usage at the test stands that may have constituted a hazard to employees. The industrial hygiene survey is available to interested persons.

More recently, in 1998, Boeing/Rocketdyne officials provided investigators additional information on chemical use patterns at the sites. They have also given investigators quantitative data on chemical use, although there is no quantitative data on personal exposure to hazardous chemicals.

This discussion will focus on those chemicals with evidence for chemical carcinogenicity. We do not have quantitative exposure data on exposure to these agents, but given the epidemiologic results it is important to review those chemicals which may have been present even if there is not direct evidence of exposure. The chemicals of principal concern are hydrazine, asbestos, beryllium and TCE. UDMH may contain impurities of dimethylnitrosamine (NDMA) and oxidation of UDMH and MMH may also result in production of NDMA and monomethylnitrosamine (NMA), both of which are considered chemical carcinogens.

Hydrazines

There is evidence that three hydrazines were used at the test stands: hydrazine, MMH, and UDMH. Records obtained by UCLA indicate that hydrazine was used from 1955 through 1977, UDMH from 1955 to 1970, and MMH from 1955 to the present. These represent primary use periods, and, while there may be exceptions, the data are likely to be reasonably accurate. Quantitative estimates of pressurants and propellants use is contained within a log supplied by Boeing. Rocketdyne/Boeing provided UCLA with some incident reports; there were reports of accidental releases of hydrazines, but there were limited estimates of worker exposure.

Hydrazine

Hydrazine is classified in Group 2B, a possible human carcinogen, based on inadequate evidence in humans and sufficient evidence in animals by the International Agency for Research on Cancer (IARC, 1974). The U.S. EPA classifies hydrazine as a probable human carcinogen

(Group B2), and the National Toxicology Program (NTP) Annual Report on Carcinogenesis considers hydrazine a substance that may reasonably be anticipated to be a carcinogen (U.S. EPA, 1984a; U.S. DHHS, 1994). The World Health Organization has concluded: "On the basis of the evidence of carcinogenicity in animals and positive results in short-term tests, it would be prudent to consider hydrazine to be a possible human carcinogen" (WHO, 1987a; 1987b).

Hydrazine induces unscheduled DNA synthesis in human cells in vitro, sister chromatid exchange, DNA strand breaks in rat hepatocytes, somatic mutations in Drosophila and chromosomal aberrations and mutations in plants. It was mutagenic to yeast and bacteria. Hydrazine was positive in five strains of bacteria in the Ames bioassay (IARC, 1974; WHO, 1987a; 1987b). Thus, there is a mechanistic basis and biological plausibility to assume hydrazine is carcinogenic to humans. Overall, this conclusion is reasonable for all the hydrazines described here. Information on the human carcinogenicity of hydrazine is inadequate according to IARC and U.S. EPA. This conclusion is based on a lack of human investigations rather than negative evidence.

There is extensive literature on the carcinogenicity of hydrazine in animals. Animal studies have demonstrated cancer of the liver, lung, and mammary tumors in mice. The routes of administration have included gavage, drinking water, inhalation, and intraperitoneal injection. Inhalation studies in mice, rats, hamsters, and dogs were conducted. Significantly increased incidences of tumors were reported for mice (lung), rats (nasal cavity), and hamsters (nasal cavity). The study duration was considered to be inadequate for dogs. Leukemias were also identified in mice exposed to hydrazine via intraperitoneal administration. Hydrazine exposure in drinking water also produced hepatocellular carcinomas in hamsters (IARC, 1974; WHO, 1987a; 1987b).

Monomethylhydrazine (MMH)

MMH is classified by the U.S. EPA (1993) as a probable carcinogen (Group B2) on the basis of animal studies. There is no evidence to date of carcinogenicity in humans. MMH is positive in the Ames assay for mutagenicity (Toth, 1972).

In a study conducted by Toth (1972), the administration of 0.01% methylhydrazine in the drinking water of 6-week-old randomly bred Swiss mice enhanced the development of lung tumors by shortening their latency period. In the MMH-treated mice, 12 females developed 17 lung tumors, all of which were identified as adenomas, with an incidence of 24%. The lung tumors had an average latency period of 51 weeks. In the male group, 11 mice developed 12 lung tumors, all of which were classified as adenomas, with an incidence of 22%. The average latency period for the tumors was also 51 weeks.

