DOW CHEMICAL U.S.A.

1803 Building
4 December 1981

MIDLAND, MICHIGAN 48640

MEMORANDUM

TO: M. F. CURRIER
~~P.~~ L. POSTON
W. E. LEDFORD

FROM: G. L. CARLO

cc: R. R. Cook

Sorry about this, but there are a couple of modifications which should be added to the copy of "A Cross-Sectional Study of Employees With Potential Workplace Exposure to Ethylene Oxide," which you should have recently received. These are the result of conversations between Ralph Cook and I regarding the draft which was previously sent to you.

On page 2 of Abstract (lines 14 and 15): strike out "...and no specific future studies were suggested."

On page 13 of paper (line 17): strike "Both urine protein and urinary", and also strike lines 18, 19 and 20.

On page 15 of paper (line 8): strike "As noted above", and also strike lines 9, 10 and 11. At the beginning of line 12, insert "Elevated...". Also strike line 15 through the end of the page.

On page 15, also, after line 14, insert: "little importance relative to potential EO exposures. Each individual with abnormal urine findings was evaluated clinically. Two of the potentially exposed had sperm in their urine, while one other had acute urethritis. In all others, the findings were transitory in nature and no disease was diagnosed."

On page 16 (lines 7 and 8): strike "...and no specific future studies were suggested."

DOW CHEMICAL U.S.A.

1803 Building
2 December 1981

MIDLAND, MICHIGAN 48640

MEMORANDUM

TO: M. F. CURRIER
P. L. POSTON
W. E. LEDFORD

FROM: G. L. CARLO

CC: R. R. COOK

Attached please find a draft of our report, "A Cross-Sectional Study of Employees with Potential Workplace Exposure to Ethylene Oxide." This draft reflects the input of the Epidemiology Group whose comments were incorporated after their review of an earlier draft. Please note that Table 3 is only partially complete, since Perry is working on preparing the missing data. That table, however, has no bearing on our results and review without the missing data presents no real problem.

If you have no major criticisms, please sign the approval sheet and send it back to me so that I might initiate the CRI review process here. (We need the original signatures here.) If you do have major concerns, please call me and we can discuss them.

My feeling is that, after CRI approval, the paper should be submitted to the Journal of Occupational Medicine for publication.

Att.

APPROVAL FOR OUTSIDE RELEASE OF
PROPRIETARY TECHNICAL INFORMATION

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1. To be completed by AUTHOR AND sent to SUPERVISOR

Manuscript Title: A CROSS-SECTIONAL STUDY OF EMPLOYEES WITH POTENTIAL WORKPLACE EXPOSURE TO ETHYLENE OXIDE

Author(s): Carlo GL, Currier MF, Poston PL and Ledford WE.

To be presented or (published) (circle one): Journal of Occupational Medicine

Questions concerning manuscript are to be directed to:

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Building 1803 City Midland Date Needed 18 Dec. 1981

Suggested reviewers:

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DEPARTMENTAL APPROVAL FOR RELEASE

I have read this manuscript and approve its release at this time as being in the best interests of The Dow Chemical Company.

Immediate Supervisor and Date
R. R. Cook, M.D.

Laboratory Director and Date

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J. R. Venable, M.D.

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A CROSS-SECTIONAL STUDY OF EMPLOYEES WITH
POTENTIAL WORKPLACE EXPOSURE TO
ETHYLENE OXIDE

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A CROSS-SECTIONAL STUDY OF EMPLOYEES WITH POTENTIAL WORKPLACE EXPOSURE TO ETHYLENE OXIDE

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Acknowledgement

We would like to extend our sincerest thanks to the following individuals for their contributions to this work: Ken Bodner, M.P.H., Dow Chemical U.S.A., Ralph Cook, M.D., M.P.H., Dow Chemical U.S.A., Jed Diem, Ph.D., Tulane University, and Dirk Van Peenen, M.D., Dr. P.H., formerly of Dow Chemical U.S.A.

Abstract

A Cross-Sectional Study of
Employees with Potential Workplace
Exposure to Ethylene Oxide

Currier MF, Carlo GL, Poston PL, Ledford WE

This paper describes the results of an epidemiological inquiry conducted among a cohort of employees of a large chemical manufacturing complex. The first objective of this inquiry was to identify, for future reference, the group of workers with potential exposure to ethylene oxide (EO), and the group of workers who have never had potential EO exposure. The second objective was to determine whether the group of current workers with potential EO exposure had a higher prevalence of abnormalities of the hematopoietic, hepatic, renal and reproductive systems, as measured by data collected through periodic health examinations, than did an appropriately matched control group.

Ninety-six full time employees with potential workplace exposure to EO were identified through personnel records. One thousand three hundred and forty three full time employees not involved in the EO processes or in Research and Development or Instrumentation were identified and classified as not exposed.

In the cross-sectional portion of the inquiry, eighty-four male employees who had been working for at least 6 months in processes involving EO exposure, prior to the time of their 1980 health examination, were matched to individuals not involved in those processes, on age, hire date, race, smoking history, alcohol intake and date of health examination. Results of hematology (Hgb, Hct,

RBC, WBC, percent lymphocytes) and blood chemistry (total bibirubin, alkaline phosphatase, LDH, SGPT, SGOT and GGTP) tests yielded no statistically significant differences between the two groups. Results of kidney function (BUN, serum creatinine, urine protein, RBC and WBC) tests revealed a statistically significant excess of individuals in the potentially exposed group with urine protein levels above the reference range; however, because of other medical conditions present among some of those reported as abnormal, this finding was not considered clinically significant. Cursory review of responses to the reproductive and medical history portions of the health inventory questionnaire, from a clinical perspective, suggested that these data were noncontributory.

Within the limitations of this cross-sectional study design, there were no indications of significant problem areas and no specific future studies were suggested.

Ethylene oxide (EO) is an important industrial chemical used in the manufacture of such products as ethylene glycol, polyesters, nonionic surface-active agents, heavy duty home laundry detergents, and glycol ethers (e.g., solvents for surface coatings).[1] It is also used as a pesticide fumigant and a cold sterilant for medical equipment. At room temperature and normal atmospheric pressure it is a colorless gas; at higher pressures it may be a volatile liquid. In the United States, where 43 percent of the world production capacity is held, production of EO has increased from 1.3 billion pounds in 1960 to 5.3 billion pounds in 1979.

Acute intoxication with EO at high concentrations has been recognized as a cause of eye, respiratory tract and skin irritation, and of central nervous system depression.[2] Suspected delayed effects include headache, nausea, vomiting, incoordination, and electrocardiograph abnormalities. Levels responsible for acute effects have been estimated at above 2000 ppm for very short single exposures and above 200 ppm for continuous 8 hour exposures.[3] The American Conference of Governmental Industrial Hygienists lists an 8-hour time-weighted-average (TWA) concentration of 10 ppm for the EO threshold limit value (TLV) in its Notice of Intended Changes for 1980. The current OSHA permissible exposure limit (PEL) is 50 ppm TWA.

The first epidemiological inquiry into the possibility of adverse chronic effects resulting from EO exposure was reported in 1964.[4] This cross-sectional study involved 37 EO operators engaged in manufacturing operations, and age-matched control operators working with chemicals other

than EO. The highest air level of EO recorded was 127 ppm; however, the average levels were less than 10 ppm for the working day. In their study, the EO group reported fewer symptoms and less absenteeisms than the controls. In addition, the frequency of "abnormal" laboratory findings in the study and control groups was equivalent.

In more recent years, however, there have been epidemiological studies conducted which have suggested positive associations between EO exposure and human illness. For example, a cross-sectional study of employees involved in cold sterilization using EO, revealed varying frequencies of symptoms such as sore throat among 12 exposed employees, versus no symptoms of any kind in a control group.[5] Cytogenetic studies by these same investigators reportedly showed more frequent sister chromatid exchanges (SCE's) among the 12 employees than among the 11 controls (average SCE's 8.65 versus 6.37). In addition, another investigation reported peripheral neuropathy with decreased nerve conduction velocity among 4 men after overexposure to EO.[6]

Concern also has been expressed regarding the possible carcinogenicity of EO. Results of an industry-sponsored inhalation study showed an increased, dose-related incidence of mononuclear cell leukemia in male and female Fischer 344 rats.[7] Effects were noted at exposure levels of 100, 33, and 10 ppm. Because of the chemical's alkylating agent properties,[8] and because it is mutagenic in several test systems including Neurospora,[9] plants,[10] and the Salmonella typhimurium strain TA 1535 bacterial assay,[11] carcinogenicity is biologically plausible.

Recently, there have been two reports from Sweden regarding human malignancies allegedly associated with EO exposure. The first was of a case each of acute myelogenous leukemia, chronic myelogenous leukemia, and Waldenstrom's macroglobulinemia, diagnosed between 1972 and 1977, among employees of a small factory which used EO for sterilization.[12] In a subsequent retrospective mortality study of employees in an EO production facility, the same author reported more deaths from leukemia than would have been expected (3 observed versus less than 0.5 expected) using Swedish national death rates as a standard.[13] Two of the leukemia deaths were caused by chronic lymphatic leukemia and one was caused by acute myeloid leukemia. The significance of these epidemiologic findings are limited, however, by the small number of observed deaths and the uncertainty of worker exposure information. In addition, a more recent cohort mortality study by Morgan et al.[14] revealed no deaths from leukemia among EO workers.

Because the results of previously reported epidemiological studies of EO exposure were conflicting, the development of an additional occupational epidemiology data base was seen as an important contribution to the understanding of the relationship between EO exposure and possible adverse health effects. This paper describes an inquiry conducted among a cohort of employees in a large U.S. chemical manufacturing complex.

The first objective was to identify the group of workers with potential exposure to EO, and a group of workers who have never had potential EO exposure. The a priori definition of these groups was seen as important in expediting any future EO studies. The second objective was to determine whether current workers with potential EO exposure had a higher preval-

ence of abnormalities of the hematopoietic, hepatic, renal, and reproductive systems, as measured by data collected through periodic health examinations, than did appropriately matched current workers who never had potential exposure to EO. The results of this prevalance study were seen as valuable in generating hypotheses regarding specific questions in need of further investigation.

MATERIALS AND METHODS

A. Cohort Identification

Process description and exposure information. Within the chemical manufacturing complex, there are two groups of employees who may have exposure to EO. The first group is comprised of those individuals involved in the production of EO and ethylene glycol. The second group, considered mainly as users of EO, is comprised of those employees involved in the production of the DOWANOLS* and ethanolamines. Personnel sampling for EO exposure has been done at various times for both groups of workers by collecting breathing air zone samples on activated charcoal. Samples are desorbed with carbon disulfide and analyzed by flame ionization gas chromatography. All measured eight-hour TWA EO exposures for those employees involved in EO and ethylene glycol production have been well below the TLV. The loading operating technicians have had the highest exposures with a range of yearly average TWA exposures from <1.0 ppm in 1977 to 1.7 ppm in 1980. Among this group the range of individual measurements has been <.1 ppm to 5.7 ppm. All other jobs have had yearly average TWA exposures below 1.0 ppm. Grab-samples taken since 1973 to determine peak exposure levels have indicated excursions for the loading job as high as 235 ppm (in 1976), while all other jobs had peak exposures below 100 ppm, with most being below 20 ppm. Since the loading job requires wearing a supplied air respirator, the exposure measurements for this job represent only potential exposures. Other chemicals to which EO and

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ethylene glycol production employees might be exposed include ethylene dichloride (EDC), DOWTHERM* A (biphenyl and biphenyl oxide), and ethylene glycol. Exposure levels for all of these have been well below their respective TLVs. The only one of any substantial toxicity, EDC, is used in very small quantities (less than one 55-gallon drum per month), and is usually handled by only one job classification for approximately one minute every other day.

The highest recorded EO exposure among personnel involved in the production of the DOWANOLS* and ethanolamines was 0.1 ppm during the bleeding down of some EO containing equipment in 1980. Other chemicals to which these employees might be exposed include propylene oxide, methanol, butanol, ammonia, the mono-, di- and tri- ethanolamines, and the DOWANOLS* EB, DB, TBH, PM, DPM and TPM. For the most part, 8-hour TWA exposures to these chemicals are generally below 1.0 ppm.

Definition of the populations potentially exposed and not exposed to EO. Figure 1 outlines the procedure through which the potentially exposed and unexposed populations were identified.** The potentially exposed group was comprised of the full-time employees ever involved in the production of EO, ethylene glycol, the DOWANOLS* or ethanolamines as identified through personnel lists. The group of individuals who did not meet the work history requirement were considered as candidates for the unexposed group. Eliminated from this group because their overall exposures would likely be ill-

**Throughout this report, reference is made to the "potentially exposed" population. Exposure measurements were not carried out on every individual included in this study; therefore, actual exposure could not technically be documented.

defined, were those who were not full-time employees, and those who were involved in either Research and Development or Instrumentation. Thus, the total number of employees considered unexposed was 1343.

B. Cross-Sectional Health Inventory Study

The major analytical portion of this research involved the assessment of whether a differential prevalance of certain abnormalities of the hematopoietic, hepatic, renal and reproductive systems existed between the workers potentially exposed and the group of appropriately matched unexposed workers. A readily accessible data base suited for this cross-sectional analysis was that maintained as part of the health inventory program, which is a voluntary annual health examination offered to all production employees of the manufacturing complex. It includes both a medical history and a laboratory work-up.

Potentially exposed and Unexposed groups. Extracted from the overall list of potentially exposed (as defined previously), were all employees who had been working for at least 6 months in the processes involving EO exposure prior to the time of their 1980 health examination. Employees with previous service in these areas were not included in the potentially exposed study group, but neither were they eligible to become matched unexposed controls. Females were not included because there were so few, and it was also necessary to exclude those for whom complete 1980 health examinations data were not available. Thus, from the 96 individuals in the original pool of potentially exposed, six females and six males with insufficient health inventory data were eliminated. The 84 employees remaining represented 93.3 percent of the total potentially exposed group.

Eliminated from the list of unexposed were 127 females, 75 individuals with less than 6 months employment within the chemical complex, and 87 individuals judged to have potential exposure to benzene (benzene is suspected of having hematopoietic effects and thus might be considered a competing exposure). Another 93 individuals were eliminated because they did not participate in the 1980 health inventory. The remaining 939 individuals eligible for control matching represented 91.1 percent of the original unexposed pool.

A single unexposed control was then matched to each member of the potentially exposed group. For each employee in the potentially exposed group, a search of the entire group of controls was initiated to determine matching candidates. If a control candidate was previously selected as a control match, he was excluded from the process for any subsequent matching. The matching criteria were, in order, as follows: age (within 5 year intervals), hire date ($\pm$ 5 years), race, smoking history (non-smoker, current cigarette smoker, ex-smokers and cigar or pipe smokers combined), and alcohol intake (light, moderate, heavy). The entire list of control candidates for a particular potentially exposed individual was thus compiled. As a final matching step, the date of the 1980 health inventory exam was utilized to control for common seasonal occurrences such as influenza, common colds, etc., which might impact on the outcome variables to be studied. In two cases, appropriate matches could not be found. In one instance, the date of hire criterion was relaxed from $\pm$ 5 to $\pm$ 6 years for the control, and in another instance, the age group criterion was relaxed to match a 19 year old in the 15-19 year age group with a 20 year old in the 20-24 year age group.

Analytical variables. The analytical outcome variables were extracted from records of results of the 1980 health inventory examinations. The laboratory test variables, their reference ranges, and the suspected directions of the change in value if an effect is present, are listed in Table 1. These tests were considered those most likely to be influenced if EO was, in fact, causing health problems based on a review of the EO related literature. Table 2 lists other non-laboratory test variables, available from the questionnaire portion of the health inventory, which might be expected to be influenced by EO. Unlike the laboratory analyses, where the results are at least applicable to the day on which the samples were collected, and thus temporally associated with the potential exposure, it was not possible to determine whether these historical data had any temporal relevance at all to the potential exposure. Because of the historical nature of these data and their quality (based on subjective recall), no rigorous statistical analyses were applied to them.

The exposure variable, or independent variable, was current involvement in the production of EO, ethylene glycol, the DOWANOLS* or the ethanolamines as described above.

The matching criteria described above made it possible to control for the potential confounding variables age, hire date, race, smoking and alcohol consumption history, and date of health inventory.

Statistical analysis. Because using matched controls made the overall study population appear as "pre-dose" (unexposed) and "post-dose" (potentially exposed) populations, and because normal distribution was not neces-

sarily assured, the non-parametric Wilcoxon Signed Rank Test[15] was utilized as the analytic statistic for the continuous data. The value for the unexposed subject was subtracted from the value for the potentially exposed subject and both the positive rank sum statistic (T+) and the large sample approximation (T*) to the normal distribution were calculated. A p-value was then calculated based on T* to test the hypothesis of a zero median difference between the two populations. The continuous variables analyzed in this manner were: Hbg, Hct, RBC, WBC, percent lymphocytes, total bibirubin, alkaline phosphatase, LDH, SGPT, SGOT, GGTP, BUN and serum creatinine. In addition, because of the clinical implications of values outside of a given reference range, these data were also analyzed as dichotomous or multichotomous variables. For those variables where the implications were important for values either above or below the reference range, (i.e. Hgb, Hct, RBC, blood chemistries and kidney functions), each value was categorized as being normal (within the reference range) or abnormal. A p-value was then calculated, based on the number of discordant pairs ("potentially exposed" versus "unexposed") which indicated more abnormals among the potentially exposed, to test the hypothesis that the values were the same in both groups (Exact Probability Test[15]). Urine protein, urine WBC, and urine RBC, were also analyzed in this manner. Because the implications of values both below and above the reference range for WBC and percent lymphocytes were thought to be important, the Maxwell-Stuart extension of McNemar's test[16] was utilized to produce a chi-square statistic from which a p-value could be derived pertinent to a multi-chotomous stratification.

Results

A. Cohort Identification for Future Follow-up. Table 3 gives the frequency distribution by race, sex, and age for both the group of employees ever involved in the production of EO, ethylene glycol, the DOWANOLS* and the ethanolamines, and the group never involved in such production. For the purpose of reference for future studies, the first group can be considered as those potentially exposed to EO, and the second group as those probably unexposed. These descriptive statistics are important in determining the proper methodological approach in future studies regarding EO exposure. Both the lists of potentially exposed and unexposed were maintained for future access as necessary.

B. Cross-sectional Health Inventory Study. As Tables 4 and 5 indicate, the process of matching the selected potentially exposed and unexposed individuals was very efficient. There were no striking differences between the potentially exposed and unexposed groups chosen for analysis, for either the matched variables or selected unmatched variables.

In Tables 6, 7 and 8 are the results of the hematology, kidney function and blood chemistry analyses. For interpretive purposes, it should be noted that the higher values for the large sample approximation in the Wilcoxon test (T) indicate that the median value of the potentially exposed group was larger than that in the unexposed. For Hgb, Hct and RBC, the critical test area was at the lower end of the probability curve; therefore, the lower values were of interest. For WBC and % lymphocytes, both low and high values were of interest; therefore, two-tailed significance tests were applied. For all other variables where the Wilcoxon test was utilized, a one-tailed test considering the higher values as critical was applied.

Also, the Wilcoxon's test applied to the continuous data was interpreted as indicative of physiologically significant effects, while the exact probability and the Maxwell-Stuart tests, applied to the categorical data, were interpreted as indicative of clinically significant effects.

Table 6 shows that none of the differences in hematology between the potentially exposed and unexposed groups approaches statistical significance. Similarly, the results of the blood chemistry analyses (Table 8) show no statistically significant differences between the potentially exposed and unexposed, from either a physiological or a clinical perspective. In Table 7, however, it can be seen that a statistically significant excess of individuals within the potentially exposed group had abnormally high urine protein levels. Of eight instances where the values for a potentially exposed individual and his matched control were discordant, seven had the abnormal value reported for the potentially exposed individual. Approaching statistical significance was the excess of individuals within the potentially exposed group with urine WBC above the reference range. Both urine protein and urinary WBC were reported and analyzed as nonparametric data; therefore, nothing can be said regarding the physiological significance of these findings. The clinical implications, however, will be addressed in the next section.

Cursory review of the responses to the reproductive and medical history portions of the health inventory questionnaire, from a clinical perspective, suggested that these data were noncontributory.

Discussion

Cross-sectional or prevalence studies are traditionally utilized as hypothesis generating instruments. Because disease incidence is not the outcome parameter, (i.e., not possible to determine whether exposure preceeded effect) the cross-sectional study is not appropriate for definitively investigating cause and effect. This type of study is, however, generally believed to be capable of suggesting the presence of profound cause-effect relationships, given a sound study design.

In this investigation, the methodological rigor was enhanced by the incorporation of the one-for-one matching of potentially exposed with unexposed individuals. However, with the inclusion of the date of health inventory as the last matching step, an additional potential bias was encountered. Because entire plants within the chemical complex were generally scheduled for the examinations each month, the matched control group could have potentially included a disproportionately large number of individuals from a particular plant or plants. If that were the case, the comparison studied might be of potential exposure to ethylene oxide and potential exposure to another chemical. To address this possible problem, the distribution of plant-specific job titles for the entire chemical complex was ascertained, and compared to the similar distribution among the matched controls. The only discrepancy between the distributions for the two groups was a disproportionably large number of workers from a cellulose production area among the matched controls (17.8 percent versus 6.6 percent of the totals).

However, the chemicals utilized in the cellulose production area were not considered to be of significance; thus, this slight discrepancy was judged to be unimportant in terms of affecting the results of the investigation.

The only positive findings of this inquiry were the statistically significant excess in the number of potentially exposed with urine protein values above the reference range, and the borderline of significance excess of potentially exposed with high urine WBC levels. As noted above, it was not possible to assess the physiological significance of these excesses. However, neither an increase in urine protein or urine WBC is considered to be indicative of specific clinical conditions. Excess of urine protein and urine WBC might be considered of medical importance when found in conjunction with other abnormal laboratory or clinical findings; however, within the context of this study, they were judged to be of little importance. The finding of clinical proteinuria on routine examination could be the result of many conditions including medically inconsequential sperm in the urine, acute febrile disorders, central nervous system lesions and genito-urinary infections. In this study, two of the potentially exposed individuals had sperm in their urine while one other had acute urethritis. The presence of excessive numbers of white blood cells in the urine is commonly associated with inflammatory processes and infections, and is also not considered alone to be a discriminator of specific disease.

This study, then, has found no major differences in the prevalence of various conditions between individuals potentially exposed to EO and unexposed individuals. This finding is consistent with earlier work reported by Joyner[4] who found the frequency of abnormal laboratory findings to be the same among 37 EO operators and matched controls. Within the limitations of this cross-sectional study design, there were no indications of significant problem areas and no specific future studies were suggested.

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Figure 1

Identification of Potentially Exposed and Unexposed Populations

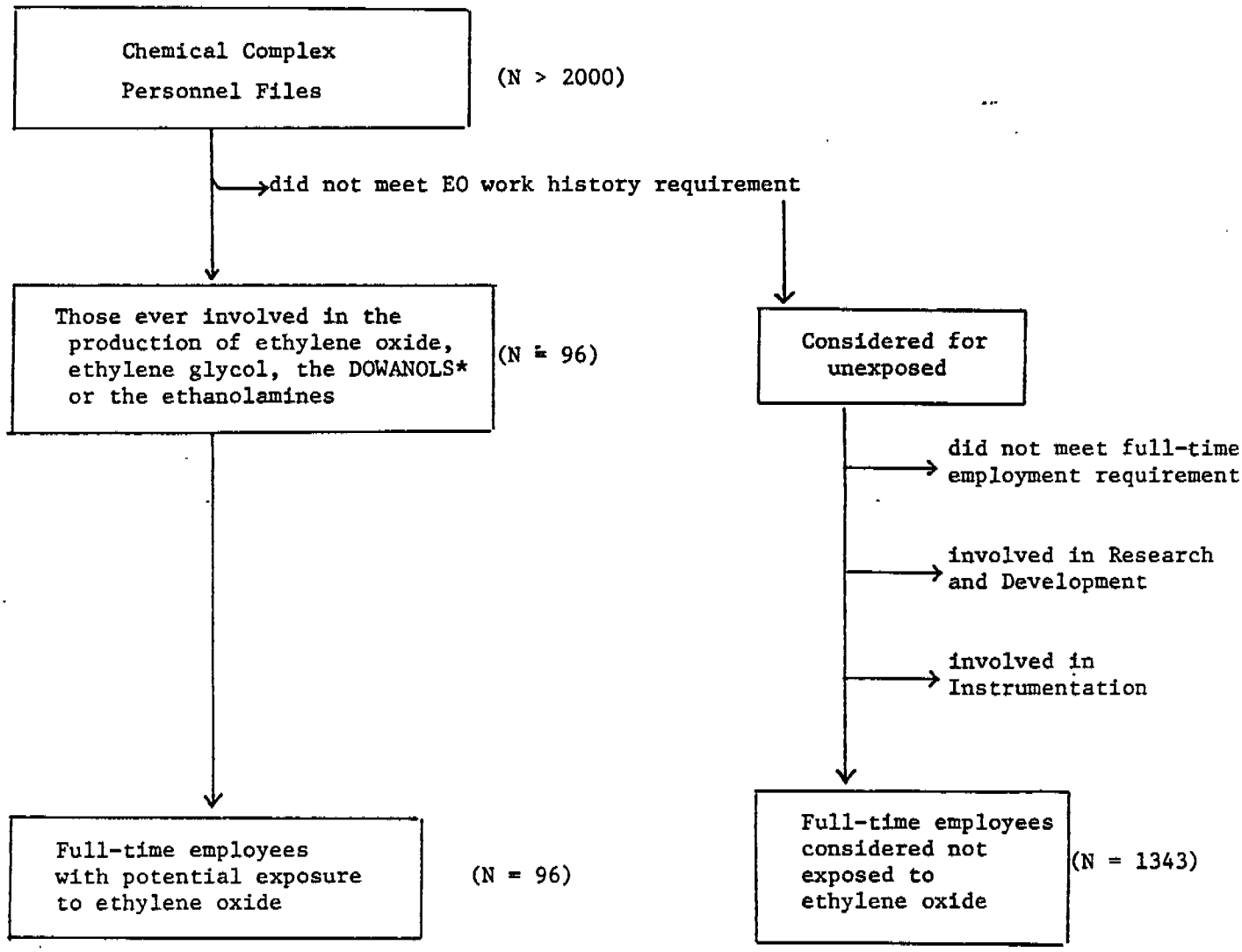

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Table 1
Laboratory Test Outcome Variables,
Reference Ranges and Suspected Direction of
Value Change If An Effect is Present

Group	Test	Reference Range	Direction of Suspected Change if Effect Present
Hematology*			
	Hgb	14-18 Gm%	low
	Hct	40-54%	low
	RBC	4.6-6.2 million/mm^3	low
	WBC	4.5-11.0 thousand/mm^3	low or high
	Percent Lymphocytes	25-33%	low or high
Kidney**	BUN	8-26 mg/dl	high
	Serum Creatinine	0.9 - 1.4 mg/dl	high
	Urine Protein (1+ or greater)	negative	high
	RBC	2	high
	WBC	0-3	high
Liver**	Total Bilirubin	<1.6 mg/dl	high
	Alkaline Phosphatase	35-148 units	high
	LDH	63-155 IU/L	high
	SGPT	12-53 units	high
	SGOT	15-55 units	high
	GGTP	<38 U/L	high

*reference range based on Conn[18]

**reference range according to Bio-Science Laboratory, Van Nuys, California

Table 2

Non-Laboratory Test Outcome
Variables Available Through
The Health Inventory Questionnaire

Questionnaire Item	Type of Response
Has your family had any of the following:	
Birth Abnormality	Yes or No for self; actual number among children
Miscarriages	Actual Number
Stillbirths	Actual Number
Death under 6 months	Actual Number
Do you have or have you had any of the following:	
Liver Trouble	Yes or No
Kidney Trouble	Yes or No
Anemia or Blood Problems	Yes or No
History of Blood dyscrasias	Yes or No
Abnormal function of Blood Elements	Yes or No
Liver or renal dysfunction	Yes or No

Table 3

Frequency Distribution by Race, Sex and Age for Employees Classified as Potentially Exposed to Ethylene Oxide and Unexposed

Race	Sex	Age	Potentially Exposed N	Potentially Exposed % of Total	Unexposed N	Unexposed % of Total
White	Males	<20	1	1.0	13	1.0
		20-29	38	39.6	333	24.8
		30-39	28	29.2	312	23.2
		40-49	9	9.4	294	21.9
		50-59	0	0.0	22	1.6
		60+	0	0.0	8	1.0
		All ages	76	79.2	982	73.1
White	Females	<20	0	0.0	2	0.0
		20-29	3	3.1	67	5.0
		30-39	1	1.0	24	1.8
		40-49	0	0.0	10	1.0
		50-59	0	0.0	1	0.0
		60+	0	0.0	0	0.0
		All ages	4	4.2	104	7.7
Non-white	Males	<20	0	0.0	2	0.0
		20-29	8	8.3	137	10.2
		30-39	6	6.3	81	6.0
		40-49	0	0.0	13	1.0
		50-59	0	0.0	1	0.0
		60+	0	0.0	0	0.0
		All ages	14	14.6	234	17.4
Non-white	Females	<20	0	0.0	15	1.1
		20-29	1	1.0	8	1.0
		30-39	1	1.0	0	0.0
		40-49	0	0.0	0	0.0
		50-59	0	0.0	0	0.0
		60+	0	0.0	0	0.0
		All ages	2	2.0	23	1.7
Overall Total			96	100.0	1343	100.0

Table 4

Results of Matching Individuals Potentially Exposed to EO and Individuals Unexposed, Absolute Frequencies in Age and Race Groups

	Potentially Exposed		Unexposed	
	Race		Race	
Age	White	Non-white	White	Non-white
<20	1	0	0	0
20-24	18	2	19	2
25-29	19	4	19	4
30-34	12	4	12	4
35-39	14	2	14	2
40 +	8	0	8	0
All Ages	72	12	72	12
Median Age (in years)	29.0		29.0	
Mean Age (in years)	30.0		30.2	

Table 5

Results of Matching Individuals Potentially Exposed to EO and Individuals Unexposed, Selected Matched and Un-matched variables Extracted from Health Inventory Questionnaire

Variable	Potentially Exposed	Unexposed
Mean length of service	7.52	7.48
Total non-smokers	30	30
Total former smokers	17	17
Total current smokers	37	37
Family histories of leukemia	5	3
Family histories of cancer	33	28
Family histories of blood disorders	1	2
History of diabetes	0	3
History of asthma	3	10
History of arthritis	4	5

Table 6

Results of Hematology Analyses,
Individuals Potentially Exposed to
Ethylene Oxide versus Individuals
Unexposed

Outcome Variable	Wilcoxon's Signed Rank T**	p	Exact Probability DEA/TD***	p	Maxwell-Stuart Extension Test X^2	p
Hgb	1.02	>.500	3/7	>.500	-	-
Hct	1.18	>.500	2/3	.500	-	-
RBC	-0.56	.288	5/9	.500	-	-
WBC*	-0.69	.490	-	-	1.14	>.500
% lymphocytes*	1.06	.390	-	-	2.06	.357

* two-tailed test

** large sample approximation to normal distribution

*** ratio of the number of discordant pairs where potentially exposed was classified as abnormal to the total number of discordant pairs.

