Health Exam Findings Among Individuals Occupationally Exposed to Benzene

Jean C. Townsend, M.S.; M. Gerald Ott, M.S.; and William A. Fishbeck, M.D.

We previously conducted a cohort mortality study of 594 individuals occupationally exposed to measured concentrations of benzene. This report presents health examination findings lor a subset of 282 men from the larger group. Although slight decreases in mean total bilirubin and RBC values were detected statistically in comparing the exposed group to controls, these changes were not regarded as clinically significant. No correlations were found between peripheral blood counts and latency. duration or intensity of benzene exposure. Presently we have no indication from our data of adverse effects of benzene having occurred in our subset. Variation in latency among individuals and the possibility of subtle changes effecting an eventual pattern contribute to the need for continued surveillance.

Effects of chronic benzene poisoning in man are related predominantly to the hematopoietic system of the body. however, central nervous and gastrointestinal involvement may also occur.[1-4] Thus, symptoms such as headache. dizziness, weakness, fatigue, insomnia. anorexia. nausea or vomiting mav or mav not appear in conjunction with blood changes. Variation in individual susceptibility is considerable and manifestations of chronic poisoning have not been predictable.[1,5] Recorded blood abnormalities associated with benzene toxicitv include leukopenia. thromhocvtopenia. macrocytosis. aplastic. anemia and leukemia: pathological effects on the kidnevs and liver have also been reported.[1,5,6]

Vigliani and Forni[7] have suggested that leukemia associated with benzene is frequentlv preceded bv a hyporegenerative anemia or pancytopenia of more or less longstanding. However. these authors reported one case in which the leukemia occurred 14 years after the initial anemia with apparentlv normal blood counts in the interim period. Also pertinent to the question of latency is evidence of chromosomal aberrations in circulating lymphocytes of persons several years after exposure to benzene and subsequent recovery.[8,9]

Historicallv. the postulated relationships between clinical findings and benzene exposure have been based on individuals exposed to apparentlv very high Concentrations of benzene. The lack of long-term environmental monitoring has been evident. and has contributed to the difficulty of extrapolating findings to lower exposure intensities.

The purposes of this study were (1) to examine rrccnt laboratorv and health history data on 282 employees with respect to latencv. duration. current intensity, and cumulative dose of benzene. and (2) to discuss these findings as thev relate to the mortalitv experience of the same target population. The individuals hid experienced potential exposure to benzene ranging from < 2 ppm time weighted average (TWA) to approximately 30 ppm TWA for an right-hour day for periods of from less than one year to 20 years or more.

Environmental Considerations

The chemical operations covered hv this investigation were grouped into three production areas: Production Area I: Chlorobenzol. date of operation 1920 to present: Production Area II: Alkvl benzene. date of operation 1935 to present; and. Production Area III: Ethyl rcllulose. date oi operation 19.36 to present. These process areas were selected because past exposures in at least several job classifications within each area exceeded 2 ppm TWA. Research and development laboratories and other production units with undefined exposure at this companv location were not included in the study.

Benzene was utilized as a raw material in the first two production units whereas. in ethyl cellulose. it was employed as a solvent. TWA estimates of benzene exposure for each job in all production areas were based on environmental measurements, process flow sheets and job descriptions provided by industrial hygienists and plant operating personnel. Everv job was evaluated on a year-by-vear basis and assigned to one of the following four intensitv categories: < 2 ppm TWA; 2-9 ppm TWA: 10-24 ppm TWA; and 25+

From Dow Chemical U.S.A., Michigan Division, 607 Building, Midland, MI 48640

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ppm TWA. The four categories were determined in advance from knowledge of the ranges of exposure that had existed in these production units.

A summary of industrial hygiene monitoring data for the period 1944 through 1974 is reported in a mortality study concerning these production areas.[12] Table 1 presents the measurements of benzene concentrations in a condensed format.