In 1973, Toth and Shimizu observed that the administration of 0.01% methylhydrazine in the drinking water to 6-week-old randomly bred Syrian Golden hamsters, for the remainder of their lifetime, gave rise to malignant histiocytomas of the liver and tumors of the cecum. While no malignant histiocytomas developed in the controls, 32% (16/49) of the females and 54%

(27/50) of the males were observed to have developed such lesions. In females, the incidence of tumors of the cecum was 18% (9/49) and 14% (7/50) in males, compared with 1% (1/99 F; 1/97 M) in the controls (Toth & Shimizu, 1973).

UDMH

UDMH is classified in Group 2B--possibly carcinogenic to humans--by IARC (1974), based on there being sufficient evidence for carcinogenicity in experimental animals. UDMH is classified as a substance that may reasonably be anticipated to be carcinogenic by the NTP (U.S. DHHS, 1994). The U.S. EPA (1984b) has classified UDMH as a probable carcinogen (group B2). Information on the carcinogenic effects of UDMH on humans is not available.

Gavage

Roe et al. (1967) report an increased incidence of pulmonary tumors as compared with the control group in 25 virgin Swiss mice given UDMH by gavage at 0.5 mg a day, five days each week for 40 weeks (test for difference: $0.5 > P > 0.2$).

Drinking Water

Administration of 0.01% UDMH in the drinking water of 6-week-old Syrian golden hamsters for the remainder of their lifetime gave rise to tumors of the cecum and blood vessels. While no vascular tumors developed in the controls, 4% (2/50) of the females and 28% (14/50) of the males were observed to have developed such lesions. In females, the incidence of tumors of the cecum was 20% (10/49) and 30% (15/50) in males, compared with 1% (1/100 F; 0/100 M) in the controls (Toth, 1977).

UDMH, when administered in the drinking water, induced a high incidence of angiosarcomas in various organs; and it induced tumors of the kidneys, lungs, and liver in mice of both sexes. In rats, the same route of administration induced liver carcinomas (U.S. EPA, 1984b).

This brief review indicates there is substantial evidence for the carcinogenicity in animals of the hydrazines used at Rocketdyne. Based on the chemical structures of the hydrazines and data from genotoxicity and animal studies, there is a clear biological basis to hypothesize that hydrazines are human carcinogens.

Nitrosodimethylamine (NDMA)

NDMA and nitrosomethylamine (NMA) are produced by the oxidation of UDMH and MMH (Urry et al, 1965; Stone, 1980; Loper, 1977; Carter et al., 1981; Lunn & Sansone, 1994). NDMA can result from vapor phase oxidation of UDMH; UDMH can be oxidized to NDMA in open air, but oxidation by NTO or other oxygenates may be another pathway for NDMA formation (ARB, personal communication). Formation and contamination from NDMA

occurred at Aerojet in Sacramento, California, and the NDMA contamination represents one of the ongoing issues at that Superfund site. Groundwater and surface water NDMA contamination occurred at Aerojet. From 1955 through 1961, at least 1,023,420 pounds of UDMH were used at Rocketdyne. After 1961, there was reduced use of UDMH, but there was some ongoing use until 1970. Environmental pollution by NDMA represents an area requiring further study although Rocketdyne/Boeing samples have apparently not detected NDMA recently.

An industrial hygiene professional, Mr. Cheng, at Edwards Air Force base in California informed us that when conducting air monitoring studies around rocket-engine test sites, he observed a high occurrence of NDMA in the air during the transport and transfer of UDMH fuels. This observation is supported by the summary of the industrial hygiene special study: "Evaluation of potential exposures, conducted at the hydrazine blending facility at the Rocky Mountain arsenal in Commerce City, Colorado." In that study, air samples for UDMH and hydrazine were below levels of analytical sensitivity, yet air samples for NDMA were above the regulatory limit. Two studies were obtained from the U.S. Air Force that reported results from industrial hygiene surveys of Titan II rockets for hydrazine, UDMH, and NDMA; and they demonstrated that measurable levels of NDMA were widespread. Fine and Rounbehler (1981) reported NDMA formation in the rocket-fuel industry. Given the above mentioned reports on the presence of NDMA at other rocket-testing sites, we believe there was a potential for exposure to NDMA at Rocketdyne during the transfer of rocket fuel propellants and testing of rockets.

