The Correlation of Clinical and Environmental Measurements for Workers Exposed to Vinyl Chloride

C. G. KRAMER, M.D., and J. E. MUTCHLER*

The Dow Chemical Company, Midland, Michigan 48640

A method is described for the statistical consolidation and correlation of environmental measurements and clinical findings using as an example a group of healthy male workers exposed routinely to vinyl chloride for periods up to 25 years. Retrospective in nature the study reveals several statistically significant effects from chronic exposures to vinyl chloride and traces of vinylidene chloride.

Introduction

For validating an industrial hygiene standard, it is essential to perform careful and comprehensive studies of the possible effects of substances on exposed workmen. In practice, however, very few substances have been the object of sufficient study to furnish reliable guidelines. Today, specialists in occupational health must recognize the need to develop programs which will better identify the relation between stresses acting on the human body in the work environment and physical changes that can be measured clinically, to explain the significance of these changes and use the results to help refine our guidelines for environmental control.

Although toxicologists are constantly predicting what exposures are likely to be safe for people, there will always be some doubt about their predictions until enough human experience has been gained to prove their accuracy. The "proof of the pudding" should result from the correlation of good environmental measurements with the results of a well planned medical surveillance program. It is likely that such feedback from human experience will differ from the animal experimental data in that it will not define a level of exposure which will actually cause injury, at least frank injury. However, except in cases where an industrial hygiene standard has not been applied, the feedback from human experience could be expected to describe levels of exposure which have been shown to be either acceptable or marginally unacceptable. This information would be valuable to toxicologists because it would strengthen their skills in predicting from experimental animal data effects of substances on humans. In a broader sense, it would be useful in substantiating criteria to be used for industrial hygiene standards.

For several years The Dow Chemical Company's medical and environmental health groups have been conducting concurrent medical and environmental surveillance of a large worker population exposed to many different chemicals. The project described in this paper analyzes the information already gained from concurrent surveillance and relates it to the determination of acceptable levels of exposure. A method is described for the statistical consolidation and correlation of environmental measurements and clinical findings, using as an example a group of 98 healthy male workers who had been exposed routinely to vinyl chloride for periods up to 25 years. Retrospective in nature, the study reveals several statistically significant clinical changes due to chronic exposures to vinyl chloride and smaller amounts of vinylidene chloride. By isolating these apparent effects and examining them in the light of our medical interpretation, we have developed what appears to be a promising technique for

*Present Address: George D. Clayton and Associates, 25711 Southfield Road, Southfield, Michigan 48075

relating clinical information to worker exposures to achieve a more refined industrial hygiene standard.

Vinyl Chloride

Vinyl chloride ($CH_2=CHCl$) is a chemical compound of increasing industrial importance. It is a monomer used as a chemical intermediate in the polymerization of polyvinyl chloride resin, in the production of copolymers such as Saran, and as a solvent.

Animal Toxicity

The toxicity of vinyl chloride has been reviewed by von Oettingen,[1] Mastromatteo, *et al.*,[2] and more recently by Torkelson, *et al.*,[3] and Lester, *et al.*[4] This gas is an anesthetic, and narcosis is the only reported effect of acute overexposure.

Torkelson,[3] Lester,[4] and their co-workers studied the chronic toxicity of vinyl chloride on rats. Torkelson and associates included rabbits, guinea pigs and dogs in a study of effects from repeated exposure, i.e., using controlled concentrations of 50-500 ppm. They found that repeated seven-hour exposure to 220 ppm caused micropathological changes in the livers of rabbits, and at 100 ppm, noted slight but statistically significant increases in the average weight of rat livers. Other animals were unaffected by 100 ppm. Using concentrations of 20,000 and 50,000 ppm, Lester found no evidence of effects on lungs or other vital organs upon repeated daily exposures lasting 92 days at the lower concentration and 19 days at the higher level. Like Torkelson, however, he detected some increase in relative weights of the rat liver and, in addition, of the rat spleen. The Committee on Threshold Limit Values (American Conference of Governmental Industrial Hygienists), weighing both studies, concluded that "although the experimental data are conflicting, the preponderance indicates a compound of relatively low toxicity with which a threshold limit of 500 ppm is consistent."[5]

Human Toxicity

Few effects have been reported as a result of human exposure to vinyl chloride except for narcosis upon acute exposure. However, at least two industrial deaths have been reported from overexposure to vinyl chloride.[6] In a controlled study, Lester, *et al.*,[4] exposed six volunteers for five-minute periods to 4,000 8,000, 12,000, 16,000, and 20,000 ppm of vinyl chloride. The first signs of intoxication appear at 8,000-12,000 ppm. No other effects were reported.

