Solvent Exposure and Leukemia Among Rubber Workers: An Epidemiologic Study

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The findings of this composite epidemiologic study indicate an association between leukemia and jobs entailing exposure to solvents.

A literature review on the epidemiologic characteristics of these cancers yields little firm evidence of chemical exposure as an etiologic factor. A four-fold increase occurred in the U.S. leukemia mortality rate between 1920-1960, followed by a gradual decline. This decline has occurred for whites of all ages, but not for non-whites.[1,2] leukemia incidence rates within the U.S. have generally been higher for males than females. This male-female acess has declined in childhood cases, while the ratio has been increasing for adult cases.[3] Internationally, males show a similar excess with the exception of only a few nations.[2] The age-specific mortality rate *rises* to a minor peak during the first five years of life, falls to a minimum during young adulthood, then ascends to a maximum peak in later adulthood and old age.[4]

Geographically, the mortality rate within the U.S. is highest for the white population in the northwestern and northcentral states (but not including Ohio, the state in which the cohort study described below was conducted). A deficit exists in the northeast and southern states. The mortality rate for the non-white population exhibits a null cluster of elevated incidence rates in the mid-southern states.[4] Various emmigrant group studies in the U.S. have not revealed any consistent trend, and there seems to be little consistent evidence of an association between leukemia and either social class or industrialization.[2,5]

Of the four major cytological types of leukemia, defined by the 8th Revision of the International Classification of Diseases, myeloid and lymphatic constitute the greatest percentage of cases. The proportion of myeloid cases peaks at 60% of all leukemia cases between the ages of 30 to 40, then declines. The lymphatic type has the highest childhood dative prevalence (50%), declines until the ages of 30 to 40, and then rises to its peak of 60% between the ages of 80 to 90. The lymphatic type surpasses the myeloid type in percentage near the age of 70. Myeloid leukemia exhibits its highest incidence in whites living in certain northcentral and northeastern states. The lympatic type demonstrates an elevated incidence among whites in northcentral and west coast states Non-whites do not show geographic clusters of elevated rates for either of these types of leukemias. The ratio of male cases to female cases is highest for the chronic lymphatic type and lowest for the chronic myeloid.[2,4] These reported differences in sex ratios could suggest either the possibility of occupational environmental factors in the etiology of the lymphatic type, with males being selectively exposed to such factors; or the possibility of differential susceptibility of males and females to environmental factors.

Considerable evidence supports the hypothesis that chromosomal aberrations are associated with the occurrence of leukemia.[2,6] Ionizing radiation may achieve its myeloid leukemogenic effect via chromosomal damage.'

Chemicals such as benzene, phenylbutazone, and chloramphenicol are suspected leukemogens, although there is little sound epidemiologic evidence.[2,7] There is also evidence that benzene can produce chromosomal aberrations.[6] However, the evidence regarding the leukemogenic effects of these chemicals can only be viewed as suggestive.

Them are some indications that the other major cancers of the lymphatic and hematopoietic systems (Hodgkin's disease. lymphosarcoma, and multiple myeloma) may have some environmental etiology. Epidemiological evidence on Hodgkin's disease indicates that high social class white males, 50 years or older, have the greatest incidence rate.[8] Akauki supports the environmental hypothesis with evidence indicating a greater incidence of Hodgkin's disease in Japanese migrants in Hawaii than in japan The evidence supporting environmental factors in lymphosarcomas and multiple myelomas is meager although Japanese studies have shown radiation and migration to effect the incidence of these diseases.[10,11]

Cohort Mortality Study

In 1970, the United Rubber Workers Union negotiated with each of the six

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major U.S. rubber companies for a program of comprehensive research into work-related health problems The School of Public Health, at the University of North Carolina, is conducting the research program within four of these companies. The data presented here derive from seven plants within one of these four companies. and refer exclusively to deaths among the hourly (i.e. factory) employees, either active or retired.

