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RESPIRATORY AND IMMUNOLOGIC EVALUATION
OF ISOCYANATE EXPOSURE IN A NEW
MANUFACTURING PLANT

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Abstract (Limit: 200 words)

The effects of isocyanate exposure on respiration and immunology were studied in workers at a toluene-diisocyanate (584849) (TDI) manufacturing facility (SIC-5161) in Louisiana. In April 1973 before TDI production began, 168 workers were given a medical questionnaire to compile smoking histories and to determine the presence of upper and lower respiratory symptoms and bronchitis. Spirometric tests were administered to determine lung volume and diffusing capacities. Follow up visits and tests continued periodically for over 5 years; the last one was made in October 1978. Eight-hour time weighted averages for TDI exposure of 1949 personal samples respiratory 42 jobs titles were obtained. TDI developed in 4.3 percent of the study population. The values of the parameters of lung function declined, and some of the workers in the study group had evidence of sensitization to TDI.

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I. INTRODUCTION

The construction of a new plant in Southwestern Louisiana for production of toluene diisocyanate (TDI) with start of operation late in 1973 led to a proposal by the National Institute of Occupational Safety and Health (NIOSH) to the investigators for a longitudinal study of respiratory health of the workers who would be exposed to TDI. The ability to begin the study prior to the start of TDI production presented the unique opportunity of obtaining pre-exposure biologic data on the study population. The proposed investigation had the full agreement and cooperation of the major chemical company operating this plant and its labor representatives.

It has been known for two decades that reversible airways obstruction develops in a small proportion of workers exposed to isocyanate vapors, either during manufacture or application processes. In addition to the recognition of the risk for developing this form of occupational asthma, there had been a suggestion that chronic progressive fixed airways obstruction was detected in an exposed population and was not related to "sensitivity", but rather was a general effect of TDI exposure.

This multi-disciplinary investigation addressed the following scientific questions:

(1) What are the characteristics of plant airborne TDI concentrations, particularly in terms of average exposures, as well as variation in short term concentrations (peaks)? This was first assessed by area monitoring using a physico-chemical method for continuous monitoring developed in the United Kingdom and introduced into this investigation by the principal investigator resulting in its first research or other application in the United States. During the course of the contract, personal sampling for continuous airborne concentrations of TDI vapor was similarly initiated and formed the basis for the comprehensive personal exposure profiles in these manufacturing workers detailed in this report.

(2) What proportion of exposed workers become reactive to TDI vapor following exposure, what are the temporal relationships between initial exposure and such reactivity, and what are the clinical manifestations in the reactive group?

(3) Are there host factors which will serve to identify those individuals who are susceptible to TDI exposure and develop the clinical picture of occupational asthma as the result of such exposure?

(4) Can the physiologic consequences (bronchoconstriction) of exposure in susceptible workers be reproduced in the laboratory by broncho-provocation; and what are the physiologic, immunologic and exposure characteristics of such a reproduced bronchoconstrictor response?

(5) What is the mechanism of TDI induced asthma? Is it immunologic or non-immunologic?

(6) Is there a generalized adverse effect on respiratory function in the exposed working population, and if so, what are its determinants (e.g., host factors, level of exposure)?

(7) Is the airways obstruction which results from development of TDI reactivity reversible in all instances, or are there permanent residual effects which are measurable by follow-up serial ventilatory function studies? If permanent changes occur in some reactive individuals, what are the determinants of such irreversibility?

(8) Does development of TDI reactivity lead to a general (non-specific) bronchial hyperresponsiveness?

(9) What are the dose-response relationships of any acute or chronic respiratory effects identified in this exposed population as determined either by the longitudinal field survey or bronchoprovocation testing?

(10) Are there levels of exposure which are not associated with any acute or chronic adverse respiratory health effects?

(11) Are there measurements, either physiologic, immunologic or other which are likely to be useful in identifying workers who may have a high risk of developing TDI reactivity prior to or during the course of their exposure?

(12) What is the course of specific and non-specific bronchial hyperresponsiveness following removal of the susceptible worker from exposure?

As the reader of this report will appreciate, considerable information impacting on the above questions has been obtained in this five-year investigation. However, our knowledge concerning TDI-induced respiratory health effects is by no means complete and several issues require additional scientific inquiry for their resolution.

II. STUDY DESIGN AND PROTOCOLS

As originally conceived, the study design sought to compare three TDI exposure categories with respect to the longitudinal course of respiratory symptoms, spirometric measurements, lung volumes and diffusing capacity. Initial measurements were made prior to TDI production (and exposure) enabling an individual to serve as his/her own control. The three exposure categories were (1) TDI production workers in daily contact with the chemical, (2) workers (primarily maintenance personnel) with intermittent TDI contact, and (3) controls employed outside the TDI production area. In April of 1973, prior to the beginning of TDI production, 168 workers were administered a modified British Medical Research Council questionnaire. It was used to gather smoking histories and to determine presence or absence of (1) upper respiratory symptoms, (2) lower respiratory symptoms, and (3) bronchitis (see longitudinal symptom analysis section for definitions). In addition, the 168 individuals underwent spirometric testing and determination of lung volumes and diffusing capacities.

Of the original 168 participants, 49 had left the plant (two died and 47 either were fired or laid off, retired, quit, or transferred away from the plant) by the last visit in October of 1978. This corresponds to a dropout rate of 4.22% per visit. In addition to the 49 participants of the original 168 who had left the plant by the last visit, 19 refused to perform forced expirations at the last visit. The decrease from 168 to 100 participants at the final visit corresponds to a dropout rate of 6.28% per visit.

Table 1 presents summary data, by visit, on spirometry participation for the 277 participants in the data file. Completing the interview seems better accepted by the workers than spirometric testing, and there are individuals with completed interviews who refused to perform forced expirations. Thus, Table 1 underestimates interview participation.

The manufacturing site was visited a second time in November, 1973, at which time pre- and post-spirometric testing was performed. No relationship between pre- and post-shift decline and TDI exposure was observed. Subsequent visits have totaled 7: September, 1974 (spirometry, lung volumes, and diffusion); March, 1975 (spirometry); October, 1975 (spirometry, lung volumes, and diffusion); March, 1976 (spirometry); November, 1976, December, 1977 (spirometry, lung volumes, and diffusion); and October, 1978 (spirometry and lung volumes). A respiratory health questionnaire was administered at each of the follow-up visits. Change in symptom status was assessed by comparing the initial visit status with that on the last available questionnaire provided it was administered at one of the last three visits.

*Not used
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Other
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exposure?
Highly
selected
to begin
with.*

As the follow-up period lengthened, the original exposure categories lost their integrity due to job changing by participants. Concurrently, detailed exposure information based on personal monitors became available allowing the original exposure categories to be replaced by cumulative exposure in ppm-months. (See the environmental section below.)

At visits two through six, new participants were added in order to preserve the size of the study population. At their entry point, the interview used at the initial April, 1973, visit was administered.

In the Fall of 1976, due to the continuing erosion of the study population because of workers leaving the plant, it was decided to follow up those who had left in order to see if their health had changed since leaving the plant. There were 42 people who had left the plant at that time and of those, 17 were successfully tested. The remainder were either impossible to locate or unwilling to be tested. The results of this follow-up were reported in the annual report of 1977.

All participants were tested at their initial session with a battery of common inhalant allergens.* The presence of two or more positive prick tests (wheal diameter 1 mm greater than control) was used to define atopy.

Pulmonary function tests were conducted in a mobile laboratory on a Cardio-Pulmonary instrument (Model 5000) Pulmolab. This unit is capable of measuring expiratory flows and volumes, lung volumes, and single breath diffusing capacity. It is equipped with an electronic dry rolling-seal spirometer which provides BTPS outputs of all volumes and flows. During a maximum forced expiration, the output is fed into an XYT recorder in order to obtain plots of flow vs volume or time. The parameters calculated from the forced expiration include the forced vital capacity (FVC), the forced expiratory volume in 0.5 and 1.0 seconds ($FEV_{0.5}$ and FEV_1), the FEV_1/FVC ratio reported as a percent, the forced expiratory flow between 25 and 75% of the FVC (FEF_{25-75}), FEF_{50} and FEF_{25} . All these parameters were measured for each individual who was available at the time of testing. However, only satisfactory data were used in the analysis. For spirometry to be satisfactory for an individual, the two largest FVC maneuvers must be within 3% of one another. In addition, these curves must have a sharp initial flow with a smooth continuous effort extending until either flow plateaus to 0.0 liters per second, or seven seconds have elapsed. Therefore, the FVC could be termed an FEV_7 . When there are more than two satisfactory curves, all data from the two maneuvers with the highest combined percent of predicted

* Allergens used were those known to be of local clinical relevance and included *Aspergillus* sp., *Homodendrum* sp., *Fusarium* sp., Bermuda grass, Johnson grass, *Helminthosporium* sp., *Alternaria* sp., white oak, giant ragweed mix, elm pecan, house dust, marsh elder, cat dander, and dog dander.

for $FEV_{.5}$ and FEF_{25-75} were stored for analysis and averaged. These two parameters should provide data with the largest initial effort indicated by the high $FEV_{.5}$ and a good sustained effort, indicated by the large FEF_{25-75} . The only change in calculation procedures occurred in 1975 when backward extrapolation was introduced to determine zero time for the beginning of timed volume ($FEV_{.5}$, FEV_1). At that time, all data previously calculated were recalculated using this procedure and the data file was updated so that all data for the entire course of the study was standardized with a backward extrapolation start of time.

The measurement of lung volumes included the slow vital capacity maneuver (VC) and the residual volume (RV) measured by the nitrogen washout technique. In addition, the alveolar volume (AV) is taken as the sum of inspired volume from the diffusion test and residual volume. The total lung capacity (TLC) is calculated as the sum of RV and the larger of VC or FVC. The diffusing capacity for carbon monoxide in units of milliliters per minute per millimeter of mercury was measured by the single breath method ($DLCOSB$). The diffusion constant K equals $DLCOSB/AV$ in units of $\text{min}^{-1} \text{mmHg}^{-1}$. For measurements of residual volume and diffusing capacity only satisfactory data were analyzed. For satisfactory data, the residual volume from two tests had to be within 10% of each other, or 200 cc, whichever is larger. The smallest RV was used in the analysis. The diffusing capacity is reported from two $DLCO$ measurements within 10% of each other in which the alveolar volume is at least 85% of the total lung capacity and the time for the test is within ten to fourteen seconds.

In 1978, a computerized data reduction system was connected on line to the Pulmolab. The output from the Pulmolab is instantaneously fed by means of a ten bit A/D converter to a Datapoint 1100 computer processor with three diskette drives. Data resolution of the computer are 10 ml for volume and 20 ml/sec for flow. The computer calculates the parameters listed previously and uses the method of backward extrapolation in determining the $FEV_{.5}$ and FEV_1 . These outputs are immediately displayed for the technician on a cathode ray tube, and if the tests are considered satisfactory by the technician, the data are reduced in the same method previously employed when data were calculated by hand. The reduced data is stored magnetically on diskettes. In order to insure that this computerized system did not systematically affect data collection, spirometry obtained on 100 individuals was calculated by hand and compared to that measured by the computerized system. The mean difference between hand and computer calculated values were within 1% and 2% of the observed volumes and flows, respectively.

CO_{20}

In addition to measuring spirometric parameters, the computer also determines residual volumes and diffusion capacity. These data were calculated and reduced with the same methods previously employed. In addition, when values obtained by computer were compared to those obtained by previous methods, identical data were produced.

In summary, pulmonary function measurements were conducted throughout the study using the same equipment and test procedures. The method of

Act up
or down

backward extrapolation was implemented after the initiation of the study, but past data were recalculated and the analysis updated. In addition, the implementation of a computerized data reduction system was carefully analyzed and proved comparable to previous methods of data reduction and calculation. Therefore, for the duration of the study, data collection was standardized to reduce variability.

The complete data file from all nine visits contains information on 277 participants. Four of these are female and have been deleted from all analyses. Table 2 presents descriptive statistics on the 274 males in the study. 85% of them are white, 73.7% are current (51.1%) or ex (22.6%) cigarette smokers, and 20.1% reacted positively to two or more skin tests. They have a mean age of 35.9 years, a mean height of 69.9 inches, and averaged 14.4 pack-years of cigarette smoking. All pulmonary function percent predicted were near 100% with the exception of FEF₂₅₋₇₅ (91.0%).

III. TDI EXPOSURE INDICES

Two thousand and ninety three personal samples on 143 workers were collected using MCM type 4000 tape samplers and 4100 MCM integrating Reader Recorder System, both manufactured by Universal Environmental Instruments and supplied by MDA Scientific Incorporated of Park Ridge, Illinois. Sampling was done in a relatively uniform manner with respect to time from June, 1975, through October, 1978. All job categories in the TDI manufacturing area are represented in the 143 people monitored.

Appendix 1 details the technical aspects of the TDI monitoring program and Appendix 2 treats the statistical methodology used to define exposure categories. In this section, the environmental data are summarized and the two exposure indices developed for each participant are described.

A. Cumulative Exposure

One hundred and forty four of the 2,093 personal samples were taken by maintenance workers during a single one-month period in 1975 (called turnaround time) of concentrated maintenance activity. Since these maintenance workers were not a representative collection of maintenance workers and since no sampling was done during subsequent turnaround times (the wearing of monitors was an impediment to work performance), these 144 samples were not used to determine cumulative exposure categories.

Since the frequency distribution of the 8-hour time-weighted averages of the remaining 1,949 samples, representing 42 job titles, was markedly skewed to the right, they were transformed using logarithms to the base 10. The frequency distribution of the transformed 8-hour time-weighted averages

was approximately symmetrical and the following categories were defined on the log scale:

Category	TWA ¹		LOG (TWA)	
	lower limit	upper limit	lower limit	upper limit
1	0	.00025	-4.00	-3.60
2	.00025	.0005	-3.60	-3.30
3	.0005	.001	-3.30	-3.00
4	.001	.002	-3.00	-2.70
5	.002	.004	-2.70	-2.40
6	.004	.008	-2.40	-2.10
7	.008	.016	-2.10	-1.80
8	.016	.032	-1.80	-1.50

(If LOG (TWA) coincided with a category boundary, it was placed in the lower category.)

Figure 1 contains histograms of the 1949 8-hour time-weighted averages used to develop exposure categories and of the 144 "turnaround time" 8-hour time-weighted averages. Table 3 contains descriptive statistics for the same two sets of 8-hour time-weighted averages.

Using clustering techniques described in Appendix 2, the 42 job titles as described by 1949 8-hour time-weighted averages were divided into three categories: HIGH, MODERATE, and LOW. The jobs which make up each category are listed in Table 4. The jobs cluster by exposure as follows:

- (1) TDI C-Operators and Drumming E-Operators in the HIGH GROUP
- (2) TDI Foreman, TDI B-Operators, TDI maintenance personnel, and the TDI Laboratory Samplers in the MODERATE GROUP, and
- (3) Primarily non-TDI area located jobs in the LOW GROUP.

Histograms on the LOG (TWA) scale and descriptive statistics in ppm for each of three exposure categories are presented in Figure 2 and Table 5 respectively. The histograms provide graphic verification of the separation between the HIGH and LOW GROUPS (80% of the samples in the LOW GROUP fall in LOG (TWA) category 4 or lower whereas 80% of the samples in the HIGH GROUP fall in LOG (TWA) category 5 or higher.) with the MODERATE GROUP lying in an intermediate position. The descriptive statistics in ppm show that the 25th percentile, the median, the geometric mean, the mean, and the 75th percentile

¹TWA - 8-hour time-weighted average

all increase approximately by multiples of two from the LOW to HIGH CATEGORY, thus establishing a definite exposure gradient.

Job histories collected from personnel records and interviews were used to determine the number of months a participant spent in each of the three exposure categories. Cumulative exposure in ppm-months was computed by multiplying the time in an exposure category by a representative measure of concentration for that category and then summing the three obtained products. The representative measure of concentration was taken to be the geometric mean of the observed 8 hour time weighted averages for the category. The geometric mean instead of arithmetic mean was used as a measure of central tendency since it is more representative of the central portion of the distribution when, as is the case here, positive skewness is removed by taken logarithms.

B. Time Above .02 ppm

In addition to calculating the 8-hour time-weighted average from each personal sample, the length of time the concentration was above each of the levels .005, .01, .02, .04, .06, and .08 ppm was recorded. This information on the 2,093 samples representing 50 job titles was used to develop "peak exposure" categories as described in Appendix 2. The job titles for each of the resulting categories are listed in Table 6. The proportion of time spent above each level is presented in Table 7 by category.

Using individual job histories, the time spent above a particular concentration level was calculated as the sum over peak exposure categories of the product of time spent in the category and proportion of time spent above the level for that category. This quantity whose units is months was used in seeking associations between health effects and peak exposure. This index is not equal to the actual time above a particular level but is only proportional to it. The constant of proportionality (approximately .25) adjusts for the fact that in a 30 day or 720 hour month, approximately 168 hours are spent in the workplace.

Although six indices of peak exposure, one for each concentration level, were calculated, they were so highly correlated (the smallest correlation coefficient was .96) that we have used only the time above .02 ppm in the health effects correlation analyses. Because of its high correlation with the other five indices, no new information would be obtained by substituting the other indices for time above .02 ppm.

C. Assignment of Exposure Indices for Correlation Studies

Four different sets of statistical analyses, one each for spirometry, lung volumes, diffusion, and respiratory symptoms are presented in the

following sections. Since the visits for which usable data is available is different for each of four analyses, exposure indices have been computed separately for each. Thus, for example, the cumulative exposure and time above .02 ppm indices for spirometry were computed from time of initial exposure at the manufacturing site through the date of the last visit for which usable spirometric data on the participant is available. In a similar manner, the two exposure indices were computed for each participant for each of the three other analyses.

In addition to treating cumulative exposure and time above .02 ppm as continuous variables as defined above, cumulative exposure and time above .02 ppm categories were also developed for use in relating a health effect to exposure. One of these categorizations dichotomized the continuous exposure index and the other created three subgroups as described below.

For cumulative exposure GROUP I consists of those participants whose cumulative exposure (for a particular analysis) was less than or equal to .0682 ppm-months and GROUP II those participants with more than .0682 ppm-months of exposure. To create three cumulative exposure categories, GROUP II was further dichotomized into GROUP IIA AND GROUP IIB using a division point of 0.1 ppm-months. $0.0682 \text{ ppm-months} = (0.0011 \text{ ppm}) \times (62 \text{ months})$ was chosen as the first division point because it corresponds to the exposure accumulated by a participant who spent 62 months, the time from initial TDI production to the end of the study, in the lowest concentration exposure category which has a geometric mean of 0.0011 ppm. This placed approximately two-thirds of the population into GROUP I. The division point to dichotomize GROUP II into GROUP IIA and IIB was chosen so as to result in approximately equal numbers in these two subgroups.

For time above 0.02 ppm GROUP I consists of those participants who spent no longer than 0.19 months above 0.02 ppm and GROUP II those participants with exposure longer than 0.19 months above .02 ppm. This division point corresponds to the time spent above 0.02 ppm for a participant who spent the full period of 62 months in the lowest peak exposure category. GROUP I determined in this way contained approximately two-thirds of the study population. To create three peak exposure categories, GROUP II was further subdivided into GROUP IIA and GROUP IIB of approximately equal numbers using a division point of one month.

IV. LONGITUDINAL RESULTS AND ANALYSIS

A. Introduction

The overall objective of this longitudinal study has been to relate change in variables representative of health status to host factors

and variables reflecting exposure to TDI. The health status variables considered in the longitudinal analysis are spirometric measurements: FEV₁, FVC, FEV%, FEV₂₅₋₇₅, FEV₅₀; diffusion capacity DL_{CO} and K; lung volumes: RV, TLC, and (RV/TLC) X 100; and respiratory symptoms: upper respiratory symptoms, lower respiratory symptoms; bronchitis and dyspnea. The host factors considered are cigarette smoking as measured by pack-years and atopic status as defined in the section on study design and protocols. TDI exposure indices as defined in the section on environmental characterization have been based on cumulative exposure and time above .02 ppm.

Each of the health status variables with the exception of respiratory symptoms are quantitative in nature and annual change for them has been computed as the slope of the least squares straight line using time since initial visit as the independent variable. Usable data from three or more visits was sufficient to include a participant in the analysis. The slopes or annual changes were regressed using the technique described in Appendix 2 on independent variables representing TDI exposure, atopic status, and cigarette smoking. For each of the pulmonary function measurements six regressions were performed. In each regression pack years of cigarette smoking and atopic status as represented by a dummy variable equal to 1 if the participant was atopic and 0 otherwise, were included in the independent variables. The coefficient of the variable representing atopic status is an estimate of the mean annual change in atopics minus the mean annual change in non-atopics after controlling for the other variables. The variables representing exposure to TDI in the six regressions are as follows:

Regression 1 Cumulative exposure in ppm-months.

Regression 2 A dummy variable called cumulative exposure category II which is 1 if cumulative exposure is greater than .0682 ppm-months (See the Environmental Characterization for the rationale behind choosing this division point.) and 0 otherwise. Thus, the coefficient of this variable estimates the mean annual change of the cumulative exposure GROUP II participants minus the mean annual change of the cumulative exposure GROUP I participants (See the Environmental Characterization Section for GROUP I and GROUP II definitions) after controlling for the other variables.

Regression 3 In this regression TDI exposure is represented by 2 dummy variables:

- (1) Cumulative exposure category IIA which is 1 if cumulative exposure is greater than .0682 ppm-months and 0 otherwise, and
- (2) Cumulative exposure category IIB which is 1 if cumulative exposure is greater than .1 ppm-months and 0 otherwise.

Thus, the coefficient of cumulative exposure category IIA estimates the difference in mean annual change between GROUP IIA and GROUP I (GROUP IIA-GROUP I). The coefficient of cumulative exposure category IIB estimates the difference in mean annual changes between GROUP IIB and GROUP IIA (GROUP IIB-GROUP IIA). Both of these estimated differences in means are after controlling for the other variables.

Regression 4

Time above .02 ppm in months.

Regression 5

A dummy variable called peak exposure category II indicating that a participant belongs to time above .02 ppm GROUP II (See the Environmental Characterization Section for definitions of GROUP I and II). The coefficient of this variable has been an interpretation analogous to that of the coefficient of cumulative exposure category II in Regression 2.

Regression 6

Two dummy variables called peak exposure category IIA and peak exposure category IIB which indicate respectively membership in time above .02 ppm GROUPS II and IIB. The coefficients of these variables have interpretations analogous to those of cumulative exposure category IIA and cumulative exposure category IIB of Regression 3.

Tables 8 through 13 present the results of these regressions. The numbers in parentheses in these tables are the regression coefficients divided by their standard errors and should be compared to percentiles of the normal distribution for tests of significance. Thus, a regression coefficient is significantly different from 0 at the $\alpha = .05$ level if it divided by its standard error exceeds 1.96 in absolute value.

Each observed annual change is the sum of the unobserved true annual change and an estimation error term. It is the variability of the true annual changes which we are trying to explain by the independent variables in the regression equations. The last column headed "% variability explained" in Tables 8 through 13 is the percent of true annual change variance explained by independent variables in the regression equations. Estimates of the true annual change standard deviation for each pulmonary function considered are given in Table 14.

The estimation error term is the result of the variation in individual pulmonary function determinations about a participants regression on time. The differences between individual determinations and the fitted regression on time are called residuals. The variation in these residuals depends on, among other things, technical measurement error, seasonal variability in pulmonary function, technician effects if they exist, and daily variability in pulmonary function not affecting physiologic state. The residual error standard deviation for each pulmonary function considered is given in Table 14.

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Estimated mean annual changes and their standard errors are presented in Table 14. The remaining columns of Table 14 are more fully discussed in Appendix 2. Here we only note that for each pulmonary function approximately 50% of the observed annual change variability in a participant studied at all nine visits is true annual change variability and hence is available for explanation by host factors and exposure to TDI.

With the possible exceptions of FEF₂₅₋₇₅ and FEF₅₀ the spirometric mean annual changes found in this longitudinal study are not markedly different from cross-sectional studies. The FEF₅₀ longitudinal mean annual change is 3.5 to 7.5 times that expected from cross-sectional results, depending on which prediction equations are used.

Estimates of the mean annual changes in this study population for K $[-.716 \text{ (min-mmHg-year)}^{-1}]$ and TLC (.32 ml/year) differ from Cotes' (1) cross-sectional age coefficients. Mean annual change for K differs by a factor of 18 and TLC annual change is statistically significantly positive whereas Cotes' cross-sectional age coefficient is 0.

Longitudinal RV and (RV/TLC) X 100 annual changes, although larger, are not markedly different from that expected from cross-sectional studies.

B. Spirometry Results

Two hundred and twenty-six participants had complete spirometry from three or more visits. Table 15 presents summary statistics on these 226 participants and the 48 who did not have complete data for the required number of visits. There were no important differences between the two groups. Three participants of the 226 lacked data on at least one of the explanatory variables and consequently have been deleted from the analysis.

In each of the six regressions, both FEV₁ and FVC annual declines were significantly positively related to pack-years of smoking with each pack-year contributing .6 ml/yr to FEV₁ annual decline and .7 ml/yr to the FVC annual decline. Neither FEV₁ nor FVC annual decline were significantly related to atopic status. Neither FEV%, FEF₂₅₋₇₅, nor FEF₅₀ annual decline were associated with pack-years of cigarette smoking. Atopics showed consistently smaller FEF₂₅₋₇₅ and FEF₅₀ annual declines than non-atopics at p-values ranging from .12 to .18.

No spirometric measurement was significantly associated with cumulative exposure treated as a continuous variable. However, with the exception of FVC all annual declines became greater with increasing cumulative exposure.

Using one-tailed tests of significance FEV₁ (p = .034), FEV% (p = .014), and FEF₂₅₋₇₅ (p = .004) estimated mean annual declines (after controlling for

atopy and pack years of smoking) were significantly greater (12 ml/yr , $.20(\text{yr})^{-1}$, and 41 ml/sec-yr respectively) in cumulative exposure GROUP II (i.e., those participants with cumulative exposure greater than .0682 ppm-months) than in GROUP I. At 14 pack years of cigarette smoking, the mean number of pack years for the group of the 223 participants used in this analysis, the estimated mean annual declines (See Table 16) for non-atopics in GROUP I are 20 ml/year , $.28 \text{ yr}^{-1}$, and 84 ml/sec-yr respectively. Thus, even though there is a dose-related effect for FEV_1 and $\text{FEV}\%$ annual decline, the absolute level of the mean annual declines in the higher exposure group are approximately the same as expected from cross-sectional studies. However, the GROUP I and GROUP II FEF_{25-75} estimated mean annual declines of 80 ml/sec-yr and 121 ml/sec-yr for non-atopics with 0 pack years of cigarette smoking are significantly greater than the cross-sectional annual decline of 31 ml/sec-year reported by Knudson, et al (2) for male "never-smokers" over age 25. The GROUP I estimated mean annual FEF_{50} decline of 103 ml/sec-yr for non-atopics at 0 pack-years is also significantly greater than cross-sectional annual decline of 15 ml/sec-yr reported by Knudson, et al (2). The biological significance of the discrepancy between FEF_{25-75} and FEF_{50} annual changes as computed from longitudinal data and that expected based on cross-sectional studies is not known. It could mean either that the population under study has abnormally large declines in these flow rates, indicating a deleterious effect on respiratory health, or that it is inappropriate to compare flow rate annual changes from these two types of studies. The magnitude of the differences between GROUP I and GROUP II (-41 ml/sec-yr for FEF_{25-75} and -29 ml/sec-yr for FEF_{50}) reflecting a relationship to TDI exposure together with large annual declines for these pulmonary functions is suggestive of a hazardous local environment with TDI exposure increasing the risk. In any event, independent of the level of annual change, there is an exposure related effect for FEV_1 , $\text{FEV}\%$, and FEF_{25-75} annual decline.

