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To: Members, Benzene Epidemiology Task Force

From: Neill K. Weaver, M.D.

The attached preprint, "A Retrospective Assessment of Solvent Exposure and the Relationship to Lymphatic Leukemia," by Earl W. Arp, Jr., et al, is very intriguing. In exploring the relationship between lymphatic leukemia and solvent exposures in the rubber industry, there appears to be an association with coal-derived (but not petroleum-derived) solvents.

Attachment
a/s

cc: Epidemiology Task Force
I. R. Tabershaw, M.D.
D. Schottenfeld, M.D.
J. J. Thorpe, M.D.

NKW/eew

A RETROSPECTIVE ASSESSMENT OF SOLVENT EXPOSURE AND THE RELATIONSHIP TO LYMPHATIC LEUKEMIA

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INTRODUCTION

Prior research in occupational health has demonstrated an apparent association between leukemia and solvent exposure in an industrial setting. McMichael, et al.,[7] in a 1975 Occupational Health Studies Group (OHSG) report, first demonstrated an increased risk of lymphatic leukemia among rubber workers with a history of solvent exposure as judged by OHSG researchers. The results of that study are presented in Table 1, with the presumed level of exposure based on Occupational Title Groups (OTG's), an OHSG scheme for grouping of workers by contact with common product components and/or process equipment. McMichael notes that for some period of time in the past, benzene was the solvent of choice in the industry.

Wolf, et al.,[26] in a 1977 CHSG study, investigated the same set of leukemia cases using new occupational title groups based on more recent environmental data. Results showed an increased relative risk similar to that of the McMichael finding for one study population, but the lack of an association between leukemia and solvents in another company. An associ'ation between myeloid leukemia and benzene exposure was demonstrated by Infante, et al.,[3] among pliofilm workers exposed between 1940 and 1949.

In the OHSG studies, no direct measurements of past benzene or other solvent exposures were available, 'thus the analyses were based on subjective categories assigned by industrial hygienists. Even with a homogeneous group such as an OTG, however, there exists a gradient of exposure potential, as individual jobs will vary with respect to ex-

posure by virtue of geographical location, engineering controls, or work practice.

McMichael noted the need for more detailed information about solvents used in the rubber industry in order to more accurately assess their impact on worker health. The objective of this research project was to develop a detailed history of solvent usage and potential worker exposure in a rubber tire plant and to use this infomation to reassess the association of lymphatic leukemia and solvent exposure.

