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NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH)
SUBMISSION OF NIOSH MANUSCRIPT
ENTITLED "BENZENE AND LEUKEMIA: AN EPIDEMIOLOGIC RISK ASSESSMENT"
TO THE
OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

29 CFR 1910
Docket No. 11-059C

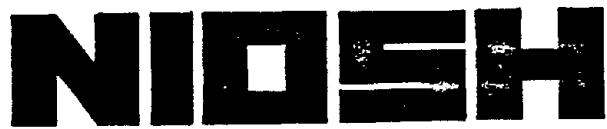
U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health
Cincinnati, Ohio

August 9, 1985

REPORT DOCUMENTATION PAGE		1. REPORT NO.	2.	3. Recipient's Accession No.
				PB 90 153776 /AS
4. Title and Subtitle NIOSH Testimony on Benzene and Leukemia: An Epidemiologic Risk Assessment by J. D. Millar, August 9, 1985		An	5. Report Date	85/08/09
			6.	
7. Author(s) NIOSH		8. Performing Organization Rept. No.		
9. Performing Organization Name and Address NIOSH		10. Project/Task/Work Unit No.		
		11. Contract (C) or Grant(G) No. (C) (G)		
12. Sponsoring Organization Name and Address		13. Type of Report & Period Covered		
		14.		
15. Supplementary Notes				
16. Abstract (Limit: 200 words) In this testimony, the mortality experience of a cohort with occupational exposure to benzene (71432) was updated in efforts to learn more about a possible connection to leukemia. Job/exposure matrices were used to derive cumulative exposure concentrations. These matrices were based on available air sampling data. The standardized mortality ratio (SMR) for leukemia was 328 and the SMR for multiple myeloma was 398. SMRs for leukemia increased from 105 in workers with less than 40 part per million years (ppm-y) cumulative exposure to 314 in workers with from 40 to 199.99ppm-y; to 1,757 in those with from 200 to 399.99ppm-y; and to 4,535 in those with 400 ppm-y or more. A 40 year working lifetime exposure at 10 parts per million was equivalent to a cumulative benzene exposure of 400ppm-y. When the boundaries of the exposure categories were varied, this strongly positive trend in SMRs remained evident. A conditional logistic regression was performed to examine the shape of the exposure/response relation. A log linear model best explained the association between cumulative benzene exposure and leukemia. It was calculated from this model that protection against benzene induced leukemia will be increased exponentially by any reduction in the permissible exposure limit.				
17. Document Analysis a. Descriptors				
b. Identifiers/Open-Ended Terms NIOSH-Publication, NIOSH-Author, NIOSH-Testimony, Millar-J-D, Cancer-rates, Mortality-data, Benzene-poisoning, Mortality-rates, Risk-analysis, Epidemiology, Risk-factors				
c. COSATI Field/Group				
18. Availability Statement		19. Security Class (This Report)	21. No. of Pages	
			41	
		22. Security Class (This Page)	22. Price	
			A03	

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Comments to DOL

AUG 15 1985

Mr. Patrick Tyson
Acting Assistant Secretary for
Occupational Safety and Health
U.S. Department of Labor
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Dear Mr. Tyson:

Enclosed for your information is a copy of a manuscript entitled "Benzene and Leukemia: An Epidemiologic Risk Assessment" by Robert A. Rinsky, et al. As you may know, Mr. Rinsky is a member of our staff. The model described in this manuscript updates and extends previously published observations of a cohort of benzene-exposed workers in which a significant relationship between benzene and the incidence of leukemia, was observed. This analysis, in my opinion, provides support for the NIOSH position that a reduction in the current OSHA PEL for benzene, is warranted.

Please feel free to call on me if you have any questions.

Sincerely yours,

J. Donald Millar, M.D.
Assistant Surgeon General
Director

1 Enclosure

This manuscript also submitted to the Environmental Protection Agency

**Benzene and Leukemia:
An Epidemiologic Risk Assessment**

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ABSTRACT

To assess quantitatively the association between benzene and leukemia, we examined the updated mortality experience of a cohort with occupational exposure to benzene, and we calculated a cumulative benzene exposure index (ppm x years) for each cohort member. Cumulative exposures were derived from job-exposure matrices. These matrices were based on available air sampling data and, in instances when no sampling data existed, on a number of assumptions about exposures for location and time period. In the cohort analysis, we found that the standardized mortality ratio (SMR) for leukemia was 328 [95% confidence interval (CI)=150-623], and the SMR for multiple myeloma was 398 (CI=107-1019). With stratification of the cohort by cumulative exposure, SMRs for leukemia were found to increase from 105 in workers with less than 40 ppm-years' cumulative exposure; to 314 in workers with from 40 to 199.99 ppm-years; to 1,757 in those with from 200 to 399.99 ppm-years; and to 4,535 in those with 400 or more ppm-years. Cumulative benzene exposure of 400 ppm-years is equivalent to mean annual exposure over a 40-year working lifetime at 10 ppm, the currently enforceable U.S. standard. This strongly positive trend in SMRs remained evident when the boundaries of the exposure categories were varied. To examine the shape of the exposure-response relation, we performed a conditional logistic regression; in this analysis, ten controls were matched to each leukemia case. A log-linear model was found best to explain the association between cumulative benzene exposure and leukemia. From this model, it can be calculated that protection against benzene-induced leukemia will be increased exponentially by any reduction in the permissible exposure limit.

INTRODUCTION

The association between benzene and leukemia was suggested in a series of case reports beginning more than 50 years ago. [Delore, 1928; Mallory, 1939; Browning, 1965; Cavignaux, 1962; Vigliani, 1964] Those clinical observations were subsequently corroborated by epidemiologic studies [Vigliani, 1964; Aksoy, 1974; Vigliani, 1976; Infante, 1977; Ott, 1978; Rinsky, 1981; Goldstein, 1983] and more recently, by carcinogenesis bioassays. [Goldstein, 1980; Snyder, 1980; Maltoni, 1983; NTP, 1983] Benzene is now generally considered by national and international scientific bodies to be a human carcinogen. [NIOSH, 1976; EPA, 1979; IARC, 1982]

To reduce the risk of leukemia in industrial workers exposed to airborne benzene, the U.S. Occupational Safety and Health Administration (OSHA) in 1978 promulgated an occupational exposure standard which reduced permissible workplace concentrations for benzene ten-fold, [OSHA, 1978] from the previously acceptable 8-hour time-weighted average (TWA) of 10 ppm in air to a new 8-hour TWA of 1 ppm. This decision was based on the qualitative demonstration of the carcinogenicity of benzene in case reports and epidemiologic studies. [OSHA, 1978].

In 1980, in a decision of profound importance for governmental risk assessment [Ashford, 1982], the U.S. Supreme Court invalidated the new OSHA benzene standard of 1 ppm. [U.S. Supreme Court, 1980] The Court stated that OSHA had failed to provide "substantial evidence" of the need for regulation in that

OSHA had not demonstrated a "...significant risk of material health impairment" at the former standard of 10 ppm. Since that decision, epidemiologic research on benzene has moved from qualitative evaluation of carcinogenicity to quantitative assessment of the dose-response relationship between benzene and leukemia. At least three quantitative assessments have recently been published. [U.S.EPA, 1979; IARC, 1982; White, 1982] Each has relied heavily upon epidemiologic studies conducted by the National Institute for Occupational Safety and Health, (NIOSH) [Infante, 1977; Rinsky, 1981] and by the Dow Chemical Company [Ott, 1978]. In each, the amount of benzene exposure has been found to correlate positively with risk of death from leukemia. All three analyses were, however, based on estimates of group exposure rather than on estimates of the exposure of individual workers. The resultant risk estimates were subject, therefore, to wide variances.

To reduce the uncertainties of those assessments, we re-examined the mortality experience of a cohort of rubber workers with previously documented exposure to benzene. This cohort is the largest of those used in the previous risk assessments, and it offers the most extensive historical record on airborne exposures to benzene. Since our previous evaluation of the mortality of this cohort, [Rinsky, 1981] the NIOSH Life-Table Analysis System has been modified to allow incorporation of data on individual exposures [Waxweiler, 1983]; previously, only duration of employment could be used as a surrogate for exposure. Also, an additional 6.5 years of observation had elapsed since the previous evaluation, allowing us to update this analysis to 1982. We report here on our quantitative analysis in this cohort of the relationship between occupational exposure to benzene and death from leukemia.

BACKGROUND

This study is based on the experience of three plants at two locations in Ohio which manufactured a natural rubber film (rubber hydrochloride). The details of the process have been described previously. [Rinsky, 1981] In brief, natural rubber was dissolved in benzene and spread on a conveyor. Benzene was then evaporated and recovered, and the resultant thin film was stripped from the conveyor, rolled, and milled to specifications. Rubber hydrochloride was manufactured at Location 1 from 1939 until April 1976. Production at Location 2 occurred in two separate plants. The first began as a research and development project; it then began commercial production in 1936 or 1937 and continued until 1949, when the second plant began operation. This operation continued until 1965. Operations at all three plants were essentially identical. In fact, both the plant at Location 1 and plant 2 at Location 2 represented expansions of plant 1 at Location 2. Although hydrochloric acid, soda ash, natural rubber, and small amounts of plasticizers were present, benzene was the only chemical in the rubber hydrochloride plants which could reasonably be associated with hematologic toxicity. The rubber hydrochloride plants were located within larger industrial facilities. Employees were likely during their working careers to have worked in areas of these facilities where materials other than rubber hydrochloride were produced.