NDMA is considered a probable carcinogen. It is classified as a probable carcinogen by the U.S. EPA. It is classified as a substance reasonably anticipated to be carcinogenic by the NTP. It is classified as a probable carcinogen by IARC (Group 2A) on the basis of sufficient evidence in animals.

Human Studies

In 1996, DeStefani et al. conducted a hospital-based case-control study in Uruguay in which the dietary intake of NDMA and its food sources was measured in 320 cases of lung cancer and in a control group of 320 patients afflicted with diseases not related to tobacco use or diet. NDMA displayed a marked dose-response pattern, after adjusting for total energy intake and tobacco smoking, with a 3-fold increase in risk for the higher category of intake. The risks were slightly more elevated for adenocarcinomas of the lung.

Animal Studies

Oral administration results in tumors of the liver (hepatocellular carcinomas and hemaniosarcomas), kidney, and lung. Administration via inhalation produces cancers of the lung, liver, and kidney in mice. Inhalation exposure to rats results in tumors of the lung, liver, kidney and nasal cavity. Tumors have resulted from exposure to NDMA in rabbits, guinea pigs, ducks, fish, hamsters, and newts. Tumors have resulted from different routes of administration in animal studies. Other tumor sites are the nervous system, bile duct and forestomach. NDMA is carcinogenic in all animal species tested. NDMA is highly genotoxic as well as being an animal

carcinogen. Ethanol administration enhances the carcinogenicity of NDMA in mice (Anderson et al., 1992). NDMA must be considered a compound of major significance where human exposure is likely to occur, based on the large number of publications (more than 2,000) demonstrating carcinogenic risk. The evidence for NDMA as a carcinogen has now been known for approximately 40 years.

UDMH was known to contain approximately 0.1% NDMA as an impurity, but exposure to workers may also occur if NDMA is formed from oxidation of the parent compound. Unfortunately, there was no quantitative estimation of NDMA at Rocketdyne and we have no evidence regarding worker exposure to the compound. However, NDMA is considered a potent carcinogen; for example, the TD_{50} (the dose producing tumors in 50% of test animals) is 0.124 mg/kg/day. The EPA unit risk estimate for inhalation is 1.4×10^{-2} $(ug/m^3)^{-1}$.

Nitrosomethylamine (NMA)

The nitrosation of secondary amines, e.g., UDMH, is widely recognized as producing relatively stable nitrosamines, whereas nitrosation of primary amines, e.g., MMH, leads to unstable nitrosamines that break down to alcohols. There is no published evidence for the formation of NMA from rocket testing that we were able to identify, but oxidation of MMH is a pathway to NMA. Huber and Lutz (1984a; 1984b) have investigated NMA formation and reaction with DNA and concluded NMA has a sufficiently long lifetime to react with DNA *in vitro*. Results of *in vivo* studies also indicated that nitrosamine has a sufficent lifetime to methylate DNA in the stomach and small intestine of rats following oral administration of methyl amine and nitrite.

A study by Hussain and Ehrenberg (1974) indicated the product of methyl amine and nitrite produces NMA and this nitrosamine is mutagenic. There are no carcinogenicity studies of NMA because of its short life. The data on mutagenicity and DNA adduct formation would lead to a prediction that this compound would be similar to other nitrosamines and would likely be carcinogenic.

Further research on nitrosamine formation from MMH oxidation at test sights is required In our judgement exposure to NMA is likely to have been small because of the instability of the compound, but we mention it to identify areas of uncertainty.

Hydrazine Nitrosation

Lambert and Shank (1988) have suggested that reaction of endogenous formaldehyde with hydrazine may result in the formation of a nitrosamine, which further reacts to form a formaldehyde hydrazone that is capable of methylating DNA. Methylation of DNA is considered a potentially carcinogenic pathway. The pathway proposed by Lambert and Shank requires formation of NMA; therefore, there are possible similarities between the carcinogenicity of hydrazine and MMH.

