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MEMORANDUM

SUBJECT: Pirate Qualitative Risk Assessment Based On Sprague-Dawley Crl:CD BR Rat Dietary Study

P.C. Code 129093

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Background

A chronic oral toxicity study with Pirate in Sprague-Dawley Crl:CD BR rats was conducted by Hazleton Washington, Incorporated, Vienna, Virginia, for American Cyanamid Company, Agricultural Research Division, Princeton, New Jersey, and completed August 23, 1994 (ID HWA 362-206; MRID No. 434928-37).

The study design allocated groups of 55 rats per sex to dose levels of 0, 60, 300, or 600 ppm of Pirate for 105 weeks. An additional 10 rats per sex per dose were designated for interim sacrifice at week 53.

Survival Analyses

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Pirate in male rats. Female rats showed a significant decreasing trend for mortality with increasing doses of Pirate. See Tables 1 and 2 for mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Male rats had significant increasing trends in hepatocellular adenomas, hepatocellular adenomas and/or carcinomas combined, malignant histiocytic sarcomas, and testes interstitial cell tumors, all at $p < 0.05$. Male rats also had a significant increasing trend in malignant histiocytic sarcomas and/or malignant lymphocytic lymphomas combined at $p < 0.01$. There was a significant difference in the pair-wise comparison of the 600 ppm dose group with the controls for malignant histiocytic sarcomas and/or malignant lymphocytic lymphomas combined at $p < 0.05$. Malignant histiocytic sarcomas and malignant lymphocytic lymphomas were combined at the request of the reviewer.

Female rats had a significant increasing trend in uterine endometrial stromal polyps at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls for uterine endometrial stromal polyps. Mammary gland fibroadenomas and carcinomas showed no statistically significant increasing trends for either tumor type. There was a significant difference in the pair-wise comparison of the 60 ppm dose group with the controls for mammary gland fibroadenomas at $p < 0.05$.

The statistical analyses of the male rats were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. The statistical analyses of the female rat mammary tumors were based upon Peto's Prevalence Test since there was a statistically significant negative trend for mortality with increasing doses of Pirate in female rats. Female rat uterine polyps were analyzed using the Exact trend test and the Fisher's Exact test for pair-wise comparisons because all tumors were observed at terminal sacrifice. See Tables 3 through 7 for tumor analysis results.

Table 1. Pirate - Sprague-Dawley Crl:CD BR Rat Study

Male Mortality Rates* and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53[i]	53-78	79-105[f]	Total
0	2/65	1/63	10/62	0/52	19/51[a]	22/54 (41)
60	0/65	0/65	10/65	9/55	10/46	19/55 (35)[n]
300	0/64[b]	0/64	10/64	2/54	23/52	25/54 (46)
600	1/64[c]	2/63	10/61	7/50[c]	8/43	18/53 (34)[n]

*Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

[a]One accidental death at week 104, dose 0 ppm.

[b]One accidental death at week 13, dose 300 ppm.

[c]Two accidental deaths, one each at weeks 26 and 78, dose 600 ppm.

[n]Negative change from control.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Pirate - Sprague-Dawley Crl:CD BR Rat Study

Female Mortality Rates[*] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	0/65	1/65	10/64	11/54	23/42[a]	35/54 (65)**[n]
60	0/65	0/65	10/65	6/55	29/46[b]	35/52 (67)
300	1/65	1/64	10/63	7/53	22/46	31/55 (56)[n]
600	0/65	0/65	10/65	2/55	23/53	25/55 (45)**[n]

[*]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

[a]One accidental death at week 78, dose 0 ppm.

[b]Three accidental deaths, one at week 78 and two at week 104, dose 60 ppm.

[n]Negative trend or negative change from control.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Pirate - Sprague-Dawley Crl:CD BR Rat Study

Male Liver Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	60	300	600
Adenomas (%)	0/51 (0)	0/55 (0)	3[a]/54 (6)	3/50 (6)
p =	0.022*	1.000	0.132	0.118
Carcinomas (%)	3/51 (6)	0/55 (0)	2[b]/54 (4)	2/50 (4)
p =	0.421	0.108[n]	0.473	0.510
Combined (%)	3/51 (6)	0/55 (0)	5/54 (9)	5/50 (10)
p =	0.045*	0.108[n]	0.390	0.346

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54. Also excludes week 53 interim sacrifice animals.

[a]First adenoma observed at week 105, dose 300 ppm.