Industrial hygiene records describing past atmospheric concentrations of benzene at the plants were available from the Industrial Commission of Ohio, the Ohio Department of Health, the University of North Carolina, NIOSH, and

company records. These records have been described previously. [OSHA Docket 1977; Rinsky, 1981] Because most of the measurements in these records were not taken to support an epidemiologic study, but rather for compliance purposes, there are gaps in the data. These gaps were filled by estimating exposures (see methods). Nonetheless, they represent an unusually complete record of past exposures for a retrospective cohort study covering this time period. They indicate that as the knowledge of the toxicity of benzene increased, (and recommended exposure levels were revised downward), the company kept pace with those revisions. Thus, for the most part, employees' 8-hour time-weighted average exposures to airborne benzene were within the standard in effect at any given time (Table 1). As is, however, characteristic of industrial processes, there were occasional excursions above these limits. A detailed description of those excursions in relation to individual exposures has been presented previously. [OSHA Docket, 1977; Rinsky, 1981]

METHODS

Estimation of Past Exposures

Detailed job history information on each employee was obtained from company personnel records. Each employee's record was reviewed to identify the department symbol which indicated work in a rubber hydrochloride (RH) plant at either location. Each unique RH job title (which was described in a short narrative on the personnel record) was then assigned a numeric code (Appendix 1 & 2). Job codes and employment dates were then abstracted for each employee who had worked in an RH department. Because of the large number of job codes in the record system (resulting from numerous variations in job titles), codes were fit to broader categories, referred to as "exposure-classes", which could be associated with specific manufacturing areas. In general, these exposure-classes represented areas in which industrial hygiene data had been collected. In some instances job titles did not readily fit into a single area, and in such situations, hybrid exposure-classes were developed.

Job-exposure matrices, which tabulated exposure-class codes by year, were constructed (Appendix 3 & 4). For Location 1, actual results from past industrial hygiene measurements, [Rinsky, 1981] were placed into their respective cells in this matrix. Cells for which no data were available were completed according to rules that were established. These rules called for interpolation between available previous and subsequent values, or projection

of values forward or backward when no measured value existed to be used in interpolation (Appendix 5). Industrial hygiene measurements obtained at Location 2 were applied to the matrix in similar fashion. Few historical industrial hygiene data were available from this location. Since, however, the processes and job assignments were essentially identical at both locations, benzene exposure levels measured at Location 1 were assumed as naturally occurring simulations of exposure levels in corresponding areas at Location 2, when actual exposure measurements did not exist.

The exposure-classes, job-exposure matrices, and rules for interpolation were developed by a statistics intern who had neither prior involvement with the study, nor knowledge of how his decisions might affect the placement of cohort members in the analysis. The principal investigators were available to him for consultation, but in these areas the intern made all final decisions.

Population

All non-salaried white males employed in an RH department for at least one day between January 1, 1940 and December 31, 1965 were eligible for inclusion in the study population. Individuals whose initial exposure occurred subsequent to December 31, 1965 were excluded, as 1965 was the year in which production of rubber hydrochloride ceased at location 2. Very few individuals were first hired at location 1 after 1965.

Vital status was ascertained for the cohort through December 31, 1981. Those cohort members not traced were considered to be alive as of the study end date. Death certificates for all known deaths were obtained and were coded by a qualified nosologist according to the rules of the International Classification of Disease Adapted for Use in the United States (ICDA) which were in effect at the time of death. Each code was then converted to one of 89 "death categories" for use in the NIOSH Life-Table Analysis System.

Analytical Methods

The NIOSH Life-Table Analysis System [Waxweiler, 1983] was used to generate expected numbers of cause-specific deaths, within 5-year age and 5-year calender time periods. These calculations were based on United States white male death rates specific for the same 5-year age and calender time periods, applied to the number of person-years at risk of dying. Person-years were further stratified by cumulative benzene exposure and by 5-year latency periods (interval since initial exposure). To determine cumulative benzene exposure, an individual's daily benzene exposure was obtained from the appropriate cell in the exposure-class/year matrix. Exposures were then accumulated by summation of the daily values over a man's entire working career.

Accumulation of observed deaths and of an individual's person-years at risk of dying began on January 1, 1950, or on the first day on which his cumulative personal exposure to benzene reached 1.0 ppm-day (1 day of employment in an

exposed department), whichever occurred later. Observation ceased on December 31, 1981, or on the date of death, whichever occurred earlier.

The cohort was divided into 4 categories of exposure. These exposure strata were less than 40 part per million years (ppm-years), 40 to 199.99 ppm-years, 200 to 399.99 ppm-years, and more than 400 ppm-years. These boundaries correspond to the cumulative exposures which would result from average annual exposures to less than 1, 1 to 4.99, 5 to 9.99, and 10 or more parts per million benzene respectively, accumulated over a 40-year working lifetime.

Observed numbers of deaths for each cause were divided by the expected to obtain cause-specific standardized mortality ratios (SMRs). Ninety-five percent confidence intervals (CI) were calculated for each cause of death examined. [Rothman, 1979] Additionally, a matched case-control analysis was performed using conditional logistic regression. This analysis was intended: 1) to evaluate the exposure terms which govern the relationship between risk of death from leukemia and exposure to benzene; 2) to evaluate the effect of potential confounders and effect modifiers on this relationship; and 3) to identify the functional form of the exposure-response relationship.

The exposure terms evaluated were cumulative exposure, duration of exposure, and rate of exposure (cumulative exposure divided by duration of exposure). Ten controls were matched to each leukemia death by year of birth and year first employed. As suggested by Thomas, [Thomas, 1977] these controls were selected from among those cohort members still alive at the time of death of the corresponding case.

Because it is generally believed that some latency period subsequent to an initiating exposure is required to develop leukemia, a separate analysis which "lagged" exposures was also performed. Within each matched set, all benzene exposures that had occurred within the 5-year time period prior to the death of the case was ignored in calculating the individual's cumulative total.

RESULTS

Cohort Analysis

A total of 1196 white males with at least a ppm-day of cumulative exposure to benzene through December 31, 1965 were included in the cohort. They contributed a total of 32,438 person-years at-risk. On December 31, 1981, 838 (70.1%) were alive, 342 (28.6%) were dead, and 16 (1.3%) were lost to follow-up. Those persons lost to follow-up were considered to be alive as of the study end date.

Neither mortality from all causes of death combined (342 observed vs. 341.1 expected) nor mortality from all malignant neoplasms combined (71 observed vs. 68.7 expected) was elevated over expectation (Table 2). There was, however, a statistically significant increase in deaths from all lymphatic and hematopoietic neoplasms (15 observed versus 6.8 expected, SMR=221, CI=124-366). This increase was due mainly to excess numbers of deaths from leukemia (9 observed versus 2.7 expected, SMR=328, CI=150-623) and from multiple myeloma (4 observed versus 1 expected, SMR=398, CI=107-1019).

SMRs for leukemia, over the four exposure strata (less than 40 ppm-years, from 40 to 199.99 ppm-years, from 200 to 399.99 ppm-years and more than 400 ppm-years) demonstrated a marked, progressive increase with increasing exposure to benzene (SMRs = 105, 314, 1757, and 4535, respectively) (Table 3; Figure 1a). No apparent pattern was evident for these deaths with regard to

latency, which ranged from under 5 to over 30 years; however, seven of the nine leukemia cases had less than 20 years of latency.

Because this observation was based on only 9 leukemia deaths there was the possibility that this strongly positive trend in leukemia mortality might be an artifact produced by our choice of boundaries for the exposure categories. To examine this possibility we arbitrarily changed the sizes of the categories, first by halving their ranges, and then by doubling them. The resultant SMRs continued in both instances to show a strongly positive trend of increasing risk with increasing exposure. (SMRs for exposure ranges $\times 1/2 = 128, 139, 402, 2326$; SMRs for exposure ranges $\times 2 = 136, 806$, and 4672) These findings demonstrate the robustness of the observed association (Figures 1b and 1c).

SMRs for multiple myeloma, over the four original exposure strata, did not increase with increasing exposure (Table 4). Three of the four myeloma cases had less than 40 ppm-years exposure (based upon our assumptions of dose), and all four occurred after 20 years of latency. All four of these deaths were from Location 1. Case descriptions of the deaths due to leukemia and multiple myeloma are provided in Table 5.

Case-Control Analysis

Examination of data from the case-control analysis indicated that mean cumulative benzene exposure was higher for cases than for controls (242

ppm-years versus 53 ppm-years). Also, average duration of exposure was longer for cases (8.0 years versus 2.8 years). Finally, there was a difference in rates of exposure between cases and non-cases, with cases averaging approximately 24 ppm of benzene per day versus approximately 18 ppm per day for controls.

To evaluate the exposure terms which govern the exposure-response relationship between benzene and leukemia, and to assess potential confounders and effect modifiers, we analysed the case-control data using conditional logistic regression. [Kleinbaum, 1982] This analysis produces odds ratios (OR) of the general form:

$$OR = \exp(B_1 X_1 + \dots + B_n X_n)$$

where X_i are exposure variables, potential confounders, and/or effect modifiers, and B_i are coefficients to be estimated. Odds ratios calculated by this technique are expressed relative to that of an unexposed worker, in which X_i are considered to be 0.

We examined several models to identify that which would adequately explain the risk of death from leukemia with the minimum number of terms. In our first examination, we considered three exposure variables separately - cumulative exposure, duration of exposure and average exposure rate - and we fit three separate models, one for each of these variables. In these three models, cumulative exposure (ppm-years) was found to be the strongest single predictor of death from leukemia ($\beta = 0.0135$, CI = 0.0039-0.0230, $\chi^2=7.6$; $p=0.006$). Then to examine in more complexity the same three intercorrelated exposure

variables, we constructed another model in which all three were entered simultaneously. In this model, only cumulative exposure was found to contribute significantly to risk of death from leukemia. Interactions among cumulative exposure, duration, and rate of exposure also were examined. None of those interaction terms were found to be statistically significant.

