Am. Ind. Hyg. Assoc. J. 45(12):809-811 (1984)

101

Cancer Mortality and Solvent Exposures in the Rubber Industry

TIMOTHY C. WILCOSKY, HARVEY CHECKOWAY, ELIZABETH G. MARSHALL and HERMAN A. TYROLER
Occupational Health Studies Group, School of Public Health, University of North Carolina, Chapel Hill, NC 27514

Some evidence suggests that solvent exposures to rubber industry workers may be associated with excess cancer mortality, but most studies of rubber workers lack information about specific chemical exposures. In one large rubber and tire-manufacturing plant, however, historical documents allowed a classification of jobs based on potential exposures to all solvents that were authorized for use in the plant. A case-control analysis of a 6678 member cohort compared the solvent exposure histories of a 20% age-stratified random sample of the cohort with those of cohort members who died during 1964-1973 from stomach cancer, respiratory system cancer, prostate cancer, lymphosarcoma, or lymphatic leukemia. Of these cancers, only lymphosarcoma and lymphatic leukemia showed significant positive associations with any of the potential solvent exposures. Lymphatic leukemia was especially strongly related to carbon tetrachloride (OR = 15.3, $p < .0001$) and carbon disulfide (OR = 8.9, $p = .0003$). Lymphosarcoma showed similar, but weaker, associations with these two solvents. Benzene, a suspected carcinogen, was not significantly associated with any of the cancers.

Introduction

Occupational studies suggest that benzene exposure may cause some types of leukemia[1] and lymphoma,[2] but other solvent-cancer associations have received less attention. Such studies can be difficult to conduct because many years may elapse between causal exposures and the occurrence of disease and measurements of exposures from earlier decades are often sparse or nonexistent. However, detailed records of authorized solvent use in one large rubber and tire-manufacturing plant allowed a classification of jobs based on potential exposures to 25 specific solvents. Workers from this plant have shown excess mortality from several different cancers,[3] and these cancers were associated with jobs that involved the use of solvents.[4] The exploratory case-control study reported here examined the associations of these cancers with each of the specific solvents, including benzene, used in the plant.

Methods

As described in an earlier publication,[3] researchers from the Occupational Health Studies Group at the University of North Carolina at Chapel Hill followed a closed cohort of 6678 active and retired male rubber workers for a 10-year period that began in 1964. These production workers from a large plant in Akron, Ohio, were aged 40-84 at the beginning of follow-up, and a trained nosologist coded the underlying cause of death for all decedents under the Eighth Revision of the International Classification of Diseases (ICD). A 20% age-stratified random sample of the cohort[4] served as the control group for this analysis; the cases were decedents from cancers for which an earlier study of the cohort[3] had shown excess mortality: stomach (ICD 151), prostate (ICD 185), lymphosarcoma and reticulum cell sarcoma (ICD 200), and lymphatic leukemia (ICD 204). (For the sake of brevity, the ICD 200 category will be referred to as lymphosarcoma.) Respiratory system cancer (ICD 160-163) was also included, because other research suggests a possible association with benzene exposure.[5]

The methodology for reconstructing past solvent exposures has been previously described.[6] For each calendar year, a review of the product specifications and operating procedures indicated which solvents were authorized for use at each stage of tire production, and the specifications for raw materials identified the specific solvent components of the commercial grade materials. These documents gave the history of all authorized solvent usage in the plant by process area and calendar year. Worker exposures were linked to the solvent data through the work history records, which specify the job title, the department, and the dates of employment for each job that a worker holds in the plant; complete machine-retrievable work histories were available through 1973 for cases and controls aged 40-79 in 1964.

