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An Evaluation of the Associations of Leukemia and Rubber Industry Solvent Exposures

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Excessive leukemia mortality has appeared consistently in epidemiological studies of British and U.S. rubber industry workers. Attempts to identify causative factors have focused on exposure to benzene and other solvents. Interpretations of findings from these studies have often been influenced by expectations of a benzene/nonlymphocytic leukemia association, seen from previous wort in other settings. However, data from the rubber industry studies have not been consistent with this expectation, as lymphocytic and nonlymphocytic leukemia have shown similar mortality excesses. Data from a small casecontrol study of lymphocytic leukemia are presented to illustrate an approach that considers multiple solvent exposures. The associations with lymphocytic leukemia risk observed for a number of solvents, most notably carbon tetrachloride and carbon disulfide, were stronger than those detected for benzene.

Key words: leukemia, rubber industry, epidemiology, solvents, benzene, occupational health

INTRODUCTION

Background

Leukemia mortality excesses have been prominent among the findings from numerous epidemiological studies conducted in the British and U.S. rubber industries. Recognition of the extensive use of organic solvents in rubber and tire manufacturing stimulated a priori suspicions that there might exist leukemia hazards in the industry. The well-documented causal association between benzene exposures and leukemia seen in the rotogravure and shoe industries [Vigliani and Saita, 1964; Aksoy and Erdem, 1978] served as a guide in this regard.

The relationship between leukemia risk and solvent exposures in the rubber industry has been, at most, indirectly inferred. The main reason has been that these investigations were retrospective designs—a common, often necessary feature of epidemiological studies of rare, chronic diseases—with either nonexistent or unsystematically obtained environmental exposure data. Nonetheless, the consistently

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observed patterns of elevated leukemia mortality rates, accompanied by apparent localization of risks to workers with the greatest potential for past solvent exposures. prompted the International Agency for Research on Cancer to conclude in a recent monograph on the rubber industry [IARC, 1982a] that therc is sufficient evidence to consider the association as causal.

In this paper we review the studies of leukemia and solvent exposures in the British and U.S. rubber industires. Particular attention is paid to the specificity of this relationship, in terms of leukemia cell type. and with regard to the various solvents used in the industry. Much of the interpretation of the findings from previous research has been influenced by how well or poorly the results accord with expectations derived from studies of benzene-exposed workers in other occupational settings. In particular, the presence or absence of a benzene/acute nonlymphocytic leukemia association has been the standard for causality, despite some conflicting evidence. The implications of this approach are discussed.

In addition, we present findings from a small-scale casecontrol study that are suggestive of etiological associations between lymphocytic leukemia and a number of rubber industry solvents other than benzene. most notably carbon tetrachloride and carbon disulfide.

A detailed summary of the findings from the British and U.S. studies of leukemia among rubber workers is given in Table I. Selected important findings and conclusions drawn from these investigations are discussed below.

British Rubber Industry Studies

Two companion series of epidemiologic studies have been undertaken by the Employment Medical Advisory Service (Fox et al, 1974; Fox and Collier, 1976; Baxter and Werner, 1980] and the British Rubber Manufacturers' Association [Veys, 1981; Parkes et al, 1982]. Modest excesses of leukemia have been observed generally. The most direct evidence pertaining to solvent exposures was a marked excess of acute myeloid leukemia in one tire plant (SMR = 714) where plastic film manufacturing, entailing benzene exposure, had occurred in past years [Baxter and Werner, 1980]. In contrast, Parkes et al [1982] discounted the likelihood of a causal association between leukemia mortality and solvents because the observed excesses occurred in years when benzene was no longer used, and there was no unusual leukemia cell type distribution.

U.S. Rubber Industry Studies

Epidemiologic research in the U.S. rubber industry has revealed fairly consistent patterns of elevated leukemia mortality rates (see Table I). While there has been considerable variability in the reported relative risks, most have been in the range of 1.5 to 3.0, and lymphocytic leukemia excesses generally have been as prominent as those from the nonlymphocytic leukemias. Cell type distinctions were not made in many of the studies. however.

Etiological associations with solvents have been examined by some investigators who used work history information to indicate the likelihood for past exposure. Several of these studies warrant comment.

