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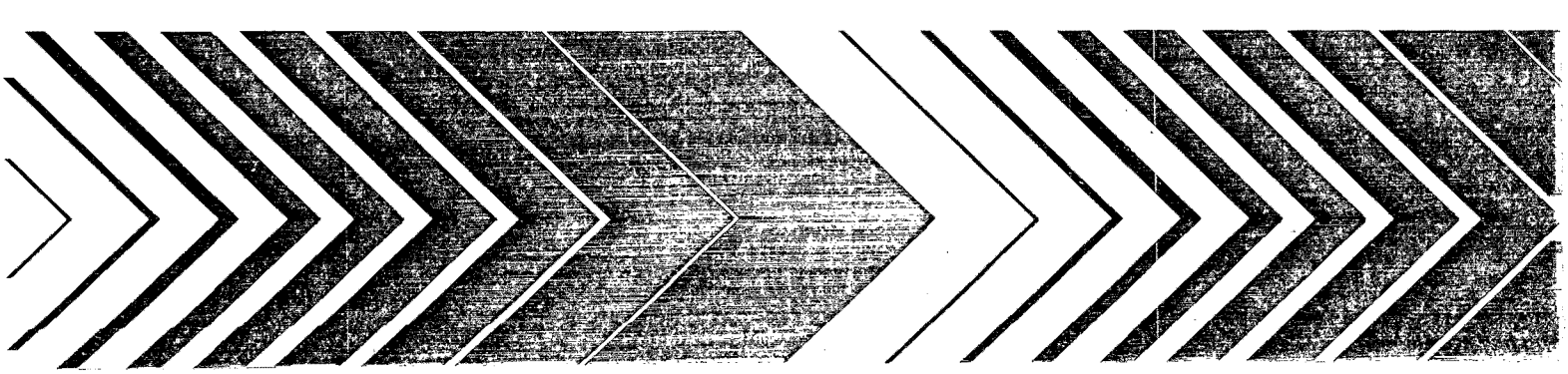
Evaluation of the Carcinogenicity of Unleaded Gasoline



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April 1987

EVALUATION OF THE CARCINOGENICITY

OF

UNLEADED GASOLINE

Carcinogen Assessment Group
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C.

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PREFACE

The Carcinogen Assessment Group of the Office of Health and Environmental Assessment has prepared this evaluation at the request of the Office of Air Quality Planning and Standards and the Office of Mobile Sources. The purpose of the document is to review the available evidence regarding the carcinogenicity of gasoline vapors to people exposed to vapor emissions during refueling of motor vehicles. This review characterizes the likelihood that gasoline vapors are carcinogenic to exposed humans and provides an upper-bound quantitative estimate of the human risk per unit of exposure. This information is needed to assist the Agency in evaluating risk management options for reducing the hazard from exposure to gasoline vapors. In the development of this document the available scientific literature has been reviewed through 1985.

ABSTRACT

In this document the likelihood that unleaded gasoline vapors are carcinogenic to humans is evaluated. From carcinogenicity data in animals, an estimate is made of the magnitude of cancer risk a person would experience, under the assumption that gasoline vapors are carcinogenic. All biological factors believed to be relevant to carcinogenesis are reviewed including: (a) chronic and shorter-term animal studies of aerosolized whole gasoline, various gasoline fractions, and analogous hydrocarbon mixtures; and (b) epidemiologic studies of occupations involving exposure to gasoline vapors. Fifty-five epidemiologic studies involving gasoline exposure are reviewed. A quantitative analysis of cancer incidence in the two long-term animal gasoline inhalation studies is performed, an upper-bound cancer risk potency estimate is calculated, and the uncertainties in the estimate are discussed. The major conclusions are: (1) although employment in the petroleum refineries is possibly associated with cancers of the stomach, respiratory system, and lymphopoietic and hematopoietic tissues, exposure to gasoline cannot be implicated as a causative agent because of confounding exposure to other chemicals and inadequate information on gasoline exposure; (2) the occurrence of liver cancer in female mice and kidney cancer in male rats provides "sufficient" evidence in animals that inhalation of wholly aerosolized gasoline is carcinogenic; and (3) gasoline vapors from vehicle refueling might be less carcinogenic than indicated by animal experiments using wholly aerosolized gasoline, if the less volatile components, which are apparently responsible for acute kidney toxicity, also contribute to the observed carcinogenic response.

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1. SUMMARY AND CONCLUSIONS

1.1. SUMMARY

1.1.1. Qualitative

1.1.1.1. Animal Studies--A lifetime inhalation bioassay of unleaded gasoline in Fischer 344 rats and B6C3F1 mice has induced a statistically significant increased incidence (6/100) of renal carcinomas in the kidney cortex of male rats and a larger, also statistically significant, increase in the incidence (20/100) of hepatocellular carcinomas in female mice. Female rats and male mice had no significant treatment-related increase in tumors at any organ site. The increase of renal carcinomas in male rats was statistically significant at the highest dose tested (2,056 ppm) but not at the two lower doses (292 ppm and 67 ppm). However, the combined incidence of adenoma/carcinoma/sarcoma was also significantly increased at the intermediate dose. In mice, the incidence of liver carcinomas alone and adenoma and carcinoma combined was significantly increased in the highest but not the two lower dose groups. Moderate decrements in the body weight gain in the high-dose groups indicate that the maximum tolerated dose was reached. Glomerulonephrosis occurred in nearly all of the male rats, and mineralization of the pelvis was correlated with dose. However, there was no correlation between animals with tumors and those with mineralization.

The same pattern of glomerulonephritis, as well as positive tumor responses, occurred with chronic inhalation exposure to synthetic fuels (RJ-5 and JP-10). Chronic inhalation studies with jet fuels used by the Air Force and Navy (JP-4 and JP-5) have resulted in the same nephrotoxic lesions, but no information is available about the carcinogenic response.

In a series of exposures of male rats to a variety of distillate fractions as well as to individual components of gasoline, toxicity was correlated with the paraffin compounds present in the 145° to 280°F distillate fractions and not with aromatic compounds in the mixture. The most toxic compounds were branched-chain aliphatics, generally in the C6-C9 range, although some larger molecules such as 2,2,4,4-tetramethyl octane also showed a high level of activity. The acute and subchronic renal toxicity of decalin, a volatile hydrocarbon of the same general type as those found in gasoline, is confined to male rats and did not occur in female rats or in mice, dogs, or guinea pigs.

The renal toxicity pattern observed with exposure to hydrocarbon mixtures involving protein accumulation in renal tubules is clearly different than the kidney lesions occurring spontaneously in old rats, and occurs in males of both Fischer 344 and Sprague-Dawley strains, but not in females of these strains or in mice or monkeys. Mutagenesis tests of unleaded gasoline have been carried out in Salmonella, yeast, mouse lymphoma *in vivo* cytogenetics, in mouse dominant lethal systems, and in a rat kidney cell DNA repair model. Various gasoline feedstocks have been tested in mouse lymphoma and *in vivo* cytogenetics assays. The results of most of these assays have not met the criteria for positive responses.

1.1.1.2. Epidemiologic Studies--Fifty-five studies were reviewed to determine if there is any epidemiologic evidence for an association between gasoline exposure and cancer risk. Since unleaded gasoline was only introduced in the mid-1970s, even recent epidemiologic studies are not likely to show an unleaded gasoline effect because of the long latency period generally associated with cancer. Therefore, this review was not limited to unleaded gasoline exposure, but addressed any potential gasoline exposure.

None of the studies reviewed provided qualitative as well as quantitative estimates of gasoline exposure.

Seven studies were identified that evaluated the association between employment in the gasoline service industry and cancer risks; the industry here includes gasoline service station owners and attendants, garage workers, gasoline and fuel truck drivers, and those who reported working with gasoline. The study by Stemhagen et al. (1983) provided some evidence of an association between gasoline service station employment and risk of primary liver cancer. The remaining six studies were judged inadequate.

Twenty-five studies were reviewed that evaluated the association between employment in a petroleum refinery (a work environment with potential gasoline exposure) and cancer risk. Judged individually, these studies provided inadequate evidence of an association. However, judged collectively these studies provide suggestive evidence of an association between employment in a petroleum refinery and risk of stomach cancer, respiratory system cancer (i.e., lung, pleura, nasal cavity, and sinuses), and cancer of the lymphatic and hematopoietic tissues.

Nineteen case-control studies were reviewed which evaluated employment in the petroleum industry as a cancer risk factor. The study by Howe et al. (1980) provided limited evidence of an association between petroleum industry employment and risk of bladder cancer.

Also reviewed were four protocols of epidemiologic studies in progress. These studies may provide evidence of an association between gasoline exposure and cancer risk; however, these findings are 3 to 5 years in the future.

1.1.2. Quantitative

Data from the API study on kidney tumors in male rats and liver adenomas and carcinomas in female mice were used to derive an estimate of the incremen-

tal upper-limit unit risk due to continuous human exposure to 1 ppm of unleaded gasoline. Since the animals breathed an aerosol of whole gasoline under laboratory conditions, whereas humans are expected to breathe only the more volatile components of the mixture, the estimates are uncertain. If tumor induction is caused by the same, relatively nonvolatile C6-C9 branched hydrocarbons that are primarily responsible for the nephrotoxicity in male rats, then the quantitative estimates of the risk of breathing gasoline vapors may be overly conservative. The carcinogenic potency estimate for unleaded gasoline was derived from a continuous exposure study, whereas the actual human exposure is periodic in most cases. The available information is not adequate to determine if this will result in an overestimation or an underestimation of risk. The estimates from the mouse and rat data are similar: 2.1×10^{-3} $(ppm)^{-1}$ from mouse data and 3.5×10^{-3} $(ppm)^{-1}$ from rat data.

The presence of 2% benzene in the unleaded gasoline mixture could theoretically contribute to the response, although the mouse liver and rat kidney have not been the target organs in animal experiments with benzene. Based on those experiments, it is estimated that the contribution of benzene to the response observed in the API unleaded gasoline studies could be on the order of 20%. However, there is no qualitative evidence that benzene actually is contributing to the response.

1.2. CONCLUSIONS

On the basis of a small but definite kidney tumor response in male rats and a significant hepatocellular response in female mice, using EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) to classify the weight of evidence for carcinogenicity in experimental animals, there is sufficient evidence to conclude that gasoline vapors are carcinogenic in animals. The similar pattern of response in rats to the synthetic fuels RJ-5 and JP-10,

and the renal toxicity observed in chronic bioassays with JP-4 and JP-5, support the findings with unleaded gasoline, indicating that some agent or combination of agents common to these mixtures is responsible for the observed effects.

The relevance of the rat kidney response to human carcinogenicity has been questioned on the basis of experiments showing that early-occurring kidney toxicity is apparently caused by the interaction of gasoline hydrocarbon components with a unique protein (alpha-2-microglobulin) produced in large quantities only by the male rat and not other species. If this toxicity were the cause of the kidney tumor response, the case for human carcinogenicity would be weakened. However, given the current evidence, the Carcinogen Assessment Group cannot disregard the rat kidney tumor response as an indication of potential human carcinogenicity for several reasons: (a) the link between hydrocarbon nephropathy and tumor induction is not proven; (b) with very few exceptions, chemicals causing cancer in humans also cause cancer in animals, indicating a similarity of response across the animal kingdom; and (c) the kidney of experimental animals is a demonstrated target organ for more than 100 carcinogenic chemicals.

The EPA Science Advisory Board and the Health Effects Institute have independently reviewed the earlier draft of this report. Both groups agreed that the evidence for carcinogenicity in animals meets the EPA Guidelines criteria for sufficient evidence in animals and inadequate evidence in humans. They both pointed out the uncertain relevance of rat kidney tumors as an indication of human response and the difficulty in making quantitative estimates of gasoline vapor potency from the animal study of whole gasoline when the identity of the carcinogenic component is unknown.

The epidemiologic studies collectively provide limited evidence that occupational exposure in the petroleum industry is associated with certain types of cancer. However, the evidence for evaluating gasoline as a potential carcinogen is considered inadequate under the EPA Guidelines criteria for epidemiologic evidence.

Based on sufficient evidence in animal studies and inadequate evidence in epidemiologic studies, the overall weight of evidence for unleaded gasoline is EPA category B2, meaning that unleaded gasoline is a probable human carcinogen.

The carcinogenic potency of unleaded gasoline, using data from the most sensitive species tested, is 3.5×10^{-3} per ppm. This is a plausible upper bound for the increased cancer risk from unleaded gasoline, meaning that the true risk is not likely to exceed this estimate and may be lower.

2. INTRODUCTION

This document presents an evaluation of the likelihood that unleaded gasoline is a human carcinogen and provides a basis for estimating its possible public health impact, including a potency evaluation in relation to other carcinogens. The evaluation of carcinogenicity depends heavily on animal bioassays and epidemiologic evidence. However, other factors, including mutagenicity, metabolism (particularly in relation to interaction with DNA), and pharmacokinetic behavior have an important bearing on both the qualitative and quantitative assessment of carcinogenicity. This document presents an evaluation of the animal bioassays and relevant toxicity studies, the human epidemiologic evidence, the quantitative aspects of assessment, and finally, a summary and conclusions dealing with all of the relevant aspects of the carcinogenicity of unleaded gasoline.

3. ANIMAL STUDIES

Although a number of experiments have been carried out to assess the acute and subchronic toxicity of gasoline vapors, only one long-term study has been conducted to date for the purpose of evaluating the carcinogenicity of unleaded gasoline. This inhalation study, using Fischer 344 rats and B6C3F1 mice, was conducted at the request of the American Petroleum Institute (API) and has been published by MacFarland et al. (1984). This chapter contains a review by EPA's Carcinogen Assessment Group (CAG) of the chronic inhalation study and other studies related to the health impact of gasoline vapors or its constituents.

3.1. LIFETIME INHALATION BIOASSAY IN RATS AND MICE (INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION, 1983)

The following is a review of a final report of a study on the carcinogenicity of unleaded gasoline vapor in Fischer 344 rats and B6C3F1 mice. The study was completed by the International Research and Development Corporation (IRDC) for the API in 1983 and has been published by MacFarland et al. (1984).

The physicochemical properties and the formulation of unleaded gasoline test sample, as described by the sponsor, are presented in Tables 3-1 and 3-2. The unleaded gasoline used in the API inhalation study was blended specifically for the experiment. The test gasoline contained no EDB or EDC (as does leaded gasoline). The benzene content of the test gasoline was 2.0%. In comparison to commercial unleaded gasoline the test gasoline contained a higher proportion of benzene (average percentage in commercial gasoline was 1.3 in 1977) and of heavy catalytic-cracked naphtha (HCCN).

Exposures in the API animal inhalation study to the total gasoline vapor were conducted in 16-m^3 glass and stainless steel chambers. Humidity and temperature within the chambers were approximately 55% and 25°C, respectively.

TABLE 3-1. PHYSICOCHEMICAL CHARACTERISTICS[a] OF THE TEST MATERIAL

Research octane no.	92.0
Motor octane no.	84.1
(R+M)/2	88.1
Reid vapor pressure, lbs.	9.5
Distillation, ASTM D-86	
IBP, °F	93
10% evap., °F	116
50% evap., °F	216
90% evap., °F	340
End point, °F	428
API gravity	60.6
Gum, ASTM D381, mg/gal	1
Sulfur, ppm	97
Phosphorus, g/gal	< 0.005
Lead, g/gal	< 0.05
Stability, hours	24+
HC analysis, ASTM D1319	
Aromatics, vol. %	26.1
Olefins, vol. %	8.4
Saturates, vol. %	66.5
Benzene content, vol. %	2.0

[a]All of the above information was supplied by the sponsor, the American Petroleum Institute.

SOURCE: IRDC, 1982.

TABLE 3-2. FORMULATION OF UNLEADED GASOLINE

Generic stream[a]	CAS number	Volume %
Light catalytic-cracked naphtha	64741-55-5	7.6
Heavy catalytic-cracked naphtha	64741-54-5	44.5
Light catalytic-reformed naphtha	64741-63-5	21.3
Light alkylate naphtha	64751-66-8	22.0
Benzene added to bring to 2%		0.8
Butane added to increase Reid vapor pressure		3.8
Plus: Antioxidant 5 lbs/1,000 bbl		
Metal deactivator 5 lbs/1,000 bbl		

[a]Toxic Substance Control Act (TSCA) PL 94-469: Candidate List of Chemical Substances, Addendum 1, Generic Terms Covering Petroleum Refinery Processed Streams, January 1978.

Gasoline vapor was generated by metering liquid through a heated vaporization column; the vapor was carried by dry nitrogen to the inlet port of the chamber, where the vapor was diluted with filtered air at a flow rate of 910 to 1,900 L/min to achieve the desired atmospheric concentrations.

Exposure concentrations are given in Table 3-3. Actual concentrations, measured by gas chromatography, and nominal concentrations approximated desired concentrations rather closely.

The same protocol was used for the study in rats and mice. Rats and mice were about 6 weeks old when the study began. Initial body weights were: male rats, 95 to 129 g; female rats, 79 to 105 g; male mice, 14 to 26 g; female mice, 12 to 20 g. Animals were randomly assigned to exposure groups according to body weight. Three treatment groups, each composed of 100 males and 100 females, were exposed to measured levels of 67, 292, or 2,056 ppm of gasoline vapor. An untreated group of 100 males and 100 females was exposed to filtered chamber air only. Animals were exposed 6 hours/day, 5 days/week until final sacrifice at 107 weeks (male rats and male mice), 109 weeks (female rats), and 113 weeks (female mice). Ten males and 10 females per group were sacrificed at 3, 6, 12, and 18 months.

Animals were observed daily, and body weights were recorded monthly for the first 17 months and biweekly thereafter. Hematology was evaluated for seven males and seven females per group at 18 and 24 months. Serum from seven males and seven females per group was biochemically analyzed at 3, 6, 12, 18, and 24 months. Ten animals from each dose/sex group were killed after 3, 6, 12, and 18 months of exposure to provide for periodic histopathologic evaluation.

Survivors, interim sacrificed animals, and decedents were necropsied, and tissues, organs, and tumors were examined microscopically. Major organs were weighed.

TABLE 3-3. INHALATION EXPOSURE CONCENTRATIONS FOR A CARCINOGENICITY STUDY ON UNLEADED GASOLINE VAPOR IN FISCHER 344 RATS AND B6C3F1 MICE

Exposure group	Desired concentration (ppm)	Nominal concentration[a] (ppm)	Actual concentration[a] (ppm)
Low	50	129	49.7
Mid	275	596	273
High	1,500	2,963	1,501

[a]The actual concentration data have not been corrected for the "nitrogen effect" on instrument calibration. Furthermore, an error in chamber airflow rate calibrations was reported which increased the actual airflow rate to approximately twice the assumed flow rate. If the corrections discussed in the study report are applied, the most probable nominal and actual concentrations were as follows:

Exposure group	Nominal concentration (ppm)	Actual concentration (ppm)
Low	72	67
Mid	310	292
High	1,713	2,056

SOURCE: IRDC, 1982.

Exposure to unleaded gasoline vapor did not affect survival. All groups of rats and female mice had greater than 50% survival for the entire study, and survival for all groups of male mice was greater than 50% for at least 95 weeks.

Body weight trends are given in Tables 3-4 and 3-5. Modest reduction of weight gain was found in male and female rats and male mice in the high-dose groups. No effect of gasoline vapor on weight gain in female mice was observed.

Organ weights (absolute and organ/body) did not appear to be affected by treatment with gasoline vapor, with the exception of significant ($p < 0.05$) increases in kidney weights and kidney/body weight ratios in high-dose male rats, as shown in Table 3-6.

At the 3-month interim sacrifice, dose-related nonneoplastic histopathologic changes were observed in the male rats. These consisted of cortical multifocal renal tubular basophilia, protein casts, and chronic interstitial inflammation. The basophilia was present in epithelial cells of renal tubules. The proteinaceous tubular casts occurred within dilated renal tubules and were commonly located at the corticomedullary junction. The incidence was 70 and 100% in mid- and high-dose males, respectively. Chronic interstitial inflammatory foci with a predominantly lymphoid cell type were observed at 20 and 70% incidence in mid- and high-dose males, respectively. In addition, renal congestion and very small foci of renal cortical mineralization were noted in several rats.

In animals dying in the 3- to 6-month interval or sacrificed at 6 months, the nonneoplastic renal changes in male rats described above were again evident. The incidence of tubular basophilia was 0%, 40%, 100%, and 100% in control, low-, mid-, and high-dose male rats, respectively. Proteinaceous casts were observed

TABLE 3-4. BODY WEIGHT TRENDS IN A CARCINOGENICITY STUDY OF UNLEADED GASOLINE VAPOR IN FISCHER 344 RATS

Study week	Mean body weight + S.D. (grams)			
	Control	67 ppm	292 ppm	2,056 ppm
Males				
0	112 ± 8	113 ± 8	113 ± 9	112 ± 8
13	306 ± 18	316 ± 15[b]	312 ± 16[a]	290 ± 18[b]
26	348 ± 19	361 ± 19[b]	350 ± 20	340 ± 16[b]
52	409 ± 27	412 ± 27	398 ± 24[a]	376 ± 20[b]
78	401 ± 31	406 ± 41	393 ± 20	376 ± 25[b]
106	416 ± 29	403 ± 44	388 ± 33	364 ± 32
Females				
0	93 ± 6	93 ± 6	92 ± 6	92 ± 6
13	173 ± 11	186 ± 11[b]	177 ± 12[a]	173 ± 9
26	209 ± 12	210 ± 11	201 ± 12[b]	192 ± 10[b]
52	250 ± 18	256 ± 16[a]	249 ± 18	225 ± 13[b]
78	264 ± 19	274 ± 19[a]	263 ± 21	246 ± 16[b]
108	288 ± 35	282 ± 31	289 ± 48	255 ± 27

[a]Statistically different from control group at $p \leq 0.05$.
[b]Statistically different from control group at $p \leq 0.01$.

SOURCE: Adapted from IRDC, 1982.

TABLE 3-5. BODY WEIGHT TRENDS IN A CARCINOGENICITY STUDY OF UNLEADED GASOLINE VAPOR IN B6C3F1 MICE

Study week	Control	Mean body weight + S.D. (grams) 67 ppm	292 ppm	2,056 ppm
Males				
0	22 ± 2	21 ± 2	22 ± 2	22 ± 2
13	30 ± 2	29 ± 2	31 ± 2[b]	31 ± 2
26	33 ± 2	32 ± 2[a]	32 ± 2[a]	34 ± 2[a]
52	38 ± 4	36 ± 3[b]	35 ± 3[b]	35 ± 3[b]
78	38 ± 4	37 ± 4	37 ± 3[a]	35 ± 3[b]
102	39 ± 4	37 ± 5	38 ± 3	35 ± 3
Females				
0	18 ± 2	18 ± 2	18 ± 2	18 ± 2
13	25 ± 1	25 ± 1	26 ± 1[a]	26 ± 1[b]
26	28 ± 1	28 ± 2	28 ± 1	29 ± 2
52	31 ± 3	32 ± 4	30 ± 2	30 ± 2[a]
78	35 ± 3	35 ± 5	34 ± 3[b]	32 ± 3[b]
112	34 ± 3	35 ± 4	34 ± 3	32 ± 3

[a]Statistically different from control group at $p \leq 0.05$.
[b]Statistically different from control group at $p \leq 0.01$.

SOURCE: Adapted from IRDC, 1982.

TABLE 3-6. EFFECT OF CHRONIC EXPOSURE TO UNLEADED GASOLINE VAPOR ON KIDNEY WEIGHTS AND KIDNEY/BODY WEIGHT RATIOS IN MALE FISCHER 344 RATS

Weight measured	Month of study	Kidney weights and kidney/body weight ratios: Dose group 0 ppm (control)	67 ppm	272 ppm	2,056 ppm
Kidney	3	2.39 ± 0.32[a](10)[b]	2.39 ± 0.32 (10)	2.41 ± 0.20 (10)	2.70 ± 0.24[c] (10)
Kidney/body	3	8.19 ± 0.80 (10)	7.82 ± 0.80 (10)	8.13 ± 0.54 (10)	9.35 ± 0.49[d] (10)
Kidney	6	2.62 ± 0.32 (10)	2.71 ± 0.26 (10)	2.64 ± 0.16 (10)	2.84 ± 0.17 (10)
Kidney/body	6	7.87 ± 0.55 (10)	7.76 ± 0.64 (10)	8.03 ± 0.36 (10)	8.86 ± 0.39[d] (10)
Kidney	12	3.07 ± 0.19 (10)	3.13 ± 0.19 (10)	3.30 ± 0.32 (10)	3.13 ± 0.38 (10)
Kidney/body	12	8.02 ± 0.55 (10)	7.94 ± 0.40 (10)	8.29 ± 0.31 (10)	8.78 ± 0.74[d] (10)
Kidney	18	2.70 ± 0.19 (10)	2.64 ± 0.19 (10)	2.73 ± 0.13 (10)	2.80 ± 0.11 (10)
Kidney/body	18	6.94 ± 0.49 (10)	7.26 ± 1.18 (10)	7.37 ± 0.51 (10)	7.83 ± 0.44[d] (10)
Kidney	24	2.80 ± 0.33 (26)	2.91 ± 0.34 (38)	2.87 ± 0.24 (34)	3.13 ± 0.34[d] (32)
Kidney/body	24	6.93 ± 0.95 (26)	7.38 ± 1.09 (38)	7.55 ± 0.71[c] (34)	8.75 ± 1.01[d] (32)

[a]Mean ± S.D.
[b]Number of animals evaluated.
[c]Statistically significant difference compared to control group ($p \leq 0.05$).
[d]Statistically significant difference compared to control group ($p \leq 0.01$).

SOURCE: IRDC, 1982.

in 27% of the control male rats, 80% of the mid-dose male rats, and 100% of the high-dose male rats. The incidence of chronic interstitial inflammation was 18, 20, 100, and 100% in control, low-, mid-, and high-dose male rats, respectively. Mineralization in a radial pattern within the renal pelvis, with material located within tubules or the collecting ducts of the renal pelvis, was observed in 20% of the high-dose males.

At the 12-month interim sacrifice, the occurrence of proteinaceous casts in the kidneys of male rats was nearly equal in all groups: 20%, 30%, 30%, and 30% in control, low-, mid-, and high-dose male rats, respectively. Mineralization in the renal pelvis occurred in 20% of the mid-dose male rats and in 80% of the high-dose male rats. Progressive glomerulonephrosis was diagnosed in one high-dose male rat. Another new finding was karyomegaly (very large nuclei within renal tubular epithelial cells) in male rats.

The complexity of nonneoplastic morphologic alterations observed in the kidneys of all rats, especially males, increased after 18 months of exposure. Progressive glomerulonephrosis occurred with higher incidence than previously. The lesion was characterized by atrophied or sclerosed glomeruli, dilated renal tubules containing proteinaceous casts, tubular damage with regeneration or scarring, and the presence of foci of chronic inflammatory cells. The incidence of glomerulonephrosis in male rats was 20% in controls, 30% in the mid-dose group, and 20% in the high-dose group; the incidence in female rats was slightly lower. Proteinaceous casts in the kidneys of male rats were noted in 50, 50, 40, and 60% of control, low-, mid-, and high-dose male rats, respectively. Mineralization in the renal pelvis was seen in 20% of the mid-dose and 80% of the high-dose male rats. Renal congestion was commonly seen, and karyomegaly was again noted in male rats. A benign renal cortical adenoma was diagnosed in a high-dose male rat. Mononuclear cell leukemia was diagnosed in the kidney of

a female rat that died during the 12- to 18-month interval.

At the final sacrifice, nearly all male rats exhibited progressive glomerulonephrosis. The incidence rates were 100, 95, 97, and 100% in control, low-, mid-, and high-dose male rats, respectively. A slightly lower rate of occurrence was seen in female rats. Mineralization in the renal pelvis occurred in 0, 5, 63, and 91% of the control, low-, mid-, and high-dose males, respectively. Karyomegaly was observed occasionally in the male rats. One mid-dose male rat had renal tubular epithelial hyperplasia at termination. The lesion was characterized by the presence of a large dilated tubule containing a cystic lumen lined by epithelial cells. Renal cysts, epithelial cell pigmentation, hydronephrosis, chronic interstitial inflammation, congestion, cortical and pelvic mineralization in female rats, and necrosis were among the nonneoplastic lesions observed in the 18-month to terminal sacrifice period.

Pathologic examination of the rats revealed a small incidence of renal tumors in each treated group of male rats (Table 3-7). The first of these tumors was detected at the 18-month interim kill. Renal carcinomas were found in each treated group of male rats, with those in high-dose males being significantly ($p < 0.05$) increased compared to controls (Table 3-7). A statistical test for linear trend was significant at the 0.05 level. Among females, one renal sarcoma was reported in the mid-dose group. Renal carcinomas generally consisted of epithelial cells in a tubular or acinar pattern in the cortex, and renal adenomas mainly included small masses of epithelial cells forming tubular or papillary structures in the cortex. Renal sarcomas consisted primarily of spindle cells in a more pelvic location. The following percentages of final sacrificed male rats had mineralization of the renal pelvis: control, 0%; low-dose, 5%; mid-dose, 63%; high-dose, 91%. Mineralization of the renal pelvis was not found in each kidney with a tumor (Table 3-8); hence, mineraliza-

TABLE 3-7. KIDNEY TUMOR INCIDENCE IN MALE FISCHER 344 RATS FROM CHRONIC EXPOSURE TO UNLEADED GASOLINE VAPOR

Tumor type	Exposure group (ppm gasoline vapor) 0 (control)	67	292	2,056	Time to first tumor (day)
Renal adenoma/ adenoma cortex	0/100[a]	0/100	2/100	1/100	546
Renal carcinoma/ renal carcinoma undifferentiated	0/100[b]	1/100[c]	2/100	6/100[c,d,e]	692
Renal sarcoma[f]	0/100	0/100	1/100	0/100	748
Total	0/100[b]	1/100	5/100[d,e]	7/100[c,d,e]	

[a]Number with tumor/number examined.
[b]Statistical analysis for linear trend was significant at the 0.05 level.
[c]In the IRDC (1982) interim report, renal carcinomas were diagnosed in 2 low-dose and 5 high-dose male rats. Further analysis of the kidney sections, as indicated in the subsequent final report on the study, resulted in the observation of renal carcinomas in 1 low-dose and 6 high-dose male rats.
[d]The 100 animals in each denominator in this table include 40 animals sacrificed at 3, 6, 12, and 18 months, and decedents and survivors in the remaining 60 animals which were allowed to survive for the duration of the study. If the 40 interim sacrificed animals are excluded from each denominator to allow replacement of the 100 total animals with the 60 animals allowed to survive for the duration of the study, the statistically significant differences shown in this table remain significant at $p < 0.05$.
[e]Statistically significant ($p < 0.05$) increase compared to control group by Fisher Exact Test.
[f]A renal sarcoma was also found in a female rat in the 292-ppm exposure group.

SOURCE: IRDC, 1982; MacFarland et al., 1984.

TABLE 3-8. INDIVIDUAL DATA ON MINERALIZATION OF THE RENAL PELVIS AND KIDNEY TUMORS IN MALE AND FEMALE FISCHER 344 RATS EXPOSED TO UNLEADED GASOLINE VAPOR[a]

Dose group	Rat identification number[b]	Kidney tumor type (grade)[bc]	Renal pelvis mineralization (grade)[c]
Males			
67 ppm	1339	Carcinoma (3)	None
272 ppm	1442	Carcinoma (2)	None
	1381	Carcinoma, undifferentiated (0-4)	None
	1447	Sarcoma (4)	None
	1420	Adenoma (3)	Present (1)
	1380	Adenoma (2)	Present (3)
2,056 ppm	1467	Carcinoma (3)	Present (3)
	1550	Carcinoma (3)	None
	1481	Carcinoma (3)	Present (3)
	1490	Carcinoma	Present (3)
	1506	Carcinoma, undifferentiated (3)	Present (2)
	1544	Carcinoma, undifferentiated (3)	Present (3)[d]
	1501	Adenoma, cortex (2)	Present (2)
Females			
292 ppm	1842	Sarcoma (0-4)	None

[a]These data are taken from the IRDC (1982) report except where indicated.
[b]These data represent the final review of the kidney slides as presented by Kitchen (1983) at the Workshop on the Kidney Effects of Hydrocarbons.
[c]Grading system: 1 = very slight
2 = slight or small
3 = moderate
4 = severe
[d]Mineralization located in renal cortex instead of renal pelvis.

tion of the renal pelvis does not appear to have been a requirement in the etiology of kidney tumor formation in rats exposed to unleaded gasoline vapor.

Spontaneous kidney tumor formation is rare in male Fischer 344 rats; for example, Goodman et al. (1979) reported a historical control incidence of one kidney adenoma (0.05%), two kidney adenocarcinomas (0.11%), and three benign mixed kidney tumors (0.17%), for a total of six kidney tumors (0.33%) formed spontaneously in 1,794 untreated Fischer 344 rats evaluated in the National Cancer Institute's Carcinogenesis Testing Program from 1972 through 1978. The historical control incidence of 0.11% reported by Goodman et al. (1979) is 20-fold less than the 2% incidence of kidney adenocarcinomas in low-dose males shown in Table 3-7.

A significantly ($p < 0.01$) increased incidence of hepatocellular carcinomas alone and of hepatocellular adenomas and carcinomas combined was found in high-dose female mice as compared to control mice (Table 3-9). Except for a hepatocellular carcinoma in a high-dose female mouse that died at between 12 and 18 months, the observation of hepatocellular adenomas and carcinomas in female mice, as shown in Table 3-9, was confined to those animals necropsied from 18 months through final sacrifice. Hepatocellular carcinomas were described as having invasive, trabecular, and solid patterns with areas of necrosis and cytoplasmic vacuolization. Macroscopic findings in the liver of male and female mice included lobulated masses of raised red firm foci which correlated with histopathologic diagnoses of adenomas and carcinomas in liver. Mucoserous nasal discharge, possibly related to an irritant effect of gasoline vapor, was noted for male and female high-dose mice. A papillary cystic adenoma of the renal cortex was found in a high-dose female mouse killed at final sacrifice, and bilateral renal tubular adenocarcinomas were found in a high-dose female mouse which died in the period between 18 months and final sacrifice.

TABLE 3-9. HEPATOCELLULAR TUMOR INCIDENCE IN FEMALE B6C3F1 MICE FROM CHRONIC EXPOSURE TO UNLEADED GASOLINE VAPOR

Hepatocellular tumor type	Exposure group (ppm gasoline vapor)			
	0 (control)	67	292	2,056
Adenoma	1/100[a]	4/100	3/100	7/100
Carcinoma	7/100	6/100	9/100	20/100[b,c]
Adenoma and carcinoma combined	8/100	10/100	12/100	27/100[b,c]

[a]Number with tumor/number examined.
[b]Statistically significant ($p < 0.01$) increase compared to control group.
[c]The 100 animals in each denominator in this table includes 40 animals sacrificed at 3, 6, 12, and 18 months and decedents and survivors in the remaining 60 animals which were allowed to survive for the duration of the study. If the 40 interim sacrificed animals are excluded from each denominator to allow replacement of the 100 total animals with the 60 animals allowed to survive for the duration of the study, the statistically significant differences shown in this table remain significant at $p < 0.01$.

SOURCE: IRDC, 1982.

In summary, exposure to unleaded gasoline vapor produced a small but statistically significant ($p < 0.05$) increase in renal carcinomas in male Fischer 344 rats, and a statistically significant increase ($p < 0.01$) in hepatocellular carcinomas in female B6C3F1 mice under the conditions of this bioassay. Moderate body weight gain decreases with no reduction in survival in high-dose groups suggest that a maximum tolerated dose was approached; however, mineralization in the kidney indicates that exposure to unleaded gasoline vapor produced toxicity in this organ in each treated group of male rats. Applying the International Agency for Research on Cancer (IARC) classification approach for carcinogens, as well as EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), the EPA's Carcinogen Assessment Group (CAG) concludes that these studies furnish sufficient evidence for the carcinogenicity of unleaded gasoline vapor in animals under the conditions of the bioassay.

3.2. 90-DAY INHALATION EXPOSURE STUDY WITH GASOLINE VAPOR IN RATS AND MONKEYS (MacFARLAND, 1983)

A 90-day inhalation exposure study of the toxicity of unleaded gasoline vapor in Sprague-Dawley rats and squirrel monkeys was performed as a prechronic test in preparation for the carcinogenicity study with unleaded gasoline in rats and mice. In the 90-day study, rats and monkeys were exposed 6 hours/day, 5 days/week for 13 weeks to totally vaporized unleaded EPA reference gasoline and a leaded commercial gasoline, as shown in Table 3-10. The hydrocarbon composition of the two gasolines was similar, but the unleaded gasoline contained 5 mg/gallon of lead and the leaded gasoline contained 1.94 g/gallon of lead. The animals were examined for mortality, body weight, food consumption, toxic signs, hematological changes, urinary changes, tissue lead levels, and pathology. Pulmonary function tests and cortical flash-evoked response tests were also done on the monkeys.

TABLE 3-10. DESIGN OF THE 90-DAY INHALATION EXPOSURE STUDY

Concentration group	Number[a] and species of animals		Dose (ppm)
	Rats	Monkeys	
I. Control	40	8	0
II. Unleaded gasoline	40	8	384
III. Unleaded gasoline	40	8	1,552
IV. Leaded gasoline	40	8	103
V. Leaded gasoline	40	8	374

[a]Equally divided as to sex.

Some female monkeys in Groups III and V showed emesis. Body weights in male rats in Groups II and IV were significantly greater at termination. Female rats in Group III had increased reticulocyte counts, and some rats in Group V had increases in hematocrit and mean corpuscular volume, and decreases in white cell count and mean corpuscular hemoglobin concentration.

Male monkeys in Groups III and V had an increased minute volume. Female monkeys in Group III had a reduced respiratory rate, and female monkeys in Group V had a decreased tidal volume at termination.

Liver weights were increased in male rats in Groups II and IV and decreased in Group V female rats. Kidney weights were increased in Group IV female rats and Group V male monkeys. Thyroid weights were increased in male monkeys in Groups II and III. Heart/body weights were decreased in male rats in Groups IV and V, and brain weights were decreased in male rats in Groups II and III. Group V female rats had decreases in liver/body and adrenal/body weights.

The initial pathological examinations showed no treatment-related effects. Histopathologic reexamination of tissue sections showed subtle but discernible changes in kidneys of Group III male rats. These changes were described as an increase in the incidence and severity of regenerative epithelium, and proteinaceous material in dilated tubules was found.

3.3. RENAL TOXICITY OF GASOLINE AND RELATED PETROLEUM NAPHTHA IN MALE RATS (HALDER ET AL., 1984)

The renal effects of subchronic inhalation exposure of male and female Sprague-Dawley rats to wholly vaporized unleaded gasoline and related petroleum naphthas described in Table 3-11 were reported by Halder et al. (1984). The results of this study are presented in Tables 3-12 through 3-20. This study is especially pertinent to the unleaded gasoline carcinogenicity study in that it gives an indication as to which fractions in unleaded gasoline can produce kidney toxicity.

Exposure of male and female Sprague-Dawley rats to unleaded gasoline for 21 days induced mild tubular degenerative and regenerative changes with increases in hyalin droplets in the renal cortex in males. Corticomedullary tubular dilatation and necrosis were found in one high-dose male rat.

A 90-day exposure to unleaded gasoline resulted in a treatment-related incidence of tubular dilatation and necrosis at the corticomedullary junction in male rats, along with a dose-related severity. The persistence of these lesions during a 4-week recovery period suggests an irreversible effect.

Similar 21-day exposures of rats to full-range alkylate naphtha, polymerization naphtha, light catalytic-reformed naptha, and light straight-run naphtha induced renal lesions in males similar to those obtained with unleaded gasoline treatment. Milder renal lesions were found in males exposed to light catalytic-cracked naphtha. No renal effects were noted with exposure to heavy

TABLE 3-11. SUMMARY OF THE COMPOSITION AND BOILING RANGES OF THE TEST MATERIALS

Material	Composition (%)			Boiling range (°F)	
	Paraffins[a]	Olefins	Aromatics	10% bp	90% bp
Light straight-run naphtha	96	0	4	71	222
Light catalytic-cracked naphtha	39	32	29	174	346
Light catalytic-reformed naphtha	67	2	31	137	230
Heavy catalytic-reformed naphtha	7	0	93	290	364
Full-range alkylate naphtha	98	2	0	124	315
Polymerization naphtha	8	92	<1	205	353
Unleaded gasoline blend	45[b]	12[b]	43[b]	112	326

[a]Includes cyclo-, normal, and branched.
[b]Estimated.

TABLE 3-12. NEPHROTOXIC EFFECTS IN RATS FOLLOWING A 21-DAY INHALATION EXPOSURE TO LIGHT STRAIGHT-RUN NAPHTHA

Group and concentration[a]	Incidence[b] M	Incidence[b] F
Environmental control	0/10	0/10
Sham control	0/10	0/10
1.50 mg/L (395 ppm)	0/10	0/10
5.13 mg/L (1,349 ppm)	0/10	0/10
14.56 mg/L (3,829 ppm)	3/10	0/10

[a]Analytical time-weighted average in mg/L (ppm).
[b]Incidence of tubular dilation and necrosis at corticomedullary junction.

TABLE 3-13. NEPHROTOXIC EFFECTS IN RATS FOLLOWING A 21-DAY INHALATION EXPOSURE TO LIGHT CATALYTIC-CRACKED NAPHTHA

Group and concentration[a]	Effects
Sham control	
0.20 mg/L (43 ppm)	
2.04 mg/L (434 ppm)	Evidence of early degenerative changes in kidneys of treated male rats.
13.06 mg/L (2,777 ppm)	

[a]Analytical time-weighted average in mg/L (ppm).

TABLE 3-14. NEPHROTOXIC EFFECTS IN RATS FOLLOWING A 21-DAY INHALATION EXPOSURE TO LIGHT CATALYTIC-REFORMED NAPHTHA

Group and concentration[a]	Incidence[b] M	Incidence[b] F
Environmental control	0/10	0/10
Sham control	0/10	0/10
2.00 mg/L (544 ppm)	0/10	0/10
5.85 mg/L (1,591 ppm)	1/10	0/10
20.30 mg/L (5,522 ppm)	3/10	0/10

[a]Analytical time-weighted average in mg/L (ppm).
[b]Incidence of tubular dilation and necrosis at corticomedullary junction.

TABLE 3-15. NEPHROTOXIC EFFECTS IN RATS FOLLOWING A 21-DAY INHALATION EXPOSURE TO HEAVY CATALYTIC-REFORMED NAPHTHA

Group and concentration[a]	Incidence[b] M	Incidence[b] F
Environmental control	0/10	0/10
Sham control	NE[c]	NE
1.03 mg/L (215 ppm)	NE	NE
2.81 mg/L (587 ppm)	0/10	0/10
10.20 mg/L (2,132 ppm)	0/10	0/10

[a]Analytical time-weighted average in mg/L (ppm).
[b]Incidence of tubular dilation and necrosis at corticomedullary junction.
[c]NE = Not examined. Pathology was not done due to lack of adverse effects at higher concentrations.

TABLE 3-16. NEPHROTOXIC EFFECTS IN RATS FOLLOWING A 21-DAY INHALATION EXPOSURE TO FULL-RANGE ALKYLATE NAPHTHA

Group and concentration[a]	Incidence[b]	
	M	F
Environmental control	0/10	0/10
Sham control	0/10	0/10
1.54 mg/L (345 ppm)	10/10	0/10
4.92 mg/L (1,104 ppm)	10/10	0/10
15.31 mg/L (3,434 ppm)	10/10	0/10

[a]Analytical time-weighted average in mg/L (ppm).
[b]Incidence of tubular dilation and necrosis at corticomedullary junction.

TABLE 3-17. NEPHROTOXIC EFFECTS IN MALE RATS FOLLOWING A REPEAT 21-DAY INHALATION EXPOSURE TO FULL-RANGE ALKYLATE NAPHTHA

Group and concentration[a]	Incidence in males[b]
Sham control	0/40
0.015 mg/L (3 ppm)	0/20
0.152 mg/L (34 ppm)	4/10
1.538 mg/L (345 ppm)	11/20

[a]Analytical time-weighted average in mg/L (ppm).
[b]Incidence of tubular dilation and necrosis at corticomedullary junction.

TABLE 3-18. NEPHROTOXIC EFFECTS IN RATS FOLLOWING A 21-DAY INHALATION EXPOSURE TO POLYMERIZATION NAPHTHA

Group and concentration[a]	Incidence[b] M	F
Environmental control	0/10	0/10
Sham control	0/10	0/10
1.04 mg/L (215 ppm)	0/10	0/10
3.05 mg/L (632 ppm)	2/10	0/10
9.89 mg/L (2,049 ppm)	4/10	0/10

[a]Analytical time-weighted average in mg/L (ppm).
[b]Incidence of tubular dilation and necrosis at corticomedullary junction.

TABLE 3-19. NEPHROTOXIC EFFECTS IN RATS FOLLOWING A 21-DAY INHALATION EXPOSURE TO AN UNLEADED GASOLINE BLEND

Group and concentration[a]	Incidence[b] M	F
Environmental control	0/10	0/10
Sham control	0/10	0/10
0.11 mg/L (29 ppm)	0/10	0/10
1.58 mg/L (416 ppm)	0/10	0/10
12.61 mg/L (3,316 ppm)	1/10	0/10

[a]Analytical time-weighted average in mg/L (ppm).
[b]Incidence of tubular dilation and necrosis at corticomedullary junction.

TABLE 3-20. NEPHROTOXIC EFFECTS IN RATS FOLLOWING A 90-DAY INHALATION EXPOSURE TO AN UNLEADED GASOLINE BLEND

Group and concentration[a]	Incidence[b]			
	Terminal sacrifice		Four-week recovery	
	M	F	M	F
Environmental control	0/10	0/10	0/10	0/10
Sham control	0/10	0/10	0/10	0/10
0.15 mg/L (40 ppm)	1/10	0/10	1/10	0/10
1.44 mg/L (379 ppm)	7/10	0/10	5/10	0/10
14.70 mg/L (3,866 ppm)	5/10	0/10	4/10	0/10

[a]Analytical time-weighted average in mg/L (ppm).
[b]Incidence of tubular dilation and necrosis at corticomedullary junction.

catalytic-reformed naphtha.

The results of these studies suggest that paraffin and alkene fractions are effective as renal toxicants and that aromatics are relatively nontoxic. The unleaded gasoline blend included some of the naphtha materials tested in this study, and although the unleaded gasoline composition is proprietary, it was mentioned that it contained 22% full-range alkylate naphtha, a fraction which could be a significant factor in renal toxicity induced by unleaded gasoline exposure.

3.4. TOXICITY OF ORGANIC CHEMICALS PRESENT IN UNLEADED GASOLINE

In order to more accurately determine which compounds present in unleaded gasoline are the primary sources of nephrotoxicity in rats, a series of studies sponsored by the American Petroleum Institute were carried out. Unleaded gasoline was distilled into 0° to 145°F, 145° to 220°F, 220° to 280°F, and 280°F+ fractions. Each of these fractions, as well as the individual aliphatic hydrocarbons comprising the major portion of each fraction, were evaluated in a series of subchronic studies. The individual studies are described below.

3.4.1. 13-Week Inhalation Toxicity Study of a 0° to 145°F Gasoline Distillate Fraction in Rats (IIT Research Institute, 1985a)

Fischer 344 rats of both sexes were exposed to a 0° to 145°F gasoline distillate fraction 6 hours/day, 5 days/week via inhalation over a 13-week period. The concentration was maintained at 1,000 or 4,500 ppm. No evidence of hydrocarbon nephropathy or other toxic signs were detected in either male or female rats.

3.4.2. 13-Week Inhalation Toxicity Study of C4/C5° Hydrocarbon Blends in Rats (IIT Research Institute, 1985b)

Fischer 344 rats were exposed to the same concentrations under the same experimental conditions as those in the previous study. Two vapor mixtures

were used. One was a 50:50 mixture of n-butane and n-pentane. The other was a 50:50 mixture of isobutane and isopentane. These four chemicals comprise over 70% of the hydrocarbons present in the 0° to 145°F distillate fraction of unleaded gasoline. The exposure-related effects were nominal with no evidence of hydrocarbon nephropathy.

3.4.3. Renal Toxicity of Whole Unleaded Gasoline, Fractions of Unleaded Gasoline, Various Naphthas, and Some Individual Components, in Male Rats (Halder et al., 1984)

This study was designed to evaluate, in greater detail, the components of unleaded gasoline in the less volatile fractions responsible for the induction of renal toxicity in rats. Test materials included whole unleaded gasoline, 145° to 220°F, 220° to 280°F, 280°F+ distillate fractions, four naphthas, and a variety of individual organic components. Fischer 344 male rats were exposed to the test materials via oral gavage at 0.5 or 2.0 mg/kg/day, 5 days/week for 4 weeks. The kidneys were scored for three types of lesions, hyaline droplet formation, regenerative epithelium, and tubular dilation with granular material. The lesions were graded on a severity of 1 to 5, with the scores for the three lesions added, then summed over 10 animals per group.

The results are listed in Tables 3-21, 3-22, and 3-23. Of the individual compounds tested, straight-chain alkanes and alkenes, cyclic alkanes, and aromatics were relatively nontoxic. The most toxic compounds were aliphatic hydrocarbons in the C6-C9 range with multiple branching. Of the chemicals tested, 2,2,5-trimethylpentane and 2,2,5-trimethylhexane were the most active. Since the majority of the C6-C9 branched-chain alkanes are found in the 145° to 220°F and the 220° to 280°F fractions, the finding that these two fractions were highly toxic agreed well with the results for individual chemicals. The high degree of toxicity of the light alkylate naphtha was also in good agreement

TABLE 3-21. EFFECTS OF 4 WEEKS' ORAL EXPOSURE TO FRACTIONS OF UNLEADED GASOLINE

Test material	Dose (g/kg/day, 5 days/week)	Average nephropathy score
Saline	--	27
PS-6 unleaded gasoline	0.5	84[a]
	2.0	83[a]
Light catalytic-cracked naphtha	0.5	37[a]
	2.0	53[a]
Heavy catalytic-cracked naphtha	0.5	36[a]
	2.0	34[a]
Light catalytic-reformed naphtha	0.5	33
	2.0	38[a]
Light alkylate naphtha	0.5	96[a]
	2.0	88[a]
145-220°F gasoline fraction	0.5	60[a]
	2.0	89[a]
220-280°F gasoline fraction	0.5	99[a]
	2.0	104[a]
280-end°F gasoline fraction	0.5	42[a]
	2.0	31

[a] $p \leq 0.05$, Mann-Whitney U test.

TABLE 3-22. EFFECTS OF 4 WEEKS' ORAL EXPOSURE TO ORGANIC CHEMICALS PRESENT IN GASOLINE (SERIES 1)

Test material	Dose (g/kg/day, 5 days/week)	Average nephropathy score
Saline	--	30
PS-6 unleaded gasoline	0.5	92[a]
	2.0	91[a]
n-Pentane	0.5	27
	2.0	23
2-Methylbutane	0.5	25
	2.0	21
2-Methylpentane	0.5	46[a]
	2.0	59[a]
2,3-Dimethylbutane	0.5	76[a]
	2.0	61[a]
2,2,5-Trimethylhexane	0.5	94[a]
	2.0	96[a]
2-Methyl-2-pentene	0.5	30
	2.0	35
Methylcyclopentane	0.5	29
	2.0	34
m-Xylene	0.5	27
	2.0	26

[a] $p \leq 0.05$, Mann-Whitney U test.

TABLE 3-23. EFFECTS OF 4 WEEKS' ORAL EXPOSURE TO ORGANIC CHEMICALS PRESENT IN GASOLINE (SERIES 2)

Test material	Dose (g/kg/day, 5 days/week)	Average nephropathy score
Saline	--	29
PS-6 unleaded gasoline	0.5	64[a]
	2.0	55[a]
n-Hexane	0.5	27
	2.0	31
2-Methylhexane	0.5	42[a]
	2.0	36
2,3-Dimethylpentane	0.5	61[a]
	2.0	66[a]
2,2,4-Trimethylpentane	0.5	76[a]
	2.0	85[a]
Trans-2-pentene	0.5	27
	2.0	29
Toluene	0.5	34
	2.0	19
1,2,4-Trimethylbenzene	0.5	33
	2.0	31

[a] $p \leq 0.05$, Mann-Whitney U test.

with results for individual chemicals since 45% of an analyzed sample was found to consist of trimethyl pentane.

3.4.4. 4-Week Oral Nephrotoxicity Screening Study in Male F344 Rats (Tegeris Laboratories, 1985)

This study was designed to evaluate the nephrotoxicity of a variety of aliphatic hydrocarbons present in the 280°F+ distillate fraction of unleaded gasoline. The following chemicals were tested:

API PS-6-fuel
2,3-Dimethyloctane
2-Methyldecane
Decane
3-Methyloctane
Octane
2,2,3-trimethyloctane
2,2,7,7-Tetramethyloctane
2,2,4,4-Tetramethyloctane
2,3,3-Trimethyldecane
2,2,4,4-Tetramethyldecane
2,3-Dimethyldecane
2,2,4,4,5,5,7,7-Octamethyloctane

Fischer 344 male rats were exposed to the test materials via oral gavage, 5 days/week for 4 weeks. Total dosage was 2.0 g/kg body weight. Only three of the individual chemicals induced detectable toxic effects in the kidney. In comparison with the API PS-6 fuel, which was given a moderately severe rating for induction of nephropathy, 2,2,4,4-tetramethyloctane was rated as severe; 2,2,3-trimethyloctane as moderate; and 2,2,4,4-tetramethyldecane was rated as inducing only slight effects.

3.5. RENAL EFFECTS OF DECALIN IN SEVERAL LABORATORY MAMMALIAN SPECIES (ALDEN ET AL., 1983)

A comparison of the renal effects in various laboratory mammalian species exposed to decalin (a prototype volatile hydrocarbon composed of two cyclohexane rings) was discussed by Alden et al. (1983). One of the observations presented was that a 91-day inhalation exposure to 5 ppm and 50 ppm decalin induced renal toxicity in male Fischer 344 rats and not in females, male or female mice, male or female dogs, and male or female guinea pigs (Table 3-24).

TABLE 3-24. BIOLOGICAL TESTING OF DECALIN, A PROTOTYPE VOLATILE HYDROCARBON

Species tested	Renal injury	Reference
Rats (male/female)	+/-	AFAMRL-TR-79-121 (Wright-Patterson AFB)
Mice (female)	-	
Dogs (male/female)	-/-	
Guinea pigs (male/female)	-/-	AFMRL-TR-78-55 (Wright-Patterson AFB)
Mice (male)	-	Dr. Logan Stone (personal communication)

The observed renal effects in male rats included hyalin droplets in the cytoplasm of proximal convoluted tubular epithelial cells, granular casts at the junction of the inner and outer band of the outer zone of the medulla, and augmented chronic glomerulonephropathy. These droplets consist of an alpha-2-microglobulin, a protein synthesized in the male rat liver under the control of testosterone and endogenous corticosterone. They occur spontaneously in sexually mature male rats but not in castrated males, in female rats, or in humans.

3.6. TOXICITY OF SYNTHETIC FUELS AND MIXED DISTILLATES IN LABORATORY ANIMALS (MacNAUGHTON AND UDDIN, 1983)

Toxicity studies on mixed distillates and synthetic fuels in experimental animals have been or are being done by the United States Air Force, and preliminary results of these studies were reported by MacNaughton and Uddin (1983). The studies are summarized below. The design of the experiments, in which the agents were given by inhalation, is shown in Table 3-25. Beagle dogs, Fischer 344 rats, Syrian Golden hamsters, and C57BL/6 mice were used.

3.6.1. Studies with RJ-5 Synthetic Fuel

RJ-5 fuel consists of hydrogenated dimers of norbornadiene with a vapor pressure of 1.3 kPa at 103°C.

Results of the studies with a 1-year exposure to 30 mg/m^3 and 150 mg/m^3 were as follows:

1. Decreased body weight gain in rats and dogs, with possible appetite suppression.
2. Acute lung inflammation and some bronchopneumonia in rats and dogs sacrificed immediately after 6 months of treatment.
3. After a 1-year holding period, there was a 25% incidence of alveolar carcinomas in CF-1 mice (the strain shown in the workshop proceedings), a strain predisposed to this tumor type.

The results of the studies in which dogs, mice, hamsters, and rats were exposed to 30 or 150 mg/m^3 for 1 year followed by a 1-year holding period were as follows:

1. Decreased body weight gain in exposed male rats and male hamsters throughout the study. Increased body weight gain in exposed female rats during treatment was reversed during the post-treatment period.
2. Decreased ($p < 0.05$) kidney/body weights in exposed female rats.

TABLE 3-25. DESCRIPTION OF FUEL INHALATION EXPOSURES

Fuel	Exposure (months)	Concentration (mg/m^3)	Species[a]	End date
Synthetic				
JP-10	12, int[b]	560	D,R,M/F,H	Completed
RJ-5	6, cont[c]	155	D,R,M/F,M	Completed
RJ-5	12, int	30, 150	D,R,M/F,H	Completed
Mixed distillate				
JP-4	8, int	2,500, 5,000	D,R,M,M/F	Completed
JP-4	3, cont	500, 1,000	D,R,M/F	Dec. 1983
JP-4	12, int	500, 1,000	R,M/F	Jul. 1984
JP-5	3, cont	150 750	D,R,M/F	Completed
JP-5 (S)[d]	3, cont	250, 750	D,R,M/F	Completed
JP-7	12, int	150, 750	R,M/F	Dec. 1985
JP-8	3, cont	500, 1,000	R,M/F	Jul. 1985
JP-TS	12, int	200, 1,000	R,M/F	Dec. 1985
DFM	3, cont	50, 300	R,M/F	Completed
DFM (S)	3, cont	50, 300	R,M/F	Completed

[a]D (dogs); R (rats); M (monkeys); M/F (mice, female); H (hamsters).
[b]Intermittent (6 hours/day, excluding weekends and holidays).
[c]Continuous.
[d]Shale.

3. Four (7%) renal cell adenomas and five (8%) renal cell carcinomas in high-dose male rats; one (2%) renal cell carcinoma in a low-dose male rat. No renal cell carcinomas were seen in controls.

4. Other kidney lesions in exposed male rats were:

Lesion	Incidence		
	150 mg/m^3	30 mg/m^3	Control
Renal medullary mineralization	57/62 (92%)	2/59 (3%)	0%
Moderate pelvic urothelial hyperplasia	58%	7%	2%
Hyaline droplets	18%	19%	2%
Cortical cysts	24%	2%	0%

3.6.2. Studies with JP-10 Synthetic Fuel

JP-10 fuel is a bicyclic, bridged compound; exotetrahydrodi(cyclopentadiene), with a vapor pressure of 1.87 kPa.

Results of the studies with a 1-year exposure at 562 mg/m^3 followed by a 1-year recovery period were:

1. Slight weight loss in exposed rats and hamsters.
2. Hepatocellular vacuolization in 50% of the control and 75% of the exposed female mice.
3. Nine renal cell carcinomas in treated male rats compared to one in contols; poorly differentiated malignant neoplasms in one control and one treated male rat.
4. Other renal effects in male rats were:

Lesion	Incidence	
	Treated	Control
Augmented renal tubule degeneration compatible with old-rat nephropathy	43/49 (87%)	32/49 (65%)
Medullary mineral deposits (mineralized cell debris)	100%	0%
Papillary hyperplasia of renal pelvic epithelium	26/49 (53%)	2/49 (4%)

5. No toxic lesions in female mice.
6. Adrenal cortical adenomas and carcinomas were found in 27% of the control and 28% of the treated male hamsters; however, adrenal zona glomerulosa adenomas and adrenal zona glomerulosa hyperplasia were found in 14% and 72% of treated male hamsters, respectively, and 5% and 45% of control male hamsters, respectively.

3.6.3. Studies with JP-4 Mixed Distillate

JP-4 mixed distillate has characteristics similar to gasoline and has a vapor pressure of 13 kPa. JP-4 represents 85% of the turbine fuel used by the Department of Defense.

Results of studies with an 8-month intermittent exposure to 2,500 and 5,000 mg/m^3 (containing 80 mg/m^3 benzene) were:

1. Increased organ and organ/body weights for kidney, liver, spleen, and lung in exposed male rats.
2. A 27% incidence of bronchitis in exposed rats.
3. A transient increase in red blood cell fragility in female dogs.

Results of studies with a 90-day continuous exposure to 500 and 1,000 mg/m^3 with a 19-month holding period were:

1. Increases in serum globulin and total protein and BUN in low-dose and high-dose dogs.
2. Decreased body weight gain in exposed male and female rats during treatment.
3. Centrilobular hepatocellular fatty change in 88% of the low-dose and 89% of the high-dose female mice.
4. Kidneys of all exposed male rats contained hyalin droplets in the proximal tubular epithelium, and focal dilatation of renal tubules near the corticomedullary junction with plugging by cellular debris was found in 96% of the low-dose and 100% of the high-dose male rats.