The shape of the exposure-response function was then evaluated using several models. First, since the distribution of cumulative exposures was highly skewed, we examined a logarithmic transformation of cumulative exposures. Results of this analysis indicated that the fit for this model ($\chi^2=4.77$, $p=0.029$) was less adequate than that determined above for the untransformed measure ($\chi^2=7.6$; $p=0.006$). Then, to investigate the possibility of a more general form of curvature, we added a quadratic term for cumulative exposure. However, this maneuver did not significantly improve the fit of the model ($p=0.89$). From these findings, we determined that the untransformed model provided the best representation of the exposure-response relationship. From this model, the equation best describing the odds ratio for leukemia in relation to cumulative exposure to benzene was determined to be:

$$OR = \exp (0.0135 \times \text{ppm-years}).$$

The exposure-effect curve defined by this equation was plotted. Upper and lower 95% confidence intervals were calculated for cumulative lifetime exposures to benzene ranging from 0 to 450 ppm-years (Figure 2). From this equation, the average cumulative exposure attained by the cases and controls (70 ppm-years) was found to produce an OR, relative to the unexposed workers,

of 2.6 (CI=1.3-5.0). To ensure that the odds ratios for the matched sets of cases and controls were homogeneous (a prerequisite to the above analyses), interactions between cumulative exposure and the matching variables (year of birth and year of first exposure) were introduced into the model. Neither of these interactions was found to be significant.

To take into account an induction period for leukemia, benzene exposures occurring within the 5 year period prior to the death of a case were eliminated from the calculated cumulative exposure of each individual in a matched set. We then re-examined the effect of cumulative exposure. The odds ratio increased slightly from 0.0135 to 0.0177 as did the statistical significance of the observation. ($\chi^2=7.8$; $p=0.005$)

DISCUSSION

The major findings of this analysis were: (1) that a strongly positive exposure-response relationship exists between benzene and leukemia; (2) that, based upon the model, this relationship extends downward to mean annual exposure levels of less than 1 ppm, cumulated over a 40-year working lifetime; and (3) that there also exists in the population studied a statistically significant excess of deaths from multiple myeloma.

The environmental data used in this risk assessment are admittedly incomplete. Measured environmental levels did not exist for all years and had to be constructed from extant data. In some cases this meant allowing a single measured exposure to serve for a number of years. Episodes of high exposure due to such temporary circumstances as spills and process upsets were probably overlooked by the industrial hygiene surveys. In addition, percutaneous absorption of benzene, a route of exposure which recently has been shown to be of potential importance, was not examined. [Susten, 1985] Nevertheless, the existing environmental data are unusually comprehensive in comparison to those typically available for retrospective cohort studies. They permit a reasonable estimate of cumulative benzene exposure for each member of this study population. Examination of the exposure data led us to conclude that employees' historical 8-hour time-weighted average exposures to airborne benzene had generally been within the standards in effect at any given time. Missing data were estimated using rules pre-established by an intern who had no knowledge of individual's disease outcome. (Appendix 1-6)

If the environmental data are in error, we believe they likely err by overestimating actual average exposures, for two reasons. First, the majority of the measurements were taken by industrial hygienists looking for trouble spots within the process rather than trying to document typical personal exposures. Second, the economic viability of the rubber hydrochloride manufacturing process depended upon efficient recovery of costly solvent; indeed, much of the process was dedicated toward this end. Continuous high-level contamination by benzene of a large ventilated area would not have been economically acceptable.

The model becomes unstable in the higher dose ranges considered, as indicated by the extreme width of the 95% confidence interval in Figure 2. This is primarily a function of there being only 9 leukemia deaths in the series. However, both the categorical and the conditional logistic regression analyses indicate exponential increases in relative risk with increasing cumulative exposure to benzene. Therefore, while the exact estimate of relative risk at higher dose levels lies within a wide range of estimates, it should follow that an exponential decrease in risk will result from any lowering of exposures.

An association such as that observed here becomes more credible if it remains evident after imposition of a lag period reflecting induction-latency. In this instance a lag period was imposed by discounting from all individuals in the matched sets, all exposure which had been experienced in the 5-years prior to the death of the case. Following that maneuver the association between

benzene exposure and death from leukemia not only remained evident, but actually increased slightly in strength.

Multiple myeloma, which was the cause of death in four members of this cohort, has been observed previously in persons exposed to benzene, although also in small numbers. [Decoufle, 1983] In addition, several recent toxicologic studies have demonstrated lymphoid malignancies in both rats and mice exposed to benzene. [Goldstein, 1980; Snyder, 1980; Maltoni, 1983; NTP, 1983] It is of interest that three of the four deaths from multiple myeloma which were observed in this cohort occurred among the group with lowest cumulative exposure to benzene (<40 ppm-years), and that all four required exceptionally long latency periods for hematologic malignancies (>20 years). These two observations raise the possibility that relatively low cumulative exposures to benzene may produce a relatively well differentiated malignancy such as multiple myeloma, whereas higher exposures lead to leukemia. In this construct, it is conceivable that the progressive reduction of exposures to benzene, which has been achieved over the last several decades, may lead to a situation in which multiple myeloma will in the future become manifest in a large population of workers with relatively low cumulative exposures to benzene. The present observations must, however, be interpreted cautiously in the absence of further corroboration.

The analyses performed in this study exemplify the strengths and weaknesses of quantitative risk assessments which are based on epidemiologic data. The great strength of such analyses is that they are based on the experience of

man; that they avoid all of the problems attendant upon inter-species extrapolations. However, the obvious weakness of such analyses is the dependence on observations made over many years by multiple observers of a naturally occurring and unplanned experiment. Thus estimates of exposure, even in the relatively complete case as that described here, are perfectly imperfect.

In conclusion, the results of this risk assessment indicate that an exponential decrease in risk of death from leukemia would be achieved by a lowering of occupational exposures to benzene. Thus according to the model derived in the present study, a worker exposed to benzene at an average exposure of 10 ppm daily at work for forty years would have an increased risk of dying from leukemia of 221.4 (C.I. 4.8 to 9897). If the average daily exposure were lowered to 1 ppm, the risk would decrease to 1.7 (C.I. 1.2 to 2.5). At 0.1 ppm the risk would be nearly indistinguishable from background (OR = 1.06, C.I. 1.02 to 1.10).

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Table 1

Schedule of Recommended Limits for Occupational Exposure to Benzene
United States, 1941 to Present

<u>Year</u>	<u>Recommended Exposure Limit</u>	<u>Reference</u>
1941	100 ppm	Drinker, 1941
1947	50 ppm 8-hour TWA*	American Conference of Governmental Industrial Hygienists, 1947
1948	35 ppm 8-hour TWA	American Conference of Governmental Industrial Hygienists, 1948
1957	25 ppm 8-hour TWA	American Conference of Governmental Industrial Hygienists, 1957
1963	25 ppm ceiling	American Conference of Governmental Industrial Hygienists, 1963
1969	10 ppm 8-hour TWA	American National Standard Institute, 1969
1976	1 ppm	National Institute for Occupational Safety and Health, 1976

*TWA = time-weighted average

Table 2

Observed and Expected Deaths from
All Causes, All Malignant Neoplasms,
and Lymphatic and Hematopoietic Malignancies.
January 1, 1950 through December 31, 1981.
Rubber Hydrochloride Workers, Ohio.

<u>Cause of Death</u>	<u>Observed Deaths</u>	<u>Expected Deaths</u>	<u>SMR; (95% C.I.)</u>
All causes	342	341.1	100; (90-111)
All Malignant Neoplasms	71	68.7	103; (81-130)
Lymphatic and Hematopoietic Malignancies	15	6.8	221; (124-366)
Leukemia	9	2.7	328; (150-623)
Multiple Myeloma	4	1.0	398; (107-1019)

Table 3

Observed and Expected Deaths from Leukemia in
 White Males with at Least One Day of Exposure to Benzene
 from January 1, 1940, through December 31, 1965
 by Cumulative Exposure and by Years of Latency.
 January 1, 1950 through December 31, 1981.
 Rubber Hydrochloride Workers, Ohio.

		<u>EXPOSURE (ppm-yrs)</u>				
		<40	40-200	200-400	>400	TOTAL
<u>LATENCY (yrs)</u>		2	0			2
	<5	0.10	0.02			0.12
	5-10	0.16	0.05	0.01		0.22
	10-15	0.22	0.07	0.02	0.00	0.32
	15-20	0.28	0.09	0.03	0.01	0.41
	20-25	0.33	0.10	0.03	0.01	0.48
	25-30	0.38	0.12	0.04	0.01	0.55
	>30	0.41	0.17	0.04	0.01	0.64
	TOTAL	2	2	3	2	9
		1.89	0.63	0.17	0.04	2.74
SMR =	105	314	1757	4535	328	
C.I. =	12-382	35-1137	353-5135	509-16374	150-623	

Table 4

Observed and Expected Deaths from Multiple Myeloma in
 White Males with at Least One Day of Exposure to Benzene
 from January 1, 1940, through December 31, 1965
 by Cumulative Exposure and by Years of Latency.
 January 1, 1950 through December 31, 1981.
 Rubber Hydrochloride Workers, Ohio.