When GROUP II is dichotomized into GROUP IIA and GROUP IIB using a division point of .1 ppm-months, a larger mean decline is to be expected in GROUP IIB than in GROUP IIA if there is a dose-response relationship. For FEV_1 , $\text{FEV}\%$, and FEF_{25-75} annual declines, which showed an association with the cumulative exposure dichotomized at .0682 ppm-months, this was not found. Although the declines were smaller in GROUP IIB than IIA, statistical significance (two-tailed p-values = .19, .68, and .50 respectively) did not obtain. Estimated mean annual changes for these pulmonary function measurements are presented in Table 17 by exposure group for non-atopics with 14 pack years of smoking. Since large cumulative exposures are associated with participation from the beginning of the study to the later visits, the highest exposure group is possibly a survivor population. Such a selection could explain the non-significant decreases in annual declines from GROUP IIA to GROUP IIB.

With the exception of FVC annual decline, all spirometric annual declines increased with increasing time above .02 ppm treated as a continuous

variable. Using one-tailed tests of significance, p-values for the relationship between FEV_1 , $FEV\%$, FEF_{25-75} and FEF_{50} annual changes after controlling for atopic status and pack years of smoking were .15, .027, .034, and .32 respectively.

Again, using one-tailed tests of significance FEV_1 ($p = .05$), $FEV\%$ ($p = .05$), FEF_{25-75} ($p = .023$), and FEF_{50} ($p = .038$) estimated mean annual declines after controlling for atopy and pack years of smoking were significantly greater (11 ml/year, .15 (yr)⁻¹, 32 ml/sec-yr, and 40 ml/sec-yr) in time above .02 ppm GROUP II (i.e., those participants with time above .02 greater than .19 months) than in GROUP I. At 14 pack-years of cigarette smoking estimated mean annual declines (See Table 18) for non-atopics in GROUP I are 21 ml/year, .31 (yr)⁻¹, 88 ml/sec-year, and 106 ml/sec-year respectively. Thus, as in the dichotomized cumulative exposure regression, FEV_1 and $FEV\%$ annual declines are approximately the same as those expected from cross-sectional results whereas FEF_{25-75} and FEF_{50} declines are greater than expected.

When the time above .02 ppm GROUP II is dichotomized into GROUP IIA and GROUP IIB using a division point of 1 month, annual declines were smaller in GROUP IIB than in GROUP IIA for FEV_1 and FEF_{50} and larger for $FEV\%$ and FEF_{25-75} . In no case was the GROUP IIB decline significantly different at the .05 level from GROUP IIA. Estimated mean annual changes for these pulmonary function measurements are presented in Table 19 by exposure group for non-atopics with 14 pack years of smoking.

Previous authors, notably Fletcher, et al (3), Berry (4), and Berry, et al (5), have noted that observed annual change for FEV_1 is the sum of two components: true annual change and estimation error. The magnitude of the estimation error is determined primarily by length of follow-up, the variability of an individual FEV_1 determination about the true value, and to a lesser extent by the distribution of visits between end points. Fletcher et al (3) estimate the standard deviation of an individual FEV_1 determination about its true values as 160 ml. Berry's (4) estimate, derived from several studies, is 120 ml. Our estimate of 133 ml is comparable to these two.

We have estimated in our 5.5 year study that approximately 50% of the total variability (i.e., variability between observed FEV_1 annual changes) is real variability (i.e., variability between true annual changes) and not due to estimation error. Berry, et al (5) and Fletcher et al (3) also estimate this percentage at 50% for studies 2.5 and 9 years in length, respectively. We expected that Berry's estimate of this percentage would be less than ours because his follow-up was shorter and that Fletcher's would be larger because his follow-up time was longer. This expectation is not realized because the three total variances differ.

Berry's total variance is larger than would be expected from the increase in estimation error caused by the comparatively short follow-up period. Thus, although Berry's real variance as percentage of total variance is the same as in this study, his absolute real variance is larger. This may be due to the cotton dust exposure of his population producing abnormally large FEV₁ annual declines in some individuals. Similarly, Fletcher's total variance is smaller than would be expected from the decrease in estimation error caused by the comparatively long length of his follow-up period. This results in a smaller real variance possibly reflecting the relative homogeneity of his population with regard to FEV₁ annual change. In addition, the statistical methodology employed by Fletcher assigns more of the total variance to estimation error than does our methodology. This would tend to decrease real variability as a percentage of true variability.

Our conclusion is that these three studies for which length of follow-up and variability among true annual changes were quite different, nevertheless, exhibited remarkably comparable standard deviations of a single FEV₁ determination about its true value and that the unexpected comparability of real variance as a percentage of total variance is explained by the differing population characteristics and statistical methodology. In short, the three studies produce no conflicting results.

In a previous annual report dated March 15, 1976, and in Butcher, et al (6), we reported an annual increase in FEV₁ of approximately 55 ml/year. This increase, based on the first five visits, was recognized as being abnormally high but was reported because extensive checking at the time revealed no reason to doubt its validity.

Before proceeding with the analysis reported here, we examined FEV₁ for the 33 participants with complete spirometry at all nine visits in order to determine if there might have been a systematic bias at any of the visits. A graph of the mean FEV₁'s by visit for these 33 participants is presented in Figure 3 together with a least squares straight line fit to the means. This straight line gives an FEV₁ annual change of -21 ml/year. There is an evident peak in mean FEV₁ at the October, 1975, or 5th visit. A linear model as in Fletcher, et al (3), containing a secular bias term for each visit resulted in a significant ($p < .001$) bias term of 134 ml at visit 5.¹ No other visit exhibited a secular bias. A straight line fit to the FEV₁ means for the first five visits results in an annual change of +37 ml/year which together with the now known positive bias at visit 5 suggests that the FEV₁ annual increase reported earlier was due to the systematically high FEV₁'s at visit 5.

We considered not using the visit 5 data in the current analysis but decided against that course for three reasons:

¹ Both FVC and FEF₂₅₋₇₅ also exhibited significant biases at visit 5.

(1) After extensive searching, we have found no explanation for the visit 5 bias; (2) Because visit 5 is approximately midway in the follow-up period, it has little effect on an individual participant's FEV₁ slope provided the participant has at least one data point available on either side of visit 5; (3) when those participants with visit 5 as either their first or last usable visit were not used in the FEV₁ analysis, the results were similar.

C. Diffusion and Lung Volume

One hundred and sixty-five participants had diffusing capacity determinations from three or more visits, and 183 participants had complete lung volume determinations from three or more visits. Tables 20 and 21 present summary statistics on those participants with and without three or more complete determinations for these two sets of pulmonary functions. No important differences between the two sub-groups of participants were revealed.

Of the 165 participants with diffusing capacity determinations, one lacked data on at least one of the explanatory variables and was deleted from the analysis. Similarly, three participants have been deleted from the lung volume longitudinal analysis.

In each of the six regressions RV and (RV/TLC) X 100 annual increase was significantly correlated with pack-years of smoking adding 1 ml/year to the RV annual increase and $.01 \text{ (yr)}^{-1}$ to the (RV/RC) X 100 annual increase. None of the other pulmonary functions (DL_{CO}, K, or TLC) considered were related to pack-years of smoking.

Of the five pulmonary functions considered, only K was significantly ($p < .05$) related to atopic status. This relationship was evident in each of the six regressions with K in the atopics declining approximately $.4 \text{ (min-mmHg)}^{-1}$ per year faster than non-atopics. This finding is inexplicable.

With respect to the exposure indices, TLC was not significantly related to any of the six exposure indices. K and DL_{CO} had a significant ($p < .05$) relation to exposure in all six regressions but it was paradoxical in nature, i.e., annual declines decrease with increasing exposure. RV and (RV/TLC) X 100 were not related to cumulative exposure as a continuous variable or when it was categorized into two or three groups. They both showed a significant ($p < .05$) paradoxical relationship with the time above .02 ppm variables, i.e., annual increases in these two pulmonary functions decreased with increasing time above .02 ppm.

D. Respiratory Symptoms

Four patterns of symptoms as determined by the questionnaire are examined in this analysis:

(1) upper respiratory symptoms: drip at the back of the nose, hay fever or its symptoms, sinus trouble or postnasal drip;

(2) lower respiratory symptoms: usual cough, phlegm, wheezing, attacks of shortness of breath with wheezing, or breathlessness when walking with other people;

(3) bronchitis: usual cough and phlegm more than three months in the preceding year;

(4) dyspnea: Grade 2 or higher where Grade 2 = when hurrying on level, Grade 3 = when walking with others, Grade 4 = stop for breath when walking at own pace.

To be included in the longitudinal respiratory symptom analyses a participant must have had both an initial interview and a final (i.e., the latest of the last three visits) follow-up interview in order to determine respiratory symptom status for each of these visits. Two hundred and three of the total of 274 participants had sufficient information to determine at least one of the four respiratory symptom complexes considered. Table 22 presents summary statistics on these 203 participants and the 71 without sufficient information. There were no important differences between the two groups. One participant lacked data on the explanatory variables and was discarded from the analyses.

Tables 23 and 24 present for each of the four symptom complexes the number of participants in each of the four categories: (1) symptoms present at both the initial and last usable interview, (2) symptoms present at initial interview and absent at last usable interview, (3) symptoms absent at initial interview and present at the last usable interview, and (4) symptoms absent at both the initial and last usable interview. These numbers are broken down by cumulative exposure category using .0682 ppm months as the dividing point in Table 23 and by time above .02 ppm category using .19 months as the dividing point in Table 24. Each table further subdivides the exposure category by atopic and cigarette smoking status.

If a higher proportion of participants in the higher exposure category acquired a symptom pattern between the initial and last usable interview (using those with any type of change as the denominator), this was taken as evidence of an exposure related effect. All four symptom patterns exhibited this effect using either cumulative exposure or time above .02 ppm category to represent exposure. However, statistical significance was not obtained. The lowest p-value was .13 for the relationship between bronchitis and cumulative exposure category.

For upper respiratory symptoms and dyspnea the percentage of participants changing symptom category who went from asymptomatic to symptomatic significantly exceeded 50%. This together with high prevalence rates for upper (38%) and lower (30%) respiratory symptoms at the initial interview suggests a hazardous local environment, either general or work-related, or both. However, we found no statistically significant relationship between acquiring respiratory symptoms and exposure to TDI.

E. Immunology

IgE (I.U./ml) and eosinophil levels (ccm^{-1}) were determined at all nine visits and the first six, respectively. To control for possible seasonal effect on these two variables, a Fall and a Spring average were calculated for each participant. Average IgE levels across participants were higher in the Fall than in the Spring (269.0 vs 155.0, $p < .001$). There was no difference between average Fall and Spring eosinophil levels (227.0 vs 224.0).

Associations were sought between Fall IgE and eosinophil levels with atopy as defined by two or more positive skin test reactions to common allergens, pulmonary function at the time of initial visit, and longitudinal course of pulmonary function.

Fall IgE level was moderately correlated with skin test atopy (point biserial coefficient = .17, $p = .01$) while Fall eosinophil level was not correlated with it (point biserial coefficient = .09, $p = .12$).

Pulmonary function (in percent predicted) at initial interview was not significantly associated with IgE level dichotomized at 300. Only K was significantly associated ($p = .01$) with eosinophil level dichotomized at 250. Those with an eosinophil level less than 250 had mean K percent predicted equal to 101.9 as opposed to 94.4 for those with eosinophil levels greater than 250. No pulmonary function annual change showed a significant relationship between either IgE dichotomized at 300 or eosinophil level dichotomized at 250 after controlling for the cumulative exposure greater than .0682 variable and pack-years of smoking.

V. TDI REACTORS

A. Clinical and Epidemiologic Features

We consider those persons TDI clinically "sensitive" who develop recurrent respiratory signs and symptoms upon repeated exposure to low concentrations of TDI, or in some cases unidentified reactants or by-products of TDI manufacture. The definition must be qualified because some workers develop reversible airways obstruction in the TDI area, obtain relief upon transferring to other areas, but fail to react to pure TDI vapor in bronchoprovocation challenges.

TDI is an irritant and is detectable in relatively low concentrations by non-sensitized persons. This probably explains why sensitization is most often described by the subject as a "loss of tolerance" to the material. Dry cough is the most frequent symptom, but chest tightness, exertional breathlessness, wheezing and shortness of breath are also common. Orthopnea is usually present in nocturnal attacks. Sputum is uncommonly reported unless it was present prior to sensitization. Reduced strength or stamina were common complaints of those who continued to have TDI exposure, and these symptoms abated following cessation of exposure.

A delay of about one-half hour was the most commonly reported interval between known exposure and onset of symptoms. A majority of persons, however, reported increased symptoms after leaving the plant, suggesting either a dual or late reaction. Immediate onset, that is, within a few minutes of exposure, was rarely reported.

Of 277 persons in the study population, 12 men (4.3%) became clinically "sensitive" to TDI (see Table 25). Nine of these 12 men became sensitized after less than 12 months of TDI exposure, eight of those after less than four months of exposure. Six of the 12 had known major exposure in TDI spills. Three of the 12 were atopic, that is, had two or more positive reactions to skin testing with common inhalant allergens. Six persons underwent bronchoprovocation challenge with pure TDI vapor: two of these reacted, and four did not react, to levels of less than .02 ppm. Five of the 12 had never smoked. The sensitized persons were rather evenly divided between operators in the TDI area and maintenance workers in the same area. The lone sensitized subject from outside the TDI area was a chemical engineer who may have been exposed in laboratory work.

Figures 4 and 5 display the results of longitudinal lung function testing for the nine TDI clinically "sensitive" individuals with lung function testing after sensitization. Eight of the 12 sensitized men were tested prior to start-up of TDI production, and therefore prior to exposure. The others were transferred

into the TDI area or hired at different times, and were first studied at the succeeding visit for data collection. Three subjects (numbers 110, 197, and 200) have shown declines in both FEV₁ and FEF₂₅₋₇₅ despite removal from the TDI area. Two subjects (033 and 035) have shown stable FEV₁ values but declines in FEF₂₅₋₇₅. Four persons show stable to slightly increasing values for FEV₁ after removal from TDI exposure. Two of the subjects still work in the TDI area and both have stable expiratory flow rates.

Under the present conditions, however, removal from the TDI area cannot be considered an absolute guarantee of no further exposure. Large accidental TDI emissions and certain wind conditions can disperse the material to other parts of the chemical complex. Perceptible amounts of TDI can also be detected around workers with contaminated clothing and shoes, and this can be responsible for temporary contamination of such facilities as lunch rooms and the medical department. There are thus opportunities for intermittent, low-level exposures to TDI or to other materials from TDI synthesis, in distant areas of the chemical manufacturing complex.

B. Immunologic Findings

In this longitudinal study, immunologic tests were performed to determine whether exposure to TDI had an effect on total immunoglobulin levels; whether presence of atopy was a factor in development of TDI "sensitivity"; whether total blood eosinophil levels alter following exposure to TDI; and whether development of humoral antibodies was a mechanism in TDI "sensitivity."

The results of skin testing with common inhalant allergens showed that there was a similar distribution of atopic individuals among the various exposure groups and that this presence of atopy was not a factor in development of TDI "sensitivity" (7, 8). Total blood eosinophil counts were not significantly altered by exposure to TDI (8). Immunoglobulins G, A, M, D, and E were not significantly changed by TDI exposure (8, 9, 10). Quantitation of specific antibodies was undertaken by skin testing with a TDI-human serum albumin (TDI-HSA) conjugate. Results of skin testing indicated that TDI-HSA was a poor antigen and that anti-TDI antibodies of IgE type could not be detected using this material (9). Further, the radioallergosorbent test (RAST) was of little use with this antigen. Prausnitz-Küstner (P-K) testing in monkeys was also evaluated as a method for determining development of TDI specific IgE antibodies. All results were negative (9). Passive cutaneous anaphylaxis (PCA) in guinea pigs was used to detect heterocytotropic antibodies. No positive PCA tests were obtained on serum samples from workers following exposure (9).

C. Provocative Inhalation Challenge with TDI

During our prospective studies we found that approximately 5% of workers developed clinical "sensitivity" (i.e., they complained of wheezing and shortness of breath when in a TDI containing area) (9). These subjects, where possible, were challenged with TDI (3, 10). They were brought to Tulane University and exposed for 15 minutes to saline vapor on day 1, 0.005 ppm TDI on the second day, and on subsequent days to 0.01 and 0.02 ppm until a 20% drop in FEV₁ was observed. Expiratory flows were derived from a forced vital capacity maneuver and determined with an electric dry rolling seal spirometer which provided output for volume-time and volume-flow plots of maximum forced expiration. Peak flow was also determined in a separate maneuver using a Wright's peak flow meter. Lung function testing was performed prior to exposure, and at 5, 10, 15, 30, 45, 60, 90, and 120 minutes and thereafter at hourly intervals following challenge. The workers were challenged in a single blind fashion in an exposure chamber with dimensions of 2.25 X 1.89 X 2.55 meters (10.84 m³) which was under slight negative pressure (Figure 6) (10). The atmospheres of TDI were generated by controlled evaporation of TDI accomplished by passing air over the surface of TDI contained in a 250 ml gas washing bottle with effective surface area 60.8 cm². The flow rate was controlled by a calibrated rotameter at between 2 to 6 liters per minute, depending on concentration of isocyanate vapor required. Circulation was obtained by a small fan; temperature in the room was maintained at 23 to 24° C and humidity was 45 to 55%. TDI quantitation was accomplished with a model 7000 TDI monitor. The subject was seated throughout the challenge with his breathing zone close to the end of the monitor to ensure accurate measurement of the concentration of TDI inhaled. Throughout the challenge, the subject was observed through a glass window in the air lock door by a physician. Persons reacting to TDI inhalation challenge showed three types of response (6, 8, 11). A total of 28 TDI clinically "sensitive" individuals (six of whom were in the original study population) were tested by provocative inhalation challenge with TDI. Of these 28 persons tested, 10 reacted to TDI with a drop in FEV₁ of greater than 20%. Six showed an immediate bronchospastic response, beginning within 15 minutes after the challenge. In two workers, a late response was seen beginning at least one hour after the challenge and, in a further two individuals, a dual response was seen with the characteristics of both the immediate and late reaction. In some individuals, a dose response was also seen, i.e., challenge with 0.005 ppm did not elicit an adverse response but challenge with 0.01 ppm would elicit a bronchospastic reaction (Figure 7).

D. Challenge Testing with Methacholine Chloride (Mechoyl)

A total of 10 workers reporting "sensitivity" to TDI and 10 non-sensitive, non-exposed workers were challenged with methacholine at the work plant. Seven of the ten "sensitive" individuals responded to challenge with a greater than 20% drop in FEV₁, whereas only one of the 10 non-sensitive workers reacted (12).

All subjects were tested for pulmonary function prior to commencement of challenge and demonstrated baseline flow parameters within 80% of predicted normal values. Five breaths of physiologic phosphate buffered saline were inhaled through a Bird Mark 8 nebulizer and lung function was measured at 1, 5 and 3 minutes after administration. Methacholine was administered, starting at a concentration of 5 and increasing through 10 to 25 mg/ml. One breath of the 5 mg/ml solution was followed by progressive increases in number of breaths with each of the three concentrations to a maximum of five breaths of the 25 mg/ml concentration. The procedure was stopped when either a 20% drop in FEV_1 occurred or, in the absence of any airway response, when the maximum of five breaths of 25 mg/ml was reached. Methacholine dose response regression slopes were graphed for the subjects, where possible, with a cumulative breath unit equivalent to one breath of 1 mg/ml methacholine on the abscissa and percentage drop in FEV_1 on the ordinate (11). All subjects who were shown to be reactive to TDI by provocative inhalation challenge also demonstrated high sensitivity to methacholine.

E. Study of the Effect of Pretreatment with Disodium Cromoglycate:

Some of the workers reacting to TDI were pretreated with 40 mg of disodium cromoglycate (DSCG) which was administered by spinhaler 30 minutes before re-exposing to the concentration of TDI which had initiated the adverse pulmonary reaction. Workers with both immediate and dual responses were tested. Lung function measurements were determined as for the regular TDI inhalation challenge. In all three TDI reactive individuals tested, (two showing an immediate response to the challenge with TDI and the one showing a dual response) their adverse bronchial responses were inhibited by pretreatment with disodium cromoglycate (11, 13) (Figure 8).

F. Lymphocyte Transformation and Leukocyte Histamine Release:

Cellular studies included lymphocyte transformation following exposure of cells to the TDI-HSA conjugate and histamine release from leukocytes following exposure to TDI-HSA was measured. These tests were performed on samples collected from individuals reporting "sensitivity" to TDI. No lymphocyte stimulation was measured and no histamine released from leukocytes was detected (6).

G. Lymphocyte cAMP Dose Response Studies:

As previously reported (12, 14), we showed that TDI acts as a partial adrenergic agonist, however, this effect was seen with cells of normal individuals. We therefore examined the effect of TDI upon lymphocytes from TDI reactive individuals. Quantitation was performed by means of a method

developed in our laboratory (14) where lymphocytes were separated by Ficoll-Hypaque density gradient centrifugation, incubated with dilutions of isoproterenol, prostaglandin E₁ or TDI, followed by washing, precipitation with trichloroacetic acid, freeze thawing, extraction with ether, and quantitation by radioimmunoassay. Results were interpolated from a standard graph and expressed as percent stimulation of cAMP formation. Dose response regression lines were determined by means of the linear ascending portion of the slopes. Blood samples for lymphocyte cAMP dose response studies of TDI reactors were obtained prior to, and at 15 and 120 minutes after provocative inhalation challenge (PIC). In lymphocytes of the two TDI reactors tested to date, dose response slopes following stimulation with either TDI, isoproterenol or prostaglandin E₁ were markedly reduced when compared with those of normal individuals and non-TDI reactors (Figure 9). Dose response slopes did not differ from pre-exposure baseline levels, following challenge with TDI (11).

H. Plasma Histamine Levels:

Samples for venous plasma histamine determination were collected prior to exposure, and at 1, 5, 10, 15, and 120 minutes after exposure. Histamine was determined by the enzyme isotopic method of Beaven, et al, with an internal control of ³H-histamine to measure recovery (15). All samples from individual patients were assayed in quadruplicate. Plasma histamine levels of six subjects were tested. Two were individuals with a strong history of TDI sensitivity who reacted to provocative inhalation challenge (PIC) with TDI. Two had a weak history of sensitivity and did not react to PIC. In no case was histamine release into venous plasma demonstrable following inhalation challenge with TDI. Baseline plasma histamine levels were all within normal limits (11).

I. Determination of Serum Complement and Split Products of Complement

Functional levels of total complement (CH₅₀) were quantitated by standard techniques in fresh serum or serum frozen at -70° C on samples collected before exposure and 1, 5, 10, 15, and 120 minutes after TDI exposure (11). A hemolytic assay was also used to measure the alternative complement pathway proteins (APCH₅₀). Split products and factor B in plasma were measured by an immunoelectrophoretic assay and split products of C3 were determined by the counterimmunoelectrophoretic assay of Arroyave and Tan. Two TDI reactors and five persons demonstrated to be negative by provocative inhalation challenge were tested. Baseline CH₅₀ and APCH₅₀ levels were all within normal limits (60 to 120 and 15 to 45 units, respectively) for all workers and no significant changes in these complement levels were seen following inhalation challenge with TDI (11).

J. Loss of TDI and Methacholine Reactivity after Removal from Isocyanate Exposure:

One of the TDI reactive individuals, who had been studied intensively, has been followed longitudinally after moving to a new job which does not entail exposure to isocyanates. This individual reacted originally to an exposure for 10 minutes of 0.005 ppm of TDI with an immediate bronchospastic response. He was highly sensitive to methacholine, showing a 38% drop in FEV₁ when he received one breath of 5 mg/ml of methacholine (16).

Six months after removal from an isocyanate containing environment, he was re-challenged with TDI and did not react to 15 minutes exposure to 0.02 ppm of TDI. He was re-tested for methacholine sensitivity and it was found that three breaths of the 5mg/ml concentration were required to initiate a 20% reduction in FEV₁. After a further six months (i.e., one year following removal from TDI), he was again tested by methacholine challenge. At this testing, he failed to react to 3 breaths of 25mg/ml of methacholine.

Concurrent with methacholine and TDI inhalation challenges, blood samples were drawn for cyclic AMP dose-response slopes following stimulation of his lymphocytes by prostaglandin E₁, isoproterenol and TDI. Initially, he was shown to have a markedly reduced dose response slope to all three agonists compared with normals. Six months later, there was a slight improvement in the dose response slopes. The results of the dose response slopes on his latest testing await completion.

K. Concurrent Development of Food Allergy and Isocyanate Reactivity

A further interesting aspect of this worker was that he claimed to have become highly sensitive to radishes at about the same time he became sensitive to TDI. He was challenged by permitting him to eat one small 5 gram radish and pulmonary function testing was performed. He had an immediate severe reaction following one bite of the radish with a 75.4% decrease in FEV₁. He now reports that, at one year following removal from the TDI area, he has eaten a radish which is approximately four times as large as the one used in the testing with no ill effects. Interestingly, radishes contain allyl isothiocyanate and benzyl isothiocyanate (17). A manuscript reporting our findings with this worker is in preparation (18).

L. Tolyl-specific IgE Antibodies in Serum of TDI Reactive Individuals:

We assisted Dr. M. Karol of the University of Pittsburgh by providing serum samples from TDI reactors to enable her to develop a new

antigen for RAST. This antigen consists of p-tolyl isocyanate conjugated to human serum albumin (TMI-HSA). The serum samples we supplied were from highly reactive individuals. Four of the five serum samples sent to Dr. Karol were shown to contain tolyl-specific IgE antibodies (19). Using antigen provided by Dr. Karol, we were able to confirm these results on the same serum samples in our laboratories. Later we prepared our own TMI-HSA antigen and compared this with the antigen produced by Dr. Karol. The Pearson's correlation of coefficient test was applied to the results of RAST using the same sera with both antigens. A value of 0.96 was obtained, indicating that our antigen was essentially identical to that produced by Dr. Karol. Using our antigen, we tested serum samples from a total of 26 individuals who had been shown by ourselves and another center to be reacting to provocative inhalation challenge with TDI. Depending on the method of evaluation of the results of the RAST, only 15 to 18% of the individuals were shown to have tolyl-specific IgE antibodies (20) (Figure 10). These results show that there are antibodies involved in TDI asthma in a few individuals but would suggest that a humoral mechanism is not the definitive mechanism of TDI reactivity.

