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Mutagenesis, teratogenesis and carcinogenesis in man

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Survey of mortality among employees engaged in the manufacture of styrene and polystyrene at the BASF Ludwigshafen works

by R. FRENTZEL-BEYME,[1] A. M. THIESS[2] and R. WIELAND[2]

FRENTZEL-BEYME, R., THIESS, A. M. and WIELAND, R. Survey of mortality among employees engaged in the manufacture of styrene and polystyrene at the BASF Ludwigshafen works. *Scand. j. work environ. & health* 4 (1978): suppl. 2, 231—239. A mortality survey of 1,960 employees currently or previously exposed to styrene at work has shown that the observed number of deaths from cancer or other causes is no higher than the number expected in the German population or in a group of BASF employees. Analyses of deaths occurring after a minimum period of five years in groups exposed for different durations (5 years, 10 years, 15 years, more than 15 years) indicated no increase in mortality with exposure time. This latter observation also applied to malignant tumors; therefore it may be inferred that prolonged exposure to styrene is not a cancer hazard.

Key words: cancer, chemical industrial workers, mortality, prospective study, styrene.

A survey of mortality among persons that have been exposed to styrene during their employment in the BASF Aktiengesellschaft has been carried out in order to discover whether there was an excess incidence of malignant tumors. The cohort included all past and present employees engaged in the manufacture of styrene or polystyrene for more than one month since production started in 1931.

The date when exposure started, the date of birth, the date of leaving the plant, and the reason for leaving the plant were extracted from the plant records of each employee or exemployee and recorded. When a person was no longer engaged in styrene or polystyrene production, a follow-up procedure was carried out; this was successful for 93 % of all former German employees. The follow-up was more difficult in the case of former non-German employees, many of whom had returned home to countries without registration systems comparable to those

1 Deutsches Krebsforschungszentrum, Heidelberg, Federal Republic of Germany.

2 Occupational Medicine and Health Protection, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Federal Republic of Germany.

Table 1. Numbers of person-years of observation for the styrene cohort (1,960 persons) and the vinyl chloride cohort (1,681 persons).

Group	Total period of observation for group	
	Styrene	Vinyl chloride
15— 24	2,732.9	3,156.08
25— 34	6,819.4	6,718.35
35— 44	5,532.4	5,609.79
45— 54	3,407.7	2,892.14
55— 64	1,379.5	1,175.00
65— 74	258.4	194.77
75— 84	7.8	20.94
85—100	0.0	0.00
Total	20,138.1	19,767.07

in Germany, and it was successfully carried out for only 29 % of the personnel, who however had been exposed in almost the half of all cases for less than six months.

The technical data and the respective recordings of workplace concentrations have been reported in another presentation in these proceedings (4).

It was not possible to ascertain how long an individual employee had been exposed to lower or higher levels of styrene, because most employees had carried out various tasks within the plants. However, since both the equipment and safety precautions had been considerably improved over the years (for instance, now there are only closed systems), the cohort was

Table 2. Causes of death in the styrene cohort (1,960 persons) [a] and comparisons of incidences with expectancies.

Serial number	ICD number	Cause of death	Observed	Expected									
				Rhinehessia-Palatinate 1970—1975					Ludwigshafen 1970—1975				
					p	Age group	(O/E)	p		p	Age group	(O/E)	p
1	011	Tuberculosis	1	1.046					1.160				
2	0—136	Infections and parasites	2	1.538	0.455				1.648	0.490			
3	151	Stomach cancer	2	2.586					2.378				
4	153	Colon cancer	1	1.201		30—34	(1/0.42)	0.041	1.198		30—34	(1/0.0)	0.0
5	154	Rectal cancer	1	1.010					0.874	0.583			
6	157	Pancreatic cancer	2	0.721	0.163				0.705	0.157			
7	158	Peritoneal carcinosis	1	0.141	0.132	40—44	(1/0.013)	0.013	0.228	0.202	40—44	(1/0.0)	0.0
8	162	Lung cancer	3	5.442					5.726				
9	189	Malignant neoplasm of the urinary system	1	0.538	0.416				0.415	0.340			
10	202	Splenic tumor	1	0.087	0.083	50—54	(1/0.014)	0.014	0.058	0.057	50—54	(1/0.0)	0.0
11	250	Diabetes	1	1.014					0.956	0.616			
12	252—279	Other metabolic diseases	1	0.207	0.187	55—59	(1/0.020)	0.020	0.222	0.199	55—59	(1/0.024)	0.024
13	400	Malignant hypertension	1	0.171	0.158	30—34	(1/0.0)	0.0	0.136	0.127	30—34	(1 0.0)	0 0
14	410	Acute myocardial infarction	13	13.718					13.792				
15	411	Acute ischemic heart disease	1	0.377	0.314	50—54	(1/0.044)	0.043	0.492	0.389			
16	412	Chronic ischemic heart disease	1	1.826					2.0				
17	420—427	Other heart diseases	2	1.530	0.452				1.443	0.423	50—54	(1 0.036)	0.022
18	428	Myocardial diseases	2	1.930	0.575				1.174	0.328			
19	432—435	Cerebrovascular diseases	1	0.275	0.240	50—54	(1/0.052)	0.051	0.295	0.256	50—54	(1 0.059)	0.057
20	436	Apoplexy	4	3.420	0.446				2.908	0.332			
21	440	Arteriosclerosis	1	0.263	0.231				0.315	0.270			
22	490—491	Bronchitis	1	1.049					1.239				
23	493	Asthma	1	0.671	0.489				0.550	0.423			
24	517—519	Pneumonopathy	1	0.242	0.215	55—59	(1/0.033)	0.033	0.200	0.181	55—59	(1 0.024)	0.024
25	571	Hepatic cirrhosis	5	6.652					5.920				
26	572—573	Other liver diseases	1	0.331	0.282	40—44	(1/0.025)	0.025	0.329	0.281	40—44	(1 0.036)	0 036
27	577	Pancreatopathy	1	0.424	0.346				0.306	0.264	30—34	(1. 0.049)	0.045
28	795—796	Uncertain or unknown	3	0.533	0.017	30—34	(2/0.025)	0.0	0.754	0.041	30—34	(2 0.045)	0 001
29	800—807	Railroad accidents	1	0.290	0.252	50—54	(1/0.011)	0.011	0.179	0.164	50—54	(1 0.0)	0 0
30	810—819	Automobile accidents	7	9.440					7.992				
31	820—827	Accidents with vehicles not in traffic	1	0.302	0.261	20—24	(1/0.020)	0.020	0.260	0.229	20—24	(1 0.0)	0.0
32	910—929	Other accidents	3	2.199	0.377				2.297	0.403			
33	953	Suicide	3	2.165	0.368	40—44	(2/0.342)	0.047	2.014	0.327	40—44	(2 0.248)	0.026
34	960—969	Homicide	1	0.513	0.401				0.546	0.421			
35	980—989	Wounding, possibly intentional	1	0.162	0.149	50—54	(1/0.009)	0.009	0.055	0.053	50—54	(1/0.0)	0.0
36	0—796	Natural causes	56	74.369					71.372				
37	800—999	Unnatural causes	17	22.096					19.748				
38	0—999	All causes	73	96.465					91.120				

[a] Total period of observation 20.138 years.

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0 036)	0.035
0 059)	0.057
0 024)	0.024
0 036)	0.036
0 049)	0.048
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0.0)	0.0

Table 3. Incidence of deaths in the styrene cohort by age and year.