<u>LATENCY (yrs)</u>	<u>EXPOSURE (ppm-yrs)</u>				<u>TOTAL</u>
	<40	40-200	200-400	>400	
<5	0	0			0
	0.02	0.01			0.02
5-10	0	0	0		0
	0.04	0.02	0.00		0.06
10-15	0	0	0	0	0
	0.07	0.02	0.01	0.00	0.10
15-20	0	0	0	0	0
	0.10	0.03	0.01	0.00	0.15
20-25	1	0	0	1	2
	0.12	0.04	0.02	0.00	0.18
25-30	2	0	0	0	2
	0.15	0.05	0.02	0.01	0.23
>30	0	0	0	0	0
	0.17	0.07	0.02	0.01	0.27
TOTAL	3	0	0	1	4
	0.68	0.24	0.07	0.02	1.01
SMR =	445	-	-	4716	398
C.I. =	89-1297			72-30740	107-1019

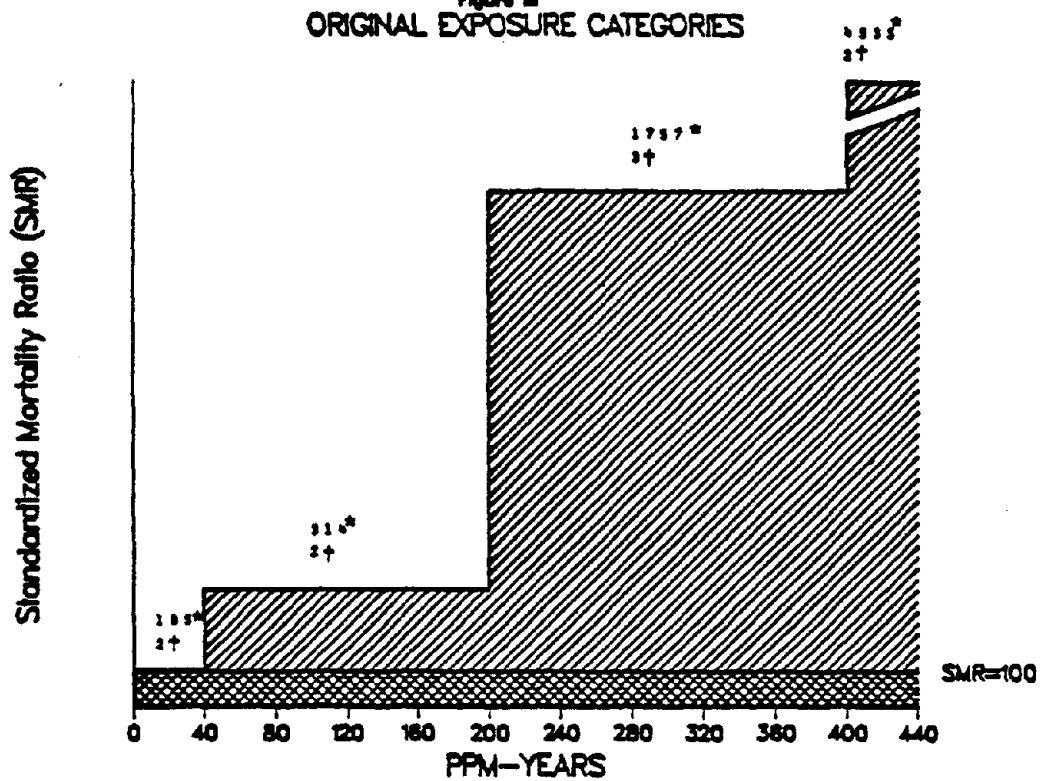
Table 5
Case Descriptions of Leukemia and Multiple Myeloma Deaths
Rubber Hydrochloride (RH) Workers, Ohio, 1950 - 1981

Case Number	Age at Death	Year of Death	Latency* (yrs)	Cause of death†	Corroborating Medical Reports	Plant Location & Duration of Employment (RH)	Cumulative Benzene Exposure (ppm-years)
1	36	1958	17	monocytic leukemia (204)	none available	Location 1 1 1/2 years	62.93
2	29	1950	2	chronic myelogenous leukemia (204)	hospital, autopsy, tissue slides	Location 1 1 month	.10
3	60	1958	13 1/2	acute myelocytic leukemia (204)	hospital, hematologist	Location 2 11 1/2 years	256.79
4	65	1960	10 1/2	acute myelogenous leukemia (204)	hematologist, hospital, tissue slides	Location 2 8 1/2 years	311.38
5	62	1961	22	DiGuglielmo's acute myelocytic leukemia (204)	hospital, physician	Location 2 13 years	421.97
6	57	1961	20	acute granulocytic leukemia (204)	hospital, tissue slides, autopsy	Location 2 20 years	629.97
7	57	1957	15 1/2	acute monocytic leukemia (204)	tissue slides	Location 2 5 years	105.28
8	28	1954	3 1/2	myelogenous leukemia (204)	none available	Location 1 1 1/2 years	11.22
9	67	1979	37	acute myeloblastic leukemia (204)	none available	Location 2 14 years	266.08
10	69	1980	25 1/2	multiple myeloma (203)	none available	Location 1 1 1/2 years	19.95
11	52	1963	22 1/2	multiple myeloma (203)	hospital	Location 1 4 days	.11
12	62	1968	24 1/2	plasma cell sarcoma (203)	hospital	Location 1 23 years	652.66
13	68	1981	26 1/2	multiple myeloma (203)	none available	Location 1 9 months	7.75

*Latency = time (in years) from date first exposed until death

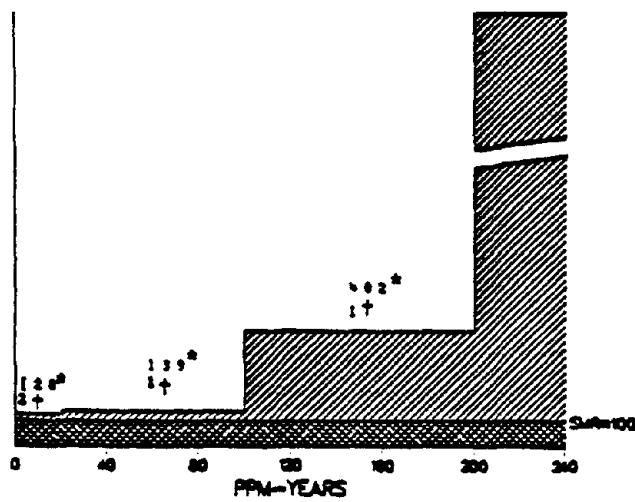
†International Classification of Disease code as determined by nosologist from death certificate indication