In summary, our studies of TDI "sensitive" individuals show that asthmatic reactions can be elicited by brief exposure to very low concentrations of TDI. These reactions may be immediate, late or dual reactions such as those induced by avian protein, certain organic dusts or Aspergillus fumigatus allergens. However, our negative findings with plasma histamine and complement are evidence against an immunologic mechanism. Our findings, that persons who react to TDI are also reactive to methacholine, confirm that TDI reactive individuals have irritable airways. However, our demonstration that not all methacholine sensitive individuals react to TDI suggests that reactivity to TDI is not a non-specific reaction (11). Whether methacholine reactivity is pre-existing or develops concurrently with development of sensitivity to TDI is not known and awaits results of prospective studies although the results of our longitudinal study of one sensitive worker suggest the latter (N).

The demonstration of the partial agonistic activity of TDI (12,14) is of great interest. TDI reactive individuals have decreased adrenergic agonist dose-response slopes which are associated with in vivo responses to TDI challenge (11). These results are in agreement with current concepts of asthma. Szentivanyi's theory of the mechanism of asthma proposes that a defective beta adrenergic response is present in asthmatic individuals and that this deficiency may be responsible for two effects: First, it may prevent production of sufficient levels of cyclic AMP in mast cells to protect against release of pharmacological mediators such as histamine and slow reactive substance of anaphylaxis which are ultimately responsible for the bronchospastic response. Second, a deficiency in the ability to produce cyclic AMP can have a deleterious effect on the delicate cyclic nucleotide

balance required to maintain smooth muscle tone. Thus, our studies of TDI reactive individuals, to date, suggest that the most likely mechanism of TDI asthma is pharmacologic rather than allergic, although the latter possibility still cannot be excluded.

Our findings that DSCG may inhibit asthmatic reactions under controlled conditions (11, 16) agree with the concept of the action of this drug and suggest that DSCG may be a useful prophylactic measure for workers who develop TDI reactivity. Expanded testing in both the laboratory and the field will be necessary before a definitive statement can be made however.

Our findings in the worker who has been studied extensively following removal from the TDI containing area, suggest that TDI reactivity is reversible when the isocyanate exposure is stopped (18). The demonstration of increased reactivity to methacholine and diminished cAMP dose response suggests that TDI in some way acts to alter receptors on the cells to cause decreased cholinergic and adrenergic function. The loss of methacholine sensitivity suggests that this effect of TDI upon receptors may be transient and may be reversed, with the worker reverting to his prior health following removal from isocyanate exposure. Similar loss of bronchial hyperreactivity has been demonstrated following removal of reactive individuals from Western red cedar wood dust exposure.

VI. CONCLUSIONS

(1) Throughout the five-year period of this study, a comprehensive environmental survey of the plant and its workers using state of the art, continuous area and personal monitors demonstrated that all workers in the study population had some degree of TDI exposure, which depended upon job and location. There were frequent excursions above the current threshold limit value of 0.02 ppm ceiling. These exposures occurred even though the plant is modern and uses currently available control technology.

(2) During annual one-month periods of concentrated maintenance activity in which the plant is completely overhauled, there were higher than usual TDI concentrations measured at the breathing zones of maintenance workers.

(3) Although there was daily variation in TDI concentration, there were no systematic exposure trends demonstrated over the five-year period of the study.

(4) In this five-year longitudinal study, FEV_1 , $FEV\%$ and $FEF_{25-75\%}$ annual declines are significantly related (after controlling for smoking and atopic status) to TDI dose, where dose is measured by either (a) two cumulative exposure categories (division point = .0682 ppm-months) or (b) two "time above 0.02 ppm" categories (division point = .19 months).

(5) FEV_1 and $FEV\%$ annual declines in the high exposure categories were not significantly different from annual declines predicted for members of the general population from cross-sectional studies. FEF_{25-75} and FEF_{50} annual declines were significantly greater than expected in both exposure categories. K (diffusion constant) annual decline was significantly greater than expected, but was inexplicably negatively related to dose. The same held for RV and RV/TLC annual increases. TLC annual change showed a significant increase instead of expected no change.

(6) TDI dose as estimated by cumulative exposure and peak exposure as measured by time spent above 0.02 ppm correlated equally well with annual change in lung function.

(7) FEV_1 , FVC, RV and RV/TLC annual changes were significantly related to pack-years of cigarette smoking with associations in the expected direction. Only K annual decline was related to atopic status and that association was an inexplicable negative one.

(8) Prevalences of bronchitis and dyspnea increased from pre-exposure baseline in the high exposure category, as measured by cumulative exposure, to a greater extent than in the low category. These differences in symptom increases between exposure categories were not statistically significant (p-values equal to .13 and .18, respectively).

(9) Clinically important bronchial hypersensitivity to TDI developed in 4.3% of the study population, usually within a few months of first exposure.

(10) Neither atopy nor smoking served to identify persons at higher risk of developing TDI reactivity. Half of the TDI reactors had been exposed to high levels during a spill or equipment malfunction.

(11) Some TDI reactors have failed to attain pre-exposure or pre-sensitization values of FEV_1 or $FEF_{25-75\%}$, despite transfer to other areas in the chemical complex.

(12) There is persuasive clinical evidence for sensitization in some persons who fail to react to low concentrations (less than or equal to 0.02 ppm for 15 minutes) of pure TDI vapor in the exposure chamber.

(13) TDI, at certain concentrations, acts as a partial agonist upon lymphocytes to stimulate cyclic adenosine monophosphate levels. At lower concentrations, it can block cyclic AMP stimulation by isoproterenol, and prostaglandin E₁ but not histamine.

(14) TDI reactors are hypersensitive to methacholine (heightened bronchoconstriction as determined by a standard inhalation multiple breath technique), but not all methacholine sensitive individuals are TDI reactive.

(15) Lymphocytes of TDI-sensitive individuals have decreased ability to respond to cyclic AMP stimulants such as the beta agonists isoproterenol, prostaglandin E₁ and TDI.

(16) Provocative inhalation challenge studies show that airways reactivity to TDI is reproducible in the laboratory environment and can be blocked by disodium cromoglycate. During bronchial reactions, no changes in serum complement components are observed and there is no release of histamine detectable in peripheral plasma.

(17) RAST with p-tolyl isocyanate conjugated to human serum albumin only detects tolyl specific IgE antibodies in serum of 15-18% of subjects proven by provocative inhalation challenge to be TDI reactive. Thus, demonstration of tolyl specific serum IgE antibody cannot be used to diagnose clinical sensitivity to TDI.

(18) In addition to the above mentioned immunologic and pharmacologic activities, TDI does not appear to have an effect upon:

(a) Induction of specific antibodies in man as demonstrable by hemagglutination, RAST, Prausnitz-Küstner, passive cutaneous anaphylaxis or direct skin testing with TDI human serum albumin conjugates.

(b) Changes in levels of serum IgG, A, M or E.

(c) Induction of non-specific histamine release from leukocytes in vitro or in vivo.

(d) Induction of peripheral blood lymphocyte blastogenic transformation employing cells from "sensitive" subjects.

ENVIRONMENTAL CHARACTERIZATION

A. Introduction

This report summarizes the environmental characterization activities in a new TDI manufacturing plant for a period of five years (1973-78). This exposure characterization survey was perhaps the most extensive and thorough survey undertaken of any TDI manufacturing plant in the world. Vast amounts of data were collected using the best and the state of the art monitoring techniques and methods. During the course of the study several papers were published (21-27), covering various aspects and findings of environmental characterization as related to the other parts of the study. Five annual progress reports containing environmental characterization sections have also been submitted.

As expected in such longitudinal studies, the study goes through an evolutionary process. During the period of five years there were tremendous advancements made in the fields of personal and area monitoring, laboratory and field calibration of monitors, and also the recognition of the advantages and limitations of the measurement techniques. Also during the study, the Tulane industrial hygienist developed a good rapport with his counterpart in the plant and also with the supervisors, shift foreman and other workers of the plant. Better insight was gained about the administrative set up and manufacturing operation of the plant. Appropriate refinements and changes in environmental characterization survey had to be made throughout the course of the study to adapt to these evolutionary changes. This progress report will delineate these evolutionary changes during the study and the necessary refinements made to accommodate these changes.

B. Monitoring Techniques

At the time of the writing of the proposal, the method widely used for analysis of TDI in air was a wet chemical method based on impinger sampling and colorimetry developed by Marcali (23). Until recently this was the standard recommended method for analysis of TDI. Because it is an impinger sampling method it is not ideally suited for personal sampling and the method can give only the integrated time weighted average. During the latter part of 1973 a continuous paper tape monitor for area measurement of TDI became commercially available. This instrument is based on a paper tape method developed by Reilly in 1963 (29). Three of these portable area monitors were acquired for the study. The TDI monitor based upon an original design by Dunlap Limited, in collaboration with ICI, Ltd. of U.K., continuously monitors concentrations of TDI in the atmosphere in the range of 0.0 to 0.08 ppm. It has a meter readout

as well as audible and visible alarms and output connections for an external recorder. Sensitivity and specificity to TDI is obtained by utilizing a continuous reel of chemically impregnated paper tape to sample the air. The tape is supplied in a cassette which will run for 168 hours or one week continuously.

In operation, the metered volume of atmosphere is drawn through the tape as it moves past the exposure orifice. If TDI is present, a stain is developed on the tape; the intensity being proportional to the concentration of TDI. The exposed tape then moves past two photo detectors. One detector measures reflected light from the unexposed half and the other from the exposed half. The two signals are compared electronically and an output signal, proportional to the TDI concentration compensated for minor tape variations, is displayed in parts per million of TDI. The concentration is also continuously recorded on a strip chart recorder. A typical recorder printout is given in Figure 11.

This was a major development in monitoring of TDI. These monitors were initially evaluated in the laboratory. For the evaluation the monitors needed to be dynamically calibrated in the laboratory. There were no simple methods available at the time to generate standard atmosphere of TDI for dynamic calibration. Therefore, the diffusion cell method based on the work of Allshiller and Cohen (30) was used to generate standard atmospheres of TDI and was subsequently used to dynamically calibrate the monitors (25). Although no exhaustive interference study was performed at this time, under ideal conditions of the laboratory the monitors correlated ($r = .994$) well with the standard Marcali method. The monitors were then evaluated in the field against the standard method by simultaneous sampling at various locations. Although the correlation ($r = 0.81$) in the field testing was not as good as in the laboratory looking at the graph of concentration by standard method vs the monitor indicates (see Figure 12) that at higher TDI concentrations ($> .005$ ppm) the Marcali method was reading consistently higher than the paper tape monitor. This could be explained by the positive interference in the standard method due to the primary aromatic amines. The primary aromatic amine (Toluene diamine) can be potentially present in the air because it is one of the raw materials used in the manufacture of TDI and it can also be formed by the hydrolysis of TDI itself either with moisture or by hydrochloric acid in the air. Hydrochloric acid can be in the air because it is one of the by-products in the manufacture of TDI. Although not confirmed by our unit, it has been reported that the toluene diamine does not interfere with the paper tape monitor method. Therefore, it was concluded the standard method would be overestimating the TDI concentration and cannot be used for TDI exposure characterization. Since then, the paper tape monitors were used exclusively for measuring exposures to TDI.

C. Area Monitoring

Three model 7000 TDI Area Monitors (31) were used beginning August, 1973, until the end of 1975. The TDI Drumming Building and several locations in the plant were monitored. The concentration profile for the two years (August 73 to July 75) in the plant and the Drumming Building is given in Figure 13, where the ordinate indicates the "weekly time weighted averages" expressed as ppm TDI and the abscissa the dates. It is clear from Figure 13 that there is no consistent pattern of exposure. There are a few discontinuities in the profile; they represent periods where no exposure data are available because of breakdown or malfunction of the TDI monitor. The levels of TDI both in the plant and the Drumming Building vary randomly and the exposures for the operators in the Drumming Building are different and independent of the exposure levels for the plant operators.

During this period there were a number of excursions above the proposed threshold limit value (TLV) of 0.005 ppm TWA and also a few excursions above the current TLV value of 0.02 ppm. The percent excursions of weekly time weighted averages above both these levels is given in Table 26. Although from Table 26 it appears that in general the operators working in the plant have higher TDI exposures than those working in the Drumming Building, the table could be misleading for the following reasons: (1) The plant's physical structure is open and unprotected and direction, wind speed, humidity, temperature and precipitation. The Drumming Building is a closed system and the wind direction, wind speed and precipitation will have minimal effect on the concentration inside the building. (2) The operators in the plant are not stationary at one location in the plant; they move around considerably. In the Drumming Building, the operator's movements are localized and restricted. (3) The plant is much more complex with multiple potential sources of emissions of TDI. To completely characterize and define the environmental levels of TDI, several area monitors would be needed. Even then, since the operators move about the plant it would be extremely difficult to monitor the exact individual exposure. The obvious alternative for quantitation of dose each worker receives is through personal monitoring which will be discussed in the following section.

In order to evaluate whether the levels of TDI in the plant and the Drumming Building have increased or decreased an histogram or a frequency distribution of the weekly time weighted averages was prepared, showing the number of weeks for each exposure interval. The two-year period was divided to coincide approximately with the pulmonary function and clinical tests of the workers. The histograms for the plant and the Drumming Building are shown in Figures 14 and 15 respectively. The mean value and the standard deviation for each time period is shown along with the histogram. The values indicate that there was little improvement in TDI levels in the plant until March, 1975, and in the Drumming Building there was slight increase in the exposure levels at that time.

The area monitoring activities were suspended for the studies because as is shown later on in this section, there was no correlation at all because the area monitor estimates of exposure to personal breathing zone estimates of concentration for people working in any general area where the area monitor is located.

D. Personal Monitoring

In June of 1975, continuous TDI personal monitors, based on the paper tape method, capable of continuously monitoring TDI; in the breathing zone of workers for up to eight hours, became commercially available for the first time. Our group acquired 12 personal monitors (Model MCM 4000) along with a reader/recorder (Model MCM 4100); a required accessory to get the exposure profile. The personal TDI monitor essentially works on the same principle as the area TDI monitor. The only differences are in the personal monitor the tape moves at a rate of 2 cm/hr compared to 10 cm/hr in the area monitor. However, in order to compensate for the stain intensity the sampling rate of personal monitor is 100 ml/min compared to 500 ml/min for the area monitor. The personal monitor only collects the air sample on paper tape. After the collection period, the stain intensity on the paper tape is read using the reader recorder. The concentration profile is recorded on a chart paper called the TDI Datagram. A typical datagram is shown in Figure 16. The datagram also electronically integrates the area under the curve and records the total dose for eight hours in ppm-hrs unit. In other words, the datagram provided by the personal TDI monitor, gives a total history of the TDI exposure to the worker for eight hours on a work shift.

The TDI personal monitors were thoroughly evaluated in the laboratory before they were routinely used in the field. The flow rates were checked and adjusted and the battery packs were checked to see if they are capable of sampling at 100 ml/min for eight hours when they are fully charged according to manufacturer's specification. The rate of movement of the tapes was checked in all monitors and was confirmed to be 2.0 cm/hr. The monitors which could not sustain 100 ml/min flow rate or if the tape movement was erratic were sent back to the manufacturer. The reasons for not sustaining 100 ml/min could either be because of a bad battery or because of breakdown of the pump. In either case, appropriate measures were taken to assure proper performance of the personal monitor. The personal monitors were also dynamically calibrated against the standard method. The details of calibration are given in the next section.

Beginning in July, 1975, the workers in the TDI plant, TDI Drumming Building and Tank Farm, Hydrogen and Carbon Monoxide (HYCO) plant, Toluene diamine (TDA) plant, Phosgene plant, Hydrazine plant and all the maintenance personnel in these plants were monitored almost continuously till the middle of 1978 (three years). Programming schedules were drawn up for six month

periods in advance. The plant manager, superintendent, safety director and all senior supervisors and shift foremen were given a copy of the schedule. A typical schedule is given in Table 27. The personal samplings were done based on the job title rather than the personnel. In this plant, each job title associated with a certain plant uniquely defined a certain job function. All the job titles in the TDI plant, TDI Drumming, HYCO, Phosgene, TDA plants were monitored. All the job titles were monitored during all the three shifts (8-4, 4-12, and 12-8), except the maintenance, drumming personnel and the control population. The maintenance and drumming personnel work only during the day shift and so were monitored only in day shifts. The control population were also personally monitored only in the day shift.

Before embarking on a comprehensive personal monitoring survey, a study was made to determine how well the area monitoring data in the plant and Drumming Building and personal monitoring of job titles who should be working in the respective areas compared. In other words, whether the TDI levels measured by area monitors truly reflected the personnel exposures. Table 28 summarizes the results of this study. It clearly shows that the area monitors cannot be reliably used for measuring worker exposure. Even those 8-hour-TWA where the correlation was good between area and personal monitors inspection of the respective concentration profiles revealed that the integrated TWA correlation was only coincidental. The individual peaks and excursions were not similar in the datagram and the area monitor strip chart. This study reinforced the need for extensive personal monitoring for exposure characterization.

E. Quality Assurance Programs for Monitoring

(1) General Precautions:

Recognizing the importance of quality control in data collection for such long range prospective studies appropriate measures were taken early in the study. Quality control checks and measures were made in every step of data collection. The technician responsible for checking and issuing the area and personal monitor was given a written protocol of the procedures. He was properly instructed and trained to use the monitoring instrument in terms of calibration, testing of optics, flow rate, zero adjustments, changing of tapes, testing tape movement, etc. The technician maintained a log book, where he entered date, monitor number, calibration, flow rate adjustments and any other relevant adjustments he makes to the personal monitors before it is issued to the workers. He notes the time, date, the monitor number and the name of the person it was issued to for that day. During the shift the monitors were randomly checked to see if they are properly worn. At the end of the shift, the flow rates are checked

again and noted. Within 24 hours after collection, the paper tapes are read in the reader recorder. During that time, the paper tapes are stored in the dark. As soon as the paper tape is read, the name, job title, the date, shift, time of monitoring and the location of work is entered on the datagram in the field. The datagrams were then checked by the industrial hygienist at Tulane and then were read and coded for storage in computer. The analysis of the personal monitoring and other data is described elsewhere in the report. All the personal monitors were sent back to the manufacturer for service maintenance and quality control after about 18 months use.

(2) Calibration

The area and personal monitors were routinely calibrated according to the manufacturer's specification. In the case of area TDI monitor the calibration is checked every day with the "calibration strip" provided with the instrument and the flow meter is checked and necessary adjustments made if necessary. In the case of personal monitors, the battery packs were charged for 14 hours at the end of every eight hour use. The flow rate of the personal monitors were checked using a calibrated rotameter before and after each use. The reader recorder is properly zeroed and the calibration checked before using each day.

In order to establish that the "calibration strip" provided by the manufacturer is accurate, the area monitor is first calibrated with the "calibration strip". Then it is dynamically calibrated against the Marcali method by generating an atmosphere of known TDI concentration. Initially, the standard atmosphere of TDI was generated using the diffusion cell method. Later on in the study a new and more convenient generating method based on permeation was developed (6). When both the area monitor and the Marcali method indicate within experimental errors the same concentration, it is assumed the monitor is calibrated; if not, the standard method concentration is assumed correct and the reasons for differences are investigated. The personal monitors along with the reader/recorder system were also dynamically calibrated the same way.

(3) Interference Studies

One of the reasons for not using the standard Marcali method for exposure characterization is because the primary amines such as toluene diamine positively interfere in the determination. The toluene diamine (TWA) is a potential air contaminant in the manufacture of TDI because TDA is one of the raw materials used. TDA can also be produced in the air by hydrolysis reaction of TDI with moisture or HCl in the air. Relative humidity levels in the plant range between 70-80% through the year. Hydrochloric acid also can potentially be present in the air because for every mole of

TDI manufactured, four moles of HCl is obtained as a by-product. HCl will readily hydrolyze TDI to TDA.

In the paper tape method, TDA is not an interferent. Investigation in our laboratory has shown that chlorine and nitrogen dioxide react with the paper to produce a diffuse brown stain. This brown stain is distinctly different from the characteristic bluish-purple stain produced by TDI. The technician handling the paper tape for the personal monitor was specifically instructed to check the tapes usually for unusual stains and void them if there were any on the tapes. Also a preliminary survey of chlorine concentrations in the air was made using Matheson-Kitagawa chlorine detector tubes. Generally, the chlorine levels at different locations in the plant were less than the detection limit of 0.3 ppm at which level the interference in the monitor is not significant. Figure 17 shows the extent of interference of chlorine and nitrogen dioxide with the paper tape monitor.

How many units?
2 Ref

(4) Evaluation of Response of Reader/Recorder for Personal Monitor Tape

The miniature continuous paper tape personal monitors (Model MCM-4000) and the Reader/Recorder Model MCM-4100 were evaluated for short term response on exposures to TDI. This kind of an evaluation was felt to be very important because in the real life situation the monitor is seeing an environment where the concentration of TDI is rapidly fluctuating and changing in time and space. At the end of the work shift when the tape is removed from the monitor and fed into the reader/recorder the recorder draws out a nice datagram in 30 seconds as shown in Figure 16. Until now, no one has investigated the degree of accuracy with respect to time, resolution and a combination of time-concentration exposure patterns. The personal monitor has been dynamically calibrated at known concentrations for long periods of time and it has been proved that it reads accurately. This kind of testing does not tell anything about short-term responses, resolution of peaks, or effects on peak broadening, etc. This kind of analysis was important for the study because in one of the analyses of the exposure data we were interested in the amount of time an operator spends above levels of .005, .01, .02, .04, .06, and .08 ppm. The study has revealed a significant limitation of the personal monitoring system. Figure 18 will be used to explain this limitation. As an example, if a worker wearing the monitor were to be exposed as follows (see Figure 8), 0-10 mins at 0 ppm exposure; 10 to 30 mins at .02 ppm exposure, 30 to 40 min at 0 ppm exposure, and 40 to 50 min again at .02 ppm. Figure 18 shows approximately the shape of peaks obtained compared to what theoretically should be obtained. The worker has been exposed to 30 mins at .02 ppm. Thus, the times measured will be underestimated at lower concentrations. These kind of errors is both time and concentration dependent. Thus, every time the concentration changes up or down because of this response and resolution effect the time estimated would be erroneous. These kinds of rapid changes in concentration and time exposed

is a very feasible situation in the TDI plant. We also noted that in spite of the peak broadening and shortening effect, the total dose which is the area under all the peaks is correct. Therefore, the calculation of the time weighted average concentration is correct.

The reasons for these response effects are:

(a) Because the paper tape in the personal monitor moves at a speed of 2 cm/hr, the whole history of exposure for 8 hours is recorded in 16 cm length of the tape.

(b) The tape runs through the reader/recorder at a speed of a 1 cm/second. In other words, the eight hours of exposure history is read in 16 seconds.

(c) The recorder pen does not respond with the same speed. Therefore, the time estimate errors are amplified at higher concentrations and lower times of exposure. At concentration less than .01 ppm, the errors do not seem to be very significant.

(d) Because the photometer scans the stain throughout its length, the peak broadening compensates for peak height and the total effective area under the curve is measured accurately. Therefore, the total dose and time weighted average measurements are accurate.

In spite of these limitations considering the accuracy of TWA measurements, the capability of indicating the exposure profiles and the versatility and simplicity of the paper tape monitors we feel the paper tape personal monitors are the best method currently available for environmental characterization of TDI for long-term epidemiologic studies.

(5) Effect of Temperature on Measurements of TDI with Continuous Reading Monitors

There are no published reports so far about the effect of temperature on the measurement of TDI using the Model 7000 TDI monitor. The personal and/or area monitoring was done throughout the year and the monitors were subjected to a wide range of temperatures (0-35° C). Therefore, a study was conducted to evaluate the performance of these monitors at various temperatures. Figure 19 shows a plot of the ratio of Marcali method concentration to the Model 7000 reading vs temperature for various TDI concentrations.

The monitor seems to agree well (< 20% error) with the Marcali method at 0°, 9°C, 17°C and 23°C. At 4°C, there are 3 points: one with

40% error and two with less than 30% error. Because the study was conducted outdoors during winter time, we could not repeat the study at 40°C. Considering the variability of temperature, humidity, formation of TDI condensation aerosols, etc., we feel there is no significant temperature effect on measurement with continuous monitor.

(6) Effect of Humidity on Measurement of TDI with Continuous Reading Monitors

Standard atmospheres of TDI were generated at various humidities and simultaneously measured with the Model 7000 monitor and the Marcali method. Figure 20 shows the results of this study. The paper tape monitor consistently reads lower at 0% RH. Between 20 to 100% RH, the average errors are within 20%. Since the average relative humidity at the plant is between 70 to 80%, we assumed that the humidity does not have any significant effect on measurements of airborne TDI.

F. Miscellaneous Studies

Because phosgene is one of the raw materials used in the manufacture of TDI and it is a well known respiratory irritant, a pilot scale survey was made to determine the extent of exposure to the study population. Personal phosgene monitors (MCM-4000) similar to the TDI monitors were used for this evaluation. Table 29 summarizes the results of this survey. It is clear from this table that the phosgene exposures were relatively minimal (0.004 ppm) when compared to the NIOSH recommended TWA of 0.1 ppm for up to 10 hour-day work week and a ceiling of 0.2 ppm.

STATISTICAL CONSIDERATIONS

A. Statistical Methodology Used to Define Exposure Categories

In the Environmental Characterization section, three exposure categories based on TDI concentration as measured by 8-hour time-weighted averages and four exposure categories based on peak TDI exposure as measured by time, the instantaneous TDI concentration was above .02, .04, .06, and .08 ppm were defined. This section describes the statistical methodology used to construct these exposure categories.

The construction of the exposure categories based on TDI concentration begins with 8-hour time-weighted averages for 1949 personal samples on 42 job titles. Since the frequency distribution of the time-weighted averages was markedly skewed to the right, the time-weighted averages were transformed by taking logarithms to the base 10. The logarithm scale was divided into eight categories using division points -3.60, -3.30, -3.00, -2.70, -2.40, -2.10, and -1.80, corresponding to division points .00025, .0005, .001, .002, .004, .008, and .016 ppm on the original scale. The lowest category on the $\log_{10}$ scale is called category 1, the next highest category 2, etc.

The frequency distribution by $\log_{10}$ category for the 1949 personal samples is given in Figure 1. It is approximately symmetrical.

Each of the 42 jobs is represented by its cumulative distribution function:

$$(p_1, p_2, p_3, p_4, p_5, p_6, p_7) = (p_i)_i^7 = 1$$

where p_i is equal to the proportion of time-weighted averages in $\log_{10}$ scale category i or less. The distance between two jobs represented by:

$$(p_{1i})_i^7 = 1 \quad \text{and} \quad (p_{2i})_i^7 = 1$$

is then defined to be:

$$\left[\sum_{i=1}^7 (p_{1i} - p_{2i})^2 \right]^{1/2}$$

Then two jobs are "similar" if the distance between them is small and "dissimilar" if the distance between them is large.

Figures 21 and 22 contain histograms for several jobs together with the distances between them.

The distance between E-operators in drumming and the bug pond operators is 1.13 making them far apart. The histogram in Figure 21 visually confirms this separation. On the other hand, the TDI foreman and the D-operators in phosgene (Figure 22) are quite similar with .097 distance between them. Intermediate between those two extremes are A-operators in TDI and D-operators in phosgene (Figure 22) with .37 distance between them, TDI foreman and bug pond operators (Figure 21) with distance .56 between them, and E-operators in drumming and TDI foreman (Figure 21) with distance .67 between them.

Using those 21 jobs with 10 or more personal samples, a cluster analysis was performed utilizing the above distance function. The BMDP2M (32) cluster analysis of cases algorithm using options SUMOFSQ and NO STANDARDIZE with weights equal to the number of samples in job was used to perform the computations. When this algorithm combined clusters, the cumulative distribution of the new cluster was computed as the weighted average of the two component cumulative distributions using weights equal to the number of samples in each component.