Baretta, *et al.*,[7] exposed human volunteers to 50, 250 and 500 ppm for 7 1/2 hours in an investigation concerned primarily with expired air studies. No clinical changes nor neurological responses were found in the thirteen volunteers upon thorough physical examination.

Filatova and Gronsberg[8] reported angioneurosis of spastic character in workers exposed to the monomer in a polyvinyl chloride polymerization process. Air samples usually varied between 20 ppm and 315 ppm.

Wilson, *et al.*,[9] reported several cases of acroosteolysis in hands of workmen working in vinyl chloride polymerization processes. No vinyl chloride exposure estimates are cited, but the nature of the disorder and the circumstances of its appearance suggest that the effect may have resulted from a "combination of physical insult, chemical insult, and personal idiosyncrasy." Dinman, *et al.*,[10] Cook, *et al.*,[11] and Dodson, *et al.*,[12] reported on a comprehensive epidemiological, industrial hygiene and clinical study of over 5,000 employees engaged in vinyl chloride and polyvinyl chloride manufacturing throughout the United States and Canada. A clear association of acroosteolysis and manual cleaning of polymerization reactors was revealed, with an expected prevalence of one case per 37 reactor cleaners. The study did not implicate vinyl chloride as the etiological agent but, using certain assumptions about the monomeric content of polymer residue within the reactors, there appeared to be a semi-quantitative correlation between the prevalence of acroosteolysis and the degree of degassing prior to vessel entry.[11]

Suciu, *et al.*,[13] studied the clinical manifestations of a group of 186 male employees working in polyvinyl chloride plants. They reported the presence of the "narcotic syndrome," asthenic nervous

symptoms, Raynaud's syndrome and hepatomegaly, but did not furnish data regarding the number of exposures to vinyl chloride and other substances in the work environment.

Environmental Aspects

The Work Environment

Subjects included in our investigation had worked in one or both of two manufacturing facilities which had been using vinyl chloride in polymerization processes. In both plants the environmental stresses of the work area were essentially equivalent. There were two airborne materials present in the work environment, vinyl chloride and vinylidene chloride. The concentrations of vinyl chloride were much higher than those of vinylidene chloride, due to the much larger quantities of vinyl chloride used and its greater volatility.

During the first of two decades covered in the present study, the exposure of the workers to vinyl chloride and vinylidene chloride were estimated solely by nonspecific combustion techniques.[15,16] The concentrations were expressed as vinyl chloride, although both materials were known to be present. In more recent measurements, infrared and gas chromatographic techniques have established that the vinyl chloride concentrations average 10 ppm, while virtually all vinylidene chloride concentrations amount to less than 5 ppm, and most frequently are detectable only in trace amounts. For this reason, all exposure estimates used in this study have been indexed as "vinyl chloride." Our conclusions, however, must be viewed in the proper context — that is, a work environment with two airborne materials: vinyl chloride in substantial amounts combined with very small amounts of vinylidene chloride. It should be noted, however, that a continuous 90-day inhalation exposure of rats and guinea pigs, at a concentration of 5 ppm vinylidene chloride,[14] revealed no significant changes in hematologic, biochemical, pathologic and growth-rate parameters.

Environmental Surveillance

Industrial hygiene surveys of the operations in which the workers under study were exposed started in 1950. From that time until 1959, environmental surveillance was conducted on a regular basis, but using only the traditional techniques of grab sampling and portable analyzers.[15,16] Since 1959, permanent multipoint continuous monitors have been used to estimate the exposures received by the workers studied. The application of data processing and computer technology to environmental control has allowed us to document the intensity of exposures more thoroughly and validate our continuous monitoring technique by breath sampling surveys.[7,17]

The environmental sampling related to this investigation has focused on the exposure levels of men working in eight critical job classifications. Sampling for one or more of these classifications was performed in 1950, 1951, 1952, 1953, 1954, 1955, 1958, 1959, and each year thereafter. Before continuous monitors were installed in 1959, the periodic exposure estimates were based on job studies supplemented by the examination of several discreet samples gathered over a few days. In later surveys, the exposure estimates were based on hundreds of thousands of samples gathered on a continuous basis over long time periods using multi-point analyzers. Thus the quantity of environmental sampling has increased and the quality has improved over the years in a manner that parallels the intensification of the medical surveillance program.

Suitable Air Quality Parameters

Obviously, a study of the possible effects of repeated inhalation of an airborne material which varies in concentration requires the use of a quantitative expression of air quality. We also recognize the need for an expression of air quality that will help characterize the tremendous variation in vinyl chloride concentration that may occur, together with a measure of central tendency. We base our choice, the "time-weighted average concentration" (TWA), on consideration both of the problem under study and of availability of data. For this study, from a practical viewpoint, the heterogeneity of the environmental sampling limits our choice of an air-quality parameter to the time-weighted

average concentration, which is a convenient expression for integrating a variable exposure pattern. However, we wish to point out that theoretically this expression has no relationship to the degree of toxic response.