Age (years)	Number of deaths				Total for age	
	1956—1960	1961—1965	1966—1970	1971—1976	N	%
15—24	1	1	0	3 [a]	5	6.7
25—34	0	3	2	4	9	12.2
35—44	1	1	5	2	9	12.2
45—54	0	3	5	8	16	21.6
55—64	1	2	11	8	22	29.7
65—74	0	0	4	7	11	14.9
75—84	0	0	0	2	2	2.7
Totals						
N	3	10	27	34	74	—
%	4.1	13.5	36.5	45.9	—	100.0

[a] One of the dead had been exposed for 15 d only.

divided into groups of those who had been exposed before 1960 and those who had not been exposed before 1960. This procedure gave a crude differentiation between possible levels of exposure. Another reason for dividing the cohort in this way was the comparatively high proportion of non-German employees working in the plant after 1960; this changed the composition of the cohort and, as mentioned before, reduced the follow-up rate considerably.

For the analysis of the data with reference to period of exposure, the cohort was further subdivided into groups of employees exposed for periods of up to 5 years, 5 years or more but less than 10 years, 10 years or more but less than 15 years, and 15 years or more.

The total number of years of observation for the 1,960 exposed persons has been broken down by age groups in table 1. Table 2 gives the number of deaths observed, by causes of death, and the expected numbers based on the 1970—1975 statistics for Rhinehessia-Palatinate and the 1970—1975 statistics for the town of Ludwigshafen. Where appropriate, the expectancies for the pertinent age group are given, too. Whenever the observed number of deaths exceeded expectancy, the probability of such a deviation by chance was determined, under the assumption of the Poisson distribution.

Another basis of comparison was provided by the use of an internal reference group consisting of a cohort of similar composition and size that resulted from studies on exposure to vinyl chloride. Data relating to mortality in this group are being published elsewhere. The total numbers of years of observation and the breakdown by age of this cohort are given in table 1.

RESULTS

General mortality

Table 3 reveals the breakdown of the 74 deaths by age and year of death. Mortality was highest in the age group 55—64 years.

Table 4 shows the proportional breakdown by causes of all deaths observed in the cohort and the corresponding distribution for the whole population of the Federal Republic of Germany. When the two sets of relative frequencies of particular causes of death are compared, it is noticeable that within the cohort of those exposed to styrene the proportion of deaths due to malignant neoplasms was less than in the country as a whole, namely, 14.9 % compared with 18.5 %. Similarly, the proportion of deaths due to cardiovascular diseases was appreciably less in the cohort than in the country as a whole. The proportion of deaths due to

Table 4. Cause of death in the styrene cohort compared with causes of death in the Federal Republic of Germany, 1968—1972.

ICD number	Cause of death	Styrene cohort		Federal Republic of Germany	
		N	%	%	PMR[b]
000—136	Infections & parasites (respiratory tuberculosis)	2 (2)	2.7 (2.7)	1.5 (0.9)	180 (300)
140—199	Malignant neoplasms	11	14.9	18.5	81
200—209	Neoplasms of lymphatic and hematogenic systems	1	1.3	1.2	108
240—279	Metabolic and nutritional diseases	2	2.7	2.0	135
390—458	Cardiovascular diseases	27	36.5	43.2	84
460—519	Diseases of the respiratory tract	3	4.1	9.0	46
520—577	Diseases of the digestive tract (hepatic cirrhosis)	7 (5)	9.4 (6.7)	6.1 (2.7)	154 (248)
E950—959	Suicide	3	4.1	2.2	186
E960—999	Other violent deaths	1	1.3	0.3	434
780—796	Unknown, unexplained causes	4	5.4	3.8	142
E800—949	Accidents (traffic) (others)	13 (9)[a] (4)	17.6 (12.2) (5.4)	6.3 (3.6) (2.7)	279 (339) (260)
280—289 290—389 580—629 680—738	Other causes	0	0.0	6.3	0
000—999	Total	74	100.0	100.0	—

[a] One of the dead had been exposed for 15 d only.
[b] PMR = proportional mortality ratio.

diseases of the liver and other digestive organs was, however, higher in the cohort than in the rest of the country, but this should perhaps be considered in the light of the generally high incidence of deaths due to hepatic cirrhosis in Rhinehessia-Palatinate (table 2) — where most German wine is produced.

The fact that the proportion of accidental deaths was nearly three times as large in the cohort as in the total population points to the uselessness of comparisons of this sort. The age structures of the two populations are simply too different. For this reason, the expectancies for particular age groups were calculated (making use of the total number of years of observation for each group) and compared with the numbers of deaths observed, as shown in table 2.

The 56 deaths from natural causes within the cohort were considerably fewer than the numbers expected for populations with the same age structure. namely, 71 (based on Ludwigshafen statistics) and 74 (based on statistics for the administrative region Rhinehessia-Palatinate). There was, however, good agreement between observed and expected figures for specific causes of death when the expectancies were based on the total number of years of observation for the whole cohort. Certain events were observed that would have occurred very rarely in the general population, had this been observed over the whole period of time. These causes of death were: peritoneal carcinosis in the age group 40—44 years; colon-rectum cancer in the age group 30—34 years; pancreatic tumor in the age group 50—54 years; metabolic disease in the age group 55—59 years; malignant hypertension in the age group 30—34 years; and disease of the liver in the age group 40—44 years.

Since, however, none of these events occurred more than once in the whole cohort, they cannot be regarded as indicative of specific hazards involved in exposure to styrene.

The causes of three deaths could not be determined in spite of efforts made by the authorities.

Mortality in relationship to period of exposure

In accordance with a suggestion made by Fox (3), the cohort was modified by the elimination of all those who had been under observation for less than five years from the time of first exposure and the

Table 5. Deaths in the reduced styrene cohort (members observed at least 5 years): Comparison of observed and expected deaths by duration of exposure.

Exposure (years)	Exposure started	Natural deaths			Unnatural deaths			All deaths		
		N	N_E	P	N	N_E	P	N	N_E	P
0— 4	pre 1960	6	11.291	—	1	3.342	—	7	14.633	—
	post 1960	8	18.126	—	0	5.187	—	8	23.313	—
5— 9	pre 1960	8	9.960	—	1	1.657	—	9	11.616	—
	post 1960	8	3.105	0.014	3	0.677	0.031	11	3.782	0.002
10—14	pre 1960	4	6.589	—	3	0.877	0.059	7	7.466	
	post 1960	1	0.128	0.12	0	0.027	—	1	0.155	0.144
> 15	pre 1960	13	9.316	0.148	1	0.716	0.48	14	10.032	0.137
	post 1960	—	—	—	—	—	—	—	—	—
Total	pre 1960	31	37.156	—	6	6.591	—	37	43.747	—
	post 1960	17	21.36	—	3	5.891	—	20	27.25	—

The expected deaths are based on the reference population mortality of Rhinehessia-Palatinate in 1972—1975.

Table 6. Deaths in the reduced styrene cohort (members observed at least 5 years): Comparison of observed and expected deaths by age groups.