Visual inspection, without knowledge of job titles, of the cluster tree produced by BMDP2M resulted in three distinct clusters of jobs forming the basis of three exposure categories. Each of the remaining 21 jobs was then assigned to the category corresponding to the cluster to which it was nearest.

Histograms on the log scale and descriptive statistics in ppm for each of the three exposure categories are presented in Figure 2 and Table 5 respectively. The jobs which make up each category are listed in Table 4. The distances between the HIGH and MODERATE categories and between the MODERATE and LOW categories are .56 and .41 respectively.

In determining the peak exposure categories described on the Environmental Section, all 2093 personal samples were used. A job was represented by four numbers

$$(q_2, q_4, q_6, q_8)$$

where q_i equals the proportion of time above .01 ppm for $i = 2, 4, 6, 8$.

Distance between jobs was defined in a manner analogous to that in the cumulative exposure case and a similar clustering performed. This resulted in four peak exposure categories as described in Tables 6 and 7.

B. Statistical Methodology Used in Longitudinal Pulmonary Function Analysis

A large part of our effort in accessing the respiratory health effects of exposure to TDI has been directed at relating, after controlling for smoking and atopic status, pulmonary function annual change to an index of exposure. Annual change for a particular pulmonary function parameter, say FEV_1 , was computed for each study participant with three or more usable determinations of FEV_1 as the slope of the least squares regression line using FEV_1 as dependent variable and time since initial visit as the independent variable. In this section, the statistical methodology for relating annual changes determined in this way to explanatory variables is developed.

For the i^{th} ($i = 1, 2, \dots, N$) study participant, let

$$y_{ij} = \alpha_i + \beta_i (t_{ij} - \bar{t}_i) + \eta_{ij}$$

denote the linear regression of FEV_1 on time. Here the t_{ij} 's ($j = 1, \dots, n_i$) represent those time points for which usable FEV_1 's are available for the i^{th} participant, $\bar{t}_i$ is the mean of the t_{ij} 's, the error terms η_{ij} are assumed independent and normally distributed with mean 0 and variance τ^2 independent of study participant, α_i is the value of the i^{th} study participant's true regression line at $\bar{t}_i$, and β_i is the slope of the true regression line. Then each α_i and β_i are estimated respectively by the usual least squares estimators:

$$a_i = \frac{1}{n_i} \sum_{j=1}^{n_i} y_{ij} \quad \text{and}$$

$$b_i = \frac{\sum_{j=1}^{n_i} y_{ij} (t_{ij} - \bar{t}_i)}{\sum_{j=1}^{n_i} (t_{ij} - \bar{t}_i)^2}$$

In addition, τ^2 is estimated by

$$\tau^2 = \frac{\sum_{i=1}^N \sum_{j=1}^{n_i} (y_{ij} - a_i - b_i (t_{ij} - \bar{t}_i))^2}{\sum_{i=1}^N (n_i - 2)}$$

with $\sum_{j=1}^{n_i} (n_i - 2)$ degrees of freedom. Moreover, the variance of the

estimator b_i is given by

$$\frac{\tau^2}{\sum_{j=1}^{n_i} (t_{ij} - \bar{t}_i)^2}$$

which depends on the observation times for the i^{th} participant.

Now let $x_{i1}, x_{i2}, \dots, x_{ik}$ denote the independent variables for the i^{th} participant with $x_{i1} = 1$ for all i . For example with $k = 4$, x_{i2} might be cumulative exposure, x_{i3} a dummy variable representing atopic status, and x_{i4} = pack-years of cigarette smoking. Then we wish to estimate the coefficients in the expression

$$\beta_i = \sum_{j=1}^k \gamma_j x_{ij} + \epsilon_i$$

where β_i is the true slope for the i^{th} participant, the ϵ_i are independent and normally distributed with mean 0 and variance σ^2 . Thus σ^2 is the variance of the time annual changes β_i not accounted for by explanatory variables $x_{i1}, \dots, x_{ik}$.

Standard regression techniques using the observed slopes as dependent variable can not be used to estimate the γ 's in (1) because the variance of the observed slopes is not homogeneous. In order to take this lack of homogeneity into account, we proceed as follows.

Assume b_i and β_i are related by

$$b_i = \beta_i + \delta_i$$

where the δ_i are independent and normally distributed with mean 0 and

variance $\tau^2 / \sum_{j=1}^n (t_{ij} - \bar{t}_i)^2$. Furthermore, assume that the ϵ_i in (1)

and the δ_i are independent. It then follows that the observed slopes b_i

satisfy

$$b_i = \sum_{j=1}^k \gamma_j x_{ij} + \epsilon_i + \delta_i$$

where the δ_i are independent and normally distributed with mean 0 and variance

$$\sigma^2 + \tau^2 / \sum_{j=1}^n (t_{ij} - \bar{t}_i)^2.$$

In model (2) $\sigma^2 = \text{Variance}(\epsilon_i)$ is the variance of the true slopes

not accounted for by the $x_{i1}, x_{i2}, \dots, x_{ik}$, τ^2 is the residual variance about

an individual participant's regression line, and $\tau^2 / \sum_{j=1}^n (t_{ij} - \bar{t}_i)^2$ is the

variance of the estimation error associated with the observed slope b_i .

Since the coefficients γ_j in (2) are the same as those in (1), model (2) which relates the observed slopes to explanatory variables, can be used to estimate the coefficients in model (1) which relates true slopes to the explanatory variables. Because the variances of the $\varepsilon_i + \delta_i$ in (2) are heterogeneous, unweighted multiple regression techniques should not be used to estimate the γ_j 's in (2). Since consistent estimators of

$\sigma^2 + \tau^2 / \sum_{j=1}^{n_i} (t_{ij} - \bar{t}_i)^2$, as required by weighted regression procedures are

not available, the γ_j 's and σ^2 have been estimated by maximizing the

likelihood of b_i 's with respect to the γ_j 's and σ^2 at the observed value of

$$\tau^2 = \frac{\sum_{j=1}^N \sum_{i=1}^{n_i} (y_{ij} - a_i - b_i (t_{ij} - \bar{t}_i))^2}{\sum_{i=1}^N (n_i - 2)}$$

Specifically, letting $K_i = \sum_{j=1}^{n_i} (t_{ij} - \bar{t}_i)^2$, the log likelihood of

the β_i 's is

$$- \frac{N}{2} \ln 2\pi - \sum_{i=1}^N \frac{1}{2} \ln (\sigma^2 + \tau^2 / K_i) - \sum_{i=1}^N \frac{(b_i - \sum_{j=1}^k \gamma_j x_{ij})^2}{2(\sigma^2 + \tau^2 / K_i)}$$

which yield likelihood equations at the observed value of τ^2 :

$$\sum_{i=1}^N \frac{(b_i - \sum_{j=1}^k \gamma_j x_{ij}) x_{1i}}{(\sigma^2 + \tau^2/K_i)} = 0 \quad (i = 1, 2, \dots, k),$$

$$\sum_{i=1}^N \left\{ \frac{(b_i - \sum_{j=1}^k \gamma_j x_{ij})^2}{(\sigma^2 + \tau^2/K_i)^2} - \frac{1}{\sigma^2 + \tau^2/K_i} \right\} = 0$$

A solution to these equations was obtained using the International Mathematical and Statistical Libraries' subroutine ZSYSTEM which solves systems of non-linear equations.

Starting values for this iterative procedure were obtained in the following manner:

1. Letting $b_i = \theta + \epsilon_i + \delta_i$ with the variance of ϵ_i equal to σ_0^2 and

$$\bar{b} = \frac{\sum_{i=1}^N K_i b_i}{\sum_{i=1}^N K_i},$$

it follows (See Section 16.5 of (34) for an analogous computation) that the expected value of

$$\frac{1}{N-1} \sum_{i=1}^N K_i (b_i - \bar{b})^2 \text{ is } \tau^2 + \frac{W_0}{N-1} \sigma_0^2$$

where $W_o = \sum_{i=1}^N K_i - \frac{\sum_{i=1}^N K_i^2}{\sum_{i=1}^N K_i}$. This results in

$$\hat{\sigma}_o^2 = \frac{\sum_{i=1}^N K_i (b_i - \bar{b})^2 - (N-1) \tau^2}{W_o}$$

as an estimate of σ_o^2 .

2. Regress b_i on the $x_{i1}, x_{i2}, \dots, x_{ik}$ using weights equal to

$(\hat{\sigma}_o^2 + \frac{\tau^2}{K_i})^{-1}$ and take as starting values for the iterative equation solving

procedure, $\hat{\sigma}_o^2$ and the coefficients $\gamma_{01}, \gamma_{02}, \dots, \gamma_{0k}$ obtained from this

weighted regression.

The variance-covariance matrix of the estimators was estimated by the inverse of the negative of the information matrix evaluated at the solution of the likelihood equations. Inference on the estimated regression coefficients was based on the asymptotic normality of maximum likelihood estimators.

As examples of above procedure, consider the following two cases

using FEV_1 annual change:

(1) $k = 1$ and $x_{i1} = 1$ for all i .

(2) $k = 4$ and $x_{i1} = 1$ for all i .

$$x_{i2} = \begin{cases} 0 & \text{if cumulative exposure} \leq .0682 \text{ ppm-months} \\ 1 & \text{otherwise} \end{cases}$$

$$x_{i3} = \begin{cases} 0 & \text{if } i^{\text{th}} \text{ participant is non-atopic} \\ 1 & \text{otherwise} \end{cases}, \text{ and}$$

$$x_{i4} = \text{pack-years of cigarette smoking},$$

In this situation $N = 223$,

$$\hat{\tau}^2 = .017572 \lambda^2 \text{ with 928 degrees of freedom,}$$

$$\frac{\sum_{i=1}^N K_i b_i}{\sum_{i=1}^N K_i} = -.02402,$$

$$\sum_{i=1}^N K_i$$

$$\sum_{i=1}^N K_i (b_i - \bar{b})^2 = 6.2107, \text{ and}$$

$$\sigma_o^2 = .000791 \lambda^2.$$

Then for example (1) using $-.0240 \lambda$ for γ_{01} and $.000791 \lambda^2$ for

$\hat{\sigma}_0^2$, we obtain: $\hat{\gamma}_1 = -.02442$ with standard error = .00316 and

$\hat{\sigma}^2 = .000652$ d^2 . In this case, $\gamma_1 = -.0244$ is the maximum likelihood estimate of mean FEV₁ annual change and $\hat{\sigma} = .02552$ is the maximum likelihood estimate of between true slopes standard deviation.

$$\text{The quantity } .000652 + \frac{.017572}{\sum (t_j - \bar{t})^2}$$

is the estimated variance of an observed slope calculated from time points

$t_1, t_2, \dots, t_n$ and $.000652 / (.000652 + \frac{.017572}{\sum (t_j - \bar{t})^2})$ is the proportion

of this variance due to "between true slopes". This is the variability we

are attempting to explain by exposure to TDI, atopic status, and pack years

of smoking. For a participant with FEV₁ readings at all nine visits

$\sum (t_j - \bar{t})^2 = 26.45$ so that 49.5 per cent of variability in such a participant's

annual change is available for explanation by the explanatory variables.

For example (2) starting values $-.0118, -.0123, .0010, -.00059,$

and .000791 were obtained for the intercept, coefficient of exposure

categorization, coefficient of atopic status, coefficient of pack-years,

and σ^2 respectively. Five iterations were required to satisfy the ZSYSTEM stopping criteria with $EPS = 10^{-6}$ and $NSIG = 9$ (See IMSL ZSYSTEM documentation for definitions of EPS and NSIG.) The resulting regression equation is:

FEV_1 annual change =

$$-.0120 - .0118 EXP + .0010 ATOPY - .00058 PACK-YEARS$$

(.0056) (.0064) (.0071) (.00022) where

$$EXP = \begin{cases} 1 & \text{if cumulative exposure} > .0682 \text{ ppm-months} \\ 0 & \text{otherwise} \end{cases}$$

$$ATOPY = \begin{cases} 1 & \text{if participant is positive on two or more skin tests} \\ 0 & \text{otherwise} \end{cases}$$

and the numbers in parentheses are the standard errors of the regression coefficient. The maximum likelihood estimate of σ^2 (the between true slope variability after removing variability explained by exposure category, atopic status, and pack years of smoking) is .000591 λ^2 . Thus using the results of previous example, 9.4 percent of the true slope variability is explained by these three variables.

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PARTICIPATION BY VISIT

SPIROMETRY

Visit Date	4-73	11-73	9-74	3-75	10-75	3-76	11-76	12-77	10-78	TOTAL
Number Added	168	27	25	34	23	-	-	-	-	277
Permanently Lost	-	6	9	3	11	13	7	13	9	71
Eligible from Previous Visit	-	162	180	202	225	235	228	215	206	
Total Eligible	168	189	205	236	248	235	228	215	206	
Refused (% of Elig. from Prev.)	0	3 (1.9)	7 (3.9)	12 (5.9)	21 (9.3)	25 (10.6)	37 (16.2)	35 (16.3)	36 (17.5)	
Temporarily Lost (% of Elig. from Prev.)	2 (1.2)	11 (6.8)	13 (7.2)	21 (10.4)	17 (7.6)	24 (10.2)	25 (11.0)	34 (15.8)	29 (14.1)	
Complete Spirometry (% of Total Eligible)	144 (85.7)	145 (76.7)	168 (81.9)	197 (83.5)	200 (80.6)	175 (74.5)	161 (70.6)	142 (66.0)	135 (65.5)	
Complete Spirometry (% of Eligible - Refused - Temp. Lost)	144 (86.7)	145 (82.8)	168 (90.8)	197 (97.0)	200 (95.2)	175 (94.1)	161 (97.0)	142 (97.3)	135 (95.7)	

Table 2

DESCRIPTIVE STATISTICS AT INITIAL VISIT
FOR THE 274 MALE PARTICIPANTS

			<u>n</u>
1. Race:	85%	white	274
2. Cigarette Smoking:	51.1%	current	273
	22.6%	Ex	
	25.9%	Never	
3. Atopy (positive to 2 or more skin tests)	20.1%	Atopic	274
4. Upper respiratory symptoms	38.7%	Positive	273
5. Lower respiratory symptoms	29.6%	Positive	272
6. Bronchitis	3.6%	Positive	273
7. Dyspnea	84.3%	GRADE I	271
	11.7%	GRADE II	
	2.9%	GRADE III	

	<u>n</u>	<u>Mean</u>	<u>Standard Deviation</u>
8. Age (years)	274	35.9	11.3
9. Height (inches)	274	69.9	2.56
10. Pack-years	273	14.37	16.3
11. IgE IU/ml	271	181.8	287.7
12. FEV% P ⁽¹⁾	244	100.2	13.3
13. FVC% P	244	102.7	12.3
14. FEF ₂₅₋₇₅ % P	244	91.0	26.5
15. RV% P	217	99.4	25.7
16. TLC% P	217	101.0	11.6
17. DLCO% P	212	99.0	16.7
18. KZ P	212	99.7	17.3

(1) % predicted are taken from the pulmonary function measurements at the time of the initial interview or the next visit at which the pulmonary function measurement was taken if it was not done at the visit of the initial interview.

Table 3

DESCRIPTIVE STATISTICS (in ppm)
FOR 8-HOUR TIME-WEIGHTED AVERAGES

8-Hour Time-Weighted Averages Used to Develop Exposure Categories		"Turnaround Time" 8-Hour Time-Weighted Averages
MAX	.0250	.0250
P ₇₅	.0036	.0067
MEAN	.0035	.0055
MEDIAN	.0023	.0030
P ₂₅	.0011	.0020
MIN	.0001	.0001
S. D.	.0045	.0059
GEO. MEAN	.0020	.0036
GEO. S. D.	2.94	2.55
n (samples)	1949	144

Table 4

JOB TITLES BY TIME-WEIGHTED
AVERAGE EXPOSURE CATEGORY

<u>Exposure Category</u>	<u>Job Code</u>	<u>Job</u>	<u>Location</u>	<u>Number of Samples</u>
HIGH	13001	C Operator	TDI	222
	15050	E Operator	Drumming	199
	15051	E Operator	Tank Farm	5
	31030	Millwright	Phosgene	12
	33030	Welder	Phosgene	1
MODERATE	1001	Foreman	TDI	239
	12001	B Operator	TDI	208
	14030	D Operator	Phosgene	224
	30001	Unsp. Maint.	TDI	7
	30021	Unsp. Maint.	Machine Shop	4
	31001	Millwright	TDI	51
	32001	Boilermaker	TDI	17
	33001	Welder	TDI	31
	34001	Pipefitter	TDI	30
	36001	Instruments	TDI	7
	36019	Instruments	Shop	5
	41002	Unspec. Sampl.	TDI Lab	7
	42002	A Sampler	TDI Lab	14
	43002	B Sampler	TDI Lab	7
LOW	1014	Foreman	Soda Ash	4
	1017	Foreman	T101	4
	11001	A Operator	TDI	69
	11010	A Operator	TDA	60
	12020	B Operator	Hyc	88
	13010	C Operator	TDA	89
	13040	C Operator	POL-DNT	14
	14040	D Operator	POL-DNT	124
	15010	E Operator	TDA	35
	15030	E Operator	Phosgene	1
	19052	Operator	Bug Pond	99
	31012	Millwright	Sodium Nitrate	2
	33009	Welder	Ammonia	6
	33027	Welder	Pilot Plant	3
	35001	Electrician	TDI	15
	35018	Electrician	Shop	6
	36009	Instruments	Ammonia	6
	37028	Carpenter	Shop	4
	40002	Chemist	TDI Lab	15
	53029	Clerical	CAR Warehouse	2
	57012	Truck Driver	Sodium Nitrate	4
	58012	Warehouseman	Sodium Nitrate	5
	71021	Machinist	Shop	4

Table 5

8-HOUR TIME-WEIGHTED AVERAGE DESCRIPTIVE
STATISTICS (in ppm) BY EXPOSURE CATEGORY

<u>CATEGORY</u>	<u>HIGH</u>	<u>MODERATE</u>	<u>LOW</u>
MAX.	.0250	.0250	.0248
P ₇₅	.0088	.0035	.0020
MEAN	.0068	.0032	.0016
MEDIAN	.0050	.0020	.0013
P ₂₅	.0025	.00130	.0007
MIN.	.0001	.0001	.0001
S. D.	.0062	.0039	.0018
GEO. MEAN	.0045	.0020	.0011
GEO. S. D.	2.69	2.68	2.37
n	439	851	659

JOB TITLES BY PEAK EXPOSURE CATEGORY

Category I:	15050	E Operator in Drumming
	30001	Unspecified Maintenance in TDI
	31030	Millwright in Phosgene
	33030	Welder in Phosgene
Category II:	12001	B Operator in TDI
	13001	C Operator in TDI
	31001	Millwright in TDI
	33001	Welder in TDI
	34001	Pipe Fitter in TDI
Category III:	01001	Foreman in TDI
	14030	D Operator in Phosgene
	15051	E Operator in TK Farm
	32001	Boilermaker in TDI
	37001	Carpenter in TDI
	42002	A Sampler in TDI Lab
Category IV:	01014	Foreman in Soda Ash
	01017	Foreman in T-101
	11001	A Operator in TDI
	11010	A Operator in TDA
	12020	B Operator in HYCO
	13010	C Operator in TDA
	13040	C Operator in POL-DNT
	14040	D Operator in POL-DNT
	15010	E Operator in TDA
	15030	E Operator in Phosgene
	19052	Operator in Bug Pond
	30021	Unspecified Maint. in Machine Shop
	31010	Millwright in TDA
	31012	Millwright in Sodium Nitrate
	33009	Welder in Ammonia
	33010	Welder in TDA
	33020	Welder in HYCO
	33027	Welder in Pilot Plant
	35001	Electrician in TDI
	35018	Electrician in Electric Shop
	36001	Instruments in TDI
	36009	Instruments in Ammonia
	36019	Instruments in Instr. Shop
	36020	Instruments in HYCO
	36030	Instruments in Phosgene
	37028	Carpenter in Carpenter Shop
	38001	Insulator in TDI
	39001	Maint. Supervisor in TDI
	40002	Chemist/Analyst in TDI Lab
	41002	Unspecified Sampler in TDI Lab
	43002	B Sampler in TDI Lab
	53029	Clerical in CAR Warehouse
	57012	Truck Driver or Laborer in Sodium Nitrate
	58012	Warehouseman in Sodium Nitrate
	71021	Machinist in Machine Shop

Table 7

PERCENTAGE OF TIME SPENT ABOVE SELECTED CONCENTRATION
LEVELS BY PEAK EXPOSURE CATEGORY

Category	Percentage of time above:					
	.005 ppm	.01 ppm	.02 ppm	.04 ppm	.06 ppm	.08 ppm
I	36.1	20.1	10.6	5.5	3.9	3.4
II	24.0	12.1	5.0	2.4	1.6	1.4
III	10.7	4.0	1.4	0.5	0.3	0.2
IV	3.2	0.7	0.3	0.1	0.1	0.0

Table 8

ANNUAL CHANGE REGRESSION COEFFICIENTS⁽¹⁾ USING CUMULATIVE EXPOSURE,
ATOPIC STATUS AND PACK-YEARS AS EXPLANATORY VARIABLES

	n	Intercept	Cumulative Exposure	Atopy	Pack- Years	% Variability Explained
L/yr	223	-.0103 (-1.09)	-.0770 (-.81)	.0011 (.15)	-.00057 (-2.55)	7.36
L/yr	223	-.0039 (-.40)	.0455 (.47)	-.0070 (-.97)	-.00071 (-3.13)	20.3
(yr) ⁻¹	223	-.2041 (-1.52)	-1.372 (-1.01)	.1246 (1.21)	-.00332 (-1.03)	3.0
-75 L/sec-yr	223	-.0736 (-3.23)	-.00275 (-1.19)	.0249 (1.44)	-.00024 (-.43)	4.1
L/sec-yr	223	-.1115 (-3.50)	-.000386 (-.12)	.0374 (1.54)	-.00036 (-.48)	6.5
$\frac{\text{ml}}{\text{min-mmHg-yr}}$	164	-.169 (-4.99)	1.276 (3.31)	-.0155 (-.58)	-.00072 (-.85)	28.8
min-mmHg-yr^{-1}	164	-1.127 (-4.97)	7.926 (3.07)	-.433 (-2.43)	-.0015 (-.27)	47.5
./yr	179	.0391 (3.09)	-.126 (-.99)	-.00222 (-.24)	.00104 (3.58)	30.9
./yr	179	.0275 (1.81)	.00371 (.02)	-.0106 (-.93)	.00048 (1.38)	5.5
FLC) x 100 (yr) ⁻¹	179	.4400 (3.04)	-1.112 (-.77)	-.0181 (-.17)	.0114 (3.44)	46.4

The numbers in parentheses are the regression coefficients divided by their standard errors. They should be compared to normal distribution percentiles for tests of significance.

Table 9

ANNUAL CHANGE REGRESSION COEFFICIENTS⁽¹⁾ USING DICHOTOMIZED
CUMULATIVE EXPOSURE, ATOPIC STATUS, AND PACK-YEARS AS EXPLANATORY VARIABLES

		Cumulative ⁽²⁾ Exposure			Pack- Years	% Variability Explained
	n	Intercept	Category II	Atopy		
L/yr	223	-.0120 (-2.14)	-.0118 (-1.82)	.0009 (.13)	-.00058 (-2.60)	9.4
L/yr	223	-.0006 (-.10)	.0012 (.19)	-.0069 (-.95)	-.00071 (-3.17)	19.2
(yr) ⁻¹	223	-.2358 (-2.94)	-.2024 (-2.20)	.1216 (1.19)	-.0034 (-1.08)	6.30
5-75 L/sec-yr	223	-.0801 (-5.96)	-.0406 (-2.63)	.0243 (1.42)	-.00025 (-.46)	11.1
L/sec-yr	223	-.1031 (-5.44)	-.0285 (-1.31)	.0373 (1.55)	-.00041 (-.54)	6.6
$\frac{ml}{min-mmHg-yr}$	164	-.0934 (-4.39)	.0518 (1.97)	-.00642 (-.24)	-.00101 (-1.19)	16.3
mmHg-yr) ⁻¹	164	-.6578 (-4.64)	.3246 (1.86)	-.3755 (-2.09)	-.0033 (-.58)	33.6
L/yr	179	.0286 (3.83)	-.0061 (-.07)	-.00289 (-.31)	.00107 (3.67)	27.1
L/yr	179	.0278 (3.11)	.0000 (.00)	-.0105 (-.93)	.00048 (1.38)	5.6
TLC) x 100 (yr) ⁻¹	179	.3331 (3.93)	.0313 (.32)	-.0246 (-.23)	.0117 (3.52)	41.7

See Footnote ⁽¹⁾ of Table 8.

Cumulative Exposure Category II has value if cumulative exposure is > .0682 ppm-months and 0 otherwise. Thus, its coefficient estimates the difference between the two categories after controlling for the other variables.

EXPOSURE CATEGORIES (2), ATOPIC STATUS, AND PACK-YEARS AS EXPLANATORY VARIABLES

	n	Intercept	Cumulative Exposure Category II A	Cumulative Exposure Category II B	Atopy	Pack-Years	% Variability Explained
FEV ₁ L/yr	223	-.0123 (-2.21)	-.0187 (-2.25)	.0132 (1.31)	.0020 (.28)	-.00057 (-2.59)	13.3
FVC L/yr	223	-.0008 (-.15)	-.0049 (-.56)	.0115 (1.10)	-.0060 (-.82)	-.00072 (-3.17)	21.1
FEV% (yr) ⁻¹	223	-.2374 (-2.97)	-.2339 (-1.95)	.0597 (.41)	.1262 (1.23)	-.0034 (-1.07)	7.0
FEF ₂₅₋₇₅ L/sec-yr	223	-.0806 (-6.00)	-.0494 (-2.46)	.0166 (.68)	.0256 (1.49)	-.00024 (-.44)	13.0
FEF ₅₀ L/sec-yr	223	-.1032 (-5.44)	-.0304 (-1.07)	.0035 (.10)	.0377 (1.56)	-.00041 (-.54)	6.7
DL _{CO} $\frac{\text{ml}}{\text{min-mmHg-yr}}$	164	-.0921 (-4.46)	-.0308 (-.86)	.1407 (3.26)	-.00870 (-.33)	-.00107 (-1.29)	35.1
K (min-mmHg-yr) ⁻¹	164	-.6468 (-4.68)	-.208 (-.86)	.9013 (3.12)	-.3892 (-2.22)	-.00370 (-.67)	66.1
RV L/yr	179	.0288 (3.85)	.00467 (.40)	-.00951 (-.69)	-.00334 (-.35)	.00107 (3.65)	27.1
TLC L/yr	179	.0276 (3.10)	-.00860 (-.62)	.0154 (.94)	-.00978 (-.87)	.00049 (1.40)	5.5
(RV/TLC) × 100 (yr) ⁻¹	179	.3359 (3.97)	.1122 (.86)	-.1455 (-.93)	-.0312 (-.29)	.0117 (3.51)	43.8

(1) See Footnote (1) of Table 8.