Figure 1a
ORIGINAL EXPOSURE CATEGORIES



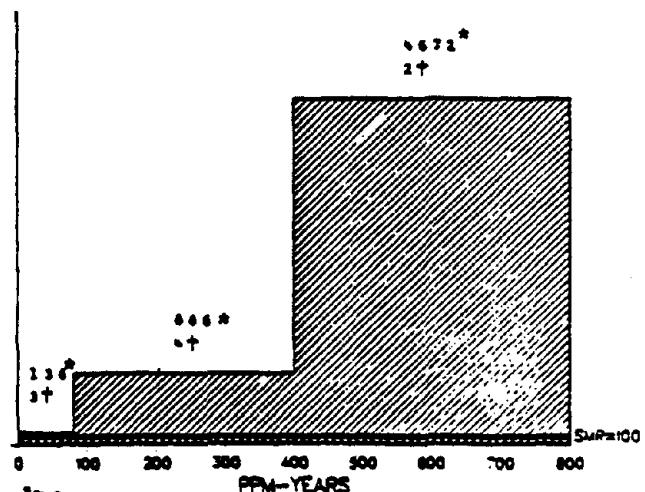
*SMR
† number of observed deaths

Figure 1b
HALVED EXPOSURE CATEGORIES



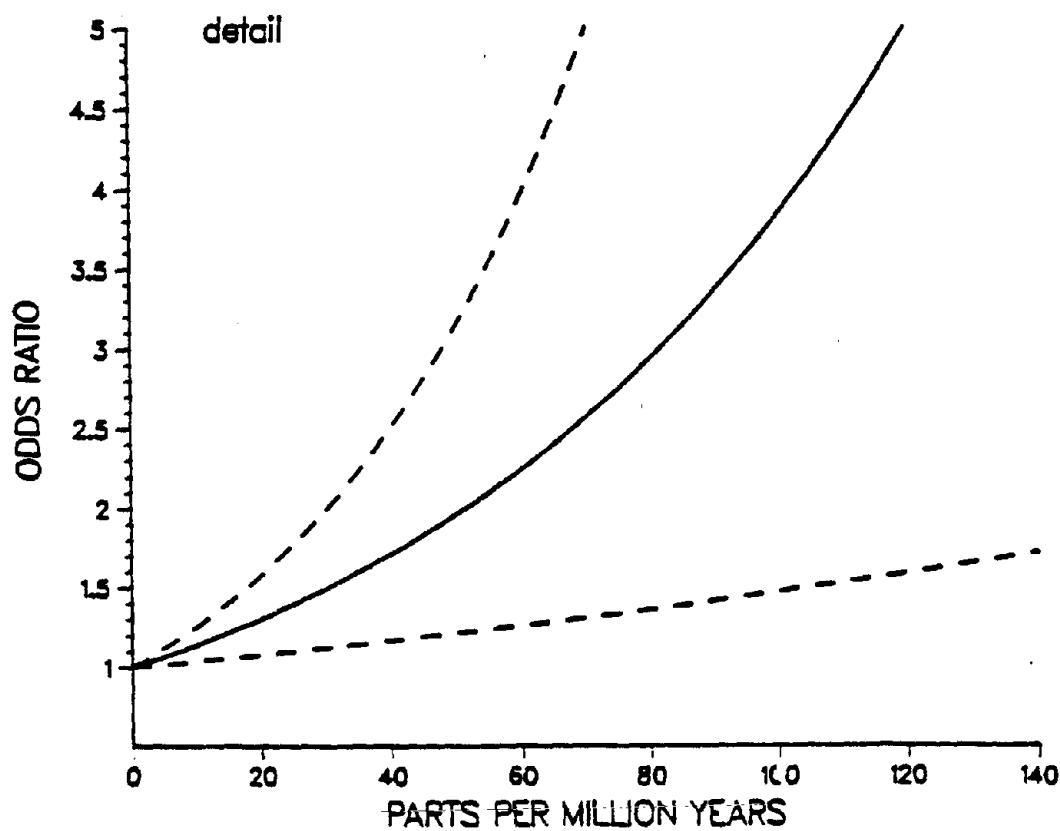
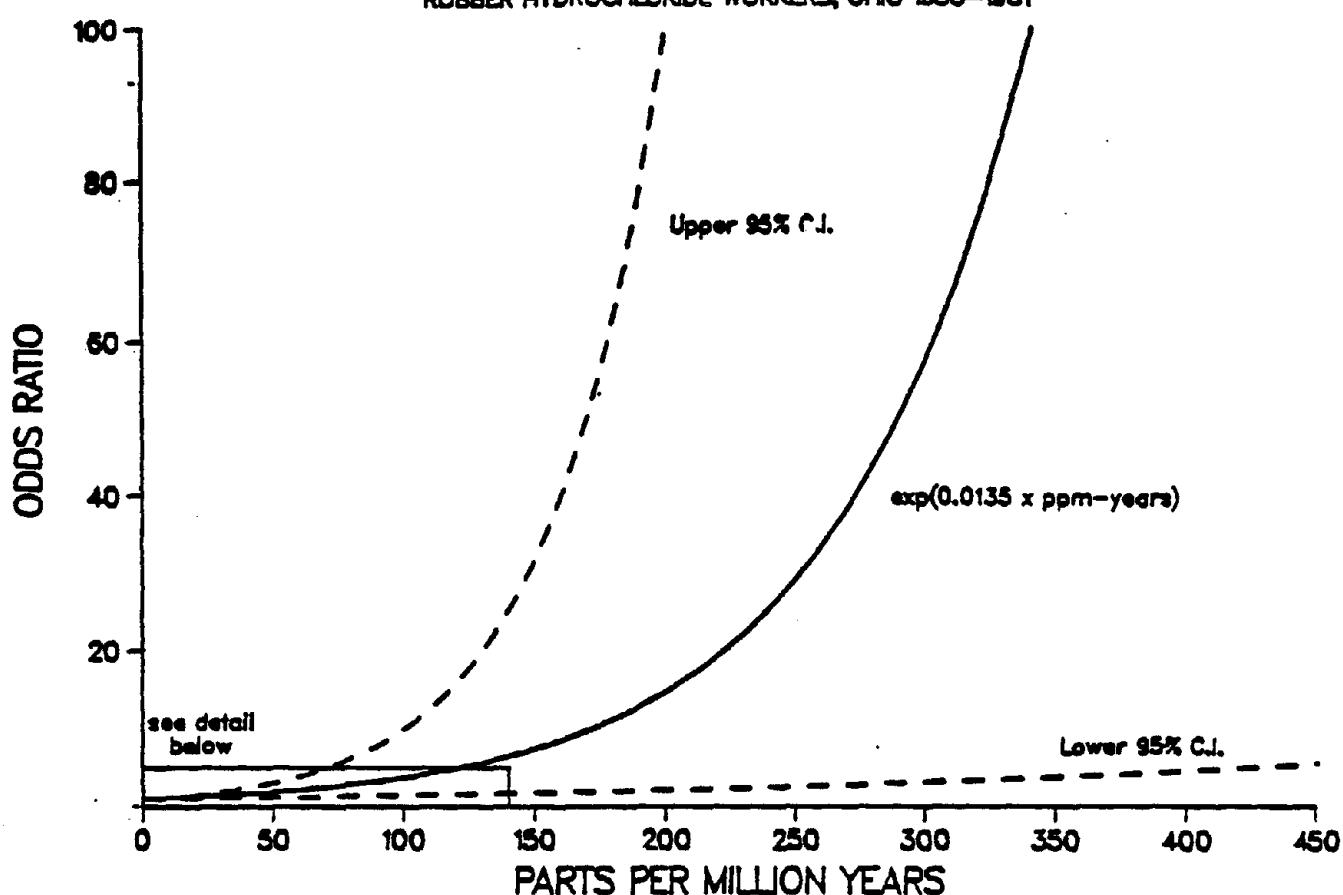
*SMR
† number of observed deaths

Figure 1c
DOUBLED EXPOSURE CATEGORIES



*SMR
† number of observed deaths

Figure 2
 RELATIONSHIP BETWEEN RISK OF LEUKEMIA
 AND CUMULATIVE EXPOSURE TO BENZENE
 RUBBER HYDROCHLORIDE WORKERS, OHIO 1950-1981



Appendix 1
 Job Titles and Exposure Classes - Location 1
 Rubber Hydrochloride Workers, Ohio

Code	Job Title	No. of Persons	Exposure Class
01	Spreader Operator	62	Casting Unit
02	Utility and Service	675	Minimum
03	Utility - Wet Side	73	Reactor
04	Quencher Operator	66	Quencher
05	Spreader Operator Helper	47	Casting Unit
06	Neutralizer Operator	135	Neutralizer
07	Reactor Operator	121	Reactor
08	Head Spreader Operator	6	Casting Unit
09	Supervisor	27	Minimum
10	Banbury	12	Minimum
11	Cement/Concentrator	78	Mixer/Reactor
12	Wet Side 1st Man	45	Reactor/Neutralizer
13	Miscellaneous	24	Minimum
14	Foreman	10	Minimum
15	Spreader Knifeman	222	Between Units
16	Scrap Sorter	27	Minimum
17	Acid Concentrator Operator	20	Reactor
18	Pack and Ship	57	Minimum
19	Mill Operator	92	no exposure
20	Fabric Wrap	95	no exposure
21	Camachine Operator	152	no exposure
22	Sheeter Operator	36	no exposure
23	Foil Inspection	29	no exposure
24	Scrap Reclaim	9	no exposure
25	Wrap Helper	5	no exposure
26	Re-troll and Inspection	20	no exposure
27	Still Operator	22	Still House
28	Tensilizer	9	no exposure
29	Secretary	13	no exposure
30	Lawson Operator	21	no exposure
31	Casting Film Operator	16	Casting Unit
32	No Job Title	1	Minimum
33	Neutralizer Preparation	3	Neutralizer
34	Prime Wrap	59	no exposure
35	No Job Title	1	Minimum

Appendix 2
Job Titles and Exposure Classes - Location 2
Rubber Hydrochloride Workers, Ohio

Code	Job Title	No. of Persons	Exposure Class
01	Miscellaneous	126	Minimum
02	Utility	43	Minimum
03	Distill and Misc.	6	Reactor
04	Water Purification	1	Minimum
~	Wet Side Operator	16	Reactor/Neutralizer
	Reroll and inspect	119	no exposure
	R.T. Unit Helper	129	Casting Unit
	2nd Asst Casting Operator	69	Casting Unit
	Supervisor	17	Minimum
	Casting Operator	22	Casting Unit
	Breakdown Mill Operator	57	Mixer
12	Clean Tanks	71	Presses open
13	Cameron Machine Operator	11	no exposure
14	Head Operator	11	Casting Unit
15	Pack and Ship	37	No Exposure
16	Reactor Operator	61	Reactor
17	(sequence code skipped)		
18	Cement Mixer	33	Mixer
19	Cut Shells and Misc.	30	no exposure
20	Pull Down to Emp. Roll	6	no exposure
21	Neutralizer Operator	126	Neutralizer
22	Quencher Operator	50	Quencher
23	Cut and Pack	26	no exposure
24	Record Orders	12	no exposure
25	Prepare stock for cutter	1	no exposure
26	T.C. Machine Operator	14	no exposure
27	Asst. Casting Operator	15	Casting Units
28	Spreader Helper	41	Casting Units
29	Prod. Balance Operator	17	Between Units
30	Film Operator	26	Between Units
31	Banbury Operator	24	Minimum
32	Preparation - Scrap	30	no exposure
33	Janitor	7	no exposure
34	Still Operator	12	Still House
35	Spreader	1^	Casting Unit
36	Reroll and Inspect		no exposure
37	Filter Cloth		no exposure
38	Finishing Operator		no exposure
39	Sheeter Operator		no exposure
40	Solution Operator	1	Neutralizer

Appendix 2 (cont.)

Job Titles and Exposure Classes - Location 2
Rubber Hydrochloride Workers, Ohio

Code	Job Title	No. of Persons	Exposure Class
41	Tensilizer Operator	10	no exposure
42	(sequence code skipped)		
43	Pliofilm	9	Minimum
44	2nd Asst Spreader Operator	36	Casting Operator
45	Preparation - Stock	5	no exposure
46	Acid Concentrator	4	Reactor
47	2nd Asst. Reactor Operator	1	Reactor
48	Asst. Operator	2	Casting Unit
49	Puncher	2	no exposure
50	Bag Machine	3	no exposure
51	Pack and Relief	1	no exposure
52	Acid Recovery	2	Neutralizer
53	Receiving Checker	1	no exposure
54	Operator	1	Minimum
55	Atomic Gauge Operator	3	Between Units
56	Mix and Mill Operator	23	Mixer
57	2nd Asst. Operator	1	Casting Unit
58	(sequence code skipped)		
59	Stock Cutter	1	no exposure
60	Preparation - Shipment	1	no exposure
61	Washer Operator	1	no exposure
62	Clean Operator	3	no exposure
63	Scrap Cutter	6	no exposure*
64	no title	5	no exposure*
65	no title	33	quencher or still house)*

* = exposure class determined on an individual basis by review of work history ..

