Lymphohematopoietic Cancers and Butadiene and Styrene Exposure in Synthetic Rubber Manufacture[a]

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Styrene and 1,3-butadiene are two chemicals that form the bases of common types of synthetic rubber. Both chemicals are carcinogenic in animals. Styrene oxide as a metabolite of styrene causes stomach cancers in species given the chemical by gavage.[1] Data from human studies are limited, and any observed effects often cannot be tied specifically to styrene, which raises questions regarding its carcinogenicity for humans.[2] Butadiene exposure limits had been set on the basis of fire and explosion hazards. However, in the early eighties, toxicology studies indicated that this chemical caused cancer at multiple sites in animals, including the lymphohematopoietic system, lung, heart, brain, and other sites.[3] Several studies in human populations exposed to butadiene have shown increased risks of cancers, especially in the lymphohematopoietic system.[4] Some have questioned the findings of these studies because the type of cancer was not the same for workers in primary butadiene production as compared to end-use industries such as rubber manufacture.[5] Specifically, studies of butadiene production workers showed risks of lymphosarcoma,[6-8] and studies in synthetic rubber production showed leukemia risks.[9-12]

The population for analysis in this paper is from the Matanoski *et al.* cohort, and the study examines exposures of the cases of lymphohematopoietic cancers and

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controls from that cohort as reported in the Santos-Burgoa *et al.* study.[10,11,13,14] That study of lymphohematopoietic cancers had shown a very high risk of leukemia from estimated exposures to butadiene based on a ranking scheme developed with the help of industry representatives (O.R. = 7.4 95% CI 1.3-41.3).[11] The purpose of the current paper is to determine the risks of these cancers in relation to both styrene and butadiene using measured monitoring data from most of the synthetic rubber production plants included in the original study. Use of measured levels of chemicals for each job may provide further clarification of the risks associated not only with butadiene but also with styrene.

PREVIOUS STUDIES OF POPULATION

The original cohort of 12,110 workers with one or more years of employment from seven United States and one Canadian plant had demonstrated low all-cause mortality.[13] However, production workers had an increased risk of deaths from "other lymphatic cancers" (ICD-9 202 and 203), and black production workers had an increased risk of leukemia. Industry representatives were asked to score each job for both styrene and butadiene exposures on a scale of 1 to 10. Jobs were given the same scores for seven of the eight plants in the study with some slight modification of scores of only one plant because of variation in production practices. For each worker in the nested case-control study of all lymphohematopoietic cancers, the job score for each job was multiplied by the number of months spent in that job, and these job-specific cumulative scores, summed over all jobs, provided a total cumulative score for an individual. The analysis indicated that butadiene cumulative scores and selected work areas (labor, laboratory, and support services) were associated with an increased odds ratio for leukemia.[11] Subsequently, a review of industrial hygiene measurements of butadiene and styrene levels for seven of the eight study plants indicated that the monitored levels differed by plant.[10] This meant that the original study design, which matched cases and controls by plant and duration worked based on the presumption that exposures were similar across plants, may have overmatched for exposure and diluted the observed association with butadiene.

MATERIAL AND METHODS

The 59 lymphohematopoietic cancer cases included in the current study are the same as those from the Santos-Burgoa study. The cases generally had 10 or more years of employment and 20 years of follow-up.[10] The cases were selected based on the classification of lymphohematopoietic cancers (LHC) as they appeared on death certificates. For the current study, hospital records were reviewed to verify diagnosis for 55 of the 59 cases. Records were available for all but one leukemia case, and diagnoses were correct in all instances. Following review, all leukemias could be classified into subtype. Classification of non-Hodgkins lymphomas and lymphosarcomas on death certificates did not correspond to the hospital diagnoses based on specific ICD code. Of the 13 cases reviewed, however, all but two fell into the combined category of ICD 200 and 202. The two cases with incorrect death certificate

diagnoses based on hospital records were omitted from this study, but one new case was added from the hospital record review of other cancers, resulting in 12 cases, 7 lymphosarcomas (ICD 200) and 5 non-Hodgkins lymphomas (ICD 202). The diagnoses of cases of multiple myeloma and Hodgkins disease were unchanged after hospital review. The new classifications resulted in 58 total cases; the case classifications based on hospital diagnoses were used to distinguish the specific cancer subgroups. For the four cases for which a complete hospital record could not be obtained, the death certificate diagnoses were used.

