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Case Control Study of Cancer in Synthetic Rubber Workers

FINAL REPORT
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16. Abstract (Limit: 200 words) A nested case/control study was conducted of gastrointestinal cancer in male workers from eight styrene-butadiene polymer manufacturing facilities in the United States and Canada to determine whether there was any association with exposures to styrene (100425) and butadiene (106990). A study on the association between hematologic neoplasms and exposure to butadiene and styrene was reexamined using different criteria for matching and exposure. Exposure levels for each job in the industry were developed, based on area and personal monitoring. The risk of lymphohematopoietic cancers was increased in the workers who had increased exposure to butadiene. Even using different methodologies such as choosing different types of controls, the risk of leukemia among these workers remained high. Among the leukemia cases, there was a higher than expected proportion of acute lymphocytic leukemia. Some of the odds ratios were high for butadiene and styrene associated with esophagal cancers, but the findings were not statistically significant. Also not significant was a suggestive trend for increasing odds ratios with increasing butadiene exposure for colorectal cancers. When short term workers were included, there was an increase in the all cause mortality, but no increase in standardized mortality ratios for cancer or circulatory diseases. Long term workers had higher risks for cancers of interest in this study than short term workers.

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1. Final Performance Report

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List of Abbreviations

SEER Surveillance, Epidemiology, and End Results, a project of the Biometry Branch of the National Cancer Institute
SMR Standardized Mortality Ratio
OR Odds Ratio
CI Confidence Interval
p probability
LRS Likelihood Ratio Statistic
ICD International Classification of Diseases

List of Tables

Significant Findings

Biologic importance of the work:

In repeated analyses using different control groups, the risk of lymphohematopoietic cancers was increased in workers who had increased exposure to butadiene. This has important implications with regard to the present consideration of a safe standard to set for anyone exposed to butadiene.

Methodologic importance of the work:

Choosing new leukemia controls who were not matched for duration of employment resulted in a slightly lower odds ratio for butadiene. However, when duration was added to the model, the odds ratio for butadiene was higher than the original odds ratio using duration matched controls. The model with both butadiene and styrene is significant at $p = .02$. These observations will need to be tested in larger populations of cancers, but it does appear that controlling for duration worked improves evaluation of risk from the chemical by removing the differences in opportunity for exposure in cases and controls. This would mean that the dose in a fixed time period is more important than total cumulative dose. This is very important since most occupational studies have used duration worked as the marker of "dose."

The application of measurement data to describe dose in a population at risk is complicated and needs to be approached with caution. The job titles abstracted from the personnel records and the jobs on the samples may not be compatible. Not all job titles are sampled and the reason for sampling is not always clear. Samples used for a purpose other than that for which they were collected may have other short-comings which are not immediately obvious.

Abstract

Butadiene is the 34th most common chemical produced in the U.S. (Morrow 1990). It is used in the manufacture of plastics, resins, rocket fuel, rubber, and rubber products. Studies in animals have shown 1,3-butadiene causes various types of tumors of the lymphohematopoietic system, lung, and other sites. The incidences of tumors are high and occur at exposure levels below current standards. The multiplicity of tissues affected with cancer in animals after exposure to butadiene, the unanswered questions about whether humans metabolize 1,3-butadiene similarly to the animals, and the widespread use of butadiene make this chemical potentially a serious hazard in humans.

The study examined butadiene associations with lymphohematopoietic and gastrointestinal cancers as well as methodologic issues related to selection of controls in a case-control study, influence of inclusion of short-term workers, and evaluation of exposure measurements. This work extends earlier work in several ways: 1) estimates of risk and interactions from lifetime estimates of exposures to butadiene and styrene were calculated for workers who died of gastrointestinal cancers; 2) methodologic issues of control selection were addressed by the selection of a new set of controls for workers who died from lymphohematopoietic cancers; 3) following collection and analysis of measurement data, methodologic issues related to using measures for exposure estimates were examined; 4) a cohort analysis of death information was used to examine the mortality of short term workers.

The study showed that even when using different methodologies such as choosing different types of controls, the risk of leukemia among workers in this industry remains high. Analysis of the case-control sets matched for duration worked have compared cases with gastrointestinal cancers and controls above and below the median butadiene exposure to subjects with no exposure in an exact analysis. Although some of the odds ratios are high for butadiene and styrene associated with esophagal cancers and there is a suggestive trend for increasing odds ratios with increasing butadiene exposure for colorectal cancers, none of the results are significant. These data need to be reexamined using measurement data and controls which are not matched for duration of exposure.

