Second Draft

THE CORRELATION OF CLINICAL AND ENVIRONMENTAL MEASUREMENTS FOR WORKERS EXPOSED TO VINYL CHLORIDE

By

J. E. Mutchler, M.S.E.

and

C. G. Kramer, M.D.

Biochemical Research Laboratory
and
Medical Department

The Dow Chemical Company
Midland, Michigan

For Presentation at

The 1968 Gordon Research Conference On

Industrial Hygiene

Tilton, New Hampshire

August 5, 1968

I. INTRODUCTION

A careful and comprehensive study of the exposed workmen is crucial in validating an industrial hygiene standard. In practice, however, the number of substances for which such studies have been reported have been very few. The chall nge today in occupational health is the development of programs that will help better define the relationships between stresses in the work environment and measurable clinical changes, both as to the significance of those changes and as those relationships can refine our guide lines for environmental control.

Although toxicologists have become quite proficient in predicting what exposures are likely to be safe for people, there is always some doubt until enough human experienc has been gained to prove that their predictions are correct. This "proof of the pudding" should result from the correlation of good environmental measurements with the results of a well planned medical surveillance program. This f d-back from human experience likely 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. Except in cases where an industrial hygiene standard has not been applied, the feed back from human experienc could be expected, however, to describe a level of exposure which has been shown to be either acceptable or marginally unacceptable.

This information would be valuable in assisting the toxicologists in strengthening their skills in predicting effects on humans from experimental animal data, and in a broader sense, this information would be useful in substantiating criteria to be used for industrial hygiene standards.

The Dow Chemical Company's medical and environmental health groups have for several years been conducting concurrent medical and environmental surveillance for a large worker population exposed to many different chemicals. The project described herein attempts to harness the information from such concurrent surveillance -- and relate it to acceptabl levels of exposure.

This paper describes a method for the statistical consolidation and correlation of environmental measurements and clinical findings using as an example a group of 98 healthy male workers who have been exposed routinely to vinyl chloride for periods up to 25 years. Retrospective in nature, the study reveals several statistically significant clinical chang s from chronic exposures to vinyl chloride, and together with medical interpretation of these apparent effects, we offer what appears to be a promising technique for relating the collective clinical information from worker exposures to a more refined industrial hygiene standard.

II. VINYL CHLORIDE

Vinyl chloride (CH_2=CHCl) is a chemical of increasing industrial importance. It is a monomer used both in the polymerization of polyvinyl chloride resin, Saran and other copolymers, as a chemical intermediate, 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] The gas is an sth tic 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. Using controlled concentrations of 50-500 ppm, Torkelson found that repeated seven-hour exposure to 200 ppm caused micropathological changes in the livers of rabbits, and at 100 ppm he 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 lung or other vital organ effects upon repeated daily exposures lasting 92 days at th lower concentration and 19 days at th higher level. However, he also detected some increase in relative weights of the rat liver as well as the 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

There are few reported effects from human exposure to vinyl chloride except for narcosis upon acute exposure. At least two industrial deaths are 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. They found the first signs of intoxication appearing 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. Their investigation primarily was concerned with expired air studies, but no clinical changes nor neurological responses were found in the thirteen volunteers upon thorough physical examination.

Filatova and Gronsberg[8] reported angioneurosis of a 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] report several cases of acroosteolysis in the hands of workmen working on vinyl chloride polymerization processes. No vinyl chloride exposure estimates are cit d, but the nature of the disorder and the circumstances of its appearance suggest that the effect may have resultd from a "combination of physical insult, chemical insult, and personal idiosyncrasy."

Suciu, et al.,[10] studied the clinical manifestations of a group of 186 employees working in polyvinyl chloride plants. Without quantifying the exposures to vinyl chloride and other substances in the work environment of these men, the authors report the presence of the "narcotic syndrome," asthenic nervous symptoms, Raynaud's syndrome and hepatomeglia.

III. ENVIRONMENTAL ASPECTS

The Work Environment

Subjects included in this investigation have worked in one or both of two manufacturing facilities which use vinyl chloride in polymerization processes. In both plants the environmental stresses of the work area have been essentially equivalent. There are two airborne materials present in the work environment: vinyl chloride and vinylidene chloride, the vinyl chloride being present in much higher concentrations than

vinylidene chloride. The overriding presence of vinyl chloride can be attributed to its relative use and higher volatility.