Age (years)	Exposure started	Natural deaths			Unnatural deaths			All deaths		
		N	N_E	P	N	N_E	P	N	N_E	P
15—24	pre 1960	—	—	—	—	—	—	—	—	—
	post 1960	0	—	—	1	0.387	0.321	1	0.495	
25—34	pre 1960	—	—	—	1	1.565		1	2.731	
	post 1960	3	1.476	0.19	0			3	3.458	
35—44	pre 1960	3	4.015	—	3	1.902	0.297	6	5.917	
	post 1960	0			1	1.786		1	5.468	
45—54	pre 1960	7	8.814		1	1.494		8	10.309	
	post 1960	4	6.779		1	0.74	0.523	5	7.947	
55—64	pre 1960	14	14.581		1	1.066		15	15.647	
	post 1960	6	6.361		0			6	6.83	
65—74	pre 1960	6	7.976		0			6	8.240	
	post 1960	4	2.954	0.342	0			4	3.053	0.365
75—	pre 1960	1	0.524	0.408	0			1	0.537	0.415
	post 1960	—			—			—		
Total	pre 1960	31	37.156		6	6.591		37	43.747	
	post 1960	17	21.36		3	5.891		20	27.25	

The expected deaths are based on the reference population mortality of Rhinehessia-Palatinate in 1972—1975.

Table 7. Details of fatal cases of cancer in the styrene cohort.

Study number	Site of tumor	Diagnosis	Date and kind of diagnosis	Date of death	Age at time of diagnosis (years)	Exposure started	Time exposed month	Time observed (years)
21250	Lungs	Carcinoma: metastasizing bronchogenic, discrete, keratinized squamous cells; many metastases, e.g., in kidneys, bones, and lymph nodes	23 Sept. 74 histological	18 Sept. 74	49	30 April 70	2	4
21055	Lungs	Pulmonary carcinoma; metastases	5 Oct. 65 radiological	20 Oct. 65	59	5 Feb. 58	93	7
20963	Lungs	Pleuritis carcinomatosa accompanying bronchial carcinoma		24 Feb. 75	74	1 Dec. 60	67	15
21003	Stomach	Tubular carcinoma of the stomach and hepatic cirrhosis	26 May 71 histological	7 June 71	56	6 Sept. 60	52	11
21256	Stomach	Carcinoma of the stomach, with metastases, partly polypous, partly diffusely infiltrating	28 April 65 histological	9 June 66	60	8 March 39	322	27
21244	Pancreas	According to case records: uncertain primary tumor, metastases in lumbar vertebrae and pancreas		11 Jan. 67	54	1 Oct. 52	171	15
21157	Peritoneum, sigmoid of the colon	Peritoneal carcinosis; adenocarcinoma of the sigma (colon/rectum) with multiple hepatic metastases, para-aortal lymphatic metastases, wide-spread adhesion of the peritoneum to the primary tumor	23 July 63 histological	3 Jan. 64	44	1 Aug. 55	32	9
20427	Rectum	Adenocarcinoma of the rectum; dense infiltration of the intestinal wall with adenoid structures	24 July 69 histological biopsy	3 Aug. 69	61	18 July 63	72	6
20997	Probably kidney	Site of primary tumor not known: iliac crest, appears as metastasis of a hypernephroid carcinoma	histological	29 June 65	53	20 Oct. 49	188	16
21370	Sigma	Infiltrating adenocarcinoma of the sigma (colon); ileus accompanying peritoneal carcinosis; recurrent tumor penetrating into the bladder	20 Jan. 72 histological 24 Oct. 72 laparotomy 24 Oct. 72 biopsy	25 Oct. 72	34	6 July 65	88	7
21292	Spleen	Splenic tumor: no histological examination! Uncertain dignity		8 Nov. 69	54	17 Aug. 59	59	10
21689	Head of pancreas	No histological diagnosis: death certificate		2 March 70	66	28 Aug. 64	47	6

subdivision of the remainder into groups of people that had been exposed for less than 5 years, 5—9 years, 10—14 years, and 15 years or more.

Within the new cohort with a minimum period of observation of five years, mortality rose with time of exposure relative to the expectancy both for natural and unnatural deaths, and particularly for initial exposures after 1960, but only became significantly higher than expectancy in the group with 5—9 years of exposure, as shown in table 5.

Table 6 shows the observed and expected numbers of deaths for the cohorts with periods of employment before and after 1960 broken down by age and cause of death (natural or unnatural). In no age group was the number of deaths significantly higher than the expectancy.

Diagnoses of fatal cancer cases

Table 7 gives details of the 12 cases in which cancer was diagnosed as the cause of death, including site of the tumor, diagnosis, date when exposure began, duration of exposure, and observation period.

DISCUSSION

According to preliminary reports on two animal experimental studies, a link is suggested between styrene monomer and tumors of the lymphatic and blood systems (7).

If an association between exposure to a substance like styrene and a specific disease with a long latency like cancer is suspected, the most logical procedure would be to compare groups with sh rt, intermediate and long duration of exposure, provided that the minimum observation period is at least five years from

Table 8. Comparison of the styrene and vinyl chloride cohorts: Relative risks of dying from specific causes, by age groups.

Age (years)	Styrene cohort				Vinyl chloride cohort		
	Deaths a	Person-years b	Expected c = bf	Relative risk g = a/c	Deaths d	Person-years e	Death rate/years f = d/e
Malignant neoplasms							
30—39	1	6,693.6	1.004	0.996	1	6,701	0.00015
40—49	2	4,460.8	3.167	0.632	3	4,220.5	0.00071
50—59	5	2,266.9	7.027	0.712	6	1,950.9	0.0031
60—69	3	713.3	7.347	0.408	6	579.7	0.0103
70—79	1	64.9	1.947	0.514	2	66.5	0.03
Cardiovascular diseases							
30—39	1	6,693.6	—	—	—	—	—
40—49	2	4,460.8	5.353	0.374	5	4,220.5	0.0012
50—59	8	2,266.9	10.428	0.767	9	1,950.9	0.0046
60—69	14	713.3	8.65	1.636	7	579.7	0.012
70—79	2	64.9	0.974	2.054	1	66.5	0.015
Other natural causes							
30—39	3	6,693.6	5.02	0.597	5	6,701	0.00075
40—49	4	4,460.8	4.238	0.944	4	4,220.5	0.00095
50—59	5	2,266.9	3.4	1.47	3	1,950.9	0.0015
60—69	5	713.3	3.71	1.348	3	579.7	0.0052
70—79	—	64.9	0	—	2	66.5	0.03
80—89	—	—	—	—	2	3.12	0.64
All natural causes							
30—39	5	6,693.6	5.957	0.839	6	6,701	0.00089
40—49	8	4,460.8	12.49	0.641	12	4,220.5	0.0028
50—59	21	2,266.9	20.855	1.607	18	1,950.9	0.0092
60—69	19	713.3	19.687	0.965	16	579.7	0.965
70—79	3	64.9	4.868	0.616	5	66.5	0.075
80—89	—	—	—	—	2	3.12	0.64
Unnatural causes							
20—29	7	5,250.8	2.85	2.456	3	5,310.2 + 993.5	0.00048
30—39	3	6,693.6	6.990	0.429	7	6,701	0.00104
40—49	4	4,460.8	6.340	0.63	6	4,220.5	0.00142
50—59	3	2,266.9	2.267	1.32	2	1,950.9	0.001
60—69	—	713.3	1.213	—	1	579.7	0.0017
70—79	—	64.9	0.976	—	1	66.5	0.015

the beginning of exposure. The rationale of this approach is that diseases and deaths before a minimum period of five years of observation are more likely to be due to previous history than to the particular exposure under study.

If, on the other hand, the incidence of cancer increases with duration of exposure and if adjustment for age is properly considered, the evidence suggests that an association between risk substance and disease may exist.

For this reason an approach to the data analysis was made that is in accordance with a recent criticism of the data presented by Duck et al. (2) concerning the mortality of British workers exposed to vinyl chloride. Several authors (1, 3, 6) have in this context reemphasized the analysis by duration of exposure (as a measure of dosage), enabling the comparison of several groups with different exposure periods. Expected deaths are calculated with the total person-years experience of a subgroup, but only after a minimum observation period (five years).