The initial mortality study was carried out at the company's largest plant, in Akron, Ohio, and has been fully reported earlier.[12] A cohort of 6,678 male, hourly rubber workers was identified (and cross-checked) retrospectively, and mortality data for the period 1964-72 were obtained from the company's life insurance records. This cohort, of active and retired workers, aged 40 to 84 at January 1, 1964, and with an average employment duration of 25 years. was followed for nine years, with 1% of persons lost to follow-up, and with complete death ascertainment on the remainder of the population.

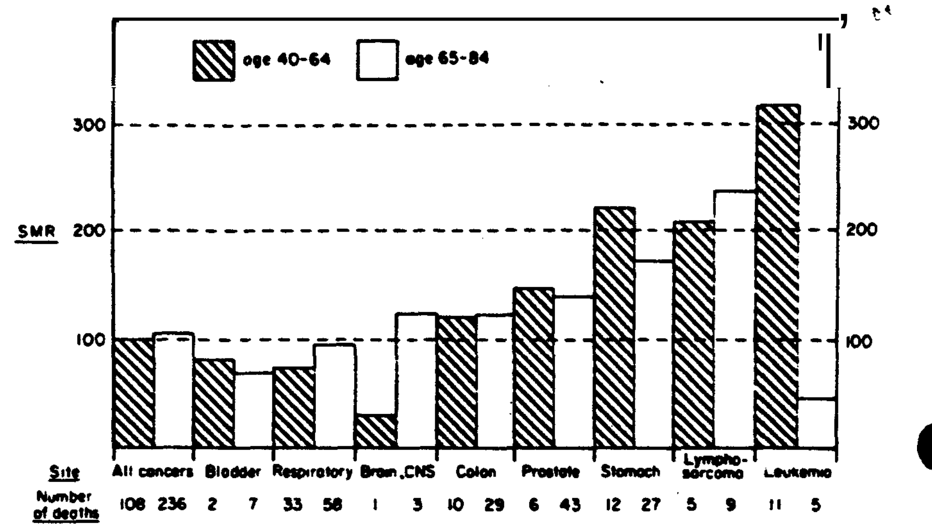
An estimate of racial composition (based on payroll records and death certificates) indicated that 13% of the cohort was black. compared to 10% within the U.S. male population of the same age-range. The similarity of these two figures allowed mortality comparison of the cohort with the U.S. male population.

By comparing the observed deaths to the number of deaths expected (calculated from 1968 U.S. male age-specific death rates), standardized mortality ratios were calculated. For all deaths, the SMR was 93 in the age-range 40 to 64, and 101 in the age-range 65 to 84. These age ranges were chosen because 65 is the age of normal retirement. It should also be noted that these SMR's are conservative because of the use of a standard population that includes the physically unemployable segment of the community — i.e. the sick, disabled and institutionalized. who are at heightened mortality risk.

Figure 1 presents the cancer mortality SMR's, for these same two age-ranges, 40 to 64, 65 to 84. While the SMR for all cancers is approximately 100, several type of cancer showed a statistically significant elevation — in particular, cancers of the stomach, the prostate, and the lymphatic and hematopoietic systems. The latter group, comprising the International Classification of Diseases (8th Revision) categories 200 to 209, includes the leukemias (see Figure 1). with a threefold excess in the age-range 40 to 64 — 11 deaths observed where 3.5 were expected. It also includes the commonest types of lymphoid tissue cancer, that is, the lymphosarcomas. reticulum cell sarcomas. and Hodgkin's Disease (Figure 1). for which there was, overall. a two fold excess across the full age-range. 40-84 — 16 deaths observed where 6.2 were expected.

