Benzene 11036 Regulation Risk Assessment Hematology

PRELIMINARY REPORT OF PLIOFILM COHORT HEMATOLOGY

Hematologic Effects of Benzene: A 35 yr Longitudinal Study of Rubber Workers

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Howard M. Kipen, H.D., M.P.H
Ronald P. Cody, ED.D
Paul J. Lioy, PH.D
Bernard D. Goldstein, H.D.

Department of Environmental & Community Medicine
UMDNJ - Rutgers Medical School
Piscataway, New Jersey
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PRELIMINARY HEMATOLOGY REPORT

INTRODUCTION

The following is a report on the quantitative relationship between estimated benzene exposures and hematologic monitoring data in a subset of a cohort of rubber hydrochloride workers. The analysis is preliminary in nature because of a number of factors which are discussed subsequently.

The mortality experience of a cohort of 748 rubber hydrochloride workers with at least one day of exposure to benzene was originally reported in 1977 and updated in 1987 to include subsequent deaths (Infante et al., 1977; Rfnsky et al., 1981). Two quantitative estimates of the benzene exposures for this cohort have been constructed (Crump and Allen, 1984; Rinsky et al. 1985). This report examines the quantitative relationship between these benzene esposure estimates and hematologic monitoring data on a group of the workers.

METHODS

The entire cohort of 748 represents workers from three separate plants in two locations. NIOSH provided to API work records on approximately 400 deceased members of the cohort. Of these 400 records, 135 (all from the St Marys plant, NIOSH location 1) included some hematologic monitoring data on the workers. We were provided with 85 individual records far this preliminary analysis as the remaining 50 had only preemployment blood counts or only single counts, or because the results were not recorded on standard record forms. Future analyses will attempt to incorporate the limited records for these 50 employees.

For each individual, a cover sheet displayed demographic data and a chronologic work history of all rubber

beginning and ending dates. Each separate job (time period) for each individual was linked to its estimated benzene exposure according to the Crump estimate of exposure (Crump and Allen, 1984, Appendix B). Similarly each job was linked to its estimated benzene exposure according to the Rinsky estimates of exposure (Rinsky et al., 1985). Some of the exposure estimates were rounded off to the nearest 5 ppm to facilitate data entry.

Hematology data consisted of RBC, WBC, hemoglobin, and differential counts (polys, large lymphocytes, small lymphocytes, monocytes, eosinophils, and basophils) recorded from blood samples on various dates. No analyses were completed on the monocytes, eosinophils, and basophils.

There were an average of three different levels of exposure for each of the 85 individuals in the analysis. Among the 85 individuals, 3991 separate blood samples were legibly recorded. For an individual there ranged from one to 200 blood samples at each separate estimated exposure level.

When individual sample values for a specific cell count could not be read from the data sheets, they were left out, but the other values for that blood sample date were recorded as long as the date of the sample was legible. Approximately 5% of the blood samples were not recorded because of illegible dates.

At any given exposure for an individual all samples were averaged, and the mean for each of the recorded parameters (WBC, RBC, etc.), was used in the subsequent analysis. This yielded 230 separate points that represented the mean of blood counts at one exposure level for one individual in each scheme of estimation, Crump or Rinsky. When a single exposure level was attributed to

one individual during discontinuous time periods (e.g., exposure at 10 ppm for one year in 1950 and again for six months in 1957) all of the corresponding blood samples would be averaged from both time periods. This gave one data point at an exposure category for that person.

STATISTICAL ANALYSIS

Correlation matrices and linear regressions were calculated between exposures and blood counts for all 85 subjects.

A one way analysis of variance with repeated measures compared the blood counts at each individual's highest and lowest exposure estimates. Those subjects with only one exposure value had to be excluded, leaving 55 to 58 subjects for each of the analyses of variance (depending on blood cell type and exposure estimate).