POTENTIAL RECORD SOURCES

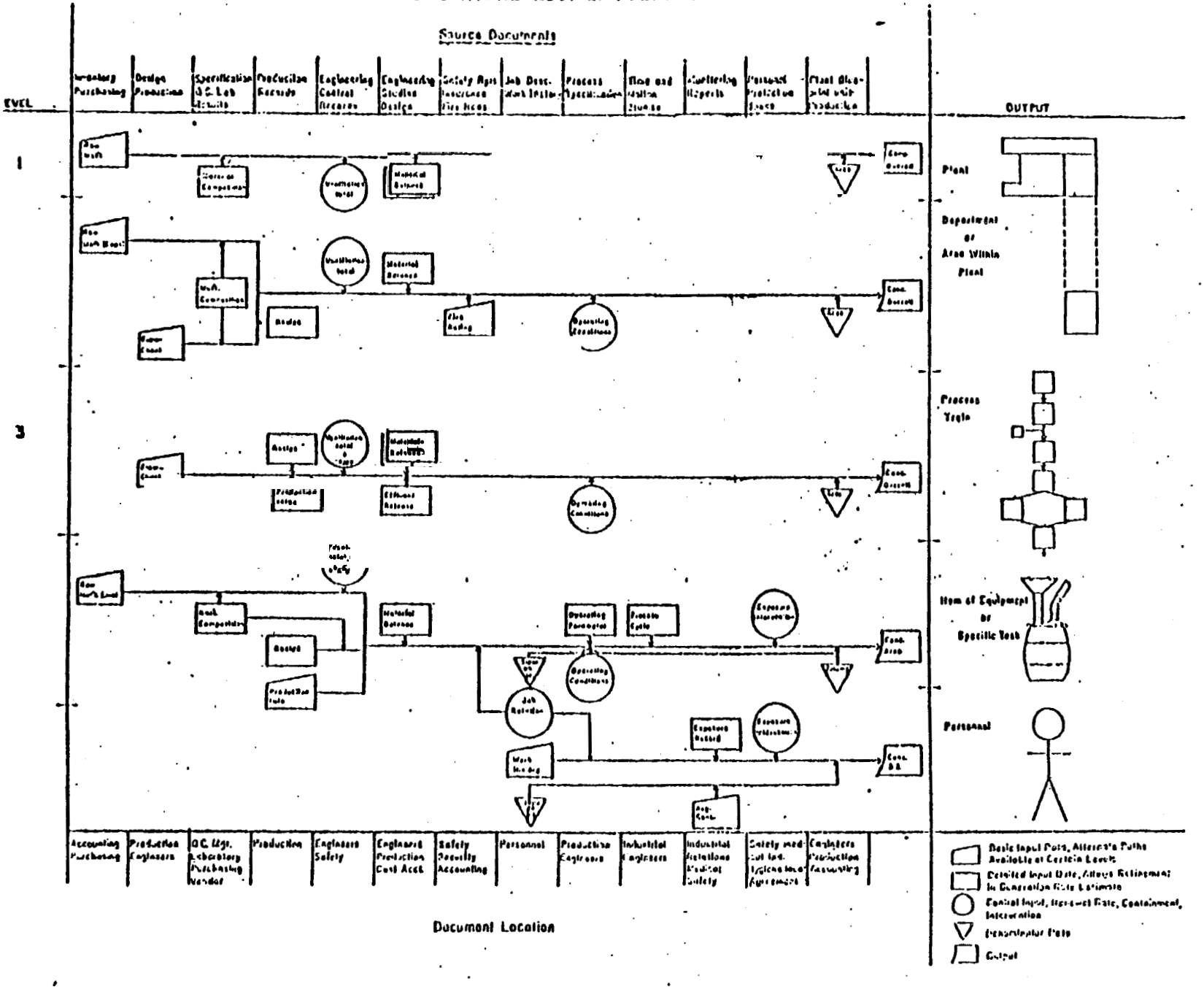

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TABLE 2 1

POTENTIAL SOLVENT EXPOSURE

PROCESS AREA: CEMENT HOUSE

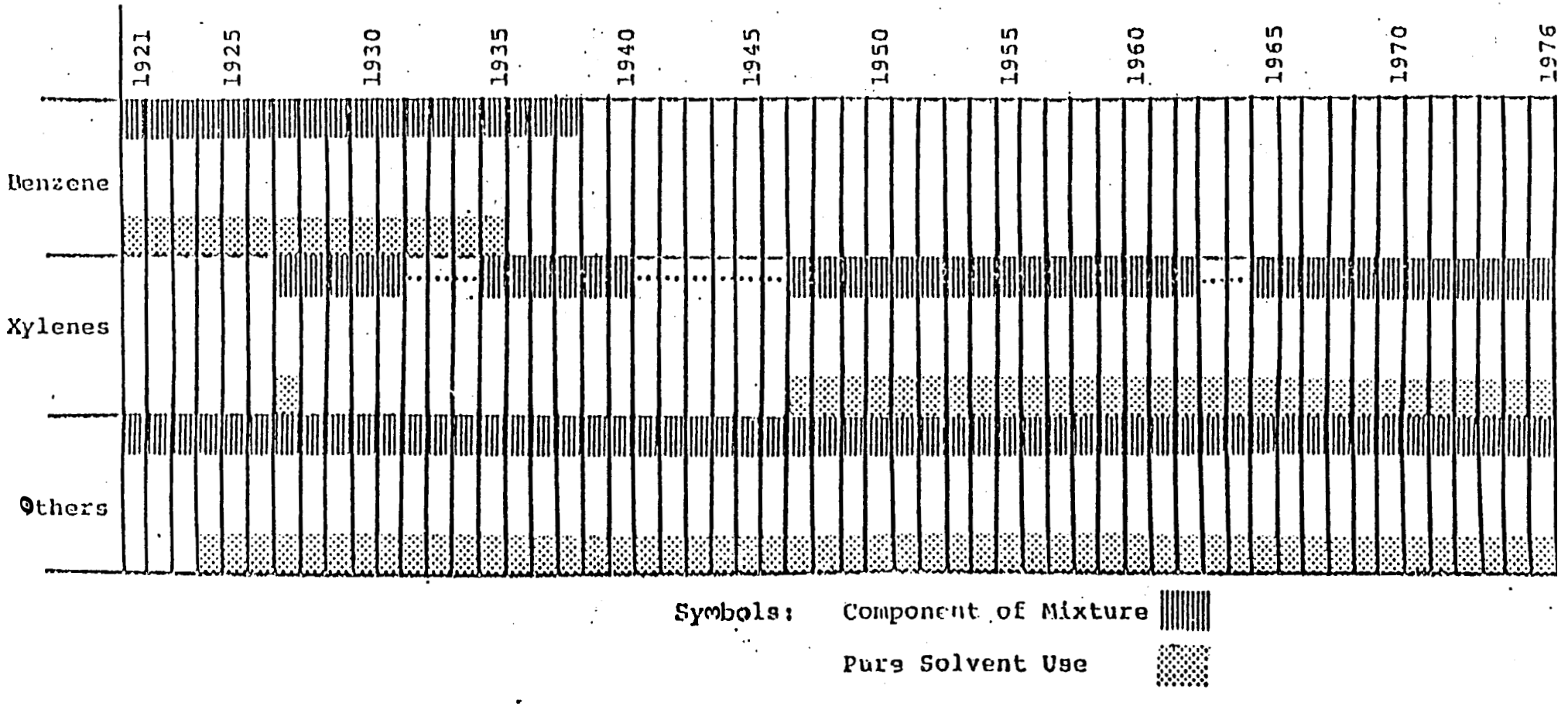


TABLE 2.3

POTENTIAL SOLVENT EXPOSURE

PROCESS AREA: BEAD ROOM

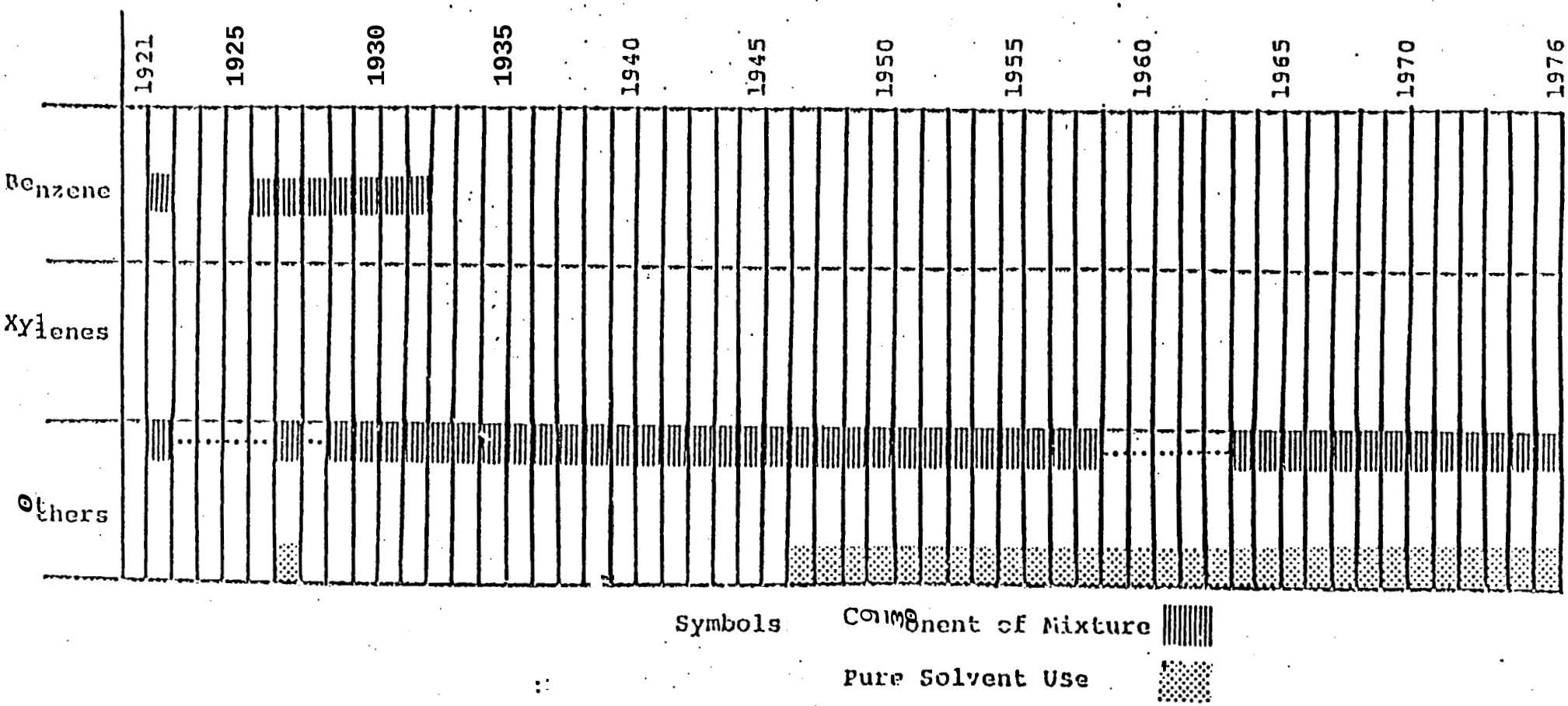


TABLE 2 5

POTENTIAL SOLVENT EXPOSURE

PROCESS AREA: CALENDER

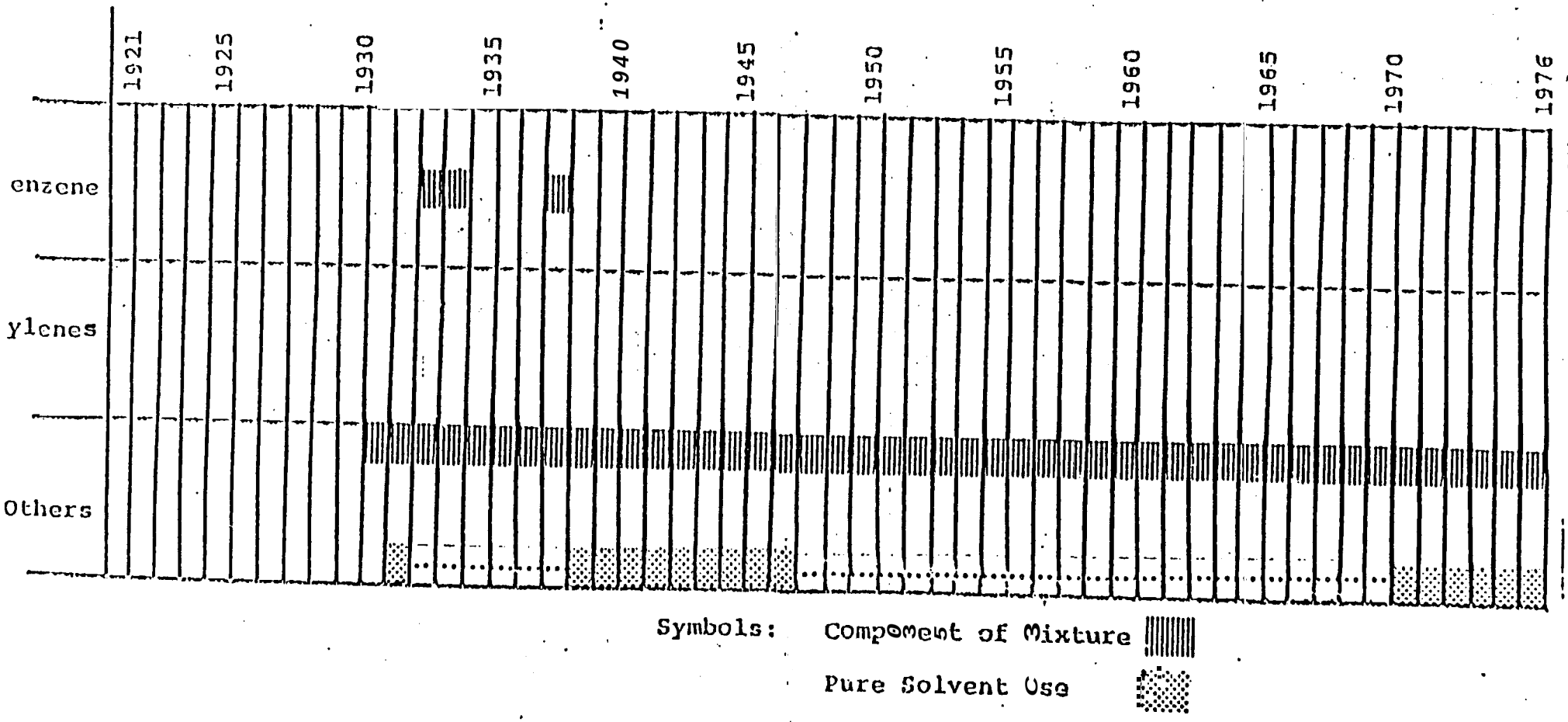


TABLE 2.6

POTENTIAL SOLVENT EXPOSURE

PROCESS AREA: STOCK CUTTING

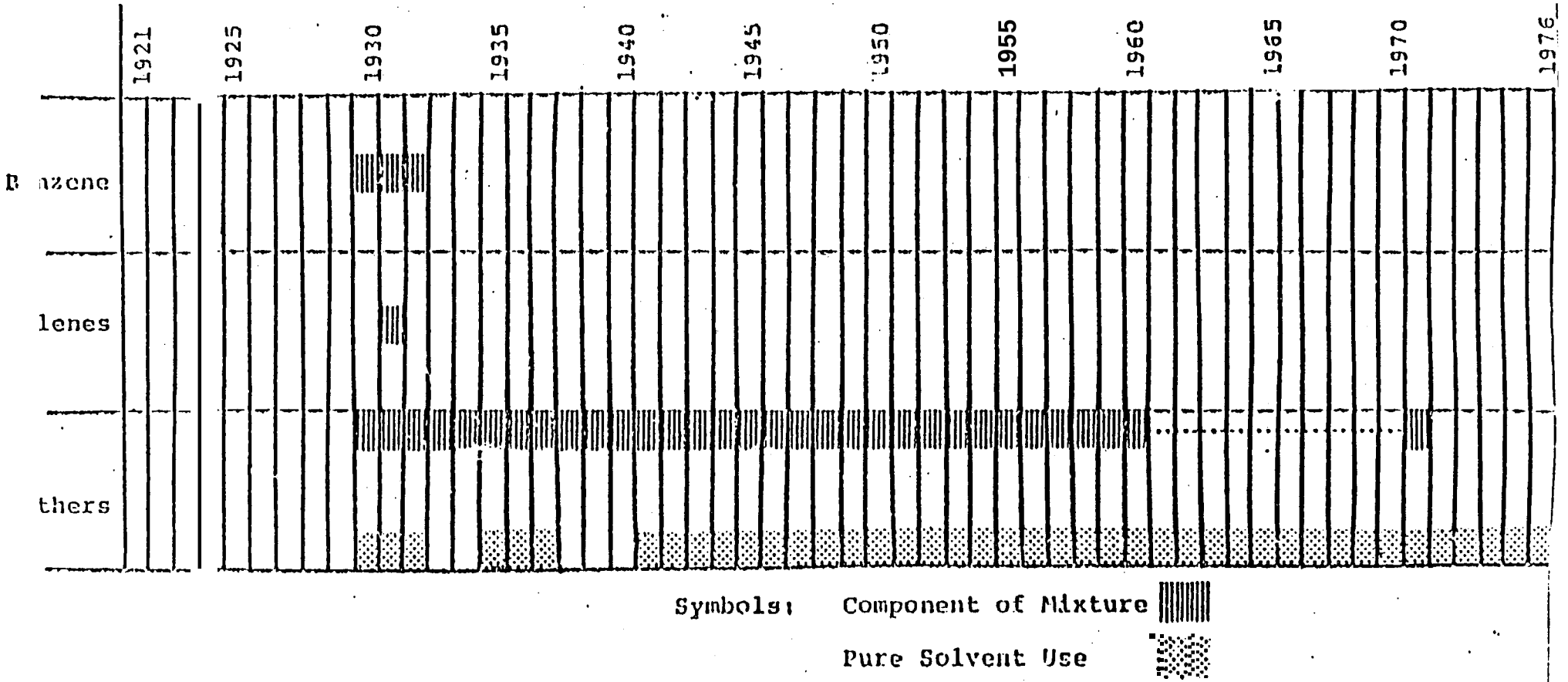


TABLE 2.7

POTENTIAL SOLVENT EXPOSURE

PROCESS AREA: TREAD & SIDEWALL

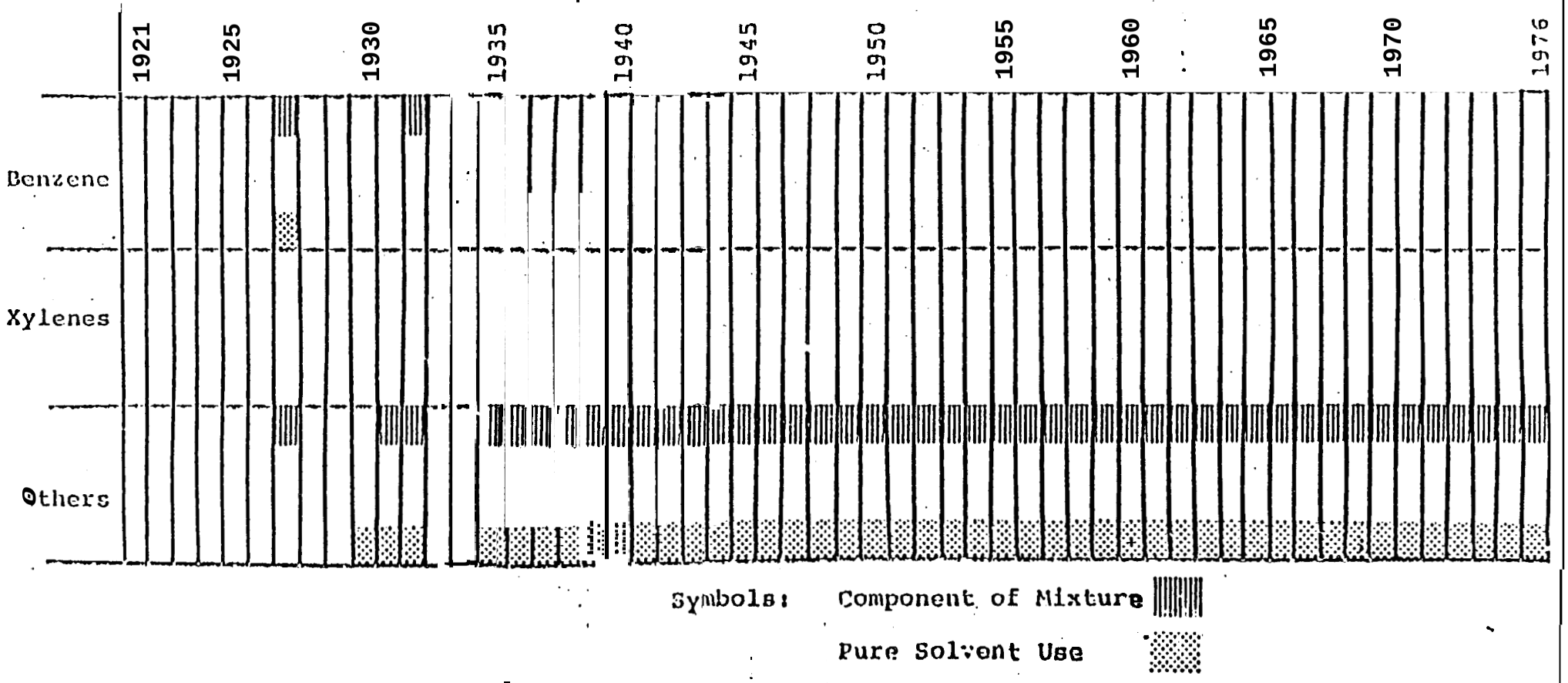


TABLE 2.9

POTENTIAL SOLVENT EXPOSURE

PROCESS AREA: FINAL FINISH

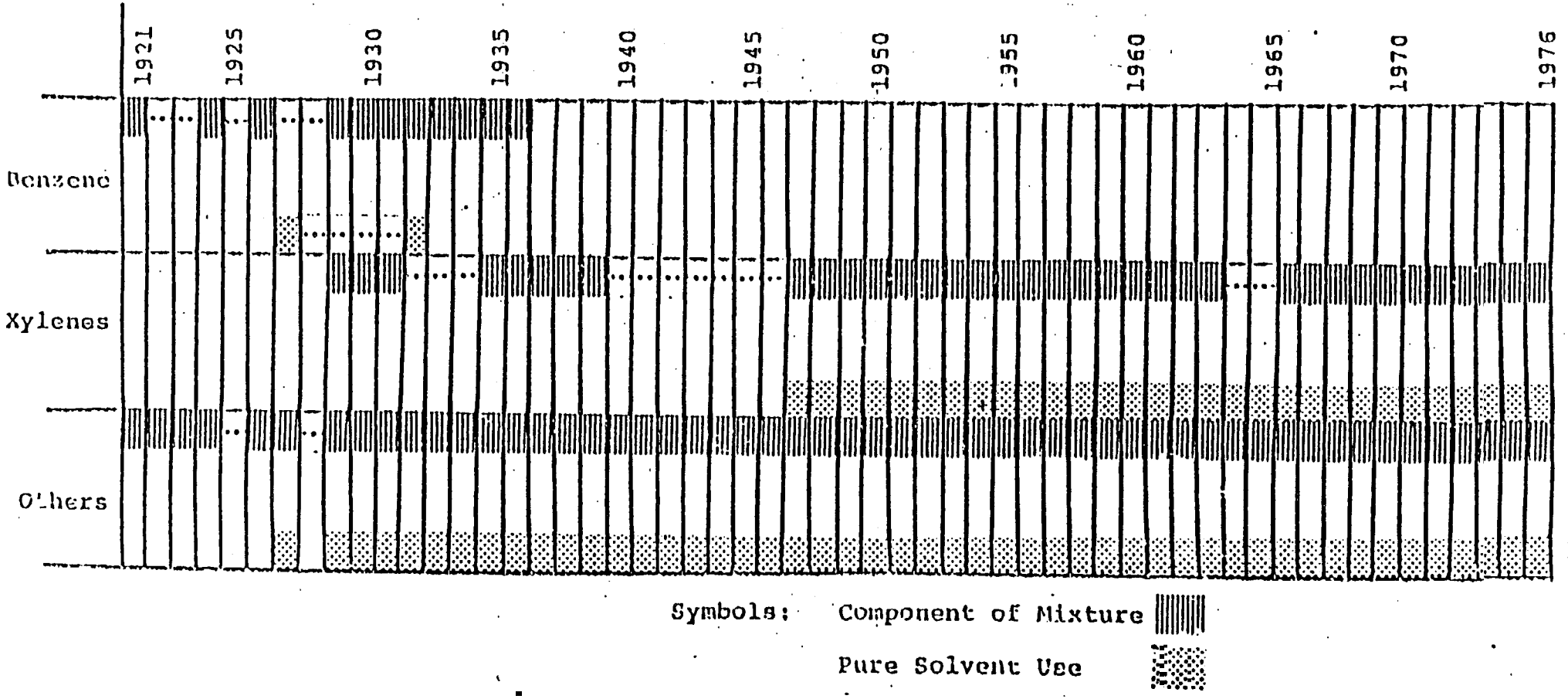


TABLE Z 1

POTENTIAL SOLVENT EXPOSURE

PROCESS AREA: AIR BAGS

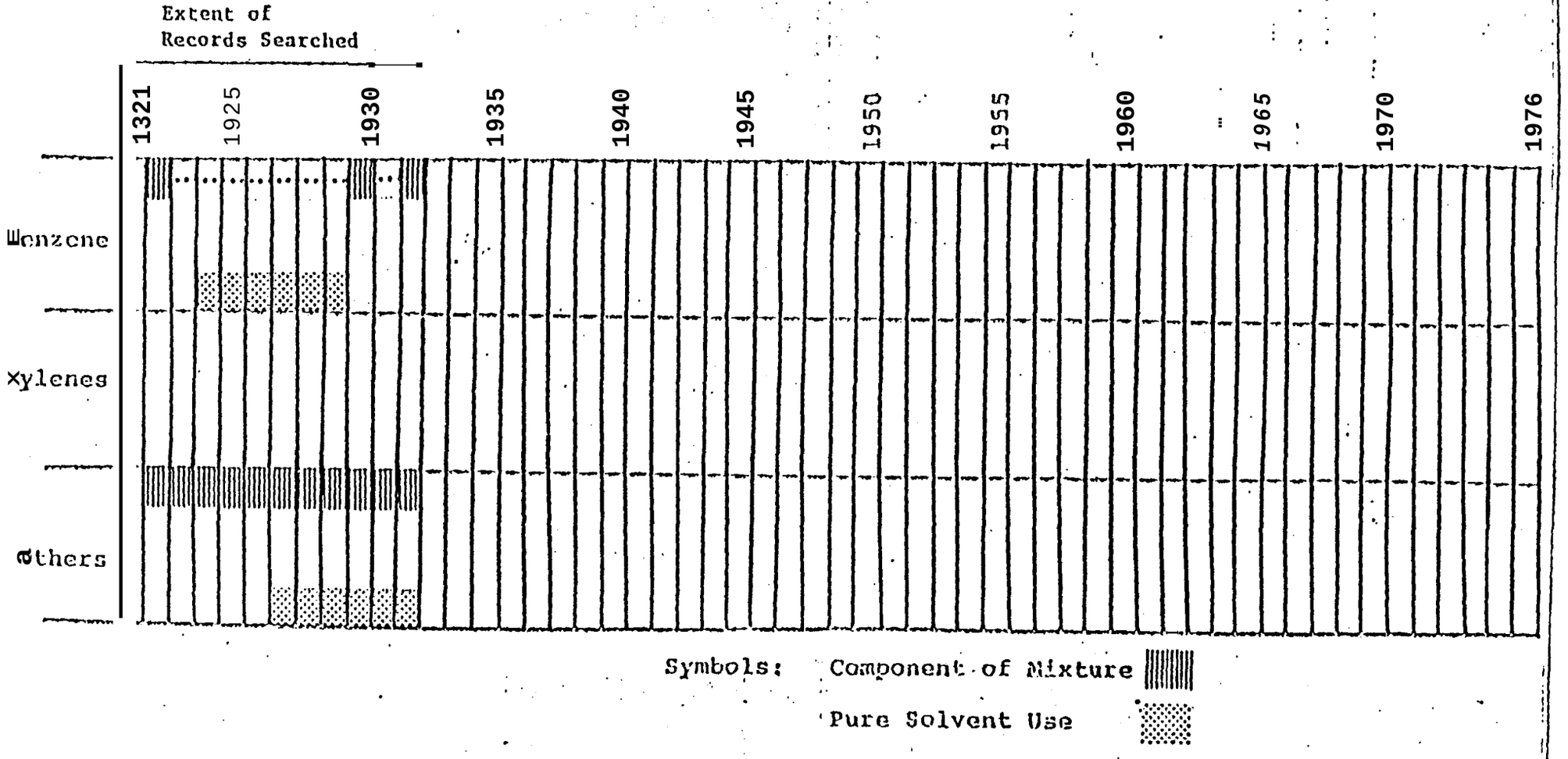
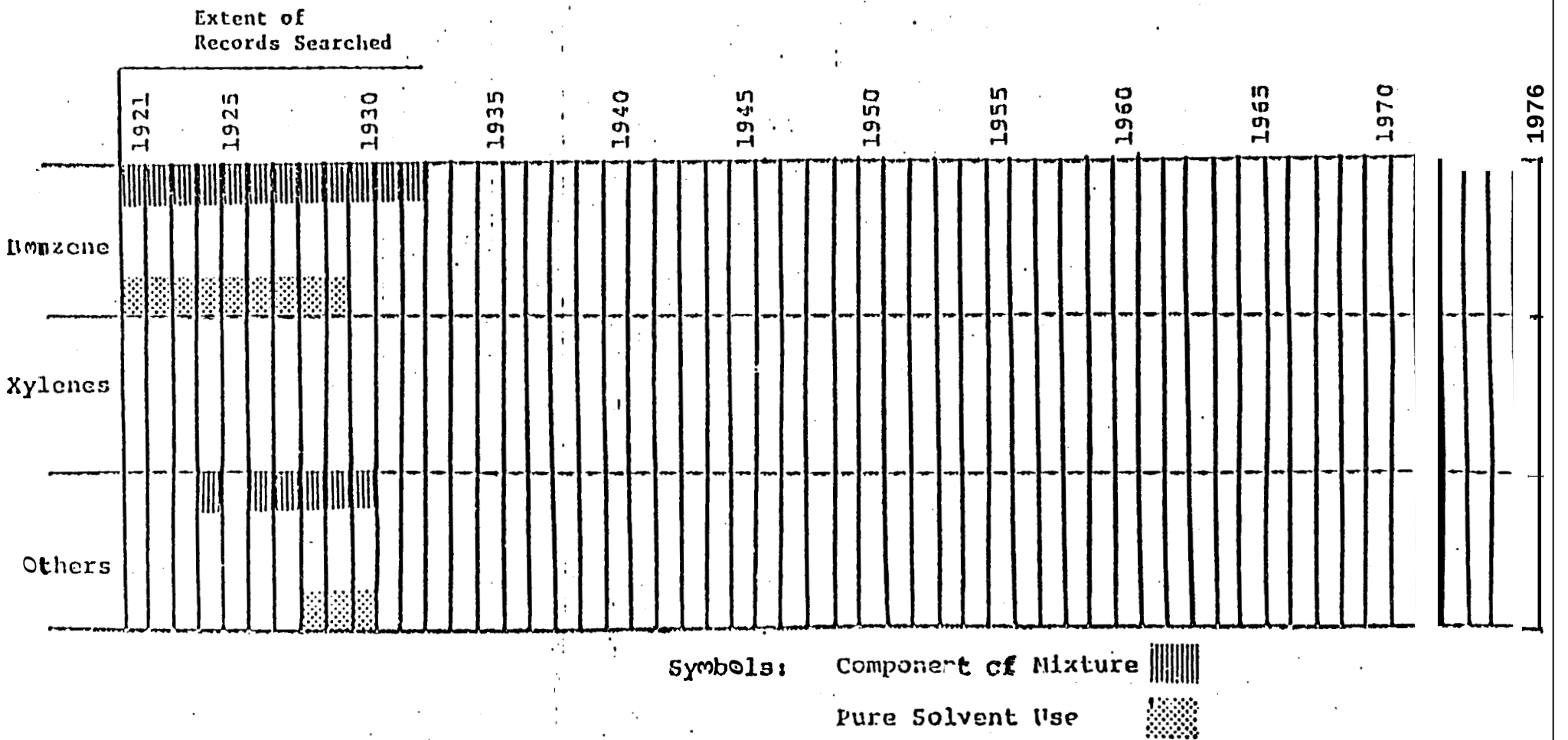


TABLE 2.13

POTENTIAL SOLVENT EXPOSURE

PROCESS AREA SOLID TIRES



Before this period, some extrapolation is necessary. This can be done with some confidence since the technology of drum-built tires was introduced at least a decade earlier. For tire building prior to the early 1930's and for other operations such as tubes, belts, and hoses, we do not have the job classification record, consequently a different approach must be taken to establish exposure potential. The standard operating procedure documents, which describe how tasks are to be performed, offer clues to