Hospital records were sought for all cases of lymphohematopoietic and gastrointestinal cancers included in the study. Of those with a diagnosis of leukemia, a higher proportion were acute lymphocytic leukemia than would be expected based on SEER data. Unusual observations were also made when reviewing hospital records of patients with gastrointestinal cancers. Two of the soft tissue sarcomas are angiosarcomas (one of the liver, the other of the femur). According to SEER data, this cell type and the fibrosarcomas are occurring at a frequency much higher than expected.

The inclusion of short-term workers (those with less than one year of employment) in the cohort analysis has increased the all cause mortality but remarkably did not increase the SMRs for cancer or circulatory diseases. For cancers of interest in the current research, the long-term workers have higher risks than short-term workers. This might suggest that those exposed in the industry the longest are at highest risk of cancer. The data indicate that inclusion of these short-term workers does not add to the risk of lymphohematopoietic and gastrointestinal cancers.

Report

Background

Animal studies: Studies in mice have shown that 1,3-butadiene causes various types of cancer which include lymphoma, hemangiosarcoma of the heart, hepatocellular carcinomas, alveolar carcinomas of lung, forestomach cancers, renal tubular adenomas, preputial gland carcinomas and Harderian gland cancers (Irons, et al. 1989; Melnick et al. 1990). The incidences of these tumors are high and occur at butadiene levels below current standards.

Other tumors that have occurred in 1,3-butadiene exposed rats include cancer of the pancreas and Leydig cell tumors of testis in males and cancers of the mammary and thyroid glands as well as sarcomas of the uterus in females (Owen et al. 1987). Cancers in mice occur at lower doses than in rats. Many cancers do not exhibit a dose response relationship with exposure but rather threshold levels which differ by tumor type (Owen et al. 1987; US OSHA 1990).

In both rats and mice, butadiene is metabolized to 1,2-epoxybutene but the rats metabolize the substance to a lesser extent than mice and have a greater capacity for detoxification (Kreiling et al. 1987; Laib et al, 1988, 1990; Bolt 1992). Metabolic studies using liver preparations suggest that the rate of 1,2-epoxybutene formation differs across species and that the species specific rates may rank as mouse > rat > human > monkey, but the human data on which this ranking is based are still limited (Schmidt et al. 1985, 1986). The importance of these observations on metabolic rates lies in the fact that 1,2-epoxybutene is thought to represent one important carcinogenic pathway by which 1,3-butadiene may cause cancers. The mouse has greater biotransformation of the epoxybutene to alkylating compound diepoxybutane via the glutathione-S-transferase pathways than in the rat. Covalent binding of reactive butadiene metabolites have been seen in mouse liver (Csanady 1992). The multiplicity of tissues affected with cancer in animal species after exposure to butadiene and the suggestion that man can metabolize 1,3-butadiene to similar compounds as these animals make this chemical a potentially serious hazard in man.

Human studies: Reports available on humans exposed to 1,3-butadiene include 3 cohort and 2 case-control studies. One cohort study (Meinhardt 1982) and one nested case-control study (McMichael et al. 1976) showed risks of leukemia associated with work in styrene-butadiene latex production. In the latter study, the risk for all lymphohematopoietic cancers associated with butadiene was OR 6.2 (95% C.I. 4.1-12.5) and for lymphatic leukemia an OR of 3.9 (95% CI 2.6-8.9). This study also showed a significant 2-fold increase in stomach cancer, but not all cancer sites were examined.

The cohort study of butadiene monomer workers reported excesses of lymphosarcoma in workers routinely exposed to butadiene and of leukemia in workers exposed intermittently to the substance (Divine 1976). The cohort study in the SBR latex industry (Matanoski et al. 1990) indicated risks of leukemia in black production workers and other lymphomas in all production workers. The case-control study within the latter cohort suggested increased risks of leukemia associated with 1,3 butadiene and not styrene based on estimated exposure scores.

Thus, studies to date have focused on risks of lymphohematopoietic cancers. However, many other cancer sites related to butadiene exposure have been reported in the animals and for some of these sites there appears to be excess cancers in human populations as well. These risks have occurred in industries which produce the butadiene as well as in industries which use it in conjunction with other chemicals to manufacture end products. Thus, it appears that butadiene is the common agent associated with these risks.

Type of exposure: Animal studies have clearly shown that the total cumulated dose is not the important measure in producing lymphomas, but rather, dose rate is important. High exposure levels over short periods cause lymphomas and low doses over long periods cause many of the other solid tumors. In the animals, the absence of the appearance of solid tumors in the high dose group may relate to the lethal effect of the exposure (Melnick et al. 1990). In Melnick's work, alveolar-bronchial neoplasms were the most sensitive marker of exposure to low doses over long periods.