During the first of two decades covered in this study the exposures of the workers to vinyl chloride and vinylidene chloride were estimated solely by nonspecific combustion techniques.[11, 12] 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 ratio of vinyl chloride to vinylidene chloride concentrations averages about 10, with virtually all vinylidene chloride concentrations less than 5 ppm,* and usually 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: a work environment with two airborne materials -- vinylidene chloride believed to be present in nearly trace amounts and vinyl chloride in substantial amounts.

*A recent study of the effects in animals of long-term inhalation exposure of vinylidene chloride showed that continuous 90-day exposures to rats and guinea pigs at 5 ppm produced no significant changes in hematologic, biochemical, pathologic and growth rate parameters.[13]

Environmental Surveillance

Industrial hygiene surveys of the operations in which the workers under study have been exposed, started in 1950. Since then and until 1959, environmental surveillance was conduct d on a regular basis, but with the traditional techniques of grab sampling and portable analyzers.[11,12] 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.[7,14]

The environmental sampling related to this investigation has focused on the exposure levels of men working in eight critical job classifications. Sampling was performed in this regard for one or more of these classifications 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 coupled with several discrete samples gathered over a few days. In later surveys, the exposure estimates were based on hundreds of thousands of samples gathered over long time periods with multipoint analyzers - on a continuous basis. Therefore, the quality and quantity of environmental sampling has increased over the years in a manner that parallels the medical surveillance program.

Suitable Air Quality Parameters

Obviously, a study of the possible effects of repeated inhalation of changing concentrations of an airborne material like vinyl chloride requires the use of a quantitative expression of air quality. We also recognize the need for an expression of air quality that would help characterize the tremendous variation in concentration that may occur, together with a measure of central tendency. We base our choice, the "time-weighted average concentration" on consideration of both the problem under study and on availability. From a practical viewpoint the heterogeneity of the environmental sampling limits the choice of an air quality parameter for this study to the time-weighted average concentration. The time-weighted average is a convenient expression for integrating a variable exposure pattern. However, we wish to point out that th oretically, this expression has no relationship to the degr of toxic response.

Bartlett and Carroll[15] note that for agents passing through the respiratory membranes, as vinyl chloride apparently do s, we know very little of how repeated or continuous exposure leads to chronic effects. However, since chronic effects coul presumably be cumulative and progressive, a suitable parameter of air quality would be the m an conc ntration; _.g., the tim - weighted average concentration.

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

IV. MEDICAL ASPECTS

Those who have worked in the industrial setting appreciat the difficulties encountered in studying a population which is subject to continuing change and often to mixed exposures. It is rare in actual practice to encounter a stable population with exposure to a single environmental contaminant. In this resp ct the population in this study is typical, in that the exposur 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 has consisted of a history, physical, chest X-ray, timed vital capacity, urinalysis and minimum hematology. To this basic examination we have added those particular laboratory tests which appeared

justified by the particular hazard which was suspected. The tests have varied from year to year as the state of medical knowledge changed.

We have now instituted a program in which all employees, in addition to being given this same basic examination, receive a far more complete battery of tests. We now include all individuals in our plant, regardless of their degree or type of exposure. By so doing we hope to accumulate data that will be useful in establishing norms for our working population, and in providing better clinical data for other projects like this.

For the sake of comparing populations, we have no comparable data on a large group of employees that would qualify as an ideal control group. Such data would be very useful for a conventional comparison of mean clinical indices for a "control" population and an "exposed" population. However, 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 -- and at this point we are seeking to establish a method with which we can study the

TABLE A

R&S 104753

FACTORS IN WHICH VCl GROUP DIFFERED SIGNIFICANTLY FROM THE "CONTROL" GROUP

(P≤0.05)

	VCl 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
DISEASE CATEGORY:		
CATEGORY IX (DISEASES OF DIGESTIVE SYSTEM)	3.0	13.2

accumulated data of the past. Over the years, our examinations have served their basic purpose of protecting the health of the individual employees and have resulted in the discovery and correction of some obvious abnormalities. However, the less obvious effects may have been missed.

The document used to record the physical exam data is reproduced in the next ten slides. By asterisk we indicate all those responses and measurements which we process for computer retrieval.

