

OBSERVATIONS ON THE VINYL CHLORIDE STUDY FROM A STATISTICAL VIEWPOINT

The Objective and Scope of the Study

The vinyl chloride study was undertaken to define an acceptable career exposure level to vinyl and vinylidene chloride in light of data collected from a human population exposed over a period of years to these chemicals. The study was retrospective in that the data analyzed was assembled from information already available. Ninety-seven employees working within the area of concern were declared in-scope of the study on the basis of having experienced no serious acute exposures and having had little or no contact with other toxic chemicals. For many of these employees, complete medical information was not available. Physical exams had been given on a voluntary basis in 1958, 1959-60, 1961, and 1965-66. A summary of lab procedures under investigation and the number of employees examined is shown in Table A. The non-response rate is high for some tests and must be considered in the final interpretation of results. The procedures appearing in Table A were selected from a broader list of lab tests available from the medical records because these showed promise of correlation with exposure variables based on a preliminary analysis of the more complete set of data.

The Industrial Hygiene section of the Bio-Chem Department was responsible for determining exposure levels experienced by plant workers in the study population. The time-weighted average concentrations of VCl and VCl_2 were measured for each job classification on a yearly basis. It was necessary in several cases to project backwards in order to estimate the exposure levels in years prior to installation of the monitoring devices. Thus, the exposure data for the i^{th} individual consists of a $1 \times n_i$ matrix of yearly TWA exposure levels for the n_i years preceding the date of medical exam. The details of measuring these yearly time-weighted averages will not be discussed here.

The Method of Analysis

The question posed by this study and the methods of data collection made it rather difficult to specify a statistical model for which all assumptions of the model could be met. Since definite medical diagnoses were not available,

the strategy of analysis was to attempt to explain variation in the observed clinical variables by first removing effects resulting from non-environmental factors such as age, and then to see if the unexplained variation could be further reduced by the introduction of variables representing some function of the exposure levels to $VC1$ and $VC1_2$. This led to the use of multiple regression analysis. Obviously, there was no way of arbitrarily selecting the levels of the independent variables. As a result, very few observations occurred at the higher exposure levels which were of most interest. The assumptions that the errors were independently normally distributed with constant variance was not rigorously tested. However, these assumptions appear to be reasonably satisfied.

Findings

(1) Six lab procedures of the eleven under study showed correlations with one or more exposure variables for at least one periodic exam series at the .05 level. These were BSP, B Protein, Icterus Index, Hemoglobin, Systolic and Diastolic Blood Pressure.

(2) All six of these lab tests showed correlations during the 1965-66 period, while only hemoglobin showed a significant correlation at the .05 level prior to this date; that being in 1958. However, two tests, B Protein and Icterus Index, were administered only in 1965-66 and one, the BSP, was obtained only on a limited basis prior to 1965.

(3) In the final analysis much weight is placed on the readings observed for those few employees who experienced high exposure levels, especially in the 1949-58 period of their careers. For example, the average exposure level in 1950 was 153 ppm, whereas the average exposure level for 1965 was 29 ppm.

(4) The BSP test showed the most pronounced correlation with one or more exposure variables.

(5) Three individuals in the study had Time-Weighted-Averages of 595 ppm in 1953. Two of these were given physicals in 1965. The weight of their relatively high exposure levels in the early 50's is evident from Figure I where they represent the two highest time-weighted averages despite average exposure levels in the 60's.

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(6) The correlation between age and TWA concentration of chemical exposure increased as exam dates became more recent with 1965-66 showing the highest correlations.

<u>Year</u>	<u>Correlation</u>
1958	.048
1959-60	.125
1961	.153
1965-66	.361

(7) The average career length as of the 1965-66 physicals was 14.4 years.

(8) A number of interrelated exposure measures were examined, such as dose, number of years of TWA greater than 50, 100, or 200 ppm and several interactions between exposure measures and age or ∇ weight. However, TWA was relied upon where possible because of the ease in presenting and interpreting results.

