NIOSH

TECHNICAL REPORT

Respiratory and Immunologic Evaluation of Isocyanate Exposure in a New Manufacturing Plant

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
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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 bronchoprovocation; 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.

The manufacturing site was visited a second time in November, 1973, at which time pre- and post-shift 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.

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 each of visits two through five approximately 25 participants were added to the study population. At their entry point, the interview used at the initial April, 1973, visit was administered. The additions brought the total size of the study population to 277. In contrast to the original 168 participants who had no prior TDI exposure, the added participants had been exposed to TDI for a short period of time prior to their entry into the study. All had prior exposure less than 11 months.

Table I 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 I underestimates interview participation.

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 with a subset of 16 common inhalant allergens*. The presence of two or more positive prick tests (wheal diameter 1 mm greater than control) was used to define atopy.

A copy of the initial and follow-up interviews together with the criteria used to define respiratory symptom categories can be found in Appendix 3. Also presented is a listing of the computer programs used to edit the interviews. Each coded interview has been machine edited to check for missing data and logical inconsistencies. When possible, errors were corrected. This procedure resulted in complete interview information for 98.5 percent of the 277 initial interviews.

There are several factors which impact on accuracy and reliability of pulmonary function measurements. They are instrumentation, calculation, data reduction methods, instrument calibration, test procedures and technician variability. These factors are now discussed in turn.

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

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*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., Alternarea sp., white oak, giant ragweed mix, elm, pecan, house dust, marsh elder, cat dander, dog dander, and plantain.

maximum forced expiration, the output is fed into an XYT recorder in order to obtain plots of flow vs volume or volume vs 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 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 ($DLCO_{SB}$). The diffusion constant K equals $DLCO_{SB}/AV$ in units of min^{-1} $mmHg^{-1}$. 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.

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.

The volume accuracy of the spirometer is calibrated with a 1,000 ml syringe, and time calibrated with a stop watch. Setting the test gas cylinders at constant pressure would produce a constant flow into the spirometer. This will produce a linear plot of volume versus time, and repeating the maneuver gives a flow versus volume plot. If flow is accurately measured, its amplitude would equal the slope of the volume time plot (volume and time having been previously calibrated). The calibration for volume, time and flow was conducted twice daily and adjustments made if the volume inaccuracy exceeded 10 ml, flow inaccuracy exceeded 50 ml per second, or the time inaccuracy exceeded 1%.

The accuracy of the gas analyzers for measuring $DLCO_{SB}$ was assessed with a gas mixing pump which precisely mixed measured gas volumes to $\pm$ .06% accuracy. Simple combinations of test gases and room air provided by this gas mixing pump were used to assess accuracy and linearity of the analyzers. If linearity changed more than 1%, new linearity curves were employed. Though this measurement was conducted monthly, changes in linearity occurred no more than once per year. Accuracy and span for the gas analyzers were conducted twice daily. This was done to determine the instrument's ability to measure 0% gas, and 100% gas for a diffusion mixture consisting of .3% CO and 10% helium in air. (Note: 100% CO gas would be .3% CO). These were adjusted twice daily if the concentrations varied by more than 1%. In addition, the technicians conducting the tests were tested weekly to insure repeatability of the diffusion measurements. In no case did the week to week variation differ by more than 2%. In addition, following the technicians over a long term, that is, more than one year, never produced variations greater than 3% in single breath diffusing capacity.

The nitrogen analyzer used in the measurement of residual volume by the multibreath washout method was checked for 0, span, and linearity at least twice daily. This was conducted by injecting 100% oxygen across the system, 80% nitrogen, or by washing out a canister of room air and displaying

a semi log plot of nitrogen versus volume. A linear decline of this plot implies that there was no leak in the overall circuitry and plumbing of the system, and that the analyzer produced a linear response throughout the span of 0 to 80% nitrogen. This test was conducted twice daily and adjustments were made if the volume inaccuracy from the washout was greater than 20 ml, or if the 0 or span inaccuracy was greater than 1%. If there was a problem in linearity it was always corrected before testing was conducted.

Test procedures remained the same for the duration of the study. All subjects were tested for spirometry in the standing position. Nose clips were used for all tests. The closed circuit procedure was used for spirometry, that is, the subject inspired from the spirometer and then expired the maximum forced vital capacity into the spirometer. In this way, the inspiration preceding the forced vital capacity could be monitored in order to assess the subject's ability to reach total lung capacity. At least four forced vital capacity measurements were conducted on each subject. At least two were displayed as volume/time curves and two as flow/volume loops. The lung volume and the diffusing capacity tests were always conducted in the seated position. Again, nose clips were always used, and at least two measures of residual volume were conducted which had to be within 10% or 200 ml, whichever is larger. The smallest residual volume measurement was used in analyses. At least three single breath diffusing capacity tests were conducted on each subject and of those, the two chosen for analyses had to be within 10% of one another. If more than two were within 10%, the two with the largest alveolar volume, alveolar volume being the sum of inspired volume plus residual volume, were used in analyses. In addition, the time duration for diffusing capacity had to be within 10 to 14 seconds, and the alveolar volume had to be at least 85% of the total lung capacity.

Technician variability was held to a minimum by always having two technicians conduct the tests. The technicians used in the field always had at least two years of in-house pulmonary function testing in our laboratories. In addition, each technician was supervised for at least four on site field studies by a bioengineer (HWG) before being allowed to conduct independent testing.

As a final precaution, once data was entered into the computer for analysis, a sample of that data was printed to insure that the correct information was coded with the correct individual and stored for analysis in the appropriate format for the data base. In this way, the raw data and the reduced data were checked for agreement prior to analysis.

In summary, pulmonary function measurements were conducted throughout the study using the same equipment and test procedures. The method of 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. Every precaution possible was taken to insure that the changes seen in this population during the duration of the study were influenced as little as possible by the random and systematic variability which often affects measurements of pulmonary function.

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 predicteds were near 100% with the exception of FEF_{25-75} (91.0%).

Each subject's chect x-rays held by the plant medical department were reviewed by a physician (RNJ) in 1974. The purpose was to detect potentially confounding disorders (e.g., tuberculosis, fibrosis) and to be certain that these were neither unusually prevalent nor unevenly distributed among groups of participants. Only a few subjects had films suspicious for inactive granulomatous infection; only one subject had diffuse linear shadows suggesting interstitial fibrosis, and the abnormality was stable, and long antedated TDI exposure. After this systematic review, an individual's later films were examined only if the investigators learned that he or she was having persistent or recurrent symptoms, or requested review of the films. No abnormal films were detected by individual case review. Review of reasons for absence due to illness in a 12-month period failed to detect cases of recurrent pneumonia, but recorded diagnostic information was often incomplete. In the entire study period we detected no case with clinical or radiographic evidence suggesting hypersensitivity pneumonia.

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

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[1] TWA - 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 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 ppm-months = (0.0011 ppm) X (62 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: FEV_1, FVC, FEV%, FEF_{25-75}, FEF_{50}; 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.

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 FEF_{25-75} and FEF_{50} the spirometric mean annual changes found in this longitudinal study are not markedly different from cross-sectional studies. The FEF_{50} 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 the study for DLCO (-.716 ml/min-mmHg-year), K (-.0947 min-mmHg-year) and TLC (.32 ml/year) differ from Cotes' (1) cross-sectional age coefficients. Mean annual changes for DLCO and K are larger by factors of 3.6 and 2.4 respectively. The 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.

The increased prevalence of atopy (23% vs 6.3%) in the group with three or more good spirometry visits is possibly counterintuitive, i.e., long exposure to TDI which is implied by having large number of visits should result in an increased risk of being atopic. A more plausible explanation lies in the manner in which the skin testing was distributed over the nine visits of the study. Of the 48 participants with two or fewer complete spirometry visits, 31 (64.6%) were not tested with seven or more of the possible 16 allergens, whereas only 30 (13.3%) of the 226 with three or more complete visits had this characteristic. This "differential exposure to skin testing" makes it more difficult for the small number of visits group to be classified atopic, thus explaining the differential rates of atopy in the two groups. The differential exposure to skin testing is a consequence of the skin testing protocol whereby such testing was spread out over the nine visits with not all of the allergens used at each visit.

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 FEV_1 and FVC annual declines were significantly positively related to pack-years of smoking with each pack-year contributing .6 ml/yr to FEV_1 annual decline and .7 ml/yr to the FVC annual decline. Neither FEV_1 nor FVC annual decline were significantly related to atopic status. Neither FEV%, FEF_{25-75}, nor FEF_{50} annual decline were associated with pack-years of cigarette smoking. Atopics showed consistently smaller FEF_{25-75} and FEF_{50} 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 FEV_1 ($p = .034$), FEV% ($p = .014$), and FEF_{25-75} ($p = .004$) estimated mean annual declines (after controlling for atopy and pack years of smoking) were significantly greater (12 ml/yr, .20(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 yr^{-1}, and 84 ml/sec-yr respectively. Thus, even though there is a dose-related effect for FEV_1 and 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/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 had 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, FEV%, and FEF_{25-75} annual decline.

Table 16A presents descriptive statistics at the time of entry into the study for each of the two cumulative exposure categories. GROUP I was older and contained more participants with respiratory symptoms than did GROUP II. Thus, the potential bias is toward underestimating the excess decline in GROUP II.

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, 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 FEV_1 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 FEV_1 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 remarkedly comparable standard deviations of a single FEV_1 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 FEV_1 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 FEV_1 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 FEV_1'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 FEV_1 annual change of -21 ml/year. There is an evident peak in mean FEV_1 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 FEV_1 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 FEV_1 annual increase reported earlier was due to the systematically high FEV_1's at visit 5.

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

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[1] Both FVC and FEF_{25-75} 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 FEV_1 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 FEV_1 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 $(yr)^{-1}$ 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 DL_{CO} was significantly ($p < .05$) related to atopic status. This relationship was evident in each of the six regressions with DL_{CO} in the atopics declining approximately .4 $(ml/min\text{-}mmHg)^{-1}$ 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 have little hard information on conditions at the plant prior to TDI exposure to support this hypothesis. Moreover, note should be taken that the symptom complex defined as lower respiratory symptoms is quite broad in nature. It only requires a positive response to any one of the following questions:

(1) Do you usually cough first thing in the morning in bad weather?

(2) Do you usually cough at other times during the day or at night in bad weather?

(3) Do you usually bring up phlegm, sputum or mucous from your chest first thing in the morning in bad weather?

(4) Do you usually bring up phlegm, sputum or mucous from your chest at any other times during the day or night in bad weather?

(5) Does your breathing ever sound wheezy or whistling?

(6) Do you have attacks of shortness of breath with wheezing at present?

(7) Do you get short of breath when walking with other people your own age on level ground?

A similar remark holds for upper respiratory symptoms. Evidence that the high prevalence of lower respiratory symptoms is possibly due to the measuring instrument was found in results from other studies of this Unit. Lower respiratory symptom prevalences from four other studies were 41.0%, 34.4%, 46.5% and 28.5%. The first three populations were exposed to either suspected or confirmed respiratory hazards: cottonseed dust, coffee dust, and asbestos, respectively. The 28.5%, which is comparable to the 29.5% observed in the study population of this report prior to TDI exposure, comes from a working population not exposed to any known respiratory hazard.

Table 24A presents prevalences for bronchitis and dyspnea at initial and final interviews by smoking-cumulative exposure category. These prevalences were obtained for Table 23 by collapsing across atopic status. For both bronchitis and dyspnea, the increase in prevalence from initial to final interview is greater in > .0682 ppm-months exposure category irrespective of smoking category. However, in no case did statistical significance obtain.

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.

F. Detailed Analysis of FEV_1 Slope

(1) Results

After performing the large number of regressions reported in Tables 8-13, a detailed analysis of the relationship between FEV_1 slope and dichotomized (at .0682 ppm-months) cumulative exposure was performed. FEV_1 slope was singled out for the following three reasons:

1. There is an extensive body of knowledge on FEV_1 slope e.g., (3), (4), (5), (35), (36), (37), (38), (39), (40) to which our results could be related.

2. FEV_1 when adjusted for body stature is a reliable and sensitive indicator of large airways obstruction.

3. The 12 ml/yr difference in FEV_1 between the two cumulative exposure categories (Table 16), although statistically significant after controlling for atopy and pack years, is biologically small; it would be helpful to compare this exposure effect to that of cigarette smoking.

The objective of the extended FEV_1 analysis was to estimate mean annual FEV_1 declines for the six smoking-exposure categories: three categories of smoking (never, ex, and current cigarette smoking) by two categories of exposure (less than or equal to .0682 ppm-months, and greater than .0682 ppm-months). This would allow a comparison of the smoking effect in the $\leq$ .0682 ppm-months group with the exposure effect in the never smokers. Atopy was not included in this analysis because the previous analyses had indicated that it was not an important influencing variable.

Fletcher et al (3) have observed that FEV_1 level as measured by FEV_1 divided by the third power of height, (i.e., FEV_1/ht^3 in units of Cl/m^3) is associated with the annual decline prior to the study period. Consequently, in determining correlation between FEV_1 slope and exposure, adjustment should be made for FEV_1/ht^3 to allow for the possibility of an excess of rapid pre-study decliners (as measured by low FEV_1/ht^3) in the high exposure group which could otherwise lead to a spurious correlation between FEV_1 slope and exposure. In addition, there should also be adjustment for age since FEV_1/ht^3 and possibly FEV_1 slope are related to age.

FEV_1/ht^3 was obtained for each participant by averaging the available FEV_1's for that participant, multiplying this average by 100 and then dividing by height cubed, height measured in meters. This quantity, referred to as FEV_1 level, was initially categorized using division points of 55, 65, 75 and 85. Average FEV_1 slopes for these categories are shown below.

MEAN FEV_1 SLOPE BY FEV_1 LEVEL CATEGORY

FEV_1/ht^3 (Cl/m^3)	n	Mean FEV_1 Slope (ml/year)
< 55	21	-47.5
55-64	58	-20.1
65-74	76	-22.6
75-84	49	-20.3
85+	19	-26.2

Because of the lack of association between FEV_1 slope and level among the four highest categories, FEV_1 level was dichotomized using a division point of 55 Centilitres per meter cubed. This lack of association is in accordance with results reported by Fletcher et al (3).

Before presenting the FEV_1 slope analyses, we give the results of an analysis relating FEV_1 level to age, smoking and exposure.

Logistic regression of the dichotomized FEV_1 level yielded a significant age effect ($p < .01$), a marginally significant ex-smoking effect as compared to never smokers (one-tailed p-value = .07) and a significant current smoking effect as compared to never smokers (one-tailed p-value = .03). In addition to these expected relationships, there was a significant association ($p = .05$) between FEV_1 level and exposure after controlling for age and smoking. There was a smaller proportion of participants with low FEV_1 level in the high exposure category than in the low category. This finding appears to argue against a TDI exposure effect as measured by FEV_1 level. However, as discussed by Fletcher et al (3), FEV_1 level measures the effect of FEV_1 slope prior to the study as opposed to FEV_1 slope over the period of study. Thus, a possible explanation for the negative association between FEV_1 level and exposure is one of selection, whereby the rapid FEV_1 decliners prior to TDI exposure selected themselves into the low exposure category. Furthermore, that there is a deficiency of participants with low FEV_1 level in the high exposure group is consistent with their younger mean age (31.7 vs 37.6 years) since FEV_1 level has not been adjusted for age. That the high exposure group is younger is consistent with the fact that the jobs which lead to the high exposure category are entry level jobs. These necessarily go to new hirees who would tend to be young.

In any event, it is important in assessing the relationship between FEV_1 slope and exposure over the period of this study to adjust for FEV_1 level because the known positive association between low FEV_1 level and large FEV_1 declines would tend to minimize the effect of exposure.

In order to estimate cell means for the six smoking-exposure categories while controlling for age and FEV_1 level, the regression procedure outlined in Appendix 2 was utilized with FEV_1 slope as the independent variable and the following dependent variables:

1. A dummy variable representing high TDI exposure - greater than .0682 ppm-months.

2. Two dummy variables, one representing ex-smokers and one representing current smokers.

3. The products of the two variables in 2, with the variable in 1.

4. Age.

5. A dummy variable representing low FEV_1 level (FEV_1/ht^3 less than 55).

The results of the regression are presented in the Table 16B by smoking-exposure-FEV_1 level category.

Cell means have been adjusted to the mean study population age of 35.6 years in order to account for differing age distributions within the cells. The esimated cell means in the low FEV_1 level category should be interpreted cautiously, especially for those cells which contain a small number of participants, since they are the result of an extrapolation.

The coefficient of age in the multiple regression was - 5.8 millilitres per decade (one-tailed p-value = .03). A weak acceleration of FEV_1 loss with increasing age of approximately 5.5 millilitres per decade was also shown by Kauffmann et al (35) in a group of Paris area workers. Kauffman's age effect disappeared after adjustment for FEV_1 level. In contrast, the age effect observed in the present study occurs after controlling for FEV_1 level, TDI exposure and smoking status.

After adjusting for age, TDI exposure, and smoking status, those with FEV_1 level $\leq$ 55 Cl/m^3 had mean FEV_1 annual decline of 20 ml/year (one-tailed p-value = .04) more than those with FEV_1 level > 55 Cl/m^3. This shows, following the arguments presented by Fletcher et al (3), that there are a group of people, namely those with low FEV_1 level, in this study who are lifelong rapid decliners. This lifelong rapid decline should not be attributed to TDI exposure. To prevent such attribution, the association between FEV_1 slope and exposure has been adjusted for FEV_1 level.

Among the never smokers, after adjusting for age and FEV_1 level, those with greater than .0682 ppm-months of TDI exposure declined on the average 38 ml/year (one-tailed p-value = .001) more than those with less exposure. In the ex smokers, 3/ml year difference between exposure groups was not significant. The 11 ml/year difference in the current smokers had a one-tailed p-value of 0.1.

Turning to the smoking effect in the $\leq$ .0682 ppm-months participants there was, after adjusting for age and FEV_1 level, a significant (one-tailed p-value = .004) difference of 27 ml per year between current smokers and never smokers. The 14 ml/year difference between current smokers and ex smokers was almost significant (one-tailed p-value = .06). The 14 ml/year difference between ex smokers and never smokers had a one-tailed p-value of .12.

The 38 ml/year exposure effect in the never smokers and the 27 ml/year current cigarette smoking effect in the low exposure group were not significantly different (p-value = .32).

The average FEV_1 decline, the precision of an individual FEV_1 determination, the precision of a participant's FEV_1 slope, and the effect of cigarette smoking observed in this study, are all consistent with the results of other investigators.

Our average FEV_1 slope of -24 ml/year (with standard error of 3.2) is comparable to the -30 ml/year measured by Fletcher et al (3). Ferris et al (36) observed a mean FEV_1 annual change of -37 ml/year over six years in a population of males with mean age 53 years. Higgins et al (37) found an average FEV_1 annual change of -34 ml/year in males aged 25 to 34 years and a -45 ml/year average annual change in males aged 55-64 years. The follow-up period for this study was nine years. Petty et al (38) observed over six years a mean FEV_1 annual change of -19 ml/year in a population of males, 27 per cent of which had (FEV_1/FVC) X 100 less than 60. Kauffmann et al (35) observed a -47 ml/year mean annual FEV_1 annual change over 12 years in a population of males with mean age 41 years. Lebowitz et al (39) and Pham et al (40) were unable to demonstrate significant changes in FEV_1 over a three year period. The average FEV_1 decline of 24 ml/year observed in this study at 7.5 times its standard error is highly significant.

As mentioned in the Spirometry Results Section, the observed standard deviation of a single FEV_1 determination of 133 ml is comparable to the 120 ml of Berry (4) and 160 ml of Fletcher et al (3). Additionally, we observed a standard error of 25 ml/year for the slope of a participant present at all nine visits over the full 5.5 years of the study. This compares with the 20 ml/year of Fletcher et al (3) for a study of eight years and sixteen visits.

Fletcher et al (3) found a 15 ml/year difference in FEV_1 slope between current and never smokers. Kauffmann's (35) estimate of this difference was 10 ml per year. Results presented by Ferris et al (36) lead to an estimate of 13 ml/year. When averaged over exposure categories, we observed a 14 ml/year difference. In the low exposure group, the difference was 27 ml/year.

The comparability of our general results, i.e., those not related to TDI exposure, with those of other investigators, demonstrates that the elevated FEV_1's at visit 5 have not produced a bias in the FEV_1 slope measurements. This external validation provides justification beyond that given in the Spirometry Results section for discounting the visit 5 FEV_1 measurements effect on FEV_1 slope. Although we were able to detect a visit 5 bias, we have provided evidence that it did not affect our results. This demonstrates an inherent strength of any longitudinal study of three or more visits; in two-visit studies, it is impossible to detect such bias.

The 38 ml/year exposure effect in the never smokers was not significantly different (p-value = .32) from the 27 ml/year smoking (current) effect in the low exposure group. This comparability of cigarette smoking with TDI exposure was also found when the smoking-exposure interactions were omitted from the regression equations. In such a regression, the exposure and cigarette smoking effects were both 16 ml/year.

At the time of entry into the study, current smokers had averaged one pack of cigarettes per day for an average length of 18 years. Thus, the data suggest that this amount of smoking produces an annual decline in FEV_1 equivalent to the decline associated with TDI exposure at a concentration of .0011 ppm for 62 months in a never smoker. The fact that the effect of TDI exposure was observed in the never smokers and not in the current cigarette smokers suggests that smoking may mask the effect of TDI exposure.

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 FEV_1 and FEF_{25-75} despite removal from the TDI area. Two subjects (033 and 035) have shown stable FEV_1 values but declines in FEF_{25-75}. Four persons show stable to slightly increasing values for FEV_1 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 hererocytotropic 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 (8, 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 FEV_1 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 m^3) 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 cm^2. 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 FEV_1 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 (Mecholyl)

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 FEV_1, 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 1mg/ml methacholine on the abcissa 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 E_1 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 E_1 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 ^{3}H-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 FEV_1 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 FEV_1. 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 5 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 E_1, 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 FEV_1. 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 coefficience 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 pharmological 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) The effect of TDI exposure on FEV_1 annual change appears primarily in the non-smokers and may be masked by smoking. In this population smoking on the average a pack of cigarettes a day for 18 years and a TDI total dose in excess of .0682 ppm-months had a similar effect on FEV_1 mean annual changes.

(6) 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. Both DL_{CO} and K (diffusion constant) annual declines were significantly greater than expected, but were 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.

(7) 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.

(8) 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.

(9) 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).

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

(11) 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.

(12) 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.

(13) 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.

(14) 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 E_1 but not histamine.

(15) 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.

(16) Lymphocytes of TDI-sensitive individuals have decreased ability to respond to cyclic AMP stimulants such as the beta agonists isoproterenol, prostaglandin E_1 and TDI.

(17) 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.

(18) 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.

(19) 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 hemaglutination, 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.

APPENDIX 1

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 (28). 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 1968 (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 <u>does not</u> 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 abcissa 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 Daumming 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.

(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 4°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.

APPENDIX 2

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. These points correspond 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:

$$(p_1, p_2, p_3, p_4, p_5, p_6, p_7) = (p_i)_{i=1}^{7}$$

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:

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

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 .0i 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} $(i = 1, 2, \ldots, N)$ 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 $(j = 1, \ldots, n_i)$ 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 $x_{i1}, x_{i2}, \ldots, x_{ik}$ 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

$$\beta_i = \sum_{j-1}^{k} \gamma_j \; x_{ij} + \varepsilon_i$$

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 $x_{i1}, \ldots, x_{ik}$.

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 $\tau^2 / \sum_{j=1}^{n_i} (t_{ij} - \bar{t}_i)^2$. Furthermore, assume that the ε_i in (1) and the δ_i are independent. It then follows that the observed slopes b_i satisfy

$$b_i = \sum_{j=1}^{k} \gamma_j x_{ij} + \varepsilon_i + \delta_i \qquad (2)$$

where the $\delta_i + \varepsilon_i$ are independent and normally distributed with mean 0 and variance

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

In this model σ^2 = Variance (ε_i) is the variance of the true slopes not accounted for by the $x_{i1}, x_{i2}, \ldots, x_{ik}$, 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

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

Specifically, letting $K_i = \sum_{j=1}^{n_i} (t_{ij} - \bar{t}_i)^2$, the log likelihood of the β_i's is

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

which yield likelihood equations at the observed value of $\hat{\tau}^2$:

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

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

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

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

1. Letting $b_i = \theta + \varepsilon_i + \delta_i$ with the variance of ε_i equal to σ_o^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

$$\frac{1}{N-1} \sum_{i=1}^{N} K_i (b_i - \bar{b})^2 \quad \text{is} \quad \hat{\tau}^2 + \frac{Wo}{N-1} \sigma_o^2$$

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

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

as an estimate of σ^2_o.