Exposure was defined as the presence of a worker in a process area when a given solvent was authorized for use, and a computer algorithm assigned exposure codes to all cases and controls. In this analysis, only workers with cumulative exposures of more than one year were considered exposed. The exposure definition was based strictly on company records, so it required no subjective investigator judgment. However, the authorization of a soivent does not guarantee that it was actually used, so an unknown number of workers may have been misclassified as exposed, and the term "exposure" should be interpreted to mean potential exposure. Race-specific analyses, stratified by 10-year birth cohorts, were used to estimate age-adjusted relative risks (as approximated by odds ratios) and chi-square values.[7]

Results

Although the review of company documents identified 25 solvents that had been authorized for use in the plant, this analysis presents data only for the 20 in Table I, because fewer than two cases of any given cancer were exposed to the remaining five solvents. Of the cancers under investigation in this study, only respiratory system cancer decedents

TABLE I
Age-Adjusted Exposure Odds Ratios for Solvents and Respiratory System Cancer by Race

	Whites[A]	Blacks[A]	Years of Authorization
Gasoline	(43) .62[B]	(2) .39	1921[C]
Specialty napthas	(43) .70	(2) .39	1921[C]
Benzene	(23) .69	(0) -	1921 - 1938
Ethanol	(21) 1.0	(0) -	1922[C]
Carbon tetrachloride	(20) .75	(0) -	1924 - 1955
Xylenes	(10) .61	(0) -	1927[C]
Carbon disulfide	(14) .61	(0) -	1927 - 1967
Ammonia	(1) -	(2) 1.1	1931[C]
Ethyl acetate	(6) .84	(0) -	1933 - 1956
Acetone	(5) .86	(0) -	1933 - 1948
Hexane	(19) .54[B]	(2) .69	1936[C]
Solvent "A"[D]	(36) .95	(2) .45	1942[C]
Isopropanol	(27) .64	(2) .56	1942[C]
Phenol	(13) .95	(2) .91	1943[C]
VM&P naphtha	(5) .54	(2) .85	1955[C]
Trichloroethylene	(11) .64	(0) -	1955[C]
Heptane	(11) .63	(2) .93	1956[C]
Toluene	(3) .55	(0) -	1959[C]
Dipentene	(2) .35	(2) .87	1960[C]
Perchloroethylene	(2) .26	(0) -	1964[C]
Total cases:	85	16	

[A]Number of exposed cases in parentheses
[B]$p < .05$
[C]Still authorized in 1973
[D]Proprietary mixture of toluene and other solvents.

TABLE II
Age-Adjusted Exposure Odds Ratios for Solvents and Selected Cancers, White Males

	Stomach Cancer[A]	Prostate Cancer[A]	Lympho-sarcoma[A]	Lymphatic Leukemia[A]
Gasoline	(18) .97	(20) 1.0	(6) 1.2	(9) 5.3
Specialty napthas	(18) 1.1	(18) .91	(6) 1.4	(8) 2.8
Benzene	(12) 1.3	(11) .73	(6) 3.0	(4) 2.5
Ethanol	(8) 1.1	(8) 1.0	(1) -	(4) 2.0
Carbon tetrachloride	(7) .76	(12) 1.3	(6) 4.2[B]	(8) 15.3[D]
Xylenes	(3) .53	(8) 1.5	(4) 3.7[B]	(4) 3.3
Carbon disulfide	(8) 1.2	(11) 1.5	(6) 5.6[C]	(7) 8.9[D]
Ammonia	(2) 2.1	(1) -	(0) -	(1) -
Ethyl acetate	(1) -	(5) 1.9	(1) -	(3) 5.3[B]
Acetone	(1) -	(4) 1.7	(1) -	(3) 6.8[C]
Hexane	(11) 1.2	(13) 1.5	(6) 4.0[B]	(7) 4.0[B]
Solvent "A"[E]	(15) 1.4	(13) .99	(6) 2.6	(7) 2.8
Isopropanol	(14) 1.4	(12) .96	(6) 2.9	(6) 1.8
Phenol	(6) 1.4	(2) .37	(0) -	(1) -
VM&P naphtha	(3) 1.1	(4) 1.6	(1) -	(3) 2.9
Trichloroethylene	(5) 1.0	(3) .62	(3) 2.4	(2) .81
Heptane	(6) 1.3	(3) .58	(3) 2.3	(2) .91
Toluene	(1) -	(3) 2.6	(0) -	(2) 3.0
Dipentene	(2) 1.3	(0) -	(0) -	(1) -
Perchloroethylene	(1) -	(1) -	(1) -	(1) -
Total cases:	30	33	9	10