All of these factors were compared with the control group by a test for difference between means using a normal approximation, and the significant differences are noted in Table A.

Though we have no ideal control group, we compared the results of the examinations on 66 of the individuals in the study group, who had examinations during 1965 and 1966, with a group of 605 employees from other departments who had examinations in the same period. This comparison was carried out by a test for difference between means using a normal approximation. The study group showed an increased number of responses to the history item on asthma which, however, was not reflected in a final diagnostic category nor was any significant difference noted between the time vital capacities

of the study group and the overall group. The study group also showed an increase in positive responses to the history item on "kidney stone or bloody urine." Again, this was not reflected in the diagnostic categories. They showed 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 positive responses were recorded was that for abnormalities of the anus and rectum. Again, since this was not born 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 x-cept for category IX which covered diseases of the digestive system where less diagnoses were recorded for the study group than for the comparison.

There were no group differences in the electrocardiograms or chest X-rays. Hand X-rays on the individuals in the "exposed" group showed no sifnificant abnormalities and no case of acroosteolysis. In comparing the mean BSP of the study group with the comparison group, only 116 measurements were available in the comparison group. The mean BSP for th study group was 2.73 (50 observations) and the mean for the control group was 2.89 (116 observations). In addition, all records were

individually reviewed for data which were not processed for computer retrieval, but no significant additional findings were noted. Considering the many factors studied, some differences would be expected. However, this conventional comparison of the two groups does not suggest there is any basic difference between the two populations in regard to general health and it appears that no significant disease has appeared in the study group as a result of their work exposure.

Table 1

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

V. STATISTICAL CONSOLIDATION OF DATA WITHIN THE EXPOSED GROUP

Dependent Variables

Upon compiling the accumulated clinical data from the 98 men in this study 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 1.

Independent Variables

In identifying factors which could explain some or all of the variation in the observed clinical variables we recognize the need to include age and obesity, important nonenvironmental variables, and level of exposure 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 (TWA). The product of TWA and time-on-the job (TOJ) gav a measure of the cumulative dosage.

Data Format

At this point we had prepared two concurrent sets of data for ach man: his medical information and his 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 . . . 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.[16]

Y_1 = clinical observation 1, 1 1,2, . . . 21.

VI. 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 regr ssion equation $Y = f(X_1, X_2)$, the method now examines the contribution X_1 would hav made if

Table 2

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	+	+	+	+
Vital capacity	-	O	O	O
Chemical				
Bromsulphalein (BSP)	O	+	+	+
Icterus Index	O	O	+	+
Alkaline phosphatase	O	O	O	O
Serum glut oxal tran (SGOT)	O	O	O	O
Thymol turbidity	O	O	O	O
Protein, serum total				
albumin	O	O	O	O
globulin				
alpha 1	+	O	O	O
alpha 2	O	O	O	O
beta	O	+	+	+
gamma	-	O	O	O
ag ratio	O	O	O	O
Hematological				
H moglobin	-	O	-	-
Hematocrit	O	O	O	O
Red blood cells	O	O	O	O
White blood cells	O	O	O	O
Prothrombin time	O	O	O	O
Urine				
Specific gravity	O	O	O	O

R&S 104760

TABLE 3

CORRELATION COEFFICIENT MATRIX - CRUCIAL VARIABLES

	AGE	OB	TWA	DOSE	BPs	BPD	BSP	II	Hb	β PROTEIN
AGE		0	0	+	+	+	0	0	−	0
OB	0		0	+	+	+	+	0	0	+
TWA	0	0		+	+	+	+	+	−	+
DOSE	+	+	+		+	+	+	+	−	+
BPs	+	+	+	+		+	+	0	0	0
BPD	+	+	+	+	+		+	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	

R&S 104761

\+ POSITIVE CORRELATION $P \leq 0.05$

0 NO CORRELATION $P \leq 0.05$

− NEGATIVE CORRELATION $P \leq 0.05$

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.[17]

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 is an empirical approach, the resulting equation could be physically meaningless, but it may nevertheless be extremely valuable for predicting the values of some dependent variable from knowledge of other variables, at least under certain stated restrictions. However, just because a particular functional relationship has been developed and a specific computational procedure followed, we cannot conclude that a casual relationship exists among the variables.