2. Regress b_i on the $x_{i1}, x_{i2}, \ldots, x_{ik}$ using weights equal to $(\hat{\sigma}^2_o + \frac{\tau^2}{K_i})^{-1}$ and take as starting values for the iterative equation solving procedure, $\hat{\sigma}^2_o$ and the coefficients $\gamma_{01}, \gamma_{02}, \ldots, \gamma_{0k}$ 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.

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

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

x_{i4} = pack-years of cigarette smoking .

In this situation $N = 223$,

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

$$\frac{\sum_{i=1}^{N} K_i b_i}{\sum_{i=1}^{N} K_i} = -.0240\ell ,$$

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

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

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

$\hat{\sigma}_o^2$, we obtain: $\hat{\gamma}_1 = -.0244\ell$ with standard error = .00316 and $\hat{\sigma}^2 = .000652\ \ell^2$. In this case, $\gamma_1 = -.0244$ is the maximum likelihood estimate of mean FEV_1 annual change and $\hat{\sigma} = .0255\ell$ is the maximum likelihood estimate of between true slopes standard deviation.

The quantity $.000652 + \frac{.017572}{\Sigma(t_j-\bar{t})^2}$ is the estimated variance of an observed slope calculated from time points $t_1, t_2, \ldots, t_n$ and $.000652/(.000652 + \frac{.017572)}{\Sigma(t_j-\bar{t})^2}$ 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 FEV_1 readings at all nine visits $\Sigma(t_j-\bar{t})^2 = 26.45$ 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) startings 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 ZSYSTM stopping criteria with EPS = 10^{-6} and NSIG = 9 (See IMSL ZSYSTM documentation for definitions of EPS and NSIG.) The resulting regression equation is:

FEV_1 annual change =

$$\underset{(.0056)}{-.0120} - \underset{(.0064)}{.0118}\,EXP + \underset{(.0071)}{.0010}\,ATOPY - \underset{(.00022)}{.00058}\,PACK\text{-}YEARS$$

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 ℓ^2. Thus using the results of previous example, 9.4 percent of the true slope variability is explained by these three variables.

APPENDIX 3

Interview Forms, Symptom Criteria, and Editorial Programs

Tul-LSU Sch. Med. Pul. Dis. -Immuno.

OCCUPATIONAL STUDY VIII
Interview
Olin

Schedule B

ready to be keypunched _____

DATA COLUMN	CODE COLUMN	
IDENTIFICATION		
1. Study number _ _ _ _	1-4	
2. Social security number _ _ _ - _ _ - _ _ _ _	5-13	
3. Name _	14-36	
4. Permanent address		
Street _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _	37-55	
City and State _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _	56-70	
Zip Code _ _ _ _ _	71-75	
5. Schedule Code 0 8	76-77	
6. Participation Number 1	78	
7. Code Card 0 1	79-80	
	1-4	_ _ _ _
8. Permanent Telephone Number _ _ _ _ _ _ _	5-11	_ _ _ _ _ _ _
9. Date of Birth _ _ - _ _ - _ _	17-22	_ _ _ _ _ _
10. Age _ _	23-24	_ _
11. Race: White 1 Negro 2 Other 3	25	_
12. Sex: Male 1 Female 2	26	_
13. Civil Status: Single 1 Married 2 Divorced 3 Widower 4 Separated 5 Other 6		
If "other" specify: _____	27	_
14. Name of Employing Agency _____	28-29	_ _
15. Plant within Agency _____	30-31	_ _
16. Date of Interview _ _ - _ _ - _ _	32-37	_ _ _ _ _ _
17. Name of Interviewer _____	38	_
18. CODE CARD 0 2	79-80	0 2

Data Column	Code Column
COUGH	1-4 ____
1. Do you usually cough first thing in the morning in bad weather? Yes 1 No 2	5 ___
2. Do you usually cough at other times during the day or at night in bad weather? Yes 1 No 2	6 ___
If "yes" to 1 or 2	
3. Do you cough on most days for as much as 3 months of the year? Yes 1 No 2 N.A. 9	7 ___
4. For how many years have you had this cough? Less than 2 years 1; 2 to 5 years 2; 5 years or more 3; N.A. 9	8 ___
SPUTUM	
1. Do you usually bring up phlegm, sputum or mucous from your chest first thing in the morning in bad weather? Yes 1 No 2	9 ___
2. Do you usually bring up phlegm, sputum or mucous from your chest at any other times during the day or night in bad weather? Yes 1 No 2	10 ___
If "yes" to 1 or 2	
3. Do you bring up phlegm, sputum or mucous from your chest on most days for as much as 3 months of the year? Yes 1 No 2 N.A. 9	11 ___
4. For how many years have you raised phlegm, sputum or mucous from your chest? Less than 2 years 1; 2 to 5 years 2; 5 years or more 3; N.A. 9	12 ___
WHEEZING	
1. Does your breathing ever sound wheezy or whistling? Yes 1 No 2	13 ___
2. Have you ever had attacks of shortness of breath with wheezing? Yes 1 No 2	14 ___
If "yes" to 1	
3. For how many years has your breathing sounded wheezy of whistling? __ __ N.A. 9 9	15-16 ____
If "yes" to 2	
4. Do you have attacks of shortness of breath with wheezing at present? Yes 1 No 2 N.A. 9	17 ___

Data Column	Code Column
BREATHLESSNESS	
1. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill? Yes 1 No 2	18 ___
2. Do you get short of breath when walking with other people your own age on level ground? Yes 1 No 2	19 ___
If "yes" to 1 or 2	
3. For how many years have you had shortness of breath? ___ N.A. 99	20-21 ___
CHEST ILLNESS	
1. During the past 3 years, how much trouble have you had with illnesses such as chest colds, bronchitis or pneumonia? 0 1 2 3 4 5 (none — great deal)	22 ___
2. During the past 3 years, how often were you unable to do your usual activities because of illnesses such as chest colds, bronchitis or pneumonia? One time 1; 2-5 times 2; more than 5 times 3	23 ___
3. Do you think you have ever had any of these chest disorders: asthma, any kind of bronchial trouble, or emphysema? Yes 1 No 2 D.K. 3	24 ___
4. Has a doctor ever told you that you had asthma, some kind of bronchial trouble, or emphysema? Yes 1 No 2	25 ___
If "yes" to 4	
5. Which type? _____ N.A. 9	26 ___
6. Have you ever had repeated attacks of pneumonia? Yes 1 No 2	27 ___
7. Have you ever been hospitalized for	
Pleurisy Yes 1 No 2	28 ___
Tuberculosis Yes 1 No 2	29 ___
8. Have you ever had a chest injury or chest operation? Yes 1 No 2	30 ___
If "yes" when? _____	
NASAL CATARRH	
1. Do you usually have a drip at the back of your nose? Yes 1 No 2	31 ___
If "yes" to 1	
2. Do you have a drip at the back of your nose for as much as three months? Yes 1 No 2 N.A. 9	32 ___
3. Have you ever had hay fever? Yes 1 No 2	33 ___

Data Column	Code Column
NASAL CATARRH (cont'd)	
4. Have you ever had a runny, stuffy or itchy nose and/or sneezing for several days at a time occuring at certain times of the year? Yes 1 No 2	34 —
5. Have you ever had sinus trouble or a postnasal drip? Yes 1 No 2	35 —
If "yes" to 1, 3, 4 or 5	
6. Do you have any such illness at present? Yes 1 No 2 N.A. 9	36 —
ADDITIONAL ALLERGY HISTORY	
1. Have you ever had atopic dermatitis, by which I mean a scaling rash that occurs in elbow creases, behind the knees and/or sometimes behind the ears? Yes 1 No 2	37 —
2. Have you ever had urticaria, by which I mean swollen red spots on the skin which may or may not be itchy? Yes 1 No 2	38 —
If "yes" to 1 or 2	
3. Do you have either such illness at present? Yes 1 No 2 N.A. 9	39 —
4. Have you had more than 2 head colds each year for some time? Yes 1 No 2	40 —
If "yes" to 4	
5. When you have a head cold, do you have runny, stuffy or itchy nose and/or sneezing for several days at a time? Yes 1 No 2 N.A. 9	41 —
6. Do any members of your immediate family (mother, father, brothers, sisters) have any of the allergies I have mentioned: a) asthma (attacks of shortness of breath with wheezing); b) hay fever; sinus trouble; post nasal drip; a runny, stuffy or itchy nose and/or sneezing for several days at a time occurring at certain times of the year; c) atopic dermatitis or d) urticaria? Yes 1 No 2	42 —
If "yes" to 6	
7. Which family member and what type allergy?	
Mother 1	45 —
Allergy: a 1 b 2 c 3 d 4	46 — — — —
Father 2	50 —
Allergy: a 1 b 2 c 3 d 4	51 — — — —
Sister 3	55 —
Allergy: a 1 b 2 c 3 d 4	56 — — — —
Brother 4	60 —
Allergy: a 1 b 2 c 3 d 4	61 — — — —

Data Column	Code Column
PRIOR EXPOSURE	
1. Have you ever worked with urathane foam, either rigid or flexible? Yes 1 No 2	65 ___
If "yes" to 1	
2. Did you work in manufacturing? Yes 1 No 2 N.A. 9	66 ___
3. Do you or have you ever owned a fiberglass boat? Yes 1 No 2	67 ___
If "yes" to 3	
4. Do you or did you do your own repairs? Yes 1 No 2 N.A. 9	68 ___
If "yes" to 4	
5. Did you use any bouyancy materials? Yes 1 No 2 N.A. 9	69 ___
CODE CARD 0 3	79-80 0 3

Data Column	Code Column
SMOKING	1-4 ____
1. Do you now smoke cigarettes: regularly 1; occasionally (usually less than 1 per day) 2; never 3	5 ___
If "regularly" now:	
2. Do you inhale? Yes 1 No 2 N.A. 9	6 ___
3. Do you smoke cigarettes: with filters 1; without filters 2; both with and without filters 3; N.A. 9	7 ___
4. How many cigarettes do you usually smoke each day at the present time? __ __ N.A. 9 9	8-9 ____
5. How old were you when you began to smoke cigarettes? __ __ N.A. 9 9	10-11 ____
6. What is the usual number you have smoked per day since you began to smoke? __ __ N.A. 9 9	12-13 ____
If "occasionally or "never" now:	
7. If you do not smoke cigarettes now, did you ever smoke them: regularly 1; occasionally (usually less than 1 per day) 2; never 3; N.A. 9	14 ___
If "regularly"	
8. What was the usual number of cigarettes you smoked per day? __ __ N.A. 9 9	15-16 ____
9. Did you inhale? Yes 1 No 2 N.A. 9	17 ___
10. How old were you when you began to smoke cigarettes? __ __ N.A. 9 9	18-19 ____
11. How old were you when you stopped smoking cigarettes regularly? __ __ N.A. 9 9	20-21 ____
12. Were you influenced to stop smoking because you had a cough, wheezing or shortness of breath? Yes 1 No 2 N.A. 9	22 ___
13. Do you now smoke pipes or cigars: regularly 1; occasionally (usually less than 1 per day) 2; never 3	23 ___
If "regularly" now	
14. How many pipefuls or cigars do you usually smoke each day? __ __ N.A. 9 9	24-25 ____
15. How old were you when you first smoked pipes or cigars? __ __ N.A. 9 9	26-27 ____

Data Column		Code Column	
SMOKING (cont'd)			
16. Do you usually inhale when you smoke either pipes or cigars? Yes 1 No 2 N.A. 9		28	—
If "occasionally" or "never" now:			
17. If you do not smoke cigars or pipes now, did you ever smoke them:	regularly 1 occasionally 2 (usually less than 1 per day) never 3 N.A. 9	29	—
If "regularly"			
18. How many pipefuls or cigars did you usually smoke each day?	__ N.A. 99	30-31	__
19. How old were you when you first smoked pipes or cigars?	__ N.A. 99	32-33	__
20. How old were you when you stopped smoking pipes or cigars?	__ N.A. 99	34-35	__
21. Did you usually inhale when you smoked either pipes or cigars?	Yes 1 No 2 N.A. 9	36	—
CODE CARD	04	79-80	04

April, 1973

OCCUPATIONAL HISTORY

Now I would like for you to tell me about each of the places you have worked and the types of jobs you have done. Please begin by telling me about your present job. Include part time jobs. Exclude jobs held for less than one (1) year.

	Present Job	Job No. 1	Job No. 2	Job No. 3
Name and Address of Company				
Kind of Business				
Years: From / To				
Job Description				

1-4 ____
5-14 ____
____

OCCUPATIONAL STUDY VIII
Interview
Olin

1-4 ____

5-14 _ _ _ _ _ _ _ _ _ _

OCCUPATIONAL HISTORY (supplementary page)

	Job No.	Job No.	Job No.	Job No.	Job No.
Name and Address of Company					
Kind of Business					
Years From / To					
Job Description					

Tul. Sch. Med.
Pul. Dis. - Immuno.

OCCUPATIONAL STUDY VIII
Follow-Up Interview
Clinic

Schedule b_1

ready to be keypunched _____

DATA COLUMN	CODE COLUM
Name: _____	
Study Number: _ _ _ _	1 _ _ _ _
Date: _ _ - _ _ - _ _ (mo. day yr.)	5 _ _ _ _
A. ACUTE EXPOSURE EXPERIENCE	
1. Have you had any reaction to a gas exposure in the last 6 months? Yes 1 No 2	12 _
If "Yes" to 1 fill out the accompanying addendum.	
"The following questions relate to your usual state of health in the last 6 months and do not include symptoms you may have had immediately following gas exposures. Please answer yes or no whenever possible."	
B. COUGH (Count a cough with first smoke or on first going out of doors but exclude clearing thorat, a single or occasional cough.)	
2. Do you usually cough first thing in the morning in bad weather? Yes 1 No 2	13 _
3. Do you usually cough during the day or night in bad weather? Yes 1 No 2	14 _
If "Yes" to 2 or 3:	
4. Have you coughed like this on most days for as much as 3 months in the last 6 months? Yes 1 No 2 N.A. 9	15 _
C. PHLEGM (Count swallowed phlegm or phlegm more than twice a day but exclude phlegm from the nose.)	
5. Do you usually bring up phlegm, sputum or mucus from your chest first thing in the morning in bad weather? Yes 1 No 2	16 _
6. Do you usually bring up phlegm, sputum, or mucus from your chest during the day or night in bad weather? Yes 1 No 2	17 _
If "Yes" to 5 or 6:	
7. Have you brought up phlegm like this on most days for as much as 3 months in the last 6 months? Yes 1 No 2 N.A. 9	18 _

DATA COLUMN		CODE COLUMN
D. CHEST ILLNESS (Count illness relating to lungs, including flu, but exclude heart trouble or external injury.)		
8. In the last 6 months have you had any chest illness which has kept you at home for a week or more?	Yes 1 No 2	19 ___
If "Yes" to 8:		
9. How many such illnesses have you had?	___ ___ N.A. 9 9	21 ___ ___
10. Did you bring up more phlegm than usual in this illness (or these illnesses)?	Yes 1 No 2 N.A. 9	23 ___
E. CHEST TIGHTNESS		
11. Has your chest been tight or your breathing difficult in the last 6 months?	Yes 1 No 2	24 ___
F. BREATHLESSNESS		
If unable to walk because of any condition other than heart or lung disease put "X" in this box and go to question 16.	[ ]	
12. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?	Yes 1 No 2 N.A. 9	25 ___
If "Yes" to 12:		
13. Do you get short of breath walking with other people at an ordinary pace on the level?	Yes 1 No 2 N.A. 9	26 ___
If "Yes" to 13:		
14. Do you have to stop for breath walking at your own pace on the level?	Yes 1 No 2 N.A. 9	27 ___
If "Yes" to 14:		
15. Are you short of breath on washing or dressing?	Yes 1 No 2 N.A. 9	28 ___
G. WHEEZING		
16. Has your breathing been wheezy or whistling in the last 6 months?	Yes 1 No 2	29 ___
17. Have you had attacks of shortness of breath with wheezing?	Yes 1 No 2	31 ___
If "Yes" to 17:		
18. Do you have attacks of shortness of breath with wheezing at present?	Yes 1 No 2 N.A. 9	32 ___

DATA COLUMN		CODE COLUMN
H. NASAL CATARRH		
19. Do you usually have a drip at the back of your nose?	Yes 1 No 2	33 ___
If "Yes" to 19:		
20. Have you had a drip at the back of your nose for as much as 3 of the last 6 months?	Yes 1 No 2 N.A. 9	34 ___
21. Do you have a runny, stuffy, or itchy nose, or sneezing for several days at a time occurring at certain times of the year?	Yes 1 No 2	35 ___
22. Do you have sinus trouble or a postnasal drip?	Yes 1 No 2	36 ___
I. ALLERGY		
23. Have you had asthma in the last 6 months?	Yes 1 No 2	37 ___
24. How many head colds have you had in the last 6 months?	___ ___	38 ___ ___
If other than "none":		
25. How many weeks did they last, all together?	___ ___ N.A. 9 9	41 ___ ___
26. When you have a head cold do you have a runny, stuffy or itchy nose, or sneezing for several days at a time?	Yes 1 No 2	43 ___
27. Do you take medication for allergies?	Yes 1 No 2	44 ___
If "Yes":		
28. What medication? _____		
29. How frequently? _____		
J. OTHER ILLNESSES		
30. Since we last saw you, has a doctor told you that you had . . .		
a. a heart condition?	Yes 1 No 2	45 ___
b. T.B.?	Yes 1 No 2	46 ___
c. emphysema?	Yes 1 No 2	47 ___
d. chronic bronchitis?	Yes 1 No 2	48 ___
e. pneumonia?	Yes 1 No 2	49 ___
If "Yes" to pneumonia: How many times?	___ ___ N.A. 9 9	51 ___ ___
31. Have you had any operations or injuries affecting your chest or been told something was wrong with your chest x-ray since we last saw you?	Yes 1 No 2	53 ___
If "Yes" to 31: Please describe: _____		

Tul. Sch. Med.
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OCCUPATIONAL STUDY VIII
Follow-Up Interview
Olin

Schedule b_4

DATA COLUMN		CODE COLUMN
K. SMOKING HISTORY		
32. Do you smoke regularly?	Yes 1 No 2	54 ___
If "Yes" to 32: 33. . . . cigarettes?	Yes 1 No 2 N.A. 9	55 ___
If "Yes" to 33: 34. How many packs do you smoke each day?	___packs = ___ ___Cig. N.A. 9 9	56 ___
35. Do you inhale?	Yes 1 No 2 N.A. 9	58 ___
36. Do you smoke pipes regularly?	Yes 1 No 2 N.A. 9	59 ___
If "Yes" to 36: 37. How many pipesful do you smoke each day?	___ ___ N.A. 9 9	61 ___
38. Do you inhale?	Yes 1 No 2 N.A. 9	63 ___
39. Do you smoke cigars regularly?	Yes 1 No 2 N.A. 9	64 ___
If "Yes" to 39: 40. How many cigars do you smoke each day?	___ ___ N.A. 9 9	65 ___
41. What type of cigar do you smoke?	_____ N.A. 9	67 ___
42. Do you inhale?	Yes 1 No 2 N.A. 9	68 ___
	Schedule Code	75 0 8 ___ 0 6
L. EXPOSURE INFORMATION		1 Study No.
43. Have you been off work for more than 3 weeks in the last 6 months?	Yes 1 No 2	5 ___
If "Yes" to 43: 44. For how many weeks?	_____	
45. What did you do in that time?	_____	
46. Which zone do you work in?	North 1 South 2 East 3 West 4 Central 5 All Over 6 Other: _____ 8	6 ___
If specific zone is given: 47. Which area in that zone?	_____ N.A. 9 9	7 ___
48. What is your complete job title?	_____	9 ___
	Study Classification	12 ___

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OCCUPATIONAL STUDY VIII
Follow-Up Interview
Olin

Schedule b_5

DATA COLUMN			CODE COLUMN
L. EXPOSURE INFORMATION (cont'd)			
49. How frequently do you notice being exposed to the following gases?	Frequency	Duration	
a) Ammonia?	_____	_____	13 _____
b) TDI?	_____	_____	21 _____
c) Phosgene?	_____	_____	31 _____
d) Chlorine?	_____	_____	41 _____
e) Residue?	_____	_____	35 _____
		Olin's Exposure Classification	42
50. Interviewer: _____			73 __
		Schedule Code	75 _____

Rev. 11/76

DATA COLUMN		CODE COLU
K. SMOKING HISTORY		
32. Do you smoke regularly?	Yes 1 No 2	54 __
If "Yes" to 32: 33. . . . cigarettes?	Yes 1 No 2 N.A. 9	55 __
If "Yes" to 33: 34. How many packs do you smoke each day? ___packs = ___ ___Cig.	N.A. 9 9	56 __ __
35. Do you inhale?	Yes 1 No 2 N.A. 9	58 __
36. Do you smoke pipes regularly?	Yes 1 No 2 N.A. 9	59 __
If "Yes" to 36: 37. How many pipesful do you smoke each day?	__ __ N.A. 9 9	61 __ __
38. Do you inhale?	Yes 1 No 2 N.A. 9	63 __
39. Do you smoke cigars regularly?	Yes 1 No 2 N.A. 9	64 __
If "Yes" to 39: 40. How many cigars do you smoke each day?	__ __ N.A. 9 9	65 __ __
41. What type of cigar do you smoke? _____	N.A. 9	67 __
42. Do you inhale?	Yes 1 No 2 N.A. 9	68 __
	Schedule Code	75 0 8 __ __ 0 6
L. EXPOSURE INFORMATION		1 Study No.
46. Which zone do you work in?	North 1 South 2 East 3 West 4 Central 5 All Over 6 Other: _____ 8	6 __
If specific zone is given: 47. Which area in that zone? _____	N.A. 9 9	7 __ __
48. What is your complete job title? _____		9 __ __
	Study Classification	12 __
	Olin's Exposure Classification	72
50. Interviewer: _____		73 __
	Schedule Code	75 _____

SYMPTOM CLASSIFICATIONS

	Initial Interview	Follow-Up Interview
Bronchitis		
Current Bronchitis Usual cough and phlegm for more than 3 months per year	1 in cc 5 or 6 and 1 in cc 7 and 1 in cc 9 or 10 and 1 in cc 11	1 in cc 13 or 14 and 1 in cc 15 and 1 in cc 16 or 17 and 1 in cc 18
Chronic Bronchitis Current bronchitis for two or more years	Current bronchitis and 2 or 3 in cc 8 and 2 or 3 in cc 12	not applicable
Lower Respiratory Symptoms Cough, phlegm, wheezing, SOB with wheezing, or SOB when walking with others of own age	1 in cc 5 or 6 or 9 or 10 or 13 or 17 or 19	1 in cc 13 or 14 or 16 or 17 or 26 or 29 or 31
Upper Respiratory Symptoms Drip at back of nose, hay fever, or current sinus trouble	1 in cc 32 or 36	1 in cc 34 or 36
Dyspnea		
Grade 1	2 in cc 18 and 19	2 in cc 25-28
Grade 2	1 in cc 18 and 1 in cc 19	1 in cc 25 and 2 in cc 26-28
Grade 3	2 in cc 18 and 19	1 in cc 25-26 and 2 in cc 27-28
Grade 4	not applicable	1 in cc 25-27 and 2 in cc 28
Grade 5	not applicable	2 in cc 25-28
Respiratory Atopy Ever had asthma or hay fever or any trouble around grass, pollen, etc.	1 in cc 14 or 33 or 34	not applicable
Dermal Atopy Ever had eczema or hives, and a positive family history of asthma or hay fever	1 in cc 37 or 38 and 1 in cc 42	not applicable
Atopy Either dermal or respiratory atopy	either of the above	not applicable
Smoking		
Current Cigarette	1 in cc 5	1 in cc 54 and 55
Ex-Cigarette	2 or 3 in cc 5 and 1 in cc 14	not applicable
Pipe/Cigar	2 or 3 in cc 5 and 1 in cc 23 or cc 29	1 in cc 54 and 1 in cc 59 or 64
Never Smoker	2 or 3 in cc 5 and 2 or 3 in cc 23	2 in cc 54