Results of studies with a 1-year exposure to 500 and 1000 mg/m^3 were:

1. Decreases in body weight and in kidney and liver weights in high- and low-dose male rats.
2. Decreases in spleen and kidney weights in low-dose female rats.

3.6.4. Studies with JP-5

JP-5 mixed distillate is the other major turbine engine fuel besides JP-4. Results of studies with a 90-day continuous exposure of dogs, rats, and mice to 150 and 750 mg/m^3 and a 19-month post-exposure period were:

1. Decreased body weight in exposed male rats.
2. Increased BUN and serum creatinine in male and female high-dose rats.
3. Mild, diffuse fatty change with small vacuoles in hepatocytes of 3% of the control, 73% of the low-dose, and 24% of the high-dose mice. "Foamy" hepatocellular cytoplasmic vacuoles were found in 18% of the control, 15% of the low-dose, and 44% of the high-dose female mice.
4. Male rats sacrificed at the end of the 90-day exposure period had dilated renal tubules filled with granular necrotic debris at the corticomedullary

junction.

5. By 19 months post-treatment, old-rat nephropathy was evident in 96%, 96%, and 84% of the high-dose, low-dose, and control males, respectively. Old-rat nephropathy was more severe in treated males. Renal medullary tubular mineralization was found in 82% of the high-dose, 59% of the low-dose, and none of the control male rats. A dose-related focal hyperplasia of the renal pelvis was reported.

In summary, chronic exposure to RJ-5 and JP-10 synthetic fuels induces a common pattern of nephrotoxicity leading to renal carcinomas. Similar studies with JP-4 and JP-5 show the same preneoplastic lesions, but no information is available about neoplastic response.

3.7. INFLUENCE OF BENZENE ON THE RENAL CARCINOGENIC EFFECTS OF UNLEADED GASOLINE VAPOR IN MALE RATS

The quantitative estimate of risk from exposure to benzene has recently been updated in an interim report (U.S. EPA, 1985). Although a number of animal studies, carried out by the appropriate route of exposure (inhalation), have shown that benzene is carcinogenic in several organs, the risk estimates derived from these studies were considered to be less reliable than epidemiologic data for estimating risk to humans. The unit risk due to a lifetime exposure to 1 ppm benzene in the air was therefore estimated from leukemia incidence data in exposed humans. Using various models and a combination of assumptions and epidemiologic studies, 21 unit risk estimates ranging from 0.9×10^{-2} to 1×10^{-1} were obtained. Based upon the criteria of using the data from all epidemiologic studies with reasonable exposure information and an average value over all mathematical models thought to be plausible, a combined unit risk estimate of 2.6×10^{-2} was derived. This was taken to be the CAG's best judgment of unit risk.

3.8. CONCLUSIONS OF THE UAREP REPORT (1983) ON TOXICOLOGICAL INTERPRETATION OF HYDROCARBON-INDUCED KIDNEY LESIONS

An analysis of the toxicology and carcinogenicity of unleaded gasoline and other hydrocarbons, issued by the Universities Associated for Research and Education in Pathology, Inc. (UAREP) was published in December, 1983. This section summarizes the review and interpretation of the data presented in that document.

3.8.1. Assessment of the API Chronic Inhalation Study with Unleaded Gasoline Vapor in Rats and Mice

1. There were significant increases in renal adenoma and carcinoma incidence in male Fischer 344 rats and in hepatocellular adenoma and carcinoma incidence in female B6C3F1 mice exposed to an aerosol of whole unleaded gasoline vapor. The bioassay was well designed and conducted, and there were several independent examinations of the kidney slides.
2. Male Rat Kidney Lesions in Exposed Groups
   a. Three-month findings: Focal degeneration in the proximal tubules, hyaline droplets in the proximal tubules, granular casts at the junction between the inner and outer stripes of the outer medulla, some evidence of regeneration. The lesions seemed dose related, with the greatest prominence in the high-dose group.
   b. Findings by 12 months: Karyomegaly, probably in the P_3 segment of the proximal tubules. Old-rat nephropathy, in treated as well as control rats, shown as atrophy of the P_1 segment of the proximal tubule with basement membrane thickening, mesangial thickening in the glomeruli, interstitial fibrosis with chronic inflammation, and periodic acid-Schiff (PAS)-positive tubular colloid casts in the

distal nephron. Calcium hydroxyapatite deposition in the papilla was evident in the exposed groups.

c. Findings after 12 months: Areas of hyperplasia. Progression of the severity of old-rat nephropathy, which was greater in the treated groups than in controls, as well as preneoplastic and neoplastic lesions.

d. Findings at 18 months: Renal adenoma in one rat.

e. Findings at 24 months (final sacrifice): Renal adenomas and carcinomas in treated rats.

3. Liver Pathology in Female Mice

No treatment-related lesions were found between 3 and 18 months. It could not be determined whether preneoplastic lesions preceded the liver tumors. Acute effects, such as fatty metamorphosis from exposure of mice to other hydrocarbons, were neither reported nor looked for in the carcinogenicity study with unleaded gasoline.

3.8.2. Interpretation of the Toxicological Carcinogenic Findings in the Carcinogenicity Study with Unleaded Gasoline by UAREP

1. Male Rat Kidney - Nonneoplastic Lesions

Signs of acute and chronic renal toxicity were evident. There was some necrosis, but more often there was cell degeneration and/or blebbing with release of cell debris forming casts between the pars recta (P_3 segment) and the thin limb. The kidney lesions in exposed male rats were unique in that they were unlike those induced by known nephrotoxins such as mercuric chloride, halogenated hydrocarbons, or nitrilotriacetic acid.

The mechanism of gasoline-induced nephrotoxicity is obscure. There was no uniform necrosis in the P_3 segment, and many lesions were

found in the P_1 and P_2 segments. It is currently not possible to accurately characterize the nature and location of the toxic lesions in male rat kidneys in this study.

The toxic kidney lesions were clearly distinguishable from old-rat nephropathy, which in the latter involved the whole kidney and showed atrophy of the P_1 segment of the proximal tubule and glomerular sclerosis. However, exposure to unleaded gasoline vapor augmented the severity of old-rat nephropathy.

The most striking chronic nonneoplastic lesion in exposed rats was severe mineralization of the tubules in the papilla. The deposits were characterized as calcium hydroxyapatite. The etiology behind the mineralization is uncertain, but it was hypothesized that chronic damage in the proximal tubule and higher segments in the nephron leads to phospholipid vesicle-induced calcification. The observed calcification pattern is unique to hydrocarbon exposures, and chronic exposure of male rats to JP-10 synthetic missile fuel has also induced mineralization in the kidney.

2. Male Rat Kidney - Preneoplastic and Neoplastic Lesions

The neoplastic process resulting from treatment of male rats with unleaded gasoline resembles that induced by several other renal carcinogens: karyomegaly, probably in the P_3 segment, followed by hyperplasia, followed by adenomas that were often cystic, and carcinomas. These preneoplastic and neoplastic lesions were found in association with the increased severity of old-rat nephropathy, but it was not possible to characterize their precise location, nature, or progression. It was not possible to establish the influence of old-rat nephropathy on these lesions, and the mechanism for the induction of these preneo-

plastic and neoplastic lesions is unknown.

3. Liver Lesions in Female Mice

Acute toxicity or preneoplastic lesions were not found in the livers of female mice, according to the carcinogenicity study report; however, hematoxylin and eosin staining is not sensitive for the detection of preneoplastic lesions. Acute toxicity studies with other hydrocarbons in mice have revealed fatty metamorphosis in the liver. The neoplasms in livers of female mice exposed to unleaded gasoline vapor resembled mouse liver neoplasms found in other studies, but such neoplasms are often phenotypically similar regardless of etiology.

3.8.3. Review of Human Kidney Lesions

1. Acute - There are no thorough studies on human kidney lesions resulting from acute exposure to hydrocarbons. Case reports indicating structural and functional changes in the kidney show the main lesions as variants of an immune complex type of glomerular nephritis, a type of lesion that has not been found in rodents. The mechanism of acute toxicity in the case reports is difficult to pinpoint because of confounding factors.
2. Chronic - There is no persuasive evidence that human exposure to gasoline is associated with renal cancer. There is no evidence for the calcification of papilla or calculi in the bladder or kidney from human exposure to gasoline. Human renal adenocarcinomas are morphologically similar to those found in male rats chronically exposed to unleaded gasoline vapor, as well as to well-characterized models of rodent renal neoplasia induced by chemical carcinogens. However, renal adenocarcinomas develop in human kidneys that are normal except for a putative increase in hyperplasia and adenomas, whereas adenocarcinomas in the kidneys of rats chronically exposed to unleaded gasoline vapor occurred

with a background of chronic, and often severe, renal disease. An apparent increase in the incidence of adenomas and carcinomas in the kidneys of dialysis patients is the only possible equivalent to adenocarcinoma induction in rats. This possible similarity between humans and rats needs to be further investigated, but it is consistent with the view that any type of chronic renal injury, e.g., old-rat nephropathy, can possibly act as a promoter and/or cocarcinogen in the induction of renal neoplasia.

Human renal cancer can occur along with chronic interstitial nephritis, e.g., chronic analgesic nephropathy. This type of cancer arises in the renal pelvic epithelium to yield transitional cell carcinomas totally different in location and structure from the lesions seen in the chronic rat study with unleaded gasoline.

3.8.4. Species and Sex Comparison of the Kidney

Renal morphology has been most thoroughly studied in the rat, rabbit, and dog. There has been no detailed ultrastructural study in the mouse kidney. A detailed ultrastructural study has been done with renal biopsies from 10 human males who were screened for renal dysfunction.

The human kidney is multilobular, without the distinct zonation caused by the alignment of nephrons in the unilobar rodent kidney. The rodent kidney has a long loop of Henle and long papillae to allow extensive concentration of urine. The human kidney has nothing like the outer stripe of the outer medulla in the rodent kidney, which contains the pars recta (P_3 segment) of the proximal tubule and the ascending limb of the loop of Henle. The human kidney has an ultrastructurally simple proximal tubule in contrast to the kidney of the rat, mouse, and rabbit. No morphological differences between the kidneys of male and female humans have been described.

The size and number of lysosomes in the P_1, P_2, and P_3 segments in the male rat kidney are larger than in the female rat kidney. This may be correlated with the unique production of alpha-2-microglobulin and resorption of this protein in the proximal tubule in the male rat kidney. Endoplasmic reticulum and microbodies are more prominent in female than in male rat kidneys, which may indicate a difference between them in metabolic capacity. Castration and hypophysectomy of male rats decrease the differences in the proximal tubule, particularly lysosomes, between male and female rat kidneys.

Hyaline droplets in the P_1 and P_2 segments have been found in kidneys of male rats exposed to hydrocarbons other than unleaded gasoline vapor, e.g., decalin. These droplets consist mainly of protein, including alpha 2-microglobulin, within the phagolysosomal system of the male rat kidney. In the male rat kidney it is presumed that, with no evidence of acute glomerular lesions, these droplets represent accumulations of endogenous proteins that are produced in the male rat liver and resorbed by the kidney, to be phagocytized by lysosomes. Protein accumulation by the kidney could be due to increased synthesis and uptake and/or decreased degradation. The mechanism of hydrocarbon nephrotoxicity is presently unclear. Exposure to decalin produces hyaline droplets in male but not in female rats, and these droplets have been observed to disappear quickly after cessation of treatment with decalin. However, it is not known whether chronic lysosomal overload can produce cell injury in rat kidney proximal tubules.

Less is known about renal mixed function oxidase (MFO) than about liver MFO. There are marked species, strain, and sex differences in the metabolic capability of the rodent kidney. There are potentially significant quantitative and, to a lesser degree, qualitative differences in renal MFO components and activity among species. In all species studied thus far, MFO activity has

been localized in the proximal tubule and usually in the P_3 and/or P_2 segments. Little data exist on MFO in the human kidney. Metabolites from other organs can possibly go to the kidney to produce toxicity in vivo. Specific studies on renal MFO and unleaded gasoline toxicity are lacking, but there is some evidence that renal MFO may play a role in the renal toxicity of other hydrocarbons.

3.8.5. Rodent Kidneys and Other Hydrocarbons

The only hydrocarbon fuel other than unleaded gasoline that has been tested in a chronic rodent bioassay is the synthetic missile fuel JP-10. Exposure to JP-10 was found to induce renal carcinomas in male Fischer 344 rats.

Most solvents and hydrocarbons have induced similar acutely toxic lesions in the rodent kidney; however, no specific mechanism of action has been determined, nor has an ultrastructural analysis been done.

Paraffin and isoparaffin fractions have been found to be more acutely toxic in rodent kidneys than are other fractions of petroleum products. The most toxic individual compounds were C6-C9 aliphatics with multiple branching.

The mutagenicity of unleaded gasoline has been reported as negative. However, in the in vitro assays, only S-9 fractions from rat liver were used, which may not relate to other organs: also, there may have been a problem with the volatility and solubility of the gasoline in these assays.

None of the tested hydrocarbons has produced a uniform necrosis in the pars recta epithelium, as is commonly seen in the rodent kidney with other renal toxins, such as mercuric chloride.

Acute lesions in the rodent kidney from hydrocarbon exposure have been characterized as hyalin droplet accumulations, focal areas of degeneration and necrosis, epithelial regeneration, and granular casts in the corticomedullary junction.

3.8.6. Old-Rat Nephropathy

Old-rat nephropathy is characterized by interstitial fibrosis, thickening of tubular basement membranes, interstitial chronic inflammation, vascular thickening in interlobular and afferent arterioles, glomerular hyalinization, and tubular atrophy, especially in the P_1 segment of the proximal tubule.

In the unleaded gasoline carcinogenicity bioassay, increased numbers of mitoses, hyperplasia, karyomegaly, and other preneoplastic lesions were not seen in control rats.

Old-rat nephropathy may start at an early age. Old females show a lesser degree of nephropathy than males. The severity of old-rat nephropathy varies among strains.

Old-rat nephropathy was morphologically different from preneoplastic lesions in the API carcinogenicity study of unleaded gasoline vapor. However, a possible etiologic relationship between old-rat nephropathy and toxic lesions from exposure to unleaded gasoline vapor cannot be ruled out.

In humans, chronic renal disease has been associated with renal adenocarcinoma only in kidney dialysis patients. Lesions in the kidneys of these patients are morphologically similar to those seen in male rats in the chronic unleaded gasoline vapor study, as well as in other rodent studies with hydrocarbons. No human control group has been studied along with the dialysis patients.

Old-rat nephropathy resembles focal and segmental glomerulosclerosis in human disease and, to a lesser extent, arteriolar and arterial nephrosclerosis in aging humans. Several patients with renal carcinoma following dialysis had renal failure secondary to nephrosclerosis, and one of these patients had multiple calculi in the kidney.

Studies with the liver indicate a greater ability of younger than of older

rats to metabolize carcinogens; however, a similar comparison with the kidney still needs to be explored.

3.8.7. Comparative Nephrotoxicity and Nephrocarcinogenicity

Species, strain, and sex differences in response to nephrotoxins are clearly evident. Many chemical classes of nephrotoxins induce similar morphological effects, and most nephrotoxic chlorinated hydrocarbons affect primarily the P_3 segment of the proximal tubule, which is apparantly lacking in humans. However, few agents have well-characterized mechanisms of acute and chronic renal toxicity. Some chlorinated hydrocarbons, e.g., chloroform, have chronic, carcinogenic effects that do not always correspond to acute effects in terms of target organ response.

Chloroform induces a selective and uniform degeneration and necrosis of proximal tubule epithelial cells, with the effect being greatest in areas with the greatest MFO activity, as supported by studies in rats and dogs. Similar patterns of proximal tubule degeneration from exposure to chloroform have been observed in these two species.

There is evidence that similarity of morphological end points does not necessarily indicate similarity between mechanisms. For example, nitriloacetic acid may act as a promoter in the induction of renal adenocarcinomas in rats, but the renal adenocarcinomas induced by this agent are morphologically similar to those observed in rats in the chronic unleaded gasoline vapor study. Acute, but not chronic, renal lesions from mercuric chloride treatment are unlike those induced by exposure to hydrocarbons. Mercuric chloride, as well as chlorinated hydrocarbons, initially induces selected necrosis in the renal P_3 segment, and with higher doses also induces progressive necrosis in the P_1 and P_2 segments.

3.8.8. Significance to Humans of the Chronic Inhalation Study with Unleaded Gasoline Vapor in Rats and Mice

1. The relationship between old-rat nephropathy and renal neoplasia in the chronic unleaded gasoline study is presently uncertain. Although renal neoplasia in male rats exposed to unleaded gasoline does not appear to stem from basophilic cells in the old-age renal lesions, a role of the old-age lesions in the etiology of renal neoplasia presently cannot be ruled out. In humans, chronic renal disease has been associated with an increased incidence of renal cancer.
2. No statistically significant association between renal epithelial neoplasia and environmental agents, except for cigarette smoke, has been found in humans. Tumors of the renal pelvis in humans have been associated with exposure to environmental agents.
3. Anatomical and physiological differences between rat and human kidneys may contribute to differences in renal responses to environmental agents, including unleaded gasoline. This issue needs further study.

3.9. RESEARCH IN PROGRESS OR PLANNED UNDER THE SPONSORSHIP OF THE AMERICAN PETROLEUM INSTITUTE

The purpose of the research sponsored by the API and being carried out principally by the Chemical Industry Institute for Technology (CIIT) is to attempt to link kidney pathology in male rats induced by gasoline vapors to the induction of cancer, and to show that this is a unique response in the male rat. According to these investigators' hypothesis, tumors of the kidney arise because of an increased rate of errors in the replication of DNA in the kidney cells. This increased replication error rate accompanies hyperplasia in the kidney tissue, which is a response to cellular damage caused by accumulation in the kidney proximal tubule cells of a low molecular weight protein (alpha-2-mi-

croglobulin) complexed with a metabolic product of the branched-chain aliphatic hydrocarbons present in gasoline vapors. After complexing with the hydrocarbons, the protein becomes resistant to breakdown by the tubule cells, resulting in accumulation of hyaline droplets, followed by cell death, the accumulation of cellular debris, and an increased rate of cell division.

In support of this hypothesis, it was shown that only male rats and not female rats, mice, hamsters, or humans produce alpha-2-microglobulin in large amounts, that radioactively-labeled hydrocarbons administered to male rats appear in kidney tissue complexed with proteins at the place where tumors arise (unpublished data), and that DNA repair, an indicator of genotoxicity, is absent in kidney cells following exposure to unleaded gasoline (Loury and Butterworth, 1986). Studies will be carried out to determine if gasoline acts as an initiator, as a promoter, or as a complete carcinogen. Finally, attempts are being made to develop an immunoassay for detection of proteins analogous to alpha-2-microglobulin in humans.

3.10. SUMMARY OF ANIMAL STUDIES

A lifetime inhalation bioassay of unleaded gasoline in Fischer 344 rats and B6C3F1 mice induced a significant increase in renal carcinomas in the kidney cortex of male rats and a larger, also significant increase in hepatocellular carcinomas in female mice. Female rats and male mice had no significant treatment-related induction of tumors at any organ site. The incidence of renal carcinomas was significantly increased only at the highest dose tested (2,056 ppm). However, if renal adenomas, carcinomas, and sarcomas are combined, the increase was significant at both the high and intermediate dose levels. In mice the increase in the incidence of liver carcinomas alone and adenoma and carcinoma combined was statistically significant only in the highest dose group. Moderate decrements in body weight gain in the high-dose groups indicate that

the maximum tolerated dose was reached. Glomerulonephrosis occurred in nearly all male rats, and mineralization of the pelvis was correlated with dose. However, there was no correlation between animals with tumors and those with mineralization.

The acute and subchronic renal toxicity of decalin, a volatile hydrocarbon of the same general type as those contained in gasoline, is confined to male rats and does not occur in female rats or in mice, dogs, or guinea pigs. In a series of 21-day inhalation exposures of male rats to a variety of chemical fractions of gasoline, renal toxicity was correlated with the paraffin components; specifically, those having C6-C9 carbons with one or more branches, and not with the aromatic compounds in the mixture. The same pattern of renal toxicity as well as a positive renal tumor response occurs in response to chronic inhalation of two synthetic fuels (RJ-5 and JP-10). Chronic inhalation studies with the jet fuels used by the Air Force and Navy (JP-4 and JP-5) have shown the same nephrotoxic lesions, but information on the carcinoma response is not available. The renal toxicity pattern observed with exposure to hydrocarbon mixtures, involving protein accumulation in renal tubules, is clearly different than the kidney lesions occurring spontaneously in old rats, and occurs in males of both Fischer 344 and Spraque-Dawley strains, but not in females of these strains or in mice or monkeys.

Mutagenesis tests of unleaded gasoline have been carried out in Salmonella, yeast, mouse lymphoma in vivo cytogenetics, and mouse dominant lethal systems. Various gasoline feedstocks have been tested in mouse lymphoma and in vivo cytogenetics assays. The results of most of these assays have not met the criteria for positive responses. A detailed examination of their adequacy is in process.

4. EPIDEMIOLOGIC STUDIES

The purpose of this section is to review the epidemiologic literature to determine if there is any epidemiologic evidence for an association between gasoline exposure and cancer risk. Since unleaded gasoline was only introduced in the mid-1970s, even recent epidemiologic studies are not likely to show an unleaded gasoline effect because of the long latency period generally associated with cancer. Therefore, this discussion is not limited to unleaded gasoline exposure but rather addresses any potential gasoline exposure.

Reviewed here are seven epidemiologic studies--six case-control studies and one proportionate mortality study--that evaluated the association between cancer risk and employment in the gasoline service industry, and 44 studies that assessed the association of cancer risk and employment in the petroleum industry, 25 of which were refinery-based. Four epidemiologic studies that are currently in progress are also reviewed. Ecological studies that evaluated the association of the petroleum industry and excess cancer risk are not reviewed (Blot and Fraumeni, 1976; Blot et al., 1977; Hearey et al., 1980; Henderson et al., 1975; Menk and Henderson, 1976; Blattner et al., 1981; Austin et al., 1984; Kaldor et al., 1984). Also excluded are early investigations of petroleum refinery workers (Gafafer, 1940; Wade, 1963; Baird, 1967); the use of non-age-adjusted mortality rates in these early studies makes any interpretation of their results questionable. Also not included are studies designed to assess specific petroleum refinery exposures of substances other than gasoline, e.g., benzene, lubricating-dewaxing (Hendricks et al., 1959; Rushton and Alderson, 1981b; Sherwood, 1972; Thorpe, 1974; Tabershaw Occupational Medicine Associates, 1980; Tsai et al., 1983; Wen et al., 1985); and studies of petrochemical workers (Alderson and Rattan, 1980; Alexander et al., 1982; Austin and Schnatter,

1983; Nicholson et al., 1982; Waxweiler et al., 1983a). Review articles are also not included; however, specific conclusions by the authors of reviews may be included (Savitz and Moure, 1984; Enterline and Viren, 1984; Raabe, 1984; Higginson et al., 1984; Bingham et al., 1980; Leese, 1982; Joyner, 1982; Weaver, 1982).

4.1. EPIDEMIOLOGIC STUDIES OF WORKERS IN THE GASOLINE SERVICE INDUSTRY

4.1.1. Stemhagen et al. (1983)

This is a retrospective case-control study of liver cancer. Cases were any New Jersey resident diagnosed with primary liver cancer between January 1, 1975, and March 1, 1980. Those diagnosed between January 1, 1975, and September 30, 1978, were identified through record searches of all New Jersey hospitals. Cases diagnosed after September 1978 were identified through the new statewide Cancer Registry. To ensure that all cases were ascertained, a search of all death certificates for the period 1975-79 was also conducted. Those with primary liver cancer (International Classification of Diseases [ICD] 155.0 and 155.1) as the underlying cause of death were traced to the hospital where the death occurred. After verifying that the initial diagnoses were made during the study period, these deceased persons were added to the study population.

A single physician reviewed medical records for all the cases to verify that cases were histologically confirmed primary liver cancers. Diagnoses were considered established if the pathologist had unequivocally diagnosed the tumors as primary malignant tumors of the liver. A consultant pathologist reviewed the medical records and/or examined histologic sections to decide doubtful cases.

Controls, two per case, were individually matched to the cases on the basis of age ($\pm$ 2 years), sex, race, and county of residence. Living controls

were matched to living cases, and deceased controls were matched to deceased cases. Living controls were selected from patient records in the hospital in which the case was diagnosed, provided that the potential control met the matching criteria and had the closest admission date to that of the case. Deceased controls were selected from state death certificate files. For deceased cases, the two controls that met the matching criteria and had the closest date of death to the case were selected. Excluded from the control population were potential controls with a known diagnosis (known either through medical or death certificate records) of liver cancer, hepatitis, cirrhosis, or other liver diseases. Also excluded as potential controls were deceased persons with homicide or suicide listed as the cause of death.

Of 959 cases of supposed primary liver cancer identified, 624 (66%) did not meet the criteria for studv inclusion. Of these, 385 (40%) were excluded because the histologic evaluation indicated a disease other than primary liver cancer (e.g., primary site other than liver), and 228 (24%) were excluded because the diagnosis was not histologically confirmed (e.g., diagnosis based on liver scan). Of the 335 cases that met the study criteria, medical records were available for 296; among these, interviews with 90% of either the next-of-kin respondents or the cases themselves were completed. Of the controls initially identified, 138 were unavailable (e.g., most moved out of study area). Of those traced, approximately 77% of either the next-of-kin or the controls themselves were finally interviewed.

The final study population consisted of 265 cases (178 males and 87 females) and 530 controls (356 males and 174 females); 81.5% of the cases were diagnosed as hepatocellular carcinoma and 9.1% as cholangiocarcinoma. The most frequent diagnoses or causes of death for the controls were ischemic heart disease, lung cancer, or cerebrovascular disease.

Interviews were conducted in the homes of the living study subjects (4%) and the proxy respondents (96%). Proxy information on the male cases and controls was usually provided by the wife. Proxy information for the female cases and controls was usually provided by the sons or daughters of the study subject. Data were collected on smoking habits, lifetime residence, medical histories, alcohol consumption, and lifetime occupational histories (since age 12). Occupational data were coded to the Census Bureau's index of industries and occupations (U.S. Bureau of the Census, 1970).

The association between liver cancer and specific exposures was determined by calculating the odds ratio (OR) by the Mantel-Haenszel procedure for multiple matched controls (Mantel and Haenszel, 1959). Comparisons within matched triplets were not maintained during the calculation of the adjusted odds ratio (adjusted for confounding or exposure level). The Mantel (1963) extension procedure was used to test for dose-response trends.

Results indicated that male primary liver cancer cases were more likely to be workers in gasoline service stations as compared to controls (OR = 2.88, 95% confidence interval [CI] 1.20-6.88). When analyses were limited to male cases with hepatocellular carcinoma and their matched controls, the risk increased more than four times (OR = 4.20, 95% CI 1.55-11.35) that of study subjects who never worked in gasoline service stations.

Also observed were significant excess risks for male subjects who worked in laundering, cleaning, and other garment services (OR = 2.50, 95% CI 1.026.14), eating and drinking places (OR = 2.19, 95% CI 1.22-3.92), as well as bartenders (OR = 2.27, 95% CI 1.03-5.04), winemakers (OR = 3.20, 95% CI 1.11-9.21), those employed in the agricultural industry (OR = 2.08, 95% CI 1.34-3.30), those employed in agricultural production or services exclusive of horticulture (OR = 2.08, 95% CI 1.33-3.23), and farm laborers (OR = 1.89, 95%

CI 1.19-3.00) as compared to the controls. The OR for miscellaneous laborers was significantly deficient (OR = 0.44, 95% CI 0.21-0.94).

A significant dose-response trend for both males ($p = 0.0014$) and females ($p < 0.012$) was found for increasing amounts of alcohol consumption (measured in milliliters of total ethanol consumed per year). No dose-response was observed for either males or females for cigarette smoking after controlling for the effects of alcohol consumption.

The authors indicated that the numbers of males with gasoline service station exposure were too few to analyze risks while simultaneously controlling for the effects of alcohol consumption (a significant confounder). However, since the risk for gasoline service station exposure (OR = 2.88, CI 1.20-6.88) was greater than the risk for alcohol consumption (OR = 2.52, CI 0.97-6.54) for those in the medium-heavy category of alcohol consumption, i.e., the category with the greatest risk, it is possible to infer that not all the excess risk observed in cases working in gasoline service stations is due to the confounding effects of alcohol.

This study provides limited data to assess the causal association between gasoline and primary liver cancer in males. Workers in gasoline service stations, while potentially exposed to gasoline, may be exposed to any number of potential carcinogens. These have neither been controlled for nor are actual quantitative measures of gasoline vapor present. No latency analyses were provided by years of employment in gasoline service. The authors noted that possible incomplete recall by proxy respondents of alcohol consumption (a significant confounder) may have resulted in an underestimation of the risk for alcohol.

4.1.2. Silverman et al. (1983)

This population-based case-control study was conducted as part of the

National Bladder Cancer Study (Hoover et al., 1980). The cases were all persons, ages 21 to 84, with histologically confirmed and newly diagnosed carcinoma (or papilloma not specified as benign) of the lower urinary tract (bladder, renal pelvis, ureter, and urethra), who were diagnosed from December 1, 1977, to November 30, 1978, and were residents of the Detroit metropolitan area (Macomb, Oakland, and Wayne Counties). The hospitals participating in the study contributed 97% of the total cases diagnosed in the area. Ninety-five percent of the cases were diagnosed with urinary bladder cancer, primary site. Therefore, the term "bladder cancer" was used to mean lower urinary tract carcinoma.

For purposes of analysis, the study population was initially limited to males. Personal interviews were obtained for 81% of the cases. Thirty-one proxy interviews were conducted because the patients were too ill or had died. Excluded were 17 cases whose physicians prohibited interviewing; 11 cases that could not be located; 29 cases that refused to cooperate; and 24 cases for which proxy respondents were not located, were too ill to be interviewed, or had died.

The age distribution of the controls was approximately that of the cases, and the controls were randomly selected from the general population of the Detroit area depending on age. Controls, ages 21 to 64, were selected by random digit dialing of all Detroit area residences with telephones. Those in the 65- to 84-year age group were randomly selected from Health Care Financing Administration records for area residents. Of the controls ages 21 to 64, 84% were interviewed; of the controls ages 65 to 84, 89% were interviewed.

Also excluded from the study was a potential control who had bladder cancer before the study period, a case with a histologic type not specified as transitional or squamous cell carcinoma, and five cases and three controls

because the subjects never held jobs longer than 6 months or the interview was considered unreliable. Analyses were finally restricted to white males because of the small numbers of non-whites. The final study population included 303 white male cases and 296 white male controls.

The questionnaire was designed to obtain detailed information on lifetime occupational history, smoking history, coffee consumption, artificial sweetener use, residential history, source of water, fluid intake, hair dye use, and medical history. Occupational data were collected for every job held for 6 or more months since age 12, and included information on job title and industry (coded according to the U.S. Bureau of the Census' alphabetical index of industries and occupations), years of employment, full-time/part-time status, job duties, materials exposed to, and frequency of exposure. Upon completion of the occupational history, interview subjects were shown checklists of known and suspected high-risk industries, occupations, and materials to elicit additional exposure information. The authors did not indicate if the interviewer was "blind" towards the status of the subject being a case or control.

The odds ratio was used to assess the association between occupational exposures and the incidence of bladder cancer. Stratified analyses were used to control for the confounding effects of age, smoking, or employment in other high-risk industries or occupations. The maximum likelihood method was used to compute summary odds ratios. The authors indicated that relative risk estimates were unaffected by adjustment unless specified. Two-sided 95% confidence intervals (CIs) for the crude odds ratios were computed by Woolf's (1954) method; CIs for the adjusted odds ratios were calculated by use of a test-based interval estimate; however, these were not always presented by the authors. The Mantel (1963) extension procedure (two-tailed) was used to test for trend. Risks were estimated relative to the risk for subjects "never employed" in that

industry or occupation. Both industry and occupational exposures were assessed.

Employment experience was defined as "ever employed" as well as by "usual" occupation or industry. Results were not presented for industries and occupations in which fewer than 15 subjects worked unless the industry or occupation had a "special interest because of previous reports."

Results were presented for 32 categories of industry employment and 54 occupational categories. The vast majority of these occupations or industries were not associated with the manufacture, marketing, or distribution of gasoline; therefore, no discussion of these occupationally related exposures is presented here.

Three of the industry categories (petroleum extracting and refining, trucking service, and gasoline service) were considered to have potential gasoline exposure. The authors reported an excess risk for "bladder cancer" cases if they worked in each of these industries. Cases were six times more likely to be in the categories of "ever employed in the petroleum extracting and refining industry" as opposed to those "never employed in the industry" (crude OR = 6.0, 95% CI 0.7-49.8). The risks were elevated for cases (crude OR = 1.6, 95% CI 0.8-3.5) if they were ever employed in the gasoline service industry, even after adjusting for the confounding effects of age and smoking (adjusted OR = 1.3, p value not reported). Cases were more likely to be ever employed in trucking service (crude OR = 2.2, 95% CI 1.1-4.4) than were controls. Of the 32 industry category comparisons made among those ever employed, only trucking service was significantly different from unity.

Results were similar whether "usual" industry or "ever employed" in each industry was considered for those in the gasoline service industry or the petroleum extraction and refining industry. However, for cases there was a "twofold increase" in risk for those usually employed in trucking service (OR =

4.3, p value not reported) in comparison to those ever employed in trucking service (OR = 2.1, p value not reported) after controlling for age and smoking.

Of the 54 occupations specified, truck driver was the only occupation in which cases experienced a significant elevation in risk (crude OR = 2.5, 95% CI 1.4-4.4). After adjusting for age and smoking, risk for cases ever employed as truckers was still twice (adjusted OR = 2.1 95% CI not reported). Among the cases who ever worked as garage workers or gas station attendants, risks were very slightly, although not significantly, elevated to 1.2 (95% CI 0.6-2.4). Risks were also elevated among those ever employed as taxicab drivers or chauffeurs (crude OR = 2.0, 95% CI 0.7-5.4), bus drivers (crude OR = 1.5, CI 0.4-5.3), and delivery men (crude OR = 1.6, 95% CI 0.9-2.6). The age- and smoking-adjusted odds ratio for delivery men rose from 1.6 for the crude to 1.8 for the adjusted (95% CIs not reported).

Risks were similar when usual occupation was considered in comparison to ever employed in an occupation. However, the age- and smoking-adjusted odds ratio for truckers rose from 2.1 for those ever employed to 5.4 for those usually employed as truckers.

To investigate an excess risk of bladder cancer, a follow-up questionnaire was administered to 36 of the 42 cases, and to 16 of the 18 controls who had worked as truckers for at least 6 months. The telephone interview solicited information on potential exposure to diesel exhausts, type of freight transported, work-related illnesses, and use of medications to stay awake.

These additional analyses (all adjusted for the effects of age and smoking) revealed that bladder cancer risks were significantly (p = 0.004) associated with an increasing duration of employment as a truck driver (10+ years of employment, adjusted OR = 5.5, 95% CI 1.8-17.3). However, no association between bladder cancer risk and duration of employment as a truck driver prior

to 1950 (when diesel trucks became more prevalent) was observed. An elevated estimate of relative risk for truck drivers who transported petroleum products was also observed (adjusted OR = 3.6, 95% CI 0.8-16.4). Truckers whose trucks were usually fueled by others were also at increased risk (adjusted OR = 1.7, 95% CI 0.8-3.9), but not of the same magnitude as those who fueled their own trucks (adjusted OR = 2.3, 95% CI 0.9-6.1). The authors pointed out that of the 52 truckers reinterviewed, only 5 cases and no controls drove a diesel truck while employed as a trucker, and that "most of their diesel exposure occurred while employed in non-trucking occupations."

This study provides weak evidence of an association between bladder cancer incidence and gasoline exposure. Workers in gasoline service, after adjusting for age and smoking, were observed to have a 30% greater risk of bladder cancer than those not working in gasoline service (adjusted OR = 1.3, p value not reported). Truck drivers were found to be at significant risk even after controlling for age and smoking (adjusted OR = 2.1). This risk increased significantly ($p = 0.004$) with increasing duration of employment as a trucker. The risk among truckers who transported petroleum products, after adjusting for age and smoking (adjusted OR = 3.6), was elevated to more than 3-1/2 times that of non-truckers. Risks were also elevated ($p > 0.05$) for cab drivers (crude OR = 2.0), bus drivers (crude = 1.5), and delivery men (adjusted OR = 1.8), all occupations with potential gasoline exposure.

The authors' analyses did control for the confounding effects of age, smoking, and other employment in high-risk industries or occupations. Analyses for other potential risk factors for bladder cancer (e.g., artificial sweeteners, coffee drinking, alcohol consumption) were also conducted.

There are limitations to the study. It was not possible to evaluate whether the excess risk could be attributed to diesel exhaust, gasoline exhaust,

diesel vapors, gasoline vapors (whether leaded or unleaded), or some other exposure. There was no quantification of gasoline vapor exposure. Some of the observed elevations in risks for bladder cancer cases for certain occupations may have been due to chance because of the large number of comparisons made in this study.

Latency analyses were not conducted for occupational exposure at the gasoline service station, or for the cab drivers, bus drivers, or delivery men. Excluded from the study population of 303 white male cases were 86 cases (race not reported) of lower urinary tract cancer. The authors presented no assessment of the impact of this potential non-response bias.

4.1.3. Mommsen et al. (1982; 1983a, b); Mommsen and Aagaard 1983a, b; 1984); Mommsen and Sell (1983)

Several publications have resulted from the authors' investigation of 212 bladder cancer cases (165 males and 47 females) and 259 controls (165 males and 94 females) in a predominantly rural area in Denmark (Mommsen et al., 1982; 1983a, b); Mommsen and Aagaard (1983a, b; 1984); Mommsen and Sell (1983). Reported here are the findings of the initial investigation of the males (1982) and a detailed analysis of male occupational factors (1984).

The case population consisted of males, ages 42 to 85, who were newly diagnosed with bladder cancer (91.5% invasive, 94.5% with transitional cell carcinoma) and admitted consecutively to the University Hospital of Aarhus, Department of Oncology and Radiotherapy, during the period September 1977 to September 1979. Terminal and intractable cases were not referred to the hospital and thus were excluded from the study population (Mommsen et al., 1983b). According to Mommsen and Aagaard (1984), the case population reflects the 2-year incidence of invasive bladder cancer among males in the area (22,000 km^2).

Information on the cases as well as controls was obtained by means of a questionnaire. Both cases and controls were given the questionnaire in advance. Subsequently, cases were interviewed by the principal investigator at the hospital following a review of the histologic specimens (Mommsen et al., 1982, 1983b; Mommsen and Aagaard, 1984).

Population-based controls were selected from the National Register for the region and individually matched to the cases on the basis of sex, age, and geographic area, including the degree of urbanization. Data on 95% of the controls were collected by telephone interview, the principal investigator serving as the interviewer. Data on 5% of the controls (those without telephones) were obtained via a mailed questionnaire (Mommsen et al., 1983b). If after a month no reply was received, a second questionnaire was mailed; and if after another month no response was received, another matched control was selected. Fifteen percent of the controls were substitute controls (Mommsen et al., 1983b).

Identical questionnaires were used for both cases and controls and solicited information on education, lifetime occupational history, socioeconomic status, medical history, family history of cancer, and subjects' use of alcohol, tobacco products, coffee, artificial sweeteners, and drug treatments.

Mommsen and Aagaard (1984) ascertained occupational histories from the time a subject completed school until he was selected as a study subject. A subject was categorized as being exposed to a particular industry based upon the job he held for the longest period of time, provided that it was held for at least 1 year. Information on possible occupational exposures was obtained from study subjects through the use of "non-structured questions" (Mommsen and Aagaard, 1984).

Bivariate associations between bladder cancer and the 13 most pronounced

independent variables were measured with the odds ratio. The 95% confidence intervals were calculated (Miettinen, 1974). Ipsen's computer program (unpublished) of the logistic regression model was used for the multivariate analyses of the data. Independent variables were categorized as dichotomous (yes/no). The dependent variable was risk of bladder cancer. A step-down procedure was used to eliminate "non-informative" independent variables from the model. Goodness-of-fit was expressed by the likelihood ratio G^2. Loss of information to the model was estimated through the increase in G^2 and ΔG^2, distributed as a chi-squared statistic with one degree of freedom (Bishop et al., 1977).

Mommsen et al. (1982) identified the following as significant ($p < 0.05$) bladder cancer risk factors in males: work with gasoline or oil (OR = 2.71, 95% CI 1.21-6.10); cigarette smoking (OR = 1.89, 95% CI 1.21-2.94); nocturia (OR = 2.05, 95% CI 1.27-3.32); prostatic surgery (OR = 2.38, 95% CI 1.16-4.90); history of venereal disease (OR = 2.42, 95% CI 1.01-5.82); and industrial work (OR = 1.82, 95% CI 1.04-3.17). Work with chemical materials (OR = 1.58, 95% CI 1.0-2.49) was found to be borderline significant. Risks for petroleum or asphalt workers were elevated (OR = 3.12) but not significantly (CI 0.91-10.75). A similar pattern of risk was seen for use of chewing tobacco (OR = 1.65, 95% CI 0.96-2.84) and alcohol (OR = 2.46, 95% CI 0.95-6.31).

The logistic regression analysis (Mommsen et al., 1982) revealed that males who worked with gasoline or oil were at significantly more risk for bladder cancer--2-1/3 times more (estimate of relative risk = 2.32, $p < 0.05$) than males who do not work with gasoline or oil even after significant confounding factors were controlled for. Inclusion of the following variables in the model (work with petroleum or asphalt, work with chemical materials, chewing tobacco user, industrial worker, alcohol user, previous venereal disease, and symptoms of cystitis) failed to significantly change the probability of blad-

der cancer. Thus, only six risk factors--work with oil or gas, cigarette smoking, nocturia, prostatic surgery, cheroot smoker, and lowest socioeconomic level were considered significant independent risk factors for invasive bladder cancer in this rural area of Denmark.

Mommsen and Aagard's (1984) detailed analysis of male occupational data provided very little new information. No one job title was indicative of work with gasoline or oil. Of the 20 exposed cases, 5 were mechanics, 3 were blacksmiths, 4 were semi-skilled workers, 2 each were printers or engineers, and 1 each was a shoemaker, tailor, stoker, or unskilled worker. Of the 8 exposed controls, 3 were semi-skilled workers, 2 were mechanics, and 1 each was a blacksmith, printer, and stoker. Both cases and controls averaged 27 years of exposure to gasoline or oil. As part of this review, odds ratios were calculated (Fleiss, 1981) by job titles for workers exposed to gasoline or oil. These data indicated that bladder cancer risks were greatest for blacksmiths (OR = 3.25) and mechanics (OR = 2.71).

The data collection methods of Mommsen et al. (1982) and Mommsen and Aagard (1984) are questionable. The interviewer (i.e., the principal investigator) was not blind towards the status of the subject as cases. Cases were interviewed at the hospital, the majority of the controls were interviewed by telephone, and 5% of the controls were interviewed by a self-administered mailed questionnaire (Mommsen and Aagard, 1984). The differences in interview methods may well have created a bias in the response. Furthermore, exposure data were collected in a non-uniform manner, i.e., with "nonstructured questions."

There was no quantitative measure of gasoline vapor exposure. The exposure category included "gasoline or oil," and there was no attempt to assess the effects of gasoline independent of those of oil. The job titles presented

for the 28 exposed cases and controls make the argument for oil or dye exposure rather than for gasoline exposure. None of the job titles presented were for jobs in which a gasoline occupational exposure could be inferred (i.e., gasoline service station attendant). Only the seven mechanics (crude OR = 2.71) appeared to have a potential for an occupational exposure to gasoline; this odds ratio was not adjusted for confounding variables such as smoking, and no latency analyses were conducted.

The authors' retrospective data were analyzed as if they were prospective data; i.e., the probability of bladder cancer was modeled rather than the probability of exposure. Because of the small size of the study population, the magnitude of the authors' relative risk estimate using the logistic model may be questioned.

Thus, this study provides insufficient data to determine the carcinogenicity of gasoline.

4.1.4. Domiano et al. (1985)

A case-control study was carried out by Domiano et al. on 92 white male cases with histologically confirmed renal cell carcinoma and 1,588 white male controls with nonneoplastic diseases admitted to Roswell Park Memorial Institute from 1957 to 1965. The age range of both cases and controls was 30 to 89. For purposes of analysis, two age groups were created: 30 to 59 and 60 to 89; approximately half of the controls were in each group. Patients admitted with urogenital, circulatory, respiratory, or mental disorders were excluded from the control population (ICD-7, 001-008, 016, 018, 022, 023, 031, 300-326, 330-334, 400-468, 470-527, 590-637, 782-783, 786, 789, 792, 794).

At the time of admission, patients filled out a questionnaire including occupational history, diet, and smoking habits. Cigarette smoking was measured in terms of pack-years, the product of the number of years a person smoked and

the average number of packs smoked per day. Occupational titles were coded according to the U.S. Department of Commerce Alphabetical Index of Occupations, and the industries were coded according to the Standard Industrial Classification Manual. An occupational title-gasoline exposure linkage system was developed based on the occupational and industrial hygiene literature. Cases and controls were compared for "possible" exposure (employment as an operative or laborer in refinery, construction, transportation, machinery, or petroleum transport and storage industries) or "definite" exposure (employment in gasoline service stations).

Four of the 92 cancer cases (4.3%) and 122 of the 1,588 controls (7.7%) had any exposure to gasoline (combines definitely and possibly exposed); three of the cases were "definitely" exposed to gasoline. The age-adjusted relative risk estimate for any gasoline exposure was a nonsignificant 0.53. All four of the exposed cases smoked 21 or more pack-years of cigarettes. After post-stratifying for age, risks were examined among males who smoked 21 or more pack-years of cigarettes. The relative risk estimate for the younger smokers exposed to gasoline was 0.90 (one exposed case); among the older smokers, renal cell carcinoma risks for gasoline exposure were 2-1/2 times those of smokers not exposed to gasoline (OR = 2.49, two exposed cases, p value not reported but was calculated as $0.20 < p < 0.30$, distributed as a chi-squared statistic with one degree of freedom).

The authors hypothesized that the interaction between heavy cigarette smoking and long-term gasoline exposure may be associated with an increased risk of renal cell carcinoma. However, because there were no males in the non-smoking gasoline exposure group, it was not possible to quantitatively examine this hypothesis. The data do suggest that smoking is a confounding factor for renal carcinoma (age-adjusted OR for smoking 21+ pack-years = 1.30, 50 exposed cases).

This study provides limited data on the association between gasoline and renal cell carcinoma. The numbers of exposed cases were very small (n = 3), and while risks were elevated among the older smokers for exposure to gasoline, they were not significantly elevated and may have occurred by chance. Furthermore, the authors' smoking category of 21+ pack-years is very broad, and thus may not have adequately controlled for the effects of smoking among the older smokers. The paper suggests that the authors' categorization of smoking into the high category at 21 pack-years may be biased, as the categorization was based on the distribution of the cases and not on the controls. The authors provided no analysis of latency or length of employment in gasoline service stations. Finally, it was not possible to control for the effects of other potential gasoline service station exposures (e.g., motor oils, engine exhausts, solvents, etc.).

4.1.5. Lin and Kessler (1981)

This case-control study of pancreatic cancer was conducted in more than 115 hospitals in five metropolitan areas of the United States: Buffalo, NY; Detroit, MI; Miami, FL; Minneapolis-St. Paul, MN; and New York, NY.

Study subjects were identified through hospital records, including pathology departments. Cancer-free controls were randomly selected from among contemporaneous admissions to the same hospital and matched individually to the cases on the basis of sex, race, age ($\pm$ 3 years), and marital status (ever/never). Patients admitted "primarily" for diabetes mellitus, pancreatitis, or gallstones were excluded from the control population. Study subjects were personally interviewed by interviewers blind towards the status of the study subjects, usually in the hospital setting.

Information was collected in detail on demographic characteristics, residential history, occupations, toxic exposures, animal contacts, smoking habits,

diet, medical history, and family history. Information on sexual practices and urogenital conditions was collected from the male subjects. For female subjects, data on marital, obstetric, and gynecologic histories were also collected. Data were not obtained on conditions diagnosed within 1 year before the cancer diagnosis.

Twenty-two percent of the eligible study subjects were not interviewed because of poor health status and were therefore excluded from the study. Of those remaining, approximately 86% of both males and females agreed to participate. The final study population consisted of 67 male pancreatic cancer cases and 42 female pancreatic cancer cases and their matched controls.

The chi-squared statistic and the t-test were used to test for significant differences between the cases and their controls. Dose-response effects were evaluated using the odds ratio as the estimate of relative risk. The odds ratios were calculated by adding one-half to each non-zero cell. Smoking exposure histories were evaluated with the use of a matched-pair analysis.

Male pancreatic cancer cases were significantly more likely than the controls to have been employed in occupations involving close exposure to gasoline (e.g., service stations and garages) or in the dry cleaning business (32.8% vs 14.9%, $p < 0.05$). This odds ratio was not presented; however, as part of this review a crude odds ratio of 2.79 was calculated (Fleiss, 1981) for males occupationally exposed to gasoline or employed in the dry cleaning business. This risk appeared to be positively associated with increasing duration of exposure. For those exposed 3 to 5 years, the risk was 1.27; for those exposed 6 to 10 years, the risk was 3.80; and for those exposed 10 or more years, a significant fivefold risk (OR = 5.07; p value not reported) was observed. (A p value for a test of linear trend was not reported.)

Decaffeinated coffee drinking ($p < 0.01$) and wine drinking ($p < 0.05$) also

occurred more frequently among male cases in comparison to the male controls. Neither odds ratios nor the data with which to calculate odds ratios were reported.

Among females, significantly more cases than controls were identified with a history of oophorectomy or myomatosis, drinking caffeine-free coffee, and heavy cigarette smoking ($\geq$ 10 per day). Odds ratios were not presented; however, using the authors' data, it is possible to calculate a crude odds ratio of 3.15 for females occupationally exposed to gasoline or employed in the dry cleaning business. This suggests an elevated, although not significant, risk for female workers.

This study provides an inadequate amount of data upon which to evaluate the association between gasoline vapors and the risk of pancreatic cancer.

While the authors did evaluate the risks for occupational exposure to gasoline-related occupations, no quantifications of gasoline vapor exposures were included. In addition, no analyses were presented for the effects of employment in the gasoline service occupations independent of the effects of employment in the dry cleaning industry. Thus, it is not possible to determine if the increase in risk observed for this occupational exposure was due to employment in gasoline occupations, dry cleaning occupations, or some combined exposure to both. However, workers in dry cleaning occupations have not previously been identified as being at an excess pancreatic cancer risk.

Although the authors did find a significant association of pancreatic cancer and cigarette smoking among females, no association was observed for males. This finding is inconsistent with numerous other studies on the relationship between smoking and pancreatic cancer (U.S. Public Health Service, 1982). Finally, the authors' analyses failed to control for the simultaneous effects of significant confounding variables. Hence, this study is considered inadequate.

4.1.6. Lin and Kessler (1979)

Lin and Kessler also reported (as a proceedings abstract) on a case-control study of testicular cancer in 410 white and black males (205 each cases and controls). The cases were selected from recently discharged hospital patients. The controls were "similar" demographically to the cases; however, the method of control selection was not specified.

The authors reported that the cases were significantly (p value not reported) more likely to be employed as gasoline station attendants, garage workers, truck drivers, firemen, smelter workers, or metal heaters. The cases and controls did not differ with respect to urban/rural residence, smoking practices, education, religion, or sexual practices. Additional details were not presented.

The lack of any methodologic detail precludes consideration of these data. Thus, this study is considered an inadequate basis upon which to determine the carcinogenicity of gasoline.

4.1.7. Milham (1983)

Milham analyzed all Washington State death certificate records for white male residents (429,926) for the years 1950-79 and white female residents (25,066) for the years 1974-79, ages 20+.

Occupational data were obtained using the death certificate item "usual occupation during most of lifetime." Male records for the years 1950-71 were abstracted, coded, keypunched, and then read onto magnetic tape for computer analysis. Male records for the years 1972-79 and all female records, excluding those with "housewife" listed as the usual occupation, were routinely abstracted, coded, and entered into the computer within 30 days of the date of death. Occupations were coded with a modified U.S. Bureau of the Census code. Data were not available for 3% of the deceased male population, e.g., occupations

listed as retired, unknown, etc.

For males whose cause of death was urinary bladder cancer or Hodgkin's disease, an interview with the decedent's next of kin was conducted to assess the accuracy of the occupational information on the death certificate. The next of kin gave the identical occupation as noted on the death certificate 75% of the time, a related occupation 10% of the time (e.g., plywood mill worker versus mill worker), and a completely different occupation 15% of the time. Death certificate information was also validated through union records for 100 engineers. Of these, all but two were correctly listed on the death certificate as an engineer.

Cause-of-death information was coded to the 7th ICD, and results were available for 160 causes of death. Age- and year-of-death standardized proportionate mortality ratio (PMR) analyses were used for both males and females. Expected deaths were computed for each year of the study using that year's mortality experience for the State of Washington as the standard. Expected deaths were then summed over 5-year age intervals and rounded to the nearest whole number before the results were printed. Differences in the observed and expected values were tested at the 1% and 5% level with a chi-squared statistic with one degree of freedom. PMRs were reported for each decade (1950-59, 1960-69, 1970-79), for the total 30-year period (1950-79), for those 20-64 years old at the time of death, and for those in each 5-year age interval. Significance testing was done only on observed values of 6 or more. Excluded from significance testing were PMR values for each 5-year age interval. Unless specified, all results reviewed here are for the period 1950 through 1979.

Cause-of-death analyses were presented for 219 occupational categories for males and 51 occupational categories for females. Two of the male occupational categories (gas station/garage owners and attendants, and fuel oil and

gasoline truck drivers) were considered to have workers with gasoline exposure, and two additional categories (fuel oil dealers and workers, and auto mechanics and repairmen) were considered to have workers with petroleum products exposure and potential gasoline exposure.

PMR results for the malignant diseases by the four occupational categories are summarized in Table 4-1. Reported by the author but not presented here are statistically nonsignificant cancer excesses of less than 20%, nonsignificant findings in which the observed numbers of death were less than three, and nonsignificant deficits.

There were 2,786 observed deaths among the gas station/garage owners and attendants during the period 1950-79. The proportion of malignant neoplasm deaths among this group was approximately equal to the proportion observed among all white male Washington State decedents (PMR = 97, observed = 480, $p > 0.05$). A statistically significant ($p < 0.05$) excess was observed for cancers of the bladder and other urinary organs for those who died during the periods 1950-59 (PMR = 219, observed = 4) and 1960-69 (PMR = 185, observed = 6); however, for the period 1970-79, a deficit was observed (PMR = 75, observed = 8, $p > 0.05$).

Significant excesses were not observed for any other malignant diseases; however, significant ($p < 0.05$) deficits were observed for cancer of the digestive organs and peritoneum (PMR = 82, observed = 124) and cancer of the large intestine, except rectum (PMR = 68, observed = 29).

PMRs were elevated ($p > 0.05$) (those less than 120 are not presented here) for malignant neoplasms of the mouth, excluding the floor of the mouth, salivary gland, tongue, and lip (PMR = 209); pharynx, unspecified (PMR = 194); liver, secondary and unspecified for the periods 1960-69 (PMR = 144) and 1970-79 (PMR = 137) only; pancreas for the periods 1960-69 (PMR = 128) and 1970-79

TABLE 4-1. SUMMARY OF PMR CANCER FINDINGS FOR FOUR OCCUPATIONAL CATEGORIES WITH GASOLINE OR PETROLEUM PRODUCTS EXPOSURE[a]
(Milham, 1983)

Type of cancer	Gas station owners/ attendants				Fuel oil/gas truck drivers				Fuel oil dealers/workers				Auto mechanics/repairmen			
	1950-1959	1960-1969	1970-1979	1950-1979	1950-1959	1960-1969	1970-1979	1950-1979	1950-1959	1960-1969	1970-1979	1950-1979	1950-1959	1960-1969	1970-1979	1950-1979
All malignant neoplasms	94	100	95	97	106	108	117	113/133*[b]	99	109	111	107	111	107	101	104
Buccal cavity/pharynx	-	-	144	121	-	-	-	160	-	273**	-	130	154	-	-	89
Mouth	-	-	-	209	-	-	-	-	-	-	-	-	-	-	-	-
Tongue	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	124[c]
Pharynx	-	296	-	194	-	-	-	-	-	-	-	282	-	206	125	144
Oral mesopharynx	-	-	-	141	-	-	-	-	-	-	-	-	-	-	-	241[c]
Digestive organs/ peritoneum	-	-	-	82*	151	-	159	134	-	-	-	-	-	-	-	-
Esophagus	-	-	-	-	-	-	-	288	-	-	-	-	181	212*	126	163*
Stomach	-	-	-	-	-	-	195	165	-	-	-	-	-	-	-	126[c]
Large intestine	-	-	-	68*	-	-	181	145	130	-	-	117	-	-	-	-
Small intestine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	184
Rectum	-	-	-	-	-	-		150	-	-	155	107	-	-	-	-
Liver (primary)	-	-	-	-	-	-	-	-	-	-	-	156[c]	173	-	-	71
Liver	-	-	-	-	-	-	-	-	-	-	-	-	243	-	-	-
Liver (secondary, unspecified)	-	144	137	117	-	-	-	-	-	-			-	-	-	-
Pancreas	-	128	126	119	-	-	-	-	155	129	-	125	-	-	-	288[e]/ 218[f]
Respiratory system	-	-	-	123	-	143	-	117	-	-	-	-	145*	-	122*	123**
Larynx	-	-	191	123	-	-	-	-	-	-	-	-	197	-	153	133
Trachea, bronchus, lung	-	-	-	-	-	130	121	120[d]	-	-	-	-	155*	-	122*	124**
Thoracic organs (secondary)	-	-	-	247	-	-	-	-	-	-	-	-	-	-	-	-
Genitourinary organs																
Prostate	-	-		-		-		-	172*	130	-	130	-			-
Testis	-	423	-	161	-	-	-	-	-	-	-	-	-	-	-	-
Bladder	219*	185*	75	144	-	-	-	138	-	127	182	129	129	166	-	119
Kidney	125	-	156	122	-	-	-	177	-	-	150	88	-	-	-	-

(continued on the following page)

TABLE 4-1. (continued)

Type of cancer	Gas station owners/ attendants				Fuel oil/gas truck drivers				Fuel oil dealers/workers				Auto mechanics/repairmen			
	1950-1959	1960-1969	1970-1979	1950-1979	1950-1959	1960-1969	1970-1979	1950-1979	1950-1959	1960-1969	1970-1979	1950-1979	1950-1959	1960-1969	1970-1979	1950-1979
Brain	-	-	-	-	-	-	-	-	122	167	140	193*[b]	-	-	-	-
Non-melanoma skin	-	-	-	157	-	-	-	-	-	-	-	-	-	-	-	132
Melanoma skin	-	-	-	-	-	-	-	-	-	-	-	206	-	-	-	-
Lymphatic/hematopoietic tissues	120	-	-	93	-	158	-	105	-	-	180**	126	123	-	-	110
Hodgkin's disease	191	148	-	129	-	-	-	-	-	350	-	164	196	-	-	104
Lympho- and reticulosarcomas	-	-	-	-	-	-	-	-	-	-	300	142	-	-	-	-
Other lymphomas	-	224	-	100	-	-	-	-	-	-	334	183	-	-	198*	175*
Multiple myeloma	-	-	-	-	-	-	-	-	-	-	208	141	-	-	-	-
Leukemia/aleukemia	160	-	-	100	-	-	-	145	131	-	-	92	134	130	-	118
Myeloid leukemia	207	175	-	155	-	-	-	-	-	-	-	-	126	-	180	181[c]
Lymphatic leukemia	-	-	-	-	-	-	-	-	-	-	-	-	-	283**	-	129
Acute leukemia	-	128	-	86	-	-	-	-	-	-	-	-	-	-	120	109
Other leukemias	-	-	-	-	-	-	-	-	-	-	-	-	-	-	125	206

* $p < 0.05$.

** $p < 0.01$.

a Not presented are findings in which the observed numbers of deaths are less than 3, non-significant excesses of 20% or less, and all non-significant deficits. Findings for the entire 30-year period are reported whenever a decade-specific finding is reported.

b Significant excess observed among those ages 20-64 only.

c Excess observed among those ages 20-64 only.

d Among those ages 20-64, the PMR = 131.

e Excess observed among those ages 40-44.

f Excess observed among those ages 45-49.

(PMR = 126); larynx (PMR = 191) for the period 1970-79; testis for the period 1960-69 (PMR = 423) (the data for the period 1970-79 were not readable); kidney (1950-59 PMR = 125; 1970-79 PMR = 156); non-melanoma skin (PMR = 157); Hodgkin's disease (1950-59 PMR = 191; 1960-69 PMR = 148); other lymphomas (1960-69 PMR = 224); leukemia and aleukemia (1950-59 PMR = 160); and myeloid leukemia (1950-59 PMR = 207).

