A Case-Control Study of Kidney Cancer Among Petroleum Refinery Workers

January 2, 1990

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Abstract

We conducted a case-control study within a combined cohort of approximately 100,000 male refinery workers from five petroleum companies to evaluate the hypothesis of increased kidney cancer risk following exposure to hydrocarbons, especially those found in unleaded gasoline. A review of 18,323 death certificates identified 102 kidney cancer cases, to each of whom four controls were matched. We defined three major hydrocarbon categories: non-aromatic liquid gasoline distillates, aromatic hydrocarbons, and the more volatile hydrocarbons. For less intensive exposure assessment, we identified asbestos, lead, chlorinated solvents, nitrosamines, ionizing radiation, polynuclear aromatic hydrocarbons, and higher-boiling hydrocarbons. Work histories were found for 98 per cent of the cases and 94 per cent of the controls. Industrial hygienists assessed all jobs, an average of 15.7 per subject, by assigning semiquantitative ratings for the intensity and frequency of the exposures of primary interest and dichotomous ratings (present or absent) for the secondary exposures. Each exposure had either no association or a weak association with kidney cancer in these data. The estimated relative risk (RR) for any above refinery background exposure to non-aromatic liquid gasoline distillates was 1.0 (95 per cent confidence interval (CI) 0.5 - 1.9). Analysis of the longest job (average duration 9.2 years or 40 per cent of the work history) produced results less inconsistent with a relation between employment and kidney cancer. In comparison with a reference group composed of office workers, professionals and technicians, three groups appeared to be at increased risk: workers in receipt, storage and movements (RR = 2.5, 95 per cent CI 0.9 - 6.6); laborers (RR = 1.9, 95 per cent CI 1.0 - 3.9); and unit cleaners (RR = 2.3, 95 per cent CI 0.5 - 9.9).

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A Case-Control Study of Kidney Cancer Among Petroleum Refinery Workers

1. SUMMARY

Epidemiology Resources Inc. (ERI) conducted a case-control study of kidney cancer within a combined cohort of current and former refinery workers from five petroleum companies. The study was undertaken to evaluate the hypothesis of increased risk of human kidney cancer following exposure to hydrocarbons, especially the hydrocarbons found in unleaded gasoline. Male rats exposed to completely volatilized, unleaded gasoline have been shown to develop kidney cancers in a dose-related manner. Toxicologic research has linked this effect to a reversible inability of the male rat kidney to metabolize and eliminate branched alkanes with six or more carbon atoms (i.e., the C6+ isoalkanes or isoparaffins). The mechanism appears not to be genotoxic and seems to involve increased and sustained proliferation of the cells of the proximal renal tubule.

A review of over 18,000 death certificates identified 102 cases of kidney cancer in the combined cohort. Four controls were randomly selected for each case from computer files of the cohort rosters. The controls were matched to the cases by company, refinery location, date of birth, and "at risk status" (i.e., being alive and free of a diagnosis of kidney cancer at the time the case was diagnosed). Supplemental controls were selected for controls whose work histories could not be found. Work histories were obtained for 98% of the cases and 95% of all controls.

All entries on the work histories were abstracted and computerized for exposure rating. The exposure ratings were assigned by industrial hygienists, including a representative of ERI (L.L.) and one or more representatives of each company, with assistance from employees and retirees with long experience at the specific refinery locations.

The exposures of primary interest consisted of three categories of hydrocarbons, defined on the basis of their atmospheric distillation temperature ranges and chemical structure: (1) non-aromatic liquid gasoline distillates (NALGD), (2) aromatic hydrocarbons in the C6-C9 range (aromatics), and (3) more volatile hydrocarbons (volatiles). The industrial hygienists assigned semiquantitative ratings for the intensity and frequency of exposure to these hydrocarbon categories. Exposures of secondary interest were higher-boiling hydrocarbons, polynuclear aromatic hydrocarbons (PAH), asbestos, lead, chlorinated solvents, nitrosamines and ionizing radiation. The industrial hygienists rated these exposures simply as present or absent in each job.

The industrial hygienists assigned a confidence score to each of the exposure ratings to reflect their degree of certainty in their judgments. The lowest confidence score ("pure guesswork") was seldom used and the average scores for each exposure fell between the intermediate and highest levels of subjective confidence ("educated guess" and "reasonably sure"). An analysis of the consistency of exposure ratings

among refineries found adequate documentation for nearly all instances of apparent inconsistency in exposure ratings, as suggested by the assignment of different exposure ratings to jobs with the same codes for job title and refinery unit. This analysis suggested that it would have been inadequate to rely exclusively upon job title and unit codes for exposure assessment.

The cases and controls were compared with respect to ever having been exposed above refinery background levels and with respect to cumulative exposure to each of the primary and secondary exposures. The comparisons were made by estimating relative risks of kidney cancer (RR), with 95 per cent (statistical) confidence intervals (CI). An RR of 1.0 indicates no association and an RR greater than 1.0 indicates a positive association between exposure and disease.

RRs were computed for each employee's entire work history at these refineries and for specified periods of time prior to kidney cancer occurrence. All comparisons revealed either no association or weak associations between kidney cancer and refinery exposures. The weak associations were quite compatible with random error. The RR for any above-background exposure to the NALGD hydrocarbon category was 1.0 (95% CI 0.5 - 1.9).

These results are most consistent with the hypothesis of no effect on kidney cancer risk of the refinery exposures examined. The upper 95% confidence limits, a rough indication of the resolving power of this study, tended to be in the range of a 50% to a 150% increase in risk. It is possible that because much refinery work has historically been performed outdoors, exposures there were too low to produce a measurable increase in risk. Because high proportions of work histories were found for the cases and controls, bias from missing data is not a reasonable explanation for the absence of strong associations in this study. Bias toward the null RR value of 1.0 from nondifferential misclassification of exposure is always a possibility, but it is difficult to imagine major improvements that could have been made in the exposure assessment given the available resources. Confounding by unmeasured kidney cancer risk factors such as cigarette smoking and obesity cannot be dismissed, but should not have been sufficient to have masked a major effect.

Analysis of the longest job held by each case and control produced results less inconsistent with a relation between refinery employment and kidney cancer. Laborers (RR = 1.9), unit cleaners (RR = 2.3), and workers in receipt, storage and movements (RR = 2.5) appeared to be at greater risk when compared with a group composed of office workers, professionals and technicians. The laborers were among the most difficult groups for the assignment of hydrocarbon exposure ratings because of their diverse duties and non-specific work locations in the refineries. Unit cleaners are generally considered to experience some of the highest hydrocarbon exposures in refineries, but they were few in number in this study. Thus, the RR estimate for this group was imprecise (95% CI 0.5 - 9.9) in comparison with the estimates for laborers (95% CI 1.0 - 3.9) and workers in receipt, storage and movements (95% CI 0.9 - 6.6). The latter group of workers is of special interest because it includes employees, such as the "downstream" workers involved in the distribution and transport of finished petroleum products, who have had higher hydrocarbon exposures than those of refinery workers in general.

2. INTRODUCTION

This study was designed to examine the hypothesis that exposure to the hydrocarbons present in gasoline increases the risk of human kidney cancer. After a recent consideration of all available research, the International Agency for Research on Cancer (IARC 1989) described the evidence of carcinogenicity of gasoline as inadequate in humans and limited in laboratory animals. The existing information comes from two major sources: toxicologic studies of non-human mammalian species and epidemiologic studies of mortality among employees in the petroleum industry.

Male rats exposed by inhalation to wholly vaporized unleaded gasoline developed nephropathy and experienced a dose-related increase in kidney cancer incidence (MacFarland et al. 1984, Kitchen 1984). These effects did not occur among female rats or mice of either gender in this study. Further investigation strongly suggested that the branched alkanes (i.e., isoalkanes or isoparaffins) with six or more carbon atoms (C6+ isoalkanes) were the compounds responsible for the nephrotoxic effects (Health Effects Institute 1988). These hydrocarbons are apparently metabolized to derivatives capable of binding to a rat-specific urinary protein, $alpha_{2u}$ globulin, forming a complex that is not readily degraded by cellular enzymes. As a result, the protein-hydrocarbon complex tends to accumulate in the cells of the proximal tubule to an extent that may disrupt normal cellular function and cause the cells to die (Busey and Cockrell 1984, Phillips 1984, Halder et al. 1984, Trump et al. 1984). These reversible effects are not seen in the following species, which all lack $alpha_{2u}$ globulin: mice, dogs, guinea pigs, and monkeys (Craig 1983, Bruner 1984, Kuna and Ulrich 1984, MacNaughton and Uddin 1984).

It is hypothesized that the development of kidney tumors in gasoline-treated male rats is the result of a non-genotoxic mechanism involving increased and sustained proliferation of the tubular epithelium as it replaces the dying cells. Exposure of rat kidney cells to C6+ isoalkanes stimulates replicative DNA synthesis, but not unscheduled DNA synthesis (Loury and Butterworth 1986). Whereas unscheduled DNA synthesis indicates repair subsequent to genotoxic insult, replicative DNA synthesis is characteristic of proliferative response to injury or necrosis. Thus, it has been suggested that "unleaded gasoline has little, if any, ability to initiate tumorigenesis in the kidney, but rather, may promote the development of spontaneously initiated tumors by mechanisms related to cell turnover" (Loury and Butterworth 1986).

The hydrocarbon composition of the completely volatilized gasoline to which the rats were exposed was unlike the composition of the vapors encountered in most situations of human gasoline exposure. In particular, the C6+ isoalkanes were proportionately more abundant in the rat bioassay. These compounds make up 30 to 35 per cent of liquid gasoline, but only 10 per cent of gasoline vapor under ordinary circumstances (McDermott and Killiany 1978, Myers et al. 1975, Halder et al. 1986). Because most workplace and other monitoring to date has measured total hydrocarbon concentrations (Westberg and Lamb 1985), it is difficult if not impossible to assess human exposures to the C6+ isoalkanes quantitatively at the present time.

More than 20 epidemiologic studies have compared cancer death rates among petroleum company employees with rates in the general population (Savitz and Moure 1984, Carcinogen Assessment Group 1987, IARC 1989, Wong and Raabe 1989). A few of these studies reported slightly elevated mortality rate ratios for kidney cancer, but most of the estimates were at or below the null value of 1.0.

Several aspects of these studies limit their informativeness. By far the most important limitation is that hydrocarbon exposures were not assessed in most of the studies. In many of them, exposure assessment did not go beyond ascertaining that an individual had been employed by a petroleum company or in a refinery for a given length of time. This kind of exposure classification scheme will capture people with relatively high and prolonged exposures, but will group them together with sizable numbers of people whose exposures are minimal. The resulting bias could mask all but the most pronounced effects. An efficient solution to this problem would be to conduct a case-control study within each cohort (a so-called "nested" case-control study). The much smaller number of individuals in such a study would permit a detailed exposure assessment to be undertaken for each of them.

The second major limitation of the mortality follow-up studies of petroleum company employees is the rarity of kidney cancer. Even in groups of thousands of people followed for decades, few kidney cancer deaths will ordinarily occur and comparisons of rates will lack statistical precision. Possible remedies would be merely to wait as follow-up continues or to aggregate several study populations into a larger, combined cohort.

The third major limitation is that cancer induction time was ignored in many of the analyses (Wong and Raabe 1989). If an agent causes cancer, its role may occur early or late in the overall carcinogenic process. For instance, a genotoxic "initiator" would act at an early stage in comparison with a "promoter" or an agent that would enhance the growth of an existing tumor. For initiators, exposure close in time to the occurrence of disease would not be etiologically relevant, whereas such exposure would be important for tumor promoters and growth enhancers. Failure to allow for different hypothetical induction times constitutes an important form of exposure misclassification (Rothman 1981). As with the use of nonspecific indicators of the degree of exposure, lack of specificity with respect to the time when exposure was sustained will diminish the estimated magnitude of any real effect.

The present study was designed to reduce each of these limitations. By consolidating several cohorts of refinery workers, the study increases the number of cases and thereby enhances statistical precision. As a case-control study, it includes a manageable number of study subjects for the purpose of detailed exposure assessment. Finally, by assessing exposure within specified periods of time prior to kidney cancer occurrence, the study attempts to reduce the bias that can result when induction time is ignored.

3. METHODS

The study began with the aggregation of several cohorts of petroleum refinery workers into a combined cohort and, concurrently, with the development of an exposure rating system. Case-finding was then accomplished by a review of all death certificates that had been collected through the most recent date of mortality follow-up of each cohort. Controls were selected at random from the cohort rosters, within categories of matching factors. Copies of all available work histories for the cases and controls were then obtained and converted to machine-readable form. Semiquantitative exposure ratings were assigned to each job by industrial hygienists familiar with the specific refineries in which the cases and controls were employed. The resulting data were then checked for errors, edited, and subjected to statistical analysis.

3.1 Cohort Assembly

Cohorts of petroleum industry employees from 36 refinery locations (Divine et al. 1985, Hanis et al. 1985, Morgan and Wong 1984, Morgan and Wong 1985, Nelson 1985, Wen et al. 1983, Wong et al. 1986) were consolidated into a combined cohort (Table 1). All of the original studies were conducted or funded by the petroleum companies. The definition of the distinct cohorts is of necessity arbitrary. Some of the cohorts were combined by the original investigators after they had been studied separately.

TABLE 1

Characteristics of the Consolidated Cohorts

Cohort	Number of refinery locations	Follow-up period (inclusive dates)	Minimum employment duration criterion
A	10	January 1, 1970 - December 31, 1980	6 months
B	2	January 1, 1950 - December 31, 1980	1 year
C	1	January 1, 1937 - December 31, 1978	1 day
D	4	February 1, 1970 - December 31, 1977[a]	1 month
E	1	January 1, 1946 - December 31, 1978	1 year
F	1	January 1, 1947 - December 31, 1979	1 year
G	17	January 1, 1947 - December 31, 1977	5 years

[a] This follow-up period is for persons entering the cohort as active employees. Follow-up began on January 2, 1970 for persons entering the cohort as annuitants, all of whom were known to be alive on January 1, 1970.

Others were not previously combined, but were composed of employees of the same companies and had identical membership criteria and follow-up periods.

Two cohorts, not listed in Table 1, could not be included as originally planned. One had to be excluded because of a lack of sufficient company resources for participation in exposure assessment. The other could not be included because the company was unable to locate the needed work histories. An estimated total of only one or two cases would have been contributed by these comparatively small cohorts.

In the aggregate, the consolidated cohorts contained approximately 100,000 employees. The cohort members were followed for an average of 15 years, producing a total of about 1.5 million person-years of observation. Some of the cohorts contained women and petrochemical workers. These employees were excluded from the present study because not all cohorts contained them and they were comparatively small in number. The restriction to men made the study more pertinent to the male-specific effect of the C6+ isoalkanes in rats. The exclusion of petrochemical workers simplified the exposure assessment, which was designed to focus on gasoline hydrocarbons.

The follow-up periods in Table 1 indicate the earliest and latest possible dates of death in each study. We assumed that vital status follow-up of each cohort member did not begin until after he had achieved the minimum employment duration criterion established by the original investigators. For example, all members of cohort E were employed for at least one year during a period that began on January 1, 1945. Therefore, the earliest possible date of death in this study was January 1, 1946.

The follow-up periods for cohorts A and D began in 1970, considerably later than the others. Cohort A contributed younger person-time on average than any of the other cohorts because each member of cohort A had to be employed for at least one day after December 31, 1969. Cohort D included annuitants who were alive on January 1, 1970, as well as employees who worked for at least one month between January 1, 1970 and December 31, 1977.

3.2 Case Ascertainment

Although the simple term "kidney cancer" is used throughout this report, the specific disease of interest is primary renal cell carcinoma, which is also known as adenocarcinoma of the kidney or hypernephroma. Malignant neoplasms of the renal pelvis, ureter, urethra, and paraurethral glands were excluded for two reasons. First, most of the malignant tumors observed among the male rats experimentally exposed to gasoline were carcinomas of the renal parenchyma (Kitchen 1984, MacFarland et al.