Listing of Computer Program to Edit Initial Interview

```
00010      C
00020      C    PROGRAM TO PROCESS T.D.I. INITIAL INTERVIEWS
00030      C    (FORMERLY CALLED INITLB. FOR)
00040      C
00050      C    WRITTEN BY LARRY JANESKI MARCH, 1978
00060      C    (WITH CODE SEGMENTS FROM TDIINV. FOR)
00070      C
00080      C    UPDATED BY RAY KERN MARCH, 1979
00090      C
00100                 IMPLICIT INTEGER (A-Z)
00110               DIMENSION CC(80), OTHER(5)
00120               DOUBLE PRECISION XFILE
00130                 REAL YEARS,PACKS,YRSTOP,AGE,S1,AGE1,AGE2,PYRS
00140               DATA OTHER/5*0/
00150      C
00160               OPEN(UNIT=01,ACCESS='SEQIN',FILE='TDINTL.INV')
00170               OPEN(UNIT=20,ACCESS='SEQOUT',FILE='TDEXTI,INV')
00180               XFILE='TDBAKI.INV'
00190               OPEN(UNIT=21,ACCESS='SEQOUT',FILE=XFILE)
00200
00210            800 FORMAT (A4,74X,12)
00220            801 FORMAT (80I1)
00230            900 FORMAT (/' DO YOU WANT DATA EXTRACTED(Y OR N)? '$)
00240            802 FORMAT (A1)
00250            908 FORMAT (A4,1X,3I2,6I2,2I1,5I2,5X,F5.2,2I2,4F6.2,1X,3A2)
00260      C
00270               TYPE 900
00280               ACCEPT 802,IEXT1
00290      C
00300      C           READ FIRST CARD FOR ID #
00310      C
00320            3 CONTINUE
00330                 READ(01,800,END=100)ID,CARD
00340                 IF (CARD.EZ.01) GO TO 4
00350                 CALL ERROR (ID,'CARD OUT OF SEQUENCE')
00360                 STOP
00370      C
00380      C           READ SECOND CARD FOR DATE INFO
00390      C
00400            4 CONTINUE
00410                 READ (01,801) CC
00420                 IF(CC(80).EQ.2) GO TO 5
00430                 CALL ERROR (ID,'CARD OUT OF SEQUENCE')
00440                 STOP
00450      C
00460      C           DATE CALCULATION
00470      C
00480      C
00490            5 CONTINUE
00500                 MO = CC(32)*10 + CC(33)
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```
00510               YR = CC(36)*10 + CC(37)
00520               DA = CC(34)*10 + CC(35)
00530     C
00540     C         AGE CALCULATION
00550     C
00560               AGE = CC(23)*10 + CC(24)
00570     C
00580     C            VISIT CALCULATION
00590     C
00600               VISIT = '00'
00610               IF(YR.EQ.73.AND.MO.GE.03.AND.MO.LE.05) VISIT = '01'
00620               IF(YR.EQ.73.AND.MO.GE.10.AND.MO.LE.12) VISIT = '02'
00630               IF(YR.EQ.74.AND.MO.GE.08.AND.MO.LE.10) VISIT = '04'
00640               IF(YR.EQ.75.AND.MO.GE.02.AND.MO.LE.04) VISIT = '05'
00650               IF(YR.EQ.75.AND.MO.GE.02.AND.MO.LE.11) VISIT = '06'
00660               IF (VISIT.NE.'00') GOTO 6
00670     C
00680     C         BAD DATE
00690     C
00700               CALL WARN (ID,'INTERVIEW DATE')
00710               SKIP RECORD 01
00720               SKIP RECORD 01
00730             GO TO 3
00740     C
00750     C    FOR EACH CLASS OF SYMPTOMS (LRS,URS,BRON.), DETERMINE IF SYMPTOM
00760     C    WAS PRESENT/ABSENT FOR INITIAL INTERVIEWS
00770     C
00780     C    LOWER RESPIRATORY SYMPTOM - INITIAL INTERVIEW
00790     C
00800             6 CONTINUE
00810               READ (01,801) CC
00820               IF (CC(80) .EQ. 3) GO TO 7
00830               CALL ERROR (ID,'CARD OUT OF SEQUENCE')
00840               STOP
00850             7 CONTINUE
00860               LRD = 0
00870               IF (CC(05).EQ.1.OR.CC(06).EQ.1.OR.CC(09).EQ.1.OR.CC(10).EQ.1
00880              *.OR.CC(13).EQ.1.OR.CC(17).EQ.1.OR.CC(19).EQ.1)
00890              *LRS = 1
00900               IF (CC(05).EQ.2.AND.CC(06).EQ.2.AND.CC(09).EQ.2.AND.
00910              *    CC(10).EQ.2.AND.CC(13).EQ.2.AND.CC(19).EQ.2.AND.
00920              *   (CC(17).EQ.2.OR. CC(17).EQ.9))
00930              *LRS = 2
00940               IF (LRS.EQ.0) CALL EXCEPT (ID,'LOWER RESP. SYMPTOM')
00950     C
00960     C         UPPER RESPIRATORY SYMPTOM - INITIAL INTERVIEW
00970     C
00980               URS = 0
00990               IF (CC(32).EQ.1.OR.CC(36).EQ.1) URS = 1
01000               IF ((CC(32).EQ.2.OR.CC(32).EQ.9).AND.
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01010              *     (CC(36).EQ.2.OR.CC(36).EQ.9)) URS = 2
01020               IF (URS.EQ.0) CALL EXCEPT (ID,'UPPER RESP. SYMPTOM')
01030      C
01040      C        BRONCHITIS - INITIAL INTERVIEW
01050      C
01060               COUGH=0; PHLEG=0; CCOUGH=0; CPHLEG=0
01070               CBRON=0; EBRON=0
01080      C
01090      C        EXPANDED DEFINITION
01100               IF ((CC(05).EQ.1.OR.CC(06).EQ.1).AND.CC(07).EQ.1) COUGH=1
01110               IF ((CC(09).EQ.1.OR.CC(10).EQ.1).AND.CC(11).EQ.1) PHLEG=1
01120               IF ((CC(05).EQ.1.OR.CC(05).EQ.2).AND.
01130              *    (CC(06).EQ.1.OR.CC(06).EQ.2).AND.
01140              *    (CC(07).EQ.2.OR.CC(07).EQ.9)) COUGH = 2
01150               IF ((CC(09).EQ.1.OR.CC(09).EQ.2).AND.
01160              *    (CC(10).EQ.1.OR.CC(10).EQ.2).AND.
01170              *    (CC(11).EQ.2.OR.CC(11).EQ.9)) PHLEG = 2
01180               IF (COUGH.EQ.1.AND.PHLEG.EQ.1) EBRON = 1
01190               IF (COUGH.EQ.2.OR. PHLEG.EQ.2) EBRON = 2
01200               IF (EBRON.EQ.0) CALL EXCEPT (ID,'CURRENT BRONCHITIS')
01210      C
01220      C        CHRONIC DEFINITION
01230               IF (COUGH.EQ.1.AND.(CC(08).EQ.2.OR.CC(08).EQ.3)) CCOUGH = 1
01240               IF (COUGH.EQ.1.AND.CC(08).EQ.1) CCOUGH = 2
01250               IF (COUGH.EQ.2.AND.CC(08).EQ.9) CCOUGH = 2
01260               IF (PHLEG.EQ.1.AND.(CC(12).EQ.2.OR.CC(12).EQ.3)) CPHLEG = 1
01270               IF (PHLEG.EQ.1.AND.CC(12).EQ.1) CPHLEG = 2
01280               IF (PHLEG.EQ.2.AND CC(12).EQ.9) CPHLEG = 2
01290               IF (CCOUGH.EQ.1.AND.CPHLEG.EQ.1) CBRON = 1
01300               IF (CCOUGH.EQ.2.OR. CPHLEG.EQ.2) CBRON = 2
01310               IF(CBRON.EQ.0) CALL EXCEPT (ID,'CHRONIC BRONCHITIS')
01320      C
01330      C        ATOPY - FROM INITIAL INTERVIEW
01340      C
01350               RATOPY=0; DATOPY=0; ATOPY=0
01360               IF(CC(14).EQ.1.or.CC(33).EQ.1.OR.CC(34).EQ.1) RATOPY = 1
01370               IF (CC(14).EQ.2.AND.CC(33).EQ.2.AND.CC(34).EQ.2) RATOPY = 2
01380               IF ((CC(37).EQ.1.OR.CC(38).EQ.1).AND.CC(42).EQ.1) DATOPY = 1
01390               IF ((CC(37).EQ.2.AND.CC(38).EQ.2).OR.
01400              *    ((CC(37).EQ.1.OR.CC(38).EQ.1)AND.CC(42).EQ.2)) DATOPY = 2
01410               IF (RATOPY.EQ.1.OR.DATOPY.EQ.1) ATOPY = 1
01420               IF (RATOPY.EQ.2.AND.DATOPY.EQ.2) ATOPY = 2
01430               IF (ATOPY.EQ.0) CALL EXCEPT (ID.'ATOPY SYMPTOM')
01440      C
01450      C        DYSPNEA (3 GRADES:  1=NO, 2-3=YES)
01460      C
01470               DYSP = 0
01480               IF (CC(18).EQ.2.AND.CC(19).EQ.2) DYSP = 1
01490               IF (CC(18).EQ.2.AND.CC(19).EQ.1) DYSP = 1
01500               IF (CC(18).EQ.1.AND.CC(19).EQ.2) DYSP = 2
01510               IF (CC(18).EQ.1.AND.CC(19).EQ.1) DYSP = 3
01520               IF (DYSP.EQ.0) CALL EXCEPT (ID,'DYSPNEA GRADE')
01530      C
```

```
01540     C         SMOKING - FROM INIITAL INTERVIEW (NEXT CARD)
01550     C
01560           15 CONTINUE
01570              READ (01,801) CC
01580              IF (CC(80) .EQ. 4) GO TO 16
01590              CALL ERROR (ID,'CARD OUT OF SEQUENCE')
01600              STOP
01610           16 CONTINUE
01620              SMOKE=0; PACKS=99.99; YEARS=99.99; YRSTOP=99.99; PYRS=-1.00
01630              IF ((CC(05).EQ.1.AND.CC(14).EQ.9).OR.
01640             *    (CC(14).EQ.1.AND.(CC(05).EQ.2.OR.CC(05).EQ.3)))
01650             *SMOKE = 1
01660              IF ((CC(05).EQ.2.OR.CC(05).EQ.3) .AND.
01670             *   (CC(14).EQ.2.OR.CC(14).EQ.3).AND.
01680             *   (CC(23).EQ.1.OR.CC(29).EQ.1))
01690             *SMOKE = 2
01700              IF((CC(05).EQ.2.OR.CC(05).EQ.3).AND.
01710             *   (CC(14).EQ.2.OR.CC(14).EQ.3).AND.
01720             *   (CC(23).EQ.2.OR.CC(23).EQ.3))
01730             *SMOKE = 3
01740              IF(SMOKE.NE.0) GO TO 17
01750              CALL EXCEPT (ID,'SMOKING STATUS')
01760              GO TO 70
01770           17 CONTINUE
01780     C
01790     C           DECISION FOR PACKS, YEARS, STOP YEARS
01800     C
01810              IF(SMOKE.EQ.1) GO TO 20
01820                   YRSTOP = 99.99
01830                   YEARS = 0.0
01840                   PACKS = 0.0
01850              GOTO 70
01860     C
01870     C    CIGARETTE SMOKER
01880           20 CONTINUE
01890              IF (CC(06).NE.1) GO TO 35
01900     C           PERSON WHO NOW SMOKES
01910     C
01920              YRSTOP = 0.0
01930              S1 = CC(12)*10 + CC(13)
01940     C
01950     C         CHECK FOR VALID PACKS
01960     C
01970              IF (S1,GT.0.0.AND.S1.LT.77.0) GO TO 21
01980              S1 = CC(08)*10 + CC(09)
01990              IF (S1.Gl.0.0.AND.S1.LT.77.0) GO TO 21
02000              GOTO 25
02010     C
02020     C         HERE IF VALID PACKS
02030     C
```

```
02040           21 CONTINUE
02050                PACKS = S1/20.
02060      C        CHECK FOR VALID AGE
02070           25 IF (AGE.GT.O.O.AND.AGE.LT.77.0) GOTO 27
02080              GOTO 70
02090      C        CHECK FOR VALID STARTING AGE
02100           27 CONTINUE
02110              AGE1 = CC(10)*10 + CC(11)
02120              IF (AGE1.GT.0 .AND. AGE1.LT.77) GO TO 30
02130              GO TO 70
02140      C
02150      C          HERE IF VALID AGE
02160      C
02170           30 CONTINUE
02180                YEARS = AGE - AGE1
02190              GOTO 70
02200      C
02210      C          HERE IF PAST SMOKER
02220      C
02230           35 CONTINUE
02240              IF (CC(14).NE.1) GO TO 70
02250              S1 = CC(15)*10 + CC(16)
02260              IF (S1.GT.0 .AND. S1.LT.77.0) GOTO 40
02270                GOTO 45
02280           40 CONTINUE
02290                PACKS = S1/20.
02300      C        CHECK FOR VALID AGE
02310           45 IF (AGE.GT.0.0.AND.AGE.LT.77.0) GOTO 47
02320                GOTO 70
02330      C        CHECK FOR VALID STARTING AGE
02340           47 CONTINUE
02350              AGE1 = CC(18)*10 + CC(19)
02360              IF (AGE1.GT.0.0 .AND. AGE1.LT.77.0) GO TO 48
02370              GO TO 70
02380      C        CHECK FOR VALID STOPPING AGE
02390           48 CONTINUE
02400              AGE2 = CC(20)*10 + CC(21)
02410              IF (AGE2.GT.0.0 .AND. AGE2.LT.77.0) GO TO 50
02420              GO TO 70
02430      C
02440      C          HERE IF AGES ARE VALID
02450      C
02460           50 CONTINUE
02470              YRSTOP = AGE - AGE2
02480              YEARS = AGE2 - AGE1
02490      C
02500      C        PACK*YEARS CALCULATION
02510      C
02520           70 CONTINUE
02530              IF (PACKS.EQ.99.99) CALL EXCEPT (ID,'PACKS/DAY SMOKED')
02540              IF (YEARS.EQ.99.99) CALL EXCEPT (ID,'YEARS SMOKED')
02550              IF (SMOKE.EQ.1.AND.YRSTOP.EQ.99.99)
```

```
02560              *CALL EXCEPT (ID,'YRS STOPPED SMOKING')
02570               IF (PACKS.EQ.99.99.OR.YEARS.EQ.99.99) GO TO 75
02580               PYRS = PACKS*YEARS
02590              75 CONTINUE
02600               IF(TEXT1.NE.'Y') GO TO 80
02610     C
02620     C         WRITE ON TO EXTRACT FILE
02630     C
02640              71 CONTINUE
02650               STUDY='08'
02660               PLANT = 0.0
02670               HAZOCC = 0
02680               RECORD = '08'
02690     C
02700               WRITE(21,908) ID,MO,DA,YR,LRS,URS,CBRON,EBRON,DYSP,ATOPY,RATOPY,
02710              *DATOPY,OTHER,PLANT,HAZOCC,SMOKE,PACKS,YEARS,YRSTOP,PYRS,
02720              *STUDY,VISIT,RECORD
02730
02740               WRITE(20.908) ID,MO,DA,YR,LRS,URS,CBRON,EBRON,DYSP,ATOPY,RATOPY,
02750              *DATOPY,OTHER,PLANT,HAZOCC,SMOKE,PACKS,YEARS,YRSTOP,PYRS,
02760              *STUDY,VISIT,RECORD
02770     C
02780     C         ID 0210 IS MISSING INITIAL INTERVIEW.  SPECIAL EXTRACT FOR HIM.
02790               IF (ID.NE.'0209') GO TO 80
02800               ID='0210'; MO=9; DA=15; YR=74; LRS=0; URS=0; CBRON=0; EBRON=0
02810               DYSP=0; ATOPY=0; DATOPY=0; RATOPY=0; SMOKE=0; PACKS=99.99
02810               YEARS=99.99; YRSTOP=99.99; PYRS=-1.00; VISIT='04'
02830               GO TO 71
02840     C
02850     C         GET NEXT RECORD
02860
02870              80 CONTINUE
02880               GO TO 3
02890     C
02900     C         HERE AT END OF FILE ON LINE 3
02910     C
02920             100 CONTINUE
02930               CALL EXIT
02940               END
02950     C
02960     C         ****************************
02970               SUBROUTINE ERROR(ID,MESSAG)
02980     C         ****************************
02990     C
03000     C    TYPES OUT ERROR MESSAGE ON TTY WITH ALPHANUMERIC ID.
03010     C    MESSAGE MUST BE LONGER THAN 10 CHARACTERS TO WORK, OTHERWISE
03020     C    YOU MAY GET GARBAGE.
03030     C
03040               DIMENSION MESSAG(2)
03050               DOUBLE PRECISION MESSAG
03060               TYPE 1, ID,MESSAG
```

```
03070            1 FORMAT (/' *** ERROR ID ',A4,':  ',2A10)
03080              RETURN
03090              END
03100      C
03110      C       ****************************
03120              SUBROUTINE EXCEPT(ID,MESSAG)
03130      C       ****************************
03140      C
03150      C    TYPES OUT EXCEPTION MESSAGE ON TTY WITH ALPHANUMERIC ID.
03160      C    MESSAGE MUST BE LONGER THAN 10 CHARACTERS TO WORK, OTHERWISE
03170      C    YOU MAY GET GARBAGE.
03180      C
03190              DIMENSION MESSAG(2)
03200              DOUBLE PRECISION MESSAG
03210              TYPE 1, ID, MESSAG
03220            1 FORMAT (/' EXCEPTION ID ',A4,':  ',2A10)
03230              RETURN
03240              END
03250      C
03260      C       ***************************
03270              SUBROUTINE WARN(ID,MESSAG)
03280      C       ***************************
03290      C
03300      C    TYPES OUT WARNING MESSAGE ON TTY WITH ALPHANUMERIC ID.
03310      C    MESSAGE MUST BE LONGER THAN 10 CHARACTERS TO WORK, OTHERWISE
03320           YOU MAY GET GARBAGE.
03330      C
03340              DIMENSION MESSAG(2)
03350              DOUBLE PRECISION MESSAG
03360              TYPE 1, ID, MESSAG
03370            1 FORMAT (/' * WARNING ID ',A4,':  ',2A10)
03380              RETURN
03390              END
```