Several of the nonmalignant diseases exhibited a significant excess or deficit among gasoline station workers ($p < 0.01$ unless specified): asthma (among those ages 20-64 only, PMR = 223, observed = 10); diabetes mellitus (PMR = 142, observed = 55); diseases of the circulatory system (PMR = 109, observed = 1,332); arteriosclerotic heart disease, including coronary disease (PMR = 109, observed = 1,048); diseases of the respiratory system (PMR = 79, observed = 126); pneumonia (PMR = 71, observed = 45, $p < 0.05$); duodenal ulcer (PMR = 193, observed = 20); cirrhosis of the liver without alcoholism (PMR = 58, observed = 28); cirrhosis of the liver with alcoholism (PMR = 31, observed = 6); and accidental falls (PMR = 37, observed = 11).

There were 73 cancer deaths of a total of 334 deceased males whose usual occupation was fuel oil or gasoline truck driver (PMR = 113, $p > 0.05$). Among those ages 20 to 64, a significant excess in total cancer was observed (PMR = 133, observed = 48, $p < 0.05$). A significant excess was also observed for diseases of the arteries (PMR = 176, observed = 15, $p < 0.05$) and for motor vehicle accidents (PMR = 214, observed = 24, $p < 0.01$).

Elevated, although not significantly, were PMRs for cancers of the buccal cavity and pharynx (among those ages 20 to 64 PMR = 244); digestive organs and peritoneum (1950-59 PMR = 151; 1970-79 PMR = 159); esophagus (PMR = 288); stomach (1970-79 PMR = 195); large intestine, except rectum (1970-79 PMR = 181); rectum (PMR = 150); respiratory system (1960-69 PMR = 143); primary lung,

bronchus, and trachea (1960-69 PMR = 130; 1970-79 PMR = 121); bronchus and lung (among those 20 to 64 PMR = 155; 1960-69 PMR = 153); kidney (PMR = 177); bladder and other urinary organs (PMR = 138); lymphatic and hematopoietic tissues (1960-69 PMR = 158); and leukemia and aleukemia (PMR = 145).

There were 1,554 deaths among white males whose usual occupation was fuel oil dealers and workers; 305 of these deaths were due to a malignant neoplasm (PMR = 107, $p > 0.05$). Significant cancer excesses were observed for cancers of the buccal cavity and pharynx (1960-69 PMR = 273, observed = 8, $p < 0.01$), prostate (1950-59 PMR = 172, observed = 13, $p < 0.05$), and lymphatic and hematopoietic tissues (1970-79 PMR = 180, observed = 19, $p < 0.01$). Cancer of the brain was significantly elevated among those between the ages of 20 and 64 at the time of death (PMR = 193, observed = 9, $p < 0.05$). There were no significant cancer deficits observed.

Statistically nonsignificant cancer excesses ($p > 0.05$) of 120 or above were observed for several forms of cancer: cancers of the pancreas (1950-59 PMR = 155; 1960-69 PMR = 129), prostate (1950-59 PMR = 130), bladder and other urinary organs (1960-69 PMR = 127; 1970-79 PMR = 182), and lympho- and reticulosarcomas (1970-79 PMR = 300); Hodgkin's disease (1960-69 PMR = 350); other lymphomas (1970-79 PMR = 334); multiple myeloma (1970-79 PMR = 208); and leukemia and aleukemia (1950-59 PMR = 131).

Nonmalignant diseases observed at significant levels (all p values were less than 0.05 unless specified) were infective and parasitic diseases (PMR = 46, observed = 6); asthma (PMR = 203, observed = 10); psychoses (PMR = 275, observed = 6, $p < 0.01$); paralysis agitans (PMR = 237, observed = 10, $p < 0.01$); diseases of the circulatory system among white males ages 20 to 64 (PMR = 115, observed = 272); arteriosclerotic heart disease, including coronary disease among males ages 20 to 64 (PMR = 119, observed = 231, $p < 0.01$), diseases

of the respiratory system (PMR = 69, observed = 68, $p < 0.01$); pneumonia (PMR = 66, observed = 26), other diseases of the lung and pleural cavity (ICD 527) (PMR = 69, observed = 28); and for the period 1970-79, other diseases of the urinary system (PMR = 215, observed = 8).

Among the white males whose usual occupation was automobile mechanics or repairmen, there were 3,445 observed deaths; 677 of these were cancer deaths (PMR = 104, $p > 0.05$). Esophageal and respiratory system cancers both exhibited a significant excess (PMR = 163, observed = 22, $p < 0.05$ and PMR = 123, observed = 255, $p < 0.01$, respectively). The overwhelming majority of the respiratory system cancer deaths were from primary cancer of the bronchus, trachea, and lung (PMR = 124, observed = 210, $p < 0.01$); however, nonsignificant excesses were observed for cancers of the larynx (PMR = 133). Excesses were observed for all of the lymphatic and hematopoietic tissue cancers, some being significant: lymphatic leukemia (ICD 204.0) (1960-69 PMR = 283, observed = 8, $p < 0.01$) and other lymphomas (ICD 202 and 202.2) for the period 1970-79 only (PMR = 198, observed = 10, $p < 0.05$). Nonsignificant ($p > 0.05$) excesses were observed for Hodgkin's disease (1950-59 PMR = 196), myeloid leukemia (ICD 204.1) among those ages 20 to 64 (PMR = 181), acute leukemia (ICD 204.3) (1970-79 PMR = 120), and other unspecified leukemias (ICD 204.4) among those ages 20 to 64 (PMR = 284).

The proportion of cancer deaths among automobile mechanics was elevated nonsignificantly ($p > 0.05$) for several other kinds of cancer: buccal cavity and pharynx (1950-59 PMR = 154); tongue among those ages 20 to 64 (PMR = 124); oral mesopharynx among those ages 20 to 64 (PMR = 241); pharynx, unspecified (1950-79 PMR = 144; 1970-79 PMR = 125, observed = 2); stomach among those ages 20 to 64 (PMR = 126); small intestine, including duodenum (PMR = 184); liver (1950-59 PMR = 243); pancreas among those ages 40 to 44 (PMR = 288) and 45 to 49

(PMR = 218); and bladder and other urinary organs for the years 1950-59 (PMR = 129) and 1960-69 (PMR = 166).

Statistically significant excesses ($p < 0.05$) were also observed for multiple sclerosis (PMR = 233, observed = 10, $p < 0.01$), paralysis agitans (PMR = 177, observed = 14), chronic rheumatic heart disease (PMR = 139, observed = 41), bronchitis with emphysema (1970-79 PMR = 188, observed = 10), other diseases of the lung and pleural cavity (1970-79 PMR = 125, observed = 81), and hernia of the abdominal cavity (PMR = 285, observed = 9, $p < 0.01$).

There are several limitations to this study. The major problem is the questionable validity associated with the use of PMRs as a method of analysis. In addition, workers in each of the four occupational categories were potentially exposed to gasoline; however, they were also potentially exposed to other petroleum products, such as diesel fuel oil, home heating oil, motor oils, and solvents, as well as to engine exhausts. It was not possible to control for these potential confounding exposures or to quantify gasoline exposure. Due to data constraints, the analyses by latency or length of employment were not carried out.

The validation study of death certificate information suggested that 15% of all death certificates had an unreliable occupation listed as the "usual lifetime occupation." Although this is probably a random occurrence, the small number of observed deaths for a particular malignant disease may be unduly influenced; thus, a PMR may be under- or overestimated for a particular job category.

Finally, there was no control for other confounding risk factors such as smoking. Thus, this study provides an insufficient basis upon which to assess the association of gasoline and cancer risk.

4.2. EPIDEMIOLOGIC STUDIES OF WORKERS IN THE PETROLEUM INDUSTRY

4.2.1. Mortality Studies of Workers in the Petroleum Refining Industry

4.2.1.1. Tabershaw-Cooper Associates, Inc. (1974 Unpublished, 1975 Unpublished)--On behalf of the American Petroleum Institute (API), Tabershaw-Cooper Associates, Inc. (1974) conducted a retrospective cohort mortality study of petroleum refinery workers at 17 refineries. The refineries were sampled from the 251 United States refineries listed in the 1971 Census of the Oil and Gas Journal. The sample was designed to give a "reasonably representative distribution" of the refinery population with respect to location, ownership, and size. The study population consisted of all hourly employees (excluding clerical) who worked in one of the refineries for at least 1 year between January 1, 1962, and December 31, 1971. Because of missing records, only pensioners were included from Refinery No. 5. The final cohort consisted of 20,163 subjects, representing 137,153 person-years of observation.

Information on each study subject was obtained from plant personnel records and included date of birth, date of hire, most recent job title, date of termination or retirement, date and place of death for those known to have died, and, for terminated employees, their last known address. Race information was not available on most employees. The authors estimated that 91.9% of the cohort was white (including Mexican and Latin Americans), 7.9% were black, and 0.2% were other. These estimates were based on information received from five of the refineries on the race distribution of their current work forces.

Exposure was categorized as high, medium, or low with respect to hydrocarbon exposure by a refinery safety engineer. The high category (Category A) included laboratory, maintenance, and salvage recovery jobs. Workers in this category would have had exposure to gasoline. The low category contained plant security, utility, purchasing, and motor transport jobs. Some of the workers

in this category (i.e., motor transport) would have had exposure to gasoline; others probably would have not. All other jobs, including laborers, were classified as medium exposure; individuals in this category had potential for gasoline exposure.

Vital status was determined as of December 31, 1971. Cohort members who had terminated employment or retirees whose vital status was unknown were traced using telephone books, the U.S. Post Office, and state drivers license bureaus. Six percent (1,120) were lost to follow-up.

In an effort to ascertain vital status for all cohort members, the authors requested that the Social Security Administration (SSA) determine, for each worker lost to follow-up, whether contributions were still being made; whether benefits were being received; and whether a death claim had been filed, and if so, where and when. This follow-up study (Tabershaw-Cooper Associates, Inc., 1975) resulted in the successful tracing of 99% of the original cohort, representing 5,499 person-years of observation. A total of 1,194 deaths were ascertained; death certificates were acquired for all but 10 of these. The authors did not indicate which revision of the ICD was used to code the death certificates.

Standardized mortality ratios (SMRs) were calculated, comparing the observed mortality experience of the cohort to what was expected, by using the United States male-, calendar-, time-, age-, and cause-specific mortality as the standard rate. It was not possible to determine if race was assumed to be white for the calculations of the expected numbers. SMRs were tested for statistical significance at the $\alpha = 0.05$ and $\alpha = 0.01$ levels using an adaptation of a formula of Chiang (1961).

Current employees represented 68% of the cohort; the others were retired, 18%; terminated, 11%, and deceased 4%. Approximately 34% of the cohort were

age 41 or younger at the end of the study period; about 31% were 57 or older. Sixty percent had 20 or more years of service, and only 28% were employed for less than 10 years.

Results were reviewed for the original study (Tabershaw-Cooper Associates, Inc., 1974) and the SSA updated study (Tabershaw-Cooper Associates, Inc., 1975); they were generally the same. Reported here are the results for the SSA updated study.

For the total cohort the SMR for all causes of death was 69 (observed = 1,194); this was statistically significant ($p < 0.01$) and suggests a healthy-worker effect for this refinery population. The SMR for all cancers was also significantly low (SMR = 83, observed = 275, $p < 0.01$). Small statistically nonsignificant excesses were observed for lymphomas (SMR = 123) and malignant neoplasms of the genital organs (SMR = 111). No other excesses were reported. Several causes of death had significant deficits in mortality including cancers of the buccal cavity and pharynx (SMR = 58, observed = 7, $p < 0.05$), the respiratory system (SMR = 82, observed = 93, $p < 0.05$), and urinary organs (SMR = 35, observed = 6, $p < 0.01$). Cause-specific SMRs were not reported for 32 cancer deaths. It appears that these deaths were for miscellaneous cancer sites including cancers of the bone, skin, brain and central nervous system (CNS), and other unspecified sites.

Nonmalignant causes of death for which significant ($p < 0.01$) deficits were observed were: diabetes mellitus (SMR = 45, observed = 11), vascular lesions affecting the CNS (SMR = 53, observed = 57), arteriosclerotic heart disease (SMR = 84, observed = 511), nonrheumatic endocarditis (SMR = 24, observed = 7), hypertensive heart disease (SMR = 30, observed = 11), influenza and pneumonia (SMR = 31, observed = 11), cirrhosis of the liver (SMR = 47, observed = 24), symptoms of senility and ill-defined conditions (SMR = 56,

observed = 14), motor vehicle accidents (SMR = 53, observed = 31), other accidents (SMR = 61, observed = 39), suicide (SMR = 63, observed = 24), and homicide = 52, observed = 10).

The authors carried out analyses of several subcohorts, first dividing the cohort into those hired before the starting date of the study (i.e., 1962) and those hired later. The mortality pattern for the former group (consisting of 75% of the cohort) was identical with that of the total cohort. Again, the only excesses were for lymphomas (SMR = 126) and cancer of the genital organs (SMR = 106); these were not statistically significant. For those hired after 1962 the numbers of observed deaths were very small, making cause-specific interpretations difficult. A statistically significant deficit was observed for all causes of death (SMR = 39, observed = 13, $p < 0.01$) and an excess of 25% (SMR = 125) was observed for all cancer deaths; however, the latter was based on only four observations and was not significant.

Mortality patterns among those hired before 1952 (i.e., the subcohort with approximately 10 or more years of occupational exposure) were generally similar to those of the total cohort; the only excess observed was for lymphomas (SMR = 129, $p > 0.05$). Cancer of the genital organs was observed at expected levels (SMR = 103, $p > 0.05$); all other causes of death considered by the authors were deficits, including the SMRs for all causes of death (SMR = 70, observed = 1,123, $p < 0.01$) and all cancers (SMR = 82, observed = 261, $p < 0.01$).

Among those hired after 1952, a significant ($p < 0.01$) deficit was observed for all causes of death (SMR = 61, observed = 71); for all cancers the SMR was observed at expected levels (SMR = 99, $p > 0.05$). However, excesses ($p > 0.05$) were observed for cancers of the buccal cavity and pharynx (SMR = 424), digestive organs and peritoneum (SMR = 156), and genital organs (SMR = 303). These were based on only a few observations (2, 5, and 2, respectively).

The SMR for all causes of death was significantly ($p < 0.01$) low for each of the three hydrocarbon exposure categories (high, SMR = 67, observed = 499; medium, SMR = 69, observed = 528; low, SMR = 80, observed = 167). Risks for all cancers were also low, but were only significant ($p < 0.01$) among workers in the medium exposure category (medium, SMR = 81, observed = 120; high, SMR = 87; low, SMR = 77). If one assumes that the age distribution of workers in the three exposure categories was similar, then SMRs across exposure categories may be compared. A positive trend associated with increasing exposure was observed for cancer of the genital organs (high, SMR = 136; medium, SMR = 117; low, SMR = 0); however, these point estimates were not statistically significant. Statistically nonsignificant excesses were also observed for lymphomas among workers in the high exposure category (SMR = 129) and in the low category (SMR = 170), and for leukemia and aleukemia among workers in the low exposure category (SMR = 271). No overall pattern of risk associated with increasing exposure was observed for the remaining site-specific cancers. These SMRs were lower than 100 in all instances and were significantly low for respiratory system cancer among those in the medium exposure category (SMR = 76, observed = 39). The overwhelming majority of the SMRs for the nonmalignant diseases were lower than 100 regardless of exposure category; a few were observed to be significant deficits, but no overall pattern related to exposure could be discerned.

The authors also evaluated risks for males who had at least 20 years of exposure and for whom the "20th year of exposure occurred at least 10 years before" the end of the study. These 5,145 workers were all hired before 1943. Cancer risks for this subcohort were generally the same as those of the total cohort except that the excess lymphoma mortality observed in the total cohort (SMR = 123) appeared to disappear in this subcohort (SMR = 93). The deficit

observed among the total cohort for digestive system cancer (SMR = 86) was observed to be significant ($p < 0.05$) for this subcohort (SMR = 76, observed = 43). No cancer excesses were observed.

This large study had excellent follow-up (99%), and death certificates were obtained for all but 0.8% of the deceased cohort members. Analyses were undertaken for exposure categories for which some job title information was available, and a latency analysis was also conducted. The period of follow-up, however, was short, only 10 years. This is important considering the young age of the cohort; approximately 70% were age 56 or younger at the time of vital status ascertainment. There was no control for confounding variables such as other chemical exposures and smoking. Considering that SMRs for all smoking-related diseases were lower than what was expected (many were significantly lower), smoking is not considered to be a serious confounder in these data.

The authors calculated their SMRs based upon the mortality experience of males, but females were not explicitly excluded from the cohort. If the study population did include females, then risks for the total cohort may be biased. It was not possible to determine if SMRs were based upon race-specific U.S. mortality figures. Since the authors estimated that 8.1% of the cohort was non-white, risks for the total cohort may be either overestimated or underestimated.

It was not possible to determine if the cause-of-death information was coded by a trained nosologist. This is important because the study period spanned two revisions of the ICD, and a comparability problem between ICD revisions may be present in the data.

The major problem with this study, as well as with the other petroleum refinery studies, is that it is not possible to determine the quantitative gasoline exposure from the available information. Although it is known that

many of the workers had the potential for gasoline exposure, it is not known how many workers were exposed, what their individual mortality outcome was, or for how long or at what levels they were exposed to gasoline. Thus, this study provides insufficient evidence to associate gasoline exposure with cancer risks.

4.2.1.2. Hanis (1977)--Hanis conducted a retrospective cohort mortality study of employees of the Imperial Oil Company, Ltd. of Canada. The cohort included all active male employees who were employed at least 1 year during the 10-year period 1964-73 and all terminated, including retired, male employees who were employed at least 5 years during the study period. Excluded from the study population were 6,681 short-term employees (i.e., male terminated employees with less than 5 years' service and males actively employed by the company but who had worked for the company less than 1 year during the study period). Also excluded from the final study population were 19 annuitant deaths for whom exposure information was missing from the company records (one of these males was identified as an intestinal cancer death). Thus, of the 21,732 males initially identified as potential cohort members, only 15,032 (120,636 person-years of observation) were included in the final study population.

Employees lost to follow-up were those who left the company prior to being vested in the pension plan, 5.8% (865). Employees vested in the pension plan were those who terminated prior to January 1, 1966, and who had at least 15 years of service at the time of termination, and those who terminated on or after January 1, 1966, but who had at least 10 years of service.

Deaths were identified through company medical department records. Cause-of-death information was verified through provincial registrars, the Vital Statistics Section of Statistics Canada, and through the U.S. Department of Health, Education, and Welfare for those employees who subsequently died in the United

States. Not verified were 18 other foreign deaths. Of the 1,551 deaths that were identified, cause-of-death information could not be verified for 1.6% (25) of these. Cause-of-death information was subsequently recoded to the 8th revision of the ICD. It could not be determined if the recoding was done by a trained nosologist.

The company supplied information on each study participant on computer tapes for the time periods 1964-68 and 1969-73. These data included name, employment number, department number, job title (e.g., warehouseman), job category (e.g., professional, administrative), age, and years of service. The 1969-73 data also contained information on employment status (active, retired, or terminated), retirement date, and date of death. Information on decedents was supplied on punched cards and included name, employee number, department number at time of last employment, date of birth, province of death, date of death, cause of death as coded on the death certificate, age at death, and whether the information was verified or not.

Ten exposure categories were used to define daily exposure to crude petroleum, gas or breakdown products: (1) refinery, exposed; (2) refinery, non-exposed; (3) non-refinery, exposed; (4) non-refinery, non-exposed; (5) mixed history of exposure/non-exposure; (6) moderate exposure group; (7) mixed history refinery, exposed/non-refinery, exposed; (8) mixed history refinery, non-exposed/non-refinery, non-exposed; (9) not enough information for a definition; and (10) no information available. An employee was classified by the company as a refinery worker on the basis of his department number.

The mortality experience of the oil company employees was compared to that of the Canadian population. SMRs were calculated using the 1969 sex-, age-, and cause-specific mortality rates to calculate the expected number of deaths. Internal comparisons of the refinery population to the non-refinery population

were made using the sex-, age-, and cause-specific death rates of the non-refinery population as the standard. Causes of death excluded from the presentation of SMR results were cancers of the buccal cavity and pharynx; the esophagus and stomach; other respiratory organs (ICD-8 160, 161, 163); the bone, connective tissue, and skin (ICD-8 170-174); and other unspecified sites (ICD-8 190-199).

The author did not test for statistical significance of SMR results. As part of this review, p values for SMRs were calculated as a one-tailed exact test assuming a Poisson distribution (Gustafson, 1984). Significance testing was at the $\alpha = 0.05$ level.

A majority (78%) of the population was present in 1964 at the beginning of the study period. Nearly 80% of the cohort was under the age of 65 at last observation; approximately 30% were under the age of 40. Over half the population (52%) was employed for 20 or more years with the company. Eight percent of the deaths occurred in the retired personnel; over 50% of the cancer deaths occurred in workers at the Quebec or Ontario sites.

The SMR for all causes of death (SMR = 83.9, observed = 1,511) was significantly ($p < 0.01$) lower than the mortality experience of the Canadian population, demonstrating the "healthy worker" effect. Significant ($p < 0.01$) SMR deficits were observed for all cancer deaths (SMR = 82.2, observed = 301), diseases of the respiratory system (SMR = 69.4, observed = 90), and accidents, poisonings, and violent deaths (SMR = 38.6, observed = 59). SMR deficits ($p < 0.05$) were also observed for diseases of the circulatory system (SMR = 94.2, observed = 905) and for lymphatic and hematopoietic system cancers (SMR = 69.7, observed = 25). An excess in mortality of 20% or more was not observed for any of the malignant diseases.

All additional analyses of the cohort's mortality experience were limited

to males 40 and older (82,057 person-years of observation), as only 1.7% of the deaths occurred in males younger than 40.

To examine the mortality experience for geographic differences, four geographic categories were established: (1) the Atlantic Provinces, including Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland; (2) Quebec and Ontario; (3) the Western Provinces of Alberta, Saskatchewan, Manitoba, and British Columbia; and (4) others including the Northwest Territories, offshore drilling personnel, foreign subsidiaries, and affiliates. The mortality experience of the four areas was generally similar to that of the total Canadian population. Significant deficits were observed for all causes of death for each of the areas: Area 1 SMR = 86.6, observed = 153, $p < 0.05$; Area 2 SMR = 91.4, observed = 920, $p < 0.05$; Area 3 SMR = 76.3, observed = 367, $p < 0.01$; and Area 4 SMR = 67.7, observed = 43, $p < 0.05$). Significant deficits were observed for all cancer deaths in the Western Provinces (Area 3 SMR = 75.0, observed 79, $p < 0.01$). Deficits for all cancer deaths were also observed for the remaining areas, but these were not observed at significant ($p < 0.05$) levels (Area 1 SMR = 94.1, Area 2 SMR = 83.7, and Area 4 SMR = 53.6).

Statistically significant deficits or excesses were not observed for any of the specific causes of death among workers in the Atlantic Provinces (Area 1); however, a 28% excess was observed for cancer of the digestive organs (ICD-8 155-159), excluding cancer of the intestines and rectum (SMR = 128.5).

Workers in Area 2 were considered to have significantly lower mortality than the population of Ontario and Quebec for diseases of the respiratory system (SMR = 78.8, observed = 56, $p < 0.05$); cancers of the trachea, bronchus, and lung (SMR = 62.6, observed = 44, $p < 0.01$); cancers of the lymphatic and hematopoietic system (SMR = 49.5, observed = 9, $p < 0.05$); and accidents, possonings, and violent deaths (SMR = 40.2, observed = 24, $p < 0.01$). Excesses

($p < 0.05$) were observed for cancers of the digestive organs, excluding intestines and rectum (SMR = 128.5, observed = 23), and for cancers of the urinary bladder and kidney (SMR = 134, observed = 11).

Workers in the Western Provinces (Area 3) were observed to have significant deficits for diseases of the circulatory system (SMR = 78.6, observed = 213, $p < 0.01$), diseases of the respiratory system (SMR = 57.3, observed = 20, $p < 0.05$), cancer of the intestines and rectum (ICD-8, 152-154) (SMR = 42.5, observed = 6, $p < 0.05$), and accidents, poisonings, and violent deaths (SMR = 42.1, observed = 15, $p < 0.01$). Excesses above 20% were not observed.

Workers in the other areas (Area 4) were observed to have a favorable mortality experience in comparison to the total population for these other areas. SMRs were lower than 100 for all reported causes except for cancers of the trachea, bronchus, and lung (SMR = 111.4). None of these was observed at significant levels.

The author next compared mortality patterns for the exposed (i.e., males who were daily exposed to crude petroleum, gas, or breakdown products regardless of whether they worked in the refineries) to those of the nonexposed. There were 6,523 employees in this subcohort of exposed persons, representing 50,534 person-years of observation. The calculations for the expected number of deaths were based on the mortality rates of the nonexposed.

The mortality experience of the exposed oil company employees was very different from that of the nonexposed oil company employees. Significant ($p < 0.01$) excesses were observed for all causes of death (SMR = 127, observed = 1,085); all cancer deaths (SMR = 134, observed 215); diseases of the circulatory system (SMR = 115, observed = 644); diseases of the respiratory system (SMR = 168, observed = 71); cancer of the trachea, bronchus, and lung (SMR = 211, observed = 67); and accidents, poisonings, and violence (SMR = 764, ob-

served = 42). A more than 40% excess was observed for cancer of the urinary bladder and kidney (SMR = 147, $p > 0.05$).

SMRs were not computed for stomach and esophageal cancer or for cancers of the bone, connective tissue, and skin. The author's descriptive statistics do suggest that esophageal and stomach cancer are two times more frequent among the exposed population as compared to the nonexposed (12.9% versus 6%), and that cancers of the bone, connective tissue, and skin are more than three times as frequent among the nonexposed (8.3% versus 2.3%) as compared to the exposed.

The author also calculated age-specific and adjusted cancer mortality rates for selected sites per 10,000 in the exposed and nonexposed populations; relative risks (RR) were then computed. Among males ages 40 to 64 years, and 80 years and above, intestinal cancer risks for the exposed were generally equal to those of the nonexposed; however, risks among males 65 to 79 were elevated (RR = 1.6, $p > 0.05$), based on chi-square with Yates correction factor and 1 degree of freedom. Intestinal cancer risks appeared not to vary by geographic location or duration of employment.

The relative risk for lung cancer in males was significantly ($p < 0.01$) elevated among those ages 40 to 64 (RR = 3.2) and 65 to 79 (RR = 1.9); these risks appeared to be inversely related to age (RR for those in the 80+ age group = 1.2). Excess risks, though not significant, were observed for males in the age group 40 to 64 years in the Atlantic Provinces (RR = 1.9); the age groups 40 to 64 years (RR = 2.2) and 65 to 79 years (RR = 2.1) in Ontario and Quebec; and among the age groups 65 to 79 years (RR = 2.9) and 80 years and above (RR = 7.0) in the Western Provinces.

The author also examined lung cancer mortality rates and relative risks by duration of employment and age. The numbers of lung cancer deaths among the nonexposed were few in the categories of 11 to 20 years' employment (observed =

1), and 21 to 30 years' employment (observed = 4), making it difficult to observe an overall pattern. The age-adjusted relative risk was elevated ($p > 0.05$) for the three categories of duration of employment (11 to 20 years, RR = 9.4; 21 to 30 years, RR = 1.6; 31+ years, RR = 1.7), but no dose-response relationship was observed. The elevation in risk appeared limited to males below the age of 80 years (i.e., ages 40 to 79).

No excess in risk for the exposed relative to the non-exposed was observed for lymphatic and hematopoietic system cancers. Risks for the exposed population relative to the nonexposed were not computed for the other cancer sites.

The author next compared the mortality experience of those employed in the refinery operations (N = 4,515, 35,604.5 person-years of observation) to those employed in the non-refinery operations. Expected numbers of deaths for the refinery workers were calculated based on the mortality experience of the non-refinery workers. Hanis reported information on job titles for these two groups of workers. As part of this review, job titles were rereviewed by a certified industrial hygienist to determine which job titles would have employees that were potentially exposed to gasoline. There were 17 job codes identified for the refinery population, nine of which were considered to have job titles in which workers would have potential gasoline exposure: (1) gauger; (2) operations, processing, field supervisors, dewaxing, asphalt stills, crude stills, and clay press; (3) packaging and shipping; (4) mechanics, boilermakers, and pipe fitters; (5) chemists; (6) garage workers; (7) electricians; (8) handymen and laborers; and (9) custodial services. There were 17 additional job codes identified for the non-refinery population, only 5 of which were considered to have job titles in which workers would have potential gasoline exposure: (1) marketing, shipping, transportation, and filling; (2) marine workers; (3) gaugers; (4) mechanics; and (5) chemists. Additional job titles

including numbers of workers in each job were not provided.

SMRs for refinery workers were generally similar to the results observed for the exposed population. SMRs were significantly elevated for all causes of death (SMR = 114, observed = 816, $p < 0.01$); all cancer deaths (SMR = 124, observed = 164, $p < 0.01$); diseases of the respiratory system (SMR = 132, observed = 54, $p < 0.05$); and for accidents, poisonings, and violent deaths (SMR = 160, observed = 27, $p < 0.05$). Not observed among the exposed workers but seen among this subcohort of refinery workers were elevated SMRs for cancers of the intestines and rectum (SMR = 185, observed = 28, $p < 0.01$) and other digestive organs (SMR = 181, observed = 21, $p < 0.01$). A statistically significant deficit was observed for malignant neoplasms of the lymphatic and hematopoietic systems (SMR = 47, observed = 7, $p < 0.05$). Statistically non-significant elevations in the SMRs were observed for cancers of the prostate (SMR = 138) and the urinary bladder and kidney (SMR = 120).

Mortality rates and relative risks for the refinery workers by geographic region were also calculated for cancers of the intestine and rectum, other digestive organs, lung, and lymphatic and hematopoietic system. The age-adjusted relative risk for intestinal and rectal cancer was significant ($p < 0.05$) at 2.0 for refinery workers as compared to non-refinery workers. A negative trend was associated with age (ages 40 to 64, RR = 2.4; ages 65 to 79, RR = 2.0; ages 80+, RR = 1.4). Risk for other digestive organ cancer was elevated significantly ($p < 0.05$) for males in age group 65 to 79 years (RR = 10.3); however, among workers in age groups 40 to 64 years and 80 years and above, no risk was apparent (RR = 1.1 and RR 1.0, respectively). Duration of employment also appeared to be inversely related, at least for the categories of employment presented, to the risk of cancer of the intestine and other digestive organs (11 to 20 years, RR = 17.5, $p < 0.01$; 21 to 30 years, RR = 2.5, $p > 0.05$; 31+

years, RR = 1.2, $p > 0.05$). The age-adjusted relative risk for total intestinal and other digestive organ cancer (ICD 153-159) was elevated among refinery workers in each of the geographic areas that had observations (Area 1, RR = 2.2; Area 2, RR = 1.5; Area 3, RR = 2.7), though none was significantly elevated. A significant ($p < 0.05$) risk was observed among refinery workers ages 65 to 79 in the Ontario and Quebec Provinces (RR = 4.8). A much smaller increase in risk (RR = 1.3, $p > 0.05$) was observed for males in the age group 40 to 64 years in the area. Risks were also elevated at nonsignificant levels for males in the age groups 40 to 64 years (RR = 3.9) and 80 years and above (RR = 3.1) in the Western Provinces. No increase in risk was observed for refinery workers in the age group 65 to 79 years in the western area; however, the number of observed deaths was small.

Lung cancer risks were not significantly elevated among the refinery workers, a pattern very different from what was observed among the exposed workers (age-adjusted RR among refinery workers as compared to non-refinery workers = 1.18, $p > 0.05$; age-adjusted RR among exposed workers against nonexposed = 2.3, $p < 0.01$). The risk among the refinery population in comparison to the non-refinery population was lower than expected for lymphatic and hematopoietic system cancers (age-adjusted RR = 0.46, $p > 0.05$).

Lastly, the author calculated SMRs by selective job titles for cancers of the intestine and rectum, other digestive organs, lung, and lymphatic and hematopoietic system. As part of this review, these job titles were rereviewed by a certified industrial hygienist to identify those job titles that would have employees with potential gasoline exposure. Four gasoline exposure categories were thus identified: (1) mechanics, boilermakers, and pipefitters (N = 1496); (2) operations, processing, field supervisors, dewaxing, asphalt stills, crude stills, and clay press (N = 1303); (3) marketing plant and clerks (N = 609);

and (4) packaging and shipping (N = 494).

In general, SMRs for workers for selected cancers in the four gasoline exposure categories were observed to be in excess, though not at significant levels ($\alpha = 0.05$), even though the numbers of observed deaths were small. Specifically, the SMR for workers in the mechanics category was elevated for cancer of the intestine and rectum (SMR = 167.8) as well as for cancer of the other digestive organs (SMR = 134). The SMR for males in the operations category was in excess for lymphatic and hematopoietic system cancers (SMR = 127.7) only. Risks among the marketing plant employees were elevated for both lung cancer (SMR = 166.2) and lymphatic and hematopoietic system cancer (SMR = 131.8). Packaging and shipping workers exhibited an elevated risk of lymphatic and hematopoietic system cancers (SMR = 230) only.

Five job title categories were considered to have employees that would not be exposed to gasoline. A statistically signficant ($p < 0.05$) excess was observed among engineers (N = 625) for other digestive organ cancer (excludes intestinal and rectal cancer) (SMR = 357.5, observed = 4). Though elevated, SMRs were not significant for intestinal and rectal cancer among males in the services, i.e., laundry, custodial, watchmen, and inspectors (N = 156, SMR = 293.8); lung cancer among garage workers and route salesmen (N = 807, SMR = 146.0); or for lung cancer among males employed in the utilities, building trades, or boilerhouse (N = 226, SMR = 200.4). No excess in risk was observed among the office workers (N = 2546).

This study provides insufficient evidence with which to associate employment in the petroleum industry with cancer risk. Gasoline exposure information was not available. Job titles, a proxy measure of gasoline exposure, were provided, but results of these analyses were inconsistent. The only significant cancer finding by job title was for digestive system cancers, excluding those

of the intestine and rectum, for a job considered not to have potential exposure to gasoline (i.e., engineers).

There are other limitations to this study. There was no control for confounding variables such as other chemical exposures (e.g., asbestos and the pipe fitters) and smoking. A major limitation is that all employees who terminated employment prior to being vested in the pension plan were excluded from the cohort (6,681) or were lost to follow-up (865). This has probably led to an underreporting of mortality for Imperial Oil Company employees. Mortality may also have been underreported for employees who were vested in the pension plan but who terminated or retired early, since the company made no attempt to contact these individuals or verify their vital status until they reached pension age. Company records were the only source of vital status ascertainment; therefore, mortality may be underreported for the total cohort. Thus, the estimate of risk for this cohort may be underestimated.

The period of follow-up was short, only 10 years. This is especially important because approximately half of the cohort was under the age of 50 at the time of last observation. Thus, this study provides insufficient evidence of an association between employment in the petroleum industry and a risk of cancer.

4.2.1.3. Hanis et al. (1979)--Hanis et al. (1979) conducted a mortality study of the employees of Imperial Oil Company, Ltd. of Canada and collected information on 21,732 male employees who were either actively working or who were annuitants during the 10-year observation period of 1964-73.

This study population is generally the same population as previously reported on by Hanis (1977); however, the methods of analyses differ.

Data were obtained on current age, years of service with the company, employment status (active, retired, terminated, or dead), date of retirement,

date of death, cause of death, and job title, function, and location. Based on the information regarding the latter, employees were classified by exposure as well as by refinery work. The exposure classification was as follows:

1. Exposed - person who had daily occupational contact with petroleum or its products.

2. Moderately exposed - person who had less than daily contact with petroleum or its products (it could be as much as 2 weeks every month).

3. Non-exposed - person who had no known occupational contact with petroleum or its products.

About 1.6% of the total employees were exposed to petroleum or its products only for a short period of time. If the exposure was for more than 5 years, the employees were included in the exposed group; if the exposure was for less than 5 years, they were included in the non-exposed group.

The classification of refinery work was based on the location of the job, as follows:

1. Refinery work - person who worked daily on a refinery site irrespective of exposure to petroleum.

2. Non-refinery work - person who worked at sites other than refinery.

The final study population was obtained by the exclusion of females, summer students, short-term employees (with less than 5 years' service with the company), employees actively working during the study period but who had had less than 1 full year of employment, 19 retired employees who had died during the study period and on whom no information was available, and 865 employees who were lost to follow-up.

The verification of underlying cause of death was achieved with the help of Provincial Registrars (except for one province) and Statistics Canada. Of a total of 1,511 deaths during the study period, information was not available

for 1.6% of the decedents.

A total of 82,057.0 person-years of observation was contributed by 15,032 individuals. Age-adjusted, cause-specific mortality rates were calculated by using the direct method of age adjustment with the total population as the reference population. This study presented the analyses of cancer deaths. Analyses were carried out by exposure group and refinery group in three geographic locations: the Atlantic provinces, Ontario/Quebec, and the western provinces. Of 301 cancer deaths, 5 deaths were in the less than 40-year age group; hence this group was omitted from the detailed analyses.

Analysis by exposure group revealed that there was statistically significant ($p < 0.05$) excess mortality in the exposed group from all cancer (RR = 1.23), cancer of the esophagus and stomach (RR = 3.25), and cancer of the trachea, bronchus, and lung (RR = 1.89) as compared to the non-exposed group. For the moderately exposed group, the mortality risk for total cancer and site-specific cancers appeared to be less than that for the non-exposed group. As pointed out by the authors, this was probably due to the very small number in this group.

The same pattern was observed for both cancers of the esophagus and stomach, and of the trachea, bronchus, and lung, when geographic locations were taken into consideration. Although none of the RRs was statistically significant, the RRs were increased among the exposed group for cancer of the esophagus and stomach in Ontario/Quebec and the Western Provinces when compared to the non-exposed group. Exposed/non-exposed group comparison for cancer of the trachea, bronchus, and lung showed increased RRs for the same two geographic locations. This cancer risk appears to increase geometrically from eastern to western Canada.

Mortality rates by length of employment demonstrated positive trends with

increasing duration of employment both for cancers of the stomach and esophagus, and of the lung, trachea, and bronchus, indicating a dose-response relationship.

The refinery group showed a higher risk for mortality from cancers of all sites, intestine and rectum, and other digestive organs when compared to the non-refinery group. The RRs were 1.29, 1.97, and 1.82 ($p < 0.05$ for all the RRs), respectively.

Although analysis by geographic location showed that there was a higher risk for cancers of the intestine and other digestive organs in the respective regions for refinery workers as compared to non-refinery workers, any meaningful interpretation is difficult due to the small numbers in the Atlantic and Western Provinces.

Analysis by length of employment in the refinery classification did not show any trends with increasing length of employment either for cancer of the intestine and rectum or for cancer of other digestive organs.

When data were examined by specific subgroups of exposure in refinery and non-refinery settings, higher mortality rates were observed for cancer of the esophagus and stomach in refinery/exposed, refinery/moderately exposed, non-refinery/exposed, and non-refinery/moderately exposed, as compared to non-exposed in their respective refinery/non-refinery settings. Similar findings were not evident in these groups for cancers of the intestine and rectum, other digestive organs, and trachea, bronchus, and lung. Most of these rates, except for the refinery-exposed groups, were based on very small numbers.

Analysis by various job titles for the same four above-mentioned cancers produced mixed results but does show some increased risk. However, these rates are based on extremely small numbers and hence are not reported here in detail.

This mortality study was conducted on a large population (15,032) and had a total of 82,057 person-years of observation. However, the follow-up period was fairly short. Age-adjusted mortality rates were used for the analyses, which makes it difficult to compare this study with other studies. The total study population of the work force was used as a standard population for direct age adjustment, which may underestimate some of the risks if there is a common exposure for this population that causes certain types of cancer. Analyses by location and exposure, however, point toward cancers of the esophagus and stomach, and trachea, bronchus, and lung. Other confounding factors, e.g., smoking and other occupational exposures, were not considered. Due to the extremely small numbers, mortality rates by job categories do not provide much help. Most important, specific exposure histories to gasoline were not presented.

In addition, in a letter to the editor, Schottenfeld et al. (1980) question: (1) the use of an exposure classification criterion that does not consider average dose level, duration, and uniformity of exposure over time; (2) Hanis et al.'s assumption that exposure within 5-year age groups is homogeneous within a particular cohort; Schottenfeld et al. suggest that the authors should have used the Mantel-Haenszel procedure (Mantel and Haenszel, 1959) as a summary measure of relative risk rather than make such an assumption; (3) the combining of esophageal epidermoid carcinoma and stomach adenocarcinoma into a single cause-of-death category, since each has a different etiology; (4) the authors' failure to use a test of linear trend to test for dose-responses; and (5) that the lung cancer excess reported by Hanis et al. may reflect an occupational association other than with petroleum products (e.g., asbestos); Schottenfeld et al. suggest that smoking information be acquired on the cohort members.

Hence, this study is considered inadequate to use as a basis for drawing any conclusions with regard to gasoline exposure.

4.2.1.4. Theriault and Goulet (1979)--The investigators conducted a retrospective mortality study of 1,205 males (race not specified) who worked at a Canadian oil refinery plant for more than 5 years between 1928 (the start of plant operations) and December 31, 1975. Vital status was determined as of December 31, 1976.

The company furnished personnel information on each person, including name, date of birth, date of employment, work termination date, last known address, social insurance and employment insurance numbers, and a classification of workers according to the type of work; i.e., operation, maintenance, or office work. Males who terminated employment were traced through several means including telephone calls, the Motor Vehicle Bureau, the Quebec Health Insurance Board, the Pension Board, the Unemployment Insurance Commission, the Quebec Population Registry, and letters to fellow workers. Lost to follow-up were 190 males (16% of the original study population) whose survival status could not be ascertained. Thus the final study population consisted of 1,015 males, representing 17,545.6 person-years of observation.

Cause of death, as reported on the death certificate, was recoded to the 8th revision of the ICD.

The SMRs were calculated using the age- and cause-specific death rates for the Province of Quebec as the standard. Expected numbers of deaths for the years 1928-62 were calculated using the 1951 rates, while the 1971 rates were used for the years 1963-76. To test the differences between the observed and the expected numbers of deaths, the Bailer-Ederer test (1964) for the ratio of a Poisson variable to its expectation was used. For purposes of analysis, the cohort was divided into two subgroups: those with more than 20 years' and

those with less than 20 years' time between the date of employment and time of death. The SMRs for the combined subgroups were also calculated. Reported by the authors but not reviewed here are nonsignificant cancer excesses based on only one or two observed deaths.

There were 108 deaths observed; 91% occurred among employees who were 40+ years of age. The age distribution of the lost-to-follow-up group was similar to those who were alive at the time of ascertainment.

The SMR for all causes of death among the combined cohort and among those with less than 20 years of exposure was significantly reduced ($p < 0.05$) (SMR = 78, observed = 108 and SMR = 63, observed = 33, respectively). Also reduced, although not significantly, was the SMR for all causes of death among those with 20+ years of exposure (SMR = 88). The SMRs for total cancer mortality among the total cohort were also lower than unity (SMR = 89, observed = 25, $p < 0.05$). Similar patterns were observed among the two exposure groups. The SMR for malignant neoplasms of the brain/CNS for those exposed less than 20 years was significantly elevated at 652 (observed = 3). The only other significant SMR (17, observed = 1) was observed among those with 20+ years of exposure whose cause of death was accidents and violence.

SMRs were elevated, though not significantly, for malignant neoplasms of the male genital organs/bladder/kidney (SMR = 152), and of the digestive system (SMR = 126) among those with 20 or more years of exposure. Similar patterns were observed among the total cohort, but the SMRs were smaller. Also elevated ($p < 0.05$) was the SMR for diseases of the digestive system (SMR = 179, observed = 7) among those with 20 or more years of exposure.

Job titles for the 25 cancer deaths were reported by the authors: 4 were in operations, 4 were office employees, 11 were maintenance workers, and 6 belonged to more than one group. Except for the office workers, all of the

workers may have been exposed to gasoline.

These results provide insufficient evidence for the carcinogenic potential of gasoline vapors. Gasoline exposure information was not presented. The refinery also operated a laboratory, and confounding variables, such as exposure to other chemicals, were not controlled for.

One hundred and ninety (16%) males were totally eliminated from the study population because they were lost to follow-up (rather than including these subjects in the study population until the point of loss). As a result, the expected numbers of deaths may be artificially low (Monson, 1980), thus potentially overestimating the SMR.

The authors' use of the 1951 age- and cause-specific death rates as the standard population for the period 1928-62 is questionable, since mortality rates have greatly changed over this period of time.

Finally, confounding factors such as smoking were not taken into consideration. Thus, these data provide insufficient information with which to assess an association between gasoline vapors and cancer.

4.2.1.5. Thomas et al. (1980)--Thomas et al. (1980) conducted a proportionate mortality study of decedents who at the time of their deaths were active members of the Oil, Chemical, and Atomic Workers International Union (OCAW). The deaths were reported to OCAW International Headquarters by the union's locals in Texas between 1947 and 1977. Of the total number of deaths that were reported, death certificates could not be located for 10%, and these were not included in the study. Of the 3,105 decedents for whom there were death certificates, about 40% were less than 50 years of age at death; about 40% were union members for less than 10 years, and 25% were union members for 20+ years.

The individual plants in which the members had worked were classified into one of five major categories, according to major industrial process. Of the

3,105 deaths, 67.2% were classified in the petroleum refining and production of petrochemicals category. Since this category was considered by the reviewers to be the most relevant of the categories to an assessment of gasoline exposure, the results of this category alone are discussed here.

The underlying cause of death was coded by a trained nosologist in accordance with the 8th revision of the ICD. Information on age at death, race, and cause of death was combined with data obtained from the union to formulate a final record on each subject.

The expected number of deaths was calculated by applying the race- and cause-specific relative frequencies of death among U.S. males to the total number of deaths in the study group, with appropriate adjustments for age and calendar year. Proportionate mortality ratios were calculated for various cancer sites by dividing the observed number of deaths from a particular cancer by the expected number. For each cancer site with an elevated PMR, Texas Proportionate Mortality Ratios (TPMRs) and Proportionate Cancer Mortality Ratios (PCMRs) were calculated using the relative frequencies for Texas males and the proportionate cancer mortality for U.S. males, respectively. Statistical significance was determined by use of the summary chi-square test.

The PMR for all cancer deaths was elevated for white (PMR = 126, observed = 394, $p < 0.01$) and non-white (PMR = 127, observed = 79, $p > 0.01$) workers. A PMR excess ($p < 0.01$) was also observed for arteriosclerotic heart disease for both racial groups (white, PMR = 119, observed = 687; non-white, PMR = 149, observed = 114). However, statistically significant deficits ($p < 0.01$) were observed among whites only for respiratory diseases (PMR = 36, observed = 27) and digestive diseases (PMR = 65, observed = 68). Non-white males had significantly elevated ($p < 0.01$) PMRs for motor vehicle accidents (PMR = 184, observed = 29) and a significantly greater PMR was observed for non-motor

vehicle accidents for whites only (PMR = 154, observed = 145, $p < 0.01$).

The cause-specific cancer PMRs showed significant ($p < 0.05$) excesses for whites, for the digestive organs and peritoneum (PMR = 124, observed = 111), respiratory system (PMR = 131, observed = 134), brain and CNS (PMR = 176, observed = 25), and skin (PMR = 194, observed = 14). Similar excesses were observed for non-whites, for cancers of the respiratory system (PMR = 139) and digestive system (PMR = 138), but these excesses were not statistically significant.

Analysis by length of union membership revealed PMR excesses for cancer of the stomach (PMR = 269, observed = 14, $p < 0.05$) and cancer of the kidney (PMR = 214, observed = 7, $p < 0.05$), both in the 20+ years' membership group in white males. In the same group, the TPMRs were also significant for both of these causes (TPMR = 278 and 251, respectively). The only other statistically significant elevation of the TPMR was observed in white males for cancer of the brain and CNS (TPMR = 245, observed = 12, $p < 0.05$) in the 10 to 19 years' membership group. A similar analysis for non-white males revealed a PMR excess for stomach cancer (PMR = 280, observed = 12, $p < 0.05$) in the 10+ years' membership group. The corresponding PCMR was 192 and the TPMR was 259 for this cause in this group, and both were significant at the 0.05 level, while the PMR was 242 (observed = 5, $p < 0.05$) for the non-white group with union membership of less than 10 years. However, the corresponding TPMR and PCMR were not significant.

These results provide very weak evidence for the carcinogenicity of gasoline vapors because of several study limitations. Death certificates were not available for 10% of the population, i.e., for about 350 deaths. This may lead to underreporting of certain causes of death and may heavily influence the cause-specific mortality frequencies, especially if the underreporting occurred

for specific causes where the numbers were small to start with. This limitation was also expressed by Wong and Tabershaw (1980) in their letter to the editor.

Since the study was limited to active members of the union, thereby excluding union members who had retired or left for other reasons as well as non-union members, the results may overrepresent diseases with very low survival rates and underrepresent diseases that tend to occur in retirees, or to have a longer latency period. These concerns were also expressed by Wong and Tabershaw (1980) and Divine (1980).

A serious inherent problem with this study is in the usefulness of the PMR statistic. In addition, exposure information on gasoline was not available. Confounding variables such as other chemical exposures and smoking were not taken into consideration.

There is another question with regard to the adequacy of the latency period used in this study. A surrogate measure of latency is length of union membership. Approximately 40% and 25% of the decedents were OCAW members for less than 10 years and more than 20 years, respectively. Thus, for a significantly large population, the period between first exposure and death was less than the generally accepted average latency period of 10 to 30 years for environmentally induced cancers.

Thus, this study provides very limited evidence of an association between gasoline and cancer risk.

4.2.1.6. Wen et al. (1981, 1982, 1983, 1984a)--This is a retrospective cohort study of all regular employees who worked at a Gulf Oil refinery located in Port Arthur, Texas. The refinery was a fullservice operation involved in refining crude oil and manufacturing fuels, oils, lubricants, and petrochemicals such as benzene, cumene, ethylene, and cyclohexane. Vinyl chloride was never

manufactured at the refinery. The authors examined mortality extending over a period of 41 to 44 years and presented analyses of the data in four papers. No information was provided by the authors as to why the period of study differed for the four analyses. Described here are the authors' methods of cohort selection and data collection; the authors' results are reviewed separately.

The cohort consisted of all regular employees who worked at the refinery between January 1, 1937, and January 1, 1978, in the study covering the shortest time interval (Wen et al., 1983, 1984a), and between June 15, 1935, and December 31, 1979, in the study covering the longest time interval (Wen et al., 1982), regardless of length of employment. Demographic and work histories were obtained from the company's personnel records. Verification and supplementation of information was done by using other corporate records such as annuitant insurance, seniority lists, and medical and mortality records. Records included vital information on date of hire, date of retirement or termination, pay status, and, if deceased, date of death. Pay status was classified as salaried or hourly, depending on the percentage of time worked in each category. Vital status was determined by tracing through the SSA, the Texas and Louisiana Departments of Motor Vehicles, and local telephone directories, followed up by inquiries made to former employees, friends, relatives, and neighbors.

Death certificates were obtained either from the company's personnel, benefit, or medical records, or from the various states' vital statistics departments. The underlying causes of death were coded by a trained nosologist according to the 8th revision of the ICD. Person-years at risk were calculated from the beginning of the follow-up period or from the date of employment, whichever was later. Those lost to follow-up were calculated in the person-years of observation up to the point of last known contact, usually employment termination. SMRs were computed by using age-, sex-, race-, year-, and cause-

specific mortality rates of the general U.S. population (Monson, 1974). Significance testing was done by using the Poisson distribution (Wen et al., 1981, 1983, 1984a) or a summary chi-square test with one degree of freedom (Wen et al., 1982). Characteristics of the cohort analyzed for each of the four papers are presented in Table 4-2. No information was provided by the authors as to why the total numbers of deaths or those lost to follow-up were not identical for the four analyses.

4.2.1.6.1. Wen et al. (1982). These analyses were originally presented in 1980 at the New York Academy of Sciences Workshop on brain tumors in the chemical industry and subsequently published in 1982; they are therefore presented here before the authors' 1981 analyses.

Analyses were restricted to the 15,698 male employees because of the small numbers of females (1,823). White males represented 83% of the study population, 316,574 person-years of observation; non-white males contributed 58,971 person-years of observation. Race was not known for 2.5% of the males, but these were assumed to be white. Lost to follow-up were 9.8% of the white males and 13.5% of the non-white males.

Approximately 40% of the males worked 20 years or more, 50% were employed less than 9 years, and 70% were hired before 1950. This pattern was observed for both race groups.

There were 4,660 observed deaths, and death certificates were not obtained for 9% of these; a breakdown by race was not reported.

The SMR for all causes of death among all males was 89. A similar pattern was observed stratifying by race (white SMR = 92, non-white SMR = 81). These risks were not significant ($p > 0.05$). Risks for all malignant neoplasms were equal to those of the U.S. population for both races (white SMR = 99, non-white SMR = 110).

TABLE 4-2. SUMMARY OF COHORT CHARACTERISTICS FROM FOUR WEN ET AL. STUDIES

	Wen et al. (1981)	Wen et al. (1982)[a]	Wen et al. (1983)	Wen et al. (1984a)
Period of follow-up	6/15/35—1/1/78	6/15/35—12/31/79	1/1/37—1/1/78	1/1/37—1/1/78
Time of employment required for inclusion	1 day	1 day	1 day	1 day
Number of years of observation	42.5	44.5	41.0	41.0
Number of persons followed (total)	17,350	17,521	16,880	16,880
Number of person-years observed (total)	406,659	408,073	406,198	406,198
Number of white males followed	12,960	13,074	12,526	12,526
Number of person-years observed (white males)	315,167	316,574	313,067	313,188
Average length of follow-up (years)	23.4	NR[b]	24.1	NR
Number lost to follow-up (total)	2,185 (13%)[c]	2,278 (13%)	1,542 (9.1%)	NR
Number lost to follow-up (white males)	1,216 (9.8%)	1,281 (9.8%)	727 (5.8%)	730 (5.8%)
Number of deaths (total)	4,434	4,766	4,361	4,358
Number of observed deaths (white males)	3,494	3,753	3,444	3,441
Death certificates unascertained (white males)	299 (8.6%)	9% (all males)	218 (6.3%)	NR

[a] Originally presented in 1980, subsequently published in 1982.
[b] NR = Not reported.
[c] Values in parentheses represent percent of total.

Analyses by specific cause of death were only presented for brain tumors. None of the SMRs reported was statistically significant. The SMR among white males for malignant brain tumors was 85; the SMR equaled 108 for benign or unspecified brain tumors. SMRs were not reported for the non-whites because of the small numbers of observed deaths (observed malignant = 3, observed benign or unspecified = 2); however, the SMRs can be calculated (Fleiss, 1981) as 150 for brain cancer and 133 for benign or unspecified brain tumors ($p > 0.05$).

SMRs for brain tumors in males by length of employment (less than or greater than 20 years) were calculated stratifying by race and diagnoses (malignant or benign). None of the SMRs was statistically significant. The data suggest that risks for white males employed less than 20 years at the refinery were less than for the U.S. population (SMR = 65), but that among white males employed 20 or more years, malignant brain tumor risks may be slightly elevated, although not significantly, over U.S. risks (SMR = 109). Risks for benign brain tumors among white males employed at least 20 years were 80% greater than for the U.S. population (SMR = 184). Risks for non-white males were not reported; however, they can be calculated as 93 for brain cancer among those employed less than 20 years (observed = 1) and 217 (observed = 2) among those employed more than 20 years. Risks for benign brain tumors were also elevated (SMR = 317, observed = 2) among those employed 20 or more years ($p > 0.05$).

This study presents insufficient data to assess the association of gasoline with brain cancer. No quantitative measures of gasoline were available. Details on job assignments and proxy measures for exposure were not reported. The refinery manufactured petrochemicals (e.g., benzene) as well as gasoline, and exposures to these other substances were not controlled for.

The cohort of 15,698 was followed for 44 years. Considering this fact, the tracing of vital status was very good, and tracing procedures were very

thorough, although one could question using SSA records before 1946, since SSA records for mortality follow-up were not very complete until after World War II, and hence their use may lead to an understatement of deaths. If a DMV license had been issued through 1980, the person was assumed to be alive, which may also lead to some understatement of mortality. Anyone who ever worked at the refinery during the study period was included in the cohort, which may lead to the inclusion of persons with little or no exposure in the denominator and hence to underestimation of risk.

The authors report analyses of brain tumor deaths by age at death, year of hire, length of employment, and year of death; however, these analyses did not post-stratify by race or brain tumor diagnosis (i.e., malignant or benign).

Another criticism of this study is that both white- and blue-collar workers were included in the cohort, and analysis failed to control for this fact; thus, risks for those involved in manufacturing of petroleum products (i.e., blue-collar workers) may be underestimated.

Finally, the brain is a common site of metastasis, and without knowing if the brain cancer is primary, it is not possible to draw conclusions of an association between brain cancer and employment in the petroleum refining industry.

4.2.1.6.2. Wen et al. (1981). This study reports detailed analyses of the brain tumor data previously presented in 1980 by the authors (Wen et al., 1982). The length of this study was 2 years shorter (June 15, 1935 to January 1, 1978) than previously reported. The cohort of 17,350 workers consisted of 15,556 (90%) males, 83% white and 17% non-white, and 1,794 (10%) females. Lost to follow-up were 1,551 (10%) of the males and 634 (35%) of the females. Thus, analyses were limited to males only (374,202 person-years of observation).

The distribution of male workers by race, time of hire, and length of

employment was similar to that reported in the previous study. Also included were details on pay status, classified as salary or hourly depending on the percent of the work in each category. These data indicated that 82% of the white males and 98% of the non-white males never worked as salaried employees.

Similar patterns of risk were observed to those previously reported for all causes of death, except that risks were reported at significant levels ($p < 0.01$); among white males the SMR equaled 88 (observed = 3,494), and among non-white males the SMR equaled 75 (observed = 842). Risks for all malignant neoplasms were slightly lower than those originally reported but were not significantly reduced (white SMR = 94; non-white SMR = 93). Brain cancer risks for white males were also lower (SMR = 76) than previously reported (SMR = 85).

Brain tumor mortalities were further examined by pay status; hourly employees were those with 100% of their employment on an hourly basis, and salaried employees were those with 75% of their employment on a salaried basis. Risks for salaried employees were slightly lower than risks for hourly employees, regardless of race or cause of death (i.e., all causes, all cancers, and brain tumors).

To further evaluate the effect of the lost-to-follow-up group, a subcohort was selected. Referred to as the 1940 cohort, this subcohort consisted of employees hired on or after January 1, 1940, with a minimum of 6 months of employment. Lost to follow-up were only 3.8% of the white males and 6.5% of the non-white males. The final 1940 cohort of 11,526 males represented 275,785 person-years of observation. Similar patterns of risk were observed ($p > 0.05$); the SMR for white males for brain cancer was observed at 66. The SMR for non-whites was not reported but can be calculated as 189.

This study has many of the same limitations as the previous study. Gasoline exposure could not be assessed. Details on job titles were not available.

Confounding factors were not controlled for.

The authors did attempt to correct a limitation of the previous study by including analyses by pay status, using hourly employees as the proxy measure for blue-collar workers; however, results were only presented for all brain tumors. No analysis was presented for malignant brain tumors by pay status. Analyses of all brain tumor risks by latency and length of employment were presented, but no analyses of these important factors were presented for malignant brain tumors.

Finally, the authors presented no rationale for why this study period was shortened by 2 years from what was originally reported, thus excluding two of the white male brain cancer deaths from the study population.

Thus, this study provides insufficient data to assess the association between gasoline and primary brain cancer in males.

4.2.1.6.3. Wen et al. (1983). This study analyzes the previously reported (Wen et al., 1981, 1982) Port Arthur, Texas, cohort for all causes of death. This period of study began 1-1/2 years later and ended 2 years sooner (January 1, 1937 to January 1, 1978) than what was initially reported by the authors in 1980 (Wen et al., 1982). No explanation was provided by the authors as to why the period of study differed.

In this study, 16,880 employees were included in the cohort, of whom 15,095 (89.4%) were males contributing 372,505 person-years. The follow-up was successful for 94% of the males and 68% of the females; however, this study presented findings for males only. Of 4,269 male deaths, death certificates were located for 3,982 (93.3%). As in the other Wen et al. (1981, 1982) studies, 70% of the male cohort began work prior to 1950; approximately 40% worked for 20 or more years.