In Production Area I benzene was chlorinated to produce mono- and di-chlorobenzenes. in a closed continuous system. It was recognized as a potential hazard during initial chlorination. Other operations in the plant included the separation of unreacted benzene for recycling and further chlorination. Mono-, di-, tri-. and tetra-chlorobenzenes were also found routinely in the work environment. Benzene concentrations in this work area were below 10 ppm TWA. The rule for categorizing jobs by exposure was as follows: Low exposure (2-9 ppm TWA) — Mechanics. chlorinator operators and still operators in the first chlorination cycle. Very low exposure (< 2 ppm TWA) — All other jobs in the production area.

Historically. less industrial hygiene monitoring for benzene took place beyond the first chlorination cycle because of the unlikelihood that exposures would exceed accepted guidelines. In 1973 exposure intensities of up to 4.6 ppm TWA were reported outside the initial chlorination area (Table 1). It should be noted that these estimates were based on measurements taken in new production facilities.

Production Area II began as a semiplant operation for ethylbenzene production. This operation was expanded in 1937 when demand for styrene increased. The benzene was alkylated with ethylene to produce ethylbenzene and diethylbenzene. In a second process benzene was alkylated with propylene to produce isopropyl benzene. After 1943 these processes were located in different building. Dehydrogenation, which took place in a separate process area. led to the end products styrene. divinylbenzene. and alpha-methyl styrene. As in the first production area, the processes were closed continuous systems. Potential for highest exposures occurred in the benzene unloading areas and during sampling of process lines. The following materials considered to be of toxicological importance were known to be regularly present in Production Area II: benzene, ethylbenzene, divinylbenzene. toluene. xylene. isopropyl benzene. styrene. diisopropyl benzene and alpha-methyl styrene. The exposure categorization rule with respect to benzene is summarized for jobs in Production Area II in abbreviated form: High exposure (25+ ppm TWA) — Operating and maintenance jobs in the ethylbenzene process prior to 1943. Moderate exposure (10-24 ppm TWA) — Operating jobs. ethylbenzene. 1943 to 1960: maintenance mechanics, ethylbenzene unit, 1943 to 1971: operating and maintenance jobs. propyl benzene unit. 1943 to 1968. Low exposure (2-9 ppm TWA) — Operating and maintenance jobs. dehydrogenation unit, 1973 to present: miscellaneous jobs in propyl and ethylbenzene over varying time periods since 1943. Very low exposure (< 2 ppm TWA) — Clerical and supervisory jobs in all areas, and several operating jobs in dehydrogenation.

Production Area III consisted of a process that produced ethyl cellulose resins and a second process where. up until 1968, sheets of ethyl cellulose were fabricated. The resin process began by treating cellulose rolls with caustic and reacting the treated material with ethyl chloride in the presence of benzene. The product was washed repeatedly and then dried before packaging. High benzene exposures occurred during sampling and also during lading and unloading of batch reactors. In the past, exposure in excess of 25 ppm TWA did occur for several jobs within the production unit: over the last ten years. exposure intensities have not exceeded 10 ppm TWA.

The highest exposures to benzene occurred in the sheeting operation. where adjustments on the casting equipment required entry into an enclosed area. Surveys in 1953 and again in 1963 indicated TWA exposures to benzene above 25 ppm for men in several job classifications. The benzene exposure categorization rule for the ethyl cellulose units is as follows: High exposure (25+ ppm TWA) — Operating, maintenance jobs in production and sheeting until 1965. Moderate exposure (10-24 ppm TWA) — Lab technicians and selected operating jobs until 1966. Low exposure

Table 1. — Summary of Industrial Hygiene Measurements of Benzene Concentrations in Production Areas.