This same approach was also used to regress the differences in blood counts against the differences in exposure at an individuals' highest and lowest exposures. As with the ANOVA above, those subjects with only one exposure had to be excluded. This analysis was performed without constraining the regression line to go through the origin.

Blood counts were additionally plotted as a function of time to assess the presence of any secular trends. The SAS statistical program was used for all analyses.

RESULTS

Crump Estimates

The Crump exposure estimate was significantly correlated with WBC ($r = -0.21$, $p = 0.0012$), explaining 4% of the WBC variance. This

correlation improved significantly ($r = -0.34$, $p = 0.001$) when only samples taken at estimated exposures greater than or equal to 40 ppm were included in the analysis. The regression explained 11.5% of the variance. If the data from estimated exposure levels greater than 250 ppm are excluded (55 samples), the correlation between WBC and the Crump estimate of exposure becomes nonsignificant ($r = -0.07$, $p = 0.29$).

For the Crump estimates, RBC counts correlated somewhat better with all exposures ($r = -0.29$, $p = 0.001$) than did the WBC counts discussed above. 8% of the variance was explained by the regression.

Hemoglobin and total lymphocyte counts were not significantly correlated with the Crump exposure estimate.

A one way analysis of variance with repeated measures compared UBC counts between an individuals' highest and lowest Crump exposure estimates. This resulted in a $p = 0.062$. Mean WBC at high exposure was 9575, and at low exposure it was 10,075. The biological significance of this difference is not apparent. For RBC this ANOVA was not significant ($p = 0.096$).

Using the Crump exposure estimates, WBC differences were not significantly correlated with exposure differences ($r = -0.198$, $p = 0.14$). For RBC differences there was a significant correlation ($r = -0.288$, $p = 0.03$). Neither intercept was significantly different from zero.

Rlnsky Estimates

The Rinsky exposure estimate correlated with mean WBC counts at $r = -0.13$ ($p = 0.056$), and explained 1.7% of the variance in WBC count. There was some improvement in the

the regression of WBC counts was conducted only with Rinsky exposure estimates greater than or equal to 20 ppm ($r = -0.19$, $p = 0.047$).

For RBC counts there was no correlation with the Rinsky exposure estimates, ($r = -0.05$, $p = 0.42$), and hemoglobin and total lymphocyte count were also not correlated with the Rinsky exposure estimates.

The one way analysis of variance with repeated measures for WBC at highest and lowest estimated exposures in an individual was not significant for the Rinsky estimates ($p = 0.98$). This ANOVA was similarly not significant for RBC counts ($p = 0.98$).

Using the Rinsky estimates for both WBC ($r = 0.248$, $p = 0.07$) and for RBC ($r = 0.118$, $p = 0.39$), the differences in counts were not significantly correlated with differences in exposures. Neither intercept was Significantly different from zero. It should also be noted that the nearly significant r value for WBC using the Rinsky estimates was for a positive slope, contrary to biological expectation of benzene's depressant action on hematopoesis.

Further Analyses

Lagging exposures by 90 days relative to the dates of blood sampling, so that a given sample was compared with exposures which occurred 90 days previously (rather than at the time of blood sampling), did not appreciably change any of the correlations for either exposure estimate. Further analysis might entail more detailed exploration of this relationship.

There was no appreciable secular trend up or down in either mean

WBC or RBC over the 35 years that members of the cohort were sampled. Individual abnormal counts may have occured more frequently during the earlier, high exposure years of the 1940's, ,suggesting further analysis.

Review of samples from seven workers known to have died of hematologic malignancies did not reveal a consistent pattern of low WBC (less than 5000) or RBC (less than 4 million) as premonitory of later development of disease. Of these seven workers however, only one had acute myelogenous leukemia , the malignancy most clearly demonstrated to be causally related to benzene exposure.