Table 7

Results of Kidney Function Analyses,
Individuals Potentially Exposed to
Ethylene Oxide versus Individuals
Unexposed

Outcome Variable	Test Statistic: Wilcoxon's Signed Rank T*	p	Exact Probability **DEA/TD	p
BUN	-2.02	>.500	0/0	-
Serum Creatinine	-0.40	>.500	0/0	-
Urine Protein	-	-	7/8	.035
RBC	-	-	4/8	>.500
WBC	-	-	8/10	.055

* large sample approximation

** ratio of the number of discordant pairs where potentially exposed was classified as abnormal to the total number of discordant pairs

Table 8

Results of Blood Chemistry Analyses, Individuals Potentially Exposed to Ethylene Oxide versus Individuals Unexposed

Outcome Variable	Test Statistic: Wilcoxon's Signed Rank T*	p	Exact Probability **DEA/TD**	p
Total bibirubin	-0.32	>.500	2/2	.250
alkaline phosphase	0.90	.184	0/1	-
LDH	-0.45	>.500	0/1	-
SGPT	0.52	.302	8/14	.395
SGOT	-0.82	>.500	3/9	>.500
GGTP	0.42	.337	5/11	>.500

* large sample approximation to normal distribution

** ratio of the number of discordant pairs where potentially exposed was classified as abnormal to the total number of discordant pairs.

PROCEDURES FOR INITIATING COMPUTERIZED HANDLING OF ETHYLENE OXIDE EXPOSURE DATA:

1) CREATE PROGRAM THAT WILL FIRST DETERMINE WHO WAS IN GLYCOL II AND/OR DOWANOLS/ETHANOLAMINES IN 1980 AND IF THEY HAD BEEN IN LONGER THAN 6 MONTHS.

2) THIS LIST WILL BE KEPT AND SENT TO PROGRAM THAT WILL ELIMINATE FEMALES AND CONTRACTORS AND THEN BREAK LIST INTO WHITE MALES AND BLACK MALES

3) THESE 2 LISTS WILL THEN BE SENT TO PROGRAM THAT WILL DETERMING IF A HEALTH INVENTORY HAD BEEN PERFORMED IN 1980 -

A) IF SO, THE EMPLOYEE will REMAIN ON THE LIST

B) IF NOT, THE EMPLOYEE will BE REMOVED FROM THE ACTIVE LIST AND will PRINT MESSAGE - THE REASON WHY THE EMPLOYEE HAD NO H.I. MUST BE MANUALLY DETERMINE

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4) THE LISTS FROM 3A WILL BE PASSED TO THE MATCHING ROUTINES FOR A CONTROL POPULATION

A) FOR EACH EMPLOYEE ON THE LIST, THE EMPLOYEE FILE WILL BE SEARCHED FOR THE FOLLOWING -

1) THE EMPLOYEE MUST NOT HAVE PREVIOUS GLYCOL I, GLYCOL II, OR DINAMOLS/ETHANOLAMINES HISTORY. THIS OBVIOUSLY PRECLUDES ANY MATCH FOR ANYONE ELSE ON THE EXPOSED LIST

2) IF THE EMPLOYEE HAS NO PREVIOUS EXPOSURE, THE MEDICAL DATA FILES WILL THEN BE SEARCHED (FORM 03) TO DETERMINE IF A HEALTH INVENTORY WAS PERFORMED IN 1980 [redacted]

A) IF SO, THE CONTROL CANDIDATE IS SENT FOR FURTHER EDITING

B) IF NOT, THE CANDIDATE IS DISCARDED AND THE SEARCH CONTINUES

NOTE: THIS WILL, FOR THE MOST PART, PRECLUDE ANY OFFICE WORKERS FROM BLOCKS 33 & 23 (WITH THE POSSIBLE EXCEPTION OF X-EXPOSURE PERSONELL)

FROM BEING IN THE CONTROL POPULATION, SINCE [redacted] ARE NOT NORMALLY OFFERED TO THESE EMPLOYEES

3) THE CONTROL CANDIDATE SENT FROM STEP 3A WILL THEN BE EDITED FOR A MATCH ON RACE AND SEX, IF BOTH OF THESE CRITERIA ARE NOT MET, THE CONTROL CANDIDATE IS DISCARDED AND THE SEARCH CONTINUES

4) IF RACE AND SEX MATCH, AGE IS THEN CALCULATED TO SEE IF THE CONTROL CANDIDATE IS WITHIN THE SAME AGE RANGE (INCREMENTS OF 5 YEARS) IF SO, THE CONTROL CANDIDATE IS PASSED TO THE NEXT MATCHING ROUTINE, IF NOT, THE CANDIDATE IS DISCARDED AND THE SEARCH CONTINUES

5) IF THE PREVIOUS MATCHES ARE SUCCESSFUL A TEST IS MADE TO SEE IF THE HIRE-DATE OF THE CONTROL CANDIDATE IS WITHIN 12 MONTHS BEFORE OR AFTER THE EXPOSED EMPLOYEE. IF THE TEST IS SUCCESSFUL, THE CONTROL CANDIDATE IS PASSED TO THE NEXT MATCHING ROUTINE,

IF NOT, THE CANDIDATE IS DISCARDED AND THE SEARCH CONTINUES

NOTE: THE 12 MONTH RANGE IN HIRE-DATE MAY BE LESSENED TO 6 MONTH RANGE IN DETERMINING THE CONTROL EMPLOYEE IF SEVERAL CONTROL CANDIDATES EXIST FOR THE EXPOSED EMPLOYEE

4) IF THE HIRE DATE TEST IS SUCCESSFUL - A CHECK TO SEE IF A MATCH ON SMOKING AND ALCOHOL HISTORY CAN BE OBTAINED. SMOKING WILL BE BROKEN INTO 3 CATEGORIES; NON-SMOKER, FORMER SMOKER, CURRENT SMOKER. ALCOHOL HISTORY WILL BE BROKEN INTO 3 CATEGORIES LIGHT DRINKER, MODERATE DRINKER, HEAVY DRINKER. IF A SUCCESSFUL MATCH ON THE SMOKING AND ALCOHOL HISTORY CAN BE OBTAINED, THE CONTROL CANDIDATE IS PASSED TO THE PROCESSING ROUTINES FOR FINAL SELECTION. IF A MATCH CANNOT BE SUCCESSFULLY OBTAINED, THE CONTROL CANDIDATE IS DISCARDED AND THE SEARCH CONTINUES.

B) ONCE A CONTROL CANDIDATE HAS BEEN FOUND TO BE ACCEPTABLE, THE ENTRY IS MADE IN A LIST OF ALL POTENTIAL CONTROL MATCHES FOR THE EXPOSED EMPLOYEE, AND THE EMPLOYEE FILE IS SEARCHED FOR ANY MORE POTENTIAL CONTROL MATCHES FOR THE EXPOSED EMPLOYEE; IF MORE ARE FOUND, THEY ARE PLACED IN THE CANDIDATE LIST.

C) ONCE A COMPLETE SEARCH OF THE EMPLOYEE FILE HAS BEEN MADE AND THE LIST OF POTENTIAL CONTROL MATCHES HAS BEEN COMPLETED, THE LIST IS SENT TO THE FINAL PROCESSING ROUTINES.

D) IF THE POTENTIAL CANDIDATE LIST CONTAINS MORE THAN 1 EMPLOYEE, A TEST IS USED TO DETERMINE IF ANY HAVE A HIRE-DATE WITHIN 6 MONTHS OF THE HIRE-DATE OF THE EXPOSED EMPLOYEE. IF ANY ONE CANDIDATE FULFILLS THE REQUIREMENT HE IS USED AS THE CONTROL MATCH.

A) IF MORE THAN ONE CANDIDATE MEETS THE REQUIREMENT, THE CANDIDATE

WITH THE CLOSEST HIRE-DATE IS CHOSEN AS THE CONTROL MATCH.

B) IF NO CANDIDATE MEETS THE CRITERIA, THE CANDIDATE WITH THE CLOSEST HIRE-DATE TO THE EXPOSED EMPLOYEE IS CHOSEN AS THE CONTROL MATCH.

NOTE: HIRE-DATE USED IN THIS SENSE REFLECTS START DATE THAT IS CLOSEST TO TOTAL TIME OF EXPOSURE FOR THE STUDY EMPLOYEE, i.e. A START DATE OF 01-01-77 IN GLYCOL II OR DOWANDLS (AND ASSUMING CONTINUED SERVICE UNTIL 01-01-81) SHOULD BE MATCHED WITH A CONTROL CANDIDATE WHOSE HIRE DATE IN DOW IS MOST CLOSELY MATCHED TO 01-01-77.

5) ONCE A MATCH IS FOUND FOR THE EXPOSED EMPLOYEE, THE PERTINENT DEMOGRAPHIC INFORMATION IS REPORTED, STORED FOR VARIOUS SUMMARY REPORTS, AND THE INFORMATION IS STORED FOR ACCESS BY THE PROGRAMS IN PHASE II OF THE STUDY, THE DATA ANALYSIS PHASE.

6) ONCE THE APPROPRIATE INFORMATION CONCERNING THE EXPOSED EMPLOYEE AND HIS CONTROL MATCH IS STORED AND/OR REPORTED, THE NEXT STUDY EMPLOYEE IS OBTAINED, AND A NEW SEARCH IS INITIATED IN THE EMPLOYEE FILE STARTING IN STEP 4.

[redacted]

AFTER MATCHING IS PERFORMED:

1) PARTICIPATION RATE (GLYCOL II & DOXIANOLS)
AS NUMBER DID PARTICIPATE / NO. ELIGIBLE)

2) MAPPING DOWN GROUP Y / 2000 (AS EVERYONE ELIGIBLE)

3) CHARACTERISTICS OF EXPOSED GROUP (X)
COMPARED TO TOTAL ELIGIBLE (Y)

AGE: MEAN, MEDIAN, FREQUENCY DISTRIBUTION
FOR X - EXPOSED AVAIL FOR MATCHING MATCH CONTROLS Y - EVERYONE

RACE: PROPORTION NON-WHITE

SEX: PROPORTION FEMALE

DATE OF HIRE: MEAN, MEDIAN, FREQUENCY DIST.

HT, WEIGHT: MEAN, MEDIAN

DBP (DIAS BLOOD PRESSURE)

SMOKING: PROPORTION NEVER, EVER, CURRENT

ALC: LIGHT, MODERATE, HEAVY

PROPORTION: MEAN OR MEDIAN YES ANSWERS TO
QUESTIONS ON TABLE III B.

AFTER CHARACTERISTICS OF EXPOSED GROUPS FOUND:

3. COMPARISON OF DEPENDENT VARIABLES

A. CONTINUOUS (TABLE III A. 2, 3, & 4)

VARIABLE	EXPOSED RANGE	MEAN	MEDIAN	CONTROL "	"	P-VALUE (MANN-WHITNEY U.)
HLB	12.5-16.0	14.2	14.4			
⋮						

B. PROPORTIONS: (TABLE III A. 1.A & B)

VARIABLE	E+C+	E+C-	E-C+	E-C-	P VALUE (MANTAMARES,
YES %					

1) CYCLE II AND 3 ANIMALS BE CONSIDERED SEPARATELY

2) HANDLING OF % IF CONGENITAL ABORTIONS, MISCARRIAGES, ETC.

3) Y OR N, THEN NUMBER AS A DESCRIPTION

STEP 4 - CHARACTERISTICS OF THE EO STUDY GROUP

STEP 4 OF THE ETHYLENE OXIDE STUDY CONSISTED OF OBTAINING CHARACTERISTICS FOR THE EXPOSED POPULATION USED IN THE ETHYLENE OXIDE STUDY. THE FOLLOWING DESCRIPTIONS INDICATE CHARACTERISTICS OF THE STUDY GROUP THAT CAN BE VIEWED IN THE FOLLOWING ENCLOSURE.

THE FIRST REPORT CHARACTERIZES THE STUDY GROUP ACCORDING TO AGE, RACE, AND SEX. SINCE SEX IS EXCLUSIVELY MALE FOR THE STUDY, THE REPORT BASICALLY INDICATES THE SEX AND RACE BREAKDOWN FOR EACH AGE CATEGORY LISTED, STARTING WITH THE AGE CATEGORY OF THOSE LESS THAN 20 YEARS, THROUGH THE CATEGORY FROM AGES 20 THRU 24, 25 THRU 29, ETC TO END UP WITH THOSE OVER 99 YEARS.

THE SECOND REPORT INDICATES THE MEAN AND MEDIAN AGE OF THE ETHYLENE OXIDE STUDY GROUP IN TERMS OF YEARS.

THE THIRD REPORT INDICATES THE FREQUENCY AND THE CUMULATIVE FREQUENCY OF THE HIRE YEARS OBTAINED FOR THE ETHYLENE OXIDE STUDY GROUP. THE YEARS LISTED SIMPLY REFLECT THE YEARS ENCOUNTERED IN OBTAINING HIRE DATES FROM THE DEMOGRAPHIC FILES, AND THE NUMBER (FREQUENCY) OF THE EMPLOYEES (STUDY) HIRED DURING THAT PARTICULAR YEAR. INCLUDED ALONG WITH THE FREQUENCY OF HIRE YEAR IS THE CUMULATIVE FREQUENCY.

THE FOURTH REPORT SIMPLY INDICATES THE MEAN LENGTH OF SERVICE FOR ALL THE MEMBERS OF THE STUDY GROUP IN TERMS OF YEARS.

THE FIFTH AND FINAL REPORT INCLUDES A NUMBER OF SUMMARY CHARACTERISTICS INCLUDED AS PART OF THE POTENTIAL CONFOUNDING VARIABLES FOR THE STUDY GROUP. INCLUDED IS A BREAKDOWN OF THE SMOKING HISTORIES INTO TOTAL NUMBER NON-SMOKERS, TOTAL NUMBER FORMER SMOKERS, AND TOTAL NUMBER CURRENT SMOKERS (BASED ON 1980 HEALTH INVENTORY EXAM). A BREAKDOWN OF THE ALCOHOL HISTORY IS ALSO INCLUDED SUCH AS LIGHT ALCOHOL DRINKERS, MODERATE ALCOHOL DRINKERS, AND HEAVY ALCOHOL DRINKERS. A BREAKDOWN OF FAMILY HISTORY IS REPORTED INCLUDING NUMBER EMPLOYEES IN EXPOSED GROUP THAT HAD FAMILY HISTORIES OF BIRTH ABNORMALITIES, FAMILY HISTORIES OF LEUKEMIA, FAMILY HISTORIES OF BLOOD DISORDERS, AND FAMILY HISTORIES OF CANCER. ALSO, OUTSIDE EXPOSURES TO VARIOUS CHEMICALS AND AGENTS WERE ALSO LISTED INCLUDING TOTAL OUTSIDE EXPOSURES TO INSULATION, PAINT, GLUE, INSECTICIDE, FURNITURE REFINISHERS, METAL CLEANERS, BRICK LAYING AGENTS AND CHEMICALS USED IN BOAT BUILDING ACTIVITIES. AND FINALLY TOTALS WERE INCLUDED ON EXPOSED EMPLOYEES IN THE STUDY THAT RESPONDED POSITIVELY TO HISTORIES OF DIABETES, ASTHMA, AND ARTHRITIS.

AGE	MALES			FEMALES		
		WHITE	BLACK	OTHER	WHITE	BLACK	OTHER
<20	1	1	0	0	0	0	0
20-24	20	18	2	0	0	0	0
25-29	23	19	4	0	0	0	0
30-34	16	12	4	0	0	0	0
35-39	16	14	2	0	0	0	0
40-44	4	4	0	0	0	0	0
45-49	4	4	0	0	0	0	0
50-54	0	0	0	0	0	0	0
55-59	0	0	0	0	0	0	0
60-64	0	0	0	0	0	0	0
65-69	0	0	0	0	0	0	0
70-74	0	0	0	0	0	0	0
75-79	0	0	0	0	0	0	0
80-84	0	0	0	0	0	0	0
85-89	0	0	0	0	0	0	0
90-94	0	0	0	0	0	0	0
95-99	0	0	0	0	0	0	0
>99	0	0	0	0	0	0	0

TOTAL NUMBER EMPLOYEES IN STUDY GROUP - 84

MEAN AGE OF STUDY GROUP IN YEARS - 30.0

MEDIAN AGE OF STUDY GROUP IN YEARS - 29.0

MEAN LENGTH OF SERVICE FOR STUDY GROUP - 6.97

HIRE YEAR	FREQUENCY	CUMULATIVE FREQUENCY
1959	2	2
1960	1	3
1963	3	6
1964	2	8
1965	2	10
1966	4	14
1967	2	16
1968	7	23
1969	5	28
1972	4	32
1973	5	37
1974	10	47
1975	7	54
1976	7	61
1977	7	68
1978	9	77
1979	7	84

TOTAL NUMBER EMPLOYEES IN STUDY GROUP = 84

22 ARR 81 POTENTIAL CONFOUNDING VARIABLES FOR STUDY GROUP - - ETHYLENE OXIDE

TOTAL NUMBER STUDY GROUP - 84

TOTAL SMOKING/ALCOHOL HISTORIES UNAVAILABLE - 0

TOTAL NON-SMOKERS - 30
TOTAL FORMER SMOKERS - 17
TOTAL CURRENT SMOKERS - 37

TOTAL LIGHT ALCOHOL DRINKERS - 59
TOTAL MODERATE ALCOHOL DRINKERS - 20
TOTAL HEAVY ALCOHOL DRINKERS - 10

TOTAL FAMILY HISTORIES OF BIRTH ABNORMALITY - 5
TOTAL FAMILY HISTORIES OF LEUKEMIA - 5
TOTAL FAMILY HISTORIES OF BLOOD DISORDERS - 1
TOTAL FAMILY HISTORIES OF CANCER - 33

TOTAL HEALTH HISTORIES UNAVAILABLE - 20

TOTAL OUTSIDE EXPOSURE TO INSULATION - 6
TOTAL OUTSIDE EXPOSURE TO PAINT - 25
TOTAL OUTSIDE EXPOSURE TO GLUE - 17
TOTAL OUTSIDE EXPOSURE TO INSECTICIDE - 25
TOTAL OUTSIDE EXPOSURE TO FURNITURE REFINISHERS - 13
TOTAL OUTSIDE EXPOSURE TO METAL CLEANERS - 7
TOTAL OUTSIDE EXPOSURE TO BRICK LAYING - 5
TOTAL OUTSIDE EXPOSURE TO BOAT BUILDING - 5

TOTAL HISTORIES OF DIABETES - 0
TOTAL HISTORIES OF ASTHMA - 3
TOTAL HISTORIES OF ARTHRITIS - 4

VARIABLE - WBC (RR:0-3)

(+ NORMAL - ABNORMAL)

	EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 1	+	+						
PAIR 2	+	+						
PAIR 3	+	+						
PAIR 4	+	+						
PAIR 5							-	+
PAIR 6	+	+						
PAIR 7	+	+						
PAIR 8	+	+						
PAIR 9	+	+						
PAIR 10	+	+						
PAIR 11							-	+
PAIR 12	+	+						
PAIR 13	+	+						
PAIR 14	+	+						
PAIR 15	+	+						
PAIR 16							-	+
PAIR 17	+	+						
PAIR 18	+	+						
PAIR 19	+	+						
PAIR 20	+	+						
PAIR 21	+	+						
PAIR 22	+	+						
PAIR 23	+	+						
PAIR 24	+	+						
PAIR 25	+	+						
PAIR 26	+	+						
PAIR 27	+	+						
PAIR 28	+	+						
PAIR 29	+	+						
PAIR 30							-	+
PAIR 31	+	+						
PAIR 32	+	+						
PAIR 33	+	+						
PAIR 34	+	+						
PAIR 35			-	-				
PAIR 36	+	+						
PAIR 37							-	+
PAIR 38	+	+						
PAIR 39	+	+						
PAIR 40	+	+						
PAIR 41	+	+						
PAIR 42	+	+						
PAIR 43	+	+						
PAIR 44							-	+
PAIR 45	+	+						
PAIR 46	+	+						
PAIR 47	+	+						
PAIR 48	+	+						
PAIR 49	+	+						

VARIABLE - WBC (PR:0-3)

	(+ NORMAL - ABNORMAL)							
	EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 50	+	+						
PAIR 51	+	+						
PAIR 52	+	+						
PAIR 53	+	+						
PAIR 54	+	+						
PAIR 55	+	+						
PAIR 56	+	+						
PAIR 57	+	+						
PAIR 58	+	+						
PAIR 59					+	-		
PAIR 60							-	+
PAIR 61							-	+
PAIR 62	+	+						
PAIR 63	+	+						
PAIR 64	+	+						
PAIR 65	+	+						
PAIR 66	+	+						
PAIR 67	+	+						
PAIR 68	+	+						
PAIR 69	+	+						
PAIR 70	+	+						
PAIR 71	+	+						
PAIR 72	+	+						
PAIR 73	+	+						
PAIR 74	+	+						
PAIR 75	+	+						
PAIR 76	+	+						
PAIR 77					+	-		
PAIR 78	+	+						
PAIR 79	+	+						
PAIR 80	+	+						
PAIR 81	+	+						
PAIR 82	+	+						
PAIR 83	+	+						
PAIR 84	+	+						
TOTAL	73		1		2		8	
PERCENTAGE	86.9%		1.1%		2.3%		9.5%	

TOTAL POPULATION SIZE - 84

$p = .0547$

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VARIABLE - URINE PROTEIN (RR:NEG)

(+ NORMAL - ABNORMAL)

	EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 1	+	+						
PAIR 2	+	+						
PAIR 3	+	+						
PAIR 4	+	+						
PAIR 5							-	+
PAIR 6	+	+						
PAIR 7	+	+						
PAIR 8	+	+						
PAIR 9	+	+						
PAIR 10	+	+						
PAIR 11	+	+						
PAIR 12	+	+						
PAIR 13	+	+						
PAIR 14	+	+						
PAIR 15	+	+						
PAIR 16	+	+						
PAIR 17	+	+						
PAIR 18	+	+						
PAIR 19	+	+						
PAIR 20	+	+						
PAIR 21	+	+						
PAIR 22	+	+						
PAIR 23	+	+						
PAIR 24	+	+						
PAIR 25	+	+						
PAIR 26	+	+						
PAIR 27	+	+						
PAIR 28	+	+						
PAIR 29	+	+						
PAIR 30			-	-				
PAIR 31	+	+						
PAIR 32	+	+						
PAIR 33	+	+						
PAIR 34	+	+						
PAIR 35	+	+						
PAIR 36	+	+						
PAIR 37	+	+						
PAIR 38							-	+
PAIR 39	+	+						
PAIR 40	+	+						
PAIR 41	+	+						
PAIR 42	+	+						
PAIR 43	+	+						
PAIR 44	+	+						
PAIR 45	+	+						
PAIR 46	+	+						
PAIR 47							-	+
PAIR 48	+	+						
PAIR 49	+	+						

VARIABLE - URINE PROTEIN (RR:NEG)

	(+ NORMAL - ABNORMAL)							
	EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 50	+	+						
PAIR 51	+	+						
PAIR 52	+	+						
PAIR 53	+	+						
PAIR 54	+	+						
PAIR 55	+	+						
PAIR 56							-	+
PAIR 57	+	+						
PAIR 58	+	+						
PAIR 59							-	+
PAIR 60	+	+						
PAIR 61							-	+
PAIR 62	+	+						
PAIR 63	+	+						
PAIR 64							-	+
PAIR 65	+	+						
PAIR 66	+	+						
PAIR 67	+	+						
PAIR 68	+	+						
PAIR 69	+	+						
PAIR 70					+	-		
PAIR 71	+	+						
PAIR 72	+	+						
PAIR 73	+	+						
PAIR 74	+	+						
PAIR 75	+	+						
PAIR 76	+	+						
PAIR 77	+	+						
PAIR 78	+	+						
PAIR 79	+	+						
PAIR 80	+	+						
PAIR 81	+	+						
PAIR 82	+	+						
PAIR 83	+	+						
PAIR 84	+	+						
TOTAL	75		1		1		7	
PERCENTAGE	89.2%		1.1%		1.1%		8.3%	

TOTAL POPULATION SIZE - 84

$P = .0352$

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VARIABLE - RBC (RR:0-2)

	(+ NORMAL - ABNORMAL) EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 1	+	+						
PAIR 2	+	+						
PAIR 3	+	+						
PAIR 4	+	+						
PAIR 5	+	+						
PAIR 6	+	+						
PAIR 7	+	+						
PAIR 8	+	+						
PAIR 9	+	+						
PAIR 10	+	+						
PAIR 11	+	+						
PAIR 12	+	+						
PAIR 13	+	+						
PAIR 14	+	+						
PAIR 15	+	+						
PAIR 16							-	+
PAIR 17	+	+						
PAIR 18	+	+						
PAIR 19	+	+						
PAIR 20	+	+						
PAIR 21	+	+						
PAIR 22	+	+						
PAIR 23	+	+						
PAIR 24	+	+						
PAIR 25	+	+						
PAIR 26	+	+						
PAIR 27					+	-		
PAIR 28	+	+						
PAIR 29	+	+						
PAIR 30					+	-		
PAIR 31	+	+						
PAIR 32	+	+						
PAIR 33	+	+						
PAIR 34	+	+						
PAIR 35					+	-		
PAIR 36	+	+						
PAIR 37	+	+						
PAIR 38							-	+
PAIR 39	+	+						
PAIR 40	+	+						
PAIR 41	+	+						
PAIR 42	+	+						
PAIR 43	+	+						
PAIR 44	+	+						
PAIR 45	+	+						
PAIR 46	+	+						
PAIR 47							-	+
PAIR 48	+	+						
PAIR 49	+	+						

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VARIABLE - RBC (RR:0-2)

(+ NORMAL - ABNORMAL)

	EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 50	+	+						
PAIR 51	+	+						
PAIR 52	+	+						
PAIR 53	+	+						
PAIR 54	+	+						
PAIR 55	+	+						
PAIR 56	+	+						
PAIR 57	+	+						
PAIR 58	+	+						
PAIR 59	+	+						
PAIR 60	+	+						
PAIR 61							-	+
PAIR 62	+	+						
PAIR 63	+	+						
PAIR 64					+	-		
PAIR 65	+	+						
PAIR 66	+	+						
PAIR 67	+	+						
PAIR 68	+	+						
PAIR 69	+	+						
PAIR 70	+	+						
PAIR 71	+	+						
PAIR 72	+	+						
PAIR 73	+	+						
PAIR 74	+	+						
PAIR 75	+	+						
PAIR 76	+	+						
PAIR 77	+	+						
PAIR 78	+	+						
PAIR 79	+	+						
PAIR 80	+	+						
PAIR 81	+	+						
PAIR 82	+	+						
PAIR 83	+	+						
PAIR 84	+	+						
TOTAL	76		0		4		4	
PERCENTAGE	90.4%		0.0%		4.7%		4.7%	

TOTAL POPULATION SIZE - 84

$P = .6367$

Pages #

5	56
11	59
16	60
27	61
30	64
35	70
37	77
38	
44	
47	

Perry Porter

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STEP 10 - DETERMINATION OF A P-VALUE FOR URINE PROTEIN, WBC, AND RBC

BECAUSE THE URINE PROTEIN, RBC, AND WBC ARE STORED AS A RANGE OF VALUES RATHER THAN A SINGLE NUMERIC VALUE, THEY COULD NOT BE PROCESSED AS CONTINUOUS TYPE DATA BUT HAD TO BE TRANSFORMED INTO CATEGORICAL TYPE DATA BY COMPARING THE DATA VALUE TO ITS REFERENCE RANGE (LISTED WITH THE VALUE IN THE ETHYLENE OXIDE PROTOCOL, TABLE III, A3), AND DETERMINING NORMALITY (+) OR ABNORMALITY (-) FOR THE STUDY AND CONTROL POPULATIONS. THIS WAS DONE BY A PROGRAM DESIGNED FOR THE MEDICAL DEPARTMENT COMPUTER. IT BASICALLY LISTS THE + OR - VALUES AS DESCRIBED IN STEP 9, WITH A TOTAL OF EACH CATEGORY LISTED AT THE END (AS ++, +-, -+, --). FROM THESE TOTALS THE PROBABILITY TABLES INCLUDED WITH STEP 9 WERE CONSULTED TO PROVIDE A P-VALUE FOR EACH DATA ELEMENT, URINE PROTEIN, WBC, AND RBC.