[A]Number of exposed cases in parentheses
[B]$p < .05$
[C]$p < .01$
[D]$p < .001$
[E]Proprietary mixture of toluene and other solvents.

included at least two blacks exposed to any of the solvents. As Table I shows, most solvents were negatively associated with respiratory system cancer in both races, and for gasoline and hexane, the negative associations achieved nominal statistical significance ($p < .05$) among whites. Table I also presents the first and last years of authorized use for these solvents, and it shows that the solvent exposures changed over time in the plant as new solvents were introduced, while other solvents were withdrawn.

Table II presents exposure odds ratios for the remaining cancers in this study. Neither stomach cancer nor prostate cancer showed significant associations with any of the solvents and almost all odds ratios were less than two. A strikingly different pattern, however, emerges for lymphosarcoma and lymphatic leukemia, where several solvents had significantly elevated odds ratios. Lymphatic leukemia was especially strongly related to carbon tetrachloride (OR = 15.3, $p < .0001$) and carbon disulfide (OR = 8.9, $p = .0003$) exposures; lymphosarcoma showed similar, but weaker, associations with these two solvents.

Discussion

Because different solvents were often used simultaneously (sometimes as components of solvent mixtures) in a given process area, a high degree of correlation exists among many solvent exposures. Consequently, the multiple significant exposure-disease associations for lymphosarcoma and lymphatic leukemia shown in Table II may reflect a single causal agent that is correlated with several of the solvents. Although this agent may not necessarily be a solvent, carbon tetracholoride and carbon disulfide were very strongly associated with both lymphosarcoma and lymphatic leukemia — two cancers that are sometimes cytomorphologically indistinguishable.[8] Other researchers[9] have also found excess lymphatic leukemia in rubber workers exposed to solvents other than benzene and they noted that one work area with excess lymphatic leukemia also had excess lymphosarcoma.

Neither carbon tetrachloride nor carbon disulfide has been shown to cause lymphosarcoma or lymphatic leukemia, but carbon tetrachloride is an apparent liver carcinogen in animals and it may promote the leukemogenicity of other chemicals,[10] while carbon disulfide exposure may cause bone marrow hyperplasia.[11] Studies of laundry and dry cleaning workers who had possible exposures to carbon tetrachloride have revealed no excess mortality from lymphatic leukemia,[12,13] but five cases were reported in a genetically-susceptible family that had worked in a dry cleaning busi-

ness.[14] Female laundry and dry cleaning workers in Wisconsin showed a slight excess of lymphosarcoma.[13]

Benzene, a suspected cause of myeloid and monocytic leukemia in an earlier study of rubber workers,[1] showed no significant associations with any of the cancers in the present analysis. However, benzene and other solvents were withdrawn from the plant before the follow-up period of the cohort, so that exposure-related deaths could have occurred before the beginning of follow-up. In fact, the leukemia cases in the earlier study[1] were exposed to benzene during 1940-49, and they all died before 1964.[15] Other solvents were authorized for use relatively recently, so that any carcinogenic effects would not necessarily have been apparent during the follow-up period.

Unlike other studies of cancer in rubber industry workers,[4,9,15-17] the analysis reported here attempted to examine the cancer risk from specific chemical exposures rather than the risks associated with job categories. An earlier study[6] demonstrated the feasibility of analyzing specific solvents in this multi-exposure setting, but the analysis was restricted to just two solvents, benzene and xylene. The present study, however, considered all 25 solvents authorized for use in the plant. Even though the use of historical documents to derive estimates of potential solvent exposure may have caused exposure misclassification, the resulting bias should be towards the null value of the odds ratio,[18] since any exposure misclassification is probably similar for cases and controls.

Confounding from nonoccupational or occupational exposures could have disguised important solvent-cancer associations in this plant, or spuriously caused the associations between solvents and leukemia and lymphosarcoma. Negative confounding from cigarette smoking, for example, may have caused the negative solvent associations with respiratory system cancer in Table I; smoking data are not available for these workers. Alternatively, the negative associations may be due to chance or to an occupational lung carcinogen that is negatively correlated with solvent exposure.

