Mortality Study of Workers in 1,3-Butadiene Production Units Identified from a Chemical Workers Cohort

Elizabeth M. Ward, John M. Fajen, Avima M. Ruder, Robert A. Rinsky, William E. Halperin, and Cindy A. Fessler-Flesch

Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH 45226 USA

The International Agency for Research on Cancer has given the designations of "sufficient evidence" of carcinogenicity of 1,3-butadiene in experimental animals and "limited evidence" of carcinogenicity in humans. To investigate the carcinogenic effect in humans, we conducted a cohort mortality study among 364 men who were assigned to any of three 1,3-butadiene production units located within several chemical plants in the Kanawha Valley of West Virginia, including 277 men employed in a U.S. Rubber Reserve Plant which operated during World War II. The butadiene production units included in this study were selected from an index developed by the Union Carbide Corporation, which listed for each chemical production unit within their South Charleston, West Virginia and Institute, West Virginia, plants all products, by-products, and reactants. Departments included in the study were those where butadiene was a primary product and neither benzene nor ethylene oxide was present. A total of 185 deaths were observed; the standardized mortality ratio (SMR) for all causes of death was 91, reflecting lower mortality among the study population than the U.S. population. The study found a significantly elevated standardized mortality ratio (SMR) for lymphosarcoma and reticulosarcoma based on four observed cases (SMR = 577; 95% CI = 157–1480), which persisted in an analysis using county referent rates. An excess of lymphosarcoma and reticulosarcoma among all workers and among workers with routine exposure to 1,3-butadiene was also observed in the only other cohort of 1,3-butadiene production workers previously studied. A statistically nonsignificant excess of stomach cancer was observed in the overall cohort (n = 5; SMR = 243; 95% CI = 79–568) that was most pronounced among workers employed in the rubber reserve plant for 2 or more years (n = 5; SMR = 657; CI = 213–1530). We conclude that the results of this study add to the weight of evidence suggesting that butadiene is carcinogenic in humans. *Key words*: butadiene, cancer, lymphosarcoma, mortality, reticulosarcoma. *Environ Health Perspect* 103:598–603(1995)

1,3-Butadiene is used in the manufacture of synthetic rubbers (such as styrene-butadiene rubber or poly-butadiene rubber) and thermoplastic resins (*1*). Approximately 3000 million pounds of butadiene are produced in the United States each year (*2*). NIOSH estimates that approximately 9500 workers in the United States are occupationally exposed to 1,3-butadiene (*1*).

The International Agency for Research on Cancer (IARC) reviewed the literature on butadiene in 1992 and concluded that there is "limited evidence" of the carcinogenicity of butadiene in humans and "sufficient evidence" of the carcinogenicity of butadiene in experimental animals based on three long-term animal bioassays (*3*). Epidemiologic studies have been conducted among workers exposed to butadiene in the manufacture of styrene-butadiene rubber (*4–7*) and among workers involved in the production of butadiene monomer (*8–10*). Meinhardt et al. (*4,5*) examined mortality among 2756 white males employed in two styrene-butadiene rubber production facilities in Port Neches, Texas. Elevated, although not statistically significant, increased mortality was observed for lymphatic and hematopoietic neoplasms at one of the two plants [standardized mortality ratio (SMR) = 155], in particular lymphosarcoma and reticulosarcoma (SMR = 181) and leukemia (SMR = 203). These excesses were most pronounced among workers hired during World War II. Matanoski et al. (*6*) analyzed the mortality experience of 13,920 rubber production workers in the United States and Canada and found no significant increase in mortality from lymphatic or hematopoietic cancer, or any other cancer site. However, a nonsignificant excess risk of "other lymphatic cancer" (SMR = 202) was noted among production workers. An update of this study was reported by Matanoski et al. in 1990 (*7*). As in the earlier study, there was no significant increase in lymphatic or hematopoietic cancer, or any other cancer site. Production workers had a significant excess of "other lymphatic cancer" (SMR = 260). A significant excess of all lymphopoietic cancers was noted for blacks (SMR = 507). A nested case–control study of lymphopoietic cancer was conducted within this cohort. This study examined lymphopoietic cancer risk in relation to indices of cumulative butadiene and styrene exposure, and found a significant excess risk of leukemia associated with butadiene exposure (*11*).