Listing of Computer Program to Edit Follow-up Interview

```
00010     C
00020     C    PROGRAM TO PROCESS T.D.I. FOLLOW-UP INTERVIEWS
00030     C    (FORMERLY CALLED FOLUPB.FOR)
00040     C
00050     C    WRITTEN BY LARRY JANESKI MARCH 21, 1978
00060     C    (WITH CODE SEGMENTS FROM TDIINV.FOR)
00070     C
00080     C    UPDATED BY RAY KERN MARCH, 1979
00090     C
00100               IMPLICIT INTEGER (A-Z)
00110               COMMUN/RAND/MAXID,TABLE(1000,2)
00120               REAL PACKS,YEARS,YRSTP,AGE,S1,DIF,DMO,YEARSI,PACKSI,PLANTI
00130               REAL YRSIPI,PYRS,PYRSI
00140               DOUBLE PRECISION IFILE,OFILE,XFILE
00150               DIMENSION CC(80),OTHER(5)
00160     C
00170            790 FORMAT (A10)
00180            791 FORMAT (A1)
00190            792 FORMAT (A2)
00200            800 FORMAT (A4,74X,A2)
00210            801 FORMAT (80I1)
00220            908 FORMAT (A4,1X,3I2,6I2,2X,5I2,5X,F5.2,2I2,4F6.2,1X,3A2)
00230     C
00240     C    INPUT AND OUTPUT FILES DETERMINED BY VISIT NUMBER
00250               TYPE 1
00260             1 FORMAT (/' PROGRAM TO PROCESS T.D.I. FOLLOW-UP INTERVIEWS.')
00270               2 TYPE 3
00280               3 FORMAT (/' ENTER 2 DIGIT VISIT NUMBER (08,09,10) - '$)
00290                 ACCEPT 792, IVISIT
00300                 IF (IVISIT.EQ.'08') GOTO 4
00310                 IF (IVISIT.EQ.'09') GOTO 5
00320                 IF (IVISIT.EQ.'10') GOTO 6
00330                 GO TO 2
00340               4 CONTINUE
00350                 IFILE='TDI8.INV'; OFILE='TDEXT8.INV'
00360                 GO TO 7
00370               5 CONTINUE
00380                 IFILE='TDI9.INV'; OFILE='TDEXT9.INV'
00390                 GO TO 7
00400               6 CONTINUE
00410                 IFILE='TD110.INV'; OFILE='TDEXTX.INV'
00420               7 CONTINUE
00430                 OPEN(UNIT=20,ACCESS='SEQIN',FILE=IFILE)
00440                 OPEN(UNIT=21,ACCESS='SEQOUT',FILE=OFILE)
00450     C
00460     C    RANDOM ACCESS ON T.D.I. BACKUP INTERVIEW EXTRACT FILE
00470               XFILE = 'TDBAKI.INV'; MAXID = 500
00480               CALL TABGEN (XFILE)
00490               OPEN(UNIT=01,ACCESS='RANDOM',RECORD SIZE=80,FILE=XFILE)
00500               TYPE 8
00510             8 FORMAT (/' DO YOU WANT DATA EXTRACTED (Y OR N)? '$)
```

```
00520              ACCEPT 791, IEXT
00530              IF (IEXT.EQ.'N') GO TO 11
00540              TYPE 9
00550            9 FORMAT ( ' DO YOU WANT TDBAKI.INV UPDATED? '$)
00560              ACCEPT 791, IBAK
00570      C
00580           11 CONTINUE
00590              READ20,800,END=100) ID,CARD
00600              IF (CARD.EQ.'06') GO TO 12
00610              CALL ERROR (ID,'CARD OUT OF SEQUENCE')
00620              STOP
00630           12 CONTINUE
00640              BACKSPACE 20
00650              READ(20,801,END=100) CC
00660      C
00670              MO = CC(05)*10 + CC(06)
00680              DA = CC(07)*10 + CC(08)
00690              YR = CC(09)*10 + CC(10)
00700      C
00710      C     FETCH PREVIOUS INTERVIEW EXTRACT FROM BACK-UP EXTRACT FILE
00720                CALL GETREC(ID,N,RNF)
00730                READ(01#N,908) IDI,MOI,DAI,YRI,LRSI,
00740               *URSI,CBRONI,EBRONI,DYSPI,ATOPYI,OTHER,PLANTI,HAZOCI,
00750               *SMOKEI,PACKSI,YEARSI,YRSTPI,PYRSI,STUDYI,VISITI,RECRDI
00760      C
00770      C     CHECK INTERVIEW DATE WITH PREVIOUS INTERVIEW DATE.
00780      C     SKIP ID IF ERROR.
00790                IF(RNF.EQ.1) GO TO 85
00800                IF(YR.GT.YRI) GO TO 15
00810                IF(YR.EQ.YRI.AND.MO.GT.MOI) GO TO 15
00820                CALL WARN (ID,'DATE > PREVIOUS DATE')
00830                GO TO 85
00840      C
00850      C     DETERMINE VISIT FROM INTERVIEW DATE AND CHECK IT.
00860      C
00870           15 CONTINUE
00880              VISIT = '00'
00890              IF(YR.EQ.76.AND.MO.GE.11.AND.MO.LE.12) VISIT = '08'
00900              IF(YR.EQ.77.AND.MO.GE.10.AND.MO.LE.11) VISIT = '09'
00910              IF(YR.EQ.78.AND.MO.EQ.10) VISIT = '10'
00920              IF(VISIT.EQ.IVISIT) GO TO 20
00930      C
00940      C     BAD DATE - SKIP PROCESSING FOR THIS ID
00950      C
00960                CALL WARN (ID,'FOLLOW-UP DATE')
00970                GO TO 85
00980
00990      C
01000      C           LOWER RESP. FINAL INTERVIEW
01010      C
01020           20 CONTINUE
```

```
01030              LRS = 0
01040              IF (CC(13).EQ.1.OR.CC(14).EQ.1.OR.CC(16).EQ.1.OR.CC(17).EQ.1
01050             *.OR.CC(26).EQ.1.OR.CC(29).EQ.1.OR.CC(31).EQ.1)
01060             *LRS = 1
01070              IF (CC(13).EQ.2.AND.CC(14).EQ.2.AND.CC(16).EQ.2.AND.
01080             *    CC(17).EQ.2.AND.CC(29).EQ.2.AND.CC(31).EQ.2.AND.
01090             *   (CC(26).EQ.2.OR.CC(26).EQ.9))
01100             *LRS = 2
01110              IF (LRS .NE. 0) GO TO 25
01120              CALL EXCEPT (ID,'LOWER RESP. SYMPTOM')
01130     C
01140     C        URS - FINAL INTERVIEW
01150     C
01160           25 CONTINUE
01170              URS = 0
01180              IF (CC(34).EQ.1.OR.CC(36).EQ.1) URS = 1
01190              IF ((CC(34).EQ.2.OR.CC(34).EQ.9).AND.CC(36).EQ.2) URS = 2
01200              IF (URS . NE. 0) GO TO 30
01210              CALL EXCEPT (ID,'UPPER RESP. SYMPTOM')
01220     C
01230     C        BRON. - FINAL INTERVIEW
01240     C
01250           30 CONTINUE
01260              COUGH=0; PHLEG=0; CBRON=0; EBRON=0
01270              IF ((CC(13).EQ.1.OR.CC(14).EQ.1).AND.CC(15).EQ.1) COUGH = 1
01280              IF ((CC(16).EQ.1.OR.CC(17).EQ.1).AND.CC(18).EQ.1) PHLEG = 1
01290              IF ((CC(13).EQ.1.OR.CC(13).EQ.2).AND.
01300             *    (CC(14).EQ.1.OR.CC(14).EQ.2).AND.
01310             *    (CC(15).EQ.2.OR.CC(15).EQ.9)) COUGH = 2
01320              IF ((CC(16).EQ.1.OR.CC(16).EQ.2).AND.
01330             *    (CC(17).EQ.1.OR.CC(17).EQ.2).AND.
01340             *    (CC(18).EQ.2.OR.CC(18).EQ.9)) PHLEG = 2
01350              IF (COUGH.EQ.1.AND.PHLEG.EQ.1) EBRON = 1
01360              IF (COUGH.EQ.2.OR. PHLEG.EQ.2) EBRON = 2
01370              IF (EBRON.EQ.0) CALL EXCEPT (ID,'CURRENT BRONCHITIS')
01380     C
01390     C        DYSPNEA GRADE (1=NO, 2-5=YES)
01400     C
01410              DYSP = 0
01420              CC25=CC(25); CC26=CC(26); CC27=CC(27); CC28=CC(28)
01430              IF (CC25.EQ.2.AND.CC26.EQ.9.AND.CC27.EQ.9.AND.CC28.EQ.9) DYSP=1
01440              IF (CC25.EQ.1.AND.CC26.EQ.2.AND.CC27.EQ.9.AND.CC28.EQ.9) DSYP=2
01450              IF (CC25.EQ.1.AND.CC26.EQ.1.AND.CC27.EQ.2.AND.CC28.EQ.9) DYSP=3
01460              IF (CC25.EQ.1.AND.CC26.EQ.1.AND.CC27.EQ.1.AND.CC28.EQ.2) DYSP=4
01470              IF (CC25.EQ.1.AND.CC26.EQ.1.AND.CC27.EQ.1.AND.CC28.EQ.1) DYSP=5
01480              IF (DYSP.EQ.0) CALL EXCEPT (ID,'DYSPNEA GRADE')
01490           40 CONTINUE
01500     C
01510     C    SMOKING UPDATE
01520     C
01530              SMOKE=0; PACKS=99.99; YEARS=99.99; YRSTP=99.99; PYRS=-1.00
```

```
01540              IF(CC(54).EQ.1.AND.CC(55).EQ.1) SMOKE = 1
01550              IF(CC(54).EQ.1.AND.CC(55).EQ.2.AND.
01560             *  (CC(59).EQ.1.OR. CC(64).EQ.1)) SMOKE = 2
01570              IF(CC(54).EQ.2.AND.CC(55).EQ.9.AND.CC(59).EQ.9.AND.CC(64).EQ.9)
01580             *SMOKE = 3
01590              IF (SMOKE.NE.0.AND.SMOKEI.NE.0) GO TO 50
01600              IF (SMOKEI.EQ.0) SMOKE = 0
01610              CALL EXCEPT (ID,'(F)SMOKING STATUS')
01620              GO TO 81
01630     C
01640     C        DIF EQUALS DIFFERENCE BETWEEN FOLLOW-UP INTERVIEW
01650     C        AND THE PREVIOUS INTERVIEW IN YEARS.
01660     C        S1 IS THE # CIGARETTES SMOKED/DAY  .
01670     C
01680           50 CONTINUE
01690              DIF = (YR-YRI)*360 + (MO-MOI)*30 + (DA-DAI)
01700              DIF = DIF/360.
01710              SI = CC(56)*10 + CC(57)
01720     C
01730              IF((SMOKE.EQ.3.OR.SMOKE.EQ.2).AND.
01740             *    (SMOKEI.EQ.2.OR.SMOKEI.EQ.3)) GO TO 79
01750     C
01760              IF(SMOKE.EQ.1.AND.SMOKEI.EQ.1) GO TO 60
01770     C
01780              IF((SMOKE.EQ.2.OR.SMOKE.EQ.3).AND.
01790             *(SMOKEI.EQ.1)) GO TO 65
01800     C
01810              IF(SMOKE.EQ.1.AND.(SMOKEI.EQ.2.OR.SMOKEI.EQ.3))
01820             *GO TO 70
01830     C
01840     C        CIGARETTE SMOKER BOTH VISITS
01850     C
01860           60 CONTINUE
01870     C        CURRENT SMOKER LAST VISIT
01880              IF (YRSTPI.EQ.0.0) YEARS = DIF
01890     C        PAST SMOKER LAST VISIT
01900              IF (YRSTPI.GT.0.0.AND.YRSTPI.LT.99.99) YEARS = DIF/2.
01910              IF (S1.GT.0.AND.S1.NE.77.AND.S1.NE.88.AND.S1.NE.99) GO TO 62
01920              CALL EXCEPT(ID, "(F)PACKS/DAY SMOKED')
01930              GOTO 63
01940           62 PACKS = S1/20.
01950           63 YRSTP = 0.0
01960              GO TO 80
01970     C
01980     C        STOPPED SMOKING BETWEEN VISITS
01980     C
01990     C
02000           65 CONTINUE
02010              PACKS = PACKSI; SMOKE = SMOKEI
02020              IF (PACKS.EQ.99.99) CALL EXCEPT (ID,'(F)PACKS/DAY SMOKED')
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```
02030              IF (YRSTPI.EQ.0.0) GO TO 66
02040              IF (YRSTPI.GT.0.0.AND.YRSTPI.LT.99.99) GO TO 67
02050     C        ERROR ON LAST VISIT YEARS STOPPED SMOKING
02060              CALL EXCEPT (ID,'(F)YRS STOPPED SMOKE')
02070              GO TO 80
02080     C        CURRENT SMOKER LAST VISIT
02090           66 CONTINUE
02100              YEARS = DIF/2.
02110              YRSTP = DIF/2.
02120              GO TO 80
02130     C        PAST SMOKER LAST VISIT
02140           67 CONTINUE
02150              YEARS=0.0; PACKS-0.0
02160              YRSTP = YRSTPI + DIF
02170              IF (YEARS.EQ.99.99) CALL EXCEPT (ID,'(F)YEARS SMOKED')
02180              GO TO 80
02190     C
02200     C        STARTED SMOKING BETWEEN VISITS
02210     C
02220           70 CONTINUE
02230              IF(S1.GT.0.AND.S1.NE.77.AND.S1.NE.88.AND.S1.NE.99) GO TO 72
02240              CALL EXCEPT (ID,'(F)PACKS/DAY SMOKED')
02250              GO TO 73
02260           72 PACKS = S1/20.
02270           73 YRSTP = 0.0
02280              YEARS = DIF/2.
02290              GO TO 80
02300     C
02310     C        NEVER SMOKED IN EITHER VISIT
02320     C
02330           79 CONTINUE
02340              PACKS = 0.0
02350              YEARS = 0.0
02360              YRSTP = 99.99
02370              IF (SMOKEI.EQ.2) SMOKE = 2
02380              GO TO 80
02390     C
02400     C        PACK-YEARS UPDATE
02410     C
02420           80 CONTINUE
02430              IF (PACKS.EQ.99.99.OR.YEARS.EQ.99.99) GO TO 81
02440              PYRS = PACKS*YEARS
02450     C
02460     C        WRITE ON TO EXTRACTION FILE
02470     C
02480           81 CONTINUE
02490              IF (IEXT.NE.'Y') GO TO 85
02500              STUDY = '08'
02510              PLANT = 0.0
02520              HAZOCC = 0
02530              RECORD = '08'
```

```
02540              WRITE (21,908) ID,MO,DA,YR,LRS,URS,CBRON,EBRON,DYSP,ATOPY,
02550             *OTHER,PLANT,HAZOCC,SMOKE,PACKS,YEARS,YRSTP,PYRS,
02560             *STUDY,VISIT,RECORD
02570     C
02580     C         BACK-UP EXTRACT FILE UPDATE
02590              IF (IBAK.NE.'Y') GO TO 85
02600              WRITE (01#N,908) ID,MO,DA,YR,LRS,URS,CBRON,EBRON,DYSP,ATOPY,
02610             *OTHER,PLANT,HAZOCC,SMOKE,PACKS,YEARS,YRSTP,PYRS,
02620             *STUDY,VISIT,RECORD
02630            85 CONTINUE
02640              SKIP RECORD 20
02650              GO TO 11
02660     C
02670     C         HERE ON END-OF-FILE
02680     C
02690           100 CONTINUE
02700              CALL EXIT
02710              END
02720     C
02730     C         ****************************
02740              SUBROUTINE ERROR(ID,MESSAG)
02750     C         ****************************
02760     C
02770     C    TYPES OUT ERROR MESSAGE ON TTY WITH ALPHANUMERIC ID.
02780     C    MESSAGE MUST BE LONGER THAN 10 CHARACTERS TO WORK, OTHERWISE
02790     C    YOU MAY GET GARBAGE.
02800     C
02810              DIMENSION MESSAG(2)
02820              DOUBLE PRECISION MESSAG
02830              TYPE 1, ID,MESSAG
02840            1 FORMAT (/' *** ERROR ID ',A4,':  ',2A10)
02850              RETURN
02860              END
02870     C
02880     C         ****************************
02890              SUBROUTINE EXCEPT(ID,MESSAG)
02900     C         ****************************
02910     C
02920     C    TYPES OUT EXCEPTION MESSAGE ON TTY WITH ALPHANUMERIC ID.
02930     C    MESSAGE MUST BE LONGER THAN 10 CHARACTERS TO WORK, OTHERWISE
02940     C    YOU MAY GET GARBAGE.
02950     C
02960              DIMENSION MESSAG(2)
02970              DOUBLE PRECISION MESSAG
02980              TYPE 1, ID,MESSAG
03000              RETURN
03010              END
03020     C
03030     C         ****************************
03040              SUBROUTINE WARN(ID,MESSAG)
03050     C         ****************************
03060     C
```

```
03070     C    TYPES OUT WARNING MESSAGE ON TTY WITH ALPHANUMERIC ID.
03080     C    MESSAGE MUST BE LONGER THAN 10 CHARACTERS TO WORK, OTHERWISE
03090     C    YOU MAY GET GARBAGE.
03200     C
03110               DIMENSION MESSAG(2)
03120               DOUBLE PRECISION MESSAG
03130               TYPE 1, ID MESSAG
03140             1 FORMAT (/' * WARNING ID ',A4,':  ',2A10)
03150               RETURN
03160               END
03170     C
03180     C         **************************
03190               SUBROUTINE TABGEN (IFILE)
03200     C         **************************
03210     C
03220     C    GENERATES LOOK-UP TABLE FOR RANDOM ACCESS BASED ON SEQUENTIAL
03230     C    SCAN FOR ID# - PAIRS ID# WITH RECORD #.  THIS SUBROUTINE SHOULD
03240     C    BE CALLED ONLY ONCE.
03250     C
03260     C    CALLING SEQUENCE:  CALL TABGEN(IFILE)
03270     C
03280     C    WHERE IFILE = INTEGER, DOUBLE PRECISION VARIABLE CONTAINING NAME
03290     C                  OF FILE TO BE SCANNED.
03300     C
03310     C    IN THE LABELLED COMMON /RAND/:
03320     C         MAXID = INTEGER VARIABLE CONTAINING MAX # OF CASES (ID#'S).
03330     C                 MUST BE LESS THAN 1000 (LINEAR DIM OF TABLE ARRAY).
03340     C         TABLE(1000,2) = 2-D INTEGER ARRAY LINKING ID# WITH ITS RECORD #
03350     C                         IN FILE.
03360     C
03370               IMPLICIT INTEGER (A-Z)
03380               DOUBLE PRECISION IFILE
03390               COMMON /RAND/ MAXID, TABLE(1000,2)
03400     C
03410              800 FORMAT (A4)
03420              900 FORMAT (/' ERROR IN SUBROUTINE TABGEN:')
03430              901 FORMAT (' ID ',A4,' HAS APPEARED TWICE IN DATA FILE ',A10.
03440                 *', RECORD # ',16' AND ',16,'.')
03450              902 FORMAT (' # OF CASES > MAX # SET UP FOR TABLE.')
03460     C
03470     C    INITIALIZATION
03480     C
03490               OPEN (UNIT=1,ACCESS='SEQIN',FILE=IFILE)
03500               IF(MAXID.LE.0) MAXID = 1000
03510               DO 10 I=1,MAXID
03520                  TABLE(I,1)='0000'
03530                  TABLE(I,2)=0
03540             10 CONTINUE
03550               I = 0
03560               N = 0
03570               ID2 = '000'
03580     C
```

```
03590     C    LOOP UNTIL YOU FIND A DIFFERENT ID.  N IS THE RECORD #.
03600     C
03610           100 CONTINUE
03620               N = N+1
03630               READ (1,800,END=999) ID1
03640               IF(ID1.EQ.ID2) GO TO 100
03650     C
03660     C    HERE TO MAKE TABLE ENTRIES.
03670     C         CHECK IF ID HAS BEEN ENTERED BEFORE.
03680     C
03690           200 CONTINUE
03700               DO 300 K=1,I
03710                  IF (TABLE(K,1).NE.ID1) GO TO 300
03720                  TYPE 900
03730                  TYPE 901, ID1,IFILE,TABLE(K,2),I
03740                  STOP
03750           300 CONTINUE
03760               I = I+1
03770               TABLE(I,1) = ID1
03780               TABLE(I,2) = N
03790               ID2 = ID1
03800     C
03810     C         CHECK IF INDEX > MAX. CONTINUE SCAN IF NOT.
03820     C
03830               IF (I.LE.MAXID) GO TO 100
03840               TYPE 900
03850               TYPE 902
03860               STOP
03870     C
03880     C    HERE ON EOF FOR CLOSE-OUT.
03890     C
03900           999 CONTINUE
03910               CLOSE (UNIT=1)
03920               RETURN
03930               END
03940     C
03950     C         ****************************
03960               SUBROUTINE GETREC(ID,N,RNF)
03970               ****************************
03980     C
03990     C    SEARCHES TABLE GENERATED BY SUBROUTINE TABGEN FOR ID# AND
04000     C    RETRIEVES RECORD # FOR RANDOM ACCESS.
04010     C
04020               IMPLICIT INTEGER (A-Z)
04030               COMMON /RAND/ MAXID,TABLE(1000,2)
04040     C
04050               RNF = 0
04060               DO 10 I=1,MAXID
04070                  IF(TABLE(I,1).NE.ID) GO TO 10
04080                  N = TABLE(I,2)
04090                  RETURN
```

```
04100           10 CONTINUE
04110              TYPE 900, ID
04120          900 FORMAT(/' RECORD NOT FOUND FOR ID ',A4)
04130              RNF = 1
04140              RETURN
04150              END
04160      C
04170      C       **********************************
04180              SUBROUTINE AERROR(ID,MESG1,MESG2)
04190      C       **********************************
04200      C
04210      C     TYPES OUT ERROR MESSAGE ON TTY WITH ALPHANUMERIC ID
04220      C
04230              DOUBLE PRECISION MESG1,MESG2
04240              TYPE 900, ID,MESG1,MESG2
04250          900 FORMAT (/' ERROR ID ',A4,':  ',2A10)
04260              RETURN
04270              END
```

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Table 1

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

				n
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	

		n	Mean	Standard Deviation
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.	DL_{CO}% P	212	99.0	16.7
18.	K% P	212	99.7	17.3

(1) % predicteds 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	.0020	.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

Exposure Category	Job Code	Job	Location	Number of Samples
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	Hyco	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

CATEGORY	HIGH	MODERATE	LOW
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

Table 6

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	Number of Samples
I	36.1	20.1	10.6	5.5	3.9	3.4	219
II	24.0	12.1	5.0	2.4	1.6	1.4	618
III	10.7	4.0	1.4	0.5	0.3	0.2	518
IV	3.2	0.7	0.3	0.1	0.1	0.0	738
All Categories Combined	14.6	6.9	3.0	1.4	1.0	0.8	2093

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
FEV_1 L/yr	223	-.0103 (-1.09)	-.0770 (-.81)	.0011 (.15)	-.00057 (-2.55)	7.36
FVC L/yr	223	-.0039 (-.40)	.0455 (.47)	-.0070 (-.97)	-.00071 (-3.13)	20.3
FEV% $(yr)^{-1}$	223	-.2041 (-1.52)	-1.372 (-1.01)	.1246 (1.21)	-.00332 (-1.03)	3.0
FEF_{25-75} L/sec-yr	223	-.0736 (-3.23)	-.00275 (-1.19)	.0249 (1.44)	-.00024 (-.43)	4.1
FEF_{50} L/sec-yr	223	-.1115 (-3.50)	-.000386 (-.12)	.0374 (1.54)	-.00036 (-.48)	6.5
K $(min\text{-}mmHg\text{-}yr)^{-1}$	164	-.169 (-4.99)	1.276 (3.31)	-.0155 (-.58)	-.00072 (-.85)	28.8
DL_{CO} $\frac{ml}{min\text{-}mmHg\text{-}yr}$	164	-1.127 (-4.97)	7.926 (3.07)	-.433 (-2.43)	-.0015 (-.27)	47.5
RV L/yr	179	.0391 (3.09)	-.126 (-.99)	-.00222 (-.24)	.00104 (3.58)	30.9
TLC L/yr	179	.0275 (1.81)	.00371 (.02)	-.0106 (-.93)	.00048 (1.38)	5.5
(RV/TLC) x 100 $(yr)^{-1}$	179	.4400 (3.04)	-1.112 (-.77)	-.0181 (-.17)	.0114 (3.44)	46.4

(1) 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

	n	Intercept	Cumulative[2] Exposure Category II	Atopy	Pack-Years	% Variability Explained
FEV_1 L/yr	223	-.0120 (-2.14)	-.0118 (-1.82)	.0009 (.13)	-.00058 (-2.60)	9.4
FVC L/yr	223	-.0006 (-.10)	.0012 (.19)	-.0069 (-.95)	-.00071 (-3.17)	19.2
FEV% $(yr)^{-1}$	223	-.2358 (-2.94)	-.2024 (-2.20)	.1216 (1.19)	-.0034 (-1.08)	6.30
FEF_{25-75} L/sec-yr	223	-.0801 (-5.96)	-.0406 (-2.63)	.0243 (1.42)	-.00025 (-.46)	11.1
FEF_{50} L/sec-yr	223	-.1031 (-5.44)	-.0285 (-1.31)	.0373 (1.55)	-.00041 (-.54)	6.6
K $(min\text{-}mmHg\text{-}yr)^{-1}$	164	-.0934 (-4.39)	.0518 (1.97)	-.00642 (-.24)	-.00101 (-1.19)	16.3
DL_{CO} $\frac{ml}{min\text{-}mmHg\text{-}yr}$	164	-.6578 (-4.64)	.3246 (1.86)	-.3755 (-2.09)	-.0033 (-.58)	33.6
RV L/yr	179	.0286 (3.83)	-.0061 (-.07)	-.00289 (-.31)	.00107 (3.67)	27.1
TLC L/yr	179	.0278 (3.11)	.0000 (.00)	-.0105 (-.93)	.00048 (1.38)	5.6
(RV/TLC) x 100 $(yr)^{-1}$	179	.3331 (3.93)	.0313 (.32)	-.0246 (-.23)	.0117 (3.52)	41.7

[1] See Footnote [1] of Table 8.

[2] 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.

Table 10

ANNUAL CHANGE REGRESSION COEFFICIENTS[1] USING THREE CUMULATIVE EXPOSURE CATEGORIES[2], ATOPIC STATUS, AND PACK-YEARS AS EXPLANATORY VARIABLES

	n	Intercept	Cumulative[2] Exposure Category II A	Cumulative[2] Exposure Category II B	Atopy	Pack-Years	% Variability Explained
FEV_1 L/yr	223	-.0123	-.0187	.0132	.0020	-.00057	13.3
		(-2.21)	(-2.25)	(1.31)	(.28)	(-2.59)	
FVC L/yr	223	-.0008	-.0049	.0115	-.0060	-.00072	21.1
		(-.15)	(-.56)	(1.10)	(-.82)	(-3.17)	
FEV% $(yr)^{-1}$	223	-.2374	-.2339	.0597	.1262	-.0034	7.0
		(-2.97)	(-1.95)	(.41)	(1.23)	(-1.07)	
FEF_{25-75} L/sec-yr	223	-.0806	-.0494	.0166	.0256	-.00024	13.0
		(-6.00)	(-2.46)	(.68)	(1.49)	(-.44)	
FEF_{50} L/sec-yr	223	-.1032	-.0304	.0035	.0377	-.00041	6.7
		(-5.44)	(-1.07)	(.10)	(1.56)	(-.54)	
K $(min\text{-}mmHg\text{-}yr)^{-1}$	164	-.0921	-.0308	.1407	-.00870	-.00107	35.1
		(-4.46)	(-.86)	(3.26)	(-.33)	(-1.29)	
DL_{CO} $\frac{ml}{min\text{-}mmHg\text{-}yr}$	164	-.6468	-.208	.9013	-.3892	-.00370	66.1
		(-4.68)	(-.86)	(3.12)	(-2.22)	(-.67)	
RV L/yr	179	.0288	.00467	-.00951	-.00334	.00107	27.1
		(3.85)	(.40)	(-.69)	(-.35)	(3.65)	
TLC L/yr	179	.0276	-.00860	.0154	-.00978	.00049	5.5
		(3.10)	(-.62)	(.94)	(-.87)	(1.40)	
(RV/TLC) x 100 $(yr)^{-1}$	179	.3359	.1122	-.1455	-.0312	.0117	43.8
		(3.97)	(.86)	(-.93)	(-.29)	(3.51)	

[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
FEV_1 L/yr	223	-.0141 (-2.51)	-.0043 (-1.05)	.0010 (.14)	-.00057 (-2.56)	9.51
FVC L/yr	223	-.0020 (-.35)	.0032 (.75)	-.0070 (-.96)	-.00071 (-3.12)	19.7
FEV% L/yr	223	-.2470 (-3.09)	-.452 (-1.93)	.1231 (1.24)	-.0035 (-1.08)	6.2
FEF_{25-75} L/sec-yr	223	-.0853 (-6.31)	-.0184 (-1.83)	.0246 (1.42)	-.00024 (-.44)	7.6
FEF_{50} L/sec-yr	223	-.1107 (5.83)	-.0066 (-.47)	.0375 (1.55)	-.00038 (-.50)	4.7
K $(\text{min-mmHg-yr})^{-1}$	164	-.0968 (-4.47)	.0380 (2.14)	-.00832 (-.31)	-.00095 (-1.10)	16.6
DL_{CO} $-\frac{\text{ml}}{\text{min-mmHg-yr}}-$	164	-.6482 (-4.45)	.1761 (1.48)	-.382 (-2.11)	-.00305 (-.53)	27.3
RV L/yr	179	.0361 (4.93)	-.0129 (-2.38)	-.0017 (-.19)	.00102 (3.55)	38.1
TLC L/yr	179	.0322 (4.69)	-.00733 (-1.11)	-.00996 (-.88)	.00045 (1.29)	9.9
(RV/TLC) x 100 $(\text{yr})^{-1}$	179	.4238 (5.08)	-.1361 (-2.20)	-.0114 (-.11)	.0112 (3.40)	55.4

[1] 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	Intercept	Peak Exposure[2] Category II	Atopy	Pack-Years	% Variability Explained
FEV_1 L/yr	223	-.0127 (-2.29)	-.0108 (-1.64)	.00058 (.08)	-.00058 (-2.61)	10.9
FVC L/yr	223	.0005 (.09)	-.0015 (-.22)	-.0069 (-.95)	-.00072 (-3.18)	18.6
FEV% yr^{-1}	223	-.2594 (-3.26)	-.1541 (-1.63)	.1158 (1.13)	-.0034 (-1.07)	6.0
FEF_{25-75} L/sec-yr	223	-.0847 (-6.34)	-.0317 (-1.99)	.0232 (1.35)	-.00024 (-.45)	10.0
FEF_{50} L/sec-yr	223	-.0999 (-5.34)	-.0396 (-1.77)	.0361 (1.50)	-.00045 (-.60)	8.7
K $(\text{min-mmHg-yr})^{-1}$	164	-.0977 (-4.64)	.0646 (2.50)	-.0058 (-.22)	-.00101 (-1.19)	24.3
DL_{CO} $\frac{\text{ml}}{\text{min-mmHg-yr}}$	164	-.6560 (-4.64)	.3170 (1.82)	-.3706 (-2.06)	-.00338 (-.60)	31.4
RV L/yr	179	.0341 (4.69)	-.0172 (-1.92)	-.00285 (-.30)	.00104 (3.60)	32.4
TLC L/yr	179	.0331 (3.81)	-.0158 (-1.48)	-.0105 (-.94)	.00045 (1.31)	11.3
(RV/TLC) x 100 $(yr)^{-1}$	179	.3911 (4.70)	-.1427 (-1.40)	-.0240 (-.22)	.0115 (3.46)	44.2

[1] See Footnote [1] of Table 8.

