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PENGAD-Bayonne, N.J.			
PLAINTIFF'S EXHIBIT 1312			
NEW YORK			
MAR 19 1979			
HEALTH DIVISION			
SS	ATG	REG	EDS

March 14, 1979

To: Members, Benzene **Epidemiology Task Force**

From: Neill K. ^{NKW}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/eev

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

By

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Presented at

The Southeastern Occupational Health and Safety Conference, Hilton
Head, S.C., November 9 - 11, 1978.

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 (OHSB) report, first demonstrated an increased risk of lymphatic leukemia among rubber workers with a history of solvent exposure as judged by OHSB 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 OHSB 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 OHSB 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 association between myeloid leukemia and benzene exposure was demonstrated by Infante, et al.,⁽³⁾ among pliofilm workers exposed between 1940 and 1949.

In the OHSB 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 information to reassess the association of lymphatic leukemia and solvent exposure.

וּלְחִיטָה מְעֻבָּדָה

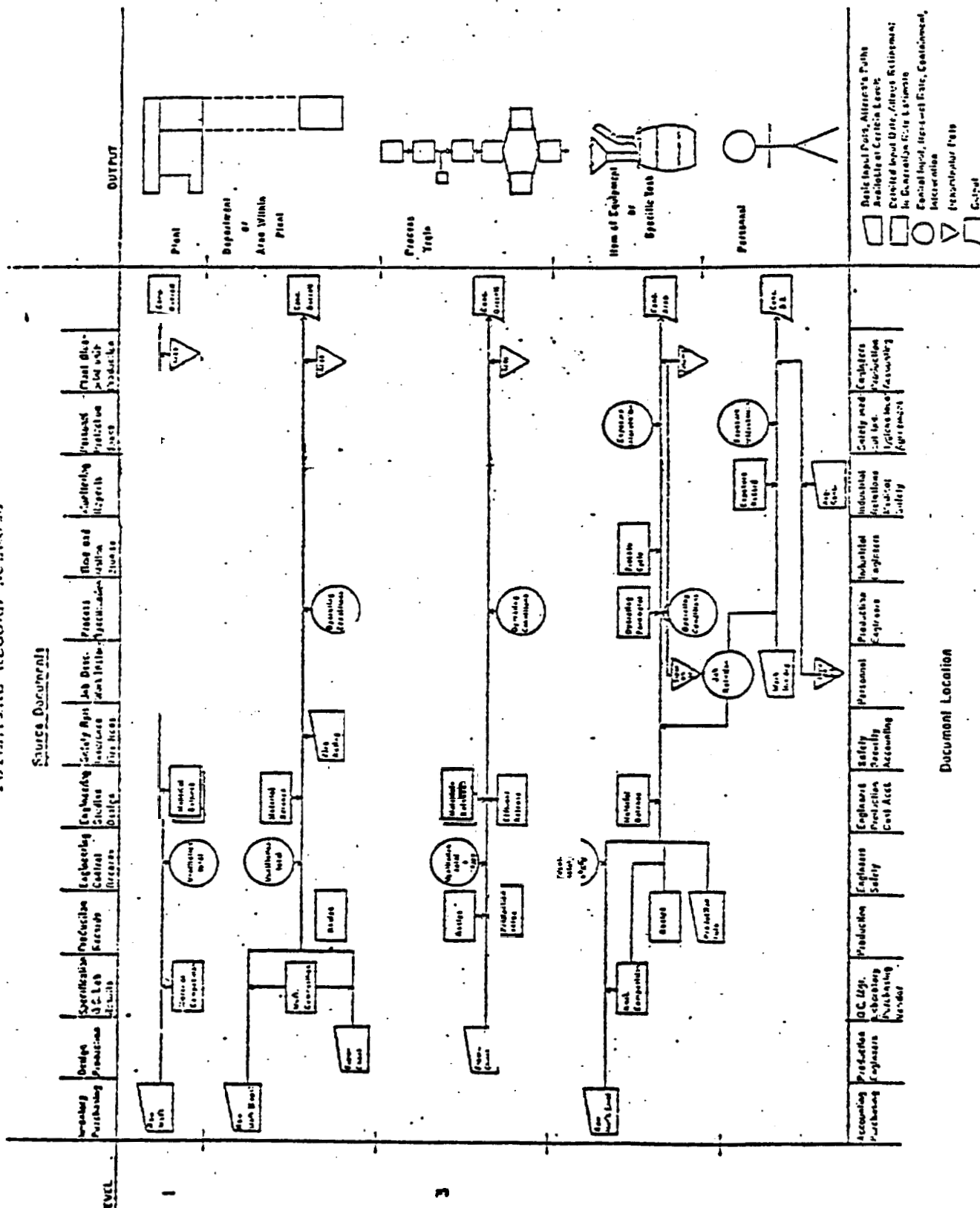


TABLE 2 1
POTENTIAL SOLVENT EXPOSURE
PROCESS AREA: CEMENT HOUSE

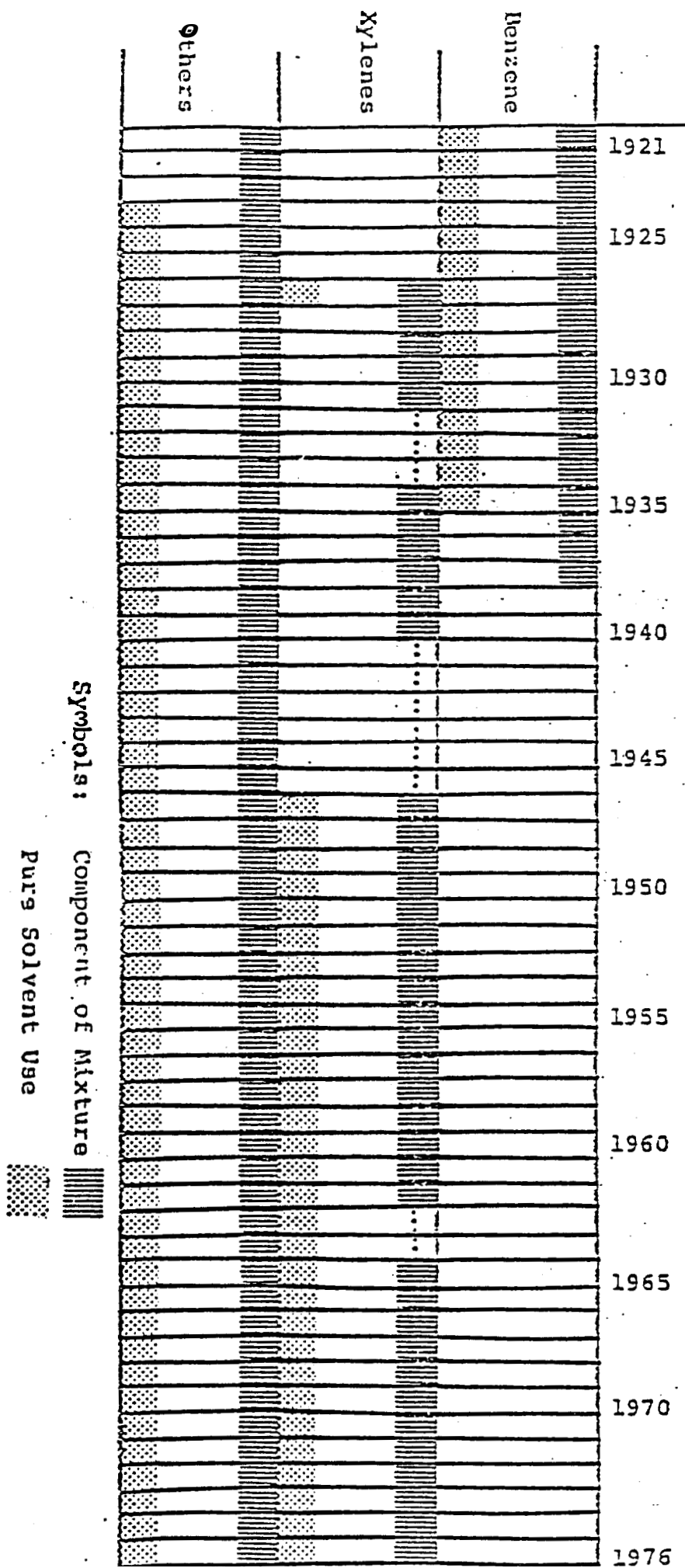


TABLE 2.3
POTENTIAL SOLVENT EXPOSURE
PROCESS AREA: BEAD ROOM

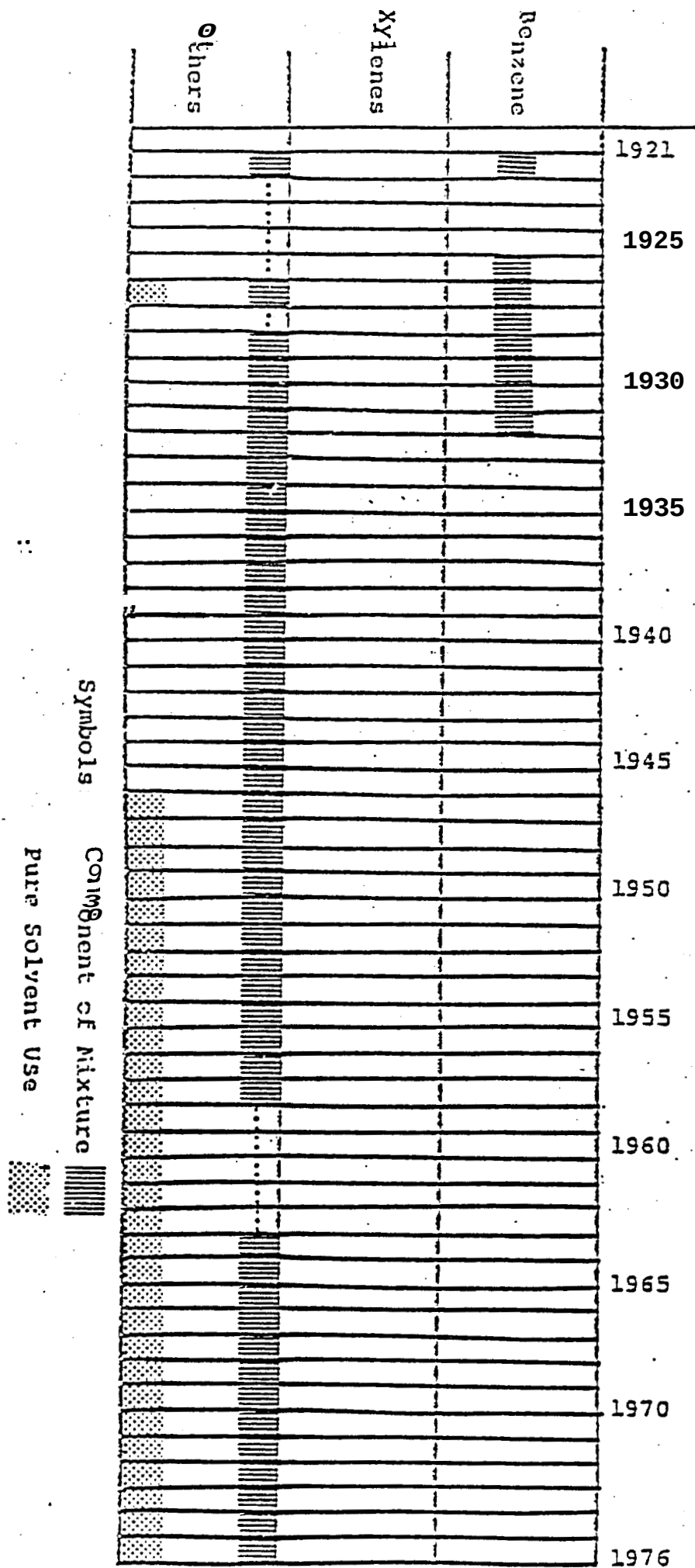


TABLE 2.5
 POTENTIAL SOLVENT EXPOSURE