Only one previous study has examined the mortality experience of butadiene production workers (*8–10*). This study included 2586 male workers employed at a facility located in Port Neches, Texas, for at least 6 months between 1943 and 1979. Butadiene was produced by the catalytic dehydrogenation of *n*-butane. The first analysis of the cohort by Downs et al. found eight deaths from lymphosarcoma and reticulosarcoma, yielding a significant SMR of 235 compared to national rates; the SMR was 185 and nonsignificant compared to county rates. In the update by Divine et al. (*9*), there was one additional lymphosarcoma and reticulosarcoma death yielding a significant SMR of 229 (CI = 104–435; county-based SMR's were not reported). In a third update (*10*), the SMR for lymphosarcoma and reticulosarcoma in the total cohort was not significant (n = 9; SMR = 209; 95% CI = 95–396). However, among the subset of 1056 workers with routine exposure to 1,3-butadiene, there were 6 deaths from lymphosarcoma and reticulosarcoma (SMR = 452; 95% CI = 165–984).

To investigate the carcinogenic effects of exposure to butadiene in humans, a cohort of workers employed in butadiene units was identified from within a large cohort (29,139 workers) of chemical workers whose mortality experience has previously been reported (*12*). Rinsky et al. analyzed the mortality experience of the overall cohort without regard to particular exposures (*12*). The primary hypothesis of the current study was that exposure to butadiene is associated with excess mortality from malignant neoplasms of the lymphatic and hematopoietic tissue. A secondary hypothesis was that butadiene would cause excess mortality from neoplasms of other sites.

Background

The study population was identified from records of 29,139 workers at three Union Carbide Corporation facilities in the Kanawha Valley, West Virginia: the South

Charleston plant, the Institute plant, and the Technical Center. The first two of these facilities produced butadiene and are included in this study. The South Charleston plant began operations in 1925, around the process of stripping ethylene from natural gas. It evolved into a chemical and plastics facility, producing a wide variety of chemical substances, including butadiene, ethylene oxide, polyethylene, vinyl chloride resins, and polyols. The Institute plant was originally built by the U.S. government (U.S. Rubber Reserve Corporation) to produce styrene-butadiene rubber to replace the supply of natural rubber that was cut off during World War II. This facility was bought by Union Carbide in 1947. The plant was then used as a larger production facility for materials developed at the South Charleston plant, such as acetone, isopropanol, butanol, and acetaldehyde. As of 1986, when the Institute plant was sold to Rhone-Poulenc, it had expanded to include the manufacture of agricultural chemicals and a wide range of ethylene oxide and propylene oxide-based products.

Butadiene production units were identified from a chemical and department index developed by Union Carbide. The index listed all products, by-products, and reactants for each chemical production unit within the South Charleston and Institute plants. Departments were identified where butadiene was a primary product and neither benzene nor ethylene oxide was present.

South Charleston (1941–1965). The butadiene production process at South Charleston involved the recovery of butadiene monomer from olefin cracking (see appendix for process description). Among the chemicals used in the process was bis(2-chloroethyl)ether, which also has been evaluated by IARC for carcinogenicity. The IARC regards bis(2-chloroethyl)ether as having limited evidence of carcinogenicity in animals (13,14), based on a bioassay in which an excess of hepatomas was observed in mice (15). This chemical showed negative results in a bioassay measuring pulmonary tumor response in mice (16) and in a long-term bioassay in rats (17).

Rubber Reserve Unit, Institute plant (1943–1946). The U.S. Rubber Reserve Corporation butadiene production unit operated from 1943 to 1946 at the Institute plant. The unit produced butadiene monomer indirectly from ethanol (see appendix for process description). As in the South Charleston unit, bis(2-chloroethyl)ether was used in this process. In addition, large quantities of acetaldehyde were present. Acetaldehyde is considered by IARC to have "sufficient evidence" of carcinogenicity in animals (18) based on its

ability to induce tumors of the larynx and nasal epithelium in hamsters (19) and rats (20).