Comparison of a cohort of workers employed for a long time with the population mortality for the entire time of observation would lead to the apparent paradox, sometimes called the "healthy worker effect," that long-term exposure is inversely related to death. Whereas in the reference population a number of deaths may and will have occurred in a given time, the study subjects cannot possibly have died during the timespan of this occupational exposure category for which they had qualified.

This effect, although observed for many decades. only sporadically begins to be considered appropriately in the analyses of cohort studies. As a consequence of the objection stated above, in order to adjust for this possible survival effect, the period of five years was a first cut-off point for the summation of person-years under observation in four categories of workers employed up to 5, 10, 15 and more than 15 years, respectively.

This adjustment was a first step towards a more-detailed interpretation. A minimum observation period of 10 or 15 years after the first exposure period will be considered in future studies.

The effect of a hazardous exposure may show more pronounced deviations from expectation in the subgroups with long-term observation.

In the case of the cohort of employees exposed to styrene, this approach has, however, led to no significant deviation from expectation.

In order to establish whether or not the results obtained for styrene exclude a specific hazard, it is recommendable to make comparisons with a group of chemical workers that have not been exposed to styrene, but are similar otherwise.

The comparison shows (table 8) that in the vinyl chloride cohort deaths occurred earlier than in the styrene cohort. Cancer mortality in the former increased with age, and in 12 cases out of 18 was associated with a period of exposure exceeding five years; in the styrene cohort, however, the period of exposure had no influence on the incidence of cancer. It thus follows that exposure to pure styrene is most probably not a cancer hazard. On the other hand, the comparison shows that mortality through natural causes other than cancer was higher in the styrene cohort than in the vinyl chloride cohort. It is thus advisable to examine the data in the same way in all future studies.

The results supplemented and completed the work reported on at the symposium on "Health Aspects of Polymers" (5).

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QUESTIONS AND ANSWERS

Question to Prof. THIESS

Dr. HERNBERG: Is it correct to compare a cohort of workers with a high proportion of guest workers to the experience of the German (or local) general population.

Prof. THIESS: The guest workers have already been considered by the fact that the styrene cohort has also been divided into the groups "exposure before 1960" and "exposure after 1960." Guest workers were employed only after 1960.

In addition, their exposure is often short-term, and the follow-up is incomplete because they return to their native country after several years. This special group does not contribute much to the knowledge and will. therefore, be considered appropriately in future evaluations. (Reference: 5th Medichem congress paper: "Problems in Following-up Foreign Labour Force in Mortality Studies").

Question to Dr. RAMSEY

Dr. VAINIO: During the meeting we have heard that also Dow Chemicals has completed a styrene carcinogenicity study on animals. Would you like to enlighten the study further?

Dr. RAMSEY: There is nothing further that I can add to knowledge about this study that is available at this time.

Scand. j. work environ. & health 4 (1978): suppl. 2, 240—246

Epidemiologic investigations of styrene-butadiene rubber production and reinforced plastics production

by THEODORE J. MEINHARDT, RONALD J. YOUNG
and RICHARD W. HARTLE [1]

MEINHARDT, T. J., YOUNG, R. J. and HARTLE, R. W. Epidemiologic investigations of styrene-butadiene rubber production and reinforced plastics production. *Scand. j. work environ. & health* 4 (1978): suppl. 2, 240—246. The United States National Institute for Occupational Safety and Health (NIOSH) began an epidemiologic study of workers employed in the styrene-butadiene rubber (SBR) industry during 1976. This study was prompted by reports of relatively high numbers of leukemia deaths occurring within SBR production work populations. Simultaneous with the initiation of this investigation, the University of North Carolina released a report associating an excess risk of death due to hematopoietic and lymphatic malignancies among workers producing several synthetic rubbers, including SBR. This report presents NIOSH's preliminary mortality observations and a discussion of progress made on the analyses of contaminants found in two SBR production facilities. Currently, NIOSH is determining the feasibility of doing an epidemiologic study in the reinforced plastics industry. Interest in this study developed as part of an effort to determine health hazards associated with occupational exposure to styrene. Most of the technology for the reinforced plastics industry developed in the 1950s, and therefore this process represents a relatively new industry. This report also includes information on environmental conditions observed in the reinforced plastics industry and enumerates some of the complicating characteristics of this industry which increase the complexity of this study.

The only epidemiologic studies of which I am aware that have considered the mortality patterns of workers exposed to styrene are the two studies being presented today by Dr. Thiess and Dr. Fischbein. These reports are concerned with the mortality patterns of individuals who have worked in industries that involve environmental exposure to low levels of styrene. My presentation outlines ongoing research efforts being made by the National Institute for Occupational Safety and Health (NIOSH) in United States industries with both low and high level environmental exposures to styrene. Unfortunately, these efforts have not as yet progressed to the point where analyses and results are available.

Potential harmful effects associated with exposure to styrene have been noted in the literature for years. It was not until leukemia cases were reported in styrene-butadiene rubber (SBR) plants in

[1] National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Industry-Wide Studies Branch, Robert A. Taft Laboratories, Cincinnati, Ohio, U.S.A.

the United States in March of 1976 that NIOSH focused its attention on the possible carcinogenicity of styrene. Almost simultaneously with NIOSH's decision in 1976 to study the SBR industry, a number of articles appeared concerning the possible mutagenicity and carcinogenicity of styrene and its metabolites.

Styrene is known to be metabolized to styrene oxide (2), which was shown by several authors to be mutagenic in the Ames microbial test system (5, 10). Finnish researchers reported that an unidentified styrene metabolite was positive for microbial mutagenesis after activation of styrene by liver microsomes (16). The mutagenesis of a styrene metabolite indicates that styrene exposure may be related to carcinogenesis since 90 % of the carcinogens, identified through various animal test systems, studied by the Ames tests have been shown to be mutagenic (6).

The eight malignancies of the hematopoietic and lymphatic systems among SBR workers were of particular concern in view of a previous study reporting a "statistically reliable" decrease in the amounts of blood hemoglobin, erythrocytes and thrombocytes in rubber processing plant workers (1). Additionally, a separate preliminary epidemiologic study of workers exposed primarily to styrene discussed what appeared to be an excessive percentage of deaths due to leukemia and lymphomas. This latter finding must be tested further because the deaths were identified from a worker population with potential concomitant exposure to benzene and other recognized chemical hazards (4).

The possibility that exposure to styrene may be associated with leukemia and other forms of cancer could represent a serious occupational health problem. In the United States alone, it is estimated that 4,082,400 t of styrene were produced in 1977 with an estimated 500,000 workers occupationally exposed to this substance. Thus, NIOSH decided to pursue further the question of human carcinogenicity of styrene by studying employees in the reinforced plastics industry where there is much greater potential for styrene exposure than in the SBR industry and not nearly as many confounding chemicals.

EPIDEMIOLOGIC INVESTIGATION IN THE STYRENE-BUTADIENE RUBBER INDUSTRY

Styrene-butadiene rubber (SBR) is the most widely used synthetic rubber in the world. The United States Government foresaw shortages of natural rubber during World War II and financed construction of fifteen SBR plants, sixteen butadiene production facilities and five styrene plants. Between 1946 and 1955, these plants were sold to various private companies (12).