At this point we had accumulated the data and selected a strategy for analysis of th 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 correlation matrix for all the independent and dependent variables available. This screening technique revealed several clinical variables that appeared related to exposure. The correlation matrix is shown in Table 2.

Six clinical parameters of the twenty-one under study showed significant ($P \leq 0.05$) correlations 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 pointed out the fact that the "independent" and "dependent" variables are interrelated, in addition to identifying a series of clinical tests which could be examined critically. Table 3 shows the correlation matrix ($P \leq 0.05$) between all of the crucial variables, dependent and independent. The general consistency of the relationships among the variables justifies 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 the model is chosen should include the independent variables themselves, together with interaction or cross-product terms which may be helpful in explaining variation in the observed variables. For example, we allow for the possibility of age and exposure operating together (interacting) in a manner differently than age and exposure acting independently. However, we faced two opposing criteria for selecting a predictive equation:

(1) For utility and accuracy we wish our model to include as many significant independent variable terms as possible so that reliable values can be predicted.

(2) For simplicity and ease of communication we wish to have the equation include as few significant independent variable terms as possible.

Operating largely from an empirical viewpoint, we drew up a list of 30 independent variable terms including transformations of the four basic independent factors. Since for any given t st we had unequal numbers of observations for each individual,

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 4.

VII. STATISTICAL RESULTS

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

Systolic Blood Pressure

$$BP_s = A_1 + B_1 (AGE)^3 + (TWA)(AGE)\left[C_1(OB) - D_1\right]$$

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

$$II = A_4 + B_4 (TWA)^4$$

Hemoglobin

$$Hb = A_5 + B_5 (AGE)^{1/2} - C_5(TWA)^3$$

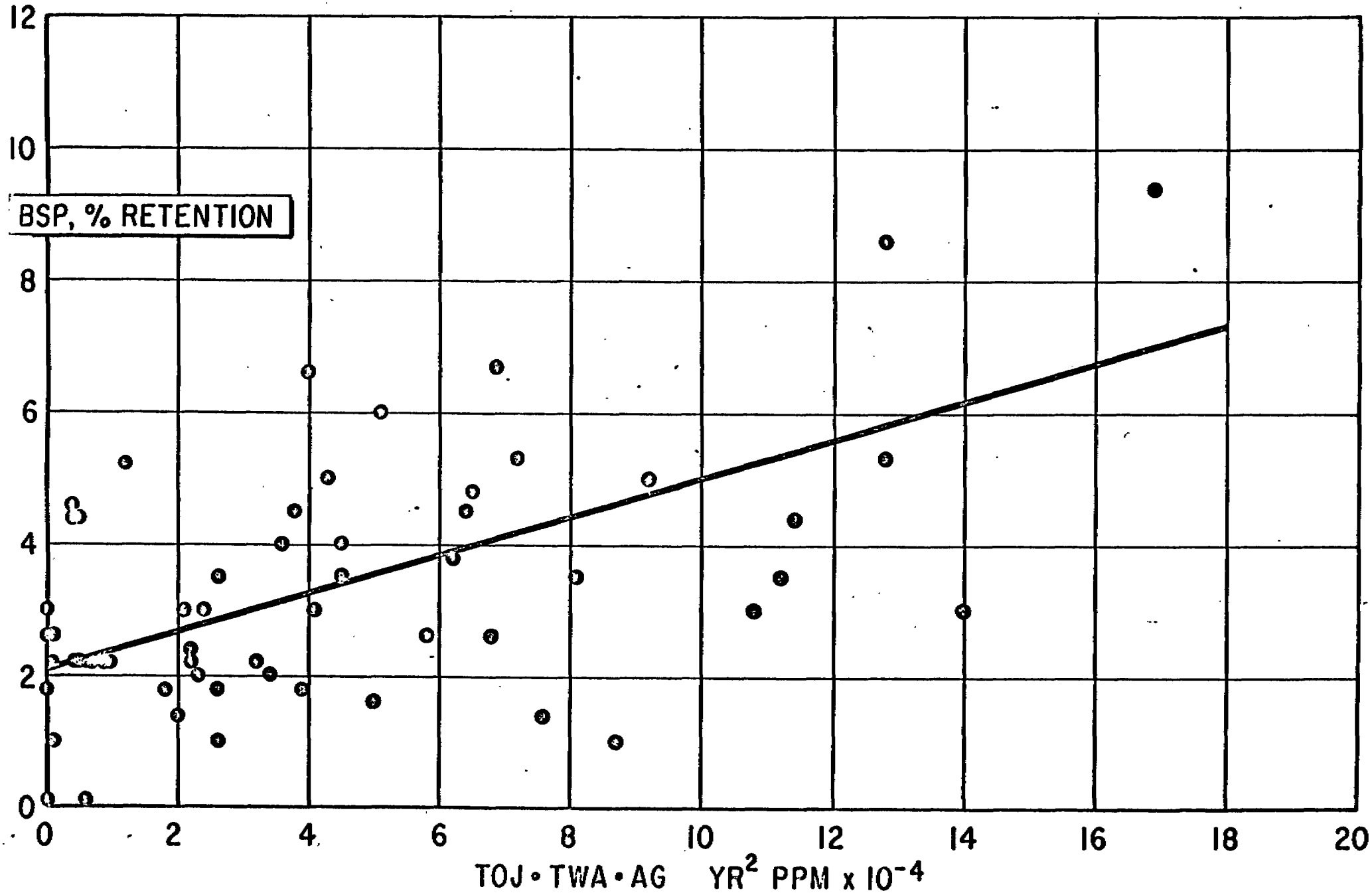
Beta-Protein

$$\text{Beta-protein} = A_6 + B_6 (DOSE)^3$$

Table 4

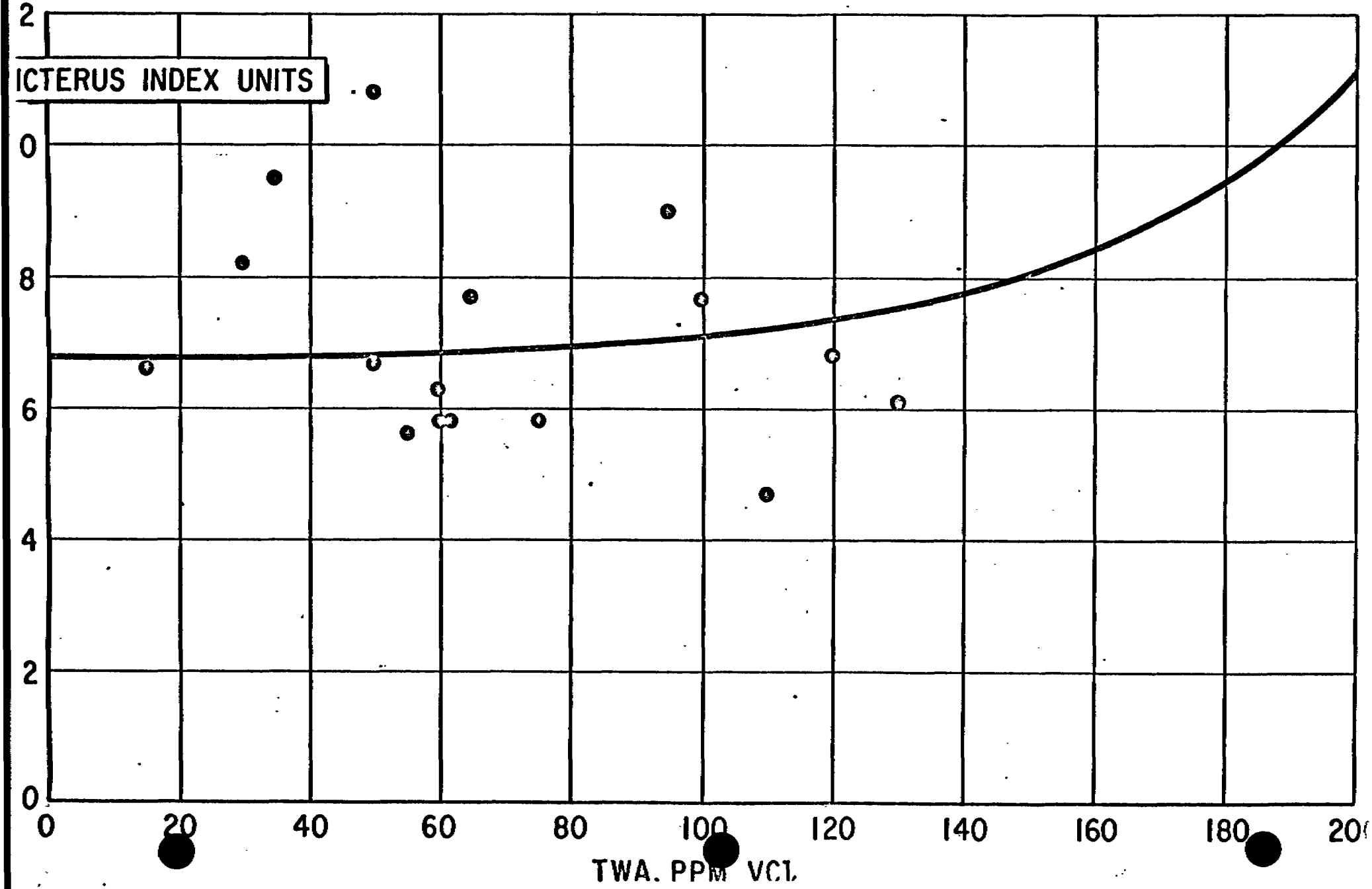
TEST	TOTAL NUMBER OF OBSERVATIONS	NUMBER OF SUBJECTS AND NUMBER OF RANDOMLY SELECTED OBSERVATIONS
Systolic Blood Pressure	323	98
Diastolic Blood Pressure	323	98
Bromsulphalein	92	65
Icterus Index	29	25
Hemoglobin	145	83
Beta-Protein	58	58