Institute plant (1959–1971). The Institute plant also produced butadiene monomer as a by-product of olefin cracking from 1959 to 1971. The process was the same as described for the butadiene production units at the South Charleston plant; however, in 1965 dimethyl acetamide was substituted for bis(2-chloroethyl)ether.

Methods

The study population was identified by searching a computer file of work history records of 29,139 workers included in a mortality study of males employed from 1940 to 1979 at any of the Union Carbide chemical plants operating in the Kanawha Valley (12). The computer file of work history records contained a code representing each department in which an individual worked, but not the starting or ending dates. A total of 527 individuals were identified as having ever worked in the department codes relating to the butadiene units in the South Charleston or Institute plants identified for study. Copies of personnel records were collected for these individuals, and the starting and ending dates of their employment in each department were coded. Only 364 individuals who worked in the departments during the years when butadiene was produced were retained in the study ($n = 364$). As in the overall Kanawha Valley chemical workers cohort, there was a high proportion of individuals whose race was unknown (28%). Among those whose race was known, 94% were white. Therefore, individuals whose race was unknown were assumed to be white.

The Rinsky et al. (12) Kanawha Valley study determined vital status through 31 December 1978. For individuals not known to be deceased as of that date, vital status through 31 December 1990 was determined by matching with records of the National Death Index (NDI). Individuals known to be alive as of 31 December 1978 who were not identified as deceased from National Death Index records 1979–1990 were assumed alive as of 31 December 1990. For workers who were deceased, death certificates were obtained from state vital statistics offices and were coded according to the International Classification of Diseases (ICD) revision in effect at the time of death. The mortality experience of the cohort was compared to United States and to Kanawha County mortality rates using a modified life-table analysis system (LTAS) developed by NIOSH (21,22). The county rate analysis was restricted to the time period 1960 through 1990 for which county

referent rates are available in the NIOSH lifetable. Standardized mortality ratios, 95% confidence intervals, and two-sided p-values were calculated. Confidence intervals and p-values were calculated using an exact method (if either the observed or expected was less than 6) or an approximate method (if observed or expected frequencies were 6 or more). Because of the small size of the cohort and therefore the small numbers of deaths, latency and duration analyses were performed by simply dichotomizing both latency and duration categories so that approximately equal numbers of expected deaths were below and above the cutpoints.

For specific cancer site categories in which a statistically significant elevated SMR was observed, concomitant chemical exposures of the deceased workers were identified. This was accomplished by listing all departments other than butadiene in which their personnel records indicated they worked and then identifying the chemicals used and produced in each department from the index assembled by Union Carbide.

Results

Among the 364 persons who were identified as working in any of the butadiene production units, 277 individuals worked in the Rubber Reserve Unit which produced butadiene from ethanol, and 87 worked in the units at the South Charleston and Institute plants which produced butadiene from olefin cracking. Among these 364 persons, 176 (48.3%) were alive, 185(50.8%) were deceased, and 3 (0.8%) had unknown vital status as of the study end date of 31 December 1990. Table 1 shows the mortality pattern of the total cohort through 1 January 1990 based on U.S. referent rates. As in the previous study of the mortality experience of 29,139 workers in the three Kanawha Valley plants through 1978 (3), the SMR for deaths from all causes in the butadiene production cohort was <1.00. The SMR for deaths from all malignant neoplasms was 1.05 (CI = 0.78–1.40), which was higher than the SMR for deaths from all malignant neoplasms in the larger chemical workers cohort (SMR = 0.93; CI = 0.88–0.99) (12). Among the 92 specific causes of death and 26 major categories examined in the NIOSH lifetable, there was only one significantly elevated SMR, which was for the category "lymphosarcoma and reticulosarcoma" ($n = 4$; SMR = 5.77; CI = 1.57–14.8). County-based analyses, which covered only the time period 1960–1990, resulted in a similar SMR (SMR = 5.78; CI = 1.57–14.8).