solvent use in a given plant area, For example, a statement that the finished tube is to be washed with "solvent X" is probably sufficient evidence to establish contact between "solvent X" and an individual whose job title was Tube Finisher during the period of time in which the standard operating procedure is an active document. Likewise, knowledge that an individual was a tire builder and that the drum cement of that specific period contains "solvent Y", can be used to establish that the builder was potentially exposed to "solvent Y".

Since the immediate interest was the impact of benzene exposure versus other solvent exposure, it was decided to focus on this simple dichotomy of potential solvent exposure. Therefore the exposure codes shown in Table 3 were developed to distinguish use of the commercial solvent benzene from all other solvents (while recognizing that other solvents may contain small quantities of benzene as a contaminant). the criteria for assigning each of the eight codes are included following the code listing. These criteria and the data listed above were used to assign one of the eight codes to each line of the 135 work histories involved in the leukemia study. This portion of the study was accomplished without the coders being aware of whether the history being coded was that of a case or control.

The assignment of potential solvent exposure codes 1 through 4 proceeded in a straightforward manner as documentation existed for all lines assigned these four codes. For the period of time covered by a line on a work history, the solvent use charts were consulted to determine which solvents, if any, were authorized for the department indicated. A positive finding was adequate to assign a potential area exposure in the appropriate solvent class, either Cade 2 or 4.

Assignment of a Code 1 exposure required that benzene be authorized for use in that department during the time covered by the work history line and that the job title be clearly associated with solvent use. Job titles such as fire Builder, Cement Tires, and Core Cementer satisfied this latter requirement. Code 3 was assigned in an analogous manner in departments where benzene was not authorized or after the tine at which the commercial benzene solvent was removed from use.

TABLE 3 (COST.)

CRITERIA FOR ASSIGNING CODES

SOL - Solvent Use Charts
SO? - Standard Operating Procedures
FPS - Final Product Specification
JCR - Job Classification Record

CODE 1: Assigned when there is documented use of the commercial solvent benzene in tha department during the job period; and documented routine, direct use or handling of solvent by job title or task description.

Documentation: SOL, SO?, FPS, JCR

CODE 2: Assigned uhen there is documented proximity to the us2 of the commercial solvent benzene during the job period; but no documented direct use or handling of solvent by the jcb title or task.

Documentation: SOL, SOP, FPS, JCR

CODE 3: Assigned uhen there is documented us2 of solvents in the department during the job period; and documented routine, direct use or handling of solvent by the job title or task.

Documentation: SOL, SOP, FPS, JCR

CODE 4: (A) Assigned uhen there is documented proximity to solvent use during the job period; but no documented direct use or handling of solvents by ehe job title or task; or

(B) Assigned when a job title or task has no documented direct use or handling of solvents; but is classified as an assistant to a job title that Goes.

Documentation: SOL, SCP, FPS, JCR

No known solvent exposure, a Code 7, was attributed to those work history lines listing departments where no solvent use was authorized or suspected or where the job description exists and makes no reference to solvent-csntaining materials. This category lists jobs such as Warehouse Man, Elevator Operator and Yard Crane Operator. Code 7 was also assigned those lines carrying job titles where solvent use would not *be* normal to the operation even though docmentation was not available. Job titles falling under this category included Cafe Helper, Steam Table, and Spot Seam Welder.

Code 9 is essentially a missing data code made necessary because a number of jobs were in production areas not covered by this study, i.e., Steel Products, and in areas where the investigator cauld not render a judgment based on personal industrial hygiene experience. In addition, some lines ot' work history were simply unintelligible and could not be assigned any other code.