SMRs for all causes of death and all cancers were 84 (observed = 4,269,

$p < 0.01$) and 96 (observed = 839, $p > 0.05$), respectively. Both showed deficits, confirming the popular belief in the "healthy worker" effect. The total cohort showed more statistically significant ($p < 0.05$) deficits than excesses, including deficits for cancers of the digestive organs (SMR = 82, observed = 231), esophagus (SMR = 44, observed = 12), rectum (SMR = 60, observed = 19), liver (SMR = 35, observed = 8), and bladder (SMR = 46, observed = 13); lympho- and reticulosarcomas (SMR = 24, observed = 4); and diseases of the circulatory system (SMR = 79, observed = 2,036), respiratory system (SMR = 68, observed = 203), gastrointestinal system (SMR = 59, observed = 75), and infective and parasitic diseases (SMR = 35, observed = 60). The only significant SMR elevation was for cancer of the bone (SMR = 205, observed = 11, $p < 0.05$). Cancer of the eye had an SMR of 286, based on only two deaths. Hodgkin's disease had an SMR of 145 and cancer of the skin had an SMR of 122, both based on 16 observed deaths. All of the other SMRs were less than 120, none being statistically significant.

Analyses of the cohort by pay status revealed deficits for all causes of death (SMR = 67, observed = 300, $p < 0.01$) and all cancers (SMR = 79, observed = 61, $p > 0.05$) in salaried workers (white and non-white; this pay group comprised 11% of the total population). All other cause-specific mortalities also showed deficits. When cancer mortality was examined in this group, two excesses were observed; these were for cancer of the pancreas (SMR = 189) and cancer of the skin (SMR = 140), based on eight and two deaths, respectively. Both of these SMRs were statistically nonsignificant. A statistically significant cancer deficit was observed for stomach cancer (SMR = 17, observed = 1) for this subcohort.

Both white and non-white hourly workers had SMR deficits for all causes of death. The SMRs for workers in this pay group were 90 (observed = 3,146) and

73 (observed = 823), respectively, both being statistically significant ($p < 0.01$) deficits. These same groups also had SMRs of 99 and 92, respectively, for all cancers, neither being statistically significant; the SMR for diabetes mellitus was elevated, but not significantly (SMR = 112) in the non-white group only. SMR deficits were seen for all other causes. Among white hourly workers, a significant cancer deficit was observed for cancers of the esophagus (SMR = 47, observed = 7), liver (SMR = 46, observed = 7), and bladder (SMR = 47, observed = 10), and for lympho- and reticulosarcomas (SMR = 8, observed = 1). Both racial groups had a higher mortality for bone cancer, with SMRs of 228 and 217 for whites and non-whites, respectively ($p < 0.05$). These excesses were based on nine and two deaths, respectively. Whites also showed an increase in the SMR for eye cancer (SMR = 341), based on two deaths, and skin cancer (SMR = 122), based on 13 deaths. All other SMR increases were under 120 and were statistically nonsignificant. When this group was analyzed according to those who had worked 1 year or more, similar excesses in bone cancer SMRs were observed in both races; among whites the SMR equaled 275 (nine deaths), and among non-whites the SMR equaled 245 (two deaths). Both were statistically nonsignificant.

This study has the same limitations as the previous Wen et al. (1981, 1982) analyses. Once again, neither exposure levels nor job titles were available. No analyses were performed either for latency or length of employment, although for a cohort of this size with a 41-year observation period, this would have been feasible.

The authors went to great lengths to calculate and show that the study had an adequate statistical power in terms of detecting increases for the various causes of cancer deaths studied, but in the absence of any occupational exposure histories the study is inadequate to use as a basis upon which to draw any

conclusions.

4.2.1.6.4. Wen et al. (1984a). These analyses examined the mortality experience of active, retired, and terminated workers. The period of study was the same as the authors' 1983 study (January 1, 1937 to January 1, 1978); however, these analyses were limited to white males only. Of a total of 12,526 white male employees contributing to 313,188 person-years, 6,199 (contributing 41% of the total person-years and 38% of the 3,441 deaths) had terminated, and 2,837 (contributing 8% of the person-years and 37% of the deaths) had retired by the end of the study. The active group numbered 2,635 and contributed 51% of the total person-years and 25% of the deaths. The mean age at death was 53 for active, 57 for terminated, and 74 for retired workers.

The SMRs for all causes for active, terminated, and retired workers were 68 (observed = 855, $p < 0.01$), 104 (observed = 1,306, $p > 0.05$), and 89 (observed = 1,280, $p < 0.01$), respectively. SMRs for all cancers for active, terminated, and retired workers were 85 (observed = 177. $p < 0.05$), 98 (observed = 234, $p > 0.05$), and 105 (observed = 270, $p > 0.05$), respectively.

There was no significant excess for any site-specific cancer cause of death among any of the three groups. Reported by the authors but not reviewed here are nonsignificant cancer excesses based on fewer than three deaths. Nonsignificant increases among the active group were observed for cancers of the pancreas (SMR = 146), kidney (SMR = 142), bone (SMR = 164), and for leukemia (SMR = 155). Excesses ($p > 0.05$) were observed among the terminated group for cancers of the buccal cavity and pharynx (SMR = 122), pancreas (SMR = 113), lung (SMR = 115), bone (SMR = 216), skin (SMR = 156), prostate (SMR = 130, and for Hodgkin's disease (SMR = 160); and among the retired group for cancers of the lung (SMR = 118), bone (SMR = 246), skin, (SMR = 118), kidney (SMR = 132), prostate (SMR = 114), brain (SMR = 117), and other lymphatic

tissues (SMR = 159), and for leukemia (SMR = 158). Statistically significant deficits were found for cancer of the lung (SMR = 67, observed = 38, $p < 0.05$) in active workers and cancer of the liver and biliary passages (SMR = 16, observed = 1, $p < 0.05$) in retired workers.

The authors divided the retired group into three subgroups for further analyses: (1) employees who retired at 65 or later, i.e., regular retired; (2) employees who retired early on the basis of a medical disability, i.e., disability retired; and (3) all employees who retired before 65 including disability retired, i.e., early retired. The SMRs for all causes of death among the regular and early retired were significantly ($p < 0.05$) lower than for the U.S. white male population (SMR = 87, observed = 246, and SMR = 89, observed = 485, respectively), while the SMR for the disability retired was significantly ($p < 0.01$) higher (SMR = 164, observed = 53) for all causes of death. The only other significant elevations in risk were for diseases of the circulatory system for the disability retired (SMR = 154, observed = 27) and diseases of the nervous system and sense organs for the disability retired (SMR = 1300, observed = 3). Significant deficits were observed for all but the latter diseases group among the early retired.

Borderline significant cancer risks were observed for regular retired employees for skin cancer (SMR = 478, observed = 3, 95% CI 0.96-13.96).

Excessive nonsignificant cancer risks of 140 or above were observed among each of the three retired groups. Among the regular retired employees, risks were elevated for cancer of the kidney (SMR = 254), leukemia (ICD 204-207, 284) (SMR = 183), and cancer of other lymphatic tissues (ICD 202, 203, 208) (SMR = 318). Among the early retired employees, risks were elevated for cancer of the kidney (SMR = 154) and for leukemia (SMR = 144). Only one of the malignant diseases had observations of three or more for the disability retired group;

risk for this site was elevated (lung cancer, SMR = 150)

This study has some of the same limitations as the authors' previous analyses (Wen et al., 1981, 1982, 1983). There is no information on gasoline exposure or job titles, length of employment, or latency analysis. Additionally, the authors failed to explain why this cohort of white males had three fewer deaths than the same cohort reported in an earlier study (Wen et al., 1983). Risks for those involved in petroleum refining operations may be underestimated, since approximately 29% of the workers at this plant are management or clerical staff (Moure-Eraso and Itaya, 1985) and therefore not likely to be exposed to petroleum products. The authors indicate that 99% of the lost-to-follow-up group were terminated employees, and therefore deaths for this group may be underascertained and risks may be artificially low.

Thus, this study provides insufficient information to assess the carcinogenicity of gasoline.

4.2.1.7. Rushton and Alderson (1981a)--The Rushton and Alderson paper is a mortality study of all male workers who had worked for at least 1 year between January 1, 1950, and December 31, 1975, at any one of eight refineries in Great Britain; the total number in this large cohort was 34,781 individuals, for a total of 575,982 person-years of observation, and the mean follow-up was 16.6 years for each person.

Tracing was successful for over 99% of the cohort. It was achieved either through social security records at Newcastle using National Insurance numbers or through National Health Service Central Registers at Southport and Edinburgh using National Health Service numbers.

Personal data were obtained on full name, date of birth, address, date of joining, and last or present job. For leavers, the date and reason for leaving were obtained. For dead individuals, the underlying cause of death and up to

three causes contributing to the underlying cause of death were coded, using the appropriate revision of the ICD. Date of entry to the study was January 1, 1951, or 1 year after joining, whichever was later, depending on whether the person was employed prior to or after January 1, 1950.

The SMRs were computed by using 5-year age and calendar-period rates for males in England and Wales for English and Welsh refineries and in Scotland for Scottish refineries. Significance testing was done by the use of the Poisson distribution.

The SMRs for all causes of death (SMR = 84, observed = 4,406), arteriosclerotic and degenerative heart disease (SMR = 90, observed = 1,428), and tuberculosis of the respiratory system (SMR = 39, observed = 25) and bronchitis (SMR = 64, observed = 253) showed statistically significant deficits ($p < 0.0001$). The only significant SMR elevation was observed for accidents that were caused by fire and explosion (SMR = 201, observed = 12, $p = 0.0196$). Although some statistically significant excesses were found for laborers for various categories in different refineries, there was in general a lowered mortality from nonmalignant causes in all the subgroups defined by job, age, duration of service, etc.

SMR deficits were also observed for all cancer deaths (SMR = 89, observed = 1147, $p = 0.0001$) and for cancer of the lung and pleura (SMR = 78, observed = 416, $p < 0.0001$). Excesses were observed for cancer of the nasal cavities and sinus (SMR = 224, observed = 7, $p < 0.04$) and for melanoma (SMR = 216, observed = 14, $p < 0.007$).

Analysis by job category revealed pronounced deficits for all cancer SMRs in engineers, scientists, foremen, and administrative and clerical workers. Other groups had an SMR of 100, with the exception of laborers (SMR = 111, observed = 325, $p < 0.05$). A similar pattern was also observed for lung can-

cer, except that the elevated SMR observed for laborers was not statistically significant.

Detailed examination of data revealed excesses from cancer of the esophagus, stomach, intestine, and rectum among workers from four of the eight refineries. At one refinery there was a negative trend for stomach cancer with increasing years of service, while the other demonstrated exactly the opposite, a positive trend with increasing duration of service. A positive trend with increasing length of service was observed in two refineries for cancer of the intestine. Statistically significant SMR excesses were observed for the following cancers: (1) cancer of the esophagus in operators in all refineries together and in laborers in one refinery; (2) cancer of the stomach in laborers in one refinery (this increase affected laborers, riggers, and fire and safety workers); (3) cancer of the intestine for scientists from all the refineries together and in one individual refinery, and for operators in another refinery; and (4) cancer of the rectum in fitters from all of the refineries. This increase was also observed in one refinery in fitters and operators.

All of the excesses were in age groups above 60 years, except for cancer of the intestine, which occurred in the 45- to 59-year age group.

The significant increase in melanoma mortality basically came from two refineries (11 of 14 deaths); of 5 deaths from one refinery, 4 were operators, while the 6 deaths from the other refinery included two boilermakers, an operator, a pipefitter, a laborer, and a clerk. Fifty percent of these deaths were in the under 45-year age group. In one refinery, an increased SMR was observed for lymphosarcoma; although this was statistically significant, it was based on very few numbers.

This study also has the same problem as the majority of the refinery studies, i.e., lack of information on exposure to gasoline. Confounding vari-

ables such as exposures to other chemicals, etc., are not taken into consideration. Although the overall analysis showed increased cancer mortality of the nasal cavities and sinus, no detailed analyses by age, latency, or length of employment are presented. At one of the refineries, increases from cancers of the larynx, prostate, and kidney and suprarenal are mentioned in the text, but no details are provided.

The eight refineries studied here are of varying sizes and complexities and may not deal with the same products. Some had chemical plants in addition to oil refinery plants. Sometimes the mortality results of the different refineries show exactly contradictory findings. For example, analysis by length of service demonstrated that in one refinery, mortality from stomach cancer had a negative trend with increasing duration of service, while another refinery showed a positive trend in stomach cancer mortality with increasing duration of service.

Although this study has a large sample size, more than adequate person-years of observation, and a long follow-up, latency analyses were not carried out. Because of the limitations discussed above, this study is considered inadequate for drawing any conclusions with respect to cancer risk.

4.2.1.8. Schottenfeld et al. (1981)--Schottenfeld et al. (1981) reported the results of a prospective mortality and morbidity study sponsored by the American Petroleum Institute (API) and conducted by the Memorial Sloan-Kettering Cancer Center (MSKCC). The study population consisted of full-time active petroleum industry employees from 19 U.S. companies involved in petroleum refining, petrochemical manufacturing, research and development, and quality control. All reports of illness (more than 5 consecutive days), cancer incidence, and mortality were to be collected. Annuitants of these companies also made up the study population; however, since they were not actively employed, reports of

illness or cancer incidence were not routinely collected. This report presents the results of mortality and cancer incidence only.

Results are reported for 76,336 white and Hispanic males who were employed at any time between January 1, 1977, and December 31, 1979. This group comprises 87.3% of the entire study population and excludes females, blacks, and races other than white or Hispanic. Only 18 employees (< 0.001%) were lost to follow-up. Active members who retired during the study period were assumed to be alive on December 31, 1979, unless mortality information was provided to MSKCC. Seventy-two percent of the white male cohort were employed in refining occupations. Forty-four percent of the refinery workers and 30% of the petrochemical workers were employed before 1960. Approximately 47% of the refinery workers and 58% of the petrochemical workers were under the age of 40.

The SMRs for all deaths and standardized incidence ratios (SIRs) for cancer occurrences were calculated, and observed deaths and incidences of cancers were compared with the expected occurrence in the general population. Mortality rates were compared with the expected occurrence in the general population. Mortality rates were compared with U.S. white male, age-specific rates for 1977. Cancer incidence rates were compared with U.S. age-specific rates from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) programs for 1977 (SEER, 1981). MSKCC used the 8th revision of the ICD to code diagnostic information.

Decreased SMRs were reported for all major classifications of disease. SMRs for all deaths and all cancer deaths were significantly ($p < 0.05$) less than 100 for refinery workers (SMR = 56 for all deaths, observed = 393; SMR = 75 for cancer deaths, observed = 127), petrochemical workers (SMR = 57 for all deaths, observed = 74; SMR = 58 for cancer deaths, observed = 17), and for all workers (SMR = 55 for all deaths, observed = 502; SMR = 72 for cancer deaths,

observed = 156). Lung cancer in refinery workers (SMR = 74, observed = 48) and all workers (SMR = 68, observed = 57) was significantly ($p < 0.05$) less than expected.

The crude average annual mortality ratio was reported to be 4.1/1,000 based on 502 deaths and 122,607 person-years of observation. The authors stated that these crude mortality results were preliminary and may be the result of various factors, including: (1) a relatively short period of observation to date, with workers having been followed for only 1.6 person-years on the average; (2) the study population being younger than the U.S. population; and (3) an underreporting of deaths due to a time lag of 4 to 5 months between the deaths and receipt of death certificates. SMRs, on the other hand, were based on age-specific rates. The authors acknowledged that the influence of the healthy worker effect may have caused the standardized rates to be lower than those expected for the general population.

SIRs were calculated for the incidence of cancers during 1977-79. There were 307 cancers reported and 118,566 person-years of observation. For all cancers, the SIRs were significantly ($p < 0.05$) less than 100 for all workers (SIR = 85, observed = 307) and refinery workers (SIR = 86, observed = 240). The SIR for petrochemical workers was 86, but this was not significant. However, specific cancer sites did show significantly increased ($p < 0.05$) SIRs: acute and chronic lymphocytic leukemias in refinery workers (SIR = 274, observed = 7), multiple myelomas in petrochemical workers (SIR = 552, observed = 3), and cutaneous melanomas in workers from the mid-Atlantic region (SIR = 278). A significant ($p < 0.05$) deficit of digestive system cancer was observed among all workers (SIR = 77, observed = 64).

The authors suggested that these figures be viewed as preliminary and interpreted cautiously. This study looks at mortality and cancer incidence

between 1977 and 1979. Exposure information was not included; however, because this study was done in cooperation with the American Petroleum Industry and specific petroleum-related companies, such information may be available. The effects of confounding factors such as smoking and other chemical exposures were not addressed. Additionally, the period of observation was quite short, only 3 years, and the number of older workers in the study was limited, which would limit the assessment of latency effects. The degree of underreporting is unknown, but could be quite high because reporting was voluntary.

The shortcomings of this study were also discussed in a report submitted to the EPA by the API and prepared by Environmental Health Associates, Inc. (Wong et al., 1985 Unpublished). The main problems listed were as follows: there was a lack of consistency in reporting of mortality and morbidity across companies; mortality experience of terminated employees was not included; many companies were not timely in reporting data; and verification of completeness of census information was lacking. Thus, the results of this study provide insufficient data to form conclusions for an association between cancer and gasoline.

4.2.1.9. Thomas et al. (1982a)--Thomas et al. (1982a) examined the cause-specific mortality experience of an expanded group of union members who were employed at three refineries that were included in an earlier study (Thomas et al., 1980). These refineries were located in the Beaumont/Port Arthur area of Texas. The number of male deaths from the original study of these three refineries was 1,161. This number was expanded to include 1,194 retiree deaths and 154 additional active union member deaths. In the earlier study, reported deaths were for the period between 1947 and 1977. The period of observation for the present study was extended through 1979. Thus, 2,509 active and retired members of OCAW were available for analysis in this 1982 study. As with the earlier study, death certificates could not be located for 8% of the reported

deaths. As opposed to the earlier study, no information was given regarding length of union membership.

PMR calculations were exactly the same as for the Thomas et al. (1980) study. Among whites, 51.2% were retirees, while less than 30% were retirees among the non-whites. Seventy percent of the white males and 59% of the non-white males were age 55 or older at the time of death.

An elevation in PMR was observed for all cancers in both whites (PMR = 119, observed = 474, $p < 0.05$) and non-whites (PMR = 123, observed = 79, $p < 0.05$). The PMR for stomach cancer was significantly elevated ($p < 0.05$) for whites (PMR = 141, observed = 36) and non-whites (PMR = 196, observed = 12). The relative frequencies of deaths, for whites only, attributable to cancers of the pancreas (PMR = 142, observed = 32), prostate (PMR = 146, observed = 39), brain (PMR = 228, observed = 27), and hematopoietic and lymphatic system (PMR = 172, observed = 68), including leukemia (PMR = 189, observed = 31), were significantly greater than expected ($p < 0.05$). Although a PMR of 151 was observed for kidney cancer for white males, it was not statistically significant. A statistically significant excess was observed for accidents, suicides, and homicides (PMR = 142, observed = 66, $p < 0.05$) for blacks only.

There were differences in the mortality patterns for white males among active and retired union members. Significant relative excesses ($p < 0.05$) of stomach (PMR = 166, observed = 21), pancreatic (PMR = 179, observed = 18), and brain cancer (PMR = 229, observed = 25) deaths were seen among active members. Among retirees, however, the PMRs were significantly elevated for prostate cancer (PMR = 142, observed = 31), Hodgkin's disease (PMR = 365, observed = 5), multiple myeloma (PMR = 295, observed = 7), and leukemia (PMR = 232, observed = 19).

Analyses by individual refinery revealed the following significant ($p < 0.05$) PMR elevations. In Refinery A, the total (active and retired) population showed increases in all cancers (PMR = 113, observed = 211), cancer of the prostate (PMR = 162, observed = 20), cancer of the brain (PMR = 213, observed = 16), and non-Hodgkin's lymphoma (PMR = 200, observed = 12). There were significant ($p < 0.05$) elevations in cancer of the brain (PMR = 236, observed = 12) and stomach cancer (PMR = 192, observed = 11) and in non-Hodgkin's lymphoma (PMR = 233, observed = 7) for active workers and retired workers.

In Refinery B, the cohort was analyzed by race. There were significant ($p < 0.05$) PMR elevations in whites for all cancers (PMR = 122, observed = 165), cancer of the skin (PMR = 302, observed = 7), and leukemia (PMR = 252, observed = 14). For leukemias, whites in both active and retired status showed significant ($p < 0.05$) increases in leukemia (PMR = 259, observed = 7, and PMR = 246, observed = 7, respectively). In non-whites, the significant ($p < 0.05$) excesses were for all cancers (PMR = 165, observed = 43), cancer of the stomach (PMR = 254, observed = 7), and cancer of the lung (PMR = 207, observed = 15). Analysis by active and retiree status was not done for this subcohort.

Refinery C showed significant ($p < 0.05$) increases for all cancers (PMR = 125, observed = 98), cancer of the prostate (PMR = 189, observed = 10), cancer of the brain (PMR = 235, observed = 7), and leukemia (PMR = 260, observed = 8). The lung cancer PMR was significant ($p < 0.05$) in the active members (PMR = 174, observed = 22), while the leukemia PMR was significant ($p < 0.05$) in retirees (PMR = 418, observed = 6).

The limitations of this study are similar to those already noted in the earlier study (Thomas et al., 1980). There are serious concerns regarding the loss of individual cases due to the unavailability of death certificates, the

lack of exposure data, and the inherent validity problems of PMRs.

4.2.1.10. Reeve et al. (1982)--The authors reported on a proportionate mortality study of members of an OCAW local in Texas City, Texas. Previous investigations had linked brain cancer with union employment in Texas (Thomas et al., 1980), at three oil refineries in the Beaumont/Port Arthur, Texas, area (Thomas et al., 1982a), and at a petrochemical plant in Texas City (Alexander et al., 1982; OSHA/NIOSH, 1980). This investigation (Reeve et al., 1982) was initiated to determine unusual patterns of cancer mortality at other refineries and petrochemical plants in Texas City.

Males who had been union members of OCAW Local 4-449 and died during the period 1947-79 comprised the study population. Active members at the time of death were identified from notifications sent by the union local to OCAW Headquarters for the purpose of maintaining an accurate count of union members; this file had been maintained since 1947. Retired and former members were identified from two "less well-structured record systems maintained by the local." One system, kept since 1942, maintained a file of all deaths among members. Names were added to the file on the basis of "word of mouth" or from newspaper obituaries. The second system, kept since 1959, was a ledger of deceased members whose survivors had been sent a Bible by the local.

The final study population consisted of 264 white males. Excluded because of insufficient numbers were black males (N = 30) and 31 deaths (11%) that could not be documented with death certificates.

Death certificates were obtained from the Texas Bureau of Vital Statistics and coded by a trained nosologist to the 8th revision of the ICD. Expected numbers of deaths were obtained by applying age-, time-, and cause-specific relative frequencies of deaths among the total U.S. white male population (Monson, 1974). PMRs were calculated if five or more deaths were observed or

expected. Significance testing ($\alpha = 0.05$) was done using a summary chi-square with one degree of freedom.

Sixty-one percent of the study population had worked at Refinery A, 23% at Refinery B, 6% at a tin smelter, 5% at a chemical plant, and the remaining 5% at miscellaneous locations. Thirty-seven percent of the deaths occurred in the age interval 50-59, and 20% of the deaths occurred during each of four 5-year time periods from 1960 to 1979. The authors only reported company-specific PMR results for the refinery workers. The authors provide no reason as to why the non-refinery workers were excluded from the PMR analyses; however, this was most probably due to the small numbers of non-refinery workers (40).

There were 37 cancer deaths observed among Refinery A workers (PMR = 118, $p > 0.05$). Skin cancer was the only cause of death to have a significantly elevated PMR (PMR = 788, observed = 5, $p < 0.05$). Although PMRs were not reported, observed deaths were at least twice those expected for cancers of the brain (observed = 3, expected = 1.23) and kidney (observed = 2, expected = 0.84). The observed deaths for liver cancer were more than four times those expected (observed = 3, expected = 0.64). An additional liver cancer death was observed, but it could not be determined if it was primary or secondary and was thus excluded from the PMR analysis. The only other elevated PMR was for non-motor vehicle accidents (PMR = 163, $p > 0.05$).

The number of expected deaths due to melanoma, using Galveston County, Texas, as the standard, was also determined for Refinery A workers. The resulting estimate was 0.54 compared to 4 observed melanoma deaths.

Among Refinery B workers, 13 cancer deaths were observed (PMR = 108, $p > 0.05$). The PMR was elevated, though not significantly, for lung cancer (PMR = 156). The only other elevated PMR was for circulatory diseases (PMR = 121). The PMR for hematopoietic and lymphatic tissue cancers was not reported, but

the observed numbers of deaths were three times those expected (observed = 4, expected = 1.22).

This study has several limitations. The study population may not be representative of all union deaths in Texas City, Texas, because of the incompleteness of the union's recordkeeping systems and losses due to the unavailibility of death certificates. There are inherent validity problems in a PMR analysis. There was no information on gasoline exposure, job titles, length of employment, analysis of latency, or control of confounding factors. Thus, this study provides insufficient data to form an association between gasoline and cancer.

4.2.1.11. Hanis et al. (1982)--In a retrospective cohort study of the Exxon refinery and chemical plant at Baton Rouge, Louisiana, the investigators included all regular refinery and chemical plant employees who had worked at that site for at least 1 month during January 1, 1970, through December 31, 1977. Also included in the cohort were the retirees who were alive as of January 1, 1970.

Of the total population of 8,666, 6,632 were known to be alive, 1,199 were known to be dead, and 835 (9.6%) were lost to follow-up at the end of the study period. Data were obtained from the company personnel files that included name, sex, race, date of birth, date of employment, social security number, date of termination, work history summaries, status at last observation, date of death, underlying cause of death, and, when available, a history of smoking and alcohol consumption. Job categories were derived from the work histories. Death certificates were available for 99% of the decedents. The underlying cause of death was coded by a trained nosologist according to the 8th revision of the ICD.

The computer program developed by Monson (1974) was used to calculate age,

sex, race, and calendar year adjusted SMRs, using U.S. death rates as the standard. Ninety-five percent confidence intervals were calculated assuming a Poisson distribution. Hence, if the confidence interval did not include 100, the SMR was statistically significant. Reported by the authors but not reviewed here are nonsignificant cancer excesses based on fewer than three observed deaths.

A total population of 8,666 contributed to 52,791.3 person-years of observation. In the case of lost-to-follow-up individuals, person-years were calculated until the last known status. Ninety-five percent of the population was male, blacks accounting for 16%. Approximately 60% of the individuals were 50 years or older, while about 50% of the individuals were employed prior to 1945. Of the study population, 72.5% belonged in the job categories of operators (32%), mechanics (60%), and laborers (8%); 25.9% belonged in all other jobs; and 1.6% of the job categories were unknown. They were classified in this manner because it was assumed that the first group was more likely to be in contact with petroleum and its products.

Analyses were carried out by total cohort and various subcohorts. For the total cohort, SMR deficits were observed for all causes of death (SMR = 92, observed = 1,199, $p < 0.05$) as well as for malignant neoplasms (SMR = 92, observed = 249, $p > 0.05$). There were more SMR deficits than increases. None of the increases observed was statistically significant. Cause-specific cancer mortality of this group showed elevated SMRs for cancers of the pancreas (SMR = 152) and kidney (SMR = 155). None of these elevations was statistically significant. There were some other SMR increases, but they were less than 120 and hence are not mentioned here. The only statistically significant SMR was observed for cancer of the buccal cavity/pharynx (SMR = 26, observed = 2), being a deficit.

A subcohort of operators, mechanics, and laborers, consisting of 6,281 employees contributing to 38,960.3 person-years of observation, showed quite a few cause-specific SMR increases, although none was statistically significant. The SMR elevations of 120 or more were for cancers of the pancreas (SMR = 154), testis/other genitalia (SMR = 286), kidney (SMR = 205), other secondary and unspecified sites (SMR = 139), lymphoreticular sarcoma (SMR = 125), and other lymphatic tissue (SMR = 125).

A subcohort of all other employees, consisting of 2,243 individuals contributing to 13,230.3 person-years of observation, showed an SMR deficit for all malignant neoplasms (SMR = 70, observed = 40, $p < 0.05$). This subcohort showed SMR deficits for virtually every cause-specific cancer examined except for cancers of the pancreas (SMR = 156) and bone, connective tissue, skin, and breast (SMR = 150), with none of the elevations being statistically significant.

Analysis of the subcohort who were alive prior to 1956, i.e., who had worked for 15 or more years in the company (5,297 individuals, 37,425 person-years of observation), revealed SMR deficits for all causes of death (SMR = 93, observed = 1180, $p < 0.05$) and malignant neoplasms (SMR = 93, observed = 247, $p > 0.05$). Statistically nonsignificant cause-specific cancer SMR elevations of 120 or more were observed for cancers of the pancreas (SMR = 153), and kidney (SMR = 155), and for lymphoreticular sarcoma (SMR = 122).

When job categories for this subcohort were considered, operators, mechanics, and laborers showed higher mortality than expected for cancers of the pancreas (SMR = 154), kidney (SMR = 205), and other secondary and unspecified sites (SMR = 141), all lymphopoietic tissue cancers (SMR = 124), and lymphoreticular sarcoma (SMR = 129). All of these elevations were statistically nonsignificant. All other job categories showed increases for cancers of the pan-

creas (SMR = 161) and bone, connective tissue, skin, and breast (SMR = 176). The p value for all of these was greater than 0.05.

A special analysis of 24 pancreatic cancers did not reveal any clues as to job category or length of employment. Importantly, alcohol consumption history for this group was not available.

This cohort study has been fairly well analyzed. Although job categories were considered for analysis, all potentially exposed people were considered together. No specific gasoline exposure histories were present, and the follow-up period was short. Analyses by latency and length of employment may have been helpful. The study area included a chemical plant, but confounding by other occupational exposures was not considered. No tracing procedure details or source of death certifications were mentioned. Pancreatic cancer was the only cancer that came very close to being a statistically significant excess mortality than expected, but this excess was observed in the total cohort as well as in every subcohort that was considered, leading to the conclusion that this excess cannot be explained entirely by exposure to gasoline. Due to the above-mentioned reasons, this study is considered inadequate to use as a basis for drawing any conclusions.

4.2.1.12. Rushton and Alderson (1983)--On behalf of the Institute of Petroleum in England, Rushton and Alderson conducted a retrospective cohort study of all males who had worked for at least 1 continuous year between January 1, 1950, and December 31, 1975, at oil distribution centers in Great Britain. Data were provided by three companies (A, B, and C). Data collection and tracing procedures were exactly the same as those described in these authors' earlier (1981a) study.

The cause of death, the underlying cause of death, and up to three contributing causes of death were coded using the appropriate revision of the ICD.

SMRs were calculated by using the rates of the male population of England and Wales for the 5-year age and calendar period. Significance testing was done by use of the Poisson distribution.

More than 99% of the population was successfully traced. The cohort consisted of 23,306 males contributing 397,569 person-years of observation, with a mean follow-up of 17.1 years for each individual. Of 3,926 found to be deceased, death certificates were obtained for all but 23 (0.5%) of the decedents. A total of 11 job categories were considered for this study.

The SMR for all causes of death was 85 (observed = 3,926, $p = 0.0001$), showing a typical "healthy worker" effect. The SMRs for all neoplasms (SMR = 87, observed = 1,002, $p < 0.0001$) and for cancers of the lung and pleura (SMR = 80, observed = 384, $p < 0.0001$), esophagus (SMR = 61, observed = 17, $p = 0.02$), and intestines (SMR = 79, observed = 57, $p = 0.04$) showed significant deficits. A deficit was also seen for cancer of the urinary bladder (SMR = 75, observed = 32); this was of borderline significance ($p = 0.05$). Lowered mortality for cancer of the lung was thought to be caused by a reduced level of smoking among these workers, as compared to the level in the general population, because of the nature of their work. The only significant SMR elevation was for myelofibrosis (SMR = 276, $p = 0.04$), which was based on five deaths.

Significant deficits were observed for many of the nonmalignant diseases: tuberculosis (SMR = 22, observed = 11, $p < 0.0001$), cerebrovascular diseases (SMR = 87, observed = 374, $p = 0.01$), chronic rheumatic heart disease (SMR = 52, observed = 31, $p < 0.0001$), other diseases of the heart excluding ischemic heart disease (SMR = 64, observed = 71, $p < 0.001$), hypertensive disease (SMR = 71, observed = 65, $p < 0.01$), influenza (SMR = 50, observed = 13, $p < 0.01$), pneumonia (SMR = 72, observed = 133, $p < 0.0001$), bronchitis (SMR = 67, observed = 240, $p < 0.0001$), chronic and other nephritis (SMR = 46, observed =

15, $p < 0.001$), and suicide (SMR = 57, observed = 38, $p < 0.0001$). The only elevation seen for nonmalignant diseases was for other diseases of the genitourinary system (SMR = 130, $p = 0.25$).

Although SMR deficits for all neoplasms and lung cancer were found in workers for companies B and C in several job categories, they tended to decrease with a later date of entry into the cohort for all neoplasms. In company B, there was an excess for all neoplasms for males joining during or after 1960 (SMR = 131, observed = 43, $p = 0.05$), which was partially accounted for by an excess in this group for lung cancer (SMR = 163, observed = 19, $p < 0.05$). An excess in lung cancer was also observed in the same company for workers who had less than 5 years of service (SMR = 140, observed = 34, $p < 0.05$).

Some other statistically significant increases were observed in some subcohorts, but they were based on very few deaths. These excesses included other neoplasms of the lymphoid tissue in workers from company C (SMR = 4.39, observed = 5, $p = 0.01$) and in operators overall (SMR = 4.05, observed = 3, $p = 0.04$); multiple myeloma in operators from company B (SMR = 3.51, observed = 4, $p < 0.05$); leukemia in individuals starting work before 1940 from company B (SMR = 1.93, observed = 15, $p < 0.01$); and myelofibrosis in workers from company B (SMR = 3.81, observed = 4, $p < 0.05$). An excess was observed from chronic lymphatic leukemia in company B employees when histological types were examined (SMR = 2.33, observed = 8, $p < 0.05$). These SMRs were not reported by the authors but were calculated from the authors' data as part of this review.

This is a well-conducted study as far as identification and follow-up of the cohort are concerned. Tracing is virtually complete, and very few studies of this size are able to achieve such a tracing success.

Although there is an indication that analyses by length of employment, latency, and job description were carried out, no details for these variables

were presented in this published paper; however, some of this information was presented in the authors' unpublished version of this paper (Rushton and Alderson, 1982 Unpublished). The information provided is very selective and sparse. Much of the report is devoted to a detailed analysis of various subcohorts for ischemic heart disease, since no deficit for this cause was observed in this study. The details of the ischemic heart disease analysis are not discussed here, since this review pertains to cancer risk. Again, no information is available for gasoline vapor exposure at the distribution centers or at the 11 job categories considered. In summary, the study is considered inadequate for drawing any conclusions with respect to cancer risk.

4.2.1.13. Morgan and Wong (1983 Unpublished)--On behalf of the Standard Oil Company of California, Environmental Health Associates, Inc. (EHA) conducted a retrospective cohort mortality study of current and former Chevron USA employees at the Richmond and El Segundo refineries in California. Included in the cohort of 14,179 were all individuals who had worked for at least 1 day between January 1, 1950, and December 31, 1980, and who had completed at least 1 year of employment at either refinery by December 31, 1980. This represented 266,470.7 person-years of follow-up.

Using company employment records, data were collected and coded on worker's name, social security number, date of birth, sex, race (if known), date of hire, date of separation, employment status (active, retired, separated, etc.), vital status, vital status source, and date of death.

Names and social security numbers of cohort members identified through employment records were matched to yearly computerized payroll tapes to verify cohort completeness. Year-end tapes for the years 1965-66, 1970-71, and 1977-78 were randomly selected for use. This method identified 279 (3.8%) individuals not included in the original cohort. Of these, 35 records from the Rich-

mond refinery and 96 from El Segundo were not located.

Vital status was ascertained as of December 31, 1980, using records from the company, SSA, the University of California at San Francisco's computerized database of individuals who died in the State of California (CAMLIS), and the California State Department of Motor Vehicles. Tracing was successful for 95% of the cohort.

Death certificates were obtained from company records or the appropriate states' vital statistics departments for 97.82% of those 2,292 individuals identified as deceased. EHA's nosologist recoded all death certificates to the 8th revision of the ICD by underlying cause of death and up to four contributing causes.

Work history data, by job title, job location, and dates, were only coded for the first and last jobs. A total of 3,324 jobs and 1,699 locations were identified. These were classified into subgroups based on the type of work. Seven subgroups were created for job codes: administrative/management, clerical/office support, laboratory, operating, maintenance, custodial/plant protection/other, and supervisory/foreman (unknown department). Six subgroupings were created for location codes: administration, laboratory, operating, maintenance, package/utilities/warehouse, and marketing/transportation.

The risk of death among the cohort members was assessed by utilizing the SMR. The expected number of deaths was calculated by using the U.S. national age-, cause-, race-, and sex-specific mortality rates for each 5-year time period from 1950 to 1980 (Marsh and Preininger, 1980). Both 95% and 99% confidence intervals were calculated. Those lost to follow-up were counted up to the last date of contact (i.e., termination date or last driver's license renewal date) and thereafter eliminated from analysis. Race was not known for 20% of the cohort. These individuals (2,772) were assumed to be white for pur-

poses of analysis. Reported by the authors but not reviewed here are nonsignificant cancer excesses based on fewer than three observed deaths.

Approximately 25% (3,465) of the cohort were active employees on the last day of the study; 22% (3,144) retired during the study; and 42% (5,979) terminated employment with Chevron. Approximately 31% were employed for 20 or more years.

Among the total cohort, the SMR for all causes of death was significantly low at 72 (observed = 2,292, $p < 0.01$) in comparison to U.S. mortality. Mortality for all cancers was also significantly low (SMR = 76, observed = 462, $p < 0.01$). Cancer deficits were noted for cancers of the buccal cavity and pharynx (SMR = 47, observed = 9, $p < 0.05$), digestive system (SMR = 72, observed = 125, $p < 0.01$), pancreas (SMR = 59, observed = 20, $p < 0.05$), large intestine (SMR = 71, observed = 40, $p < 0.05$), respiratory system (SMR = 69, observed = 135, $p < 0.01$), and lung (SMR = 67, observed = 124, $p < 0.01$).

Slight elevations ($p < 0.05$) in cancer risks were observed for cancers of the brain/CNS (SMR = 126) and lymphatic and hematopoietic tissue (SMR = 105). This latter group was limited to diagnoses of lympho- and reticulosarcomas (SMR = 127) and cancer of other lymphatic tissues (ICD 202, 203, and 208) (SMR = 142). The SMR for leukemia and aleukemia was 88, but not significantly lower than the U.S. experience.

A large number of nonmalignant causes were observed to have statistically significant mortality deficits; $p < 0.01$ unless noted. These included infective and parasitic diseases (SMR = 38, observed = 14), diseases of the nervous system (SMR = 48, observed = 12) and circulatory system (SMR = 74, observed = 1,228), arteriosclerotic heart disease (SMR = 79, observed = 924), vascular lesions of the CNS (SMR = 67, observed = 158), chronic rheumatic heart disease (SMR = 61, observed = 19, $p < 0.05$), diabetes mellitus (SMR = 37, observed =

17), diseases of the respiratory system (SMR = 56, observed = 105), digestive system (SMR = 65, observed = 97) and genitourinary system (SMR = 50, observed = 22), senility and ill-defined conditions (SMR = 27, observed = 10), and accidents (SMR = 71, observed = 146). The cause-specific SMR for suicide was significantly elevated (SMR = 128, observed = 88, $p < 0.05$) over the expected.

The SMRs for all causes of death and all cancers were significantly lower ($p < 0.01$) than expected at the Richmond (SMR = 74, observed = 1,507 and SMR = 78, observed = 302, respectively) and El Segundo (SMR = 69, observed = 785 and SMR = 72, observed = 160, respectively) refineries. A slightly elevated rate of mortality for brain/CNS cancer (SMR = 111, $p > 0.05$) was observed among El Segundo workers. SMRs for all other cancer sites were less than 100 at El Segundo, and cancers of the digestive system (SMR = 64, observed = 40, $p < 0.01$), stomach (SMR = 41, observed = 5, $p < 0.05$), respiratory system (SMR = 74, observed = 53, $p < 0.05$), and lung (SMR = 74, observed = 50, $p < 0.05$) were significantly lower than expected.

Among Richmond refinery employees, cancer mortality rates were elevated ($p > 0.05$) for cancer of the brain/CNS (SMR = 134), for lympho- and reticulosarcomas (SMR = 151), and for cancers of other lymphatic tissues (SMR = 167) and the breast (SMR = 127). The SMR for cancer of the liver was significantly lower than expected (SMR = 25, observed = 2, $p < 0.05$).

White male employees (i.e., white males combined with all males for whom race was unknown) exhibited patterns of mortality similar to that of the entire cohort. The pattern of mortality among white females was very different from that of white males. The SMR for all causes was only slightly lower than the U.S. population (SMR = 93, $p > 0.05$), and the SMR for all cancers was slightly elevated at 119 ($p > 0.05$). The only form of cancer for which a deficit was observed was breast cancer (SMR = 68, $p > 0.05$). SMRs were elevated for all

remaining cancer sites for which a death was observed. Thus, excesses ($p > 0.05$) were found for cancers of the digestive system (SMR = 162), large intestine (SMR = 297), and lung (SMR = 242). Excesses were also observed for cancers of the esophagus (SMR = 994), skin (SMR = 535), kidney (SMR = 526), and brain/CNS (SMR = 287), but these were based on only one observation.

Among those known to be non-white males, 33 total deaths were observed (SMR = 49, $p < 0.01$); only 4 of these were cancer deaths (SMR = 41, $p > 0.05$). No deaths occurred among non-white females during the study period.

Limiting analyses to cohort members who were classified by location into the laboratory subcategory (N = 844) revealed nonsignificant cancer excess for cancers of the rectum (SMR = 356), prostate (SMR = 133), and other lymphatic tissues (SMR = 357). A significant deficit was observed for all causes of death (SMR = 74, observed = 87, $p < 0.01$) and lung cancer (SMR = 27, observed = 3, $p < 0.01$).

Limiting analyses to those employees who worked in maintenance locations (N = 7,838) revealed significant cancer deficits for all cancers (SMR = 75, observed = 266, $p < 0.01$) and cancers of the buccal cavity and pharynx (SMR = 36, observed = 4, $p < 0.05$), large intestine (SMR = 52, observed = 17, $p < 0.01$), and lung (SMR = 66, observed = 72, $p < 0.01$). Statistically nonsignificant excesses were observed for cancers of the larynx (SMR = 132), brain/CNS (SMR = 140), and lympho- and reticulosarcomas (SMR = 129). Limiting analyses to maintenance workers at the Richmond refinery revealed excesses ($p > 0.05$) for cancers of the rectum (SMR = 137), skin (SMR = 128), testis (SMR = 144), other lymphatic tissue cancers (SMR = 177), and a slight excess for kidney cancer (SMR = 112).

Analyses of cohort members in operating locations (N = 5,510) revealed excesses ($p > 0.05$) for cancers of the larynx (SMR = 136) and brain/CNS (SMR

= 128), and for lympho- and reticulosarcomas (SMR = 165). Among operating workers at the Richmond refinery, risks were also elevated for Hodgkin's disease (SMR = 179) and other lymphatic tissue cancers (SMR = 191). An excess in leukemia and aleukemia was confined to cohort members at the El Segundo refinery only (SMR = 197).

Analyses by the seven job classifications and the remaining three location codes were not presented. Analyses by latency since hire (less than 10 years, 10 to 19 years, 20+ years) were presented. Among those with less than 10 years, only cancers of the kidney (SMR = 244) and other lymphatic tissues (SMR = 135) were elevated, although these were based on only two and one observations, respectively ($p > 0.05$). Among workers with 10 to 19 years since first hire, SMRs were elevated for cancers of the rectum (SMR = 132), kidney (SMR = 125), and brain/CNS (SMR = 164), and for lympho- and reticulosarcomas (SMR = 181) and other lymphatic tissue cancers (SMR = 263). None of these elevations was significant ($\alpha = 0.05$).

Among those with 20+ years of latency, elevations in cancer mortality were observed for cancer of the brain (SMR = 119, observed = 13), lympho- and reticulosarcomas (SMR = 129, observed = 12), and other lymphatic tissue cancers (SMR = 122, observed = 14). These were not statistically significant.

In addition to latency analysis, analysis for the total cohort by length of employment at the refineries (less than 5 years, 5 to 14 years, and 15+ years) was conducted. Excesses were seen for several of the site-specific cancers; however, none was statistically significant. The data suggest that excesses in kidney (SMR = 284) and lung (SMR = 128) cancer are confined to those employees with less than 5 years of employment, since no excesses were observed among those with 5 to 14 years or 15+ years of employment. An excess for skin cancer was observed only among those with 5 to 14 years of employment

(SMR = 145). An elevated SMR for cancer of the brain/CNS was observed among all three employment groups, with the greatest excess observed among those with 5 to 14 years of employment (less than 5 years, SMR = 105; 5 to 14 years, SMR = 168; 15+ years, SMR = 112). Excesses for mortality due to other lymphatic tissue cancers were not confined to any single employment category (less than 5 years, SMR = 220; 5 to 14 years, SMR = 178; 15+ years, SMR = 121). Elevated SMRs were only observed among those with 15+ years of experience for cancers of the larynx (SMR = 121), lympho- and reticulosarcomas (SMR = 163), and leukemia and aleukemia (SMR = 122). A significant deficit was observed for lung cancer for those with 15+ years of employment (SMR = 52, observed = 70, $p < 0.01$).

The study population was also stratified by date of hire: pre-1949 versus post-1948, the point in time when the recommended benzene standard (TWA) was lowered to 35 ppm from a high of 100 ppm in 1947. All 22 leukemia deaths occurred in employees hired on or before 1948; 16 of 17 lympho- and reticulosarcoma deaths occurred in pre-1949-hired employees (pre-1949, SMR = 150; post-1948, SMR = 37). Other lymphatic tissue cancer deaths followed a similar pattern but to a lesser degree. Analyses by refinery suggest that the excess was further restricted to those at the Richmond refinery. While these increases are not statistically significant ($p > 0.05$), the authors noted that the study had insufficient power (< 80%) with which to detect excess mortality from malignancies of the lymphopoietic system. Among those hired after 1948, an excess ($p > 0.05$) was observed for cancers of the esophagus (SMR = 144), skin (SMR = 133), and kidney (SMR = 158).

This study had a long follow-up period (30 years) and a high percentage of vital status ascertainment. The main limitation is the lack of information on gasoline vapor exposure. Information on job titles was obtained but not presented. Analyses by location were presented for laboratory, maintenance, and

operating locations; however, workers may have been exposed to more than one substance at a single location. The authors offer no evidence that specific high-risk jobs were accurately assessed by the coding of only first and last jobs held. Race was assumed to be white for 20% of the male cohort; however, no analyses were presented of the known white male subcohort to verify that no race bias was introduced into these data. Thus, risk estimates may be overestimated for this cohort. Finally, confounding risk factors were not taken into consideration. Thus, this study is considered inadequate to draw conclusions on the association between gasoline vapors and cancer.

4.2.1.14. Morgan and Wong (1984 Unpublished)--This retrospective cohort study was conducted on workers employed by the Mobil Oil Company in its Beaumont, Texas, refinery. The cohort consisted of all individuals employed at this refinery for at least 1 year between January 1, 1945, and January 1, 1979. Data on the cohort were actually obtained by Stanford Research International (SRI), which was associated with Environmental Health Associates (EHA). Follow-up to ascertain the vital status of the eligible cohort was done through personnel records, the SSA, Mobil corporate data, and review by refinery staff. For the deceased members, death certificates were obtained from the refinery, Mobil corporate offices, and various states' vital statistics departments. Cause of death was coded by SRI according to the 8th revision of the ICD. When death certificates were not available and the date of death was known, it was recorded. SRI prepared the computer files for the data and edited them for completeness and consistency. SRI forwarded the edited copy of the tape to EHA. EHA validated the data for completeness of the cohort by using union seniority rosters, and corrected the discrepancies due to coding errors or missing data prior to the analyses.

A total of 6,139 individuals, contributing 123,354.9 person-years of ob-

servation, were eligible for the study; of these, 5,696 (92.78%) were males and 443 (7.22%) were females. Information on race was not available for 6% of the cohort; for analysis purposes, these cases were assumed to be white. Vital status as of January 1, 1979, was as follows: 4,371 (71.2%) were alive; 1,582 (25.77%) were deceased; death certificates were obtained for 98.4%; and 186 (3.03%) were lost to follow-up. Person-years were computed from January 1, 1946, or from the date of employment, whichever was later. For the lost-to-follow-up employees, the person-years were calculated until the last date vital status was known, and thereafter they were excluded from the analysis (withdrawn alive).

The SMRs were computed by applying the U.S. national race-, sex-, age-, and cause-specific mortality rates, for 5-year periods from 1945 to 1980, to the appropriate person-years. A total of 31.63% of the cohort were hired between 1940 and 1949, providing a potential latent period of 30 years, while 20% were hired in 1970, giving a very short period for follow-up. Analyses were carried out for the total cohort and various subcohorts by race, sex, length of employment, and latency period.

For the total cohort, SMRs for all causes of death and all cancers were 81.3 (observed = 1,582) and 96 (observed = 346), respectively, the former being significant ($p < 0.01$). There were more SMR deficits observed than excesses. Some of the deficits were statistically significant, including the ones for diseases of the circulatory system (SMR = 86, observed = 896); nonmalignant respiratory diseases (SMR = 51, observed = 59); diseases of the digestive system (SMR = 59, observed = 50) and genitourinary system (SMR = 52, observed = 21); accidents, poisonings, and violence (SMR = 58, observed = 91); and cancers of the buccal cavity and pharynx (SMR = 27, observed = 3), digestive system (SMR = 76, observed = 86), and rectum (SMR = 24, observed = 3). Excess mortal-

ity ($p > 0.05$) was observed for the following causes: cancer of the skin (SMR = 139), cancer of the breast (SMR = 147, based on three cases), lympho- and reticulosarcomas (SMR = 147), and other lymphatic tissue cancers (SMR = 158). Statistically significant findings were noted for lymphatic and hematopoietic cancer (SMR = 147, observed = 47), and leukemia and aleukemia (SMR = 173, observed = 23).

The subcohort of 4,733 white males (including 358 for whom race was not known but who were classified as white), contributing a total of 98,070.4 person-years, had SMR deficits for all causes of death (SMR = 84, observed = 1,233, $p < 0.01$) and all cancers (SMR = 92, observed = 256). The only significant excess observed in this group was for lymphatic and hematopoietic cancer (SMR = 148, observed = 39, $p < 0.05$), an excess that came primarily from the leukemia and aleukemia category (SMR = 179, observed = 20, $p < 0.05$).

This group also showed an insignificant excess incidence for the same causes of cancer mortality as those of the total cohort, except for breast cancer. Significant deficits observed for cancer were similar to those observed for the total cohort, except that liver cancer was also observed at significant levels (SMR = 16, observed = 1). The SMR deficits for causes of mortality other than cancer were also similar to those of the total cohort.

The subcohort of 418 white females, contributing 6,882.4 person-years, also had lower mortality than expected for all causes of death (SMR = 59, observed = 17, $p < 0.05$) and all cancers (SMR = 97, observed = 8, $p > 0.05$). A few increased SMRs were observed, but they were neither significant nor represented by more than one case, except for breast cancer (SMR = 151), which was based on only three cases ($p > 0.05$).

The male non-white subcohort consisted of 963 individuals contributing 18,205.2 person-years of employment. The SMR for all causes of death was lower

than expected (SMR = 74, observed = 331, $p < 0.01$) but was increased slightly for all cancer deaths (SMR = 110, observed = 82, $p > 0.05$). Nonsignificant elevations of SMRs were found for some types of cancer, one of them being cancer of the respiratory system (SMR = 128). The increased SMR for respiratory cancer was caused solely by the increased incidence of death from lung cancer (SMR = 138), and was based on 25 cases. Elevated SMRs were also seen for prostate cancer (SMR = 128), stomach cancer (SMR = 133), leukemia and aleukemia (SMR = 163), other lymphatic tissue cancer (SMR = 181), and a slight increase for pancreatic cancer (SMR = 119).

The subcohort of all male employees had SMR deficits for all causes of death (SMR = 82, observed = 1,564, $p < 0.01$) and all cancers (SMR = 96, observed = 338). The findings for this subcohort were identical to those for the total cohort, with significantly increased SMRs for the same two causes of cancer mortality, lymphatic and hematopoietic cancer (SMR = 148, observed = 46, $p < 0.05$), and leukemia and aleukemia (SMR = 177, observed = 23, $p < 0.05$). Results for this group were unchanged when the 358 individuals whose race was unknown were excluded from the group.

When the data for white males were examined by length of employment and latency period, the SMRs for all causes of death and for all cancers showed positive trends, by increasing length of employment and increasing latency period. SMRs for all causes of death consistently showed a statistically significant deficit in all the groups, except in the group that had a latency period of more than 40 years. A definite positive trend was observed for mortality from lung cancer with increasing latency, although the SMRs for each group were lower than 100. Similar trends were not observed for the same cause by length of employment. Positive trends with increasing latency were also observed for brain cancer and cancer of the central nervous system, and for

lymphatic and hematopoietic cancer. A similar trend was observed for the latter cause but not the former when length of employment was considered. Surprisingly, no positive trend was observed for mortality from leukemia and aleukemia, either by length of employment or by latency. SMRs were statistically significantly increased for lymphatic and hematopoietic cancer in the group with a latency period greater than 40 years (SMR = 190, observed = 16), and for leukemia and aleukemia in the group with a latency period of 20 to 39 years (SMR = 215, observed = 11) and the group employed for more than 30 years (SMR = 235, observed = 11). A statistically significant excess of skin cancer was observed among those with less than 20 years' latency (SMR = 375, observed = 4).

Among non-whites, positive trends were observed for all causes of death when the data were analyzed by length of employment as well as by latency period. The SMRs for all causes of death showed significant deficits in both the less than 20 and the 20 to 39 years' latency groups (SMR = 60, observed = 40, and SMR = 57, observed = 127, respectively). The SMR for all causes of death in the 40+ year latency group was only slightly elevated (SMR = 106, $p > 0.05$). Although a positive trend for all cancer types was observed by latency, no such trend was evident by length of employment. The SMR for all cancers in the group with a latency period of 40+ years was 154 (observed = 45, $p < 0.05$). Increased SMRs for this group were also observed for cancer of the respiratory system (SMR = 237, $p < 0.01$), which included lung cancer (SMR = 255, $p < 0.01$); both of these increases were based on 17 cases each. Analysis by length of employment showed significant excesses in mortality from cancer of the digestive system (SMR = 439, $p < 0.05$) and cancer of the stomach (SMR = 756, $p < 0.05$), both in the group employed for less than 10 years. These SMRs were based on a very few cases (five and three cases, respectively). Curiously, the incidence

of stomach cancer showed a negative trend both by latency and length of employment.

A special analysis for lymphatic and hematopoietic cancer for all males revealed findings similar to those for white males and showed a positive trend by both latency and length of employment, although the gradient was modest. No such trends were observed for leukemia or aleukemia either by latency or by length of employment. When this cohort was subdivided into groups of persons hired prior to 1957 (when the recommended benzene 8-hour TWA exposure limit value was 35 ppm) and those hired after 1957 (when the recommended benzene 8-hour TWA exposure limit value was lowered to 25 ppm), there were 45 deaths in the former group (SMR = 148, $p < 0.05$) and one death in the latter group (SMR = 121, $p > 0.05$). Leukemia SMRs for these groups were 174 ($p < 0.01$) and 300 ($p > 0.05$), respectively.

This study has a long follow-up period of 35 years and a high percentage of vital status ascertainment for a cohort having such a long follow-up. The analyses are fairly complete and well done. The main limitation of this study with regard to the evaluation of the carcinogenicity of gasoline vapors is the lack of information on exposure. No surrogate information, such as job titles, was reported. Also, no details of the follow-up procedures are available. The SSA was the only external source of information, so it is likely that a few deaths were missed. Finally, confounding by risk factors could not be evaluated for this study.

4.2.1.15. Thomas et al. (1984)--This is a nested case-control study of deceased OCAW members who had been employed in three Texas oil refineries. The original description of decedents from active and retired union members can be found in the authors' earlier proportionate mortality study (Thomas et al., 1982a) where significant ($p < 0.05$) excesses of mortality from malignant brain

tumors, stomach cancer, and leukemia were reported. Also reported earlier were the authors' preliminary analyses of the brain tumor case-control data (Thomas et al., 1982b). However, since the number of cases has since expanded, from 25 observed deaths among active employees to 37 observed deaths among active and retired employees, only the later study (Thomas et al., 1984) is reported here.

One brain tumor case, four stomach cancer cases, and four leukemia cases were subsequently added to the original data (Thomas et al., 1982a) for this study. Of the 37 total brain tumor cases, six were excluded from analysis because the diagnoses could not be confirmed with hospital records. (Diagnoses of brain tumors were confirmed because the brain is a common site of metastasis.) One leukemia case was excluded because additional information indicated that an incorrect diagnosis was obtained originally.

The 31 brain tumor cases, 52 stomach cancer cases, and 34 leukemia cases were matched to three deceased controls selected from the records of active and retired union members. Cause of death was any other than those under study. Controls were matched to the cases for race, sex, and refinery, and were matched as closely as possible for age at death, date of death, and date of first union membership. Work history records could not be located for 16 controls, so substitute controls were selected; records for 8 of these substitutes were not located and were eliminated from the study. Thus, there were 93 controls matched to the brain tumor cases, 154 controls matched to the stomach cancer cases, and 96 controls matched to the leukemia cases.

Cases of multiple myeloma (N = 9), Hodgkin's disease (N = 9), non-Hodgkin's lymphoma (N = 23), and cancers of the skin (N = 14), prostate (N = 51), and pancreas (N = 41) were also obtained to develop crude estimates of unusual employment patterns by work categories. The controls for the brain tumor cases, stomach cancer cases, and leukemia cases served as the control population, as

the original pool of eligible controls had been exhausted.

Eleven mutually exclusive work categories were created by categorizing the types of unit operations. Assignment to work categories was accomplished by reviewing job titles and department assignments. No quantitative exposure estimates were attempted.

Five of the work categories established had unit operations in which gasoline was identified or was known to be a constituent product. Category 1 (crude oil) had jobs associated with the "first step" in the refining process, including the distillation of crude oil into five basic streams, one of which was wet gas and gasoline. Category 3 (treating) included jobs related to the production of gasoline, kerosene, light fuel oils, and diesel oils. These processes included blending of additives, alkylation to produce high-octane products, polymerization to improve the quality of gasoline products, and hydrogen-treating to remove sulfur. Category 7 (maintenance and labor) included all functions related to equipment servicing, maintenance, and construction, including still and tank cleaning. Category 8 (receipt and movement) included all processes, areas, and equipment used for the transport of bulk liquid products, e.g., gasoline. Category 9 (laboratory) included the quality control laboratories where refinery products such as gasoline are tested. The definitions for the remaining six work categories of lube oil (category 2), coking (category 4), grease paint (category 5), utilities (category 6), motor transportation (category 10), and other activities (category 11) indicated no exposure to gasoline.

A study subject was considered exposed to a work category if he was known to have worked at least 1 day in a category beginning 15 years or more prior to his death. Approximately 40% of the study population met the definition of exposure for at least one category. As many as six exposure categories per

individual were observed, but the average number of categories was two per study subject.

Estimates of relative risk (odds ratios) by work category for brain tumors, stomach cancer, and leukemia were calculated by the maximum-likelihood method, using Miettinen's procedures for matched case-control data. Odds ratios were not calculated if the number of exposed cases was less than five, and were considered statistically significant if 90% confidence intervals did not contain 1. The authors noted, however, that statistical significance testing was used as "a guide to the relative importance of the numerous comparisons made" and was "not to be interpreted in the strict(est) sense." The Mantel extension procedure was used to examine trends by length of time for those work categories in which the odds ratio was 1.5 or greater. Also reported were median durations of employment for those who were exposed in each work category. Matching was eventually dropped, and levels for duration of employment were defined as (1) not exposed, (2) exposed but worked less than 5 years in the category, and (3) exposed and worked more than 5 years in the category. Finally, standardized risk ratios (SRRs) were calculated for exposure levels 2 and 3, using the lowest exposure level as the standard.

A significantly elevated odds ratio ($p < 0.10$) of 2.8 was observed for brain tumor cases among receipt and movement workers; however, median duration of employment for the cases was 22% of that of the controls. Similarly, brain tumor cases who were pipefitters (a subcategory of maintenance and labor) (OR = 1.5), workers in the overall category of maintenance and labor (OR = 1.2), and lube oil workers (OR = 1.6) also had elevated, although not significant, odds ratios. Median duration of employment for the controls approximately equaled or exceeded that of the cases. All of these work categories, except the latter (i.e., lube oil), had potential for gasoline exposure.