Table 2 provides the SMRs for lymphosarcoma and reticulosarcoma by dura-

Table 1. Mortality (through 31 December 1990) from specific causes for butadiene production workers

Cause	Observed	Expected	SMR	95% CI
Tuberculosis	0	1.72	—	
Malignant neoplasms				
Buccal and pharynx	1	1.29	0.77	0.02–4.29
Digestive organs	11	12.2	0.90	0.45–1.61
Stomach	5	2.06	2.41	0.79–5.68
Respiratory system	19	16.6	1.14	0.69–1.79
Trachea, bronchus, and lung	19	15.8	1.20	0.72–1.88
Male genital organs	3	3.70	0.81	0.17–2.37
Urinary organs	1	2.32	0.43	0.01–2.39
Lymphatic and hematopoietic	7	3.99	1.75	0.70–3.61
Lymphosarcoma and reticulosarcoma	4	0.69	5.77	1.57–14.8
Hodgkin's disease	0	0.34	—	
Leukemia and aleukemia	2	1.62	1.23	0.15–4.44
Other lymphatic or hematopoietic	1	1.33	0.75	0.02–4.17
Other sites	6	5.36	1.12	0.41–2.44
Neoplasms of benign and unspecified nature	0	0.62	—	
Diabetes melitis	2	2.90	0.69	0.08–2.49
Blood and blood-forming diseases	0	0.54	—	
Alcoholism and mental disorders	0	1.21	—	
Nervous system diseases	1	2.14	0.47	0.01–2.59
Diseases of the heart	75	82.2	0.91	0.72–1.14
Diseases of the circulatory system	21	18.2	1.15	0.71–1.76
Respiratory system diseases	7	13.9	0.50	0.20–1.03
Digestive system diseases	5	9.36	0.53	0.17–1.25
Diseases of genitourinary system	2	2.96	0.68	0.08–2.44
Diseases of the skin and subcutaneous tissue	0	0.17	—	
Musculoskeletal diseases	0	0.35	—	
Symptoms and ill-defined conditions	2	2.48	0.81	0.09–2.91
Accidents	10	10.3	0.97	0.46–1.78
Suicide and homicide	3	4.62	0.65	0.13–1.90
All other causes	3	2.88	1.04	0.21–3.04
Certificates not obtained	6			
All cancers	48	45.5	1.05	0.78–1.40
All causes	185	202.2	0.91	0.79–1.06

SMR, standarized mortality ratio.

Table 2. Standardized mortality ratios (SMRs) for lymphosarcoma and reticulosarcoma by duration of employment and time since first employment in butadiene production processes

| Latency[a] | Duration of employment[b] | | | | | |
| | < 2 years | | ≥ 2 years | | Total | |
	Observed	SMR	Observed	SMR	Observed	SMR
< 30 years	1	4.92	0	—	1	2.41
≥ 30 years	0	—	3	19.8**	3	10.8**
Total	1	3.03	3	8.27*	4	5.77*

[a]Latency categories were selected to divide expected deaths from all causes into two approximately equal categories. There were 95 expected deaths in the < 30 years latency category and 107 in the ≥ 30 years latency category.
[b]Duration of employment categories were selected to divide expected deaths from all causes into two approximately equal categories. There were 100 expected deaths in the < 2 years duration category and 102 in the ≥ 2 years duration category.
$*p < 0.05$; $**p < 0.01$.

tion of employment in butadiene production processes and latency (defined as time since first employment in butadiene production processes). Three of the four deaths from lymphosarcoma and reticulosarcoma occurred in the >2 years' duration and >30 years' latency categories (SMR = 19.8; CI = 4.08–57.8). Table 3 provides additional information about the work histories of the four individuals, three of whom worked in the Rubber Reserve unit at the Institute plant. Aside from their assignments to butadiene production units, there were no commonalities among the

four cases except that two had been assigned to an acetaldehyde unit, one for 8 years and one for 29 years.

There was a statistically nonsignificant excess of stomach cancer in the overall cohort ($n = 5$; SMR = 2.43; CI = 0.79–5.68) that was most pronounced among workers employed in the Rubber Reserve plant for over 2 years ($n = 5$; SMR = 6.57; CI = 2.13–15.3; Table 4). County-based analyses for the overall cohort showed identical SMRs of 2.93 for the county and U.S. referent rates 1960–1990. Table 5 provides information about the work histories of the

five individuals who died of stomach cancer. Aside from their assignments to the butadiene unit, the only commonality among the work histories of the cases was that two had been assigned to "maintenance of grounds."