 PROCESS AREA: CALENDER

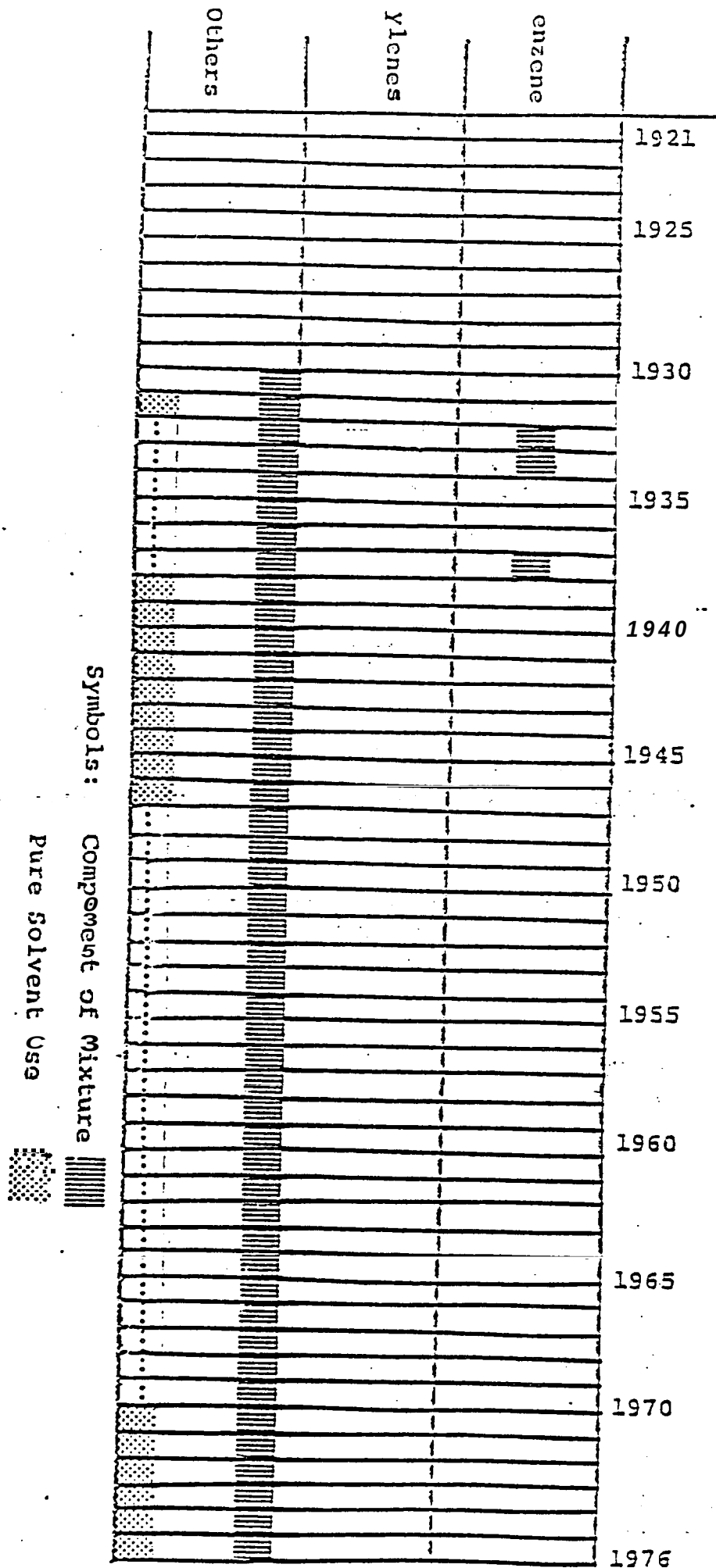


TABLE 2.6

POTENTIAL SOLVENT EXPOSURE
PROCESS AREA: STOCK CUTTING

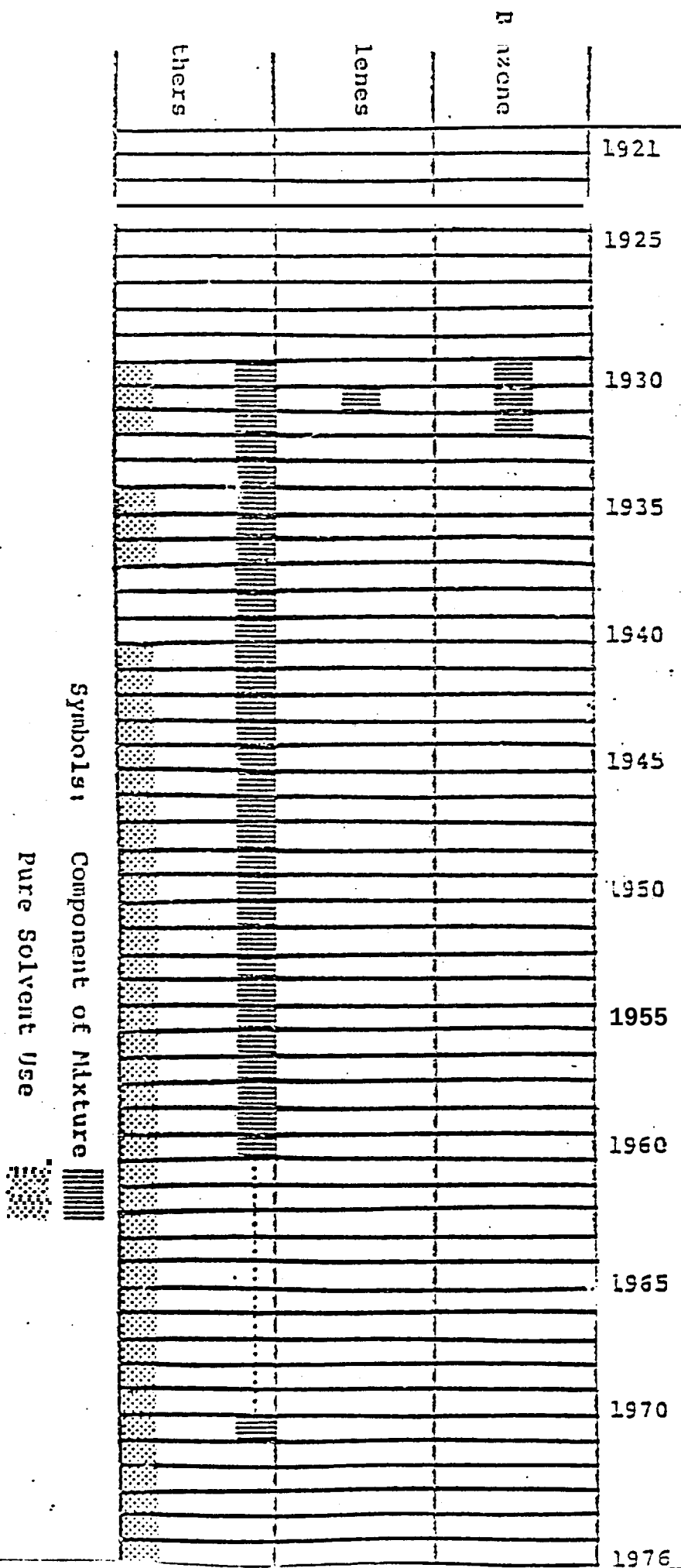


TABLE 2.7
POTENTIAL SOLVENT EXPOSURE
PROCESS AREA: TREAD & SIDEWALL

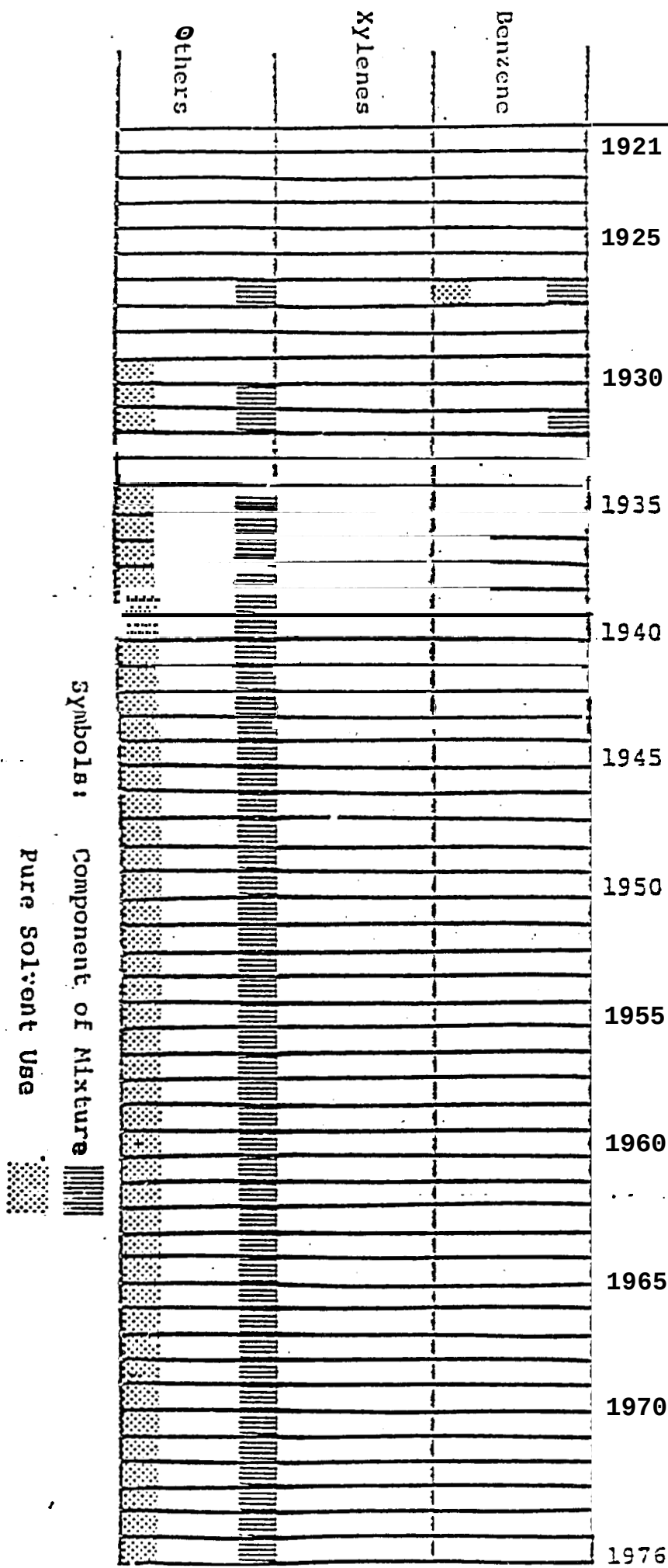


TABLE 2.9
POTENTIAL SOLVENT EXPOSURE
PROCESS AREA: FINAL FINISH

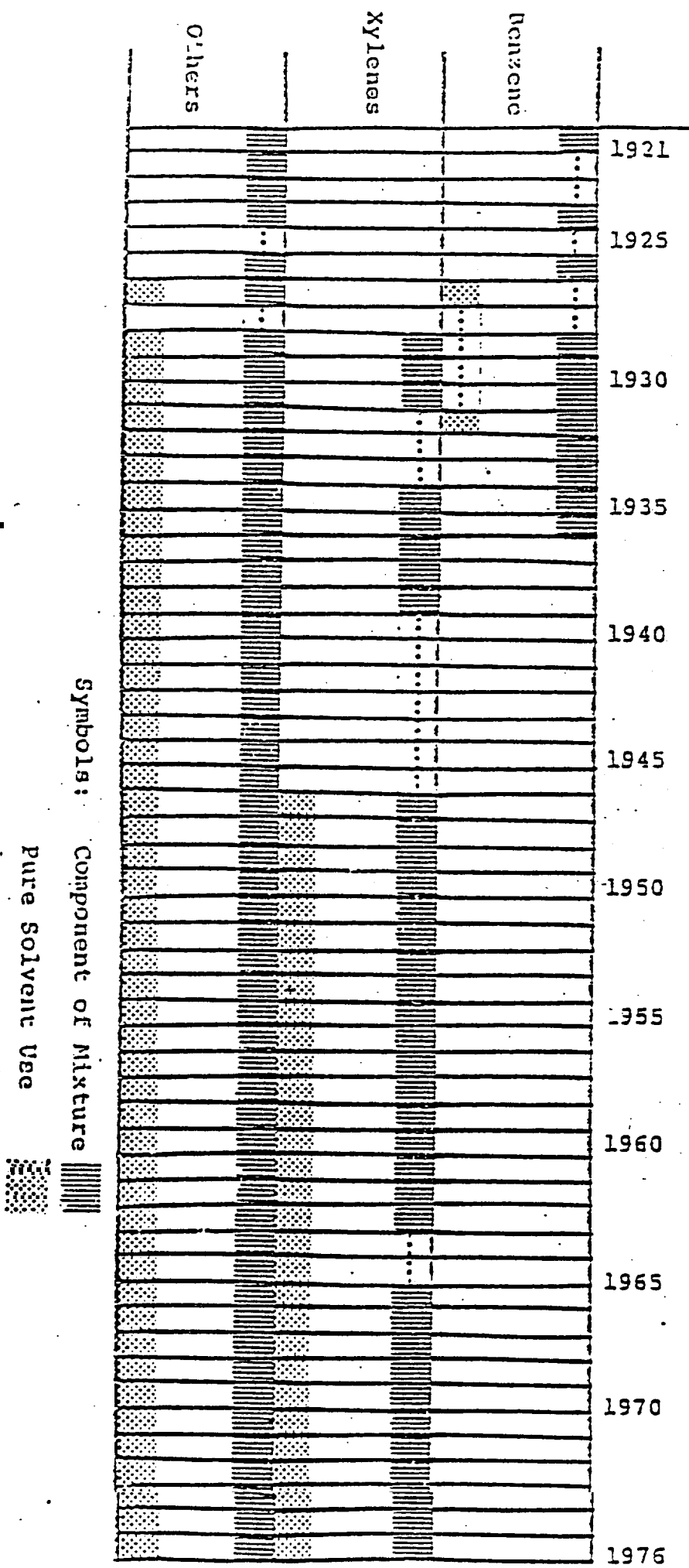


TABLE 2 1.
POTENTIAL SOLVENT EXPOSURE
PROCESS AREA- AIR BAGS

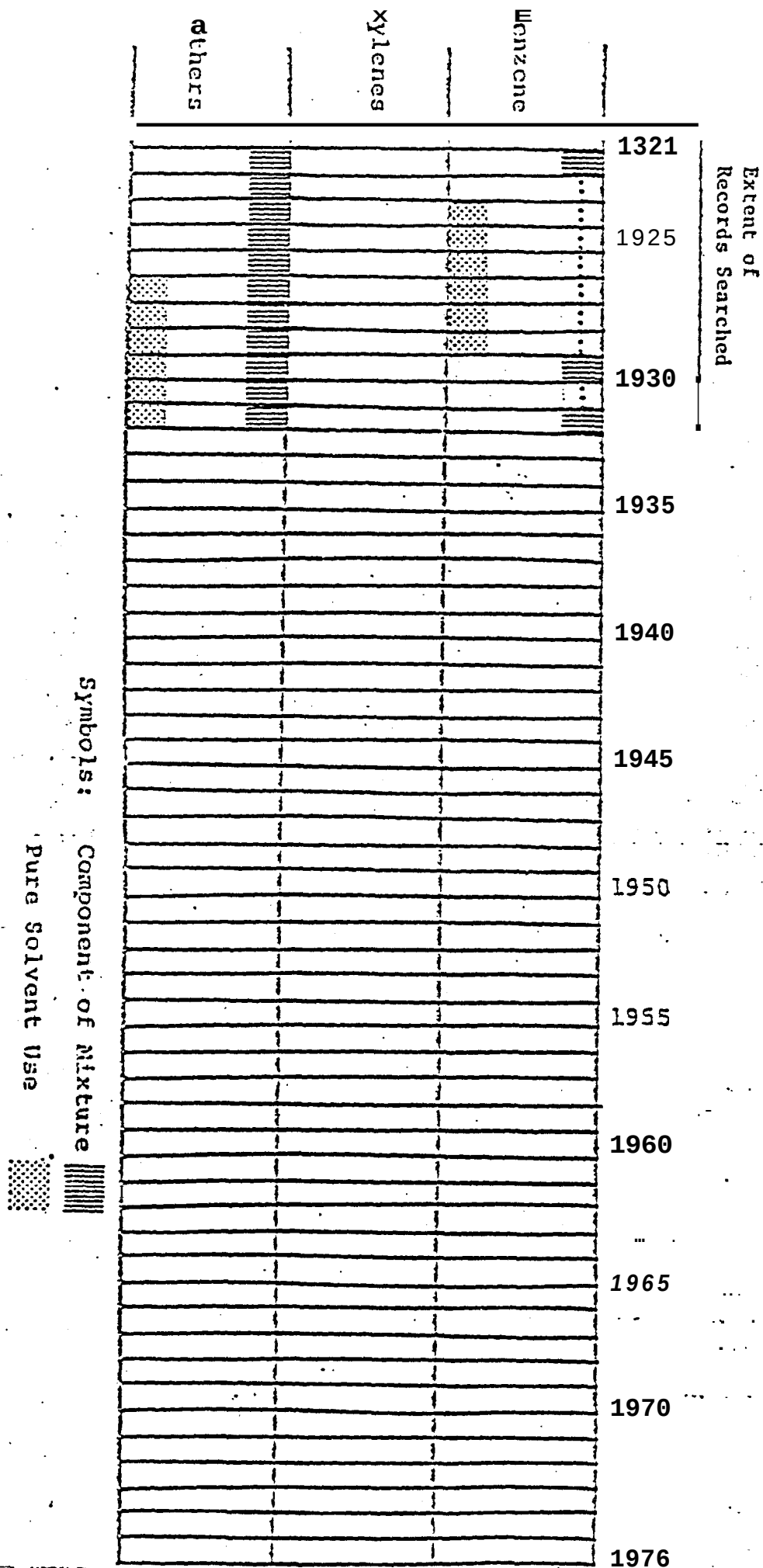
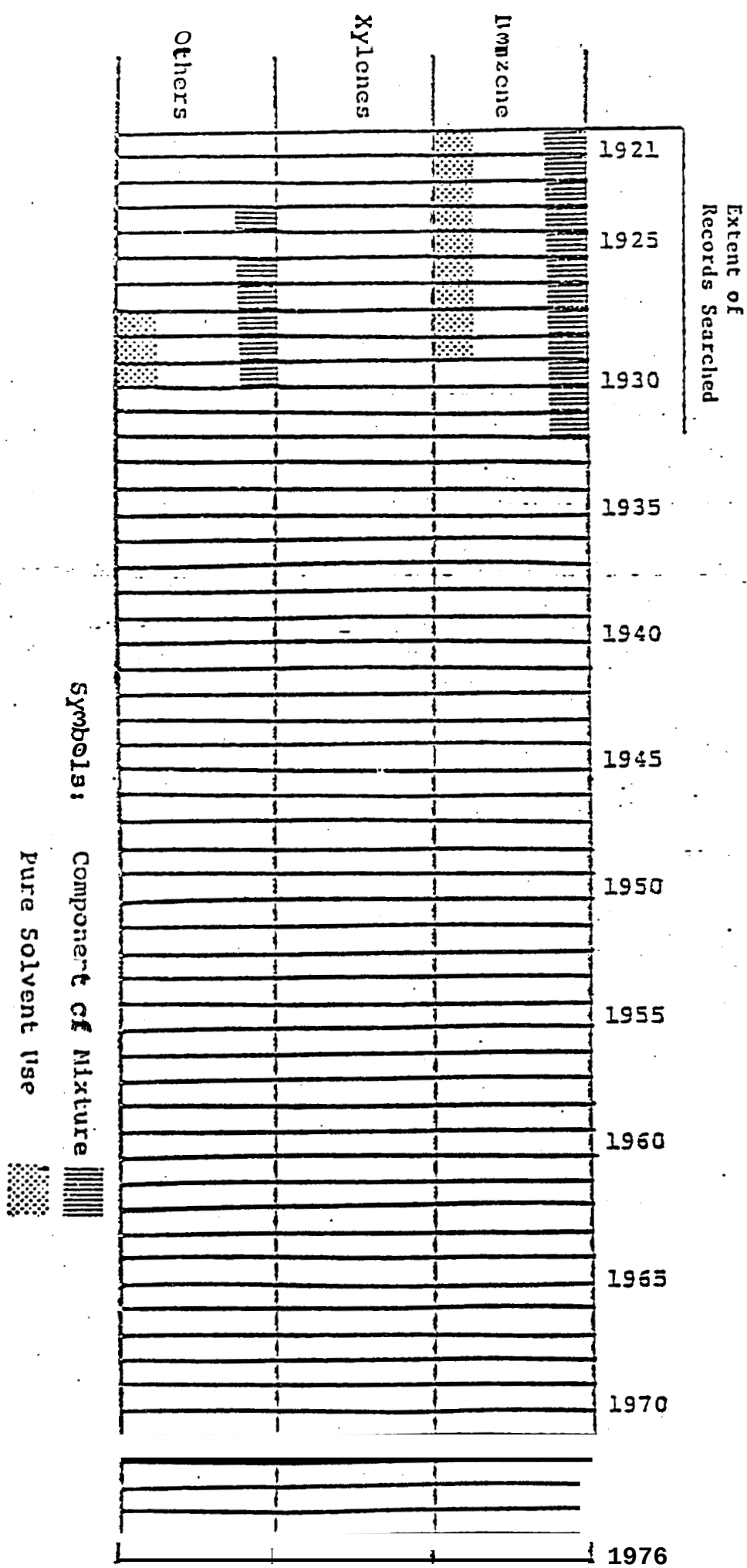


TABLE 2.13
POTENTIAL SOLVENT EXPOSURE
PROCESS AREA SOLID TIRES



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 a71 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 Code 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 time at which the commercial benzene solvent was removed from use.

TABLE 3 (COST.)
CRITERIA FOR ASSIGNING CODES

SOL - Solvent Use Charts
SOP - 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 the department during the job period; and documented routine, direct use or handling of solvent by job title or task description.

Documentation: SOL, SOP, FPS, JCR

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

Documentation: SOL, SOP, FPS, JCR

CODE 3: Assigned when there is documented use 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 when there is documented proximity to solvent use during the job period; but no documented direct use or handling of solvents by the 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-containing 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 documentation 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 could not render a judgment based on personal industrial hygiene experience. In addition, some lines of work history were simply unintelligible and could not be assigned any other code.

Assignment of a Code 5 or 6 was based primarily on the judgment of the investigator and involved jobs normally associated 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 can be assumed that Cenent House personnel were potentially 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 from plant use. A review showed that one of the cases fell into this category, having been employed as a cement mixer from 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 hand.