In January 1976 two men employed at adjacent SBR facilities in Port Neches, Texas, died of leukemia. This information, combined with knowledge of other leukemia cases at the two SBR plants, began to concern the local Oil, Chemical and Atomic Workers' Union representatives, who in turn relayed this concern to the company. Consequently, local company officials reviewed plant records and identified eight leukemia cases among employees within the past few years. This apparent excess prompted the company officials to request that NIOSH investigate the possibility of an association between employment in SBR production and the development of leukemia or related malignancies.

Simultaneous with NIOSH becoming aware of leukemia cases among workers at SBR facilities, McMichael et al. (7) from the University of North Carolina's Occupational Health Studies Group reported the cause specific mortality experience among a cohort of 6,678 male rubber and tire manufacturing workers and various subgroups of that total population (broken down by occupational job titles). A relative risk for lymphatic and hematopoietic malignancies of 6.2 was reported for a synthetic plant, a work area that included production of elastomers, particularly SBR. In a subsequent unpublished report (entitled "Toxicologic, Industrial Hygiene and Epidemiologic Considerations in the Possible Association Between SBR Manufacturing and Neoplasms of Lymphatic and Hematopoietic Tissues") by McMichael et al. the relative risk for hematopoietic and lymphatic systems was reduced to 2.4 based on a case-

Table 1. Observed leukemia initially reported among currently employed, retired or pensioned SBR workers.

Case	Duration of employment	Beginning date of employment (year)	Date of death (year)	Age at death	Cell type[a]
1	19	1950	1971	62	Lymphocytic leukemia
2	20	1955	1976	46	Acute myelogenous leukemia
3	21	1958	Alive	—	Lymphocytic leukemia
4	25	1951	1976	59	Acute myelocytic leukemia
5	17	1943	1972	77	Acute lymphoblastic leukemia
6	28	1943	1971	64	Myelocytic leukemia
7	25	—	1978	52	Acute myelocytic leukemia
8	23	1943	1967	65	Acute myeloblastic leukemia
9	22	1943	Alive	—	Chronic lymphatic leukemia

[a] Diagnosis based on company record.

Table 2. A typical SBR recipe (part per 100 parts monomer).

Ingredient	Quantity
Butadiene	75.0
Styrene	25.0
n-Dodecyl mercaptan	0.5
Paramenthane hydroperoxide	0.10
Sodium formaldehyde sulfoxylate	0.10
Soap flakes	5.0
Water	180.0

control study at the same plant, but was still statistically significant.

In addition to the eight leukemia cases initially identified by the companies, another case was identified by NIOSH shortly after it initiated the study. Table 1 presents basic information on these individuals, as well as their specific cell type of leukemia. It is important to remember that these initially observed diagnoses are based on company records and that some of these may be assigned different International Classification of Disease Codes when all of the information on the death certificates is considered. Additionally, it is known that case number five was treated for recurring respiratory infections with a drug which has been linked with blood dyscrasia and that case number nine had potential short-term exposure to benzene while he worked on an experimental project. Eight of these nine cases were diagnosed after 1971. These cases were identified from company health records which were available only on active, retired, or pensioned employees. Therefore, the health status of terminated employees, the largest segment of people who have worked at the plants, remains to be evaluated.

The two SBR plants in Port Neches, Texas, were selected for study so that the potential of a health risk in these two plants could be evaluated and the salient question of potential health hazards associated with SBR production could be addressed. The method of study chosen for this investigation was a retrospective cohort mortality design. The population, composed of approximately 5,600 workers, represents a large stable work force for which adequate personnel records are available. Later this year data collection on all members of the study population should be complete, and analysis can begin.

Process and chemical hazards

Styrene-butadiene rubber is a copolymer of styrene and butadiene. It is made through an emulsion polymerization process. An emulsion system normally contains water, monomers, initiator, and foam (12). An initiator system which usually contains paramenthane hydroperoxide and sodium formaldehyde sulfoxylate is used in combination with a mercaptan to polymerize butadiene and styrene. A typical SBR recipe is found in table 2. The styrene butadiene, soap, and initiator are pumped continuously from separate storage tanks into and through a series of agitated reactors maintained at proper conditions such that the required degree of conversion is reached at the exit of the last reactor (12). The termination of the reaction is caused by addition of a "shortstop' such as sodium dimethyldithiocarbamate or sodium polysulfide. The "shortstop" reacts rapidly with free radicals and oxidizing agents and thus destroys any remaining initiator and prevents the formation of new chains. The unreacted monomers are recovered, first the butadiene by distillation and then the styrene by steam stripping. An antioxidant, such as a mixed alkylated diphenylamine, is added to protect the product from oxidation. The latex is partially coagulated with brine and then fully coagulated with dilute sulfuric acid. The coagulated crumb is then washed, dried, and baled for shipment (12).

Representative employee 8-h time-weighted average exposures to styrene and butadiene for specific job classifications in one of the SBR facilities are depicted in table 3. The United States threshold limit values for exposure to styrene and butadiene are 100 ppm and 1,000 ppm, respectively. It is readily seen that exposures to both chemicals are low when compared with existing United States standards.

Other chemicals used in SBR production have also been associated with a carcinogenic risk. Phenyl-beta-napthylamine was historically used as an antioxidant at some SBR facilities. This chemical has been demonstrated to be metabolized in the body to beta-napthylamine, a known human bladder carcinogen. Another example is the extender oils used in approximately 70 % of SBR production (11, 13). Furthermore the Oil, Chemical, and Atomic Workers' Union arranged for Kettering Laboratories to conduct skin painting experiments with five extender oils used at one of the SBR facilities in the United States. Preliminary results indicated a positive carcinogenic response for three of these oils in the animal test system (3). Of the recognized potential chemical hazards used in the SBR industry, only styrene has been speculatively linked with a possible risk of hematopoietic and lymphatic malignancies. However, it would be inappropriate at the present time to attribute the observed leukemia cases solely to the occupational exposure of styrene because of the complex chemical nature of this industry and the presence of other chemicals which have also been associated with cancer.

Table 3. SBR — Summary plant data of employees' 8-h time-weighted average (TWA) exposure to styrene and butadiene at an SBR facility, April 1977.

Job classification	No. of samples	Styrene				Butadiene			
		Range (ppm) (high-low)	Mean (ppm)	Median (ppm)	TWA	Range (ppm) (high-low)	Mean (ppm)	Median (ppm)	TWA
Technical services personnel	12	2.14—0.09	0.55	0.37	0.55	114.55—0.21	19.85	0.63	19.68
Production foreman	1	0.15—0.15	0.15	0.15	0.15	1.16—1.16	1.16	1.16	1.16
Head production operator	5	0.55—0.11	0.28	0.14	0.27	69.61—0.25	15.50	0.27	15.61
Production operator	24	2.14—0.12	0.38	0.16	0.39	33.21—0.23	3.30	0.30	3.41
Operator helper	3	0.16—0.14	0.15	0.15	0.15	1.81—0.26	0.79	0.30	0.77
Pipefitter	8	0.22—0.09	0.13	0.10	0.13	1.78—0.18	0.74	0.41	0.73
Electrician	5	0.13—0.09	0.11	0.10	0.11	0.34—0.18	0.22	0.20	0.22
Maintenance mechanic	17	0.81—0.08	0.17	0.12	0.18	44.38—0.19	3.15	0.34	3.39
Carpenter	4	0.11—0.10	0.11	0.11	0.11	30.60—0.20	7.80	0.20	7.73
Common laborer	17	12.33—0.10	3.00	0.61	3.12	8.22—0.17	1.52	0.44	1.63
Instrument man	3	1.44—0.09	0.65	0.41	0.64	174.14—0.17	58.62	1.56	58.58

EPIDEMIOLOGIC INVESTIGATION IN THE REINFORCED PLASTICS INDUSTRY

As stated earlier, it was decided by NIOSH that a second epidemiologic study focusing on workers with a high occupational exposure to styrene and few concomitant chemical exposures should be undertaken. Three distinct industrial settings, styrene and polystyrene manufacturing, polystyrene fabrication, and reinforced plastics production, were identified. It was determined during plant visits in these three settings that styrene and polystyrene manufacturing and polystyrene fabrication are not labor intensive and represent low potential for worker exposure. The reinforced plastics production industry, on the other hand, has a large number of workers potentially exposed to higher concentrations of styrene. Therefore, this environment probably represents the best opportunity to evaluate qualitatively any potential health risk.