Discussion

The major finding of this study is excess mortality from lymphosarcoma and reticulosarcoma among workers employed in butadiene production processes located within two large chemical plants. An excess of lymphosarcoma and reticulosarcoma (SMR = 239) was observed in the only other butadiene production cohort previously studied (8–10). The latter plant used a different process (the catalytic and oxidative dehydrogenation of n-butane) from either of the two processes used by Union Carbide. A nonsignificant excess in lymphosarcoma and reticulosarcoma deaths was also found at one of two plants producing styrene-butadiene rubber (4). Elevated lymphoma incidence has also been observed in mouse bioassays (23–26).

A prior mortality study of workers at the Union Carbide's Kanawha Valley plants found a significant excess of lymphosarcoma and reticulosarcoma (SMR = 1.40; CI = 104–187) (12). An excess of deaths from this cause in the county where the plant is located (Kanawha County, West Virginia) has been noted previously (27). The county rate analyses in the current paper show that the expected number of deaths for lymphosarcoma and reticulosarcoma are approximately 15% higher in Kanawha County than in the U.S. population. Thus, geographical variation does not explain a substantial proportion of the increased risk among workers in butadiene units. A previous study which evaluated occupational risk factors for lymphopoietic cancers within Union Carbide's Kanawha Valley plants did not specifically evaluate the risks for lymphosarcoma and reticulosarcoma, but instead included these tumors in the broader grouping, "non-Hodgkin's lymphoma" (28). That study did not find an association between butadiene exposure and non-Hodgkin's lymphoma. Those results cannot be directly compared to findings of the current study because the periods of case ascertainment, disease groupings, and classification of butadiene exposure were different.

Our study also found an excess of stomach cancer among workers employed in the Rubber Reserve Unit for over 2 years. Review of the work histories of all the individuals who died of stomach cancer did not reveal any likely confounding exposures. Stomach cancer was in deficit in the overall Kanawha Valley chemical worker cohort followed through 1978 (SMR = 79; CI =

Table 3. Work histories of individuals who died of lymphosarcoma and reticulosarcoma

Age at death (years)	Beginning year of employment in butadiene unit	Approximate length of employment in butadiene (months)	Time from initial exposure to death (years)	Year of death	Butadiene department worked in	Other departments/ exposures
65	1942	39	33	1975	Rubber reserve	Acetaldehyde unit,[a] outside work
64	1943	35	36	1979	Rubber reserve	Maintenance of grounds, acetaldehyde unit,[a] upper island chemicals[b]
52	1946	9	25	1971	Rubber reserve	Isopropanol-acetone,[c] laborer, maintenance, general stores and purchasing
63	1952	96	32	1984	Olefin unit, S. Charleston	Maintenance labor, gas plants/ olefins,[d] outside work, acetylene unit,[e] weighmaster, chemicals and resins—packaging and shipping

[a]Acetaldehyde unit: A variety of chemicals, many requiring acetaldehyde as a reaction material, were produced in this department. These included vinyl isobutyl ether, vinyl ethyl ether, vinyl butyl ether, vinyl methyl ether, hexaldehyde, 2-ethyl butyraldehyde, propionaldehyde, 2-methyl pentaldehyde, methyl isoamyl ketone, 2,3-dimethyl pentaldehyde, ethyl propenal ether, ethyl acetate, and 2-methyl pentaldehyde. Refined acetaldehyde was also produced.
[b]Upper island chemicals area units: A large variety of chemicals, including ethers, ketones, alcohols, and acids were produced in these units.
[c]Isopropanol-acetone department: Materials handled in this department included propylene, diisopropanol sulfate, fuel gas, water, sulfuric acid, and "merrill oil." Products included isopropanol, diisopropyl ether, isopropyl oils, and weak sulfuric acid.
[d]Gas plants/olefins: Materials handled in this department included butane, propane, acetone, gasoline, butadiene vent gas, methanol, blowbacks from ethylene absorbers at "MB," polyethylene, chlorohydrin, propylene absorbers from isopropanol, caustic 20%, anti-oxidant, "DuPont No. 5," wood chips, and alumina pellets. Products included ethylene, propylene, and acetylene. By-products included crude butadiene, propane, "pyrofax," benzene, hydrogen-methane, sulfur saturated wood chips, hydrogen, and residues.
[e]Acetylene unit: Process materials included calcium carbide, sodium hydroxide, and sulfuric acid. Products included acetylene and calcium hydroxide.