FIGURE 1


BSP, % RETENTION
0
2
4
6
8
10
12
0
2
4
6
8
10
12
14
16
18
20
TOJ • TWA • AG YR² PPM x 10⁻⁴

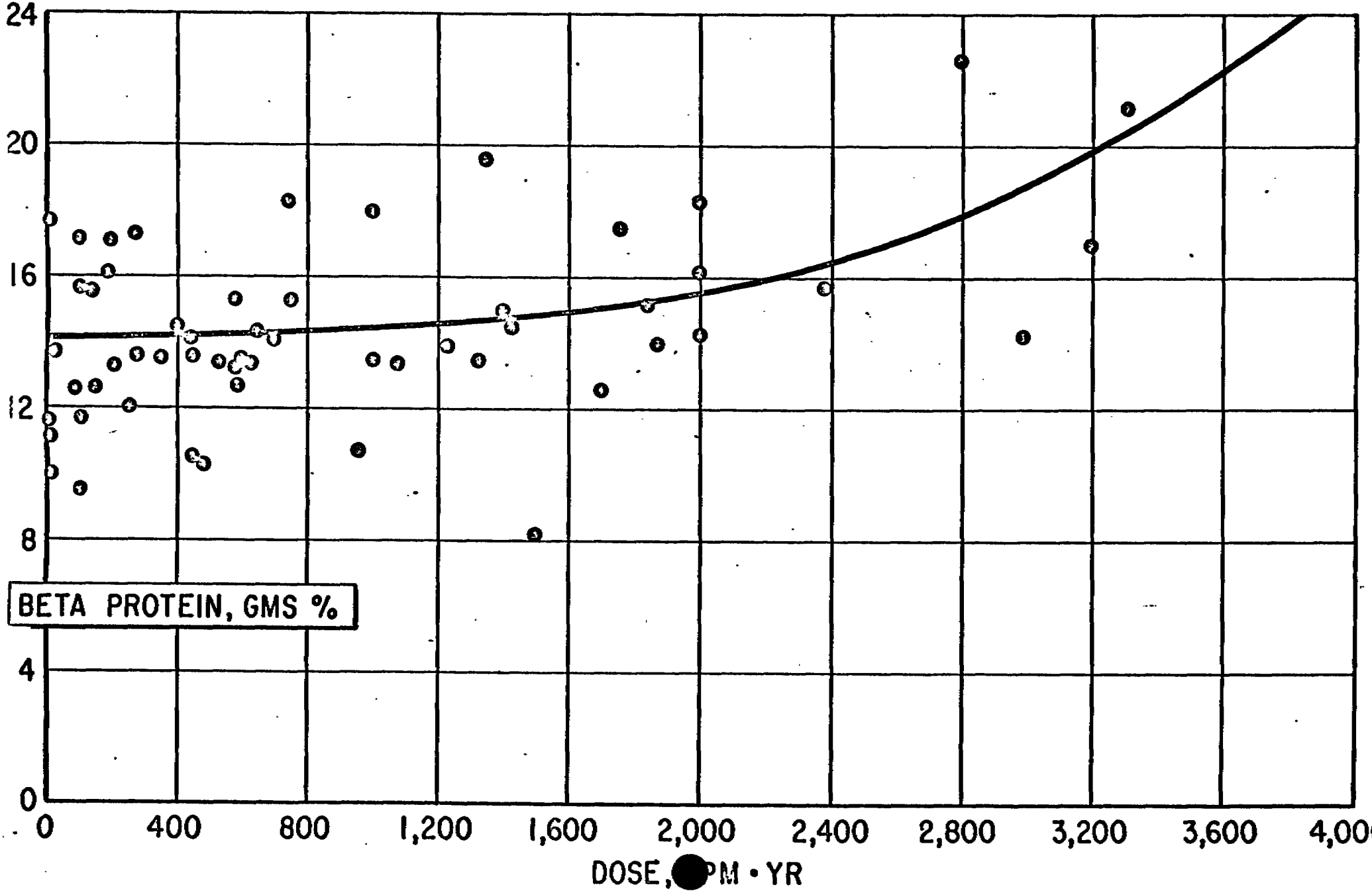
R&S 104768

FIGURE 2



R&S 104769

FIGURE 3



Figures one, two and three show the regression responses for three of the above models, BSP, Icterus Index and Beta-Protein respectively.

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 the Regression, Se, the overall F-Statistic, and the coefficient of multiple determination, R^2. These measures of the "goodness of fit" for each model of the clinical variables are listed in Table 5.

Utility of the Models

The regression models must be used with discretion. The least squares regression coefficients are adjusted for other variables in the regression procedure and, therefore, attempting to predict the response by changing only one variabl arbitrarily may be misleading; therefore, we must specify the prediction range for each variable under investigation. Such prediction ranges are shown in Table 6.

To relate the statistical results to the practical question of an industrial hygiene standard requires careful consideration. First, an acceptable workroom air quality concentration

must allow for men working in that environment for an entire career, up to 45 years; our data are useful only over a 20 year span. For effects which are cumulative, such as most of those isolated in this study apparently are, the last part of a man's career is the limiting consideration. For these reasons, and in view of our data and the predictive ranges thereof, we wish to examine the clinical variables at TOJ 20, and AGE 60.