Bartlett and Carroll [18] note that, for agents passing through the respiratory membranes, as vinyl chloride apparently does, we know very little of how repeated or continuous exposure leads to chronic effects. However, since chronic effects could presumably be cumulative and progressive, a suitable parameter for the study of air quality would be the mean concentration, *e.g.*, the time-weighted average concentration.

As a result of the environmental sampling conducted since 1950, yearly TWA estimates have been tabulated for each of the 98 individuals studied, following the work history of each man as he stayed within the group of critical job classifications during his employment. The result is a table of yearly exposure estimates for each individual. With such a table, a man's previous exposure history is available — both on a cumulative dosage basis (ppm-years) and as a career time-weighted average exposure.

Medical Aspects

Those who have worked in the industrial setting appreciate the difficulties encountered in studying a population which is subject to continuing change and often to mixed exposures. In actual experience it is rare to encounter a stable population which has had exposure to a single environmental contaminant. The population in the present study is typical in that the exposure has been mixed. Likewise, our clinical methods have varied both as to frequency of examination and use of certain laboratory tests.

Until recently, our periodic medical examination consisted of a medical history, and a physical examination, including chest x-ray, timed vital capacity, urinalysis and minimum hematology. To this basic examination we have added those particular laboratory tests which appear justified by the particular hazard to which the worker may have been exposed. The tests have varied from year to year as the state of medical knowledge has changed. We now have a program in which all employees, in addition to this basic examination, receive a far more complete battery of tests. We include all individuals in our plant, regardless of the degree or type of exposure to hazardous materials. By so doing, we hope to accumulate data that will be useful in establishing norms for our working population, and for providing better clinical data to be used in similar projects.

Data on a large group of employees that would qualify as a control group would be very useful for a conventional comparison of mean clinical indices for the "control" population and the "exposed" population. Unfortunately we have no such comparable data. Moreover, this type of analysis has the disadvantage of masking variation within the "exposed" group — variation which could be correlated with the degree of exposure if good environmental data were available.

The experience discussed in this paper is based largely on our previous methods of acquiring data. At the moment we are seeking to establish a method with which we can study the data accumulated in the past. Over the years, our examinations, which have served the basic purpose of protecting the health of individual employees, have resulted in the discovery and correction of some obvious abnormalities. However, less obvious effects may have been missed.

Though we had no ideal control group, we compared the results of the examinations on 66 of the individuals in the study group who had had examinations during 1965 and 1966 with a group of 605 employees from other departments who had had examinations in the same period. Ninety-five parameters of the history, physical examination and laboratory work were studied. This comparison was carried out by a test for difference between means, using a normal approximation. The summary of significant differences is shown in Table I. The study group showed an increased number of responses to the history item on asthma. This, however, was not reflected in a final diagnostic category, nor was any significant difference noted between the timed vital capacities of the study group and of the overall group. The study group also showed an

TABLE I

Factors in Which VC1 Group Differed Significantly from the "Control Group" ($P \leq 0.05$)

	VC1 Group, %	"Control Group," %
Number of Exams	66	605
History:		
Asthma	10.8	2.6
Stomach, liver, intestinal trouble	6.2	18.0
Kidney stone, bloody urine	9.2	3.0
Nervous trouble of any sort	4.6	13.4
Have you ever worked with radioactive substances	1.5	15.5
Physical:		
Anus-rectum	13.8	6.1
Identifying body marks	7.7	18.7

increase in positive responses to the history item "kidney stone or bloody urine." Again, this was not reflected in the diagnostic categories. There was a decrease in number of responses to the history questions on "stomach, liver, and intestinal trouble" and "nervous trouble of any sort." On physical examination, the only category in which more responses were recorded was that involving abnormalities of the anus and rectum. Again, since this finding was not borne out in the final diagnostic categories, it would indicate that the various examiners did not consider these findings to be of clinical significance.

There was no difference in overall diagnostic categories except for diseases of the digestive system, where fewer specific diagnoses were recorded for the study group than for the comparison group. There were no group differences in the electrocardiograms or chest x-rays. Hand x-rays on the individuals in the "exposed" group showed no significant abnormalities and no case of acroosteolysis. For comparing the mean BSP of the study group with that of the comparison group, only 116 measurements were available for the comparison group. The mean BSP for the study groups was 2.73 (50 observations), and the mean for the control group was 2.89 (116 observations). Although all records were individually reviewed for data which had not been processed statistically, no significant additional findings were noted. Considering the many factors studied, some differences would be expected. However, this conventional comparison of test means for the two groups does not suggest any basic difference between the two populations with regard to general health, and it appears that no significant disease has appeared in the study group as a result of work exposure.