ENCLOSE IS THE COMPUTERIZED LISTS FOR EACH OF THESE DATA ELEMENTS.

Barry Porter

STEP 3 - MATCHING THE STUDY GROUP TO THE CONTROL CANDIDATES

ONCE THE STUDY GROUP HAD BEEN DEFINED, AND THE CONTROL CANDIDATES HAD BEEN ESTABLISHED, THE PROCEDURE OF MATCHING THE STUDY POPULATION TO THE LIST OF CONTROL CANDIDATES TO CREATE A CONTROL POPULATION WAS STARTED.

THE STUDY GROUP AND THE CONTROL CANDIDATES WERE INPUT INTO A COMPUTER PROGRAM FOR MATCHING BETWEEN STUDY AND CONTROL EMPLOYEES. FOR EACH EMPLOYEE IN THE STUDY POPULATION, A SEARCH OF THE ENTIRE CONTROL CANDIDATE GROUP WAS INITIATED TO DETERMINE MATCHING CANDIDATES. IF A CONTROL CANDIDATE WAS PREVIOUSLY SELECTED FOR A CONTROL MATCH, HE WAS EXCLUDED FROM THE MATCHING PROCESS FOR ANY SUBSEQUENT MATCHING, THEREBY ELIMINATING THE POSSIBILITY OF ANY TWO STUDY EMPLOYEES RECEIVING AN EXACT MATCH WITH THE SAME CONTROL CANDIDATE.

THE FIRST CRITERIA USED IN THE MATCHING PROCESS WAS AGE. AGES FROM 15 YEARS TO GREATER THAN 99 YEARS WERE BROKEN INTO CATEGORIES OF 5 YEARS. THE CATEGORIES WERE BROKEN AS SUCH - CAT. 1 = <20 YEARS, CAT. 2 = 20 YRS THRU 24 YEARS, CAT. 3 = 25 YEARS THRU 29 YEARS, ETC. THE AGE OF THE STUDY EMPLOYEE WAS CALCULATED AND CATEGORIZED, THEN FOR EACH CONTROL CANDIDATE THE AGE (AT THE TIME OF THE HEALTH INVENTORY EXAM) WAS CALCULATED AND CATEGORIZED. IF THE AGE CATEGORIES MATCHED, THE MATCHING PROCESS CONTINUED FOR THE SAME CONTROL CANDIDATE, IF NOT, THE NEXT CONTROL CANDIDATE WAS SELECTED, AND THE MATCHING PROCESS STARTED OVER.

THE NEXT MATCHING CRITERIA WAS HIRE DATE. SINCE EACH STUDY EMPLOYEE AND THE CONTROL CANDIDATE BEING PROCESSED HAD TO HAVE HIRE DATES WITHIN 5 YEARS OF ONE ANOTHER, THE HIRE DATES OF EACH WERE EXTRACTED FROM THE COMPUTERIZED DEMOGRAPHIC FILES, AND COMPARISONS WERE MADE TO DETERMINE IF THE CRITERIA WAS MET. IF SO, THE PROCESSING CONTINUED, IF NOT, A NEW CONTROL CANDIDATE WAS SELECTED, AND THE MATCHING PROCEDURE WAS RE-INITIATED.

RACE AND SEX THEN WAS MATCHED BETWEEN STUDY EMPLOYEE AND THE CONTROL CANDIDATE BEING PROCESSED. SINCE FEMALES HAD BEEN EXCLUDED IN THE POPULATION DEFINITION PROCESS, SEX WAS NO PROBLEM FOR MATCHING, SO RACE WAS EXTRACTED FROM THE DEMOGRAPHIC FILES AND A COMPARISON WAS MADE. IF RACE MATCHED, THE MATCHING PROCESS CONTINUED, IF NOT, THE MATCHING WAS RE-STARTED WITH A NEW CONTROL CANDIDATE.

SMOKING AND ALCOHOL USE HISTORY WERE NEXT IN THE MATCHING PROCEDURES. SMOKING HISTORY FOR THE STUDY EMPLOYEE AND THE CURRENT CONTROL CANDIDATE BEING PROCESSED WERE EXTRACTED FROM THE COMPUTERIZED MEDICAL DATA FILES, AND CATEGORIZED INTO NON-SMOKER, FORMER SMOKER, AND CURRENT SMOKER. AS WELL, THE ALCOHOL HISTORIES WERE EXTRACTED FROM THE DATA FILES AND CATEGORIZED INTO LIGHT, MODERATE, OR HEAVY

ALCOHOL USERS. IF BOTH THE SMOKING AND ALCOHOL USE CATEGORIES MATCHED BETWEEN THE STUDY EMPLOYEE AND THE CURRENT CONTROL CANDIDATE, THE MATCHING PROCESS CONTINUED, IF NOT, THE PROCEDURE BEGAN AGAIN USING A NEW CONTROL CANDIDATE.

IF THE CONTROL CANDIDATE CURRENTLY BEING PROCESSED MET ALL THE PRECEEDING CRITERIA, HE WAS ADDED TO THE LIST OF "SEMI-FINAL" CONTROL CANDIDATES. ONCE THIS LIST OF "SEMI-FINAL" CANDIDATES WAS COMPLETE FOR THE STUDY EMPLOYEE BEING PROCESSED (i.e., THE ENTIRE LIST OF CONTROL CANDIDATES HAD BEEN EXHAUSTED FOR THAT STUDY EMPLOYEE), THE PROGRAM MADE A SEARCH OF THIS "SEMI-FINAL" LIST AND DETERMINED THE DATE OF THE 1980 HEALTH INVENTORY EXAM, BASED ON A MONTH-DAY-YEAR FORMAT. THAT DATE WAS THEN COMPARED TO THE DATE OF THE 1980 HEALTH INVENTORY EXAM FOR THE STUDY EMPLOYEE, AND THE CONTROL CANDIDATE WITH THE HI EXAM NEAREST TO THAT OF THE STUDY EMPLOYEE WAS SELECTED AS THE MATCH. USING THE NEAREST HI EXAM DATE APPROACH SERVED SIMPLY TO DIMINISH THE IMPACT COMMON SEASONAL OCCURRANCES OF INFLUENZA, COLDS, ETC., MAY HAVE ON THE RESULTS OF DATA ELEMENTS OBTAINED FROM THE STUDY EMPLOYEE VS. THE CORRESPONDING CONTROL MATCH.

ONCE A MATCH FOR THE STUDY EMPLOYEE HAD BEEN OBTAINED, THE MATCH WAS PLACED IN THE CONTROL POPULATION FILE FOR FURTHER PROCESSING IN THE ETHYLENE OXIDE STUDY, A NEW STUDY EMPLOYEE WAS OBTAINED, AND A NEW SEARCH OF THE CONTROL CANDIDATE FILE WAS INITIATED.

IF NO MATCH COULD BE OBTAINED FOR THE STUDY EMPLOYEE BEING PROCESSED, THE IDENTIFICATION FOR THAT PARTICULAR STUDY EMPLOYEE WAS PRINTED, AND PROCEDURES DESCRIBED BELOW WERE INITIATED TO OBTAIN A CONTROL MATCH.

FOLLOWING IS A LIST OBTAINED FROM THE MATCHING STEP. IT INDICATES THE IDENTIFICATION AND ATTRIBUTES OF THE STUDY AND CONTROL EMPLOYEES USED IN THE STUDY.

ONCE THE CONTROL MATCHING PROCEDURE HAD BEEN COMPLETED, IT WAS DETERMINED THAT TWO STUDY EMPLOYEES DID NOT HAVE CONTROL MATCHES OBTAINED. THIS WAS FOR PAIR 40 (DJ LEGLUE - WHITE STUDY GROUP), AND PAIR 70 (TRALFORD - WHITE STUDY GROUP). IN THE LEGLUE CASE, NO MATCH COULD BE FOUND IN AGE CATEGORY, SINCE LEGLUE WAS IN THE YOUNGEST AGE CATEGORY. BY LIFTING THE AGE CATEGORY REQUIREMENT (BUT NOT THE 5 YEAR AGE DIFFERENTIAL REQUIREMENT), A MATCH WAS OBTAINED WITH A 20 YEAR OLD CONTROL CANDIDATE (DIFFERENT AGE CATEGORY, BUT ONLY 1 YEAR APART IN AGE). IN THE CASE OF ALFORD, NO MATCH COULD BE OBTAINED WITHIN THE 5 YEAR HIRE DATE DIFFERENTIAL REQUIREMENT. TO OBTAIN A MATCH THE 5 YEAR DIFFERENTIAL WAS RELAXED TO 6 YEARS, AND A MATCH WAS OBTAINED WITH A DIFFERENTIAL OF 5 YEARS 8 MONTHS.

SUMMARY OF DEMOGRAPHIC/WORK HISTORY DATA FOR STUDY/CONTROL GROUPS

WHITE STUDY/CONTROL GROUP

STUDY								CONTROL							
EMPLOYEE	S	R	AGE	HIRE DATE	EXAM DATE	SM ST	AL ST	EMPLOYEE	S	R	AGE	HIRE DATE	EXAM DATE	SM ST	AL ST
BCHARRELL III	M	W	29	740909	800326	C	L	WLRUSSELL SR	M	W	29	700831	800423	C	L
LCHUGHES JR	M	W	34	680102	800319	F	L	RWWITTMANN	M	W	34	680527	800515	F	L
RLHEMMINGER	M	W	22	790514	800306	N	L	RWHOPE	M	W	22	790102	800110	N	L
GWBALDWIN	M	W	38	650602	800701	C	M	MJBROUILLETTE J	M	W	38	680115	800821	C	M
JRROSS	M	W	28	780213	800305	F	H	MEKELLY	M	W	29	751006	800415	F	H
OBDENHAM	M	W	20	790618	800328	N	L	TMBENNETT	M	W	20	790219	800627	N	L
KJTHIBODEAUX	M	W	24	780410	800709	N	M	MPWAGUESPACK	M	W	24	740905	800922	N	M
TSFALKE	M	W	20	780911	800314	C	M	DRDENOVA	M	W	21	771010	800124	C	M
CGMOUCH JR	M	W	43	590320	800728	F	M	CPSIMONEAUX	M	W	42	630606	800808	F	M
RWCOOK	M	W	38	660621	800723	F	H	DFSTOCKMAN	M	W	39	630528	800918	F	H
JAWINTZ III	M	W	35	661010	800701	N	H	MJTORRES JR	M	W	35	650429	800508	N	H
WTAUSTIN	M	W	29	740501	800326	F	L	RGBULLIARD	M	W	28	770822	800307	F	L
CCGRAVES JR	M	W	29	730220	800708	N	L	GAPERRY	M	W	29	740826	800611	N	L
RLSPILLMAN JR	M	W	24	770110	800708	N	L	WCDUCK	M	W	24	760524	801023	N	L
BLHARRIS	M	W	24	790226	800714	C	M	JCCREEL	M	W	24	740909	800708	C	M
MALANDRY	M	W	20	780828	800410	N	L	MJBARBIER	M	W	20	780605	800709	N	L
TASOLOMON	M	W	43	670605	800327	F	M	HLHEBERT	M	W	43	680408	800501	F	M
RLGOBERT	M	W	30	740805	800708	N	L	OTBONIN	M	W	30	690818	800929	N	L
CDMERCER	M	W	29	760621	800702	N	L	F SIMONSON III	M	W	29	740521	800808	N	L
TJPELLOWSKI	M	W	33	720914	800326	C	M	BJALEXIUS	M	W	31	700831	800428	C	M
JWMASEY	M	W	27	751103	800321	F	M	HMACHTERMEYER	M	W	27	740826	800509	F	M
WKMARTIN	M	W	25	740812	800709	C	L	V GLAVIANO JR	M	W	25	741216	800512	C	L
DLARMAND	M	W	25	740909	800318	N	L	WJBOURGEOIS JR	M	W	25	760105	800502	N	L
SCSMITH	M	W	25	780626	800306	N	M	JKPHILLIPS	M	W	26	741202	800111	N	M
JHCUIRER	M	W	47	640714	800311	N	L	JJERYOUX	M	W	47	600407	800411	N	L
ALWHITTINGTON	M	W	42	600801	800714	C	M	DJTERRITO	M	W	43	610501	800930	C	M
WWSCOTT	M	W	38	680520	800730	C	L	CWCHEMIN	M	W	38	641217	800812	C	L
EJBOURGEOIS	M	W	36	650517	800304	C	L	CEALMOND	M	W	36	660303	800603	C	L
CJWILLIBER	M	W	33	690818	800310	N	L	JRGOODWIN	M	W	33	690722	800206	N	L
FTHACKLER JR	M	W	36	670614	800703	C	L	RCSIBLEY	M	W	36	660608	800915	C	L
TTTUNG	M	W	34	730102	800710	N	L	CWHOOD JR	M	W	34	690728	800505	N	L
RJPEPITONE	M	W	33	690124	800319	N	L	CASPEARS	M	W	33	730416	800624	N	L
RGCOOPER	M	W	33	690210	800701	N	L	WAMILLER	M	W	33	670411	801024	N	L
WJTEMPLET	M	W	25	751110	800321	C	L	CDDUVAL	M	W	26	750120	800618	C	L
WEHORSFALL	M	W	27	740909	800716	C	L	KWMARTIN	M	W	27	740729	800910	C	L
JWGRISSOM JR	M	W	21	770705	800313	N	H	KAFRUGE	M	W	21	780116	800307	N	H
WDNORDER JR	M	W	20	790514	800313	C	M	RGKENNEDY	M	W	21	770919	800421	C	M
DAPATE	M	W	23	771205	800702	F	L	RECUTRER	M	W	23	781127	800618	F	L
KJDENOVA	M	W	22	760517	800716	N	M	GPCHUSTZ	M	W	22	790924	801015	N	M
DJLEGLUE	M	W	19	790529	800319	F	L	RJARMAND	M	W	20	790625	800904	F	L
B WHALEY	M	W	48	590212	800911	C	M	JPKINCHEN	M	W	48	561203	800826	C	M
KPBROU	M	W	43	630705	800716	F	L	CLWIGGINS	M	W	43	661213	800415	F	L
JELOVE	M	W	45	630614	800707	C	L	CJTHIBODEAUX JR	M	W	45	590102	801017	C	L
HEMURRAY	M	W	38	660228	800701	N	L	JLDEASON	M	W	38	640217	800725	N	L
DJBOECKMAN	M	W	25	760202	800327	C	M	DFBERGERON	M	W	25	780313	800403	C	M
CPLEMOINE	M	W	20	780424	800703	C	L	CEBARBER	M	W	21	790521	800915	C	L
WATURNER	M	W	32	751215	800703	N	L	GWRACHAL	M	W	32	740107	801029	N	L

SUMMARY OF DEMOGRAPHIC/WORK HISTORY DATA FOR STUDY/CONTROL GROUPS

WHITE STUDY/CONTROL GROUP

STUDY								CONTROL							
EMPLOYEE	S	R	AGE	HIRE DATE	EXAM DATE	SM ST	AL ST	EMPLOYEE	S	R	AGE	HIRE DATE	EXAM DATE		
KDCALDWELL	M	W	20	771205	800702	C	L	RJPUJOL	M	W	20	790716	800910		
JCGROSS JR	M	W	28	750908	800718	N	L	CRWHITAKER	M	W	28	740805	800509		
GAMILLER	M	W	21	790416	800704	C	L	MAARMSTRONG	M	W	21	770822	800403		
EJCATLETT JR	M	W	36	631210	800709	C	H	RAWEBB JR	M	W	36	681113	800902		
LEDAY	M	W	39	660324	800703	C	L	AJDENOVA	M	W	39	660602	800904		
DEPANEPINTO	M	W	36	640309	800702	F	L	HTKING	M	W	36	680123	800402		
RDLENOIR	M	W	35	681202	800701	C	L	JMWOOD	M	W	35	700427	800409		
TJWATKINS	M	W	25	760614	800703	C	L	MJDIDIER	M	W	25	741118	800723		
TDSMOTHERS	M	W	33	690818	800707	F	L	RJHOTARD	M	W	33	670110	800902		
LJLEMOINE JR	M	W	32	681218	800325	C	L	HRLAWES JR	M	W	33	690721	800612		
BJABADIE	M	W	25	751020	800312	N	H	RCGUSTIN	M	W	25	740722	800912		
MRVIATOR	M	W	28	721003	800305	C	L	PWRAMAGOS	M	W	28	741202	800219		
JASOLOMON	M	W	31	730608	800403	N	L	JSPARKER	M	W	31	740819	800407		
DMWILLIAMSON	M	W	26	740107	800714	N	L	RDTHORNHILL	M	W	26	751229	800815		
MLHIMEL	M	W	24	740729	800714	C	L	WCGRANT	M	W	24	740826	800723		
BAGUILLORY	M	W	24	780911	800326	C	L	TVTEMPLET	M	W	24	770926	800111		
RKBONANNO	M	W	23	770926	800320	C	L	PEGRACE	M	W	23	771219	800303		
RLAGUILLARD	M	W	23	760426	800317	N	H	WJLEGER JR	M	W	23	780417	800416		
JDGRISSOM	M	W	26	760907	800325	F	L	JDBAILEY	M	W	26	760621	800118		
WLJACKSON JR	M	W	26	760802	800321	C	H	JLSTOUTE	M	W	26	790219	800508		
JLCAZES	M	W	37	680409	800710	N	L	KRTRICE	M	W	37	640130	800723		
ASGENRE III	M	W	31	730312	800716	F	M	JLBRANCH	M	W	31	740304	800416		
JRALFORD	M	W	46	690210	800708	N	M	T BREKKEN SR	M	W	47	630603	800813		
JLSHELTON	M	W	35	680617	800312	F	L	STRICHARDSON	M	W	35	680130	800505		
JESTEARS	M	W	39	681022	800326	F	L	DADAIGLE	M	W	38	680513	800605		

SUMMARY OF DEMOGRAPHIC/WORK HISTORY DATA FOR STUDY/CONTROL GROUPS

BLACK STUDY/CONTROL GROUP

STUDY								CONTROL							
EMPLOYEE	S	R	AGE	HIRE DATE	EXAM DATE	SM ST	AL ST	EMPLOYEE	S	R	AGE	HIRE DATE	EXAM DATE	SM ST	AL ST
SSCLARK	M	B	30	740909	800708	C	M	LVTHOMAS	M	B	30	731003	800604	C	M
WRLEJEUNE	M	B	23	770829	800324	F	M	MCRUFFIN	M	B	23	780109	800401	F	M
W ROBINSON	M	B	38	721115	800303	C	H	WJARRINGTON	M	B	38	690811	800806	C	H
I PATTERSON JR	M	B	25	751013	800324	N	L	HJTAYLOR	M	B	25	740401	800403	N	L
CAAGUILLARD	M	B	31	730612	800701	C	M	DRCLARK	M	B	30	760119	800918	C	M
TSPERRY	M	B	20	790416	800711	N	L	RWPARKER	M	B	20	790521	800903	N	L
J GAGE	M	B	31	780828	800318	C	L	RAWILLIAMS	M	B	33	740909	800617	C	L
E PROVOST JR	M	B	30	781106	800328	N	L	W HARRIS JR	M	B	31	760503	800430	N	L
CBHANEY	M	B	27	750106	800311	C	H	HIMELLIEON	M	B	27	750324	800617	C	H
JAWHITE	M	B	35	690721	800318	C	L	EJFREDERICKS	M	B	38	690714	800222	C	L
LDBRADFORD	M	B	28	770418	800707	C	M	LJTILLMAN	M	B	29	790521	800709	C	M
U DELOCH JR	M	B	27	740611	800707	C	L	CATUCKER	M	B	27	740805	800826	C	L

DRAFT
4/8/81

PARTICIPATION DATA

GROUP	NUMBER	*PARTICIPATION RATIO
I. Population Universe.		
A. All employees eligible for Periodic Health Examinations (PHE) in 1980 (Total in plant except ~~clerical and~~ certain management).		
B. Total for whom 1980 PHE data available.		
C. Female employees.		
D. Population universe used as source for data ("source" ~~subtotal~~ in population = IB minus IC).		
II. Exposed population, selected from source population (all males).		
A. No. males in Glycol II at time of 1980 exam.		
B. No. males who worked in Glycol II on or before 31 Dec. 1980.		
C. No. males in Dowanols at time of 1980 exam.		
D. No. males in Dowanols on or before 31 Dec. 1980.		
E. Subtotal in exposed population = IIA + ~~IIB~~ + IIC ~~+ IID~~	85	85/91 = 93.4%
III. Control population (all males)		
A. Potential control population, selected from source population (ID) minus exposed population ~~(IIE)~~ (II A+II B+II C+II D)		
B. Employees with potential exposure to benzene in 1980		
C. Employees with unknown chemical exposures due to assignment in Research and Development or in Instrumentation.		
D III A minus III B and III C	976	976/1069 = 91.3%
~~E~~ No. in III A who had ever worked in Glycol I, Glycol II or Dowanols		
~~F~~ Subtotal in control population = ~~IIIB+IIIC~~		

*Participation Ratio = No. employees in the group for whom a 1980 PHE. available divided by no. employees in the group eligible for 1980 PHE.

CHARACTERISTICS OF EXPOSED AND MATCHED (1:1)

CONTROL POPULATIONS

Aug 1980

CHARACTERISTIC	VALUE	
	EXPOSED	CONTROL
I. MATCHED CHARACTERISTICS.		
Number		
Mean Age		
Median Age		
No. non whites		
Yrs in Plant		
Current Smokers		
Non Smokers		
Ex Smokers & Pipe Smokers		
II. OTHER CHARACTERISTICS.		
% with Hx. of diabetes		
% with Hx. of asthma		
Mean height		
Mean weight		
Mean diastolic blood pressure		
% non drinkers		

~~(A) Continuous~~ | ~~Means~~ | ~~Median~~ | ~~Range~~ | S.D. | Pr

~~Dichotomous — dis... ...~~

(B)

Question: (1) Is there an SAS program for ~~comparison~~ of continuous data which may not be normally distributed. I would suggest we wilcoxon test for ~~...~~ CV data matched (i.e. paired rank test)?

Continuous →

If not, can we check kurtosis + skewness before + after square root transformation + use the paired t test if normal.

program Peggy has come up with

(2) ~~...~~ ~~Do they have any table for~~ ~~...~~ ~~p value~~

Dichotomous → McNemar's test.

McNemar's is a simplified chi square I believe — but suggest you check with ...

(A)

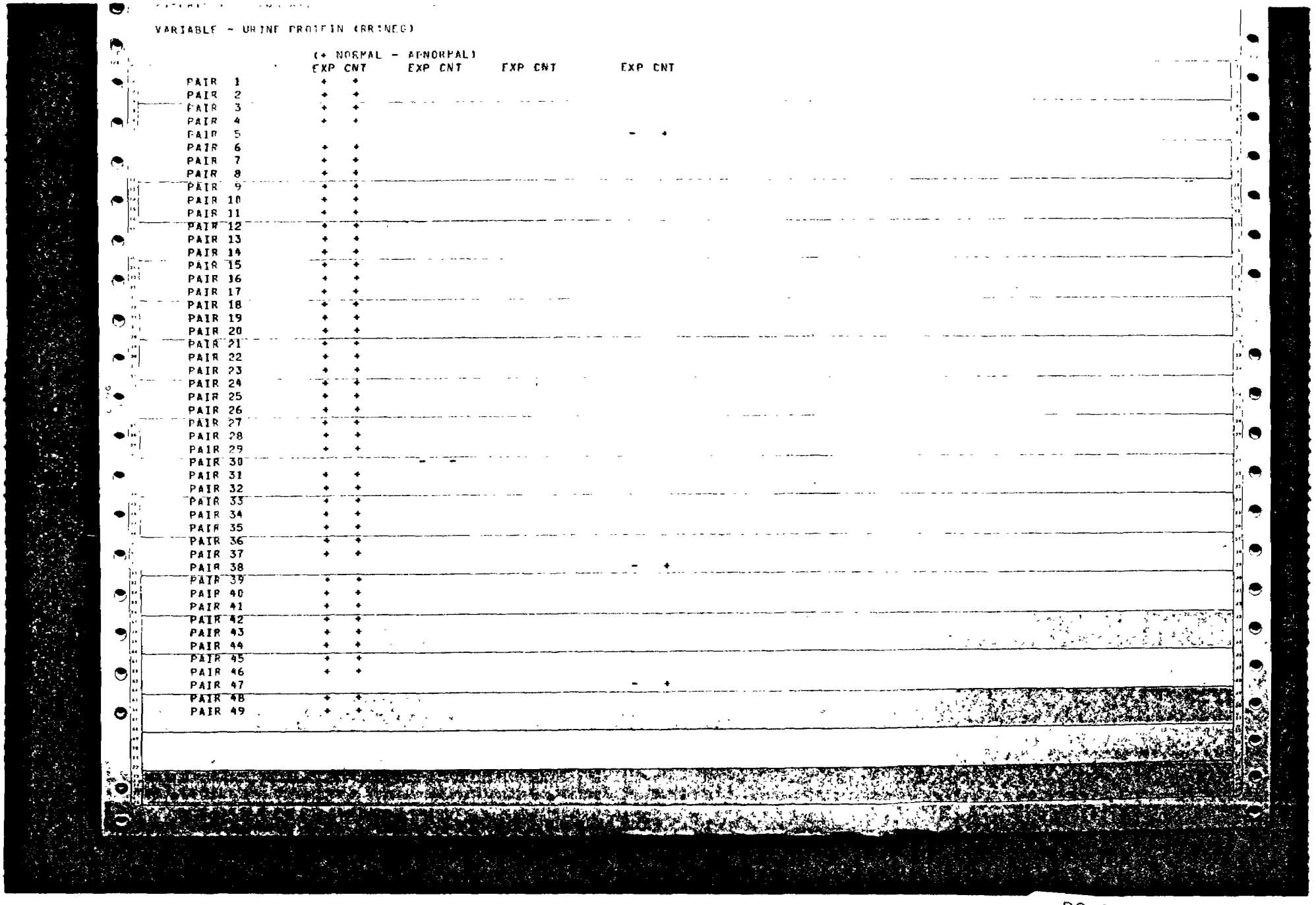
We mean ± 1/1
Deans advice on
how to present
this

Table III Continuous Data

Variable	Exposed Group				Control group				P value
	Mean	Median	S.D	Range	Mean	Median	S.D.	Range	
i.e. LDH									

Table IV: Dichotomous data

Variable	No. DISCORDANT PAIRS: Exposed +/control − : y	Exposed −/control +	P-val
Blood in urine (+ or −)			



VARIABLE - URINE PROTEIN (BRINEG)