Because this exploratory analysis examined a large number of solvents and cancers, the observed positive findings for lymphosarcoma and lymphatic leukemia require cautious interpretation. The modest number of cases of these cancers, and the possible biases discussed above further accentuate the need for guarded conclusions. Nevertheless, the study does suggest that solvent exposures played little or no role in the cohort's excess stomach cancer and prostate cancer, while some solvents other than benzene (especially carbon tetrachloride and carbon disulfide) were closely associated with lymphosarcoma and lymphatic leukemia.

References

1. **Infante, P.F., R.A. Rinsky, J.K. Wagoner and R.J. Young:** Leukemia in Benzene Workers. *Lancet ii*:76-78 (1977).
2. **Vianna, N.J. and A. Polan:** Lymphomas and Occupational Benzene Exposure. *Lancet i*:1394-1395 (1979).
3. **McMichael, A.J., R. Spirtas and L.L. Kupper:** An Epidemiologic Study of Mortality Within a Cohort of Rubber Workers, 1964-72. *JOM 16*:458-464 (1974).
4. **McMichael, A.J., R. Spirtas, J.F. Gamble and P.M. Tousey:** Mortality Among Rubber Workers: Relationship to Specific Jobs. *JOM 18*:178-185 (1976).
5. **Askoy, M.:** Different Types of Malignancies Due to Occupational Exposure to Benzene: A Review of Recent Observations in Turkey. *Environ. Res. 23*:181-190 (1980).
6. **Arp, E.W., P.H. Wolf and H. Checkoway:** Lymphocytic Leukemia and Exposures to Benzene and Other Solvents in the Rubber Industry. *JOM 25*:598-602 (1983).
7. **Mantel, N. and W. Haenszel:** Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease. *J.N.C.I. 22*:719-748 (1959).
8. **Williams, W.J., E. Beutler, A.J. Erslev and R.W. Rundles:** Hematology, 2nd Ed. pp. 1026-1039. McGraw-Hill, New York, NY (1977).
9. **Monson, R.R. and L.J. Fine:** Cancer Mortality and Morbidity among Rubber Workers. *J.N.C.I. 61*:1047-1053 (1978).
10. **International Agency for Research in Cancer,** IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans — Some Halogenated Hydrocarbons. *I.A.R.C. 20*:373-399 (1979).
11. **Briegler, H.:** Effects of Carbon Disulfide on Blood Cells and Bone Marrow. *J. Indust. Hyg. Toxicol. 31*:98-103 (1949).
12. **Blair, A., P. Decoufle and D. Grauman:** Causes of Death among Laundry and Dry Cleaning Workers. *Am. J. Public Health 69*:508-511 (1979).
13. **Katz, R.M. and D. Jowett:** Female Laundry and Dry Cleaning Workers in Wisconsin: A Mortality Analysis. *Am. J. Public Health 71*:305-307 (1981).
14. **Blattner, W.A., W. Strober, A.V. Muchmore, R.M. Blase, S. Broder and J.F. Fraumeni:** Familial Chronic Lymphocytic Leukemia — Immunologic and Cellular Characterization. *Ann. Intern. Med. 84*:554-557 (1976).
15. **Wolf, P.H., D. Andjelkovich, A. Smith and H. Tyroler:** A Case-Control Study of Leukemia in the U.S. Rubber Industry. *JOM 23*:103-108 (1981).
16. **Andjelkovich, D., J. Taulbee, M. Symons and T. Williams:** Mortality of Rubber Workers with Reference to Work Experience. *JOM 19*:397-405 (1977).
17. **Parkes, H.G., C.A. Veys, J.A.H. Waterhouse and A. Peters:** Cancer Mortality in the British Rubber Industry. *Br. J. Ind. Med. 39*:209-220 (1982).
18. **Greenland, S.:** The Effect of Misclassification in the Presence of Covariates. *Am. J. Epidemiol. 112*:564-569 (1980).

8 February 1984; Revised 27 August 1984