Summary

Workers at the test stands were likely exposed to 5 suspected hydrazine-related carcinogens: the three hydrazines and two products of oxidation, NDMA and NMA. Rocketdyne/Boeing has reported to UCLA that 355 soil samples from various chemical-handling locations at SSFL have been collected and analyzed for NDMA. They reported there have been no detects of NDMA in any sample. The date of this sampling was not given UCLA and we have seen no protocol to indicate the location and other details of the sampling. A RCRA Facility Investigation Work Plan Addendum for the Santa Susana Field Laboratory prepared by Ogden Environmental and Energy Services Co., Inc. dated September 1996 and obtained by a member of the Advisory Committee appears to indicate soil samples found concentrations of 40 and 20 ug/kg NDMA. We can not explain the variance between the data reported by Rocketdyne and this sampling report.

Rocketdyne/Boeing did report that NDMA has been detected at least once in 5 groundwater monitoring wells at SSFL. UCLA has not seen these data, nor do we have information about the date and locations of the sampling. Rocketdyne/Boeing reported that no NDMA has been detected since 1988 in four of the wells, and NDMA has not been detected in surface water at SSFL since a surface water monitoring program was begun in 1993. Thus, there is evidence for NDMA formation, but we have no quantitative information on employee exposure during the periods of high UDMH use prior to 1970. Additional sampling may be appropriate to rule out any environmental NDMA contamination.

Trichloroethylene

TCE Release Assessment at the Rocketdyne Facility

The probable major source of TCE exposure and contamination at the Rocketdyne facility resulted from the use of TCE as a rocket-engine cleaning agent. TCE was used in the cleaning operations of large and vernier (small) engines fueled by a propellant mixture of liquid oxygen (LOX) and kerosene (RP-1), and to clean engine components including thrust chamber components, turbo pumps, heat exchangers and gas generators. TCE was used as a utility solvent to clean up testing areas and tools as needed. For example, test personnel would use a 1/4-inch hose with spray nozzle to wash the turbo pump cell for approximately one minute. Kerosene burning engines required TCE flushing to remove residual hydrocarbon deposits and vapors left on the fuel jacket and in the LOX dome from previous tests or engine checkouts prior to ignition. These deposits and vapors are combustible and potentially explosive when exposed to LOX. Other fuels do not leave hydrocarbon residues and consequently did not require TCE flushing.

Prior to a planned test series, between each test and after the test series, large engines and thrust chamber components were flushed on the test stand with TCE. During the 1950s, testing personnel did not necessarily flush the domes after every engine test; on occasion, the surfaces of suspected areas would be wiped off with TCE impregnated rags, resulting in possible exposure by inhalation and dermal absorption. The vernier engines and other engine components were not

flushed or cleaned with TCE while mounted on the test stand. Instead, they were often taken to another facility, separate from the test stand, to be cleaned by hand with TCE-impregnated rags or small pressurized TCE spray systems, also resulting in possible exposure by inhalation or dermal absorption.

Prior to 1961, catch pans and recovery systems were not used to recover TCE. The TCE that did not evaporate after flushing operations was discharged from each test stand onto a concrete spillway that drained into unlined channels and then into unlined ponds. TCE recovery systems were introduced in 1961; however, it was not until the early 1970s that they uniformly achieved the minimum percent recovery allowed by environmental permits of 85%. The initial designs of the catch pans were left up to the individual test-stand engineers. The designs varied considerably in such aspects as depth of pan and size of base, resulting in considerable variation of TCE recovery due to evaporative losses and splashing. In addition, the initial materials used for the flexible drain hose were not very compatible with TCE; consequently, leaks and breaks in the hose would occur. Additional leaks occurred due to problems in TCE transfer pipes. During the 1970s, recovery systems improved; however, a 1977 picture of an Alfa test stand shows a TCE recovery catch pan leaning against a railing on the bottom platform.