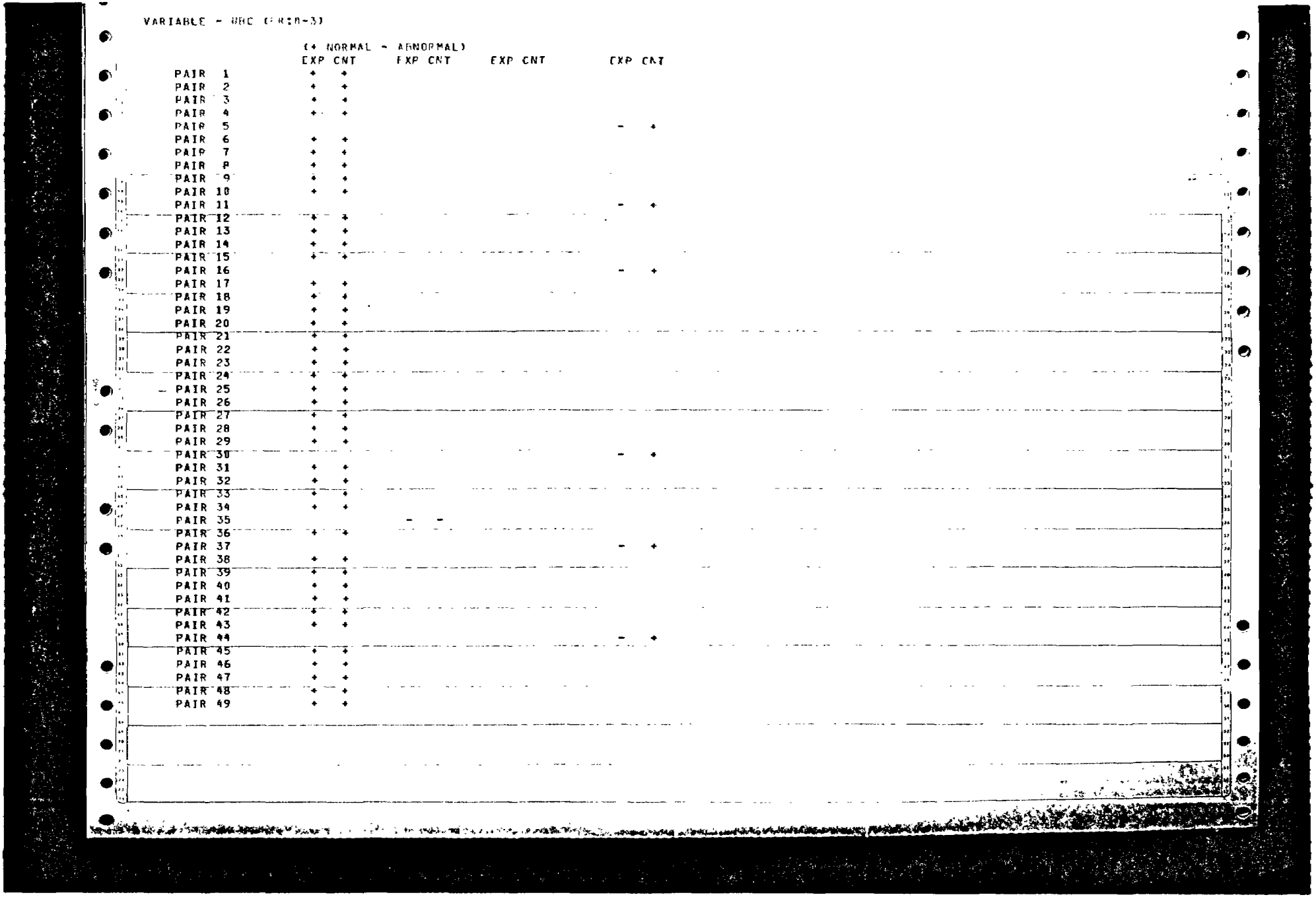
	(+ NORMAL - ABNORMAL) EXP CNT	EXP CNT	EXP CNT	EXP CNT
PAIR 1	+ +			
PAIR 2	+ +			
PAIR 3	+ +			
PAIR 4	+ +			
PAIR 5	- +			
PAIR 6	+ +			
PAIR 7	+ +			
PAIR 8	+ +			
PAIR 9	+ +			
PAIR 10	+ +			
PAIR 11	+ +			
PAIR 12	+ +			
PAIR 13	+ +			
PAIR 14	+ +			
PAIR 15	+ +			
PAIR 16	+ +			
PAIR 17	+ +			
PAIR 18	+ +			
PAIR 19	+ +			
PAIR 20	+ +			
PAIR 21	+ +			
PAIR 22	+ +			
PAIR 23	+ +			
PAIR 24	+ +			
PAIR 25	+ +			
PAIR 26	+ +			
PAIR 27	+ +			
PAIR 28	+ +			
PAIR 29	+ +			
PAIR 30	- -			
PAIR 31	+ +			
PAIR 32	+ +			
PAIR 33	+ +			
PAIR 34	+ +			
PAIR 35	+ +			
PAIR 36	+ +			
PAIR 37	+ +			
PAIR 38	- +			
PAIR 39	+ +			
PAIR 40	+ +			
PAIR 41	+ +			
PAIR 42	+ +			
PAIR 43	+ +			
PAIR 44	+ +			
PAIR 45	+ +			
PAIR 46	+ +			
PAIR 47	- +			
PAIR 48	+ +			
PAIR 49	+ +			

DO 095143
CONFIDENTIAL

VARIABLE - URINE PROTEIN (BRINEG)

	(+ NORMAL - /ABNORMAL) EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 50	+	+						
PAIR 51	+	+						
PAIR 52	+	+						
PAIR 53	+	+						
PAIR 54	+	+						
PAIR 55	+	+						
PAIR 56							-	+
PAIR 57	+	+						
PAIR 58	+	+						
PAIR 59							-	+
PAIR 60	+	+						
PAIR 61							-	+
PAIR 62	+	+						
PAIR 63	+	+						
PAIR 64							-	+
PAIR 65	+	+						
PAIR 66	+	+						
PAIR 67	+	+						
PAIR 68	+	+						
PAIR 69	+	+						
PAIR 70					+	-		
PAIR 71	+	+						
PAIR 72	+	+						
PAIR 73	+	+						
PAIR 74	+	+						
PAIR 75	+	+						
PAIR 76	+	+						
PAIR 77	+	+						
PAIR 78	+	+						
PAIR 79	+	+						
PAIR 80	+	+						
PAIR 81	+	+						
PAIR 82	+	+						
PAIR 83	+	+						
PAIR 84	+	+						
TOTAL	75		1		1		7	
PERCENTAGE	89.2%		1.1%		1.1%		8.3%	

TOTAL POPULATION SIZE - 84



VARIABLE - UBC (PRE-3)

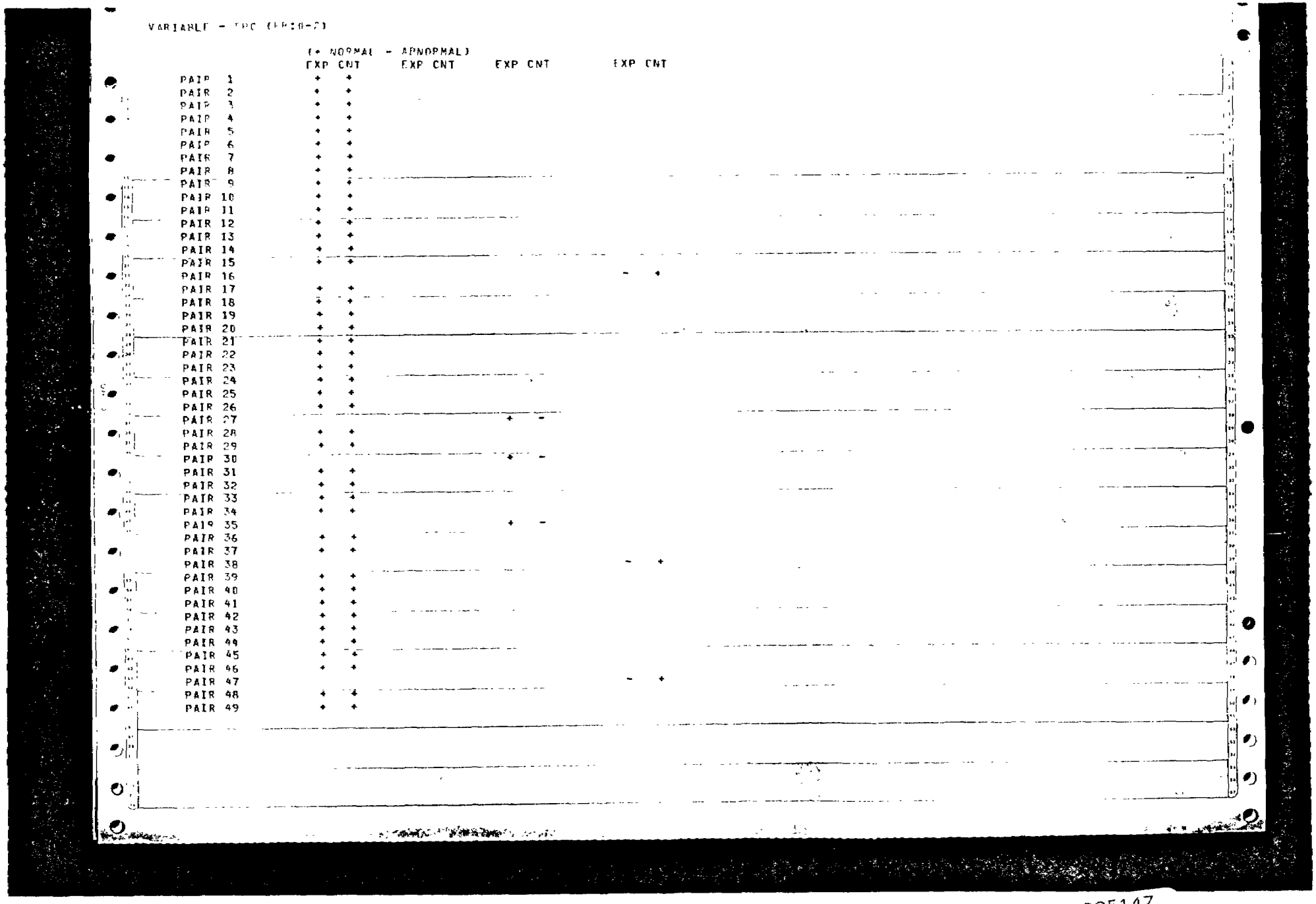
	(+ NORMAL - ABNORMAL) EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 1	+	+						
PAIR 2	+	+						
PAIR 3	+	+						
PAIR 4	+	+						
PAIR 5							-	+
PAIR 6	+	+						
PAIR 7	+	+						
PAIR 8	+	+						
PAIR 9	+	+						
PAIR 10	+	+						
PAIR 11							-	+
PAIR 12	+	+						
PAIR 13	+	+						
PAIR 14	+	+						
PAIR 15	+	+						
PAIR 16							-	+
PAIR 17	+	+						
PAIR 18	+	+						
PAIR 19	+	+						
PAIR 20	+	+						
PAIR 21	+	+						
PAIR 22	+	+						
PAIR 23	+	+						
PAIR 24	+	+						
PAIR 25	+	+						
PAIR 26	+	+						
PAIR 27	+	+						
PAIR 28	+	+						
PAIR 29	+	+						
PAIR 30							-	+
PAIR 31	+	+						
PAIR 32	+	+						
PAIR 33	+	+						
PAIR 34	+	+						
PAIR 35			-	-				
PAIR 36	+	+						
PAIR 37							-	+
PAIR 38	+	+						
PAIR 39	+	+						
PAIR 40	+	+						
PAIR 41	+	+						
PAIR 42	+	+						
PAIR 43	+	+						
PAIR 44							-	+
PAIR 45	+	+						
PAIR 46	+	+						
PAIR 47	+	+						
PAIR 48	+	+						
PAIR 49	+	+						

DO 095145
CONFIDENTTAL

VARIABLE - [illegible]

	(+ NORMAL - ABNORMAL) EXP CNT	EXP CNT	EXP CNT	EXP CNT
PAIR 50	+ +			
PAIR 51	+ +			
PAIR 52	+ +			
PAIR 53	+ +			
PAIR 54	+ +			
PAIR 55	+ +			
PAIR 56	+ +			
PAIR 57	+ +			
PAIR 58	+ +			
PAIR 59			+ -	
PAIR 60				- +
PAIR 61				- +
PAIR 62	+ +			
PAIR 63	+ +			
PAIR 64	+ +			
PAIR 65	+ +			
PAIR 66	+ +			
PAIR 67	+ +			
PAIR 68	+ +			
PAIR 69	+ +			
PAIR 70	+ +			
PAIR 71	+ +			
PAIR 72	+ +			
PAIR 73	+ +			
PAIR 74	+ +			
PAIR 75	+ +			
PAIR 76	+ +			
PAIR 77			+ -	
PAIR 78	+ +			
PAIR 79	+ +			
PAIR 80	+ +			
PAIR 81	+ +			
PAIR 82	+ +			
PAIR 83	+ +			
PAIR 84	+ +			
TOTAL	73	1	2	8
PERCENTAGE	86.9%	1.1%	2.3%	9.5%

TOTAL POPULATION SIZE - 84



VARIABLE = TPC (PRIOR)

	(+ NORMAL - ABNORMAL) EXP	CNT	EXP	CNT	EXP	CNT	EXP	CNT
PAIR 1	+	+						
PAIR 2	+	+						
PAIR 3	+	+						
PAIR 4	+	+						
PAIR 5	+	+						
PAIR 6	+	+						
PAIR 7	+	+						
PAIR 8	+	+						
PAIR 9	+	+						
PAIR 10	+	+						
PAIR 11	+	+						
PAIR 12	+	+						
PAIR 13	+	+						
PAIR 14	+	+						
PAIR 15	+	+						
PAIR 16					-	+		
PAIR 17	+	+						
PAIR 18	+	+						
PAIR 19	+	+						
PAIR 20	+	+						
PAIR 21	+	+						
PAIR 22	+	+						
PAIR 23	+	+						
PAIR 24	+	+						
PAIR 25	+	+						
PAIR 26	+	+						
PAIR 27			+	-				
PAIR 28	+	+						
PAIR 29	+	+						
PAIR 30			+	-				
PAIR 31	+	+						
PAIR 32	+	+						
PAIR 33	+	+						
PAIR 34	+	+						
PAIR 35			+	-				
PAIR 36	+	+						
PAIR 37	+	+						
PAIR 38					-	+		
PAIR 39	+	+						
PAIR 40	+	+						
PAIR 41	+	+						
PAIR 42	+	+						
PAIR 43	+	+						
PAIR 44	+	+						
PAIR 45	+	+						
PAIR 46	+	+						
PAIR 47					-	+		
PAIR 48	+	+						
PAIR 49	+	+						

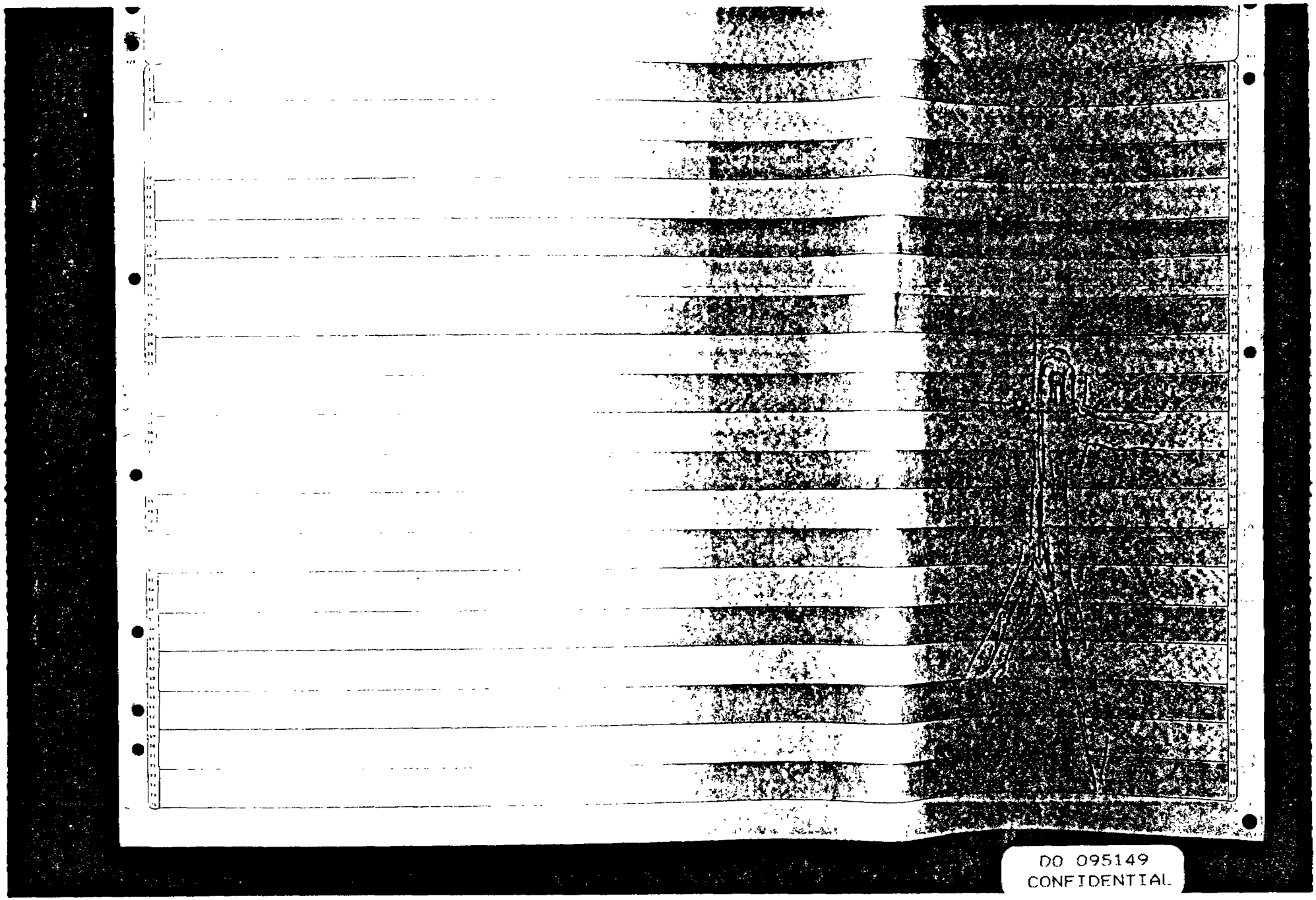
DO 095147
CONFIDENTIAL

VARIABLE - RRC (PRED-2)

	(+ NORMAL - /NNORMAL) EXP CNT	EXP CNT	EXP CNT	EXP CNT
PAIR 50	+ +			
PAIR 51	+ +			
PAIR 52	+ +			
PAIR 53	+ +			
PAIR 54	+ +			
PAIR 55	+ +			
PAIR 56	+ +			
PAIR 57	+ +			
PAIR 58	+ +			
PAIR 59	+ +			
PAIR 60	+ +			
PAIR 61				- +
PAIR 62	+ +			
PAIR 63	+ +			
PAIR 64			+ -	
PAIR 65	+ +			
PAIR 66	+ +			
PAIR 67	+ +			
PAIR 68	+ +			
PAIR 69	+ +			
PAIR 70	+ +			
PAIR 71	+ +			
PAIR 72	+ +			
PAIR 73	+ +			
PAIR 74	+ +			
PAIR 75	+ +			
PAIR 76	+ +			
PAIR 77	+ +			
PAIR 78	+ +			
PAIR 79	+ +			
PAIR 80	+ +			
PAIR 81	+ +			
PAIR 82	+ +			
PAIR 83	+ +			
PAIR 84	+ +			
TOTAL	76	0	4	4
PERCENTAGE	90.4%	0.0%	4.7%	4.7%

TOTAL POPULATION SIZE - 84

DO 095148
CONFIDENTIAL



DO 095149
CONFIDENTIAL

DESCRIPTION OF PROCEDURES USED IN THE CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

THE FOLLOWING DESCRIPTIONS GIVE A STEP-BY-STEP IN-DEPTH VIEW OF THE PROCEDURES USED BY LOUISIANA DIVISION PERSONNEL IN OBTAINING POPULATIONS USED IN THE CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION (HEREAFTER REFERRED TO AS THE "ETHYLENE OXIDE STUDY"), COLLECTION OF LABORATORY VALUES AND QUESTIONNAIRE DATA, AND ANALYSIS OF VARIOUS DATA ELEMENTS AND THEIR ASSOCIATED VALUES THROUGH THE USE OF VARIOUS STATISTICAL METHODS, TECHNIQUES, AND PACKAGES. EACH STEP WILL LIST PROCEDURES APPROPRIATE TO IT AND WILL AS WELL LIST VARIOUS TABLES AND OR RESULTS GENERATED AS OUTPUT FROM THAT PARTICULAR STEP.

Thanks Perry—

I may want to look at these again.

June

DESCRIPTION OF PROCEDURES USED IN THE CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

THE FOLLOWING DESCRIPTIONS GIVE A STEP-BY-STEP IN-DEPTH VIEW OF THE PROCEDURES USED BY LOUISIANA DIVISION PERSONNEL IN OBTAINING POPULATIONS USED IN THE CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION (HEREAFTER REFERRED TO AS THE "ETHYLENE OXIDE STUDY"), COLLECTION OF LABORATORY VALUES AND QUESTIONNAIRE DATA, AND ANALYSIS OF VARIOUS DATA ELEMENTS AND THEIR ASSOCIATED VALUES THROUGH THE USE OF VARIOUS STATISTICAL METHODS, TECHNIQUES, AND PACKAGES. EACH STEP WILL LIST PROCEDURES APPROPRIATE TO IT AND WILL AS WELL LIST VARIOUS TABLES AND OR RESULTS GENERATED AS OUTPUT FROM THAT PARTICULAR STEP.

STEP 1 - DEFINITION OF THE ETHYLENE OXIDE STUDY POPULATION

AFTER CAREFUL REVIEW OF THE FINAL DRAFT PROTOCOL WORK PROCEEDED ON OBTAINING A STUDY POPULATION FOR USE IN THE ETHYLENE OXIDE STUDY. THE SOURCE OF DATA FOR THE PROCEDURE WAS TO BE THE COMPUTERIZED WORK HISTORY AND DEMOGRAPHIC FILES RESIDING ON THE MEDICAL DEPARTMENT PDP 11-34 MINICOMPUTER USING DSM-11 (DIGITAL STANDARD MUMPS). USING PROGRAMS THAT WERE ALREADY IN EXISTENCE, A LIST WAS GENERATED OF ALL LOUISIANA PERSONNEL THAT HAD EVER WORKED IN THE PLANTS WITHIN THE DIVISION THAT COULD HAVE POTENTIAL ETHYLENE OXIDE EXPOSURE. THESE PLANTS WERE DEFINED TO BE THE DOWANOLS PLANT AND THE GLYCOL II PLANT. ONCE THE COMPUTERIZED LIST WAS GENERATED, A MANUALLY PREPARED SELECTION OF EMPLOYEES WERE MADE USING THE REQUIREMENT THAT THE EMPLOYEE BE A FULL TIME DOW EMPLOYEE [illegible] AT THIS POINT, FEMALES AND PRE-EMPLOYMENT TYPE PERSONNEL (THOSE EMPLOYEE ASSIGNED TO THE PLANTS < LESS THAN 6 MONTHS PRIOR TO THE 1980 HEALTH INVENTORY EXAM) HAD NOT YET BEEN SORTED OUT AND EXCLUDED. USING THE IDENTIFICATION OF THE 96 EMPLOYEES OBTAINED ON THE FIRST LIST, A NEW PROGRAM WAS EXECUTED THAT IDENTIFIED FEMALES FROM THE FIRST LIST, AS WELL AS PRE-EMPLOYEE STATUS PERSONNEL. AT THIS POINT THE REMAINING PERSONNEL WAS CHECKED AGAINST EXISTING MEDICAL DATA FILES TO DETERMINE WHO HAD IN FACT PARTICIPATED IN THE 1980 HEALTH INVENTORY PROGRAM. THIS FINAL LIST OF 84 EMPLOYEES WAS MAINTAINED ELECTRONICALLY FOR FUTURE MANIPULATION IN SUBSEQUENT PROCEDURES. A COMPANION LIST OF EMPLOYEES WERE GENERATED INDICATING THE IDENTIFICATION OF THOSE EMPLOYEES NOT PARTICIPATING IN THE 1980 HEALTH INVENTORY PROGRAM FROM THE EO PLANTS. A MANUAL PROCEDURE WAS THEN INITIATED TO ASCERTAIN REASONS FOR FAILURE OF THESE EMPLOYEES TO PARTICIPATE IN THE HEALTH INVENTORY PROGRAM AS PART OF LOUISIANA DIVISIONS INTERNAL AUDITING PROCEDURES.

THE COMPLETE STATISTICS ASSOCIATED WITH SELECTION OF THE STUDY POPULATION IS ENCLOSED IN THE FOLLOWING PRINTOUT.

TOTAL NUMBER EMPLOYEES IN ORIGINAL STUDY SELECTION - 96
NUMBER EMPLOYEES REMOVED FROM ORIGINAL SELECTION FOR MISCELLANEOUS REASONS -
NUMBER FEMALES IN ORIGINAL STUDY SELECTION - 6
NUMBER EMPLOYEES IN ORIGINAL STUDY SELECTION HAVING PRE-EMPLOYMENT STATUS -

TOTAL NUMBER EMPLOYEES ELIGIBLE FOR STUDY GROUP - 90
NUMBER ELIGIBLE EMPLOYEES PARTICIPATING IN 1980 HEALTH INVENTORY - 84
NUMBER ELIGIBLE EMPLOYEES NOT PARTICIPATING IN 1980 HEALTH INVENTORY - 6
PERCENTAGE PARTICIPATION OF ELIGIBLE EMPLOYEES - 93.3
TOTAL EMPLOYEES IN STUDY GROUP - 84

DESCRIPTION OF PROCEDURES USED IN THE CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

THE FOLLOWING DESCRIPTIONS GIVE A STEP-BY-STEP IN-DEPTH VIEW OF THE PROCEDURES USED BY LOUISIANA DIVISION PERSONNEL IN OBTAINING POPULATIONS USED IN THE CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION (HEREAFTER REFERRED TO AS THE "ETHYLENE OXIDE STUDY"), COLLECTION OF LABORATORY VALUES AND QUESTIONNAIRE DATA, AND ANALYSIS OF VARIOUS DATA ELEMENTS AND THEIR ASSOCIATED VALUES THROUGH THE USE OF VARIOUS STATISTICAL METHODS, TECHNIQUES, AND PACKAGES. EACH STEP WILL LIST PROCEDURES APPROPRIATE TO IT AND WILL AS WELL LIST VARIOUS TABLES AND OR RESULTS GENERATED AS OUTPUT FROM THAT PARTICULAR STEP.

STEP 1 - DEFINITION OF THE ETHYLENE OXIDE STUDY POPULATION

AFTER CAREFUL REVIEW OF THE FINAL DRAFT PROTOCOL WORK PROCEEDED ON OBTAINING A STUDY POPULATION FOR USE IN THE ETHYLENE OXIDE STUDY. THE SOURCE OF DATA FOR THE PROCEDURE WAS TO BE THE COMPUTERIZED WORK HISTORY AND DEMOGRAPHIC FILES RESIDING ON THE MEDICAL DEPARTMENT PDP 11-34 MINICOMPUTER USING DSM-11 (DIGITAL STANDARD MUMPS). USING PROGRAMS THAT WERE ALREADY IN EXISTENCE, A LIST WAS GENERATED OF ALL LOUISIANA PERSONNEL THAT HAD EVER WORKED IN THE PLANTS WITHIN THE DIVISION THAT COULD HAVE POTENTIAL ETHYLENE OXIDE EXPOSURE. THESE PLANTS WERE DEFINED TO BE THE DOWANOLS PLANT AND THE GLYCOL II PLANT. ONCE THE COMPUTERIZED LIST WAS GENERATED, A MANUALLY PREPARED SELECTION OF EMPLOYEES WERE MADE USING THE REQUIREMENT THAT THE EMPLOYEE BE A FULL TIME DOW EMPLOYEE AT THIS POINT, FEMALES AND PRE-EMPLOYMENT TYPE PERSONNEL (THOSE EMPLOYEES ASSIGNED TO THE PLANTS LESS THAN 6 MONTHS PRIOR TO THE 1980 HEALTH INVENTORY EXAM) HAD NOT YET BEEN SORTED OUT AND EXCLUDED. USING THE IDENTIFICATION OF THE 96 EMPLOYEES OBTAINED ON THE FIRST LIST, A NEW PROGRAM WAS EXECUTED THAT IDENTIFIED FEMALES FROM THE FIRST LIST, AS WELL AS PRE-EMPLOYEE STATUS PERSONNEL. AT THIS POINT THE REMAINING PERSONNEL WAS CHECKED AGAINST EXISTING MEDICAL DATA FILES TO DETERMINE WHO HAD IN FACT PARTICIPATED IN THE 1980 HEALTH INVENTORY PROGRAM. THIS FINAL LIST OF 84 EMPLOYEES WAS MAINTAINED ELECTRONICALLY FOR FUTURE MANIPULATION IN SUBSEQUENT PROCEDURES. A COMPANION LIST OF EMPLOYEES WERE GENERATED INDICATING THE IDENTIFICATION OF THOSE EMPLOYEES NOT PARTICIPATING IN THE 1980 HEALTH INVENTORY PROGRAM FROM THE EO PLANTS. A MANUAL PROCEDURE WAS THEN INITIATED TO ASCERTAIN REASONS FOR FAILURE OF THESE EMPLOYEES TO PARTICIPATE IN THE HEALTH INVENTORY PROGRAM AS PART OF LOUISIANA DIVISIONS INTERNAL AUDITING PROCEDURES.

THE COMPLETE STATISTICS ASSOCIATED WITH SELECTION OF THE STUDY POPULATION IS ENCLOSED IN THE FOLLOWING PRINTOUT.