The human situation may parallel that in animals. The previous studies (Meinhardt et al. 1982; Divine 1990) suggested that the risks of lymphohematopoietic cancers occurred in workers who were employed less than 10 years and who often had a short latency. These individuals would have had high exposures in early periods of the industry when exposures would have been high as procedures were developed. Thus, the studies 20 or so years after the beginning of the industry will see higher risks of tumors with short latency, such as leukemia, and perhaps related to high exposures. With continued follow-up, the cancers with long latency begin to appear. This situation may be analogous to that of the study of atomic bomb survivors who first manifested leukemia risks and are now showing increasing risks for the solid tumors. Some of these differences relate to the latent period of tumor development. The studies in the styrene butadiene rubber plants (Matanoski et al. 1987, 1990) have shown similar changes in risk in two time periods of follow-up. In addition, there is evidence in all previous studies of some excesses in cancers at sites other than the bone marrow.

Both the SBR latex and the butadiene monomer production worker cohorts showed some increase in the risk of colon cancer in long-term workers. Renal cancers demonstrated a 2-fold excess risk for long-term workers in the butadiene monomer plant and a 1.7-fold excess mortality risk in the SBR cohort of production workers. Larynx and lung cancers have occurred in excess in some subsets of each of the populations such as in short-term maintenance workers in the SBR cohort. In the case of the monomer plant study, since no attempt was made to control for race, the risks using white rates in a racially mixed population may have severely underestimated the risk of diseases such as lymphoma and colon cancer (Downs et al. 1987). These cancer sites are the same general tumor sites involved in animal studies.

Study cohort: The cohort population under study consists of a population of 18,470 male long-term and short-term workers in 8 styrene-butadiene polymer manufacturing plants in the United States and Canada. Women are excluded from these analyses because at the time when these workers were being exposed, the small number of women employed in the industry were often office workers and few were the blue collar workers exposed to butadiene. Minority workers, however, are included in the population.

Most of these plants began making the polymer when the synthetic rubber manufacturing process was first introduced in the early 1940s and 6 out of 8 of the plants are still in operation. The population has been followed for mortality through Social Security and the National Death Index in the United States through 1982. The Canadian population consists only of workers with 10 or more years of service who were entitled to death benefits from the company at the time of death whether employed at that time or not. Originally we had only included workers with one or more years of service, but the group has been expanded to include all workers in the United States plants in order to determine if short-term workers have the same mortality experience as the long-term workers. This is the cohort from which the cases and controls have been selected for the current studies. The cases have been identified from death certificate information on causes. The controls have been chosen from the remaining cohort regardless of vital status.

An original nested case-control study of lymphohematopoietic cancers in this population had indicated that 1,3-butadiene was associated with a risk of leukemia even when corrected for possible confounding by styrene. The current studies expand the case-control studies in this population with refinement of the exposure scheme for these two chemicals.

Specific Aims: A summary of the specific aims of this research are:

1) to conduct a nested case-control study of gastrointestinal cancers to determine whether there is any association of this category of cancers, and specific cancers within the category, with exposures to butadiene and styrene;

2) to reexamine through a nested case-control study, the association between hematologic neoplasms and exposure to butadiene and styrene, using different criteria for matching and different criteria for exposure;

3) to develop exposure levels of butadiene and styrene for each job in the industry based on actual area and personnel monitoring rather than on the previously developed estimated ranks based on industry personnel judgments;

4) to reevaluate the nested case-control studies based on the actual levels of exposure;

5) to evaluate the effects of the addition of short-term workers to a mortality analysis.

Issues:

There were several issues of particular concern to this project.

1) There was concern by some investigators that matching for duration worked in the case-control study might not give as good an estimate of risk as non-duration matched controls. Therefore, new controls which were not matched on duration worked were chosen for the set of lymphohematopoietic cases.

2) Butadiene may cause disease at several sites. The examination of specific sites of digestive cancers, some of which had shown excess SMRs over those for the all cause or all cancer SMRs, in a nested case-control format is an attempt to address this issue.

3) There was concern regarding the ranking of exposure scores based on impressions of exposure rather than on actual measurements. In addition, when ranking scores on a scale of ten, the experts tended to have preferences for some ranks. Measured data have been collected and compared with rank scores.

4) There was concern that short-term workers might have a different risk from long-term workers possibly because an initial sensitivity to the chemicals caused them to leave their jobs. The mortality analyses are an attempt to address this concern.