The 1242 controls included in this study are part of a larger case-control study of several cancer sites. These controls were selected to represent the frequency distribution of population sizes across the eight plants and are similar in age distribution to the cases. The controls represent one percent of the plant population. Since controls had to live as long as or longer than cases, their duration of employment and, thus, their exposure potential is slightly longer than that of the case group, leading to possible higher cumulative exposures. For that reason, all models using the cumulative exposures included the "duration worked" variable in the model.

EXPOSURE

A total of 3,952 butadiene and 3,649 styrene exposure measurements were gathered from seven of the eight plants and from NIOSH. Most measurements represented personal monitoring data, and these were the only values used to represent job exposures. Despite the large number of measurements, some jobs in some plants had no values. However, all jobs had a rank score from the previous exposure estimation done by industry representatives.

For the current analysis, the assumption is that the *relative* exposures of jobs are similar across plants, but the *actual* exposure values for a specific job will differ by plant. The z-score transformation was used to estimate exposure for all jobs with missing measurements for each plant. These estimations used the actual values from other plants to get the relative values by job and the measurements for the plant to calculate missing job exposures for that plant. Thus, after these calculations, every job had an exposure level that was unique by plant and was based on monitoring data for that plant. The single plant with no industrial hygiene measurements was assigned values for jobs based on the values of a similar plant in the same geographic area. These job- and plant-specific exposure levels and the job histories of cases and controls were used to calculate both a cumulated exposure in parts per million times number of months exposed (ppm-months) and a time-weighted average exposure in parts per million (ppm) based on total cumulated exposure in ppm-months divided by the total time employed for both styrene and butadiene for each individual.

ANALYSIS

Unconditional logistic regression analysis was done using SPSS with beta values calculated using a continuous variable for ln-transformed chemical exposure measures.[15] These beta values also were converted into corresponding odds ratios for a

time-weighted average exposure to each chemical at 1 ppm. Multivariate models included birth year, year of hire before or after 1950, hire age, race, and duration worked. The variables were tested for their contribution to the model using step-down modeling. Although butadiene and styrene levels are correlated, the correlation did not interfere with the use of both variables in the model.

RESULTS

The associations between specific categories of lymphohematopoietic cancers and the chemicals clearly differ by type of cancer. Leukemias and Hodgkins disease are associated with time-weighted average butadiene exposure. The other cancers in this ICD-9 group 200-209, except for non-Hodgkins lymphomas (ICD-9 202), have significant associations with exposure to styrene (TABLE 1). Although none of the demographic variables are significant in the model, leukemia cases are more likely to be younger and to have been hired after 1950 compared to controls. The observed association suggests that there is a significant increase in the risk of leukemia for each unit increase in the average measured levels of butadiene. Based on the leukemia model, as shown in TABLE 1, the odds ratio calculated for exposure to butadiene at the low average working lifetime level of 1 ppm is 1.5 (95% CI 1.1, 2.1). The odds ratio for Hodgkin's disease associated with a similar butadiene exposure at 1 ppm is 1.7 (95% CI 1.0, 3.0). The associations between the continuous measure of styrene exposure and all LHC, all lymphomas, lymphosarcomas, and multiple myeloma are also highly significant. The odds ratio for multiple myeloma associated with low-level styrene exposure at 1 ppm is 3.0 (95% CI 1.3, 7.0). The risk of lymphosarcoma is significantly associated with increasing styrene exposure, and the odds ratio at 1 ppm exposure is 3.9 (95% CI 1.6, 9.6). The association between all lymphomas and styrene is represented by an odds ratio at 1 ppm of 2.7 (95% CI 1.2, 5.8).

TABLE 2 represents use of a cumulative dose to assess associations between these two chemicals and lymphohematopoietic cancers. In all but the models for multiple myeloma, a term for duration worked contributes significantly to the model. This term usually is negative and suggests the risk is higher for those reaching a cumulative dose in a shorter time period, that is, those with a higher-intensity dose. For workers with a long duration worked and a long latency for some of these diseases, this may also represent early exposure periods in their work history. The associations of leukemia and Hodgkins disease with butadiene are still present when using the cumulative exposure measure, but for leukemia styrene exposure also plays a role. In most cases, the use of a cumulative measure does not present any different conclusions than that of time-weighted exposure variables. Only in the combined category of lymphomas (ICD-9 200 and 202) did the best model include demographic variables. The odds ratios for these cancers increased the earlier the birth year and the older the age at first hire of the subjects.