1984). Second, in their histologic appearance and epidemiologic features, the excluded tumors resemble cancers of the urinary bladder much more closely than they resemble adenocarcinoma of the kidney (Morrison and Cole 1982).

Data from the Third National Cancer Survey (Percy et al. 1981) suggested that death certificates could be used to identify nearly all incident cases because the vast majority of kidney cancer patients die within a few years of diagnosis and the diagnosis is seldom missing from the death certificate. Of 930 death certificates listing "kidney cancer" (ICD-8 189.0 - 189.9) as the underlying cause of death, 865 were among individuals who had the same diagnosis made in a hospital. Thus, only 7% of the death certificates could be considered false positives with respect to kidney cancer as the underlying cause of death. Deaths attributed mistakenly to bladder cancer (ICD-8 188) were the single greatest source of error, accounting for 18 (28%) of the false positives. Extension of these results to kidney cancers mentioned elsewhere on the death certificate is not strictly appropriate. Overall, however, the proportion of false positives is likely to be less than 10%.

The inaccuracy of death certificates among the ICD-9 categories 189.0 - 189.9 is also likely to be unimportant. There are no published data on this question, but the entity defined in this report as "kidney cancer" (ICD-9 189.0) is so predominant within this category that false positive diagnoses of other cancers in the ICD-9 189 category must be considered rare occurrences. In 1970, for instance, only 266 (7%) of the 4,078 deaths coded as ICD-8 189 among males in the United States (all ages, all races) were assigned to subcategories other than 189.0 (National Center for Health Statistics 1974).

The foregoing information suggests that, in absolute terms and in comparison with other cancers, incident cases of kidney cancer may be ascertained reasonably well by the use of death certificate information. Steps required to go beyond the death certificate to obtain medical records, pathology and autopsy reports, and histologic specimens would include contacting the next of kin for permission; such steps were determined to be infeasible in this study. In any event, the proportion of cases for which any supplemental diagnostic information might be available is unknown and could well be quite low.

Given these considerations, it was concluded that reasonably valid data on the occurrence of kidney cancer among petroleum company employees could be obtained by a qualified, uniform review of death certificates for any mention of the disease. Thus, the goal of case ascertainment was to use all available information on the death certificates to come as close as possible to a study of kidney cancer incidence, as opposed to a study of mortality from kidney cancer.

One of us (M.S.) read the 18,323 collected death certificates to find any mention of kidney cancer, using a guide developed for this study by a nosologist with substantial experience in death certificate coding (Appendix A). During this review, every death certificate that appeared to identify a kidney cancer according to this definition and every certificate for which there was any question was photocopied. In addition, every fiftieth certificate was copied and interspersed with the certificates for the potential cases. The selected death certificates were then reviewed and coded by another experienced nosologist. Only the kidney cancers that were confirmed by this nosologist were included as cases in the study.

3.3 Control Selection

Because the study made use of previously assembled cohorts, control selection was straightforward. The participating companies provided computer files of cohort rosters that included the following data: race; vital status at the close of follow-up; and dates of birth, hire and termination of employment. A random sample of controls, within categories of matching factors, was drawn from the computerized cohort rosters. A ratio of four controls per case was determined to provide an acceptable level of statistical precision at an acceptable cost.

Cases and controls were matched by refinery location (and therefore by employer), year of birth (within decades), and "at-risk status." Matching by "at-risk status" simply means that each control had to be alive and free of a known diagnosis of kidney cancer at the estimated date of the case's diagnosis. The dates of diagnosis were estimated using age-specific kidney cancer survival data from the Third National Cancer Survey (Axtell et al. 1976).

Refinery location was used as a matching criterion primarily for practical purposes in the retrieval and coding of work histories. Matching by this variable also enhanced the comparability of exposure information and improved the statistical efficiency of controlling for geographically related determinants of kidney cancer, as well as for methodologic differences among the studies that might have exerted a confounding-like bias on the results.

If a control's work history could not be located, a supplemental control was selected from the remaining cohort members who met the same matching criteria. The objective of selecting the supplemental controls was to reduce the absolute number of controls with missing work histories. To avoid undue delay, only one set of supplemental controls was chosen.

3.4 Exposure Assessment

Exposure assessment began with the retrieval and abstraction of copies of original work history records. Concurrently, refinery exposures of primary and secondary importance were defined. Next, a semiquantitative system for rating each job with respect to each exposure was developed by industrial hygienists from ERI and the participating companies. Finally, the exposure rating system was implemented through a series of refinery site visits and a procedure for review and approval of the final ratings.

3.4.1 Work History Retrieval and Abstracting

Copies of original work history records were requested from the companies for all cases and controls. All entries on the work histories were transcribed verbatim onto a computer file according to the instructions in Appendix B. Each indication of a change of employment status, job title, department or work location was considered a work history entry, or "job.".

The computerized work history transcriptions from each refinery were arranged in two complementary ways. The first was a grouping into general job title categories ("stillmen," "pumpers," etc.). Within each category, the jobs for all cases and controls from a given refinery were listed in chronologic order. The jobs for each case and control tended to be scattered throughout this listing, which was printed directly onto the forms that were used to record the exposure ratings. The chronologic listing within general job title categories enabled historical changes and trends at each refinery to be reflected easily in the exposure ratings.

The second arrangement of jobs was a chronologic listing for each case and control, exactly as the information appeared on the original paper record. This listing was used as a secondary reference during exposure rating. For example, if a job title was missing for a particular job, the jobs before and after the one in question were used as a clue as to the nature of the employee's duties during the time period in question.

3.4.2 Exposure Categories

Refinery exposures were considered in two categories. The primary exposures were defined as major categories of hydrocarbons, with an emphasis on creating a category that would classify subjects with respect to exposure to the hydrocarbons present in gasoline. The secondary exposures were defined as other chemical and physical agents that might be encountered in refinery work and that have been hypothesized to be related to cancer in general or kidney cancer in particular.

Because gasoline is a complex mixture of several hundred hydrocarbons, the only feasible way to characterize refinery exposures to these compounds was by fairly broad categories. For meaningful connection to the information on the work histories, the principal consideration in devising the categories was to find some common property that would group the hydrocarbons in relation to refinery processes. The property that proved to be most useful from this standpoint was the hydrocarbon distillation temperature range at atmospheric pressure. This characteristic is intimately linked to the stages of petroleum refining, to volatility, and therefore to the potential for exposure by inhalation. An ancillary consideration was commonality of toxic properties, which in turn tend to be related to chemical structure. In this regard the aromatic hydrocarbons are frequently distinguished from other hydrocarbon categories.

Based upon these considerations, and in close consultation with the industrial hygienists on the API task force for this project, the primary hydrocarbon categories in Table 2 were developed. The category composed of the non-aromatic, liquid gasoline distillates (NALGD), with an approximate distillation range of 40 to 200 °C, was of principal interest because it contains the C6+ isoalkanes. The aromatic compounds, with a distillation range (approximately 80 to 142 °C) that falls within the NALGD range, warranted separate assessment on toxicologic and epidemiologic grounds, as well as from the standpoint of refinery processes. The third primary hydrocarbon category was formed by the more volatile hydrocarbons, which have an approximate distillation range of -42 to 40 °C. The volatiles present the greatest potential for inhalation exposure because they constitute approximately 75 per cent of gasoline vapor.

A review of the epidemiologic and toxicologic literature revealed that the secondary exposures shown in Table 3, each of which may occur in refinery operations, have been implicated to some degree in the etiology of cancer in general or kidney cancer in particular. The mounting evidence on occupational asbestos exposure and kidney cancer has recently been reviewed (Smith et al. 1989). Three separate studies (Blair et al. 1979, Katz and Jowett 1981, Duh and Asal 1984) have reported elevated kidney cancer mortality among laundry and dry-cleaning workers, who are exposed to a variety of chlorinated solvents. There have also been isolated reports of kidney cancer excesses in relation to the polynuclear aromatic hydrocarbons (PAH) present in coke oven emissions (Redmond et al. 1972). Some nitrosamines are potent carcinogens in rodents (Sebranek and Cassens 1973). Ionizing radiation, of course, is associated with a wide variety of cancers (Committee on the Biological Effects of Ionizing Radiation 1980). For completeness, the hydrocarbons in the atmospheric distillation range above the NALGD (approximately 200 to 400 °C) were added to the

TABLE 2

Primary Hydrocarbon Exposure Categories

Category	Approximate distillation range (°C)	Examples
Volatile hydrocarbons	-42 to +40	Alkanes: n-butane, isobutane, isopentane, n-pentane
Non-aromatic liquid gasoline distillates (NALGD)	+40 to +200	Alkanes: methyl pentanes, cyclopentane, dimethyl & trimethyl pentanes Alkenes: isobutylene, methyl butane
Aromatics (C6 - C9)	+80 to +142	Benzene, toluene, xylene

TABLE 3

Secondary Exposures

Secondary Exposures	Examples of Likely Job Titles or Activities
Lead	Painter Grease manufacture
Asbestos	Insulation worker Pipefitter Maintenance
Ionizing radiation	Radiographer Operator at catalyst unit with radiation density gauge
Chlorinated hydrocarbon solvents	Laboratory chemist Shop personnel
Polynuclear aromatic hydrocarbons (PAH)	Coke unit operator Thermal asphalt manufacture
Nitrosamines	Machine shop operator Using nitrite-containing metal working fluids
Higher boiling hydrocarbons	Stillman Unit cleaner

list of secondary exposures; these higher boiling hydrocarbons or middle distillates include heavy naphtha, kerosene and light gas oil.

3.4.3 Development of the Exposure Rating System

The exposure rating scheme for the primary exposures was more detailed than for the secondary exposures. For the secondary exposures, each job was simply assigned a dichotomous rating denoting the agent's presence or absence. For the primary hydrocarbon categories, each job was assigned two semiquantitative ratings, one for exposure intensity and another for exposure frequency.

The intensity rating represented, on a three-point scale, the highest exposure level that would be encountered at least once a month in a given job. The intensity rating of 1 corresponded to "refinery background," as would be experienced by a security guard or office worker. The intensity rating of 3 was intended to approximate the upper one-fourth of all historical exposures at the refinery, in the judgment of the industrial hygienists. All remaining jobs were assigned the intensity rating of 2.

The frequency ratings were also on a three-point scale. The frequency rating of 3 represented daily or constant exposure. The frequency rating of 2 was used for exposures that occurred on the order of once a week and the rating of 1 for exposures that occurred approximately once a month.

The intensity and frequency ratings were designed to be assigned in conjunction with each other to create distinct intensity-frequency combinations. Because the intensity rating for each job represented the highest exposure that occurred at least once a month, it was assumed that whenever a frequency rating of 1 (monthly) or 2 (weekly) was assigned to a job, all remaining time on that job was spent at the next-lowest intensity level. For example, the 3-2 combination of intensity and frequency ratings meant that a job involved exposure at the highest intensity level (3) about once a week (2) and at the intermediate intensity level (2) the remainder of the time. Under this system, the intensity rating of 1 (refinery background) was always accompanied by the frequency rating of 3, to represent the jobs in which above-background exposures never or rarely occurred.

A subjective confidence score was assigned to each primary and secondary exposure rating. The confidence score indicated the degree of certainty the industrial hygienists were willing to place in their collective judgments. The confidence score of 1 indicated the lowest degree of certainty, which the industrial hygienists were asked to characterize as "pure guesswork." The confidence score of 2 represented an intermediate degree of certainty, or an "educated guess." The highest confidence score of 3 was used to indicate that the industrial hygienists were "reasonably sure" about a particular rating decision.

Each job was also assigned codes to indicate the job title and refinery unit. These codes were based on our modification of an API coding system for refinery tasks and processes (Appendix D).

3.4.4 Implementation of the Exposure Rating System

The exposure rating decisions were made during site visits to the refineries or company headquarters, using the plan described in Appendix C. Because the work history information was arranged chronologically by job category on the rating sheets, identically worded entries within given periods of calendar time could be assigned identical ratings and the same job title and unit codes.

The following people were present at the exposure rating site visits: an industrial hygienist (L.L.) representing ERI, at least one additional representative from ERI, at least one industrial hygienist representing the participating company, and current and former long-term employees of the company. Only the industrial hygienists made the rating decisions and assigned the confidence scores. The long-term employees provided key information with respect to the particular refinery or refineries under consideration, especially information about historical operations. The ERI representatives recorded the ratings on clean coding sheets and took notes on the rationales the industrial hygienists gave for their exposure rating judgments. Other people, including epidemiologists from ERI and the participating companies, were occasionally present as observers.

For some refineries, the long-term employees or retirees were not present at the rating sessions but were consulted as needed by telephone. In either case, the availability of these persons proved to be invaluable. They were nearly always able to decipher the occasionally cryptic work history entries, to describe the activities of employees with vague or obscure job titles, and to identify important differences between identical or similar job titles that were held by persons who worked in different parts of the refinery.

Procedures were instituted to keep the industrial hygienists unaware of whether the work history entries came from cases or controls. The arrangement of entries by job category and time period on the coding sheets would have made it extremely difficult for any such knowledge to have been used in any event. The experienced refinery personnel were asked not to reveal the identities of individuals whose work history entries they recognized, as happened occasionally. (In one instance, a retiree pointed out that only one person in the entire history of a refinery had ever had a certain job title that appeared on one subject's work history.) One of the duties of the ERI note taker was to watch for occurrences of unmasked scoring. None was observed.

After the first two exposure rating site visits, the ERI industrial hygiene representative expressed a concern that the masking of case and control identities might have broken down. He had noted long periods of absence near the end of work records of some of the subjects and surmised that these were the work histories of kidney cancer patients who were away from work on sick leave. (Reasons for absences from work had not been transcribed from the paper records in an attempt to avoid this kind of problem.) The ERI industrial hygiene representative was asked to provide identification numbers of the subjects he suspected were cases. It turned out that all of the subjects he identified were actually controls. Until data collection was complete, he was told only that his observations "did not correlate" with case or control status.

Shortly after each exposure rating site visit, the rating sheets were sent to the company industrial hygiene representatives for concurrence. Questions and discrepancies were resolved by telephone. The final rating sheets were then signed by the company representatives and returned to ERI.

3.4.5 Analysis of Exposure Rating Consistency

We conducted an analysis of exposure rating consistency, the purpose of which was to identify and review selected inconsistencies among the primary hydrocarbon exposure ratings that were assigned to nominally similar jobs. Nominally similar jobs were defined on the basis of the assigned job title and unit codes. An apparent inconsistency was defined as the assignment of different intensity or frequency ratings to two or more jobs with the same job title and unit codes. Apparent inconsistencies were more extreme if they were between intensity or frequency ratings of 1 and 3, as opposed to between ratings of 1 and 2 or between ratings of 2 and 3.

A substantial number of apparent inconsistencies was expected because the purpose of the job-by-job rating system was to capture exposure information too specific to be reflected by the job title and unit codes themselves. Consequently, if the rating procedure had worked well, there would not be a high degree of consistency but rather a high degree of documentation for the apparent inconsistencies.

For the NALGD hydrocarbon category, 13 title-unit combinations, comprising 2,004 jobs (25 per cent of the total of 7,943 jobs that received ratings) had apparent inconsistencies that were sufficiently extreme and numerous to merit detailed review. These title-unit combinations included 54 per cent of all jobs to which the highest intensity rating of 3 was assigned and 33 per cent of all jobs receiving the intermediate intensity rating of 2. Similar numbers and proportions of jobs were selected for detailed review with respect to the ratings for volatiles and aromatics.

In nearly all instances of apparent scoring inconsistency, we were able to find a clearly stated rationale in the notes from the rating sessions. A few transcription and keypunch errors were detected. In the aggregate, the effect of these errors was negligible, as indicated by the small number of subjects involved (fewer than one per cent) and the short duration of the jobs in question (at most 15 months).