5) Cases of cancer of the lymphohematopoietic system often are not well classified on death certificates. Thus, a review of hospital records of cases at these sites as well as those of digestive cancers has been undertaken.

Results

1) Case-control studies of gastrointestinal cancers including all long-term cases with ICD 150-159

Cases have been identified and controls have been selected using both the duration-matched procedure and the non-duration matched procedure. Worker records for these cases and controls were abstracted, edited, and keyed to machine-readable form. The job titles for all workers in the case-control data set were coded and scores assigned to the jobs based on the exposure matrix. A program was developed to assign the scores and cumulate each persons' exposures for a lifetime score.

For each specific site of cancer except pancreas, the median score for butadiene is higher for cases than for controls (table 1). Except for esophagus and pancreas cancers, styrene scores follow the same pattern.

Table 1
Median Log Transformed Score of Matched
Gastrointestinal Cases and Controls

		Butadiene		Styrene	
Cancer Site	Number of Cases/Controls	Cases	Controls	Cases	Controls
All 150-159	154/453	4.86	4.80	4.41	4.37
Esophagus	16/42	5.77	4.52	4.46	5.00
Stomach	32/85	4.55	4.19	4.87	3.56
Colon/Rectum	59/181	5.47	5.20	5.47	5.23
Pancreas	28/92	4.26	4.47	3.49	3.91

Analysis of the case-control sets matched for duration worked have compared cases and controls above and below the median to subjects with no exposure in an exact analysis. Although some of the odds ratios are high for butadiene and styrene associated with esophagal cancers and there is a suggestive trend for increasing odds ratios with increasing butadiene exposure for colorectal cancers, none of the results are significant (table 2).

Table 2
Odds Ratios (and p values) for Gastrointestinal Cancers and
Butadiene and Styrene Exposure
Above and Below Median Log Score
Exact Analysis

	Butadiene Exposure			Styrene Exposure		
Cancer Site	None	Below Median	Above Median	None	Below Median	Above Median
Esophagus	1.00	3.49 (.33)	2.48 (.47)	1.00	4.67 (.10)	1.12 (.92)
Stomach	1.00	1.10 (.87)	0.71 (.65)	1.00	0.38 (.15)	1.11 (.87)
Colon/Rectum	1.00	1.11 (.86)	1.56 (.42)	1.00	0.67 (.52)	1.08 (.86)
Pancreas	1.00	0.57 (.43)	1.19 (.83)	1.00	1.64 (.41)	0.75 (.66)

p values in parentheses

2) Case-control study of lymphohematopoietic neoplasms

The original study used duration matched controls. We have selected new non-duration matched controls. Because new controls are included in the expanded studies, all job histories of both cases and controls were reabstracted by the group of new abstractors to assure consistency. As in the original study, records were abstracted by two independent coders and rechecked by the research assistant to resolve discrepancies. Only one subject had an additional record found in this second review of the microfilm for about 1000 subjects. Additional changes resulted from gathering new job and industry data from NIOSH and other sources not available previously. These new data allowed us to classify jobs and exposure ranks more precisely. These changes result in different cumulative exposures, especially in midlevel values, which are not related to data management or data quality control. Since the analysis is sensitive to selection of dichotomous cut points around the mean or median levels, methodologically we now analyze data over a series of cut points to evaluate the sensitivity and consistency of results.

A program to estimate lifetime exposure was developed using SAS rather than Paradox which had been used in the original analyses. To assure ourselves that we were indeed using the same method of analysis as originally even though our choice of software was different, we applied the new programs to the updated files and compared the results with the original analyses. Table 3 shows the original values (adapted from Santos-Burgoa C, page 146) and the reanalysis values. Odds ratios estimates were obtained by exponentiation of the coefficents (i.e., betas) in the regression model. For a continuous variable, the odds ratio estimate represents the increase in the odds of disease per unit increment in the log of the exposure score. Table 3 shows values that were in the same direction as the original analysis. Moreover, the odds ratio estimates were slightly greater and more precise, consistent with improvements in exposure classification. An analysis of the influence of individual subjects on the estimates shows that the coefficients are relatively robust, that is, the estimates are not heavily weighted by any one observation.