Researchers from the National Institute for Occupational Safety and Health reported a Standardized Mortality Ratio (SMR) of 560 for leukemia among 748 workers engaged in rubber hydrochloride (Pliofilm) manufacturing in the 1940s

(Infante et al, 1977; Rinsky et al, 1981]. Benzene exposures were known to have occurred in the Pliofilm departments studied. An argument for a potent leukemogenic effect of benzene was offered on the basis of the estimated low exposure levels, presumed to be in compliance with existing standards, and because all seven observed leukemia deaths were either myelogenous or monocytic [Rinsky et al, 1981]. Andjelkovich et al [1976, 1977] previously had found no leukemia excess among Pliofilm workers.

McMichael et al [1974] reported a dramatic excess of lymphocytic leukemia (SMR = 764) for workers aged 40–64 in one plant. Leukemia risk was related to work experience in a number of jobs where there existed potential for solvent exposures [McMichael et al, 1976b]. An apparent dose-effect relationship between solvent exposures and lymphocytic leukemia was detected in a case-control study of 15 deaths from several plants [McMichael et al, 1975]. Specific solvents were not identified in these studies, as the exposures were considered to be mixtures of various aromatic and aliphatic compounds.

In a larger case-control study of leukemia death in four companies, Wolf et al [1981] confirmed the association of lymphocytic leukemia with solvent exposures in the company reported on earlier by McMichael et al [1975] but did not find similar results for the other three companies. Also, myeloid leukemia was apparently unrelated to solvent exposures.

In the casecontrol studies reported by McMichael et al [1975] and Wolf et al [1981], solvent exposures were inferred from occupational titles recorded on work history records, where the occupational titles were functionally homogeneous groupings of jobs, similar with respect to materials handled and machinery used [Gamble and Spirtas, 1976]. Occupational titles were useful for distinguishing jobs according to generalized solvent exposure potential; however, exposures to individual solvents could not be specified. Consequently, Arp et al [1983] devised a method to estimate worker exposures to the specific solvents encountered in the company that experienced the greatest lymphocytic leukemia excess [McMichael et al, 19741. From company documents dating back to the 19209, Arp created historically validated charts of annual authorized solvent usage by process area for all solvents used in order to study the association between solvents, especially benzene, and lymphocytic leukemia. The cases and controls in Arp's study were the same subjects from this company that were included in the larger case-control study [Wolf et al, 19811. The entries from work history records and the solvent charts indicated whether workers spent time in a process area when a solvent was authorized for use. Descriptions of the job titles listed on the work histories permitted differentiation of the jobs that involved routine handling of solvents (primary exposure) from other jobs in the process which presumably involved lesser exposure to solvents (secondary exposure).

Table II shows data from Arp's study [Arp et al, 1983) of the solvent exposure history comparisons of 15 lymphocytic leukemia cases with 30 matched controls. In this analysis, workers with potential solvent exposures of at least I year were considered exposed. Although workers with secondary solvent exposures experienced only a slight excess of lymphocytic leukemia, the data indicated a 4.5 times greater risk among workers who routinely handled solvents (primary exposure). It is noteworthy that the exposure odds ratio for the benzene categories and the aggregate 'other solvent" categories were almost identical.