Based on the uses described above, there appears to have been significant potential for employee exposure to TCE via inhalation and dermal exposure.

Carcinogenicity

The U.S. EPA has previously classified TCE as a probable human carcinogen (Group B2/C). EPA is re-evaluating the carcinogenicity of TCE at present. IARC considers TCE to be a probable human carcinogen (Group 2A). IARC last reviewed TCE in 1995. TCE is not classified by NTP.

Animal studies

Animal studies have reported increases in lung, liver, and testicular tumors via inhalation, one of the likely sources of exposure to employees at Santa Susana. TCE has been shown to cause cancer in mice and rats. The site of tumor induction varies with the route of administration of TCE and with species. An increase in lung, liver, and testicular tumors has been observed as a result of inhalation exposure to TCE, and an increase in liver tumors was observed as a result of exposure to TCE via gavage. The principle tumor site in mice are the liver and lung, while the principle tumor site in the male rat is the kidney. When administered orally, TCE induced liver tumors in mice. TCE elicits acute pulmonary cytotoxicity in mice, which involves Clara cells of the bronchioles.

Metabolites and Their Modes of Action

Absorption of TCE by inhalation, dermal, and oral exposure is very rapid. Once absorbed, TCE is readily metabolized by humans and animals to chloral hydrate (CHL),

trichloroacetic acid (TCA), dichloroacetic acid (DCA), and trichloroethanol (TCOH)--all known toxic substances. These metabolites are thought to be responsible for the cytotoxicity and/or carcinogenicity of TCE in the liver, kidney, and lung. TCA and DCA may play a major role in liver tumor formation in mice exposed to TCE.

Human Studies

The occurrence of specific cancers was increased, at least to a small extent, in each of the following 5 cohort studies; and liver cancer, in particular, was increased in four: German study (Henschler et al., 1995), NCI study (Spirtas et al., 1991), Swedish study (Axelson, et al., 1994), Finnish study (Anttila et al., 1995), and the Hughes Aircraft study (Morgan et al., 1998). Weiss (1996) has reviewed the issue of cancer in relation to occupational exposure to TCE.

Based on these studies, there is some evidence for cancers of the kidney, liver, biliary tract, and non-Hodgkins lymphoma in humans. Axelson et al. (1994) concluded there is no evidence that TCE is a human carcinogen. Weiss (1996) concluded that evidence for the cancers described is quite limited. Further research is necessary to study the effects of high exposures to TCE and to investigate cancers of the liver, kidney, and non-Hodgkins lymphoma. The finding of cancers of the liver in both human and animal studies suggests there is a biological basis for this cancer endpoint. There is no evidence to date for cancer of the lung from inhalation of TCE in humans.

Kerosene-based Fuels

As described above, TCE was used to remove residual hydrocarbon deposits and vapors left on the fuel jacket and in the LOX dome from previous tests or engine checkouts prior to ignition. The hydrocarbon deposits result from incomplete combustion of kersone-based fuels. This incomplete combustion of fuels may result in the formation of soots containing polycyclic aromatic hydrocarbons (PAHs). Dermal absorption of PAHs is now recognized as an important source of exposure to these chemical agents in other industries (Van Rooij et al., 1993a; 1993b).

PAH formation has been demonstrated from kerosene combustion, but these examples were under relatively low temperature conditions, e.g., kerosene heaters. We have not identified any literature demonstrating PAH formation from rocket testing of kerosene fuels. UCLA was able to obtain a report from an Advisory Committee member submitted to the Ventura County Air Pollution Control District for 1992. This report indicates a small amount of PAHs were released from the facility. Further investigation to rule out the hypothesis that worker exposure may have resulted from PAH contamination may be useful. We were not able to obtain information on this issue from other sites to determine if there is potential for inhalation or dermal uptake of PAHs.

Other PAH Exposures

In the mid-1970s, the bowl area was deactivated, but it was later reactivated in the late

1970s. During the interim period, the area was used for coal gasificiation and liquification. In 1976, coal hydroliquification was carried out. This process included placing of pulverized coal into a high pressure environment to produce aromatic and 2-ring PAH compounds. The liquids produced were then transferred to 55-gallon drums. Employees were exposed to the compounds principally during transfer of the aromatic hydrocarbons. Exposure would have occurred via both dermal contact and inhalation.