Our conclusion was that there was a high degree of documentation for apparent inconsistencies in exposure ratings and an acceptably low number of transcription and keypunching errors. It was clear from this analysis that sole reliance on job title and unit codes would have resulted in the loss of many details about refinery-specific factors that in the evident judgment of the industrial hygienists were important determinants of exposure. The fact that the rationale for an exposure rating decision was adequately documented does not imply that the rationale was a good one or that the decision was correct, of course. Responsibility for the adequacy of the rationales and the accuracy of the ratings lies ultimately with the participating company industrial hygienists, whose judgments were reflected in their approval of the final rating sheets.

3.4.6 Exposure Scaling

For each of the primary hydrocarbon categories, the industrial hygienists assigned the frequency rating of 1 (once a month) to fewer than 0.1 per cent of all jobs. Consequently, the intensity-frequency combinations 2-1 and 2-2 were combined for purposes of data analysis, as were the 3-1 and 3-2 intensity-frequency combinations. Five rank-ordered categories of combined intensity and frequency ratings resulted, as shown in Table 4.

A score was assigned to each of the five intensity-frequency rating categories so that measures of cumulative exposure could be computed. For the secondary exposures, the scores were simply 1 if the exposure was judged to be present and 0 if it was judged to be absent. For the primary exposures, three sets of scores were used for this purpose (Table 4). Set I, which was used in the main analyses, implied an equal difference in exposure from each intensity-frequency combination to the next in the rank ordering. Score sets II and III were used in ancillary analyses to test the sensitivity of the results to the assumption of linearity in set I. In set II, the incremental differences in actual exposure were assumed to be greater at the high end of the scale than at the low end. In score set III, the differences were assumed to be greater at the low end of the scale than at the high end.

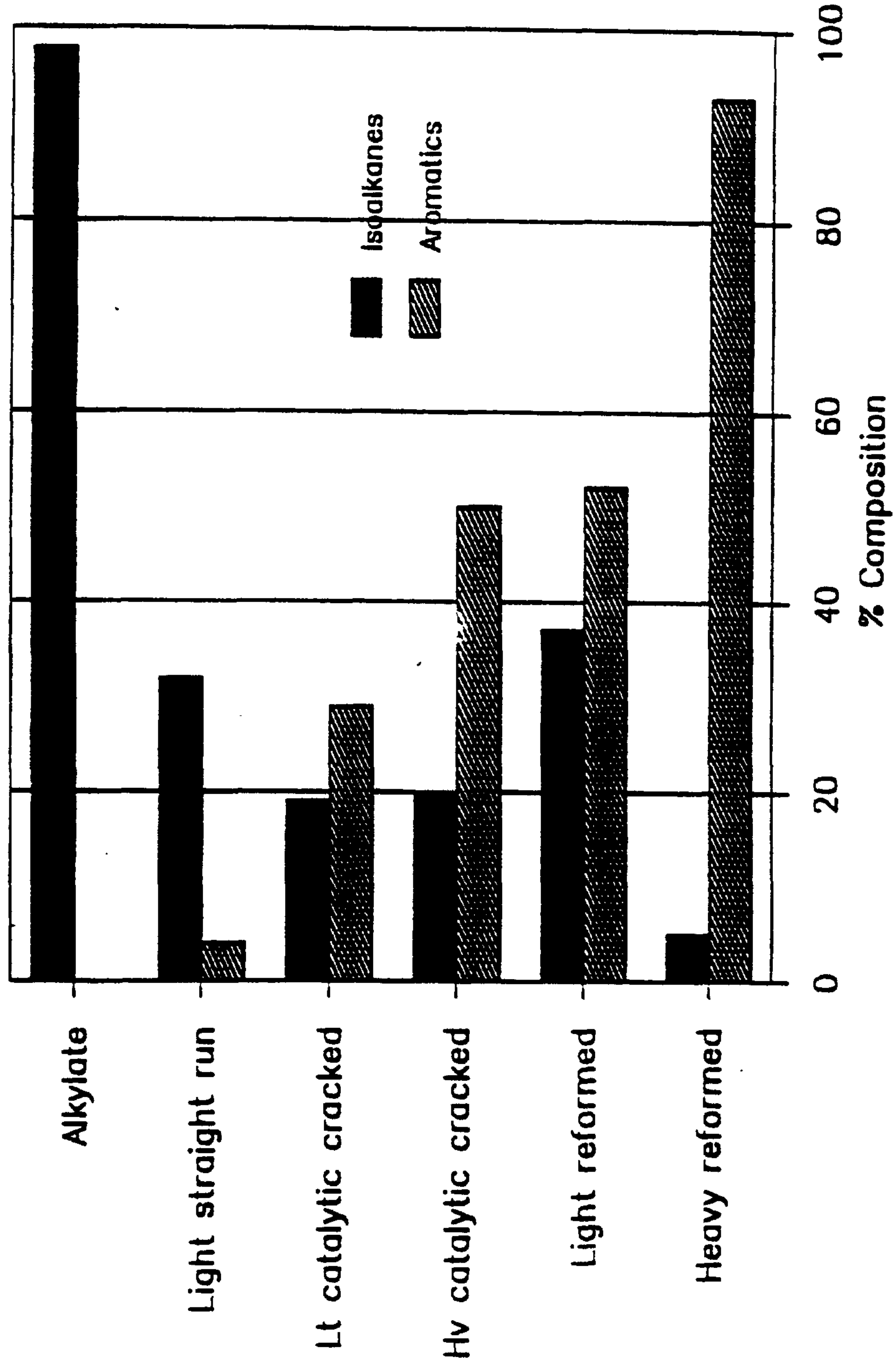
TABLE 4

Intensity-Frequency Ratings and Three Exposure Scoring Schemes for Primary Hydrocarbon Categories

Intensity-frequency ratings[a]	Description	Exposure score		
		I	II	III
1-3	Never above refinery background	0.00	0.00	0.00
2-1, 2-2	Intermediate intensity, less often than daily	0.25	0.10	0.40
2-3	Intermediate intensity, daily	0.50	0.30	0.70
3-1, 3-2	Highest intensity, less often than daily	0.75	0.60	0.90
3-3	Highest intensity, daily	1.00	1.00	1.00

[a] Intensity: 1, refinery background; 2, intermediate; 3, highest 25% in refinery history.
Frequency: 1, monthly; 2, weekly; 3, daily.

Figure 1
Isoalkane and Aromatic Content of
Typical Gasoline Blend Streams



Source: R.C. Russell, Exxon Co. USA, unpublished data

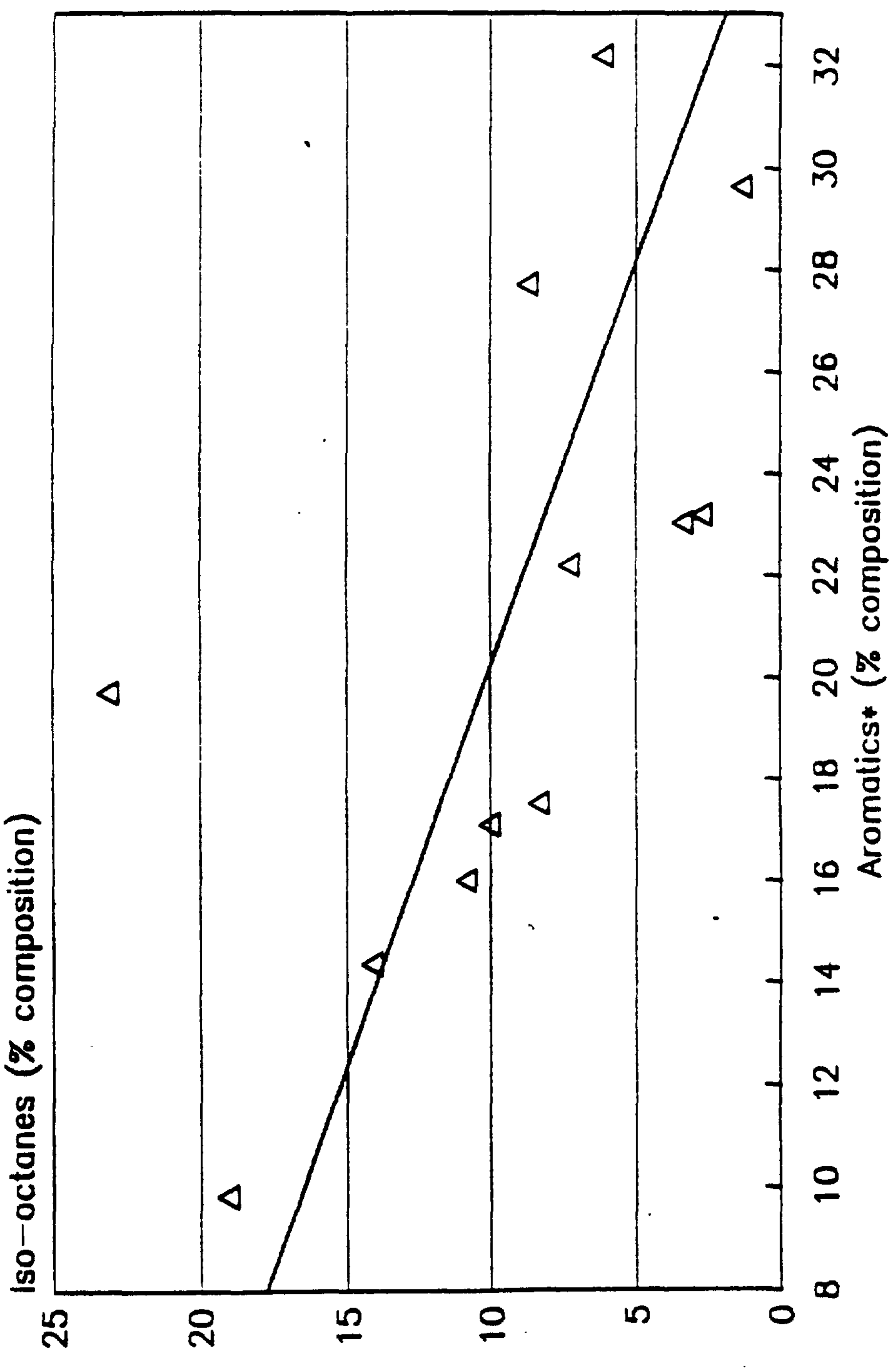
The cumulative-exposure computation for each job consisted of multiplying the score for that job by the length of time it was held. (Because the only possible job-specific ratings for the secondary exposures were 1 and 0, there was no difference between cumulative exposure and duration of exposure to these agents.) The score-years were then summed over all or a portion of the jobs in each person's work history. Summation over the whole work history produced a measure of cumulative exposure for the person's entire tenure of employment at the refinery. Because the highest exposure score in each set was 1.00, each person's highest possible number of score-years was equal to his duration of employment. A person could achieve this maximum of cumulative exposure if all his jobs throughout his work history were assigned the 3-3 combination of intensity and frequency ratings.

The score-years were also summed for each person within "windows" of hypothetical kidney cancer induction time. These summations were computed by considering only the jobs that each case and his matched controls held within specific periods of time prior to the estimated date of the case's diagnosis. The highest possible number of score-years an individual could accumulate within an exposure window was equal to the duration of that window (in years).

Consideration of exposure in time windows close to the date of diagnosis (e.g., within 10 years) corresponds to the postulation of relatively short hypothetical kidney cancer induction periods, as would be characteristic of causes that act relatively late in the carcinogenic process. Tumor promoters or growth enhancers would display an association with kidney cancer during these exposure windows. Consideration of exposure windows in the more distant past (e.g., 10-19 years or $\geq$20 years prior to diagnosis) corresponds to hypotheses involving causes of kidney cancer with comparatively long induction times, such as mutagenic initiators.

After the exposure rating system for this study was developed and implemented, API and Exxon Company USA provided information indicating an inverse association between the concentration of isoalkanes and the concentration of aromatic compounds in gasoline blend streams. Light straight run naphtha and alkylate naphtha are higher in isoalkanes and lower in aromatics, whereas other gasoline blend streams are higher in aromatics and lower in isoalkanes (Figure 1). Commercial unleaded gasoline also appears to exhibit a strong inverse association between its aromatic content and its C6+ isoalkane content (Figure 2). It is therefore possible that when the industrial hygienists assigned a lower rating for aromatics than for NALGD to a particular job, this combination of ratings might have reflected to some degree an NALGD exposure that was relatively rich in C6+ isoalkanes.

Figure 2 – Relation Between Iso-octane and Aromatic Content of 12 Samples of Commercial Unleaded Gasoline



*Benzene, ethylbenzene, toluene, xylene
From: Mobil Oil Corp. Mobil Methanol-to-Gasoline Process Environmental Rpt. 1982

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To take advantage of this possibility, we devised a scheme to weight each exposure score for NALGD in a manner that depended on the rating for aromatics that had been assigned to the same job. If exposure to aromatics was rated lower than NALGD exposure, according to the rank ordering in Table 4, we multiplied the NALGD exposure score by four-thirds (1.33); if the aromatics rating was equal to or greater than the NALGD rating, we multiplied the NALGD exposure score by two-thirds (0.67).

This weighting procedure had the effect of doubling the NALGD score for the jobs in which exposure to aromatics was rated as lower than NALGD exposure (with each exposure assessed on its own relative, historical scale). By increasing the NALGD scores for some jobs and decreasing the scores for the others, this weighting system produced distributions of weighted NALGD score-years that were similar to the unweighted distributions. Thus, the same cut-points could be used in categorical analyses of weighted and unweighted cumulative NALGD exposures. For instance, with the unweighted scores in set I as the base (Table 4), the weighted scores for NALGD were 0.00, 0.33, 0.67, 1.00 and 1.33 when aromatics were rated lower than NALGD. When aromatics were rated equal to or higher than NALGD, the weighted NALGD scores in set I were 0.00, 0.17, 0.33, 0.50 and 0.67.

In the analysis of weighted NALGD scores, the highest cumulative exposure (in score-years) for any individual was equal to 1.33 times his employment duration or 1.33 times the length of a particular exposure window. An individual could achieve this maximum if all of his jobs were assigned the 3-3 intensity-frequency combination for NALGD <u>and</u> the rating for aromatics was below 3-3 for each of these jobs.

4. DATA PREPARATION AND ANALYSIS

The work history data, including the exposure ratings and job title and unit codes, were keypunched directly from the exposure rating sheets. A second data file consisting of covariate data, such as date of birth and race, was created by extracting information from the cohort data files provided by the companies. A code for Hispanic and non-Hispanic ethnic background was derived from a U.S. Census Bureau list of Spanish surnames (see Appendix E) and added to the covariate file.

Verification and editing of the exposure rating and covariate files entailed an extensive series of computer-assisted checks for missing, out-of-range, and inconsistent values. Every cohort member's work history was checked to ensure that all work history entries were in sequential order with no gaps or duplicate entries, and that all start and stop dates were correct.

Estimates of relative risk (RR) were obtained by computing ratios of exposure-odds between cases and controls (original and supplemental controls combined). Conditional logistic regression analysis was used to control matched and unmatched covariates. RRs were estimated for ever having been exposed above refinery background levels over each employee's entire work history and within the specified periods of induction time. RRs were also estimated for cumulative exposure to each of the primary and secondary exposures. In addition, RRs were computed for the longest jobs held by the cases and controls, within categories based on the assigned job title and unit codes. The precision of the RR estimates was assessed by means of 95 per cent confidence intervals (CI). The statistical analyses were performed with the EPILOG software system. Tests of statistical significance were neither performed nor implied in any of the analyses.

5. RESULTS

5.1 Case Ascertainment

The death certificate review produced 104 tentatively identified kidney cancer cases among members of the consolidated cohort. The nosologist confirmed 102 (98 per cent) as cases according to the definition established for the study. None of the questionable or systematically sampled death certificates was classified as a case.

5.2 Work History Retrieval

Initial requests were made to the participating companies to provide 510 work histories, 102 for the cases and 408 for their matched controls. Of the total, 480 (94 per cent) were found. Work histories were missing for two cases (two per cent) and 21 controls (five per cent). The employment durations of these 23 subjects ranged from 4.7 years to 47.7 years, with a mean of 31.7 years. The low proportions of these missing records severely limit the degree of bias that could have been produced by completely missing work histories.