Appendix 3
Location 1, 1939-1976
Daily Benzene Concentrations (ppm)
Exposure Class Codes by Year

Exposure Class	39-46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76
Reactor	10 ^K	10 ^K	10 ^K	10 ^K	10 ^K	10 ^K	10 ^K	10 ^K	10 ^K	10 ^K	10 ^A	9 ^H	8 ^H	7 ^H	6 ^H	5 ^H	5 ^D	5 ^D	5 ^D	5 ^D	5 ^H	5 ^D	5 ^D	5 ^D	5 ^D	7 ^H	2 ^B				
Neutralizer	23 ^K	23 ^K	23 ^K	23 ^K	23 ^K	23 ^K	23 ^K	23 ^K	23 ^K	23 ^K	23 ^A	22 ^H	22 ^H	21 ^H	21 ^H	20 ^H	20 ^H	19 ^D	28 ^D	7 ^D	7 ^D	12 ^D	15 ^H	18 ^H	5 ^D	5 ^D	5 ^D	16 ^H	25 ^B		
Quencher	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	30 ^J	34 ^D	25 ^H	16 ^D	26 ^H	35 ^D	25 ^H	16 ^H	6 ^D	26 ^D	18 ^D	17 ^D	5 ^D	7 ^H	9 ^B	
Between Units	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	20 ^J	35 ^D	5 ^D	19 ^D	16 ^H	12 ^H	9 ^H	5 ^D	5 ^D	5 ^D	5 ^I	5 ^I		
Casting Unit	34 ⁰	28 ⁰	34 ⁰	50 ⁰	42 ⁰	34 ⁰	33 ⁰	34 ⁰	23 ⁰	39 ⁰	59 ⁰	16 ⁰	23 ⁰	26 ⁰	23 ⁰	18 ⁰	13 ⁰	15 ⁰	12 ⁰	15 ⁰	16 ⁰	16 ⁰									
Still House	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^J	10 ^D	10 ^H	12 ^D	10 ^D	9 ^H	7 ^H	5 ^D	5 ^D	5 ^D	16 ^H	5 ^D	5 ^D	5 ^I	5 ^I	
Mixer	45 ^K	45 ^K	45 ^K	45 ^C	40 ^H	35 ^H	30 ^H	25 ^H	20 ^H	15 ^H	10 ^A	10 ^H	10 ^H	9 ^H	9 ^H	9 ^H	8 ^D	34 ^D	26 ^D	5 ^D	8 ^D	8 ^H	8 ^D	5 ^I	5 ^I						
Minimum	5 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L	1 ^L			
Mixer/ Reactor	28 ^H	28 ^H	28 ^H	28 ^H	26 ^H	23 ^H	20 ^H	18 ^H	15 ^H	13 ^H	10 ^H	10 ^H	9 ^H	9 ^H	8 ^H	7 ^H	7 ^H	7 ^H	20 ^H	16 ^H	5 ^H	7 ^H	7 ^H	7 ^H	5 ^H	5 ^H	5 ^H	6 ^H	7 ^H		
Reactor/ Neutralizer	17 ^H	17 ^H	17 ^H	17 ^H	17 ^H	17 ^H	17 ^H	17 ^H	17 ^H	17 ^H	17 ^H	17 ^H	16 ^H	15 ^H	14 ^H	14 ^H	13 ^H	13 ^H	12 ^H	17 ^H	6 ^H	9 ^H	10 ^H	12 ^H	5 ^H	5 ^H	5 ^H	5 ^H	17 ^H		
Platform*	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^J	25 ^D	35 ^H	60 ^D	5 ^D	5 ^D	13 ^H	20 ^D	5 ^D	5 ^D	5 ^D	5 ^D	5 ^I	5 ^I		
Stripper*	155 ^G	89 ^C	155 ^C	680 ^C	350 ^C	155 ^G																									
Spreader/* Dryer	188 ^G	61 ^C	188 ^G	250 ^C	188 ^G	188 ^A	188 ^G	261 ^E	188 ^G	188 ^G																					

* - these exposure classes do not directly correlate to a particular job. They are used in the calculation of other exposure classes.

Note: Underlined values are averages of actual measurements; values not underlined are estimates; superscripts refer to source or estimation procedure as described in Appendix 5

Appendix 4
Location 2, 1936-1965
Daily Benzene Concentrations (ppm)
Exposure Class Codes by Year

Exposure Class	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65
Mixer	45 ^P	16 ^P	10 ^P	10 ^P	9 ^P	9 ^P	8 ^P	34 ^P	26 ^P																					
Neutralizer	23 ^P	16 ^P	22 ^P	21 ^P	21 ^P	20 ^P	20 ^P	19 ^P	28 ^P	7 ^P																				
Reactor	10 ^P	22 ^P	8 ^P	7 ^P	6 ^P	5 ^P	5 ^P	5 ^P	6 ^P																					
Casting Unit	34 ^P	23 ^P	39 ^P	59 ^P																										
Quencher	30 ^P	34 ^P	25 ^P	16 ^P																										
Between Units	20 ^P	35 ^P																												
Still House	10 ^P	12 ^P																												
Presses Open	45 ^Q	60 ^Q	25 ^Q	5 ^Q																										
Minimum	1 ^P																													
Reactor/Neutralizer	17 ^P	6 ^P																												

Note: Underlined values are averages of actual measurements; values not underlined are estimates; superscripts refer to source or estimation procedure as described in Appendix 3

Appendix 5
Rules for Interpolation of Daily Benzene Concentrations
(Footnotes for Appendices 3 and 4)

The designation A through G in the exposure class matrices in appendices 3 and 4 indicates that the value used was the average of actual measured values. The specific character indicates the source, as follows:

- A = Ohio Department of Health (1956) Table II in the 1981 paper
- B = NIOSH survey (1976) Table IV in the 1981 paper
- C = Company Monitoring Data (1946-1950) Table V in the 1981 paper
- D = Company Monitoring Data - 112 Surveys [1963-1974 (96 since 1970] Figures 3 through 14 in the 1981 paper. All values of less than 5 ppm made equal to 5 ppm
- E = University of North Carolina (1974) Table III in the 1981 paper
- F = Ohio Department of Health (1957) Table IX in the 1981 paper
- G = For all years, Stripper was assumed to have the value of 155 ppm and Spreader/Dryer was assumed to have the value of 188 except where actual measured data was available. Assumed values of 155 and 188 are averages of the available measured data.
- H = Values were the result of linear interpolation between two measured values
- I = When no latter measured value existed to interpolate to, the latest measured value was projected forward.
- J = The average of the measured values for 1963 and 1964 were rounded up to the nearest 5 and then projected backward. For between units, 1965 and 1966 values were used.
- K = When no earlier measured value existed to interpolate to, the first measured value was projected backward.
- L = The minimum exposure value was set equal to 5 ppm up to 1946, and 1 ppm after 1946. In 1946 the presses were enclosed. Up until that time, the open presses may have contributed to overall building concentrations.
- M = This value was the average of the Reactor value and the Mixer value. It was assigned to workers exposed to both areas.
- N = This value was the average of the Reactor value and the Neutralizer value. It was assigned to workers exposed to both areas.
- O = The value for the Casting Unit was derived by taking the average of the Between-units value and the Platform value, and adding to it 1/32 of the sum of the spreader value and stripper value. [Casting Unit = (Between-unit + Platform)/2 + 1/32(Stripper + Spreader)] It was assigned to various workers in the casting area who were exposed to both between-units and platform areas and exposed infrequently (approximately 15 minutes/day) to the stripper and spreader areas.
- P = Values used for Location 2 workers were taken from equivalent location from Location 1
- Q = The values used for the Presses-open for Location 2 for the years 1963-1965 are taken from the Location 1 data. The average of the values for 1963 and 1964 was rounded up to the nearest 5 and then projected backward.

Appendix 6
Tables and Figures from
LEUKEMIA IN BENZENE WORKERS
Rinsky, Young, and Smith
American Journal of Industrial Medicine
1981

TABLE III. Atmospheric Benzene Concentrations, Location 1, 1974

Area	No. of samples	Concentration, ppm		
		Mean	Max	Min
Mix	10	10.4	29.0	0.0
Fabrication	5	7.6	21.0	2.8
Inside drier	3	260.6	355.0	193.0
Finishing 146A	1	30.0	30.0	30.0
Finishing 146B	3	10.6	20.0	0.0

Source: University of North Carolina (1974).