Statistical Consolidation of Data for the Exposed Population

Dependent Variables

After the accumulated clinical data from the 98 men in this study had been compiled, there were 21 clinical parameters for which sufficient data existed to warrant inclusion in further statistical analysis. The criterion for inclusion was at least one observation per man for 25 men for any given test. The 21 clinical parameters are listed in Table II.

Independent Variables

In identifying factors which could explain some or all of the variation in the observed clinical variables, we recognize the need for including a record of age and obesity (important nonenvironmental variables), and the level and duration of exposure (essential environmental variables). Age was recorded to the nearest whole year. Obesity was defined as the ratio of actual weight to "standard weight." The level of exposure was expressed as the cumulative time-weighted average concentration. The product of TWA and time-on-the-job (TOJ) gave a measure of the cumulative dosage.

TABLE II

Twenty-one Clinical Parameters Screened for Correlation with Exposure

Test
Physical
Systolic blood pressure
Diastolic blood pressure
Timed vital capacity
Chemical
Bromsulphalein (BSP)
Icterus index
Alkaline phosphatase
Serum glut oxal tran (SGOT)
Thymol turbidity
Protein, serum total
albumin
globulin
alpha 1
alpha 2
beta
gamma
AG ratio
Hematological
Hemoglobin
Hematocrit
Red blood cells
White blood cells
Prothrombin time
Urine
Specific gravity

Data Format

At this point we had prepared two concurrent sets of data for each man: medical information and environmental information. All that remained was the individual matching process and collective analysis. At the time of each clinical observation, both types of data for each man were registered in the following format:

Man No., Date, Age, TOJ, TWA, Ht, Wt, Std Wt, $Y_1 \ldots Y_{21}$

Where TOJ = time-on-job (time of exposure), yrs.

TWA = Career time-weighted average exposure

Std Wt = Standard (desired) weight as tabulated by the Metropolitan Life Insurance Company.[19]

Y_i = Clinical observation i, i = 1, 2 ... 21.

Statistical Analysis

The technique used for extracting relationships hidden in the available data was "step-wise multiple linear regression analysis." This procedure, made powerful by the advent of digital computers, systematically builds a mathematical model from a choice of independent variable terms based on the fundamental independent variables. In the step-wise regression procedure, the independent variable (X_1) most highly correlated with the response is entered into the model, and the coefficients are determined by the method of least squares. Using partial correlation coefficients, the next variable (X_2) to enter the regression is that whose partial correlation with the response is highest. Given the regression equation $Y = f(X_1, X_2)$, the method now examines the contribution X_1 would have made if X_2 had been entered first. Repeatedly, the step-wise method selects as the next variable in the regression the one most highly partially correlated with the response. At each stage, the "best" regression equation $Y = f(X_1, X_2, \ldots X_n)$ is determined by the method of least squares, after checking the partial F criterion for each variable to verify the significance of each term included.[20]

The object of this technique is to express a relationship by some relatively simple mathematical function such as polynominal which contains appropriate variables and which approximates the true response of the dependent variable over some limited ranges of all the variables involved. Since this approach is empirical, the resulting equation might be considered to be physically meaningless; nevertheless, it may prove extremely valuable for predicting the values of some dependent variable from knowledge of other variables, at least under certain stated restrictions. In using the technique, it was kept in mind that, just because a particular functional relationship has been developed and a specific computational procedure is followed, it cannot be concluded that a causal relationship exists among the variables. After data had been accumulated and a strategy had been selected for analysis of the information, the remaining steps could be broadly classified as screening and refinement.

Correlation Matrix

The first step in analyzing the consolidated information was to examine the linear

TABLE III

Correlation of All Dependent Variables with All Independent Variables ($P \leq 0.05$)

Test	Age	OB	TWA	Dose
Physical				
Systolic blood pressure	+	+	+	+
Diastolic blood pressure	+	+	+	+
Timed vital capacity	–	0	0	0
Chemical				
Bromsulphalein (BSP)	0	+	+	+
Icterus index	0	0	+	+
Alkaline phosphatase	0	0	0	0
Serum glut oxal tran (SGOT)	0	0	0	0
Thymol turbidity	0	0	0	0
Protein, serum total				
albumin	0	0	0	0
globulin				
alpha 1	+	0	0	0
alpha 2	0	0	0	0
beta	0	+	+	+
gamma	–	0	0	0
AG ratio	0	0	0	0
Hematological				
Hemoglobin	–	0	–	–
Hematocrit	0	0	0	0
Red blood cells	0	0	0	0
White blood cells	0	0	0	0
Prothrombin time	0	0	0	0
Urine				
Specific gravity	0	0	0	0

correlation matrix for all the independent and dependent variables available. This screening technique revealed several clinical variables that appeared to be related to exposure. The correlation matrix is shown in Table III.