Missing work histories were most prevalent in cohort F, for which the employment records of one of the six cases and eight of the 24 original controls could not be found. Cohort F's company investigated the matter and determined that a record-maintenance practice could explain the missing work histories. During the time period of the cohort F study, the general policy at this refinery was to retain personnel folders for at least 10 years for a select group of individuals, including those who terminated employment or stopped receiving company benefits. At the time of record destruction, information on these employees was added to a roster. The cohort membership information on these employees was created from this roster. Because of the relatively small contribution of cohort F to the combined cohort, any bias in the overall study results from this disproportionately high prevalence of missing work histories would be minor.

Supplemental controls were selected for the 21 original controls whose work histories were not found. Supplemental controls were also selected for two controls within cohort A whose work histories were truncated. Thus, the study contained a total of 23 supplemental controls, 19 of whose work histories were found.

In total, work histories were available for 100 of 102 cases (98 per cent) and for 406 of 431 controls (94 per cent). Within the 506 work histories, we found a total of 683 "gaps." Nearly all of these gaps were time periods during which the employee was not working (e.g., he was laid off or on military or sick leave). At least one such gap was present in the work histories of 54 per cent of the cases and 48 per cent of the controls; the work histories of 10 per cent of the cases and 10 per cent of the controls had more than three gaps. The gaps ranged in length from one day to 23.1 years, with a mean of 1.1 years. Fifty-three per cent of the gaps were for periods of three months or less and 24 per cent were for periods longer than one year.

5.3 Exposure Ratings

Each missing work history and each gap within a work history was treated as a "job" and all exposure ratings were coded as unknown. Under this expanded definition of a "job," there were 710 jobs with unknown exposure ratings, or eight per cent of the total of 8,653 jobs.

Of the 7,943 jobs that received exposure ratings, roughly half were assigned to the background exposure category (intensity rating of 1) for each of the primary exposures (Table 5). The proportions ranged from 42% for NALGD to 52% for aromatics. The intermediate intensity rating of 2 was assigned much more often than the highest intensity rating of 3. For a given intensity rating, there was an almost equal division between frequency ratings of 2 (once a week) and 3 (daily) (Table 6). Thus, the industrial hygienists atrributed real distinctions in exposure to all three intensity ratings and, for above-background exposures, to the frequency ratings of 2 and 3.

As previously noted, the frequency rating of 1 (approximately once a month) was almost never assigned (Tables 5 and 6). The industrial hygienists assigned frequency ratings of 2 and 3 with a great deal of confidence, as more than 85 per cent of all

TABLE 5

Distribution of Jobs by Intensity and Frequency Ratings and Confidence Scores for Primary Hydrocarbon Exposures

Exposure	Characteristic	Rating	Jobs	Confidence Level Low	Intermediate	High
NALGD	Frequency	1	7	0	5	2
		2	2148	92	214	1842
		3	5788	10	186	5592
	Intensity	1	3362	5	144	3213
		2	3926	98	570	3258
		3	655	10	227	418
Aromatics	Frequency	1	7	0	.5	2
		2	1948	92	181	1675
		3	5988	12	230	5746
	Intensity	1	4108	6	161	3941
		2	3336	107	559	2670
		3	499	0	247	252
Volatiles	Frequency	1	7	0	5	2
		2	2072	92	172	1808
		3	5864	10	172	5682
	Intensity	1	3898	5	168	3725
		2	3673	98	509	3066
		3	372	10	171	191

[a] Frequency: 1, monthly; 2, weekly; 3, daily.
Intensity: 1, refinery background; 2, intermediate; 3, upper 25% in refinery history.

Abbreviation: NALGD, non-aromatic liquid gasoline distillates.

TABLE 6

Distribution of Jobs by Intensity-Frequency Rating Combinations and Mean Confidence Scores for Primary Hydrocarbon Exposures

	NALGD		Aromatics		Volatiles	
Intensity-frequency combination[a]	No. of jobs	Mean confidence score[b]	No. of jobs	Mean confidence score[b]	No. of jobs	Mean confidence score[b]
1-3	3362	5.9	4108	5.9	3898	5.9
2-1	4	5.5	4	5.5	7	4.9
2-2	1932	5.5	1726	5.5	1909	5.5
2-3	1990	5.8	1606	5.8	1757	5.8
3-1	3	4.0	3	4.0	0	NA
3-2	216	5.0	222	5.0	163	5.0
3-3	436	5.8	274	5.3	209	5.7
Unknown	710	NA	710	NA	710	NA

[a] Frequency: 1, monthly; 2, weekly; 3, daily.
Intensity: 1, refinery background; 2, intermediate; 3, upper 25% in refinery history.

[b] The minimum combined confidence score is 2 ("pure guesswork" for both the intensity and frequency ratings). The maximum is 6 ("reasonably sure" about both ratings).

Abbreviations: NALGD, Non-aromatic liquid gasoline distillates; NA, Not applicable.

such ratings received the highest confidence score. The confidence scores assigned to the intensity ratings, on the other hand, were inversely proportional to the intensity ratings themselves. Refinery background intensity ratings of 1 were assigned with an extremely high degree of confidence, with more than 95% of such ratings receiving the highest score. The industrial hygienists were somewhat less confident about assigning the intermediate intensity rating of 2 and considerably less confident when they assigned the highest intensity rating of 3.

As with the primary exposures, the secondary exposure ratings were seldom assigned with the lowest degree of confidence (Table 7). The industrial hygienists displayed a greater degree of confidence when they judged that a job did not involve above-background exposure to the secondary exposures than when they judged these exposures to have been present.

Nitrosamines were judged to have been present in only one job, which was held by a control (Table 7). Ionizing radiation was identified as an exposure in 24 jobs for five subjects, all of whom were controls. Because of their low frequency, these two exposures were not considered further in the analysis.

5.4 Case-Control Comparisons

A modest inverse association between Spanish surname and kidney cancer risk in our data (Table 8) (RR = 0.66, 95% CI 0.14 - 3.00) is consistent with incidence rates in New Mexico, where the rate among Hispanic males is also about two-thirds the rate among non-Hispanic males (Young et al. 1981). In contrast with national data, in which white and nonwhite males have roughly equal kidney cancer incidence rates (Morrison and Cole 1982), nonwhites appeared to be at somewhat higher risk than whites in this cohort (Table 8) (RR = 1.59, 95% CI 0.74 - 3.39).

The single refinery represented by cohort C contributed approximately one-fourth of the cases in the study, as did multi-refinery cohorts D and G (Table 8). The cases and controls had very similar distributions of employment duration (Table 8), age at termination of employment, year of termination, and age at the time of the case's diagnosis (Table 9). These similarities may be attributed to the matching of the cases and controls by decade of birth and "at-risk status" at the estimated date of diagnosis. The distributions of year of hire were also nearly identical. The cases tended to have been hired at older ages than the controls, however. The relative risk associated with being hired at age 20 or older was 1.48 (95% CI 0.71 - 3.09). In comparison with being hired under age 20, the relative risk for beginning employment at age 45 or older was 1.92 (95% CI 0.58 - 6.37).

TABLE 7

Distribution of Jobs by Exposure Ratings and Confidence Scores for the Secondary Exposures

Exposure	Rating	Jobs	Confidence Level		
			Low	Intermediate	High
Lead	Absent	5,255	2	235	5,018
	Present	2,688	1	1,136	1,551
Asbestos	Absent	2,939	0	192	2,747
	Present	5,005	3	1,416	3,586
Ionizing radiation	Absent	7,920	0	40	7,880
	Present	24	0	21	3
Chlorinated solvents	Absent	7,104	2	383	7,104
	Present	441	5	198	238
PAH	Absent	3,899	0	194	3,705
	Present	4,044	25	1,809	2,210
Nitrosamines	Absent	7,943	0	50	7,893
	Present	1	0	0	1
Higher boiling hydrocarbons	Absent	3,359	0	150	3,209
	Present	4,584	86	962	3,536

Abbreviation: PAH, polynuclear aromatic hydrocarbons.

TABLE 8

Distribution of Cases and Controls by Cohort, Duration of Employment, Race and Surname

Variable	Cases	Controls	Variable	Cases	Controls
Cohort			Duration of employment[a]		
A	9	39	< 10 years	14	65
B	10	40	10-19 years	13	41
C	25	100	20-29 years	23	122
D	23	103	30-39 years	43	158
E	4	16	≥ 40 years	9	45
F	6	32	Total	102	431
G	25	101			
Total	102	431			
Race			Surname		
Nonwhite	11	31	Spanish	2	12
White	88	388	Other	100	419
Unknown	3	12	Total	102	431
Total	102	431			

[a] The actual duration of employment or the time from hire to the case's estimated date of diagnosis, whichever was shorter.

TABLE 9

Distribution of Cases and Controls by Age at Hire, Termination and Diagnosis and Year of Hire, Termination and Diagnosis

Variable	Cases	Controls	Variable	Cases	Controls	Variable	Cases	Controls
Age at Hire			Age at Termination[a]			Age at Diagnosis[b]		
< 20	10	58	< 40	11	45	< 50	17	74
20-24	31	113	40-44	3	27	50-54	10	44
25-29	23	102	45-49	8	37	55-59	14	81
30-34	19	64	50-54	11	44	60-64	20	51
35-39	6	48	55-59	25	110	65-69	10	70
40-44	6	24	60-64	29	114	70-74	14	47
≥ 45	7	22	≥ 65	15	54	≥ 75	17	64
Total	102	431	Total	102	431	Total	102	431
Year of Hire			Year of Termination[a]			Year of Diagnosis		
< 1920	15	59	< 1950	13	51	< 1950	5	
1920-24	13	61	1950-54	11	43	1950-54	8	
1925-29	20	68	1955-59	24	71	1955-59	12	
1930-34	4	26	1960-64	17	72	1960-64	10	NA
1935-39	10	43	1965-69	8	46	1965-69	14	
1940-44	23	89	1970-74	18	64	1970-74	32	
≥ 1945	17	85	≥ 1975	11	84	≥ 1975	21	
Total	102	431	Total	102	431	Total	102	

[a] The actual date of termination or the case's estimated date of diagnosis, whichever was earlier

[b] For the controls, the age at the matched case's estimated date of diagnosis.

Abbreviation: NA, Not applicable.

When the cases and controls were compared with respect to ever having a job that the industrial hygienists rated as above refinery background, the relative risks for all primary and secondary exposures were close to the null value (Table 10). (The two cases and 25 controls with missing work histories have been omitted from Table 10 and all subsequent tables.)

The relative risk estimates remained close to the null value in categories of cumulative exposure to the primary hydrocarbon exposures, with the exception of a weak positive association in the lowest and highest cumulative exposure categories for aromatics (Table 11). The weighting of the NALGD ratings had a negligible impact on the results. The use of alternative exposure scores (see Table 4) exposure scores produced virtually identical results (Tables 12 and 13).

As with the primary hydrocarbon exposures, we found an absence of strong positive associations in relation to duration of exposure to the secondary exposures (Table 14). (There were too few cases and controls rated as exposed to chlorinated solvents to distinguish between 5-9 years and ≥ 10 years of exposure.)

Analysis within specified time periods prior to diagnosis produced no associations with either the primary (Table 15) or secondary exposures (Table 16) that were not readily compatible with random error in sampling variability, as reflected in the widths of the confidence intervals. For the primary exposures, we examined cumulative exposure and hypothetical induction time in conjunction with each other. For neither NALGD (Table 17), aromatics nor volatiles (Table 18) were any appreciably elevated relative risks evident.

We analyzed NALGD within categories of cohort, age at diagnosis, age at hire, and year at hire (Table 19). Within categories of these variables, the numbers of cases and controls who had never been in jobs rated as having above background exposure were too small to support a meaningful analysis. We consequently divided cumulative NALGD exposures at five score-years. Nonetheless, the confidence intervals for all the relative risk estimates are comparatively wide because each estimate is based on a relatively small number of subjects (Table 19).

We grouped cohorts A and D because of their previously noted methodologic similarity in beginning follow-up later in calendar time than the other cohorts (Table 1). Cohorts C and G were analyzed separately because they were the cohorts that provided the greatest numbers of cases. All other cohorts (B, E and F) were considered together as a group. There was a tendency toward positive associations between kidney cancer and NALGD exposure in cohorts A, D and C, and toward inverse associations in the remaining cohorts. An inverse association among the youngest cases (age < 55 at diagnosis) was balanced by a direct association in the

TABLE 10

Relative Risks for Any Above-Background Exposure to the Primary and Secondary Exposures

Exposure	Never Exposed Cases	Never Exposed Controls	Ever Exposed Cases	Ever Exposed Controls	Relative Risk[a]	95% CI
NALGD	13	53	87	353	1.00	0.51 - 1.94
Aromatics	20	96	80	310	0.95	0.50 - 1.80
Volatiles	15	59	85	347	1.31	0.72 - 2.39
Lead	28	109	72	297	0.93	0.57 - 1.54
Asbestos	15	49	85	357	0.76	0.40 - 1.44
Chlorinated solvents	88	344	12	62	0.69	0.32 - 1.50
PAH	24	76	76	330	0.69	0.40 - 1.21
Higher boiling hydrocarbons	14	55	86	351	0.95	0.49 - 1.84

[a] Controlling for the matching factors by conditional logistic regression.

Abbreviations: CI, confidence interval; NALGD, non-aromatic liquid gasoline distillates; PAH, polynuclear aromatic hydrocarbons

TABLE 11

Relative Risks within Categories of Cumulative Exposure to the Primary Exposures Using Score Set I[a]

Exposure	Group or measure	Never exposed	Score-years <5	Score-years 5-9	Score-years ≥10
NALGD, unweighted	Cases	13	41	22	24
	Controls	53	159	107	87
	RR[b]	1.00	1.03	0.83	1.08
	95% CI		0.51 - 2.08	0.38 - 1.83	0.50 - 2.33
NALGD, weighted	Cases	13	48	25	14
	Controls	53	204	87	62
	RR[b]	1.00	0.96	1.20	0.89
	95% CI		0.48 - 1.92	0.55 - 2.61	0.38 - 2.09
Aromatics	Cases	20	43	17	20
	Controls	95	145	93	73
	RR[b]	1.00	1.45	0.91	1.30
	95% CI		0.76 - 2.77	0.42 - 1.99	0.62 - 2.73
Volatiles	Cases	15	46	23	16
	Controls	59	185	95	67
	RR[b]	1.00	0.96	0.96	0.92
	95% CI		0.49 - 1.88	0.45 - 2.04	0.40 - 2.09

[a] See Table 4.
[b] Controlling for the matching factors by conditional logistic regression.

Abbreviations: NALGD, non-aromatic liquid gasoline distillates; RR, relative risk; CI, confidence interval.

TABLE 12

Relative Risks within Categories of Cumulative Exposure to the Primary Exposures Using Score Set II[a]

Exposure	Group or measure	Never exposed	Score-years <5	Score-years 5-9	Score-years ≥10
NALGD, unweighted	Cases	13	56	21	10
	Controls	53	249	68	36
	RR[b]	1.00	0.91	1.24	1.10
	95% CI		0.46 - 1.82	0.56 - 2.74	0.43 - 2.78
NALGD, weighted	Cases	13	64	17	6
	Controls	53	264	62	27
	RR[b]	1.00	0.99	1.10	0.88
	95% CI		0.50 - 1.95	0.48 - 2.54	0.30 - 2.62
Aromatics	Cases	20	57	16	7
	Controls	95	225	60	26
	RR[b]	1.00	1.27	1.33	1.30
	95% CI		0.68 - 2.39	0.61 - 2.91	0.48 - 3.51
Volatiles	Cases	15	64	16	5
	Controls	59	268	58	21
	RR[b]	1.00	0.92	1.08	0.90
	95% CI		0.48 - 1.78	0.48 - 2.43	0.28 - 2.82

[a] See Table 4.
[b] Controlling for the matching factors by conditional logistic regression.