Odds ratios for stomach cancer were significantly elevated ($p < 0.10$) for maintenance and labor workers (OR = 4.5), the yard labor subcategory (of maintenance) (OR = 2.4), and lube oil workers (OR = 1.7). Odds ratios were elevated for the maintenance subcategories of pipefitting (OR = 1.8) and miscellaneous maintenance (OR = 1.7). Median duration of employment for cases was longer than for the controls for each of these work categories/subcategories. Odds ratios were also elevated for the maintenance subcategories of boilermaking (OR = 1.5) and construction (OR = 1.2) and the category of motor transportation (OR = 1.7); however, median duration of employment was longer for the controls in comparison to the cases for each of these latter groups. Again, all of these work categories, except lube oil, may have had potential for gasoline exposure.

No significantly elevated odds ratios were observed for leukemia among the study population. Risks were elevated for the treating category (OR = 1.6) and the boilermaking subcategory of maintenance (OR = 1.5). The median duration for the cases was longer than that for the controls for both of these work category employees. Both of these work categories had potential for gasoline exposure. Odds ratios for lube oil workers were slightly elevated (OR = 1.1), but the median duration of employment for the controls was nine times longer than for the cases.

A nonsignificant dose-response trend for duration of employment (measured as no employment in a work category, less than 5 years' employment in a work category, and 5 or more years' employment in a work category) was observed for stomach cancer for lube oil workers (0 years, SRR = 1.0; < 5 years, SRR = 1.5; > 5 years, SRR = 1.8) and maintenance workers (0 years, SRR = 1.0; < 5 years, SRR = 2.4; > 5 years, SRR = 3.1), and for leukemia among workers in treating (0 years, SRR = 1.0; < 5 years, SRR = 1.2; > 5 years, SRR = 2.0) and boiler-

making (0 years, SRR = 1.0; < 5 years, SRR = 1.2; > 5 years, SRR = 1.8). The stomach cancer data for which a dose-response trend was evident were further analyzed by refinery. (Leukemia data were not analyzed because of the small number of cases per refinery.) Risks for cases who worked with lube oil (OR = 3.1, $p < 0.10$) and maintenance (OR = 3.6, $p > 0.10$) were more than three times those of the controls at Refinery A. Elevated risks ($p > 0.10$) were also observed at Refinery B among lube oil workers (OR = 1.5) and maintenance workers (OR = 2.4). At Refinery C, risks were elevated for maintenance workers (OR = 3.3). Again, each of these work categories, except lube oil, had potential for gasoline exposure.

A comparison of the multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, skin, prostate, and pancreas cancer cases with the pooled controls revealed no pattern by work category.

These results provide very weak evidence for an association between work in the petroleum industry and stomach cancer. A dose-response trend was observed for stomach cancer among the maintenance workers, a work category for which a potential for gasoline exposure exists. Among all maintenance workers, the estimate of relative risk was high (OR = 4.5) and significant ($p < 0.10$). The median duration of employment for the cases was longer than for the controls. Similar patterns were observed for lube oil workers (a work category not considered to have potential for gasoline exposure), but the estimates of risk were not as elevated as they were for maintenance workers.

The major limitation of this study, as with most of the studies of refinery workers, is the inability to determine gasoline exposure. As the authors noted, "It is not known if the work categories were truly indicative of exposure, since the number of potential exposures in any particular category was extensive, and because workers may not have had contact with a specific sub-

stance in more than one category." The authors set α at 10% rather than at the customary 5%; thus a larger porportion of the significant findings may be due to chance alone. Also, there was no control for confounding factors such as alcohol and other chemical exposures.

The cases and controls, all of whom worked at the oil refineries, may be overmatched with respect to occupational exposures within the refinery if there is a common exposure for this population that causes certain types of cancer. However, this would tend to underestimate the estimate of relative risk and thus is not considered a serious limitation.

4.2.1.16. Wen et al. (1984b Summary)--This document, hereinafter referred to as Wen et al. (1984b Summary), describes and summarizes the findings from seven different studies. Six of these studies were carried out on Gulf Oil Company refinery employees, and one was carried out on populations from counties in which refineries are located. Data were presented primarily for kidney cancer.

1. Study of kidney cancer mortality in Jefferson and Orange Counties (Texas)

These two counties have a heavy concentration of refineries and petrochemical plants and hence were chosen for the study. Of 24,766 deaths in these counties between 1965 and 1981, 99 deaths were due to kidney cancer. When compared with the rate for the U.S. general population by age, race, and calendar time, the SMR was found to be 100. There was a modest increase in kidney cancer in the 1970-74 period (SMR = 138, 95% CI 99-188), but no positive trend was found.

2. A cohort study of Gulf's Port Arthur refinery

This study was published in 1983 and is reviewed earlier in the document as Wen et al. (1983).

3. A mortality surveillance study of all of Gulf's employees and annuitants

A total of 246,263 person-years were contributed to this study by 48,417

males and 12,916 females during the 1977-81 mortality surveillance period. Of 3,046 deaths occurring during this period, 16 were attributed to kidney cancer in males. The SMR of 92 was based on the U.S. population and was not statistically significant (95% CI 53-150). No deaths were observed among the females. Deficits were also observed for deaths from bladder cancer (SMR = 49) and genitourinary system diseases (SMR = 58). No other details of the analysis were provided.

4. A cancer incidence study of Gulf's refineries and petrochemical plants

A cancer registry established in 1977 for Gulf's 18 refineries and petrochemical plants monitors about 15,000 employees; among these employees, two kidney cancer deaths (observation period unknown) were seen, which gave a standardized incidence ratio of 70 (95% CI 8-252), i.e., indicating no increase in kidney cancer in this population.

5. A historical mortality analysis of Gulf employees and annuitants (PMR analysis)

A total of 17,511 death certificates were collected during the period 1932-82 for Gulf employees and annuitants who had died either while employed or after retirement. A PMR analysis was conducted using Monson's (1974) program. The PMR for kidney cancer was 114 for whites (observed = 81), 139 for non-whites (observed = 4), and 115 for all males (observed = 85). None of these was statistically significant. PMR deficits were seen for bladder cancer among whites (PMR = 75, observed = 82) and among non-whites (PMR = 83, observed = 4).

6. Case-control study for the Port Arthur cohort

Twenty-two deaths from kidney cancer were identified in the retrospective cohort study described earlier (Wen et al., 1983). For each case, three non-cancer-deceased controls (d.c.), matched on race, sex, date of birth, and date of death, and three mixed controls (no exclusion for cancer, dead or alive)

(m.c.), matched with the entire cohort for race, sex, date of birth, date of hire, and length of service, were selected. Matched analyses using Rothman and Boice's (1982) program were done for gasoline, jobs ever held, longest job held, smoking, and alcohol.

Eleven certified industrial hygienists derived estimates of exposure to gasoline; the hygienists individually assessed exposure for 1,000 job titles. Smoking and alcohol histories were obtained from medical records of either preplacement or voluntary health examinations.

Comparison with each of the control groups and for the different lengths of exposure to gasoline vapors showed no significant excess in relative risk of kidney cancer for the cases (RR m.c. = 1.09, 95% CI 0.34-3.55; RR d.c. = 0.82, 95% CI 0.24-2.81). There was also no evidence of a dose-response relationship by duration of exposure. Similar results were observed for the subgroup of cases with 20 or more years of employment. A modest increase in relative risk was observed for these cases when compared with the m.c. group exposed for 6 months up to 5 years (RR = 2.37, 95% CI 0.62-9.09). This result contradicts the expectation that comparison with the d.c. group would show an increase in relative risk, since this control group was made up of non-cancer individuals, as opposed to the m.c. group, which did not exclude persons with cancer.

Relative risks using m.c. were higher than those using d.c. when the analyses were done by job titles: lube oil workers (RR m.c. = 6.00, 95% CI 0.73-49.34; RR d.c. = 3.00 95% CI 0.46-19.36), garage and transportation workers (RR m.c. = 3.16, 95% CI 0.42-24.20; RR d.c. = 2.20, 95% CI 0.35-14.10), and receipt and movement workers (RR m.c. = 2.30 95% CI 0.32-16.43; RR d.c. = 1.22, 95% CI 0.22-6.92) for the longest-held jobs. Relative risk for kidney cancer was increased for cases working in the utility department when compared with

the d.c. group (RR = 4.37, 95% CI 0.44-43), but not when compared with the m.c. group (RR = 1.00). The authors point out here that in the workers from the garage and transportation department, the controls had worked longer in this department than the cases.

When the risks for groups of employees from the various departments were examined by job ever held, the grease plant workers showed an increased relative risk for cases when compared with the m.c. group (RR = 3.00, 95% CI 0.21-41.92). Again, the authors note that the controls had spent a longer time than the cases in the grease plant.

None of the relative risks was statistically significant, and the numbers on which they were based are very small. The authors also state that these excesses were due to non-gasoline causes, since gasoline exposure effects were already examined. This is a little difficult to accept in the absence of any simultaneous multiple adjustment analysis for confounding factors, since the risks may be additive or multiplicative.

Smoking and alcohol intake information was available for fewer than one-third of the cases (i.e., seven individuals) as well as for the controls; nevertheless, an analysis by these factors was carried out, and twofold and threefold increases in the relative risk for kidney cancer were found for these cases, respectively. It is interesting to note that smoking and sometimes alcohol consumption have been cited as risk factors for kidney cancer.

7. A comparison of exposure between "refinery workers" and workers at marketing and gasoline stations

Total hydrocarbon exposure was measured at refineries and at marketing and gasoline terminals. Personal samples for the entire work period (7 hours or more) or partial samples (short-term peak periods) and area samples were collected. Results for the entire work period sampling indicated that marketing

terminal workers had slightly higher exposures than refinery workers; the 95th percentile was 30 ppm and 20 ppm, respectively, but neither of them was anywhere near the recommended TLV of 300 ppm. Service station workers also had a very low exposure, with an average of 3.1 ppm TWA; the TWAs for refinery and marketing terminal workers were 5 and 11 ppm, respectively. The area samples showed a mean of 15.2 ppm for refineries and 13.4 ppm for marketing terminals. The partial samples showed a mean of 13.7 ppm for refineries and 71.5 ppm for marketing terminals; the 95% percentile for marketing was 340 ppm.

Conclusions of the Wen et al. (1984b Summary) Study

This conclusion section describes the kidney cancer results reported by Wen et al.; in this paper, the authors compiled data from seven studies, six of which involved Gulf Oil Company employees and one that concerned kidney cancer deaths among individuals living in Texas counties containing a large number of refineries and petrochemical plants. Each of these seven studies is reviewed above; studies 5, 6, and 7 are discussed here, since only these three studies of the group of studies discussed by Wen et al. have relevance for a review of the cancer epidemiology of gasoline-exposed workers.

Study No. 5 looked at PMRs and therefore suffers from all the inherent validity problems of a PMR study.

Study NO. 6 is the most important of the studies in the Wen et al. paper. However, this case-control study has a number of limitations. The sample size is extremely small. No indication is given of the population from which the deceased and/or mixed-control individuals were selected. No information is provided for the assumptions used to interpret the results obtained by comparison with the mixed-control group. The mixed-control group contains individuals with cancer, which may have led to an underestimation of risk for these cases if kidney cancer and the types of cancer found in the controls had the

same risk factors. Adjustment for confounding factors was not done. Histories of smoking and alcohol consumption are lacking in two-thirds of the cases as well as for the controls, and probably would not have been of use even if available because they were obtained from preplacement and/or voluntary health examinations. Exposure history to gasoline vapor is available by length of exposure but not by the level of exposure.

The final Wen et al. study (Study No. 7) was supposed to address the problem of the lack of information on exposure intensity. It does not, however, because the exposure levels measured in that study cannot readily be applied retrospectively, since past exposures may have been considerably different. Furthermore, the method of collection of personal as well as area samples, the method of estimation of hydrocarbons, the duration of the collection period, and whether or not the samples were collected for different shifts were not explained. Also, the study did not report exposure levels by job titles. In summary, the studies reported in the Wen et al. summary paper are considered inadequate for qualitative risk assessment.

4.2.1.17. Kaplan (1982 Unpublished, 1985 Unpublished)--On behalf of the American Petroleum Institute, Kaplan (1982 Unpublished, 1985 Unpublished) conducted additional follow-up and analyses on API's retrospective cohort mortality study of approximately 20,000 people from 17 refineries. Previously reported by Tabershaw-Cooper Associates, Inc. (1974 Unpublished, 1975 Unpublished), Kaplan's initial analyses (1982) added an additional 5 years of follow-up. He subsequently (1985) added an additional 4 years of follow-up for a total of 19 years of cohort follow-up. Reported here is the latest of these analyses (Kaplan, 1985 Unpublished).

Included in the cohort were male, non-clerical, hourly workers on their last job (except for petrochemical workers, who were excluded wherever possible)

who had worked continuously for at least 1 year between 1962 and 1971. Females, petrochemical workers, clerical workers, and salaried workers were excluded. Refinery No. 5 was excluded from the analysis because it did not have records beyond 1 year for workers who had left or been terminated.

Vital status of the cohort was updated through December 31, 1980, through the SSA as well as through participating refineries. Between these two sources, the SSA information was assumed to be correct except where vital status was known to the refinery and unknown to the SSA. Refineries also updated employment status for each individual and provided information on race where possible. Race information was missing for approximately 7.5% of the cohort. Death certificates were obtained from various state vital statistics departments. The author did not indicate the ICD revision used to code the death certificates.

Person-years of observation were used for the analysis. The expected mortality for black males was derived using the mortality experience of non-white males. Mortality for "other males" was compared with white male mortality. The results from both were then combined. SMRs were computed by using the modified life table program adapted from Monson (1974). For analysis of brain cancer and brain neoplasms, the NIOSH program was used (Waxweiler et al., 1983b). For the multiple myeloma mortality analysis, U.S. population rates were used.

Of 20,169 individuals, 178 (0.9%) were excluded from the cohort for various reasons, reducing the cohort size to 19,991. Through December 31, 1980, 15,935 were alive, 3,349 were dead, and 707 (3.5%) were lost to follow-up. The mean age at time of hire for this cohort was 26.2, and over 66% of the cohort was employed for more than 20 years as of this update.

For the total cohort analysis, including 297,591.9 person-years of employment, significant ($p < 0.05$) SMR deficits were observed for all causes of death

and for mortality from all cancers (SMR = 78, observed = 3,349, and SMR = 87, observed = 793, respectively). More SMR deficits than excesses were observed in this population. Some of the noteworthy statistically significant deficits were for cancer of the respiratory system (SMR = 83, observed = 278, 95% CI 73-93), lung cancer (SMR = 85, observed = 270, 95% CI 75-96), diseases of the circulatory system (SMR = 79, observed = 1,727, 95% CI 75-83), and ischemic heart disease (SMR = 80, observed = 1,267, 95% CI 76-85). SMRs above 120 were observed for mortality from cancer of the thyroid (SMR = 122), cancer of other lymphatic tissue (SMR = 131), and from benign neoplasms (SMR = 133). These excesses were based on 2, 30, and 14 deaths, respectively. None of these SMRs was statistically significant.

The SMRs for the subcohort of whites only, for the subcohort having at least 10 or 20 years of latency, and for the subcohort employed for at least 10 years were similar to the SMRs for the total cohort (as stated in the text, although no tables are given). For the subcohort that had 20 or more years of employment, the results were also similar, except for mortality from cancer of the thyroid, which showed an SMR deficit, and an excess ($p > 0.05$) of mortality from neoplasms of the lymphatic and hematopoietic tissue (SMR = 111).

Three special analyses were carried out; two of these were for causes of excess mortality observed in the total cohort and in virtually all of the subcohorts. They are as follows:

A special analysis of mortality from cancer of other lymphatic tissue revealed that of 30 deaths, 16 were attributed to multiple myeloma, with a mean age at death of 63.5 years and an SMR of 123 ($p > 0.05$). Other deaths in this group were caused by polycythemia vera (4 deaths) and other neoplasms of the lymphoid tissue (10 deaths).

A special analysis of mortality from benign neoplasms revealed that of 14

deaths, 7 were due to unspecified brain neoplasms, with an SMR of 127 ($p > 0.05$).

The third special analysis was for mortality from mesothelioma. In the total cohort, there were nine mesothelioma deaths; six of them were caused by pleural mesotheliomas, while for the other three it was not clear whether pleural or peritoneal surfaces were involved. The job status of these cohort members was as follows: one insulator, one maintenance supervisor, one pipefitter, one utility worker, two welders, and three machinists. The average duration of employment was 30.22 years and the SMR was 241 ($p < 0.05$).

This study of 19,991 individuals definitely has good statistical power, and the follow-up to date is very good. The cohort is quite young, however. Analyses are done by race, length of employment, and latency, though no tables are provided. Once again, vital information on exposure to gasoline vapor is missing, as is an analysis by job titles. Confounding factors are not considered.

It is interesting to note the increase in mortality attributed to mesothelioma. This may be a real increase, because the author notes that some of the workers might have worked during World War II in shipyards where there may have been asbestos exposure. The history of current and/or past potential exposures to other occupational substances is missing. There is also a slight chance of misclassification, as pointed out by the author, but misclassification can lead either to overestimation or to underestimation, depending on whether the error is one of commission or omission.

4.2.1.18. McGraw et al. (1985)--The authors conducted a retrospective mortality study of white male Shell Oil Company employees from the Wood River Refinery in Southern Illinois. The refinery produces a "full line of refinery products." A research laboratory operated on the site from 1933 to 1975. The

cohort of 3,976 (person-years of observation not reported) consisted of all white male employees (hourly and salaried) who had worked at the refinery for at least 1 day during the period January 1, 1973, through December 31, 1982. Retirees who were alive as of January 1, 1973, and whose last work location was the refinery were also included. Vital status was ascertained as of January 1, 1983, by company pension and life insurance departments. Lost to follow-up were all employees (8%) who terminated employment for reasons other than retirement; 94% of this group was under 40 years of age, and 73% had 5 years or less of employment.

Death certificates were obtained from company pension files or state vital statistics departments. Underlying cause of death was coded to the 8th revision of the ICD by a trained nosologist. Person-years were accumulated from January 1, 1973 (or date of employment if after January 1, 1973) to date of death, date of termination, or study end date, whichever came first. The SMRs adjusted for age were calculated (Monson, 1974) using U.S. white male death rates as the standard. Cell-type-specific SMRs were calculated using the Surveillance, Epidemiology and End Results (SEER) mortality rates for white males, all regions combined, 1973-77 (SEER, 1981). The SMR 95% confidence intervals were also estimated.

On the day of entry into the cohort, the mean age of the population was 49 years. Half of the cohort began employment before 1948; approximately two-thirds were pensioners before the end of the study period.

There were 640 deaths observed. The SMR for all causes was 76 ($p < 0.05$) and for all cancers was 91 ($p > 0.05$). A significant elevated SMR was observed for leukemia/aleukemia (SMR = 213, observed = 14, 95% CI 117-358). Significant deficits in the SMR were observed for nonmalignant diseases of the circulatory system (SMR = 77, observed = 361, 95% CI 69-85), respiratory tract (SMR = 44,

observed = 28, 95% CI 29-63), and digestive system (SMR = 49, observed = 15, 95% CI 27-81). Not reported, but representing 139 observed deaths, were cancers of the buccal cavity and pharynx, stomach, large intestine, rectum, liver, pancreas, larynx, lung, skin, prostate, testes, bladder, kidney, brain, and central nervous system.

Cell type for 12 of the 14 observed leukemia deaths was specified on the death certificate. Eight of these were acute myelogenous cell type (AML) (SMR = 394, 95% CI 172-788). No deaths due to lymphosarcoma or reticulosarcoma were observed. Work histories for cohort members whose cause of death was leukemia were reviewed using payroll records and preemployment application forms. None of these employees were "operators in the benzene units or loaders in the dispatching department." Five were maintenance workers, three held laboratory jobs, and six (two draftsmen, one patrolman, and three compounders) "probably had no benzene exposure above refinery background level."

No data on exposure to gasoline vapors were presented in this study. The study site also included a research laboratory. All employees who terminated employment for reasons other than retirement were lost to follow-up (approximately 318). This may lead to an underreporting of cohort mortality, particularly if those employees who terminated did so for reasons of disability. No analysis by latency was presented, although the authors stated that about half of the cohort began employment before 1948. The follow-up period was short. Analysis by specific cancer sites was limited to lymphatic and hematopoietic tissues. Finally, confounding factors were not considered. Because of the above-mentioned reasons, this study provides insufficient evidence of an association between gasoline and cancer.

4.2.1.19. Hanis et al. (1985a)--In the first part of this multiple-objective study, the authors used a retrospective cohort study designed to examine the

mortality experience of regular employees who had worked for at least 1 month in the plants under study during the period January 1, 1970 through December 31, 1977. The cohort population came from three Exxon refineries and chemical plants situated in the United States. It also included retirees who were alive as of January 1, 1970. Employees who worked in more than two plants were counted only once in the total population, although their duration of employment at all plants combined was counted appropriately in person-years. Data on name, date of birth, sex, race, date of employment, date of termination, and vital status at last observation were obtained through company, personnel, and medical records. Data on the underlying cause of death were extracted from death certificates. The underlying cause of death was coded by a trained nosologist according to the 8th revision of the ICD. Where death certificates were unavailable, death notices or company medical records were used. SMRs were computed by using the U.S. cause-specific mortality rates by age, race, sex, and calendar year for each 5-year age group.

The total cohort consisted of 21,698 individuals, which included 15,437 regular and 6,261 retired employees contributing 137,702 person-years of employment. Forty-two percent of the cohort were still actively employed at the end of the study period, 46% had retired (29% of these died during the study period), 10% had terminated their employment, and 1% had died while still employed.

Follow-up for vital status was successful for 99% of the cohort, and there were 3,198 deaths. Death certificates were procured for all but 25 (0.8%) of the people in the cohort.

Eighty-five percent of the cohort were white males. The remaining 15% was distributed as follows: 9% black males, 5% white females, and 1% black females.

The total cohort had a statistically significant lower mortality than ex-

pected for all causes of death (SMR = 91, observed = 3,198), mental disorders (SMR = 40, observed = 6), diseases of the digestive system (SMR = 71, observed = 93), and for all external causes (SMR = 56, observed = 111). There were slight elevations in SMRs for benign/unspecified neoplasms (SMR = 132, $p > 0.05$) and for diseases of the blood and blood-forming organs (SMR = 120, $p > 0.05$).

The SMR for mortality from all cancers also showed a statistically non-significant deficit (SMR = 94). Deficits ($p > 0.05$) were also observed for mortality from cancer of the lung, skin, and genitourinary organs, leukemia, and lymphopoietic system cancer. There were six sites for which greater-than-expected cancer mortality was observed, based on five or more deaths; these sites included liver/gallbladder/bile duct (SMR = 133), pancreas (SMR = 107), bone/connective tissue/skin/breast (SMR = 119), kidney (SMR = 143), brain/CNS (SMR = 115), and lymphosarcoma/reticulosarcoma (SMR = 114). None of these elevated SMRs was statistically significant.

A subcohort of workers employed during the study period showed reduced SMRs for all causes of death and for all cancers. These SMRs were 62 (observed = 670) and 76 (observed = 183) ($p < 0.05$ for both), respectively. Four of six causes of death that were elevated in the total cohort were also elevated for this subgroup but were not statistically significant. These causes of death included cancer of the liver/gallbladder/bile duct (SMR = 139), kidney (SMR = 148), and brain/CNS (SMR = 130).

Analysis by latency in employees who had more than 15 years of employment showed the same pattern as that for the total cohort. The SMR for all cancers showed a significant deficit (SMR = 90, observed = 613, $p < 0.05$).

A total of 18,402 white males contributing 120,053 person-years showed SMR deficits for all the cause-specific deaths considered.

For black males (2,026 contributing to 11,550.9 person-years), SMRs of 97

(observed = 284) and 92 (observed = 54) were observed for all causes of death and for mortality from all cancers, respectively. Increased SMRs were observed for mortality from cancers of all the digestive organs (SMR = 131), stomach (SMR = 159), large intestine (SMR = 116), pancreas (SMR = 182), diseases of the circulatory system (SMR = 116), and diseases of the genitourinary system (SMR = 120). All of these increases were statistically nonsignificant.

When data were analyzed by plant, cohorts from the Baton Rouge, Lousiana, and Baytown, Texas, plants showed SMRs of less than 100 for all causes of death. The only exception to this was an observed nonsignificant SMR increase for symptoms/senility/ill-defined conditions in the Texas plant cohort and an SMR of 100 for circulatory system diseases at the Baton Rouge plant.

The Bayway/Bayonne, New Jersey, plant cohort had an SMR of 100 for all causes of death and a statistically significant excess in mortality from all cancers (SMR = 116, observed = 259) and from endocrine/nutrition/metabolic diseases (SMR = 148, observed = 32). Two nonsignificant increases in the SMR were observed for diseases of the circulatory system (SMR = 106) and for symptoms/senility/ill-defined conditions (SMR = 135).

Further examination of cancer mortality in these three plants revealed SMR deficits for the Baton Rouge (SMR = 92, observed = 249) and Baytown (SMR = 75, observed = 158, $p < 0.05$) plant cohorts. There were statistically nonsignificant increases in the SMRs for pancreatic cancer (SMR = 152) among the Baton Rouge cohort, kidney cancer for both the Baton Rouge (SMR = 155) and the Baytown (SMR = 123) cohorts, brain and CNS cancer for the Baytown cohort (SMR = 131), and for all lymphopoietic cancer (SMR = 108) for the Baton Rouge cohort. The Bayway/Bayonne plant cohort had statistically significant ($p < 0.05$) increases for all cancer deaths (SMR = 116, observed = 259) and for mortality from cancer of the digestive organs (SMR = 132, observed = 84); mortality from

respiratory system cancer was of borderline ($p = 0.05$) statistical significance. The same cohort had no statistically significant SMR increases for the other cancer sites considered.

When local, state, and county rates were applied to the statistically significant cause-specific cancer mortality results for the Bayway/Bayonne plant, such as all cancer deaths, cancer of the digestive system, and cancer of the respiratory system, these SMRs were reduced, leading the authors to the conclusion that regional factors were affecting mortality from these causes.

This study is the first phase of a multiphase study. It has a short follow-up period, although some retirees (who were alive on the starting date) were included. No data on exposure to gasoline vapors or job titles were available. The study sites also include chemical plants. A very weak analysis by latency using the subcohort hired prior to 1956 is presented. The total cohort, including both sexes and races, was analyzed as a homogeneous population, making it difficult to draw any conclusions. Confounding factors are not taken into consideration. Thus, this study is considered inadequate to use as a basis from which to draw any conclusions with regard to gasoline exposure.

4.2.1.20. Hanis et al. (1985b)--This is the second part of a multi-objective retrospective cohort mortality study of employees at three Exxon refineries and chemical plants. The cohort of 21,698, contributing 137,702 person-years, was observed from 1970 to 1977. The study design, cohort definition, and data collection techniques, except for smoking history data, were handled in exactly the same manner as those described in these authors' earlier (1985a) study.

Smoking histories were obtained from employee medical records kept since the mid-1960s; however, "consistency of detail varied by plant." The measure of smoking exposure was ever, never, or unknown. Histories were available for 70% of the cohort.

To derive the occupation for which each employee had spent the largest portion of his/her working time, work histories were reviewed; 3% of these were missing. Nine occupational categories were created for analyses: official/manager, professional, technician, office worker/clerk, process operator, mechanical worker, unskilled laborer, service worker, and laboratory technician/field professional. Job titles within each category were presented. Occupational categories were further classified into two exposure groups. The nonexposed group consisted of officials/managers, professionals, technicians, and office workers/clerks. The remaining occupational categories were classified as potentially exposed to "petroleum, petrochemicals, and other related substances."

The total study population was used as the standard population unless otherwise specified. Age-, sex-, race-, and calendar year-specific death rates in the subgroup of interest (e.g., smoking males) were multiplied by the number of person-years in the appropriate cell in the standard population to obtain directly adjusted death rates. The expected number of deaths resulting was then summed over all the cells and divided by the total number of person-years in the standard population, and then multiplied by 10,000 to yield the directly adjusted rates per 10,000 person-years. The Mantel-Haenszel procedure was used to test the rate ratios (relative risk) for statistical significance.

Thirty-three percent of the cohort were classified as mechanical workers, 28% as process operators, and 11% as professionals. Of the study population, 75% had potential for "daily exposures" to petroleum, petrochemicals, or other related substances, 22% had "little" potential for exposure, and 3% had unknown potential.

Analyses by mortality outcome, either a mortality rate or a rate ratio, were presented by geographic site, occupational subgroup, and smoking category.

Results were not reported for those cause-specific diseases in which there were fewer than five observed deaths per geographic site or exposure group.

Mortality rates among plants were fairly consistent, and for all causes of death were virtually identical. The only cause of death whose rates were higher than those of the U.S. population for all three plant cohorts was kidney cancer; the highest rate ratio (HRR), ratio of the highest plant mortality rate to the U.S. rate observed, was 1.5 (observed = 9, i.e., number of observed deaths at the plant with the highest mortality). Pancreatic cancer rates were higher than U.S. rates at the Baton Rouge and Baytown plants (HRR = 1.7, observed = 23). Rates at the Bayway/Bayonne plant for cancers of the stomach (HRR = 1.1, observed = 16), large intestine (HRR = 1.3, observed = 32), and lung (HRR = 1.1, observed = 77) were slightly higher than the U.S. rates. Mortality rates for endocrine/nutritional/metabolic diseases were higher at the Baytown and Bayway/Bayonne plants in comparison to the U.S. rates (HRR = 1.7, observed = 9). At all three plants, mortality rates for diseases of the respiratory system (HRR = 0.9, observed = 48) were lower than the U.S. rates.

Mortality rates of the potentially exposed group were generally higher than those of the nonexposed group, and for all causes of death a significant ($p < 0.05$) rate ratio of 1.2 was observed. Elevated ($p > 0.05$) over those of the nonexposed group were mortality rates of the potentially exposed for all malignant neoplasms (RR = 1.2) and cancers of the digestive system (RR = 1.4), pancreas (RR = 1.1), lung (RR = 1.3), genitourinary organs (RR = 1.6), and prostate (RR = 1.9). Mortality rates for cancer of the brain/CNS (RR = 0.3), respiratory system diseases (RR = 0.7), and digestive system diseases (RR = 0.8) were all lower ($p > 0.05$) than the U.S. rates. Also significantly elevated was the rate ratio for diseases of the circulatory system (RR = 1.4).

Directly adjusted mortality rates were also presented for the nine occu-

pational categories for selected causes of death. The nonexposed technicans had the highest rates for all causes of death and for all cancers. The exposed laborers had the second highest rates for all causes of death and for all cancers. A consistent pattern could not be discerned for specific cancers, and only limited data were presented. However, mortality rates for mechanical workers (MR/10,000) for kidney cancer were approximately 45% higher than the U.S. rates (MR = 1.6 vs. MR = 1.1).

As part of this review, all job titles and occupational categories (as presented by Hanis et al.) were rereviewed by a certified industrial hygienist to identify those job titles and occupational categories that would have employees with potential gasoline exposure. The occupational category of laboratory technician/field professional (N = 909) was identified as containing workers exposed to gasoline during the sampling and testing of gasoline in the quality control laboratories. The laborer category (N = 1,572) contained workers who were potentially exposed to gasoline during transport loading operations or during maintenance activities. The process operators category (N = 6,135) contained process operators and technicians who may be exposed to gasoline during sampling procedures. All three of these categories were classified by the authors as potentially exposed to petroleum, petrochemicals, or other related substances.

A review of the authors' data by occupational category indicated that directly adjusted mortality rates for laborers (MR = 56) and processors (MR = 53) were only slightly higher than U.S. rates (MR = 51) for all cancers. Lung cancer mortality rates for laborers (MR = 16.4), processors (MR = 18.9), and laboratory technicians (MR = 18.6) were higher than U.S. rates (MR = 16.0). Digestive system cancer rates for laborers (MR = 16.1) and processors (MR = 18.3) were also higher than the U.S. rates (MR = 14.2).

Smokers were generally observed to have a higher risk of death when compared to nonsmokers. Significant ($p < 0.05$) rate ratios for all causes of death (RR = 1.9) and all cancer deaths (RR = 2.3) were observed. An elevated rate ratio was observed for smoking exposure for all digestive organ cancers (RR = 1.6). Conversely, smokers were at reduced risk for cancers of the pancreas (RR = 0.8), genitourinary organs (RR = 0.9), and prostate (RR = 0.6). Rate ratios for other malignant neoplasms were not presented.

The authors further examined the relationship of smoking to refinery exposure by post-stratifying smoking exposure (ever/never) by occupational categories (potentially exposed to petroleum products/not exposed). Smokers were observed to be at increased risk of death when compared to nonsmokers regardless of refinery exposure. The only exception was for cancer of the pancreas; smokers potentially exposed to refinery products were at reduced risk of death compared to nonsmokers (RR = 0.8).

Occupational exposures were then stratified by smoking categories. The risk of death among smokers potentially exposed to refinery products was always greater than among those not exposed to refinery products. Significant ($p < 0.05$) rate ratios were observed for all causes of death (RR = 1.2) and diseases of the circulatory system (RR = 1.4). Risks for all malignant neoplasms (RR = 1.2) and cancers of the digestive organs (RR = 1.2) and respiratory system (RR = 1.7) were also elevated among smokers.

Detailed results were not presented for the nonsmoking population; however, the risks for those potentially exposed to refinery products were slightly elevated over the nonexposed group for all malignant neoplasms (RR = 1.2). The pancreatic cancer mortality rate among the potentially exposed nonsmokers was higher (MR = 4.8) than the rate among the two smoking groups (MR = 4.8 vs. 3.4).

This study has many of the same limitations as the authors' earlier study (1985a). There was a lack of information on gasoline exposure. The follow-up period was short. No latency analyses were included. The study sites also included chemical plants, and the only confounding factor taken into consideration was smoking. Smoking information was missing for 30% of the cohort. Since smoking is associated with both the outcome variable (mortality) and exposure (smoking is generally prohibited in certain areas of the plant), a selection bias is potentially introduced into the analysis of the smoking data. In addition, the authors presented no data with which to evaluate dose-response effects. This is unfortunate, as this is one of the few studies where, because mortality rates were adjusted by the direct method rather than by the indirect method used to calculate SMRs, subcohort risks could be directly compared.

Based on the above-mentioned reasons, this study provides insufficient evidence for the carcinogenicity of gasoline vapors.

4.2.1.21. Divine et al. (1985)--This is a retrospective cohort study consisting of 19,077 white male employees of Texaco, Inc., who worked for a minimum of 5 years prior to December 31, 1977, at refinery, petrochemical, and research facilities owned by the company; at least 1 day of employment had to occur between January 1, 1947, and December 31, 1977. There were 358,029 person-years of observation. Employees who transferred from other company facilities could not be identified. Excluded from the cohort were employees of the administrative, engineering, and medical services departments, and employees of a former subsidiary who terminated employment before 1955.

Data on the employees, obtained from company records or the SSA, included employee's name, social security number, race, sex, date of birth, and a complete occupational history, when available.

Of the 19,077 white males included in the study, 4,024 (21.1%) were deceased as of December 31, 1977. The vital status of 444 (2.3%) of the employees was unknown. Death certificates were obtained for 3,872 (96.2%) of the decedents from company records or state vital statistics departments.

The underlying cause of death was recoded by a trained nosologist according to the 7th revision of the ICD. SMRs were calculated by using the U.S. white male population as the comparison group (Monson, 1974). Ninety-five percent confidence intervals were also calculated. The calculation for the overall SMR included the decedents for whom no death certificates were recovered; cause-specific SMRs were calculated without using these decedents. Those lost to follow-up were assumed lost on the date of last employment.

The overall SMR was 75 (4,024 deaths observed, $p < 0.05$). In most major cause of death categories, the SMR was significantly ($p < 0.05$) less than unity (100), including all malignant neoplasms (SMR = 75, observed = 767) and cancers of the digestive organs (SMR = 70, observed = 215), stomach (SMR = 70, observed = 45), large intestine (SMR = 68), observed = 64), lung (SMR = 59, observed = 182), and bladder (SMR = 56, observed = 19). The SMR for benign neoplasms was 148 (20 deaths observed, $p > 0.05$), which was the highest SMR observed. The elevated cancer SMRs were for cancers of the pancreas (SMR = 107, observed = 62, 95% CI 82-138), brain (SMR = 111, observed = 31, 95% CI 75-157), and for Hodgkin's disease (SMR 108, observed = 13, 95% CI 58-185), leukemia (SMR = 118, observed = 48, 95% CI 87-156), and cancer of other lymphatic tissue (SMR = 115, observed = 25, 95% CI 74-170). Significantly ($p < 0.05$) reduced SMRs were observed for all non-cancer causes except benign neoplasms (endocrine and metabolic diseases SMR = 78, observed = 78; vascular lesions of the CNS SMR = 79, observed = 322; diseases of the circulatory system SMR = 79, observed = 1,975; arteriosclerotic heart disease SMR = 81, observed = 1,623; respiratory

diseases SMR = 52, observed = 159; emphysema SMR = 60, observed = 52; diseases of the digestive system SMR = 56, observed = 141; cirrhosis of the liver SMR = 47, observed 56; diseases of the genitourinary system SMR = 53, observed = 43; external causes of death SMR = 54, observed = 227; and accidents SMR = 53, observed = 152).

It is difficult to draw conclusions from this study. Although the study population is quite large and covers an appreciable period of time, 30 years, job-specific data were not included, which makes exposure assessment difficult. The cohort consisted of employees who worked at "the refinery, petrochemical, and research facilities"; these and other confounding factors (e.g., smoking) were not controlled for. The authors failed to state that the calculations of their SMRs were time-specific; however, the Monson program will calculate time-specific SMRs if instructed to do so.

The lack of information on length of employment, latency, or type of exposure makes this study insufficient for forming conclusions as to an association between gasoline and cancer.

4.2.1.22. Barron and Divine (1985)--At a 1985 meeting of the Society for Epidemiologic Research, Barron and Divine presented preliminary results from a nested case-control study using the cohort studied by Divine et al. (1985). Cases consisted of 31 white male employees with cancer of the brain and 12 with benign and unspecified tumors of the brain. Controls (four per case) were matched for age and date of hire. Significant rate ratios were found in two work areas: research laboratories and lube oil refining units when comparing those ever employed to those never employed. Specific odds ratios and p values were not reported. For cases, the average employment duration in the work area was 5 years longer than controls in the laboratory and 2 years shorter in lube oil refining. The authors reported that employment histories of cases in the

laboratory setting appeared to be concentrated in the 1940s. No additional details were presented.

The lack of any information on control selection, case verification, or details on the magnitude of the risk preclude using this study as a basis for forming conclusions as to an association between gasoline and primary brain cancer.

4.2.1.23. Nelson (1985 Unpublished)--This is a retrospective cohort mortality study of Amoco Oil refinery employees from 10 geographically dispersed U.S. refineries that used generalized processes to produce a variety of petroleum products, including unleaded gasoline. The cohort of 10,763 individuals (104,954 person-years of follow-up) consisted of all full-time regular employees who worked in one of the refineries for at least 6 months, at least 1 day of which was between January 1, 1970, and December 31, 1980.

The vital status of each cohort member was assessed as of December 31, 1982, through the SSA, the National Death Index, or company records. The completeness of the cohort was verified against Social Security 941 forms. Only 2.1% of the cohort members (1.5% of the white males) were lost to follow-up. Death certificates were obtained for 971 of the 983 decedents from company files or from the appropriate state's records of its vital statistics department. The underlying cause of death was coded by an experienced nosologist to the 8th revision of the ICD.

Information on cohort members was extracted from computerized company work records and included social security number, name, sex, race, birth date, employment type (salaried or "ever hourly"), hire date, termination date, and refinery where employed. Smoking information was available for 59% of the total cohort (i.e., those individuals who had company-sponsored medical examinations from 1976 to 1982). However, this information was not available for

90% of the decedents.

Computerized job history information was used to group cohort members by exposure categories. "Most frequent" job title and in-plant locations were assumed to be representative of a worker's entire employment history. A validation study of this method was conducted in the Salt Lake Refinery (N = 387) where the author found that "most frequent computerized job title was . . . representative of an employee's complete job history approximately 89% of the time."

Four mutually exclusive exposure groups were established: (1) job type (administrative, maintenance, operations, and unknown), (2) contact with refinery products, (3) contact with light aromatic hydrocarbons (benzene, toluene, xylene), and (4) contact with heavy oils (catalytically cracked oil or coker gas oil). The latter three exposure groups were categorized as none, occasional, routine, and unknown. Cohort members were categorized into exposure categories by an industrial hygienist, using the most frequent job title and location information. The exposure category selection process was based on a qualitative evaluation of job categories.

SMRs were calculated using the Monson program (Monson, 1974) updated through 1980, which compares observed deaths to those expected based on U.S. death rates. SMRs and two-sided 95% confidence intervals were calculated by race and sex for 42 selected causes of death.

White males comprised 85.4% of the cohort; black males, white females, and black females comprised 8.2, 5.4, and 1%, respectively. The majority of the cohort members (66%) were employed at the Whiting and Texas City refineries. Over half (51%) of the employees were employed by the company for 25 years or more; 37% were employed for 9 years or less.

Among the white male cohort members, the SMRs for all causes of death (SMR

= 73, observed = 921) and all cancer deaths (SMR = 84, observed = 259) were reduced significantly ($p < 0.05$). Conversely, a significantly elevated ($p < 0.05$) SMR of 201 was observed for skin cancer (observed = 11). Elevated (but not significantly) were cancers of the rectum (SMR = 149) and stomach (SMR = 148). SMRs were slightly elevated for cancers of the large intestine (SMR = 113), liver (SMR = 116), pancreas (SMR = 110), and bladder (SMR = 109). The SMR for benign neoplasms (SMR = 178) was also elevated. Statistically significant deficits were observed for several causes of death, including cancers of the buccal cavity and pharynx (SMR = 20, observed = 2) and lung (SMR = 63, observed = 75); lymphatic and hematopoietic tissue cancers (SMR = 60, observed = 16); and diseases of the circulatory system (SMR = 75, observed = 461, nonmalignant respiratory system (SMR = 50, observed = 38), digestive system (SMR = 60, observed = 39), and genitourinary system (SMR = 38, observed = 4); and accidents, poisonings, and violence (SMR = 53, observed = 55).

The SMR among black males for all causes of death (SMR = 68, observed = 50) was significantly reduced. Nonsignificant increases in the SMR were observed for cancers of the large intestine (SMR = 224), kidney (SMR = 443), and brain/CNS (SMR = 510); however, these SMRs were based on only one or two observations.

Among white females, the SMR was depressed for all causes of death (SMR = 69) and elevated for cancers of the large intestine (SMR = 178, observed = 1), liver (SMR = 902, observed = 1), and diseases of the circulatory system (SMR = 114). None of these SMRs was significant. No deaths occurred among the black female cohort members.

Subcohort analyses were limited to white males. Statistically significant elevated SMRs for digestive system (SMR = 137, observed = 49) and stomach cancer (SMR = 207, observed = 11) were observed among white males employed at

the Whiting, Indiana, refinery and among all white cohort males hired before 1940 (digestive cancer SMR = 163, observed = 36; stomach cancer SMR = 243, observed = 8). A statistically significant SMR for digestive system cancer (SMR = 139, observed = 53) was also observed among those who were routinely exposed to light aromatic hydrocarbons.

Statistically significant elevations in the skin cancer SMR were found among several subcohorts. All of those who died of skin cancer (observed = 11) were ever-hourly employees (SMR = 263) and tended to be maintenance workers (SMR = 378, observed = 8) who were routinely exposed to refinery products (SMR = 268, observed = 10), light aromatic hydrocarbons (SMR = 262, observed = 7), or heavy oils (SMR = 259, observed = 7). Others at risk for skin cancer were those hired after 1945 (SMR = 292, observed = 8) and those with less than 15 years of latency (SMR = 524, observed = 3).

SMRs were elevated, although not significantly, for cancers of the rectum and liver among maintenance workers; ever-hourly employees; those who were exposed (occasionally or routinely) to refinery products, light aromatic hydrocarbons, or heavy oils; those hired before 1940; and those with 15 years or more of latency. Elevated kidney cancer SMRs were observed among salaried employees; administrators; those with no exposure to refinery products, light aromatic hydrocarbons, or heavy oils; and those hired before 1940.

SMRs for all causes of death, by refinery, were also calculated using state and county death rates as the standard. SMRs for 7 of 10 refineries were slightly lower than U.S.-based rates. For example, the SMR based on U.S. rates for all causes of death at the Whiting refinery was 81 versus an SMR of 77 based on state rates. County-based rates were slightly lower than state rates, the SMR for all causes of death at Whiting equaling 74. SMRs, using county mortality rates as the expected rates, were also calculated for selected causes

of cancer death. The overall pattern of risk remained unchanged--those causes of death with elevated rates continued to exhibit similar patterns of excess risk. Noticeable differences were observed among Whiting employees whose cause of death was malignant melanoma of the skin (SMR = 213 based on U.S. rates versus SMR = 267 based on county rates).

The author also calculated, by the direct method, the SMRs for all causes of death and all cancer deaths to examine dose-response effects of white male exposure to refinery processes, light aromatics, or heavy oils. The relationship among rates standardized to the U.S. rates were similar to those based on rates standardized to the study population. There appeared to be a dose-response effect for all causes of death for the three exposure categories. Patterns for all cancer deaths were not so clear-cut. Among those with occasional exposure to refinery processes, the risks appear to be less in comparison to those with no exposure, whereas among those occasionally exposed to heavy oils, the risks appear to be greater than those of the nonexposed or routinely exposed groups.

There are several limitations to this study with regard to evaluation of gasoline exposure. The main limitations are the lack of information on gasoline vapor exposures and the fact that products other than gasoline were routinely manufactured in all the refineries. For example, four of the refineries, representing 77% of the study population, also manufactured petroleum coke. Also, there was some redundancy among the four exposure groups. For example, 43% of the total cohort was routinely exposed to light aromatics and heavy oils (Nelson et al., 1985). There was no control during these analyses for these multiple exposures.

Results were not consistent among refineries. For example, excess stomach cancer was observed at five of the seven refineries for which deaths were

observed; at the Whiting refinery (N = 3,474) there were significant elevations (SMR = 207), whereas at the Texas City refinery (N = 2,472) a deficit (SMR = 48) was observed.

There was excellent follow-up; however, the period of follow-up was short. This is especially important considering that one-third of the study population were employed for less than 9 years (10 to 30 years generally being the latency for environmental carcinogenesis).

Finally, confounding factors such as smoking were not taken into consideration. Thus, this study provides insufficient evidence for the carcinogenicity of gasoline vapors.

4.2.2. Case-Control Studies that Evaluated Employment in the Petroleum Industry as a Risk Factor

4.2.2.1. Cole et al. (1972)--During an 18-month period, Cole et al. (1972) attempted to identify all residents, ages 20 to 89, with newly diagnosed bladder cancer in eastern Massachusetts, including Boston. Six hundred and sixty-eight cases were identified that included transitional or squamous-cell malignancies of the renal pelvis, ureter, bladder, or urethra. Of these, a random sample of 510 was selected for interview, and usable occupational interviews were obtained for 461 cases (356 males, 105 females). Controls were selected from the age- and sex-stratified sample of the adult population of the study area and matched for sex and year of birth. Of 668 persons initially identified as potential controls, 485 (374 males, 111 females) provided usable occupational histories.

Questionnaires administered to both cases and controls provided detailed information on occupational history. Occupations were classified according to occupational exposures and occupation titles. Based on a literature review, 13 occupational categories were created and ranked from "presumed highest risk of

bladder cancer" (dyestuffs manufacture and use) to lowest (office workers), based on "similar" exposures. The suspect category, rankings 1 to 8, included dyestuffs, rubber, leather, printing, painting, petroleum, organic chemicals, and other chemicals, respectively. The nonsuspect category, rankings 9 to 13, included fumes and smoke, manufacturing not elsewhere classified, ranching and farming, service occupations, and office work, respectively. The category involving petroleum products was ranked 6, a suspect category.

Occupations were also classified according to job titles. This was done, according to the authors, in order to look for previously unrecognized hazardous occupations. Occupations were assigned title codes based on description of work alone, without regard to exposure. From the detailed work histories, each person was assigned up to nine occupations.

Relative risks were calculated from observed number of cases and expected number of cases. Expected numbers of cases were calculated based on the frequency distribution of the control's occupational categories. All risk estimates were controlled for age (20 to 59, 60 to 74, and 75 to 89). To evaluate the association between occupation and cigarette smoking, risk estimates were controlled for smoking using three categories of maximum daily cigarette consumption: nonsmokers, up to one-half pack a day, and more than one-half pack a day. Relative risks and their associated 95% confidence limits were calculated by Sheehe's modification (1966) of Woolf's technique. This may, according to the authors, result in conservative estimates of relative risk.

Risk estimates were presented comparing cases to controls for each of the suspect exposure categories. All risks were calculated relative to the nonsuspect categories. Estimates based upon the total number of cases and controls occurring in each of the 13 categories were calculated controlling for age and smoking. In total, the case population contributed 1,241 different

observations (i.e., occupations).

Significantly ($p < 0.05$) elevated relative risks of 1.57 (95% CI 1.04-2.36) and 2.00 (95% CI 1.37-2.90) were observed for the rubber and leather occupational categories, respectively. The relative risk for petroleum product occupations was 1.00, showing no increase or decrease in risk.

When the cases were classified according to the single mutually exclusive category of "usual occupational exposure," results were similar to those cited above. Increased relative risks were seen for rubber, leather, paint, and other organic chemical occupations, though none of these was significantly different than for the nonsuspect workers. The relative risk for petroleum occupations was 1.05 (95% CI 0.65-1.71). These risks are age-adjusted only.

Cases were also classified according to whether or not they were "ever employed" in each of the suspect categories. When controlled for age and smoking, increased risks were observed for all suspect categories except "other chemicals." Significant ($p < 0.05$) increases were seen for the rubber and leather categories, with relative risks of 1.63 (95% CI 1.04-2.56) and 2.25 (95% CI 1.46-3.46), respectively. The relative risk for the petroleum category was 1.18 (95% CI 0.82-1.69). This was not significant.

The authors discussed an interesting feature of the petroleum exposure category. It is the largest of the eight suspect categories in that more of the cases were classified as ever working in the petroleum industry. One subcategory, machinists and mechanics, accounts for 81% of the observations in the petroleum category (RR = 0.92 for this subgroup). When this group is excluded, other petroleum work has a relative risk of 1.61 (95% CI 0.932.79), although this is not significant. Not reported was whether this risk estimate was adjusted for age and/or smoking.

The data were also studied with respect to occupation title. It could not

be determined if the authors' categorization by job title was for "usual job title" or "ever employed" in a particular job title. Relative risk estimates by job title were similar to those seen for "usual" occupation for those employed in the rubber, leather, and paint industries; however, none of these risks was statistically significant. Petroleum work showed no increase in risk, exhibiting a relative risk of 0.96. The authors stated that for petroleum work, as in the earlier analysis, the nonsignificant relative risk may mask increased risk within subgroups. This, however, is not investigated in more detail.

This study failed to established a link between bladder cancer and petroleum work when based on a classification of occupation according to either a priori exposure categories or job title classifications. By the authors' own admission, individuals identified as petroleum workers made up a large portion of the study population; further analysis by subgroups may have been warranted, but no data were presented. The authors do suggest that certain subgroups of bladder cancer cases may have increased risk if they worked in the petroleum industry, but specific job classifications or exposure history, duration, or concentrations were not presented, although this information may have been available through the detailed occupational history questionnaires. Thus, this study is inadequate to link gasoline exposure or refinery exposure to bladder cancer.

4.2.2.2. Howe et al. (1980)--The authors conducted a population-based case-control study of bladder cancer in the Canadian provinces of British Columbia, Newfoundland, and Nova Scotia. Cases were identified through the population-based cancer registry for each province; they were identified as all patients with newly diagnosed bladder cancer occurring between April 1974 and June 1976. Interviews were obtained for 77% of the cases identified. Neighborhood controls

were individually matched to the cases on the basis of sex and age (± 5 years). The authors reported that 20% of the potentially eligible controls in British Columbia refused to be interviewed, as did 4% in Nova Scotia; all potential controls were interviewed in Newfoundland. The final study population consisted of 480 pairs of males and 152 pairs of females.

Subjects were interviewed in their homes. Respondents provided details on their smoking practices, employment history, occupational exposures, use of hair dyes and analgesics, beverage consumption patterns, history of kidney and bladder conditions, and consumption of possible nitrite sources in their diet. Information was also obtained on the use of artificial sweeteners; these results were reported elsewhere (Miller and Howe, 1977; Howe et al., 1977).

A matched analysis with the linear logistic model (Breslow et al., 1978) was used to assess relative risk. Two-sided 95% confidence intervals were calculated for the risk estimates. Tests of significance and interval estimation were based on the binomial distribution (Miettinen, 1970). The Mantel extension procedure was used to test for trend (Mantel, 1963).

Fourteen industries or occupations were considered a priori as high-risk industries; the petroleum industry was one of these. The male cases were 5.3 times more likely than their controls to have ever been employed in the petroleum industry (95% CI 1.5-28.6). Employment in the chemical industry was also found to be a significant risk factor (RR = 7.5, 95% CI 1.7-67.6). Elevated, though not significantly, were the rubber (RR = 5.0), photographic (RR = 3.0), medicine (RR = 2.6), and food processing (RR = 1.6) industries; the authors subsequently treated these as high-risk industries for males. Risks were also elevated ($p > 0.05$) for males employed in the cloth dyeing (RR = 2.0), tanning (RR = 1.2), and tailoring (RR = 1.5) industries; however, the authors did not subsequently treat these industries as high-risk industries, probably because

of the small numbers of exposed males. All of these estimates remained "unchanged" after controlling for cigarette smoking.

The risk for subjects who reported exposure to dust and fumes in other industries was observed at a significant 2.5 for males (95% CI 1.8-3.6) and a nonsignificant 4.5 for females. These estimates were not affected by those who reported working in the a priori high-risk industries. Dust exposures were then regrouped into four subcategories based on "logical groupings of similar fumes or dusts." The risk for diesel and traffic fume exposure was elevated (RR = 2.8), although not significantly. Exposures to welding fumes (RR = 2.8, 95% CI 1.1-8.8) and railroad dust and fumes (RR = 9.0, 95% CI 1.2-394.5) were both significantly elevated. Exposure to crop spraying was reported by the authors as significantly elevated (RR = 7.0, $p < 0.05$), but the confidence interval included 1 (95% CI 0.9-315.5).

The authors also examined occupational exposures for males by considering specific job titles that were coded to the 4-digit 1971 Canadian census code. Risks were elevated for the following job titles: guards and watchmen (RR = 4.0, 95% CI 1.3-16.4), nurserymen (RR = 5.5, 95% CI 1.2-51.1), metal machinists (RR = 2.7, 95% CI 1.1-7.6), and material recorders (RR = 2.6, 95% CI 1.0-7.3). Elevated ($p > 0.05$) were risks for glass processors (RR = 6.0) and mechanics (RR = 1.6). All of these risks remained unchanged after controlling for cigarette smoking, whereas risks for those in the armed services (RR = 1.4) or those employed as clerical workers (RR = 1.4) were reduced to statistically nonsignificant excesses after controlling for smoking.

Male study subjects responded positively to only two chemicals listed on the questionnaire: benzidine and its salts and bis(chloromethyl)ether. Though elevated (RR = 1.3 and RR = 5.0, respectively), risks for exposure to these substances were not observed at significant levels.

Age (< 60, $\geq$ 60) appeared to confound the results for males exposed to an a priori high-risk industry. Risk for the individuals less than 60 years of age and exposed to an a priori high-risk industry was more than four times (RR = 8.5, 95% CI 2.0-75.8) that for individuals ages 60 and above (RR = 2.1, 95% CI 1.1-4.2) who were also exposed to an a priori industry. Age appeared not to confound the risks for exposure to dust or fumes.

Bladder cancer risks were elevated for females employed in tailoring (RR = 2.0), medicine (RR = 1.2), and for clerical occupations (RR = 1.3); however, these elevated risks were not statistically significant.

For both sexes, a statistically significant ($p < 0.01$) dose-response relationship was observed for cigarette smoking, measured as average frequency of cigarettes smoked per day and categorized as more than 0 to 10 cigarettes (RR = 2.6, 95% CI 1.7-4.4), 10 to 20 cigarettes (RR = 3.8, 95% CI 2.6-6.0), and more than 20 cigarettes (RR = 5.1, 95% CI 3.5-8.6) per day. A similar dose-response relationship ($p < 0.01$) was observed for duration of cigarette smoking (up to 20 years: RR = 1.8, 95% CI 1.1-3.3; 21 to 40 years: RR = 3.9, 95% CI 2.6-6.4; and greater than 40 years: RR = 4.8, 95% CI 3.3-7.7) and total lifetime consumption of cigarette packs (up to 10,000 packs: RR = 2.5, 95% CI 1.7-4.0; 10,000 to 20,000 packs: RR = 4.4, 95% CI 3.0-7.2; and more than 20,000 packs: RR = 5.8, 95% CI 3.9-10.3).

Risks were also assessed for consumption of coffee (regular or instant), tea, alcohol, non-diet colas, other non-diet soft drinks, and diet drinks. The only excesses observed among males were for those who consumed regular coffee (RR = 1.5, 95% CI 1.0-2.2) or instant coffee (RR = 1.5, 95% CI 1.2-2.0). No statistically significant findings were reported among the female group, though risks for subjects who consumed non-diet colas (RR = 2.0) and instant coffee (RR = 1.4) were elevated.

Statistically significant risks were also observed for males who were users of non-public water supplies (i.e., "a source of higher than average quantities of nitrates and nitrites"), but there was no dose-response relationship observed ($\leq$ 10 years of exposure: RR = 2.2, 95% CI 1.5-3.6; 10 to 20 years: RR = 1.9, 95% CI 1.2-3.2; > 20 years: RR = 2.1, 95% CI 1.5-3.2). No increase in risk among males or females was observed for consumption of preservative-containing meats or fiddlehead greens (i.e., a green similar to bracken ferns, a bladder carcinogen in cows).

Both males and females had an excess risk (p values and CIs not reported) for conditions of the kidney or bladder that occurred up to 5 years prior to diagnosis (male bladder conditions, RR = 4.9; female bladder conditions, RR = 2.8). Analgesics containing aspirin were observed to be a significant risk factor for males (RR = 1.5, 95% CI 1.0-2.3). Analgesics appeared not to be a risk factor for females. Significantly (p = 0.004) more male cases than male controls (8 cases, 0 controls) reported using hair dyes; relative risk estimates were not reported. No increase in risk was observed for females (RR = 0.7, 95% CI 0.3-1.4) who used hair dyes.

The authors used the linear logistic model (logistic regression) to assess the simultaneous effects of smoking, occupational exposures, and other variables of interest. For males, the effects of cigarette and pipe smoking, occupational exposures, use of non-public water supplies, and grades of school "were very similar" to the univariate analysis; however, occupational exposures were measured as exposure to any of the six a priori high-risk industries rather than exposure to just the petroleum industry.

In conclusion, the authors reported that male bladder cancer cases who worked in the petroleum industry were at si nificantly high risk (RR = 5.3, 95% CI 1.5-28.6) and that this estimate remained unchanged after controlling for

the confounding effects of cigarette smoking. They did not present an estimate of relative risk for males employed in the petroleum industry while simultaneously controlling for significant risk factors other than smoking (i.e., coffee, artificial sweeteners, use of non-public water supplies, aspirin, other high-risk industries, and dust and fumes); however, since the size of the risk estimate for males in the petroleum industry, while controlling for smoking, is approximately three times more than the univariate risk estimates for these other risk factors, it can be inferred that risk in the petroleum industry would still be elevated after adjusting for these other risk factors.

The paper suggests that the authors modeled the probability of bladder cancer rather than modeling the probability of exposure, since they reported their risk estimates as relative risks (the method used to calculate risk in a prospective study) rather than as odds ratios (the method used to estimate risk in a case-control study). If this assumption is true, it is not possible to estimate the magnitude of risk for exposure to petroleum products given the available data. In addition, it was not possible to determine if the individuals in the petroleum industry were specifically exposed to gasoline, since specific job titles were not presented. No information was presented on duration of employment or latency. This study provides weak evidence of an association between bladder cancer and employment in the petroleum industry.

4.2.2.3. Bladder Cancer Mortality Studies in Louisiana

4.2.2.3.1. Gottlieb and Pickle (1981). Gottlieb and Pickle (1981) conducted a case-control study of urinary bladder cancer in Louisiana. Death certificates were collected for all deaths attributed to bladder cancer from 1960 to 1975 in 19 parishes. Decedent controls were matched to the cases on the basis of sex, race, parish of residence, and age (within 5 years), excluding those whose cause of death was bladder cancer. This resulted in 347 bladder cancer cases

(176 white males, 62 white females, 61 black males, and 48 black females) and an equal number of matched controls. The objective of the study was to determine possible occupational, environmental, or ethnic influences on mortality from bladder cancer in Louisiana.