Assignment of a Code 5 or 6 was base4 primarily on the judgment of the investigator and involved jobs normally associattd with solvent use such as Painters, Degreaser Operators, and Electricians *whose* materials list would not be carried in a company document devoted to production materials. In total, the 135 work histories included 2163 individual lines to be *coded.* The distribution of codes assigned is shown in Table 4. Approximately 80 percent are documented *codes* while Code 9 was invoked 326 times or 15 percent of the listing,

A potentially major shortcoming in this coding process has *to* do with the lack *of* a record specific to Cement House workers. These personnel dispense solvent, mix and dispense cement to user departments, and formulate mixtures for outside shipment. They are assumed to be

exposed to the cumulative solvent Jirt for the plant at any point in time. However, there is no way of knowing, from the available information, what materials were being processed for outside shipment *or* for users entirely outside of the rubber industry. It czn be assumed that Cenent House personnel were potentia?Jy exposed to at least *the* solvents that appear on the cumulative list, but there is no certainty that they were not-exposed to a material, such as benzene, after it was removed fmm plant use. *A review* showed that one of the cases fell into this category, having been employed as a cement mixer frcm 1942 to 1948. He was coded as a "3"--contact with solvent other than benzene. This *may* be an under-coding, however it is the only coding that could be justified by the data in nand.

One other caution should be mentioned. The standard operating procedure documents for Tire Building concentrate an passenger tires although materials 3r2 specifically designated for use with racing tires, truck and bus tires, and others. Nonetheless, *it* is conceivable that the data are less accurate for a plant building truck and bus tires than for a passenger tire plant. Five cases included in this *study* had work experience in the company's truck tire plant. Three of these we're considered as benzene-exposed (code 1 or 2) in the early part of the study, while two who began work in 1942 were considered "code 3" exposed. It is unlikely but possible that mixtures containing solvents other than those shown could have been authorized for the truck tire plant by a specification not reviewed for this study.

TABLE 5
RELATIVE RISK ESTIMATES (ODDS RATIOS)
FOR EXPOSURE >0 MONTHS
BY TYPE OF LEUKEMIA

EXPOSURE CATEGORY (CELL TYPE)	ALL LEUKEMIAS UCD 204-207		LYMPHATIC UCD 204		MYELOID UCD 205		OTHER AND UNSPECIFIED UCD 207	
	O.R.	χ^2	O.R.	χ^2	O.R.	χ^2	O.R.	χ^2
Code 1	0.94	0.01	3.50	3.13	0.00	3.37	0.50	0.22
2	3.29	3.77	14.00*	5.28	0.80	0.05	5.00	1.00
3	1.37	0.45	9.50*	4.98	0.50	0.74	0.29	1.56
4	1.19	0.14	1.75	0.62	0.90	0.02	0.67	0.08
5	1.69	1.24	1.00	0.00	6.50*	4.32	1.00	0.00
6	1.00	0.00	0.73	0.196	2.00	0.38	--	--
7	2.00	0.32	--	0.90	0.33	0.40	--	0.50
9	1.09	0.03	1.54	0.49	0.80	0.08	0.00	0.67
Benzene (Codes 1-2)	2.40	2.33	5.09+*	7.71	0.13	1.89	1.00	0.00
Other Solv (Codes 3-6)	2.15	2.21	5.00	2.77	1.67	0.44	0.75	0.71
Solv Exp (Codes 1-6)	2.64	3.24	17.00*	4.92	1.67	0.44	0.50	0.33
Primary Exp (1,3,5)	2.46	3.28	10.50*	5.82	1.29	0.11	0.50	0.33
Area Exp (2,4,6)	1.17	0.13	1.60	0.54	0.70	0.21	1.33	0.56

*Statistically Significant ($p < .05$)

+Unmatched Data Layout

ample, all 15 cases at some paint in their work histories received a coding of 7 (No Known Solvent Exposure), while only two of the 15 ever received a coding of 6 (Judgment Secondary Other Solvent). The results indicate that Secondary Benzene exposure (Cod2 2) and Primary Other Solvent exposure (Code 3) are associated with an increased risk of lymphatic leukemia, with fourteen-fold and ten-fold increases, respectively.

The exposure codes were combined to form groupings of particular interest: benzene, non-benzene solvent, all. solvent (including benzene), primary solvent, and area solvent exposures. The resulting relative *risk* estimates for any work experience with these exposures are given in Table 7. Exposure to the all solvents category (codes 1-61 shows an elevated ratio of 17.0 with 14 of the 15 lymphatic cases ever exposed. Primary exposure to solvents (codes 1, 3, and *5)* results in an elevated ratio of 10.50, while ares exposure [codes 2, 4, and 6) *shows* a ratio *of* only 1.60. Benzene, the principal solvent *of* interest shows an elevated ratio of 5.09 with eight of the 15 cases having direct contact or in the vicinity *of* potentia? use at some point in their working careers.

Other solvents *(codes* 3-6) also show a *strong* association with the disease. As was mentioned previously, these other solvents may contain benzene as a Contaminant, which suggests that low level concentrations of this chemical may be potentially as hazardous as the raw material itself. Alternatively, benzene might not be the active agent, and the production *of* the disease might be the result of exposure to other solvents, or some material common to both benzene and other solvents.