[2] 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 (-.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
K $(min\text{-}mmHg\text{-}yr)^{-1}$	164	-.0975 (-4.63)	.0687 (2.16)	-.00979 (2.24)	-.0054 (-.20)	-.00102 (-1.21)	24.3
DL_{CO} $\frac{ml}{min\text{-}mmHg\text{-}yr}$	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	.0598	.3242	928	47.5
FEF_{50} L/sec-yr	223	-.1100	.0106	.0790	.4653	928	43.3
K $(min\text{-}mmHg\text{-}yr)^{-1}$	164	-.0947	.0123	.0757	.3651	301	53.2
DL_{CO} $\frac{ml}{min\text{-}mmHg\text{-}yr}$	164	-.7160	.0834	.4629	2.559	301	46.4
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

	Number of visits ≥3			Number of visits <3		
	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) % predicteds 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 (ppm-months $\leq$ .0682)		GROUP II (ppm-months $>$ .0682)
	n	149		74
FEV_1	ml/yr	-20	(p = .034)[1]	-32
FVC	ml/yr	-11	(p = 1.0)	-9
FEV%	$(yr)^{-1}$	-0.28	(p = .014)	-.48
FEF_{25-75}	ml/sec-yr	-84	(p = .004)	-125
FEF_{50}	ml/sec-yr	-109	(p = .095)	-137

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

Table 16A

Descriptive Statistics at Entry to Study
by Cumulative Exposure Category

	Cumulative Exposure ≤.0682 ppm-months	Cumulative Exposure >.0682 ppm-months
n	149	74
Race (% White)	84.1	87.8
Age (years)	37.6 ± 11.0	31.7 ± 9.8
Height (inches)	69.8 ± 2.5	70.3 ± 2.4
Smoking (% current cigarette)	51.0	50.0
(% ex-cigarette)	24.8	21.6
(% never)	24.2	28.4
% LRS	31.1	27.4
% URS	46.4	33.8
% Bronchitis	4.6	1.4
Dyspnea (% Grade I)	83.3	90.4
(% Grade II)	12.7	8.2
(% Grade III)	4.0	1.4
% Atopic	21.9	25.7

Table 16B

FEV_1 Slope (ml/year)* by Smoking Exposure Category
Controlling for Age and FEV_1 Level

CIGARETTE SMOKING	$FEV_1/h^3 \geq 55$ Exposure ≤.0682 ppm-months	$FEV_1/h^3 \geq 55$ Exposure >.0682 ppm-months	$FEV_1/h^3 < 55$ Exposure ≤.0682 ppm-months	$FEV_1/h^3 < 55$ Exposure >.0682 ppm-months
never	1 n = 35	-37 n = 21	-18 n = 1	-57 n = 0
ex	-12 n = 31	-15 n = 16	-32 n = 6	-35 n = 0
current	-26 n = 64	-37 n = 35	-46 n = 12	-57 n = 2

*Cells means were estimated using the multiple regression procedure described in the text. This procedure used age as one of the covariates. The cells means presented above are adjusted to the average age (35.6 years) of the study group.

Tests of Significance

(1) age effect -5.8 ml/decade one-tailed p-value = .03

(2) low FEV_1 effect -20 ml/year one-tailed p-value = .04

(3) exposure effect in never smokers -38 ml/year one-tailed p-value = .001

(4) Smoking effect in ≤.0682 exposure category

exsmoker - never smoker effect -13 ml/year one-tailed p-value = .12

current smoker - ex-smoker effect -14 ml/year one-tailed p-value = .06

current smoker-never smoker effect -27 ml/year one-tailed p-value = .004

Table 17

ESTIMATED MEAN ANNUAL CHANGES IN FEV_1, FEV%, AND FEF_{25-75} BY CUMULATIVE EXPOSURE FOR NON-ATOPICS WITH 14 PACK-YEARS OF SMOKING

	GROUP I (ppm-months $\leq$.0682)		GROUP II A (.0682 $<$ ppm-months $\leq$.1)		GROUP II B (ppm-months $>$.1)
n	149		37		37
FEV_1 ml/yr	-20	(p = .025)[1]	-39	(p = .19)	-26
FEV% $(yr)^{-1}$	-.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 ≤.19)		GROUP II (months >.19)
n	140		83
FEV_1	-21	(p = .051)[1]	-32
FVC	-10	(p = .413)	-11
FEV%	-.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, FEV%, 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 $\leq$1)		GROUP II B (months $>$1)
n	140		47		36
FEV_1 ml/yr	-21	(p = .087)	-35	(p = .52)	-28
FEV% $(yr)^{-1}$	-.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

	Number of Visits ≥3			Number of Visits <3		
	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) % predicteds 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

	Number of Visits ≥3			Number of Visits <3		
	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) % predicteds 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

	Complete			Incomplete		
	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) % predicteds 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

Cumulative Exposure ≤ .0682

Initial INTRVW	Last Usable INTRVW	Non-Atopic			Atopic			
		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	51
YES	NO	0	3	0	2	1	0	6
NO	YES	3	9	7	2	6	1	28
NO	NO	6	9	11	2	0	3	31
YES	YES	1	8	9	0	5	2	25
YES	NO	0	7	4	3	1	1	16
NO	YES	2	10	7	1	1	1	22
NO	NO	13	11	18	4	4	3	53
YES	YES	0	0	0	0	1	0	1
YES	NO	0	5	1	0	0	0	6
NO	YES	1	0	5	0	1	0	7
NO	NO	15	31	32	8	9	7	102
YES	YES	0	5	5	0	0	0	10
YES	NO	1	1	2	1	2	0	7
NO	YES	1	3	5	2	1	1	13
NO	NO	14	27	26	5	8	6	86

Cumulative Exposure > .0682

Initial INTRVW	Last Usable INTRVW	Non-Atopic			Atopic			
		Zero PK-YRS	0-15 PK-YRS	>15 PK-YRS	Zero PK-YRS	0-15 PK-YRS	>15 PK-YRS	TOTAL
YES	YES	2	5	10	3	4	1	25
YES	NO	1	0	1	0	0	1	3
NO	YES	8	8	3	2	2	0	23
NO	NO	9	14	6	1	4	1	35
YES	YES	1	2	5	1	4	1	14
YES	NO	0	7	0	0	0	0	7
NO	YES	3	3	6	0	0	1	13
NO	NO	16	15	9	5	5	1	51
YES	YES	0	0	0	0	0	0	0
YES	NO	0	1	0	0	0	0	1
NO	YES	1	2	1	1	1	1	7
NO	NO	19	24	19	5	9	2	78
YES	YES	1	3	2	0	0	0	6
YES	NO	0	0	3	0	0	0	3
NO	YES	1	4	5	1	2	2	15
NO	NO	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

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

(URS = Usable INTRVW; LRS = Last Usable INTRVW; EBRON = Ever Bronchitis; DYSPNEA = Dyspnea)

Time above .02 > 0.19

Initial INTRVW	Last Usable INTRVW	Non-Atopic Zero PK-YRS	Non-Atopic 0-15 PK-YRS	Non-Atopic >15 PK-YRS	Atopic Zero PK-YRS	Atopic 0-15 PK-YRS	Atopic >15 PK-YRS	TOTAL
YES	YES	3	4	8	2	3	1	21
YES	NO	1	1	1	0	0	0	3
NO	YES	7	7	3	2	3	0	22
NO	NO	6	12	6	1	3	1	29
YES	YES	0	4	6	0	5	0	15
YES	NO	0	5	0	0	0	0	5
NO	YES	3	4	4	0	0	1	12
NO	NO	14	11	8	5	3	1	42
YES	YES	0	0	0	0	0	0	0
YES	NO	0	2	0	0	0	0	2
NO	YES	1	2	1	0	1	1	6
NO	NO	16	20	17	5	8	1	67
YES	YES	1	4	1	0	0	0	6
YES	NO	0	0	3	0	1	0	4
NO	YES	0	4	5	1	2	1	13
NO	NO	16	16	9	4	5	1	51

(URS = Usable INTRVW; LRS = Last Usable INTRVW; EBRON = Ever Bronchitis; DYSPNEA = Dyspnea)

Table 24A

Prevalences for Selected Respiratory Symptom Complexes
at the Initial and Final Interviews
by Smoking-Cumulative Exposure Categories

Bronchitis

	Never Smokers				Current or Ex-Smokers				
	n	Initial	Final	Mean Age	n	Initial	Final	Mean Pack-Years	Mean Age
≤.0682 ppm-months	24	0%	4.2%	36.2	92	7.6%	7.6%	20.0	38.9
>.0682 ppm-months	26	0%	7.7%	28.2	60	1.7%	8.3%	15.6	33.1

Dyspnea

	Never Smokers				Current or Ex-Smokers				
	n	Initial	Final	Mean Age	n	Initial	Final	Mean Pack-Years	Mean Age
≤.0682 ppm-months	24	8.3%	12.5%	36.2	92	16.3%	21.7%	20.0	38.9
>.0682 ppm-months	26	3.8%	11.5%	28.2	59	13.6	30.5%	15.6	33.1

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

Name	Plant	Date	Exposure in Minutes						Total ppm.	Time-weighted average	Shift
			.005	.01	.02	.04	.06	.08			
Area	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
Area	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
Area	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
Area	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
Area	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
Area	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
Area	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.

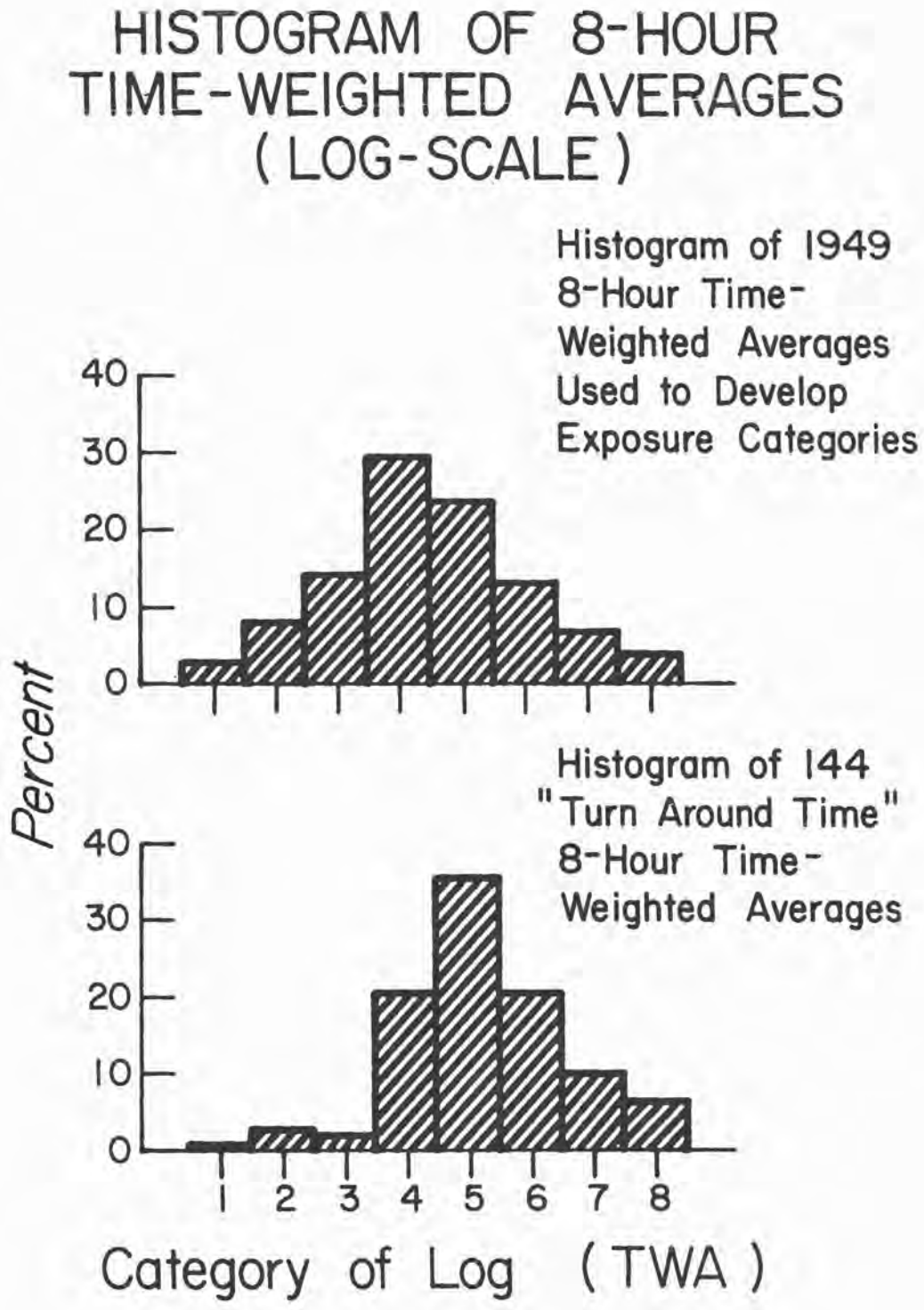

HISTOGRAM OF 8-HOUR
TIME-WEIGHTED AVERAGES
(LOG-SCALE)
Histogram of 1949
8-Hour Time-
Weighted Averages
Used to Develop
Exposure Categories
Histogram of 144
"Turn Around Time"
8-Hour Time-
Weighted Averages
Percent
40
30
20
10
0
1 2 3 4 5 6 7 8
Category of Log (TWA)

Figure 1

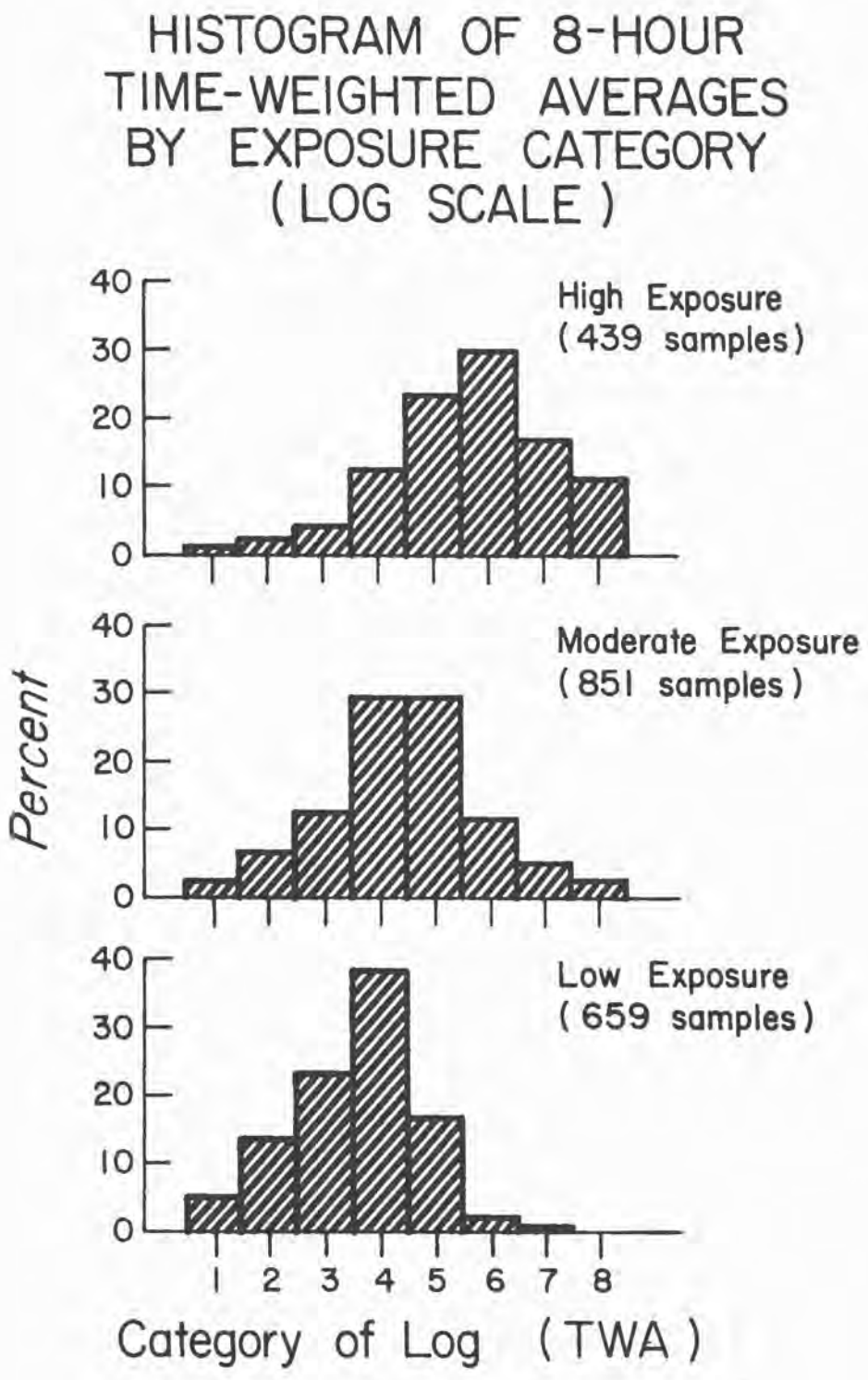

HISTOGRAM OF 8-HOUR
TIME-WEIGHTED AVERAGES
BY EXPOSURE CATEGORY
(LOG SCALE)
High Exposure
(439 samples)
Moderate Exposure
(851 samples)
Low Exposure
(659 samples)
Percent
40
30
20
10
0
1 2 3 4 5 6 7 8
Category of Log (TWA)

Figure 2

FEV_1 MEAN BY VISIT FOR THE 33 PARTICIPANTS WITH COMPLETE SPIROMETRY AT ALL NINE VISITS

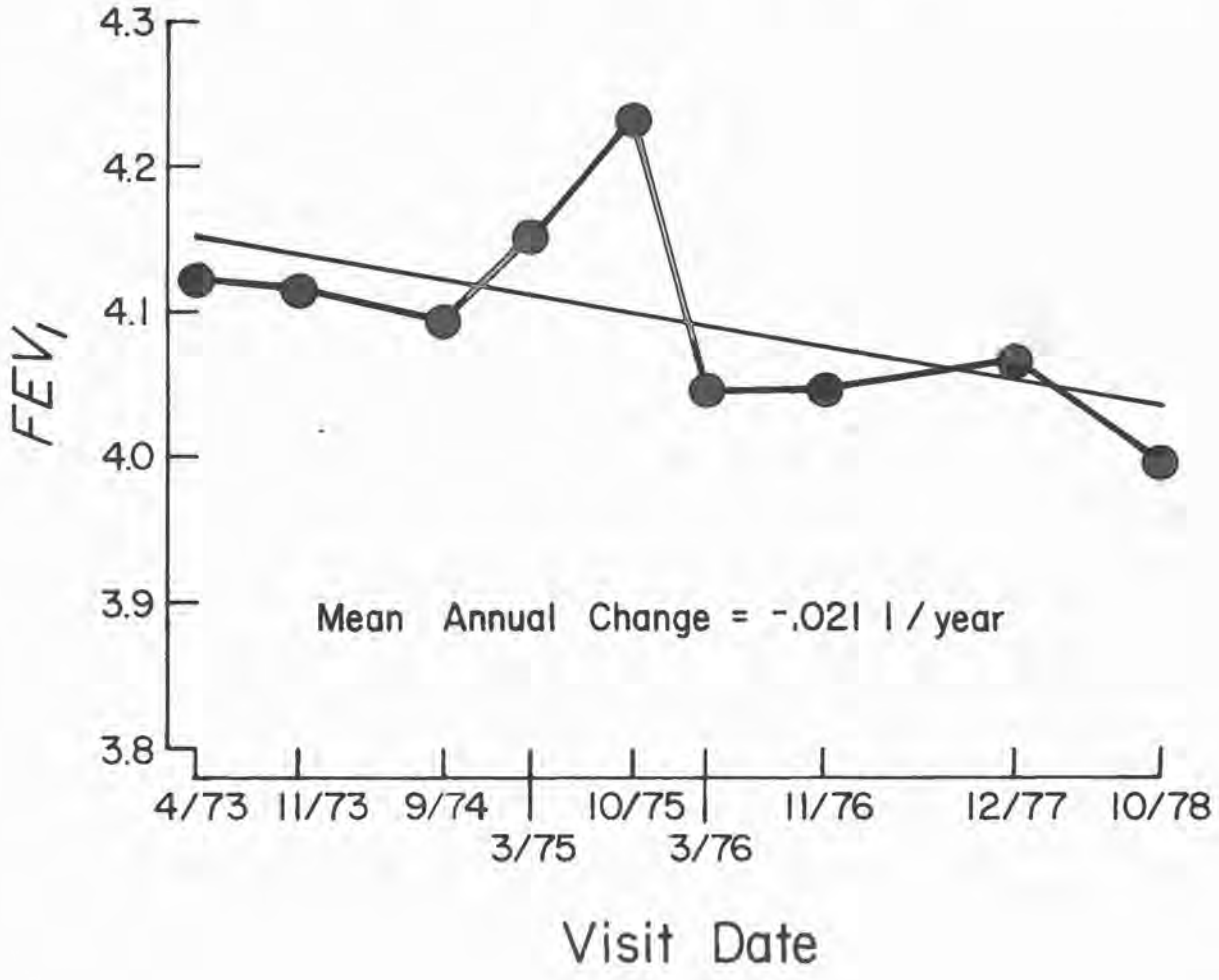


Figure 3

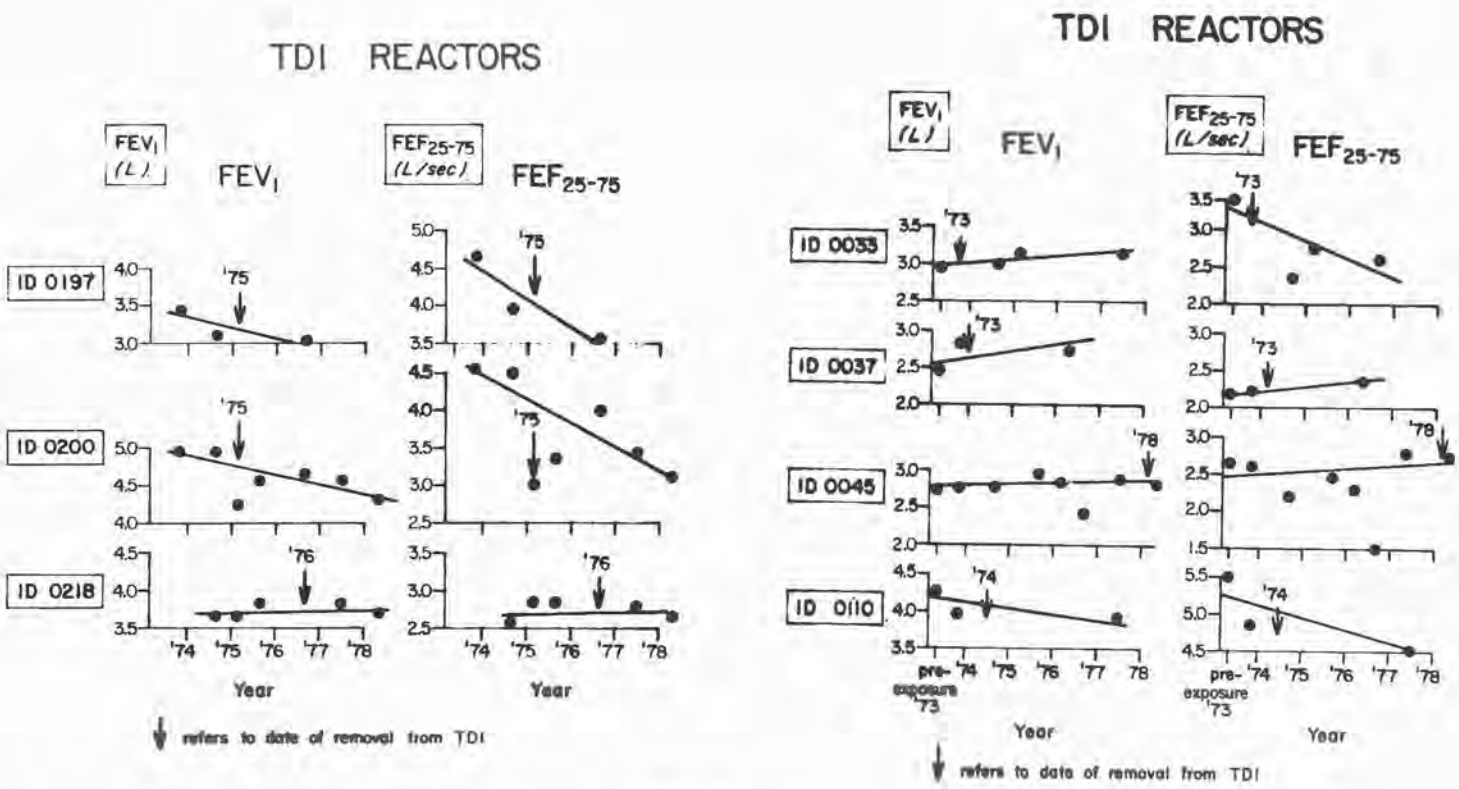

TDI REACTORS
FEV1 (L)
FEV1
FEF25-75 (L/sec)
FEF25-75
ID 0197
ID 0200
ID 0218
ID 0033
ID 0037
ID 0045
ID 0110
'73
'74
'75
'76
'78
pre-exposure
Year
refers to date of removal from TDI