Job Categories	Years of Survey	Number of Area and Breathing Zone Samples per Job	Range of Samples (ppm Benzene)	Estimated TWA (ppm Benzene)
Chlorobenzene				
Job not specified	1944 48	43	0 259	
Jobs in initial chlorination	1965	25	2 3 9	< 1 to 3
and distillation	1913	18 24	1 62	4 to 6
Other jobs in area	1964	1 7	0 2 I	< 1 io I
	1913	3 39	1 42	< 1 to 4
Alkyl benzene				
Alkylation operators	1953	5 25	0 > 100	9 to 11
(across production units)	1965	2 36	0 56	I to 7
	1971 72	39 135	0 283	< I io 13
Mechanics	1965	3 5	0 250	1 io 10
(across production units)	1971 12	30 94	0 283	1 to 14
Other jobs in production units	1965	239	0 55	1 to 5
	1971 12	13 195	0 74	< 1 to 5
Ethyl Cellulose				
Jobs in manufacturing	1952	13 25	0 > 100	17 to 35
	1965	4 24	2 515	5 to 17
	1973	25 38	1 321	3 io 4
Jobs in fabricating	1953	9	10 937	35
	1965	continuous monitoring with infrared analyses	0 > 100	11 to 32

*Indicates TWAs were not estimated

(2-9 ppm TWAI — Jobs downstream from sections using benzene directly throughout the time period. and high exposure area jobs after 1965. Very low exposure (< 2 ppm TWA) — lobs in production area removed from sections of the process utilizing benzene (1935+). Ethyl chloride. ethyl ether. and ethyl alcohol were also present in the work environment on a routine basis in Production Area III.

In all areas. TWAs reflect average exposures for employees on a given job. rather than those particular to an individual whose work practices mav differ from the norm. By combining the environmental assessment with complete work historv information for each emplovee. it was possible to determine latencv and duration of exposure and to estimate cumulative dose and intensity of benzene exposure.

Methods

Since 1967. a health examination program has been offered to all employees at the Midland. Michigan location ot Dow Chemical. U.S.A. The time required for the program to cvcle through the entire manufacturing complex is approximately two years. Data used in the present studv were derived from existing records oi health examinations conducted during the period February 1967 to March 1974. Although there were modifications in the questionnaire and in the specific laboratorv test5 periormed over the seven-year period. the basic structure of the program has remained unchanged. For each benzene exposed emplovee the most recent exam was utilized in the analvsis so that possible latent or chronic effects ot benzene could hc screened.

In addition *to* relevant health historv questions. the following quantitative health measures were studied: Blood chemistries — total bilirubin. creatinine. total protein. protein albumin. protein globulin. blood urea nitrogen (BUN). LDH. and SCOT. Hematology — hematocrit. hemoglobin. WBC. RBC. MCV. MCH. and MCHC.

A control population for comparative purposes was selected using a matched pairs design. Over 19.000 health inventorv exams were given emplovees during the period ot studv. A control for each exposed emplovee was chosen according to the following criteria: (1) The control participated in the health inventorv program during the same month as the exposed individual. (2) The pairs belonged to the same five-year age interval. (3) Cigarette smoking historv ot the control agreed with that of the exposed individual (current smokers: < 1 pack/dav: 1+ packs/days; former smokers; and never smoked). (4) Among potential control employees. the individual whose hire date was nearest the hire date of the exposed emplovee was selected.

Individuals in the control population mav have experienced exposure to a variety oi chemicals exclusive of benzene. These exposures would he expected to differ trom person to person and would also he expected to parallel background exposures of the study population during the years these persons were employed outside oi benzene areas. In addition to overall matched pair comparisons. the health measures. expressed a~ pair differences. were examined in relation to estimated dose current exposure index highest TWA exposure snd duration ot benzene exposure using a multiple regression approach. The current and highest TWA exposure intensities were expressed in coded form: 0 for not exposed: 1 for < 2 ppm: 2 tor 2-9 ppm: 3 tor 10-24 ppm: and 4 for 25+ ppm benzene. Estimated current exposure intensities at the time oi examination did not exceed 10 ppm TWA for anv ot the individuals in the studv. Hematological data were also compared with laboratory findings reported bv a nonchemical companv.