Rock coal was ground through a fine mesh in a pressurized system to obtain pulverized coal. Employees would have been exposed to particulate matter during this operation. These operations occurred between 1976 and 1981.

The control center building (B-900) was used to carry out a coal hydrogasification process from the mid-1970s to 1981. In this process, pulverized coal was fed into a pressurized system to produce methane gas. The coal was cooked for a longer period than in the coal hydroliquification process. In addition to methane, other hydrocarbons, including benzene, were likely produced, but we do not have information on the nature and amounts of their various side products. The heavy residues from these processes were further refined. Exposure to aromatic hydrocarbons and some PAHs may have occurred during these processes.

Asbestos

Asbestos is a known human carcinogen. Exposure to asbestos results in cancer of the lung, mesothelioma, and perhaps other sites. Asbestos was used at the Santa Susana Field for insulation and floor tiles. High-temperature asbestos wires and asbestos-wrapped lines were found at the Bravo, Atlas, Delta, Coca, and Bowl test stands. The same asbestos lines were located at APTF, Building 206, and STL-4. In these areas, workers (mostly with the job title of mechanic or technician) would repair torn lines and thermocouple cables with asbestos insulation around the test areas. UCLA industrial hygienists noted there were likely more buildings associated with asbestos use, principally as insulation. Exposure to asbestos would have occurred from cutting, removing, and installing asbestos materials.

A employee interviewed by a UCLA industrial hygienist is illustrative: She stated that she used to file asbestos containing material. She stated there were asbestos wires at the test stands and that they would break apart due to the high heat conditions. She was personally involved in cutting, removing, and installing of asbestos insulation.

UCLA was not able to obtain quantitative information on asbestos monitoring, which was required by the OSHA standard on asbestos, but it appears highly likely there was exposure to asbestos at the test stands by personnel involved in installation and repair of asbestos insulation.

Beryllium

UCLA industrial hygienists were informed by management that beryllium was used at the Happy Valley area from 1962 to 1967. Powdered beryllium was reported to have been mixed

with oxidizers for use in rocket propellants (B-917). Beryllium was burned as a solid propellant in a tank ventilated with HEPA filters and a water scrubber system. This work was conducted in a closed system to minimize employee exposure. The residue collected on the HEPA filters was gathered and disposed of by employees. Respirators were used to minimize exposure, and workers' clothes were removed on site and sealed in bags for cleaning. Showers were required every day during operating periods.

UCLA was not able to obtain monitoring data from this period and cannot estimate the degree of personal exposure that may have occurred to beryllium, but it is likely that some exposure may have occurred. We have obtained one incident report on beryllium which occurred in 1967 when a malfunction resulted in 0.87 pounds of beryllium being released. The report indicates there were no personal exposures and wipe tests indicated resultant contamination was within acceptable levels.

Beryllium and beryllium compounds are carcinogenic to humans according to IARC. The U.S. EPA considers beryllium a probable carcinogen (group B1). There is considerable evidence that the current occupational standard for beryllium is inadequate to prevent occupationally related beryllium lung disease and the U.S. Department of Energy (DOE) is currently developing a new occupational beryllium standard. Dr. Froines served on the Federal Advisory Committee on beryllium established by the Secretary of DOE to address health issues associated with workplace exposure to beryllium.

Control of beryllium exposure is very difficult, and the most advanced facilities in the world have difficulty keeping exposures below the current standard, even today when the hazards of beryllium are more widely recognized. UCLA is currently working closely with Los Alamos National Laboratory in the design and maintenance of a beryllium facility used in the production of nuclear weapons, and the control of beryllium exposure is a matter of concern. It is very unlikely that the same level of control would have occurred in the 1960s when the general level of sophistication and concern were more limited. We conclude there may have been exposure to beryllium during this period, but it is unclear of the magnitude and duration.

Conclusion

Over the period of this study, there may have been exposure to hydrazines, nitroso compounds, TCE, beryllium, and asbestos among test-stand personnel. There is toxicologic evidence for all of these compounds being capable of producing lung and/or other cancers. With the exception of TCE, all the compounds might be considered probable human lung carcinogens.