(9) Although no significant correlations in the 1958-61 BSP readings were detected after removing the weight affect, the mean BSP value for the 16 observations was a high 4.06 and the average exposure level was 120 ppm.

(Tentative) Conclusions

There is strong evidence that several clinical results were influenced by the amount of exposure to VCl and VCl_2 experienced by study subjects. It is not known if the effects are the result of accumulative action over the entire career of the individual or the result of the higher exposure levels experienced prior to 1958. The latter possibility seems more plausible at this time. Effects were detected in 1958 and 1965-66; none were observed in 1959-60 or 1961. A delayed response would account for the effects detected in 1965-66 after the over-all exposure levels had been lowered considerably. Assuming this explanation to be correct, the upper exposure limit could then be set by following back on the careers of those subjects showing effect in 1965 to their exposure levels prior to 1958.

TABLE A. Clinical Measurements Obtained on Members of the Study Population
by Year of Periodic Exam

Clinical Variable	Number of Employees				
	Last PE Prior to VCl Exp	1958	1959	1961	1965
Number of In-Scope Employees	97	87	89	88	92
Weight	96	69	80	72	70
Height	96	69	80	72	70
Blood Pressure, Sys.	96	69	80	69	69
Blood Pressure, Dia.	96	69	80	69	69
BSP		11	4	1	61
Hemoglobin		35		60	44
Hematocrit			74	59	66
Thymol Turbidity				44	66
SGOT					66
Prothrombin			73		
B Protein					58
Icterus Index					16
Alk. Phosphatase			71		

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APPENDIX I

ANOVA TABLES FOR LAB PROCEDURES SHOWING SIGNIFICANT CORRELATIONS WITH ONE OR MORE EXPOSURE VARIABLES

Table 1. ANOVA for BSP readings obtained on 61 employees during 1965-66.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	60	202.7		
Regression	2	108.1	54.05	33.1**
Residuals	58	94.6	1.63	
Lack of Fit	30	61.5	2.05	1.7
Pure Error	28	33.1	1.18	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	Dose prior to 1954	321.6	.70	2.57*
X2	(Yrs of 200+ Exp) ²	3.95	.69	2.24*

Prediction Equation

$$\text{BSP} = 2.28 + .0014 \text{ X1} + .0636 \text{ X2}$$

Table 2. Alternate ANOVA for BSP readings obtained on 61 employees during 1965-66.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	60	202.7		
Regression	2	110.1	55.05	34.4**
Residuals	58	92.6	1.59	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	▽Weight	- 4.59	.20	1.58
X2	(TWA/200) ⁴	.069	.71	8.00**

Prediction Equation

$$\text{BSP} = 2.56 + .011 \text{ X1} + 7.09 \text{ X2}$$

* Significant at .05 level.

** Significant at .01 level.

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Table 3. ANOVA for B Protein readings obtained on 58 employees during 1965-66.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	57	445.0		
Regression	2	63.7	31.85	4.60*
Residuals	55	381.3	6.93	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	▽ Weight	- 5.07	.237	1.60
X2	(TWA/200) ²	.145	.322	2.36*

Prediction Equation

$$B \text{ Prot} = 14.22 + .026 X1 + 3.82 X2$$

Table 4. ANOVA for Icterus Index readings obtained on 16 employees during 1965-66.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	15	50.7		
Regression	3	30.5	10.17	6.03**
Residuals	12	20.2	1.68	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	Age	38.5	- .378	2.92*
X2	(TWA) ²	5601.7	.460	2.44*
X3	(▽ Weight) ²	398.2	- .452	1.99

Prediction Equation

$$\text{Icterus Index} = 12.74 - .143 X1 + .00009 X2 - .0013 X3$$

Table 5. ANOVA for Hemoglobin readings obtained on 35 employees during 1958.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	34	34.20		
Regression	4	15.97	3.99	6.57**
Residuals	30	18.23	.608	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	Age	37.2	-.484	2.27*
X2	History of Jaundice	.20	.303	2.75 *
X3	▽ Weight	-6.66	.070	1.91
X4	(TWA)	108.7	-.368	3.05**