DISCUSSION

When all exposure/samples were used in the analysis, for both RBC and WBC the Crump estimates seemed better correlated with the observed fluctuations in blood counts than the Rinsky estimates . For both Crump and Rinsky the higher- ends of their exposure estimates (greater than or equal to 40 and *20,* repectively) were better correlated with counts than were the lower ends. Although truncating the data by eliminating lower exposures still favored the Crump estimate at higher exposures, the absence of Crump exposure estimates between 120 and 259 makes it hard to rely on the findings. These data do not allow any conclusions with regard to lower exposures on the order of 40 ppm and less.

The Crump estimate has obvious statistical outliers at the exposure estimates of *250* to 260 ppm during which time 55 samples were drawn on 12 individuals. The next lower exposure estimates are 50% less at approximately 120 ppm. If these *55* data points are excluded (approximately 1% of all samples), the correlation

0.07, p = 0.29).

The fact that the Crump exposure estimates correlate more strongly with WBC and RBC does not confirm his absolute exposure levels. Even though the results do suggest that a high exposure did occur, the absolute concentration of the high value had little impact on the analysis. For instance a preliminary analysis of a modified Crump estimate was conducted arbitrarily substituting 150 ppm for all 55 values in the 250 to 260 ppm range. The correlation with WBC was decreased only slightly from r = -0.21 (p = 0.001) to r = -0.19 (p = 0.003), explaining 3.7% rather than 4.4% of the variance in blood counts.

Mathematically identical relationships would have been found had Crump's exposure values been, for example, ten tines loner, or Rinsky's ten times higher. The fact that Crump rated the exposures for these twelve workers proportionally higher than his other exposure values was responsible for the significant exposure / blood count relationships. It bears reemphasizing that even the Crump data fail to show any significant relationship with hematologic variables when these highest values are removed.

A number of limitations of this data set and the analysis applied need--to be acknowledged. This is a partial data set, and it is not known exactly how individuals were selected for surveillance nor why only workers from one of the three locations were monitored. We have already acknowledged the illegibility of some blood count data. Additionally bias may have been introduced in deciphering handwritten figures (e.g., similar appearance of the numbers "2" and "7").

In the correlation tables, hemoglobin and and RBC are only correlated at r = 0.36, and biologically this is expected to be higher since they essentially measure the same parameter. Furthermore although not statistically significantly, they correlated in opposite directions with the exposure estimates. This implies some degree of inaccuracy and unreliablility in the measurement of the blood sample data.

The earlier and higher exposures tended to be represented by. fewer blood samples than did the later exposures. This was apparently due to changes in surveillance protocols, as well as shorter durations at any individual exposure level in earlier years. At times, abnormally low and occasionally abnormally high counts seemed to generate repeated samples on almost a daily basis for short periods of time, It is likely that workers also were transferred from areas of higher estimated exposure when counts were demonstrably abnormal. Both of these practices may produce bias in the sample. The correlations obtained in this analysis are relatively weak and may be related to other factors in addition to benzene exposure such as intercurrent illness, medications, or alcohol use.

The data points are not independent because of the multiple levels of exposure that were experienced by one person. The analyses conducted used the average of the blood counts determined for a worker at a given exposure. Therefore the regressions have some covariance between data points. However the ANOVA was performed within individual subjects and is not subject to this limitation. Results of the ANOVA were relatively consistent with the regressions.

Although we did not observe a secular trend in the counts,

changes in techniques for counting (e.g., the introduction of automated counting techniques) may have systematically influenced the sample data, possibly obscuring real trends which were present, or falsely suggesting the presence of trends.