TABLE IV. Eight-Hour Time-Weighted Average Benzene Exposures, Location 1, 1976

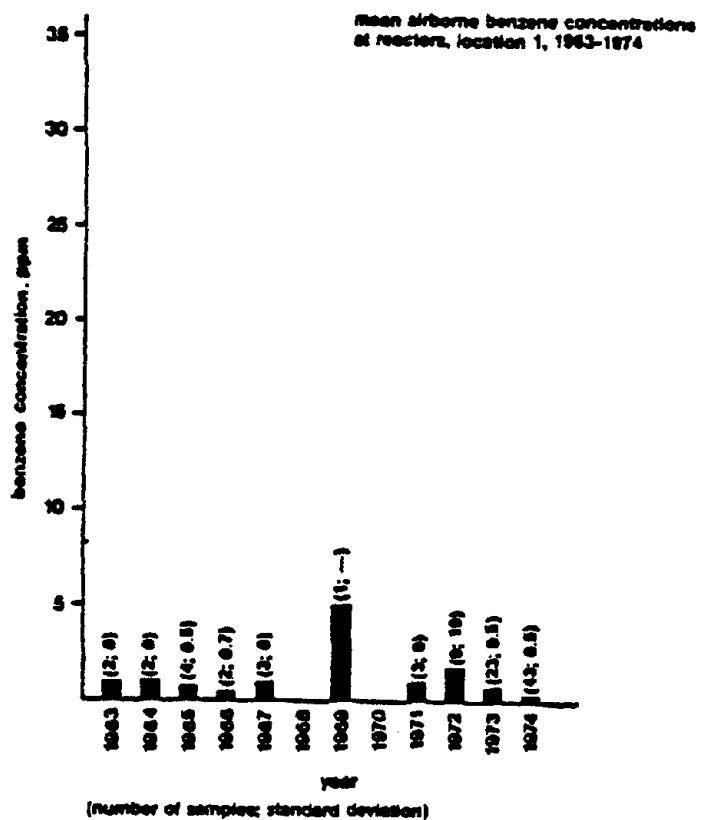
Occupational title	Number of individual samples	Range, ppm	8-hour TWA
Barbary quencher operator	2	5.9 - 11.0	8.4
Reactor operator	2	4.9 - 13.1	9.0
Neutralizer operator	4	6.9 - 67.8	24.9
Canning unit operator	6	3.8 - 9.6	7.2
Canning unit helper	4	6.5 - 12.6	8.2
First pass operator	2	16.7 - 18.4	17.5

Source: Young et al (1977).

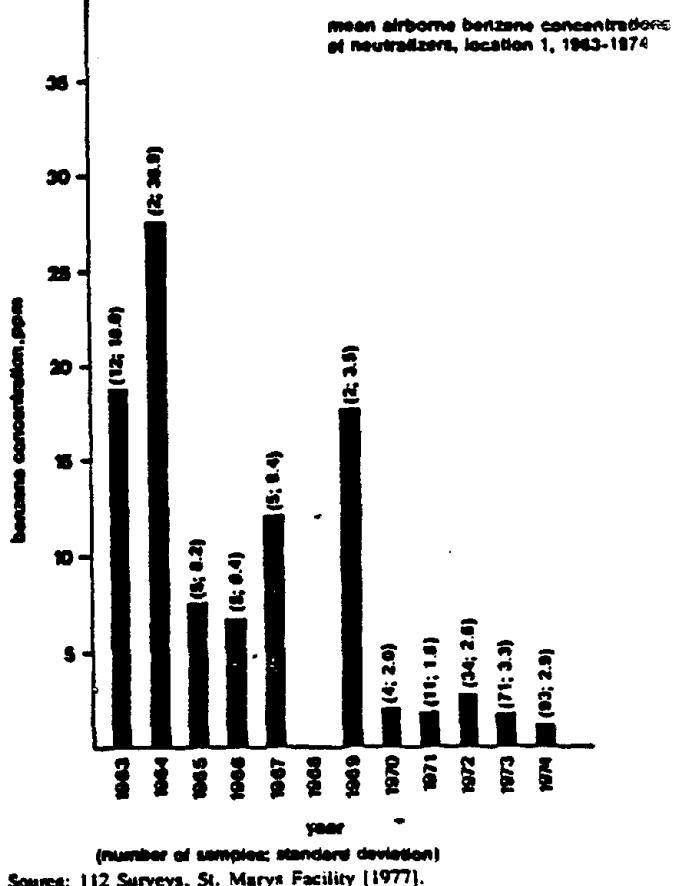
TABLE V. Company Detector Tube Determinations for Atmospheric Benzene, Location 1, 1946-50

Date	Location	Benzene concentration, ppm
10-17-46	Storage room	250
4-10-47	Storage room	19
4-10-47	Stripper roll - Unit A	75
4-10-47	Inside drier - Unit A	60
4-10-47	Stripper roll - Unit B	66
4-10-47	Inside drier - Unit B	64
4-10-47	Stripper roll - Unit C	125
4-10-47	Inside drier - Unit C	57
12-14-49	Mixers	45
12-14-49	Storage room	10
12-14-49	Stripper roll - Unit A	680
12-14-49	Presses - Unit E	15
3-01-50	Stripper roll - Unit C	350
3-01-50	Inside drier - Unit C	250
3-01-50	Storage room	35

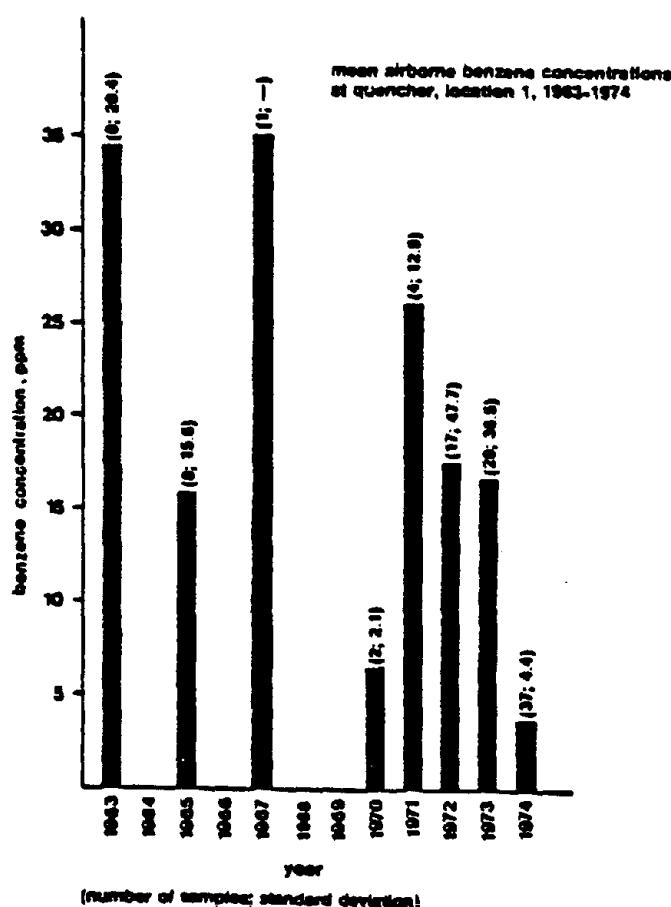
Source: Tabulations of Environmental Data of St. Marys (1977).



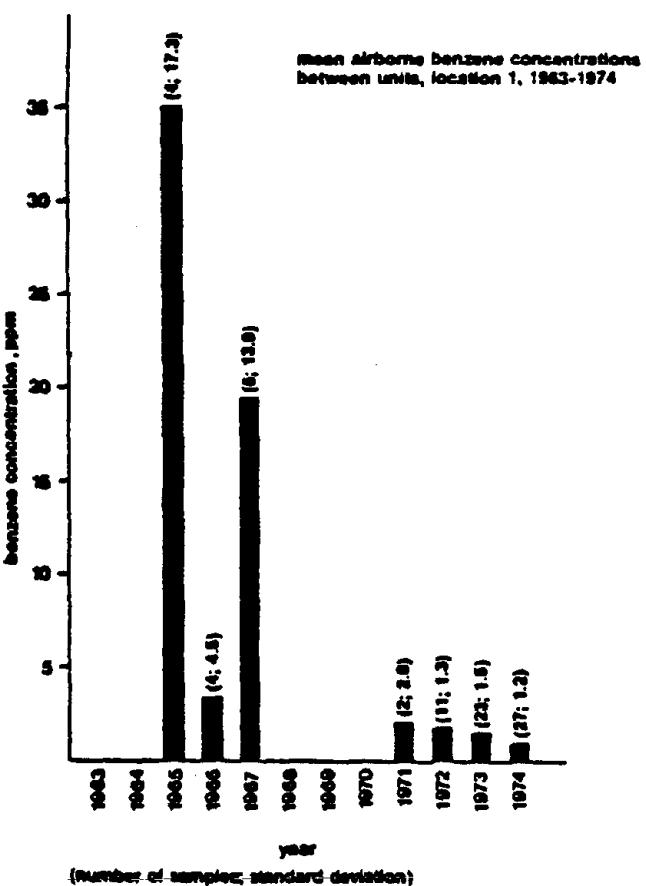
Source: 112 Surveys, St. Marys Facility (1977).



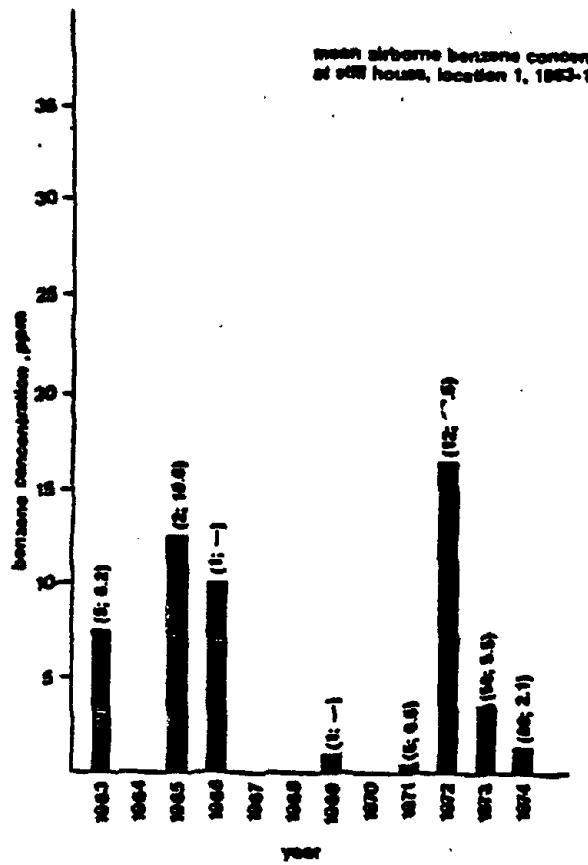
Source: 112 Surveys, St. Marys Facility (1977).