Table 3
Comparison of Regression Analyses
All Lymphohematopoietic Cancers
59 sets; 252 Observations; Duration Matched Controls

	Original analysis		Reanalysis	
Models	OR (p)	Model p	OR (p)	Model p
Continuous-ln				
butadiene	1.11 (.14)	.13	1.26 (.008)	.003
styrene	1.11 (.14)	.13	1.14 (.06)	.052
butadiene	1.07 (.45)	.24	1.27 (.028)	.012
styrene	1.07 (.46)		0.99 (.89)	
butadiene	1.15 (.22)	.28	1.23 (.089)	.028
styrene	1.19 (.21)		0.88 (.59)	
b.s interaction	0.97 (.32)		1.02 (.59)	
Exposed = above mean of log				
butadiene	2.42 (.025)	.019	3.34 (.004)	.002
styrene	1.90 (.09)	.082	2.00 (.065)	.057
butadiene	2.12 (.10)	.054	3.18 (.02)	.009
styrene	1.29 (.57)		1.09 (.85)	
butadiene	4.12 (.03)	.052	4.44 (.026)	.018
styrene	2.59 (.15)		1.76 (.46)	
b.s interaction	0.30 (.16)		0.48 (.45)	

Because the exposure scores are skewed, log transformations have been used. As shown in the table, using exposure as a continuous score results in an increased risk from butadiene for all lymphohematopoietic cancers (OR = 1.26 for each increment in exposure rather than 1.11 in the previous analysis). The reanalysis model, using better classification of the data as described above, is a statistically significant model. The model with only butadiene is the best of the models (compared to models using styrene alone, butadiene and styrene, and butadiene, styrene, and an interaction term). These results indicate an increasing risk with increasing exposure score of butadiene but not of styrene. There is no evidence of a statistical interaction.

When using the mean of the exposure scores as a cut point to define exposure, the reanalysis also shows better fit and a higher odds ratio for butadiene exposure (OR=3.3 compared to 2.4 in the original analysis). Again, the model achieves a higher level of statistical significance than in the previous study.

Although not shown here, results for the five lag periods of 2, 5, 10, 15, and 20 years indicate there is a significant increase in risk associated with butadiene exposure for each lag period up to 15 years but there is no increase in the magnitude of the odds ratios. This may result because the design has controlled for duration worked and, to some extent, also controlled for dose rate. The evaluation of the latency period will need to be examined further in future analysis.

Detailed analyses have been done to evaluate lymphohematopoietic neoplasms, especially leukemia. We examined odds ratios for multiple myeloma and leukemia using medians (table 4).

Table 4
Odds Ratios Associating ICD 200-209 Cancers
Above and Below the Median of Control Butadiene and Styrene Exposures
Compared to No Exposure
All ICD 200-209, 59 sets; Leukemia, 26 sets; Multiple Myeloma, 10 sets

	Butadiene Exposure			Styrene Exposure		
Cases	None	Below Median	Above Median	None	Below Median	Above Median
All ICD 200-209	1.00	1.90 (.22)	2.40 (.08)	1.00	2.68 (.06)	1.89 (.16)
Leukemia	1.00	5.84 (.12)	8.94 (.04)	1.00	8.19 (.04)	4.56 (.08)
Multiple Myeloma	1.00	0.92 (.94)	1.72 (.61)	1.00	3.62 (.32)	5.43 (.24)

p value in parentheses

Only the trend for leukemia showed a significant increasing risk with increasing dose of butadiene only, although the risk of styrene was also high, probably due to the correlation of chemicals. Styrene was associated with the risk of multiple myeloma but due to small numbers, neither the odds ratio nor trend were significant.

We tested the odds ratios for leukemia associated with butadiene and styrene using controls matched and not matched for duration of employment (table 5). The data are compared for the log 3 cut point to separate exposed and non-exposed. The new controls were not matched for duration of employment, but were selected randomly from data matched for age, plant and date of first hire as for the previous controls. The odds ratios were only slightly lower than in duration worked matches but the p value was higher. In order to test whether this was related to the removal of the matching variable or the specific set of controls selected, we added a variable for length of employment. This increased the odds ratios for butadiene and reduced variance. The model with the duration term included is highly significant compared to one without this term. These observations will need to be tested in larger populations of cancers, but it does appear that controlling for duration worked improves evaluation of risk from the chemical by removing the differences in opportunity for exposure in cases and controls. This would mean that the dose in a fixed time period is more important than total cumulative dose. This is very important since most occupational studies have used duration worked as the marker of dose.