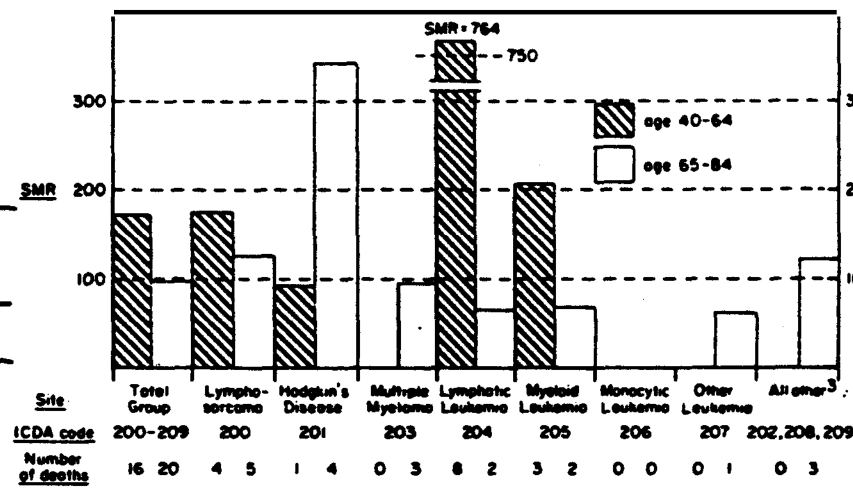
To examine the mortality from lymphatic and hematopoietic cancers in more detail. SMRs were calculated for the individual ICD categories. The results are presented in Figure 2. The greatest mortality excesses are for lymphosarcoma, Hodgkin's Disease. lymphatic leukemia. and myeloid leukemia. There was a sevenfold excess of deaths from lymphatic leukemia in the younger age-range. Six of these eight deaths were from chronic lymphatic leukemia.

Thus, this cohort mortality analysis at the Akron plant focussed attention upon



1 "Expected" deaths calculated from 1968 U.S. male age-specific death rates

Fig 1. — Standardized mortality ratios[1] (SMR): Cancer mortality analysis, in a cohort of 6,678 male hourly rubber workers, Akron plant, 1964-1972.



1. "Expected" deaths calculated from 1968 U.S. male age-specific death rates
2. International Classification of Diseases (Adapted), [redacted]
3. Other lymphoid tissue cancers, polycythemia vera, and myelofibrosis

Fig 2. — Standardized mortality ratios[1] for specific cancers of the lymphatic and hematopoietic systems (ICDA[2]: 200-209), male rubber worker cohort, 1964-1972.

cancers of the lymphatic and hematopoietic systems. For reasons of cost and time, information about the source populations-at-risk at the smaller. non-Akron plants was not obtained. Instead, a proportional mortality analysis was carried out. using an age-standardization procedure exactly analogous to that used in calculating SMR's. Within the age-range 20 to 90, proportional mortality excesses were observed, at these six non-Akron plants combined, of 15% for lymphosarcoma and Hodgkin's Disease, and 45% for leukemia These figures suggest a rather smaller mortality excess from these cancers at the non-Akron plants, compared to the Akron plant. (The considerable variation observed in age-standardized proportional mortality ratios between the individual non-Akron plants could reflect either a real difference in cancer risk because of differing in-plant work environment. or it could simply reflect the "instability" of the values of the ratios because of the small numbers of deaths involved.)

The question then arises: Are these observed mortality excesses spurious (due to chance or artefact). or are they real? Further, if real. are they associated with specific categories of jobs within the rubber industry? An analytic study was thus called for.

Case-Control Study

Because of the absence of source population information at the non-Akron plants, it was decided to carry out a case-control study. capitalizing on the total of 88 deaths (from cancers of this type) at the Akron and the non-Akron plants.

The cases were defined as any active or retired hourly worker, dying in the period 1964-73, whose death certificate included reference to a cancer of this type, irrespective of whether the cancer was the underlying cause of death, or simply a contributory cause. For 77 of the 88 cases. the cancer was the assigned underlying cause of death. The plant. race, sex. and age-at-death information for these 88 cases is presented in Table 1. Table 2 shows the distribution of specific types of cancer, at the Akron and non-Akron plants. Numerically, lymphatic and myeloid leukemias were the commonest cancer types, accounting for 35 of the 88 cases.

The controls were defined, in principle, as rubber workers not dead of this type of cancer. But further, because we only had information on deceased rubber workers at the six non-Akron plants, control selection was necessarily confined to rubber worken dead of other causes. To be eligible for selection. the control had to have died within the *same* period. 1964-73, and had to have died from a cause other than a cancer or a Mood disorder (such as aplastic anemia). To ensure control of potential confounding effects, the controls were individually matched with the cases, in a ratio of three controls per case. Age, race. sex and, probably. plant were regarded as risk indicators of leukemia and related cancers, and were also judged lo be associated with the type of job an individual does within the rubber industry. Controls were therefore individually matched with cases on sex. race. plant, and age-at-death (control age-atdeath was required to be 0 to 5 years greater than that of the case).