The review of hospital records allowed classification of leukemias into the major types, lymphoid and myeloid, but further subclassification into acute and chronic categories resulted in insufficient numbers for modeling. It should be noted that among the lymphoid leukemias 5 out of 10 were classified as acute. This ratio is in marked contrast to that reported by the national cancer registries, in which only eight

TABLE 1. Associations between Lymphohematopoietic Cancers[a] and Exposure to Average Time-Weighted Butadiene [ln(ppm + 1)] and Styrene [ln(ppm + 1)] Levels as Continuous Variables

		Butadiene			Styrene			Final Model[c]	
Cause[a] (ICD - 9 No.)	No. of Cases	Beta	*p*	OR at 1 ppm[b] (95% CI)	Beta	*p*	OR at 1 ppm[b] (95% CI)	Variables	Model *p*
LHC (200-209)	58				1.140	0.000	2.20 (1.46, 3.33)	STY only	0.001
Lymphomas (200 & 202)	12				1.415	0.014	2.67 (1.22, 5.84)	STY only BY, agehire	0.020
Lymphosarcoma (200)	7				1.956	0.003	3.88 (1.57, 9.59)	STY only	0.011
Lymphoma (202)	5						2.62 (0.40, 17.15)	None	>0.050
Hodgkins[d] (201)	8	0.787	0.056	1.73 (0.99, 3.02)				BD only	0.077
Myeloma (203)	10				1.604	0.009	3.04 (1.33, 6.96)	STY only	0.021
Leukemia (204-207)	26	0.588	0.018	1.50 (1.07, 2.10)				BD only	0.026

[a] Cause as diagnosed from hospital records. LHC = all lymphohematopoietic cancers.

[b] Odds ratio for exposure at 1 ppm compared to 0 ppm: OR = exp[beta*ln(1 ppm + 1)]. 95% CI = exp[(beta = 1.96SE)*ln(1 ppm + 1)]. Example LHC: OR = exp[1.14*ln(1 ppm + 1) = 2.20].

[c] Step-down unconditional logistic regression models included birth year (BY), age of hire (agehire), year of hire before 1950 (Hirebf50), race, duration, styrene [ln(ppm + 1)](STY), and butadiene [ln(ppm + 1)] (BD) as continuous variables. In all cases, the most parsimonious model included only a single chemical variable.

[d] The association between Hodgkins disease and butadiene is stronger if time and age variables are in the model, but the model is not significantly better.

TABLE 2. Associations between Lymphohematopoietic Cancers[a] as Related Cumulative Exposure to Butadiene and Styrene [ln(ppm months + 1)] as Continuous Variables

Cause[a] (ICD - 9 No.)	No. of Cases	Butadiene		Styrene		Final Model[b]	
		Beta	*p*	Beta	*p*	Variables	Model *p*
LHC (200-209)	58			0.400	0.000	STY & duration	0.000
Lymphomas (200 & 202)	12					none	>0.050
Lymphosarcoma (200)	7					None	>0.050
Lymphomas (202)	5					None	>0.050
Hodgkins (201)	8	0.573	0.032			BD only, duration	0.042
Myeloma (203)	10			0.447	0.023	STY only	0.013
Leukemia (204-207)	26	0.240	0.054	0.481	0.006	BD, STY, duration	0.001

[a] Causes as diagnosed from hospital records. LHC = all lymphohematopoietic cancers.

[b] Step-down unconditional logistic multiple regression models included birth year (BY), age of hire (agehire), year of hire before 1950 (Hirebf50), race, duration, styrene [ln(ppm months + 1)](STY), and butadiene [ln(ppm months + 1)] (BD).

percent of adult lymphoid leukemia cases are listed as acute.[16] Because of the unusual distribution of lymphoid leukemias in this population, the subgroups have been examined separately in TABLE 3.