Table 5
Odds Ratios for Leukemia and Chemicals
Above Log 3 Exposed: Conditional Logistic Regression
With and Without Matching for Duration Employment

Models	Duration Controls (p)	Non-Duration Controls (p)	Non-Duration Controls with Length of Employment in Model (p)
1 Butadiene only	8.48 (.04)	6.02 (.09)	9.21 (.04)
2 Styrene only	5.45 (.04)	2.60 (.14)	2.74 (.13)
3 Butadiene and	4.88	5.20	10.30
Styrene	2.56	1.20	0.88
LRS	8.28	4.74	9.83
model p	.02	.09	.02

Previous work had indicated that longest job held in a work area and butadiene independently increased the risk of leukemia. We have examined last work area or division codes from current data with butadiene in the model (table 6). The combined areas associated with risks included those where the p value for the individual area was p=.25 or less. These include service, laboratory and labor pool. The data confirmed the previous findings that the work area as well as butadiene but not styrene was associated with a risk. This finding suggests that butadiene levels may not be appropriately estimated for some work areas or there may be marked variation in exposure in these areas or, less likely, there is another exposure related to these jobs and butadiene exposure.

Table 6
Odds Ratios for Leukemia and Chemicals and Division
Above Log 3 Exposed; Expert Ranks for Determination of Exposure
Conditional Logistic Regression

Models	OR	p	LRS	Model p
1 Last Division	4.26	.01	6.8	.009
2 Butadiene	8.48	.04	7.1	.008
3 Styrene	5.45	.04	5.9	.02
4 Buta x Division	8.11	.002	11.8	< .001
*5 Last Division	5.28	.008	15.2	< .001
Butadiene	11.60	.03		
6 Last Division	4.99	.01	15.5	.001
Butadiene	7.82	.10		
Styrene	1.73	.56		

*Model with interaction term does not converge

Analysis of hospital data. Hospital records were sought for all cases of lymphohematopoietic and gastrointestinal cancers included in the study. Patient data including biopsy, pathology, and/or autopsy reports were obtained for 93 percent of cases (55 of the 59 cases). In only two of these was the information limited to a confirmation of the diagnosis by the hospital or state tumor registrar. Of the 55 cases of hematopoietic cancers with records available, 50 (91 percent) were correctly classified in the lymphohematopoietic group. One case of lymphosarcoma was actually a very rare retroperitoneal fibrosarcoma and one lymphoma was rediagnosed at autopsy as an undifferentiated adenocarcinoma of the pancreas. Of the 10 cases in the 200 and 202 ICD codes, review indicates four histiocytic lymphomas and 6 malignant lymphomas of which three are well differentiated and one is poorly differentiated and two are not specified. The death certificate classification of four of these were lymphosarcomas and six were lymphomas. All 25 leukemias with hospital record confirmation can now be classified: 14 are acute and 11 chronic with a higher proportion of acute lymphocytic leukemia than would be expected based on SEER data (table 7). In the 50 confirmed cases, 61 lympho-hematopoietic cancers were diagnosed. In addition, solid tumors at other sites were found in seven cases, frequently with autopsy identification of the lesion.

Table 7
Distribution of Leukemia Cases by Type

Classification	Cases	%	SEER%*
Acute Lymphocytic	6	24	8
Acute Myelocytic	8	32	30
Chronic Lymphocytic	6	24	42
Chronic Myelocytic	5	20	18
Monocytic	0	0	2
Total	25		

* Proportion ratio of incidence rates adjusted to include adults only

The gastrointestinal cancers and non-specific cancer categories have also been reviewed. The proportion of esophageal lesions in the upper esophagus are about one-third that expected based on hospital registry data. Soft tissue sarcomas, especially in the gastrointestinal tract, have been identified. Two of the sarcomas are very rare angiosarcomas (one of the liver, the other of the femur). According to SEER data, this cell type and the fibrosarcomas are occurring at a frequency much higher than expected. The several leiomyosarcomas and rhabdomyosarcomas which have been identified in the review of hospital records of gastrointestinal cancers will need to be compared to SEER based on cell types by specific sites. However, these data are limited since only gastrointestinal lesions and unspecified cancers have been reviewed to identify these sarcomas. There may be sarcomas at other cancer sites.

The exact hospital diagnoses of cases has been used to examine the data for lymphohematopoietic cancers without much change in results. The number of cases in subsets is so small that models frequently do not converge. The association between butadiene and leukemia remains, and for acute leukemia there is no apparent confounding by styrene.

3) Industrial hygiene measurements

Industrial hygiene data from 7 of the 8 companies were collected in the original study. Only one of the databases included random samples of jobs taken on a routine basis. The reasons for sampling in the other plants are unknown. The grouped data for job provided by the International Institute of Synthetic Rubber Producers (IISRP) did not permit the calculation of standard deviations as did the company data. The company and IISRP information is from the 1977-1983 period. NIOSH provided data for 1986 for three of the plants which were in the original study. All data were screened for obvious outliers such as one value of 2800 ppm which seemed unlikely to be a personal exposure. Then the data were divided into sample type, short-term or long-term, when indicated. Any information about method or conditions of collection and analysis methods were also recorded. It is important to recognize that all industry records preceded the development of new testing techniques after 1984.