59–104) (*12*). Prior epidemiologic studies of butadiene-exposed workers have reported a decreased SMR for digestive cancers overall (*4*), a decreased SMR for stomach cancer (*8–10*) and a slightly elevated SMR (1.05) for stomach cancer which was higher among black workers (SMR = 1.45) and maintenance workers (SMR = 1.51) (*7*). Carcinomas of the forestomach have been found to be elevated in two mouse bioassays of 1,3-butadiene (*23–26*).

The current study has several limitations. One limitation is that cancer mortality, rather than incidence, was considered, and thus any increased risk at cancer sites with high survival rates might not be detected. This limitation could not be readily overcome because there is no population-based cancer registry in the Kanawha Valley area. It is not known whether there are living individuals in the cohort who have been diagnosed with lymphosarcoma or reticulosarcoma. An important limitation is the potential for confounding exposure both within the butadiene production units and outside the units. We attempted to address the issue of confounding in the design of the study by selecting *a priori* only departments where butadiene was a primary product and benzene and ethylene oxide were not present. We also identified potential confounding exposures outside the butadiene units by examining the work histories of cases to determine whether there were common exposures. Among the potential confounding exposures which could not be controlled for in the study design, acetaldehyde was of the greatest concern both

Table 4. Standardized mortality ratios (SMRs) for malignant neoplasms of the stomach by duration of employment and time since first employment in the rubber reserve plant

	Duration of employment[b]					
	< 2 years		≥ 2 years		Total	
Latency[a]	Observed	SMR	Observed	SMR	Observed	SMR
< 30 years	0	—	2	5.63	2	2.25
≥ 30 years	0	—	3	7.40	3	3.69
Total	0	—	5	6.57*	5	2.94*

[a]Latency categories were selected to divide expected deaths from all causes into two approximately equal categories. There were 73 expected deaths in the < 30 years latency category and 91 in the ≥ 30 years latency category.
[b]Duration of employment categories were selected to divide expected deaths from all causes into two approximately equal categories. There were 87 expected deaths in the < 2 years duration category and 77 in the ≥ 2 years duration category.
*$p < 0.01$.

because it was present in the rubber reserve process and because two of the four individuals who died of lymphosarcoma and reticulosarcoma worked in the acetaldehyde unit. In addition, a case–control study of risk factors for lymphopoietic cancer within Union Carbide's Kanawha Valley chemical plant (*28*) found an elevated odds ratio for non-Hodgkin's lymphoma associated with exposure to acetaldehyde, but noted that odds ratios and duration trends were similar for acetaldehyde and acrylonitrile because of concomitant use of the two chemicals.

To examine further whether the risk of lymphosarcoma and reticulosarcoma might be attributable to an elevated risk associated with the acetaldehyde unit, to which two of the four cases had been assigned, we identified 233 workers from the large cohort of 29,139 who had ever been assigned to this unit and followed their mortality through 1991. A total of 48

deaths were identified. Aside from the two deaths from lymphosarcoma and reticulosarcoma previously identified among workers who had been included in the butadiene production study, there were no other deaths from this cause.