Figure 4

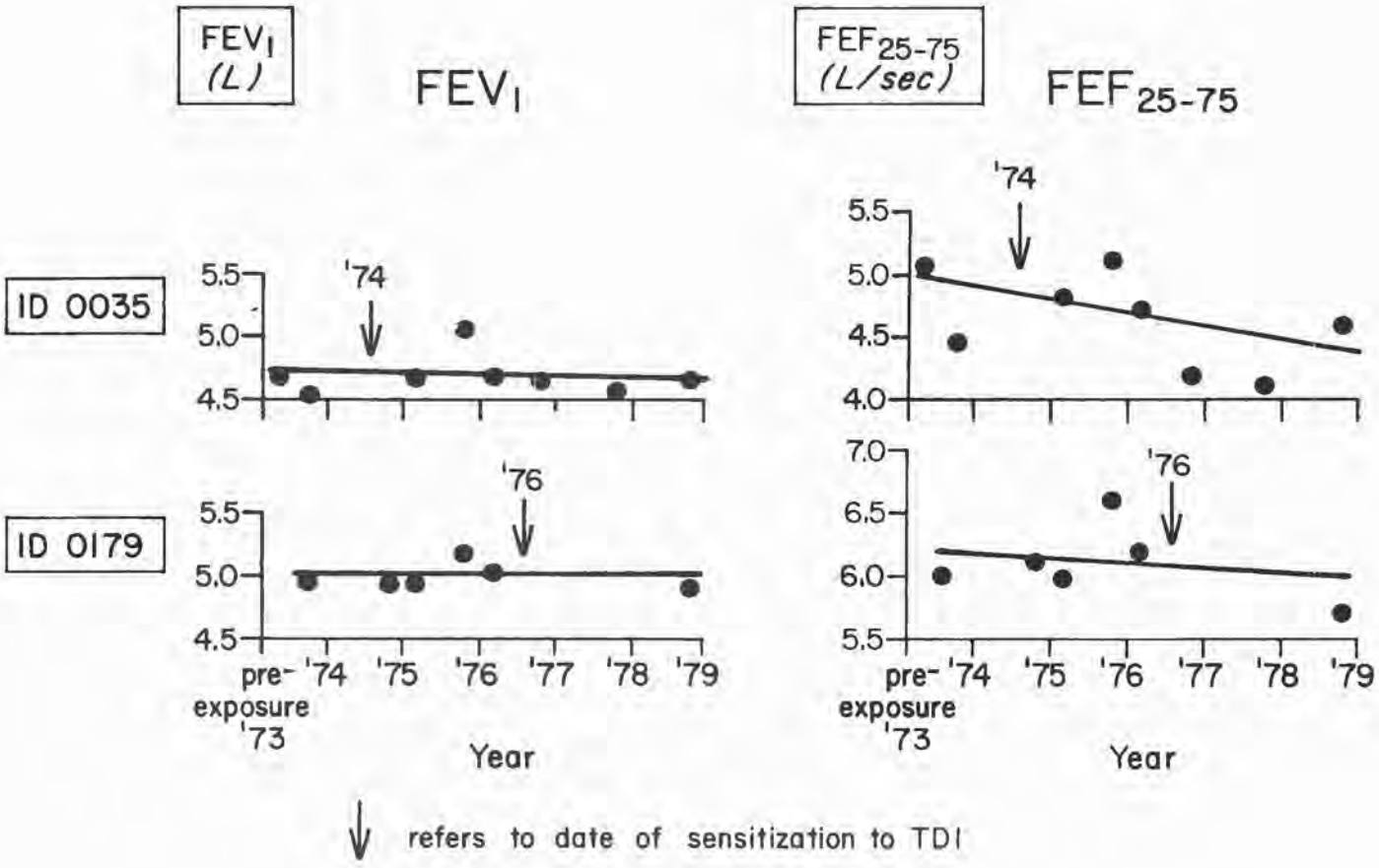
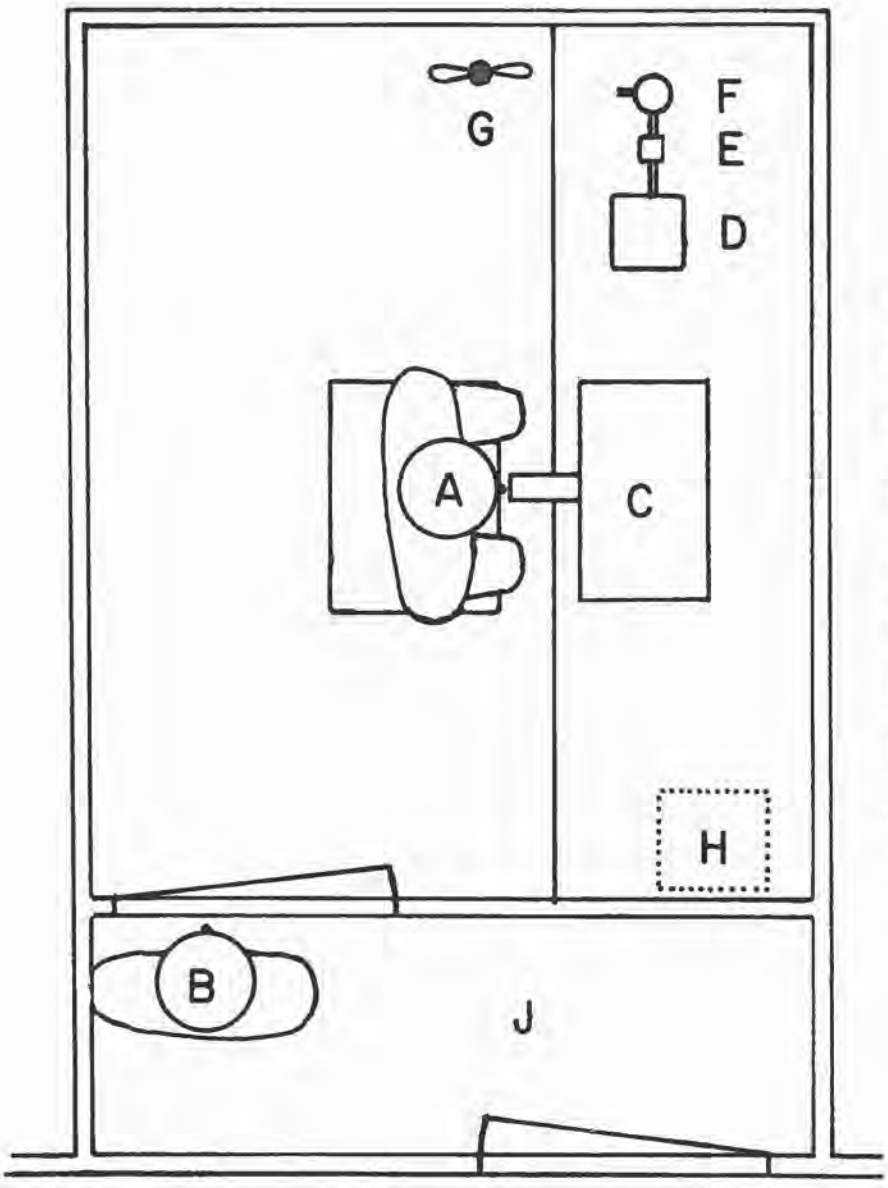

TDI REACTORS
FEV1 (L)
FEV1
FEF25-75 (L/sec)
FEF25-75
ID 0035
ID 0179
'74
'76
5.5
5.0
4.5
4.0
7.0
6.5
6.0
pre-exposure
'73
'74
'75
'76
'77
'78
'79
Year
refers to date of sensitization to TDI

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

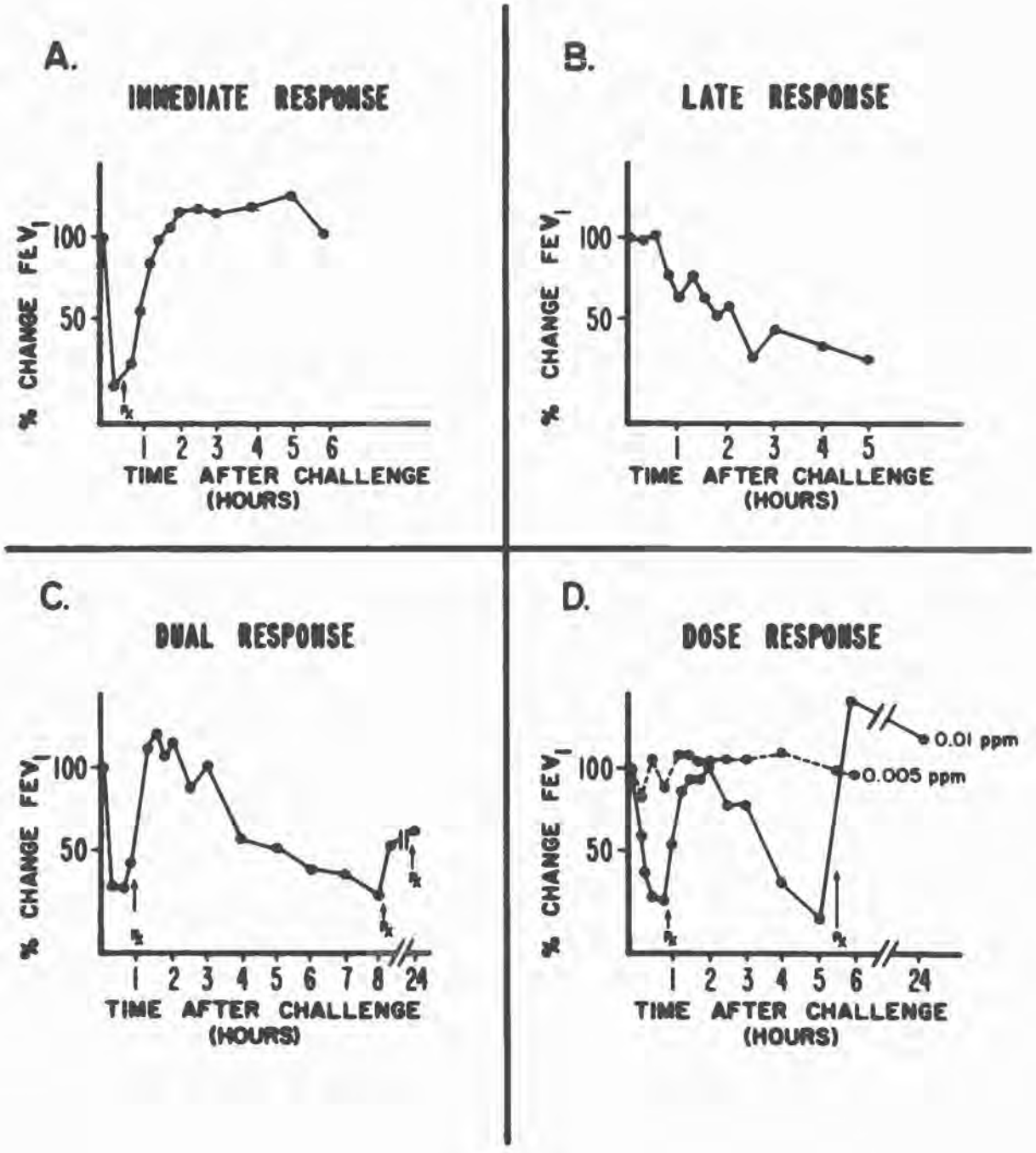


Figure 7

Respiratory Response to Provocative Inhalation
Challenge with TDI

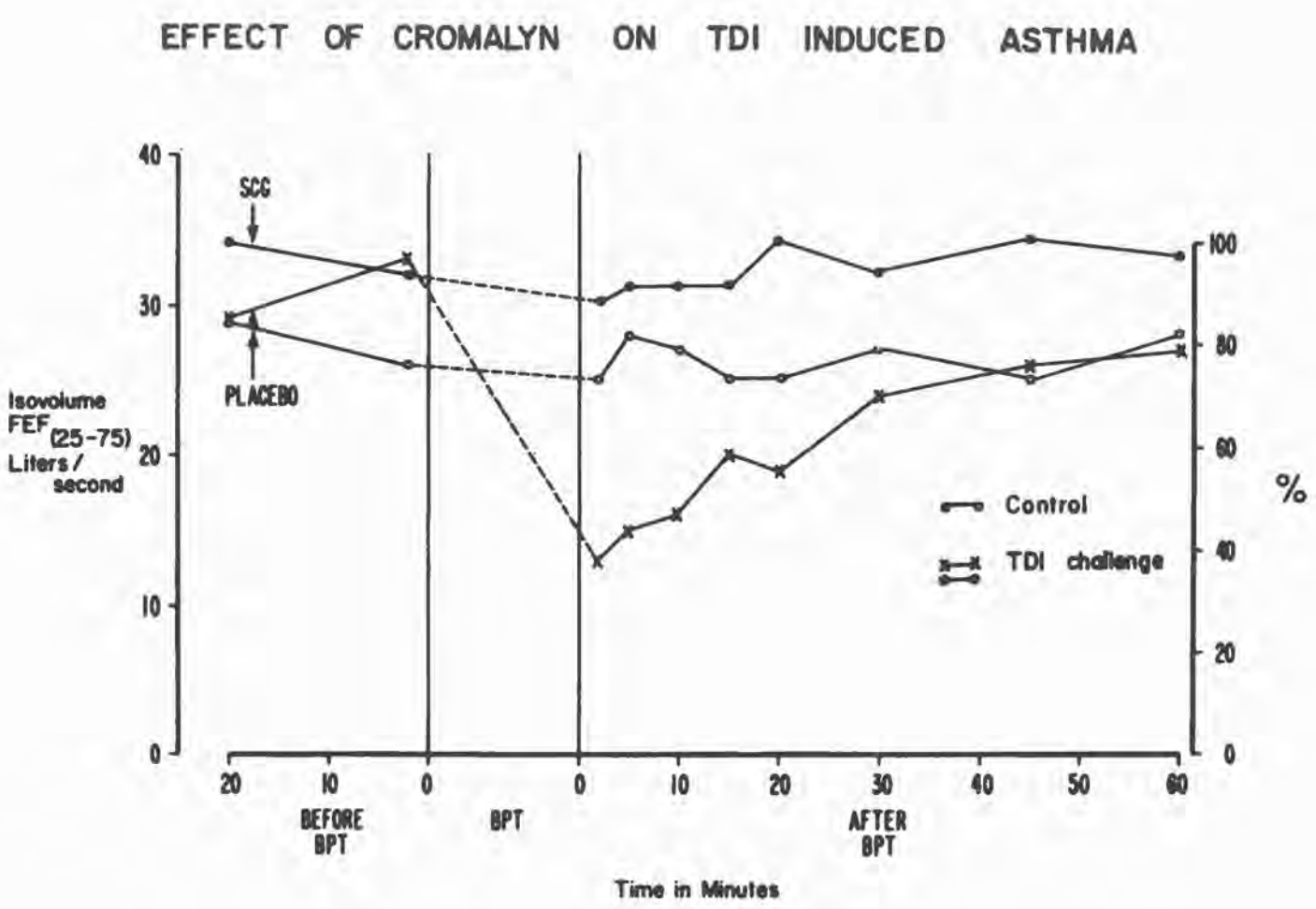

EFFECT OF CROMALYN ON TDI INDUCED ASTHMA
SCG
PLACEBO
Isovolume FEF(25-75) Liters / second
40
30
20
10
0
100
80
60
40
20
0
%
Control
TDI challenge
20
10
0
0
10
20
30
40
50
60
BEFORE BPT
BPT
AFTER BPT
Time in Minutes

Figure 8

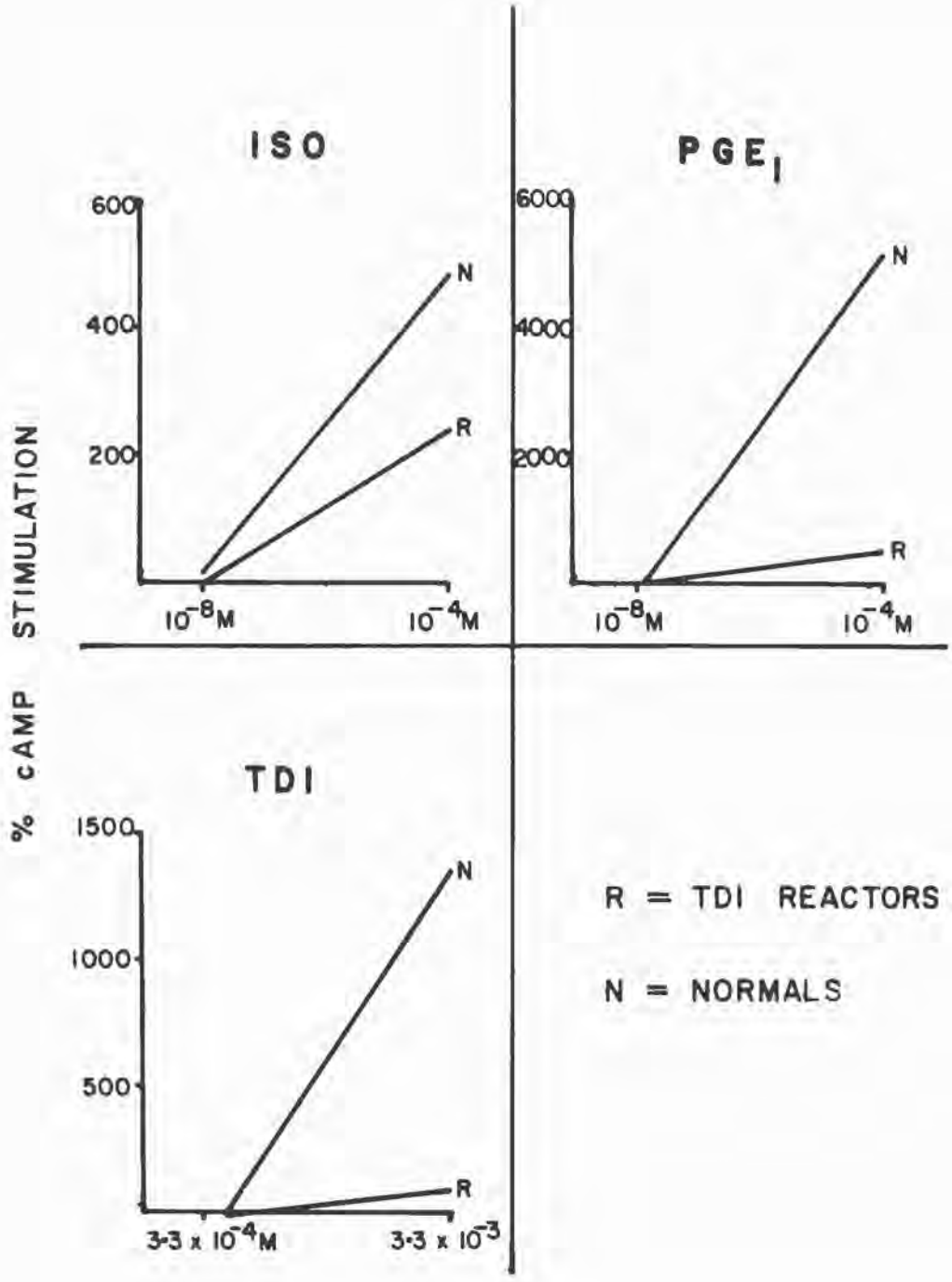


Figure 9

Cyclic Adenosine Monophosphate Dose Response Slopes of TDI Reactors and Normal Individuals to Stimulation with Agonists: Isoproterenol, Prostaglandin E_1, and TDI