Several problems become apparent in trying to use the data:

1) The job titles abstracted from the personnel records and the jobs on the samples were often not compatible. This resulted because the sample was described according to the tasks which were sampled and not by job titles. Jobs also could have changed because of a later calendar period.

2) Not all job titles were sampled. The frequency of sampling of any job varied by plant.

3) One plant had questionable data and one had non-specific titles which did not identify groups homogeneous for exposure.

4) Many job titles were non-specific even though it was clear that different jobs were included. An example is the title "lab technician" which was not clearly identified on records even though samples showed differences in exposures depending on the type of laboratory.

To resolve these issues, it will be necessary to discuss the jobs with older workers to determine their tasks for the job titles. However, it is encouraging that the measured exposures correlated very closely with the ranks assigned by the industrial hygienists and engineers (table 8). All the correlations are significant.

Table 8
Correlations Between Ranks & Personal Measures for Jobs
(Log Transformed)

Sources of Data	No.	Butadiene Correlation	No.	Styrene Correlation
Company Data (7 companies)	88	.46**	71	.06
NIOSH (3 companies)	31	.50*	-	-
IISRP	67	.74**	-	-
All Data	281	.36**	258	.13

* $p < .01$
** $p < .001$
Note: Total job titles = 560; jobs without data are omitted

The next question was whether the plants differed in measurements. The means for butadiene and styrene are seen in tables 9 and 10. The data suggest marked variability in the measurements by plant. The range of values is very high and the high geometric standard deviation (GSD) reflects that variability.

The rank scores for jobs have been compared to the means and geometric means for each job category developed for the dictionary. In general, the geometric means are similar to ranks, especially at upper and lower values, but the intermediate values do not rank as do the estimates.

Table 9
Mean Butadiene and Styrene Levels by Source of Information

	Butadiene			Styrene		
	Mean	SD	No.	Mean	SD	No.
Plant Measures						
All Plants	7.96	53.96	3952	3.53	14.32	3649
Plant 1	.96	2.85	328	6.17	20.89	324
Plant 2	4.47	7.47	36	-	-	-
Plant 3	2.30	6.92	89	-	-	-
Plant 4	5.00	18.01	1091	.86	4.67	1009
Plant 5	14.93	87.11	1435	6.66	19.64	1434
Plant 6	2.33	5.97	165	.29	.48	145
Plant 7	6.58	17.17	407	.57	1.04	737
NIOSH Measures						
Plant 3	.59	2.43	89			
Plant 6	1.31	4.36	123			
Plant 7	3.68	11.09	119			
IISRP Measures	2.61	-	74			

Table 10
Butadiene Exposure by Plant

Plant	Mean	SD	Range	GM	GSD	No.
1	.96	2.85	0.00 - 22.0	.58	5.19	328
2	4.47	7.47	0.07 - 39.0	1.25	6.03	36
3	2.30	6.92	0.05 - 14.7	.46	4.93	89
3N*	.59	2.43	0.00 - 14.4	.09	9.07	89
4	5.00	18.01	0.00 - 175.8	.18	15.48	1091
5	14.93	87.11	0.05 - 672.0	1.90	6.74	1435
6	2.33	5.97	0.00 - 48.0	.47	7.12	165
6N*	1.31	4.36	0.01 - 37.3	.12	7.10	123
7	6.58	17.17	0.01 - 217.0	1.55	6.10	407
7N*	3.68	11.09	0.00 - 99.6	.40	8.93	119
I**	2.61	-	-	1.97	-	74

* NIOSH data
** IISRP data submitted only by numbers in a category

Tables 9 and 10 indicate some obvious problems which must be dealt with in reviewing the data. The means and the ranges of values differ markedly by plant. Plant 1 has a low mean for butadiene but a high mean for styrene. This leads one to suspect that these values were exchanged. However, since no justification can be found to substantiate this suspicion, it will be necessary to omit these values. Plant 2 has few values and they represent primarily the data from two jobs so this is not useful to assess all jobs within that plant. Plant 4 has very non-specific job titles and all data from that plant will need to be examined separately because the jobs and the exposure data will have to be grouped in a similar manner to reflect the majority of the jobs.

The exposure variables are being tested to determine how much variation there is across jobs, across plants and across time. Although the time interval during which samples have been taken is short and samples have only been collected in recent years, there are some differences by time. Therefore, an algorithm will have to be developed to extrapolate the information to past periods.