The toxicologic data are consistent with the conclusion that the excess of lymphosarcoma and reticulosarcoma found in the study are likely to be related to butadiene rather than confounding exposure to acetaldehyde. Acetaldehyde has only been demonstrated to induce upper respiratory tumors in rodents at levels (1000 ppm and above) substantially above the levels at which acetaldehyde has been demonstrated to cause eye irritation in humans (29). In contrast, butadiene has been shown to cause an increase in incidence of lymphocytic lymphomas and histiocytic sarcomas in mice (formerly known as type A reticulum cell sarcomas) at concentrations as low as 200 ppm, with marginally signifi-

Table 5. Work histories of individuals who died of stomach cancer

Age at death (years)	Beginning year of employment in butadiene unit	Approximate length of employment in butadiene (months)	Time from initial exposure to death (years)	Year of death	Butadiene department worked in	Other departments/exposures
75	1943	37	21	1964	Rubber reserve	None
67	1944	30	18	1962	Rubber reserve	None
65	1943	42	33	1976	Rubber reserve	Maintenance of grounds, polyethylene department[a]
65	1943	54	33	1976	Rubber reserve and S. Charleston	Gas plants/olefins[b]
74	1943	29	32	1975	Rubber Reserve	Maintenance of grounds, janitors and watchmen, general maintenance, building services, and guards

[a]"Dowtherm," "Ucon," "Heat transfer fluid 500," butyl hydroxy toluene, "Super floss" and "Vazo." Products were various grades of homopolymers and copolymers, recovered vinyl acetate, unreacted ethylenes, and oils.
[b]Gas plants/olefins: Materials handled in this department included butane, propane, acetone, gasoline, butadiene vent gas, methanol, blowbacks from ethylene absorbers at "MB," polyethylene, chlorohydrin, propylene absorbers from isopropanol, caustic 20%, anti-oxidant, "DuPont No. 5," wood chips, and alumina pellets. Products included ethylene, propylene, and acetylene. By-products included crude butadiene, propane, "pyrofax," benzene, hydrogen methane, sulfur saturated wood chips, hydrogen, and residues.

cant increases in histiocytic sarcomas down to 20 ppm (24,25).

When studying workers employed at large chemical production complexes, it is impossible to rule out the potential importance of confounding exposures. Ott et al. (28) noted that the average production worker at these plants was exposed to 58 different chemicals, many of which were correlated. Other studies conducted in the same chemical worker population have identified associations of lymphosarcoma and reticulosarcoma with maintenance (Teta J, unpublished data) and strong acid ethanol production (30), and the broader category non-Hodgkin's lymphoma with units using acetaldehyde (28). These observations were made in efforts to investigate the observed excess of death for the original cohort study of 29,139 workers or in surveillance studies. The current study, on the other hand, was initiated in 1986 to examine the hypothesis that exposure to butadiene might be related to hematopoietic cancer. If exposure data were available, the association between mortality from lymphosarcoma and reticulosarcoma might be evaluated by determining whether there is evidence for an exposure–response relationship. However, there are no air monitoring data for any of the butadiene production processes, and thus air concentrations of butadiene (and other chemicals) cannot be estimated. Personnel records do not indicate the types of tasks or job assignments an individual worker had; thus, there is no way to know whether the four individuals who developed lymphosarcoma or reticulosarcoma were exposed to higher concentrations of butadiene than other members of the cohort. Finally, the U.S. Rubber Reserve plant operated for only 4 years, and thus we could not evaluate the effects of prolonged exposure to this process.

Despite the limitations outlined above, the study has demonstrated an excess of mortality from lymphosarcoma and reticu-

losarcoma, which is consistent with the only other butadiene production cohort previously studied. Finding an excess of neoplasms of the lymphatic system in relation to butadiene exposure is consistent with the mouse bioassay data as well (18,19). We conclude that the results of this study add to the weight of the evidence suggesting that butadiene is carcinogenic in humans.

Appendix. Process Description

Rubber Reserve Process: Production of Butadiene from Ethanol (Institute Plant, Early 1940s)

The rubber reserve plant was operated by the Union Carbide Corporation during World War II under contract with the U.S. government. The rubber reserve process produced butadiene indirectly from ethanol. To better understand the process, the plant may be considered as being composed of four major divisions: 1) an acetaldehyde conversion system, 2) a butadiene conversion system, 3) a butadiene purification system, and 4) a recovery distillation system.