REFERENCES

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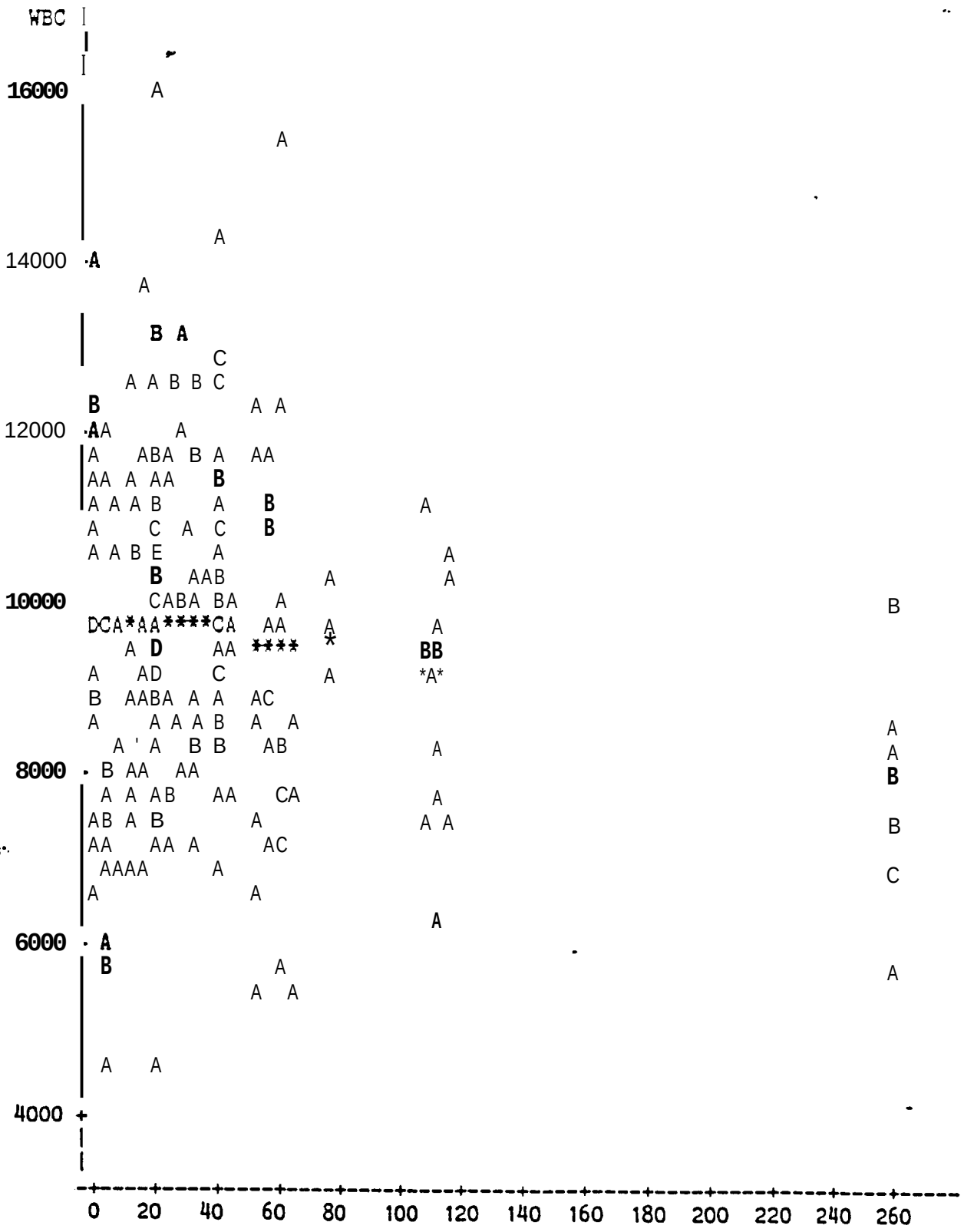
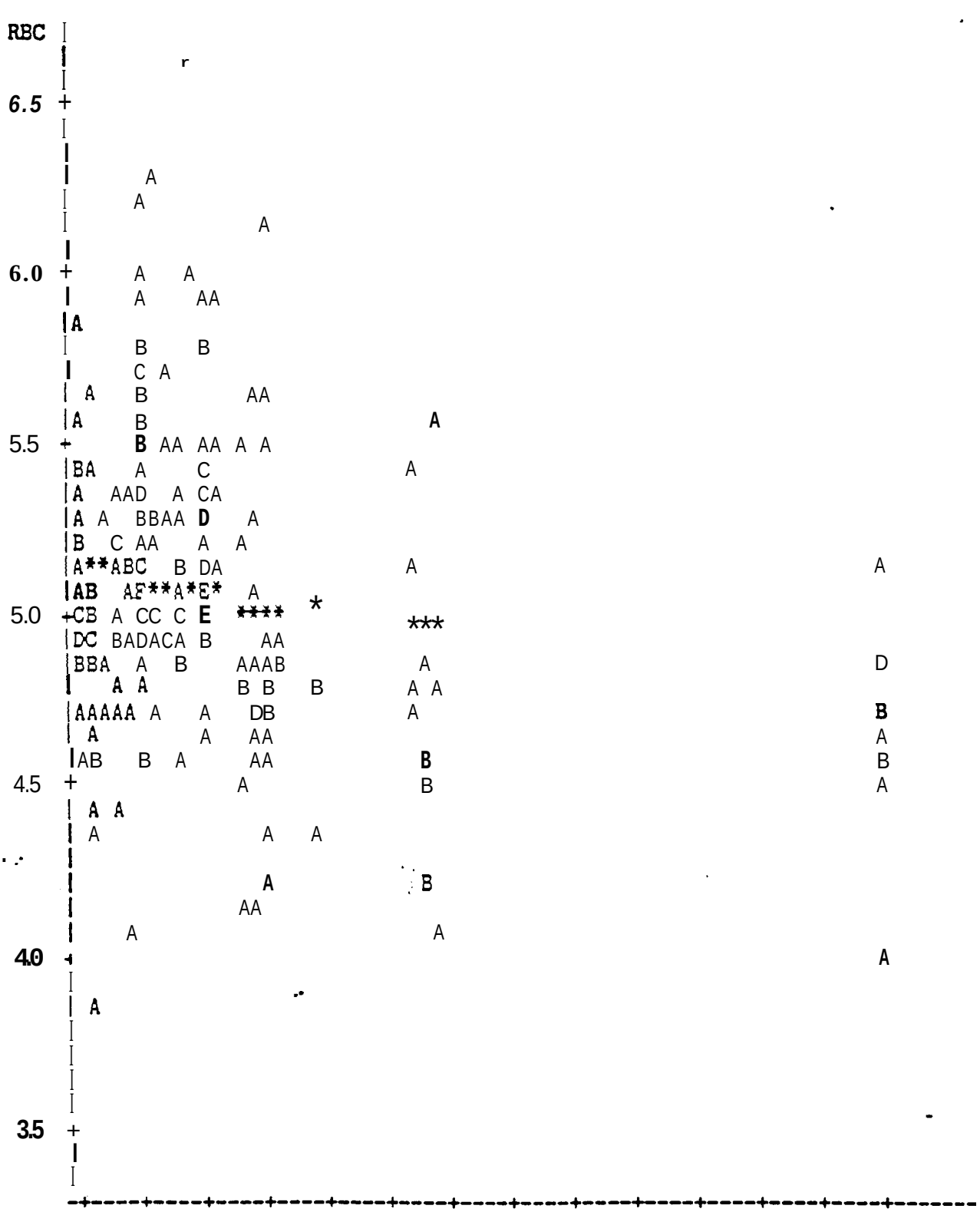
4.) Rinsky RA, Smith AB, Hornung R, Filloon TC, Young RJ, Okun AH, Landrigan PJ (1985): Benzene and leukemia: An epidemiologic risk assessment. USDHEW, PHS, CDC, NIOSH.