The data on jobs and exposure scores have divided the plants into two groups, those which furnished data about which nothing is known as to why a sample has been taken and a single plant which has routinely collected random samples of selected jobs. The geometric standard deviation varies from 3.5 to 15.3 in the combined plants

and from 2.2 to 6.3 in the single plants. This indicates that the variability is greater where more plants are included than from the single plant with random sampling. The internal comparison of the jobs within each plant shows major differences in some of the jobs. This indicates that it will be necessary to examine the exposures by plant when adding them to the case and control job histories. However, the data also must be evaluated as to the error around samples because the number of samples for any one job varies.

The analysis by job cannot be completed and the scores added to the work histories until several issues are resolved. Unfortunately, these tasks were not included in this grant and we are still trying to determine how to fund that work. These tasks include a specific description of the tasks related to jobs in the industry over time for those jobs where the exposure data indicated that the job category is not homogeneous within or between plants. This problem could not be anticipated until the exposure data were analyzed for differences. The second problem is to discuss with the workers in each of the plants how work assignments changed over time. Recent discussions with some workers from one plant have indicated that the previous information provided by the industry may be incomplete. The third problem will be to develop an appropriate algorithm for analysis. This should be done and then the decisions reviewed with NIOSH scientists so that we can analyze our data both by our independent algorithm and also by the same procedures used by NIOSH so that data from several studies can be compared.

4) Reevaluate case-control studies based on actual measures

Because the measurement data are still being studied for the most appropriate way to use them in the case-control studies, they have not yet been used in the case-control models.

5) Mortality analysis of long- and short-term workers

Mortality for long-term workers was available at the start of this study. However, short-term worker mortality was not. Death certificates for short-term workers were obtained from state vital records offices, coded for all causes of death, keyed to machine readable form, and matched to the existing data for each individual.

In addition to updating the records for short-term worker deaths, several other updates were accomplished.

1) Data from one plant had many missing birth dates. The records of workers with birth dates were examined in two ways: first, by social security number and birth date, and second, by hire year and hire age. Algorithms were constructed to estimate the missing birth dates based on these two methods. The results from the two methods were remarkably consistent, thus, the easier method to execute, that based on hire year and age, was used to assign a birth date to workers in the plant so that they could be included in the mortality analysis.

2) Data from one plant was missing race for quite a few of its workers. In the original analyses, these were included with the analysis of whites even though it was recognized that deaths among blacks (with race verified by death certificate) would be included in the analysis of blacks while person-years for living blacks whose race was unknown to us were included in the analysis of whites. This misclassification of blacks would overestimate mortality ratios in the blacks and underestimate them in the whites. Since it was known that many of the workers in one plant were black, it was desirable to account for these missing values.

   To develop an algorithm for imputing race, records of workers from that plant who had race were examined by age at hire and decade of hire. Proportions were determined, random numbers assigned, and an assignment was made by those determined proportions and the random numbers.

3) Miscellaneous updates resulting from editing the data were also made.

Results of the mortality reanalysis of long-term workers showed the expected increase in SMRs among whites (since a proportion of people were removed from the denominator when race was imputed) and decrease among blacks (since the black denominator was increased). The cohorts were restricted as in the original analyses to exclude women, workers who left before the start of complete record keeping at the plants, those hired after 1976, and in Canada, workers who worked less than 10 years, since follow-up was available only for long-term workers in Canada.

The inclusion of short-term workers (those with less than one year of employment) in the analysis has increased the all cause mortality but remarkably did not increase the SMRs for cancer or circulatory diseases. Almost all of the excess is accounted for by external causes of death, respiratory disease and respiratory cancer, and deaths in a residual class rather than in specific causes because although date of death was known, death certificates were not received. For cancers of the lympho-hematopoietic system, the long-term workers have higher risks than short-term workers. This might suggest that those exposed in the industry the longest are at highest risk of cancer. The data indicate that inclusion of these short-term workers does not add to the risk of lymphohematopoietic cancers.

To duplicate previous analysis by work areas, the jobs of about 6500 short-term workers were coded. Analysis of short-term workers for the production and maintenance area show the only remarkable finding to be that respiratory cancers are higher in short term compared to long term workers, primarily in the maintenance area.

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3. Equipment Inventory

Description:	Northgate 386 Computer
Manufacturer serial number:	KB1140151
Acquisition date:	05/31/91
Cost:	$4328
Percentage of Federal funds:	100
Condition:	Good

Description:	Alos Rollfile Microfilm Reader 22E
Manufacturer serial number:	166054
Acquisition date:	06/04/91
Cost:	$1117
Percentage of Federal funds:	100
Condition:	Fair

4. Final Invention Statement

No inventions were conceived under this grant.