In addition, the previous study of lymphohematopoietic cancers in this cohort had reported an association between leukemia and longest job held for each individual in three work area categories: laboratory, service, and labor.[11] Service work is defined by jobs that support other activities in the plant, including special tank-cleaning teams. Laboratory work could include jobs in both chemical as well as physical labs. The latter labs test the physical strength of a product and would have lower exposures to butadiene and styrene. Research and development labs are also included here and have very diverse exposures. Chemical laboratory workers would have the highest butadiene and styrene exposures in this group. Each worker was classified to the work area where he had worked the longest. For this study, the same three work areas were combined into a single "job" variable (service, labor, or laboratory), which was compared to all other job groups as reference (process, utility, maintenance, warehouse, administration, pilot plant, and engineering).

The results shown in TABLE 3 indicate that the model for all leukemias with the job variable added still shows an association with exposure to butadiene similar to the model without job (TABLE 1); but the variable for work in service, labor, or laboratory areas also explains some of the difference between cases and controls.

TABLE 3. Associations between Leukemia and Major Subtypes and Exposures to Average Time-Weighted Butadiene [ln(ppm + 1)] and Styrene [ln(ppm + 1)] as Continuous Variables and Longest Job in Services, Labor, or Laboratory

		Butadiene			Job			Final Model[c]	
Cause[a] (ICD-9 No.)	# Cases	Beta	*p*	OR at 1 ppm[b] (95% CI)	Beta	*p*	OR (95% CI)	Variables	Model *p*
All Leukemias (204-207)	26	0.572	0.026	1.49 (1.05, 2.11)	0.973	0.015	2.64 (1.21, 5.30)	BD, job	0.005
Lymphoid (204)	10	0.757	0.042	1.69 (1.02, 2.80)				BD	0.060
Myeloid (205)	15				1.591	0.012	3.70 (1.33, 10.29)	Job	0.013

[a] Causes as diagnosed from hospital records.

[b] Odds ratio for exposure at 1 ppm compared to 0 ppm: OR = exp[beta*ln(1 ppm + 1)]. 95% CI = exp[(beta = 1.96SE)*ln(1 ppm + 1)]. Example leukemia: OR = exp[0.572*ln(1 ppm + 1) = 1.49].

[c] Step-down unconditional logistic regression models included birth year (BY), age of hire (agehire), year of hire before 1950 (Hirebf50), race, duration, job, styrene [ln(ppm + 1)](STY), and butadiene [ln(ppm + 1)] (BD) as continuous variables. In all cases, the most parsimonious model included only a single chemical variable.

The model is much more significant than one with butadiene alone. Styrene is not associated with all leukemia or with either the lymphoid or myeloid subtypes. The odds ratio for exposure to butadiene at 1 ppm is 1.5 (95% CI 1.1, 2.1); and the odds ratio associated with holding a longest job in the service, labor, or laboratory areas is 2.6 (95% CI 1.2, 5.3).

The risks differ for the two leukemia cell types (TABLE 3). Lymphoid leukemia is associated with exposure to butadiene with an odds ratio of 1.7 (95% CI 1.0, 2.8) at average exposures of 1 ppm. There is no association of this leukemia with the work area variable. Myeloid leukemia is associated only with work area with an odds ratio of 3.7 (95% CI 1.3, 10.3). These data would suggest either that the risks from industrial exposures associated with the various leukemia cell types differ or that some jobs have not been correctly measured for exposure to the chemicals. The numbers of cases were too small to divide the cell types further into acute and chronic subsets.

DISCUSSION

The results of the analysis of lymphohematopoietic cancers and their subgroups of cancer indicate that, while all are associated with industrial exposures in synthetic rubber manufacture, the agents associated with the risks differ. Lymphosarcoma and myeloma cases are associated with styrene exposure, and Hodgkins disease and leukemia cases are associated with butadiene exposure. The analysis of risks is difficult because the population in this industry are exposed to two possible carcinogens, butadiene and styrene, and their uses are closely linked in the work environment. The use of actual measured data by job as in this study helped to distinguish the effects from the two exposures. The data suggest that each agent may be related to different cancers. In some cases, the differences are very clear. For example, the 10 myeloma cases show a strongly positive association with styrene and a negative but nonsignificant association with butadiene. A relationship between styrene and myeloma has appeared in previous reports describing risks in the styrene manufacturing industry, which strengthens the finding.[17,18] The recent international study in the polystyrene industry did not report the risks of styrene associated with subclasses of lymphohematopoietic cancers.[19]