The reinforced plastics industry in the United States developed during World War II with the demand for rigid materials of high strength and low weight. This industry has rapidly expanded from a production level of 3,402 t of reinforced plastics in 1945 to an estimated 795,614 t in 1977. It has been projected that this industry will continue to expand at an average annual growth rate of 15 % through 1981 (14). The Reinforced Plastics and Composite Institute of the Society of Plastics Industry has estimated that between 60,000 and 120,000 people work in the U.S. reinforced plastics industry.

After the various processes used to make reinforced plastic products within the United States were evaluated, the reinforced plastics boatbuilding process was selected for study. This process was selected because of its relatively long operational history compared to most reinforced plastic processes and because of the high potential for worker exposure to styrene.

Method of study and efforts to identify cohort

The epidemiologic method which will be used in this study is the same as that used in the study of the styrene-butadiene rubber industry — a retrospective cohort mortality study. The reinforced plastic boatbuilding industry did not begin full operation until the mid to early 1950s and tends to be comprised of modest-sized operations (facilities with 200 to 300 employees or fewer). Before a statistically meaningful number of person-years at risk can be obtained, the working population from several facilities with a relatively long operational history will need to be included in the study. Additionally, these person-years at risk must have occurred long enough in the past to allow for clinical manifestatior of any chronic health problems associated with occupational exposure.

The preliminary field visits were made to the larger boat manufacturing facilities in the state of Washington. Based on the information gathered at these plants, it has been determined, so far, that the workers from two facilities could be identified and included in the study population. The number of production workers currently employed in one of these plants is approximately 290 and has grown constantly since the start of the operations in 1952. The other facility began operation in the mid 1950s with a work force that has steadily expanded over the years to a current population of 485 individuals. To increase the size of the cohort, additional boatbuilding facilities are being identified for inclusion in the study.

Process and chemical hazards

Before the manufacturing process can be initiated, a prototype hull or deck which is made of wood, fiber glass, and resins is produced. The prototype is an exact duplicate of the reinforced fiber glass boat which is to be produced. This prototype is used to make a mold by building up layers of fiberglass cloth and polyester plastic on its surface.

The interior surface of the mold has the exact shape of the exterior of the boat being built. The mold is waxed on the inside before the manufacturing process starts. The manufacturing process begins with a worker spraying the inside of the mold with a substance known as gelcoat, which makes up the smooth solid surface of the boat's exterior. Next, layers of fiber glass and polyester resins are applied by spray gun and by hand. The reinforced fiber glass is rolled, brushed, and squeegeed to work out airpockets and other imperfections. At this point the structure of the hull and deck has been formed. The resin and fiber glass are cured while on the mold for a prescribed amount of time, and then the deck or hull is taken off the mold and is ready for finishing (8).

The following description outlines the chemistry of the reinforced plastic process. The basic reaction is the polymerization of an organic acid and alcohol to form an ester. Styrene monomer is used in the reaction as a solvent and a reactant (8). It is a solvent because it dilutes the acid and alcohol and thereby keeps them in solution until mixed with a catalyst. Styrene is also a reactant because the soluble polymers formed by the acid and the alcohols are cross-linked (i.e., connected by styrene) to produce polymers which are insoluble in most common solvents. Prior to the formation of these insoluble polymers, the chemicals are mixed with glass fibers so that the desired end product is produced (15).

The major chemical hazard resulting from the handling and application of reinforced plastics is associated with sytrene. Styrene comprises 40 % or more of the gelcoat and the resin, and is a volatile substance under normal conditions (9). Exposure to styrene can occur through several different routes: inhalation of atomized mist from the spray gun, dermal absorption during the hand work-up of the resin and fiber glass, and inhalation of styrene vapor evaporated during the curing process.

In my concluding remarks I would like to mention several additional ongoing epidemiologic investigations which may be pertinent:

1. In the United States the Society for the Plastics Industry (SPI) is conducting a cross-sectional medical study on approximately 300 active and a few retired employees at a reinforced plastic boat plant.

2. SPI is also considering the feasibility of having a mortality study conducted in various segments of the reinforced plastics industry.

3. In addition Dr. Ahlmark from Sweden is currently conducting mortality and carcinogenic assessments of reinforced plastics workers from a number of plants. The assessments are based on national record systems and cancer registries in Sweden.

At this point, NIOSH would like to solicit any comments or suggestions on how these ongoing studies or new epidemiologic studies could better address the important questions raised so far at this conference. NIOSH is also interested in learning about any further epidemiologic research being conducted by governmental agencies, labor associations, or private industries in other countries.

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QUESTIONS AND ANSWERS

Question to Mr. MEINHARDT and Dr. FISCHBEIN

Dr. A. LEHTNIEMI: Upper respiratory tract infections are more common in employees exposed to various chemicals in the rubber and plastic industries, including styrene-butadiene-acrylonitrile; on the other hand, viral etiology has been proposed for human leukemia. Have you taken into account the frequency and type of respiratory infections among those workers who died to leukemia or lymphoma? In other words, the high incidence in leukemia could be an indirect effect related to irritative properties and not to mutagenic properties of styrene. (all "flu" will never be recorded!)

Mr. MEINHARDT: In the ongoing NIOSH epidemiologic study of SBR workers, this hypothesis has not been considered to date, but it is very interesting. Respiratory health hazards in this industry are of interest, and the analysis of mortality patterns in this investigation will pay specific attention to respiratory problems.

Dr. FISCHBEIN: The causal relationship between respiratory infections and leukemia is well known, since patients with leukemia have a decreased resistance to infectious diseases in general. This may be due to impaired function of leucocytes or impairment of immunological competence. This is a post *facto* phenomenon, however.

In our clinical, cross-sectional study there was a higher prevalence of respiratory symptoms among those with high exposure than among the workers with low exposure.

In addition there was a trend towards a higher prevalence of pulmonary function abnormalities ($FEV_1/FVC < 0.75$) among workers with higher urinary mandelic acid excretion.

With regard to the mortality study I have no information about the incidence of respiratory infections among the individuals who subsequently developed leukemia. It seems that it would be very difficult to obtain accurate data on this matter in a retrospective-prospective study. Generally, there was a very low mortality in respiratory disease in the mortality study presented (1 case observed against 7 expected).