352 study subjects. were thus identified. and copies of each of these individual's complete work history were obtained from the company. Two methodological problems within this study relate to the treatment of information from these work histories: (1) there is, within the rubber industry, a large diversity of job types and a variety of chemical exposures; (2) there is considerable job mobility, whereby the average worker moves through 10 to 30 different jobs during an employment of, say. 30 to 40 years.

Table 1. — Demographic Characteristics of the 88 Cases.

	Akron Plant	Non-Akron Plants
Male		
White	46	21
Black	5	3
	51	24
Female, white	9	4
Total	60	28
Average age at death	US	51.3

To take account of the diversity of jobs a d exposures, a classification system was developed whereby the several hundred departments and the thousand or so jobs that have existed at the various plants, now or in the past, were reduced to a set of 70 occupational titles. Each occupational title includes jobs with a commonality of process and materials handled. Each job entry on a work history could thus be assigned an occupational title code, and this was done blind, with no knowledge of the individual worker's status as case or control.

To take account of job mobility, data analysis techniques were used which incorporated the complete set of job entries on each individual's work history. That is, the exposure variable was of a multivariate kind; no attempt was made to assign a "most representative job" classification to each individual, because of the large information losses this would have entailed.

Table 2. — Distribution of Deaths, 1964-73, Male and Female, by ICD Category, for Akron and non-Akron Plants. IN CASE-CONTROL STUD

ICD Category	Akron	Non-Akron	Total
200: Lymphosarcoma, and reticulum cell sarcoma	13	3	16
201: Hodgkin's Disease	6	4	10
202: Other lymphoid tissue neoplasms	6	3	9
203: Multiple myeloma	7	3	10
204: Lymphatic leukemia	15	3	18
(Acute)	(3)	(1)	(4)
(Chronic)	(9)	(2)	(11)
(Unspecified)	(3)	—	(3)
205: Myeloid leukemia	9	8	17
(Acute)	(3)	(4)	(7)
(Chronic)	(6)	(2)	(8)
(Unspecified)	—	(2)	(2)
206: Monocytic leukemia	0	0	0
207: Other and unspecified leukemia	3	4	7
208: Polycythemia vera	0	0	0
209: Myelofibrosis	1	0	1
200 - 209	60	28	88

Results of Case-Control Study

The data analysis proceeded in 2 ways. Firstly, the data were explored, in hypothesis-generating fashion, in an attempt to detect differences between cases and controls with respect to the occupational titles in which they had worked. A moderate number of occupational titles were more evident among cases than controls, but typically the difference was small — of the order of, say, 4% of case jobs being within that occupational title compared to 2% of control jobs. This tendency applied to the comparison for all lymphatic and hematopoietic cancers when considered together, and also for specific categories of these cancers — although there were some slightly greater case-control differences for lymphatic leukemia.

The second approach to data analysis involved testing the hypothesis that leukemia and related cancers are associated with exposure to solvents, particularly benzene. Organic solvents are used in large amounts within the rubber industry, and benzene was once the solvent of choice. The 70 occupational titles had previously been grouped according to industrial hygienists' assessments of solvent exposure. Three such solvent-exposure occupational title groups were created, and are referred to as heavy, medium and light solvent exposure. These three occupational title groups accounted for 19 of the 70 occupational titles — that is, about one quarter of them. The remaining 51 no-solvent-exposure occupational titles were grouped into seven functionally similar classes in case there were some other unsuspected leukemogenic differences between those seven occupational title groups that would be revealed in the analysis. Figure 3 shows, in simplified fashion, the location of solvent-exposure jobs within the major production areas.