(2) Cumulative Exposure Category II A has value 1 if cumulative exposure is >.0682 ppm-months and 0 otherwise. Cumulative Exposure Category II B has value 1 if cumulative exposure is >.1 ppm-months and 0 otherwise. The coefficient of Cumulative Exposure Category II A (resp. Cumulative Exposure Category II B) estimates the difference between the two lowest (resp. highest) categories after controlling for the other variables.

Table 11

ANNUAL CHANGE REGRESSION COEFFICIENTS⁽¹⁾ USING TIME ABOVE .02 ppm,
ATOPIC STATUS, AND PACK-YEARS AS EXPLANATORY VARIABLES

	n	Intercept	Time Above .02 ppm	Atopy	Pack- Years	% Variability Explained
1 L/yr	223	-.0141 (-2.51)	-.0043 (-1.05)	.0010 (.14)	-.00057 (-2.56)	9.51
L/yr	223	-.0020 (-.35)	.0032 (.75)	-.0070 (-.96)	-.00071 (-3.12)	19.7
2 L/yr	223	-.2470 (-3.09)	-.452 (-1.93)	.1231 (1.24)	-.0035 (-1.08)	6.2
25-75 L/sec-yr	223	-.0853 (-6.31)	-.0184 (-1.83)	.0246 (1.42)	-.00024 (-.44)	7.6
50 L/sec-yr	223	-.1107 (5.83)	-.0066 (-.47)	.0375 (1.55)	-.00038 (-.50)	4.7
$\frac{ml}{0 \text{ min-mmHg-yr}}$	164	-.0968 (-4.47)	.0380 (2.14)	-.00832 (-.31)	-.00095 (-1.10)	16.6
min-mmHg-yr)	164	-.6482 (-4.45)	.1761 (1.48)	-.382 (-2.11)	-.00305 (-.53)	27.3
L/yr	179	.0361 (4.93)	-.0129 (-2.38)	-.0017 (-.19)	.00102 (3.55)	38.1
L/yr	179	.0322 (4.69)	-.00733 (-1.11)	-.00996 (-.88)	.00045 (1.29)	9.9
/TLC) x 100 (yr) ⁻¹	179	.4238 (5.08)	-.1361 (-2.20)	-.0114 (-.11)	.0112 (3.40)	55.4

See Footnote (1) of Table 8.

Table 12

ANNUAL CHANGE REGRESSION COEFFICIENTS⁽¹⁾ USING DICHOTOMIZED
TIME ABOVE .02 ppm, ATOPIC STATUS, AND PACK-YEARS AS EXPLANATORY VARIABLES

	n	Peak Exposure ⁽²⁾		Atopy	Pack- Years	% Variability Explained
		Intercept	Category II			
L/yr	223	-.0127 (-2.29)	-.0108 (-1.64)	.00058 (.08)	-.00058 (-2.61)	10.9
L/yr	223	.0005 (.09)	-.0015 (-.22)	-.0069 (-.95)	-.00072 (-3.18)	18.6
yr ⁻¹	223	-.2594 (-3.26)	-.1541 (-1.63)	.1158 (1.13)	-.0034 (-1.07)	6.0
15-75 L/sec-yr	223	-.0847 (-6.34)	-.0317 (-1.99)	.0232 (1.35)	-.00024 (-.45)	10.0
50 L/sec-yr	223	-.0999 (-5.34)	-.0396 (-1.77)	.0361 (1.50)	-.00045 (-.60)	8.7
$\frac{ml}{min-mmHg-yr}$	164	-.0977 (-4.64)	.0646 (2.50)	-.0058 (-.22)	-.00101 (-1.19)	24.3
min-mmHg-yr)	164	-.6560 (-4.64)	.3170 (1.82)	-.3706 (-2.06)	-.00338 (-.60)	31.4
L/yr	179	.0341 (4.69)	-.0172 (-1.92)	-.00285 (-.30)	.00104 (3.60)	32.4
L/yr	179	.0331 (3.81)	-.0158 (-1.48)	-.0105 (-.94)	.00045 (1.31)	11.3
/TLC) x 100 (yr) ⁻¹	179	.3911 (4.70)	-.1427 (-1.40)	-.0240 (-.22)	.0115 (3.46)	44.2

See Footnote ⁽¹⁾ of Table 8.

Peak Exposure Category II has value 1 if time above .02 ppm is > .19 months and 0 otherwise. Thus, its coefficient estimates the difference between the two categories after controlling for the other variables.

Table 13

ANNUAL CHANGE REGRESSION COEFFICIENTS (1) USING THREE TIME ABOVE
.02 ppm CATEGORIES, ATOPIC STATUS, AND PACK-YEARS AS EXPLANATORY VARIABLES

	n	Intercept	Peak Exposure Category II A	Peak Exposure Category II B	Atopy	Pack- Years	% Variability Explained
FEV ₁ L/yr	223	-.0127 (-2.30)	-.0139 (-1.71)	.0070 (.65)	.00042 (.06)	-.00057 (-2.57)	10.7
FVC L/yr	223	.0003 (.06)	-.0088 (-1.05)	.0167 (1.49)	-.0073 (-1.00)	-.00071 (-3.11)	18.5
FEV% (yr) ⁻¹	223	-.2581 (-3.25)	-.0972 (-1.84)	-.0129 (-.84)	.1185 (1.16)	-.0035 (-1.11)	6.3
FEF ₂₅₋₇₅ L/sec-yr	223	-.0847 (-6.34)	-.0303 (-1.55)	-.0031 (-.12)	.0233 (1.35)	-.00024 (-.46)	9.9
FEF ₅₀ L/sec-yr	223	-.1005 (-5.40)	-.0682 (-2.50)	.0660 (1.80)	.0345 (1.44)	-.00037 (-.49)	11.7
DL _{CO} $\frac{\text{ml}}{\text{min-mmHg-yr}}$	164	-.0975 (-4.63)	.0687 (2.16)	-.00979 (2.24)	-.0054 (-.20)	-.00102 (-1.21)	24.3
K (min-mmHg-yr) ⁻¹	164	-.6541 (-4.62)	.3615 (1.69)	-.1051 (-.36)	-.3670 (-2.05)	-.00357 (-.63)	36.0
RV L/yr	179	.0345 (9.81)	-.00661 (-.61)	-.0242 (-1.63)	-.00166 (-.18)	.00100 (3.48)	39.5
TLC L/yr	179	.0332 (3.83)	-.0128 (-.97)	-.00679 (-.38)	-.0102 (-.91)	.00044 (1.27)	12.5
(RV/TLC) x 100 (yr) ⁻¹	179	.3952 (4.84)	-.00866 (-.07)	-.3102 (-1.82)	-.00783 (-.07)	.0109 (3.33)	57.8

(1) See Footnote (1) of Table 8.

(2) Peak Exposure Category II A has value 1 if time above .02 ppm > .19 months and 0 otherwise. Peak Exposure Category II B has value of time above .02 ppm > 1 month and 0 otherwise. Thus, the coefficient of peak Exposure Category II A (resp., Peak Exposure Category II B) estimates the difference between the two lowest (resp. highest) categories after controlling for the other variables.

Table 14

ESTIMATED POPULATION MEAN ANNUAL CHANGES AND OTHER STATISTICS

	n	Estimated Mean Annual Change	Standard Error of Mean Annual Change	Estimated Standard Deviation of True Annual Change	Residual Error Standard Deviation	Degrees of Freedom in Residual Sum of Squares	Percent of (1) Total Variability Due to True Annual Change
FEV ₁ L/yr	223	-.0244	.00316	.0255	.1326	928	49.5
FVC L/yr	223	-.0121	.00330	.0272	.1372	928	51.0
FEV% (yr) ⁻¹	223	-.3928	.0451	.3985	1.7752	928	57.1
FEF ₂₅₋₇₅ L/sec-yr	223	-.0928	.00762	.0189	.3242	928	22.6
FEF ₅₀ L/sec-yr	223	-.1100	.0106	.0790	.4653	928	43.3
DL _{CO} $\frac{\text{ml}}{\text{min-mmHg-yr}}$	164	-.0947	.0123	.0757	.3651	301	29.3
K (min-mmHg-yr) ⁻¹	164	-.7160	.0834	.4629	2.559	301	53.6
RV L/yr	179	.0435	.00434	.0306	.1616	448	48.6
TLC L/yr	179	.0322	.00498	.0328	.1910	448	43.9
(RV/TLC) x 100 (yr) ⁻¹	179	.5121	.0495	.2925	1.980	448	36.6

(1) Percent of total variability due to true annual change for a participant with usable data at all nine visits.
For a participant present at fewer than nine visits, the percent of total variability due to true annual change will be smaller.

Table 15

SUMMARY STATISTICS ON 274 PARTICIPANTS BY NUMBER OF VISITS WITH COMPLETE SPIROMETRY

	Number of visits >3	Number of visits <3
n	226	48
% White	85.4	83.3
% Lower Respiratory Symptoms	29.8	29.8
% Upper Respiratory Symptoms*	42.0	23.4
% Bronchitis	3.5	4.3
% Interview Atopic	33.8	25.5
% Atopic*	23.0	6.3
% Dyspnea	14.3	17.0
% Current Cigarette Smokers	50.9	53.2

	73			23		
	Mean	Standard Deviation	n (1)	Mean	Standard Deviation	n
Age (years)	35.6	11.0	226	35.5	12.6	48
Height (inches)	70.0	2.5	226	69.8	2.9	48
Pack-years	13.7	14.9	226	17.4	21.9	47
FEV ₁ % P (2)	100.4	13.4	207	99.2	13.3	37
FVC % P	102.9	12.4	207	101.4	12.0	37
FEF % P	91.5	26.9	207	88.2	24.5	37
RV % P	99.3	25.2	186	100.4	28.8	31
TLC % P	101.3	11.6	186	99.5	11.6	31
K % P	99.7	17.7	181	99.7	14.2	31
Cumulative Exposure* (ppm-months)	.0725	.0354	225	.0231	.0169	30
Time above .02 ppm (months)*	.55	.72	225	.29	.33	30

*p < .05

(1) n represents number of participants with usable data.

(2) % predicted are taken from the pulmonary function measurement at the time of the initial interview or the next visit at which the pulmonary function measurement was taken if it was not done at the visit of the initial interview.

Table 16

ESTIMATED MEAN ANNUAL CHANGES
IN SPIROMETRIC TESTS BY
TWO CUMULATIVE EXPOSURE CATEGORIES
FOR NON-ATOPICS WITH
14 PACK-YEARS OF SMOKING

		GROUP I		GROUP II	
		(ppm-months $\leq$.0682)		(ppm-months $>$.0682)	
	<u>n</u>	<u>149</u>		<u>74</u>	
FEV ₁	ml/yr	-20	(p = .034) ¹	-32	
FVC	ml/yr	-11	(p = 1.0)	-9	
FEVZ	(yr) ⁻¹	-0.28	(p = .014)	-.48	
FEF ₂₅₋₇₅	ml/sec-yr	-84	(p = .004)	-125	
FEF ₅₀	ml/sec-yr	-109	(p = .095)	-137	

¹p-values are significance levels for one-tailed tests of significance for differences between the two groups after controlling for other variables.

Table 17

ESTIMATED MEAN ANNUAL CHANGES IN FEV₁, FEVZ, AND
FEF₂₅₋₇₅ BY CUMULATIVE EXPOSURE FOR NON-ATOPICS WITH 14 PACK-YEARS OF SMOKING

	GROUP I (ppm-months $\leq .0682$)	GROUP II A ($.0682 < \text{ppm-months} \leq .1$)	GROUP II B (ppm-months $> .1$)
1	149	37	37
FEV ₁ ml/yr	-20 (p = .025) ¹	-39 (p = .19)	-26
FEVZ (yr) ⁻¹	-.29 (p = .05)	-.52 (p = .68)	-.46
FEF ₂₅₋₇₅ ml/sec-yr	-84 (p = .014)	-133 (p = .50)	-117

(1) p-values are significance levels for differences between adjacent categories after controlling for other variables.

Table 18

ESTIMATED MEAN ANNUAL CHANGES IN SPIROMETRIC TESTS
 BY TWO TIME ABOVE .02 ppm CATEGORIES
 FOR NON-ATOPICS WITH 14 PACK-YEARS OF SMOKING

	GROUP I (months $\leq .19$)		GROUP II (months $> .19$)
n	140		83
FEV ₁	-21	(p = .051) ¹	-32
FVC	-10	(p = .413)	-11
FEVZ	-.31	(p = .052)	-.46
FEF ₂₅₋₇₅	-88	(p = .023)	-120
FEF ₅₀	-106	(p = .038)	-146

(1) p-values are significance levels for one-tailed tests of significance for differences between the two groups after controlling for the other variables.

Table 19

ESTIMATED MEAN ANNUAL CHANGES IN FEV_1 , $FEVZ$,
 FEF_{25-75} , AND FEF_{50} BY TIME ABOVE .02 ppm
 CATEGORY FOR NON-ATOPICS WITH 14 PACK-YEARS OF SMOKING

	GROUP I (months $\leq .19$)		GROUP II A (.19 < months ≤ 1)		GROUP II B (months > 1)
n	140		47		36
FEV_1 ml/yr	-21	(p = .087)	-35	(p = .52)	-28
$FEVZ$ (yr) ⁻¹	-.31	(p = .40)	-.40	(p = .40)	-.42
FEF_{25-75} ml/sec-yr	-88	(p = .12)	-118	(p = .90)	-121
FEF_{50} ml/sec-yr	-106	(p = .012)	-174	(p = .072)	-108

(1) p-values are significance levels for differences between adjacent categories after controlling for other variables.

Table 20

SUMMARY STATISTICS ON 274 PARTICIPANTS BY NUMBER
OF VISITS WITH COMPLETE DIFFUSING CAPACITY
DETERMINATIONS

	Number of Visits ≥3			Number of Visits <3		
n	165			109		
% White	88.5			80.7		
% Lower Respiratory Symptoms	29.3			30.6		
% Upper Respiratory Symptoms*	46.7			26.9		
% Bronchitis	4.2			2.8		
% Interview Atopy	34.5			29.0		
% Atopic	24.8			12.7		
% Dyspnea	14.6			14.9		
% Current Cigarette Smokers	48.5			55.6		

	<i>Caption 2</i>					
	Mean	Standard Deviation	n ⁽¹⁾	Mean	Standard Deviation	n
Age (years)	36.0	11.0	165	35.9	11.8	109
Height (inches)	70.1	2.5	165	69.7	2.6	109
Pack-years	14.0	15.0	165	14.9	18.2	108
FEV ₁ % P ⁽²⁾	100.7	12.7	151	99.5	14.4	93
FVC % P	103.2	12.1	151	101.8	12.7	93
FEF % P	91.1	26.1	151	90.9	27.4	93
RV % P	100.0	24.5	139	99.0	27.9	78
TLC % P	102.0	11.7	139	100.0	11.5	78
K % P	99.9	17.4	135	99.4	17.1	77
Cumulative Exposure* (ppm-months)	.068	.031	164	.039	.023	77
Time above .02 ppm (months)	.49	.67	164	.42	.49	77

* $p < .05$

(1) n represents the number of participants with usable data.

(2) % predicted are taken from the pulmonary function measurement at the time of the initial interview or the next visit at which the pulmonary measurement was taken if it was not done at the visit of the initial interview.

Table 21

SUMMARY STATISTICS ON 274 PARTICIPANTS BY NUMBER OF VISITS WITH COMPLETE LUNG VOLUME DETERMINATIONS

	Number of Visits ≥3			Number of Visits <3		
n	182			92		
% White	87.4			81.5		
% Lower Respiratory Symptoms	28.7			31.9		
% Upper Respiratory Symptoms*	44.0			28.6		
% Bronchitis	3.8			3.3		
% Interview Atopy	34.1			28.9		
% Atopic	24.2			12.0		
% Dyspnea	13.3			17.7		
% Current Cigarette Smokers	48.4			57.1		

	Mean	Standard Deviation	n ⁽¹⁾	Mean	Standard Deviation	n
Age (years)	35.7	11.0	182	36.5	11.9	92
Height (inches)	70.1	2.5	182	69.5	2.6	92
Pack-years	13.5	14.8	182	16.2	19.0	91
FEV ₁ % ⁽²⁾	101.3	12.9	165	98.0	14.0	79
FVC % P	103.6	12.3	165	100.8	12.3	79
FEF % P	92.0	25.9	165	88.9	28.0	79
RV % P	98.8	24.6	151	100.9	28.3	66
TLC % P	101.7	11.6	151	99.5	11.6	66
K % P	99.5	17.4	146	100.2	17.1	66
Cumulative Exposure* (ppm-months)	.08	.03	181	.03	.02	60
Time Above .02 ppm (months)	.57	.75	181	.38	.45	60

*p < .05

(1) n represents the number of participants with usable data.

(2) % predicted are taken from the pulmonary function measurement at the time of the initial interview or the next visit at which the pulmonary function measurement was taken if it was not done at the visit of the initial interview.

Table 22

SUMMARY STATISTICS ON 274 PARTICIPANTS BY
COMPLETENESS OF INITIAL AND FINAL INTERVIEW

	Complete			Incomplete		
n	203			71		
% White	87.1			80.3		
% Interview Atopy	37.0			30.4		
% Atopic	22.2			14.1		
% Current Cigarette Smokers	52.2			48.6		

	Mean	Standard Deviation	n ⁽¹⁾	Mean	Standard Deviation	n
Age (years)	35.4	10.8	203	37.5	12.6	71
Height (inches)	69.9	2.6	203	69.9	2.4	71
Pack-years	13.6	14.8	203	16.5	20.1	70
FEV ₁ % P ⁽²⁾	100.5	13.4	182	99.5	13.4	62
FVC % P	103.1	12.0	182	101.6	13.2	62
FEF % P	91.4	27.2	182	89.8	24.6	62
RV % P	98.6	25.8	165	102.2	25.7	52
TLC % P	101.5	11.5	165	99.7	11.9	52
K % P	100.1	16.9	160	98.7	18.6	52
Cumulative Exposure* (ppm-months)	.082	.033	202	.013	.015	23
Time Above .02 ppm* (months)	.62	.80	202	.019	.19	23

* p < .05

(1) n represents the number of participants with usable data.

(2) % predicted are taken from the pulmonary function measurements at the time of the initial interview or the next visit at which the pulmonary function measurement was taken if it was not done at the visit of the initial interview.

Table 23

LONGITUDINAL CHANGE IN SYMPTOMS
BY CUMULATIVE EXPOSURE CATEGORY

Percent in subcategory pathway -

Cumulative Exposure $\leq$.0682

Cumulative Exposure $>$.0682

		Non-Atopic				Atopic				Non-Atopic				Atopic					
Initial INTRVW	Last Usable INTRVW	Zero PK-YRS	0-15 PK-YRS	> 15 PK-YRS	Zero PK-YRS	0-15 PK-YRS	> 15 PK-YRS	Zero PK-YRS	0-15 PK-YRS	> 15 PK-YRS	Zero PK-YRS	0-15 PK-YRS	> 15 PK-YRS	Zero PK-YRS	0-15 PK-YRS	> 15 PK-YRS	TOTAL		
YES	YES	7	15	20	2	4	3	2	4	3	2	5	10	3	4	1	25		
YES	U NO	0	3	0	2	1	0	2	1	0	1	0	1	0	0	1	3		
NO	R YES	3	9	7	2	6	1	2	6	1	2	8	3	2	2	0	23		
NO	S NO	6	9	11	2	0	3	2	0	3	2	14	6	1	4	1	35		
YES	YES	1	8	9	0	5	2	0	2	5	1	2	5	1	4	1	14		
YES	L NO	0	7	4	3	1	1	3	1	1	0	7	0	0	0	0	7		
NO	R YES	2	10	7	1	1	1	1	1	1	3	3	6	0	0	1	13		
NO	S NO	13	11	18	4	4	3	4	4	3	16	15	9	5	5	1	51		
YES	E YES	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0		
YES	B NO	0	5	1	0	0	0	0	0	0	0	1	0	0	0	0	1		
NO	R YES	1	0	5	0	1	0	0	1	0	1	2	1	1	1	1	7		
NO	O NO	15	31	32	8	9	7	8	9	7	19	24	19	5	9	2	78		
YES	D YES	0	5	5	0	0	0	0	0	0	1	3	2	0	0	0	6		
YES	Y NO	1	1	2	1	2	0	1	0	3	0	0	3	0	0	0	3		
NO	S YES	1	3	5	2	1	1	2	1	1	1	4	5	1	2	2	15		
NO	P NO	14	27	26	5	8	6	5	8	6	18	20	10	5	7	1	61		

Table 24

LONGITUDINAL CHANGE IN SYMPTOMS
BY TIME ABOVE .02 ppm CATEGORY

Time above .02 ppm ≤ 0.19

Last Usable Initial INTRVW		Non-Atopic				Atopic			
		Zero PK-YRS	0-15 PK-YRS	>15 PK-YRS	TOTAL	Zero PK-YRS	0-15 PK-YRS	>15 PK-YRS	TOTAL
YES	YES	6	16	22		3	5	3	55
YES	NO	0	2	0	6	2	1	1	6
NO	YES	4	10	7	29	2	5	1	29
NO	NO	5	11	11	37	2	1	3	37
YES	YES	2	6	8	24	1	4	3	24
YES	NO	0	9	4	18	3	1	1	18
NO	YES	2	9	9	23	1	1	1	23
NO	NO	15	15	19	62	4	6	3	62
YES	YES	0	0	0	1	0	1	0	1
YES	NO	0	4	1	5	0	0	0	5
NO	YES	1	0	5	8	1	1	0	8
NO	NO	18	35	34	113	8	10	8	113
YES	YES	0	4	6	10	0	0	0	10
YES	NO	1	1	2	6	1	1	0	6
NO	YES	2	3	5	15	2	1	2	15
NO	NO	16	31	27	96	6	10	6	96

Time above .02 > 0.19

		Non-Atopic				Atopic			
		Zero PK-YRS	0-15 PK-YRS	>15 PK-YRS	TOTAL	Zero PK-YRS	0-15 PK-YRS	>15 PK-YRS	TOTAL
		3	4	8		2	3	1	21
		1	1	1	3	0	0	0	3
		7	7	3	22	2	3	0	22
		6	12	6	29	1	3	1	29
		0	4	6	15	0	5	0	15
		0	5	0	5	0	0	0	5
		3	4	4	12	0	0	1	12
		14	11	8	42	5	3	1	42
		0	0	0	0	0	0	0	0
		0	2	0	2	0	0	0	2
		1	2	1	6	0	1	1	6
		16	20	17	67	5	8	1	67
		1	4	1	6	0	0	0	6
		0	0	3	4	0	1	0	4
		0	4	5	13	1	2	1	13
		16	16	9	51	4	5	1	51

Table 25

"Clinical Reactors" to TDI

I. D.	Age in 1973	Smoking in Pack-Years (Initial)	Challenge Results	Atopic ≥2 Skin Test	Known Major Exposure	Time in Plants Before Symptoms	Job When Became Symptomatic	Comments
0033	47	47	-	0	+	<1 week	B Op TDI	transferred out of TDI, then resigned from plant
0035	26	7		0	0	7 months	D Op TDI	still works in TDI
0037	27	7	+	0	0	2 months	D Op TDI	transferred out of TDI then quit for medical reasons
0045	53	11		0	0	"weeks"	Foreman TDA	transferred out of TDI
0046	26	6	-	+	+	<2 months	Chemical Engineer, East Zone	resigned from plant
0110	30	8	-	+	+	4 months	Welder TDI/TDA	transferred out of TDI
0179	20	0		+	0	3 years	C Op TDA	still works in TDI
0187	26	0	+		+	4 months	Pipefitter TDI/TDA	transferred out of TDI
0197	61	0	-	0	+	4 months	Pipefitter TDI/TDA	resigned from plant
0200	32	0		0	0	2½ years	Pipefitter TDI/TDA	transferred out of TDI
0218	57	0		0	0	3 months	Insulator TDI/TDA	transferred out of TDI
0256	33	7		0	+	2 years	Pipefitter TDI/TDA	transferred out of TDI

Table 26

TDI Environmental Exposure Evaluation (8/73 to 7/75)

Location	Percent Weekly TWA Excursions Above .005	Percent Weekly TWA Excursions Above 0.02
TDI Plant	82.7%	24.7%
TDI Drumming Building	60.3%	6.4%

Table 27

PERSONNEL MONITORING SCHEDULE

(January 7 - May 28, 1976)

January	7 thru January	11	"A" Shift	4 p.m. - 12 a.m.
January	14 thru January	18	"B" Shift	4 p.m. - 12 a.m.
January	21 thru January	25	"C" Shift	4 p.m. - 12 a.m.
January	28 thru February	1	"D" Shift	4 p.m. - 12 a.m.
February	6 thru February	10	"D" Shift	8 a.m. - 4 p.m.
February	13 thru February	17	"A" Shift	8 a.m. - 4 p.m.
February	20 thru February	24	"B" Shift	8 a.m. - 4 p.m.
February	27 thru March	2	"C" Shift	8 a.m. - 4 p.m.
March	6 thru March	10	"C" Shift	12 a.m. - 8 a.m.
March	13 thru March	17	"D" Shift	12 a.m. - 8 a.m.
March	20 thru March	24	"A" Shift	12 a.m. - 8 a.m.
March	27 thru March	31	"B" Shift	12 a.m. - 8 a.m.
April	5 thru April	9	Maintenance	8 a.m. - 4 p.m.
April	12 thru April	16	Maintenance	8 a.m. - 4 p.m.
April	19 thru April	23	Maintenance	8 a.m. - 4 p.m.
April	26 thru April	30	Maintenance	8 a.m. - 4 p.m.
May	3 thru May	7	Drumming Lab	8 a.m. - 4 p.m.
May	10 thru May	14	Drumming Lab	8 a.m. - 4 p.m.
May	17 thru May	21	Drumming Lab	8 a.m. - 4 p.m.
May	24 thru May	28	Drumming Lab	8 a.m. - 4 p.m.

Table 28

COMPARISON OF TDI MONITOR VS. PERSONAL MONITOR

duced from
available copy.