Abbreviations: NALGD, non-aromatic liquid gasoline distillates; RR, relative risk; CI, confidence interval.

TABLE 13

Relative Risks within Categories of Cumulative Exposure to the Primary Exposures Using Score Set III[a]

Exposure	Group or measure	Never exposed	Score-years		
			<5	5-9	≥10
NALGD, unweighted	Cases	13	29	20	38
	Controls	53	132	68	153
	RR[b]	1.00	0.90	1.27	1.04
	95% CI		0.43 - 1.85	0.55 - 2.92	0.50 - 2.14
NALGD, weighted	Cases	13	34	27	26
	Controls	53	156	96	101
	RR[b]	1.00	0.89	1.21	1.04
	95% CI		0.43 - 1.81	0.55 - 2.64	0.49 - 2.21
Aromatics	Cases	20	31	19	30
	Controls	95	113	67	131
	RR[b]	1.00	1.36	1.49	1.15
	95% CI		0.70 - 2.63	0.68 - 3.26	0.57 - 2.30
Volatiles	Cases	15	35	19	31
	Controls	59	155	70	122
	RR[b]	1.00	0.87	1.09	1.01
	95% CI		0.44 - 1.74	0.49 - 2.43	0.49 - 2.07

[a] See Table 4.
[b] Controlling for the matching factors by conditional logistic regression.

Abbreviations: NALGD, non-aromatic liquid gasoline distillates; RR, relative risk; CI, confidence interval.

TABLE 14

Relative Risks within Categories of Duration of Exposure
to the Secondary Exposures

Exposure	Group or measure	Never exposed	Years of exposure		
			< 5	5-9	≥10
Lead	Cases	28	34	9	29
	Controls	109	157	32	108
	RR[a]	1.00	0.84	1.09	1.05
	95% CI		0.48 - 1.47	0.44 - 2.66	0.58 - 1.92
Asbestos	Cases	15	20	10	55
	Controls	49	94	36	227
	RR[a]	1.00	0.68	0.90	0.78
	95% CI		0.32 - 1.46	0.36 - 2.26	0.40 - 1.55
Chlorinated solvents	Cases	88	5	7[b]	
	Controls	344	39	23	NA
	RR[a]	1.00	0.44	1.09	
	95% CI		0.15 - 1.30	0.41 - 2.89	
PAH	Cases	24	26	12	38
	Controls	76	129	38	163
	RR[a]	1.00	0.60	0.94	0.72
	95% CI		0.31 - 1.16	0.39 - 1.35	0.39 - 1.35
Higher boiling hydrocarbons	Cases	14	17	12	57
	Controls	55	106	36	209
	RR[a]	1.00	0.60	1.33	1.13
	95% CI		0.27 - 1.35	0.54 - 3.24	0.56 - 2.25

[a] Controlling for the matching factors by conditional logistic regression.

[b] ≥5 years.

Abbreviations: RR, relative risk; CI, confidence interval; NA, not applicable; PAH, polynuclear aromatic hydrocarbons.

TABLE 15

Relative Risks for Any Above-Background Exposure to the Primary Exposures within Time Periods Prior to Diagnosis

Exposure	Years prior to diagnosis	Never exposed Cases	Never exposed Controls	Ever exposed Cases	Ever exposed Controls	Relative risk[a]	95% CI
NALGD	< 10	51	220	49	186	1.25	0.74 - 2.11
	10-19	39	174	61	232	1.22	0.75 - 1.97
	≥20	33	107	67	299	0.64	0.36 - 1.11
Aromatics	< 10	61	235	39	171	0.89	0.53 - 1.49
	10-19	47	191	53	215	1.03	0.64 - 1.65
	≥20	38	142	62	264	0.82	0.48 - 1.42
Volatiles	< 10	55	233	45	173	1.20	0.72 - 2.00
	10-19	45	190	55	216	1.06	0.69 - 1.79
	≥20	35	112	65	294	0.63	0.37 - 1.07

[a] Controlling for the matching factors by conditional logistic regression.

Abbreviations: CI, confidence interval; NALGD, non-aromatic liquid gasoline distillates.

TABLE 16

Relative Risks for Any Above-Background Exposure to the Secondary Exposures within Time Periods Prior to Diagnosis

Exposure	Years prior to diagnosis	Never exposed		Ever exposed		Relative risk[a]	95% CI
		Cases	Controls	Cases	Controls		
Lead	< 10	70	301	30	105	1.31	0.77 - 2.23
	10-19	67	258	33	148	0.85	0.53 - 1.38
	≥20	45	153	55	253	0.68	0.42 - 1.11
Asbestos	< 10	52	206	48	200	0.97	0.58 - 1.62
	10-19	39	174	61	232	1.22	0.75 - 2.00
	≥20	37	99	63	307	0.44	0.26 - 0.76
Chlorinated solvents	< 10	94	382	6	24	1.02	0.38 - 2.71
	10-19	94	375	6	31	0.72	0.27 - 1.91
	≥20	92	362	8	44	0.65	0.27 - 1.59
PAH	< 10	68	255	32	151	0.80	0.47 - 1.34
	10-19	53	221	47	185	1.09	0.68 - 1.77
	≥20	42	130	58	276	0.54	0.32 - 0.91
Higher boiling hydrocarbons	< 10	50	224	50	182	1.37	0.82 - 2.30
	10-19	39	175	61	231	1.22	0.75 - 1.98
	≥20	34	105	66	301	0.57	0.32 - 1.00

[a] Controlling for the matching factors by conditional logistic regression.

Abbreviations: CI, confidence interval; PAH, polynuclear aromatic hydrocarbons

TABLE 17

Relative Risks for Non-Aromatic Liquid Gasoline Distillates within Categories of Cumulative Exposure and Time Prior to Diagnosis

Years prior to diagnosis	Score-years	Cases	Controls	RR[a]	95% CI
Unweighted NALGD					
< 10	0	51	220	1.00	
	< 3	34	121	1.35	0.76 - 2.40
	≥ 3	15	65	1.06	0.51 - 2.20
10-19	0	39	174	1.00	
	< 3	41	142	1.38	0.81 - 2.36
	≥ 3	20	90	0.99	0.53 - 1.86
≥ 20	0	33	107	1.00	
	< 3	30	163	0.53	0.28 - 0.99
	≥ 3	37	136	0.80	0.42 - 1.52
Weighted NALGD					
< 10	0	51	220	1.00	
	< 3	35	134	1.25	0.71 - 2.21
	≥ 3	14	52	1.24	0.59 - 2.63
10-19	0	39	174	1.00	
	< 3	42	159	1.24	0.73 - 2.10
	≥ 3	19	73	1.18	0.62 - 2.24
≥ 20	0	33	107	1.00	
	< 3	37	195	0.55	0.30 - 1.00
	≥ 3	30	104	0.82	0.42 - 1.59

[a] Controlling for the matching factors by conditional logistic regression.

Abbreviations: RR, relative risk; CI, confidence interval; NALGD, non-aromatic liquid gasoline distillates.

TABLE 18

Relative Risks for Aromatics and Volatiles within Categories of Cumulative Exposure and Time Prior to Diagnosis

Years prior to diagnosis	Score-years	Cases	Controls	RR[a]	95% CI
Aromatics					
< 10	0	61	235	1.00	
	< 3	28	115	0.96	0.54 - 1.70
	≥ 3	11	56	0.76	0.35 - 1.64
10-19	0	47	191	1.00	
	< 3	35	136	1.09	0.64 - 1.87
	≥ 3	18	79	0.93	0.49 - 1.75
≥ 20	0	38	142	1.00	
	< 3	29	150	0.67	0.36 - 1.25
	≥ 3	33	114	1.06	0.56 - 2.01
Volatiles					
< 10	0	55	233	1.00	
	< 3	31	123	1.15	0.65 - 2.02
	≥ 3	14	50	1.32	0.62 - 2.81
10-19	0	45	190	1.00	
	< 3	39	140	1.25	0.74 - 2.13
	≥ 3	16	76	0.89	0.46 - 1.73
≥ 20	0	35	112	1.00	
	< 3	37	180	0.60	0.34 - 1.05
	≥ 3	28	114	0.71	0.37 - 1.37

[a] Controlling for the matching factors by conditional logistic regression.

Abbreviations: RR, relative risk; CI, confidence interval.

Table 19

Relative Risks for Cumulative Exposure to Non-Aromatic Liquid Gasoline Distillates (Unweighted Scores) Within Categories of Cohort, Age at Diagnosis, Age at Hire and Year of Hire

	< 5 score-years		≥ 5 score-years			
Variable	Cases	Controls	Cases	Controls	RR[a]	95% CI
Cohort						
A, D	12	63	19	65	1.46	0.57 - 3.73
C	15	68	10	32	1.46	0.66 - 3.21
G	17	52	8	48	0.46	0.17 - 1.28
B, E, F	10	29	9	49	0.56	0.20 - 1.54
Age at diagnosis[b]						
< 55	22	75	5	41	0.46	0.16 - 1.37
55 - 64	11	61	22	69	2.04	0.82 - 5.07
65 - 74	13	49	10	57	0.72	0.27 - 1.94
≥ 75	8	27	9	27	1.04	0.34 - 3.24
Age at Hire						
< 25	23	85	16	78	0.75	0.33 - 1.70
25 - 29	11	46	12	55	1.14	0.33 - 3.89
30 - 34	10	23	9	34	1.00	0.06 -15.99
≥ 35	10	58	9	27	2.50	0.72 - 8.72
Year of Hire						
< 1925	13	44	14	64	1.04	0.38 - 2.84
1925 - 34	12	35	11	52	1.43	0.44 - 4.65
1935 - 44	18	79	15	48	1.29	0.51 - 3.29
≥ 1945	11	54	6	30	0.61	0.14 - 2.58

[a] Controlling for the matching factors by conditional logistic regression.

[b] For controls, age at the estimated date of the matched case's diagnosis.

Abbreviations: RR, relative risk; CI, confidence interval.

next age group (55-64). There appeared to be a positive association among cohort members who were relatively old at hire ($\geq$35 years). No strong associations were evident in categories of year of hire.

For the analysis of job titles and refinery units, we focused on the longest job held by each case and control. These jobs were held for a mean of 9.2 years, or 40 per cent of each subject's total duration of employment. On average, the longest job was the twelfth job on the work history. This job began an average of 11 years after the date of hire and ended an average of 13 years prior to termination of employment (or the estimated date of the matched case's diagnosis, whichever came first).

We grouped the job title and unit codes (Appendix D) into categories for this analysis. There proved to be too few subjects in some highly specific categories of interest to permit a meaningful analysis. For instance, only one subject's longest job was specifically identified as being in an alkylation unit (unit codes 0700 - 0900) and only one subject's longest job was in an aromatics recovery unit (unit code 1700). Thus, we grouped the longest jobs of all 100 cases and 406 controls for whom work histories were available into eight general categories (Table 20).

For the reference job title and unit category, we compiled all the jobs of office workers and professional and technical staff. This category consisted of all subjects whose longest job was in an office or non-field unit (unit code 2700), or in any of the following job titles: administration and supervision (code 10), professional (code 11) or technical (code 12) field services, janitor (code 13), security (code 14), fire fighter (code 15), first aid or medical (code 17), or professional (code 51) or technical (code 52) laboratory staff.

Next, we created a category composed of workers in receipt, storage and movements (unit codes 2900-2963), excluding those who had already been placed in the administrative and services category. Monitoring data indicate that some jobs in these units, such as jobs in the transport and distribution of finished petroleum products, tend to entail higher hydrocarbon exposures than jobs in refining processes (Wen et al. 1984, IARC 1989, Rappaport et al. 1985). The jobs in this category for the cases and controls in the study consisted of jobs on pumping units (unit codes 2910-2913), on tank farms (codes 2920-2923), in wharf operations connected with water transport (codes 2940-2943), in truck and rail transport (codes 2950-2952), and in pipeline transport (codes 2960-2963). Nearly all of the cases' and controls' jobs in this category were specifically identified as involving the distribution, transport and movement of petroleum products, as opposed to the receipt and movement of crude oil.

The remaining categories were constructed by selecting common job titles with unit codes other than those that made up the previously defined categories (Table 20). The most general categories were laborers and yard workers (job title codes 24 and 47), and operators (codes 21-23). The maintenance and maintenance crafts category was

Table 20

Job Title and Unit Categories

Category	Job title codes[a]		Unit codes[a]
Administration and services	10-15, 17, 51, 52	OR	2700
Receipt, storage and movements	Any other than 10-15, 17, 51, 52	AND	2900-2963
Laborer	24, 47	AND	Any other than 2700, 2900-2963
Operator	21-23	AND	Any other than 2700, 2900-2963
Pipefitter	42	AND	Any other than 2700, 2900-2963
Machinist	43	AND	Any other than 2700, 2900-2963
Maintenance	3, 30-41, 44-46	AND	Any other than 2700, 2900-2963
Unit Cleaner	48	AND	Any other than 2700, 2900-2963

[a] Job titles and units are listed in Appendix D

diverse and included sandblasters (job title code 03), carpenters (code 31), masons (code 32), painters (code 33), insulators (code 36), electricians and instrument men (codes 37-39), boilermakers (code 40), welders (code 41), mobile equipment operators (code 44), and lead burners (code 46). Two job title codes from the maintenance crafts category were numerous enough for separate analysis: pipefitters (title code 42) and machinists and blacksmiths (code 43). Finally, we created a category for relatively small number of subjects whose longest jobs were as unit cleaners (code 48). In the exposure rating sessions, the industrial hygienists repeatedly singled out unit cleaners for their particularly high hydrocarbon exposures. The small numbers of cases and controls within categories precluded analysis by duration of the longest-held jobs.

Compared with employees whose longest jobs were in administration and services, operators and maintenance workers did not differ appreciably in their kidney cancer risk from employees in administration and services (Table 21). Machinists and pipefitters appeared to be at lower risk of kidney cancer. Receipt, storage and movements workers, laborers and unit cleaners appeared to be at increased risk. Because of the small numbers involved, the estimated relative risk for unit cleaners was much less statistically stable (as indicated by its much wider confidence interval) than the others. The laborers and yard workers, with a relative risk of 1.9, were for the most part assigned the most general unit codes (e.g., code 2500, "multi-process to plant-wide"). The longest jobs of the receipt, storage and movements workers (relative risk of 2.5) were in the following specified units: receipt, storage and movements, unspecified (unit code 2900, two cases and five controls); pump (code 2910, two cases and three controls); tank farms (code 2920, one case and one control); water transport (wharf) (code 2940, two cases and one control); truck and rail transport (code 2950, two cases and three controls); and pipeline transport (code 2960, no cases and two controls).

6. CONCLUSION

The results of the analysis of exposure ratings are most consistent with the hypothesis of no effect, or an effect too small to be measured with precision. The upper limits of the 95 per cent confidence intervals, which for many of the relative risk estimates were in the range of 1.5 to 2.5, give an indication of the effective size of this study.

Toxicologic studies indicate that the carcinogenicity of unleaded gasoline in male rats results from a non-genotoxic mechanism of tumor promotion due to chronic, reversible renal toxicity from long-term exposure to the C6+ isoalkanes and the consequent proliferation of the cells of the proximal renal tubule. If the same mechanism were operating in humans, one would expect to find positive associations

Table 21

Relative Risks for Longest Jobs Held

Category	Cases	Controls	RR[a]	95% CI
Administration and services	23	97	1.00	
Receipt, storage and movements	9	15	2.49	0.95 - 6.56
Laborer	24	53	1.94	0.96 - 3.92
Operator	17	90	0.73	0.36 - 1.48
Pipefitter	4	49	0.33	0.10 - 1.05
Machinist	3	21	0.53	0.13 - 2.13
Maintenance	17	76	0.94	0.46 - 1.92
Unit Cleaner	3	5	2.28	0.53 - 9.93

[a] Controlling for the matching factors by conditional logistic regression

Abbreviations: RR, relative risk; CI, confidence interval between NALGD exposure and kidney cancer risk after among older employees, after long-term exposure, and in relation to exposures that occurred relatively close in time to diagnosis. To the contrary, strong associations were not present in this study in the highest categories of cumulative exposure, in exposure periods close in time to the kidney cancer occurrence, or in the highest categories of age at diagnosis.