TABLE I. Summary of Rubber Industry Studies of Leukemia

Author (year)	Study characteristics	Leukemia type	Exposure	Number observed	Estimated relative risk[a]
British studies					
Fox et al (1974)	Cohort 10,867 males (1967–71)	Unspecified[b]	Overall[c]	14	SMR = 108
Fox and Collier (1976)	Cohort 0,867 males (1972–74)	Unspecified	Overall	14	SMR = 128
		Unspecified	Tire sector	6	SMR = 143
Baxter and Werner (1980)	Cohort 0,867 males (1967–76)	Unspecified	Overall	33	SMR = 98
		Acute myeloid	Tire sector	6	SMR = 134
		Acute myeloid	Plastic film	3	SMR = 714
Parkes et al (1982)	Cohort 3,815 males (1946–75)	Unspecified	Overall	31	SMR = 110
U.S. studies					
Mancuso et al (1968)	Cohort 1,877 white males (1940–64)	Unspecified	Office (ages 65+)	2	RR = 4.27
Mancuso (1975)	Cohort 8,234 males (1938–72)	Leukemia and multiple myeloma combined	Chemical plant	1	RR = 2.38
			Stock prep.	2	RR = 2.38
			Compounding and milling	5	RR = 2.35
			Maintenance and tire shop	3	RR = 1.40
			Machine shop	1	RR = 1.37
Monson and Nakano (1976b)	Cohort 13,571 white males (1940–74)		Overall	55	SMR = 128
			Tire building and curing	18	SMR = 150
			Raw materials processing	10	SMR = 240
Monson and Nakano (1967a)	Cohort 5,816 females 986 black males 3,727 salaried white males	Unspecified	Overall	9	SMR = 97
				0	SMR = 0
				8	SMR = 93
Monson and Fine	Cohort				

Monson and Nakano (1967a)	Cohort 5,816 females 986 black males 9,427 salaried white males (1940-74)	Unsp d	Overall	9 0 8	SMR = 97 SMR = 0 SMR = 93
Monson and Fine (1978)	Cohort 13,570 white males (1940–76)	Unspecified	Calendering Rubber fabrics Tire curing Elevators Tubes	4 4 5 3 4	RR = 3.6 RR = 3.5 RR = 2.9 RR = 2.9 RR = 2.5
Delzell and Monson (1981)	Cohort 15,643 white males (1940–78)	Unspecified	Overall	68	SMR = 121
Delzell and Monson (1982)	Cohort 2,666 white males (1940–78)	Unspecified	All processing Front processing Back processing	16 7 14	SMR = 171 RR = 1.3 RR = 1.7
Delzell et al (1981)	Cohort 1,792 white males (1954–77)	Unspecified	Overall	1 3	SMR = 45 SIR = 100
McMichael et al (1976a)	Cohort 18,903 white males (1964–73)	Unspecified Lymphocytic	Overall Overall	—[d] —	SMR = 130 SMR = 158
Andjelkovich et al (1976)	Cohort 8,418 white males (1964–73)	Unspecified Lymphocytic Myeloid Monocytic	Overall Overall Overall Overall	19 10 6 3	SMR = 147 SMR = 152 SMR = 87 SMR = 311
Andjelkovich et al (1977)	Cohort 8,418 white males (1964–73)	Unspecified	General servi e	6	SMR = 246
Rinsky et al (1981)	Cohort 748 white males (1950–75)	Nonlymphocytic	Rubber Hydrochloride (benzene)	7	SMR = 560
McMichael et al (1974)	Cohort 6,678 males all races (1964–72)	Unspecified	Overall	16	SMR = 128
McMichael et al (1976b)	Cohort 6,678 males all rac e (1964–73)	Lymphocytic Lymphocytic Lymphocytic Lymphocytic	Synthetic rubber Inspection and repair Extrusion Janitorial	— — — —	RR = 3.7 RR = 3.2 RR = 3.0 RR = 2.6

TABLE I. Summary of Rubber Industry Studie of Leukemia *(Continued)*

Author (year)	Study characteristics	Leukemia type	Exposure	Number observed	Estimated relative risk[a]
McMichael et al (1975)	Case-control 17 cases 51 controls males & females all r es (1964–73)	Lymphocytic	Solvents	12	3.3
Wolf et al (1981)	Case-control 72 cases 286 controls males & females all r ocess (1964–73)	Unspecified	Solvents	8	RR = 0.8
		Lymphocytic	Solvents	5	RR = 1.6
		Lymphocytic	Solvents	4	RR = 3.2
		Myeloid	Solvents	2	RR = 1.0
		Monocytic	Solvents	0	RR = 0
		Other	Solvents	1	RR = 0.3
Arp et al (1983)	Case-control 15 cases 10 controls females all r.c.s. (1964–73)	Lymphocytic	Benzene	3	RR = 4.5
				11	RR = 4.5

[a]SMR (standardized mortality ratio = obs ÷ exp × 100); SIR (standardized incidence ratio); RR (rate ratio); OR (odds ratio from case-control studies).
[b]Unspecified, refers to all types of leukemia, combined.
[c]Overall, refers to results for entire plant, ie, unspecified exposure.
[d]Cannot determine observed number of cases exposed from published data.

