

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

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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

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

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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 carcinoma	1	0.141	0.132	40-44 (1/0.013)	0.013	0.226	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)	0.035
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)	0.048
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	0.363	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.

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)	13 (9) ^a	17.6 (12.2)	6.3 (3.6)	279 (339)
	(others)	(4)	(5.4)	(2.7)	(260)
280—289	} Other causes	0	0.0	6.3	0
290—389					
580—629					
680—738					
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	16 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 short, 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
<i>Malignant neoplasms</i>							
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
<i>Cardiovascular diseases</i>							
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
<i>Other natural causes</i>							
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
<i>All natural causes</i>							
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
<i>Unnatural causes</i>							
20—29	7	5,250.8	2.85	2.456	3	5,310.2	0.00048
30—39	3	6,693.6	6.990	0.429	7	+ 993.5 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.