One other caution should be mentioned. The standard operating procedure documents for Tire Building concentrate on passenger tires although materials are 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 were 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

CELL
TYPE

EXPOSURE CATEGORY	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	0.30	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	0.98
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 point 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 (Code 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 area 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 potential 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.

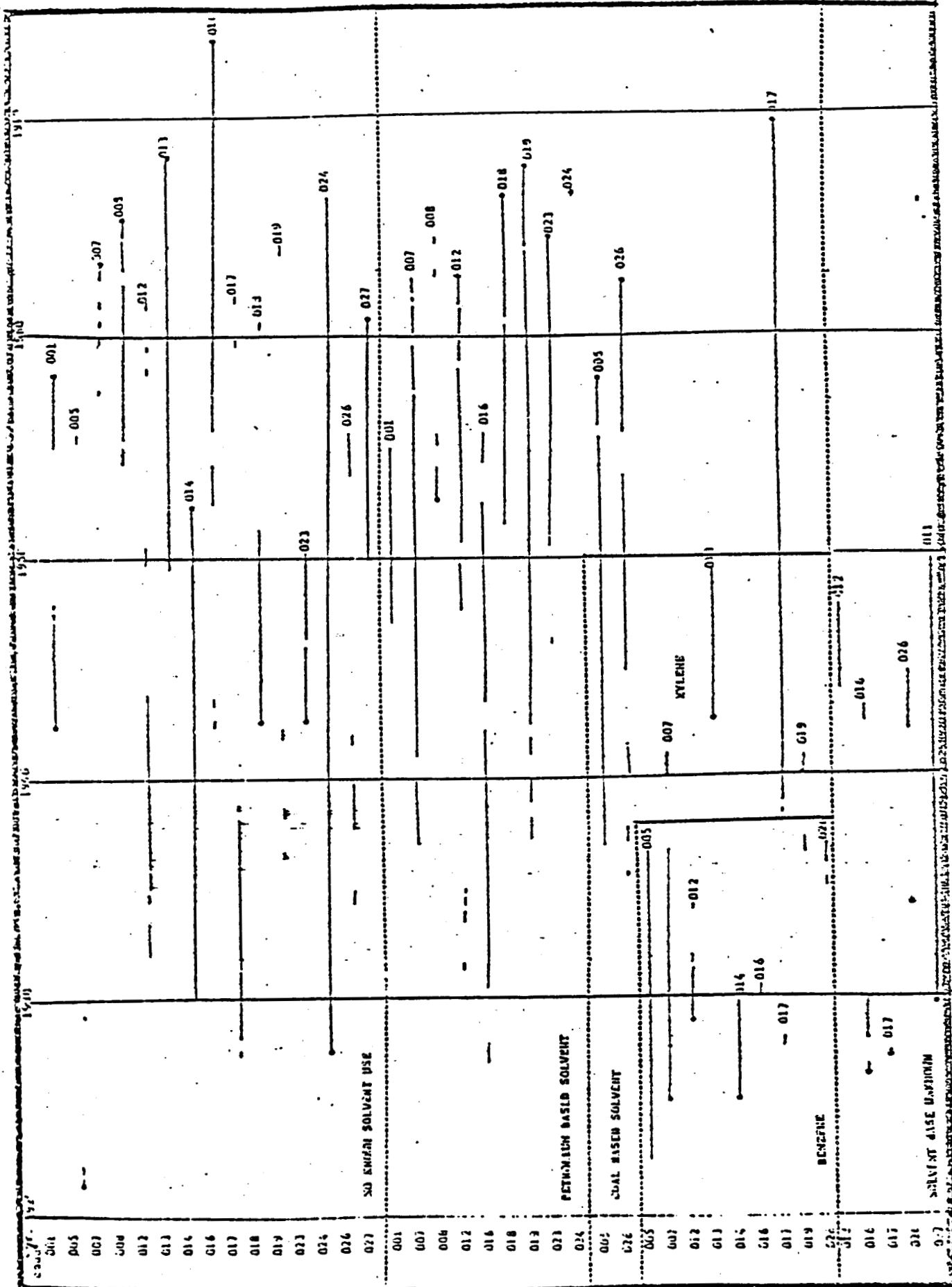
COAL-BASED SOLVENTS

During the record search described earlier, a raw material specification for xylene was found, dated 1939, that listed a source of supply which indicated the chemical might be 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 by Hamilton⁽²⁾ the coal-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 of 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--and the same chemical identity--benzene.

This due to the 1939'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 from petroleum in 1943, followed by xylene in 1944. Benzene became 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 SYSTEMATIC LIEKEND A TEST CONTROLS BY POTENTIAL EXPOSURE CATEGORIES