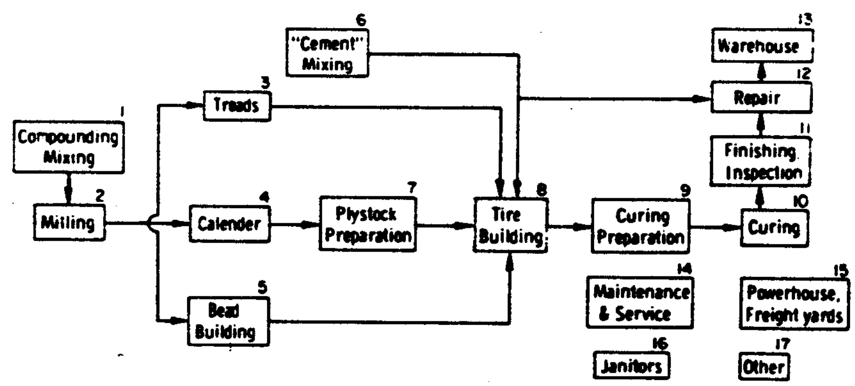
A preliminary discriminant function analysis was carried out to assess the power of the multivariate exposure variable (comprising the individual's configuration of time spent in the ten groups) to discriminate between that individual's status as case or control. The result for all lymphatic and hematopoietic cancers was statistically insignificant. However, for the lymphatic leukemia group, the analysis revealed a statistically significant positive association between solvent exposure and lymphatic leukemia. Because of this finding, together with the observed seven-fold mortality excess from lymphatic leukemia, and the previously suggested association of benzene with leukemia, subsequent analyses presented here are confined to the lymphatic leukemia cases and their controls. Of the 18 cases, 17 were male, and one female, and so the analysis was restricted to the male subset, to avoid having to include sex as an additional covariable in the analyses.

Table 3 shows the length of time, in years, spent by the male cases and controls in any of the three solvent-exposure OTG's. On average, the cases spent 11.27 years in these jobs, while the controls spent 4.06 years. The average of seven more years spent by cases in these areas represents an almost three-fold difference in exposure time between cases and controls.

To take advantage of the individual case-control matching, a matched set analysis was carried out (each set, or quadruplet, comprising one case and its three matched controls). In matched set analysis, one typically examines the distribution of intra-set differences, with the exposure variable categorized as a binary, "yes-no" variable. However, because of the need to retain the ten occupational title groups as a multivariate exposure variable, and to treat the length of "exposure" time spent in any group as a continuous (rather than a categorical) variable, therefore for each of the 17 quadruplets, the matched set analysis evaluated the difference (for each group) between the exposure time of the case and the mean exposure time of the three controls.

The results of the matched set analysis are presented in Table 4. The case-control difference (or "estimated contrast"), in years, is positive for the three solvent-exposure groups, indicating that the lymphatic leukemia cases spent longer there than did their controls. For six of the seven non-exposure groups, the difference is negative. Interestingly, the one other grouping that shows a positive difference, general service, includes jobs that would sometimes have taken the worker into the solvent exposure areas, and may, for example, have involved him in cleaning and degreasing machinery with solvents. A comparison of cases and controls for time spent in the combined solvent-exposure groups showed a statistically significant difference, using both a paired t test and a Wilcoxon signed rank test.

To determine if this observed association was at least partially spurious, because of confounding effects due to variables not matched for in control selection, multivariate analysis of covariance was next carried out. In this analysis, the matched sets were ignored, the population of cases being compared with the population of controls. This analysis revealed some degree of overmatching, in that of the three matching variables, race, age, and plant (sex having been excluded), age was not strongly associated with having worked in solvent-exposure OTG's. On the other



High solvent exposure : 3 (tread cementing), 4 (calender tending), 6
Medium " " : 4 (calender operating), 9, 11, 12, 14
Light " " : 5, 7, 8
No " " : 1, 2, 10, 13, 15, 16, 17

(Note: All jobs in each box do not necessarily have identical or even closely similar exposure characteristics. The diagram groups, in simplified fashion, several hundred different jobs.)

Fig 3. — Diagrammatic representation of rubber tire production stages, classified as sources of solvent-exposure jobs.

hand, the analysis revealed an association of educational level with type of job done. Therefore, by treating race, age. plant, and educational level as covariables along with the case-versus-control variable, it was found that, when adjusting for the effects of these covariables, the lymphatic leukemia cases effectively spent about four years more in solvent-exposure groups than did the controls. This adjusted difference (although less than the seven years indicated in the initial tabulation of work-history data) was highly statistically significant ($p = .005$).