The cohort for the mortality study included all persons who appeared on annual emplovment lists (1938-1970) of the benzene work areas. The present study covered only those perrons irom thr mortalitv cohort who were still working for the companv as oi 1967 and who participated in the health examination program after their first benzene exposure and prior to March. 1974. Table 2 summarizes the employment status of the original cohort as of Januarv 1967 .and as of January 1974. and identifies the number oi emplovees participating at least once in the health screening program during this period. Health examinations were given to 482 persons (47% of the original cohort). This coverage mav be tvpical of situations where manufacturing units date back many years and indicates a potential shortcoming of cross-sectional sampling'in occupational settings.

Results

The age distribution of men participating in the studv is weighted heavily toward older age groups. as would be expected from the method used to define the population. At the time of examination. the average age of benzene exposed and matched control individuals was 48.4 and 48.3 years respectivelv. Of the exposed employees. 209 (74%) were 45 years of age or older.

Table 3 describes the benzene exposure experience of the cohort by duration. estimated career dosage. and latencv (years between first exposure and examination date). The information is summarized by production area. highest TWA exposure for 1+ months. and current versus past exposure. Currently exposed individuals had worked in benzene areas longer. on the average. than past exposed employees and thus median career dose was larger for this group. The low median career dose among Production Area III employees was also due to short exposure durations.

The means and standard deviations of 17 selected lab measures are shown in Table 4 for the total exposed and matched control groups. Statistically significant differences were observed for total bilirubin and red blood cell counts. In each instance. the mean of the benzene group was lower than the controls. Particular attention was paid to the hematological tests. The distribution of red and white blood cell counts and hematocrit values of the exposed and control groups are seen in Fig 1. The graphs are plotted according to percentage of participants whose values fall within the various intervals. with resulting probability densities. The distributions of exposed and control emplovees are similar except for the RBC counts. where the exposed group shows a slight shift toward lower values.

Clinical records were reviewed for those individuals in the exposed population with unusually high or low readings. One person had a WBC-count of over 19,000 on his health inventory dated 6/28/73; a repeat count on 8/16/73 was 10,700. The employee's record revealed a history of chronic sinusitis and WBC's con-

Table 2. — Employment Status and Participation in Health Exam Program Between 1967 and March 1974 by Production Area. Benzene Cohort.

Employment Status and Participation in Health Exam Program	Total	Number of Employees: Production Area I	Production Area II	Production Area III
Total cohort	594	120	153	321
Left company prior to 1967	239	37	62	140
Working as of 1/1/67	355	83	91	181
Working as of 1/1/74	254	54	66	134
Participated at least once in health exam program 2/67-3/74	282	68	76	139

Table 3. — Selected Measures of Exposure by Production Area and Level of Highest TWA Exposure Intensities. Health Exam Participants:

	No. of Employees	Duration of Exposure				Exposure Dosage (grams*)		Years Since First E	
		< 1 yr.	1-9 yrs.	10-19 yrs.	20+ yrs.	Mean	Range	Mean	< 1-40 / < 1-38
Total group	282	50	129	4[illegible]	52	1298	1 6994	20 2	1-40
Currently exposed	1 IB	2	36	22	58	1336	1 6798	19 3	4-38
Past exposed	164	48	92	20	4	443	1 6994	20 8	2-36
Production Area I	58	5	2s	14	24	403	1-1338	21 7	
Production Area II	75	8	33	10	25	892	7-4636	21 1	
Production Area III	I38	31	10	18	13	704	1 6994	I8 9	4 1-40
Highest TWA benzene exposed for 1+ months									
25+ ppm	71	10	27	13	21	1605	4 6994	25 5	8 40
10 24 ppm	35	5	16	4	10	963	4 3145	22 6	4-37
4 10 ppm	I76	35	85	25	31	256	1-1338	16 9	4 1-31

*1000 ppm months exposure equivalent to 670 grams assuming 21 working days per month and that a workman breathes 10 cubic meters of air per 8 hour day

sistently ranging from **9,000** to 10.300 preceding the employee's first exposure to benzene. and extending well beyond his last benzene exposure.

