Huntingdon Life Sciences

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MESSAGE: Study No. 96-4080 - Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats

This fascimile includes the following summary data for the above referenced study for your review:

Tables

1. Summary of In-Life Physical Observations
2. Mean Body Weights
3. Mean Food Consumption
4. Percent Difference in Body Weight from Control

Appendix
A. Methodology and References

Please contact me with any questions.

Best Regards,

Raymond E. Schroeder
Study Director

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TABLE 1
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

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SUMMARY OF IN-LIFE PHYSICAL OBSERVATIONS - MALES

| | WEEK: | -1 | 0 | 1 | 2 |
|---|---|---|---|---|---|
| # OF ANIMALS EXAMINED | I | 30 | 0 | 30 | 30 |
| | II | 30 | 0 | 30 | 30 |
| | III | 30 | 0 | 30 | 30 |
| | IV | 30 | 0 | 30 | 30 |
| NORMAL | | | | | |
| WITHIN NORMAL LIMITS | I | 30 | - | 29 | 29 |
| | II | 30 | - | 30 | 29 |
| | III | 30 | - | 30 | 29 |
| | IV | 30 | - | 30 | 30 |
| DERMAL-GENERAL | | | | | |
| ULCERATION - CERVICAL | I | 0 | - | 0 | 1 |
| | II | 0 | - | 0 | 0 |
| | III | 0 | - | 0 | 0 |
| | IV | 0 | - | 0 | 0 |
| ALOPECIA - EXTREMITIES/SNOUT | I | 0 | - | 0 | 0 |
| | II | 0 | - | 0 | 1 |
| | III | 0 | - | 0 | 0 |
| | IV | 0 | - | 0 | 0 |
| OCULAR | | | | | |
| LACRIMATION - UNILATERAL | I | 0 | - | 1 | 0 |
| | II | 0 | - | 0 | 0 |
| | III | 0 | - | 0 | 0 |
| | IV | 0 | - | 0 | 0 |
| CHROMODACRYORRHEA - UNILATERAL | I | 0 | - | 1 | 0 |
| | II | 0 | - | 0 | 0 |
| | III | 0 | - | 0 | 0 |
| | IV | 0 | - | 0 | 0 |
| ORAL/BUCCAL | | | | | |
| INCISORS MALOCCLUDED | I | 0 | - | 0 | 0 |
| | II | 0 | - | 0 | 0 |
| | III | 0 | - | 0 | 1 |
| | IV | 0 | - | 0 | 0 |

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TABLE 1 (cont.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

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SUMMARY OF IN-LIFE PHYSICAL OBSERVATIONS - FEMALES

| | WEEK: | -1 | 0 | 1 | 2 |
|---|---|---|---|---|---|
| # OF ANIMALS EXAMINED | I | 30 | 0 | 30 | 30 |
| | II | 30 | 0 | 30 | 30 |
| | III | 30 | 0 | 30 | 30 |
| | IV | 30 | 0 | 30 | 30 |
| NORMAL | | | | | |
| WITHIN NORMAL LIMITS | I | 30 | - | 30 | 30 |
| | II | 30 | - | 30 | 30 |
| | III | 30 | - | 30 | 30 |
| | IV | 30 | - | 30 | 29 |
| OCULAR | | | | | |
| LACRIMATION - UNILATERAL | I | 0 | - | 0 | 0 |
| | II | 0 | - | 0 | 0 |
| | III | 0 | - | 0 | 0 |
| | IV | 0 | - | 0 | 1 |
| CHROMODACRYORRHEA - UNILATERAL | I | 0 | - | 0 | 0 |
| | II | 0 | - | 0 | 0 |
| | III | 0 | - | 0 | 0 |
| | IV | 0 | - | 0 | 1 |
| ORAL/BUCCAL | | | | | |
| ORAL SORE | I | 0 | - | 0 | 0 |
| | II | 0 | - | 0 | 0 |
| | III | 0 | - | 0 | 0 |
| | IV | 0 | - | 0 | 1 |

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TABLE 2
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