[b]First carcinoma observed at week 88, dose 300 ppm.

[n]Negative change from control.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Pirate - Sprague-Dawley Crl:CD BR Rat Study

Male Malignant Histiocytic and Lymphocytic Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	60	300	600
Histiocytic Sarcomas	0/51	1/55	1/54	[a]4/50
(%)	(0)	(2)	(2)	(8)
p =	0.012*	0.519	0.514	0.056
Lymphocytic Lymphomas	[b]1/54	2/55	0/54	4/53
(%)	(2)	(4)	(0)	(8)
p =	0.087	0.507	0.500[n]	0.176
Combined	1/54	3/55	1/54	8/53
(%)	(2)	(5)	(2)	(15)
p =	0.005**	0.316	0.752	0.015*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54 for histiocytic sarcomas, or before week 19 for lymphocytic lymphomas and combined. Also excludes week 53 interim sacrifice animals.

[a]First histiocytic sarcoma observed at week 58, dose 600 ppm.
[b]First lymphocytic lymphoma observed at week 19, dose 0 ppm.

[n]Negative change from control.

Note: One animal in the 600 ppm dose group of the interim sacrifice group had a lymphocytic lymphoma. Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. Pirate - Sprague-Dawley Crl:CD BR Rat Study

Male Testes Interstitial Cell Tumor Rates[†] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	60	300	600
Interstitial Cell Tumors (%)	3/51 (6)	1[a]/55 (2)	3/54 (6)	7/50 (14)
p =	0.019[*]	0.281[n]	0.633	0.151

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54. Also excludes week 53 interim sacrifice animals.

[a]First interstitial cell tumor observed at week 84, dose 60 ppm.

[n]Negative change from control.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 6. Pirate - Sprague-Dawley Crl:CD BR Rat Study

Female Mammary Gland Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0	60	300	600
Fibro-adenomas (%)	27/52 (52)	35/50 (70)	24/46 (52)	19[a]/55 (35)
p =	0.9995[n]	0.024*	0.440	0.992[n]
Carcinomas (%)	11/52 (21)	12/50 (24)	16/46 (35)	15[b]/55 (27)
p =	0.227	0.451	0.053	0.225

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor. Also excludes week 53 interim sacrifice animals.

[a]First fibroadenoma observed at week 60, dose 600 ppm.

[b]First carcinoma observed at week 60, dose 600 ppm.

[n]Negative trend or negative change from control.

Note: One animal in the control group and two animals in the 60 ppm dose group of the interim sacrifice group had mammary gland fibroadenomas. Two animals in the 300 ppm dose group and one animal in the 600 ppm dose group of the interim sacrifice group had mammary gland carcinomas. Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 7. Pirate - Sprague-Dawley Crl:CD BR Rat Study

Female Uterine Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	60	300	600
Endometrial Stromal Polyps (%)	0/19 (0)	0/7 (0)	0/8 (0)	5[a]/30 (17)
p =	0.019*	-	-	0.075

[+]Number of tumor bearing animals/Number of animals examined at the terminal sacrifice.

[a]Endometrial stromal polyps were only observed at week 105 in terminally sacrificed animals at the 600 ppm dose group.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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References

Armitage, P. (1955) Tests for Linear Trends in Proportions and Frequencies. Biometrics 11, 375-386.

Cochran, W.G. (1954) Some Methods for Strengthening the Common X^2 Test. Biometrics 10, 417-451.

Cox, D.R. (1972) Regression Models and Life Tables (with discussion). J. Royal Stat. Soc. Ser. B. 34, 187-220.

Gart, J.J., D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf (1986) The Design and Analysis of Long-Term Animal Experiments. In: Statistical Methods in Cancer Research, Volume III. IARC Scientific Publications No. 79. Lyon, France: International Agency for Research on Cancer, p. 18.

Peto, R., M. Pike, N. Day, R. Gray, P. Lee, S. Parish, J. Peto, S. Richard, and J. Wahrendorf (1980) Guidelines for Simple, Sensitive, Significant Tests for Carcinogenic Effects in Long-Term Animal Experiments. In: Monographs on the long-term and short-term screening assays for carcinogens: a critical appraisal. IARC Monographs, Supplement 2. Lyon, France: International Agency for Research on Cancer, pp. 311-426.

Thomas, D.G., N. Breslow, and J.J. Gart (1977) Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research 10, 373-381.