TOTAL NUMBER EMPLOYEES IN ORIGINAL STUDY SELECTION - 96
NUMBER EMPLOYEES REMOVED FROM ORIGINAL SELECTION FOR MISCELLANEOUS REASONS - 0
NUMBER FEMALES IN ORIGINAL STUDY SELECTION - 6
NUMBER EMPLOYEES IN ORIGINAL STUDY SELECTION HAVING PRE-EMPLOYMENT STATUS - 0

TOTAL NUMBER EMPLOYEES ELIGIBLE FOR STUDY GROUP - 90
NUMBER ELIGIBLE EMPLOYEES PARTICIPATING IN 1980 HEALTH INVENTORY - 84
NUMBER ELIGIBLE EMPLOYEES NOT PARTICIPATING IN 1980 HEALTH INVENTORY - 6
PERCENTAGE PARTICIPATION OF ELIGIBLE EMPLOYEES - 93.3
TOTAL EMPLOYEES IN STUDY GROUP - 84

STEP 2 - DEFINITION OF THE ETHYLENE OXIDE CONTROL POPULA

AFTER DEFINITION OF THE ETHYLENE OXIDE STUDY POPULATION WAS COMPLETE, WORK BEGAN ON DEFINITION OF THE ETHYLENE OXIDE CONTROL CANDIDATE GROUP AND SUBSEQUENT CONTROL POPULATION. THE PROCEDURE BEGAN WITH OBTAINING A LIST OF ALL PLANTS THAT HAD BEEN SCHEDULED BY THE MEDICAL DEPARTMENT FOR 1980 PERIODIC HEALTH EXAMS AND THE MONTH IN WHICH EACH PLANT WAS SCHEDULED. FROM THIS POINT, A MANUAL CHECK WAS MADE ON THE LIST TO DETERMINE WHAT PLANTS COULD SUPPLY CONTROL CANDIDATES FROM THE TOTAL LIST OF PLANTS AVAILABLE. PLANTS THAT WERE DROPPED FROM POTENTIAL CANDIDATE SUPPLIERS WERE THE RESEARCH & DEVELOPMENT GROUP AND INSTRUMENT GROUPS, SINCE DETERMINATION OF DAY TO DAY EXPOSURE FOR THESE GROUPS CANNOT BE HANDLED WITH THE PRESENT DAY WORKHISTORY PROGRAMS. ALSO ELIMINATED FROM THE LIST WERE THE LIGHT HYDROCARBONS PLANTS, SINCE POTENTIAL EXPOSURE FROM BENZENE COULD HAVE PROVED TO HAVE CONFOUNDING IMPLICATIONS.

ONCE THE FINAL LIST OF PLANTS WERE CHOSEN, THE LIST WAS ENTERED INTO A COMPUTERIZED PROGRAM DESIGNED TO OBTAIN EMPLOYEES WORKING DURING 1980 IN THOSE PARTICULAR PLANTS. ONCE THESE EMPLOYEES HAD BEEN OBTAINED, THE COMPUTERIZED WORK-HISTORY FILES WERE CHECKED FOR EACH EMPLOYEE TO DETERMINE IF THE EMPLOYEE HAD BEEN PREVIOUSLY EXPOSED TO EO, DETERMINED BY WORK HISTORY INDICATING WORK IN DOWANOLS, GLYCOL II, OR GLYCOL I (GLYCOL I WAS INCLUDED BECAUSE A SAFETY FACTOR WAS USED TO INSURE NO EO EXPOSURE, SINCE QUESTIONS ABOUT EO USE IN GLYCOL I WAS RAISED BY LA PERSONNEL). ONCE AN EMPLOYEE HAD BEEN DETERMINED TO HAVE PREVIOUS EO EXPOSURE, HE WAS EXCLUDED FROM THE LIST, IF NOT THE EMPLOYEE WAS ADDED TO THE CONTROL CANDIDATE LIST. ONCE THIS LIST WAS COMPLETE, ALL FEMALES, EMPLOYEES HAVING PRE-EMPLOYMENT STATUS WERE EXCLUDED. THE FINAL LIST WAS THEN CHECKED AGAINST THE LO. DIVISION MEDICAL FILE FOR DETERMINATION OF PARTICIPATION IN THE 1980 HEALTH INVENTORY PROGRAM. A LIST OF THOSE EMPLOYEES NOT PARTICIPATING IN THE 1980 HEALTH INVENTORY WAS PRINTED FOR MANUAL AUDITING AND FOLLOW-UP, AND THEY WERE EXCLUDED FROM THE LIST. OF THOSE PARTICIPATING, AN ELECTRONICALLY MAINTAINED FILE OF THE CONTROL CANDIDATES WAS CREATED, AND THE MATCHING PROCEDURE WAS BEGUN.

THE SUMMARY STATISTICS ASSOCIATED WITH SELECTION OF THE CONTROL CANDIDATES FOLLOWS.

26 APR-81 SUMMARY STATISTICS FOR FINAL SELECTION OF ETHYLENE OXIDE CONTROL POI

TOTAL NUMBER EMPLOYEES IN ORIGINAL CONTROL SELECTION - 1343
NUMBER FEMALES IN ORIGINAL CONTROL SELECTION - 127
NUMBER EMPLOYEES IN ORIGINAL CONTROL SELECTION HAVING PREVIOUS EXPOSURE - 87
NUMBER EMPLOYEES IN ORIGINAL CONTROL SELECTION HAVING PRE-EMPLOYMENT STATUS -

TOTAL NUMBER EMPLOYEES ELIGIBLE FOR CONTROL GROUP - 1054
NUMBER ELIGIBLE EMPLOYEES PARTICIPATING IN 1980 HEALTH INVENTORY - 961
NUMBER ELIGIBLE EMPLOYEES NOT PARTICIPATING IN 1980 HEALTH INVENTORY - 93
PERCENTAGE PARTICIPATION OF ELIGIBLE EMPLOYEES - 91.1
TOTAL EMPLOYEES ELIGIBLE FOR CONTROL MATCHING - 939

DO 095158
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APPROVALS

EPIDEMIOLOGY
HEALTH AND ENVIRONMENTAL SCIENCES
DOW CHEMICAL U.S.A.

PROTOCOL STATUS: PRELIMINARY-DRAFT FINAL ~~11th~~ 12th DRAFT

TITLE: CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

PROTOCOL NUMBER: EPI-DR-9999-9999-2081 DATE: January 26, 1981

PROPOSED STARTING DATE: February 1, 1981 March 1, 19

ESTIMATED DATE OF FINAL REPORT: June 1, 1981 Feb 1, 19

SIGNATURES:

Primary Investigator: _____ 26 Jan 1981
P. F. D. VanPeenen, M.D. (Date)

Approvals: _____
R. R. Cook, M.D. (Date)

_____
J. R. Venable, M.D. (Date)

_____ 2-18-81
R. L. Dostal (Date)

Distribution: Approved _____ 2/16/81
M. F. Currier, M.D. (Date)

DO 095159
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EPIDEMIOLOGY
HEALTH AND ENVIRONMENTAL SCIENCES
DOW CHEMICAL U.S.A.

PROTOCOL STATUS: PRELIMINARY-DRAFT FINAL 12 DRAFT

TITLE: CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

PROTOCOL NUMBER: EPI-DR-0114-1975-2081 DATE: February 3, 1981

PROPOSED STARTING DATE: February 1, 1981

ESTIMATED DATE OF FINAL REPORT: June 1, 1981

SIGNATURES:

Primary Investigator: _____ 26 Jan 1981
P. F. D. VanPeenen, M.D. (Date)

Approvals: _____ 28 Jan 1981
R. R. Cook, M.D. (Date)

_____ 4-Feb 81
J. R. Venable, M.D. (Date)

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R. L. Dostal (Date)

Distribution:

_____
M. F. Currier, M.D. (Date)

EPIDEMIOLOGY
HEALTH AND ENVIRONMENTAL SCIENCES
DOW CHEMICAL U.S.A.

PROTOCOL STATUS: PRELIMINARY-DRAFT FINAL ~~11th~~ 12th DRAFT

TITLE: CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

PROTOCOL NUMBER: EPI-DR-9999-9999-2181 DATE: January 26, 1981

PROPOSED STARTING DATE: February 1, 1981

ESTIMATED DATE OF FINAL REPORT: June 1, 1981

SIGNATURES:

Primary Investigator: _____ 26 Jan 1981
P. F. D. VanPeenen, M.D. (Date)

Approvals: _____
R. R. Cook, M.D. (Date)

_____
J. R. Venable, M.D. (Date)

_____
R. L. Dostal (Date)

Distribution: Approved _____ 2/6/81
M. F. Currier, M.D. (Date)

DO 095161
CONFIDENTIAL

EPIDEMIOLOGY
HEALTH AND ENVIRONMENTAL SCIENCES
DOW CHEMICAL U.S.A.

PROTOCOL STATUS: PRELIMINARY-DRAFT FINAL 12 DRAFT

TITLE: CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

PROTOCOL NUMBER: EPI-DR-0114-1975-2181 DATE: February 3, 1981

PROPOSED STARTING DATE: February 1, 1981

ESTIMATED DATE OF FINAL REPORT: June 1, 1981

SIGNATURES:

Primary Investigator: _____ 26 Jan 1981
P. F. D. VanPeenen, M.D. (Date)

Approvals: _____ 28 Jan 1981
R. R. Cook, M.D. (Date)

_____
J. R. Venable, M.D. (Date)

_____
R. L. Dostal (Date)

Distribution:

_____
M. F. Currier, M.D. (Date)

DO 095162
CONFIDENTIAL

12th DRAFT
February 3, 1981

TITLE: CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

SHORT TITLE: Ethylene Oxide Study

PRIMARY INVESTIGATOR:
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OBJECTIVES: To determine whether Dow employees who are exposed to ethylene oxide (EO) have more abnormalities of the hematopoietic, hepatic, renal and reproductive systems, as measured by data collected for periodic health examinations, than do employees without such exposure.

IMPORTANCE OF THE CHEMICAL: Ethylene oxide (EO) is an important industrial chemical, produced from feedstock ethylene, which is used primarily for making ethylene glycol or polyesters (Anon, 1979a). It is significant from a health viewpoint that EO is also used for cold sterilization of medical equipment, although this usage is minimal from a commercial viewpoint. U.S. production of EO increased from 1.3 billion pounds in 1960 to 5.3 billion pounds in 1979 (Anon, 1979a).

Dow has produced EO since 1941 at the Texas Division and since 1959 at the Louisiana Division. At these locations, McClimans et al, (unpublished manuscript) estimated that at least 550 employees experienced some workplace exposures to EO in the past, while Moore et al, (1979) estimated that 300 employees had worked in EO production for one year or more. At the present time, there are 88 employees with potential exposure to EO at the Louisiana facility (44 each in Glycol II and Dowanols^{R}).

The American Conference of Governmental Industrial Hygienists (AGGIH) lists an 8 hour time-weighted-average concentration (TWA) of 10 ppm for EO in its Notice of Intended Changes for 1980; an 8 hour 10 ppm TWA was also the Dow IHG, but this has very recently (1980) changed to 3 ppm with excursion limit of 50 ppm. The current OSHA permissible exposure limit (PEL) is 50 ppm TWA.

REVIEW OF LITERATURE: Acute intoxication with EO at high concentrations has long been recognized as a cause of irritation of eyes, respiratory tract and skin, and central nervous system (CNS) depression. Delayed effects include headache, nausea, vomiting, incoordination, and electrocardiograph abnormalities (Proctor & Hughes, 1978). Peripheral neuropathy with decreased nerve conduction velocity has recently been reported in 4 men after overexposure to EO (Gross et al, 1979); whether cause and effect can be assumed in these cases is debatable. Levels responsible for acute effects have been estimated at above 2000 ppm for very short single exposures and above 200 ppm for continuous 8 hour exposures (Hine and Rowe, 1963). According to Dr. Ray Flake of the Texas Division, acute overexposure of humans to EO may cause an increase in serum SGOT and SGPT levels (Fishbeck, personal communication).

The experimental toxicity of EO was reported by Dow toxicologists more than 20 years ago (Hollingsworth et al, 1956). There were no effects at 49 ppm, but histologic changes in liver, kidney, and testes were observed in some animal species at repeated seven-hour vapor exposures at levels of 204 and 357 ppm. Reversible impairment of nervous function and muscular paralysis were observed in rats, rabbits and monkeys at the 204 ppm level dose. Interestingly, laboratory results, including blood urea nitrogen and blood counts, were normal in the species studied even at the higher (357 ppm) exposure levels (Hollingsworth et al, 1956).

Recently, there has been renewed concern about possible chronic toxicity of EO. Results of an industry-sponsored 24-month experimental inhalation study showed an increased, dose-related incidence of mononuclear cell leukemia in male and female Fischer 344 rats (Snelling et al, 1981). Effects were voted at all level of exposures: 100, 33, and 10 ppm. Past literature in these regards included a 1964 report of tumorigenicity in female mice (Reyniers, 1964), alkylating agent properties (Ehrenberg et al, 1974), and demonstrations of mutagenicity in several test systems (Anon, 1979b), including Neurospora (Watson, 1966), plants (Ehrenberg and Gustafsson, 1957), and the Salmonella typhimurium strain TA 1535 bacterial assay (Embree, 1975).

As regards human disease, there are two recent published reports from Sweden of malignancies purportedly linked to EO exposure. The first report was of a case each of acute mylegenous leukemia, chronic myelogenous leukemia, and Waldenstrom's macroglobulinemia diagnosed between 1972 and 1977 in employees of a small factory which used EO for sterilization (Hogstedt et al, 1979a). These cancers may, of course, be unrelated; but in a subsequent retrospective mortality study of employees of an EO production facility, the same senior author reported more observed deaths from leukemia (3) than would have been expected (less than 0.5) using Swedish national death rates (Hogstedt et al, 1979b). Two of the leukemia deaths were caused by chronic lymphatic leukemia, one by acute myeloid leukemia. It is difficult to interpret results from this paper because of the finding of an elevated overall standard mortality ratio (SMR) with 47 deaths vs. 27 expected. Such a finding would be extremely unusual in the U.S. where most U.S. employed populations reflect the "healthy worker effect", and experience overall SMRs less than 100%. Another unusual finding was an increased SMR for diseases of the circulatory system (20 observed vs. 13 expected), which is reported only in office employees in the U.S. Finally, chronic lymphatic leukemia has not, to this author's knowledge, been linked to environmental factors.

A retrospective cohort mortality study of employees with work-place exposure to EO is planned by British colleagues at Imperial Chemical Industries Limited (ICI). Results of the ICI study will be helpful in interpretating the Hogstedt reports.

The Russian literature includes two reports of a variety of health problems associated with workplace exposures to EO. Yabukova et al (1976) reported an increased gynecological sick rate, increased complications of pregnancy, and increased incidence of interruptions of pregnancy among employees of an EO manufacturing plant compared to pregnancies in management personnel and from outside the factory. However, if I read a translation of the paper correctly, although spontaneous abortion occurred in 10.5% of pregnancies of the exposed group of instrument controllers compared to about 8% of laboratory workers (also exposed) and about 8% of management controls, there were more stillbirths among management employees (4/65) than in instrument controllers (1/57). According to Yabukova et al (1976) the "overall corresponding contamination of the factory air did not exceed 1 mg/m^3" (= about 0.6 ppm).

Ostravskaya et al (1971) reported a variety of subjective complaints from 76 individuals with 3-6 years work experience, presumably in EO manufacturing. In addition, they reported "bradycardia", "vegetative shifts" and "EKG changes" in some; the significance, if any, of the quoted abnormalities is difficult to assess from the translation. Ostravskaya et al (1971) reported a leukopenia (4000-4400 WBC/mm^3) in 9 of the 76 employees.

There was only one U.S. epidemiology study of EO prior to the recent interest in carcinogenesis. A cross-sectional study of 37 EO operators engaged in manufacturing operations and of age-matched controls (operators working with chemicals other than EO) was reported by Joyner in 1964. The highest air level of EO recorded was 127 ppm but average exposures were less than 10 ppm for the working day (Joyner, 1964). The EO group actually had fewer symptoms and less absenteeism than the controls; and there were no more "abnormal" laboratory findings in the study group than among the controls (Joyner, 1964).

More recently, in a Dow Chemical U.S.A. response document (Moore et al, 1978), it is stated (page 7) that health surveillance data from 129 Dow employees "revealed no unusual medical effects, i.e., no effects were observed in employees potentially exposed to EO within the TLV". Tests apparently included blood counts and a battery of clinical laboratory tests. A cross-sectional study of individuals involved in cold sterilization using EO was recently published by Garry et al, 1979, who found various frequencies of symptoms (up to 9 with histories of sore throat) among 12 EO-exposed employees versus no symptoms of any kind in a control group. Similarly, cytogenetic studies by these authors reportedly showed more frequent sister chromatid exchanges (SCE) (average 8.65) among the 12 employees than among 11 controls (average 6.37).

A cross-sectional study was also sponsored by the American Hospital Supply Corporation (AHSC). As yet unpublished, the AHSC study was of employees of 9 U.S. manufacturing facilities which utilize EO as a sterilant gas. According to data kindly provided by Ronald H. Abrahams, Ph.D., director of Regulatory Compliance of the AHSC, 6 of 75 exposed* employees had slight anemia and one had a slight increase in lymphocytes (there were apparently no controls for this phase of the study). Sperm counts were obtained from some of the employees: 8 of 46 exposed and 1 of 9 controls had sperm counts less than 20 million/cc. The AHSC study also included cytogenetic data: except for stable forms (Cs), all modalities of chromosome aberration including number of breaks, unstable forms (CV), and SCEs, were statistically increased in the exposed group when compared to control groups of office workers.

RATIONALE FOR RESEARCH: There is a growing volume of experimental toxicological data indicating that EO, at chronic vapor exposure levels much higher than experienced in the Dow workplace, can cause detectable health effects. Whether measurable effects might also occur at lower levels of exposure is unknown, but, if so, they might include those listed in Tables I and II. A major concern about long-term effects of workplace exposures to EO is carcinogenesis, so

*Industrial Hygiene data were not given, but vapor levels were stated to be less than the OSHA 8 hour TWA limit of 50 ppm.

it would seem reasonable that any epidemiological study be designed not only to detect the phenomena listed in Table I over the short term, but to detect excess cancers over the long term. In fact, a draft proposal for a retrospective cohort mortality study of EO production personnel at the Texas Division, with leukemia as a primary concern, was prepared by McClimans and colleagues in July 1979 (unpublished data). Very recently, Bond and colleagues have prepared the protocol for a case-control study of leukemias at Texas Division. Our proposal is for a cross-sectional study of Louisiana Division employees involved in jobs with potential EO exposure, to be followed by continuous surveillance of the same group of employees. Since cross-sectional studies are preliminary and do not usually yield definitive results, it will be necessary to plan for appropriate follow-on research depending on these preliminary findings. Alternatives for follow-on research are detailed on page 11.

Abnormalities which might be expected if workplace exposures to EO were exerting a chronic toxic effect include hematological, hepatic, reproductive, renal, cytogenetic, and carcinogenic (Glaser, 1977). As proposed at the present time, however, our project will be limited to analysis of results from existing medical surveillance data. Hematological abnormalities reportedly associated with exposure to EO include anemia and absolute lymphocytosis (Ehrenberg and Halstrom, 1967), leucopenia (Ostravskaya et al, 1971) or, simply "changes in peripheral blood" (Spasovsky et al, 1978). Because of the reported dose-related

alkylation of hemoglobin by EO (Osterman-Golkar et al, 1976; Calleman et al, 1978) it would not be unreasonable to expect increases in laboratory tests associated with hemolysis, including total serum bilirubin and lactic acid dehydrogenase (LDH), as well as anemia and reticulocytosis. Similarly, direct hepatic and renal tubular damage, causing abnormal results in simple measures of liver and kidney function, might be expected from any alkylating agent and, in fact, have been reported experimentally at high levels of EO vapor exposure (Hollingsworth et al, 1956).

Questionnaire data from the periodic health examinations are available and can be used. We recognize the weaknesses and biases of using questionnaire data as evidence for disease or for adverse reproductive function, but by judicious and a priori designation of which questions will be analyzed it should be possible to compare the prevalences of symptoms relating to diseases of the blood and of adverse pregnancy outcomes.

The list of effects which can be studied using existing data is in Table I. Table II is a more comprehensive list, including tests which cannot, and, in certain cases, probably should not, be studied at the present time. As more reliable techniques become available, however, it may become appropriate to examine for additional effects in the future. Table III lists data elements which are presently available for extraction and analysis.

APPROACH:

Exposed Population. The exposed population will consist of active Louisiana Division MALE employees who were assigned to Glycol II or Dowanols for at least 6 months prior to participating in the Health Inventory examination during 1980. Since intensity of exposure categories by job cannot be estimated because detailed historical industrial hygiene data are lacking, length of employment in the 2 plants will be used to divide the exposed group into subsets of longer and shorter durations of exposure.

Control Population. There are 88 persons eligible; but since it is anticipated that ~~non-whites and~~ females will be few, only data from ~~white~~ males will be included in the study. The control group will consist of an equal number of males matched by age (within 5 years or better), race, date of hire, and smoking and alcohol use history. The job category will be as of the date of health inventory and, of course, results of the 1980 health inventory examination must be available. Finally, to be eligible as a control, the employee must have no history of EO exposure. It is recommended that the initial pool for controls consist of all Louisiana Division employees, and that eliminations be made by matching criteria, the best age match being the final decision step.

Dependent Variables. Dependent variables are listed in Table III, and consist of answers to questions regarding reproductive history and past medical history, complete blood count values, and results of the liver and kidney function tests. Test results will be considered abnormal if outside the reference ranges shown; a summary of some recently published ranges is in Appendix i.

Covariables. Covariables or potential confounding variables other than those used in matching include family history of illness, use of medications, exposure to chemicals other than EO, radiation exposure, and substance abuse. The effects of some of these covariables cannot be analysed, and others, such as known substance abuse or use of certain medications might best be handled by elimination from both control and exposed groups. Those with a family history of blood disorders need not be eliminated, but the frequencies of such histories in the 2 groups should be checked. Obviously, affirmative answers to questions such as "Did you have a birth abnormality?" should be considered if the abnormality were considered hereditary.

Analysis of Data. Data will be collated and analysed using the computer system available to the Louisiana Division Medical Department and capably programmed by Perry Poston. The SAS statistical software system will be used for analyses. The null hypothesis of no statistically significant difference in values from the exposed and control samples will be by the Wilcoxon signed rank test for continuous data and McNemar's test in the case of dichotomous data. Continuous data will also be analyzed by McNemar's test using the categories of within or without the normal range as defined in Table III.

RESULTS, WEAKNESSES, AND FOLLOW-ON STUDIES: This proposed cross-sectional study should indicate whether or not employees potentially exposed to EO have relatively depressed red cell indices or depressed or elevated white cell counts compared to their non-EO-exposed colleagues; whether results of their laboratory tests of renal and hepatic function are comparable; and whether their reported prevalences of adverse pregnancy outcomes are similar. Identification of potentially exposed groups will also permit continued future surveillance and such groups would also be available for testing as new techniques become available. Concern has been expressed about ability of this study to detect leukemia. By definition, leukemia would, in fact, be detected by the combination of anemia associated with increased number of white cells in peripheral blood, and the diagnosis is easily confirmed by microscopic examination of bone marrow.

Cross-sectional studies have many weaknessess which need not be detailed here. The proposed study, however, additionally suffers from the following:

1. Pregnancy outcome data from fathers are less reliable than from mothers.
2. The questionnaires permit bias towards "socially-acceptable" answers.
3. The "power" or ability to detect subtle differences between exposed and control populations may be low.
4. It is difficult to separate out age and work-ethic effects when exposure categories are defined by duration rather than intensity.

For these reasons, we suggest that a negative result (i.e., no significant difference in dependent variables between exposed and control groups) not be considered the final word. Thus, it will be appropriate to continue to monitor employees with potential EO exposures.

Populations to be included in continuing surveillance (prospective morbidity) studies will be those identified for this cross-sectional study, with addition of those entering or leaving jobs with potential EO exposures. Controls who enter such jobs will join the exposed group and will be replaced as controls using the original matching criteria. Personnel new to EO exposure jobs, and staying there for 6 months, will be added to the study along with new matched controls. Personnel leaving EO exposure jobs will continue in the study, but, of course, in a different category.

Similarily a positive result (i.e., statistically significant difference in dependent variables between exposed and control groups) cannot be considered definitive either. In order to avoid decisions based on chance due to multiple comparisons, it is suggested that future studies at this time be stimulated only if a positive result is found for more than 2 laboratory tests (of the 15 to be analysed) or for more than 2 questionnaire responses (of the 11 analysed). In such an event, a retrospective morbidity study of a cohort of all EO-exposed employees at some point in the past (I'd recommend a period prior to the first Health Inventory) should be designed. Such a study might permit evaluation of the question of "which came first, exposure or morbidity?"

People. Estimated personnel needs are as follows:

Individual	Time (Hours)
VanPeenen - Epidemiologist, Midland	120
Currier - Medical Director, Louisiana	80
Cook - Director of Epidemiology, U.S. Area	20
Poston - Computer Specialist, Louisiana	60 → 120 hrs
Ledford - Industrial Hygienist, Louisiana	40
TOTAL	320 Hours

Increased by Statistical research

Dollars: For personnel, 320 x $55.00/hr = $17,600.00

For computer time, estimate about 4,000.00

The computer estimate is for analyses only and does not include gathering and storing health data; It is based on a one month's cost incurred in our department during a period of heavy computer usage.

For travel and miscellaneous 3,000.00

TOTAL $24,600.00

TIME TO COMPLETION: Approximately 3 months from approval of protocol to final report.

T A B L E I.

EFFECTS WHICH CAN BE MEASURED
USING EXISTING DATA

Expected Effect (Dependent Variable)	How Measured	Why
1. Hematopoietic		
Anemia lymphocytosis or lymphocytopenia	Red and white blood cell counts	Direct toxic effects on red and white cell precursors: stimulation of the lymphocytic system
2. Hepatotoxicity	Liver function tests, liver enzymes	Direct toxic effect
3. Mutagenesis	"Adverse pregnancy outcomes" according to questionnaire	Alteration of germinal stem cells
4. Renal tubule toxicity	Kidney function tests	Direct toxic effect

TABLE II

EFFECTS WHICH MIGHT OCCUR IF EO EXPOSURE WERE TO CAUSE ADVERSE LONG TERM EFFECTS ON HUMAN HEALTH, BUT WHICH CANNOT BE MEASURED USING EXISTING DATA AND WILL NOT BE ANALYSED IN THIS STUDY

Expected Effect (Dependent Variable)	How Measured	Why
1. Hematopoietic		
Anemia	Reticulocyte count	Hemolysis
2. Cytogenetic	(Chromosome aberrations, sister chromatid exchanges)	Direct effect on DNA* in dividing cells
3. Spermatocidal		
Depression of spermatogenesis	Sperm counts FSH levels	Toxicity to germinal tissue
4. Immunotoxicity	Counts of T&B cells Mitogen stimulation Depressed antibody formation	DNA effect; direct toxic effect on bone marrow and blood
5. Neurotoxicity	Measures of nerve conduction Tests for tremor	Reports of neurological effects

*Abbreviations: DNA = deoxynucleic acid;

FSH = follicle stimulating hormone;

T&B cells = thymus and bursa derived cells.

T A B L E III

DATA ELEMENTS WHICH CAN BE EXTRACTED FROM HEALTH INVENTORY EXAMS LOUISIANA DIVISION

A. Dependent Variables.

1. Prevalence of Positive Answers on Questionnaire Items.

a. "Has your family had any of the following:

(1) Birth Abnormality. "Analysis will be by those who checked child only as well as by those who checked child and self.

(2) "Any Miscarriages?" Analyze by "Yes" or "No" and by numbers per 100 respondents.

(3) "Any children with abnormality at birth?" As above.

(4) "Any children stillborn?" As above.

(5) "Any death under 6 months?" As above.

b. "Do you have or have you had any of the following?"* Analyses will be by prevalences of "Yes" answers.

(1) "Liver trouble."

(2) "Kidney trouble."

(3) "Anemia or blood problems."

(4) "History of blood dyscrasias."

(5) "Abnormal function of blood elements."

(6) "Liver or renal dysfunction."

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*Analyzed with and without an additional yes answer to "Exposure to drugs or chemicals that injure the liver"; "Exposure to benzene or other bone marrow depressants" and/or "Outside exposure to possible marrow toxins."

T A B L E III
(continued)

2. Results of Laboratory Tests - Hematology**

a.	Hgb Reference range	(RR)	:14-18 Gm%
b.	Hct	RR	:40-54%
c.	RBC	RR	:4.6-6.2 million/mm^3
d.	WBC	RR	:4.5-11,000/mm^3
e.	Percent lymphocytes	RR	:25-33%

3. Results of Laboratory Tests - Kidney

a.	Blood Urea Nitrogen	RR***	:8-26 mg/dl
b.	Serum Creatinine	RR	:0.9-1.4 mg/dl
c.	Urine Protein 1+ or greater	RR	:neg
d.	RBC; WBC	RR	:2; 0-3

4. Results of Laboratory Tests - Liver

a.	Total Bilirubin	RR	: Less than 1.6 mg/dl
b.	Alkaline Phosphatase	RR	:35-148 units
c.	LDH	RR	:63-155 IU/L
d.	SGPT	RR	:12-53 units
e.	SGOT	RR	:15-55 units
f.	GGTP	RR	:under 38 U/L

**Reference ranges for blood tests according to Conn (1971), which are the most conservative of those reviewed - See Appendix i.

***Normal ranges for liver and kidney tests according to Bio-Science Laboratories, 7600 Tyrone Ave., Van Nuys, Calif.

T A B L E III
(continued)

B. Characteristics (Potential confounding variables).

1. Prevalence of routine answers on questionnaire items.

a. Past history of birth abnormality, leukemia, blood disorder or cancer in any family member.

b. "Yes" on "Exposures other than at work"

c. Diabetes

d. Asthma

e. Arthritis

2. Physical Exam

a. Height

b. Weight

c. Diastolic blood pressure

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Paired Replicates Analyses by Way of Signed Ranks

DATA. We obtain $2n$ observations, two observations on each of n subjects (blocks, patients, etc.).

Subject i	X_i	Y_i
1	X_1	Y_1
2	X_2	Y_2
.	.	.
.	.	.
.	.	.
n	X_n	Y_n

Assumptions

A1. We let $Z_i = Y_i - X_i$ and take as our model

$$Z_i = \theta + e_i, \qquad i = 1, \ldots, n, \tag{1}$$

where the e's are unobservable random variables and the parameter of interest θ is the unknown "treatment" effect.