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 functions are evaluated and presented in Table 7 as a function of TWA.

Table 5

MODEL	N	Se	$F(df_1; df_2)$	R^2
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 6

				AGE			TOJ			TWA		
	Mean	SD	Limit	Mean	SD	Limit	Mean	SD	Limit	Mean	SD	Limit
olic Blood Pressure	128	14	188	40	10	65	10	5.0	25	80	75	375
tolic Blood Pressure	81	8	109	40	10	65	10	5.0	25	80	75	375
sulphalein	3.3	1.9	9.4	41	11	65	11	5.3	25	75	70	340
rus Index	7.0	1.8	11.1	40	7.1	52	14	5.7	25	55	45	200
globin	14.5	0.9	16.4	40	10	64	9.4	4.8	20	70	70	315
-Protein	14.7	2.9	22.6	42	10	65	12	5.0	23	60	50	200

ble 7. EXPECTED RESPONSE OF CRUCIAL TESTS VERSUS CAREER TWA (AGE = 60, OBES = 1.06, TOJ = 20)

Test	TWA, ppm 0	50	100	150	200	250	300
stolic Blood Pressure (AGE = 60, OBES = 1.06)	136.8	138.5	140.2	141.9	143.6	145.3	147.0
stolic Blood Pressure (AGE = 60, OBES = 1.06)	84.7	85.7	86.6	87.6	88.5	89.4	90.4
msulphalein (TOJ = 20, AGE = 60)	2.1	3.8	5.6	7.3	9.0	10.8	12.5
berus Index	6.8	6.8	7.0	8.1	11.0	X	X
moglobin (AGE = 60)	14.0	14.0	13.9	13.8	13.6	13.3	12.7
ta-Protein (TOJ = 20)	14.1	14.3	15.5	18.8	25.1	X	X

X - No DATA

VIII. INTERPRETATION OF CLINICAL CHANGES

As we review Table 7, we note six factors which appear to be related to exposure. Within the scope of our study, the blood pressures, systolic and diastolic, do not appear to rise to levels which can be considered to signify overt disease. The hemoglobin likewise does not reach levels low enough to be considered significant of disease. The Beta-Protein, Icterus index and BSP lend significant support to the possibility that some hepatic injury may occur at higher levels of exposure. The BSP appears to be most significantly correlated with exposure.