01-1	01-2	01-3	01-4	01-5	01-6	01-7	01-8	01-9	01-10	01-11	01-12	01-13	01-14	01-15	01-16	01-17	01-18	01-19	01-20	01-21	01-22	01-23	01-24	01-25	01-26	01-27	01-28	01-29	01-30	01-31	01-32	01-33	01-34	01-35	01-36	01-37	01-38	01-39	01-40	01-41	01-42	01-43	01-44	01-45	01-46	01-47	01-48	01-49	01-50	01-51	01-52	01-53	01-54	01-55	01-56	01-57	01-58	01-59	01-60	01-61	01-62	01-63	01-64	01-65	01-66	01-67	01-68	01-69	01-70	01-71	01-72	01-73	01-74	01-75	01-76	01-77	01-78	01-79	01-80	01-81	01-82	01-83	01-84	01-85	01-86	01-87	01-88	01-89	01-90	01-91	01-92	01-93	01-94	01-95	01-96	01-97	01-98	01-99	01-100	01-101	01-102	01-103	01-104	01-105	01-106	01-107	01-108	01-109	01-110	01-111	01-112	01-113	01-114	01-115	01-116	01-117	01-118	01-119	01-120	01-121	01-122	01-123	01-124	01-125	01-126	01-127	01-128	01-129	01-130	01-131	01-132	01-133	01-134	01-135	01-136	01-137	01-138	01-139	01-140	01-141	01-142	01-143	01-144	01-145	01-146	01-147	01-148	01-149	01-150	01-151	01-152	01-153	01-154	01-155	01-156	01-157	01-158	01-159	01-160	01-161	01-162	01-163	01-164	01-165	01-166	01-167	01-168	01-169	01-170	01-171	01-172	01-173	01-174	01-175	01-176	01-177	01-178	01-179	01-180	01-181	01-182	01-183	01-184	01-185	01-186	01-187	01-188	01-189	01-190	01-191	01-192	01-193	01-194	01-195	01-196	01-197	01-198	01-199	01-200	01-201	01-202	01-203	01-204	01-205	01-206	01-207	01-208	01-209	01-210	01-211	01-212	01-213	01-214	01-215	01-216	01-217	01-218	01-219	01-220	01-221	01-222	01-223	01-224	01-225	01-226	01-227	01-228	01-229	01-230	01-231	01-232	01-233	01-234	01-235	01-236	01-237	01-238	01-239	01-240	01-241	01-242	01-243	01-244	01-245	01-246	01-247	01-248	01-249	01-250	01-251	01-252	01-253	01-254	01-255	01-256	01-257	01-258	01-259	01-260	01-261	01-262	01-263	01-264	01-265	01-266	01-267	01-268	01-269	01-270	01-271	01-272	01-273	01-274	01-275	01-276	01-277	01-278	01-279	01-280	01-281	01-282	01-283	01-284	01-285	01-286	01-287	01-288	01-289	01-290	01-291	01-292	01-293	01-294	01-295	01-296	01-297	01-298	01-299	01-300	01-301	01-302	01-303	01-304	01-305	01-306	01-307	01-308	01-309	01-310	01-311	01-312	01-313	01-314	01-315	01-316	01-317	01-318	01-319	01-320	01-321	01-322	01-323	01-324	01-325	01-326	01-327	01-328	01-329	01-330	01-331	01-332	01-333	01-334	01-335	01-336	01-337	01-338	01-339	01-340	01-341	01-342	01-343	01-344	01-345	01-346	01-347	01-348	01-349	01-350	01-351	01-352	01-353	01-354	01-355	01-356	01-357	01-358	01-359	01-360	01-361	01-362	01-363	01-364	01-365	01-366	01-367	01-368	01-369	01-370	01-371	01-372	01-373	01-374	01-375	01-376	01-377	01-378	01-379	01-380	01-381	01-382	01-383	01-384	01-385	01-386	01-387	01-388	01-389	01-390	01-391	01-392	01-393	01-394	01-395	01-396	01-397	01-398	01-399	01-400	01-401	01-402	01-403	01-404	01-405	01-406	01-407	01-408	01-409	01-410	01-411	01-412	01-413	01-414	01-415	01-416	01-417	01-418	01-419	01-420	01-421	01-422	01-423	01-424	01-425	01-426	01-427	01-428	01-429	01-430	01-431	01-432	01-433	01-434	01-435	01-436	01-437	01-438	01-439	01-440	01-441	01-442	01-443	01-444	01-445	01-446	01-447	01-448	01-449	01-450	01-451	01-452	01-453	01-454	01-455	01-456	01-457	01-458	01-459	01-460	01-461	01-462	01-463	01-464	01-465	01-466	01-467	01-468	01-469	01-470	01-471	01-472	01-473	01-474	01-475	01-476	01-477	01-478	01-479	01-480	01-481	01-482	01-483	01-484	01-485	01-486	01-487	01-488	01-489	01-490	01-491	01-492	01-493	01-494	01-495	01-496	01-497	01-498	01-499	01-500	01-501	01-502	01-503	01-504	01-505	01-506	01-507	01-508	01-509	01-510	01-511	01-512	01-513	01-514	01-515	01-516	01-517	01-518	01-519	01-520	01-521	01-522	01-523	01-524	01-525	01-526	01-527	01-528	01-529	01-530	01-531	01-532	01-533	01-534	01-535	01-536	01-537	01-538	01-539	01-540	01-541	01-542	01-543	01-544	01-545	01-546	01-547	01-548	01-549	01-550	01-551	01-552	01-553	01-554	01-555	01-556	01-557	01-558	01-559	01-560	01-561	01-562	01-563	01-564	01-565	01-566	01-567	01-568	01-569	01-570	01-571	01-572	01-573	01-574	01-575	01-576	01-577	01-578	01-579	01-580	01-581	01-582	01-583	01-584	01-585	01-586	01-587	01-588	01-589	01-590	01-591	01-592	01-593	01-594	01-595	01-596	01-597	01-598	01-599	01-600	01-601	01-602	01-603	01-604	01-605	01-606	01-607	01-608	01-609	01-610	01-611	01-612	01-613	01-614	01-615	01-616	01-617	01-618	01-619	01-620	01-621	01-622	01-623	01-624	01-625	01-626	01-627	01-628	01-629	01-630	01-631	01-632	01-633	01-634	01-635	01-636	01-637	01-638	01-639	01-640	01-641	01-642	01-643	01-644	01-645	01-646	01-647	01-648	01-649	01-650	01-651	01-652	01-653	01-654	01-655	01-656	01-657	01-658	01-659	01-660	01-661	01-662	01-663	01-664	01-665	01-666	01-667	01-668	01-669	01-670	01-671	01-672	01-673	01-674	01-675	01-676	01-677	01-678	01-679	01-680	01-681	01-682	01-683	01-684	01-685	01-686	01-687	01-688	01-689	01-690	01-691	01-692	01-693	01-694	01-695	01-696	01-697	01-698	01-699	01-700	01-701	01-702	01-703	01-704	01-705	01-706	01-707	01-708	01-709	01-710	01-711	01-712	01-713	01-714	01-715	01-716	01-717	01-718	01-719	01-720	01-721	01-722	01-723	01-724	01-725	01-726	01-727	01-728	01-729	01-730	01-731	01-732	01-733	01-734	01-735	01-736	01-737	01-738	01-739	01-740	01-741	01-742	01-743	01-744	01-745	01-746	01-747	01-748	01-749	01-750	01-751	01-752	01-753	01-754	01-755	01-756	01-757	01-758	01-759	01-760	01-761	01-762	01-763	01-764	01-765	01-766	01-767	01-768	01-769	01-770	01-771	01-772	01-773	01-774	01-775	01-776	01-777	01-778	01-779	01-780	01-781	01-782	01-783	01-784	01-785	01-786	01-787	01-788	01-789	01-790	01-791	01-792	01-793	01-794	01-795	01-796	01-797	01-798	01-799	01-800	01-801	01-802	01-803	01-804	01-805	01-806	01-807	01-808	01-809	01-810	01-811	01-812	01-813	01-814	01-815	01-816	01-817	01-818	01-819	01-820	01-821	01-822	01-823	01-824	01-825	01-826	01-827	01-828	01-829	01-830	01-831	01-832	01-833	01-834	01-835	01-836	01-837	01-838	01-839	01-840	01-841	01-842	01-843	01-844	01-845	01-846	01-847	01-848	01-849	01-850	01-851	01-852	01-853	01-854	01-855	01-856	01-857	01-858	01-859	01-860	01-861	01-862	01-863	01-864	01-865	01-866	01-867	01-868	01-869	01-870	01-871	01-872	01-873	01-874	01-875	01-876	01-877	01-878	01-879	01-880	01-881	01-882	01-883	01-884	01-885	01-886	01-887	01-888	01-889	01-890	01-891	01-892	01-893	01-894	01-895	01-896	01-897	01-898	01-899	01-900	01-901	01-902	01-903	01-904	01-905	01-906	01-907	01-908	01-909	01-910	01-911	01-912	01-913	01-914	01-915	01-916	01-917	01-918	01-919	01-920	01-921	01-922	01-923	01-924	01-925	01-926	01-927	01-928	01-929	01-930	01-931	01-932	01-933	01-934	01-935	01-936	01-937	01-938	01-939	01-940	01-941	01-942	01-943	01-944	01-945	01-946	01-947	01-948	01-949	01-950	01-951	01-952	01-953	01-954	01-955	01-956	01-957	01-958	01-959	01-960	01-961	01-962	01-963	01-964	01-965	01-966	01-967	01-968	01-969	01-970	01-971	01-972	01-973	01-974	01-975	01-976	01-977	01-978	01-979	01-980	01-981	01-982	01-983	01-984	01-985	01-986	01-987	01-988	01-989	01-990	01-991	01-992	01-993	01-994	01-995	01-996	01-997	01-998	01-999	02-000	02-001	02-002	02-003	02-004	02-005	02-006	02-007	02-008	02-009	02-010	02-011	02-012	02-013	02-014	02-015	02-016	02-017	02-018	02-019	02-020	02-021	02-022	02-023	02-024	02-025	02-026	02-027	02-028	02-029	02-030	02-031	02-032	02-033	02-034	02-035	02-036	02-037	02-038	02-039	02-040	02-041	02-042	02-043	02-044	02-045	02-046	02-047	02-048	02-049	02-050	02-051	02-052	02-053	02-054	02-055	02-056	02-057	02-058	02-059	02-060	02-061	02-062	02-063	02-064	02-065	02-066	02-067	02-068	02-069	02-070	02-071	02-072	02-073	02-074	02-075	02-076	02-077	02-078	02-079	02-080	02-081	02-082	02-083	02-084	02-085	02-086	02-087	02-088	02-089	02-090	02-091	02-092	02-093	02-094	02-095	02-096	02-097	02-098	02-099	02-100	02-101	02-102	02-103	02-104	02-105	02-106	02-107	02-108	02-109	02-110	02-111	02-112	02-113	02-114	02-115	02-116	02-117	02-118	02-119	02-120	02-121	02-122	02-123	02-124	02-125	02-126	02-127	02-128	02-129	02-130	02-131	02-132	02-133	02-134	02-135	0
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shows the greatest association with a relative risk of 7.3.3, while the 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.