A2. The e's are mutually independent.

A3. Each e comes from a continuous population (not necessarily the same one) that is symmetric about zero.

1. A DISTRIBUTION-FREE SIGNED RANK TEST (WILCOXON)

Procedure. To test

$$H_0: \theta = 0, \tag{2}$$

1. Form the absolute differences $|Z_1|, \ldots, |Z_n|$. Let R_i denote the rank of $|Z_i|$ in the joint ranking from least to greatest of $|Z_1|, \ldots, |Z_n|$.

2. Define indicator variables ψ_i, $i = 1, \ldots, n$, where

$$\psi_i = \begin{cases} 1 & \text{if } Z_i > 0, \\ 0 & \text{if } Z_i < 0. \end{cases}$$

3. Form the n products $R_1\psi_1, \ldots, R_n\psi_n$, and set

$$\sum_{i=1}^{n} R_i\psi_i \tag{3}$$

The product $R_i\psi_i$ is known as the positive signed rank of Z_i. It takes on the value zero if Z_i is negative and is equal to the rank of $|Z_i|$ when Z_i is positive. The statistic T^+ is the sum of the positive signed ranks.

4. For a one-sided test of H_0 (2) versus the alternative $\theta > 0$, at the α level of significance,

$$\begin{aligned} &\text{reject } H_0 \quad \text{if} \quad T^+ \geq t(\alpha, n), \\ &\text{accept } H_0 \quad \text{if} \quad T^+ < t(\alpha, n), \end{aligned} \tag{4}$$

where the constant $t(\alpha, n)$, which satisfies the equation $P_0\{T^+ \geq t(\alpha, n)\} = \alpha$, is obtained from Table A.4. (Also see Comment 8.)

For a one-sided test of H_0 (2) versus the alternative $\theta < 0$, at the α level of significance,

$$\begin{aligned} &\text{reject } H_0 \quad \text{if} \quad T^+ \leq \frac{n(n+1)}{2} - t(\alpha, n), \\ &\text{accept } H_0 \quad \text{if} \quad T^+ > \frac{n(n+1)}{2} - t(\alpha, n). \end{aligned} \tag{5}$$

For a two-sided test of H_0 (2) versus the alternative $\theta \neq 0$, at the α level of significance,

$$\begin{aligned} &\text{reject } H_0 \quad \text{if} \quad T^+ \geq t(\alpha_2, n) \text{ or } T^+ \leq \frac{n(n+1)}{2} - t(\alpha_1, n), \\ &\text{accept } H_0 \quad \text{if} \quad \frac{n(n+1)}{2} - t(\alpha_1, n) < T^+ < t(\alpha_2, n), \end{aligned} \tag{6}$$

where $\alpha = \alpha_1 + \alpha_2$.

Large Sample Approximation. When H_0 is true, the statistic

$$T^* = \frac{T^+ - E_0(T^+)}{[\text{var}_0(T^+)]^{1/2}} = \frac{T^+ - [n(n+1)/4]}{[n(n+1)(2n+1)/24]^{1/2}} \tag{7}$$

has an asymptotic (n tending to infinity) $N(0, 1)$ distribution. The normal theory approximation to procedure (4) is

$$\begin{aligned} &\text{reject } H_0 \quad \text{if} \quad T^* \geq z_{(\alpha)}, \\ &\text{accept } H_0 \quad \text{if} \quad T^* < z_{(\alpha)}. \end{aligned} \tag{8}$$

Ties. If there are zero values among the Z's, discard the zero values and redefine n to be the number of nonzero Z's. If there are ties among the (nonzero) $|Z|$'s, use average ranks to compute T^+, and carry on as in (4) to (6). For the large sample approximation, compute T^+ using average ranks, and replace $\text{var}_0(T^+)$ in (7) by

$$\text{var}_0(T^+) = (24)^{-1}\left[n(n+1)(2n+1) - \frac{1}{2}\sum_{j=1}^{g} t_j(t_j - 1)(t_j + 1)\right], \tag{9}$$

where g = number of tied groups and t_j is the size of tied group j.*

* In (9) an untied observation is considered to be a tied group of size 1. Hence, if there are no ties at all, $g = n$, $t_j = 1$ for $j = 1, \ldots, n$, and the right-hand side of (9) reduces to $(24)^{-1}[n(n+1)(2n+1)]$.

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Table 1. Hamilton depression scale factor IV values

Patient i	X_i	Y_i
1	1.83	0.878
2	0.50	0.647
3	1.62	0.598
4	2.48	2.05
5	1.68	1.06
6	1.88	1.29
7	1.55	1.06
8	3.06	3.14
9	1.30	1.29

Source. D. S. Salsburg (1970).

Example 1. The data in Table 1 were obtained by Salsburg (1970). The data, based on nine patients who received tranquilizer T, were taken from a double-blind clinical trial involving two tranquilizers. The measure used was the Hamilton (1960) depression scale factor IV (the "suicidal" factor;) the X value was taken at the first patient visit after initiation of therapy, the Y value at the second visit after initiation of therapy. The patients had been diagnosed as having mixed anxiety and depression.

In this example involving tranquilizers, an improvement would correspond to lower factor values. We will perform test (5). From Table A.4 we find that the critical value at the $\alpha = .049$ level is $(9(10)/2) - t(.049, 9) = 45 - 37 = 8$. We illustrate the computations leading to (3) in tabular form.

i	Z_i	$\lvert Z_i\rvert$	R_i	ψ_i	$R_i\psi_i$
1	−.952	.952	8	0	0
2	.147	.147	3	1	3
3	−1.022	1.022	9	0	0
4	−.430	.430	4	0	0
5	−.620	.620	7	0	0
6	−.590	.590	6	0	0
7	−.490	.490	5	0	0
8	.080	.080	2	1	2
9	−.010	.010	1	0	0

We then have

$$T^+ = \sum_{i=1}^{9} R_i\psi_i = 5,$$

and, since $T^+ = 5 < (9(10)/2) - t(.049, 9) = 8$, we reject H_0 in favor of $\theta < 0$ at the $\alpha = .049$ level. Note that the lowest level at which we could reject H_0 using this one-sided test is .020, since $(9(10)/2) - t(.020, 9) = 45 - 40 = 5$.

For the large sample approximation we find, using (7),

$$T^* = \frac{5 - (9(10)/4)}{[9(10)(19)/24]^{1/2}} = \frac{-17.5}{8.44} = -2.07.$$

Thus we see from Table A.1 that the lowest level at which we reject H_0 with the normal approximation is .0192. Hence both the exact test and the large sample approximation indicate that there is strong evidence that the tranquilizer does lead to an improvement as measured by the Hamilton scale factor IV values.

Comments

1. Assumption A1 does not require that X_i and Y_i be independent, and indeed in most applications they are dependent.

2. For paired replicates data, the symmetry part of Assumption A3 is often inherently satisfied. In particular, if X_i and Y_i arise from populations differing only in location (i.e., the only treatment "effect" is a change in location), then $e_i = Z_i - \theta$ comes from a population that is symmetric about zero. This is also true under more general conditions.

3. To test the hypothesis $\theta = \theta_0$, where θ_0 is a specified nonzero number, obtain the modified observations $Z_i' = Z_i - \theta_0$, for $i = 1, \ldots, n$, and compute T^+ using the Z''s (instead of the Z's). Procedures (4) to (6) may then be applied as described.

4. When H_0 (2) is true, the distribution of T^+ (3) is symmetric about its mean $n(n+1)/4$; this implies that

$$P_0\{T^+ \geq x\} = P_0\left\{T^+ \leq \frac{n(n+1)}{2} - x\right\},$$

for $x = 0, \ldots, (n(n+1)/2)$. From this it follows that the lower α percentile for the null distribution of T^+ is $[n(n+1)/2] - t(\alpha, n)$. This explains the use of $[n(n+1)/2] - t(\alpha, n)$ as the critical value in procedure (5).

5. Whereas in order to perform the sign test (Section 4) for paired replicates we need only the signs of the Z_i differences, in the case of the signed rank test we need to know both the signs of the Z's and the ranks of the $|Z|$'s.

6. The statistic T^+ (3) is the sum of the ranks (of the absolute values) corresponding to the positive Z observations. Define T^- to be the sum of ranks (of the absolute values) corresponding to the negative Z observations. Note that T^- can be defined by (3) with ψ_i replaced by $1 - \psi_i$, for $i = 1, \ldots, n$. Test procedures (4) to (6) could equivalently be based on T^-, since $T^- = [n(n+1)/2] - T^+$. (See Problem 3.)

7. Let B be the number of positive Z's and let $r_1 < r_2 < \cdots < r_B$ denote the ranks of the absolute values of these positive Z's. For $\theta > 0$, these ranks tend to be larger than the corresponding ranks of the absolute values of the observations that are negative. This suggests rejecting H_0 (2) in favor of $\theta > 0$ for large values of $\sum_{i=1}^{B} r_i$. As mentioned in Comment 6, $T^+ = \sum_{i=1}^{B} r_i$. This is partial motivation for the procedure defined by (4).

8. The null distribution of T^+ can be obtained using the equation $T^+ = \sum_{i=1}^{B} r_i$ (see Comment 7), recognizing that, under H_0 (2), each of the 2^n possible outcomes for the configuration $(r_1, \ldots, r_B)$ occurs with probability $(\frac{1}{2})^n$. For example, in the case $n = 3$, the $2^3 = 8$ possible outcomes for $(r_1, \ldots, r_B)$ and associated values of T^+ are given in the following table.

B	$(r_1, r_2, \ldots, r_B)$	$P_0\{(r_1, r_2, \ldots, r_B)\}$	$T^+ = \sum_{i=1}^{B} r_i$
0		$\frac{1}{8}$	0
1	$r_1 = 1$	$\frac{1}{8}$	1
1	$r_1 = 2$	$\frac{1}{8}$	2
1	$r_1 = 3$	$\frac{1}{8}$	3
2	$r_1 = 1, r_2 = 2$	$\frac{1}{8}$	3
2	$r_1 = 1, r_2 = 3$	$\frac{1}{8}$	4
2	$r_1 = 2, r_2 = 3$	$\frac{1}{8}$	5
3	$r_1 = 1, r_2 = 2, r_3 = 3$	$\frac{1}{8}$	6

Thus, for instance, $P_0\{T^+ \geq 5\} = P_0\{T^+ = 5\} + P_0\{T^+ = 6\} = (\frac{1}{8}) + (\frac{1}{8}) = (\frac{1}{4})$. (Cf. Table A.4.)

The derivation of the null distribution of T^+ does not depend on the underlying e populations beyond the point of requiring them to be continuous and symmetric about zero. This is why the procedures based on T^+ are called distribution-free procedures. For example, when we choose the critical constant $t(\alpha, n)$ of procedure (4) so that the equation $P_0[T^+ \geq t(\alpha, n)] = \alpha$ is satisfied, we control the probability of (falsely) rejecting H_0 when H_0 is true; subject to Assumptions A1 to A3, moreover, this error probability does not depend on the underlying populations of the e's.

9. Replace Assumptions A1 to A3 by the Assumptions A1′: each Z comes from the same continuous population and A2′: the nZ's are mutually independent. Then letting

$$\theta^* = P(Z_1 + Z_2 > 0) - (\tfrac{1}{2}),$$

where Z_1 and Z_2 are random members from the Z population and Z_1, Z_2 are independent, the test procedures (4), (5), and (6) are consistent against alternatives for which $\theta^* >$, $<$, and $\neq 0$, respectively [see Pratt (1959)].

For the special situation covered by Assumptions A1 and A2 and the stronger version of A3 used in Property 1, this consistency statement implies the consistency statement given in Property 1.

Properties

1. Consistency: For our consistency statement we strengthen Assumption A3 so that each e comes from the same continuous population that is symmetric about 0. Then the tests defined by (4), (5), and (6) will be consistent against the alternatives $\theta > 0$, < 0, and $\neq 0$, respectively. See Pitman (1948), van Eeden and Benard (1957b), Pratt (1959), and Comment 9.

2. Efficiency: See Pitman (1948), Hodges and Lehmann (1956), and Section 10.

REFERENCES. The T^+ statistic was introduced by Wilcoxon (1945). Fraser (1957b) proposed a normal scores analog of the signed rank test that has desirable efficiency properties. Pratt (1959) presented a detailed discussion of methods for handling zero observations and tied ranks in the signed rank procedure [see also Cureton (1967)]. Hollander (1971) considered a procedure for testing the absence of a treatment effect under a more general model than that of (1) (see Section 10.3).

Other competitors of the T^+ test include a binary test due to Savage (1959), a generalization of the binary test considered by Doksum and Thompson (1971), and various classes of tests considered by Hemelrijk (1950a, 1950b), van Eeden and Benard (1957a, 1957b, 1957c), Govindarajulu (1960), Gross (1966), and Doksum and Thompson (1971). See also References of Section 4.

PROBLEMS

1. The data in Table 2 are a subset of the data obtained by Kaneto, Kosaka, and Nakao

Table 2. Data on blood levels of immunoreactive insulin ($\mu U/ml$)

Dog i	X_i	Y_i
1	350	480
2	200	130
3	240	250
4	290	310
5	90	280
6	370	1450
7	240	280

Source. A. Kaneto, K. Kosaka, and K. Nakao (1967).

CHAPTER 3

The One-Sample Location Problem

The procedures of this chapter are designed for statistical analyses in which primary interest is centered on the location (median) of a population. We encounter two types of data for which such analyses are important. The first of these, referred to as paired replicates data, represents pairs of "pretreatment" and "posttreatment" observations; here we are concerned with a shift in location due to the application of the "treatment." The second type of data, referred to as one-sample data, consists of observations from a single population about whose location we wish to make inferences.

In Sections 1 to 3, procedures are considered for analyzing paired replicates data using signed ranks. In particular, Section 1 presents a distribution-free signed rank test, Section 2 a point estimator associated with the signed rank statistic, and Section 3 a related distribution-free confidence interval. In Section 7 these procedures are applied to some one-sample data. An asymptotically distribution-free test for symmetry of the underlying population (one of the assumptions in Sections 1 to 3 and 7) is considered in Section 9.

Procedures for analyzing paired replicates data using signs are discussed in Sections 4 to 6. A distribution-free sign test is considered in Section 4, a point estimator associated with the sign statistic in Section 5, and a related distribution-free confidence interval in Section 6. These sign procedures are applied to some one-sample data in Section 8.

The asymptotic relative efficiencies for translation alternatives of the procedures based on the signed rank statistic and those based on the sign statistic with respect to their normal theory counterparts based on the sample mean are discussed in Section 10. In this section we also deal with the asymptotic relative efficiency of the test for symmetry covered in Section 9.

APPENDIX i

SUMMARY OF REFERENCE VALUES FOR
ADULT MALES BLOOD COUNTS

Author	Hemoglobin (Gm %)	Hematocrit (%)	Erythrocytes ($Million/mm^3$)	Leukocytes ($Thousand/mm^3$)
Coulter	14-18	42-52	4.7-6.1	4.8-10.8
Todd & Sanford	13.5-18	40-54	4.6-6.2	4.5-10
Merck	13-16	42-50	4.2-5.9	4.8-10.8
Conn	14-18	40-54	4.6-6.2	4.5-11
Jandl	13.5-17.5	41-49	4.4-6.0	
SKF	14-18	38-54	4.5-6.0	5-10
NIOSH	14-18	-	4.4-6.3	4.2-10
Bio Science	13-18	40-54	4.5-6.0	N/A

T A B L E I.

EFFECTS WHICH CAN BE MEASURED
USING EXISTING DATA

Expected Effect (Dependent Variable)	How Measured	Why
1. Hematopoietic		
Anemia lymphocytosis or lymphocytopenia	Red and white blood cell counts	Direct toxic effects on red and white cell precursors: stimulation of the lymphocytic system
2. Hepatotoxicity	Liver function tests, liver enzymes	Direct toxic effect
3. Mutagenesis	"Adverse pregnancy outcomes" according to questionnaire	Alteration of germinal stem cells
4. Renal tubule toxicity	Kidney function tests	Direct toxic effect

T A B L E II

EFFECTS WHICH MIGHT OCCUR IF EO EXPOSURE WERE TO CAUSE ADVERSE LONG TERM EFFECTS ON HUMAN HEALTH, BUT WHICH CANNOT BE MEASURED USING EXISTING DATA AND WILL NOT BE ANALYSED IN THIS STUDY

Expected Effect (Dependent Variable)	How Measured	Why
1. Hematopoietic		
Anemia	Reticulocyte count	Hemolysis
2. Cytogenetic	(Chromosome aberrations, sister chromatid exchanges)	Direct effect on DNA* in dividing cells
3. Spermatocidal		
Depression of spermatogenesis	Sperm counts FSH levels	Toxicity to germinal tissue
4. Immunotoxicity	Counts of T&B cells Mitogen stimulation Depressed antibody formation	DNA effect; direct toxic effect on bone marrow and blood
5. Neurotoxicity	Measures of nerve conduction Tests for tremor	Reports of neurological effects

*Abbreviations: DNA = deoxynucleic acid;

FSH = follicle stimulating hormone;

T&B cells = thymus and bursa derived cells.

Perry Paston

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Orchid & Coporate
Chairs Systems Research

TABLE I. PARTICIPATION DATA

GROUP	NUMBER	*PARTICIPATION RATIO
I. Population Universe		
A. All employees eligible for Periodic Health Examinations (PHE) in 1980 (Total in plant except administrative and some management).		
B. Total for whom 1980 PHE data available.		
C. Female employees.		
D. Population universe used as source for exposed and control populations (= IB minus IC).		
II. Exposed population, selected from source population (all males).		
A. No. males in Glycol II at time of 1980 exam.		
B. No. males who worked in Glycol I & II on or before 31 Dec. 1980.		
C. No. males in Dowanol/Ethanolamine at time of 1980 exam.		
D. No. males in Dowanol/Ethanolamine on or before 31 Dec. 1980.		
E. Subtotal in exposed population = IIA + IIC.	85	

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4/21/81

TABLE 1 (Con't)
Page 2

GROUP	NUMBER	*PARTICIPATION RATIO
III. Control population (all males).		
A. Source population (ID) minus exposed population (IIA + IIB + IIC + IID).		
B. Employees with potential exposure to benzene in 1980.		
C. Employeees with unknown chemical exposures due to assignment in Research and Development or in Instrumentation.		
D. Subtotal from whom matched controls selected = III A minus IIIB and IIIC.	976	

*Participation Ratio = No. employees in the group for whom a 1980 PHE available divided by no. employees in the group eligible for 1980 PHE.

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TABLE II.

CHARACTERISTICS OF POPULATIONS FROM LOUISIANA DIVISION: EO EXPOSED, EO MATCHED CONTROLS (1:1), AND ALL PHE PARTICIPANTS.

CHARACTERISTIC VALUE

	Exposed	Control	ALL
I. MATCHING CHARACTERISTICS.			
✓ Number			
✓ Mean Age			
✓ Median Age			
✓ Number non whites			
✓ Yrs. in Plant (mean)			
✓ % Current Smokers			
✓ % Non Smokers			
✓ % Ex Smokers & Pipe Smokers			
✓ % Non Drinkers			
II. OTHER CHARACTERISTICS.			
✓ % with Hx. of diabetes			
✓ % with Hx. of asthma			
Mean Height			
Mean Weight			
Mean diastolic blood pressure			

*From whom a 1980 PHE available

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Orchid Chairing & Corporate Systems Research

TABLE I. PARTICIPATION DATA

GROUP	NUMBER	*PARTICIPATION RATIO
I. Population Universe		
A. All employees eligible for Periodic Health Examinations (PHE) in 1980 (Total in plant except administrative and some management).		
B. Total for whom 1980 PHE data available.		
C. Female employees.		
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CHARACTERISTIC	VALUE		
	Exposed	Control	ALL
I. MATCHING CHARACTERISTICS.			
✓ Number			
✓ Mean Age			
✓ Median Age			
✓ Number non whites			
✓ Yrs. in Plant (mean)			
✓ % Current Smokers			
✓ % Non Smokers			
✓ % Ex Smokers & Pipe Smokers			
✓ % Non Drinkers			
II. OTHER CHARACTERISTICS.			
✓ % with Hx. of diabetes			
✓ % with Hx. of asthma			
Mean Height			
Mean Weight			
Mean diastolic blood pressure			

*From whom a 1980 PHE available

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People. Estimated personnel needs are as follows:

Individual	Time (Hours)
VanPeenen - Epidemiologist, Midland	120
Currier - Medical Director, Louisiana	80
Cook - Director of Epidemiology, U.S. Area	20
Poston - Computer Specialist, Louisiana	60
Ledford - Industrial Hygienist, Louisiana	40
TOTAL	320 Hours

Dollars:	For personnel, 320 x $55.00/hr =	$17,600.00
	For computer time, estimate about	4,000.00

The computer estimate is for analyses only and does not include gathering and storing health data; It is based on a one month's cost incurred in our department during a period of heavy computer usage.

	For travel and miscellaneous	3,000.00
	TOTAL	$24,600.00

TIME TO COMPLETION: Approximately 3 months from approval of protocol to final report.

3/6/81 Last version

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HEALTH AND ENVIRONMENTAL SCIENCES
DOW CHEMICAL U.S.A.

PROTOCOL STATUS: PRELIMINARY-DRAFT FINAL ~~11th~~ 12th DRAFT

TITLE: CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

PROTOCOL NUMBER: EPI-DR-9999-9999-2181 DATE: January 26, 1981

PROPOSED STARTING DATE: February 1, 1981

ESTIMATED DATE OF FINAL REPORT: June 1, 1981

SIGNATURES:

Primary Investigator: _____ 26 Jan 1981
P. F. D. VanPeenen, M.D. (Date)

Approvals: _____
R. R. Cook, M.D. (Date)

_____
J. R. Venable, M.D. (Date)

_____
R. L. Dostal (Date)

Distribution: Approved _____ 2/6/81
M. F. Currier, M.D. (Date)

DO 095206
CONFIDENTIAL

EPIDEMIOLOGY
HEALTH AND ENVIRONMENTAL SCIENCES
DOW CHEMICAL U.S.A.

PROTOCOL STATUS: PRELIMINARY-DRAFT FINAL 12 DRAFT

TITLE: CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

PROTOCOL NUMBER: EPI-DR-0114-1975-2181 DATE: February 3, 1981

PROPOSED STARTING DATE: February 1, 1981

ESTIMATED DATE OF FINAL REPORT: June 1, 1981

SIGNATURES:

Primary Investigator: _____ 26 Jan 1981

P. F. D. VanPeenen, M.D. (Date)

Approvals: _____ 28 Jan 1981

R. R. Cook, M.D. (Date)

_____

J. R. Venable, M.D. (Date)

_____

R. L. Dostal (Date)

Distribution:

_____

M. F. Currier, M.D. (Date)

DO 095207
CONFIDENTIAL

12th DRAFT
February 3, 1981

TITLE: CROSS-SECTIONAL STUDY OF EMPLOYEES WITH WORKPLACE EXPOSURES TO ETHYLENE OXIDE AT LOUISIANA DIVISION

SHORT TITLE: Ethylene Oxide Study

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OBJECTIVES: To determine whether Dow employees who are exposed to ethylene oxide (EO) have more abnormalities of the hematopoietic, hepatic, renal and reproductive systems, as measured by data collected for periodic health examinations, than do employees without such exposure.

IMPORTANCE OF THE CHEMICAL: Ethylene oxide (EO) is an important industrial chemical, produced from feedstock ethylene, which is used primarily for making ethylene glycol or polyesters (Anon, 1979a). It is significant from a health viewpoint that EO is also used for cold sterilization of medical equipment, although this usage is minimal from a commercial viewpoint. U.S. production of EO increased from 1.3 billion pounds in 1960 to 5.3 billion pounds in 1979 (Anon, 1979a).

Dow has produced EO since 1941 at the Texas Division and since 1959 at the Louisiana Division. At these locations, McClimans et al, (unpublished manuscript) estimated that at least 550 employees experienced some workplace exposures to EO in the past, while Moore et al, (1979) estimated that 300 employees had worked in EO production for one year or more. At the present time, there are 88 employees with potential exposure to EO at the Louisiana facility (44 each in Glycol II and Dowanols^{R}).

The American Conference of Governmental Industrial Hygienists (AGGIH) lists an 8 hour time-weighted-average concentration (TWA) of 10 ppm for EO in its Notice of Intended Changes for 1980; an 8 hour 10 ppm TWA was also the Dow IHG, but this has very recently (1980) changed to 3 ppm with excursion limit of 50 ppm. The current OSHA permissible exposure limit (PEL) is 50 ppm TWA.

REVIEW OF LITERATURE: Acute intoxication with EO at high concentrations has long been recognized as a cause of irritation of eyes, respiratory tract and skin, and central nervous system (CNS) depression. Delayed effects include headache, nausea, vomiting, incoordination, and electrocardiograph abnormalities (Proctor & Hughes, 1978). Peripheral neuropathy with decreased nerve conduction velocity has recently been reported in 4 men after overexposure to EO (Gross et al, 1979); whether cause and effect can be assumed in these cases is debatable. Levels responsible for acute effects have been estimated at above 2000 ppm for very short single exposures and above 200 ppm for continuous 8 hour exposures (Hine and Rowe, 1963). According to Dr. Ray Flake of the Texas Division, acute overexposure of humans to EO may cause an increase in serum SGOT and SGPT levels (Fishbeck, personal communication).

The experimental toxicity of EO was reported by Dow toxicologists more than 20 years ago (Hollingsworth et al, 1956). There were no effects at 49 ppm, but histologic changes in liver, kidney, and testes were observed in some animal species at repeated seven-hour vapor exposures at levels of 204 and 357 ppm. Reversible impairment of nervous function and muscular paralysis were observed in rats, rabbits and monkeys at the 204 ppm level dose. Interestingly, laboratory results, including blood urea nitrogen and blood counts, were normal in the species studied even at the higher (357 ppm) exposure levels (Hollingsworth et al, 1956).

Recently, there has been renewed concern about possible chronic toxicity of EO. Results of an industry-sponsored 24-month experimental inhalation study showed an increased, dose-related incidence of mononuclear cell leukemia in male and female Fischer 344 rats (Snelling et al, 1981). Effects were voted at all level of exposures: 100, 33, and 10 ppm. Past literature in these regards included a 1964 report of tumorigenicity in female mice (Reyniers, 1964), alkylating agent properties (Ehrenberg et al, 1974), and demonstrations of mutagenicity in several test systems (Anon, 1979b), including Neurospora (Watson, 1966), plants (Ehrenberg and Gustafsson, 1957), and the Salmonella typhimurium strain TA 1535 bacterial assay (Embree, 1975).

As regards human disease, there are two recent published reports from Sweden of malignancies purportedly linked to EO exposure. The first report was of a case each of acute mylegenous leukemia, chronic myelogenous leukemia, and Waldenstrom's macroglobulinemia diagnosed between 1972 and 1977 in employees of a small factory which used EO for sterilization (Hogstedt et al, 1979a). These cancers may, of course, be unrelated; but in a subsequent retrospective mortality study of employees of an EO production facility, the same senior author reported more observed deaths from leukemia (3) than would have been expected (less than 0.5) using Swedish national death rates (Hogstedt et al, 1979b). Two of the leukemia deaths were caused by chronic lymphatic leukemia, one by acute myeloid leukemia. It is difficult to interpret results from this paper because of the finding of an elevated overall standard mortality ratio (SMR) with 47 deaths vs. 27 expected. Such a finding would be extremely unusual in the U.S. where most U.S. employed populations reflect the "healthy worker effect", and experience overall SMRs less than 100%. Another unusual finding was an increased SMR for diseases of the circulatory system (20 observed vs. 13 expected), which is reported only in office employees in the U.S. Finally, chronic lymphatic leukemia has not, to this author's knowledge, been linked to environmental factors.

A retrospective cohort mortality study of employees with work-place exposure to EO is planned by British colleagues at Imperial Chemical Industries Limited (ICI). Results of the ICI study will be helpful in interpretating the Hogstedt reports.

The Russian literature includes two reports of a variety of health problems associated with workplace exposures to EO. Yabukova et al (1976) reported an increased gynecological sick rate, increased complications of pregnancy, and increased incidence of interruptions of pregnancy among employees of an EO manufacturing plant compared to pregnancies in management personnel and from outside the factory. However, if I read a translation of the paper correctly, although spontaneous abortion occurred in 10.5% of pregnancies of the exposed group of instrument controllers compared to about 8% of laboratory workers (also exposed) and about 8% of management controls, there were more stillbirths among management employees (4/65) than in instrument controllers (1/57). According to Yabukova et al (1976) the "overall corresponding contamination of the factory air did not exceed 1 mg/m^3" (= about 0.6 ppm).

Ostravskaya et al (1971) reported a variety of subjective complaints from 76 individuals with 3-6 years work experience, presumably in EO manufacturing. In addition, they reported "bradycardia", "vegetative shifts" and "EKG changes" in some; the significance, if any, of the quoted abnormalities is difficult to assess from the translation. Ostravskaya et al (1971) reported a leukopenia (4000-4400 WBC/mm^3) in 9 of the 76 employees.