TABLE II. Solvent Exposure and Lymphocytic Leukemia Relative Risk Estimates*

Exposure category	Number of cases exposed	Odds ratio	Chi square
Primary benzene	3	4.5	1.50
Secondary benzene	2	1.5	0.13
Primary other solvent	11	4.5	3.06
Secondary other solvent	8	1.6	0.41

*Data from Arp et al [1983].

NEW RESULTS FROM A STUDY BASED ON MULTIPLE SOLVENT EXPOSURES

Methods and Results

The casecontrol analysis of lymphocytic leukemia reported by Arp *et* al (19831 was extended to consider risks associated with 24 specific solvents. *As* before, solvents exposure charts for process areas were reconstructed from historical plant records. The determination of workers' exposure histories differed from the method used previously in that exposure codes for each solvent were assigned *to* the department rather than to the individual job title entries on the work history records. This simplified method of exposure coding enabled the use of a computer algorithm, and it proved to be more cost- and time-efficient for examining risks related to multiple agents than did the manual coding process used in the previous analysis, which was restricted to an evaluation *of* only two classes of exposure, benzene and ail other solvents grouped together. The only information sacrificed was the judgmental distinction between primary and secondary exposures.

The *cases* in the present analysis were 11 male, hourly workers whose underlying cause of death was lymphocytic leukemia (ICD8th Revision Code *204)* who were identified from the cohort reported on by McMichael et al.[1975]. These cases were also included in the studies by Wolf *et* al [1981] and Arp *et* al [1983]. Controls were a *20%* age-stratified random sample of the cohort [McMichael et al, 1976b]. A total of 1,350 controls (1.280 whites and *70* blacks) was included.

Age-adjusted relative risk *estimates,* as approximated by the odds ratio, and associated with chi-square tests of statistical significance were computed according to procedures described by Mantel and Haenszel [1959]. Workers were considered exposed to a particular solvent if their cumulative duration *of* work in a solvent-related department exceeded 12 months.

Table III shows the odds ratios associated with each of the 24 solvents. *As* mentioned above, no distinction was made between primary and secondary exposure to benzene, which accounts for the lower relative risk estimate; however, the odds ratio (2.5) is within the range of the estimates found in the previous analysis (see Table II). Among the solvents listed in Table III, carbon tetrachloride (OR=14.8) and carbon disulfide (OR = 8.7) showed the strongest associations with lymphocytic leukemia. Several other solvents were also related to leukemia mortality, and these multiple associations probably reflect simultaneous exposures to different solvents used concurrently in the industry.

Neither carbon tetrachloride nor carbon disulfide has been shown previously to be leukemogenic, and it is possible chat the present findings are spurious. Nevertheless, the high odds ratios forthese solventssuggest that, even if they are not etiological

TABLE III. Case-control Analysis of Lymphocytic Leukemia Risk Associated With Exposures to 24 solvents

Solvent	Number of cases exposed	Odds ratio	Chi square
Acetone	3	5.1	6.33*
Aqua ammonia	1	2.4	0.71
Benzene	4	2.5	1.59
carbon disulfide	7	8.7	12.82**
Carbon tetrachloride	8	14.8	18.00**
Dipentene	1	1.0	0.00
Ethanol	4	2.0	1.14
Ethyl acetate	3	5.1	6.33*
Gasoline	9	4.9	3.10
Heptane	2	0.9	0.01
Hexane	7	3.8	4.32*
Isopropanol	6	1.8	0.84
Methanol	1	8.3	5.31*
Methylene chloride	0	—	0.32
Mineral spirits	1	1.5	0.15
Perchloroethylene	1	0.7	0.09
Phenol	1	0.5	0.40
Solvent A[a]	7	2.7	2.14
Special naphthas	8	2.7	1.62
Toluene	2	3.0	1.81
Trichloroethane	0	—	0.52
Trichloroethylene	2	0.8	0.07
VM and P naphthas	3	2.9	2.68
Xylenes	4	3.2	3.35

[a]Proprietary mixture of toluene and other solvents.
*$p < 0.05$.
**$p < 0.001$.

agents themselves, they are probably closely associated with the actual causative exposure(s).