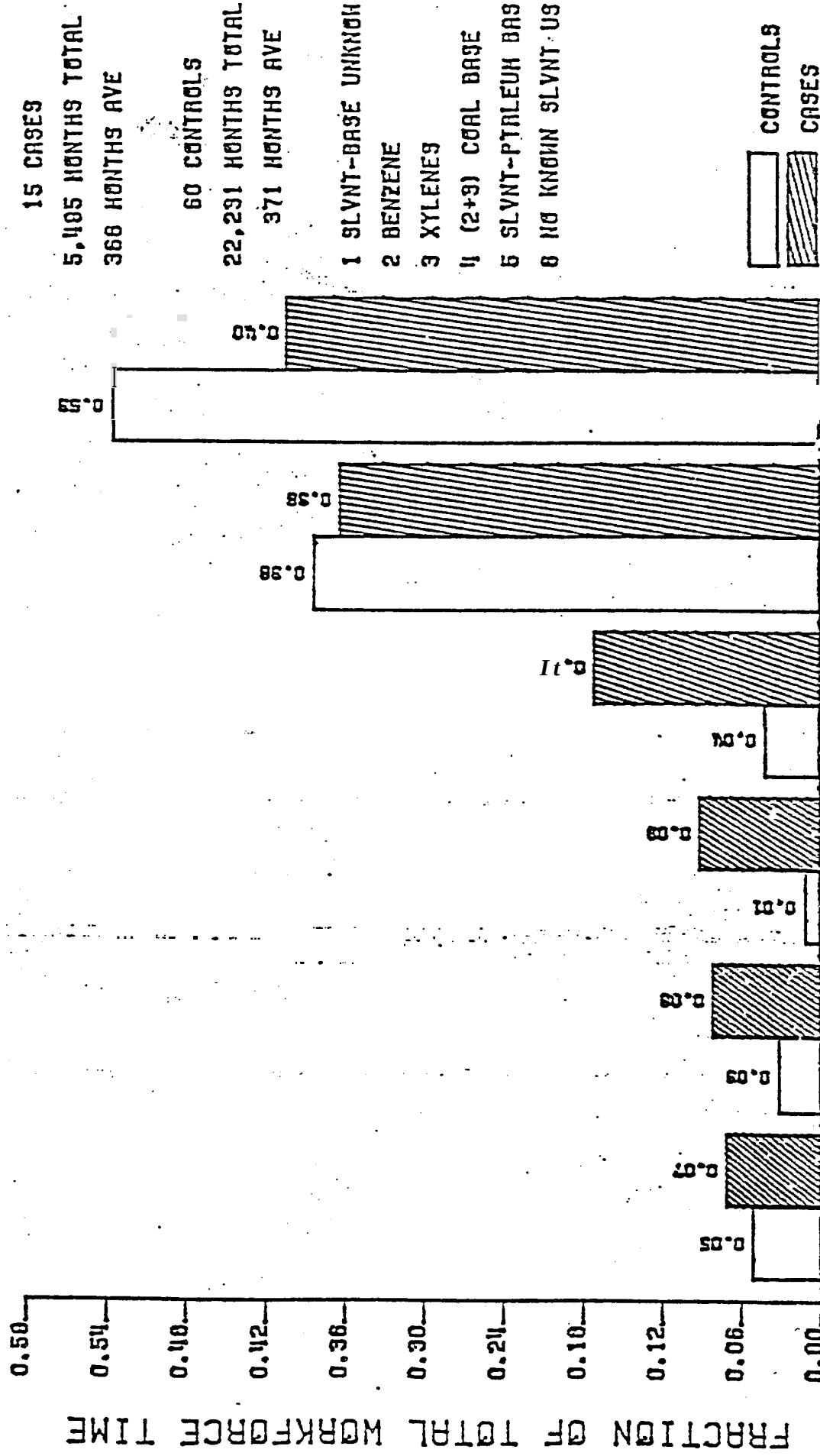
Another way to assess the effect of these different solvent sources is to assign the cases and controls to mutually exclusive exposure severity groups. Table 9 displays the number of cases and controls assigned to each category, and their ratio. An individual with any time in the Coal Based Solvent category 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, 10-Dimethyl-1,2-Benzanthracene,⁽⁴⁾ 3,4-Benzpyrene, and Methylcholanthrene.⁽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 OHSO investigators of an apparent association of lymphatic leukemia with solvent-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 antireaffirmed but was substantially strengthened. Whereas McMichael reported relative risks up to 9 for workers in the group presumed to have high solvent exposure, this study showed risk estimates of 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 from records developed for purposes far different from occupational health research. These data from existing company records have provided the capability to determine the raw material, location, time and duration of use, and identity of workers potentially 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 set i of a leukemia case and the four matched controls as follows :

	Exposed	Bot Exposed	Total
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:

$$O.R. = A_i D_i / B_i C_i$$

and for the entire study population we use:

$$O.R. = \frac{\sum_i \frac{A_i D_i}{T_i}}{\sum_i \frac{B_i C_i}{T_i}}$$

The chi-square statistic is calculated as:

$$\chi^2 = \frac{(\sum_i A_i - \frac{\sum_i U_i \sum_i V_i}{\sum_i T_i})^2}{\sum_i \frac{U_i V_i W_i X_i}{T_i^2 (T_i - 1)}}$$

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