A second emplovee had a hematocrit reading of 29% and a hemoglobin of 10.2 grams in **1970.** with referral to his family physician. (His record also showed **anemia** secondary to gastrointestinal bleeding when hired in March 1967). Subsequently. he was diagnosed with idiopathic thrombocvtopenia purpura. His job of three months' duration in the benzene area (11/67-2/68) was classified as low. and was judged not to be related to the clinical condition.

Multiple regression analvses performed for each lab measure bv regressing the lab response on the four environmental variables separatelv for each production area. and for the production areas combined. are summarized in terms of statistically significant associations in Table 5. In this analvsis. the lab response was the observed reading of the exposed individual less his matched control. None of the hematological measures were significantly correlated with anv environmental variable. The two lab measures for which associations were observed in the total cohnrt were not correlated with environmental variables in more thin one of the individual production areas. In Production Area II, cumulative dose was highly correlated with duration of exposure (r = .75) and current TWA intensity (r = .49). Thus. duration of exposure and current TLVA intensity were individually associated with total bilirubin. for example. although neither added significantlv to the regression equation after cumulative dose had been taken into account.

Health history items were utilized tn indicate individuals who may have had pertinent conditions in the past. The review of specific medical records was undertaken for persons responding positively to a history of (1) anemia or blood problems: (2) cancer or malignant growth: (3) fits, convulsions, seizures; or (4) loss of memory. No results of interest in regard to benzene toxicity were found among the latter three health history questions.

Six persons in the benzene group reported a history of anemia or blood problems. Company medical records on four of these showed no evidence of anemia — three employees were taking medications for cardiovascular problems at the time of exam. and the fourth had a hemophiliac condition known to the company since 1957. The fifth employee had a history of blood counts which hive fluctuated between normal and slight decreases since 1951. Hemoglobin values have ranged from **12.9** g to 15.5 g. hematocrit from 38.5% to 46%. and WBC from 3.600 to 5.150. This person began working at our company in **1941.** His potential benrent? exposure included 34 months in the high category (+25 ppm), 300 months in moderate (10-24 ppm), and 60 months in low (2-9 ppm). He retired in February 1974 at the age of 62 years; one month prior to this time. his hemoglobin value was 13.5 g. hematocrit 40.1%. and WBC 4500. A 1976 report irom his personal physician indicated this individual to hc in good health.

The sixth person was referred to his family physician in 1971 with an increased white cell count. He was subsequently diagnosed with hypertension and mild diabetes: the increased white counts were presumed to be the results of a splenectomy performed on the employee after an automobile accident in 1969.