The exploratory nature of this analysis and the small sample size preclude firm conclusions about specific solvent–leukemia associations. However, these findings illustrate clearly the danger of focusing exclusively on a single exposure, ie, benzene, in a multiexposure environment.

DISCUSSION

The examinations of leukemia risk factors in the British and U.S. rubber industries have proceeded sequentially from the identification of mortality excesses, relative to the generally unexposed national and regional populations, to more intensive investigations of [illegible]lly related work environments and exposures within the industry. Leukemia mortality excesses of varying magnitudes have been observed in most studies. The use of solvents in various processes of rubber and tire manufacturing (eg, tire building) and the well-recognized leukemogenic potential of benzene suggest an obvious etiological association: however, the findings from many investigations of rubber worker populations do not fit especially well with a benzene-related effect. In this regard it is noteworthy that the animal data on experimental benzene

carcinogenesis also have been conflicting [Ward et al, 1975; Maltoni and Scarnato, 1979; Snyder et al, 1980; IARC, 1982b], and the reported mutagenicity results have been largely negative [Dean, 1978; IARC, 1982b]. Contradictory results in human populations are therefore not surprising.

Benzene was used in the industry as a general purpose solvent in the 1920s [Davis, 19291, but following reports of toxicity [Hunter, 1939], benzene was supplanted by toluene and other aromatic and aliphatic solvents [Mellan, 19571. While benzene exposure still occurs in the industry, it is present primarily as a contaminant of other substances [Van Ert et al, 1980], and exposures are much lower than in the 1920s; thus it is quite likely that only small proportions of the cohorts studied were ever exposed to benzene in concentrations known to induce leukemia.

The strongest causal associations for benzene historically have been with the acute myeloid types of leukemia, including erythroleukemia [Goldstein, 1977], yet are also case reports of lymphocytic leukemia as a sequela of benzene poisoning [Delore and Borgomano, 1929; Hunter, 1939; Vigliani, 1975]. Excessive mortality from lymphocytic leukemia has been as great as that from the nonlymphocytic variants in a number of rubber industry cohorts, a result that has prompted several investigators to discount an etiologic relationship with solvents [Monson and Fine, 1978; Parkes et al, 1982].

The NIOSH study of Pliofilm workers [Rinsky et al, 1981] perhaps offers the most convincing demonstration of a benzene/nonlymphocytic leukemia association. The importance placed on the fivefold mortality excess detected in this study is evidenced by the fact that the IARC working group [IARC, 1982b] recently used this relative risk approximation to estimate excess lifetime risk associated with benzene exposures. Even in view of the magnitude of the reported risk for nonlymphocytic leukemia associated with benzene exposure, the specificity of the association remains uncertain, as exposures to other rubber industry solvents were not evalutated in the analysis. Findings from a reanalysis of the case-control data of Arp et al [1983], that were presented in this paper, demonstrate the extent to which interpretations of seemingly causal relationships can change in light of newly considered exposure information.

Additional research into the etiology of leukemia in the rubber industry should be guided by several considerations made apparent from previous work. It should be recognized that the presumed class of causative agents, solvents, is a mixed group of compounds, of which benzene is generally a minor quantitative component. The indication therefore is to examine possible etiological relationships with other solvents.

As shown from the data presented in Table III, numerous solvents were used in the industry. Moreover, usage has varied qualitatively and quantitatively over time, and there has been considerable temporal overlap of exposures. Consequently, the identification of the specific agent(s) responsible for leukemia excesses is likely to be a complicated process requiring investigator judgement as to which solvents are likely to be leukemogenic, based on previous experimental and human observational data.

While the foregoing discussion suggests the need to investigate the potential leukemogenic effects of solvents other than benzene, we do not imply that continued research into benzene toxicity in the rubber industry should be abandoned. Rather, the scope of the research should be expanded to include assessment of effects of multiple exposures, and the interpretations of the findings should not be evaluated necessarily with respect to a benzene/nonlymphocytic leukemia association.

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