Information on occupation and employment industry was abstracted from each death certificate and coded according to the three-digit industries and occupation classification of the U.S. Bureau of the Census. The "usual" residence listed on the death certificate was used to classify each individual as to proximity to possible industrial sources. In addition, each individual was assigned an Acadian ancestry code based on parent's last name and whether or not his/her birthplace was in "Acadiana," a band of counties in southern Louisiana. The authors stated that Acadians were of interest because they are thought to be highly intermarried and thus represent a stable population.

Crude odds ratios were calculated for race, sex, age (dichotomized at 63 years), and type of parish strata to estimate risk associated with usual occupation and Acadian ancestry. Parish types were classified according to industrial activities and included six parishes with wood or paper plants, nine parishes with chemical industries, three parishes with oil refineries, and five parishes classified as other. These total to more than 19, as some parishes had more than one industrial activity. The authors presented no information on the method used to calculate the crude odds ratio. However, a review of their data indicated that two methods were used, that of Fleiss (1981) (i.e., ad/bc) or that of Haldane (1955) (i.e., adding one-half to each cell). No rationale is presented as to why two different methods were used. Confidence intervals were not reported by the authors for crude odds ratios; however, they were calculated ($\alpha = 0.05$) as part of this review by Cornfield's method (1956). Analysis also included logistic multiple regression, where there were suffi-

cient numbers for each sex and race group. However, the results reviewed here are for crude odds ratios, since logistic regression odds ratios were not presented for the variables of interest.

Results indicate that bladder cancer was more common in white males whose usual industry of employment was the oil refining industry. The risk relative to employment in other industries was reported as 4.46 (95% CI 0.73-63.9). Further analysis of these workers showed a high relative risk that decreased with age, but no values were reported. Of the seven workers in the oil refining industry, four of the cases and one control lived in the same parish and all but one lived in the same zip code area.

When studying usual occupations, elevated bladder cancer risks were observed for white male mechanics (OR = 3.07, 95% CI 0.55-23.83), black male transport equipment operators (OR = 3.10, 95% CI 0.28-244.35), and white male transport equipment operators (OR = 2.06, 95% CI 0.63-7.09). Further analysis of these data shows that of six white cases with occupations as mechanics, one worked at an oil refinery, three were auto mechanics, and two were railroad mechanics. Of the 10 white and 3 black transport equipment operators, 9 were bus or truck drivers. Specific occupations of the other four were not described by the authors.

When studied by residential proximity to industries, elevated odds ratios were seen for white males and females living near paper manufacturing (OR = 1.34, 95% CI 0.73-2.49) and oil refining (OR = 1.12, 95% CI 0.63-2.01) plants. For black males and females, elevated odds ratios were also seen for those living near paper manufacturing (OR = 1.48, 95% CI 0.57-4.03) and oil refining (OR = 1.41, 95% CI 0.20-X) plants. None of these elevated risks was significant.

There are limitations to this study. Death-certificate studies are inher-

ently limited in the conclusions that can be drawn from them. Occupational and cause-of-death information is subject to misclassification bias. For example, occupational information may be subject to a recall bias on the part of the next-of-kin supplying the death certificate information. Inaccuracies inherent in death certificate diagnoses of cancer are well documented (Percy et al., 1981; Copeland et al., 1977). Usually no information is available on length of employment, and hence analyses by length of employment and latency are not possible. Information on confounding variables such as cigarette smoking did not exist on the death certificate and cannot be controlled for. The authors calculated odds ratios for different groups by different methods. Thus, it is not possible to directly compare results between different groups of workers. Another limitation to this study is that reported results were not adjusted for age, a confounding factor that could have been controlled for. There was no control for exposure to other petroleum products. In addition, bladder cancer does not always result in a mortality; therefore, the results of this study are not comparable to studies of bladder cancer incidence. Finally, this study is limited in its documentation of gasoline exposure. Thus, this study is inadequate for determining an association between gasoline and bladder cancer.

4.2.2.3.2. Gottlieb and Carr (1981). Gottlieb and Carr (1981) described the results of several death certificate case-control studies in Louisiana that investigated the occurrence of cancers of the lung, pancreas, bladder, and other sites. Because of the heavy influx of petroleum refining, chemical, and petrochemical industries in parishes along the Mississippi, the possible contributions of these industries to cancer mortality were studied. The first study involved a survey of death certificates for lung, pancreas, and bladder cancer deaths for 1960-75 in 19 parishes of Louisiana. The second study, which was expanded/to include cancers of the brain, kidney, and esophagus and

leukemia, was designed to study the influence of the source of drinking water on cancer mortality. Reviewed here are the results of the bladder cancer study. The pancreatic cancer data are presented later under the heading Pancreatic Cancer Mortality Studies in Louisiana. Likewise, the lung cancer data are presented under the heading Lung Cancer Mortality Studies in Louisiana. The data on brain, kidney, and esophageal cancers and leukemia are presented under the heading Other Cancer Mortality Studies in Louisiana.

Data from the principal investigators' previous bladder cancer case-control study (Gottlieb and Pickle, 1981) were used for additional analyses; the reanalyses (Gottlieb and Carr, 1981) are reviewed here.

Odds ratios were recalculated for white male oil refinery workers. Risks were relative to those not employed as oil refinery workers. Gottlieb and Pickle (1981) originally reported an odds ratio of 4.46 (6 of 176 cases were exposed and 1 of 176 controls were exposed). The confidence interval was not reported by the authors. For the same data, Gottlieb and Carr (1981) now report an odds ratio of 6.12 (95% CI 0.73-283.1). The methods used to calculate the odds ratios were not reported by any of the authors; however, a review of the data indicates that the method of Haldane (1955) (i.e., adding one-half to each cell) was used to calculate the 4.46 estimate. It was not possible to determine which method was used to calculate the 6.12 estimate (Gottlieb and Carr, 1981) except that it was not by the methods of Fleiss (1981) (OR = 6.10) or Cornfield (1956) (OR = 6.17, 95% CI 0.73-63.9). However, none of the calculated odds ratios was significant.

This study has the same limitations as those previously reported by Gottlieb and Pickle (1981). Thus, this study is inadequate to determine an association between gasoline and bladder cancer.

4.2.2.4 Najem et al. (1982)--A case-control study of bladder cancer in northern New Jersey was conducted by Najem et al. (1982). The cases consisted of 75 white, living, biopsy-confirmed bladder cancer patients who were consecutively admitted to the private practice clinics of four urologists and to two community hospitals in northern New Jersey during 1978. Of the 75 cases, 65 were males and 10 were females; the mean age was 66.8 years. Controls were obtained from the same clinic and hospital populations as the cases and matched for age (± 5 years), place of birth (born in New Jersey; born out of state), sex, race, and place of current residence (by census tracts). Potential controls with a history of neoplasms or "tobacco-related heart disease" were excluded from the study. Two controls were selected for each case; however, since eight of the initially accepted controls did not meet all of the matching criteria, eight cases had only one control each.

Data were obtained from the 75 cases and 142 controls on demographic and socioeconomic history, lifetime occupational history, residency, personal and family medical and surgical history, blood type, history of smoking, ingestion of coffee, cola beverages, alcohol, saccharin, and hair dye use. Occupational history was determined for the period beginning at age 16 and ending at the diagnosis of bladder cancer for cases. One year of employment was required for a study participant to be classified as being employed in a particular industry. Questions about specific jobs and chemical exposure were also used.

The data were analyzed by calculating estimates of the relative risk (odds ratios) for each risk factor of interest. Ninety-five percent two-tailed confidence intervals were calculated by the modified exact confidence intervals procedure (Rothman, 1975). Post-stratification of the data into never smoked, ex-smoker, and current smoker subgroups addressed the influence of cigarette smoking as a confounder. The homogeneity of stratum-specific odds ratios was

tested by the method proposed by Breslow and Day (1980). The Mantel-Haenszel odds ratio was used as the summary measure of association.

Of the 75 cases, 22 (29%) worked in what was classified as the petroleum (fuel) industry, compared to 19 (14%) of the 142 controls. The odds ratio was 2.5 (95% CI 1.2-5.4). Adjusting for the effect of smoking, the odds ratio was 2.4 (95% CI 1.2-4.7), showing that the association of bladder cancer with employment in the petroleum (fuel) industry was not associated with the smoking status of the cases. Among those who never smoked, the odds ratio was 5.6; the confidence interval was not reported by the authors.

The major limitation of this work is the authors' partial selection of the control population from a urology clinic. Patients from a urology clinic may have conditions that have etiological features in common with bladder cancer. Specifically, cystitis (Howe et al., 1980; Dunham et al, 1968; Wynder et al., 1963), urinary stones (Wynder et al., 1963), and obstructive lesions from prostatic disease (Dunham et al., 1968) have all been found to be bladder cancer risk factors. If these conditions (i.e., cystitis, urinary stones, and obstructive lesions from prostatic disease) are associated with exposure to gasoline, the selection of controls with these conditions may have resulted in an underestimation of the relative risk.

Other limitations are a lack of information on gasoline exposure or job titles, no analysis of latency or length of employment, a lack of detail on the data collection procedures, and no adjustment for other high-risk occupations identified by the authors as significant risk factors (work in the dye industry and work in the plastics industry).

Thus, this study provides insufficient evidence for the carcinogenicity of gasoline vapors.

4.2.2.5. McLaughlin et al. (1984)--A population-based case-control study of renal cell carcinoma was conducted by McLaughlin et al. (1984). This study was also presented at a workshop on the renal effects of petroleum hydrocarbons (McLaughlin, 1984). Cases were white residents, ages 30 to 85, of the seven-county Minneapolis-St. Paul, Minnesota, SMSA who were diagnosed with renal cell carcinoma (ICD-8 189.0) from January 1, 1974, to June 30, 1979. Cases were identified from records obtained from all hospitals in the SMSA and from the Mayo Clinic 70 miles away. The authors believed that "complete case ascertainment" was achieved, resulting in the identification of 506 cases (sex not specified). Next-of-kin interviews were obtained for all cases that were deceased (237) or too ill to be interviewed (14). Of the cases ascertained, interview data were obtained for 495 (98%) cases, 313 males and 182 females.

An age- and sex-stratified random sample of white controls, ages 30 to 64, was selected from the telephone listings of the SMSA (additional details on this sampling frame were not provided). An age- and sex- stratified systematic sample of white controls, ages 65 to 85, was selected from Medicare listings for the SMSA. A total of 714 population-based controls were identified from these two sources; of these, interviews were obtained from 697 (98%).

To evaluate the possible bias of proxy interviews, a supplementary death certificate control group was randomly selected from state mortality records for the SMSA and frequency-matched to the cases on the basis of sex, age at death, and year of death. Excluded as controls were those persons whose cause of death was urinary tract cancer. Of the 495 supplementary controls identified, next-of-kin interviews were obtained for 493 (98%).

In-person interviews were conducted in the homes. For 14% of the subjects who had moved out of the study area or who could not be interviewed at home, interviews were conducted by telephone. Data were collected on demographic and

ethnic variables; diet, beverage, and smoking history; drug use; and medical, occupational, and residential history. "Exposures after 1973" were excluded from the analysis. Details as to which exposures were excluded, and why, were not reported by the authors.

Odds ratios were calculated to estimate relative risk (Fleiss, 1981). Confounding was controlled by calculating summary odds ratios by the maximum likelihood method. Confidence intervals were calculated by a modification of Cornfield's exact method (Gart, 1970). The logistic regression procedure was used for further multivariate analysis (Breslow and Day, 1980). Dose-response effects were tested with the Mantel extension test for linear trend. All odds ratios were adjusted for age and calculated with data for all cases compared to the population-based controls. To evaluate differences by respondent status (i.e., personal or next-of-kin), odds ratios were also calculated adjusting for respondent type by comparing directly interviewed cases to directly interviewed population-based controls and comparing next-of-kin cases to next-of-kin interviewed death certificate controls.

Renal cell carcinoma risks were assessed for 12 industries of usual employment and 28 industries or occupational activities "associated with high risk for urinary tract cancer." None of these was found to be statistically significant; however, risks for employment in the chemical and petroleum industry were elevated (OR = 1.4) among males even after adjusting for age and cigarette smoking. Risks were also elevated for males employed in the agricultural industry (OR = 1.4) and the food products industry (OR = 1.4).

Risks were also assessed for 25 occupational "materials previously linked to urinary tract cancer." Of the 25, only one--petroleum, tar, and pitch products--exhibited a significant ($p = 0.046$; McLaughlin, 1984) excess in risk among males even after adjusting for age and smoking (OR = 1.7, 95% CI 1.0-2.9).

This risk appeared greater for those exposed to petroleum products for 20 or more years (OR = 2.6, 95% CI 1.2-5.7) than for those exposed for less than 20 years (OR = 1.1, 95% CI 0.05-2.5). (The p value for a test of linear trend was not reported.) Risks were also elevated among females (OR = 4.6) but not significantly. The authors report that adjusting for respondent status (i.e., personal or next-of-kin) made "no appreciable change" in these results.

Renal cell carcinoma risks were also assessed for several other risk factors. Many exhibited significant excesses. A significant ($p < 0.01$) dose-response trend was observed among both males and females for increasing levels of cigarette smoking; risks were relative to those who never used tobacco products on a "regular basis," and all odds ratios were adjusted for age. Each of the three point estimates for females were also significant (light smoking, OR = 1.8, 95% CI 1.0-3.9; moderate smoking, OR = 1.9, 95% CI 1.0-3.5; heavy smoking, OR = 2.1, 95% CI 1.1-4.6). The point estimate for males in the heavy cigarette smoking category was also significant (OR = 2.3, 95% CI 1.4-3.8).

A significant ($p < 0.01$) dose-response trend for progressive weight gain, as measured by quartiles of the Body Mass Index (BMI) (i.e., weight/height^2), was observed for females after adjusting for age and smoking (OR = 1.2, 95% CI 0.6-2.0; OR = 1.7, 95% CI 0.9-2.9; OR = 2.3, 95% CI 1.3-4.1). Risks were relative to those in the lowest quartile. This pattern was not observed in males.

All remaining analyses were adjusted for age and smoking in males and for age, smoking, and relative weight in females.

A statistically significant increase in risk was associated with increasing duration of use of phenacetin-containing analgesics among females (p for trend < 0.05). After adjusting for respondent status (i.e., personal or next-of-kin), the risk associated with long-term use was reduced to 0.8 in males and

2.0 in females. A statistically significant positive trend remained among females.

Among males, a significant risk was also associated with self-reported urologic diseases diagnosed before 1970: kidney infection (OR = 2.8, 95% CI 1.3-5.7), bladder stone (OR = X, 95% CI 1.6-X), kidney stone (OR = 2.3, 95% CI 1.1-4.5), and kidney cysts (OR = 9.2, 95% CI 1.8-62.0). Among females, a significant odds ratio was observed for kidney infection (OR = 2.2, 95% CI 1.1-4.4), and a borderline excess was observed for kidney cysts (OR = X, 95% CI 1.0-X, Fisher Exact Test). The authors stated that adjusting for respondent status (i.e., personal or next-of-kin) tended to increase the risk estimate. Self-reported cardiovascular diseases (i.e., high blood pressure and stroke) were also found to be significant risk factors in males (OR = 1.9, 95% CI 1.3-2.8, and OR = 3.5, 95% CI 1.9-10.6, respectively). Statistically nonsignificant excesses were observed among the females for high blood pressure (OR = 1.5), stroke (OR = 2.8), and diabetes (OR = 1.8).

Risks were elevated in both sexes for German and Irish heritage (i.e., both parents were of the same ethnic background relative to those born in the United States and who were not of the same ethnic background). Odds ratios among the German and Irish males were statistically significant (OR = 2.2, 95% CI 1.1-4.2, and OR = 3.5, 95% CI 1.0-12.0, respectively). Odds ratios among the German and Irish males were elevated ($p > 0.05$) (OR = 1.5 and 1.9, respectively). Risks were also elevated among both sexes for both those with Scandinavian (male OR = 1.3; female OR = 1.3) or Czechoslovakian (male OR = 1.3; female OR = 1.8) heritage, although none of these was significant. Adjusting for respondent status (i.e., personal or next-of-kin) appeared not to change the results.

Coffee and tea consumption appeared unrelated to risk in males. There was

an excess risk for heavy tea consumption (OR = 3.4, 95% CI 1.48.9) in females, and no risk was apparent for coffee consumption. The use of diet soda or artificial sweeteners was associated with a statistically nonsignificant excess risk in males (OR = 1.8); a dose-response trend was not observed. No excess was seen among females. Risks for beer consumption were elevated in both sexes, although no clear trend was ascertained. Wine and hard liquor appeared not to be associated with an increased risk of renal cell carcinoma.

To assess a possible protective effect for renal cell carcinoma, nutrient indices for intake of vitamin A, retinol, carotene, and vitamin C were developed. The authors reported that "there was no clear trend of decreasing risk with increasing consumption except perhaps for carotene and vitamin C in men." Additional details were not presented. Increasing broccoli consumption among females was associated with a lessening in risk ($p < 0.05$). A positive dose-response trend ($p < 0.05$) was observed for meat consumption in both sexes.

The authors used a logistic regression analysis to examine the effects of exposure to petroleum, tar, and pitch while simultaneously controlling for the effects of age, cigarette smoking, relative weight (as measured by the BMI), phenacetin use, ethnicity, kidney infection, kidney stones, and coffee, tea, beer, and meat consumption. Risks were similar to those of the stratified analysis with a regression OR of 1.6 (95% CI 0.92.7) compared to the stratified OR of 1.7 (95% CI 1.0-2.9) for males. The evaluation of risk among females was statistically nonsignificant (OR = 4.6). Logistic regression results were also similar to the stratified analysis; smoking, relative weight, kidney infection, and Scandinavian heritage were all found to be statistically significant after simultaneously controlling for all the other confounders.

This is a well-conducted study. The case identification methods used were good, and the response rate for both cases and controls was excellent.

The major limitation of this study is the lack of any information on gasoline exposure. Thus, this study provides insufficient data on the association of renal cell carcinoma and gasoline; however, this study does provide evidence of an association of renal cell carcinoma and exposure to petroleum, tar, or pitch products among those exposed 20 or more years.

4.2.2.6. McLaughlin et al. (1983)--In conjunction with the authors' case-control study of renal cell carcinoma (McLaughlin et al., 1984), a population-based case-control study of renal pelvis cancer was conducted (McLaughlin et al., 1983). This study was also presented at the workshop on the effects of petroleum hydrocarbons (McLaughlin, 1984). The study area, period of study, methods of data collection and analysis, and the control population were exactly the same as previously reported in this review (McLaughlin et al., 1984).

Cases were white residents of the area who were diagnosed with renal pelvis cancer (ICD-8 189.1). Of the 78 cases ascertained, interviews were obtained for 74 (98%); 73 of these were histologically confirmed, and 70 were transitional cell carcinomas. Fifty percent of the cases were deceased by the time of interview. Next-of-kin respondents provided interview data for these cases. The final study population consisted of 74 cases (50 males, 24 females) and 697 controls (428 males, 269 females).

A significant ($p < 0.001$) dose-response was observed for increasing amounts of cigarette smoking (measured as pack-years) in both sexes after adjusting for age. Not only was the trend significant, but each of the point estimates was significant among males (light smoking, OR = 5.5, 95% CI 1.425.5; moderate smoking, OR = 9.6, 95% CI 2.5-43.4; heavy smoking, OR = 10.7, 95% CI 2.7-48.9) and females (light smoking, OR = 4.9, 95% CI 1.2-20.2; moderate smoking, OR = 7.6, 95% CI 1.9-31.3; heavy smoking, OR = 11.1, 95% CI 1.868.7).

Additional analyses adjusted for age and cigarette smoking. Renal pelvis cancer risks were assessed for 13 industries of usual employment; none revealed a significant association. Risks were also assessed for 21 "potentially high-risk materials suspected to be related to urinary tract cancer." The risk for exposure to petroleum, tar, or pitch was elevated (OR = 2.4), though not significantly. Excess risks were significantly associated with exposure to coal or natural gas (OR = 2.9, 95% CI 1.0-8.2) and mineral or cutting oils (OR = 2.8, 95% CI 1.1-7.0). Statistically nonsignificant elevations were observed for herbicides (OR = 3.4), organic solvents (OR = 2.4), paint thinners (OR = 1.6), pesticides, rodenticides, or insecticides (OR = 3.0), rubber dust (OR = 2.5), soot (OR = 3.0), welding or soldering material (OR = 1.7), pigments (OR = 2.3), and leather dust (OR = 6.9).

Persons who used drugs containing phenacetin or acetaminophen on a regular basis for periods of 3 or more years were at increased risk (male OR = 3.9; female OR = 3.7), but the excesses were not statistically significant. Females who used estrogen-containing drugs were also at increased risk (OR = 2.7, $p > 0.05$).

Males who drank coffee were at an increased risk (defined as those who ever drank coffee, OR = 1.6, $p > 0.05$); a dose-response pattern was not observed. There was no apparent increased risk for coffee consumption for females. A significant ($p < 0.001$) dose-response trend was observed for increasing consumption of tea in females; risks for females who drank three or more cups per day were very high (OR = 18.8, 95% CI 5.3-68.5) even after adjusting for age and cigarette smoking. Tea consumption was not a risk factor in males. Adjustment for respondent status (i.e., personal or next-of-kin) did "little" to alter these results.

This is a well-conducted study on a cancer about which little was previ-

ously known. As with many of the studies cited earlier, the major limitation is a lack of exposure information on gasoline. Risks for the material exposures were not assessed by duration of exposure or latency. This is unfortunate because limiting analysis to those exposed to petroleum, tar, or pitch for 20 or more years may have revealed a significant excess, a pattern that was observed for renal cell carcinoma (McLaughlin et al., 1984). In conclusion, this study provides insufficient evidence of an association between renal pelvis cancer risk and gasoline exposure.

4.2.2.7. Pancreatic Cancer Mortality Studies in Louisiana

4.2.2.7.1. Pickle and Gottlieb (1980). Death certificates of 876 persons (399 white males, 259 white females, 125 black males, and 93 black females) who died of pancreatic cancer between 1960 and 1975 in 19 parishes of Louisiana were matched to death certificates of persons dying of other causes. Each certificate was individually matched by sex, race, age (within 5 years), year of death (within 1 year), and parish of usual residence. Information abstracted from each death certificate included usual residence and usual occupation and industry. Data handling methods were the same as those used for the Gottlieb and Pickle (1981) study described above.

Crude odds ratios were calculated (Woolf, 1954; Haldane, 1955) by sex and race for pancreatic cancer risk associated with 16 industrial categories, 6 occupation groups, and residential proximity to 5 industries, including food processing, sawmills, chemical manufacturing, oil refining, and paper. Confidence intervals were reported in the form exp [ln $\theta \pm 2$ std error (ln θ)] where θ is the point estimate of relative risk (i.e., approximately 95% confidence intervals). Positive associations were examined in more detail by logistic regression techniques.

The odds ratio for white males was elevated in the oil refining industry

(OR = 2.11, CI 0.86-5.20), but this was not significant. The odds ratios were elevated for other industries of employment, including metal and transport manufacturing (OR = 1.23, CI 0.34-4.40), paper manufacturing (OR = 1.77, CI 0.77-4.04), chemical manufacturing (OR = 1.16, CI 0.393.41), and the communications and utilities industries (OR = 1.58, CI 0.40-6.25).

When studied by usual occupation, elevated odds ratios were seen for white female white-collar workers (OR = 1.37, CI 0.78-2.42), white and black males who were classified as operatives (white OR = 1.17, CI 0.77-1.79; black OR = 1.26, CI 0.48-3.28), and white male farmers (OR = 1.16, CI 0.82-1.65). The only significant odds ratios occurred for married white female white-collar workers at 3.09 (CI 1.04-9.17). The numbers of cases and controls for each group were not given.

Both white males and white females showed elevated risks for pancreatic cancer associated with residence near oil refineries (male OR = 1.16; female OR = 1.19). Confidence intervals were not reported. Elevated risks were also seen for black males living near chemical manufacturers (OR = 1.20) and for black females living near oil refineries (OR = 1.42) and paper manufacturers (OR = 1.33). The authors did not give the statistical significance of these findings. The association between pancreatic cancer and nearness of residence to the paper, chemical, and oil industries was further examined by calculating the distance to each plant within 3 miles of the individual's residence. However, results were inconsistent, and confounding of duration at residence made any association inconclusive.

There are limitations to this study. Occupations within oil refineries that may be indicators of gasoline exposure were not presented. Death certificate data are for the most part only fragmentary, depicting residence and occupational histories for only a portion of the individual's lifetime. Data

were not available from this type of study on possible duration of exposure or latency. Possible confounding effects of risk factors such as smoking and alcohol consumption were not taken into consideration. Thus, this study is inadequate to link gasoline exposure with pancreatic cancer.

4.2.2.7.2. Gottlieb and Carr (1981). Data from the previous Pickle and Gottlieb (1980) study on pancreatic cancer were reanalyzed; this new analysis is reviewed here as Gottlieb and Carr (1981). Odds ratios and 95% confidence intervals for white male oil refinery workers were recalculated. It was not possible to determine the methods used. Risks for the oil refinery workers were two times greater than those of workers not employed as oil refinery workers (OR = 2.21, 95% CI 0.836.48). Fifteen of the cases and seven of the controls were employed as oil refinery workers. For the same study data, Pickle and Gottlieb (1980) originally reported an odds ratio of 2.11 (95% CI 0.86-5.20). However, neither estimate, 2.21 or 2.11, showed a significant excess in pancreatic cancer risk.

This study has the same limitations as those previously reported for Pickle and Gottlieb (1980). Thus, this study is inadequate to link gasoline exposure with pancreatic cancer.

4.2.2.8. Wigle (1977)--Wigle reported on a lung cancer case-control study and a lung cancer ecological study conducted in the urban centers of the cities of Sarnia and London in Canada during the period 1969-73. Only the case-control study is reported here. Cases were all deceased males whose cause of death was cancer of the trachea, bronchus, and lung (ICD-A 162). Controls were deaths other than lung cancer and were randomly selected by computer from the same mortality tapes and individually matched to the cases on the basis of sex, city, 5-year age group, and 5-year calendar period.

The final study population consisted of 348 cases and an equal number of

controls. The distribution of the control deaths by major cause was reported to be not significantly different ($p = 0.16$) from what was expected based on the age-, sex-, and cause-specific proportionate mortality frequencies for the two cities combined for the period 1969-73 (tested with a chi-squared statistic with 11 degrees of freedom; additional details were not reported).

Information on the study population was obtained from microfilmed death certificate records and included information on dates and places of birth, death, and residency; marital status; occupation, including kind of work done during "most of working life" and kind of industry; immediate, antecedent, and underlying causes of death; information from autopsy; and history of surgery. The 1971 Census of Canada Occupation Classification Manual was used to code occupations. The Standard Industrial Classification Manual of Canada was used to code industry of occupation. Residence was coded to census tracts. It was not possible to determine if the matching criterion for "city" was place of death, place of residence, or usual residence.

The "major lifetime" occupation was recorded on the death certificate for approximately 85% of the cases and controls. Approximately 82% of the cases and 85% of the controls had information on the death certificate to indicate that the decedent was employed at least 10 years in the recorded occupation.

The author reported a high risk of lung cancer for males employed in motor vehicle repair shops; five cases and no controls were so employed. No estimate of relative risk of lung cancer from working in motor vehicle repair shops was presented, but it can be calculated by Anscombe's (1956) method (i.e., adding 1/2 to each cell) as 11.16, relative to those not employed in vehicle repair shops. Those employed in petroleum refining appeared not to exhibit an excess risk of lung cancer (5 cases and 12 controls were exposed).

The overriding limitation of this study is the lack of statistical control

for smoking. Without smoking history information on the study population, it is virtually impossible to interpret the data from a lung cancer case-control study. Other limitations include a lack of information on gasoline exposure, no analysis for latency or length of employment, and no control for other confounding factors, e.g., other high-risk occupations or industries. These limitations make this study inadequate as a basis for determining the carcinogenicity of gasoline.

4.2.2.9. Lung Cancer Mortality Studies in Louisiana

4.2.2.9.1. Gottlieb et al. (1979). Due to exceptionally high mortality from lung cancer in southern Louisiana and correlation studies linking lung cancer to occupations found in southern Louisiana, Gottlieb et al. (1979) undertook a case-control study to determine the influence of occupational, residential, and ethnic factors associated with lung cancer. Nineteen Louisiana parishes were selected either because they had elevated rates of lung cancer among white males during 1950-69 and/or because petroleum, chemical, or paper manufacturing were industries in the parish. Death certificates from 3,327 people who died of lung cancer between 1960 and 1975 were obtained and matched to the death certificates of persons who died of causes other than cancer for sex, race, age within 5 years, year of death within 1 year, and parish of usual residence. Information concerning name, birthplace, residence at time of death, employment industry, usual occupation, marital status, and parent's names were abstracted from each death certificate. Occupation and industry were coded using the 1970 U.S. Bureau of the Census Index of Occupations and Industries. Each person was classified into 1 of 22 industrial categories and 1 of 9 occupational categories. Place of usual residence was used to classify each person as to proximity to seven industries. Likelihood of Acadian ancestry was also determined for each individual and coded as probable, possible, or unlikely.

Odds ratios were calculated by the Woolf (1954) and Haldane (1955) methods (i.e., adding 1/2 to each cell) for each sex and race category (male, female and black, white) for each of the 22 industrial codes, 9 occupational codes, 7 proximity to industry codes, and the 3 Acadian ancestry categories. Positive associations were examined in more detail by logistic regression models.

Significantly ($p < 0.05$) high odds ratios were seen for the following occupational categories: fishermen (OR = 1.81, 95% CI 1.22-2.69), transport equipment manufacture (OR = 2.20, 95% CI 1.14-4.25), and transportation services (OR = 1.27, 95% CI 1.02-1.58). Smaller increases were seen for oil refining (OR = 1.32, 95% CI 0.93-1.87), auto repair businesses (OR = 1.33, 95% CI 0.90-1.97), and metal and machinery manufacturing industries (OR = 1.27, 95% CI 0.75-2.14). Significant ($p < 0.05$) odds ratios were also calculated for older (age greater than 62) workers in fishing (OR = 1.7, 95% CI 1.02-2.86) and oil production (OR = 1.6, 95% CI 1.03-2.61) and younger workers (age less than 63) in the fishing and transportation industries (OR = 1.9, 95% CI 1.00-3.42, and OR = 2.7, 95% CI 1.21-6.22, respectively). Younger workers in the auto repair business showed a doubling of risk (OR = 2.0, 95%); this was considered of borderline significance (95% CI = 0.96-4.24). Logistic regression showed a threefold increase (OR, observed numbers, and CI not reported) in risk associated with oil exploration and drilling in workers over 62 years of age in parishes with petroleum or paper industries. Confounding factors controlled for with the use of the logistic model included age, marital status, year of death, birthplace, parish of residence, Acadian ancestry, three broad occupational categories (white- and blue-collar workers and others), and interactions between these variables.

Odds ratios for usual occupation were significantly ($p < 0.05$) increased for white male craftsmen (OR = 1.16, 95% CI 1.01-1.34), operators (OR = 1.27,

95% CI 1.04-1.55), and white female clerical workers (OR = 3.31, 95% CI 1.11-9.85). Elevated risks ($p > 0.05$) were estimated for all four sex-age groups for persons living in close proximity to oil refineries; risk estimates ranged from 1.16 (95% CI 0.97-1.38) for white males to 1.88 (95% CI 0.99-3.57) for black males. This could not be explained by employment in the industry, although risks were elevated for oil refinery workers, particularly in parishes that had both petroleum and chemical industries. Among those with probable Acadian ancestry who died at 63 years of age or older, lung cancer risks were increased approximately 1.5-fold in males and twofold in females.

This case-control study showed a number of occupations and industries linked to lung cancer risk. Risks for persons living close to oil refineries were elevated for the four age-race groups, but these were not significant. Although risks were considered of borderline significance for males, risks were also considered borderline significant for young males employed in the auto repair business. However, results from this study cannot be used to indicate that gasoline is associated with lung cancer. Information presented on job categories was too broad to indicate if a job would have potential for gasoline exposure, except perhaps among males employed in the auto repair business. In addition, death certificate studies are inherently limited. Industry, occupation, and residence data provide at best only a crude description with no details on changes, duration, or latency for these variables. A study of lung cancer that does not include the effects of cigarette smoking, which is not available from death certificates, may grossly confound the results. This study indicates that more detailed work is needed to link cancer with petroleum and gasoline exposure.

4.2.2.9.2. Gottlieb (1980). This study investigated lung cancer and the petroleum industry in Louisiana. The data collection methods and the study

population were the same as that previously reported (Gottlieb et al., 1979) except that this study reported on males only (2,161 white, 642 black). The author failed to explain why this study population (Gottlieb, 1980) had one less black male death than the population reported in the earlier study (Gottlieb et al., 1979). Relative risks were estimated along with 95% confidence intervals by modification of Miettinen methods (Rothman and Boice, 1976).

A total of 200 cases (181 white, 7 black, and 12 cases in which occupation was not specified) were employed in the petroleum industry, 125 in mining and 75 in refining. Of the controls, 170 (153 white, 5 black, and 12 controls in which occupation was not reported) were employed in the petroleum industry, 112 in mining, and 58 in refining. The overall relative risk for lung cancer in the petroleum industry was significant: 1.19 (95% CI 1.05-1.35). For the subcategory of oil-field workers, welders, operators, boilermakers, and painters, the estimate of relative risk was also significant (OR = 2.33, observed cases = 69, 95% CI 1.42-3.85). When dichotomized on age at 60 years, those classified as oil-field workers, both the younger (OR = 1.36, 95% CI 0.24-22.48) and older workers (OR = 1.86, 95% CI 0.91-3.8), showed increases in relative risk. However, these were not significant. The odds ratio for those classified as skilled workers in pumping or refining was barely significant ($p < 0.05$) at 2.43 (95% CI 1.01-5.86).

The controls were generally younger than the cases, with 59% of the controls under 34 compared to 35% of the cases. The authors stated that this reflects premature death from causes other than lung cancer, such as accidents in individuals who might have later become cases. This may underestimate the risk for lung cancer in this study population.

This study has shown that certain occupations in the petroleum industry such as welders, operators, boilermakers, painters, oil-field workers, and

workers in pumping and refining may be at increased risk of lung cancer. However, this study is limited by the same problems as those in the previously reported study. There was no control for confounding factors such as smoking. There are inherent problems in death-certificate studies. Information on gasoline exposure could not be determined from the job title information presented on death certificates. Thus, this study is inadequate to link gasoline exposure to lung cancer.

4.2.2.9.3. Gottlieb and Carr (1981). Gottlieb and Carr (1981) presented a reanalysis of the principal investigator's original lung cancer data (Gottlieb et al., 1979; Gottlieb, 1980).

Odds ratios and 95% confidence intervals were recalculated for males (both races combined) whose usual occupation was in the oil refinery industry or the petroleum industry. The authors did not report the methods used to calculate these odds ratios or confidence intervals.

A comparison of the authors' original findings (Gottlieb et al., 1979; Gottlieb, 1980) and recalculated findings (Gottlieb and Carr, 1981) is shown in Table 4-3. Initially, findings were not reported as significant for workers in the oil refinery industry; however, significant findings were later reported after the data were recalculated (OR = 1.32, 95% CI 0.93-1.87 and OR = 1.31, 95% CI 1.04-1.65, respectively). The increase in risk appeared limited to males older than 63 (OR = 1.90, 95% CI 1.13-3.19). The authors present no rationale for these differences.

A serious limitation to Gottlieb and Carr's reanalysis is that it is not possible to duplicate, with the available information, their calculations of the 95% confidence intervals. Additional limitations to this study were previously presented under Gottlieb et al. (1979) and Gottlieb (1980). Thus, this study is inadequate to link gasoline exposure to lung cancer.

TABLE 4-3. COMPARISON OF GOTTLIEB'S ORIGINAL AND RECALCULATED ODDS RATIOS AND CONFIDENCE INTERVALS FOR LUNG CANCER AMONG ALL MALES, BY AGE

	Cases	Controls	Original findings[a,b] OR (95% CI)	Recalculated findings[c] OR (95% CI)
Oil refining industry	76	58	1.32 (0.93 - 1.87)[a]	1.31 (1.04 - 1.65)
< Age 63	38	38	1.1 (0.71 - 1.79)[a]	0.99 (0.79 - 1.25)
≥ Age 63	38	20	1.7 (0.98 - 2.94)[a]	1.90 (1.13 - 3.19)
All occupations in petroleum	200	170	1.19 (1.05 - 1.35)[b]	1.2 (1.04 - 1.34)
Skilled pumping and refining occupations	54	36	Not reported	1.5 (1.08 - 2.07)
< Age 60	29	26	1.32 (0.92 - 190)[b]	1.1 (0.82 - 1.50)
≥ Age 60	25	10	2.43 (1.01 - 5.86)[b]	2.5 (1.01 - 6.17)
Total	2,805	2,805		

[a]Gottlieb et al. (1979); ORs and CIs were calculated by using Woolf's (1954) and Haldane's (1955) methods.

[b]Gottlieb (1980); ORs and CIs were calculated by using Rothman and Boice's (1976) modification of Miettinen's methods.

[c]Gottlieb and Carr (1981); methods used to calculate ORs and CIs were not reported. Using the available data, it is not possible to determine what methods were used by the authors.

4.2.2.10. Other Cancer Mortality Studies in Louisiana

4.2.2.10.1. Gottlieb and Carr (1981). In addition to the previously reviewed bladder, pancreatic, and lung cancer data, Gottlieb and Carr (1981) reported on a second case-control study designed to determine if drinking water sources were associated with cancer.

The study area was parishes in southern Louisiana, many of which were included in the bladder, pancreatic, and lung cancer studies; however, this study area also included urban parishes to maintain a "balance" in availability of subjects by water source. The data processing methods were the same as previously described (see Gottlieb and Pickle, 1981). Cases were identified during the period 1960-75 and were decedents whose cause of death was brain (N = 497) or kidney (N = 351) cancer. These were matched to non-cancer decedents (i.e., controls) on the basis of age at death ($\pm$ 5 years), years of death ($\pm$ 1 year), race, and sex. Results were also presented for esophageal cancer and leukemia; however, the sizes of these study populations were not reported.

For individuals with occupations in the petroleum or petrochemical industry, risks were significantly elevated for kidney cancer (OR = 2.27, 95% CI 1.01-5.43) and for esophageal cancer (OR = 3.19, 95% CI 1.35-8.37, $p < 0.005$). Leukemia risks were considered of borderline significance (95% CI 0.99-2.92, chi-squared statistic $p < 0.05$) and were observed to be 70% greater than for those not employed in these industries (1.70, observed cases = 41, observed controls = 24).

The risk of brain cancer for workers in the chemical industry was significantly elevated (OR = 3.52, 95% CI 1.09-14.8). Kidney cancer risks were elevated (OR = 6.06), though not significantly (95% CI 0.73-279.6, $p < 0.10$).

This study has the same limitations as the authors' other Louisiana case-control studies. Death certificate studies have inherent problems; data are

not available on length of exposure or latency, and confounding variables such as smoking cannot be controlled for. It was not possible to determine actual gasoline exposure or determine if petroleum-related exposures were for refining or petrochemical occupations. Thus, this study is inadequate to link gasoline exposure to cancer.

4.2.2.11. Brandt et al. (1978)--The authors reported on the occupational exposure to petroleum products of 50 male subjects, ages 20 to 65, diagnosed with acute non-lymphocytic leukemia (ANLL) at the University Hospital at Lund, Sweden, during the period 1969 through May 1977. Their occupational exposure to petroleum products was compared to the exposure of subjects in three clinical groups (controls): (1) 100 consecutive male patients, ages 20 to 65, treated for nonmalignant disorders from the outpatient department; (2) 100 consecutive male patients, ages 20 to 65, treated at the allergic diseases outpatient department; and (3) 22 males, ages 20 to 62, with chronic myeloid leukemia (CML) and 10 males ages 41 to 63, with chronic lymphocytic leukemia (CLL) seen during the same period as the patients with ANLL.

The authors found that 36% (18 of 50) of the cases were occupationally exposed to petroleum products, whereas only 10% (10 of 100) of each of the outpatient control groups were similarly exposed. Typical petroleum-related exposures reported were workers at filling stations, bus or truck drivers, operators of excavating machines or power saws, and road haulers. The difference in exposure between the cases and controls was significant ($p = 0.002$, Fisher Exact Test). The differences between the occupational exposures of the cases and the CML controls (3 of 22 were exposed) or the CLL controls (0 of 9 were exposed) were also significant ($p = 0.04$ and $p = 0.03$, respectively).

The authors did not estimate the risk of the exposed group relative to the nonexposed group in their study population; however, using the authors' data,

it can be estimated that the ANLL cases are five times more likely (crude OR = 5.06) to have worked in petroleum-related occupations than either of the outpatient control groups and four times more likely (crude OR = 4.3) than the CML controls.

This study provides insufficient data and insufficient analysis with which to draw conclusions on the causal association of gasoline vapors and acute non-lymphocytic leukemia. The authors undertook this study after discovering that several of the ANLL patients worked in petroleum occupations. Hence, to be objective the investigators should have chosen a different time period from which to select cases. In addition, the authors provided no details on the control population. The category of petroleum-related occupations was very broad and included exposures other than gasoline. Actual gasoline exposures were not quantified. No latency analyses were conducted. There were no controls for confounding factors such as age.

4.2.2.12. Plotnikov (1978)--Plotnikov reported on the results from a retrospective epidemiologic study of leukemia and lymphogranulomatosis (LG). This study was originally reported by the author in Russian (1978); reviewed here is an English abstract of that paper (CANCERLINE, 1978).

Leukemia or LG was diagnosed in 1,165 patients (acute leukemia, 314; chronic myeloid leukemia, 220; chronic lymphoid leukemia, 388; LG, 239) in Kuibyshev Province, U.S.S.R., between 1965 and 1974. These patients answered a detailed questionnaire concerning occupational exposures. A control population was used for comparison purposes, but the only detail provided on control selection was that controls were "healthy" individuals.

Petroleum industry employees and employees who had occupational exposure to dyes or organic solvents were 1.3 times more likely to be cases rather than controls. It was also reported that cases were exposed more frequently to

ionizing radiation or ultrahigh-frequency electromagnetic fields than were controls. Conclusions were that these exposures increased relative risk for leukemia and LG; however, relative risk estimates were not reported in the English abstract.

The lack of any methodologic detail or relative risk estimates precludes consideration of these data. Thus, this study is considered an inadequate basis upon which to determine the carcinogenicity of gasoline.

4.3. EPIDEMIOLOGIC STUDIES IN PROGRESS

4.3.1. Historical Prospective Mortality Study of Employees Exposed to Downstream Gasoline in the Petroleum Industry

The American Petroleum Institute (API) has undertaken a historical prospective mortality study of marketing employees exposed to downstream gasoline in the petroleum industry. This work is being performed by Environmental Health Associates, Inc. (EHA) (Wong and Morgan, 1984 Unpublished). Marketing employees are those workers involved in the bulk distribution operations at gasoline distribution centers, excluding service stations. These workers are primarily exposed to downstream gasoline (or gasoline after processing of petroleum) during the flow into tank trucks and from leaking fill lines and gasoline spillage. This study will involve 50,000 workers with a minimum of 6 months' employment. Identifying data and employment history will be retrieved and coded, with vital status ascertainment conducted through the SSA using the National Death Index as a supplemental means of follow-up. Cause-specific SMRs will be calculated using the U.S. national age-, cause-, race-, and sex-specific mortality rates for 5-year time periods. The study is just under way, and it is estimated that it will take approximately 4 years to complete.

4.3.2. Case-Control Study of Kidney Cancer and Hydrocarbon Exposure Among Petroleum Company Workers

A case-control study has been undertaken by Epidemiology Resources, Inc. (ERI), on behalf of the American Petroleum Institute (API). The study will evaluate the risk of kidney cancer in relation to occupational exposure to hydrocarbons, with particular attention given to those found in unleaded gasoline. A feasibility study recently done by ERI identified two case-control study populations judged to be feasible (ERI, 1985 Unpublished). One, a nested design, involves the utilization of existing cohorts of workers that had already been assembled at 7 of the 11 petroleum companies that have agreed to participate in the study. These companies already have the results of mortality follow-up, and some data have been reported (Theriault and Goulet, 1979; Hanis et al., 1982, 1985a, 1985b; Morgan and Wong, 1983 Unpublished; Wen et al., 1984a; Morgan and Wong, 1984 Unpublished; Divine et al., 1985; Nelson, 1985 Unpublished). The second study involves the analysis of death certificates through company mortality records. All participating companies maintain some sort of mortality registry, though extent of coverage varies from company to company. The use of both case-control study populations will serve to complement the limitations of each.

ERI will assess exposure to light hydrocarbons, such as those found in unleaded gasoline, by dividing the work category of "refinery work" into specific subcategories that permit a more detailed analysis of exposure while adjusting for the confounding effects of other petroleum products such as asbestos. To accomplish this task, job titles from each of the participating companies will be recoded to a uniform coding scheme. All job titles and/or departments, by company and plant for each study participant, would be so coded. The data collections phase has recently begun. API expects the case-control work to take

approximately 2 to 3 years to complete.

4.3.3. Registry of Mortality of Refinery Workers

The American Petroleum Institute is sponsoring a mortality study in refinery workers; it will be conducted by Environmental Health Associates, Inc. (EHA) (Wong et al., 1985 Unpublished). The objective of the study is to identify and monitor the mortality experience of refinery workers throughout the petroleum industry. Data collection will involve gathering of identifying information and work history for all eligible workers in participating refineries. The criteria for eligibility and the identity of the participating refineries were not available. The vital status of active and terminated employees and active annuitants will be ascertained through company identification for active employees and annuitants with positive evidence of death, and through the SSA and the National Death Index for terminated employees and annuitants without positive evidence of death. Under this study, an attempt may be made to consolidate Schottenfeld et al.'s (1981) previously collected data (from API's MSKCC Health Registry of Refinery Workers) with this new data (Weaver, 1986). The EHA mortality registry work is currently ongoing. Data are expected to be collected for a 10-year period (Weaver, 1986).

4.3.4. The Australian Petroleum Industry Health Watch Surveillance Program

This prospective cohort study, known as Health Watch, is being conducted by the Australian Institute of Petroleum Ltd. (AIP) in conjunction with the University of Melbourne, Department of Community Medicine (UM/DCM) (AIP-UM/DCM, 1983; Christie et al., 1984). The feasibility study was begun in 1979; actual data collection began in 1981 with a baseline cross-sectional survey of all eligible employees.

The study population includes all payroll employees who have worked at an Australian petroleum industry site having 10 or more employees, and who have

completed at least 5 years of employment in the petroleum industry. Transport drivers and office workers are included if their place of employment is physically an offshore drilling platform or a production, processing, storage, or manufacturing site. Excluded are all employees working in Head Offices. The study population is not fixed in numbers, since each year people who complete 5 years of service are added to the study population.

The baseline survey, carried out in 1979-80, obtained information on potential confounding variables. Data were collected on age, sex, previous employment, smoking and drinking history, and self-reported past medical history. Information on job descriptions was obtained by personal interview; all other data were obtained by self-administered questionnaire. Of the 12,500 eligible workers, 11,596 subjects (10,970 men, 626 women) completed the survey, representing a response rate of 92%.

Ultimately, Health Watch aims to incorporate directly measured exposure data into the system; however, this remains a long-term goal. Currently, precise job descriptions serve as indirect measures of exposure, and occupations are classified according to the system developed by the American Petroleum Institute (Tabershaw Occupational Medicine Associates, 1979). Employees in the Australian petroleum industry, particularly in refineries, typically carry out several tasks simultaneously. Therefore, workers are asked to apportion the amount of working time spent on each job task. These are coded separately for up to six tasks. If a person performs more than six tasks simultaneously, that person is coded "multiprocess." At each refinery site, and at one in every five job sites, a 10% sample of self-stated job descriptions are validated for accuracy.

Data are provided twice yearly by the oil companies on (1) the mortality of active employees and employees receiving pension benefits, (2) changes in

employee status (i.e., retired, terminated, or transferred), and (3) new employees. Death certificates for deceased employees are obtained from the states and coded to the ICD-9; a diagnosis of cancer is coded to the ICD-Oncology. ICD coding is undertaken by the Australian Bureau of Statistics. Follow-up status of the surviving study subjects is determined at the end of each calendar year. Tracing of terminated employees is by certified mail, and vital status is ascertained through the Government Statist of the State.

Cancer morbidity is self-reported by study participants and certified by the diagnosing physician, who supplies copies of relevant histological reports. Cancer morbidity information is also obtained from each State Cancer Registry. Non-cancer morbidity information is not obtained, since self-reported serious illness data was found to be unreliable during the feasibility stage of the study.

By the end of 1984, the Health Watch study population consisted of 9,142 persons (8,736 men, 406 women), representing 20,715 person-years of observation (AIP-UM/DCM, 1985). Of these, 47, or 0.005%, were lost to follow-up. Of the total study population of men, 27% were considered office workers; 25% worked in refining process; 20% in transport; 13% in maintenance; 5% in storage and handling; 5% in manufacturing, marketing, and packaging; 3% in offshore production; and 2% in chemical manufacturing. Approximately a third of the men were younger than 40, a third were ages 40 to 49, and a third were 50 or older (38%, 31%, and 31%, respectively).

Preliminary results are available on data collected as of December 31, 1984 (AIP-UM/DCM, 1985). Among the 9,142 subjects, 64 deaths (2 female) were observed. SMRs were calculated using the 1982 sex-, age-, and cause-specific Australian mortality experience as the standard. SMRs were not calculated if

the observed numbers of deaths or the expected numbers of deaths were less than five.

The SMR for all causes of death among male workers was a nonsignificant 61 (observed = 62, 95% CI 46-78). This deficit suggests the healthy worker effect. To further analyze this possibility, SMRs were also calculated using the mortality experience of a working population, i.e., Australian Government employees (AGRBO), as the standard. The SMR for males age 64 or younger, when compared to the AGRBO, was 104 (95% CI 79-134) for all causes of mortality.

Using the Australian mortality experience as the standard, the SMR among men for all causes of death by major job category revealed deficits for all job categories except storage and handling (SMR = 107, observed = 7, 95% CI 43-221). Significant deficits were observed for workers in refining (SMR = 38, observed = 9, 95% CI 17-71), transport (SMR = 50, observed = 9, 95% CI 23-94), and office work (SMR = 60, observed = 19, 95% CI 36-93). Using the AGRBO as the standard, nonsignificant excesses ($p > 0.05$) were observed for male workers (age < 65) in storage and handling (SMR = 196, observed = 7); marketing, manufacture, and packaging (SMR= 63, observed = 5), and maintenance (SMR = 141, observed = 11). The SMR among the male office workers (age < 65) was 100 (observed = 18), while deficits ($p > 0.05$) were observed among workers in refining occupations and transport occupations (SMR = 59, observed = 8, and SMR = 86, observed = 9, respectively).

Relative risks were calculated for all causes of mortality among the men, using the mortality experience of the petroleum industry office workers as the comparison population. Risks were again elevated ($p > 0.05$) for male workers in storage and handling (RR = 1.87); marketing, manufacture, and packaging (RR = 1.58); and among maintenance workers (RR = 1.36). Deficits ($p > 0.05$) were observed for workers in refining (RR = 0.64) and transport (RR = 0.82).

SMRs among men for major causes of death were calculated using the 1982 Australian mortality experience as the standard. The SMR for all cancers was 79 (observed = 22, 95% CI 49-119). Deficits ($p > 0.05$) were observed for all major causes of death, and for respiratory diseases the deficit was statistically significant (observed = 0, expected = 5.15, 95% CI 0-72). Mortality data by specific cause of death among the AGRBO population are not available; therefore, SMRs could not be calculated using the AGRBO as the standard.

The standardized incidence ratio (SIR) for all cancers was calculated using the Victorian Cancer Registry 1982 data as the standard. The SIR for men for all malignant neoplasms was 73; this was not significant (95% CI 46-109).

Relative risks were also calculated for all cancers by job category among men, using office workers as the reference population. The relative risk among maintenance workers was slightly elevated (RR = 1.13, 95% CI 0.34-3.75), and deficits ($p > 0.05$) were observed among refining (RR = 0.78) and transport (RR = 0.89) workers. Risks were not calculated for the remaining job categories because the number of observed deaths was less than five.

Health Watch estimates that by the year 1990, 85,000 person-years of observation will have accumulated. Future activities include the 1986 re-survey of petroleum industry employees. This re-survey will provide updated information on the present study population and collect baseline information on new employees. Also in preparation is a paper on the smoking behavior of the study population (AIP-UM/DCM, 1985). This may provide some very useful information, since smoking information on workers in the American petroleum industry is not available. It is anticipated that Health Watch will continue to issue annual reports on the study's progress.

At the present time, this study provides insufficient data on which to

evaluate the association between gasoline and cancer risk. However, study activities planned for the future include quantitative estimates of exposure. In addition, future analyses will be able to control for some very important confounding variables (e.g., smoking, alcohol). Thus, at some future time, the Health Watch project may provide sufficient data with which to evaluate the association between gasoline and cancer risk.

4.4. SUMMARY OF EPIDEMIOLOGIC STUDIES

Fifty-five studies were reviewed to determine if there is any epidemiologic evidence for an association between gasoline exposure and cancer risk. Since unleaded gasoline was only introduced in the mid-1970s, even recent epidemiologic studies are not likely to show an unleaded gasoline effect because of the long latency period generally associated with cancer. Therefore, this review was not limited to unleaded gasoline exposure but rather addressed any potential gasoline exposure.

Of the 55 studies reviewed, 7 evaluated the association between employment in the gasoline service industry and cancer risk, 25 assessed cancer risks in petroleum refineries, 19 evaluated employment in the petroleum industry as a risk factor, and 4 were epidemiologic studies currently in progress. The types of study design used were varied; 26 were case-control (hospital and population-based), 20 were cohort mortality, 1 was cohort morbidity, 5 were proportionate mortality, and 3 were nested case-control studies. Table 4-4 summarizes these studies, excluding the four studies that are currently in progress.