Six clinical parameters of the 21 under study showed significant correlations ($P \leq 0.05$) with the exposure variables, cumulative TWA and cumulative dose. These were: systolic and diastolic blood pressure, bromsulphalein, icterus index, hemoglobin and beta-protein. Of these, three showed correlation with age and four with obesity. Three other clinical parameters were significantly associated with age.

The correlation-screening procedure helped us develop and show that the "independent" and "dependent" variables are interrelated. Table IV shows the correlation matrix ($P \leq 0.05$) for all the crucial variables, dependent and independent. The general consistency of the relationships indicated among the variables justified more rigorous analysis.

Development of Regression Models

In the development of a linear regression equation for each clinical test Y in terms of independent variables, age, obesity, TWA, and dose, we took the view that the complete set of terms from which a model would be chosen should include the independent variables themselves, together with interaction or cross-product terms which might be helpful in explaining variation in the observed variables. For example, we allowed for the possibility of age and exposure operating together (interacting) in a manner which would be different from that of age and exposure acting independently. However, we faced two opposing criteria for selecting a predictive model:

1. For utility and accuracy we wished our model to include as many significant

TABLE IV

Correlation Coefficient Matrix – Crucial Variables

	Age	OB	TWA	Dose	BP_S	BP_D	BSP	II	Hb	β Protein
Age		0	0	+	+	+	0	0	–	0
OB	0		0	+	+	+	+	0	0	+
TWA	0	0		+	+	+	+	+	–	+
Dose	+	+	+		+	+	+	+	–	+
BP_S	+	+	+	+		+	+	0	0	0
BP_D	+	+	+	+	+		+	0	0	0
BSP	0	+	+	+	+	+		0	0	+
II	0	0	+	+	0	0	0		0	0
Hb	–	0	–	–	0	0	0	0		0
β Protein	0	+	+	+	0	0	+	0	0	

\+ Positive correlation $P \leq 0.05$
0 No correlation $P \leq 0.05$
– Negative correlation $P \leq 0.05$

TABLE V

Number of Subjects and Number of Clinical Tests within the Study Group

Test	Total Number of Observations	Number of Subjects & Number of Randomly Selected Observations
Systolic blood pressure	323	98
Diastolic blood pressure	323	98
Bromsulphalein	92	65
Icterus index	29	25
Hemoglobin	145	83
Beta-protein	58	58

independent variable terms as possible so that reliable values could be predicted.

2. For simplicity and ease of communication, we wanted the equation to include as few significant independent variable terms as possible.

Operating largely from an empirical point of view, we drew up a list of 30 independent variable terms including transformations of the four basic independent factors. Since we had unequal numbers of observations for each individual in any given test, it was necessary to choose randomly one observation per individual for each test in order to weight each man equally. This random selection reduced the number of observations for each test as indicated in Table V.

Statistical Results

The results of the regression analyses for each of the six crucial clinical variables are given below:

Systolic Blood Pressure

$BP_s = A_1 + B_1 (Age)^2 + (TWA)(Age)[C_1 (OB) - D_1]$

Diastolic Blood Pressure

$BP_d = A_2 + B_2 (Age)^{1/2} (OB)^{1/2} + C_2 (TWA)(OB)$

Bromsulphalein

$BSP = A_3 + B_3 (Age)(Dose)$

Icterus Index

$II = A_4 + B_4 (TWA)^2$

Hemoglobin

$Hb = A_5 + B_5 (Age)^{1/2} - C_5 (TWA)^2$

Beta-protein

$Beta\text{-}protein = A_6 + B_6 (Dose)^2$

Figures 1, 2 and 3 show the regression responses for three of the above models, BSP, Icterus Index and Beta-protein, respectively.

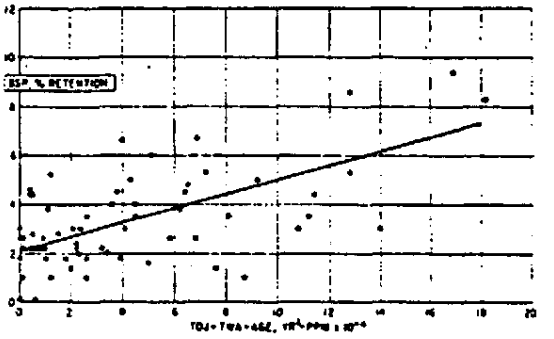

Figure 1. Regression model for bromsulphalein retention.