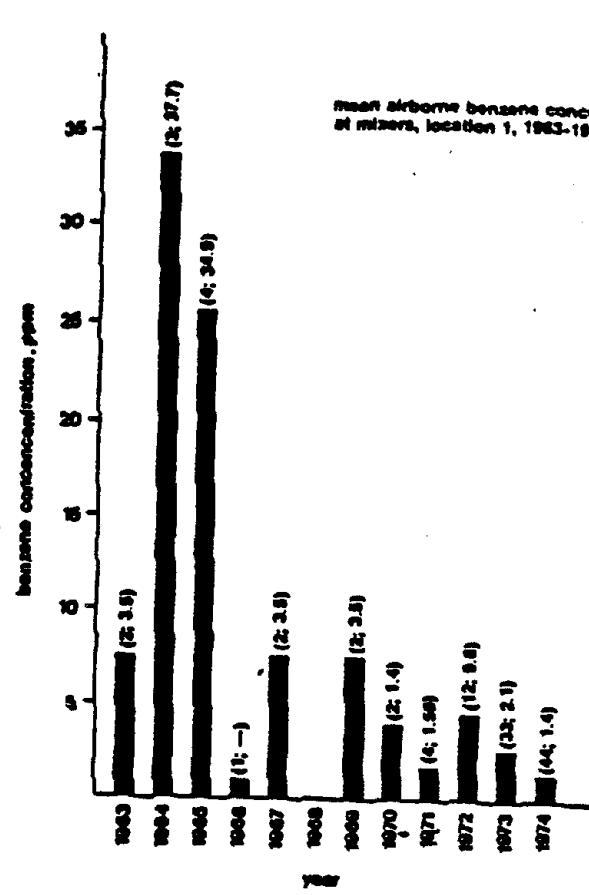
Source: 112 Surveys, St. Marys Facility (1977).



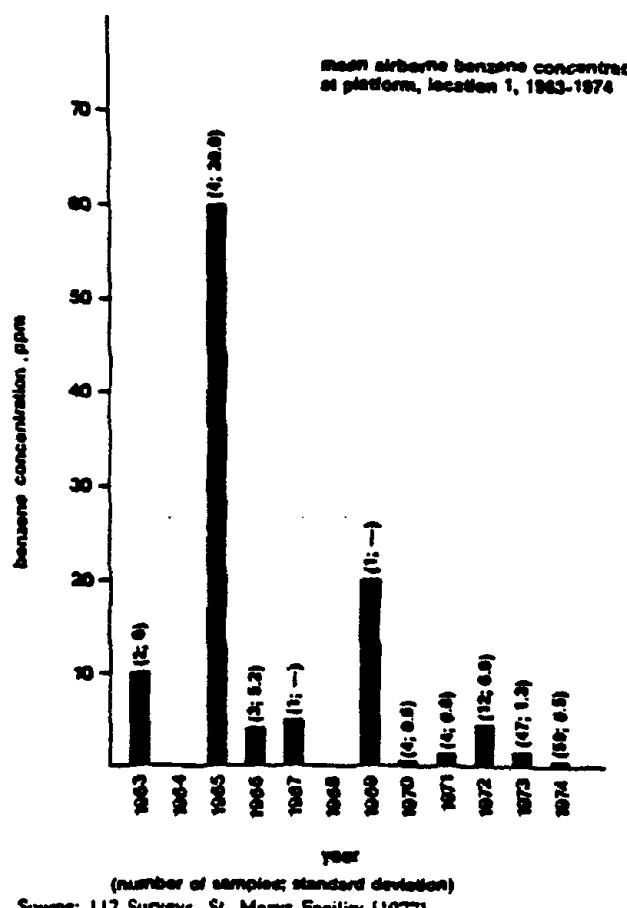
Source: 112 Surveys, St. Marys Facility (1977).



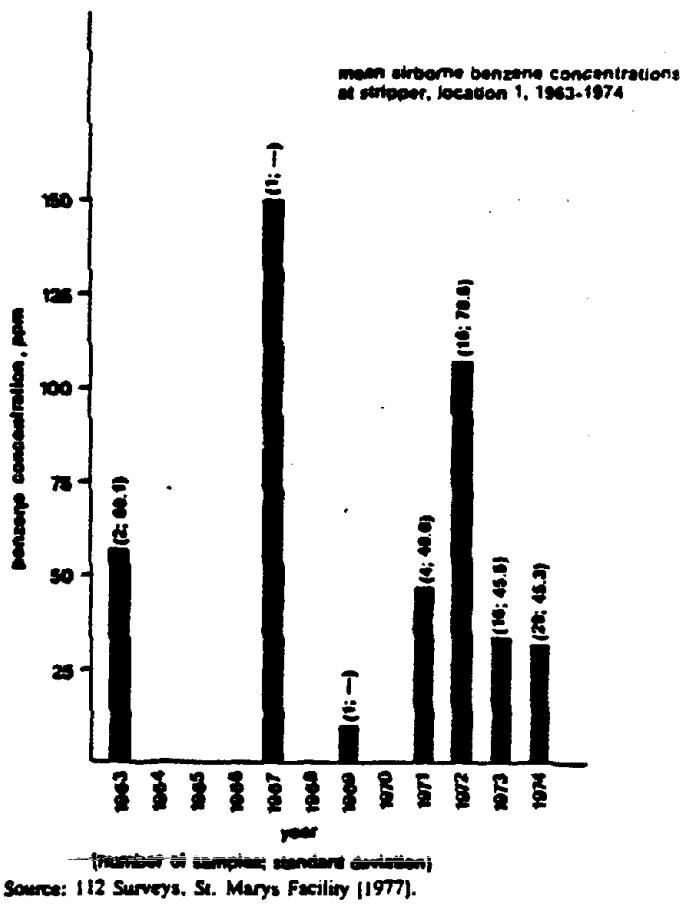
(number of samples; standard deviation)
Source: 112 Surveys, St. Marys Facility (1977).



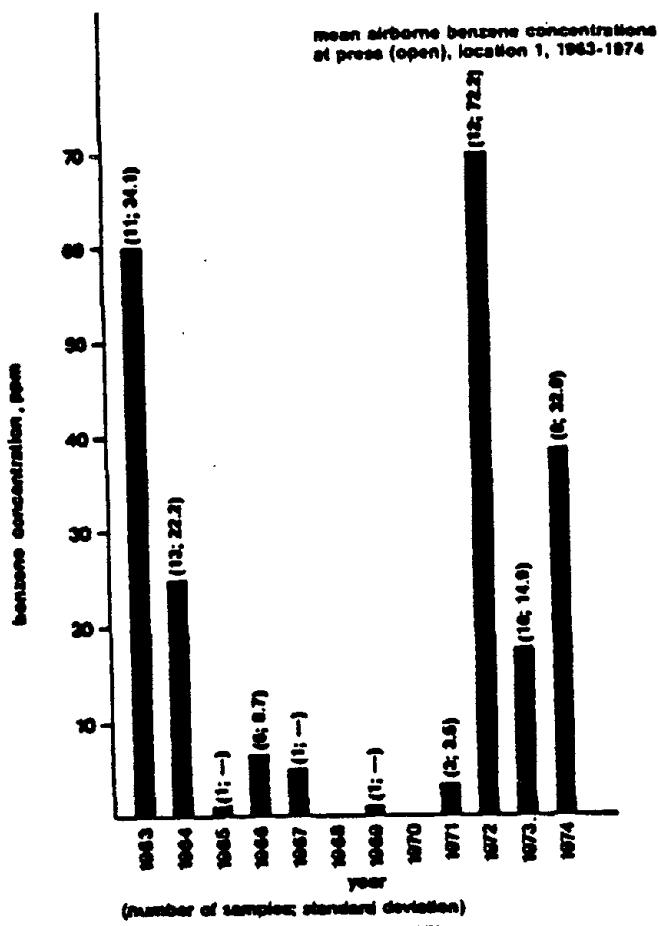
(number of samples; standard deviation)
Source: 112 Surveys, St. Marys Facility (1977).



(number of samples; standard deviation)
Source: 112 Surveys, St. Marys Facility (1977).



(number of samples; standard deviation)
Source: 112 Surveys, St. Marys Facility (1977).



Source: 112 Surveys, St. Marys Facility (1977).

TABLE IX. Atmospheric Benzene Concentrations (PPM), Location 2, Plant 2

Location	No. of samples	Range	Mean
Mixing	6	0-50	16
E. neutralizer room	36	0-50	16
W. reactor room	37	0-100	22
E. storage room	32	20-100	43
W. storage room	34	5-100	40
No. 1 casting platform	34	5-100	41
No. 2 casting platform	39	5-100	39
No. 3 casting platform	44	0-100	42
No. 4 casting platform	34	5-100	39
No. 5 casting platform	36	5-100	34
Quencher area	12	10-100	39
Engineering area	6	0-100	36
Aisle 1, 2 units	31	0-100	34
Aisle 2, 3 units	2	40-100	70
Aisle 3, 4 units	30	0-35	26
Aisle 4, 5 units	1	15	15

Source: NIOSH (1977).