Name	Plant	Date	Exposure in Minutes						Total ppm.	Time- weighted average	Shift
			.005	.01	.02	.04	.06	.08			
la	TDI	5-19-75	101.2	32.2	0	0	0	0	.0349	.0044	8 AM 4 PM
Production Worker 1	TDI	5-19-75	324	306	270	207	192	189	.200	.025	8 AM 4 PM
Production Worker 2	TDI	5-19-75	168	87	54	9	0	0	.054	.0068	8 AM 4 PM
ea	TDI	5-20-75	16.1	11.5	0	0	0	0	.0139	.0017	8 AM 4 PM
Production Worker 1	Unknown	5-20-75	195	162	120	39	0	0	.090	.0113	8 AM 4 PM
Production Worker 2	TDI	5-20-75	330	174	93	39	24	21	.105	.0131	8 AM 4 PM
ea	TDI	5-22-75	0	0	0	0	0	0	.0104	.0013	8 AM 4 PM
Production Worker 1	Unknown	5-22-75	407	384	183	39	9	0	.154	.0193	8 AM 4 PM
Production Worker 2	TDI	5-22-75	327	138	48	15	9	9	.080	.010	8 AM 4 PM
ea	TDI	6-25-75	200.1	140.3	87.4	20.7	0	0	.124	.0155	4 PM 11 PM
Production Worker 1	TDI	6-25-75									4 PM 11 PM
Production Worker 2	TDI	6-25-75	12	0	0	0	0	0	.019	.0024	4 PM 11 PM
Production Worker 3	TDI	6-25-75	9	0	0	0	0	0	.018	.0023	4 PM 11 PM
ea	TDI	6-26-75	190.9	165.6	115	20.7	13.8	13.8	.1213	.0152	4 PM 11 PM
Production Worker 1	TDI	6-26-75	69	15	0	0	0	0	.020	.0025	4 PM 11 PM
Production Worker 2	Phosgene	6-26-75	36	6	0	0	0	0	.002	.00025	4 PM 11 PM
Production Worker 3	TDI	6-26-75	207	84	15	0	0	0	.047	.0059	4 PM 11 PM
Production Worker 4	TDI	6-26-75	51	21	6	0	0	0	.036	.0045	4 PM 11 PM
ea	Drumming	5-20-75	400.2	299	69	43.7	41.4	41.4	.1490	.0186	8 AM 4 PM
Production Worker 1	Drumming	5-20-75	309	72	45	9	0	0	.066	.0083	8 AM 4 PM
Production Worker 2	Drumming	5-20-75	174	48	0	0	0	0	.036	.0045	8 AM 4 PM
Production Worker 3	Drumming	5-20-75	51	30	0	0	0	0	.022	.0028	8 AM 4 PM
ea	Drumming	5-23-75	11.5	6.9	0	0	0	0	.0297	.0037	8 AM 4 PM
Production Worker 1	Drumming	5-23-75									8 AM 4 PM
Production Worker 2	Drumming	5-23-75	360	6	0	0	0	0	.050	.0063	8 AM 4 PM
Production Worker 3	Drumming	5-23-75	21	0	0	0	0	0	.016	.002	8 AM 4 PM

Table 29

SUMMARY OF PERSONAL MONITORING FOR PHOSGENE
IN A TDI MANUFACTURING PLANT

Job Title	Location	Monitoring Period Month-Year	Shifts*	Number of Workers	Number of Readings	Concentration of Phosgene - PPM		
						Mean 8-hr TWA	±	SD
Phosgene Operator	Phosgene Plant	3/76-12/76	1,2,3	10	71	0.004	±	0.004
TDI Operator	TDI Plant	3/76- 4/76	1,3	2	6	0.004	±	0.003
DNT Operator	TDA Plant	3/76	3	3	14	0.004	±	0.003
Maintenance	TDI and Phosgene Plant	5/76-12/76	1	6	22	0.011	±	0.017

*Shift 1 8 a.m. - 4 p.m.
 Shift 2 4 p.m. -12 midnight
 Shift 3 12 midnight - 8 a.m.

HISTOGRAM OF 8-HOUR TIME-WEIGHTED AVERAGES (LOG-SCALE)

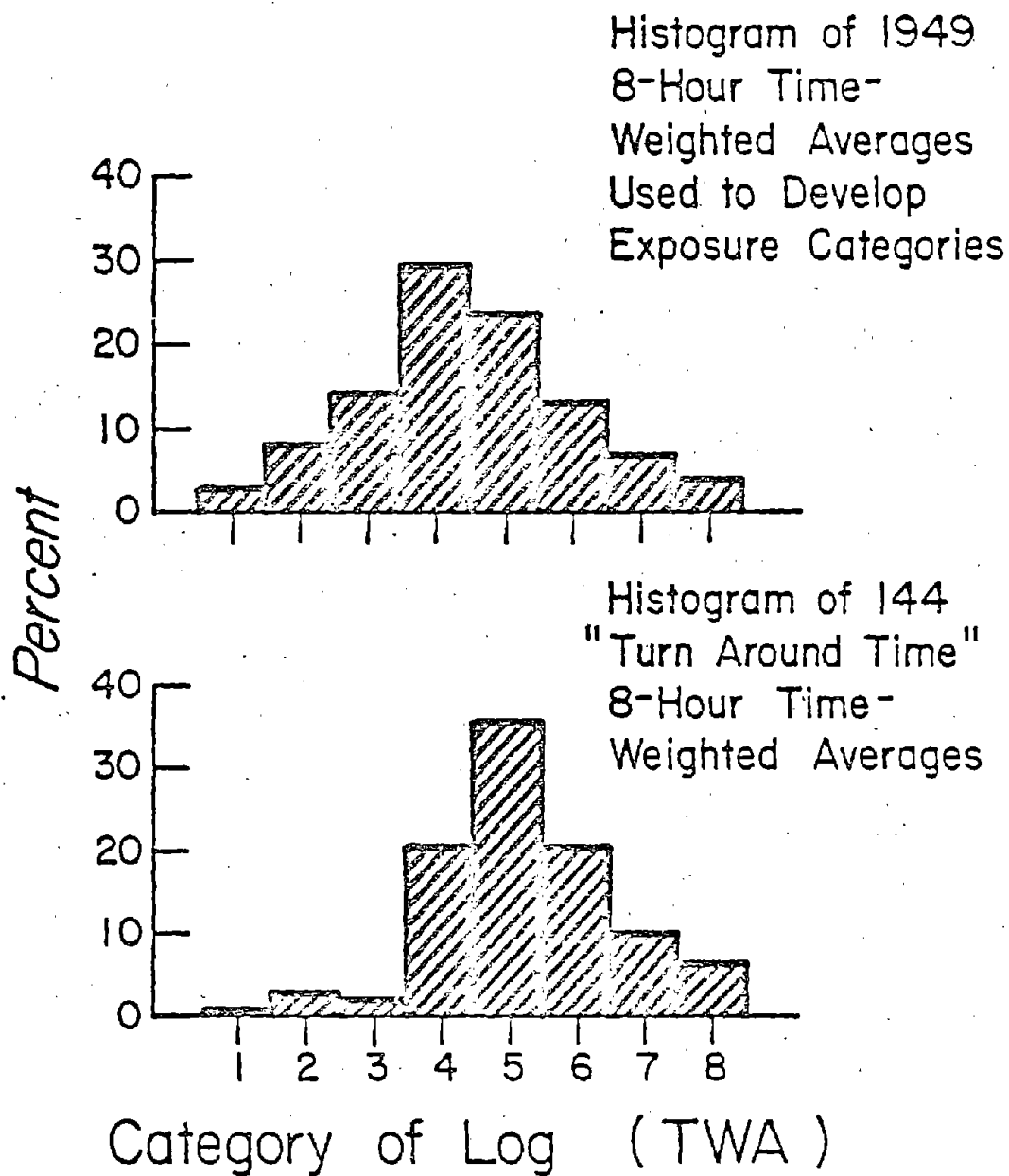


Figure 1

HISTOGRAM OF 8-HOUR TIME-WEIGHTED AVERAGES BY EXPOSURE CATEGORY (LOG SCALE)

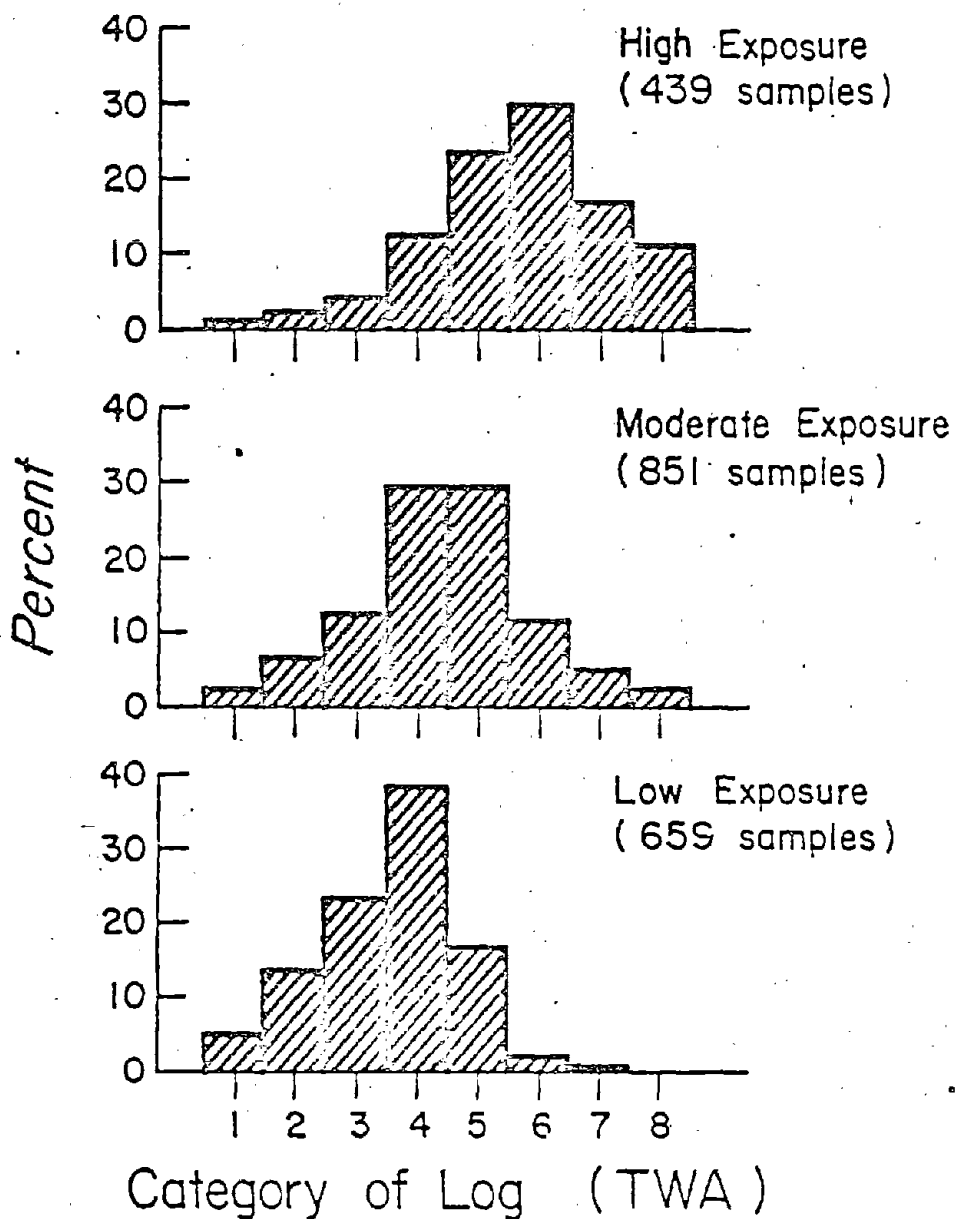
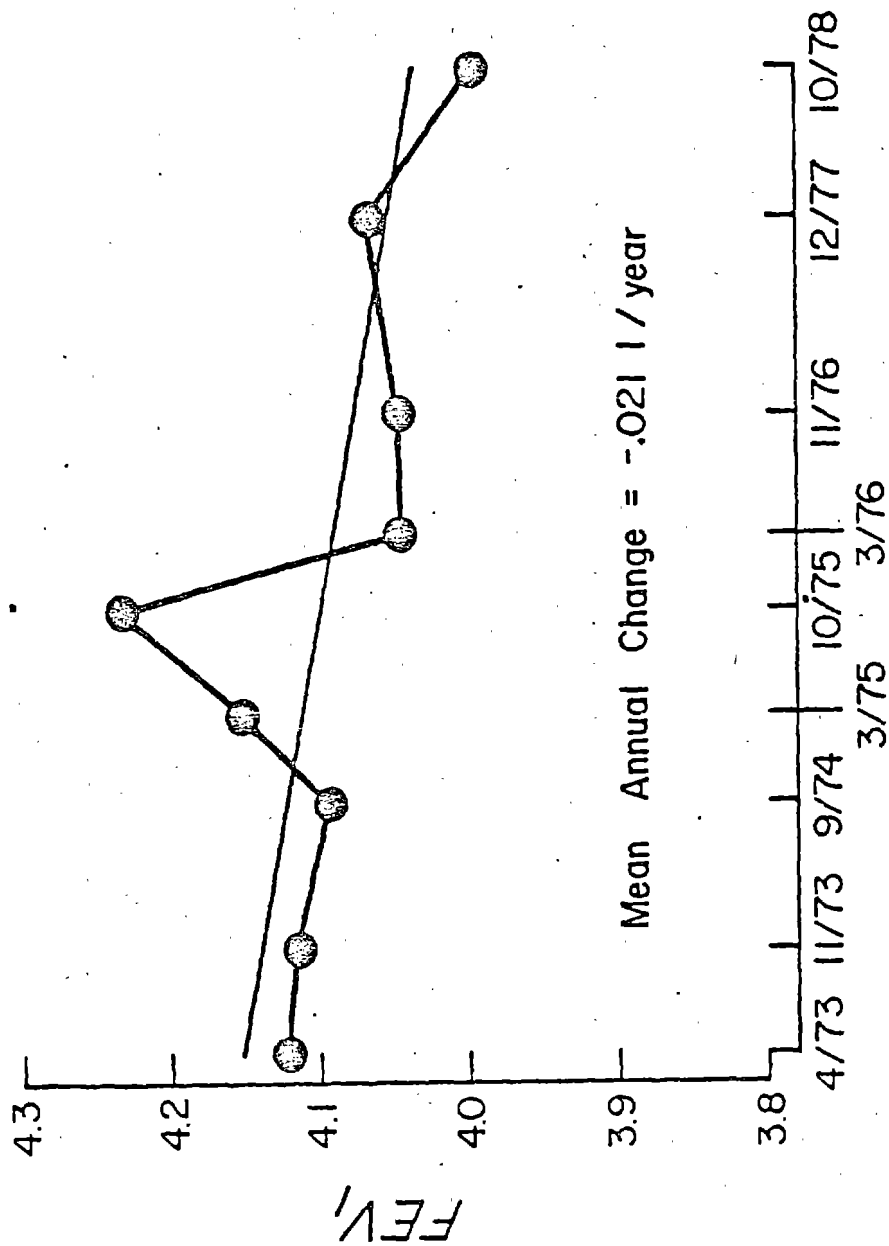


Figure 2

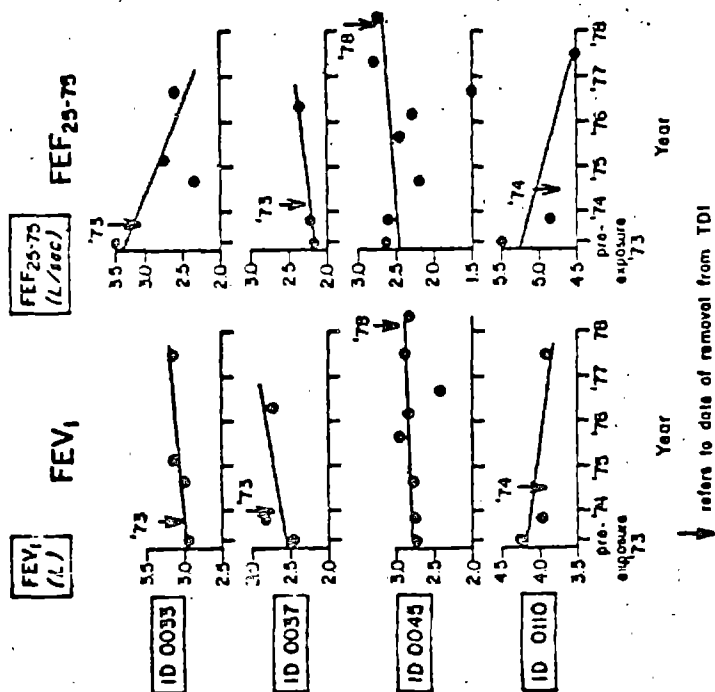
FEV₁ MEAN BY VISIT FOR THE 33 PARTICIPANTS WITH COMPLETE SPIROMETRY AT ALL NINE VISITS



Visit Date

Figure 3

TDI REACTORS



TDI REACTORS

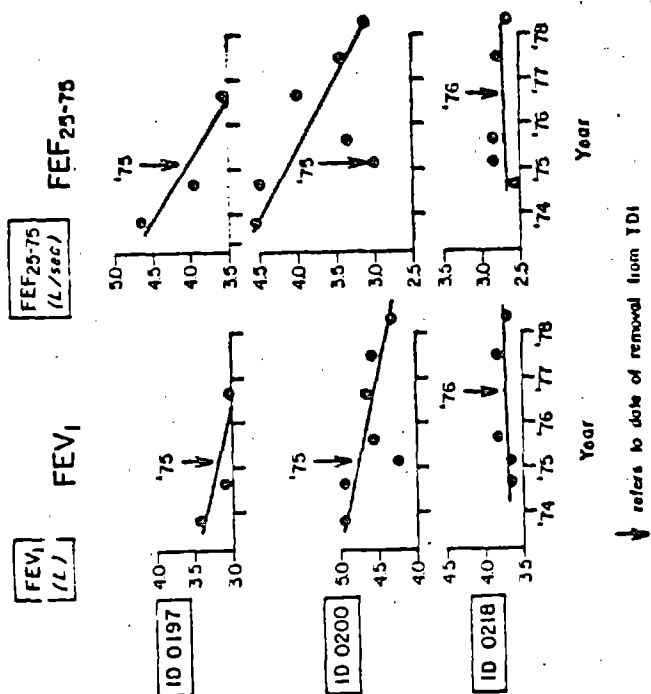


Figure 4

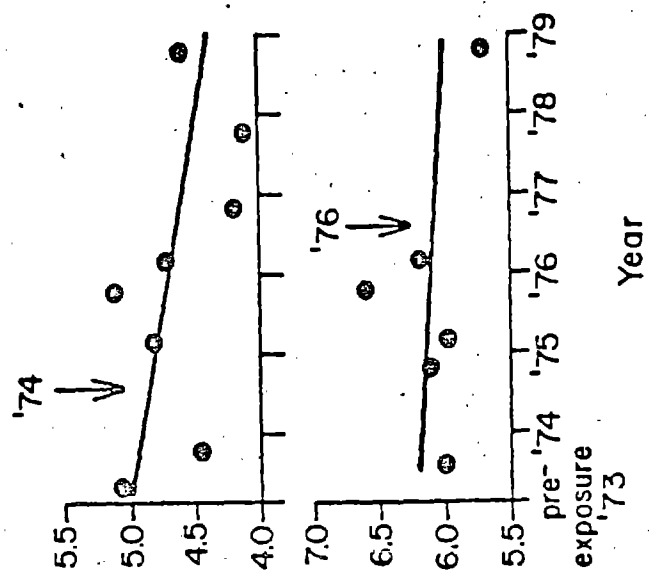
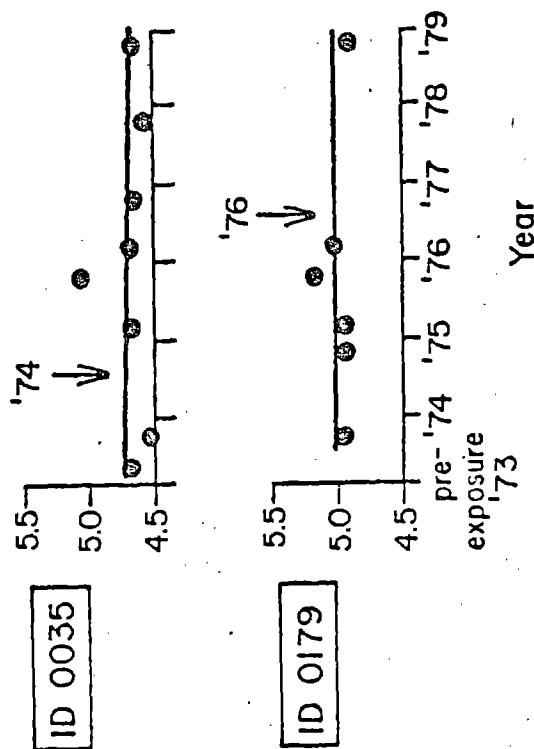
TDI REACTORS

FEV₁
(L)

FEV₁

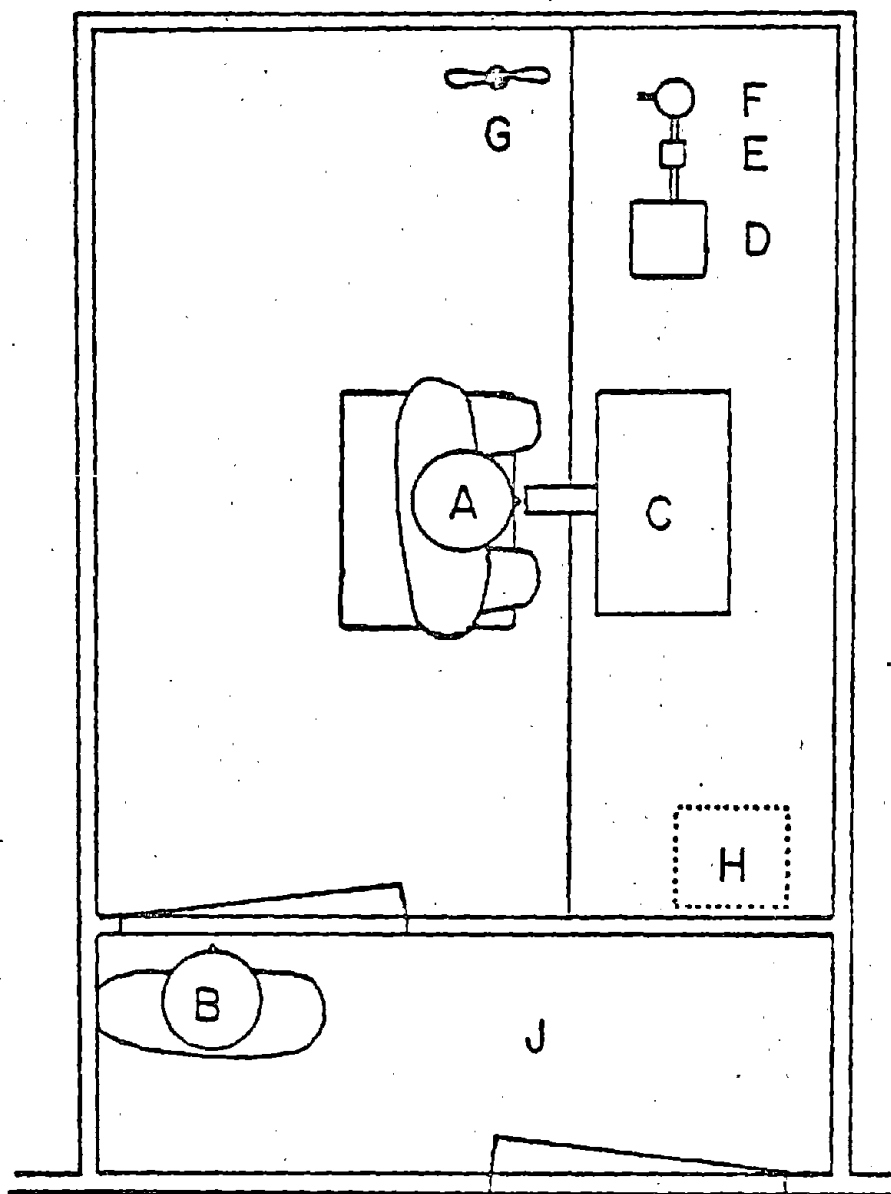
FEF₂₅₋₇₅
(L/sec)

FEF₂₅₋₇₅



↓ refers to date of sensitization to TDI

Figure 5



- A = challenge subject
- B = observer
- C = TDI monitor
- D = air pump
- E = rotameter
- F = TDI container
- G = circulation fan
- H = exhaust (overhead)
- J = air lock

FIGURE 6

SCHEMATIC DIAGRAM OF PROVOCATIVE
INHALATION CHALLENGE CHAMBER

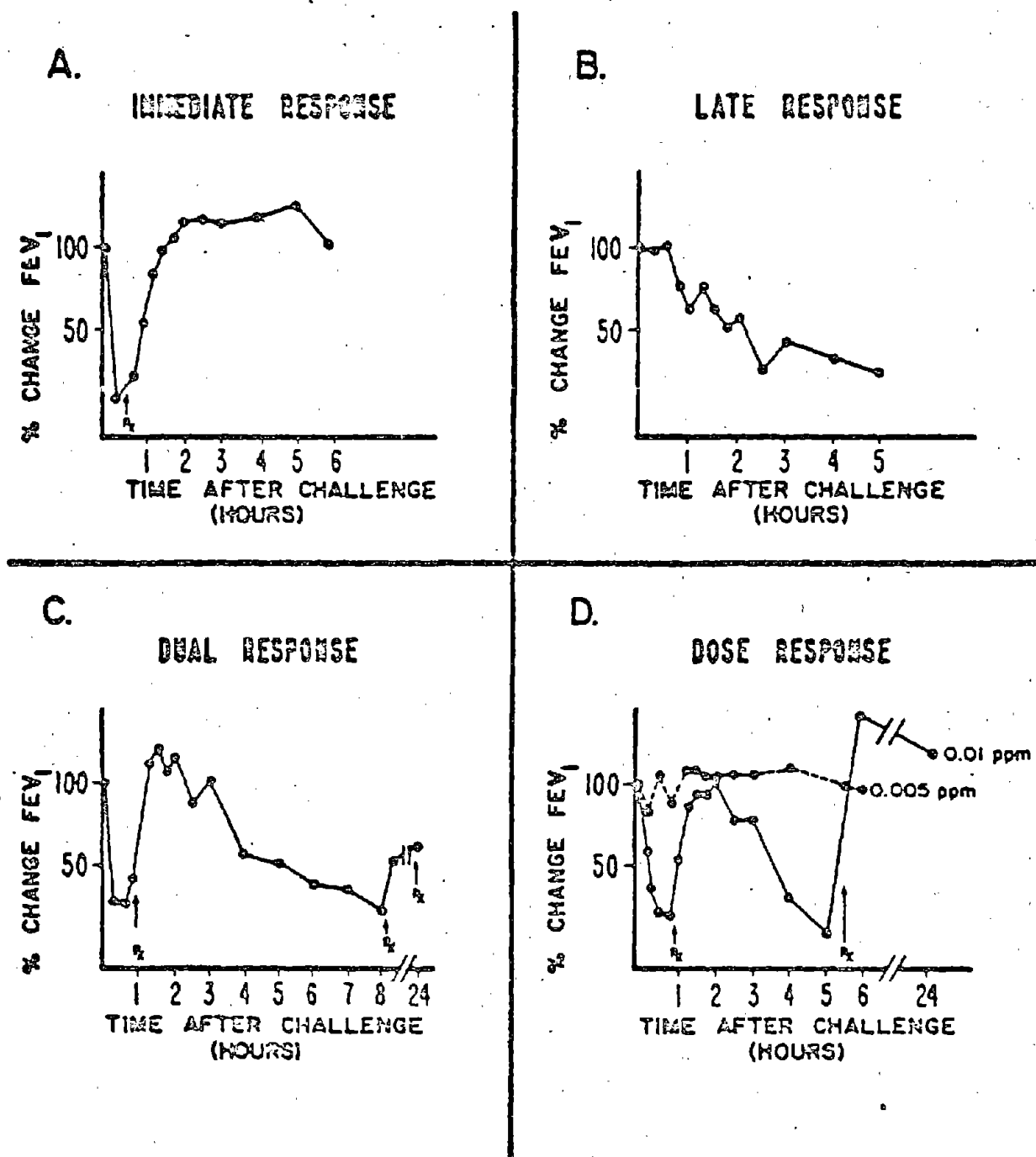
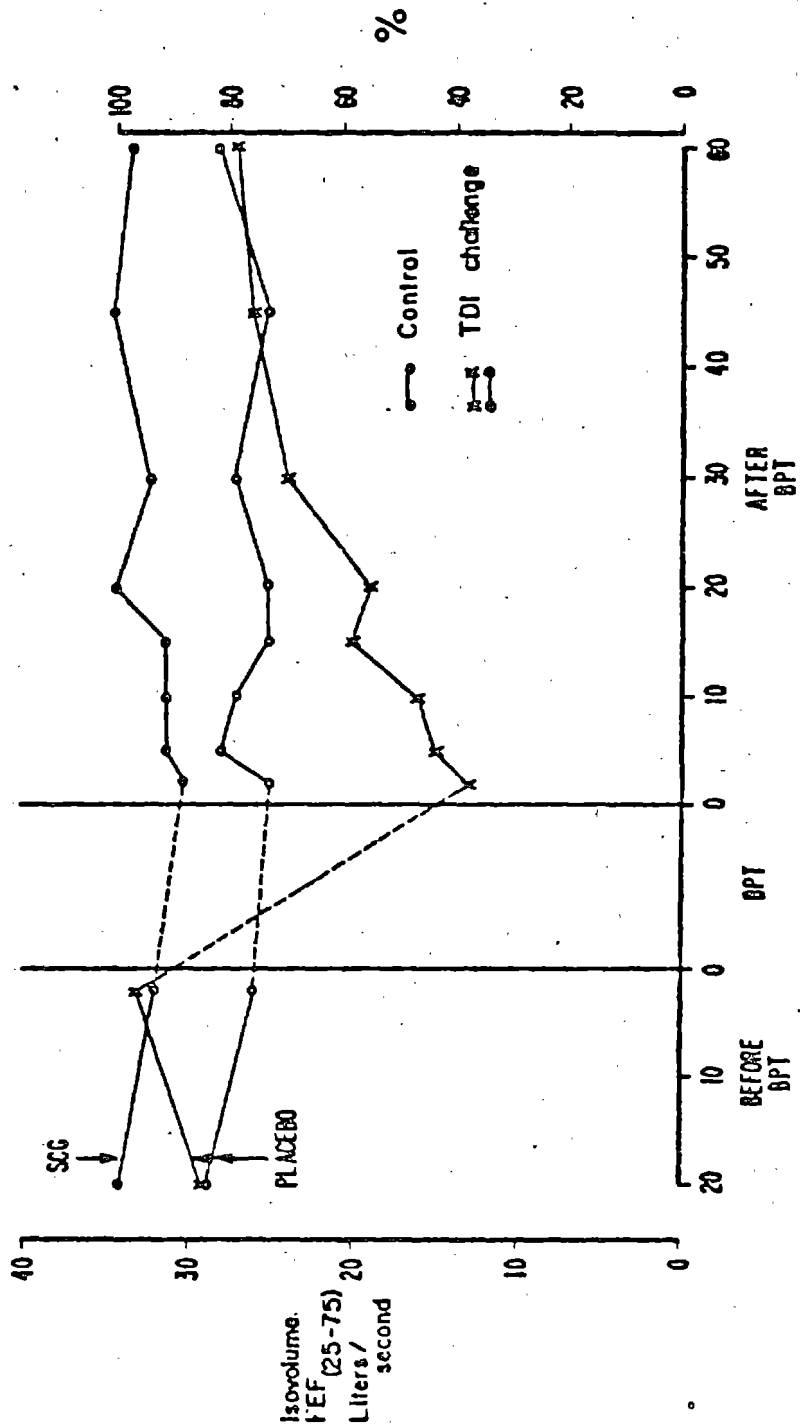