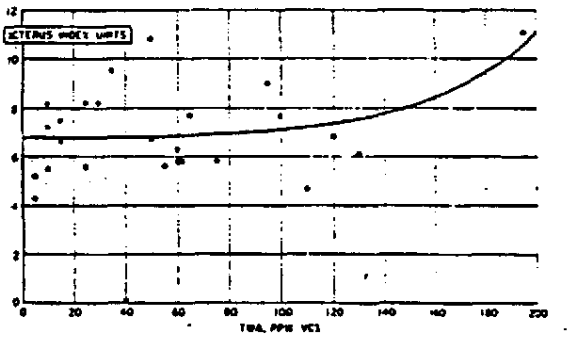

Figure 2. Regression model for icterus index.

Statistical Significance of Models

An appropriate question is: What measures of precision can be attached to the regression models? Three useful indices are the standard error of regression, Se, the overall F-Statistic, and the coefficient of multiple determination,

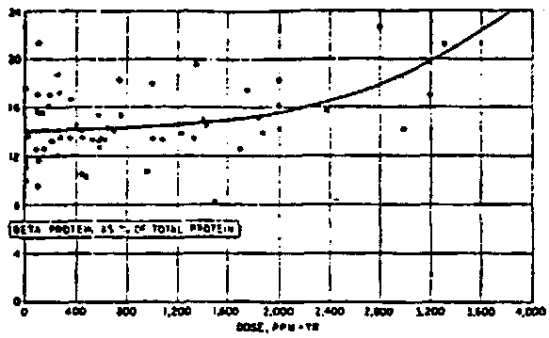

Figure 3. Regression model for beta-protein.

R^2. These measures of the "goodness of fit" for each model of the clinical variables are listed in Table VI. All of the regression models are significant at the $P=0.001$ level, except the Icterus Index model, which is significant at the $P=0.03$ level.

Utility of the Models

The regression models must be used with discretion. Since the least square regression coefficients are adjusted for other variables in the regression procedure, attempting to predict the response by changing only one variable arbitrarily may be misleading. Because of this, we must specify the prediction range for each variable under investigation. Such prediction ranges are shown in Table VII.

To relate the statistical results to the practical question of an industrial hygiene standard requires careful consideration. First, an acceptable workroom air concentration must allow for men working in the environment for an entire career, up to 45 years; our data are useful only over a 20-year span. For effects which are cumulative, as most of those isolated in this study apparently are, the last part of a man's career is the limiting consideration. In view of our data and their ranges, we can examine the clinical variables at TOJ = 20, and Age = 60, the highest legitimate values of our predictive parameters. In the case of blood pressure, obesity must be fixed also if we are to predict the effect of the level of exposure, TWA. For this purpose, we hold "OB" constant at 1.06, the overall mean for the blood pressure data. The following functions result:

Systolic Blood Pressure
$= 136.80 + 0.034035$ (TWA)

Diastolic Blood Pressure
$= 84.74 + 0.018845$ (TWA)

Bromsulphalein
$= 2.12 + 0.034599$ (TWA)

Icterus Index
$= 6.82 + 0.000000002309522$ (TWA)^4

Hemoglobin $= 13.97 - 0.0000000457339$ (TWA)^3

Beta-protein $= 14.15 + 0.000001371545$ (TWA)^3

These clinical changes are tabulated in Table VIII as a function of TWA.

Discussion of Clinical Changes

In reviewing Table VIII, we note six factors which relate empirically to exposure. Within

TABLE VI

Statistical Significance of the Regression Models

Model	Number of Observations	Standard Error of Regression	Overall F-Statistic	Coefficient of Multiple Determination
Systolic blood pressure	98	12.9	24.53 (3:94)*	0.180
Diastolic blood pressure	98	7.6	39.46 (2:95)*	0.193
Bromsulphalein	65	1.5	43.85 (1:63)*	0.407
Icterus index	25	1.6	5.66 (1:23)**	0.191
Hemoglobin	83	0.83	8.95 (2:80)*	0.162
Beta-protein	58	2.6	12.65 (1:56)*	0.170

*$P < 0.001$
**$P = 0.03$

TABLE VII

Mean, Standard Deviations and Limits for Clinical Tests

	Mean	SD	Limit	Age Mean	Age SD	Age Limit	TOJ Mean	TOJ SD	TOJ Limit	TWA Mean	TWA SD	TWA Limit
Systolic blood pressure	128	14	188	40	10	65	10	5.0	25	80	75	375
Diastolic blood pressure	81	8	109	40	10	65	10	5.0	25	80	75	375
Bromsulphalein	3.3	1.9	9.4	41	11	65	11	5.3	25	75	70	340
Icterus index	7.0	1.8	11.1	40	7.1	52	14	5.7	25	55	45	200
Hemoglobin	14.5	0.9	16.4	40	10	64	9.4	4.8	20	70	70	315
Beta-protein	14.7	2.9	22.6	42	10	65	12	5.0	23	60	50	200

the scope of this study the predicted blood pressures, systolic and diastolic, did not rise to levels which would be considered abnormal. The hemoglobin, though statistically decreased, does not fall outside the normal limits for our laboratory. The significance of the change in ratio of the beta-protein is not known. We are left with two factors which give some cause for concern. The changes in the Icterus Index and in the BSP lend some support to the hypothesis that some changes in liver function have occurred in a few individuals exposed at the higher levels. The BSP appears to be most significantly correlated with exposure.