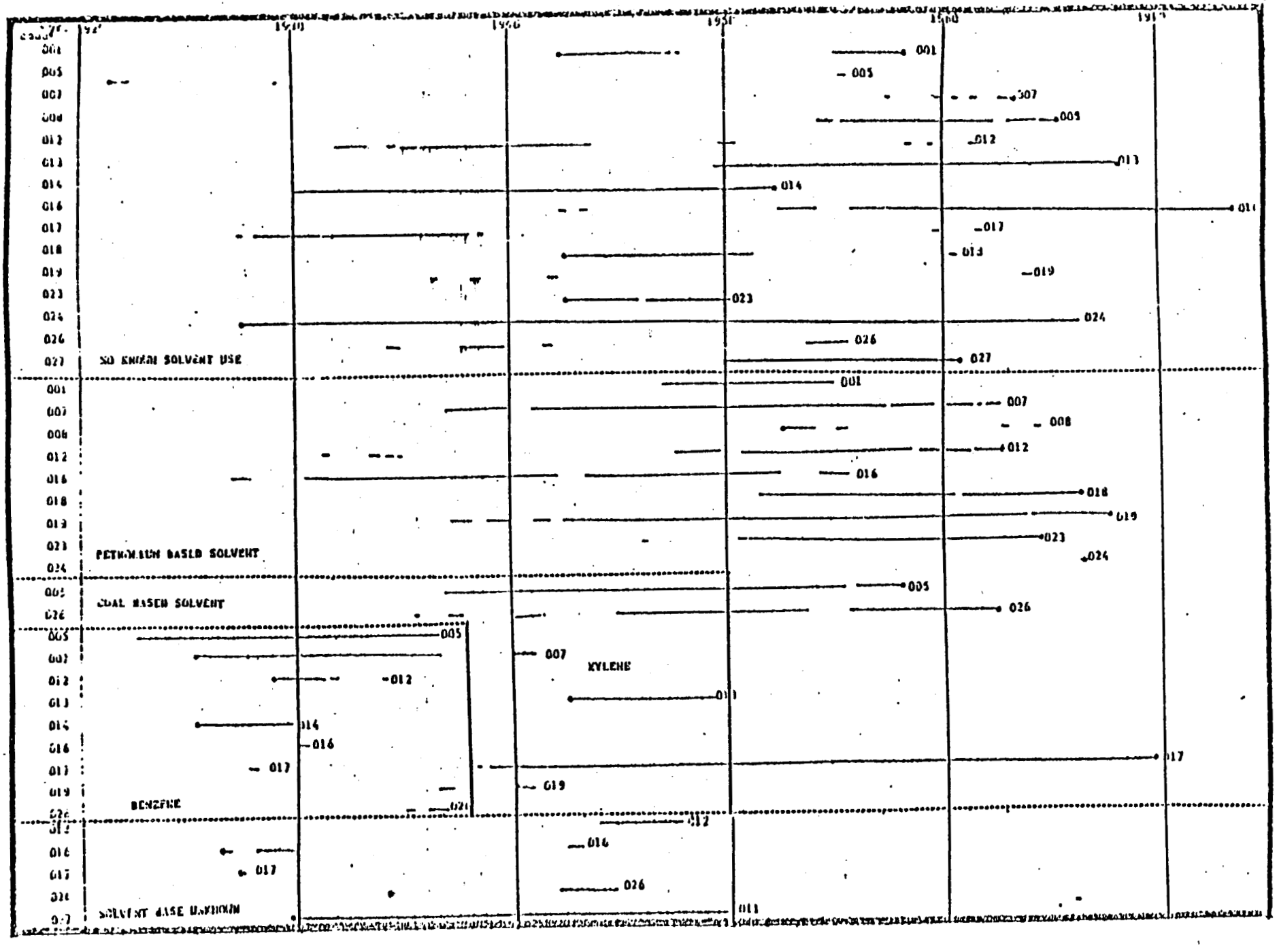
COAL-CASED SOLVENTS

During tk2 record search describe4 earlier, a raw material specification *for* xylene was found, dated 1939, that listed a source of supply which indicated the chemical might he derived from a material other than petroleum: According to Mellen,[9] in 1939 aromatic solvents were coal-based materials; and according *to* the history offered Cy Hamilton[2] the ccal-based aromatic solvent industry of the United States could trace its origin *to* the time of World War I. It seems possible that this study may have encountered a set or materials, aromatic solvents, that were derived from a different source in the 1920's and 1930's than those of more recent years, If so, those raw materials could contain a significantly different set of contaminants in both scope and level from those same raw materials of today. This could occur even though the materials would carry the same generic classification--aromatic solvents--2nd the same chemical identity—benzene.

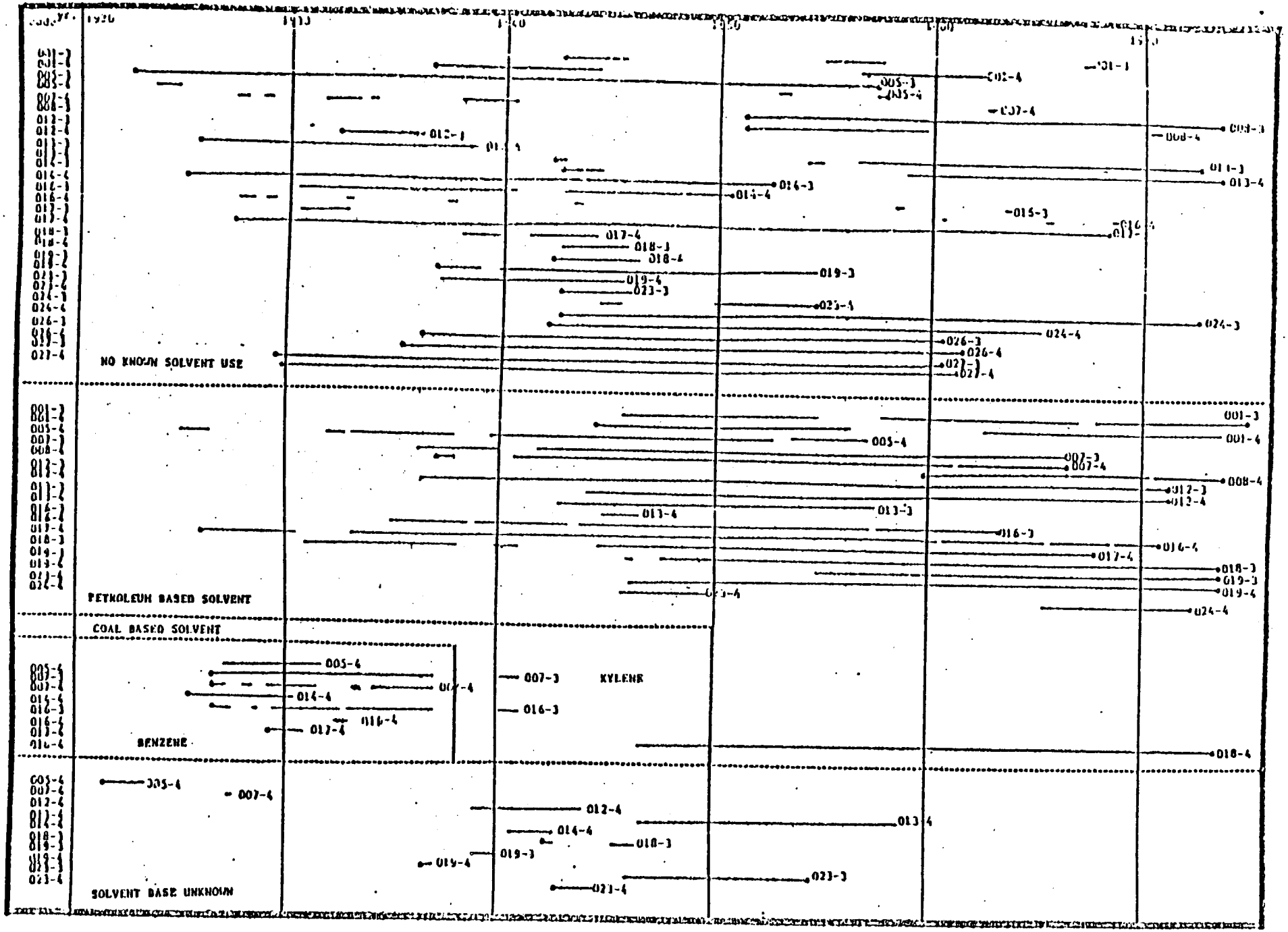
This due from the —any's *raw material specification* led to a search of the literature for the source of supply and possible origin of the aromatic solvents over the study period, According to the U.S. Tariff Commission reports,[14-25] virtually all the aromatic solvents—benzene, toluene, solvent naphtha, xylene—were produced from coal up to the early 1940's. Toluene was produced fmm petroleum in 1943, followed by xylene in 1944. Benzene berme available from petroleum in 1951. These dates, of course, do not include the small supply *of* each of these chemicals which has always been available from petroleum by fractional distillation. Probably governed by the economics of the two chemical

paralleled, of course, by the Cement House. Tire Building and Stock Cutting show a brief use history as does Miscellaneous Rubber Goods. Since there was no precise date documented for the presumed change in aromatic supply, any choice will be somewhat arbitrary. The year 1950 was chosen as the assumed cross-over date. This date is mid-way between the first appearance of xylene from petroleum and the company's earliest record of a petroleum-based supplier. It is also the last year of the coal carbonization industry's total domination of the domestic benzene supply.

WORK HISTORY PLOT OF LYMPHATIC LEUKEMIA CASES BY POTENTIAL EXPOSURE CATEGORIES



WORK HISTORY PLOT OF LYMPHATIC LEUKEMIA LIGHT CONTROLS BY POTENTIAL EXPOSURE CATEGORIES



shows the greatest association with a relative risk of 7.3.3, *while* tk2 elevation *for* benzene is slightly lower at 5.09. The measure of association for both the xylene and benzene categories combined, comprising the coal-based solvent, exposure, is significantly elevated at 5.42. When only the tight controls are considered, the only significantly elevated risk corresponds to xylene exposure.