Figure 7

Respiratory Response to Provocative Inhalation
Challenge with TDI

EFFECT OF CROMALYN ON TDI INDUCED ASTHMA



Time in Minutes

Figure 8

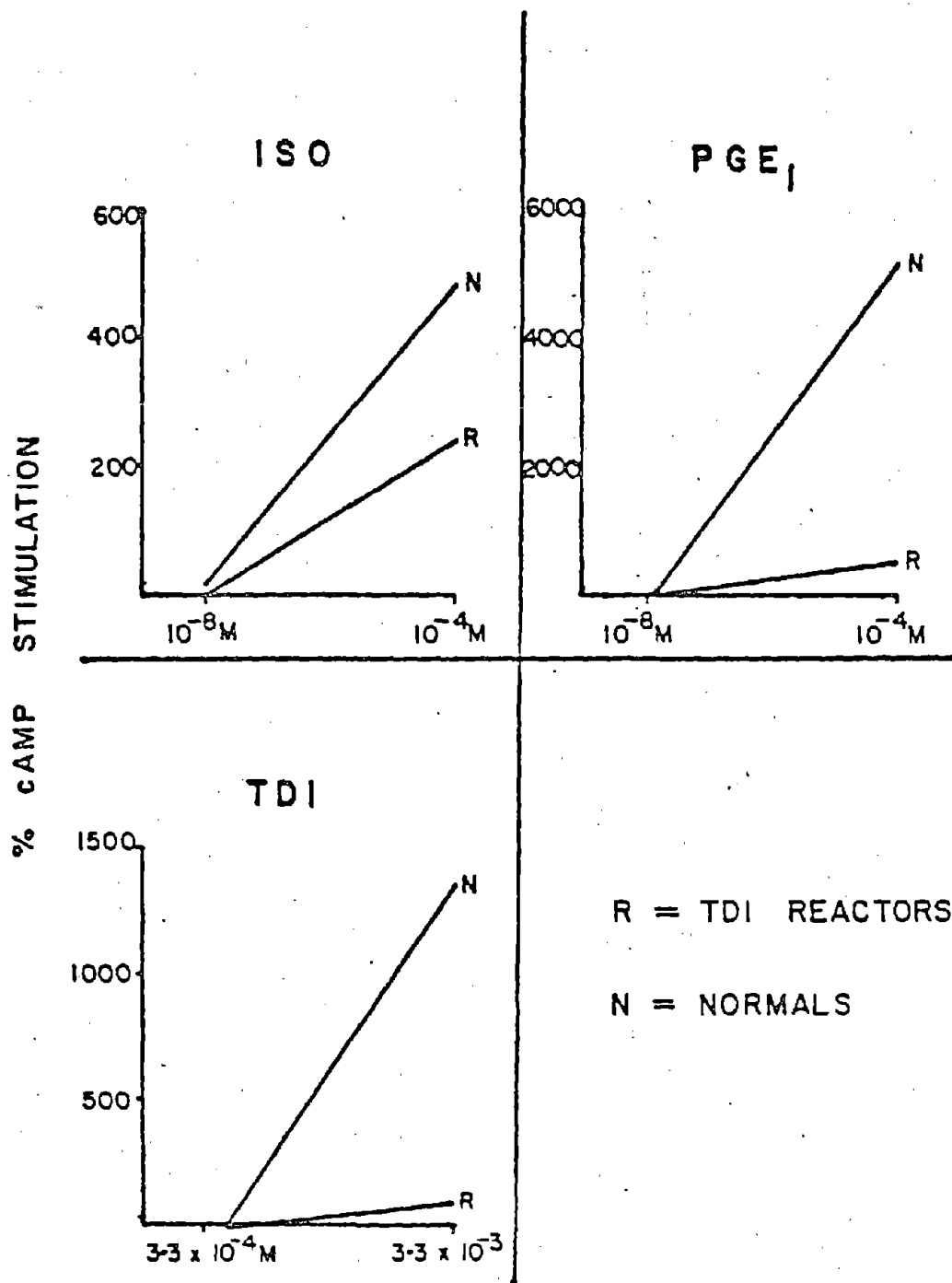


Figure 9

Cyclic Adenosine Monophosphate Dose Response
Slopes of TDI Reactors and Normal Individuals
to Stimulation with Agonists: Isoproterenol,
Prostaglandin E₁, and TDI

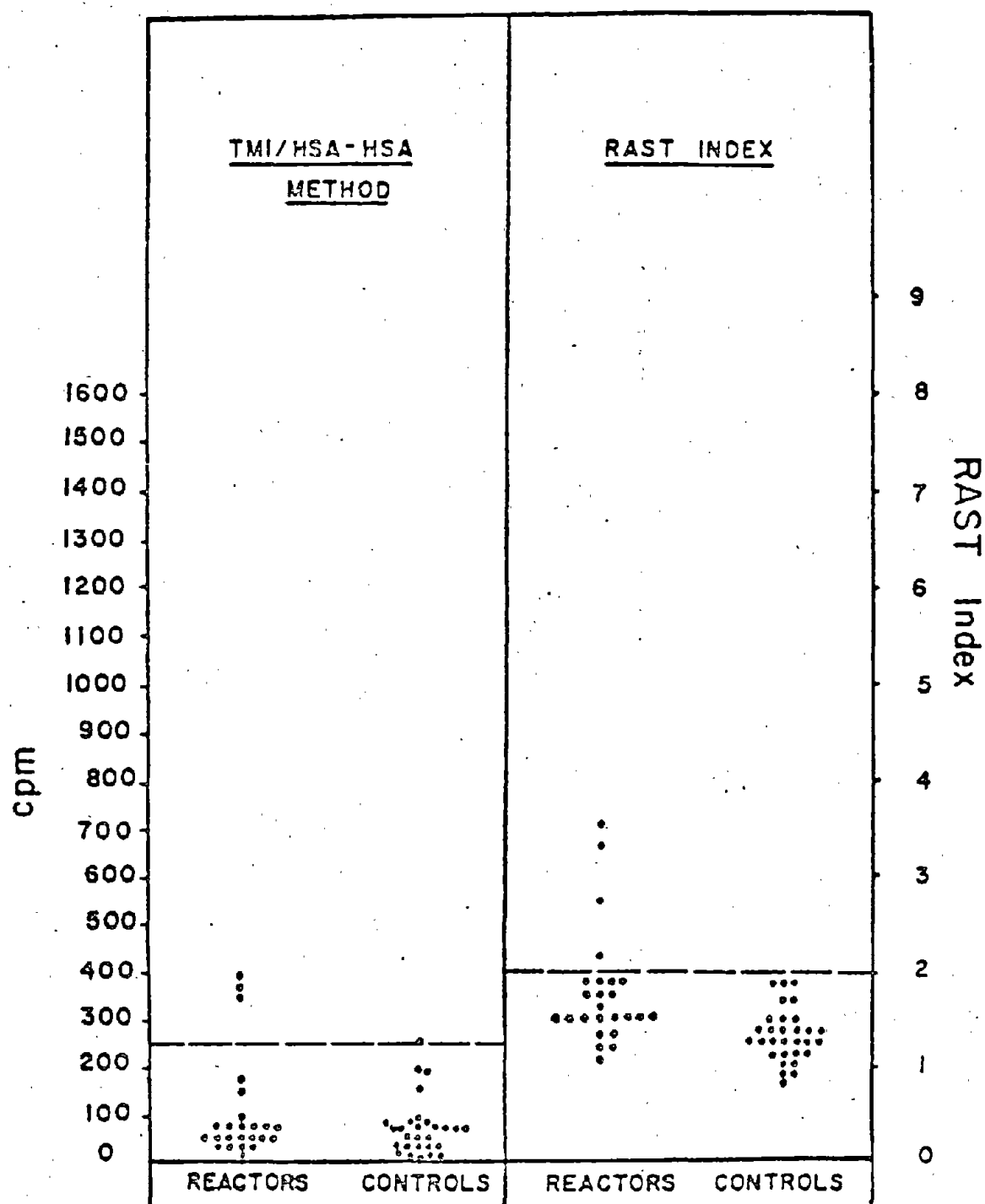


Figure 10

Radioallergosorbent Tests with p-tolyl Monoisocyanate
of Sera from TDI Reactors and Controls

TYPICAL RECORDER PRINTOUT FROM TDI AREA MONITOR

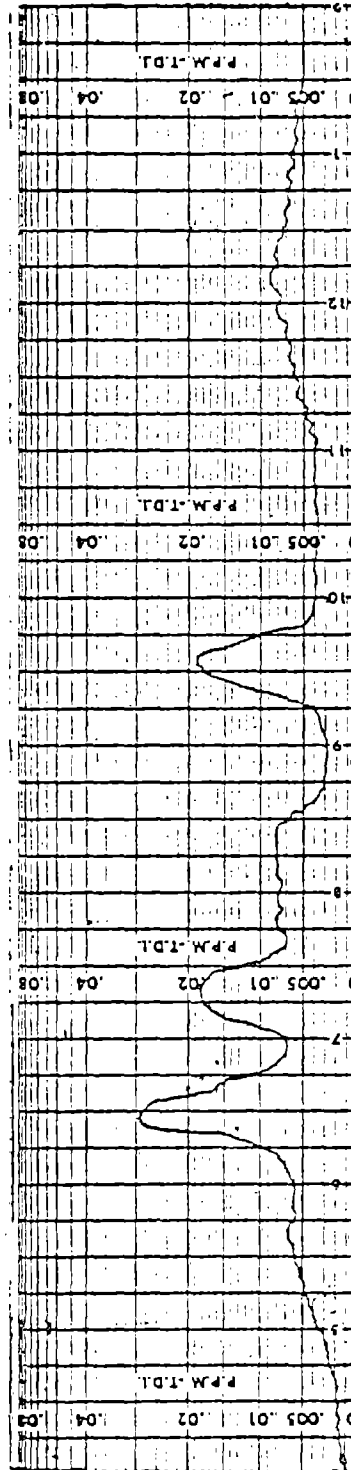


Figure 11

CONCURRENT IMPINGER
AND MONITOR TDI LEVELS
(field)

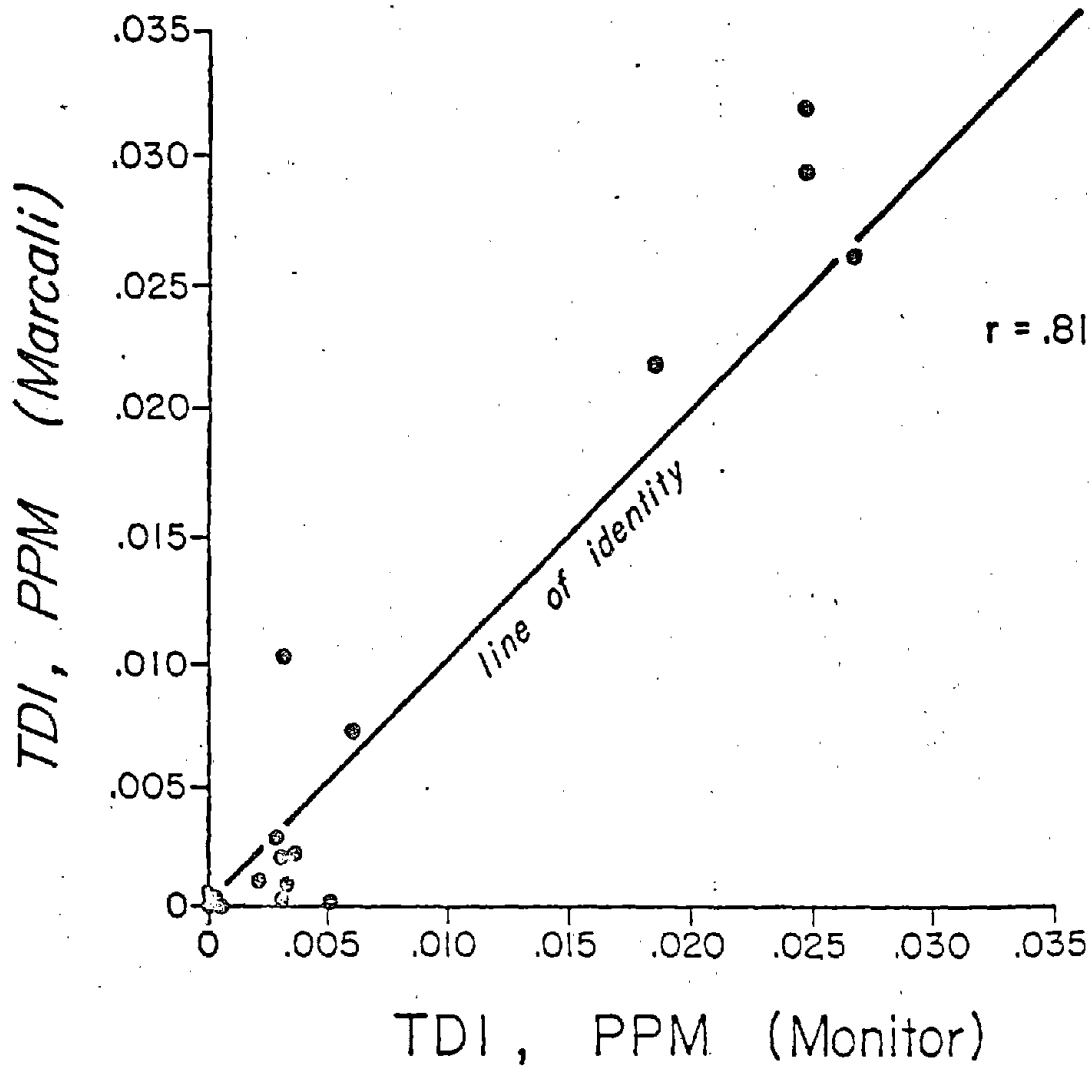
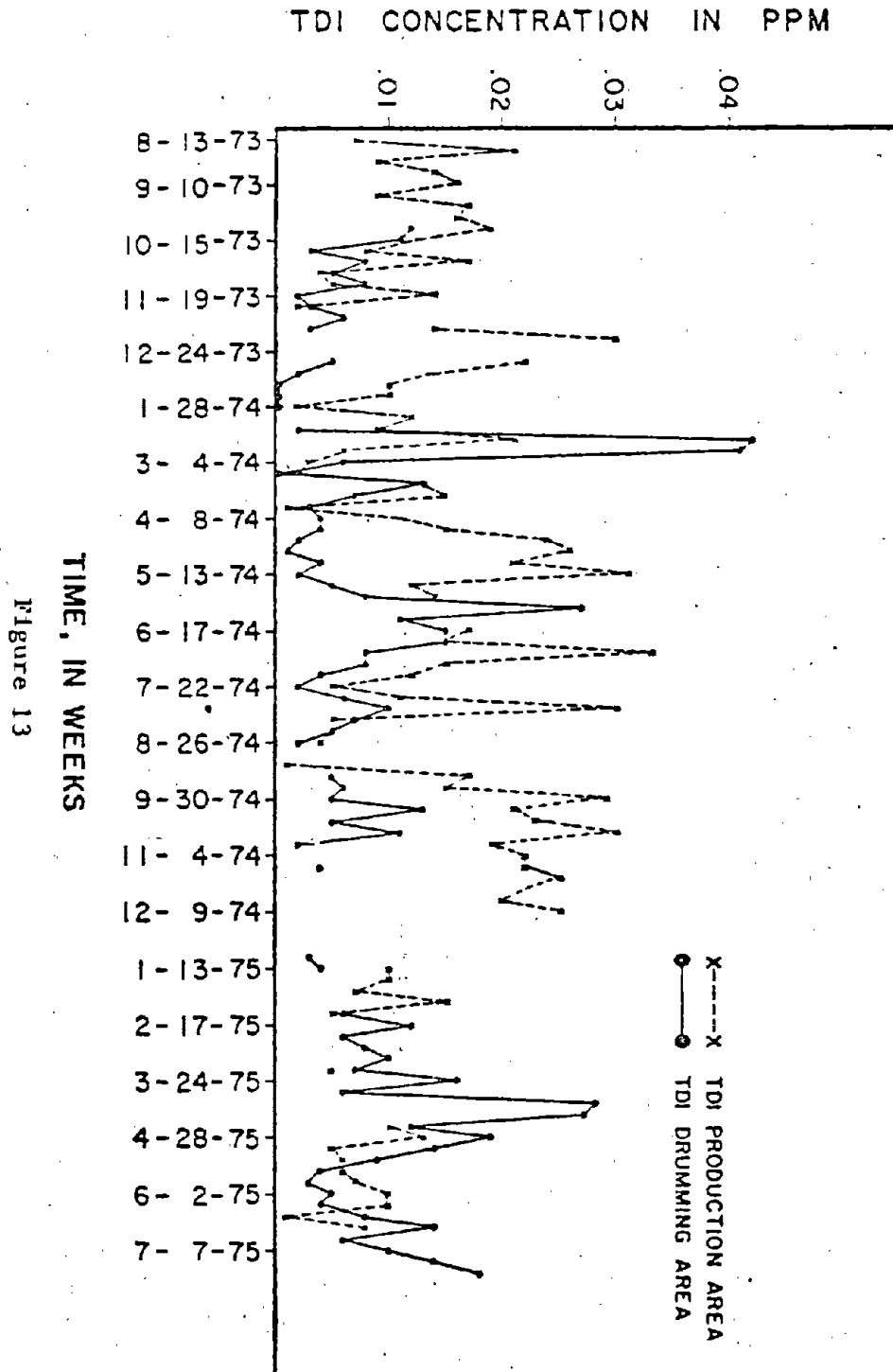