Although the number of matched lymphatic leukemia sets is not large, a series of simplified matched set analyses were carried out to compare the estimated relative risk for the three individual solvent-exposure groups. Relative risk can be estimated from the matched set data layout with a formula b a d on the formula discussed by Mantel a d Haenszel.[13]

Table 5 lists the values of the dative risk for two different times of first exposure (first, exposure to solvents at any time; and first exposure at some time between 1940-1960). The 1940-1960 period was chosen as a likely "etiologic period" for deaths occurring from the mid-1960's onward, on the assumption of a 5 to 20 year latency period, as suggested by the approximately 10 to 12 year latency period for radiation-induced leukemia. For both exposure-time definitions, there is a dose-response relationship, with the high solvent-exposure OTC having the highest relative risk Overall, the relative risk for solvent-exposed worken compared to non-exposed workers appears to be of the order of 3. When relative risk is estimated. using the relative odds approximation[14] (and ignoring individual matching), the overall value for solvent-exposed versus solvent-non-exposed worken is 2.1. However, it must be stressed that these estimates are based on modest numbers, and statistical tests indicate that the distributions of cell frequencies used in estimating the relative risk figures in Table 5 do not achieve statistical significance, except for the two high solvent exposure OTG figures (5.50, 9.00).

Finally, of the 19 individual occupational titles included within these three solvent-exposure groups. one showed a marked difference between cases and controls. For tire repair jobs, there was a sixfold discrepancy between uses and controls. The repairing of tires involves considerable swabbing of tires with solvent, and, at some time in the past, the solvent predominantly used was benzene. Of further interest, each of these four cases had started working there only at some time since 1945, whereas the two controls had started working there before 1945. This may indicate that the leukemogenic agent is a chemical that has been present in recent decades, and may still be present; rather than one that was eliminated prior to World War II or earlier.

Table 3. — Total Time (in Years) Spent in the 3 Solvent-Exposure Occupational Title Groups, Male Lymphatic Leukemia Cases and Controls.

Quadruplet No.	Case	Control 1	Control 2	Control 3	Control Mean
1	0	2.82	7.56	1.49	3.96
2	31.94	0	10.77	9.22	6.66
3	14.15	9.74	0	10.16	6.63
4	16.29	13.32	.14	2.34	5.33
5	0	0	0	22.88	7.63
6	6.78	4.85	0	27.02	10.62
7	18.45	4.07	0	.78	1.62
8	2.57	.52	8.35	3.37	4.08
9	0	0	0	0	0
10	.43	1.15	0	0	.38
11	35.63	0	8.67	0	2.89
12	35.60	0	.68	15.92	5.53
13	0	0	0	0	0
14	17.93	0	0	.25	.08
15	0	0	0	0	0
16	8.17	27.42	0	0	9.14
17	3.70	6.77	6.68	.36	4.50
Total	191.63	70.65	42.84	93.80	69.02
Average	11.27				4.06

18-1 (excluded 1 ♀)

Table 4. — Matched Quadruplet Analysis (Lymphatic Leukemia), Showing Average Intra-Quadruplet Case-Control Difference in Occupational Title Groups Exposure Time.

Occupational Title Group	Case-Control Contrast (Years)
1. Heavy solvent exposure	.55
2. Medium solvent exposure	3.09
3. Light solvent exposure	3.57
4. Compounding and Mixing	-.16[1]
5. Milling	-.19
6. Extrusion	-.16
7. Curing	-2.82
8. [illegible] Service	1.71
9. [illegible]	-.97
10. [illegible]	-4.74

[1]A negative sign indicates that the average exposure to that OTG of the control exceeded that of the case.

Table 5. — Estimation of Relative Risk of Lymphatic Leukemia, Using Matched Set Data Layout (and Binary Response Variable).