Plot of WBC*CRUMP Legend: A = 1 obs, B = 2 obs, etc.
Plot of PREDICTED WBC*CRUMP Symbol used is *



Plot of RBC*CRUMP Legend: A = 1 obs. B = 2 obs. etc.
Plot of PREDICTED RBC*CRUMP Symbol used is *



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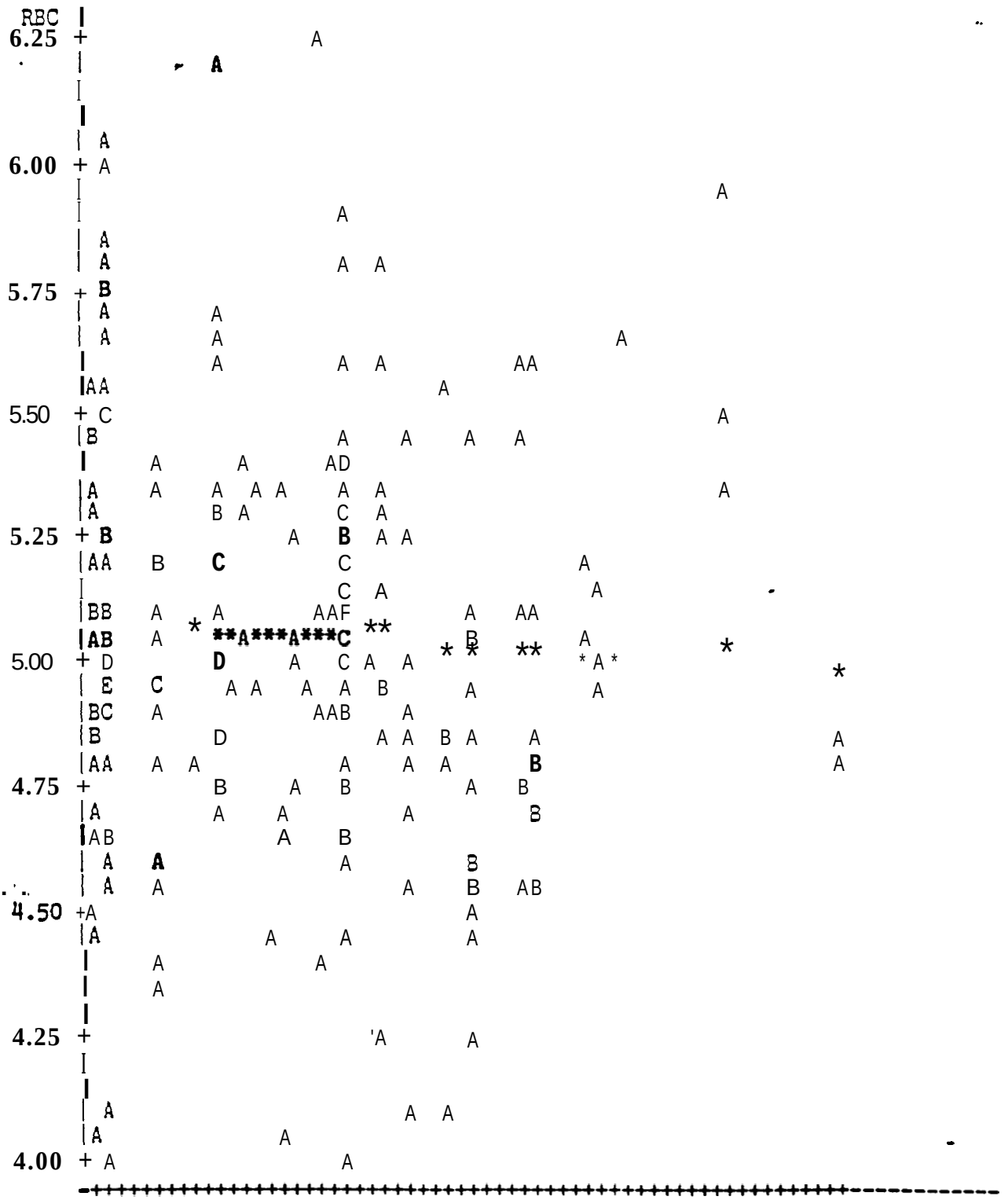

Plot of WBC*RINSKY Legend: A = 1 obs, B = 2 obs, etc.
Plot of PREDICTED WBC*RINSKY Symbol used is *