In the acetaldehyde conversion system, the ethanol was introduced into a catalytic converter containing a copper-chromium catalyst and was partially converted to acetaldehyde. The converters were heated by circulating liquid Dowtherm. The reaction involved was

$$\text{Ethanol} \xrightarrow{\text{Cu - Cr}} \text{Acetaldehyde} + \text{Hydrogen}$$
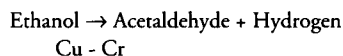
In this step, side reactions occurred that resulted in the formation of acetic acid, ethyl acetate, butylaldehyde, and butanol.

The equipment in the butadiene converter system is similar to that used in the acetaldehyde conversion system. The process was as follows:

$$\text{Ethanol} + \text{Acetaldehyde} \xrightarrow{\text{Titanium Oxide}} \text{Butadiene} + \text{Water}$$
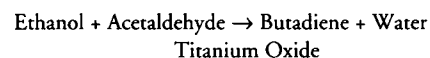
In passing through the titanium oxide, the combined ethanol and acetaldehyde are 15–20% converted to butadiene at an efficiency of 60–65%. Conversion of this mixture resulted in the formation of a large number of by-products. Among these were ethylene, ethane, propylene, propane, butylene, butane, carbon dioxide, carbon monoxide, diethyl ether, butyraldehyde, ethyl acetate, methyl ethyl ketone, carbon, acetic acid, butanol, and other unidentified hydrocarbons.

The major process steps in the purification phase were as follows: 1) stripping the crude butadiene from the condensed liquids of the butadiene converters, 2) removal of acetaldehyde from the butadiene, and 3) removal of butane and butylene from the butadiene.

The crude butadiene was removed from the condensate collected from the catalytic converter by distillation in a heated column. The crude butadiene at this point is a mixture of butenes, butane, and the binary azeotrope of butadiene and acetaldehyde. The crude mixture, including the azeotrope with acetaldehyde, was passed through a water scrubber to absorb the acetaldehyde present in the vapor. The acetaldehyde-free vapor from the scrubber was then fed to another column and the butadiene was absorbed by Chlorex (di-2-chloroethyl ether). The Chlorex preferentially absorbed the butadiene and allowed the butylenes and butane to pass out of the column. The remaining vapors consisted largely of butadiene, water, and some Chlorex. Chlorex, when heated, breaks down and forms dilute hydrochloric acid. Caustic soda was used in the solvent system to neutralize the hydrochloric acid. The final step in the purification process required the water and the Chlorex to be condensed and separated. The resulting product is butadiene at a purity of 99.5%.

The function of the recovery distillation system was to reconcentrate the unre-

acted acetaldehyde and ethanol from the conversion system, remove the by-products from the material cycle and to feed the converters.

Union Carbide Process: Recovery of Butadiene from Olefin Cracking (Institute Plant, 1959–1971 and South Charleston Plant, 1941–1965)

The Union Carbide olefin unit used a high-temperature cracking process to produce ethylene from hydrocarbons. The process was developed to recover butadiene as a by-product of the normal ethylene process. The relatively pure mixture of the four carbon molecules (less than 50% butadiene) was supplied from three sources in 10,000-gallon capacity feed tanks.

Crude feed from the feed tanks was fed to an absorber column, and Chlorex was the solvent used to desorb the butadiene. The Chlorex, after absorption of the majority of the butadiene, was routed to a stripping column. The crude butadiene at this phase of the process was 88–90% pure. The material was then scrubbed with water to remove any aldehydes which might have been present. The condensed, partially refined butadiene was then compressed and piped to the 10,000-gallon capacity intermediate storage tanks prior to recracking. To control the formation of popcorn-type polymers, sodium nitrite was added to the process stream to remove the oxygen.

Final refining of butadiene was a distillation process carried out in a two-column system. The 88–90% butadiene stream was introduced to a fore column where vinyl acetylene was removed from the process stream. The butadiene was now 97% pure and final purity of 99.5% was obtained from the refined butadiene condenser and then pumped to the refined storage tanks. Before loading or shipping the final product, Catechol (*p*-tertiary butyl catechol) was injected into the product to inhibit polymerization.

Subsequent process changes, 1965 and later, used dimethyl acetamide as the absorbent solvent in place of Chlorex.

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