The association between lymphosarcoma and styrene is represented with a high odds ratio similar to that seen with multiple myeloma, but the association is unexpected based on reports from butadiene production facility studies.[6-8] These previous reports indicated an association between butadiene exposure and the risk of lymphosarcoma identified from death certificates. In this current study, hospital records have been used to identify cases since death certificates have been shown to frequently misclassify lymphoma deaths, exchanging causes between the ICD 200 and ICD 202 categories. After using medical records to correctly diagnose cases, both cancers appear to be associated with styrene in this study. This finding does not rule out the possibility of a risk of lymphosarcoma from butadiene exposure. Styrene exposure is associated with a very high risk of lymphosarcoma, but styrene was not present in the butadiene production industry. If both agents are carcinogenic for the lymphatic system, it may be difficult to distinguish risks from exposure to each independently without more

precise dose information. The risk associated with styrene exposure may have masked a risk associated with butadiene exposure.

The risks of leukemia and Hodgkins are significantly associated with butadiene exposure and not styrene in models where both chemicals are included and when the average time-weighted intensity of exposure is used. However, styrene usually remained as the last variable for withdrawal in a step-down model of leukemia but did not contribute significantly to the models. Since exposures to both chemicals are correlated and precise measures over 30 to 40 years are not available, distinguishing between the 2 chemicals is obviously difficult. The risk of leukemia is related not only to butadiene exposure but also to work area. Based on the odds ratio, the risk of leukemia is estimated to increase by 50% from exposure to as low as 1 ppm of butadiene on average over a working lifetime. The risk increases 160% from work in three selected areas, laboratory, labor, and service. Leukemia may represent multiple diseases with multiple risk factors. The risks from chemicals may differ by cell type, in which case combining all leukemias conceals and dilutes effects.

To examine the issue regarding homogeneity of risks by subtype, leukemia subgroups were examined. Although the number of cases by group were small, the data suggest that the risks differ by leukemia type. Lymphoid leukemias are associated with exposure to butadiene, and myeloid leukemias are associated with working in laboratory, labor, or service areas. These data may represent not true differences in risk by subtype but imprecisely measured exposures by job. The fact that myeloid leukemia did not demonstrate a significant association with either styrene or butadiene does not mean that one or both of the chemicals are not related to myeloid leukemia. In fact, if job is not considered and both chemicals are examined for their association with myeloid leukemia, butadiene is associated with a risk of myeloid leukemia but with a p value = 0.14. Based on that model, the data suggest that myeloid leukemia is associated with exposure to butadiene with an odds ratio similar to that reported for lymphoid leukemia. Therefore, these jobs need to be reexamined for the levels and patterns of exposure to butadiene.

The three work areas associated with a risk of leukemia are likely to have serious problems of underreporting of exposures. The service classification included tank cleanup crews, but few measurements were recorded for this group, which has the potential for high intermittent levels. The laboratories had very different measured exposures depending on the type, location, and responsibilities of the lab as well as the specific jobs the workers held in that work area. However, it is often difficult to distinguish the exact laboratory that is related to a measurement. The measured levels of recent years undoubtedly represented a lower exposure than would have been present in the past since various types of controls to reduce exposures have been introduced in the industry. These factors could have diluted differences in exposures according to the exact laboratory and its operations. For many laboratory workers in some plants, the personnel data did not permit a separation of jobs according to specific activities in specific laboratories, and therefore the data are diluted still further by using an average exposure level for all jobs across laboratories to calculate average weighted exposures of individuals in some plants. Limiting the analysis only to the plants where jobs could be specified as to exact laboratory work would reduce the already small number of cases for analysis. Similar problems exist for the "labor" classification. Thus, (1) inadequate measurements of exposures in these work areas,

current and past, (2) adding together laboratory measurements from locations with major exposure differences into a single category, and (3) imprecision in defining exact work location and job from personnel records in work areas with marked variation in exposures by job make it difficult to distinguish the chemical exposures that are associated with these work areas. The association between the job category and leukemia indicates that specific jobs within these areas need better definition of exposures in order to determine why this association between work area and leukemia exists.