Solvent Exposure OTG	Relative Risk: First Exposed at any Stage of Work History	Relative Risk: First Exposed Between 1940-1960
High	5.50*	9.00*
Medium	2.00	1.75
Low	2.50	0.83
All three	3.25	2.33

* Underlying cell distribution achieves statistical significance ($p < .025$)

a

Conclusions

Within this case-control study, prompted by an observed excess mortality from cancers of the lymphatic and hematopoietic systems, the association of these types of cancer with specific work-environment exposure has been investigated. Of the various possible relationships examined, the one that stands out is the association of death from lymphatic leukemia with a history of having worked in solvent-exposure jobs. Both the matched quadruplet analysis and the multivariate analysis of covariance demonstrated a significant positive association of lymphatic leukemia with having worked in these jobs. (The fact that both types of analysis are similarly informative about this association reflects the fact that of all the potential confounding factors included in the series of multivariate analyses, the ones found to be most associated with the exposure variable were three of the four that had been initially used in the matching process — that is. sex, race and plant.) The nsk of death from lymphatic leukemia appears to have been approximately *seven* for worken in high solvent-exposure jobs (compared to other workers), and approximately twofold for workers in medium *or* light solvent-exposure lobs

The detailed scrutiny of lymphatic leukemia work-histories yielded some evidence that the greatest contrast between *cases* and controls was for jobs in the Tire Repair Occupational Title. Further. it appears that the relevant exposure agent (probably an organic solvent) may be *one* still present, if not first introduced, in the period since 1945.

Modern solvents used in the rubber industry include xylene, toluene, trichlorethylene, a d various aliphatic hydrocarbons. While these are generally believed. to be non-carcinogenic, this belief may partly have arisen because insufficient epidemiologic study of the carcinogenic potential of these solvents has yet been done

Four other observations should be made regarding these results

Firstly. these results call for several follow-up tasks It is clearly important to determine whether a similar association exists within the data available from the other rubber companies within the research program. Meanwhile. information must be obtained about the details of chemicals (especially solvents) currently and previously used in each *of* the jobs within the solvent-exposure groups.

Secondly. it is *of* interest-that it is lymphatic rather than myeloid leukemia that appears to be associated with solvent exposure jobs. The sparse literature in this area indicates that. at least for cases *of* gross benzene poisoning, the leukemia tends to be of either the hemocytoblastic (or stem cell) kind or the myeloblastic kind The association of lymphatic leukemia with exposure to organic chemicals appears to have no reported precedent.

Thirdly, the reconciliation of the lymphatic leukemia SMR (which is a dative risk of mortality from that cause of death for rubber workers versus the general community) with the relative risk for "exposed" versus "non-exposed" rubber workers poses an interesting question. The SMR indicates a seven-fold mortality risk for all active-age (ages 40 to 64) rubber workers; yet the relative risk calculated in Table 5 indicates a *mere* three-fold excess for "exposed" workers when all 17 cases are examined (and a two-fold excess for "exposed" workers when the 10 active-age quadruplets are examined). If *one* assumes that "non-exposed" rubber workers are at the same mortality risk as the general community, then, logically, *one* expects the "exposed" sub-group of workers to be at a risk somewhat greater than seven-fold. That the calculated figure is less. rather than greater, than seven could either reflect the limitations imposed by the size of this data set. or, it could indicate the presence of a more widely distributed leukemogen within the rubber industry. involving many of the jobs in the "no solvent-exposure" groups. That is, there might be a heightened "background" risk of leukemia that affects most, if not all, rubber workers. while. for certain sub-groups of workers, there is an additional super-imposed risk that arises from their specific job characteristics. This question is currently under follow-up. and necessarily includes further environmental assessment.

Finally. although this study has focussed upon lymphatic leukemia and solvent exposure, it is not possible to discount an association of lymphosarcoma. Hodgkin's Disease and lo eukemia with work- ! or exposure within the rubber industry. Within the data set described above, there were too few cases of these three cancer types to allow any conclusion of no association to be drawn. Indeed. the observed excess mortality from these three cancer types, for the total cohort of rubber workers, could well indicate the presence of carcinogenic agents within the work environment responsible for various cancers of the lymphatic and hematopoietic system. Further study is necessary.

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