There is an unknown amount of overlap between study populations, especially among the refinery populations, since multiple studies were conducted at single refinery locations at about the same time. Therefore, the results reviewed here may not represent independent events. The known geographic overlap of study populations can be seen in Table 4-5. Locations for four nation-

TABLE 4-4. SUMMARY OF EPIDEMIOLOGIC STUDIES REVIEWED

Author	Study population/Comparison population	Type of study	Occupational exposure
Stemhagen et al. (1983)	Primary liver cancer cases/Patients selected from hospital records	Case-control	Gasoline service station employment
Silverman et al. (1983)	Lower urinary tract cancer cases/Sample of area telephone users and Medicare participants	Case-control	Gasoline service industry; garage workers and gas station attendants; trucking transporter of petroleum products
Mommsen et al. (1982; 1983a,b); Mommsen and Aagard (1983a,b; 1984); Mommsen and Sell (1983)	Bladder cancer cases/Registrants from the Denmark National Register	Case-control	Work with oil or gasoline; work with petroleum or asphalt
Domiano et al. (1985)	Renal cell carcinoma cases/Patients selected from hospital admissions records	Case-control	Gasoline service station employment
Lin and Kessler (1981)	Pancreatic cancer cases/Patients selected from hospital admissions records	Case-control	Employment in gasoline service stations and garages or the dry cleaning business
Lin and Kessler (1979)	Testicular cancer cases/Patients selected from hospital discharge records	Case-control	Employment in gasoline service stations; employment in garages
Milham (1983)	Gasoline station owners and attendants; gasoline and fuel truck drivers; fuel oil dealers; auto mechanics and repairmen/ Washington State's mortality experience	PMR	Usual lifetime occupation as gasoline station owners or attendants; gasoline or fuel truck drivers; fuel oil dealers; or auto mechanics or repairmen
Tabershaw-Cooper (1974 Unpublished, 1975 Unpublished)	Petroleum refinery hourly workers at 17 U.S. refineries/U.S. mortality experience	Cohort mortality	Employment in one of the refineries for at least 1 year; "high, "medium," or "low" hydrocarbon exposure
Hanis (1977)	Male employees of the Imperial Oil Co./ Canadian mortality experience; an internal "non-exposed" group; an internal "non-refinery" group	Cohort mortality	Employment by the company for at least 1 year if an active employee and 5 years if a terminated employee; daily exposure to crude petroleum, gas,or breakdown products; daily refinery site exposure

(continued on the following page)

TABLE 4-4. (continued)

Author	Study population/Comparison population	Type of study	Occupational exposure
Hanis et al. (1979)	Male employees of the Imperial Oil Co./ An internal "non-exposed" group; an internal "non-refinery" group	Cohort mortality	Employment by the company for at least 1 year if an active employee and 5 years if a terminated employee; daily contact with petroleum or its products, moderately exposed to petroleum or its products; employment daily on a refinery site
Theriault and Goulet (1979)	Male employees at a Canadian oil refinery plant/Quebec, Canada mortality experience	Cohort mortality	Employment at the refinery for 5 or more years
Thomas et al. (1980)	Decedent males who at their time of death were active members of the Oil, Chemical, and Atomic Workers International Union (OCAW) in TX/U.S. and Texas mortality experiences	PMR	Union membership and employment at a plant where the major operation was petroleum refining or production of petroleum products
Reeve et al. (1982)	Decedent males who had been members of OCAW Local 4-449 in Texas City, TX/U.S. mortality experience	PMR	OCAW Local 4-449 membership and employment at one of two petroleum refineries in Texas City, TX
Hanis et al. (1982)	Regular plant employees who worked at the Exxon Baton Rouge, LA refinery and chemical plant/U.S. mortality experience	Cohort mortality	Employment at the refinery or chemical plant for at least 1 month
Rushton and Alderson (1983)	Men who had worked at three oil distribution companies in Great Britain/ Combined mortality experience of England and Wales	Cohort mortality	Employment of at least 1 year at one of the oil distribution centers
Morgan and Wong (1983 Unpublished)	Employees at two Chevron refineries/ U.S. mortality experience	Cohort mortality	Employment of at least 1 year at one of the refineries
Morgan and Wong (1984 Unpublished)	Employees at a Mobil Oil Co. refinery in Beaumont, TX/U.S. mortality experience	Cohort mortality	Employment of at least 1 year at the refinery

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TABLE 4-4. (continued)

Author	Study population/Comparison population	Type of study	Occupational exposure
Thomas et al. (1984)	Decedent cases who were active or retired members of OCAW and whose cause of death was brain tumors, stomach cancer, or leukemia/Decedents selected from records of active and retired OCAW members, excluding those whose cause of death was the same as the cases' cause	Nested case-control	Union membership and employment at one of the three Beaumont-Port Arthur, TX area refineries. Refinery exposures were categorized as crude oil, lube oil, treating, coking, grease plant, utilities, maintenance and labor, receipt and movement, laboratory, motor transport, and other work categories
Wen et al. (1981, 1982, 1983, 1984a)	Employees at a Gulf Oil refinery/U.S. mortality experience	Cohort mortality	Employment at the Port Arthur, TX site. The refinery was engaged in refining crude oil and manufacturing fuels, oils, lubricants, and petrochemicals such as benzene, cumene, ethylene, and cyclohexane
Rushton and Alderson (1981a)	Male workers at any one of eight petroleum refineries in Great Britain/Combined mortality experience of England and Wales for English and Welsh refineries and the mortality experience of Scotland for Scottish refineries	Cohort mortality	Employment of at least 1 year at one of the refineries
Schottenfeld et al. (1981)	White and Spanish surnamed men from 19 U.S. petroleum industry companies/U.S. mortality experience; SEER program results	Cohort mortality and cohort morbidity	Employment by one of the 19 petroleum industry companies, subsequently categorized as refinery employment or petrochemical employment
Thomas et al. (1982a)	Decedent males who at their time of death were active or retired members of the OCAW from three refineries in Beaumont-Port Arthur, TX area/U.S. and county mortality experience	PMR	Union membership and employment at one of the three Beaumont-Port Arthur, TX area refineries. The refineries were engaged in refining crude oil and manufacturing fuels, petroleum solvents, lubricating oils, petroleum wax, greases, and petrochemicals
Wen et al. (1984b Summary) Study 5	Gulf Oil Co. employees and annuitants/U.S. mortality experience	PMR	Employed by Gulf Oil Co. at a U.S. site

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TABLE 4-4. (continued)

Author	Study population/Comparison population	Type of study	Occupational exposure
Wen et al. (1984b Summary) Study 6	Kidney cancer cases at a Gulf Oil Co. refinery in Port Arthur, TX/Non-cancer decedents; mixed controls, i.e., no exclusion for cancer or vital status	Nested case-control	Employment at the Port Arthur, TX refinery
Kaplan (1982 Unpublished, 1985 Unpublished)	Petroleum refinery hourly workers at 17 U.S. refineries/U.S. mortality experience	Cohort mortality	Employment in one of the refineries for at least 1 year
McGraw et al. (1985)	White male employees at Shell Oil Co. Wood River Refinery/U.S. mortality experience; SEER mortality experience	Cohort mortality	Employment of at least 1 day at the refinery or the onsite research laboratory
Hanis et al. (1985a)	Regular employees from three Exxon refineries and chemical plants/U.S. mortality experience	Cohort mortality	Employment of at least 1 month at one of the refineries
Hanis et al. (1985b)	Regular employees from three Exxon refineries and chemical plants with potential exposure to petroleum, petrochemicals, and other related substances/ An internal "non-exposed" group	Cohort mortality	Employment of at least 1 month at one of the refineries and a job title of process operator, mechanical worker, unskilled laborer, service worker, laboratory technician, or field professional
Divine et al. (1985)	All employees of Texaco, Inc. who worked at the refinery, petrochemical, and research facilities/U.S. mortality experience	Cohort mortality	Employment by Texaco, Inc. at one of their refinery, petrochemical, or research facilities for a minimum of 5 years
Barron and Divine (1985)	Decedent brain cancer cases; decedent benign and unspecified brain tumor cases/Controls selected from the original Texaco, Inc. cohort	Nested case-control	Employment by Texaco, Inc. at one of their refinery, petrochemical, and research facilities; research laboratories; lube oil refining units

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TABLE 4-4. (continued)

Author	Study population/Comparison population	Type of study	Occupational exposure
Nelson (1985 Unpublished)	Full-time regular employees from 10 U.S. refineries of Amoco Oil Co./U.S. mortality experience	Cohort mortality	Employment at one of the refineries for at least 6 months; job type (administrative, etc.); contact with light aromatic hydrocarbons; contact with heavy oils; contact with refinery products; the latter 3 exposures were categorized as none, occasional, routine, or unknown.
Cole et al. (1972)	Bladder cancer cases/An age- and sex-stratified sample of the adult population of the area	Case-control	Petroleum product occupations; petroleum workers excluding machinists and mechanics
Howe et al. (1980)	Bladder cancer cases/Neighborhood controls	Case-control	Employment in the petroleum industry
Gottlieb and Pickle (1981)	Decedent bladder cancer cases/Decedents from the same parish of residence, excluding those whose cause of death was bladder cancer	Case-control	Usual industry of employment in the oil refining industry; living "near" oil refineries
Gottlieb and Carr (1981)	Decedents whose cause of death was cancer of the lung, pancreas, bladder, brain, kidney or esophagus, or leukemia/Decedents from the same parish of residence as the cases, excluding those whose cause of death was the same as the cases' cause	7 Case-control studies	Usual industry of employment in the oil refining industry; living "near" oil refineries; work in oil production; employment in the petroleum industry; workers in oil exploration and drilling; oil-field workers, welders, operators, boilermakers, or painters in the petroleum industry; skilled workers involved in petroleum pumping and refining; auto repair business
Najem et al. (1982)	Bladder cancer cases/Selected from the same urology clinic and hospital population as the cases	Case-control	Employment in the petroleum (fuel) industry
McLaughlin et al. (1984)	Renal cell carcinoma cases/An age- and sex-stratified random sample selected from area telephone listings	Case-control	Petroleum, tar, or pitch products; employment in the chemical or petroleum industry

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TABLE 4-4. (continued)

Author	Study population/Comparison population	Type of study	Occupational exposure
McLaughlin et al. (1983)	Renal pelvis cancer cases/An age- and sex-stratified random sample selected from area telephone listings	Case-control	Petroleum, tar, or pitch
Pickle and Gottlieb (1980)	Decedent pancreatic cancer cases/ Decedents from the same parish of residence, excluding those whose cause of death was pancreatic cancer	Case-control	Employment in the oil refining industry; residence "near" oil refineries
Wigle (1977)	Decedent lung cancer cases/Decedents from the same city, excluding those whose cause of death was lung cancer	Case-control	Employment in the oil refining industry; oil production occupations; auto repair business; employment in the oil exploration and drilling industry; living in "close proximity" to oil refineries
Gottlieb (1980)	Decedent lung cancer cases/Decedents from the same parish of residence, excluding those whose cause of death was lung cancer	Case-control	Employment in the petroleum industry; oil-field workers, welders, operators, boilermakers, or painters in the petroleum industry; employment as a skilled worker in petroleum pumping or refining
Brandt et al. (1978)	Acute non-lymphocytic leukemia cases/ Outpatient department patients treated for non-malignant disorders; outpatient department patients treated for allergic diseases; patients with chronic myeloid leukemia and chronic lymphocytic leukemia	Case-control	Petroleum products. Typical job titles were workers at filling stations, bus or truck drivers, operators of excavating machines or powersaws, and road haulers
Plotnikov (1978)	Patients diagnosed with leukemia or lymphogranulomatosis/"Health" individuals	Case-control	Employment in the petroleum industry

TABLE 4-5. STUDY SITE LOCATIONS[a] OF EPIDEMIOLOGIC STUDIES REVIEWED

Study site location	Study author
CALIFORNIA	
Chevron refinery in Richmond	Morgan and Wong (1983 Unpublished)
Chevron refinery in El Segundo	Morgan and Wong (1983 Unpublished)
FLORIDA	
Miami	Lin and Kessler (1981)
GEORGIA	
Amoco Oil Co. refinery in Savannah	Nelson (1985 Unpublished)
ILLINOIS	
Shell Oil Co. refinery in Wood River	McGraw et al (1985).
Amoco Oil Co. refinery in Wood River	Nelson (1985 Unpublished)
INDIANA	
Amoco Oil Co. refinery in Whiting	Nelson (1985 Unpublished)
LOUISIANA	
Exxon Co. refinery in Baton Rouge	Hanis et al. (1982) Hanis et al. (1985a) Hanis et al. (1985b)
18 parishes in southern Louisana	Gottlieb and Carr (1981)
19 parishes throughout Louisiana	Gottlieb et al. (1979) Gottlieb (1980) Pickle and Gottlieb (1980) Gottlieb and Pickle (1981) Gottlieb and Carr (1981)
MARYLAND	
Amoco Oil Co. refinery in Baltimore	Nelson (1985 Unpublished)
MASSACHUSETTS	
Eastern Massachusetts including Boston	Cole et al. (1972)
MICHIGAN	
Detroit metropolitan area	Lin and Kessler (1981) Silverman et al. (1983)

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TABLE 4-5. (continued)

Study site location	Study author
MINNESOTA	
Minneapolis-St. Paul area	Lin and Kessler (1981) McLaughlin et al. (1983) McLaughlin et al. (1984)
MISSOURI	
Amoco Oil Co. refinery in Sugar Creek	Nelson (1985 Unpublished)
NEW JERSEY	
Exxon Corp. refinery in Bayway/ Bayonne	Hanis et al. (1985a) Hanis et al. (1985b)
Northern New Jersey	Najem et al. (1982)
New Jersey State	Stemhagen et al. (1983)
NEW YORK	
Buffalo	Lin and Kessler (1981) Domiano et al. (1985)
New York City	Lin and Kessler (1981)
NORTH DAKOTA	
Amoco Oil Co. refinery in Mandan	Nelson (1985 Unpublished)
TEXAS	
Gulf Oil Corp. refinery in Port Arthur	Thomas et al. (1980)[b] Thomas et al. (1982)[b] Thomas et al. (1984)[b] Wen et al. (1981, 1982, 1983, 1984a) Wen et al. (1984b Summary)
Mobil Oil Corp. refinery in Beaumont	Thomas et al. (1980)[b] Thomas et al. (1982a)[b] Thomas et al. (1984)[b] Morgan and Wong (1984 Unpublished)
Texaco, Inc. refinery in Beaumont	Thomas et al. (1980)[b] Thomas et al. (1982a)[b] Thomas et al. (1984)[b] Divine et al. (1985) Barron and Divine (1985)

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TABLE 4-5. (continued)

Study site location	Study author
TEXAS (continued)	
Exxon Corp. refinery in Baytown	Hanis et al. (1985a) Hanis et al. (1985b)
Amoco Oil Co. refinery in Texas City	Thomas et al. (1980)[b] Reeve et al. (1982)[b] Nelson (1985 Unpublished)
Marathon Oil Co. refinery in Texas City	Thomas et al. (1980)[b] Reeve et al. (1982)[b]
OCAW locations in Texas	Thomas et al. (1980) Wen et al. (1984b Summary) Divine et al. (1985) Barron and Divine (1985)
UTAH	
Amoco Oil Co. refinery in Salt Lake City	Nelson (1985 Unpublished)
VIRGINIA	
Amoco Oil Co. refinery in Yorktown	Nelson (1985 Unpublished)
WASHINGTON	
Washington State	Milham (1983)
WYOMING	
Amoco Oil Co. refinery in Casper	Nelson (1985 Unpublished)
U.S. NATIONWIDE	
17 Refineries	Tabershaw-Cooper (1974 Unpublished, 1975 Unpublished) Kaplan (1982 Unpublished, 1985 Unpublished)
19 Companies involved in petroleum refining and petrochemical manufacture	Schottenfeld et al. (1981)
All Gulf Oil Co. sites nationwide	Wen et al. (1984b Summary)
All Texaco, Inc., refinery, petrochemical, and research facilities	Divine et al. (1985) Barron and Divine (1985)

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TABLE 4-5. (continued)

Study site location	Study author
CANADA	
A Shell-Canada refinery[c] in Quebec	Theriault and Goulet (1979)
Provinces of British Columbia, Nova Scotia, and Newfoundland	Howe et al. (1980)
Sarnia and London, Ontario	Wigle (1977)
Imperial Oil Co. sites	Hanis (1977) Hanis et al. (1979)
OTHER FOREIGN SITES	
8 Petroleum refineries in Great Britain	Rushton and Alderson (1981a)
3 Oil distribution companies at airport and blending plants in Great Britain	Rushton and Alderson (1983)
Rural area in Denmark	Mommsen et al. (1982, 1983a, b) Mommsen and Aagaard (1983a, b; 1984); Mommsen and Sell (1983)
Lund, Sweden	Brandt et al. (1978)
Kuibyshev Province, U.S.S.R.	Plotnikov (1978)

[a]Location of the Lin and Kessler (1979) study was not reported.
[b]Identification of the refinery provided by the principal author as a personal communication.
[c]Company identification of the refinery provided by Epidemiology Resources, Inc. (1985).

wide cohort mortality studies of refinery workers were not known. It is estimated that the overlap between study populations may be even greater than that which is already known.

Statistically significant cancer findings for the studies reviewed are presented by exposure in the following sections. Some of these findings may have been due to chance because of the large number of multiple comparisons made in a majority of these studies.

It should be noted that positive studies, rather than negative studies, were more likely to be identified during the literature search phase of this review. Studies, especially those of the case-control design, that failed to find an association, may not have been identified.

4.4.1. Summary of Epidemiologic Studies of Workers in the Gasoline Service Industry

A few studies have been conducted on workers in the gasoline service industry (defined here as gasoline service station owners and attendants, garage workers, gasoline and fuel truck drivers, and those who reported working with gasoline). Of the gasoline studies that were identified, six were case-control studies. Specific cancer sites investigated were liver as a primary site (Stemhagen et al., 1983), lower urinary tract (Silverman et al., 1983), bladder (Mommsen et al., 1982; 1983a, b; Mommsen and Aagard, 1983a, b; 1984; Mommsen and Sell, 1983); kidney (Domiano et al., 1985), pancreas (Lin and Kessler, 1981), and testis (Lin and Kessler, 1979). The seventh study, a proportionate mortality study of gasoline service station owners and attendants, and gasoline and fuel truck drivers, was conducted by Milham (1983) in Washington State. No cohort mortality studies were identified on workers in the gasoline service industry.

The majority of these studies assessed employment in the gasoline indus-

try as a surrogate to gasoline exposure. In addition, the analyses were not as thorough as they could have been. For example, latency analyses were generally not conducted, and adjusting for confounders was not always done.

The major limitation of these studies is the lack of information on gasoline vapor exposure; there are no quantitative estimates in any of the studies reviewed. In addition, workers in gasoline service stations are potentially exposed to other petroleum products--motor oils, diesel fuel oils, and solvents--as well as to exhaust from automobile and truck engines. It was not possible to assess the effects of gasoline exposure independently of these other exposures.

Table 4-6 shows the site-specific statistically significant ($p < 0.05$) results for the case-control studies. Stemhagen et al. (1983) found that male primary liver cancer cases were more likely to work in gasoline service stations than were their matched controls (OR = 2.88), that this difference was significant (95% CI 1.20-6.88), and that limiting analyses to hepatocellular carcinoma cases and their matched controls increased the risk to 4.20 (95% CI 1.55-11.35). This study provides some evidence of an association between work in the gasoline service industry and cancer risk. However, there are other methodological limitations in addition to the exposure limitations already mentioned. No latency analysis was conducted, and no estimate was presented of risk while simultaneously controlling for the effects of alcohol consumption (a known risk factor).

Mommsen et al. (1982) and Mommsen and Aagard (1984) found that males who reported working with gasoline or oil were at significant excess bladder cancer risk (OR = 2.71, 95% CI 1.21-6.10) even after significant confounding factors (i.e., cigarette smoking, nocturia, prostatic surgery, cheroot smoker, and lowest socioeconomic level) were controlled for (OR = 2.32). However, this

TABLE 4-6. SUMMARY OF SITE-SPECIFIC STATISTICALLY SIGNIFICANT CANCER FINDINGS FROM CASE-CONTROL STUDIES THAT EVALUATED EMPLOYMENT IN THE GASOLINE SERVICE INDUSTRY AS A RISK FACTOR[a]

Type of cancer	Author	Occupational exposure
Primary liver	Stemhagen et al. (1983)	Gasoline service station employment
Bladder	Mommsen et al. (1982) Mommsen and Aagaard (1984)	Work with gasoline or oil
Pancreas	Lin and Kessler (1981)	Any work in gasoline service stations and garages or the dry cleaning business; 10+ years employment in similar work
Testis	Lin and Kessler (1979)	Work in gasoline service stations; work in garages

[a]All findings are positive ($p < 0.05$).

study provides insufficient data with which to evaluate the carcinogenicity of gasoline. The authors' data collection methods may have created a bias in the response, since the interviewers were aware of the case or control status of the subjects. Furthermore, cases were interviewed in person or in the hospital, while controls were interviewed in their homes by telephone. The exposure category included oil as well as gasoline. No latency analysis or analysis by duration of exposure was conducted.

Lin and Kessler (1981) reported that male pancreatic cancer cases were significantly more likely to have been employed in occupations involving close exposure to gasoline (e.g., service stations and garages) or in the dry cleaning business than were the controls (OR = 2.79). This risk appeared to be positively associated with increasing duration of exposure (3 to 5 years' exposure, OR = 1.27; 6 to 10 years' exposure, OR = 3.80; 10 or more years' exposure, OR = 5.07). However, it was not possible to determine if the observed increase in risk was due to employment in gasoline occupations, dry cleaning occupations, or some combined exposure to both. In addition, the authors' analysis failed to control for the effects of other confounding variables, such as alcohol consumption. Thus, this study provides insufficient data upon which to evaluate the association between gasoline and pancreatic cancer.

Lin and Kessler (1979) also reported that cases of testicular cancer were significantly more likely to be gasoline station attendants and garage workers than were the controls. Only an abstract of this work was published and no estimates of risk were presented. The lack of any methodologic detail precludes consideration of the data.

Table 4-7 presents statistically significant ($p < 0.05$) findings by study population for Milham's (1983) proportionate mortality study of white males in Washington State. Gas station owners and attendants had a significantly great-

TABLE 4-7. SUMMARY OF SITE-SPECIFIC STATISTICALLY SIGNIFICANT CANCER FINDINGS FROM MILHAMS'S 1983 WASHINGTON STATE PHR STUDY, BY STUDY POPULATIONS EXPOSED[a]

Type of cancer (ICD-7 code)	Gas station owners/attendants	Fuel oil/gas truck drivers	Fuel oil dealers/workers	Auto mechanics/repairmen
All cancer (140-205)		+		
Buccal cavity/pharynx (140-148)			+	
Digestive organs/peritoneum (150-159)	-			
Esophagus (150)				+
Large intestine (153)	-			
Respiratory system (160-165)				+
Trachea/bronchus/lung (162)				+
Genitourinary organs				
Prostate (177)			+	
Bladder/urinary organs (181)	+			
Brain (193.0)			+	
Lymphatic/hematopoietic tissues (200-205)			+	
Other lymphomas (202, 200.2)				+
Lymphatic leukemia (204.0)				+

[a]Significant ($p < 0.05$) excesses (+) or deficits (-) are reported.

er proportion of deaths due to cancer of the bladder and other urinary organs than did Washington State decedents whose usual occupation was not gas station owner or attendant. Among the same study population, a significant deficit was observed for cancer of the digestive organs and peritoneum, and for cancer of the large intestine. Among fuel oil and gas truck drivers, a significant excess was observed for all cancers. There were no site-specific cancer excesses or deficits observed for this latter group.

Milham also evaluated the mortality experience of white males whose usual occupation was fuel oil dealer and worker, and auto mechanic and repairman, who were assumed to have petroleum products exposure and potential gasoline exposure. Significant cancer excesses were observed among the fuel oil dealers for cancers of the buccal cavity and pharynx, prostate, brain, and lymphatic and hematopoietic tissues. Among the auto mechanics, a significant excess mortality was observed for esophageal and respiratory system cancers, including a significant excess for primary cancers of the bronchus, trachea, and lung.

There are several problems associated with the validity of any PMR analysis. First, a PMR analysis is generally used when the population at risk is not known. PMRs use only the deaths from a given study, but not the entire population from the study setting. Hence, this type of study cannot give any idea of the population's risk of dying from any given cause.

Second, a PMR analysis assumes that overall mortality is equal in the two populations being compared. If this is not true, and if the mortality rate for the study group is lower than for the comparison group for all causes of death, the PMR will inflate the estimate of cause-specific mortality.

Milham (1983) used as his comparison population the mortality experience of Washington State. The general population of Washington State will include sick and disabled nonworking individuals, and thus is likely to have a higher

mortality rate from all causes of death than the gasoline station workers or the gasoline truck drivers. Therefore, Milham's cause-specific proportionate mortality rate as an indicator of risk is inflated.

Third, PMRs for two or more causes of death are interdependent rather than independent, since the sum of the observed numbers of deaths equals the sum of the expected numbers. Hence a deficit in one cause-specific mortality will force an excess in another cause-specific mortality. Fourth, a PMR analysis assumes that the classification and reporting of deaths in the study population and in the comparison population are complete and comparable. Fifth, this type of analysis, in compiling causes of deaths, assumes that both populations are comparable.

In addition, no attempt was made to control for confounding factors such as smoking. No latency analysis or analysis by duration of exposure was conducted. This study is considered inadequate for evaluating an association of gasoline exposure and cancer risk.

4.4.2. Summary of Epidemiologic Studies of Workers in the Petroleum Refining Industry

Twenty-five studies were reviewed that assessed the risk of cancer among petroleum refinery workers. Four of these were proportionate mortality studies, 17 were cohort mortality studies, 1 was a cohort morbidity study, and 3 were of the nested case-control design. These studies are summarized in Table 4-4. Table 4-5 shows the known locations for each of the refineries.

The refinery studies provided no qualitative or quantitative estimates of gasoline exposure, although some data on total hydrocarbon exposure are available (Wen et al., 1984b Summary).

Typical of modern refineries is the operation of the equipment from a computerized remote panel, which reduces the potential of exposures to work-

ers. However, the system is such that some airborne contamination by the various hydrocarbon components, and presumably gasoline, will occur. The "greatest risk" is faced by maintenance workers who may be exposed for "sustained periods of time" (Clayton Environmental Consultants, Inc., Undated). Some exposure will also occur during gasoline quality control sampling and testing procedures, especially by workers in gasoline treating and blending, and during the bulk loading of the gasoline for distribution and marketing (Clayton Environmental Consultants, Inc., Undated). The amount of exposure in these processes will vary depending upon many factors, including a worker's particular job and the extent of refinery automation.

Little is known about the historical exposure of refinery workers to gasoline. Technological developments of the automobile engine have historically been coupled with changes in gasoline composition. For example, post-1940 gasoline had higher aromatic and isoparaffinic hydrocarbon content than earlier gasoline, and unleaded gasoline has higher concentrations of isoparaffins and aromatics than leaded gasoline (Domask, 1984).

These changes over time in the refinery processes, coupled with the passage and implementation of health and safety standards, make an assessment of historical gasoline refinery exposure difficult. However, it has been estimated that the potential for gasoline exposure prior to the late 1960s is greater than the present-day potential for exposure (conversation between D.E.B. Potter, Dynamac Corporation, and Robert Reisdorf, Dynamac Corporation, 1986).

For some of these studies, employee job titles or work categories provided some information on potential for gasoline exposure; however, it is not known how indicative of exposure a particular job title or work category is. In addition, a majority of the refinery studies failed to report any information on job titles or employee work categories.

Refinery workers are exposed not only to gasoline but also to other petroleum and petrochemical products manufactured within the refinery. It was not possible to assess the effect of gasoline exposure independently of these other refinery exposures. Hence, any of the results reviewed here may be confounded by these other chemical exposures.

Statistically significant site-specific cancer findings from the cohort, nested case-control, and PMR studies are shown in Tables 4-8, 4-9, and 4-10, respectively. The results for all cancer sites combined are equivocal: three studies found statistically significant ($p < 0.05$) excesses of mortality (Tables 4-8 and 4-10), four studies found statistically significant excesses among subcohort populations and statistically significant deficits among the total cohort (Table 4-8), and eight studies found statistically significant deficits for all cancer mortality (Table 4-8). However, there are several possible explanations for the deficits observed in all cancer mortality, the most obvious being that the results are indicative of the healthy worker effect (McMichael, 1976). Some evidence of the effect is provided in these data. All of the American studies that found statistically significant deficits in all cancer mortality used the U.S. general population as the comparison population. However, when a working population (i.e., nonexposed petroleum industry workers) was used as the comparison population, a statistically significant excess of all cancer mortality was observed (Hanis, 1977; Hanis et al., 1979). A similar, but nonsignificant, pattern was seen in the Australian petroleum industry data (AIP-UM/DCM, 1985). Therefore, these data provide evidence to suggest that the deficits observed for all cancer sites combined are due to the healthy worker effect, and that cancer risks from many of these refinery studies may be underestimated because the healthy worker effect was not controlled for.

TABLE 4-8. SUMMARY OF SITE-SPECIFIC STATISTICALLY SIGNIFICANT[a] CANCER FINDINGS FROM COHORT MORTALITY STUDIES THAT EVALUATED EMPLOYMENT IN THE PETROLEUM REFINERY INDUSTRY AS A RISK FACTOR

Type of cancer (ICD-8 Code)	Tabershaw-Cooper Assoc. (1975 Unpublished)	Hanis (1977)	Hanis et al. (1979)	Theriault & Goulet (1979)	Wen et al. (1983)	Wen et al. (1984a)	Rushton & Alderson (1981a)	Schottenfeld et al. (1981)	Hanis et al. (1982)	Rushton & Alderson (1983)	Morgan & Wong (1983 Unpub.)	Morgan & Wong (1984 Unpub.)	Kaplan (1985 Unpublished)	McGraw et al. (1985)	Hanis et al. (1985)	Divine et al. (1985a)	Nelson (1985 Unpublished)
All cancer (140-209)	-	+/-	+			-	+/-	-	-	+/-	-		-		+/-	-	-
Buccal cavity/pharynx (140-149)	-				-				-		-	-	-		-		-
Digestive system (150-159)	-				-						-	+/-			+/-	-	+
Esophagus (150)					-		+			-							
Esophagus/stomach (150-151)			+														
Stomach (151)					-		+				-	+/-				-	+
Other digestive system (152-159)		+															
Intestines/rectum (152-154)		+/-															
Intestines (152-153))							+			-							
Large intestine (153)											-	-				-	
Large intestine/rectum (153-154)		+	+														
Rectum (154)					-		+					-					

(continued on the following page)

TABLE 4-8. (continued)

Type of cancer (ICD-8 Code)	Tabershaw-Cooper Assoc. (1975 Unpublished)	Hanis (1977)	Hanis et al. (1979)	Theriault & Goulet (1979)	Wen et al. (1983)	Wen et al. (1984a)	Rushton & Alderson (1981a)	Schottenfeld et al. (1981)	Hanis et al. (1981)	Rushton & Alderson (1982)	Morgan & Wong (1983)	Morgan & Wong (1983 Unpub.)	Morgan & Wong (1984 Unpub.)	Kaplan (1985 Unpublished)	McGrew et al. (1985)	Hanis et al. (1985)	Divine et al. (1985a)	Nelson (1985 Unpublished)
Other Digestive (155-159)		+	+															
Liver/gallbladder (155-156)					-	-					-	-						
Pancreas (157)											-							
Respiratory system (160-163)	-										-	+	-		-			-
Nasal cavity/sinuses (160)							+											
Lung/pleura/other resp. (162-163)						-	-			+/-	-	+						
Trachea/bronchus/lung (162)		+/-	+					-					-		-	-		-
Mesothelioma													+					
Bone (170)				+														
Skin (172-173)												+						+
Melanoma (172)							+											

(continued on the following page)

TABLE 4-8. (continued)

Type of cancer (ICD-8 Code)	Tabershaw-Cooper Assoc. (1975 Unpublished)	Hanis (1977)	Hanis et al. (1979)	Theriault & Goulet (1979)	Wen et al. (1983)	Wen et al. (1984a)	Rushton & Alderson (1981a)	Schottenfeld et al. (1981)	Hanis et al. (1982)	Rushton & Alderson (1983)	Morgan & Wong (1983 Unpub.)	Morgan & Wong (1984 Unpub.)	Kaplan (1985 Unpublished)	McGraw et al. (1985)	Hanis et al. (1985)	Divine et al. (1985a)	Nelson (1985 Unpublished)
Genitourinary organs (180-189)																	
Prostate (185)									-					-			
Urinary organs (188-189)	-																
Bladder (188)					-				-b			-			-		
Brain/other nervous system (191-192)			+														
Lymphatic/hematopoietic tissues (200-209)		-				+				+							-
Lympho- and reticulosarcoma (200)				-													
Lymphosarcoma (200.1)						+											
Non-Hodgkin's lymphoid (202)									+								
Multiple myeloma (203)									+								
Leukemia/aleukemia (204-207)									+	+			+				
Lymphatic leukemia (204)							+c										
Chronic lymphatic leukemia (204.1)									+								
Myelofibrosis (209)									+								

(continued on the following page)

TABLE 4-8. (continued)

[a]$p < 0.05$; "+" is where a positive finding ($p < 0.05$) was found among one or more cohorts or subcohorts, "-" is where a negative finding ($p < 0.05$) was found among one or more cohorts or subcohorts, "+/-" is where a positive finding ($p < 0.05$) was found among one or more cohorts or subcohorts and a negative finding ($p < 0.05$) was also found among one or more cohorts or subcohorts.

[b]$p = 0.05$.

[c]Significant excess of morbidity rather than mortality.

TABLE 4-9. SUMMARY OF SITE-SPECIFIC STATISTICALLY SIGNIFICANT CANCER FINDINGS FROM COHORT MORTALITY STUDIES THAT EVALUATED EMPLOYMENT IN THE PETROLEUM REFINERY INDUSTRY AS A RISK FACTOR[a]

Type of cancer	Author (p values)	Occupational exposure
Stomach	Thomas et al. (1984) ($p < 0.10$)	Employment in the unit operations of maintenance and labor; employment in the yard subcategory of maintenance; lube oil workers
Brain and benign and unspecified brain tumors	Barron and Divine (1985) ($p < 0.05$)	Employment in Texaco research laboratories

[a]Excluded from this table are significant findings where the authors reported that the measure of central tendency (i.e., mean, median) of the length of employment was longer for the controls than for the cases.

TABLE 4-10. SUMMARY OF SITE-SPECIFIC STATISTICALLY SIGNIFICANT CANCER FINDINGS FROM PMR STUDIES THAT EVALUATED EMPLOYMENT IN THE PETROLEUM REFINERY INDUSTRY AS A RISK FACTOR[a]

Type of cancer (ICD-8 code)	OCAW decedents from refineries in Texas (Thomas et al., 1980)	OCAW decedents from three refineries in Beaumont-Port Arthur, TX (Thomas et al., 1982a)	OCAW Decedents from a refinery in Texas City, TX (Reeve et al., 1982)
All cancer (140-209)	+	+	
Digestive organs/peritoneum (150-159)	+		
Stomach (151)	+	+	
Pancreas (157)	+	+	
Respiratory system (160-163)	+		
Lung/pleura/other respiratory (162-163)	+	+	
Skin (172-173)	+	+	+
Genitourinary organs (180-189)			
Prostate (185)		+	
Bladder (188)		-	
Kidney (189)	+		
Brain/other nervous system (191-192)	+	+	
Lymphatic/hematopoietic tissues (200-209)		+	
Hodgkin's disease (201)		+	
Non-Hodgkins lymphoma (202)		+	
Multiple myeloma (203)			+
Leukemia (204-207)		+	

[a]Significant ($p < 0.05$) excesses (+) or deficits (-) are reported.

In addition, most of the refinery cohorts were composed of all workers at the refinery, including clerical and administrative personnel, refinery operators, technicians, and maintenance personnel. Thus, total cohort analyses will dilute the estimate of risk for those most likely to be exposed (i.e., operators, etc.) and, in fact, an estimated 29% of the Wen et al. (1983, 1984b Summary) cohort (Moure-Eraso and Itaya, 1985) and 27% of the Australian cohort (AIP-UM/DCM, 1985) consisted of management and clerical workers. Thus, cancer risks among workers involved in the actual refinery processes are probably underestimated in the refinery cohort data.

Finally, for safety reasons, smoking is prohibited in many parts of the refinery (conversation between D.E.B. Potter, Dynamac Corporation, and Robert Reisdorf, Dynamac Corporation, 1986). Thus, deficits in all cancer mortality may be due to lower rates of mortality from smoking-related cancers among refinery workers in comparison to the general population.

These data suggest that cancer risks may be underestimated in these studies. A review of the site-specific cancer results follows.

The results for digestive system cancer are ambiguous. This may be due to the combined nature of the digestive system cancer category, which included cancer sites for which excesses were observed (e.g., stomach cancer) as well as sites for which deficits were observed (e.g., liver cancer). Four studies did report statistically significant excesses of digestive system cancer mortality among petroleum refinery workers (Tables 4-8 and 4-10). These excesses were among selected subcohort populations: non-white males, those with routine exposure to light aromatic hydrocarbons (i.e., benzene, toluene, and xylene), and those with at least 30 years' employment in the refinery industry. Significant excesses were also observed at refinery locations in Whiting, Indiana and Bayway/Bayonne, New Jersey. Significant deficits for digestive system cancer were

observed among total cohort populations and selected subcohort populations (Tables 4-8 and 4-10).

Cancers of the esophagus, intestines, and rectum were detected in at least one study (Table 4-8), and statistically significant excesses of stomach cancer were observed by five teams of researchers among several refinery subcohort populations (Tables 4-8, 4-9, and 4-10). These subcohorts included non-white males; workers in specific refinery work categories--laborer, rigger, fire and safety worker, lube oil worker, maintenance and labor employee, and yard maintenance worker; and workers at specific refinery locations in Whiting, Indiana and in Great Britain (Table 4-9). One study, a nested case-control study of stomach cancer (Thomas et al., 1984), reported a statistically nonsignificant positive dose-response trend for duration of employment among refinery maintenance workers, a work category considered to have potential gasoline exposure.

Significant deficits of stomach cancer were observed among salaried employees, a group not likely to be exposed; among the total cohort at the El Segundo refinery in California; and among refinery workers with 20 to 39 years latency at a Beaumont, Texas refinery. However, the Beaumont refinery is located in a county where the white male age-adjusted stomach cancer mortality rate is significantly lower ($p < 0.05$) than the mortality rate of the U.S. population (Mason et al., 1975). Thus, the deficit among males with 20 to 39 years' latency may be due to the comparison population used. This study used the U.S. general population, which has a higher stomach cancer mortality rate than the county in which the plant is located. It is concluded that limited evidence to suggest an association of stomach cancer risk and employment in the petroleum refining industry.

As previously mentioned, for safety reasons tobacco smoking is generally prohibited within a refinery setting, and this is reflected in the lung cancer

mortality patterns of the refinery workers. Specifically, ten studies found significant ($p < 0.05$) deficits of lung cancer mortality when refinery workers were compared to the general population. This provides supporting evidence to suggest that refinery workers, excluding office workers, smoke less--at least at work (conversation between D.E.B. Potter, Dynamac Corporation, and Robert Reisdorf, Dynamac Corporation, 1986)--than the general population.

Only three of the cohort mortality studies used a nonexposed petroleum industry group as the comparison population. Each of these found excesses of respiratory system cancer (Hanis, 1977; Hanis et al., 1979; Hanis et al., 1985b). Hanis (1977) and Hanis et al. (1979) found a statistically significant ($p < 0.05$) excess of lung cancer among Imperial Oil Co. workers known to have daily exposure to petroleum or its products, in comparison to the nonexposed workers. Among Exxon refinery workers, Hanis et al. (1985b) found a 70% excess ($p < 0.05$) of respiratory system cancer among potentially exposed refinery workers when compared to the nonexposed workers after post-stratifying for smoking. An excess of lung cancer was also observed by Morgan and Wong (1984 Unpublished) among non-white males with at least 40 years' latency. Thus, some limited evidence exists to suggest an association between respiratory system cancer risk and petroleum refinery industry employment.

Six studies found statistically significant ($p < 0.05$) excesses of skin cancer mortality (ICD-8 172-173) among petroleum refinery workers (Tables 4-8 and 4-10). Three of these studies provide evidence that the skin cancer excess was melanoma (ICD-8 172) (Rushton and Alderson, 1981a; Nelson, 1985 Unpublished; Reeve et al., 1982). However, there is some overlap of study populations between the Reeve et al. (1982) and the Nelson (1985 Unpublished) studies (Table 4-5); at least three of the deaths reported by Reeve et al. were also included in the Nelson cohort.

Three cohort mortality studies and one cohort morbidity study found statistically significant ($p < 0.05$) excesses of leukemia among refinery workers (Table 4-8). (The term leukemia is used here to mean all of the leukemias, ICD-8 204-207.) A fifth study, a nested case-control study by Thomas et al. (1984), found a statistically nonsignificant positive dose-response relationship between duration of employment and leukemia mortality among refinery workers involved with treating processes, a work category with potential gasoline exposure.

Excess of leukemia mortality and morbidity may be associated with the presence of benzene in gasoline or in the petroleum refinery. Epidemiologic studies have suggested significant increases in leukemia among workers with probable past exposure to benzene (Rinsky et al., 1985), and the CAG/EPA considers the evidence for carcinogenicity to humans to be sufficient (Linet, 1986). Morgan and Wong (1983 Unpublished) found evidence to suggest that the leukemia excess observed among the Chevron cohort was associated with a history of refinery employment prior to 1949, when the recommended benzene standard was lowered to 35 ppm from 100 ppm.

The literature does suggest that benzene-induced leukemia tends to be myelocytic (Heath, 1982); however, two of the refinery studies found significant excesses of lymphatic leukemia (Table 4-8), a leukemia not associated with benzene exposure. Additionally, some evidence suggests the possibility that organic solvents other than benzene may play a role in the development of leukemia (McMichael et al., 1975). Significant excesses were also observed among the other lymphatic and hematopoietic tissues, specifically lymphosarcoma, non-Hodgkin's lymphoma, multiple myeloma, and myelofibrosis (Table 4-8). Thus, these refinery studies provide limited evidence to suggest an association between lymphatic and hematopoietic tissue cancer risk and employment in

the petroleum refinery industry.

There were no cohort mortality studies of refinery workers that found statistically significant excesses of bladder cancer; statistically significant deficits of bladder cancer were observed by five research study teams. This is in contrast to three case-control studies that found that males who reported working with gasoline or oil or in the petroleum industry were at significant excess bladder cancer risk (Tables 4-6 and 4-11). This inconsistency may be explained by the fact that the 5-year survival for white male bladder cancer cases is high (54%) in comparison to the survival of white males diagnosed with stomach cancer (12%), lung cancer (9%), or acute leukemias (15%) (Silverberg, 1984). Thus, cohort mortality studies that evaluate the risk of bladder cancer do not represent the true incidence of bladder cancer in the population, and bladder cancer risk may be more truly reflected in case-control studies.

Four studies found statistically significant mortality deficits among refinery workers whose cause of death was cancer of the liver, gall bladder, or other biliary passages (ICD-8 155-156). No significant excesses were observed. These data are difficult to interpret because of the combined nature of the category and because alcohol consumption is a strong confounding factor that was not controlled for. However, evidence of an association between liver cancer and refinery employment was not observed in these data.

There are serious limitations to all of these refinery study findings, one of the most important being that the majority of the studies did not conduct analyses of latency, nor did they evaluate possible dose-response effects or analyze for duration of employment. Failure to examine cancer risks within the context of time or dose lessens the chance that an excess cancer risk will be identified. Rather, a dilution of risk is likely to occur in the absence of these analyses.

TABLE 4-11. SUMMARY OF SITE-SPECIFIC STATISTICALLY SIGNIFICANT CANCER FINDINGS FROM CASE-CONTROL STUDIES THAT EVALUATED EMPLOYMENT IN THE PETROLEUM INDUSTRY AS A RISK FACTOR[a]

Type of cancer exposure	Author	Occupational exposure
Esophagus	Gottlieb and Carr (1981)	Occupations in the petroleum or petrochemical industry
Lung	Gottlieb et al. (1979)	Employment in the oil production industry among those older than 62 years
Lung	Gottlieb (1980)	Employment in the petroleum industry; petroleum industry oilfield workers, welders, operators, boilermakers, or painters; skilled workers involved in petroleum pumping and refining
Bladder	Howe et al. (1980)	Employment in the petroleum industry
Bladder	Najem et al. (1982)	Employment in the petroleum (fuel) industry
Kidney	Gottlieb and Carr (1981)	Occupations in the petroleum or petrochemical industry
Renal cell	McLaughlin et al. (1984)	20+ years' exposure to petroleum, tar, or pitch
Leukemia	Gottlieb and Carr (1981)	Occupations in the petroleum or petrochemical industry
Acute non-lymphocytic leukemia	Brandt et al. (1978)	Petroleum products. Typical job titles were workers at filling stations, bus or truck drivers, operators of excavating machines or powersaws, and road haulers
Leukemia/ lymphogranulomatosis	Plotnikov (1978)	Employment in the petroleum industry

[a]All findings are positive ($p < 0.05$).

The lack of statistical control for confounding factors such as smoking, alcohol consumption, or diet is a major limitation in all of these studies. This is especially important when interpreting bladder, liver, or lung cancer findings. However, since smoking is generally prohibited within a refinery, confounding due to cigarette smoking may actually have resulted in an underestimation, rather than an overestimation, of occupationally-related cancer risk in comparison to the general population.

Many of the cohort studies had other limitations. The inclusion in the cohort of employees not likely to be exposed was commonplace for most of the refinery studies. The length of cohort follow-up was short for some of the studies. Some of the methods employed for vital status ascertainment (e.g., searching only company records) may have resulted in an underreporting of mortality for some of the study populations. All of these limitations can result in underestimation of cancer risk.

In addition, the number of persons lost to follow-up was sufficiently large, for some of the studies, to call into question the author's findings. Other limitations included a lack of detail on cohort tracing procedures and cause-of-death coding procedures employed by some of the researchers (e.g., version of the ICD used, and whether coding was done by a trained nosologist). At least two of the cohort studies did not use time-specific mortality rates to calculate SMRs, thus possibly biasing the risk estimates.

For two of the cohort studies, information on race was not available for the entire cohort. Those individuals for whom race was unknown were assumed to be white (this accounted for 20% of the cohort in one of these studies). This assumption may have led to a biased estimate of risk.

Savitz and Moure (1984) have suggested that ethnicity is especially pertinent to an analysis of refinery data because of Texas' large Hispanic popula-

tion. Lung cancer incidence rates among white male Hispanics were 34% of those of "Anglo" males. The incidence of melanoma among Hispanics was 14% of that among "Anglos" (Key, 1981). Thus, ethnicity may be an important confounder in the data that could not be controlled for.

There are methodological limitations as well. Those associated with a PMR analyses were discussed previously in detail (see section 4.4.1.). Most of these same limitations apply to the PMR studies of refinery workers. Other limitations include those associated with the healthy worker effect, also discussed previously.

Finally, the cohort mortality studies are limited by the inconsistency of their results (see Tables 4-8, 4-9, and 4-10), some of which may be explained by geographic variations or changes in cancer mortality patterns over time. Some may also be due to differences in refinery practices or exposure definitions. For example, many of the statistically significant deficits were observed among the total cohort, while significant excesses were observed among subcohorts of workers known to be exposed.

In spite of these limitations, there is evidence to suggest a possible association between employment in the petroleum refining industry and risk of stomach cancer, respiratory system cancer (i.e., lung, pleura, nasal cavity and sinuses), and cancer of the lymphatic and hematopoietic tissues.

4.4.3. Summary of Case-Control Studies That Evaluated Employment in the Petroleum Industry as a Risk Factor

Nineteen case-control studies were reviewed that evaluated employment in the petroleum industry as a risk factor (Tables 4-4 and 4-5). These studies, like the gasoline and refinery studies, are limited by their lack of gasoline exposure information. No quantitative estimates of exposure were available, and it was not possible to determine if these workers were actually exposed to

gasoline, although that potential existed. As in the gasoline and refinery studies, the results reviewed here may be confounded by the other chemical exposures associated with employment in the petroleum industry. Table 4-11 presents a summary of the site-specific statistically significant ($p < 0.05$) cancer findings for these studies.

Of the 19 case-control studies that were reviewed, 2 provided limited evidence of an association between cancer and employment in the petroleum industry. This evidence was provided by McLaughlin et al. (1984) for renal cell carcinoma and by Howe et al. (1980) for bladder cancer. Both studies were population-based.

McLaughlin et al. (1984) found that renal cell carcinoma cases were more likely than controls to be exposed to petroleum, tar, or pitch products ($p = 0.046$). This risk remained even after adjusting for the confounding effects of age and smoking (OR = 1.7, 95% CI 1.0-2.9), and this excess risk appeared to be positively associated with length of exposure (< 20 years, OR = 1.1, 95% CI 0.05-2.5; 20 or more years OR = 2.6, 95% CI 1.2-5.7). A logistic regression analysis was also used to examine the effects of exposure while simultaneously controlling for the effects of all significant confounding variables (age, cigarette smoking, relative weight, phenacetin use, ethnicity, a history of kidney infections or kidney stones, and consumption of coffee, tea, beer, and meat). The logistic regression odds ratio of 1.6 was similar to that of the stratified analysis (age and smoking adjusted OR = 1.7), although the logistic estimate was not statistically significant (95% CI 0.9-2.7). This result was to be expected, considering the small number of exposed persons.

Howe et al. (1980) found that bladder cancer cases were more likely to be employed in the petroleum industry than controls (RR = 5.3, 95% CI 1.5-28.6) and that this estimate remained unchanged after controlling for the confound-

ing effects of smoking. (The authors' matched analyses also controlled for the effects of age.) The findings of this study are considered limited because of lack of latency and duration-of-employment analyses.

Each of the remaining 17 case-control studies that evaluated employment in the petroleum industry as a risk factor provided insufficient data with which to draw conclusions on the association between cancer risk and petroleum industry employment.

4.4.4. Summary of Epidemiologic Studies in Progress

The American Petroleum Institute has recently begun three epidemiologic studies that are directly relevant to this review: (1) a historical prospective mortality study of employees exposed to downstream gasoline in the petroleum industry, (2) a case-control study of kidney cancer and hydrocarbon exposure among petroleum company workers, and (3) a prospective study of mortality of refinery workers. Findings from the downstream gasoline study will be available in 4 years, and the results of the case-control study in 2 to 3 years. It will be at least 5 years before the prospective study will have sufficient power to detect an approximate doubling of risk for kidney cancer or stomach cancer.

These studies also may have methodological limitations. Smoking histories will not be available for cohort members in the downstream gasoline mortality study. As was noted by the authors of the API feasibility study, "With no data on smoking it . . . (will) be difficult to determine whether any observed mortality excess from tobacco-related diseases was due to employment, smoking, or an interaction between both." (Wong and Morgan, 1984 Unpublished). In addition, it appears that an internal nonexposed group cannot be used as the comparison population (Wong and Morgan, 1984 Unpublished). Thus, these data may be biased by the healthy worker effect as well as by smoking.

The case-control study only identifies cases of kidney cancer that resulted in a mortality; it does not identify incidence cases. As noted by the authors of this feasibility study, "mortality data might reveal as little as 50% of the number of incident cases in some age groups." (ERI, 1985 Unpublished). Thus, a bias from incomplete ascertainment of the cases might exist in this study. Data on the smoking habits of individual study participants will not be available (ERI, 1985 Unpublished), and some studies have found a dose-response relationship between smoking and kidney cancer (U.S. Public Health Service, 1982; McLaughlin et al., 1984). Therefore, these data may be affected by the confounding effects of smoking.

A prospective cohort study is being conducted by the Australian Institute of Petroleum Ltd. in conjunction with the University of Melbourne, Department of Community Medicine (AIP-UM/DCM, 1983; AIP-UM/DCM, 1985; Christie et al., 1984). This well-designed study will, at some future time, permit the calculation of risk estimates while simultaneously controlling for important confounding variables (e.g., smoking and alcohol). Quantitative estimates of exposure will also be available. However, these results are several years away.

Three other refinery studies are known to be in progress or very recently completed: a Shell Oil Co. study of the company's Deer Park refinery; a Mobil Oil Paulsboro refinery study, with follow-up from 1946-79; and a Mobil Torrence refinery study, with follow-up from 1959-80 (ERI, 1985 Unpublished). Additional details on these studies are not available as of this writing.

4.4.5. Conclusions

Fifty-five studies were reviewed to determine if there is any epidemiologic evidence for an association between gasoline exposure and cancer risk. Since unleaded gasoline was only introduced in the mid-1970s, even recent epidemiologic studies are not likely to show an unleaded gasoline effect be-

cause of the long latency period generally associated with cancer. Therefore, this review was not limited to unleaded gasoline exposure, but addressed any potential gasoline exposure.

None of the studies reviewed provided qualitative as well as quantitative estimates of gasoline exposure.

Seven studies were identified that evaluated the association between employment in the gasoline service industry and cancer risks; the industry here includes gasoline service station owners and attendants, garage workers, gasoline and fuel truck drivers, and those who reported working with gasoline. The study by Stemhagen et al. (1983) provided some evidence of an association between gasoline service station employment and risk of primary liver cancer. The remaining six studies were judged inadequate.

Twenty-five studies were reviewed that evaluated the association between employment in a petroleum refinery (a work environment with potential gasoline exposure) and cancer risk. Judged individually, these studies provided inadequate evidence of an association. However, judged collectively (Tables 4-8, 4-9, and 4-10) these studies provide suggestive evidence of an association between employment in a petroleum refinery and risk of stomach cancer, respiratory system cancer (i.e., lung, pleura, nasal cavity and sinuses), and cancer of the lymphatic and hematopoietic tissues.

Nineteen case-control studies were reviewed which evaluated employment in the petroleum industry as a cancer risk factor. The study by Howe et al. (1980) provided limited evidence of an association between petroleum industry employment and risk of bladder cancer.

Also reviewed were four protocols of epidemiologic studies in progress. These studies may provide evidence of an association between gasoline exposure and cancer risk; however, these findings are 3 to 5 years in the future.

In conclusion, these epidemiologic studies collectively provide limited evidence that employment in the petroleum industry is associated with certain types of cancer. However, the epidemiologic evidence for evaluating gasoline as a potential carcinogen is considered inadequate.

5. QUANTITATIVE RISK ESTIMATION

This quantitative chapter deals with the estimation of cancer risk due to exposure to unleaded gasoline vapor. The unit risk is defined here as the lifetime incremental cancer risk from exposure to 1 ppm of gasoline vapor in air. Uncertainties about the risk estimate and the possible role of benzene content in gasoline vapor are also addressed in this chapter.

The risk estimate for gasoline vapor represents an extrapolation below the dose range of experimental data. There is currently no solid scientific basis for any mathematical extrapolation model that relates exposure to cancer risk at the extremely low concentrations, including the unit concentration given above, that must be dealt with in evaluating environmental hazards. For practical reasons the correspondingly low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. Low-dose extrapolation must, therefore, be based on current understanding of the mechanisms of carcinogenesis. At the present time the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is based in part on the fact that a very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal response that is characteristic of mutagenesis is associated with a linear nonthreshold dose-response relationship. Indeed, there is substantial evidence from mutagenicity studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at high doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear nonthreshold dose-response relationship is also consistent with the

relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). Some supporting evidence also exists from animal experiments (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the nonthreshold model, which is linear at low doses, has been adopted by the Carcinogen Assessment Group (CAG) as the primary basis for risk extrapolation to low levels of the dose-response relationship. The risk estimates made with such a model should be regarded as conservative, representing the most plausible upper limit for the risk (i.e., the true risk is not likely to be higher than the estimate, but it could be lower).

For several reasons, the unit risk estimate based on animal bioassays is only an approximate indication of the absolute risk in populations exposed to known carcinogen concentrations. First, there are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species differences in target site susceptibility, immunological responses, hormone function, dietary factors, and disease. Second, the concept of equivalent doses for humans compared to animals on a mg/surface area basis is virtually without experimental verification as regards carcinogenic response. Finally, human populations are variable with respect to genetic constitution and diet, living environment, activity patterns, and other cultural factors.

The unit risk estimate can give a rough indication of the relative potency of a given agent as compared with other carcinogens. Such estimates are, of course, more reliable when the comparisons are based on studies in which the

test species, strain, sex, and routes of exposure are similar.

The quantitative aspect of carcinogen risk assessment is addressed here because of its possible value in the regulatory decision-making process, e.g., in setting regulatory priorities, evaluating the adequacy of technology-based controls, etc. However, the imprecision of presently available technology for estimating cancer risks to humans at low levels of exposure should be recognized. At best, the linear extrapolation model used here provides a rough but plausible estimate of the upper limit of risk from exposure to a unit concentration of gasoline vapor (i.e., with this model it is not likely that the true risk would be much more than the estimated risk, but it could be considerably lower).

The risk estimates in this paper relate only to exposure to gasoline vapor. Risks related to the entire range of compounds that may be present in air are not estimated here.

5.1. PROCEDURES FOR THE DETERMINATION OF UNIT RISK

5.1.1. Low-Dose Extrapolation Model

The mathematical formulation chosen to describe the linear nonthreshold dose-response relationship at low doses is the linearized multistage model. This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data, and it incorporates a procedure for estimating the largest possible linear slope (in the 95% confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment.

Let P(d) represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form:

$$P(d) = 1 - \exp\left[-(q_0 + q_1 d + q_1 d^2 + \ldots + q_k d^k)\right]$$

where

$$q_i \geq 0,\ i = 0, 1, 2, \ldots, k$$

Equivalently,

$$P_t(d) = 1 - \exp\left[-(q_1 d + q_2 d^2 + \ldots + q_k d^k)\right]$$

where

$$P_t(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate in the animal control group at dose d.

The point estimate of the coefficients q_i, i = 0, 1, 2, ..., k, and consequently, the extra risk function, $P_t(d)$, at any given dose d, is calculated by maximizing the likelihood function of the data. At low doses, upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit, q_1^*, on parameter q_1. Whenever $q_1 > 0$, at low doses the extra risk $P_t(d)$ has approximately the form $P_t(d) = q_1^* \times d$. Therefore, $q_1^* \times d$ is a 95% upper confidence limit on the extra risk and R/q_1^* is a 95% lower confidence limit on the dose, producing an extra risk of R. Let L_0 be the maximum value of the log-likelihood function. The upper-limit q_1^* is calculated by increasing q_1 to a value q_1^* such that when the log-likelihood is remaximized subject to this fixed value q_1^* for the linear coefficient, the resulting maximum value of the log-

likelihood L_1 satisfies the equation:

$$2\ (L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, which corresponds to a 95% upper-limit (one-sided). This approach of computing the upper confidence limit for the extra risk $P_t(d)$ is an improvement on earlier models. The upper confidence limit for the extra risk calculated at low doses is always linear. This is conceptually consistent with the linear nonthreshold concept discussed earlier. The slope, q_1^*, is taken as an upper-bound of the potency of the chemical in inducing cancer at low doses.

In fitting the dose-response model, the number of terms in the polynomial is chosen equal to (h-1), where h is the number of dose groups in the experiment, including the control group.

Whenever the multistage model does not fit the data sufficiently well, data at the highest dose is deleted and the model is refit to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square statistic

$$\chi^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i (1-P_i)}$$

is calculated where N_i is the number of animals in the i^{th} dose group, X_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the

multistage model to the data, and h is the number of remaining groups. The fit is determined to be unacceptable whenever X^2 is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients.

5.1.2. Selection of Data

For some chemicals, several studies in different animal species, strains, and sexes, each run at several doses and different routes of exposure, are available. A choice must be made as to which of the data sets from several studies to use in the model. It may also be appropriate to correct for metabolism differences between species and for absorption factors via different routes of administration. The procedures used in evaluating these data are consistent with the approach of making a maximum-likely risk estimate. They are as follows:

1. The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of the lifetime carcinogenic risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals. That is, if two sets of data show a similar dose-response relationship, and one has a very small sample size, the set of data having the larger sample size is selected for calculating the carcinogenic potency.

2. If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean

of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers A_1, A_2, ..., A_m is defined as

$$(A_1 \times A_2 \times \ldots \times A_m)^{1/m}$$

3. If two or more significant tumor sites are observed in the same study, and if the data are available, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

5.1.3. Calculation of Human Equivalent Dosages

Following the suggestion of Mantel and Schneiderman (1975), it is assumed that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the two-thirds power of the weight, as would be the case for a perfect sphere, the exposure in mg/day per two-thirds power of the weight is also considered to be equivalent exposure. In an animal experiment, this equivalent dose is computed in the following manner:

Let

L_e = duration of experiment

l_e = duration of exposure

m = average dose per day in mg during administration of the agent (i.e., during l_e), and

W = average weight of the experimental animal

Then, the lifetime exposure is:

$$d = \frac{l_e \times m}{L_e \times W^{2/3}}$$

5.1.3.1. Oral--Often exposures are not given in units of mg/day, and it becomes necessary to convert the given exposures into mg/day. Similarly, in drinking water studies, exposure is expressed as ppm in the water. For example, in most feeding studies exposure is given in terms of ppm in the diet. In these cases, the exposure in mg/day is:

$$m = ppm \times F \times r$$

where ppm is parts per million of the carcinogenic agent in the diet or water, F is the weight of the food or water consumed per day in kg, and r is the absorption fraction. In the absence of any data to the contrary, r is assumed to be equal to one. For a uniform diet, the weight of the food consumed is proportional to the calories required, which in turn is proportional to the surface area, or two-thirds power of the weight. Water demands are also assumed to be proportional to the surface area, so that

$$m \propto ppm \times W^{2/3} \times r$$

or

$$\frac{m}{rW^{2/3}} \propto ppm$$

As a result, ppm in the diet or water is often assumed to be an equivalent exposure between species. However, this is not justified for the present study, since the ratio of calories to food weight is very different in the diet of man as compared to laboratory animals, primarily due to differences in the moisture content of the foods eaten. For the same reason, the amount

of drinking water required by each species also differs. It is therefore necessary to use an empirically-derived factor, f = F/W, which is the fraction of an organism's body weight that is consumed per day as food, expressed as follows:

Species	W	Fraction of body weight consumed as f_{food}	f_{water}
Man	70	0.028	0.029
Rats	0.35	0.05	0.078
Mice	0.03	0.13	0.17

Thus, when the exposure is given as a certain dietary or water concentration in ppm, the exposure in $mg/W^{2/3}$ is

$$\frac{m}{rW^{2/3}} = \frac{ppm \times F}{W^{2/3}} = \frac{ppm \times f \times W}{W^{2/3}} = ppm \times f \times W^{1/3}$$

When exposure is given in terms of mg/kg/day = m/Wr = s, the conversion is simply

$$\frac{m}{rW^{2/3}} = s \times W^{1/3}$$

5.1.3.2. Inhalation--When exposure is via inhalation, the calculation of dose can be considered for two cases where (1) the carcinogenic agent is either a completely water-soluble gas or an aerosol and is absorbed proportionally to the amount of air breathed in, and (2) where the carcinogen is a poorly water-soluble gas which reaches an equilibrium between the air breathed and the body

compartments. After equilibrium is reached, the rate of absorption of these agents is expected to be proportional to the metabolic rate, which in turn is proportional to the rate of oxygen consumption, which in turn is a function of surface area.

5.1.3.2.1 Case 1. Agents that are in the form of particulate matter or virtually completely absorbed gases, such as sulfur dioxide, can reasonably be expected to be absorbed proportionally to the breathing rate. In this case the exposure in mg/day may be expressed as:

$$m = I \times v \times r$$

where I = inhalation rate per day in m^3, v = mg/m^3 of the agent in air, and r = the absorption fraction.

The inhalation rates, I, for various species can be calculated from the observations of the Federation of American Societies for Experimental Biology (FASEB, 1974) that 25 g mice breathe 34.5 liters/day and 113 g rats breathe 105 liters/day. For mice and rats of other weights, W (in kilograms), the surface area proportionality can be used to find breathing rates in m^3/day as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ m^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ m^3/\text{day}$$

For humans, the value of 20 m^3/day is adopted as a standard breathing rate (International Commission on Radiological Protection, 1977).* The equivalent

*The average breathing rate is 10^7 cm^3 per 8-hour workday and 2 x 10^7 cm^3 in 24 hours.

exposure in $mg/W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, $i = I/W$, based upon the previously stated relationships, are tabulated as follows:

Species	W	i = I/W
Man	70	0.29
Rats	0.35	0.64
Mice	0.03	1.3

Therefore, for particulates or completely absorbed gases, the equivalent exposure in $mg/W^{2/3}$ is

$$d = \frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed, r, is assumed to be the same for all species.

5.1.3.2.2. Case 2. The dose in mg/day of partially soluble vapors is proportional to the O_2 consumption, which in turn is proportional to $W^{2/3}$ and is also proportional to the solubility of the gas in body fluids, which can be expressed as an absorption coefficient, r, for the gas. Therefore, expressing the O_2 consumption as $O_2 = k\ W^{2/3}$, where k is a constant independent of species, it follows that:

$$m = k\ W^{2/3} \times v \times r$$

or

$$d = \frac{m}{W^{2/3}} = kvr$$

As with Case 1, in the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction, r, is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or g/m^3 in experimental animals is equivalent to the same concentration in humans. This is supported by the observation that the minimum alveolar concentration necessary to produce a given "stage" of anesthesia is similar in man and animals (Dripps et al., 1977). When the animals are exposed via the oral route and human exposure is via inhalation or vice versa, the assumption is made, unless there is pharmacokinetic evidence to the contrary, that absorption is equal by either exposure route.

5.1.4. Calculation of the Unit Risk from Animal Studies

The risk associated with d $mg/kg^{2/3}/day$ is obtained from the linearized multistage model and, for most cases of interest to risk assessment, can be adequately approximated by $P(d) = 1 - \exp(-q_1^* d)$. A "unit risk" in units X is simply the risk corresponding to an exposure of X = 1. This value is estimated by finding the number of $mg/kg^{2/3}/day$ that corresponds to one unit of X, and substituting this value into the above relationship. Thus, for example, if X is in units of g/m^3 in the air, then for case 1, $d = 0.29 \times 70^{1/3} \times 10^{-3}$ $mg/kg^{2/3}/day$, and for case 2, d = 1, when g/m^3 is the unit used to compute parameters in animal experiments.

If exposures are given in terms of ppm in air, the following calculation may be used, assuming sea level barometric pressure and a temperature of 24°C:

$$1 \text{ ppm} = 0.041 \times \text{molecular weight mg/m}^3$$

Note that an equivalent method of calculating unit risk would be to use mg/kg for the animal exposures, and then to increase the j^{th} polynomial coefficient by an amount:

$$(W_h/W_a)^{j/3} \quad j = 1, 2, \ldots, k,$$

and to use mg/kg equivalents for the unit risk values.

5.2. LIFETIME RISK ESTIMATES

5.2.1. Data Available for Risk Estimation

The chronic inhalation study of unleaded gasoline vapor conducted by the International Research and Development Corporation (IRDC, 1983; MacFarland et al., 1984) and sponsored by the American Petroleum Institute (API) is the only study that can be used to derive the carcinogenic potency of unleaded gasoline vapor. Tables 5-1 and 5-2 present dose-response data used in these calculations. The data in Table 5-2 were taken from Tables 23 and 24 of Volume 6 of the API report. All of the tumors reported in Tables 5-1 and 5-2 were observed after 18 months of study, with the exception of one kidney adenoma detected in the high-dose group at 18 months.