There was a positive association between NALGD exposure among employees in the highest category of age at hire (≥35 years of age). The exposures of these employees would have been sustained on average at older ages than the exposures of the other cases and controls. This is the result in the analysis of exposure ratings that is perhaps most consistent with a causal interpretation with respect to NALGD. In the light of the null or near-null results overall and within categories of cumulative exposure, time prior to diagnosis, and age at diagnosis, however, this result cannot be accorded a great deal of interpretive weight.

Misclassification of exposure is worthy of consideration as a possible explanation for the absence of strong positive associations between kidney cancer and the exposure ratings in this study. It proved to be impossible for the industrial hygienists to assess exposures to the specific class of compounds responsible for the preneoplastic effects in the kidneys of male rats, the C6+ isoalkanes. Moreover, no refinery job entails exposure to this class of hydrocarbons alone. The closest the industrial hygienists could come was NALGD category, which includes many other hydrocarbons in addition to the C6+ isoalkanes. The exposure assessment was neither quantitative nor based directly on measurements of hydrocarbons in the refinery environment. Instead, it was based on the experience and judgment of industrial hygienists, aided by information from highly experienced refinery personnel. Thus, a substantial potential existed for exposure misclassification.

Because the industrial hygienists were unaware of the case or control status of the jobs they were rating, the frequency of classification errors should not have differed between the cases and controls. Consequently, bias in the relative risk estimates from exposure misclassification would be expected to be toward the null value of 1.0, and substantial bias toward the null from nondifferential misclassification of exposure cannot be ruled out in this study. Nevertheless, the exposure assessment was far more detailed than in the original cohort mortality studies from which the cases and controls were identified. In most of the original studies, which have been found sufficiently informative to be the basis for several reviews and meta-analyses (Savitz and Moure 1984, Carcinogen Assessment Group 1987, IARC 1989, Wong and Raabe 1989), exposure assessment consisted of nothing more than the mere fact that a person worked for a petroleum company or in a refinery. The present study should have reduced the degree of exposure misclassification considerably in comparison with those studies. If there were a major effect on kidney cancer by a refinery exposure that is even modestly associated with any of the primary or secondary exposures we considered, larger relative risk estimates would have been expected than the ones our analysis produced.

The exposure rating process seemed to work well, as indicated by the generally high degree of subjective confidence the industrial hygienists assigned to their exposure ratings and the high degree of documentation we found for the judgments in the notes from the rating sessions. The absolute accuracy of the ratings, of course, must remain a matter of speculation. There is some concern that, even though the exposure rating procedure worked well in general, there may have been inconsistencies among the ratings from refinery to refinery. The intensity ratings in particular were assigned on a semiquantitative scale in relation to the industrial hygienists' judgment of the range of historical exposures at each specific refinery. Clearly, it is possible for the highest historical exposures at one refinery to have been among the intermediate exposures at another refinery.

The fact that each company provided its own industrial hygiene expertise, with the ERI industrial hygiene representative as the only expert common to all the rating sessions, presents another cause for concern. On a small number of occasions the industrial hygienist from one company or another insisted that certain exposure ratings should be assigned to job titles and units that received different ratings at other refineries. One of the functions of the ERI industrial hygiene representative was to identify and mention these inconsistencies at the exposure rating sessions, but the judgment of the company industrial hygienists was the deciding factor in all such situations. Thus, on the justifiable presumption that exposure misclassification was nondifferential between cases and controls at all refineries, different degrees of misclassification -- and different degrees of bias toward the null relative risk value of 1.0 -- were possible at some refineries.

An improvement in future use of the exposure assessment procedure developed in this study would be to have all participating exposure raters review each others' judgments after all ratings are assigned. Such a process might produce more consistency in the exposure ratings from refinery to refinery. The expected result would be a more equal distribution of exposure misclassification errors throughout the study, if not a reduced degree of misclassification overall.

In comparison with exposure misclassification in the assignment of exposure ratings, misclassification of disease is a much less tenable explanation for the absence of strong associations between kidney cancer and refinery exposures in these data. Kidney cancer diagnoses seldom fail to appear on death certificates.

Confounding also needs to be considered. In estimating the relative risks for refinery exposures, we found that controlling for race and Spanish surname did not materially alter the results. Thus, we reported relative risk estimates for which only the matching factors were controlled (by conditional logistic regression). For two related reasons, we did not explore the possibility of mutual confounding among the refinery exposures. First, no refinery exposure had the strong, independent association with kidney cancer it would have to possess in order to be an important confounder of the relative risks for the other exposures. If a strong association had been found between kidney cancer and one or more of the refinery exposures, a much greater incentive would have existed to explore possible confounding among the exposures. Since none of the exposures appeared to be a strong risk factor in its own right, it follows that none of them should have been a strong confounder of the estimated relative risk for any of the others.

Second, the refinery exposures tended to be strongly and positively associated with each other. Thus, the inclusion of several refinery exposures in the same logistic regression model would have produced wild and uninterpretable vacillations in the relative risk estimates. Given the absence of a strong *positive* association between kidney cancer and any of the refinery exposures on their own, strong confounding could only have been produced by a refinery exposure that was *inversely* associated with kidney cancer. Such an association, indicating prevention at face value, would be considered implausible because all the exposures were selected for assessment as known or suspected causes of the disease.

We had no information on several nonoccupational risk factors for kidney cancer. Some of them, such as polymastia or excessive phenacetin use, are too rare to have exerted appreciable confounding on any of the associations. Obesity has been reported to be associated with kidney cancer but primarily among women. Obesity would produce a bias toward lower relative risks if it is positively associated with kidney cancer among men and more predominant among office workers, of whom the "refinery background" category was predominantly composed. Cigarette smoking is another kidney cancer risk factor for which information was not available. If the "refinery background" category contained a higher proportion of smokers than the other exposure categories, the resulting bias would have been toward underestimation of increased relative risks.

The degree to which obesity, smoking or any other uncontrolled risk factor could have biased the results is limited by the magnitude of the independent effects of these factors themselves on kidney cancer risk. Even the extreme categories of these two factors have not been associated with relative risks greater than a doubling or trebling of risk. Thus, one would observe a relative risk of 1.0 due to confounding by obesity or smoking only if all of the following were true: (1) The true relative risk for the refinery exposure does not exceed the range of 2.0 to 3.0. (2) All the cases and controls in the exposed category were nonsmokers or thin. (3) All the cases and controls in the "refinery background" category were heavy smokers or obese. If the actual situation was less extreme than any, or all three, of these conditions, the degree of confounding would be even less pronounced. For smoking in particular, there is evidence that differences between hourly and salaried employees and between refinery and nonrefinery personnel do not vary nearly this extent (Van Peenen et al. 1984). Thus, the algebra for assessing uncontrolled confounding by unmeasured risk factors (Axelson 1978) leads to the conclusion that it would be more reasonable to attribute the few, weakly positive associations for some of the refinery exposures in this study to confounding by risk factors such as smoking or obesity than to suspect that a pronounced effect of one or more of the refinery exposures was masked by such confounding. Only a risk factor that is common in refinery work and that has a relative risk of its own that is much larger than 2.0 or 3.0 could have obscured such an effect. No such factor is known at the present time.

Continued research on the causes of kidney cancer may identify risk factors that have stronger associations with this disease than cigarette smoking does and that are more common than phenacetin abuse or extreme obesity. As such risk factors are identified, their effects should be taken into account in future studies of kidney cancer and occupational hydrocarbon exposure.

In contrast with the exposure ratings, the analysis of job titles and units for the longest-held jobs did produce positive associations consistent with a causal effect of gasoline hydrocarbons on kidney cancer risk. The jobs that would be expected to entail the greatest exposures (receipt, storage and movements jobs, laborers and unit cleaners) had the highest relative risks. It is possible that in the bulk of jobs within refineries, especially the refinery unit operators and the diverse jobs in the maintenance crafts, the variations in exposure were all within a range that was too low to produce measurable increases in kidney cancer risk in a study of this size. The only sizable group with an elevated relative risk, the laborers, was also the most difficult to assess with respect to refinery exposures because of a lack of specificity of duties and refinery locations. The other jobs with elevated relative risks, the unit cleaners and the receipt, storage and movements workers, were too few in number in this study to permit a more detailed analysis.

The positive associations we found with these job titles and units are analogous to the similar associations that have been reported from case-control studies of kidney cancer in general populations (MacLaughlin 1984, Siemiatycki et al. 1987). In the general-population studies, of course, the employment information is less reliable and the proportions of subjects in specific jobs are much lower than in studies of employed groups that have been selected because of their potential for specific exposures.

Studies of occupational groups with greater exposures to hydrocarbons, especially the C6+ isoalkanes, would be highly informative. For this reason, receipt, storage and movements workers constitute a group that it would be particularly important to study. It is encouraging that API-sponsored research of "downstream" workers (i.e., employees engaged in the transport and distribution of finished petroleum products) is underway to address this research need.

In summary, the most important drawbacks of this study were the limited number of kidney cancer cases available, the potential for bias from exposure misclassification, the lower range of hydrocarbon exposures in refineries compared with some other workplace sites, and the dearth of knowledge of major kidney cancer risk factors. The last limitation affects any study of kidney cancer for which, unlike some other cancers (e.g., breast cancer), there are relatively few known major causes. Continued follow-up of the consolidated cohorts and expansion of the study base by the addition of other cohorts of refinery workers would increase the study size and limit the possible influence of random error.

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APPENDIX A

API KIDNEY CANCER CASE-CONTROL STUDY

Guide to Case Identification

I. General Procedures

A. Cases of kidney cancer were identified through a systematic review of all death certificates previously collected by the participating companies for their own mortality studies.

B. All causes of death, as well as other significant conditions, listed on the certificates were read for any mention of kidney cancer.

C. Death certificates were photocopied if they met one or more of the following criteria:

1. The cohort member qualified as a kidney cancer case according to the criteria for case identification described in section II below.

2. It was the fiftieth certificate read (check for false negatives).

3. There was any question as to whether the individual qualified as a case for this study.

D. After each site visit, the existing International Classification of Disease (ICD) codes on the death certificates copied were blocked out. The certificates were then sent to a trained nosologist for recoding to detect false-positive and false-negative classification errors.

II. Terms Indicating Kidney Cancers Qualifying as Cases

A. We are interested in any condition that would be assigned the code 189.0 in the ninth revision of the coding manual for the International Classification of Diseases (ICD-9). This code is defined as "primary malignant neoplasm of the kidney, except kidney pelvis." However, identification of any cases should depend upon the terminology on the certificate, and not on any previously assigned ICD codes that may appear.

B. Terms most often seen on death certificates are:

Renal carcinoma
Cancer/carcinoma of the kidney/renal parenchyma

Although 189.0 includes only cancer of the renal parenchyma, any kidney cancers not otherwise specified are also classified as 189.0 and for our purposes are considered kidney cancer cases.

C. Terms no longer used, but which may appear on older certificates:

Hypernephroma
Hypernephroid carcinoma
Grawitz tumor
Wilm's Tumor (A very rare type of kidney cancer)
-also known as Embryonal adenomyosarcoma of kidney
Embryonal carcinoma of kidney
Embryonal nephroma
Nephroblastoma
Embryonal mixed tumor of kidney
Carcinosarcoma of kidney
Embryoma of kidney

III. Other Kidney Cancers and Conditions

These terms may appear on the death certificates, but for a variety of reasons do not qualify as kidney cancer cases for this study.

A. Secondary neoplasms of the kidney (see Section IV A below). These neoplasms are rare. They are coded as 198.0 in ICD-9.

B. Benign tumors of the kidney, coded as 223.0 in ICD-9. Terms for these tumors include:

Nephradenoma
Lymphangioma of kidney
Fibroma
Angioma
Lipoma
Cortical adenoma

If the certificate does not specify whether a tumor is benign or malignant, it is considered benign.

C. Malignant neoplasms of other parts of the kidney, and other urinary organs. These neoplasms include:

Renal pelvis (also renal calyx, renal hilus, ureteropelvic junction), 189.1
Ureter, 189.2
Urethra, 189.3
Paraurethral glands, 189.4
Urinary organ, site unspecified, 189.9

D. Other diseases of the kidney, including:

Nephritis
Nephrosclerosis
Hydronephrosis
Polycystic kidneys
End stage renal disease

IV. Reading the Death Certificate

See attached sample of the U.S. standard death certificate.

A. Part I

Part I lists the immediate cause of death and any conditions giving rise to that cause. Generally, these lines can be read as, "Condition (a) is the immediate cause of death and was due to condition (b), which was due to condition (c)." The duration of each disease or condition is also given. The order and duration of the conditions listed are important in determining, for this study, the distinction between primary and secondary cancers.

Example 1. A death certificate may list:

I(a) Carcinoma of lung
(b) Renal cell carcinoma

-- If (b) is of longer duration than (a), then renal cell carcinoma is coded as primary and carcinoma of lung is coded as secondary.

-- If (a) and (b) are of the same duration, or if (a) is of longer duration than (b), then both cancers are coded as primary.

Example 2. Often the physician who filled out the certificate will ignore the distinctions between lines and will write one run-on "string" of conditions:

I(a) Carcinoma of the kidney with metastases to bladder
(b) and colon

-- The kidney is coded as the primary site, with the bladder and colon coded as secondary sites.

B. Part II

Part II lists other significant conditions that contributed to death, but were not related to the immediate cause. Any kidney cancer mentioned in Part II qualifies as a case for our study as long as it falls under the categories described in Section II of this guide.

PHYSICIAN, MEDICAL EXAMINER OR CORONER

U.S. STANDARD

CERTIFICATE OF DEATH

Form Approved
OMB No. 68R 1901

TYPE OR PRINT IN PERMANENT INK FOR INSTRUCTIONS SEE HANDBOOK

DECEDENT

DECEDENT—NAME FIRST MIDDLE LAST 1 | SEX 2 | DATE OF DEATH 3

RACE 4 | AGE—Last Birthday 5a | UNDER 1 YEAR MOS. DAYS 5b | UNDER 1 DAY HOURS MINS. 5c | DATE OF BIRTH 6 | COUNTY OF DEATH 7a

CITY, TOWN OR LOCATION OF DEATH 7b | HOSPITAL OR OTHER INSTITUTION 7c | IF HOSP. OR INST. 7d

STATE OF BIRTH 8 | CITIZEN OF WHAT COUNTRY 9 | MARRIED, NEVER MARRIED, WIDOWED, DIVORCED 10 | SURVIVING SPOUSE 11 | WAS DECEDENT EVER IN U.S. ARMED FORCES? 12

IF DEATH OCCURRED IN INSTITUTION SEE HANDBOOK REGARDING COMPLETION OF RESIDENCE ITEMS

SOCIAL SECURITY NUMBER 13 | USUAL OCCUPATION 14a | KIND OF BUSINESS OR INDUSTRY 14b

RESIDENCE—STATE 15a | COUNTY 15b | CITY, TOWN OR LOCATION 15c | STREET AND NUMBER 15d | INSIDE CITY LIMITS 15e

PARENTS

FATHER—NAME FIRST MIDDLE LAST 16 | MOTHER—MAIDEN NAME FIRST MIDDLE LAST 17

INFORMANT—NAME 18a | MAILING ADDRESS STREET OR R.F.D. NO. CITY OR TOWN STATE 18b

DISPOSITION

BURIAL, CREMATION, REMOVAL, OTHER 19a | CEMETERY OR CREMATORY—NAME 19b | LOCATION CITY OR TOWN STATE 19c

FUNERAL SERVICE LICENSEE 20a | NAME OF FACILITY 20b | ADDRESS OF FACILITY 20c

CERTIFIER

21a | DATE SIGNED 21b | HOUR OF DEATH 21c M | NAME OF ATTENDING PHYSICIAN IF OTHER THAN CERTIFIER 21d

22a | DATE SIGNED 22b | HOUR OF DEATH 22c M | PRONOUNCED DEAD 22d ON | PRONOUNCED DEAD 22e AT M

NAME AND ADDRESS OF CERTIFIER (PHYSICIAN, MEDICAL EXAMINER OR CORONER) 23

REGISTRAR 24a | DATE RECEIVED BY REGISTRAR 24b

CAUSE OF DEATH

CONDITIONS IF ANY WHICH GAVE RISE TO IMMEDIATE CAUSE STATING THE UNDERLYING CAUSE LAST

25 IMMEDIATE CAUSE (ENTER ONLY ONE CAUSE PER LINE FOR (a), (b), AND (c))

PART I (a)

DUE TO, OR AS A CONSEQUENCE OF (b)

DUE TO, OR AS A CONSEQUENCE OF (c)

PART II OTHER SIGNIFICANT CONDITIONS | AUTOPSY 26 | WAS CASE REFERRED TO MEDICAL EXAMINER OR CORONER 27

ACC. SUICIDE, HOM., UNDET. OR PENDING INVEST. 28a | DATE OF INJURY 28b | HOUR OF INJURY 28c M | DESCRIBE HOW INJURY OCCURRED 28d

INJURY AT WORK 28e | PLACE OF INJURY 28f | LOCATION STREET OR R.F.D. NO. CITY OR TOWN STATE 28g

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APPENDIX B

API KIDNEY CANCER CASE-CONTROL STUDY

Guide to Abstracting Work Histories

A. Work History Entry

1. Defined as a specific job in a specific department of a refinery held for a specific continuous length of time. In other words, every time the employee changes job title or department, or has an interruption in the time spent at a particular job, it is considered a new work history entry.