The use of a cumulative exposure measure resulted in only minor differences in overall conclusions regarding risks but did demonstrate a tendency to emphasize risks associated with styrene. A possible explanation for this finding is that intensity of exposure is a more important measure of risk associated with butadiene exposure than is total cumulative dose. This hypothesis is supported by experiments in animals that indicated that exposure intensity is more important in carcinogenicity than is exposure duration.[20] In this study, an association with intensity of exposure is suggested by the fact that models using cumulative dose are improved with the addition of a variable for duration, which usually is negative. This indicates that the longer the worker is employed to reach the observed cumulative dose, the lower that worker's risk. Use of a cumulative exposure measure dilutes the effect of high-intensity exposures. However, exposure measures used in this study have not emphasized "intensity" as a variable. The exposure measures themselves are subject to repeated averaging. The exposures by job have been averaged over a workday, over many individual measures, over many jobs included in a single common job class and even over similar jobs across the industry, and, perhaps most importantly, over long time periods. Thus, any high exposure levels are diluted. Some jobs have exposure to both chemicals, and cumulative exposures to both styrene and butadiene will then be multiplied by a constant number of months in the job. That increases the levels for both chemicals. However, unlike butadiene exposure, styrene has low exposures for *most* industry jobs, which adds to the cumulative exposure for styrene and not butadiene. Thus, low-level styrene exposure tends to dominate cumulative measures.

The major strength of the data derived from this study is that the associations are based on measured values for each job of individual workers in each plant. While there are many obvious drawbacks to such data, the foremost being the fact that the measures represent more recent exposures in the industry, the fact that they are actual values removes possible biases that can arise from professional estimates of exposure that reflect individual beliefs about what exposures should be assigned to what jobs. The use of the data to assign exposures to each individual is based on two assumptions: that the relative exposures by jobs are constant across plants and time and that exposure levels for all jobs differ by plant. The latter assumption appears to be correct when measurements by plant weighted by jobs are examined. A review of relative exposures by jobs across plants suggests similar constant relationships, which would support the first assumption. However, the data cannot be used to examine changes in relationships over time since the measurements cover only the recent 15 to 20 years of plant operations and are sparse. Further modeling could be done using estimates of differences in exposures by job over time. If the relative exposure differences for specific jobs have changed greatly over time, this would be an important correction, which could influence the associations, especially for the jobs with the

highest exposures in the past. Further work is needed to correct for these differences over time.

Work in the synthetic rubber manufacturing industry is clearly associated with a risk of leukemia. Not only has our examination of this cohort identified the risk, but also the study of Delzell *et al.*, which independently investigated a population that included a high proportion of the present cohort, identified a similar risk.[12,21] Using a different approach from the one in this study and estimating chemical exposures for jobs based on interviews and using cumulative exposure-years to determine risk ratios, Macaluso *et al.* has reported a stronger association between butadiene and leukemia than with styrene in the Delzell cohort.[21] The data from the current analysis using measured values indicates the same association between leukemia and butadiene. The fact that this association does not hold for other lymphohematopoietic cancers except for Hodgkins strengthens the probability that the associations between the specific chemicals and cancers are real. The positive association between styrene and myeloma in models where there is a negative association with butadiene would indicate that these measured values can distinguish the differences in risk for the two chemicals. Despite the small number of cases of lymphosarcoma in this population, there is a significant association between this cancer and styrene but not butadiene. These findings indicate that both chemicals appear to be possible carcinogens for lymphohematopoietic cancers in this population. The combined presence of both chemicals in many jobs may actually conceal some of the risks from each agent alone. Further efforts will be needed to separate these effects.

SUMMARY

The described nested case-control study of lymphohematopoietic cancers occurring in a cohort of synthetic rubber production workers was conducted to determine the associations of these cancers with exposure to butadiene and styrene. Cases have been confirmed through hospital record review of 95 percent of the cancers. Exposures are based on measured values of the two chemicals from personal monitoring data in seven of the eight plants under study.

The results indicate that the risk of leukemia increases with exposure to a time-weighted average butadiene measure. The odds ratio at only 1 ppm average butadiene exposure is 1.50 (95% CI 1.07, 2.10). Work in specific areas also contributes to the risk, possibly because these areas have not been completely characterized for differences in butadiene exposure. Hodgkins disease is also associated with butadiene exposure. Multiple myeloma, lymphosarcoma, and all lymphomas are associated with exposure to styrene. Since workers in this industry are apparently exposed to two carcinogenic agents, further effort must be made to distinguish the exposures to each chemical over time and to characterize their interrelationship with the risk of cancers of the lymphohematopoietic system.

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