Prediction Equation

$$\text{Hemoglobin} = 16.44 - .038 X1 + 1.1 X2 + .015 X3 - .0048 X4$$

Table 6. ANOVA for Hemoglobin readings obtained on 44 employees during 1965-66.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	43	51.44		
Regression	2	8.24	4.12	3.89*
Residuals	41	43.20	1.06	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	History of Jaundice	.09	.176	2.10*
X2	TWA	61.8	-.270	2.55*

Prediction Equation

$$\text{Hemoglobin} = 14.98 + 1.2 X1 - .0088 X2$$

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Table 7. ANOVA for Systolic Blood Pressure readings on 69 employees during 1965-66.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	68	13983.5		
Regression	3	5002.1	1667.4	12.1**
Residuals	65	8981.4	138.2	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	Age	43.2	.474	2.97**
X2	▽ Weight	- 2.1	.205	2.10*
X3	Age X(Yrs of 100+ Exp)	134.3	.489	2.80**

Prediction Equation

$$\text{Sys. BP} = 104.39 + .48 \text{ X1} + .13 \text{ X2} + .025 \text{ X3}$$

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Table 8. ANOVA for Systolic Blood Pressure readings on 69 employees during 1965-66 (Alternate)

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	68	13983.5		
Regression	3	4530.8	1510.3	10.4**
Residuals	65	9452.7	145.4	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	Age	43.2	.474	3.64**
X2	▽ Weight	- 2.1	.205	2.10*
X3	TWA	60.6	.395	2.05*

Prediction Equation

$$\text{Sys. BP} = 99.47 + .58 \text{ X1} + .13 \text{ X2} + .069 \text{ X3}$$

Table 9. ANOVA for Diastolic Blood Pressure readings on 69 employees during 1965-66.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	68	5285.1		
Regression	3	1618.3	539.4	9.56**
Residuals	65	3666.8	56.4	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	ln Age	3.74	.461	3.50**
X2	▽ Weight	- 2.1	.200	2.13*
X3	ln Age X(Yrs of 100 + Exp)	10.79	.379	1.84

Prediction Equation

$$BP_d = 25.02 + 14.66 X1 + .081 X2 + .126 X3$$

Table 10. ANOVA for Diastolic Blood Pressure readings on 69 employees during 1965-66 (Alternate)

<u>Source</u>	<u>df.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	68	5285.1		
Regression	3	1729.9	576.6	10.54**
Residuals	65	3555.2	54.7	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	ln Age	3.74	.461	3.39**
X2	▽ Weight	- 2.1	.200	2.07*
X3	TWA	60.6	.424	2.35*

Prediction Equation

$$BP_d = 26.09 + 13.94 X1 + .078 X2 + .049 X3$$

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Table 11. ANOVA for the change in Systolic Blood Pressure readings on 68 employees between their pre-exposure physical and their 1965-66 physical.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	67	13357.8		
Regression	3	4823.8	1607.9	12.04**
Residuals	64	8534.0	133.3	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	Δ Age	14.39	.330	1.26
X2	Pre-Exp BP _{sys}	128.47	- .362	3.67**
X3	TWA	58.62	.467	3.19**

Prediction Equation

$$BP_s = 48.59 + .36 X1 - .47 X2 + .12 X3$$

Table 12. ANOVA for the change in Diastolic Blood Pressure readings on 68 employees between their pre-exposure physical and their 1965-66 physical.