Within the study group were several individuals who, after approximately 20 years of exposure with time-weighted exposures of approximately 300 ppm of vinyl chloride and smaller amounts of vinylidene chloride during the early part of their careers, demonstrated a tendency to develop changes in certain laboratory tests which appear to be related to their exposure. Reference to Figures 1-3 indicates that our interpretation of the clinical changes must be tempered by the fact that only a small number of individuals experienced the highest exposures.

Two of the individuals showing the highest rise in BSP were rechecked in 1968. One had essentially normal laboratory findings and the other showed persistent elevation of various liver function tests, even though both had been removed from further exposure since 1965. The individual whose liver function tests remained elevated had a history of hepatitis preceding his exposure, although his pre-exposure liver function tests had been normal. Whether his abnormalities represented a result of his exposure or independent sequelae of hepatitis cannot be ascertained. Certainly it would be desirable not to consider individuals with a history of hepatitis as candidates for prolonged exposure to vinyl or vinylidene chloride. Unfortunately, since many cases of subclinical hepatitis occur, there may always be some individuals in a working population who have had hepatitis.

For most individuals in the study, the highest exposure occurred in the early phases of their careers and their later exposures were much lower. In the final analysis, much weight had

TABLE VIII

Expected Response of Clinical Tests as a Function of Career TWA

Test	TWA, PPM Vinyl Chloride						
	0	50	100	150	200	250	300
Systolic blood pressure (Age = 60, OBES = 1.06)	136.8	138.5	140.2	141.9	143.6	145.3	147.0
Diastolic blood pressure (Age = 60, OBES = 1.06)	84.7	85.7	86.6	87.6	88.5	89.4	90.4
Bromsulphalein (TOJ = 20, Age = 60)	2.1	3.8	5.6	7.3	9.0	10.8	12.5
Icterus index	6.8	6.8	7.0	8.1	11.0	X	X
Hemoglobin	14.0	14.0	13.9	13.8	13.6	13.3	12.7
Beta-protein	14.1	14.3	15.5	18.8	25.1	X	X

X = beyond range of available data

to be placed on the readings observed for those employees who experienced high exposure levels, especially during the period 1950-58. For example, the average time-weighted exposure level in 1950 was 155 ppm, whereas the average exposure level in 1965 was 30 ppm.

Our findings suggest that repeated exposure to vinyl chloride at TWA levels of 300 ppm or above for a working lifetime together with a very low level of vinylidene chloride may result in slight changes in certain physiologic and clinical laboratory parameters. The possibility of some impairment in liver function tests must be considered, even though no overt clinical disease was evident in any of the individuals studied. We shall continue our study, but suggest that similar studies to help clarify the effects of this material be performed for other worker populations exposed to vinyl chloride alone.

Conclusions

The present study offers a technique of judging exposure effects on a group of exposed workmen based on an analysis which is intended to account for individual levels of exposure rather than relying on a collective comparison with a so-called "control" population. The "exposed" group, especially when it is drawn from an industrial setting, will contain individuals subject to a wide range of exposures, and the mean clinical indices for the group may well mask significant individual differences within the exposed group that could be detected only by intra-group analysis.

We have attempted to correlate the clinical manifestations of a group of men for which exposure data as well as clinical measurements were available. With this approach, the "exposed" group will contain some individuals whose exposures are low enough to serve as "controls." The regression technique we have employed treats the exposure levels (Dose and TWA) as independent variables, thereby providing an open format that allows inclusion of any degree of exposure, including none. The advantage of regression analysis in this application lies in the ability to extract more substantial information on acceptable exposure levels by relating measured clinical changes directly to measured exposure. To use this method, good environmental and medical data must be gathered and consolidated concurrently in substantial quantity.

We have demonstrated the use of this statistical technique with a group of men exposed to vinyl chloride and trace levels of vinylidene chloride. In so doing, we have found some interesting apparent effects from chronic exposure to that system but, more importantly, the methodology looks promising as a needed improvement in our quest to make

practical use of toxicological feedback from worker exposures. We hope that others will offer further refinements and suggestions that will help attain this goal.