Scand. j. work environ. & health 4 (1978): suppl. 2, 247—252

Mortality experience of styrene-polystyrene polymerization workers[1]

Initial findings

by WILLIAM J. NICHOLSON,[2] IRVING J. SELIKOFF[2] and HERBERT SEIDMAN[3]

NICHOLSON, W. J., SELIKOFF, I. J. and SEIDMAN, H. Mortality experience of styrene-polystyrene polymerization workers: Initial findings. *Scand. j. work environ. & health* 4 (1978): suppl. 2, 247—252. A group of 560 individuals has been identified as employed on 1 May 1960 with at least five years seniority in a plant manufacturing styrene and polystyrene. In this plant workplace exposures included styrene, benzene and ethylbenzene, among other materials. All of the 560 individuals have been traced through 1975 and their vital status determined. Expected and observed deaths, by cause, were determined from 1 May 1960 or the tenth anniversary of employment in the plant through 31 December 1975. Over this relatively short period of time a deficit of deaths compared to that of the general population was observed (106.41 expected versus 83 observed). Among the 83 deaths, one was of leukemia, one of lymphoma and an additional death was accompanied by leukemia. A review of 361 additional death certificates revealed five additional cases of leukemia and four of lymphoma. The available information from the limited follow-up in time of the cohort and from the randomly collected death certificates, while suggestive of a possible risk, is not definitive.

Key words: benzene, leukemia, lymphoma, mortality, polystyrene, styrene.

After the recognition in 1974 that exposure to vinyl chloride posed a significant human carcinogenic risk, producing liver hemangiosarcoma and the other malignant tumors (3, 5, 6), attention was directed to other widely used plastics in which monomer exposure to workers or the general population could be of significance. Among such monomers was styrene (vinyl benzene), widely used in the production of polystyrene, which has a chemical structure with similarities to that of vinyl chloride. Of additional concern was the possibility that worker exposure to benzene, a leukemogenic agent, could occur in the production and purification of styrene monomer. Furthermore, a potential for styrene exposure to the general population exists, albeit at considerably lower concentrations than those of the workplace. Such exposures could result from the leaching of unreacted styrene from food and beverage containers and from the combustion of polystyrene products. This latter source is of importance because polystyrene decomposes under heat to its monomer.

More recently, data have been presented that suggest styrene may be carcinogenic, producing leukemias and lymphomas (1, 4). This possibility follows the finding in 1976 of eight cases of leukemia in two styrene-butadiene production facilities in Texas, and a stated increase in deaths from

1 This paper was presented by Dr. Alf Fischbein.

2 Environmental Sciences Laboratory, Department of Community Medicine, Mount Sinai School of Medicine, New York, N.Y., U.S.A.

3 American Cancer Society, New York, N.Y., U.S.A.

leukemia and lymphoma in an Ohio styrene-butadiene rubber manufacturing plant. Of the eight cases six wer among a group of 146 known deaths and two were under treatment or in remission.

For the investigation of whether health effects can be associated with styrene production and polymerization, a clinical survey and a mortality study of a large monomer and polymerization plant was conducted in 1975. The findings of the clinical survey appear elsewhere in these proceedings. Here we report the results of a mortality investigation of 560 long-term workmen employed at the facility.

MATERIALS AND METHODS

Among other information, a seniority list, as of 1 May 1960, was made available by Local 8—74 of the Oil Chemical and Atomic Workers' Union, which represented employees at the facility. The list was comprised of 711 individuals, 563 of whom had five years of employment in the plant. These latter were considered for inclusion in a cohort in which each individual would be followed prospectively from 1 May 1960 or upon attaining his 10th anniversary of employment. The five-year work criteria was applied so that the group would have significant exposure to styrene, and the 10-year criteria was applied so that long-term health effects, such as cancer, could also be considered. Of the 563 individuals, three were eliminated, one because he served as a union representative beginning in 1948 and was not working in the plant on 1 May 1960, one because of death prior to achieving his tenth anniversary of employment, and one, who was the sole female in the group, because different mortality statistics would be required.

Table 1. Distribution of ages and times of employment of 560 individuals at a styrene production and polymerization facility as of 1 May 1960.

Age (years)	Years since onset of work			
	5—9	10—14	15—19	All years
20—29	51	4		55
30—39	81	109	12	202
40—49	72	64	41	177
50—59	35	17	40	92
60—69	8	1	22	31
≥70		2	1	3
All ages	247	197	116	560

Table 2. Major work activity of 560 individuals during employment at a styrene production and polymerization facility.

Type of work	Number
High exposure categories	
Styrene production	56
Polystyrene polymerization and extrusion	129
Development and special products	53
Maintenance	206
Low exposure categories	
Service and utilities	116

Table 1 lists the breakdown according to seniority and age of the 560 individuals. Table 2 categorizes them according to major employment activities within the plant. The categorization of the departments according to relatively high or low exposure was made on the basis of air concentrations measured in a Health Hazard Evaluation during 1974 by the National Institute for Occupational Safety and Health (NIOSH), by worker descriptions, and by body burden of styrene metabolites measured during the course of the previously mentioned clinical survey. The air concentrations of styrene generally ranged from 5 to 20 ppm in the "high" exposure areas and less than 1 ppm in the "low" areas at the time of the NIOSH survey. However, wide excursions from these ranges occurred at specific locations. A good correlation of the presence of styrene metabolites with exposure classification is shown in the paper by Lorimer et al. (2) in these proceedings. Furthermore, while group exposures generally applied, there could be some individuals within each group who had a long-term exposure different from that of the group as a whole.

The current production operations are shown in fig. 1. Ethylbenzene is received at the plant in tank cars and reacted with superheated steam and a catalyst of iron

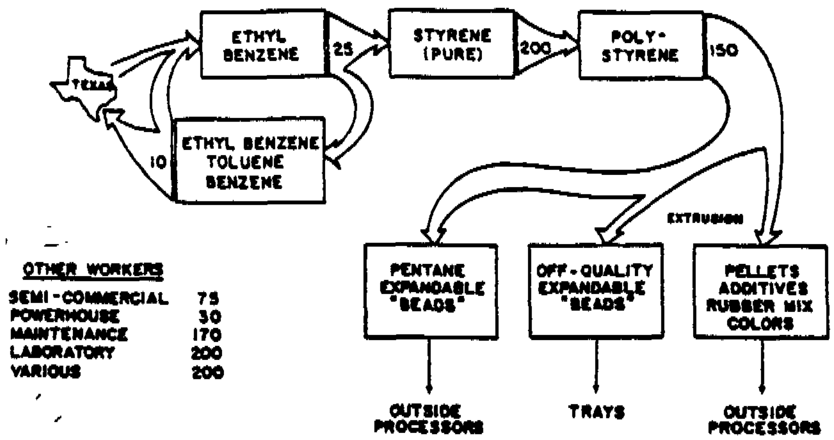

Fig. 1. Current operations and distribution of workmen in a styrene-polystyrene production facility.

oxi'e to produce styrene monomer. The crude styrene so produced is purified with the removal of unreacted ethylbenzene, benzene, toluene and xylene. These impurities are hydrogenated in another operation and distilled to separate the components for later use or distribution. Prior to 1963, benzene was produced at the plant from the by-products of coke ovens and reacted to form ethylbenzene.

In the polystyrene production, the purified styrene is reacted with water, catalysts, and various agents to produce polystyrene beads. These may later be impregnated with pentane in a closed system to form an expanded polymer. Alternatively, they may be extruded and formed into sheets. Other activities in the plant include the production of butadiene-styrene latex and pilot plant operations for research and development work on styrene polymers specific to a customer's specifications. A large maintenance force is employed at the plant and includes such trades as electricians, laborers, welders, insulators, and others. These men work throughout the plant as required, often at times of mechanical breakdown or leakage of various systems. Thus, exposure of individuals in this category could often be high. The utilities and service employees include those working in the power house and janitorial or other service jobs. Their exposures would be generally of a lower category.