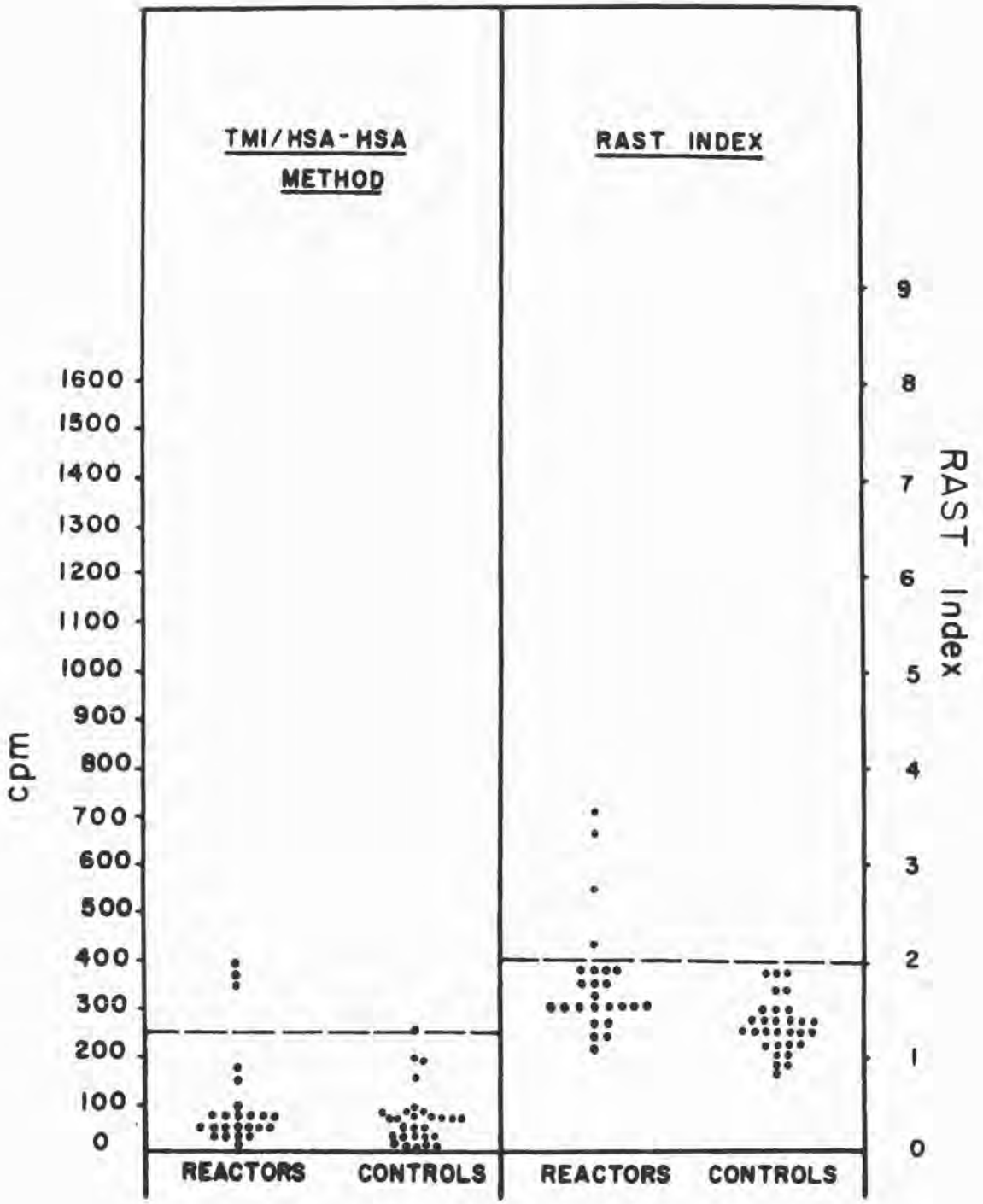


Figure 10

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

TYPICAL RECORDER PRINTOUT FROM TDI AREA MONITOR

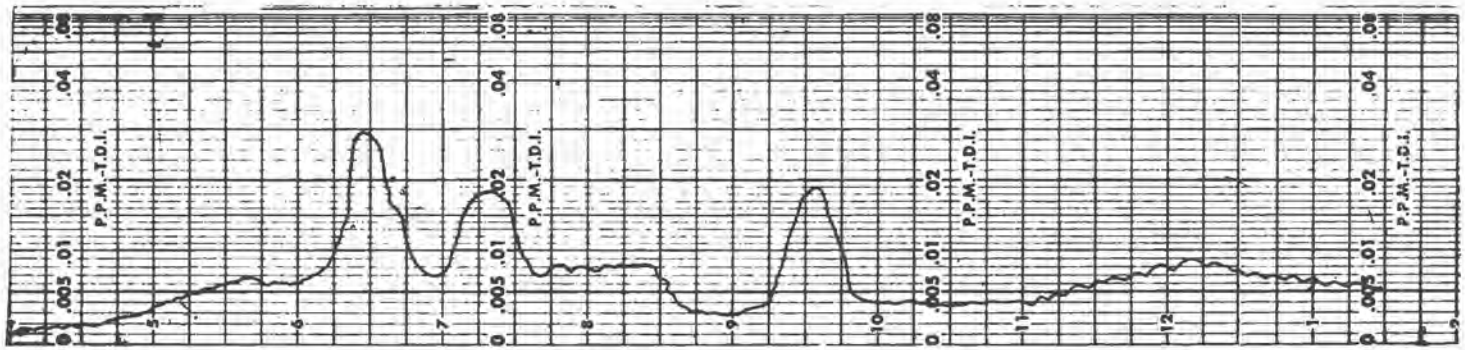


Figure 11

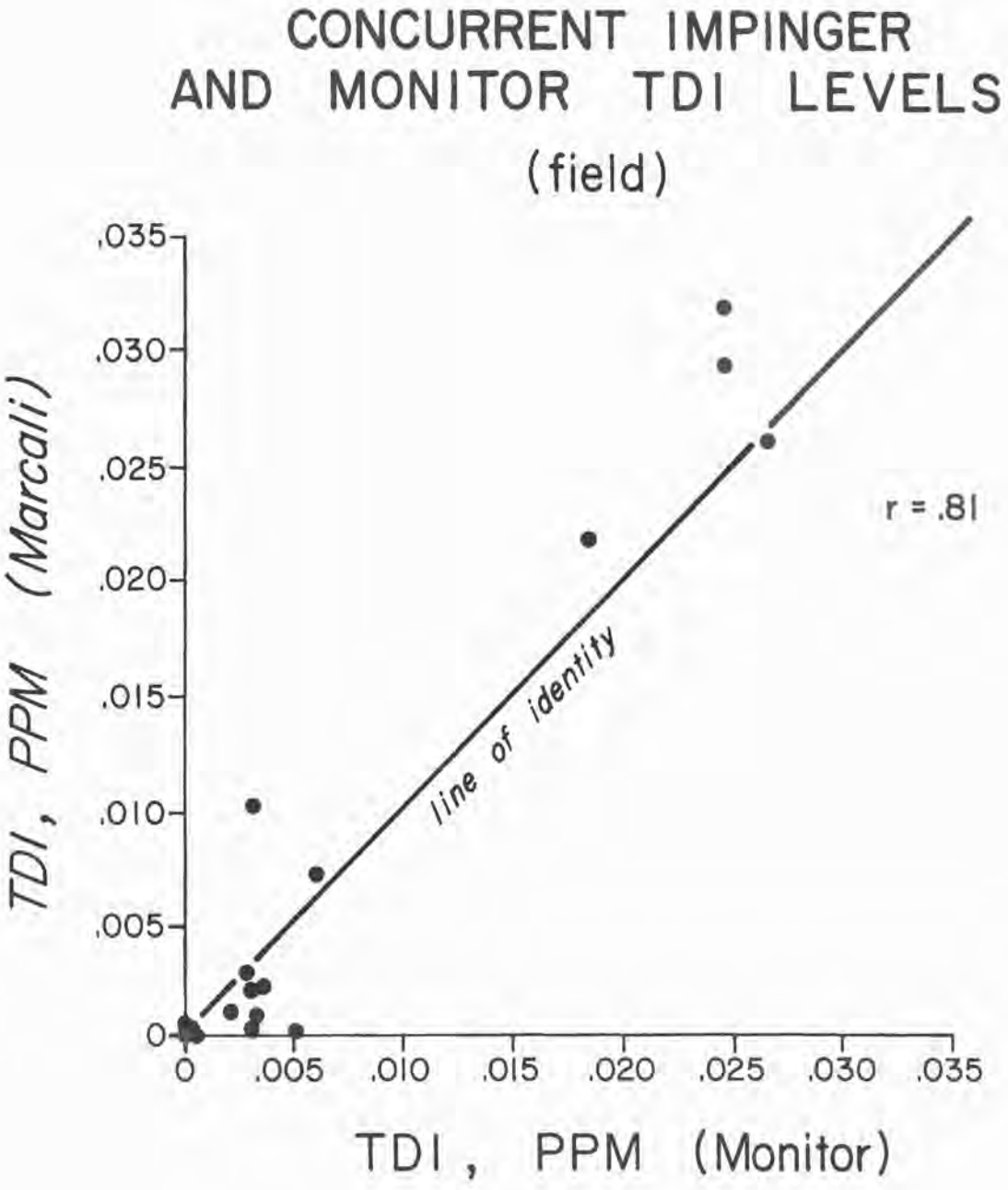

CONCURRENT IMPINGER
AND MONITOR TDI LEVELS
(field)
TDI, PPM (Marcali)
.035
.030
.025
.020
.015
.010
.005
0
line of identity
r = .81
0
.005
.010
.015
.020
.025
.030
.035
TDI, PPM (Monitor)

Figure 12

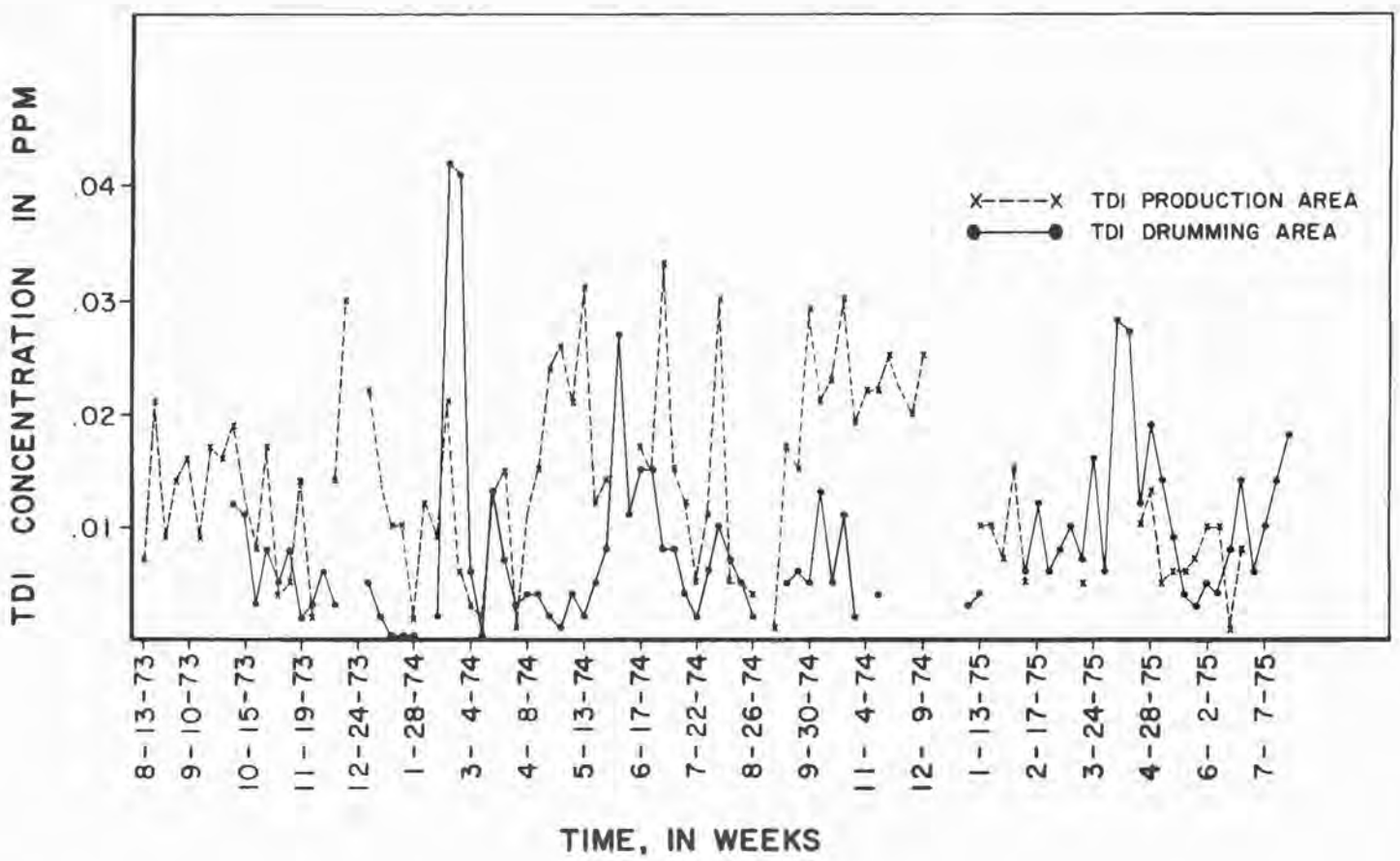

TDI CONCENTRATION IN PPM
.04
.03
.02
.01
X----X TDI PRODUCTION AREA
TDI DRUMMING AREA
8-13-73
9-10-73
10-15-73
11-19-73
12-24-73
1-28-74
3-4-74
4-8-74
5-13-74
6-17-74
7-22-74
8-26-74
9-30-74
11-4-74
12-9-74
1-13-75
2-17-75
3-24-75
4-28-75
6-2-75
7-7-75
TIME, IN WEEKS

Figure 13

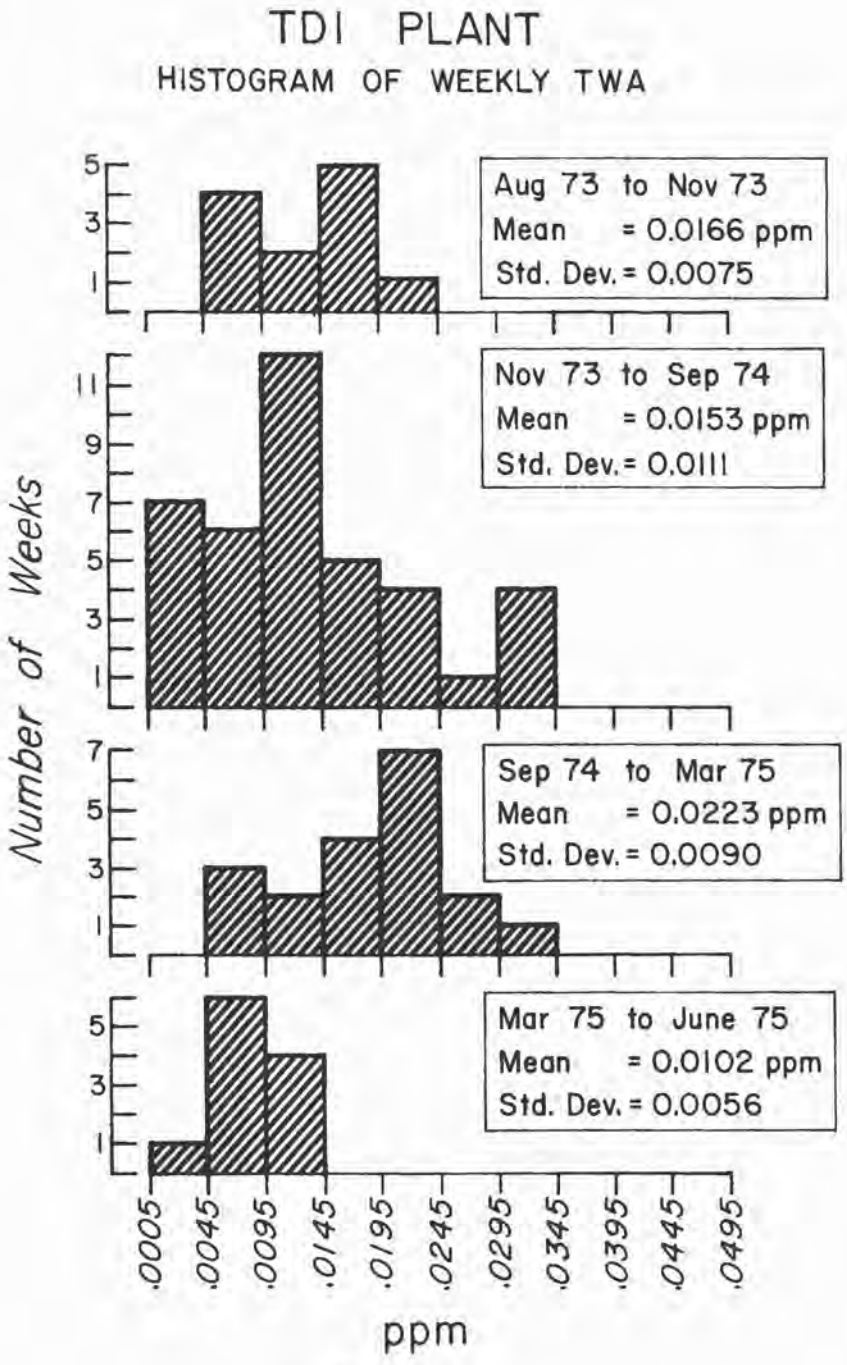

TDI PLANT
HISTOGRAM OF WEEKLY TWA
Aug 73 to Nov 73
Mean = 0.0166 ppm
Std. Dev. = 0.0075
Nov 73 to Sep 74
Mean = 0.0153 ppm
Std. Dev. = 0.0111
Sep 74 to Mar 75
Mean = 0.0223 ppm
Std. Dev. = 0.0090
Mar 75 to June 75
Mean = 0.0102 ppm
Std. Dev. = 0.0056
Number of Weeks
.0005
.0045
.0095
.0145
.0195
.0245
.0295
.0345
.0395
.0445
.0495
ppm

Figure 14

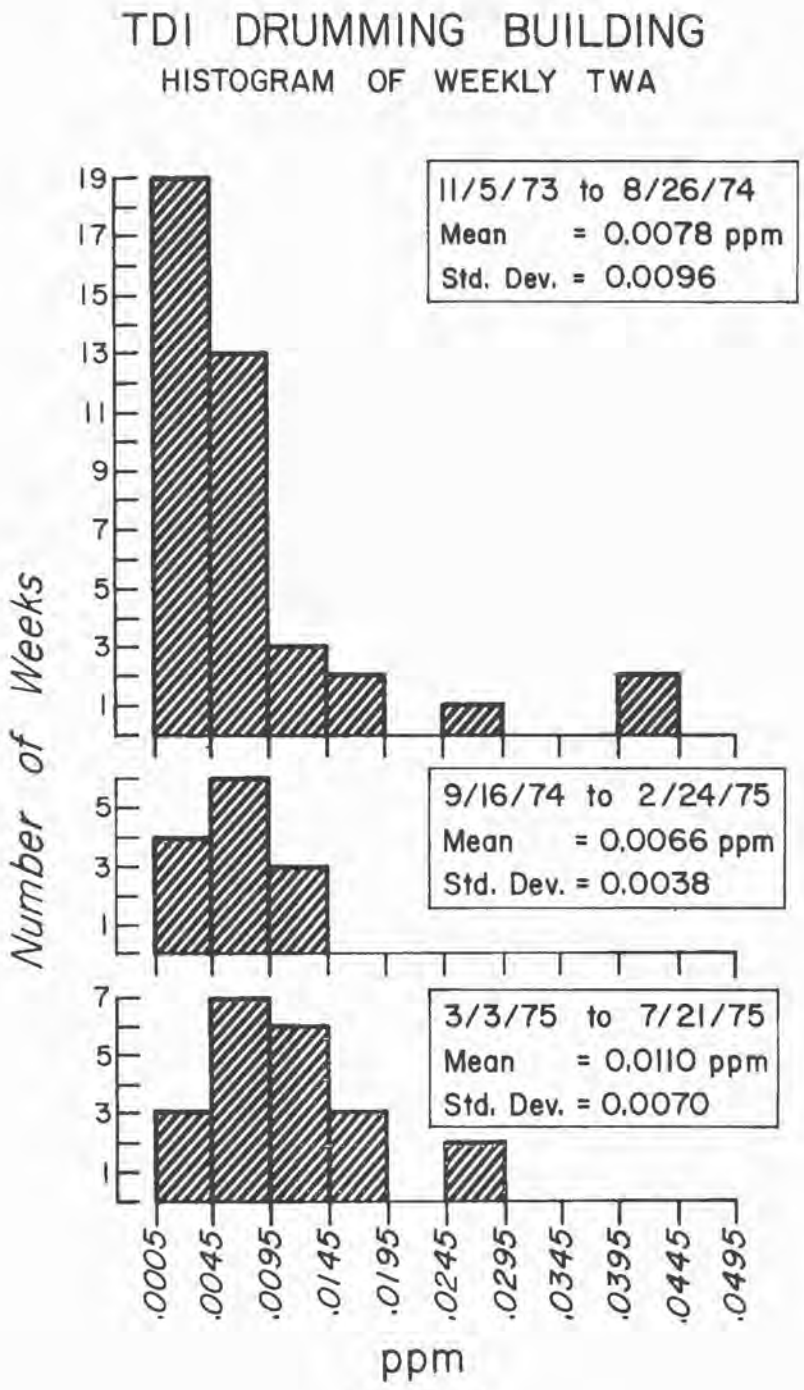

TDI DRUMMING BUILDING
HISTOGRAM OF WEEKLY TWA
11/5/73 to 8/26/74
Mean = 0.0078 ppm
Std. Dev. = 0.0096
9/16/74 to 2/24/75
Mean = 0.0066 ppm
Std. Dev. = 0.0038
3/3/75 to 7/21/75
Mean = 0.0110 ppm
Std. Dev. = 0.0070
Number of Weeks
19
17
15
13
11
9
7
5
3
1
5
3
1
7
5
3
1
.0005
.0045
.0095
.0145
.0195
.0245
.0295
.0345
.0395
.0445
.0495
ppm

Figure 15

TYPICAL RECORDER PRINTOUT
FROM TDI PERSONAL MONITOR

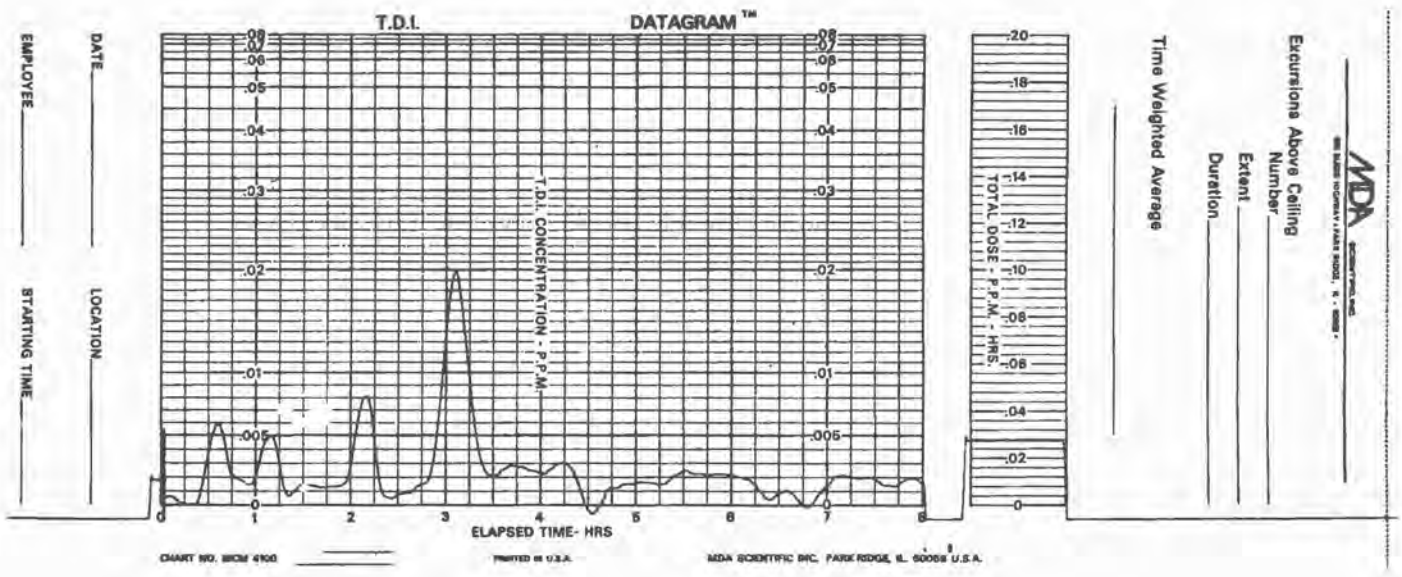


Figure 16

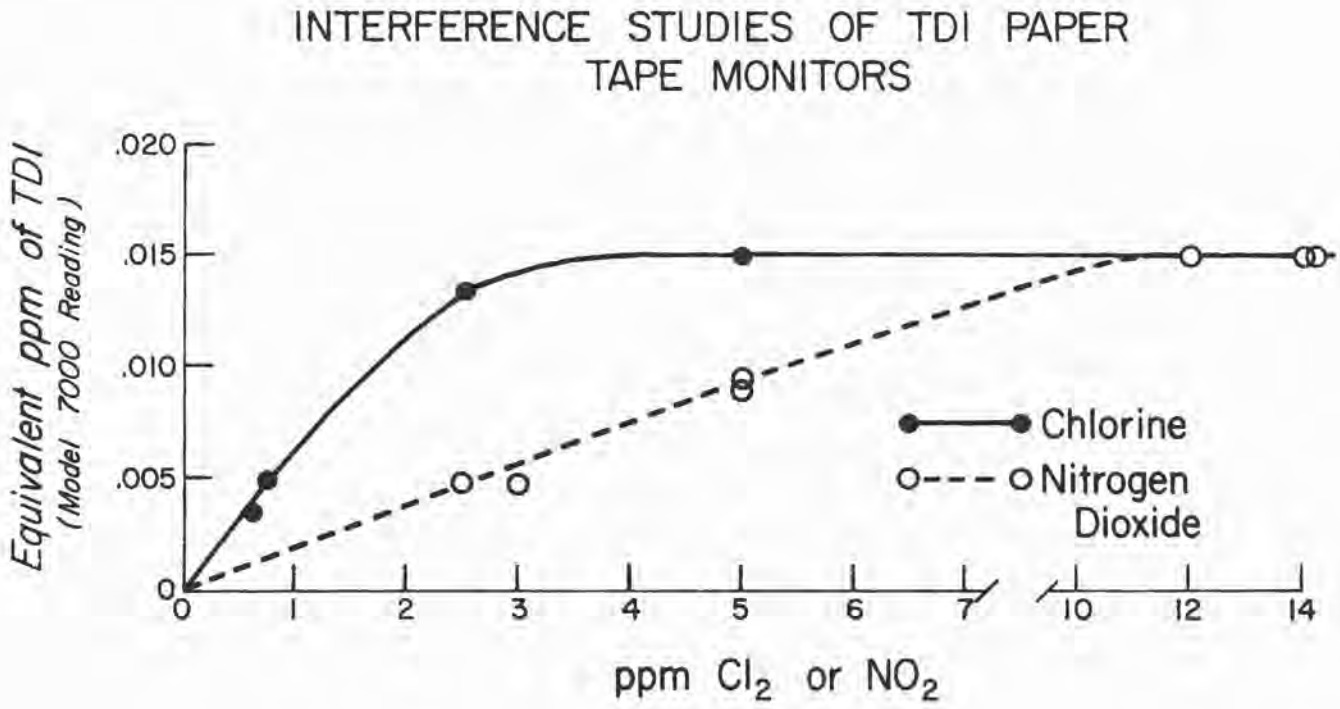

INTERFERENCE STUDIES OF TDI PAPER TAPE MONITORS
Equivalent ppm of TDI (Model 7000 Reading)
.020
.015
.010
.005
0
0
1
2
3
4
5
6
7
10
12
14
Chlorine
Nitrogen Dioxide
ppm Cl_2 or NO_2