There was only one U.S. epidemiology study of EO prior to the recent interest in carcinogenesis. A cross-sectional study of 37 EO operators engaged in manufacturing operations and of age-matched controls (operators working with chemicals other than EO) was reported by Joyner in 1964. The highest air level of EO recorded was 127 ppm but average exposures were less than 10 ppm for the working day (Joyner, 1964). The EO group actually had fewer symptoms and less absenteeism than the controls; and there were no more "abnormal" laboratory findings in the study group than among the controls (Joyner, 1964).

More recently, in a Dow Chemical U.S.A. response document (Moore et al, 1978), it is stated (page 7) that health surveillance data from 129 Dow employees "revealed no unusual medical effects, i.e., no effects were observed in employees potentially exposed to EO within the TLV". Tests apparently included blood counts and a battery of clinical laboratory tests. A cross-sectional study of individuals involved in cold sterilization using EO was recently published by Garry et al, 1979, who found various frequencies of symptoms (up to 9 with histories of sore throat) among 12 EO-exposed employees versus no symptoms of any kind in a control group. Similarly, cytogenetic studies by these authors reportedly showed more frequent sister chromatid exchanges (SCE) (average 8.65) among the 12 employees than among 11 controls (average 6.37).

A cross-sectional study was also sponsored by the American Hospital Supply Corporation (AHSC). As yet unpublished, the AHSC study was of employees of 9 U.S. manufacturing facilities which utilize EO as a sterilant gas. According to data kindly provided by Ronald H. Abrahams, Ph.D., director of Regulatory Compliance of the AHSC, 6 of 75 exposed* employees had slight anemia and one had a slight increase in lymphocytes (there were apparently no controls for this phase of the study). Sperm counts were obtained from some of the employees: 8 of 46 exposed and 1 of 9 controls had sperm counts less than 20 million/cc. The AHSC study also included cytogenetic data: except for stable forms (Cs), all modalities of chromosome aberration including number of breaks, unstable forms (CV), and SCEs, were statistically increased in the exposed group when compared to control groups of office workers.

RATIONALE FOR RESEARCH: There is a growing volume of experimental toxicological data indicating that EO, at chronic vapor exposure levels much higher than experienced in the Dow workplace, can cause detectable health effects. Whether measurable effects might also occur at lower levels of exposure is unknown, but, if so, they might include those listed in Tables I and II. A major concern about long-term effects of workplace exposures to EO is carcinogenesis, so

*Industrial Hygiene data were not given, but vapor levels were stated to be less than the OSHA 8 hour TWA limit of 50 ppm.

it would seem reasonable that any epidemiological study be designed not only to detect the phenomena listed in Table I over the short term, but to detect excess cancers over the long term. In fact, a draft proposal for a retrospective cohort mortality study of EO production personnel at the Texas Division, with leukemia as a primary concern, was prepared by McClimans and colleagues in July 1979 (unpublished data). Very recently, Bond and colleagues have prepared the protocol for a case-control study of leukemias at Texas Division. Our proposal is for a cross-sectional study of Louisiana Division employees involved in jobs with potential EO exposure, to be followed by continuous surveillance of the same group of employees. Since cross-sectional studies are preliminary and do not usually yield definitive results, it will be necessary to plan for appropriate follow-on research depending on these preliminary findings. Alternatives for follow-on research are detailed on page 11.

Abnormalities which might be expected if workplace exposures to EO were exerting a chronic toxic effect include hematological, hepatic, reproductive, renal, cytogenetic, and carcinogenic (Glaser, 1977). As proposed at the present time, however, our project will be limited to analysis of results from existing medical surveillance data. Hematological abnormalities reportedly associated with exposure to EO include anemia and absolute lymphocytosis (Ehrenberg and Halstrom, 1967), leucopenia (Ostravskaya et al, 1971) or, simply "changes in peripheral blood" (Spasovsky et al, 1978). Because of the reported dose-related

alkylation of hemoglobin by EO (Osterman-Golkar et al, 1976; Calleman et al, 1978) it would not be unreasonable to expect increases in laboratory tests associated with hemolysis, including total serum bilirubin and lactic acid dehydrogenase (LDH), as well as anemia and reticulocytosis. Similarly, direct hepatic and renal tubular damage, causing abnormal results in simple measures of liver and kidney function, might be expected from any alkylating agent and, in fact, have been reported experimentally at high levels of EO vapor exposure (Hollingsworth et al, 1956).

Questionnaire data from the periodic health examinations are available and can be used. We recognize the weaknesses and biases of using questionnaire data as evidence for disease or for adverse reproductive function, but by judicious and a priori designation of which questions will be analyzed it should be possible to compare the prevalences of symptoms relating to diseases of the blood and of adverse pregnancy outcomes.

The list of effects which can be studied using existing data is in Table I. Table II is a more comprehensive list, including tests which cannot, and, in certain cases, probably should not, be studied at the present time. As more reliable techniques become available, however, it may become appropriate to examine for additional effects in the future. Table III lists data elements which are presently available for extraction and analysis.

APPROACH:

Exposed Population. The exposed population will consist of active Louisiana Division employees who were assigned to Glycol II or Dowanols for at least 6 months prior to participating in the Health Inventory examination during 1980. Since intensity of exposure categories by job cannot be estimated because detailed historical industrial hygiene data are lacking, length of employment in the 2 plants will be used to divide the exposed group into subsets of longer and shorter durations of exposure.

Control Population. There are 88 persons eligible; but since it is anticipated that non-whites and females will be few, only data from white males will be included in the study. The control group will consist of an equal number of males matched by age (within 5 years or better), race, date of hire, and smoking and alcohol use history. The job category will be as of the date of health inventory and, of course, results of the 1980 health inventory examination must be available. Finally, to be eligible as a control, the employee must have no history of EO exposure. It is recommended that the initial pool for controls consist of all Louisiana Division employees, and that eliminations be made by matching criteria, the best age match being the final decision step.

Dependent Variables. Dependent variables are listed in Table III, and consist of answers to questions regarding reproductive history and past medical history, complete blood count values, and results of the liver and kidney function tests. Test results will be considered abnormal if outside the reference ranges shown; a summary of some recently published ranges is in Appendix i.

Covariables. Covariables or potential confounding variables other than those used in matching include family history of illness, use of medications, exposure to chemicals other than EO, radiation exposure, and substance abuse. The effects of some of these covariables cannot be analysed, and others, such as known substance abuse or use of certain medications might best be handled by elimination from both control and exposed groups. Those with a family history of blood disorders need not be eliminated, but the frequencies of such histories in the 2 groups should be checked. Obviously, affirmative answers to questions such as "Did you have a birth abnormality?" should be considered if the abnormality were considered hereditary.

Analysis of Data. Data will be collated and analysed using the computer system available to the Louisiana Division Medical Department and capably programmed by Perry Poston. The SAS statistical software system will be used for analyses. The null hypothesis of no statistically significant difference in values from the exposed and control samples will be by the Wilcoxon signed rank test for continuous data and McNemar's test in the case of dichotomous data. Continuous data will also be analyzed by McNemar's test using the categories of within or without the normal range as defined in Table III.

RESULTS, WEAKNESSES, AND FOLLOW-ON STUDIES: This proposed cross-sectional study should indicate whether or not employees potentially exposed to EO have relatively depressed red cell indices or depressed or elevated white cell counts compared to their non-EO-exposed colleagues; whether results of their laboratory tests of renal and hepatic function are comparable; and whether their reported prevalences of adverse pregnancy outcomes are similar. Identification of potentially exposed groups will also permit continued future surveillance and such groups would also be available for testing as new techniques become available. Concern has been expressed about ability of this study to detect leukemia. By definition, leukemia would, in fact, be detected by the combination of anemia associated with increased number of white cells in peripheral blood, and the diagnosis is easily confirmed by microscopic examination of bone marrow.

Cross-sectional studies have many weaknessess which need not be detailed here. The proposed study, however, additionally suffers from the following:

1. Pregnancy outcome data from fathers are less reliable than from mothers.
2. The questionnaires permit bias towards "socially-acceptable" answers.
3. The "power" or ability to detect subtle differences between exposed and control populations may be low.
4. It is difficult to separate out age and work-ethic effects when exposure categories are defined by duration rather than intensity.

For these reasons, we suggest that a negative result (i.e., no significant difference in dependent variables between exposed and control groups) not be considered the final word. Thus, it will be appropriate to continue to monitor employees with potential EO exposures.

Populations to be included in continuing surveillance (prospective morbidity) studies will be those identified for this cross-sectional study, with addition of those entering or leaving jobs with potential EO exposures. Controls who enter such jobs will join the exposed group and will be replaced as controls using the original matching criteria. Personnel new to EO exposure jobs, and staying there for 6 months, will be added to the study along with new matched controls. Personnel leaving EO exposure jobs will continue in the study, but, of course, in a different category.

Similarily a positive result (i.e., statistically significant difference in dependent variables between exposed and control groups) cannot be considered definitive either. In order to avoid decisions based on chance due to multiple comparisons, it is suggested that future studies at this time be stimulated only if a positive result is found for more than 2 laboratory tests (of the 15 to be analysed) or for more than 2 questionnaire responses (of the 11 analysed). In such an event, a retrospective morbidity study of a cohort of all EO-exposed employees at some point in the past (I'd recommend a period prior to the first Health Inventory) should be designed. Such a study might permit evaluation of the question of "which came first, exposure or morbidity?"

COMPUTER UTILIZATION [illegible] EPIDEMIOLOGIC STUDY
ETHYLENE OXIDE [illegible] FOR LOUISIANA DIVISION)

1) SELECTION [illegible] MAINTAINED WORK HISTORY RECORDS [illegible] FOR [illegible] EVALUATION OF EMPLOYEES WITH POTENTIAL ETHYLENE OXIDE EXPOSURE (STUDY POPULATION).

2) [illegible] TO DETERMINE EMPLOYEES WITHOUT [illegible] OXIDE EXPOSURE.

3) [illegible] OF VARIOUS GROUPS WITHIN DIVISION [illegible] STUDY, AS WELL AS EMPLOYEES WITH PREVIOUS ETHYLENE OXIDE EXPOSURE.

4) SELECTED EMPLOYEES CONSIDERED AS CONTROL CANDIDATES.

5) COMPUTERIZED MATCHING OF [illegible] STUDY EMPLOYEES TO 3A CONTROLS [illegible] (WHERE POSSIBLE) BASED ON CLOSEST MATCH OF AGE, [illegible] SERVICE, SMOKING AND ALCOHOL USAGE HISTORY.

6) COMPUTERIZED SEARCHING AND TOTALING WAS PERFORMED TO DEFINE AND REPORT GROUP CHARACTERISTICS AS DISEASE AND REPRODUCTIVE HISTORY.

7) [illegible] UTILIZED STATISTICAL ANALYSIS SYSTEM (S.A.S.) TO [illegible] CHARTING AND PLOTTING.

8) [illegible] OXIDE STUDY [illegible] ENHANCED, MAN POWER [illegible] SAVED, GREATER SELECTION OF ANALYSIS TOOLS MADE POSSIBLE, RELIABILITY AND ACCURACY OF FINAL RESULTS GREATLY IMPROVED.

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CONFIDENTIAL

STEP 7 - PRE-ANALYSIS CHECK ON CONTINUOUS DATA FOR NORMAL DISTRIBUTION

ONCE ALL POPULATIONS HAD BEEN DEFINED AND CHARACTERISTICS DETERMINED, THE NEXT STEP INVOLVED IN THE ETHYLENE OXIDE STUDY WAS TO MAKE A VISUAL CHECK OF THE CONTINUOUS DATA FOR HEMATOLOGY (HGB, HCT, RBC, WBC, AND PERCENT LYMPHOCYTES), CHEMISTRIES (TOTAL BILIRUBIN, ALKALINE PHOSPHATASE, LDH, SGPT, SGOT, GGTP), AND CONTINUOUS TYPE DATA ELEMENTS FOR KIDNEY (BUN AND SERUM CREATININE), WAS PERFORMED FOR DETERMINATION OF PROBABLE TYPE OF DISTRIBUTION FOR THE SAMPLES. SINCE KIDNEY ELEMENTS URINE PROTEIN, RBC, AND WBC WERE IN RANGE TYPE FORMAT (i.e. RBC .00-01), INSTEAD OF STRICTLY NUMERIC VALUES, THEY WERE ANALYZED CATEGORICALLY AND WERE NOT CONSIDERED AS PART OF THE VISUAL CHECK. (SEE TABLE III - A2, A3, AND A4, OF THE ETHYLENE OXIDE PROTOCOL FOR DATA ELEMENT LIST).

TO PERFORM THE PRE-ANALYSIS CHECK, ELEMENTS APPLICABLE WERE EXTRACTED FROM THE MEDICAL DATA FILES FOR THE [redacted] STUDY AND CONTROL POPULATIONS, PLACED ON MAGNETIC TAPE, AND THEN INPUT INTO THE STATISTICAL ANALYSIS SYSTEM (SAS) RESIDING ON THE DIVISION'S MAINFRAME IBM 370 COMPUTER SYSTEM. AT THIS POINT, EACH DATA ELEMENT WAS EXTRACTED FROM THE TAPE, AND AFTER SUBTRACTING THE VALUE OF THE CONTROL FROM THE VALUE OF THE DATA ELEMENT FOR THE EXPOSED EMPLOYEE, THE ENDING RESULTS WERE PLACED INTO SAS PROCEDURE UNIVARIATE, WHERE STATISTICS SUCH AS THE D-STATISTIC, THE STEM-LEAF PLOT, THE BOX-PLOT AND THE NORMAL PROBABILITY PLOT WERE PRODUCED. AT THIS POINT THE D-STATISTIC WAS VIEWED TO DETERMINE ITS SIZE, SINCE THE NULL HYPOTHESIS THAT THE INPUT DATA ARE A RANDOM SAMPLE FROM A NORMAL DISTRIBUTION IS REJECTED FOR LARGE VALUES OF D,* ALSO THE STEM-LEAF PLOT, BOX PLOT, AND ESPECIALLY THE NORMAL PROBABILITY PLOT WERE VIEWED, CHECKING GENERALLY FOR A NORMAL PROBABILITY PLOT THAT WOULD ROUGHLY FOLLOW A STRAIGHT LINE.** ALSO, ANY EXTREME VALUES OF THE PARTICULAR DATA ELEMENT BEING CHECKED WERE ALSO VIEWED, AND MANUAL FOLLOW-UPS WERE PERFORMED TO DETERMINE THE REASON BEHIND THE EXTREME VALUES.

AGAIN, THIS PROCEDURE WAS NOT USED TO ANALYZE THE DATA, SINCE THE NEXT PROCEDURE DEALS WITH DATA ANALYSIS, BUT WAS GENERALLY USED TO GIVE A BIRD'S EYE VIEW OF THE DATA AND ANY PROBLEMS THAT MIGHT OCCUR IN DISTRIBUTION BEFORE ANY ANALYSES WERE ACTUALLY PERFORMED.

OUTPUT FROM SAS FOR ALL 13 CONTINUOUS DATA ITEMS FOLLOWS IN THE ENCLOSURE. EACH VARIABLE BEING ANALYZED IS IDENTIFIED IN THE "VARIABLE:" PORTION OF THE PRINT IN UPPER LEFT OF THE PAGE (EXAMPLE: VARIABLE: CRTDIF IS IDENTIFICATION FOR CREATININE).

DO 095224
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* SAS USERS GUIDE, 1979 EDITION, PPG. 427-432
** SAS USERS GUIDE, 1979 EDITION, PG. 429
*** JED DIEM, STATISTICIAN, TULANE UNIVERSITY SCHOOL OF MEDICINE
STRAIGHT LINE GENERALLY INDICATES NORMAL DISTRIBUTION

DIFFERENCE OF EACH VALUE TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=HGRDIF

MOMENTS

N	84	SUM WGTS	84
MEAN	0.115476	SUM	9.7
STD DEV	1.3096	VARIANCE	1.71506
SKEWNESS	-0.303602	KURTOSIS	-0.185794
USS	143.47	CSS	142.35
CV	1134.09	STD MEAN	0.142889
T:MEAN=0	0.808151	PROB>|T|	0.421314
D:NORMAL	0.0548101	PROB>D	>0.15

QUANTILES(DEF=4)

100% MAX	2.7	99%	2.7
75% Q3	1	95%	2.375
50% MED	0.2	90%	1.8
25% Q1	-0.775	10%	-1.65
0% MIN	-3.2	5%	-2.4
		1%	-3.2
RANGE	5.9		
Q3-Q1	1.775		
MODE	-0.9		

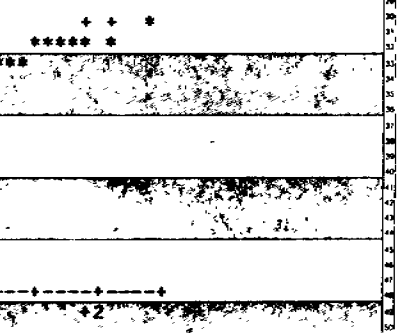
MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

EXTREMES

LOWEST	HIGHEST
-3.2	2.3
-3	2.4
-2.5	2.4
-2.4	2.5
-2.4	2.7

STEM	LEAF	#	BOXPLOT
2	57	2	
2	1344	4	
1	5567889	7	
1	0001222344	10	+-----+
0	555666778999	12	| |
0	111222334444	12	+--+--+
-0	4433332100	10	| |
-0	9999998777765	13	+-----+
-1	4320	4	
-1	8765	4	
-2	442	3	
-2	5	1	
-3	20	2	

NORMAL PROBABILITY PLOT



DIFFERENCE OF EACH VALUE TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=HCTDIF

MOMENTS

N	84	SUM WGTS	84
MEAN	0.344048	SUM	28.9
STD DEV	3.54004	VARIANCE	12.5319
SKEWNESS	-0.362313	KURTOSIS	-0.364152
USS	1050.09	CSS	1040.15
CV	1028.94	STD MEAN	0.38625
T:MEAN=0	0.890738	PROB>|T|	0.375645
D:NORMAL	0.0684682	PROB>D	>0.15

QUANTILES(DEF=4)

100% MAX	7.8
75% Q3	3.15
50% MED	0.6
25% Q1	-1.875
0% MIN	-7.9
RANGE	15.7
Q3-Q1	5.025
MODE	2

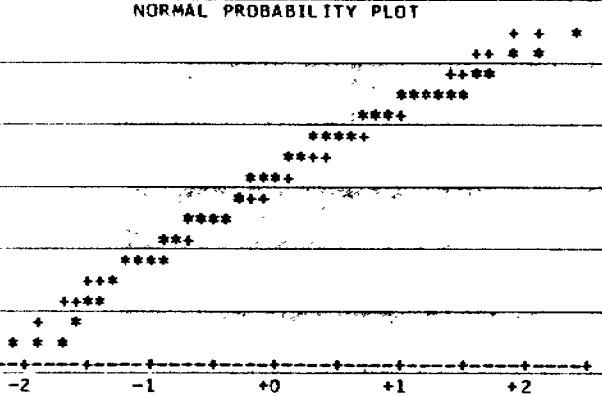
99%	7.8
95%	5.57499
90%	4.55
10%	-4.4
5%	-7.025
1%	-7.9

EXTREMES

LOWEST	HIGHEST
-7.9	5.2
-7.6	5.7
-7.3	6.1
-7.2	6.8
-6.5	7.8

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT
7	8	1	
6	18	2	
5	27	2	
4	02445689	8	
3	022347899	9	+-----+
2	0002344588	10	| |
1	2255689	7	| +-+
0	1134456678	10	*--+--*
-0	76642	5	| |
-1	9887665411	10	+-----+
-2	991	3	|
-3	95542100	8	|
-4	53	2	|
-5	52	2	|
-6	5	1	|
-7	9632	4	|



DIFFERENCE OF EACH VALUE TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=RSCDIF

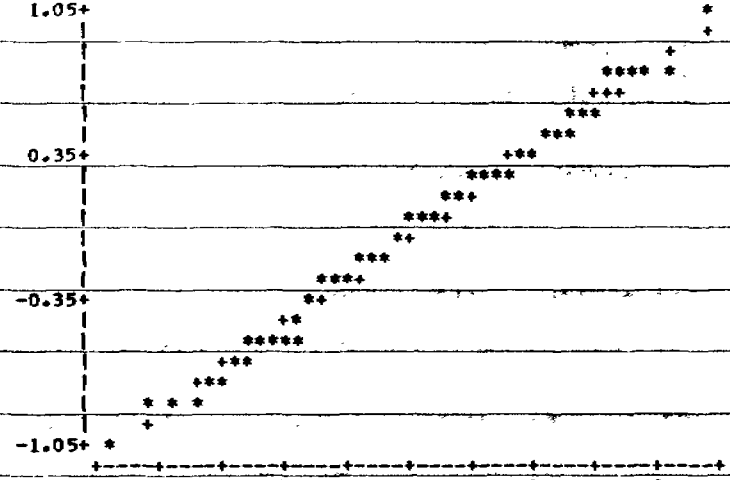
MOMENTS				QUANTILES(DEF=4)				EXTREMES	
N	84	SUM WGTS	84	100% MAX	1.01	99%	1.01	LOWEST	HIGHEST
MEAN	-0.032381	SUM	-2.72	75% Q3	0.25	95%	0.74	-1.07	0.74
STD DEV	0.426647	VARIANCE	0.182028	50% MED	-0.025	90%	0.499999	-0.86	0.74
SKEWNESS	-0.105375	KURTOSIS	-0.235921	25% Q1	-0.2875	10%	-0.605	-0.85	0.74
USS	15.1964	CSS	15.1083	0% MIN	-1.07	5%	-0.815	-0.84	0.76
CV	-1317.59	STD MEAN	0.046551			1%	-1.07	-0.74	1.01
T:MEAN=0	-0.695601	PROB>|T|	0.488622	RANGE	2.08				
D:NORMAL	0.0609964	PROB>D	>0.15	Q3-Q1	0.5375				
				MODE	0.25				

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT
10	1	1	
9			
8			
7	4446	4	
6			
5	359	3	
4	4567	4	
3	34467	5	
2	0023555789	10	+------+
1	12379	5	| |
0	14677899	8	| |
-0	9765320	7	*--+--*
-1	6644331100	10	| |
-2	9876550	7	+------+
-3	870	3	
-4	20	2	
-5	9887543	7	
-6	92	2	
-7	43	2	
-8	654	3	
-9			
-10	7	1	

MULTIPLY STEM.LEAF BY 10**-01

NORMAL PROBABILITY PLOT



DIFFERENCE OF EACH VALUE TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=WRDDIF

MOMENTS				QUANTILES(DEF=4)				EXTREMES	
N	84	SUM WGTS	84	100% MAX	5.3	99%	5.3	LOWEST	HIGHEST
MEAN	-0.170238	SUM	-14.3	75% Q3	1.55	95%	3.25	-7.3	3.1
STD DEV	2.13873	VARIANCE	4.57416	50% MED	-0.25	90%	2.45	-4.7	3.3
SKEWNESS	-0.203007	KURTOSIS	0.525557	25% Q1	-1.675	10%	-2.65	-3.6	3.3
USS	382.09	CSS	379.656	0% MIN	-7.3	5%	-3.3	-3.4	4.3
CV	-1256.32	STD MEAN	0.233355			1%	-7.3	-3	5.3
T:MEAN=0	-0.729526	PROB>|T|	0.467734	RANGE	12.6				
D:NORMAL	0.0795516	PROB>D	>0.15	Q3-Q1	3.225				
				MODE	-2.3				

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT		NORMAL PROBABILITY PLOT
5	3	1		5.25+	*
4					+
4	3	1			*
3					++
3	133	3			+****
2	578	3		2.75+	***
2	004	3			***
1	6677788999	10	+------+		*****
1	01112344	8	| |		****
0	6678889	7	| |		****
0	344	3	| |	0.25+	***
-0	443210	6	*--+--*		**
-0	987	3	| |		***
-1	4322111000	10	| |		****
-1	87766655	8	+------+		***
-2	43332111	8	|	-2.25+	****
-2	88766	5	|		*****+
-3	40	2	|		* ++
-3	6	1	|		* ++
-4			|		+
-4	7	1	|	-4.75+	*
-5					+
-5					
-6					
-6					
-7	3	1	0	-7.25+	*

-2 -1 +0 +1 +2

DIFFERENCE OF EACH VALUE TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=LYMDIF

MOMENTS				QUANTILES(DEF=4)				EXTREMES	
N	84	SUM WGTS	84	100% MAX	32	99%	32	LOWEST	HIGHEST
MEAN	1.45238	SUM	122	75% Q3	8.75	95%	20.75	-26	20
STD DEV	11.7642	VARIANCE	138.395	50% MED	3	90%	16.5	-19	21
SKEWNESS	0.0427016	KURTOSIS	-0.223499	25% Q1	-6.75	10%	-16.5	-19	26
USS	11664	CSS	11486.8	0% MIN	-26	5%	-17.75	-18	26
CV	809.991	STD MEAN	1.28357			1%	-26	-17	32
T:MEAN=0	1.13151	PROB>|T|	0.261098	RANGE	58				
D:NORMAL	0.0642366	PROB>D	>0.15	Q3-Q1	15.5				
				MODE	5				

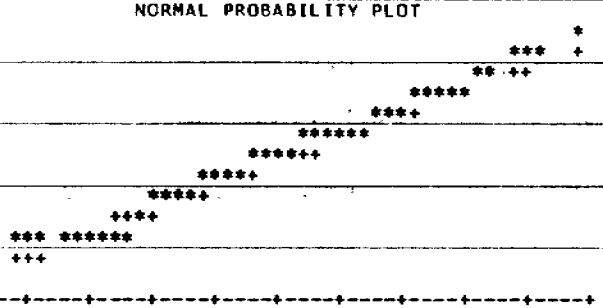
MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT
3	2	1	
2	66	2	
2	01	2	
1	556788	6	
1	00033444	8	
0	5555556777888899	16	+------+
0	111133333444	12	*--+--*
-0	44322211000	11	| |
-0	9998766555	10	+------+
-1	332000	6	|
-1	998777766	9	|
-2			|
-2	6	1	|

----+----+----+----+

MULTIPLY STEM.LEAF BY 10**+01

NORMAL PROBABILITY PLOT



DIFFERENCE OF EACH SET OF VALUES TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=TRDIF

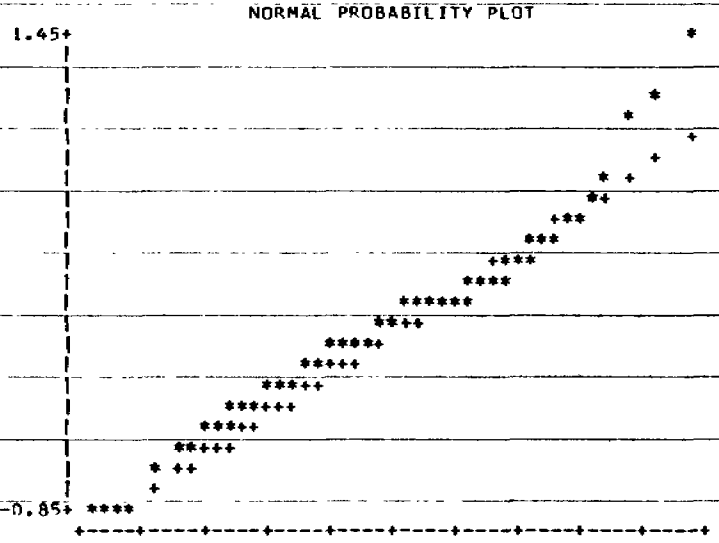
MOMENTS				QUANTILES(DEF=4)				EXTREMES	
N	84	SUM WGTS	84	100% MAX	1.4	99%	1.4	LOWEST	HIGHEST
MEAN	0.00119048	SUM	0.1	75% Q3	0.2	95%	0.674998	-0.9	0.6
STD DEV	0.387296	VARIANCE	0.149999	50% MED	0	90%	0.4	-0.9	0.7
SKEWNESS	0.659983	KURTOSIS	2.15089	25% Q1	-0.275	10%	-0.45	-0.7	1
USS	12.45	CSS	12.4499	0% MIN	-0.9	5%	-0.6	-0.6	1.1
CV	32532.9	STD MEAN	0.0422575			1%	-0.9	-0.6	1.4
T:MEAN=0	0.0281719	PROB>|T|	0.977593	RANGE	2.3				
D:NORMAL	0.125503	PROB>D	<0.01	Q3-Q1	0.475				
				MODE	0.1				

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT
14	0	1	0
13			
12			
11	0	1	0
10	0	1	0
9			
8			
7	0	1	|
6	0	1	|
5	00	2	|
4	0000	4	|
3	00000	5	|
2	0000000	7	+------+
1	000000000000000	15	| |
0			+--+--+
-0	000000000	9	| |
-1	00000000000	11	| |
-2	00000	5	+------+
-3	00000000	8	|
-4	00000	5	|
-5	000	3	|
-6	00	2	|
-7	0	1	|
-8	00	2	|

MULTIPLY STEM.LEAF BY 10**-01

NORMAL PROBABILITY PLOT



DIFFERENCE OF EACH SET OF VALUES TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=ALKDIF