BODY WEIGHT IN GRAMS
MALES
DOSE LEVEL: PPM

| STAT SYMBOL: | WEEK | | 0.0000 | 10.0000 | 100.0000 | 1100.0000 |
|---|---|---|---|---|---|---|
| A-L- | -1 | MEAN | 161.0 | 161.0 | 161.1 | 160.9 |
| | | S.D. | 9.3 | 9.3 | 9.4 | 9.4 |
| | | N | 30 | 30 | 30 | 30 |
| A-L- | 0 | MEAN | 233.3 | 237.7 | 236.6 | 234.3 |
| | | S.D. | 11.6 | 15.3 | 12.6 | 14.0 |
| | | N | 30 | 30 | 30 | 30 |
| A-L- | 1 | MEAN | 274.5 | 279.6 | 277.8 | 272.4 |
| | | S.D. | 13.4 | 19.0 | 14.5 | 16.6 |
| | | N | 30 | 30 | 30 | 30 |
| A-L- | 2 | MEAN | 314.2 | 322.1 | 321.7 | 318.3 |
| | | S.D. | 16.5 | 23.5 | 17.9 | 20.5 |
| | | N | 30 | 30 | 30 | 30 |

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TABLE 2 (cont.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

BODY WEIGHT IN GRAMS
FEMALES
DOSE LEVEL: PPM

| STAT SYMBOL: | WEEK | | 0.0000 | 10.0000 | 100.0000 | 1100.0000 |
|---|---|---|---|---|---|---|
| A-L- | -1 | MEAN | 116.5 | 116.2 | 116.5 | 116.7 |
| | | S.D. | 6.0 | 6.1 | 5.7 | 5.8 |
| | | N | 30 | 30 | 30 | 30 |
| A-L- | 0 | MEAN | 158.0 | 158.5 | 156.3 | 157.0 |
| | | S.D. | 7.5 | 9.1 | 9.3 | 7.7 |
| | | N | 30 | 30 | 30 | 30 |
| A-L- | 1 | MEAN | 177.1 | 173.8 | 178.1 | 175.8 |
| | | S.D. | 9.7 | 9.5 | 12.1 | 9.3 |
| | | N | 30 | 30 | 30 | 30 |
| A-L- | 2 | MEAN | 196.4 | 197.3 | 199.1 | 197.1 |
| | | S.D. | 11.9 | 10.4 | 14.1 | 11.7 |
| | | N | 30 | 30 | 30 | 30 |

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TABLE 3

VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

FOOD CONSUMPTION G/KG/DAY
MALES
DOSE LEVEL: PPM

| STAT SYMBOL: | WEEK | | 0.0000 | 10.0000 | 100.0000 | 1100.0000 |
|---|---|---|---|---|---|---|
| | | | | | * | |
| AL-Q | 0 | MEAN | 122.6 | 125.1 | 127.1 | 124.8 |
| | | S.D. | 6.2 | 4.4 | 5.1 | 6.6 |
| | | N | 29 | 30 | 30 | 30 |
| A-L- | 1 | MEAN | 84.3 | 84.7 | 85.3 | 83.2 |
| | | S.D. | 4.1 | 3.4 | 4.2 | 4.1 |
| | | N | 30 | 30 | 30 | 30 |
| | | | | | ** | |
| A-L-Q- | 2 | MEAN | 74.3 | 76.5 | 78.2 | 76.4 |
| | | S.D. | 5.4 | 3.3 | 3.7 | 4.0 |
| | | N | 30 | 30 | 30 | 30 |

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TABLE 3 (cont.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

FOOD CONSUMPTION G/KG/DAY
FEMALES
DOSE LEVEL: PPM

| STAT SYMBOL: | WEEK | | 0.0000 | 10.0000 | 100.0000 | 1100.0000 |
|---|---|---|---|---|---|---|
| A-L* | 0 | MEAN | 131.8 | 133.5 | 134.9 | 134.9 |
| | | S.D. | 5.9 | 9.4 | 7.8 | 8.0 |
| | | N | 29 | 29 | 28 | 26 |
| AL-B | 1 | MEAN | 92.1 | 89.4 | 93.6 | 90.4 |
| | | S.D. | 4.5 | 4.7 | 7.5 | 5.7 |
| | | N | 30 | 28 | 29 | 27 |
| K-J | 2 | MEAN | 88.8 | 89.0 | 90.8 | 89.1 |
| | | S.D. | 8.8 | 4.7 | 8.2 | 7.4 |
| | | N | 30 | 30 | 30 | 30 |

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TABLE 4
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