5.2.2. Choices of Low-Dose Extrapolation Models

In addition to the multistage model currently used by the CAG for low-dose extrapolation, estimates of risk from exposure to gasoline vapor were also determined using two other models (the probit and the Weibull models). These models cover almost the entire spectrum of risk estimates that could be generated from existing mathematical extrapolation models. These models are

TABLE 5-1. INCIDENCE RATES OF TOTAL KIDNEY TUMORS IN MALE FISCHER 344 RATS EXPOSED TO UNLEADED GASOLINE VAPOR

Experimental dose (ppm)	Standardized lifetime dose (ppm)[a]	Incidence rate[c]
0	0	0/49
67	11.96	1/59 (1.7%)[d]
292	52.14	5/56 (8.9%)
2056[b]	367.14	7/45 (15.6%)[d]

[a]The dose in ppm is assumed to be equivalent between humans and animals. Since the doses were given only 6 hours/day and 5 days/week, the lifetime dose is calculated by multiplying the factor (5 x 7) x (6/24) to each of the experimental doses.
[b]The data from this group were not used in the calculation.
[c]Tumor incidence diagnosed at termination or in rats that died after 18 months.
[d]Of the 7 tumors listed in the high-dose group, one was an adenoma that was detected at 18 months.

SOURCE: MacFarland et al., 1984.

TABLE 5-2. INCIDENCE RATES OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F1 MICE EXPOSED TO UNLEADED GASOLINE VAPOR

Experimental dose (ppm)	Standardized lifetime dose (ppm)	Carcinoma/adenoma incidence rate	Carcinoma incidence rate
0		8/57 (14.0%)	7/57 (12.3%)
67	11.96	10/52 (19.2%)	6/52 (11.5%)
292	52.14	13/57 (22.8%)	9/57 (15.8%)
2056	367.14	28/56 (50.0%)	20/56 (35.7%)

SOURCE: IRDC, 1983.

generally statistical in character, and are not derived from biological arguments, except for the multistage model, which has been used to support the somatic mutation hypothesis of carcinogenesis (Armitage and Doll, 1954; Whittemore, 1978; Whittemore and Keller, 1978). The main difference among these models is the rate at which the response function, P(d), approaches zero or P(0) as dose, d, decreases. For instance, the probit model would usually predict a smaller risk at low doses than the multistage model because of the difference of the decreasing rate in the low-dose region. However, it should be noted that one could always artificially give the multistage model the same (or even greater) rate of decrease as the probit model by making some dose transformation and/or by assuming that some of the parameters in the multistage model are zero. This, of course, is not reasonable without knowing, a priori, what the carcinogenic process for the agent is. Although the multistage model appears to be the most reasonable or at least the most general model to use, the maximum likelihood estimate generated from this model does not help to determine the shape of the dose-response curve beyond experimental exposure levels. Furthermore, maximum likelihood estimates at low doses extrapolated beyond experimental doses could be unstable depending on the amount of the lowest experimental dose; the upper-bound estimates from the multistage model at low doses are relatively more stable than maximum likelihood estimates. The upper-bound estimate can be taken as a plausible estimate at low doses if the true dose-response curve is actually linear. The upper-bound estimate means that the risks are not likely to be higher, but could be lower if the compound has a concave upward dose-response curve or a threshold at low doses. Because the estimated risk is a probability conditional to the assumption that an animal carcinogen is also a human carcinogen, the actual risk could range from a value near zero to an upper-bound estimate.

5.2.3. Calculation of Unit Risk (Risk at 1 ppm)

In the calculation of unit risk, ppm in air is assumed to be equivalent between animals and humans (see 5.1.3.2.2. Case 2). The data from the highest dose group in Table 5-1 have been excluded from the calculation because the model does not fit well if these data are included (see 5.1.1.). Furthermore, the data seem to indicate the toxic effect in the highest dose group because only two-thirds of the animals survived beyond 18 months. Using the tumor incidence data and the corresponding lifetime dose presented in Tables 5-1 and 5-2, the cancer risks at 1 ppm are calculated by means of the multistage model. The results are presented in Table 5-3. Both the 95% upper-bound estimate and the maximum likelihood estimate are given. Because the maximum likelihood estimate of the linear component in the multistage model is not zero, the upper-bound estimate is only about two times the corresponding point estimate. The cancer risk estimates in Table 5-3 can be used to represent the carcinogenic potency of unleaded gasoline vapor. The kidney data in rats and the combined hepatocellular adenoma/carcinoma data in mice are closely similar, spanning a range from 2.1×10^{-3} to 3.5×10^{-3}. This range represents one measure of uncertainty in the upper limit of potency, the lower limit being zero potency.

5.2.4. Comparison of Risk Estimates by Different Low-Dose Extrapolation Models

For comparison, the probit and the Weibull models are also used to calculate cancer risks at various dose levels. The results of these calculations are presented in Table 5-4. The maximum likelihood estimates of the parameters in each model are presented in Appendix A. The results shown in Table 5-4 indicate that all three of the models predict comparable risks (within an order of magnitude) at 1 ppm, but the difference becomes greater as the dose becomes smaller. For instance, on the basis of hepatocellular tumors, the multistage

TABLE 5-3. ESTIMATES OF CARCINOGENIC POTENCY DUE TO EXPOSURE TO 1 ppm OF UNLEADED GASOLINE VAPOR

Data base	q_1^* 95% upper-bound estimate	Maximum likelihood estimate
(1) Kidney tumor in male rats	3.1×10^{-3}	2.0×10^{-3}
(2) Hepatocelluar carcinoma/adenoma in female mice	2.1×10^{-3}	1.4×10^{-3}
Hepatocellular carcinoma in female mice	1.4×10^{-3}	8.5×10^{-4}
Geometric mean of (1) and (2)	2.7×10^{-3}	1.7×10^{-3}

TABLE 5-4. 95% UPPER-BOUND (AND MAXIMUM LIKELIHOOD) ESTIMATION OF LIFETIME RISK AT VARIOUS DOSE LEVELS, USING THREE DIFFERENT LOW-DOSE EXTRAPOLATION MODELS

Data base	Model	Dose in ppm						
		0.001	0.005	0.01	0.05	0.10	0.5	1.0
Kidney tumor, male rats	Multistage	3.53×10^{-5} (2.01×10^{-6})	1.77×10^{-5} (1.01×10^{-5})	3.53×10^{-5} (2.01×10^{-5})	1.77×10^{-4} (1.01×10^{-4})	3.53×10^{-4} (2.01×10^{-4})	1.77×10^{-3} (1.01×10^{-3})	3.53×10^{-3} (2.01×10^{-3})
	Probit	3.10×10^{-11} (7.72×10^{-13})	7.45×10^{-9} (2.48×10^{-10})	6.28×10^{-8} (2.36×10^{-9})	5.15×10^{-6} (2.74×10^{-7})	2.72×10^{-5} (1.72×10^{-6})	7.40×10^{-4} (2.39×10^{-5})	2.40×10^{-3} (3.02×10^{-4})
	Weibull	4.71×10^{-6} (3.36×10^{-7})	2.59×10^{-5} (2.15×10^{-6})	5.36×10^{-5} (4.79×10^{-6})	2.84×10^{-4} (3.07×10^{-5})	5.73×10^{-4} (6.83×10^{-5})	3.82×10^{-3} (4.38×10^{-4})	5.44×10^{-3} (9.74×10^{-4})
Hepatocellular carcinoma/ adenoma, female mice	Multistage	2.14×10^{-6} (1.44×10^{-6})	1.07×10^{-5} (7.20×10^{-6})	2.14×10^{-5} (1.44×10^{-5})	1.07×10^{-4} (7.20×10^{-5})	2.14×10^{-4} (1.44×10^{-4})	1.07×10^{-3} (7.20×10^{-4})	2.14×10^{-3}) (1.44×10^{-3})
	Probit	9.77×10^{-11} (2.85×10^{-12})	1.84×10^{-8} (6.91×10^{-10})	1.42×10^{-7} (5.97×10^{-9})	9.67×10^{-6} (5.50×10^{-7})	4.79×10^{-5} (3.14×10^{-6})	1.17×10^{-3} (1.12×10^{-4})	3.72×10^{-3} (4.24×10^{-4})
	Weibull	1.79×10^{-4} (1.94×10^{-5})	5.63×10^{-4} (6.87×10^{-5})	9.17×10^{-4} (1.18×10^{-4})	$2.81/10^{-3}$ (4.19×10^{-4})	4.53×10^{-3} (7.21×10^{-4})	1.34×10^{-2} (2.55×10^{-3})	2.11×10^{-2} (4.38×10^{-3})
Hepatocellular carcinoma only, female mice	Multistage	1.39×10^{-6} (8.53×10^{-7})	6.95×10^{-6} (4.27×10^{-6})	1.39×10^{-5} (8.53×10^{-6})	6.95×10^{-5} (4.27×10^{-5})	1.39×10^{-4} 8.53×10^{-5})	6.95×10^{-4} (4.27×10^{-4})	1.39×10^{-3} (8.53×10^{-4})
	Probit	6.79×10^{-14} (1.07×10^{-15})	5.67×10^{-11} (1.09×10^{-12})	7.88×10^{-10} (1.71×10^{-12})	1.91×10^{-7} (5.61×10^{-9})	1.56×10^{-6} (5.27×10^{-8}	1.08×10^{-4} (5.35×10^{-6})	5.13×10^{-4} (3.04×10^{-5})
	Weibull	9.26×10^{-6} (4.75×10^{-7})	4.33×10^{-5} (2.52×10^{-6})	8.38×10^{-5} (5.17×10^{-6})	3.81×10^{-4} (2.75×10^{-5})	7.17×10^{-4} (5.61×10^{-5})	3.17×10^{-3} (2.99×10^{-4})	5.88×10^{-3} (6.14×10^{-4})

model predicts a much higher risk than that predicted by the probit model at a dose level of 0.001 ppm. This observation is not surprising, since the tangent (slope) of the probit curve approaches zero as dose approaches zero, while the slope of the multistage curve is linear at low doses. The risks predicted by the Weibull model on the basis of kidney tumors and hepatocellular carcinomas/adenomas are higher on the entire exposure range (0.001 ppm to 1.0 ppm) than the multistage model because the Weibull model shows a more-than-linear dose-response relationship, which is not considered biologically plausible. For this reason, low-dose linearity has intuitive appeal. For example, the incidence of hepatocellular tumors at the lowest experimental dose (11.96 ppm) is 10/52, and the incidence in controls (0 ppm) is 8/57. In the absence of knowledge as to the shape of the dose-response relationship below the lowest experimental dose level, the only reasonable method of estimating cancer potency without having the possibility of seriously underestimating the true risk is to use linear extrapolation. That is, the slope (potency) is calculated by:

$$(10/52 - 8/57)/11.96 = 4.3 \times 10^{-3}/\text{ppm}$$

This crude estimate is about threefold greater than the maximum likelihood estimate (1.44×10^{-3}/ppm) calculated from the multistage model which utilizes all the data points, including the lowest data point used in the above calculation.

If one assumes that the dose-response curve is concave upward at low doses, the risk calculated by the low-dose linear model can be considered an upper-bound estimate of the true risk; it is the only plausible estimate that does not have the potential for underestimating the true risk on the basis of the data given. Any more precise estimate would require either further assump-

tions about the shape of the dose-response curve or biological knowledge of the mechanism of carcinogenic action.

In comparing the models in Table 5-4, it should be noted that the multistage model has higher maximum likelihood estimates than the probit model for all doses except for hepatocellular carcinoma/adenoma in female mice at 0.5 and 1.0 ppm. This result is attributed to the low-dose linearity characteristic of the multistage model's prediction of the dose-response relationship. In fact, the multistage model produces a linear relationship over the entire range of exposure estimates (0.001 ppm to 1.0 ppm) that would be produced by emissions of controlled and uncontrolled gasoline vapors. Based on its low-dose linearity characteristic, the multistage model is selected as the model EPA should rely upon to estimate risk of exposure to gasoline vapor because it provides conservative estimates at low doses and an adequately conservative approximation of risk at higher doses.

5.2.5. Uncertainties of Quantitative Risk Assessment

5.2.5.1. Uncertainties Associated with Potency Estimates--It is well known that different models, all of which might fit well with a given set of data over the experimental dose range, might nevertheless predict drastically different responses at low doses. Gasoline vapor data are no exception. As shown in Table 5-4, the multistage model predicts much higher risk than the probit model at 0.001 ppm, on the basis of liver tumor incidence. The risk estimate at low doses for unleaded gasoline vapor is calculated by using the linearized multistage model, which is linear at low doses. The potency estimate derived from such a model has been considered an upper-bound estimate on the assumption that the shape of the dose-response curve is upwardly concave at low dose levels. The carcinogenic potency, q_1^*, as derived from the multistage model, represents the 95% upper-bound confidence estimate, reflecting only the statis-

tical variability of the response data.

The low-dose risk estimate derived from animal data must further be extrapolated to humans. There are many factors that must be considered in extrapolating risk from animals to humans. Included among these factors are differences between humans and animals with respect to life span, body size, genetic variability, and pharmacokinetic effects such as metabolism and excretion patterns. In assessing the risks of gasoline vapor, it was assumed that ppm in air will induce the same tumor response in humans as in animals. It is questionable, however, whether this simple assumption is capable of accounting for all the differences between humans and the animals that were used in the gasoline experiment of the IRDC (1983).

5.2.5.2. Uncertainties Regarding the Assumption of Carcinogenicity in Humans Based on Animal Data--An important but often neglected factor in quantitative risk assessment is the weight of evidence that gasoline vapor is carcinogenic in humans. The quantitative risk estimate derived from animal data gives only a conditional probability of cancer on the assumption that the agent is carcinogenic in humans. It is not possible to test the hypothesis that all animal carcinogens are also human carcinogens since humans have not been exposed to most chemicals causing cancer in animals at sufficient dosages to detect a positive response. This hypotheses, however, is strengthened by the findings that, with very few exceptions, known human carcinogens also induce cancer in experimental animals and by the similarities in the biology of the tumorigenic response across the animal kingdom.

There is some evidence that induction of tumors by gasoline exposure is unique to male rats because this response is related to kidney damage resulting from the reaction of gasoline hydrocarbons with an alpha-2-microglobulin that only the male rat produces in large quantities. If this is true, then

the assumption that gasoline vapors are carcinogenic in humans is weakened. The CAG takes the viewpoint that the kidney of the male rat does not respond to gasoline vapors in a unique manner for several reasons:

1. The link between acute and chronic hydrocarbon nephropathy and carcinogenicity is not clear, nor can it be established from the data generated in this bioassay.
2. The kidney of experimental animals has been demonstrated to be the target for more than 100 carcinogenic chemicals (Hard, 1976).
3. A statistically significant increase in liver tumors was detected in gasoline aerosol-exposed female mice with no report of accompanying pathology (MacFarland, 1983).
4. Exposure to a synthetic fuel (RJ-5) for one year resulted in a 25% incidence of alveolar carcinomas in CF-1 mice, while exposure to another synthetic fuel (JP-10) resulted in adrenal tumors in 14% of tested versus 5% of control male hamsters (McNaughton and Uddin, 1983). In the chronic gasoline aerosol exposure (MacFarland, 1983), a renal sarcoma was reported in an intermediate-dose female rat, while three renal neoplasms were reported in two high-dose female mice. While none of these responses was considered statistically significant individually (lung tumors are considered highly inducible in CF-1 mice), collectively they provide suggestive evidence for induction of tumors in other organs as well as for induction of kidney tumors in species other than the male rat.

5.2.5.3. Uncertainties Associated with the Use of Potency Estimates to Predict Individual Risks in Real-Life Exposure Patterns--The carcinogenic potency estimate for unleaded gasoline can be used to predict the human cancer risk from continuous gasoline exposure, subject to the uncertainties previously discussed. The actual human exposure to gasoline vapor, however, is likely to

be only a few minutes per week. The questions then arise as to whether this exposure can be averaged over an entire week in order to arrive at a continuous exposure estimate, and whether overestimation or underestimation of the risk of intermittent doses would result from such averaging. The available data for analogous situations indicate that either of the two possibilities may be true. In studying factors modulating the carcinogenicity of benzidine, Vesselinovitch et al. (1975) demonstrated that twice-weekly administration of benzidine by stomach intubation was less effective in inducing liver and harderian gland tumors but more effective in inducing lung adenomas than the continuous (daily) feeding of equivalent doses.

Of possible relevance in considering exposures to gasoline vapor are studies that have been conducted on low-linear energy transfer (LET) radiation. After reviewing all available data on radiation-induced genetic and tumorigenic effects in plants, "simple" biological systems, animals, and humans, the National Council on Radiation Protection and Measurements (NCRP, 1980) concluded that, for a given total dose, the high-dose-rate exposure is more effective than the low-dose-rate exposure in producing the response, and that the difference in response between the two exposure patterns diminishes as the total dose decreases. The applicability of this observation in the case of human exposure to gasoline vapor is not known. If one assumes that gasoline vapor has the same dose-rate effect as low-LET radiation exposure, then the use of averaging dose would not overestimate the risk and would give a close approximation to the true risk when the exposure level is small. In this discussion, it is assumed that the dose-response relationship obtained previously predicts accurately the true risk when the dose is continuous.

In general, three possible circumstances can occur in estimating cancer risk due to gasoline vapor exposure in real-life situations when the averaging

dose is used:

1. The real-life (intermittent) exposure pattern and the continuous (averaging dose) exposure patterns are equally effective. In this case the risk estimate is unbiased.
2. The real-life exposure pattern is more effective than the continuous exposure pattern. In this case the risk is underestimated when the dose is averaged.
3. The real-life exposure pattern is less effective than the continuous exposure pattern. In this case the risk is overestimated when the dose is averaged.

Not enough is known about the mechanism of action to state which possibility is the most likely or to know the magnitude of either the overestimation or the underestimation.

5.2.5.4. Uncertainties Associated with Differences in Composition of Gasoline Vapors and Wholly Vaporized Gasoline--According to results of subchronic studies sponsored by the API, the 0° to 145°F distillate fraction of unleaded gasoline as well as C4-C5 aliphatic hydrocarbons, which are the primary constituents of this fraction, did not cause detectable nephrotoxicity in rats (IIT Research Institute, 1985a, b). It was further shown that the 145° to 280°F fractions contained most of the nephrotoxic activity and that the specific compounds responsible for most of the toxicity were branched-chain aliphatics 6 to 9 carbons in length. Since the 0° to 145°F distillate fraction is much more volatile at ambient temperatures than the heavier distillates, the vapor fraction would be expectd to contain a much greater percentage of short-chain hydrocarbons. Analyses of bulk liquid gasoline and vapor at various ambient temperatures have shown that the percentage of hydrocarbons in the vapor fraction equal to or greater than C6 is about 1/5 that of bulk liquid gasoline (U.S.

EPA, 1980). For the most toxic components of gasoline, such as trimethylpentane, the disparity is even greater. If in fact the development of nephrotoxicity in male rats leads directly to cancer, then the quantitative assessment of risk may be overly conservative. However, the linkage between nephrotoxicity and cancer has not been proven. Moreover, there are no data to indicate which fraction is responsible for induction of liver tumors in mice. Nevertheless, the disparity in composition of whole aerosolized gasoline used in the chronic cancer assessment study (Halder et al., 1984) and gasoline vapors results in an additional degree of uncertainty.

5.2.6. Cancer Risk Attributable to Benzene Content in Gasoline Vapor

The quantitative estimate of cancer risk from exposure to benzene has recently been updated (U.S. EPA, 1985). The unit risk was derived for leukemia in humans due to lifetime exposure to 1 ppm benzene in the air. Using various models and combinations of assumptions and epidemiologic studies, 21 unit risk estimates, ranging from 0.9×10^{-2} to 1×10^{-1}, were obtained. Based on the criteria of using the data for all epidemiologic studies with reasonable exposure information and an average value over all mathematical models believed to be plausible, a combined risk estimate of 2.6×10^{-2} was derived. This was taken to be the CAG's best assessment of unit risk.

To estimate the cancer incidence which could be attributed to the benzene content of the gasoline mixture, the following assumptions were made:

1. The tumor response to benzene is additive to the response produced by other components; that is, benzene does not act synergistically or antagonistically with other components.
2. A particular air concentration (measured as ppm) produces the same effect in animals and humans.

With these assumptions, the animal tumor incidence expected from the benzene component alone, relative to the incidence expected from the mixture is:

$$AR = (\text{benzene potency/gasoline potency}) \times 0.02$$
$$= (2.6 \times 10^{-2}/2.7 \times 10^{-3}) \times 0.02$$
$$= 0.19$$

where 0.02 was the fractional benzene content of gasoline in the rat study.

This calculation indicates that, irrespective of the tumor site, the benzene component is expected to account for about 20% of the total response. This small an incidence is undetectable, since 20% of the kidney cancer incidence at the high dose (Table 5-1) is only 0.2 x 16% = 3%, which is only about one animal out of 45 in that group. Therefore, the observed response has no detectable benzene component.

Unfortunately, there is no evidence from the benzene or gasoline literature to support or deny the additivity assumption. There is abundant evidence that a carcinogen or a noncarcinogen could modify (enhance or inhibit) the carcinogenic action of another compound. Since gasoline vapor contains more than one chemical compound, such interactive effects are possible. Further research is needed to identify which specific compounds are responsible for the carcinogenic effect and to define the factors and other chemicals which could modify their action.

5.3. CONCLUSIONS OF THE HEALTH EFFECTS INSTITUTE REGARDING THE POTENTIAL ADVERSE HEALTH EFFECTS OF EXPOSURE TO GASOLINE VAPORS

Both the Motor Vehicle Manufacturers Association and the EPA requested that the Health Effects Institute (HEI) undertake a review of the issues con-

cerning potential adverse health effects of exposure to vapors of unleaded gasoline. The HEI carried out this review, which has been published in a special report (HEI, 1985). On the basis of the API-supported chronic animal inhalation studies (MacFarland et al., 1984), the HEI concluded that wholly vaporized gasoline is an animal carcinogen and a presumptive human carcinogen. Taken collectively, the epidemiologic studies were considered to provide weakly suggestive evidence, but did not provide an association between exposure to petroleum vapors and increased kidney cancer. Thus, the available epidemiologic evidence was considered to neither negate nor confirm the interpretation that gasoline vapors are a potential human carcinogen.

Because of the uncertainty regarding the carcinogenicity of gasoline vapors in humans, the differences in composition of gasoline vapors to which humans are exposed and the wholly vaporized gasoline used in the animal studies, and because of the different patterns of exposure in humans and experimental animals, the HEI considered the development of a meaningful and realistic quantitative risk assessment to be very problematic. On the basis of the available animal studies and established guidelines, the HEI agreed that the existing data can be used to calculate an upper-bound risk factor for gasoline vapors as the EPA has done. The HEI cautions, however, that the associated health hazards, if any, cannot be established without additional data, and that the actual risk may in fact be anywhere between zero and the upper bound.

5.4. SUMMARY OF QUANTITATIVE RISK ESTIMATION

Data from the API study on kidney tumors in male rats and liver adenomas and carcinomas in female mice were used to derive an estimate of the incremental upper-limit unit risk due to continuous human exposure to 1 ppm of unleaded gasoline. Since the animals breathed the complete mixture under laboratory conditions, whereas humans are expected to breathe only the more volatile com-

ponents of the mixture, the estimates are uncertain. The estimates from the mouse and rat data are similar: 2.1×10^{-3} $(ppm)^{-1}$ from mouse data and 3.5×10^{-3} $(ppm)^{-1}$ from rat data.

The presence of 2% benzene in the unleaded gasoline mixture could theoretically contribute to the response, although the mouse liver and rat kidney have not been target organs in animal experiments with benzene. Based on those experiments, it is estimated that the contribution of benzene to the response observed in the API unleaded gasoline studies could be on the order of 20%. However, there is no qualitative evidence that benzene actually is contributing to the response.

6. REFERENCES

Alden, C.L., R.L. Kanerva, G. Ridder, and L.C. Stone. 1983. The pathogenesis of nephrotoxicity of volatile hydrocarbons in the male rat. G.P. Hemstreet III, J.J. Thorpe, and M.L. Kane, eds. Proceedings of the Workshop on the Kidney Effects of Hydrocarbons, Boston, MA, July 18-20. American Petroleum Institute, pp. 154-170.

Alderson, M. R., and N.S. Rattan. 1980. Mortality of workers in an isopropyl alcohol plant and two MEK plants. Br. J. Ind. Med. 37:85-89.

Alexander, V., S.S. Leffingwell, J.W. Lloyd, R.J. Waxweiler, and R.L. Miller. 1982. Investigation of an apparent increased prevalence of brain tumors in a U.S. petrochemical plant. Ann. N.Y. Acad. Sci. 381:97-107.

Anscombe, F.J. 1956. On estimating binomial response relations. Biometrika 43:461-464.

Armitage, P., and R. Doll. 1954. The age distribution of cancer and a multi-stage theory of carcinogenesis. Br. J. Cancer 8:1-12.

Austin, D.F., V.E. Nelson, and L.F. Johnson. 1984. Epidemiological study of the incidence of cancer as related to industrial emissions in Contra County, California. California Dept. of Health Services, Emeryville, CA. EPA-600/1-84-008. NTIS PC A05/MF A01.

Austin, S.G., and A.R. Schnatter. 1983. A cohort mortality study of petrochemical workers. J. Occup. Med. 25:304-312.

Australian Institute of Petroleum Ltd. and the University of Melbourne, Department of Community Medicine (AIP-UM/DCM). 1984. Health Watch: The Australian petroleum industry health surveillance programme triennial report, 1980-1983. 159 Barry Street, Carlton, Vic. 3053, Australia.

Australian Institute of Petroleum Ltd. and the University of Melbourne, Department of Community Medicine (AIP-UM/DCM). 1983. Health Watch: The Australian petroleum industry health surveillance programme annual report, 1984. 159 Barry Street, Carlton, Vic. 3053, Australia.

Bailer, J.C., III, and F. Ederer. 1964. Significance factors for the ratio of a Poisson variable to its expectation. Biometrics 20:639-643.

Baird, V.C. 1967. Effects of atmospheric contamination on cancer mortality in petroleum refinery employees. J. Occup. Med. 9:415-420.

Barron, V., and B. Divine. 1985. The Texaco mortality study: Case-control analysis of brain tumors in white male refinery, petrochemical and research workers. Am. J. Epidemiol. 122:519-520 (meeting abstract).

Bingham, E., R.P. Trosset, and D. Warshawsky. 1980. Carcinogenic potential of petroleum hydrocarbons: A critical review of the literature. J. Environ. Pathol. Toxicol. 3(42):483-563.

Bishop, Y.M.M., S.E. Fienberg, and P.W. Holland. 1977. Discrete multivariate analysis: Theory and practice. Cambridge, MA: The MIT Press.

Blattner, W.A., A. Blair, and T.J. Mason. 1981. Multiple myeloma in the United States, 1950-1975. Cancer 48:2547-2554.

Blot, W.T., and J.F. Fraumeni, Jr. 1976. Geographic patterns of lung cancer: Industrial correlations. Am. J. Epidemiol. 103:539-550.

Blot, W.T., L.A. Birinton, and J.F. Fraumeni, Jr., et al. 1977. Cancer mortality in U.S. counties with petroleum industries. Science 198:51-53.

Brandt, L., P.G. Nilsson, and F. Mitelman. 1978. Occupational exposure to petroleum products in men with acute non-lymphocytic leukemia. Br. Med. J. 1:553.

Breslow, N.E., N.E. Day, K.T. Halvorsen, R.L. Prentice, and C. Sabai. 1978. Estimation of multiple relative risk functions in matched case-control studies. Am. J. Epidemiol. 108:299-307.

Breslow, N.E., and N.E. Day. 1980. Statistical methods in cancer research. Vol. I. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, World Health Organization. IARC publication No. 32.

CANCERLINE. 1978. CANCERLINE DATABASE, File ID No. CARC/78/03125, Occupational characteristics of patients with leukemia and lymphogranulomatosis. Bethesda, MD: National Library of Medicine.

Chiang, C.L. 1961. Standard error of the age-adjusted death rate. Vital Statistics Special Report 47:275-285.

Christie, D., K. Robinson, I. Gordon, and I. Rockett. 1984. Health Watch: The Australian petroleum industry health study surveillance programme. Med. J. Aus. 141:331-334.

Clayton Environmental Consultants, Inc. Undated. Industrial hygiene monitoring manual for petroleum refineries and selected petrochemical operations. Prepared for the American Petroleum Institute under Contract No. LER-40-73. Washington, DC: American Petroleum Institute.

Cole, P., R. Hoover, and G.H. Friedell. 1972. Occupation and cancer of the lower urinary tract. Cancer 29:1250-1260.

Copeland, K.T., H. Checkowag, A.J. McMichael, and R.H. Holbrook. 1977. Bias due to misclassification in the estimation of relative risk. Am. J. Epidemiol. 105:488-495.

Cornfield, J. 1956. A statistical problem arising from retrospective studies. In: Neyman, J., ed. Proceedings of the Third Berkeley Symposium, Vol. IV. Berkeley, CA: University of California Press, pp. 135-148.

Divine, B.J. 1980. Another view: Comments on mortality among workers employed in petroleum refining and petrochemical plants (letter). J. Occup. Med. 22:640.

Divine, B.J., V. Barron, and S.D. Kaplan. 1985. Texaco mortality study. I. Mortality among refinery, petrochemical, and research workers. J. Occup. Med. 27:445-447.

Domask, W.G. 1984. Introduction to petroleum hydrocarbons: Chemistry and composition in relation to petroleum-derived fuels and solvents. In: Mehlman, M.A., ed. Renal effects of petroleum hydrocarbons: Advances in modern environmental toxicology, Vol. VII. Princeton, NJ: Princeton Scientific Publishers, Inc., pp. 1-25.

Domiano, S.F., J.E. Vena, and M.K. Swanson. 1985. Gasoline exposure, smoking, and kidney cancer. J. Occup. Med. 27:389-399.

Dripps, R.D., J.E. Eckenhoff, and L.D. Vandem. 1977. Introduction to anesthesia: The principles of safe practice. 5th ed. Philadelphia, PA: W.B. Saunders Company, pp. 121-123.

Dunham, L.J., A.S. Rabson, H. L. Stewart, et al. 1968. Rates, interview, and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. J. Natl. Cancer Inst. 41:683-709.

Enterline, P.E., and J. Viren. 1984. Letter from Neil K. Weaver of the American Petroleum Institute to William D. Ruckelshaus, Administrator, U.S. EPA, June 4, 1984. Kidney cancer and gasoline exposure--A literature review. FYI-AX-1181-0148.

Epidemiology Resources, Inc. (ERI). 1985. Feasibility of case-control studies of kidney cancer and hydrocarbon exposure among petroleum company workers. Submitted to the American Petroleum Institute and subsequently submitted to the U.S. EPA. FYI-AX-0685-0280 Supplement Sequence 0. Unpublished.

Federation of American Societies for Experimental Biology (FASEB). 1974. 2nd ed. Vol. III. Philip L. Altman and Dorothy S. Dittmen, eds. Bethesda, MD. Library of Congress No. 72-87738.

Fleiss, J.L. 1981. Statistical methods for rates and proportions. New York, NY: John Wiley and Sons, pp. 87-90.

Gafafer, W.M. 1940. Disabling morbidity and mortality from cancer among the male employees of an oil refining company with reference to age, site, and duration, 1933-1938 inclusive. Public Health Rep. 55:1517-1526.

Gart, J.J. 1970. Point and interval estimation of the common odds ratio in the combination of 2 x 2 tables with fixed marginals. Biometrika 57: 471-475.

Goodman, D.G., J.M. Ward, R.A. Squire, K. C. Chu, and M.S. Linhart. 1979. Neoplastic and nonneoplastic lesions in aging F344 rats. Toxicol. Appl. Pharmacol. 48:237-248.

Gottlieb, M.S. 1980. Lung cancer and the petroleum industry in Louisiana. J. Occup. Med. 22:384-388.

Gottlieb, M.S., and J.K. Carr. 1981. Mortality studies on lung, pancreas, esophageal, and other cancers in Louisiana. In: Peto, R., and M. Schneiderman, eds. Branbury Report 9: Quantification of Occupational Cancer. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, pp. 195-204.

Gottlieb, M.S., and L.W. Pickle. 1981. Bladder cancer mortlaity in Louisiana. J. La. State Med. Soc. 133:6-9.

Gottlieb, M.S., L.W. Pickle, W.J. Blot, and J.F. Fraumeni, Jr. 1979. Lung cancer in Louisiana: Death certificate analysis. J. Natl. Cancer Inst. 63:1131-1137.

Gustafson, T.L. 1984. EPISTAT statistical package for the IBM personal computer. Available from the author, 1705 Gattis School Road, Round Rock, TX.

Haldane, J.B.S. 1955. The estimation and significance of the logarithm of ratio of frequencies. Ann. Hum. Genet. 20:309-311.

Halder, C.A., T.M. Warne, and N.S. Hatoum. 1984. Renal toxicity of gasoline and related petroleum naphtha in male rats. G.P. Hemstreet III, J.J. Thorpe, and M.L. Kane, eds. Proceedings of the Workshop on the Kidney Effects of Hydrocarbons, Boston, MA, July 18-20. In: Advances in environmental toxicology, Vol. 7. Princeton, NJ: Princeton Scientific Publishers.

Hanis, N.M. 1977. A study of intestinal cancer mortality in a population of Canadian oil workers. Submitted in partial fulfillment of the requirements for the degree of doctor of philosophy. The University of Western Ontario. London, Ontario.

Hanis, N.M., T.M. Holmes, L.G. Shallenberger, and K.E. Jones. 1982. Epidemiologic study of refinery and chemical plant workers. J. Occup. Med. 24:203-212.

Hanis, N.M., K.M. Stavraky, and J.L. Fowler. 1979. Cancer mortality in oil refinery workers. J. Occup. Med. 21:167-174.

Hanis, N.M., L.G. Shallenberger, and D.L. Donaleski, and E.A. Sales. 1985a. A retrospective mortality study of workers in three major U.S. refineries and chemical plants. Part I. Comparisons with U.S. population. J. Occup. Med. 21:283-292.

Hanis, N.M., L.G. Shallenberger, and D.L. Donaleski, and E.A. Sales. 1985b. A retrospective mortality study of workers in three major U.S. refineries and chemical plants. Part II. Internal comparison by geographic site, occupation and smoking history. J. Occup. Med. 27:361-369.

Hard, G.C. 1976. Tumors of the kidney, renal pelvis, and ureter. In: Turosov, J.S., ed. Pathology of tumors in laboratory animals--tumors of the rat. IARC Scientific Publication No. 6, 1(Part 2):73-102.

Health Effects Institute (HEI), Boston, MA. 1985 (Sept.) Gasoline vapor exposure and human cancer: Evaluation of existing scientific information and recommendations for future research. Report of the Institute's Health Review Committee.

Heary, C.D., H. Ury, and A. Siegelaub, et al. 1980. Lack of association between cancer incidence and residence near petrochemical industry in the San Francisco Bay area. J. Natl. Cancer Inst. 64:1295-1299.

Heath, C.W., Jr. 1982. The leukemias. In: Schottenfeld, D., and J.F. Fraumeni, Jr., eds. Cancer epidemiology and prevention. Philadelphia, PA: W.B. Saunders Company, pp. 728-738.

Henderson, B.E., R.J. Gordon, H. Menck, J. Soohoo, S.P. Martin, and M.C. Pike. 1975. Lung cancer and air pollution in south-central Los Angeles County. Am. J. Epidemiol. 101:477-488.

Hendricks, N., C.M. Berry, J.G. Lione, and J.J. Thorpe. 1959. Cancer of the scrotum in wax pressmen. Arch. Environ. Health 19:524-529.

Higginson, J., C. Muir, and P.A. Buffler. 1984. The epidemiology of renal carcinoma in humans with a note on the effect of exposure to gasoline. In: Mehlman, M.A., ed. Renal effects of petroleum hydrocarbons: Advances in modern environmental toxicology, Vol. VII. Princeton, NJ: Princeton Scientific Publishers, Inc., pp. 203-226.

Hoover, R.N., P.H. Strasser, M. Child, et al. 1980. Artificial sweeteners and bladder cancer: preliminary results. Lancet 1:837-840.

Howe, G.R., J.D. Burch, and A.B. Miller, et al. 1977. Artificial sweeteners and bladder cancer. Lancet 2:578-581.

Howe, G.R., J.D. Burch, A.B. Miller, G.M. Cook, J. Esteve, B. Morrison, P. Gordon, L.W. Chambers, G., Fodor, and G.M. Winsor. 1980. Tobacco use, occupation, coffee, various nutrients, and bladder cancer. J. Natl. Cancer Inst. 64:701-713.

Howe, R.B., and K.S. Crump. 1982. GLOBAL82: A computer program to extrapolate quantal animal toxicity data to low doses. OSHA Contract No. 41 USC252C3.

IIT Research Institute, Chicago, IL. 1985a (Feb.). Thirteen-week inhalation toxicity study of a 0+145°F gasoline distillate fraction in rats. Sponsored by the American Petroleum Institute.

IIT Research Institute, Chicago, IL. 1985b (Mar.). Thirteen-week inhalation toxicity study of C4/C5 hydrocarbon blends in rats. Sponsored by the American Petroleum Institute.

International Commission on Radiological Protection (ICRP). 1977. Recommendation of the ICRP. Pub. No. 26, adopted Jan. 17, 1977. Oxford, England: Pergamon Press.

International Research and Development Corporation (IRDC), Mattawan, MI. 1982. Motor fuel chronic inhalation study. 6 vols. Sponsored by the American Petroleum Institute. Interim report.

International Research and Development Corporation (IRDC), Mattawan, MI. 1983 (Sept. 15). Motor fuel chronic inhalation study. 6 vols. Sponsored by the American Petroleum Institute.

Ipsen, J. Computer program available from: The Institute of Social Medicine, University of Aarhus, Denmark. Unpublished.

Joyner, R.E. 1982. American Petroleum Institute research activities, and U.S. aspects of regulatory scene concerning oil employees and publich health. In: Health & hazards in a changing oil scene. Proceedings of the Institute of Petroleum, 1982 annual conference, London, U.K. Chicester, U.K.: John Wiley & Sons, pp. 79-88.

Kaldor, J., J.A. Harris, E. Glazer, S. Glazer, R. Neutra, R.V. Mayberry, L. Robinson, and D. Reed. 1984. Statistical association between cancer incidence and major-cause mortality, and estimated residential exposure to air emissions from petroleum and chemical plants. Environ. Health Perspect. 54:319-332.

Kaplan, S.D. 1982. Mortality study of petroleum refinery workers: Update of follow-up. Draft Final Report. Submitted to the American Petroleum Institute, Washington, DC. Unpublished.

Kaplan, S.D. 1985. Second follow-up update, independent verification of vital status, and clarification of cohort definition and initial data collection of OH-1 cohort. Final Report. Submitted to the American Petroleum Institute, Washington, DC. Unpublished.

Key, C.R. 1981. Cancer incidence and mortality in New Mexico, 1973-1977. In: J.L. Young, Jr., C.L. Percy, and A.J. Asire, eds. Surveillance, epidemiology, and end results: Incidence and mortality data, 1973-7. DHHS (NIH) Pub. No. 81-2330. Washington, DC: Government Printding Office, pp. 489-595.

Kitchen, D.N. 1983. Neoplastic renal effects of unleaded gasoline in Fischer 344 rats. G.P. Hemstreet III, J.J. Thorpe, and M.L. Kane, eds. Proceedings of the Workshop on the Kidney Effects of Hydrocarbons, Boston, MA, July 18-20. American Petroleum Institute, pp. 92-102.

Kovar, J., and D. Krewski. 1981. RISK81: A computer program for low-dose extrapolation of quantal response toxicity data. Department of Health and Welfare, Canada.

Leese, W.L.B. 1982. Institute of Petroleum health research activities. In: Health and hazards in a changing oil scene. Proceedings of the Institute of Petroleum, 1982 annual conference, London, U.K. Chicester, U.K.: John Wiley & Sons, pp. 79-88.

Lin, R.S., and I.I. Kessler. 1979. Epidemiologic finding in testicular cancer. Am. J. Epidemiol. 110:357.

Lin, R.S., and I.I. Kessler. 1981. A multifactorial model for pancreatic cancer in man. J. Am. Med. Assoc. 245:147-152.

Linet, M.S. 1986 (Apr.). Benzene epidemiology review. Prepared for the Carcinogen Assessment Group, U.S. Environmental Protection Agency, by ICF, Inc., Washington, DC. Draft report.

Loury, D.J., and B.E. Butterworth. 1986. Kidney-specific DNA repair assay: an evaluation of unleaded gasoline. CIIT Activities, Chemical Industry Institute of Toxicology 6:2-7.

MacFarland, H.N. 1983. Xenobiotic-induced kidney lesions: Hydrocarbons--the PS-6 90-day and 2-year gasoline studies. G.P. Hemstreet III, J.J. Thorpe, and M.L. Kane, eds. Proceedings of the Workshop on the Kidney Effects of Hydrocarbons, Boston, MA, July 18-20. American Petroleum Institute, pp. 68-74.

MacFarland, H.N., C.E. Ulrich, C.E. Holdsworth, D.N. Kitchen, W.H. Halliwell, and S.C. Blum. 1984. A chronic inhalation study with unleaded gasoline vapor. J. Am. Coll. Toxicol. 3:231-248.

MacNaughton, M.G., and D.E. Uddin. 1983. Toxicology of mixed distillates and high-energy synthetic fuels. G.P. Hemstreet III, J.J. Thorpe, and M.L. Kane, eds. Proceedings of the Workshop on the Kidney Effects of Hydrocarbons, Boston, MA, July 18-20. American Petroleum Institute, pp. 171-185.

Mantel, N. 1963. Chi-square tests with one degree of freedom: Extension of the Mantel-Haenszel procedure. J. Am. Stat. Assoc. 58:690-700.

Mantel, N., and W. Haenszel. 1959. Statistical aspect of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22: 719-748.

Mantel, N., and M.A. Schneiderman. 1975. Estimating "safe" levels, a hazardous undertaking. Cancer Res. 35:1379-1386.

Marsh, C.M., and M. Preininger. 1980. OCMAP: A user-oriented occupational cohort mortality analysis program. Am. Stat. 34:254.

Mason, T.J., F.W. McKay, R. Hoover, W.J. Blot, and J.F. Fraumeni, Jr. 1975. Atlas of cancer mortality for U.S. counties: 1950-1969. DHEW Pub. No. (NIH) 75-780, Washington, DC: U.S. Government Printing Office.

McGraw, D.S., R.E. Joyner, and P. Cole. 1985. Excess leukemia in a refinery population. J. Occup. Med. 27:220-222.

McLaughlin, J.K. 1984. Risk factors from a population-based case-control study of renal cancer. In: Mehlman, M.A., ed. Renal effects of petroleum hydrocarbons: Advances in modern environmental toxicology, Vol. VII. Princeton, NJ: Princeton Scientific Publishers, Inc., pp. 227-244.

McLaughlin, J.K., W.J. Blot, J.S. Mandel, L.M. Schuman, E.S. Mehl, and J.F. Fraumeni, Jr. 1983. Etiology of cancer of the renal pelvis. J. Natl. Cancer Inst. 71:287-291.

McLaughlin, J.K., J.S. Mandel, W.J. Blot, L.M. Schuman, E.S. Mehl, and J.F. Fraumeni, Jr. 1984. A population-based case-control study of renal cell carcinoma. J. Natl. Cancer Inst. 72:275-284.

McMichael, A.J. 1976. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. J. Occup. Med. 18:165-168.

McMichael, A.J., R. Spirtas, L.L. Kupper, et al. 1975. Solvent exposure and leukemia among rubber workers: An epidemiologic study. J. Occup. Med. 17:234-239.

Menk, H.R., and B.E. Henderson. 1976. Occupational differences in rates of lung cancer. J. Occup. Med. 18:797-801.

Miettinen, O.S. 1970. Estimation of relative risk from individually matched series. Biometrics 26:75-86.

Miettinen, O.S. 1974. Simple interval estimation of risk ratio. Am. J. Epidemiol. 100:515-516.

Milham, S., Jr. 1983. Occupational mortality in Washington State 1950-1979. Prepared for the Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH. NTIS No. PB84-199769.

Miller, A.B., and G.B. Howe. 1977. Artificial sweeteners and bladder cancer (letter). Lancet 2:1221-1222.

Mommsen, S., and J. Aagaard. 1983a. Tobacco as a risk factor to bladder cancer. Carcinogenesis 4:335.

Mommsen, S., and J. Aagaard. 1983b. A case-control study of bladder cancer A multivariate, stratified analysis of a low risk population. Dan. Med. Bull. 30:427.

Mommsen, S., and J. Aagaard. 1984. Occupational exposures as risk indicator of male bladder carcinoma in a predominantly rural area. Acta Radiol. Oncol. 23:147-152.

Mommsen, S., and A. Sell. 1983. Prostatic hypertrophy and venereal disease as possible risk factors in the development of bladder cancer. Urol. Res. 11:49.

Mommsen, S., J. Aagaard, and A. Sell. 1982. An epidemiological case-control study of bladder cancer in males from a predominantly rural district. Eur. J. Cancer Clin. Oncol. 18:1205-1210.

Mommsen, S., J. Aagaard, and A. Sell. 1983a. A case-control study of female bladder cancer. Eur. J. Cancer Clin. Oncol. 19:725.

Mommsen, S., J. Aagaard, and A. Sell. 1983b. An epidemiological study of bladder cancer in males from a predominantly rural district. Scand. J. Urol. Nephrol. 17:307-312.

Monson, R.R. 1974. Analysis of relative survival and proportional mortality. Comput. Biomed. Res. 7:325-332.

Morgan, R.W., and O. Wong. 1983. Cause-specific mortality among employees at the Chevron Richmond and El Segundo refineries. Submitted by Environmental Health Associates, Inc., to Standard Oil of California. Unpublished.

Morgan, R.W., and O. Wong. 1984. An epidemiologic analysis of the mortality experience of Mobil Oil Corporation employees at the Beaumont, Texas, Refinery. Unpublished. Submitted by Environmental Health Associates, Inc. Unpublished.

Moure-Eraso, R., and S. Itaya. 1985. Erroneous comparisons in oil refinery workers mortality studies (letter). J. Occup. Med. 237:464-465.

Najem, G.R., D.B. Louria, J.J. Seebode, I.S. Thind, J.M. Prusakowski, R.B. Ambrose, and A.R. Fernicola. 1982. Lifetime occupation, smoking, caffeine, saccharine, hair dyes and bladder carcinogenesis. Int. J. Epidemiol. 11:212-217.

National Council on Radiation Protection and Measurements (NCRP). 1980. Influence of dose and its distribution in time on dose-response relationships for low-LET radiation. Report No. 64. Washington, D.C.

Nelson, N.A. 1985. Mortality in Amoco oil refinery employees. Phase I. TSCA Section 8 (e) Report, 8EHQ-0585-0557. Unpublished.

Nelson, N.A., D.M. Barker, P.F.D. Van Peanen, and A.G. Blanchard. 1985. Determining exposure categories for a refinery retrospective cohort mortality study. TSCA Section 8 (e) Report, 8EHQ-0585-0557. Unpublished. Submitted to the Am. Ind. Hyg. J. for publication.

Nicholson, W.J., H. Seidman, I.J. Selikoff, D. Tarr, and E. Clark. 1982. Brain tumor among operating engineers in the chemical and petrochemical industry in Texas and Louisiana. Ann. N.Y. Acad. Sci. 381:172-180.

Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH). 1980. Glioblastoma cluster in a chemical plant--Texas. Morbid. Mortal. Rep. 29:359-360.

Percy, E., E. Stanek III, and W. Gloecker. 1981. Accuracy of cancer death certificates and its effects on cancer mortality statistics. Am. J. Public Health 71:242-250.

Pickle, L.W., and M.S. Gottlieb. 1980. Pancreatic cancer mortality in Louisiana. Am. J. Public Health 70:256-259.

Plotnikov, Y.K. 1978. Characteristics of occupational reference of patients with leukemia and lymphogranulomatosis (according to the data of the Kaibyshev region). Probl. Gematol. Pereliv. Krovi 23:18-21.

Raabe, G.K. 1984. Kidney cancer epidemiology in petroleum-related studies. In: Mehlman, M.A., ed. Renal effects of petroleum hydrocarbons: Advances in modern environmental toxicology, Vol. VII. Princeton, NJ: Princeton Scientific Publishers, Inc., pp. 259-271.

Reeve, G.R., T.L. Thomas, V.F. Kelly, R.J. Waxweiler, and S. Itaya. 1982. A proportionate mortality study of an Oil, Chemical and Atomic Workers local in Texas City, Texas. Ann. N.Y. Acad. Sci. 381:54-61.

Rinsky, R.A., A.B. Smith, R. Hornung, T.G. Filloon, R.J. Young, A.A. Okun, and P.J. Landrigan. 1985 (Aug.). Benzene and leukemia: an epidemiologic risk assessment. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health. Cincinnati, OH.

Rothman, K. 1975. Computation of exact confidence intervals for the odds ratios. Int. J. Bio-Med. Comput. 6:33-39.

Rothman, K., and J.D. Boice, Jr. 1976. Modifications of Miettinen, O.S.: Estimability and estimation in case reference studies. Am. J. Epidemiol. 103:225-235.

Rothman, K., and J.D. Boice, Jr. 1982. Epidemiologic analysis with a programmable calculator. Boston, MA: Epidemiology Resources, Inc.

Rushton, L., and M.R. Alderson. 1981a. An epidemiological survey of eight oil refineries in Britain. Br. J. Ind. Med. 38:225-234.

Rushton, L., and M.R. Alderson. 1981b. A case-control study to investigate the association between exposure to benzene and deaths from leukemia in oil refinery workers. Br. J. Cancer 43:77-84.

Rushton, L., and M.R. Alderson. 1982. An epidemiological survey of oil distribution centers in Breat Britain: Final report submitted to the Institute of Petroleum, England. Subsequently submitted to U.S. EPA, FYI-OTS-0882-0206. Unpublished.

Rushton, L., and M.R. Alderson. 1983. An epidemiological survey of oil distribution centers. Br. J. Ind. Med. 40:330-339.

Savitz, D.A., and R. Moure. 1984. Cancer risk among oil refinery workers. A review of epidemiologic studies. J. Occup. Med. 26:662-670.

Schottenfeld, D., R.W. Morgan, and A.G. Zauber. 1980. Questions raised by study on cancer mortality in oil refinery workers (letter). J. Occup. Med. 22:69-70, 72.

Schottenfeld, D., M.E. Warshauer, A.G. Zauber, J.G. Meikle, and B.T. Hart. 1981. A prospective study of morbidity and mortality in petroleum industry employees in the United States--A preliminary report. In: R. Peto and M. Schneiderman, eds. Banbury Report 9: Quantification of occupational cancer. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, pp. 247-265.

Sheehe, P.R. 1966. Combination of log relative risk in retrospective studies of disease. Am. J. Public Health 56:1745-1750.

Sherwood, R.J. 1972. Evaluation of exposure to benzene vapor during loading of petrol. Br. J. Ind. Med. 29:65.

Silverberg, E. 1984. Cancer statistics, 1984. CA 34:7-23.

Silverman, D.T., R.N. Hoover, S. Albert, and K.M. Graff. 1983. Occupation and cancer of the lower urinary tract in Detroit. J. Natl. Cancer. Inst. 70:237-245.

Stemhagen, A., J. Slade, R. Altman, and J. Bill. 1983. Occupational risk factors and liver cancer. A retrospective case-control study of primary liver cancer in New Jersey. Am. J. Epidemiol. 117:443-454.

Surveillance, Epidemiology and End Results (SEER). 1981. Incidence and mortality data 1973-1977. National Institutes of Health, Bethesda, MD. NIH publication 81-2330.

Tabershaw-Cooper Associates, Inc. 1974. A mortality study of petroleum refinery workers. Project OH-1. Submitted to the American Petroleum Institute, Washington, DC. Unpublished.

Tabershaw-Cooper Associates, Inc. 1974. A mortality study of petroleum refinery workers: Social security follow-up. API Project OH-1 No. 129. Submitted to the American Petroleum Institute, Washington, DC. Unpublished.

Tabershaw Occupational Medicine Associates. 1979. Job code classification system: Petroleum refineries and selected petrochemical operations. Washington, DC: American Petroleum Institute.

Tabershaw Occupational Medicine Associates. 1980. A historical prospective mortality study of workers potentially exposed to benzene and the lubricating-solvent units of the Gulf Port Arthur refinery. Rockville, MD. Unpublished.

Tegeris Laboratories Inc., Temple Hills, MD. 1985 (Sept. 30). Four-week oral nephrotoxicity screening study in male F344 rats. Sponsored by the American Petroleum Institute.

Theriault, G., and L. Goulet. 1979. A mortality study of oil refinery workers. J. Occup. Med. 21:367-370.

Thomas, T.L., P. Decoufle, and R. Moure-Eraso. 1980. Mortality among workers employed in petroleum refining and petrochemical plants. J. Occup. Med. 22:97-103.

Thomas, T.L., R.J. Waxweiler, R. Moure-Eraso, S. Itaya, and J.F. Fraumeni, Jr. 1982a. Mortality patterns among workers in three Texas oil refineries. J. Occup. Med. 24:135-141.

Thomas, T.L., R.J. Waxweiler, M.S. Crandall, D.W White, R. Moure-Eraso, S. Itaya, and J.F. Fraumeni, Jr. 1982b. Brain cancer among OCAW members in three Texas oil refineries. Ann. N.Y. Acad. Sci. 381:120-129.

Thomas, T.L., R.J. Waxweiler, M.S. Crandall, D.W White, R. Moure-Eraso, and J.F. Fraumeni, Jr. 1984. Cancer mortality patterns by work category in three Texas oil refineries. Am. J. Ind. Med. 6:3-6.

Thorpe, J.J. 1974. Epidemiologic survey of leukemia in persons potentially exposed to benzene. J. Occup. Med. 16:375-382.

Tsai, S.P., C.P. Wen, N.S. Weiss, O. Wong, W.A. McClellan, and R.L. Gibson. 1983. Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. J. Occup. Med. 25:685-692.

Universities Associated for Research and Education in Pathology, Inc. (UAREP), Bethesda, MD. 1983 (Dec.). Hydrocarbon toxicity: Acute, subchronic and chronic effects in relation to unleaded gasoline exposure of rodents, with comments on the significance to human health. Prepared for the American Petroleum Institute.

U.S. Environmental Protection Agency. 1980. Northeast corridor regional modeling project: Determination of organic species profiles for gasoline liquids and vapors. EPA-450/4-80-036a.

U.S. Environmental Protection Agency. 1985. Interim quantitative cancer risk estimates due to inhalation of benzene. Office of Health and Environmental Assessment. EPA-600/X-85-022. Internal report.

U.S. Environmental Protection Agency. 1986 (Nov.). Guidelines for carcinogen risk assessment. Federal Register 51(185):33992-34003.

U.S. Public Health Service. 1982. The health consequences of smoking: Cancer, a report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health. DHHS(PHS)82-50179, pp. 21-169.

Vesselinovitch, S.D., K.V.W. Rao, and N. Mihailovich. 1975 (Oct.). Factors modulating benzidine carcinogenicity bioassay. Cancer Res. 35:2814-2819.

Wade, L. 1963. Observation on skin cancer among refinery workers: Limited to men exposed to high-boiling fractions. Arch. Environ. Health 6:730-735.

Waxweiler, R.J., V. Alexander, S.S. Leffingwell, M. Haring, and J.W. Lloyd. 1983a. Mortality from brain tumor and other causes in a cohort of petrochemical workers. J. Natl. Cancer Inst. 70:75-81.

Waxweiler, R.J., J.J. Beaumont, J.A. Henry, D.P. Brown, C.F. Robinson, G.O. Ness, J.K. Wagoner, and R.A. Lemen. 1983b. A modified life table analysis system for cohort studies. J. Occup. Med. 25:115-124.

Weaver, N.K. 1982. U.S. oil industry epidemiology. In: Health and hazards in a changing oil scene. Proceedings of the Institute of Petroleum, 1982 annual conference, London, U.K. Chicester, U.K.: John Wiley & Sons, pp. 43-56.

Weaver, N.K. 1986. Telephone conversation between N.K. Weaver, American Petroleum Institute, and D.E.B. Potter, Dynamac Corp., on January 14.

Wen, C.P., S.P. Tsai, N.S. Weiss, W.A. McClellan, and R.L. Gibson. 1981. A population-based cohort study of brain tumor mortality among oil refinery workers with a discussion of methodological issues of SMR and PMR. In: Peto, R., and M. Schneiderman, eds. Quantification of occupational cancer. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, pp. 413-432.

Wen, C.P., S.P. Tsai, and R.L. Gibson. 1982. A report on brain tumors from a retrospective cohort study of refinery workers. Ann. N.Y. Acad. Sci. 381:130-138.

Wen, C.P., S.P. Tsai, R.L. Gibson, and W.A. McClellan. 1984a. Long-term mortality of oil refinery workers. II. Comparison of experience of active, terminated, and retired workers. J. Occup. Med. 26:118-127.

Wen, C.P., S.P. Tsai, K.B. Moffitt, M. Bondy, and R.L. Gibson. 1984b. Summary. Epidemiologic studies of the role of gasoline hydrocarbon exposure in kidney cancer risk. In: Mehlman, M.A., ed. Renal effects of petroleum hydrocarbons: Advances in modern environmental toxicology, Vol. VII. Princeton, NJ: Princeton Scientific Publishers, Inc., pp. 245-257.

Wen, C.P., S.P. Tsai, W.A. McClellan, and R.L. Gibson. 1983. Long-term mortality of oil refinery workers. I. Mortality of hourly and salaried workers. Am. J. Epidemiol. 118:526-542.

Wen C.P., S.P. Tsai, N.S. Weis, R.L. Gibson, O. Wong, and W.A. McClellan. 1985. Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. J. Natl. Cancer Inst. 74:11-18.

Whittemore, A. 1978. Quantitative theories of carcinogenesis. In: Advances in cancer research, Vol. 27. New York: Academic Press, pp. 55-58.

Whittemore, A., and B. Keller. 1978. Quantitative theory of carcinogenesis. Society for Industrial and Applied Mathematics Review 20:1-30.

Wigle, D.T. 1977. The distribution of lung cancer in two Canadian cities. Can. J. Public Health 68:463-468.

Wong, O., and R.W. Morgan. 1984. Draft final report: Feasibility analysis for an historical prospective mortality study of employees exposed to downstream gasoline in the petroleum industry. Submitted to the American Petroleum Institute, and subsequently submitted to the U.S. EPA. FYI-AX-0285-0382 Initial Sequence A. Unpublished.

Wong, O., R.W. Morgan, and M.D. Whorton. 1985. Draft report: Registry of Mortality of Refinery Workers, Phase I. Submitted by Environmental Health Associates, Inc., to the American Petroleum Institute, and subsequently submitted to the U.S. EPA. FYI-AX-0685-0418 Initial Sequence A. Unpublished.

Wong, O., and I.R. Tabershaw. 1980. Comments on mortality among workers employed in petroleum refinery and petrochemical plants (letter). J. Occup. Med. 22:638-640.

Woolf, B. 1954. On estimating the relationship between blood group and disease. Ann. Hum. Genet. 19:251-253.

Wynder, E.L., J. Onderdonk, and N. Mantel. 1963. An epidemiological investigation of cancer of the bladder. Cancer 16:1388-1407.

APPENDIX A

COMPARISON AMONG DIFFERENT EXTRAPOLATION MODELS

Three models used for low-dose extrapolation, assuming the independent background, are:

Multistage: $$P(d) = 1 - \exp\left[-(q_1 d + \ldots + q_k d^k)\right]$$

where q_i are non-negative parameters;

Probit: $$P(d) = \int_{-\infty}^{A + B \ln(d)} f(x)\, dx$$

where f(.) is the standard normal probability density function; and

Weibull: $$P(d) = 1 - \exp\left[-bd^k\right]$$

where b and k are non-negative parameters.

The maximum likelihood estimates (MLE) of the parameters in the multistage model are calculated by means of the program GLOBAL82, which was developed by Howe and Crump (1982). The MLE estimates of the parameters in the probit and Weibull models are calculated by means of the program RISK81, which was developed by Kovar and Krewski (1981). Table A-1 presents the MLE of parameters in each of the four models.

TABLE A-1. MAXIMUM LIKELIHOOD ESTIMATES OF THE PARAMETERS FOR THE THREE EXTRAPOLATION MODELS BASED ON THREE DATA SETS IN API UNLEADED GASOLINE STUDY

Data base	Multistage model	Probit model	Weibull model
Kidney tumor in male rats	$q_1 = 2.01 \times 10^{-3}$ $q_2 = 0$	A = -3.43 B = 0.53	$b = 9.75 \times 10^{-4}$ k = 1.15
Hepatocellular carcinoma/adenoma in female mice	$q_1 = 1.44 \times 10^{-3}$ $q_2 = q_3 = 0$	A = -3.29 B = 0.52	$b = 5.15 \times 10^{-3}$ k = 0.78
Hepatocellular carcinoma in female mice	$q_1 = 8.53 \times 10^{-4}$ $q_2 = 3.83 \times 10^{-8}$	A = -3.98 B = 0.57	$b = 6.95 \times 10^{-4}$ k = 1.04

SOURCE: IRDC, 1983.

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