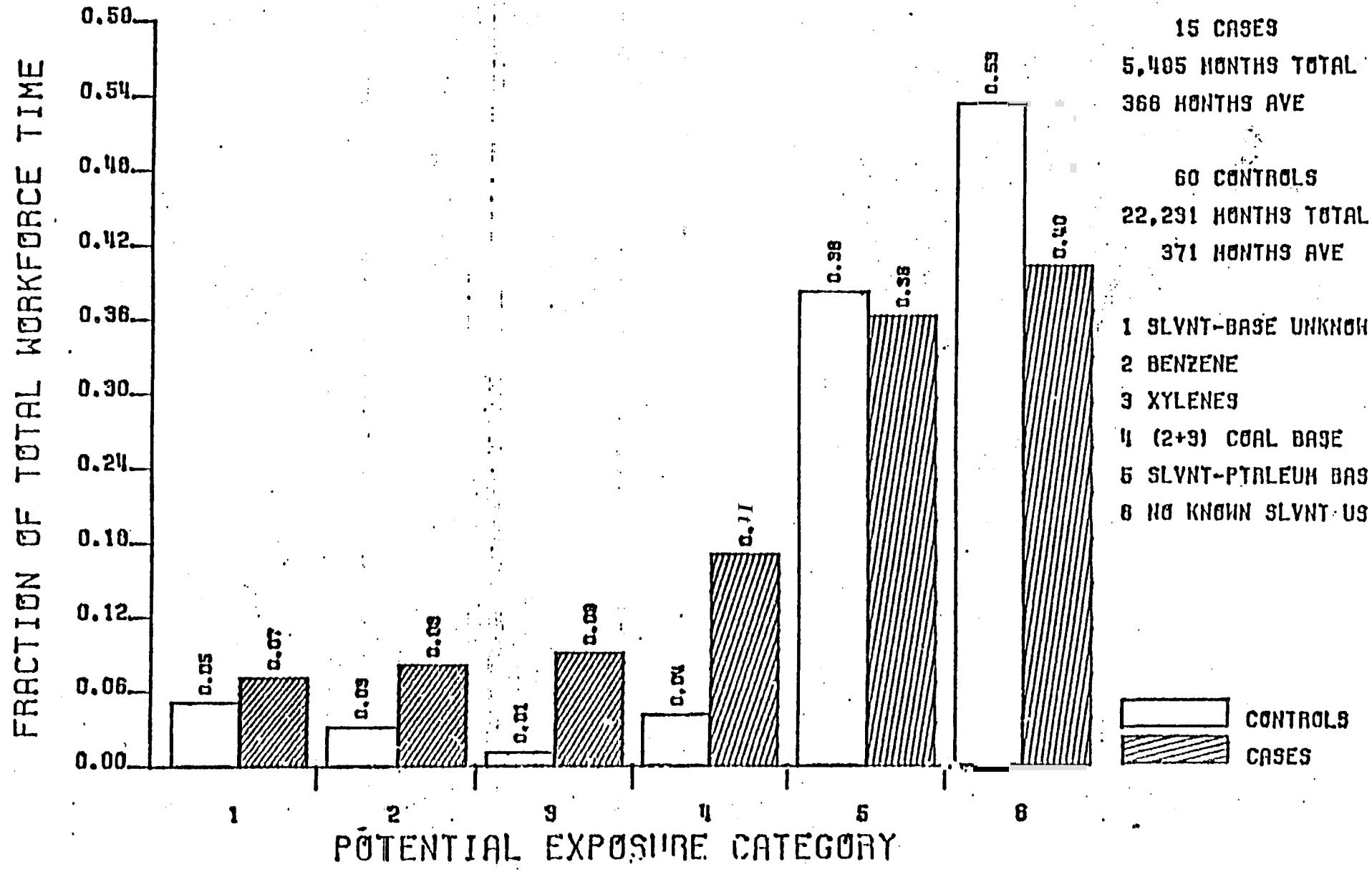
Another way to assess the effect *of* these different solvent sources is to assign the *cases* and controls to mutually exclusive exposure severity groups. Table 9 displays the number *of* cases and controls assigned to each category, and their ratio. An individual *with* any time in the Coal Based Solvent category received that severity assignment. An individual with time in the Petroleum Based Solvent category but no Coal Based Solvent time was classified as Petroleum Based exposure. Those with Judgment Other Solvent exposure (codes 5 and 6) but never codes 1-4 were placed in the Base Unknown category, while those with codes 7 and/or 9 only were No Known Solvent Exposure. With the 4:1 matching:ratio of the 15 cases and 63 controls, a ratio of .250 would be expected. Once again the Coal Based category shows an elevated ratio.

Finally, these findings under the coal-based chemical hypothesis are examined one further way. Figure *4* shows *the* fraction of *total* workforce time spent in each of the potential exposure categories by case and control. The basis *for* this chart is the work experience of 60 controls totalling 22,237 months and 15 cases totaling 5,495 months. The potential *exposure* categories of the earlier analyses are repeated on this chart. Note that the fourth entry is the combined entry of (2) benzene and (3) xylene and is labeled Coal-Based Solvents. Again, this category of exposure shows a marked contrast between case and

FIGURE 4

CASES VS MATCHED CONTROLS

FRACTION OF TOTAL WORKFORCE TIME BY POTENTIAL EXPOSURE CATEGORY



DISCUSSION

Two points should be mentioned with regard to these findings. First, many of the coal-based exposure individuals continued to work and entered petroleum-base exposure categories. Second, many of the petroleum-derived solvents probably contained a small quantity of benzene as a contaminant as do the gasolines of today, and certainly refined solvent naphtha -- xylene(s) -- would have contained measurable levels of benzene. Yet in all three methods of analysis--relative risk estimates, severity code assignment, and fraction of workforce time--the findings are consistent with the hypothesis of an agent common to coal-based materials which is either absent or not present in sufficient quantity in petroleum-based solvents to produce the disease entity under study.

As coal is aromatic in nature, while petroleum is more aliphatic[8] it is possible that coal-based products would be contaminated by cyclic compounds to a greater extent than would the petroleum-based counterparts. As a class of chemicals, the polycyclic hydrocarbons have few peers as cancer-causing agents. Coal is the source of production for a number of polycyclic chemicals. A brief literature review of the lymphatic leukemogens unearthed references to three materials apparently capable of inducing lymphatic leukemia in laboratory animals. These three are 9, IO-Dimethyl-1,2-Benzathracene,[4] 3,4-Benzpyrene, and Metnylcholanthrene.[10] Interestingly, all three materials were applied to the skin of test animals using benzene as the solvent carrier. All three are soluble in the aromatic solvents and would likely remain in the commercial material if no special attempts were made toward separation. This was pointed out by Lijinsky and Raha[5] with reference

CONCLUSION

Following earlier findings by OHSG investigators of an apparent association of lymphatic leukemia with sclvent-using job groups, an attempt was made to extend the analysis through more precise estimates of potential exposure, This was accomplished by a recreation of solvent use at a rubber tire operation over a 55-year period, utilizing company-developed business records.

When this more precise method of assigning potential exposures was applied to individual workers in the case-control study, the reported association between lymphatic leukemia and solvent exposure was not ant~ reaffirmed but was substantially strengthened. Whereas McMichael reported relative risks up tu 9 for workers in the group presumed to have high solvent exposure, this study showed risk estimates or' 3.5 to 14 for workers exposed to benzene and 1.75 to 9.5 for those who contacted other solvents. If the assigned causes of death for the cohort are assumed to be valid, the risk of death from lymphatic leukemia does indeed appear to be associated with prior history of work with solvent.

This extension of the solvent-leukemia study was made possible by data extracted frcm records develcped for purposes far different from occupational health research. These data frcm existing company records have provided the capability to determine the raw material, location, time and duration of use, and identity of workers pctentially in contact with or in the vicinity of the potential exposure agents. In the absence of actual workplace measurements, the approach presented here may offer the next best alternative. A search of company records uncovered

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APPENDIX I

MANTEL - HAENSZEL ODDS RATIO

We can represent the data for each ser i of a leukemia case and the four matched controls as follows:

	Exposed	Bot Exposed	Totai
Leukemia case	A_i	B_i	W_i
Matched controls	C_i	D_i	X_i
Total	U_i	V_i	T_i

The Mantel - Haenszel Odds Ratio for each set is:

$$O.R. = A_iD_i \; / \; B_iC_i$$

and for the entire study population we use:

$$O.R. = \frac{\sum_i \frac{(A_iD_i)}{T_i}}{\sum_i \frac{(B_iC_i)}{T_i}}$$

The chi-square statistic is calculated as:

$$\chi^2 = \frac{(\sum_i A_i - \sum_i (\frac{U_iV_i}{T_i}))^2}{\sum_i [U_iV_iW_iX_i/T_i^2(T_i-1)]}$$

which is distributed as chi-square with one degree of freedom

[From 6]