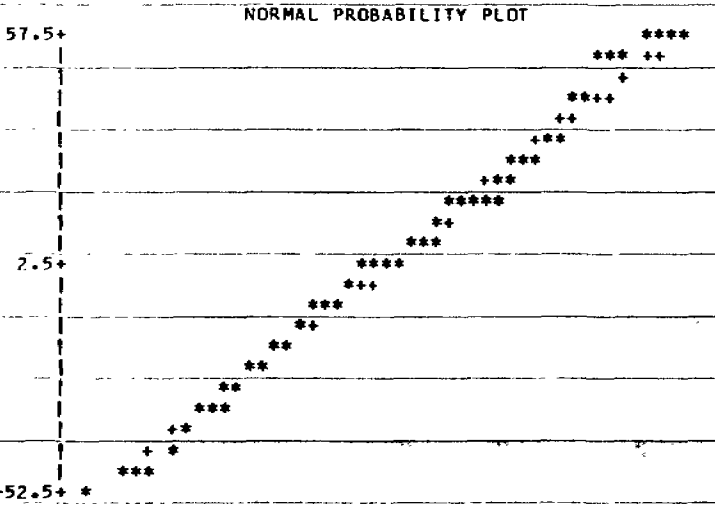
MOMENTS				QUANTILES(DEF=4)				EXTREMES	
N	84	SUM WGTS	84	100% MAX	59	99%	59	LOWEST	HIGHEST
MEAN	2.2381	SUM	188	75% Q3	17	95%	51.2498	-53	43
STD DEV	23.7317	VARIANCE	563.196	50% MED	2	90%	31	-50	54
SKEWNESS	0.0762609	KURTOSIS	0.274504	25% Q1	-13	10%	-29.5	-50	54
USS	47166	CSS	46745.2	0% MIN	-53	5%	-40.25	-41	59
CV	1060.35	STD MEAN	2.58935			1%	-53	-38	59
T:MEAN=0	0.864348	PROB>|T|	0.389688	RANGE	112				
D:NORMAL	0.0592763	PROB>D	>0.15	Q3-Q1	30				
				MODE	2				

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT
5	99	2	
5	44	2	
4			
4	13	2	
3			
3	113	3	
2	5699	4	
2	012	3	
1	556777789	9	+-----+
1	0134	4	| |
0	56778889	8	| |
0	11222222444	11	*--+--*
-0	444310	6	| |
-0	8888766	7	+-----+
-1	4330	4	
-1	7766	4	
-2	42210	5	
-2	86	2	
-3	211	3	
-3	8	1	
-4	1	1	
-4			
-5	300	3	

MULTIPLY STEM.LEAF BY 10**+01

NORMAL PROBABILITY PLOT



DIFFERENCE OF EACH SET OF VALUES TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=DDHDIF

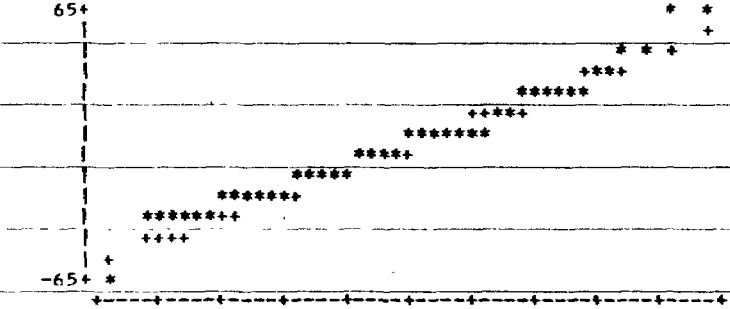
MOMENTS				QUANTILES(DEF=4)			EXTREMES	
N	84	SUM WGTS	84	100% MAX	69	99%	69	LOWEST HIGHEST
MEAN	-0.166667	SUM	-14	75% Q3	11.75	95%	42.4999	-68 38
STD DEV	22.3444	VARIANCE	499.273	50% MED	-1	90%	26	-37 44
SKEWNESS	0.436589	KURTOSIS	1.53298	25% Q1	-13	10%	-24.5	-37 49
USS	41442	CSS	41439.7	0% MIN	-68	5%	-35.5	-37 65
CV	-13406.7	STD MEAN	2.43798			1%	-68	-31 69
T:MEAN=0	-0.0683627	PROB>|T|	0.945661	RANGE	137			
D:NORMAL	0.095467	PROB>D	0.057	Q3-Q1	24.75			
				MODE	2			

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT
6	59	2	0
5			
4	49	2	0
3	68	2	|
2	0001345667	10	|
1	122336	6	+-----+
0	1122223444555567788	18	| |
-0	9887655444322110	16	*--+--*
-1	988833222110	12	+-----+
-2	98632221100	11	|
-3	7771	4	|
-4			
-5			
-6	8	1	0

MULTIPLY STEM.LEAF BY 10**+01

NORMAL PROBABILITY PLOT



DIFFERENCE OF EACH SET OF VALUES TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=SGPTDIF

MOMENTS				QUANTILES(DEF=4)				EXTREMES	
N	84	SUM WGTS	84	100% MAX	245	99%	245	LOWEST	HIGHEST
MEAN	5.2619	SUM	442	75% Q3	13.75	95%	56.7499	-71	53
STD DEV	35.3782	VARIANCE	1251.62	50% MED	-1	90%	35.9999	-41	58
SKEWNESS	3.91728	KURTOSIS	25.2055	25% Q1	-12.5	10%	-22.5	-30	60
USS	106210	CSS	103884	0% MIN	-71	5%	-29.25	-30	86
CV	672.346	STD MEAN	3.86008			1%	-71	-27	245
T:MEAN=0	1.36316	PROB>|T|	0.176519	RANGE	316				
D:NORMAL	0.189177	PROB>D	<0.01	Q3-Q1	26.25				
				MODE	-4				

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT		NORMAL PROBABILITY PLOT
24	5	1	*	250+	*
22				|	
20				|	
18				|	
16				|	
14				|	
12				|	
10				|	
8	6	1	0	90+	* +
6	0	1	0	|	++ * +
4	4838	4	0	|	++++++++
2	133556739	9	|	|	+++++++++
0	1234456688992233344558	22	+--+--+	|	++++++++++
-0	887555443109876655444433332221 1000	34	*-----*	|	**********
-2	0076332210	10	|	|	**********
-4	1	1	|	|	* ++++++
-6	1	1	0	-70+	* + +

MULTIPLY STEM.LEAF BY 10**+01

-2 -1 +0 +1 +2

DIFFERENCE OF EACH SET OF VALUES TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=GGTPDIF

MOMENTS

N	84	SUM WGTS	84
MEAN	0.0238095	SUM	2
STD DEV	20.8535	VARIANCE	434.867
SKEWNESS	-0.536854	KURTOSIS	5.71657
USS	36094	CSS	36094
CV	87584.5	STD MEAN	2.2753
T:MEAN=0	0.0104643	PROB>|T|	0.991676
D:NORMAL	0.172058	PROB>D	<0.01

QUANTILES(DEF=4)

100% MAX	78	99%	78
75% Q3	8	95%	33.4998
50% MED	0	90%	20
25% Q1	-5	10%	-18.5
0% MIN	-79	5%	-37
		1%	-79
RANGE	157		
Q3-Q1	13		
MODE	-2		

EXTREMES

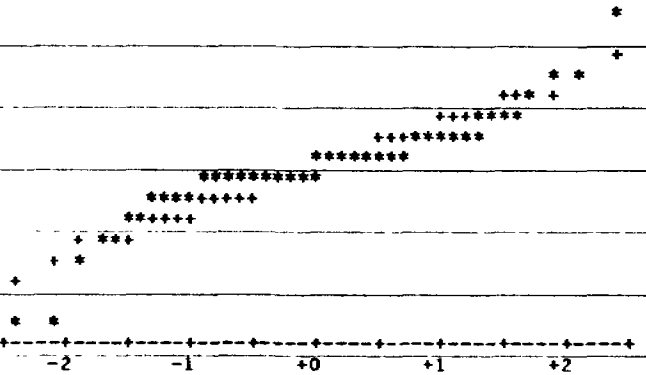
LOWEST	HIGHEST
-79	23
-76	37
-44	40
-39	48
-31	78

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT
7	8	1	*
6			
5			
4	08	2	*
3	7	1	0
2	1123	4	|
1	22234455669	11	|
0	1123344445566778889	18	*--+--*
-0	98766555444433332222221111000000	32	+-----+
-1	6554322	7	|
-2	741	3	0
-3	91	2	0
-4	4	1	0
-5			
-6			
-7	96	2	*

MULTIPLY STEM.LEAF BY 10**+01

NORMAL PROBABILITY PLOT



DIFFERENCE OF EACH SET OF VALUES TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=SGOTDIF

MOMENTS				QUANTILES(DEF=4)				EXTREMES	
								LOWEST	HIGHEST
N	84	SUM WGTS	84	100% MAX	294	99%	294	-123	25
MEAN	0.428571	SUM	36	75% Q3	7	95%	25.75	-41	26
STD DEV	37.9598	VARIANCE	1440.95	50% MED	-1	90%	17.5	-40	29
SKEWNESS	5.23923	KURTOSIS	44.7611	25% Q1	-9	10%	-25	-38	33
USS	119614	CSS	119599	0% MIN	-123	5%	-36	[illegible]	294
[illegible]	[illegible]	STD MEAN	4.14175			1%	-123		
[illegible]	[illegible]	PROB>|T|	0.917835	RANGE	417				
[illegible]	0.245587	PROB>D	<0.01	Q3-Q1	16				
				MODE	3				

MISSING VALUE .
COUNT 1
% COUNT/NOBS 1.18

```
 STEM LEAF                        #   BOXPLOT              NORMAL PROBABILITY PLOT
   28 4                           1      *        290+                                          *
   26                                                |
 [illegible]                                         |
   18                                                |
   16                                                |
   14                                             150+
 [illegible]                                         |
    6                                                |                                  ++ +
    4                                                |                              +++++
    2 155693                      6      0           |                         +++++  **** * *
 [illegible]88000001445669       33   [illegible]  10+            [illegible]
 [illegible]21099887665555444433322110  34   *-----*  |          ***********
 [illegible]                      7      0           |      * ****** +++++
   -4 10                          2      0           |    *    +++++
   -6                                                |    + + ++
   -8                                                |  +
 [illegible]                      1                -130+ *
             ----+----+----+----+----                  +----+----+----+----+----+----+----+----+
 MULTIPLY STEM.LEAF BY 10**+01                            -2        -1        +0        +1        +2
```

DO 095235
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DIFFERENCE OF EACH VALUE TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=RUNDIF

MOMENTS				QUANTILES(DEF=4)			EXTREMES	
N	84	SUM WGTS	84	100% MAX	12	99%	12	LOWEST HIGHEST
MEAN	-1.16667	SUM	-98	75% Q3	3	95%	6.74998	-14 6
STD DEV	5.02244	VARIANCE	25.2249	50% MED	-2	90%	5	-13 7
SKEWNESS	-0.0618393	KURTOSIS	0.054549	25% Q1	-4	10%	-8	-11 7
USS	2208	CSS	2093.67	0% MIN	-14	5%	-9.75	-10 10
	-430.495	STD MEAN	0.547993			1%	-14	-9 12
T:MEAN=0	-2.12898	PROB>|T|	0.0362195	RANGE	26			
Q:NORMAL	0.0777953	PROB>Q	>0.15	Q3-Q1	7			
				MODE	-2			

MISSING VALUE .

COUNT 1

% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT		NORMAL PROBABILITY PLOT
12	0	1		12.5+	*
11					
10	0	1			
9					
8					
7	00	2			***
6	000	3			***
5	000	3			***
4	000000	6			****
3	000000	6	+-----+		****
2	000	3			***
1	0000000	7			****
0					****
-0	000000	6		-0.5+	***
-1	0000	4			
-2	0000000000	10			****
-3	00000	5	+-----+		****
-4	000000000	9			****
-5	0000	4			****
-6	0000	4			***
-7	00	2			
-8	000	3			***
-9	00	2			***
-10	0	1			*
-11	0	1			+
-12					*
-13	00	2		-13.5+	*

-2 -1 0 +1 +2

DIFFERENCE OF EACH VALUE TAKEN FOR ANALYSIS

UNIVARIATE

VARIABLE=CRTDIF

MOMENTS				QUANTILES(DEF=4)				EXTREMES	
N	84	SUM WGTS	84	100% MAX	0.6	99%	0.6	LOWEST	HIGHEST
MEAN	-0.0047619	SUM	-0.4	75% Q3	0.1	95%	0.3	-0.4	0.3
STD DEV	0.192576	VARIANCE	0.0370855	50% MED	0	90%	0.2	-0.4	0.3
SKEWNESS	0.234997	KURTOSIS	0.137036	25% Q1	-0.175	10%	-0.3	-0.3	0.3
USS	3.08	CSS	3.0781	0% MIN	-0.4	5%	-0.3	-0.3	0.4
	0.044109	STD MEAN	0.0210118			1%	-0.4	-0.3	0.6
MEAN=0	-0.226631	PROB>|T|	0.821268	RANGE	1				
NORMAL	0.128911	PROB>D	<0.01	Q3-Q1	0.275				
				MODE	0				

MISSING VALUE

COUNT 1

% COUNT/NOBS 1.18

STEM	LEAF	#	BOXPLOT		NORMAL PROBABILITY PLOT
6	0	1		0.625+	
5			0		*
5				0.525+	
4					
4	0	1		0.425+	
3					+ *
3	00000	5		0.325+	+++
2					******
2	0000000000	10		0.225+	+++
1					******
1	0000000000000	13		0.125+	+++
0			+------+		******
0			*------*	0.025+	*******
-0	00000000000000000000	21	+		+++
-0				-0.075+	
-1	00000000000	11	+------+		++++++
-1				-0.175+	
-2	000000000000	12			++
-2				-0.275+	*******
-3	0000000	7			++
-3	00	2		-0.375+	

MULTIPLY STEM.LEAF BY 10**-01

-2 -1 0 +1 +2

STEP 12 - DETERMINING A P-VALUE FOR REPRODUCTIVE ELEMENTS

THE TWELVTH STEP OF THE ETHYLENE OXIDE STUDY INCLUDED DETERMINING A P-VALUE FOR DATA ELEMENTS INVOLVED IN THE REPRODUCTIVE HISTORY FOR THE STUDY AND CONTROL POPULATIONS. THE PROCEDURE INCLUDED EXTRACTING DATA ELEMENTS FOR BIRTH ABNORMALITY (FOR BOTH EMPLOYEE AND/OR OFFSPRING), MISCORRIDGES, CHILDREN STILLBORN, AND CHILDREN WITH DEATH UNDER 6 MONTHS. AS THE ELEMENTS WERE EXTRACTED, TABLES WERE PRODUCED LISTING THE POSITIVE AND NEGATIVE RESPONSES AS WELL AS DESCRIPTIVE STATISTICS AS NUMBER BIRTH ABNORMALITIES PER LIVE CHILDREN, NUMBER MISCARRIAGE PER LIVE CHILDREN, ETC., FOR BOTH THE STUDY AND CONTROL POPULATIONS. THE TOTALS OF POSITIVE RESPONSES WERE LISTED AT THE END OF THE REPORT. SINCE THE TOTAL NUMBER OF UNMATCHED PAIRS WERE RELATIVELY LOW, THE EXACT TEST COULD BE PERFORMED, AND A P-VALUE OBTAINED FROM THE UPPER PROBABILITY TABLES (SEE STEP 9). FOR EACH DATA ELEMENT, THE EXACT TEST WAS PERFORMED AND A P-VALUE OBTAINED FROM THE TABLES.

ENCLOSED IS A LIST OF THE REPORTS PRODUCED FOR THE REPRODUCTIVE HISTORY ELEMENTS AS OBTAINED FROM TABLE III, A1c OF THE ETHYLENE OXIDE PROTOCOL.

VARIABLE - BIRTH ABNORMALITY

	EXPOSED		CONTROL	
	RESPONSE	NUMBER/TOTAL	RESPONSE	NUMBER/TOTAL
PAIR 1	NO		NO	
PAIR 2	NO		NO	
PAIR 3	NO		NO	
PAIR 4	NO		NO	
PAIR 5	NO		NO	
PAIR 6	NO		NO	
PAIR 7	NO		NO	
PAIR 8	NO		NO	
PAIR 9	NO		NO	
PAIR 10	YES*		NO	
PAIR 11	NO		NO	
PAIR 12	NO		NO	
PAIR 13	NO		NO	
PAIR 14	YES*		NO	
PAIR 15	NO		NO	
PAIR 16	NO		NO	
PAIR 17	NO		NO	
PAIR 18	NO		NO	
PAIR 19	NO		NO	
PAIR 20	NO		NO	
PAIR 21	NO		NO	
PAIR 22	YES**	1/2	NO	
PAIR 23	NO		NO	
PAIR 24	YES**	1/2	NO	
PAIR 25	NO		NO	
PAIR 26	NO		NO	
PAIR 27	NO		NO	
PAIR 28	YES**	1/2	NO	
PAIR 29	NO		NO	
PAIR 30	NO		NO	
PAIR 31	NO		NO	
PAIR 32	NO		NO	
PAIR 33	NO		YES**	1/2
PAIR 34	NO		NO	
PAIR 35	NO		NO	
PAIR 36	NO		NO	
PAIR 37	NO		NO	
PAIR 38	NO		NO	
PAIR 39	NO		NO	
PAIR 40	NO		YES**	1/2
PAIR 41	NO		NO	
PAIR 42	NO		NO	
PAIR 43	NO		NO	
PAIR 44	YES**	1/0	NO	
PAIR 45	NO		NO	
PAIR 46	NO		NO	
PAIR 47	NO		NO	
PAIR 48	NO		NO	

VARIABLE - BIRTH ABNORMALITY

	EXPOSED		CONTROL	
	RESPONSE	NUMBER/TOTAL	RESPONSE	NUMBER/TOTAL
PAIR 49	NO		NO	
PAIR 50	NO		NO	
PAIR 51	NO		NO	
PAIR 52	NO		NO	
PAIR 53	NO		NO	
PAIR 54	NO		NO	
PAIR 55	NO		NO	
PAIR 56	NO		NO	
PAIR 57	NO		NO	
PAIR 58	NO		NO	
PAIR 59	NO		NO	
PAIR 60	YES**	1/2	NO	
PAIR 61	NO		NO	
PAIR 62	NO		NO	
PAIR 63	NO		NO	
PAIR 64	NO		NO	
PAIR 65	NO		NO	
PAIR 66	NO		NO	
PAIR 67	NO		NO	
PAIR 68	NO		NO	
PAIR 69	NO		NO	
PAIR 70	NO		NO	
PAIR 71	NO		NO	
PAIR 72	NO		NO	
PAIR 73	NO		NO	
PAIR 74	NO		NO	
PAIR 75	NO		NO	
PAIR 76	NO		NO	
PAIR 77	NO		NO	
PAIR 78	NO		NO	
PAIR 79	NO		NO	
PAIR 80	NO		YES*	
PAIR 81	NO		NO	
PAIR 82	NO		NO	
PAIR 83	NO		NO	
PAIR 84	YES**	1/4	NO	
TOTAL POS RES	8	6/12	3	2/4
PERCENTAGE POS RES	9.5%		3.5%	

TOTAL POPULATION SIZE - 84

P-VALUE BY EXACT TEST: P = .1133

C6610G

VARIABLE - MISCARRIAGES

	EXPOSED		CONTROL	
	RESPONSE	NUMBER/TOTAL	RESPONSE	NUMBER/TOTAL
PAIR 1	NO		NO	
PAIR 2	NO		NO	
PAIR 3	NO		NO	
PAIR 4	YES	1/2	NO	
PAIR 5	NO		NO	
PAIR 6	YES	1/1	NO	
PAIR 7	NO		NO	
PAIR 8	NO		NO	
PAIR 9	YES	2/2	NO	
PAIR 10	NO		NO	
PAIR 11	NO		YES	1/0
PAIR 12	NO		NO	
PAIR 13	NO		NO	
PAIR 14	YES	2/2	NO	
PAIR 15	YES	1/1	NO	
PAIR 16	NO		NO	
PAIR 17	NO		NO	
PAIR 18	NO		NO	
PAIR 19	NO		NO	
PAIR 20	NO		NO	
PAIR 21	NO		NO	
PAIR 22	NO		NO	
PAIR 23	NO		NO	
PAIR 24	NO		YES	1/2
PAIR 25	NO		YES	2/2
PAIR 26	NO		NO	
PAIR 27	NO		NO	
PAIR 28	NO		NO	
PAIR 29	NO		NO	
PAIR 30	NO		NO	
PAIR 31	NO		NO	
PAIR 32	NO		YES	1/4
PAIR 33	NO		NO	
PAIR 34	YES	1/3	YES	1/2
PAIR 35	NO		NO	
PAIR 36	YES	1/4	NO	
PAIR 37	NO		NO	
PAIR 38	NO		NO	
PAIR 39	NO		NO	
PAIR 40	YES	1/2	NO	
PAIR 41	NO		NO	
PAIR 42	NO		NO	
PAIR 43	NO		NO	
PAIR 44	NO		NO	
PAIR 45	NO		NO	
PAIR 46	NO		NO	
PAIR 47	NO		NO	
PAIR 48	NO		NO	

C8610G

VARIABLE - MISCARRIAGES

	EXPOSED		CONTROL	
	RESPONSE	NUMBER/TOTAL	RESPONSE	NUMBER/TOTAL
PAIR 49	NO		NO	
PAIR 50	YES	1/3	NO	
PAIR 51	NO		NO	
PAIR 52	NO		NO	
PAIR 53	NO		NO	
PAIR 54	NO		NO	
PAIR 55	NO		NO	
PAIR 56	NO		NO	
PAIR 57	NO		YES	1/2
PAIR 58	NO		YES	1/1
PAIR 59	NO		NO	
PAIR 60	NO		NO	
PAIR 61	NO		NO	
PAIR 62	NO		NO	
PAIR 63	NO		NO	
PAIR 64	NO		NO	
PAIR 65	YES	1/0	NO	
PAIR 66	NO		NO	
PAIR 67	NO		NO	
PAIR 68	NO		NO	
PAIR 69	NO		NO	
PAIR 70	NO		NO	
PAIR 71	YES	1/1	NO	
PAIR 72	NO		NO	
PAIR 73	NO		NO	
PAIR 74	NO		NO	
PAIR 75	NO		NO	
PAIR 76	NO		NO	
PAIR 77	NO		NO	
PAIR 78	NO		YES	2/1
PAIR 79	NO		YES	1/2
PAIR 80	NO		NO	
PAIR 81	NO		NO	
PAIR 82	NO		NO	
PAIR 83	NO		NO	
PAIR 84	NO		NO	
TOTAL POS RES	11	13/21	9	11/16
PERCENTAGE POS RES	13.0%		10.7%	

TOTAL POPULATION SIZE - 84

P-VALUE BY:

EXACT TEST: P = .5

VARIABLE - CHILDREN STILLBORN

	EXPOSED		CONTROL	
	RESPONSE	NUMBER/TOTAL	RESPONSE	NUMBER/TOTAL
PAIR 1	NO		NO	
PAIR 2	NO		NO	
PAIR 3	NO		NO	
PAIR 4	YES	1/2	NO	
PAIR 5	NO		NO	
PAIR 6	NO		NO	
PAIR 7	NO		NO	
PAIR 8	NO		NO	
PAIR 9	NO		NO	
PAIR 10	NO		NO	
PAIR 11	NO		NO	
PAIR 12	NO		NO	
PAIR 13	NO		NO	
PAIR 14	NO		NO	
PAIR 15	NO		NO	
PAIR 16	NO		NO	
PAIR 17	NO		NO	
PAIR 18	NO		NO	
PAIR 19	NO		NO	
PAIR 20	NO		NO	
PAIR 21	NO		NO	
PAIR 22	YES	1/2	NO	
PAIR 23	NO		NO	
PAIR 24	NO		NO	
PAIR 25	NO		NO	
PAIR 26	NO		NO	
PAIR 27	NO		NO	
PAIR 28	NO		NO	
PAIR 29	NO		NO	
PAIR 30	NO		NO	
PAIR 31	NO		NO	
PAIR 32	NO		NO	
PAIR 33	NO		NO	
PAIR 34	NO		NO	
PAIR 35	NO		NO	
PAIR 36	NO		NO	
PAIR 37	NO		NO	
PAIR 38	NO		NO	
PAIR 39	NO		NO	
PAIR 40	NO		NO	
PAIR 41	NO		NO	
PAIR 42	NO		NO	
PAIR 43	NO		NO	
PAIR 44	NO		NO	
PAIR 45	NO		NO	
PAIR 46	NO		NO	
PAIR 47	NO		NO	
PAIR 48	NO		NO	

ARIABLE - CHILDREN STILLBORN

	EXPOSED		CONTROL	
	RESPONSE	NUMBER/TOTAL	RESPONSE	NUMBER/TOTAL
PAIR 49	NO		NO	
PAIR 50	NO		NO	
PAIR 51	NO		NO	
PAIR 52	NO		NO	
PAIR 53	NO		NO	
PAIR 54	NO		NO	
PAIR 55	NO		NO	
PAIR 56	NO		NO	
PAIR 57	NO		NO	
PAIR 58	NO		NO	
PAIR 59	NO		NO	
PAIR 60	NO		NO	
PAIR 61	NO		NO	
PAIR 62	NO		NO	
PAIR 63	NO		NO	
PAIR 64	NO		NO	
PAIR 65	NO		NO	
PAIR 66	NO		NO	
PAIR 67	NO		NO	
PAIR 68	NO		NO	
PAIR 69	NO		NO	
PAIR 70	NO		NO	
PAIR 71	NO		NO	
PAIR 72	NO		NO	
PAIR 73	NO		NO	
PAIR 74	NO		NO	
PAIR 75	NO		NO	
PAIR 76	NO		NO	
PAIR 77	NO		NO	
PAIR 78	NO		NO	
PAIR 79	NO		NO	
PAIR 80	NO		NO	
PAIR 81	NO		NO	
PAIR 82	NO		NO	
PAIR 83	NO		NO	
PAIR 84	NO		NO	
TOTAL POS RES	2	2/4	0	0/0
PERCENTAGE POS RES	2.3%		0.0%	

TOTAL POPULATION SIZE - 84

P-VALUE BY:

EXACT TEST: P=.2

DO 095244
CONFIDENTIAL

VARIABLE - DEATH UNDER 6 MONTHS

	EXPOSED		CONTROL	
	RESPONSE	NUMBER/TOTAL	RESPONSE	NUMBER/TOTAL
PAIR 1	NO		NO	
PAIR 2	NO		NO	
PAIR 3	NO		NO	
PAIR 4	NO		NO	
PAIR 5	NO		NO	
PAIR 6	NO		NO	
PAIR 7	NO		NO	
PAIR 8	NO		NO	
PAIR 9	NO		NO	
PAIR 10	NO		NO	
PAIR 11	NO		NO	
PAIR 12	NO		NO	
PAIR 13	NO		NO	
PAIR 14	NO		NO	
PAIR 15	NO		NO	
PAIR 16	NO		NO	
PAIR 17	NO		NO	
PAIR 18	NO		NO	
PAIR 19	NO		NO	
PAIR 20	NO		NO	
PAIR 21	NO		NO	
PAIR 22	NO		YES	2/2
PAIR 23	NO		NO	
PAIR 24	NO		NO	
PAIR 25	NO		NO	
PAIR 26	NO		NO	
PAIR 27	NO		NO	
PAIR 28	YES	1/2	NO	
PAIR 29	NO		NO	
PAIR 30	NO		NO	
PAIR 31	NO		NO	
PAIR 32	NO		NO	
PAIR 33	YES	1/3	NO	
PAIR 34	NO		NO	
PAIR 35	NO		NO	
PAIR 36	NO		NO	
PAIR 37	NO		NO	
PAIR 38	NO		NO	
PAIR 39	NO		NO	
PAIR 40	NO		NO	
PAIR 41	NO		NO	
PAIR 42	NO		NO	
PAIR 43	NO		NO	
PAIR 44	YES	1/0	NO	
PAIR 45	NO		NO	
PAIR 46	NO		NO	
PAIR 47	NO		NO	
PAIR 48	NO		NO	

VARIABLE - DEATH UNDER 6 MONTHS

	EXPOSED		CONTROL	
	RESPONSE	NUMBER/TOTAL	RESPONSE	NUMBER/TOTAL
PAIR 49	NO		NO	
PAIR 50	NO		NO	
PAIR 51	NO		NO	
PAIR 52	NO		NO	
PAIR 53	NO		NO	
PAIR 54	NO		NO	
PAIR 55	NO		NO	
PAIR 56	NO		NO	
PAIR 57	NO		NO	
PAIR 58	NO		NO	
PAIR 59	NO		NO	
PAIR 60	NO		NO	
PAIR 61	NO		NO	
PAIR 62	NO		NO	
PAIR 63	NO		NO	
PAIR 64	NO		NO	
PAIR 65	NO		NO	
PAIR 66	NO		NO	
PAIR 67	NO		NO	
PAIR 68	NO		NO	
PAIR 69	NO		NO	
PAIR 70	NO		NO	
PAIR 71	NO		NO	
PAIR 72	NO		NO	
PAIR 73	NO		NO	
PAIR 74	NO		NO	
PAIR 75	NO		NO	
PAIR 76	NO		NO	
PAIR 77	NO		NO	
PAIR 78	NO		YES	1/1
PAIR 79	NO		NO	
PAIR 80	NO		NO	
PAIR 81	NO		NO	
PAIR 82	NO		NO	
PAIR 83	NO		NO	
PAIR 84	NO		NO	
TOTAL POS RES	3	3/5	2	3/3
PERCENTAGE POS RES	3.5%		2.3%	

TOTAL POPULATION SIZE - 84

P-VALUE BY:

EXACT TEST: P: .5000