2. Example 1. An excerpt from a work history might look like the following:

Dept	Position	Pay rate*	Change Date	
Cracking	Asst Operator	----	10/02/53	1
"	Operator	----	03/06/56	2
"	"	----	03/06/57	
"	"	----	09/01/58	
Light Oils	"	----	12/22/63	3
"	Foreman	----	02/23/65	4

*Pay rates have been blocked out on the copies for this study.

There are four work history entries in the above example, as numbered in the right margin.

B. ID Number

1. Each work history entry has its own "ID #," which consists of the employee's ID# plus the order of appearance of the entries on the work history. If the study subject in Example 1 were #6-09-1234-10, then the work history entry numbers would be, respectively, 6-09-1234-10-01, 6-09-1234-10-02, 6-09-1234-10-03, and 6-09-1234-10-04.

C. Job Title and Department

1. Should be abstracted exactly as listed on the original record.

2. Department names are often listed as "Locations" (i.e., location in the refinery).

3. Sick time, military service, layoffs, and other periods of time not spent working for the company are counted as work history entries. In this case, the job "title" is written as "Not working," and there is no department name.

4. Example 2. A work history excerpt might look like the following:

Dept	Position	Change Date	Notes
Constr	Helper	07/01/35	
Maint	Mechanic	09/24/35	Sick 02/03/37-04/11/37
"	Hd Mechanic	11/20/39	

There would be 5 work history entries in this case, because the Mechanic-Maint Dept job counts as two entries (9/35-2/37, and 4/37-11/39), with the sick time forming a separate entry between them.

D. Place of Work

Often someone will spend time working at another refinery or facility owned by the same company. These jobs are counted as separate work history entries. If the facility is not specified, then it is assumed to be the main refinery of interest.

E. Dates Held

1. Defined as the start and stop dates for the work history entry.

2. Often the term "change date" is used on the records; this date is considered to be the start date. If the stop date is not specified, it is assumed to be the day before the start of the next work history entry.

3. If a date is missing or completely illegible, the symbols < (before) and > (after) are used.

4. Example 3. A work history excerpt might look like the following:

Dept	Position	Change Date	Notes
Acctg	Payroll Clerk	03/15/46	
"	Sr Payroll Clk	10/25/50	
"	Supv-Payroll		Normal Retirement 7/1/56

To give an approximate range of time in the "Sr Payroll Clk" job, the dates for that work history entry would be abstracted as 10/25/50 - <07/01/56. Similarly, the dates for "Supv-Payroll" would be >10/25/50 - 07/01/56.

F. Job Category

1. Work history entries are grouped into categories according to job title or department (e.g., "operators," "pumpers," etc.) to facilitate assignment of exposure scores.

2. Each category has a two-digit numerical code, which is assigned to a work history entry during data entry.

3. A list of job categories is attached. This list will expand as work histories from more refineries are abstracted.

G. Output

The form to be used by industrial hygienists at the exposure scoring site visits is attached.

API KIDNEY CANCER CASE-CONTROL STUDY
WORK HISTORY ABSTRACTS - SAMPLE LIST OF JOB CATEGORIES
06/12/86

Code	Category
01	Miscellaneous
02	Working for the company at another facility
03	Not working (includes sick leave, military service, layoffs, etc.)
04	Boiler
05	Engineering
06	Foreman/Supervisor, not otherwise categorized
07	Helper, not otherwise categorized
08	Fireman
09	Laborer, Not otherwise categorized
10	Laboratory
11	Mechanic
12	Office/Clerk
13	Operator
14	Pipe
15	Pump
16	Still
17	Shipping
18	Machine
19	Coils
20	Case & Can
21	Instrument

Exposure Scoring Form

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APPENDIX C

API KIDNEY CANCER CASE-CONTROL STUDY

Exposure Rating Plan

A "work history entry" is defined as a job title, location or department, date started and date stopped as recorded on the employment history of a case or control. For recording ratings, one of us (L.L.) and the company industrial hygiene representative worked with work history entries sorted by job title. They also referred to the chronologic listing of work history entries for each employee. The forms for recording the ratings are pre-coded for data entry (see Figure 1 of main report for coding form); i.e., each work history entry was given a unique identifier so that it could be linked back to the appropriate case or control without additional coding or data entry.

For the three hydrocarbon categories of principal interest (volatile hydrocarbons, non-aromatic liquid gasoline distillates, and aromatics), ratings were assigned for the frequency and intensity of exposure. Each assigned frequency and intensity rating was given a confidence rating, expressing the degree of certainty that Mr. Levin and the designated company representative attached to the rating they assigned jointly.

<u>Frequency</u>

The frequency ratings roughly quantify the proportion of time on the job that employees with the given job title and department spent exposed to hydrocarbons in the designated category during the years in question:

(0 = unknown)
1 = infrequent, if at all
2 = intermittent; weekly
3 = regular or routine exposure; daily

Intensity

The exposure intensity ratings rank the airborne and/or dermal exposures to the hydrocarbons in the designated category during the periods of exposure to which the corresponding frequency rating refers. A rating of "1" is assigned if exposure intensity did not exceed "background," i.e., typical concentrations found within the refinery in "non-exposed" environments. A rating of "3" is assigned if exposure intensity is judged to have been in the top 25% of the range of concentrations for that hydrocarbon category throughout the refinery during the time frame of reference for this study. All other work history entries are assigned intensity ratings of "2".

(0 = unknown)
1 = equal to or not substantially above background at the refinery
2 = intermediate
3 = upper 25% of historical levels at the refinery

In practice, determining the intensity rating proved to be the key factor, since the frequency rating follows logically. For example, if the intensity level for a given exposure is 1 ("background for the refinery"), the frequency rating must be 3 ("daily").

The seven workplace exposures of secondary interest (lead, asbestos, ionizing radiation, chlorinated hydrocarbon solvents, polynuclear aromatic hydrocarbons, nitrosamines, and higher boiling hydrocarbons) were classified by the dichotomy of "present" or "absent":

(0 = unknown)
1 = absent
2 = present

Confidence

In addition to the actual exposure ratings, all primary and secondary exposure ratings were assigned confidence ratings as described below:

1 = lowest confidence (pure guesswork)
2 = intermediate confidence (educated guess)
3 = highest confidence (reasonably sure)

The confidence ratings enabled us to specify areas of uncertainty so that the data could be analyzed to account for confidence in the assessment.

Duration

The dates of starting and stopping in each work history entry define the overall duration of exposure associated with the job title and department. Consequently, there was no need for the coding system to include duration of exposure.

EXAMPLES

The following examples are hypothetical work history entries that could be found in an employment record at any one of the refineries. They show how the exposure rating system was used.

Example 1:

			Intensity:		Frequency:	
Job Title	Location	Years	Rating	Confidence	Rating	Confidence
Tank truck Loader	Tank farm/ Loading Rack	1946	3	3	3	3

In this example, we judged that this job regularly involved exposure to volatile distillates (3 = regular or routine exposure) at the highest level of intensity. The intensity assessment does not imply a quantitative estimate, i.e. a range of concentrations in parts per million or use of any workplace standard or threshold limit value. It merely reflects a judgment that of all job exposures to volatile distillates over the operating history of that refinery, tank truck loading (without benefit of vapor recovery, respiratory protection, etc.) is in the upper 25% of such exposures. Because this job assignment clearly falls into these frequency and intensity categories, our confidence ratings for both would be 3 (highest confidence).

Example 2:

Job Title	Location	Years	Intensity: Rating	Intensity: Confidence	Frequency: Rating	Frequency: Confidence
Welder	Welding Shop	1945-64	2	3	2	3
Not available	Iran	1965-68	3	2	3	2
Welder	Welding Shop	1969-76	2	3	2	3

The key to evaluating this employee's exposure lies in reviewing his individual work history. The inference that this individual was a welder while in Iran lowers the confidence rating from 3 to 2. The rationale for inferences such as this one would be discussed and agreed to at the site visit meeting as well as recorded in the meeting notes.

Example 3:

Job Title	Location	Years	Intensity: Rating	Intensity: Confidence	Frequency: Rating	Frequency: Confidence
Guard	Refinery Gate	1957-65	1	3	3	3

As a non-operations worker, a guard stationed at a physical location not in or near any process units was judged to have been exposed to volatile distillates at levels not significantly different from background levels at the refinery and was therefore assigned an intensity rating of 1 and a frequency rating of 3. Again, our certainty that this job assignment fell into these categories was high, and so the confidence ratings for intensity and frequency was 3.

APPENDIX D

API KIDNEY CANCER CASE-CONTROL STUDY

Job Title and Location Code List

Adapted from the Texaco/API Standardized Task List for
the API Kidney Cancer Case-Control Study
June 30, 1987

I. JOB TITLE CODES

ERI CODE	API CODE	TASK	COMMENT
00		Unknown	
10	AX	ADMINISTRATION AND/OR SUPERVISION	Occupations concerned with specialized administrative and managerial functions, or "clerical" work (i.e. general white collar), or those whose primary function is to supervise and coordinate activities of others. Includes stockman, order filler, records clerk, storekeeper, buyer, sales, and engineers involved with management and technical supervision.
2-	BX	OPERATIONS	
21	BA	Inside (Control Room)	Operates control panel to regulate temperature, pressure, rate of flow, and tank level in petroleum refining, processing, and treating units and petrochemical units, according to process schedules.
22	BB	Outside Apprentice	An operator whose duties are primarily outside, and who has not yet completed sufficient on-the-job training to be considered a qualified, skilled worker. In general, assists and reports to outside journey man (Task 23).

ERI CODE	API CODE	TASK	COMMENT
23	BC	Outside Journeyman	An operator whose duties are primarily outside of the control room and who has completed a specified training program. Duties include moving controls to regulate valves, pumps, compressors, auxiliary equipment to direct flow of products; checking temperature and pressure gauges and flow meters; checking equipment for malfunctions; and patrolling units to verify safe and efficient operating conditions. May perform minor repair and maintenance of equipment; sample liquids and gases, and test products for chemical characteristics and color; lubricate equipment; clean interior of processing units by circulating chemicals through them; and treat products. Includes blender, pumper, stillman, gauger, fireman.
24		Laborer, General	Laborers who are not in the yard department. Includes (if Labor designation also present) helper, packer, rigger, loader, winchman, wharfman, oiler, trackman, mechanic, utility, maintenance, shop, warehouse, tanks, garage.
4-	CX	MAINTENANCE CRAFTS-METAL	
40	CA	Boilermaking	Includes occupations concerned with assembling, erecting, and repairing boilers and related equipment, attachments and accessories. Includes laying out, cutting, fitting, and bolting, welding, or riveting heavy metal plates, boiler tubes, and castings.

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ERI CODE	API CODE	TASK	COMMENT
41	CF	Welding	Excludes those known as lead burners (Task 46) whose primary occupation is welding with lead materials. This group includes occupations primarily concerned with joining, surfacing, or otherwise fabricating or repairing structures or parts of metal or other weldable materials, such as plastic or glass, applying the following welding or cutting processes: arc; gas; resistance; solid state (friction, ultra-sonic, cold, explosion, diffusion); and other processes, such as electro-slag, electron beam, induction, thermit, and laser beam.
42	CC	Pipefitting	Includes occupations concerned with assembling and installing gas, steam, plumbing, and related fixtures, pipes, and fittings in structures, using pipe-cutting and pipe-threading tools, welding equipment, and other pipefitting tools and equipment.
46	CB	Lead Burning	Welds lead or alloy, using gas torch or arc welding equipment, to install and repair lead items. Installs or repairs equipment such as lead pipes, valves, floors, and tank linings. Cuts lead sheets or pipe using powered saws, hand shears or chopping knife. (See also Welders, Task 41)
34	CD	Structural Steel	Includes occupations concerned with joining (includes rigging) structural parts and components with bolts, screws, and related fasteners, or by fitting (placing) reinforcing steel or iron in forms to strengthen concrete. Rigging: assembles rigging to fit and move equipment of material; selects cable, ropes, pulleys, winches, blocks and sheaves, according to weight and size of load to be moved.

ERI CODE	API CODE	TASK	COMMENT
35	CE	Tinsmithing	Includes occupations concerned with laying out, cutting to size, bending or shaping, and soldering, brazing, riveting, or crimping sheet metal, such as copper, steel, aluminum, galvanized iron, and tin cold air vents, cabinets, and light tanks.
30		MISCELLANEOUS MAINTENANCE & BUILDING TRADES	Includes handyman, builder, tool inspector, inspector, utility man, repairman, construction mechanic
	DX	MAINTENANCE CRAFTS-NON-METAL	
31	DA	Carpentry	Includes occupations concerned with fabricating, installing and repairing structures and structural members made of wood and materials that can be worked like wood, such as plastic and fiberglass, using bank saws, rip saws, planers, braces, hammers and other carpentry tools and woodworking machines.
32	DC	Masonry	Includes occupations working with artificial stone, brick, concrete, stone and the like. Includes those classified as bricklayer, cement mason, stone mason, etc.
33	DD	Painting	Includes occupations concerned with applying decorative or protective materials, such as paint, enamel, varnish, shellac, stain or oil to articles by brushing, spraying, wiping, or hand-dipping; includes preparing surface of the article, mixing coating ingredients, hand-rubbing, filled or coated surfaces, and related activity.

ERI CODE	API CODE	TASK	COMMENT
03		Sandblasting	As distinct from painting
36	DB	Insulating	Includes occupations concerned with covering and lining structure with asbestos, cork, canvas, tar paper, magnesia, and related materials for insulation purposes, using saws, knives, rasps, trowels, and other tools and implements.
04		Miscellaneous Shop Services	For example, gasket cutting
EX		MAINTENANCE CRAFTS-ELECTRICAL SYSTEMS	
37	EA	Electrical Only	Excludes those individuals whose jobs are combined to electrician and instrument man or instrument man only (see also Tasks 38 and 39). Includes occupations concerned with assembling, installing, erecting, and repairing electrical equipment and related structures designed for electric power generation, transmission, and distribution; communication, signaling, and object detection; process control, fire control, and data processing; transportation and materials handling; heating, air conditioning, refrigeration, illumination; and other industrial, commercial, and domestic electrical applications.
38	EC	Electrical and Instrument	Combines the duties of electrical (Task 37) and instrument (Task 39).