The lack of quantitative industrial hygiene information prevents the UCLA investigators from making estimates of actual employee exposures, but there is sufficient anecdotal evidence from interviews and records that exposures did occur to the chemicals described above.

APPENDIX B: Job Titles Used to Classify Probable Hydrazine Exposure of Workers, by Exposure Level

High Exposure Level

MECHANIC - CHIEF - ROCKETS
MECHANIC - ENGINE PROPULSION TEST
MECHANIC - ENGINE PROPULSION TEST SR
MECHANIC - ENGINE PROPULSION TESTER SR
MECHANIC - ENGINEERING PROPULSION TESTING
MECHANIC - ENGINEERING PROPULSION TESTING SR
MECHANIC - PROPULSION RESEARCH SR
MECHANIC - PROPULSION TEST
MECHANIC - RESEARCH
MECHANIC - ROCKET ENGINE
MECHANIC - ROCKET ENGINE COMPONENTS
MECHANIC - ROCKET FIELD
MECHANIC - ROCKET SR
MECHANIC - TEST
MECHANIC - TEST SR
MEMBER TECHNICAL STAFF - PROPULSION TESTER
PROPULSION TESTING - RESEARCH
TECHNICIAN - ENGINE TEST
TECHNICIAN - ENGINE TESTING
TECHNICIAN - ENGINEERING PROPULSION TESTING
TECHNICIAN - PROPULSION RESEARCH
TECHNICIAN - PROPULSION TEST
TECHNICIAN - PROPULSION TESTING

Medium Exposure Level

ENGINEER - FLIGHT TESTING SR
ENGINEER - RESEARCH
ENGINEER - RESEARCH SR
ENGINEER - TEST
ENGINEER - TEST SR
ENGINEERING SUPERVISOR (GROUP 1)
INSPECTOR - MECHANICAL TEST EQUIPMENT FINAL
INSPECTOR - PROPULSION
INSPECTOR - PROPULSION SR
INSPECTOR - PROPULSION TESTING
INSPECTOR - PROPULSION TESTING SR
INSPECTOR - RESEARCH AND DEVELOPMENT

INSPECTOR - RESEARCH P/T
INSPECTOR - RESEARCH P/T SR
INSPECTOR - ROCKET ENGINE TESTING SR
INSPECTOR - ROCKET ENGINES SR
INSTALLATION - ROCKET ENGINES - MECHANIC
INSTRUMENTATION - MECHANIC - RESEARCH
INSTRUMENTATION - PROPULSION TEST
INSTRUMENTATION MECHANIC - ENGINEERING DEVELOPMENT SR
INSTRUMENTATION MECHANIC - PROPULSION TESTING
INSTRUMENTATION MECHANIC - TESTING
INSTRUMENTATION MECHANIC - TESTING SR
INSTRUMENTATION TECHNICIAN - PROPULSION RESEARCH
INSTRUMENTATION TECHNICIAN - PROPULSION RESEARCH SR
MECHANIC - INSTRUMENTATION
MECHANIC - INSTRUMENTATION - ELECTRONICS
MECHANIC - INSTRUMENTATION - ELECTRONICS
MECHANIC - INSTRUMENTATION - PROP & FAC
MECHANIC - INSTRUMENTATION - PROPULSION TESTING
TESTER - ROCKET ENGINE MAJOR COMPONENTS
TESTER - ROCKET ENGINE MAJOR COMPONENTS SR

Low Exposure Level

A/S ENGINE TESTING DEVELOPMENT
ENGINEER - PROPULSION - MAJOR
ENGINEER - PROPULSION GROUP
FLIGHT TESTING ENGINE CHECKOUT INST
INSPECTOR - ENGINEERING TESTING
MECHANIC - ENGINE
MECHANIC - ENGINE FLIGHT TEST
MECHANIC - ENGINE FLIGHT TEST CHIEF
MECHANIC - ENGINE INSPECTION
MECHANIC - ENGINEERING CHIEF
PROPULSION SPECIALIST