Figure 17

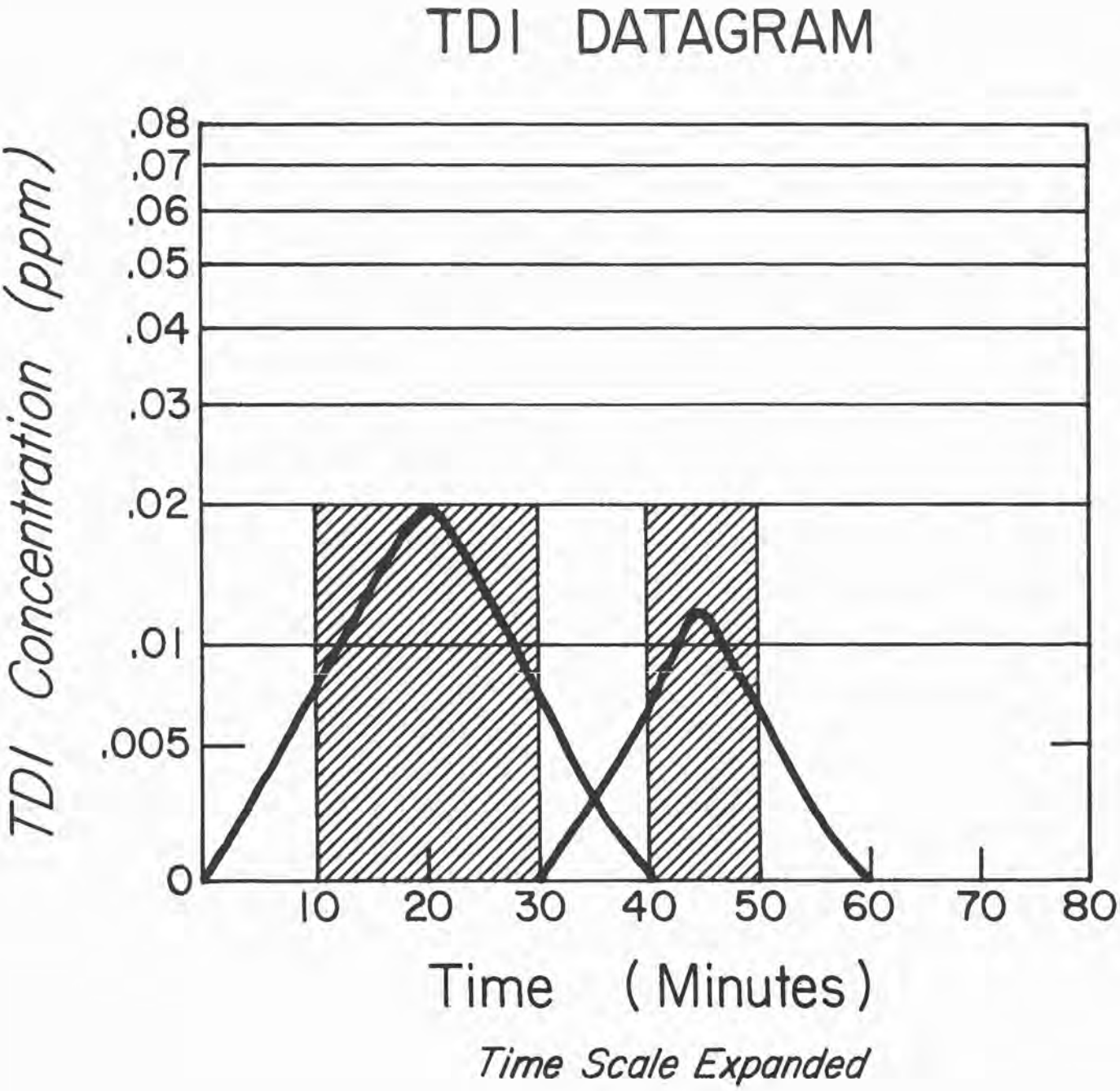

TDI DATAGRAM
TDI Concentration (ppm)
.08
.07
.06
.05
.04
.03
.02
.01
.005
0
10
20
30
40
50
60
70
80
Time (Minutes)
Time Scale Expanded

Figure 18

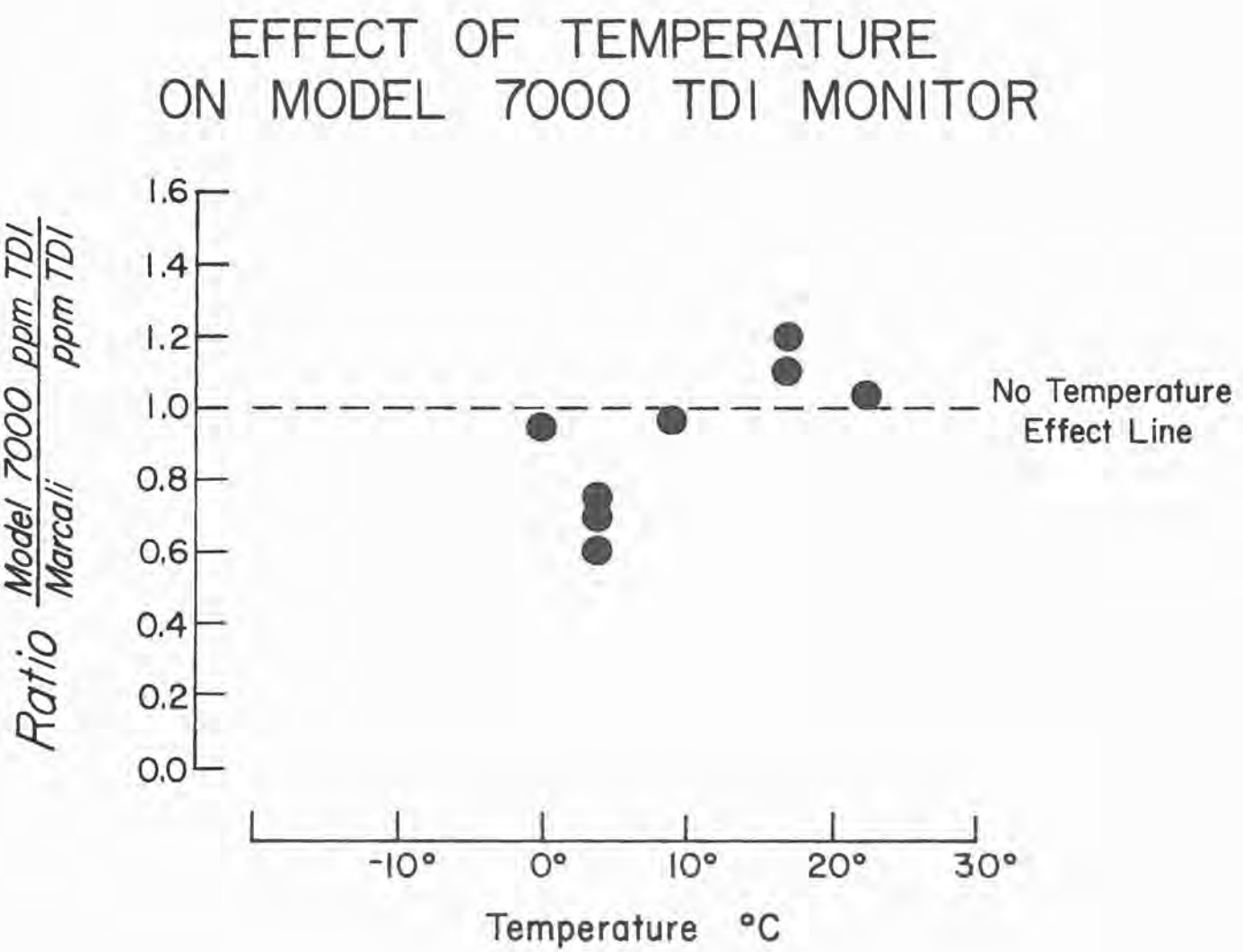

EFFECT OF TEMPERATURE
ON MODEL 7000 TDI MONITOR
Ratio Model 7000 ppm TDI / Marcali ppm TDI
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
No Temperature
Effect Line
-10°
0°
10°
20°
30°
Temperature °C

Figure 19

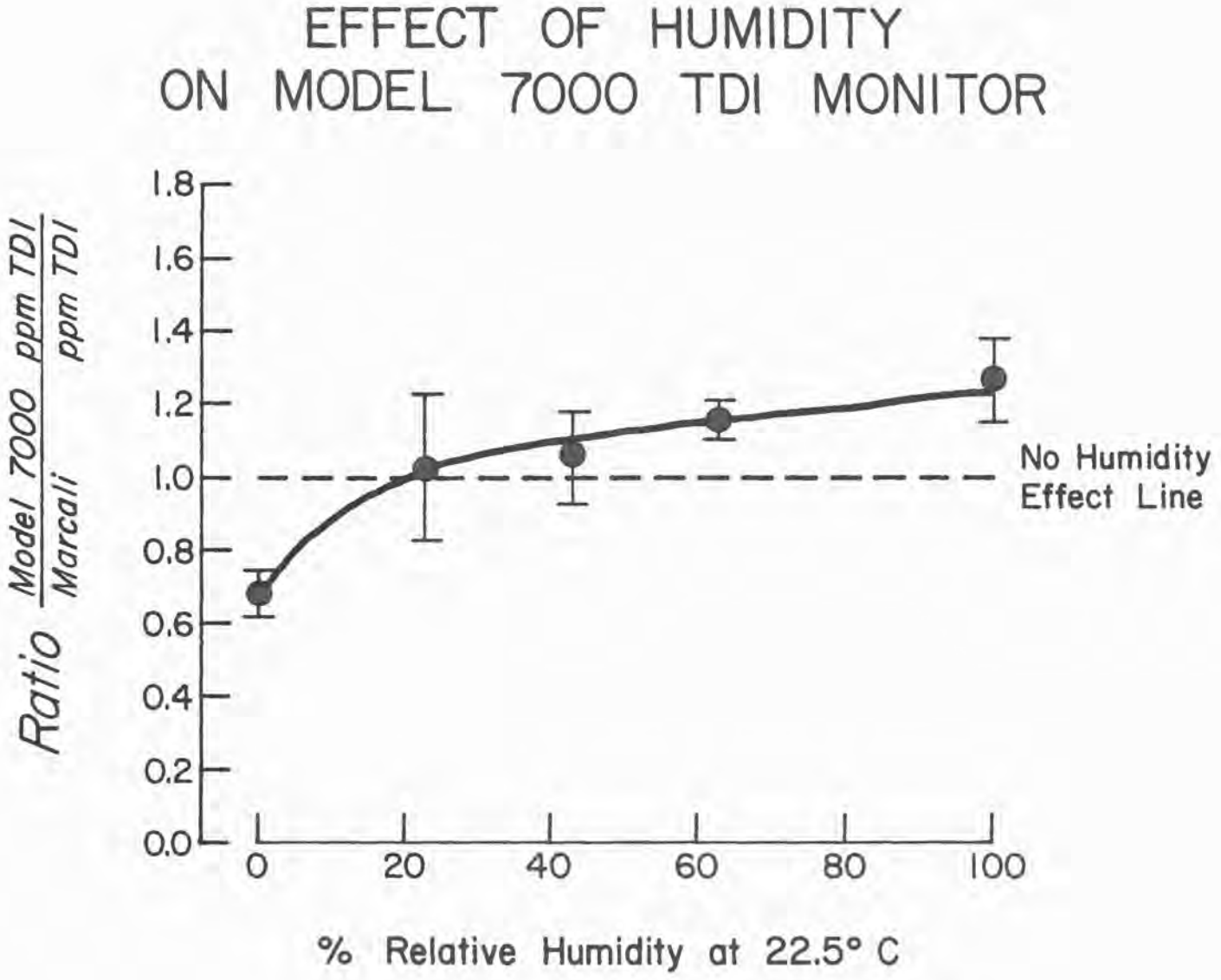

EFFECT OF HUMIDITY
ON MODEL 7000 TDI MONITOR
Ratio Model 7000 ppm TDI / Marcali ppm TDI
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
No Humidity
Effect Line
% Relative Humidity at 22.5° C

Figure 20

DISTANCE BETWEEN SELECTED JOBS

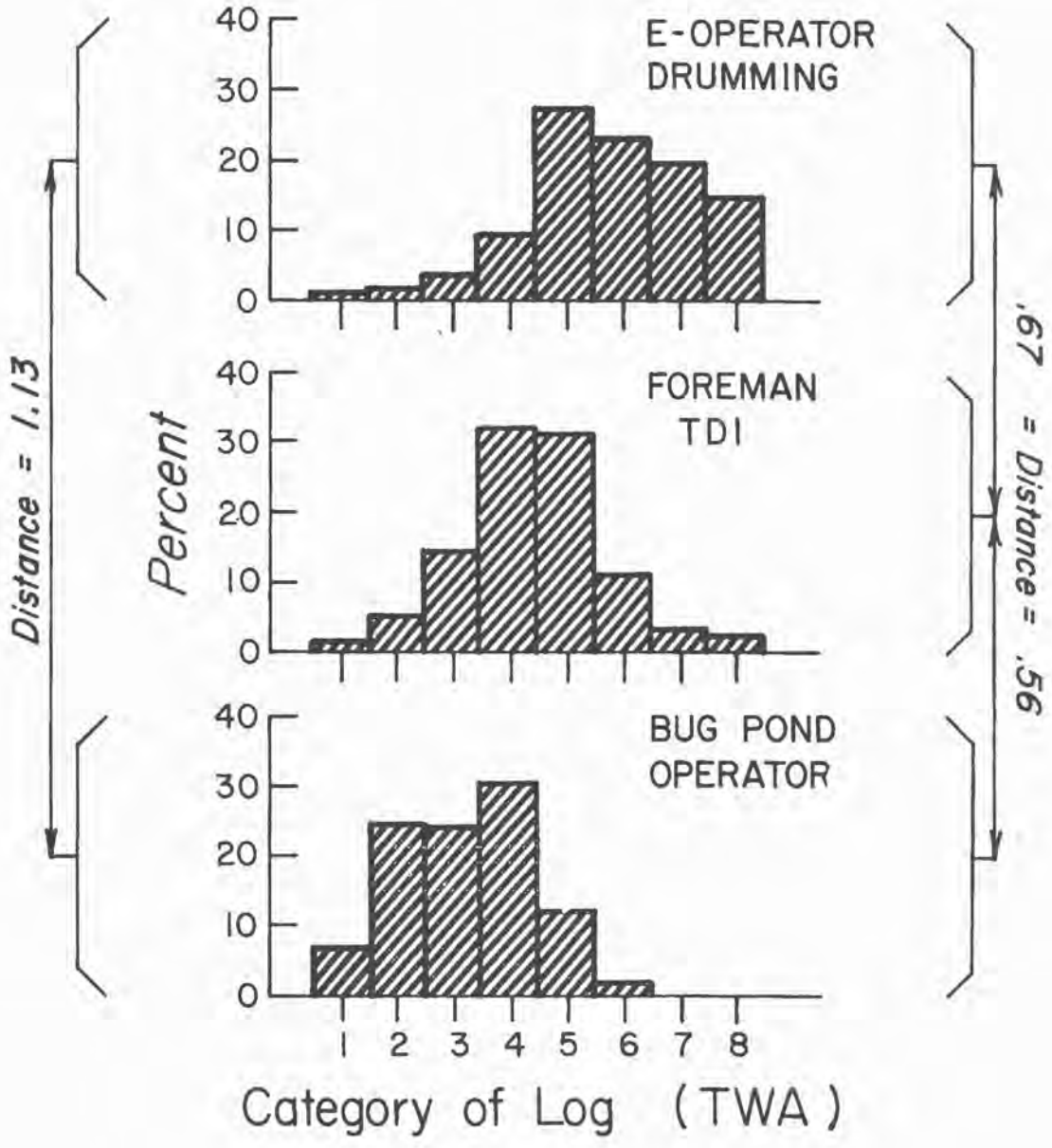


Figure 21

DISTANCE BETWEEN SELECTED JOBS

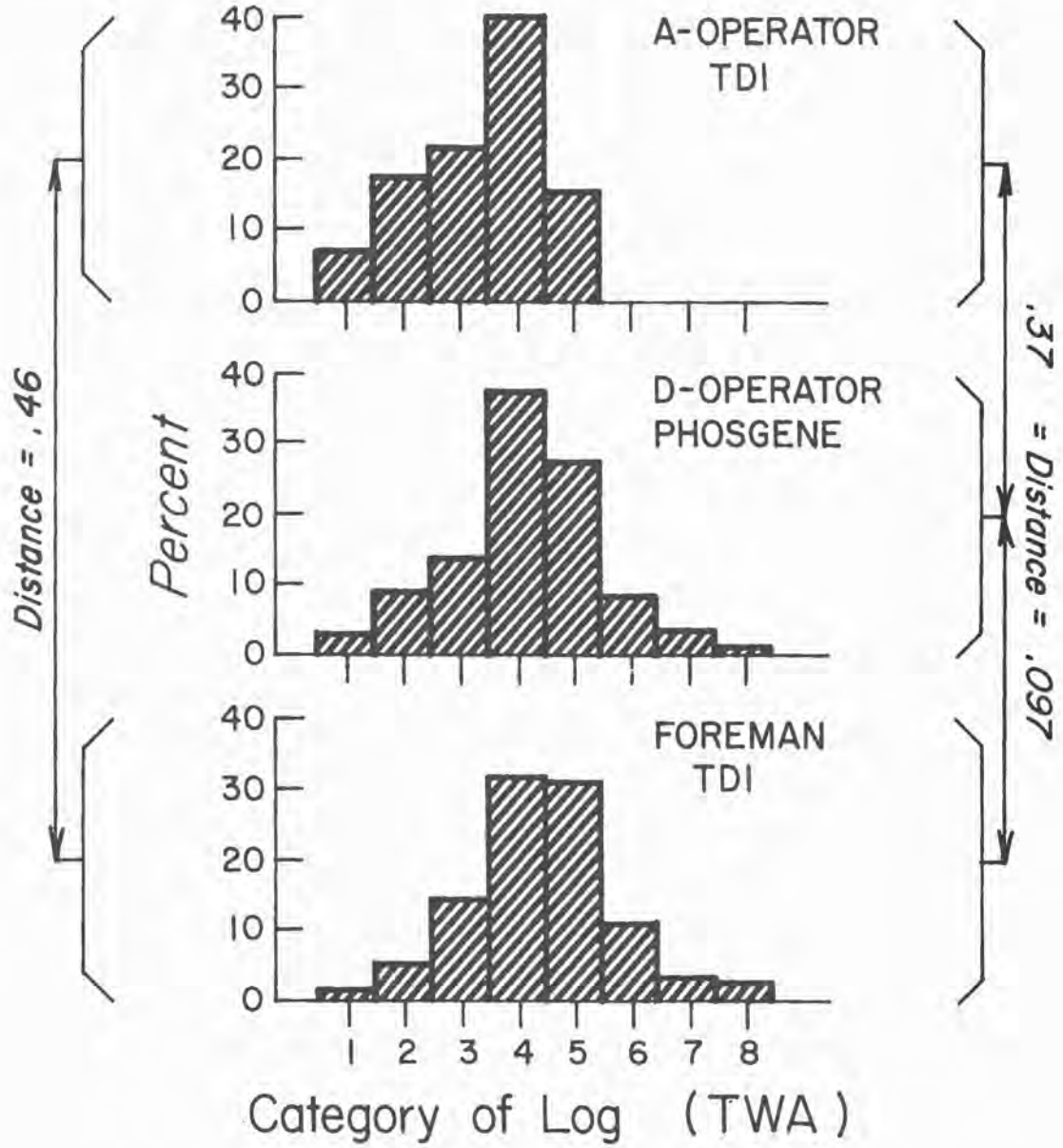


Figure 22

REPRINTS INCLUDED IN NIOSH FINAL REPORT - 10/12/79

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

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Respiratory and Immunologic Evaluation of Isocyanate Exposure in a New Manufacturing Plant

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ABSTRACT

In April, 1973, pre-exposure (baseline) information was obtained on 168 workers who were to begin manufacturing toluene diisocyanate (TDI) in four months. None of these workers had prior exposure to TDI. Subsequent follow-up in this longitudinal investigation was five and one-half years in length, during which time eight additional visits were made to the manufacturing site. At each of visits 2, 3, 4 and 5, approximately 25 participants were added to the study population, bringing the total size of the study population to 277. The added participants had no more than 11 months of TDI exposure prior to inclusion in the study.

Exposure to TDI vapor was determined by personal monitors utilizing the paper tape stain method for continuous 8-hour measurement. The approximately 2,000 personal samples collected had median 8-hour time-weighted averages of .002 ppm. The 25th and 75th percentiles were .0011 and .0036 respectively. Percentage of time above .02 ppm, the current threshold limit value, averaged 3% in these personal samples. All members of the study population had some degree of TDI exposure, which depended on both job and location. No systematic trends in exposure were observed over the course of the study.

Detailed job histories allowed for the construction of cumulative exposure as a product of concentration and time. Cumulative exposure was used to define two exposure categories (division point = .0682 ppm-months) with the low category chosen to represent the exposure received by a worker who spent the full follow-up period in a group of jobs (median 8-hour time-weighted average = .0011 ppm) with the lowest TDI concentration.

Pulmonary function annual changes for spirometric measurements, lung volumes and diffusing capacities were computed for each participant as the slope of the least squares straight line using time as the independent variable.

The average annual decline of FEV_1 was 24 ml per year, comparable to that expected on the basis of cross sectional studies of "normal" populations. Average annual declines of FEF_{25-75} and FEF_{50} were 93 and 110 ml, larger than expected on the basis of cross sectional data. Average annual declines for single breath carbon monoxide diffusing capacity and the diffusion constant (K) were also larger than expected on the basis of cross sectional results.

After controlling for pack years of smoking and atopic status, FEV_1, FEV% and FEF_{25-75} annual declines were significantly related to the TDI exposure categories. Lung volume and diffusing capacity annual change was not related to TDI exposure.

The effect of TDI exposure on FEV_1 annual change was manifest primarily in those who never smoked cigarettes; its effect in smokers may be masked by smoking. In the never smokers, there was a 38 ml per year ($p = .001$) difference between the low and high exposure categories. Among current smokers there was no observed effect of TDI. In the low exposure category, there was a 27 ml per year ($p = .004$) difference between never and current cigarette smokers. This difference is comparable to the effect of TDI in the never smokers. Current smokers averaged 18 pack years of smoking. Never smokers in the low exposure group had an average annual increase in FEV_1 of 1 ml per year.

TDI exposure as determined by cumulative dose and peak exposure as measured by time spent above 0.02 ppm correlated equally well with annual change in pulmonary function.

Clinically important bronchial hypersensitivity to TDI developed in 4.3% of the study population. A number of these workers were shown to develop bronchoconstriction in the laboratory following inhalation challenge using a maximum concentration of 0.02 ppm TDI. Half of the TDI reactors had been exposed to high levels during a spill or equipment malfunction. 75% of the reactors became symptomatic within seven months of first exposure to TDI. 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 of the chemical complex. Neither atopy nor smoking served to identify persons at higher risk of developing TDI reactivity.

TDI at certain concentrations acts as a partial agonist on lymphocytes to stimulate cyclic adenosine monophosphate (AMP) levels. At lower concentrations, it can block cyclic AMP stimulation by isoproterenol and prostaglandin E_1 but not histamine. Lymphocytes of TDI sensitive individuals have decreased ability to respond to cyclic AMP stimuli such as beta agonists, isoproterenol, prostaglandin E_1 and TDI.

RAST with p-tolyl isocyanate conjugated to human serum albumin only detects tolyl specific IgE antibodies in the serum of 15-18% of subjects proven by provocative inhalation challenge to be TDI reactive. This demonstrates that the presence of tolyl specific serum IgE antibodies cannot be used to diagnose clinical sensitivity to TDI.

All other humoral or cellular indicators of immunologic sensitization were non-revealing.

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