ERI CODE	API CODE	TASK	COMMENT
39	EB	Instrument Only	Includes occupations concerned with fabricating and repairing instruments for measuring, controlling, and indicating temperature, pressure and vacuum, fluid flow, liquid level, mechanical motion, rotation, humidity, density, acidity or alkalinity, and combustion; dial pressure gauges; scales and balances; and apparatus for testing such physical properties as hardness, tension, torsion, compression, and elasticity.
	FX	MAINTENANCE CRAFTS-ENGINES	
	FA	Gas	Repairs and maintains gas-driven, internal-combustion engines that power electric generators, compressors, and similar equipment, using hand tools and precision measuring devices.
49	FB	Gasoline/Diesel	Repairs and maintains gasoline and/or diesel engines used to power machines such as ships, trucks, railroad trains, electric generators, and construction machinery, using hand tools, precision measuring instruments, and machine tools.
43	GX	MACHINING AND BLACKSMITHING	Includes occupations concerned with shaping metal parts by milling, turning, planing, abrading, boring, chipping, sawing, and shaving with a variety of metal working machines. Includes laying out, job-setting, fitting, assembling and repairing.

ERI CODE	API CODE	TASK	COMMENT
44	HX	TRUCK/TRAILER/RAIL CRANE (MOBILE EQUIPMENT OPERATOR)	Includes occupations concerned with the transportation of people and cargo from one geographical location to another, or in or around establishments, by various methods. Includes truck/vehicle drivers, chauffeurs.
	IX	MAINTENANCE-RELATED ACTIVITIES	
45	IA	Recovery/Salvage	Recovers and/or salvages reusable materials and disposes of waste. May involve collection, inspection, separation, weighing, and minor repairs to scrap containers.
47	IB	Yard	Performs any combination of following tasks in refinery: dig ditches, build dikes and levees, and fill holes using pick and shovel. Smooth ground surfaces and roadways, using hand tamper. Clean refining equipment. Move debris from roadways and work areas, and spray and hoe weeds. Mix and pour cement. Unload material, such as tools, equipment, cement, etc., manually or with handtruck; and stack barrels and sacks for storage. Uncrate equipment and parts. Rip open sacks, and dump chemicals and catalysts into mixing, treating, or storage tanks. Dope pipelines to prevent corrosion. Change hoist cables, and rig chain hoists rope blocks, etc., used to move or raise equipment. Skim oil from cooling water in water boxes. Job titles include laborer and roustabout.
48		Unit Cleaners	

ERI CODE	API CODE	TASK	COMMENT
	JX	FIELD/SERVICES STAFF	
11	JA	Professional	An individual who can work relatively independently by virtue of educational qualifications, work experience, and/or legal certification.
12	JB	Technical	An individual who works in direct support of a professional (See Task 11). Includes craftsman.
	JC	Non-Technical	An individual who provides support of an essentially non-technical nature to professional (Task 11) or technical (Task 12) staff.
13	"	"	Janitor
14	"	"	Guard, watchman, and other security
15	"	"	Firefighter
17	"	"	First aid and other medical
	KX	LABORATORY STAFF	
51	KA	Professional	An individual who can work relatively independently by virtue of educational qualifications, work experience, and/or legal certification. Includes chemist, industrial hygienist.
52	KB	Technical	An individual who works in direct support of a professional (See Task KA). Includes inspector, lab technician.

ERI CODE	API CODE	TASK	COMMENT
53	KC	Non-technical	An individual who provides support of an essentially non-technical nature to professional (Task KA) or technical (Task KB) staff.
	PA	Pipeliner	Maintains and repairs pipelines, pumping stations, and tank frames by performing any combination of the following duties: corrosion control by sandblasting, application of corrosion resistant materials and pipe wrapping; operate heavy earthmoving equipment; position materials for carpenters, mechanics and welders; install screwpipe and manifold connections; clean storage tanks; yardwork; may use chemicals to clear foliage; may load or unload trucks; walk along pipeline to detect leaks.

II. JOB LOCATION CODES

CODE	JOB LOCATION
0000	Unknown
0100	CRUDE PROCESSING UNIT
0110	Desalting and Dehydrating
0111	Chemical desalting
0112	Electrical desalting
0120	Topping Unit/Atmospheric Distillation with desulfurization (may have secondary stills)
0121	Light topping
0122	Deep topping
0130	Topping Unit/Atmospheric Distillation without desulfurization (may have secondary stills)
0131	Light topping
0132	Deep topping
0140	Vacuum Distillation (may occur at primary refinery or lube oil refinery - both process topped crude. Synonym: residuim stripping)
0150	Virgin naphtha rerun
0160	Virgin light ends rerun
0200	CATALYTIC CRACKING UNIT

CODE	JOB LOCATION
0210	Fixed-bed
0211	With H_2S removal/recovery facilities
0212	Without H_2S removal/recovery facilities
0220	Fluid-bed (includes moving bed - involves regenerator)
0221	With H_2S removal/recovery facilities
0222	Without H_2S removal/recovery facilities
0240	Fuels plant - Light ends processing
0300	THERMAL CRACKING UNIT (Includes Visbreaking and batch stills - no catalyst used)
0400	COKING UNIT
0410	Fluid coking
0411	With H_2S removal/recovery facilities
0412	Without H_2S removal/recovery facilities
0420	Delayed coking
0421	With H_2S removal/recovery facilities
0422	Without H_2S removal/recovery facilities
0500	CATALYTIC REFORMING UNITS (utilize precious metal catalysts)
0510	Without hydrogenation
0511	With H_2S removal/recovery facilities
0512	Without H_2S removal/recovery facilities

CODE	JOB LOCATION
0520	With hydrogenation
0521	With H_2S removal/recovery facilities
0522	Without H_2S removal/recovery facilities
0600	STEAM REFORMING UNIT
0700	HF ALKYLATION UNIT
0800	H_2SO_4 ALKYLATION UNIT
0900	$AlCl_3$ ALKYLATION UNIT
1000	RETORTING UNIT
1010	Shale oil
1020	Tar sand
1100	GASOLINE POLYMERIZATION UNIT
1110	Phosphoric acid
1120	Sulfuric acid
1200	NON-AROMATIC ISOMERIZATION UNIT (e.g., Butamer, pentane, hexane, etc.)
1300	AROMATIC ISOMERIZATION UNIT (when not combined with an aromatic recovery unit)
1400	KETONE DEWAXING UNIT
1410	MEK
1411	Alone
1412	With benzene

CODE	JOB LOCATION
1413	With toluene
1420	MIBK
1421	Alone
1422	With benzene
1423	With toluene
1430	Acetone
1431	Alone
1432	With benzene
1440	MBK
1450	Wax presses
1500	LUBE/BASE OIL EXTRACTION UNIT
1510	Phenol
1520	Duo-Sol
1530	Furfural
1540	DMSO
1550	Di-Me
1560	Bariso
1570	Propane
1571	Dewaxing
1572	Deasphalting

CODE	JOB LOCATION
1600	SO_2 (EDELEANU) EXTRACTION UNIT
1700	AROMATICS RECOVERY UNIT (includes combined isomerization and recovery)
1710	Distillation
1720	Extraction
1721	Glycols (e.g., Udex, Tetra)
1722	1,1-dioxycyclopentane (e.g., Shell-Sulfolane)
1730	Crystallization
1740	Selective adsorption
1800	CLAY TREATING UNIT
1810	Lube/base oil
1820	Benzene, toluene, xylene (BTX)
1830	Middle distillates
1900	BAUXITE TREATING UNIT (WAX)
2000	SULFURIC ACID TREATING UNIT
2010	Lube/base oil
2020	Wax
2030	Middle distillates
2100	TREATING (SWEETENING) LIGHT OILS UNIT
2110	Caustic and inhibitor

CODE	JOB LOCATION
2111	Gasoline and components
2112	Middle distillates
2113	Solvents
2120	Doctor
2121	Gasoline and components
2122	Middle distillates
2123	Solvents
2130	Cupric chloride
2131	Gasoline and components
2132	Middle distillates
2133	Solvents
2140	Others, e.g. cycloversion
2200	HYDROGEN TREATING UNIT (if operated as a separate unit)
2210	Desulfurization and/or denitrification
2211	Gasoline and components
2212	Middle distillates
2213	Solvents
2220	Saturation
2221	Olefin
2222	Aromatic

CODE	JOB LOCATION
2223	Lube/base oil polishing (hydrofining)
2230	Cracking
2231	Distillate
2232	Residuim
2233	Lube/base oil
2234	For petrochem plant
2300	WASTE TREATMENT UNIT
2310	Aqueous waste
2311	Sanitary
2312	Storm
2313	Process (e.g., API separator, charcoal filtration, secondary or tertiary treatment)
2320	Solid waste
2321	Collection
2322	Incineration
2323	Land-fill
2324	Land-farm
2330	Gaseous waste (e.g., tail gas clean-up)
2400	MAINTENANCE SHOP UNIT

CODE	JOB LOCATION
2500	MULTI-PROCESS TO PLANT-WIDE UNIT
2510	Maintenance
2511	Routine
2512	Turnaround
2520	Operations (e.g., labor pool, yard, shiftbreakers, supervisors/foremen)
2525	Transportation (cranes, trucks, buses, Ross carriers)
2530	Services
2531	Fire, safety, industrial hygiene, security (guard, watchman), medical/first aid
2532	Engineering, inspection
2600	LABORATORY UNIT
2610	Quality control (QC)
2620	Research and development (R & D)
2700	OFFICE - NON-FIELD UNIT
2800	UTILITY UNIT
2810	Water treatment
2820	Boiler house (includes electrical and steam)
2830	Pump house (cooling tower)
2840	Air compressors

CODE	JOB LOCATION
2900	RECEIPT, STORAGE, AND MOVEMENTS UNIT
2910	Pump
2911	Product
2912	Intermediate
2913	Crude
2920	Tank farms
2921	Product
2922	Intermediate
2923	Crude
2930	Blending (includes additives)
2931	Product
2932	Intermediate
2933	Crude
2940	Water transport (wharf)
2941	Product
2942	Intermediate
2943	Crude
2950	Truck and rail transport
2951	Product
2952	Intermediate

CODE	JOB LOCATION
2953	Crude
2960	Pipeline transport
2961	Product
2962	Intermediate
2963	Crude
3000	NGL (NATURAL GAS LIQUIDS) RECOVERY UNIT
3010	Expansion
3011	With H_2S removal/recovery facilities
3012	Without H_2S removal/recovery facilities
3020	Refrigeration
3021	With H_2S removal/recovery facilities
3022	Without H_2S removal/recovery facilities
3030	Cryogenic (colder than propane refrigeration)
3031	With H_2S removal/recovery facilities
3032	Without H_2S removal/recovery facilities
3040	Absorption
3041	With H_2S removal/recovery facilities
3042	Without H_2S removal/recovery facilities
3100	NGL (NATURAL GAS LIQUIDS) FRACTIONATION UNIT
3200	HELIUM-RECOVERY UNIT

CODE	JOB LOCATION
3300	SULFURIC ACID MANUFACTURING UNIT
3310	Chamber
3320	Contact
3400	SULFUR RECOVERY UNIT
3410	Direct oxidation
3420	Claus
3500	HYDROGEN MANUFACTURING UNIT
3510	Steam reforming
3520	Partial oxidation (Texaco)
3530	RKN reforming (specifically to produce H_2)
3600	ASPHALT MANUFACTURING UNIT
3610	Steam distillation
3620	Vacuum distillation
3630	Air blowing with catalyst
3640	Air blowing without catalyst
3650	Barrel and drum manufacture
3700	GREASE MANUFACTURING UNIT (includes both batch and continuous)
3800	LUBE/BASE OIL MANUFACTURING UNIT

CODE	JOB LOCATION
3300	SULFURIC ACID MANUFACTURING UNIT
3310	Chamber
3320	Contact
3400	SULFUR RECOVERY UNIT
3410	Direct oxidation
3420	Claus
3500	HYDROGEN MANUFACTURING UNIT
3510	Steam reforming
3520	Partial oxidation (Texaco)
3530	RKN reforming (specifically to produce H_2)
3600	ASPHALT MANUFACTURING UNIT
3610	Steam distillation
3620	Vacuum distillation
3630	Air blowing with catalyst
3640	Air blowing without catalyst
3650	Barrel and drum manufacture
3700	GREASE MANUFACTURING UNIT (includes both batch and continuous)
3800	LUBE/BASE OIL MANUFACTURING UNIT

CODE	JOB LOCATION
3900	PACKAGING UNIT (EXCLUDING WAX)
3910	Lube/base oil and grease only
3920	Lube/base oil, grease, and other consumer products
4000	WAX PACKAGING UNIT
4100	AROMATICS PRODUCTION UNIT
4110	Catalytic reforming - BTX (dehydrogenation)
4120	Hydrogen dealkylation (platforming)
4130	Thermal reforming
4200	CUMENE PRODUCTION UNIT
4210	Phosphoric
4220	Chlorine
4230	Hydroperoxide/phenol
4300	ETHYLENE PRODUCTION UNIT
4310	Steam/furnace/tube
4320	Other
4400	NITROGEN PRODUCTS UNIT
4410	Ammonia plants
4420	Other nitric products
4500	SALVAGE/RECOVERY
4600	CATALYST/BEAD PLANT

CODE	JOB LOCATION
4700	CHEMICAL PROCESSING
4710	Alcohol Unit (Ethanol Unit)
4750	Ther - Polymerization
4800	BOOSTER STATION
4900	ROOFING PLANT
5000	REFRIGERATION PLANT
5100	OXYGEN PLANT

APPENDIX E

API KIDNEY CANCER CASE-CONTROL STUDY

Spanish Surname Analysis

The purpose of this analysis of Spanish surnames is to distinguish Hispanics from non-Hispanics (Anglos). As an indicator of ethnic background, the Hispanic/Anglo dichotomy supplements the white/non-white distinction already available from the cohort data tapes.

In their review of epidemiologic studies of cancer in refinery workers, Savitz and Moure (1984) suggested that ethnicity may be an important confounder in assessing cancer rates for these workers. It could particularly be a problem for the refineries in Texas, which has a high Hispanic population. This concern was reiterated by the Environmental Protection Agency (1987) in its recent publication on the carcinogenicity of unleaded gasoline. Samet et al. (1980) reported lung cancer incidence rates in New Mexico to be approximately three times higher for non-Hispanic whites than for Hispanic whites. Humble et al. (1985) conducted a case-control study to investigate this disparity and concluded that the difference in lung cancer incidence rates between the two ethnic groups could largely be due to differing cigarette smoking patterns.

Kidney cancer rates also seem to be linked to ethnicity. Using the New Mexico SEER data for 1973 - 1977, the rate in non-Hispanic males is one and a half times greater than that in Hispanic males (SMR = 1.5) (ERI, unpublished).

The use of surnames has proved to be a highly reliable method for determining ethnicity in the absence of self-reported information. Wiggins et al. (unpublished) compared the accuracy of several Census Bureau methods for determining Hispanic status with respondents' self-reporting of ethnicity. The 1980 List of Spanish Surnames proved highly accurate in classifying participants as Hispanic or non-Hispanic (see Table F-1, Test 2).. In addition, Howard et al. (1983) investigated the accuracy of the 1980 Census Bureau list and the GUESS (Generally Useful Ethnic Search System) computer program, which also uses surnames to determine ethnicity, in assessing Hispanic status. They found that both methods were highly accurate in classifying Hispanics and non-Hispanics when compared to the self-reported ethnicity of the participants in their survey (see Table E-1, GUESS program and Test 1).

The GUESS program is no longer widely used, however. The 1980 List of Spanish Surnames was readily available from the Census Bureau. We obtained a copy and manually checked the surnames of all study subjects against the list.

TABLE E-1

Hispanic Surname Analysis:
Validation With Self-Reports (Males)

Method	Sensitivity	Specificity
GUESS Program (Howard et al.)	87	92
1980 Census List		
Test 1 (Howard et al.)	85	95
Test 2 (Wiggins et al.)	84	99

Sources: Howard et al., 1983
Wiggins et al., unpub.

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