Acknowledgments

We wish to acknowledge the assistance of other members of the Medical Department and Environmental Research Laboratory of The Dow Chemical Company who, over two decades, gathered the basic information which has made this study possible. Our special thanks to go Mrs. Shirley Walker, R.N., who conditioned much of the medical data, to M. Gerald Ott for his suggestions with the statistical strategies, and to our supervisors and colleagues for their steady support.

References

1. von Oettingen, W.F.: *The Halogenated Hydrocarbons: Toxicity and Potential Dangers.* U.S. Public Health Service. Publication 414, Government Printing Office, Washington, D.C. (1955).
2. Mastromatteo, E., A.M. Fisher, H. Christie, and H. Danziger: Acute Inhalation Toxicity of Vinyl Chloride to Laboratory Animals. *Amer. Ind. Hyg. Assoc. J. 21:*394 (Oct. 1960).
3. Torkelson, T.R., F. Oyen, and V.K. Rowe: The Toxicity of Vinyl Chloride As Determined By Repeated Exposure of Laboratory Animals. *Amer. Ind. Hyg. Assoc. J. 22:*354 (Oct 1961).
4. Lester, D., L.A. Greenberg, and W.R. Adams: Effects of Single and Repeated Exposures of Humans and Rats to Vinyl Chloride. *Amer. Ind. Hyg. Assoc. J. 24:*265 (May 1963).
5. Committee on Threshold Limit Values: *Documentation of Threshold Limit Values,* Rev. Ed., American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio (1966).
6. Damziger, H.: Accidental Poisoning by Vinyl Chloride: Report of Two Cases. *Canadian Med. Assoc. J. 82:*828 (April 1960).
7. Baretta, E.D., R.D. Stewart, and J.E. Mutchler: Monitoring Exposures to Vinyl Chloride Vapor: Breath Analysis and Continuous Air Sampling. *Amer. Ind. Hyg. Assoc. J. 30:*537 (1969).
8. Filatova, U.S., and E.S. Gronsberg: Hygienic Working Conditions in Polyvinyl Chloride Tar Plants. *Gig i Sanit 38-42* (Jan 1957).
9. Wilson, R.H., W.E. McCormick, C.F. Tatus, and J.L. Creech: Occupational Acroosteolysis. *J.A.M.A. 201:*577 (Aug 1967).
10. Dinman, B.D., W.A. Cook, W.M. Whitehouse, H.J. Magnuson, and T. Ditcheck: Occupational Acroosteolysis: An Epidemiological Study. *Arch. Environ. Health 22:*61 (Jan 1971).
11. Cook, W.A., P.M. Giever, B.D. Dinman, and H.J. Magnuson: Occupational Acroosteolysis: An Industrial Hygiene Study. *Arch. Environ. Health, 22:*74 (Jan 1971).
12. Dodson, V.N., B.D. Dinman, W.M. Whitehouse, A.N.M. Nasr, and H.J. Magnuson: Occupational Acroosteolysis: A Clinical Study. *Arch. Environ. Health, 22:*83 (Jan 1971).
13. Suciu, I., J. Drejman, and M. Valaski: Contributions to the Study of Affections Caused by Vinyl Chloride. *Medicina Interne 15:*967 (Aug 1963).
14. Prendergast, J.A., R.A. Jones, L.J. Jenkins, Jr., and J. Siegel: Effects on Experimental Animals of Long-Term Inhalation of Trichloroethylene, Carbon Tetrachloride, 1,1,1-Trichloroethane, Dichlorodifluoromethane, and 1,1-Dichloroethylene. *Toxicol. and Appl. Pharm. 10:*270 (March 1967).
15. Peterson, J.E., H.R. Hoyle, and E.J. Schneider: The Analysis of Air for Halogenated Hydrocarbon Contaminants by Means of Absorption of Silica Gel. *Amer Ind. Hyg. Assoc. Quart. 17:*429 (Dec 1956).
16. Schaffer, A.W., and H.R. Hoyle: Nine Years Experience with the Davis Halide Meter. *Amer Ind. Hyg. Assoc. J. 22:*93 (April 1961).
17. Peterson, J.E., H.R. Hoyle, and E.J. Schneider: The Application of Computer Science to Industrial Hygiene. *Amer. Ind. Hyg. Assoc. J. 22:*180 (March 1966).
18. Bartlett, D., Jr., and R.E. Carroll: Air Quality Parameters for Epidemiologic Studies. *Arch. Environ. Health 16:*182 (Feb. 1968).
19. Desirable Weights for Men of Ages 25 and Over, Metropolitan Life Insurance Company.
20. Draper, N.R., and H. Smith: *Applied Regression Analysis.* John Wiley and Sons, Inc., New York (1966).

Received May 28, 1971