% DIFFERENCE IN BODY WEIGHT
MALES
DOSE LEVEL: PPM

| WEEK | | 0.0000 | 10.0000 | 100.0000 | 1100.0000 |
|---|---|---|---|---|---|
| -1 | % DIFF | 0.0 | 0.0 | 0.1 | -0.1 |
| | N | 30 | 30 | 30 | 30 |
| 0 | % DIFF | 0.0 | 1.9 | 1.4 | 0.4 |
| | N | 30 | 30 | 30 | 30 |
| 1 | % DIFF | 0.0 | 1.9 | 1.2 | -0.8 |
| | N | 30 | 30 | 30 | 30 |
| 2 | % DIFF | 0.0 | 2.5 | 2.4 | 1.3 |
| | N | 30 | 30 | 30 | 30 |

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TABLE 4 (cont.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

% DIFFERENCE IN BODY WEIGHT
FEMALES
DOSE LEVEL: PPM

| WEEK | | 0.0000 | 10.0000 | 100.0000 | 1100.0000 |
|---|---|---|---|---|---|
| -1 | % DIFF | 0.0 | -0.3 | 0.0 | 0.2 |
| | N | 30 | 30 | 30 | 30 |
| 0 | % DIFF | 0.0 | 0.3 | -1.1 | -0.6 |
| | N | 30 | 30 | 30 | 30 |
| 1 | % DIFF | 0.0 | -1.9 | 0.6 | -0.7 |
| | N | 30 | 30 | 30 | 30 |
| 2 | % DIFF | 0.0 | 0.5 | 1.4 | 0.4 |
| | N | 30 | 30 | 30 | 30 |

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Appendix A
Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats

Methodology and References - Statistical Analysis

Parameters analyzed statistically for this status report: body weights and food consumption

| MULTIPLE GROUP ANALYSIS STAT SYMBOL | | | STATISTICAL STATEMENT |
|---|---|---|---|
| No Sig | p≤0.05 | p≤0.01 | |
| Parametric | | | |
| A- | | | No statistical differences among the means (parametric ANOVA). |
| | A | A+ | The means differ significantly (parametric ANOVA). |
| L- | | | The response is not linearly related to the dose levels. |
| | L | L+ | The response is linearly related to the dose levels. |
| | Q | Q+ | The response shows a lack of fit. |
| | * | ** | Significantly different from control (Dunnett's). |

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Appendix A (cont.)
Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats

Methodology and References - Statistical Analysis

| MULTIPLE GROUP ANALYSIS STAT SYMBOL | | | STATISTICAL STATEMENT |
|---|---|---|---|
| No Sig | p≤0.05 | p≤0.01 | |
| Nonparametric | | | |
| K- | | | No statistical differences among the means (Kruskal-Wallis, nonparametric). |
| | K | K+ | The means differ significantly (Kruskal-Wallis nonparametric). |
| J- | | | There is not an ordered response to dosage. |
| | J | J+ | There is an ordered response to dosage. |
| | * | ** | Significantly different from control (Dunn's Rank Sum). |
| NT | | | Not tested due to lack of variance. |

Statistical evaluation of equality of means was made by the appropriate one way analysis of variance technique, followed by a multiple comparison procedure if needed. First, Bartlett's test was performed to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not, nonparametric procedures were used. The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from the control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from control.

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Appendix A (cont.)
Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats

Methodology and References - Statistical Analysis

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A statistical test for trend in the dose levels was also performed. In the parametric case (i.e., equal variance) standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1%, two-sided risk level. All other statistical tests were conducted at the 5% and 1%, two-sided risk level.

References for these techniques are Snedecor, G.W., and Cochran, W.G., *Statistical Methods*. 6th edition, Iowa State University Press (1967); Hollander, M. and Wolfe, D.A., *Nonparametric Statistical Methods*. John Wiley and Sons, New York (1973); Dunnett, C.W., *J. Am. Sta. Assn.* Vol. 50 (1955) and *Biometrics*. Vol. 20 (1964).

| | | |
|---|---|---|
| Bartlett's Test | pp. 296-298 | S&C |
| ANOVA | pp. 277-279 | S&C |
| Dunnett's | pp. 1096-1121 | D |
| | pp. 482-491 | Bio |
| Kruskal-Wallis | pp. 114-116 | H&W |
| Summed Rank Test (Dunn) | p. 131 | H&W |
| Regression Analysis | | |
| Trend | pp. 135-153 | S&C |
| Lack of Fit | pp. 456-459 | S&C |
| Jonckheere's Statistic | pp. 120-123 | H&W |