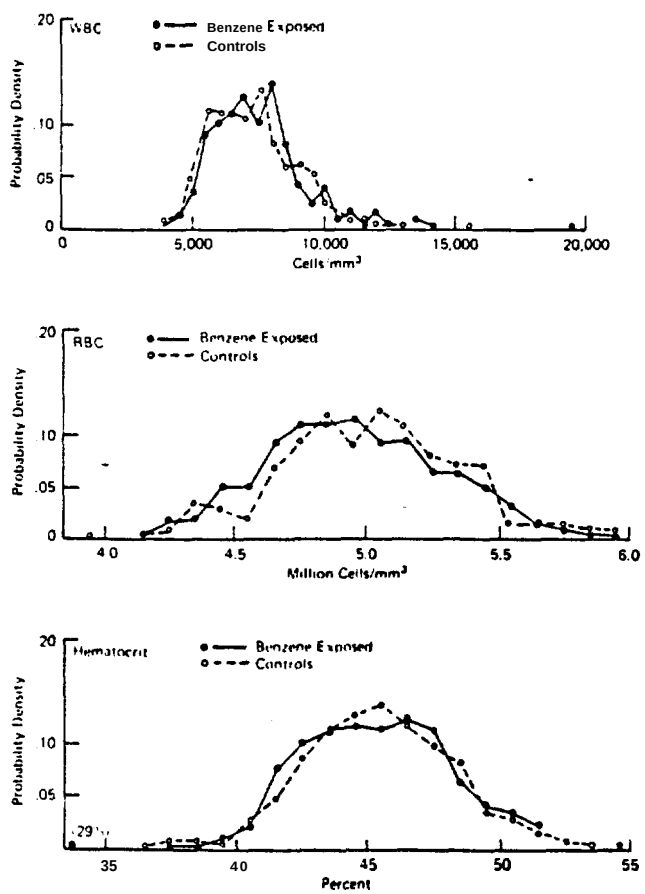

Fig 1 — Distribution of WBC, REC and hematocrit readings for total exposed and matched control populations.

Table 4. — Comparison of Benzene Exposed Population with Matched Controls for 17 Selected Laboratory Tests. 1967-1974

Test Procedures	No. of Pairs	Benzene Group (M ± SD)	Control Group (M ± SD)	Benzene Group Less Controls (M ± SD)
Blood chemistries				
Total bilirubin mg%	255	.44 ± .76	.48 ± .24	-.01 ± .38 (P < .05)
Creatinine mg%	218	1.20 ± .18	1.19 ± .19	.01 ± .24
Total protein gm%	224	7.12 ± .36	7.16 ± .39	-.04 ± .51
Protein albumin gm%	224	4.33 ± .51	4.36 ± .52	-.03 ± .55
Protein globulin gm%	224	2.79 ± .54	2.80 ± .49	-.01 ± .62
BUY mg%	241	17.3 ± 4.3	17.0 ± 4.3	.3 ± 5.8
LDH units	187	162.1 ± 31.7	163.3 ± 30.1	-1.8 ± 40.8
SGOT units	189	26.3 ± 9.9	26.6 ± 12.3	.2 ± 15.0
Hematology				
Hematocrit %	290	45.2 ± 3.0	45.1 ± 2.8	-.2 ± 4.0
Hemoglobin gm	237	15.2 ± 1.0	15.3 ± 1.0	-.1 ± 1.4
WBC per mm	232	7239 ± 1910	7030 ± 1740	210 ± 2190
RBC in millions	236	4.95 ± .34	5.01 ± .35	-.06 ± .48 (If < .05)
MCV	235	91.0 ± 4.7	90.5 ± 4.7	.6 ± 5.2
HDW	236	30.9 ± 1.6	33.6 ± 1.6	.2 ± 2.0
MCHC	236	33.9 ± 1.0	33.9 ± 1.0	.0 ± 1.2

Discussion

Greenburg et al in 1939[3] and Aksov et al in 1971[11] published results of cross-sectional surveys of benzene exposed workmen somewhat comparable to the present study. These investigations involved more extensive medical evaluations, but appear to have less supporting environmental observations. Aksov's investigation was in response to cases of aplastic anemia and acute myeloblastic leukemia detected among shoemakers in Istanbul. Greenburg studied benzene exposure in the rotogravure printing industry.

A major difference between the Greenburg study and the current investigation lies in the exposure patterns experienced by workers in the two situations. Exposures in the pressrooms had been occurring for a maximum of five years at concentrations presumably much higher than those experienced in the present study of chemical plant employees. Greenburg recognized and stressed the limitation of not knowing an individual's specific exposure experience due to variable work practices and the use of benzene to remove ink from hands and arms. In turn, the current study included many individuals exposed to benzene for more than 20 years at concentrations below 10 ppm TWA in recent years. Unfortunately, TWAs were not calculated for pressroom workers, thereby limiting comparisons of exposure intensity. In the Aksov study the concentration of benzene in the workplace reportedly ranged from 30 to 210 ppm, with employees' exposure durations varying from three months to 17 years.