Figure 12



TDI PLANT

HISTOGRAM OF WEEKLY TWA

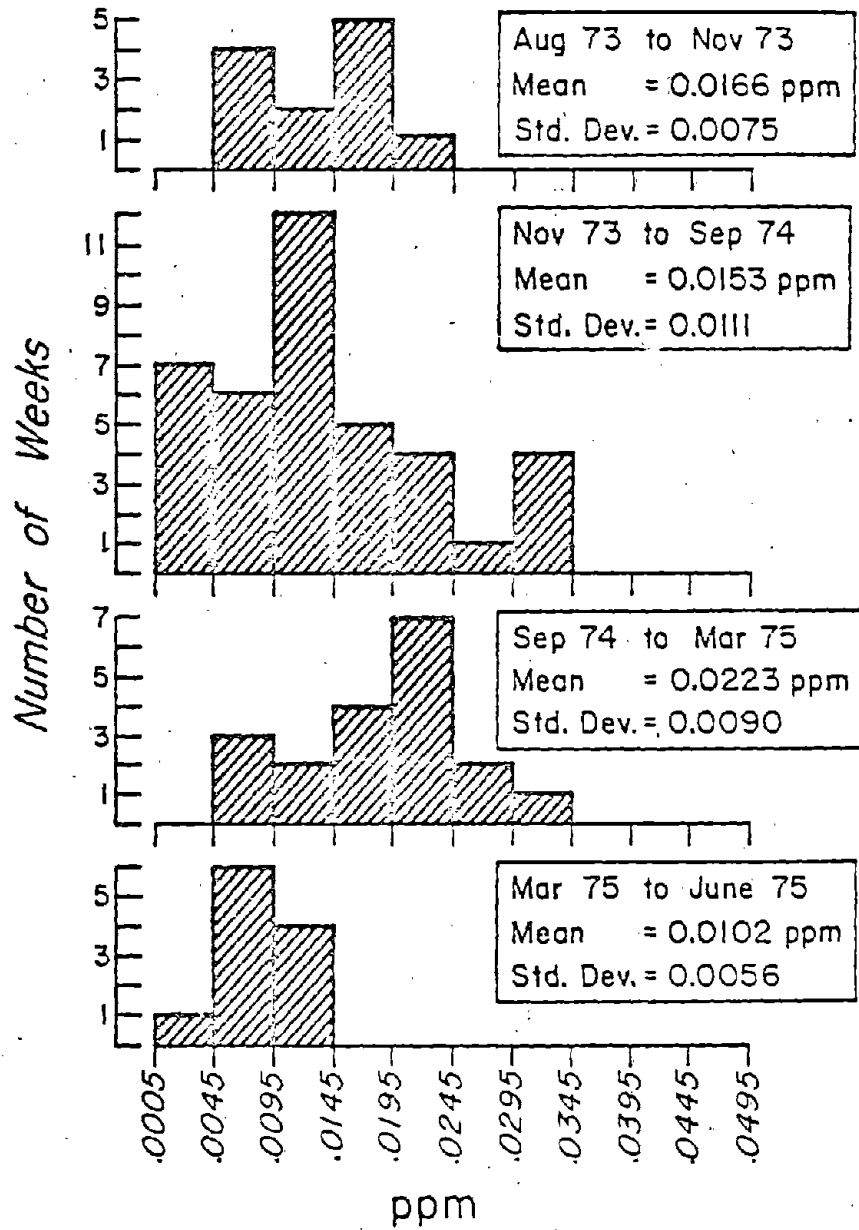


Figure 14

TDI DRUMMING BUILDING

HISTOGRAM OF WEEKLY TWA

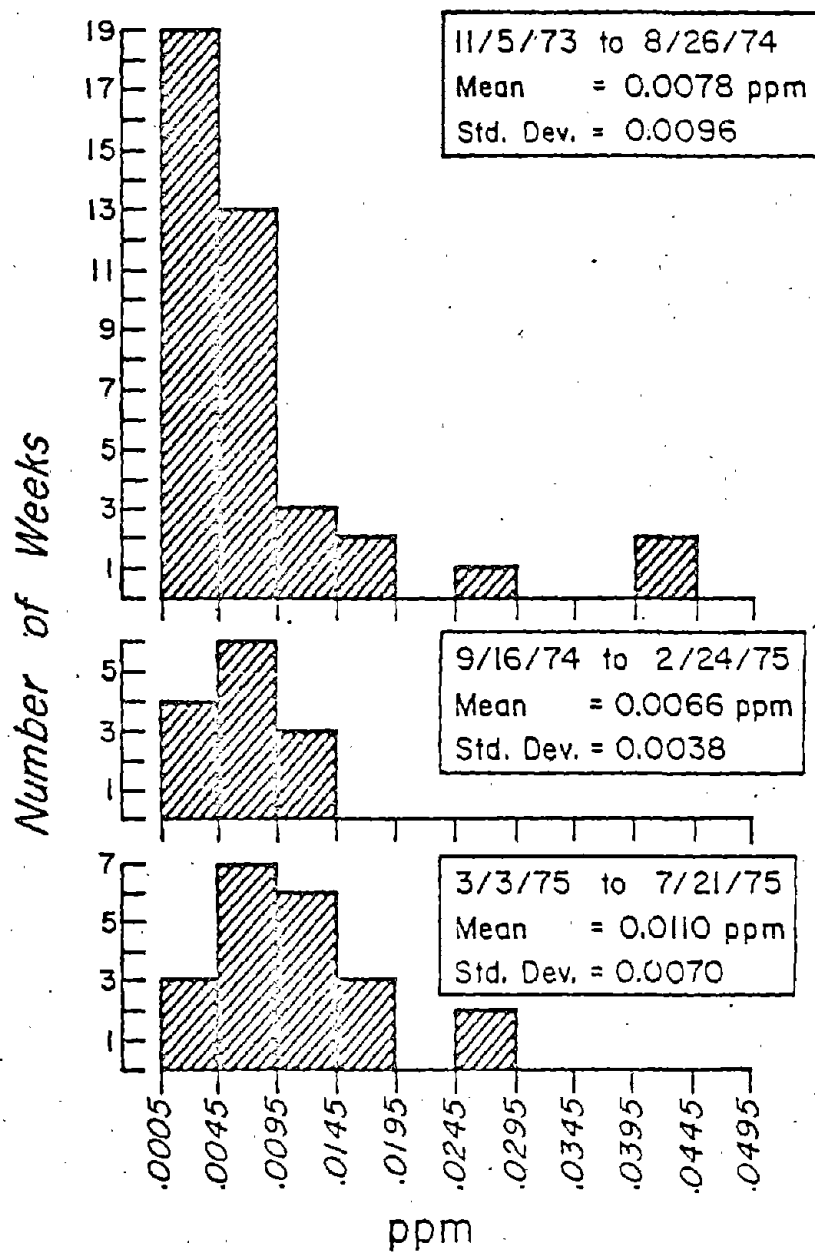


Figure 15

TYPICAL RECORDER PRINTOUT FROM TDI PERSONAL MONITOR

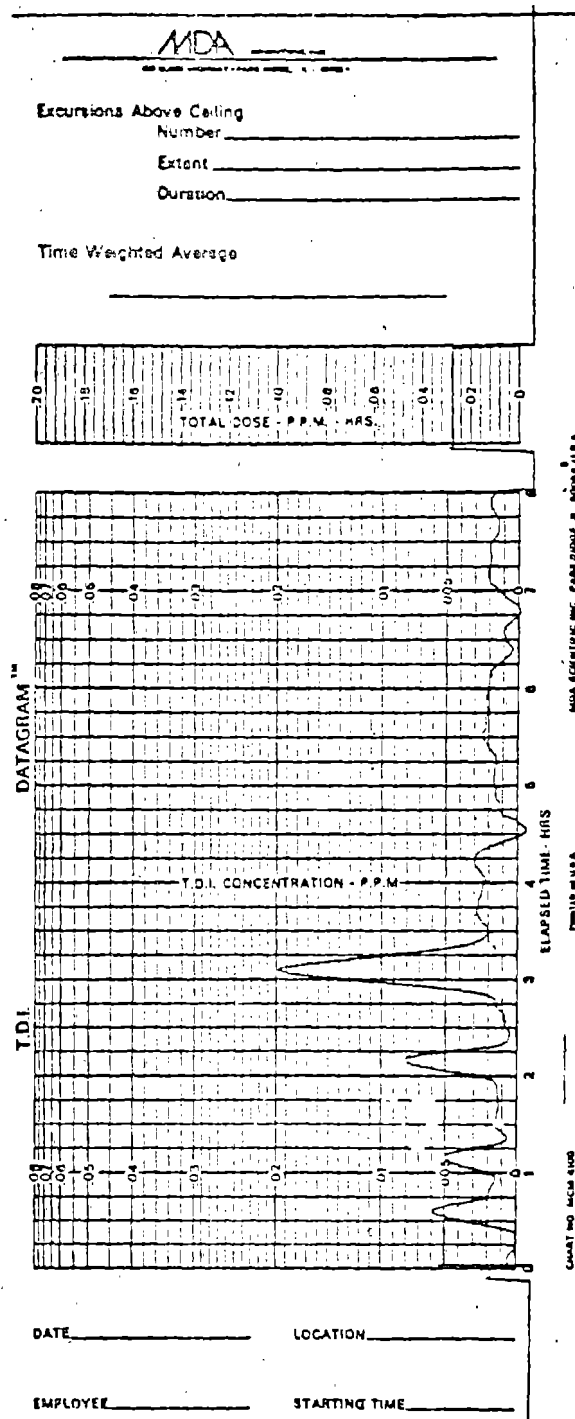


Figure 16

INTERFERENCE STUDIES OF TDI PAPER TAPE MONITORS

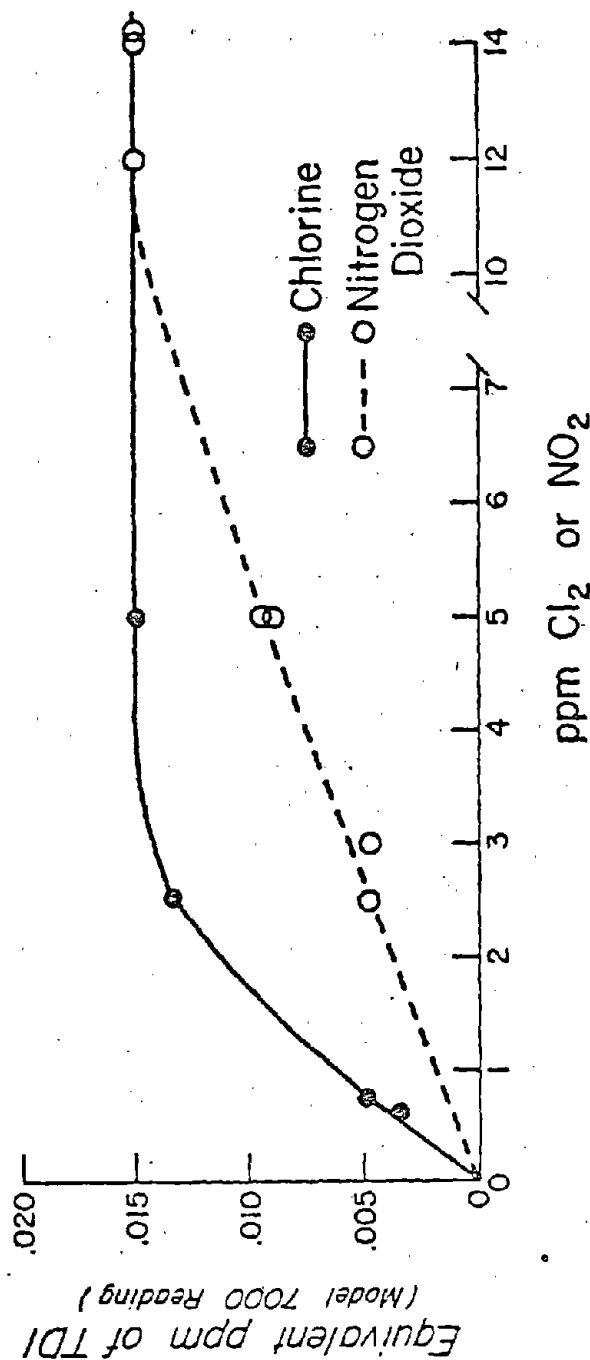
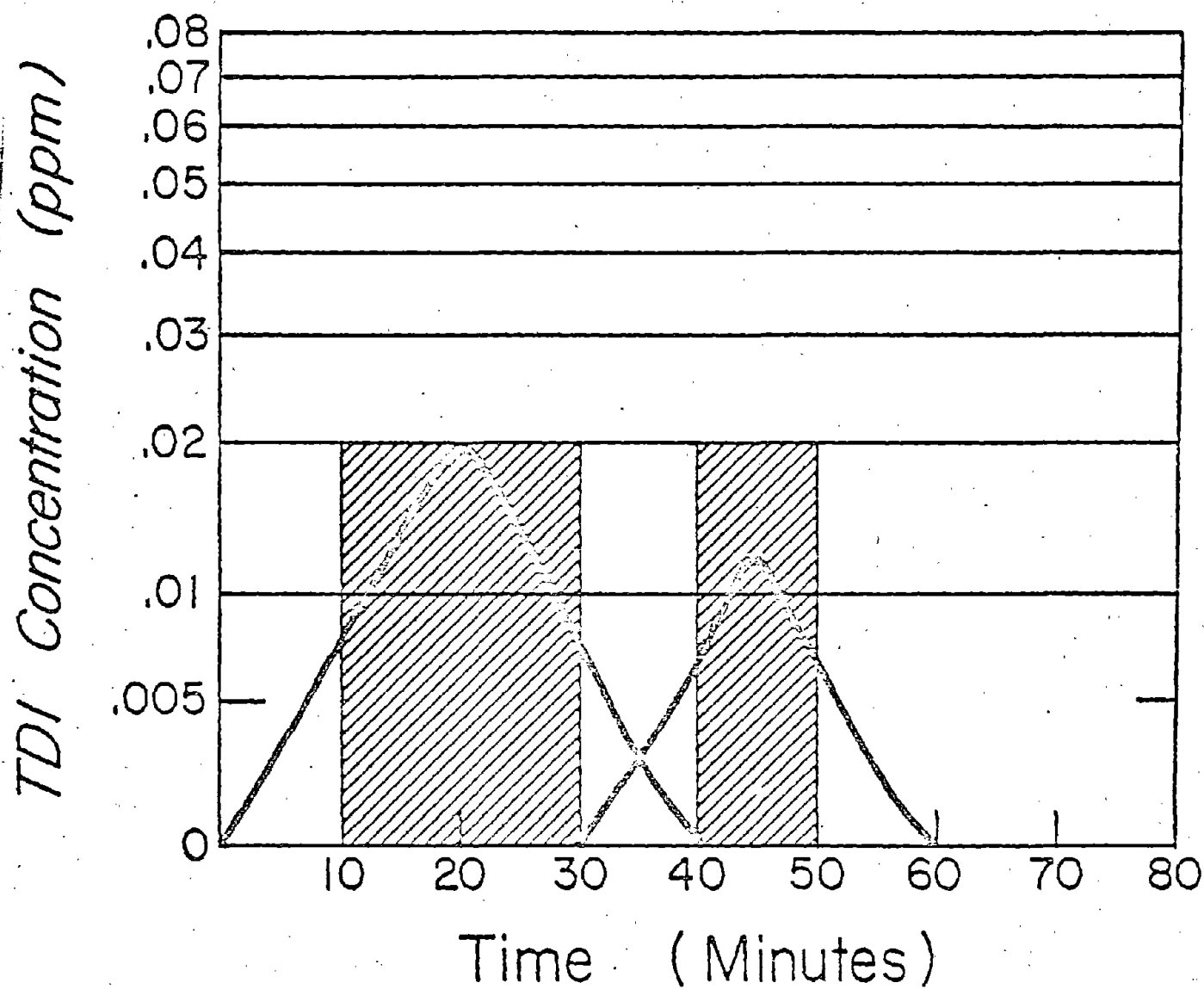


Figure 17

TDI DATAGRAM



Time Scale Expanded.

Figure 18

EFFECT OF TEMPERATURE ON MODEL 7000 TDI MONITOR

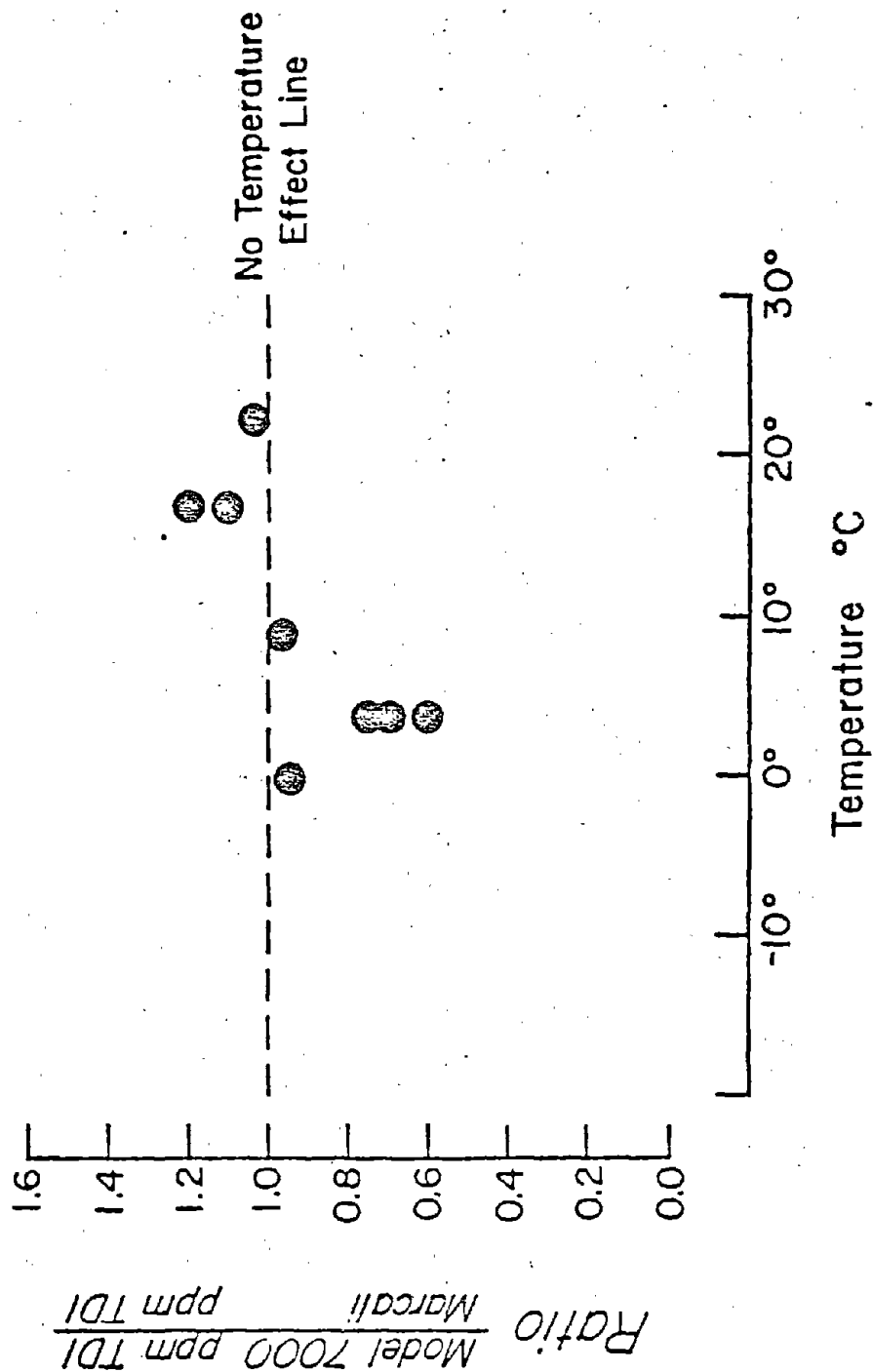


Figure 19

EFFECT OF HUMIDITY ON MODEL 7000 TDI MONITOR

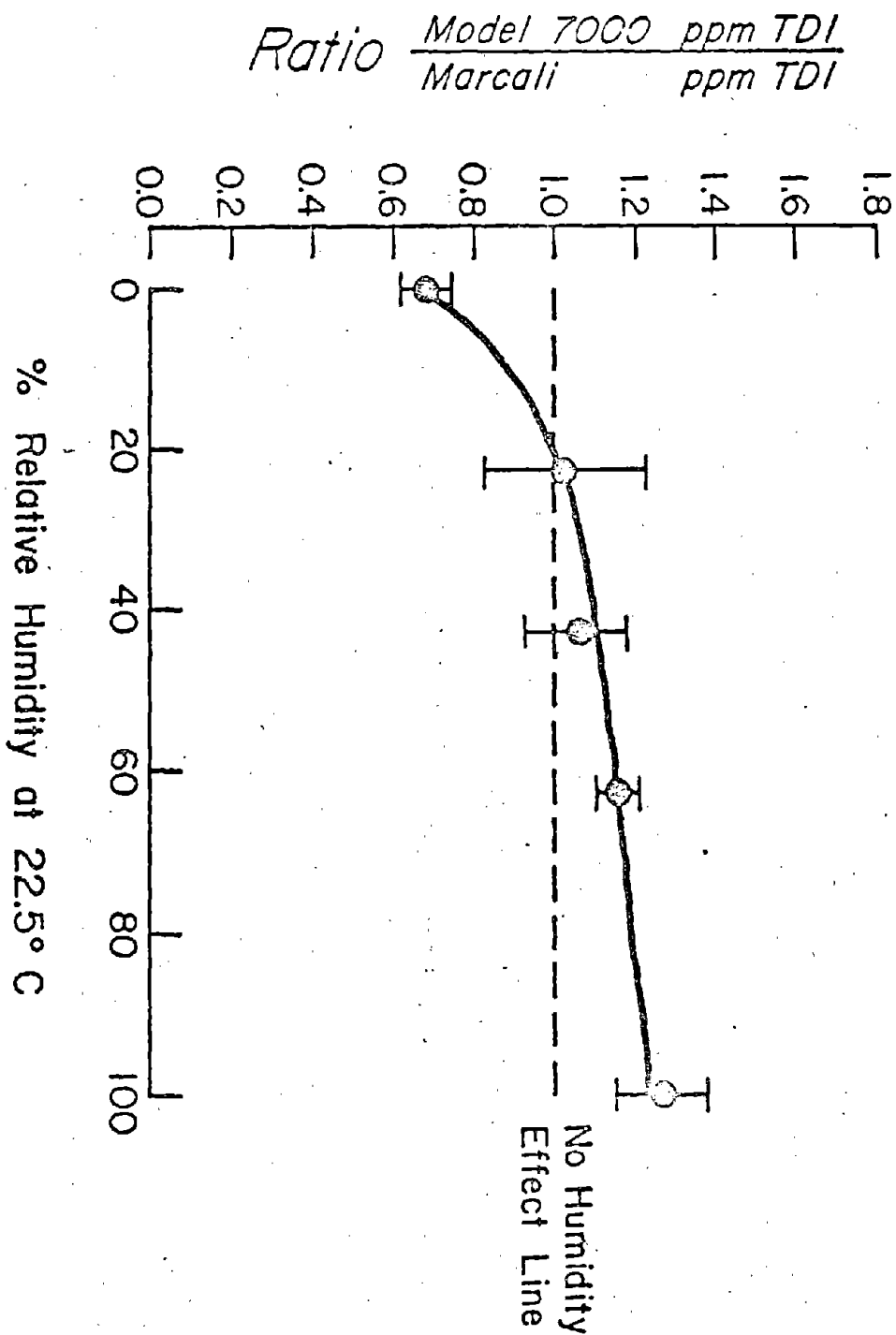


Figure 20

DISTANCE BETWEEN SELECTED JOBS

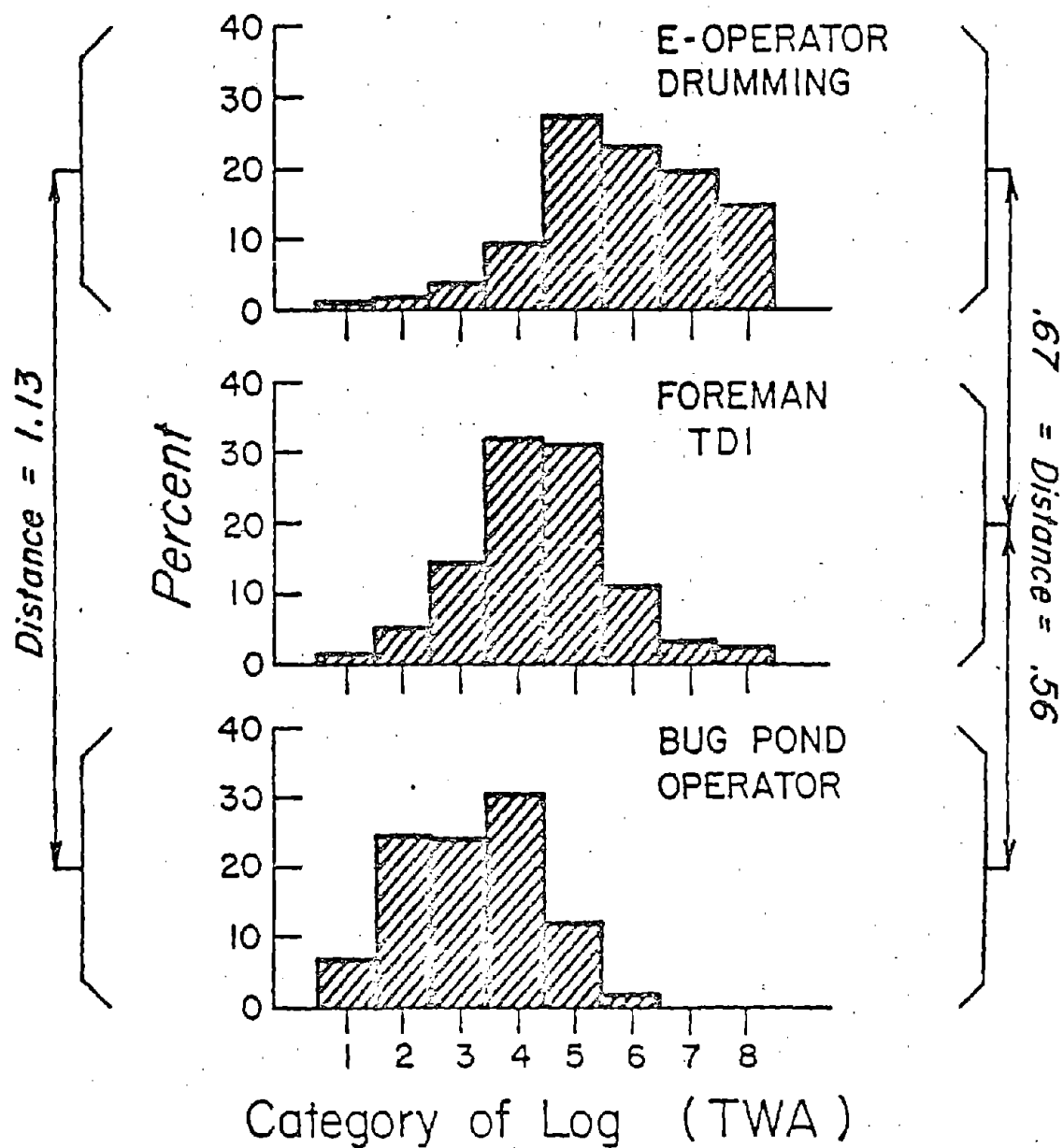


Figure 21

DISTANCE BETWEEN SELECTED JOBS

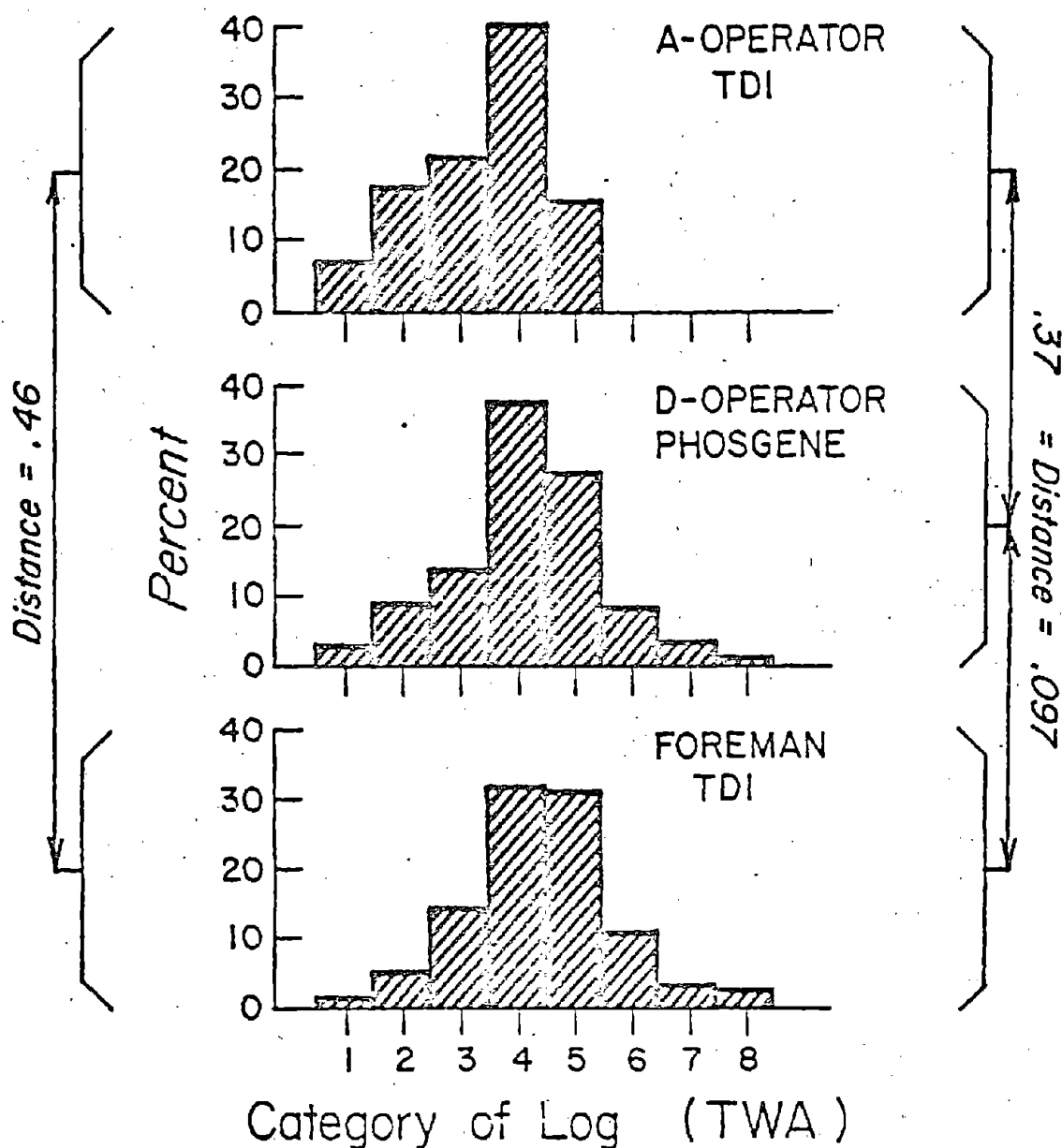


Figure 22

1. Respiratory Effects in Toluene Diisocyanate Manufacture: A Multidisciplinary Approach - Weill, Salvaggio, Neilson, Butcher, Ziskind
2. Longitudinal Study of Workers Employed in the Manufacture of Toluene-Diisocyanate - Butcher, Jones, O'Neil, Glindmeyer, Diem, Dharmarajan, Weill, Salvaggio
3. Environmental characterization of toluene diisocyanate (TDI) in a manufacturing plant - Dharmarajan, Weill, Self
4. Physical state of airborne p.p' diphenylmethane diisocyanate (MDI) and its measurement - Dharmarajan and Weill
5. Occupational Exposures to Methylene Bisphenylisocyanate (MDI): Gaseous or Aerosol - Dharmarajan
6. Analysis of Toluene Diisocyanate (TDI) and p.p'-Diphenylmethane Diisocyanate (MDI) in Air - Dharmarajan
7. The in vitro effect of toluene diisocyanate on lymphocyte cyclic adenosine monophosphate production by isoproterenol, prostaglandin, and histamine - Davies, Butcher, O'Neil, Salvaggio
8. Occupational asthma caused by low molecular weight chemical agents - Davies, Butcher, Salvaggio
9. Occupational Asthma - Karr, Davies, Butcher, Lehrer, Wilson, Dharmarajan, Salvaggio
10. Toluene diisocyanate (TDI) pulmonary disease: Immunologic and inhalation challenge studies - Butcher, Salvaggio, Weill, Ziskind
11. Toluene diisocyanate Pulmonary Disease: Immunopharmacologic and Mecholyt Challenge Studies - Butcher, Salvaggio, O'Neil, Weill, Garg
12. Inhalation challenge and pharmacologic studies of toluene diisocyanate (TDI) - sensitive workers - Butcher, Karr, O'Neil, Wilson, Dharmarajan, Salvaggio, Weill
13. Inhalation challenge testing with toluene diisocyanate (TDI) - Butcher
14. Radioallergosorbent Testing (RAST) of TDI Reactive Individuals using p-Tolyl Isocyanate (TMI) Antigen - Butcher, O'Neil, Salvaggio
15. A new method for the generation of standard atmospheres of organo isocyanates - Dharmarajan, Rando.