Within the study group we find several individuals who, after approximately 20 years of exposure with time-weighted exposures of approximately 300 ppm of vinyl chloride during the early part of their careers (and smaller amounts of vinylidene chloride) have shown a tendency to develop laboratory abnormalities which appear to correlate with 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 have 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 had 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 preceeding his exposure, although his pre-exposure liver function tests were normal. Whether his abnormalities represent a result of his exposure or independent sequelae of his hepatitis cannot be ascertained. Certainly, it would be desirable that individuals with a history of hepatitis not be considered candidates for prolonged exposure to vinyl or vinylidene chloride. Unfortunately, since many cases of subclinical hepatitis occur, we will always have in a working population some individuals 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 have been much lower. In the final analysis much weight is placed on the readings observed for those employees who experienced high exposure levels, especially in the 1950-58 period of their careers. 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, may result in a future decline in the general health of some of the individuals so exposed, probably as a result of hepatic injury. We shall continue our study, but suggest that others who have a worker population exposed to vinyl chloride would perform similar studies which will help clarify the effects of this material on the human organism.

X. CONCLUSIONS

This study offers a technique of judging exposure effects on the basis of an analysis within a group of exposed workmen accounting for the individual levels of exposure rather than relying on a collective comparison with a so-called "control" population. The "exposed" group, especially when 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 individual differences that could be detected only by an 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 are available. With this approach, the "exposed" group contains some individuals whose exposures are low enough

to serve as "controls." The regression technique we have utilized 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 intensities. To use this method, good environmental and good medical data must be gathered in substantial quantity and consolidated concurrently.

We have demonstrated the use of this statistical technique with a group of men exposed to vinyl and vinylidene chloride. In so doing we find some interesting apparent effects from chronic exposure to that system, but more importantly, this methodology looks promising as a needed improvement in our quest to harness the toxicological feedback from worker exposures. We hope that others will offer further refinements and suggestions that will help us attain our common goal.

ACKNOWLEDGEMENTS

We wish to acknowledge and thank those many members of the Medical Department and Environmental Research Laboratory who, over two decades, gathered the basic information that makes this study possible.

Our special thanks go to Mrs. Shirley Walker, R.N., who conditioned much of the Medical data, to 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. J. 24:265 (May, 1963).

5. Committee on Threshold Limit Values: Documentation of Threshold Limit Values, Rev. Ed., American Conference of Governmental Industria Hygienists, Cincinnati, Ohio (1966).

6. Danziger, 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," presented at the American Industrial Hygiene Conference, May 13-17, 1968, St. Louis, Missouri (Manuscript in Preparation).

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. Suciu, I., J. Drejman, and M. Valaski: "Contributions to the Study of Affections Caused by Vinyl Chloride," Medicina Interne 15:967 (Aug., 1963).

11. Peterson, J. E., H. R. Hoyle, and E. J. Schneider: "The Analysis of Air for Halogenated Hydrocarbon Contaminants by Means of Absorption on Silica Gel." Amer. Ind. Hyg. Assoc. Quart. 17:429 (Dec., 1956).

12. Schaffer, A. W., and H. R. Hoyle: "Nine Years Experience with the Davis Halide Meter." Amer. Ind. Hyg. Assoc. J. 22:93 (April, 1961).

13. 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" Tox. and Appl. Pharm. 10:270 (March, 1967).

14. 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).

15. Bartlett, D., Jr., and R. E. Carroll: "Air Quality Parameters for Epidemiologic Studies." Arch. Environ. Health 16:182 (Feb., 1968).

16. "Desirable Weights for Men of Ages 25 and Over." Metropolitan Life Insurance Company.

17. Draper, N. R., and H. Smith: Applied Regression Analysis. John Wiley and Sons, Inc., New York (1966).