Contrasts in medical findings between these previous studies and the present study indicate a further likelihood of considerable differences in exposure intensities. Significant results were observed by Greenburg in regard to hemoglobin, hematocrit, and WBC — none of which were found in our study. Findings for serum bilirubin were statistically significant in opposite directions between the two studies. Only with RBC did the results relative to controls deviate in the same direction. These deviations were much larger in the rotogravure printing industry study: mean difference in RBC estimated at .84 million cells versus .09 million cells for currently exposed individuals in the present study.

In the Aksov study of 217 persons, ranging in age from 12 to 58, 23.5% were reported to have hematological abnormalities attributable to chronic benzene poisoning. The incidence of persons showing hematological changes was not related to duration of employment. WBCs of less than 4,000 cell/mm³ were found for 21 persons (9.7%) by Aksov and for only one person (.4%) in the present study. Hemoglobin and hematocrit readings were not compared between the two studies since Aksov mentioned the anemia he observed could have resulted from poor nutrition.

In the present study neither the RBC counts nor other hematologic parameters were found to correlate with current TWA exposure intensity, highest TWA intensity, duration of exposure, or estimated career dosage. The hematological results for the exposed and control groups agreed well with those published by Frederik[14] based on multiphasic health screening of New York Telephone Company employees. The findings were similar both in terms of means and standard deviations. Although significant individual regressions were observed for other lab measures, no consistent pattern suggesting a clinically meaningful relationship to benzene exposure was apparent.

Individual records were assessed of persons with hematologic values outside the normal ranges and of those who answered positively to anemia or blood problems and other pertinent questions. No findings were observed that could be related to potential benzene toxicity.

Our mortality survey of the same production units covered the years 1940 through 1973. In that study the overall standard mortality ratio (SMR) was 80 (102 observed deaths versus 128 expected deaths). No statistically significant increases in mortality,

Table 5. — Summary of Statistically Significant findings (P < .05) for Regression of Each Lab Test (Matched Pair Differences) on Current TWA Exposure Intensity Category, Highest TWA Intensity Category, Duration of Exposure and Estimated Career Dosage (ppm Months), Total Population and Each Production Area.

Test Procedure	Environmental Variable, Correlation Coefficient and Significance Level
Total population	
Total bilirubin	Current TWA .19 (P < .01)
Total protein	Highest TWA -.16 (P < .05)
Production Area II	
Total bilirubin	Cumulative dosage .34 (P < .01)
Total protein	Cumulative dosage .36 (P < .01)
Protein globulin	Cumulative dosage .26 (P < .05)
BUN	Cumulative dosage .28 (P < .05)
SGOT	Current TWA .29 (P < .05)
Production Area III	
Creatinine	Cumulative dosage .24 (P < .05)

relative to the US. white male population were observed with respect to production area or estimated career dosage of benzene. The mortality analysis did direct our attention to five individuals whose death certificates contained information of clinical interest in regard to benzene toxicity. Two deaths were due to anemia — one person died in 1955 (pernicious anemia), and the second person died in 1957 (aplastic anemia). Leukemia was indicated on three death certificates for persons dying in 1965, 1970 and 1971, respectively (one case of acute granulocytic and two cases of myelogenous leukemia). Details regarding these cases are discussed in the mortality article.[12]

The individual who died most recently from leukemia had participated in the health examination program and is included among the 282 persons in the present study. His blood counts over a ten-year period, including one as recent as ten months before death, were within normal ranges. Thus, our medical records did not indicate a prior history of blood abnormalities typical of leukemia attributable to benzene.

This health examination study indicates that readily detectable latent hematopoietic changes have not occurred in our population of employees, many of whom had past TWA exposures of 10 ppm or more. The question that remains unanswered is what is the likelihood that serious health effects (such as leukemia) will occur in individuals years after benzene exposure at concentrations as described in this article, particularly when hematologic findings were normal during the years of employment. Health surveillance of this population will be continued and perhaps will one day provide a more definitive answer to the question.

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