<u>Source</u>	<u>d.f.</u>	<u>SS</u>	<u>MS</u>	<u>F-Value</u>
Total	67	6939.2		
Regression	2	2944.3	1472.1	23.95**
Residuals	65	3994.9	61.46	

Coefficients

<u>No.</u>	<u>Variable</u>	<u>Mean</u>	<u>Original Correlation</u>	<u>Coeff/S.E.</u>
X1	Pre-Exp BP _{diad}	80.60	- .546	6.13**
X2	TWA	58.62	.311	3.80**

Prediction Equation

$$BP_d = 54.59 - .73 X1 + .082 X2$$

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APPENDIX II

ANALYSIS OF LAB PROCEDURES FOR YEARS DURING WHICH NO SIGNIFICANT CORRELATION WITH ONE OR MORE EXPOSURE VARIABLES WAS DETECTED AT THE .05 LEVEL AFTER REMOVAL OF AFFECTS DUE TO NON-EXPOSURE VARIABLES

Year	N	Mean	Std Dev	Regression of Non-Exposure Variables	F-Value
<u>Alkaline Phosphatase</u>					
1959	73	7.2	2.0	Alk Phos = 5.4 + .044 (age)	$F_{1,69} = 3.1^1$
<u>Blood Pressure, Diastolic</u>					
PE	96	80.3	8.1	$BP_d = 59.66 + 6.33(\ln \text{ age}) + .055 (\nabla \text{ wt})$	$F_{2,93} = 2.82^1$
1958	69	81.2	9.0	$BP_d = 56.27 + 7.08 (\ln \text{ age}) + .10 (\nabla \text{ wt})$	$F_{2,66} = 3.36^*$
1959	80	79.8	7.7	$BP_d = 49.03 + 8.57 (\ln \text{ age}) + .046 (\nabla \text{ wt})$	$F_{2,77} = 3.84^*$
1961	71	79.9	8.4	$BP_d = 42.41 + 10.36 (\ln \text{ age}) + .13 (\nabla \text{ wt})$	$F_{2,68} = 10.01^{**}$
1965	69	81.0	8.8	See Appendix I	
<u>Blood Pressure, Systolic</u>					
PE	96	127.3	11.6	$BP_s = 119.57 + .31 (\text{age}) + .14 (\nabla \text{ wt})$	$F_{2,93} = 4.78^*$
1958	69	129.2	12.9	$BP_s = 118.75 + .29 (\text{age}) + .10 (\nabla \text{ wt})$	$F_{2,66} = 2.45^1$
1959	80	126.5	11.7	$BP_s = 118.08 + .23 (\text{age}) + .11 (\nabla \text{ wt})$	$F_{2,77} = 3.29^*$
1961	71	130.0	13.4	$BP_s = 114.66 + .40 (\text{age}) + .19 (\nabla \text{ wt})$	$F_{2,68} = 7.69^{**}$
1965	69	128.4	14.3	See Appendix I	
<u>Bromsulphalein</u>					
1959	16	4.06	2.0	Wt itself is not significant at the .10 level - 16 obs. - but after removing its affects no exposure variables can remain in the regression equation.	
1965	61	3.00	1.8	See Appendix I	

1 Significant at .10 level.

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APPENDIX II (Continued)

Year	N	Mean	Std Dev	Regression of Non-Exposure Variables	F-Value
<u>Hematocrit</u>					
1959	74	39.3	2.9	Not sign. correlated with non-exposure variables at .1 level	$F_{1, 58} = 3.82^1$
1961	59	45.1	2.7	48.11 - .072 (age)	
1965	67	47.3	2.5	Not sign. correlated with non-exposure variables at .1 level	
<u>Hemoglobin</u>					
1958	35	14.6	1.0	See Appendix I	$F_{3, 56} = 3.54^*$
1961	60	14.4	.8	Hgb = 15.34 - .023 (age) + .58 (HistJaun) + .0067 (▽ wt)	
1965	44	14.6	1.1	See Appendix I	
<u>Prothrombin</u>					
1959	73	96.0	8.0	P = 89.32 + .17 (age)	$F_{1, 72} = 2.98^1$
<u>Serum Glutamic Oxaloacetic Transaminase</u>					
1965	66	21.1	7.7	SGOT = 27.9 - .16 (age)	$F_{1, 65} = 2.92^1$
<u>Thymol Turbidity</u>					
1961	45	1.53	1.2	T = 1.59 + .014 (▽ wt)	$F_{1, 44} = 3.17^1$
1965	66	2.30	1.5	Not sign. correlated with non-exposure variables at .1 level	