RESULTS

All of the 560 individuals had been traced as of 31 December 1975, and their vital status determined. At that time, 233 were still employed at the facility, 83 were deceased, and 241 had retired or terminated employment. Each of this last group w re contacted directly for verification as a member of the cohort and for information on work acitivities. For the 83 deceased, certificates of death were obtained in all cases. Additionally, when appropriate, clinical information, radiographs, and pathological specimens were sought from hospitals. Autopsy protocols were received for 18 cases and other information for 13.

Table 3. Expected and observed mortality experiences of 560 individuals employed at a styrene production and polymerization facility prior to 1 May 1955, followed 10 years after onset of exposure (1 May 1960 — 31 December 1975).

Cause of Death	Expected	Observed
All causes of death	106.41	83
Cancer	21.01	17
Cancer of the lung	6.99	6
Leukemia	0.79	1
Lymphomas	1.25	1
Other cancer	11.98	9
Heart and circulatory diseases	56.35	52
Respiratory diseases	6.64	1
Other causes of death	22.41	13

A review of these additional data revealed that one individual, listed as deceased from pancreatic cancer on the certificate of death, actually died from acute pancreatitis.

Table 3 shows the expected and observed mortality experience, as verified for the 560 individuals from 1 May 1960 through 31 December 1975. The expected rates of death were calculated with a modified life table analysis and data on the mortality experience of the general population of the United States. The results indicate that about 79 % as many deaths as expected occurred during this period of time. Deficits of this order are commonly found in studies comparing the mortality experience of working groups with that of the general population. This deficit results, in part, because groups of employed workmen are healthier than a corresponding age group in the general population which would include individuals terminally ill and others unable to hold jobs because of disability. This "healthy worker effect" can influence total mortality data for ten or more years and that of cancer for two to five years. While the data are limited because of small numbers, some information on these expected time effects can be seen in tables 4 and 5, where the cohort mortality experience in different calendar years indicates that death rates more closely approach those of the general population as time from identification of the cohort increases. This change is also seen in an analysis of mortality patterns according to time from first exposure where the highest ratios of observed to expected deaths are found in the groups having more than 20 years since first employment.

An analysis of mortality experience by extent of exposure is shown in table 6, where maintenance and production workers are compared to utility and service employees. No particular patterns were identified in this separate mortality analysis, but again the data were limited by small numbers.

Because of the high exposure to benzene experienced by some individuals in the cohort during the 1943—1962 period of time, and to a lesser extent thereafter, special attention was paid to leukemia as

Table 4. Expected and observed mortality experiences of 560 styrene production and polymerization workmen in three calendar periods of time.

Cause of death	1960—1965		1966—1970		1971—1975	
	Expected	Observed	Expected	Observed	Expected	Observed
All causes of death	26.76	14	35.68	28	43.97	41
Cancer	4.78	2	6.87	6	9.36	9
Heart and circulatory diseases	14.01	8	18.42	18	23.92	26
Respiratory diseases	1.54	0	2.25	0	2.85	1
Other	6.43	4	8.14	4	7.84	5

Table 5. Expected and observed mortality experiences of 560 styrene production and polymerization workmen according to years from onset of employment.

Cause of death	10—19		20—29		≥30	
	Expected	Observed	Expected	Observed	Expected	Observed
All causes of death	39.78	20	59.84	59	6.79	4
Cancer	7.25	2	12.33	15	1.43	0
Heart and circulatory diseases	20.06	11	32.34	37	3.95	4
Respiratory diseases	2.30	0	3.84	1	0.50	0
Other	10.17	7	11.33	6	0.91	0

Table 6. Expected and observed mortality experiences of 560 styrene production and polymerization workmen according to work activity.

Cause of death	Production and polymerization		Maintenance		Utilities service	
	Expected	Observed	Expected	Observed	Expected	Observed
All causes of death	40.26	31	42.49	36	23.66	16
Cancer	8.17	4	8.05	10	4.79	3
Heart and circulatory diseases	20.56	20	23.22	23	12.57	9
Respiratory diseases	2.41	0	2.74	0	1.49	1
Other	9.12	7	8.48	3	4.81	3

a cause of death. While one death in the cohort was directly attributed to leukemia, a second individual, deceased of a coronary, also had leukemia at the time of death. During the course of this study, an additional 21 death certificates of individuals who died in recent years were made available to us from union files. These were of individuals that did not have five years of employment as of 1960 and were thus not included in the cohort under consideration. Among these 21 deaths, there was an additional leukemia and an additional lymphoma. Thus, in 104 deaths, there were two of leukemia, one with leukemia and two lymphomas. While the total number is small, the finding of five leukemias and lymphomas among 104 deaths suggested that further investigations of the plant mortality experience would be useful. This information was provided to the company and the union representing the plant workers. Following its receipt, the company initiated an epidemiologic study of all individuals employed for six months or more at that particular plant and supplied information on its progress to NIOSH. From information on 444 death certificates it was determined that seven deaths involved leukemia and an additional five, diseases of the lymph system. The work histories and exposures of the 444 individuals, however, were not available. The breakdown was as follows:

Acute lymphoblastic leukemia	1
Acute blastic leukemia	1
Acute myelogenous leukemia	3
Chronic lymphatic leukemia	1
Chronic myelogenous leukemia	1
Hodgkins disease	3
Lymphosarcoma	1
Retroperitoneal lymphoma	1

Unfortunately, the small numbers and limited follow-up in time of the cohort does not provide definitive information on the risk of death from leukemia or lymphoma in this plant (other than to indicate that it was not extraordinary). Similarly, available information from the randomly collected death certificates, while suggestive of an excess risk, is not definitive. More extensive epidemiologic studies, over longer time periods, will be required. Such studies, however, must take into account the possible exposures to benzene in the consideration of the etiology of leukemia.

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QUESTIONS AND ANSWERS

Question to: Dr. ALF FISCHBEIN

Dr. RANTANEN: We can expect that styrene is a weak carcinogen. Your exposure time was about 20—25 years and latency time maximally 20—25 years. Could we expect that we now are registering only latency period and 10 to 20 years more are needed to show excess malignancy frequencies?

Dr. FISCHBEIN: The period of clinical latency is an important consideration in the evaluation of environmentally induced malignant disease. For certain asbestos related tumors, pleural and peritoneal mesothelioma, for example, the latency period may be very long and the tumors usually do not become clinically manifest until 30—40 years after onset of exposure. The mortality study presented did not give any conclusive evidence because of the relatively young population and short latency period. Conclusive information is urgently needed, however, in order to protect those currently exposed. Methodological approaches other than mortality studies may also contribute to the speedy solution of this problem.

Interaction and synergism between styrene and other chemicals in the work environment should also be taken into account. Both carcinogenic potential and latency period may be affected by such factors.

Comments on the statement of Dr. Rantanen in which he to *placed styrene as a weak carcinogen.*

Prof. THIESS: From my point of view there isn't any evidence that allows us to call styrene a weak carcinogen at this moment. We have experiences since 1931; that means *46 years.* We should avoid that unskilled people will take any action due to this remark of Dr. Rantanen. Our duty is to inform people but not to raise fears.

Dr. HILDEBRAND: I would like to put the remark of Dr. Rantanen into the correct perspective. You only could assume styrene to be a weak carcinogen, but up to now there is no experimental evidence for that. This is based on three other major studies which are now complete (NCJ, MCA, MALTONI) and the results, though not all conclusive, do not show any clear evidence for styrene to be a clearcut carcinogen, not even a weak one.