

Huntingdon Life Sciences

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ATTENTION OF: Dr. J. Knaak

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DATE: 27 February 1997

CC: Dr. Hasmukh Shah
Chemical Manufacturers
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Arlington, VA 22209

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

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

Tables

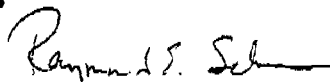
1. Summary of In-Life Physical Observations
2. Mean Body Weights
3. Percent Difference in Body Weight from Control
4. Mean Food Consumption

Appendix

- A. Methodology and References

Please contact me with any questions.

Best Regards,


Raymond E. Schroeder
Study Director

CMA 118813

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T 1-1

TABLE 1

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

96-4080

SUMMARY OF IN-LIFE PHYSICAL OBSERVATIONS - MALES

WEEK:	-1	1	2	3	4	5	6	7
# OF ANIMALS EXAMINED								
I	30	30	30	30	30	30	30	30
II	30	30	30	30	30	30	30	30
III	30	30	30	30	30	30	30	30
IV	30	30	30	30	30	30	30	30

NORMAL

WITHIN NORMAL LIMITS								
I	30	29	29	29	29	27	27	
II	30	30	29	28	26	26	27	27
III	30	30	29	28	28	28	26	24
IV	30	30	30	29	28	27	27	27

DERMAL-GENERAL

ULCERATION - CERVICAL								
I	0	0	1	1	1	1	1	1
II	0	0	0	0	0	0	0	0
III	0	0	0	0	0	0	0	0
IV	0	0	0	0	0	0	0	0

ALOPECIA - EXTREMITIES/SNOUT								
I	0	0	0	0	0	0	0	1
II	0	0	1	1	2	2	1	1
III	0	0	0	0	0	0	0	0
IV	0	0	0	0	0	0	0	0

ALOPECIA - GENERAL								
I	0	0	0	0	0	0	0	0
II	0	0	0	1	1	1	1	1
III	0	0	0	0	0	0	0	0
IV	0	0	0	0	0	0	0	0

LACRIMATION - UNILATERAL								
I	0	1	0	0	0	0	1	0
II	0	0	0	0	0	0	0	1
III	0	0	0	0	0	0	0	0
IV	0	0	0	0	1	0	0	1

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TABLE 1 (cont.)

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

96-4080

SUMMARY OF IN-LIFE PHYSICAL OBSERVATIONS - MALES

	WEEK: -1	1	2	3	4	5	6	7
# OF ANIMALS EXAMINED	I 30	30	30	30	30	30	30	30
	II 30	30	30	30	30	30	30	30
	III 30	30	30	30	30	30	30	30
	IV 30	30	30	30	30	30	30	30
CHROMODACRYORRHEA - UNILATERAL	I 0	1	0	0	0	0	1	0
	II 0	0	0	0	0	1	1	1
	III 0	0	0	0	0	0	0	2
	IV 0	0	0	1	2	1	1	1
CHROMODACRYORRHEA - BILATERAL	I 0	0	0	0	0	0	0	0
	II 0	0	0	0	1	0	0	0
	III 0	0	0	0	0	0	1	0
	IV 0	0	0	0	0	0	0	0
<u>ORAL/BUCCAL</u>								
INCISORS MALOCCLUDED	I 0	0	0	0	0	0	2	2
	II 0	0	0	0	1	1	1	0
	III 0	0	1	2	2	2	4	3
	IV 0	0	0	1	2	3	3	3
INCISORS BROKEN/MISSING	I 0	0	0	0	0	0	0	1
	II 0	0	0	0	0	0	0	0
	III 0	0	0	0	0	0	0	3
	IV 0	0	0	0	0	0	0	0

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

96-4080

SUMMARY OF IN-LIFE PHYSICAL OBSERVATIONS - FEMALES

WEEK:	-1	1	2	3	4	5	6	7
# OF ANIMALS EXAMINED	I 30 II 30 III 30 IV 30	30 30 30 30 30 30 30	30 30 30 30 30 30 30	30 30 30 30 30 30 30	30 30 30 30 30 30 30	30 30 30 30 30 30 30	30 30 30 30 30 30 30	30 30 30 30 30 30 30
<u>NORMAL</u>								
WITHIN NORMAL LIMITS	I 30 II 30 III 30 IV 30	30 30 30 29 29 28 28	30 30 30 30 30 30 30	30 30 30 29 29 28 28	29 29 28 27 25 26	28 28 27 25 26	28 28 27 25 26	28 28 27 25 26
<u>GENL. APPEARANCE</u>								
EARS SWOLLEN/RED - BILATERAL	I 0 II 0 III 0 IV 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0
<u>OCULAR</u>								
LACRIMATION - UNILATERAL	I 0 II 0 III 0 IV 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0
CHROMODACRYORRHEA - UNILATERAL	I 0 II 0 III 0 IV 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0
CHROMODACRYORRHEA - BILATERAL	I 0 II 0 III 0 IV 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0
<u>ORAL/BUCCAL</u>								
INCISORS MALOCCLUDED	I 0 II 0 III 0 IV 0	0 0 0 1 1 1 1	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0	0 0 0 0 0 0 0

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

96-4080

SUMMARY OF IN-LIFE PHYSICAL OBSERVATIONS - FEMALES

	WEEK: -1	1	2	3	4	5	6	7
# OF ANIMALS EXAMINED								
I	30	30	30	30	30	30	30	30
II	30	30	30	30	30	30	30	30
III	30	30	30	30	30	30	30	30
IV	30	30	30	30	30	30	30	30
ORAL SORE								
I	0	0	0	0	0	0	0	0
II	0	0	0	0	0	0	0	0
III	0	0	0	0	0	0	0	0
IV	0	0	1	1	0	0	0	0
INCISORS BROKEN/MISSING								
I	0	0	0	0	0	0	1	0
II	0	0	0	0	0	0	0	0
III	0	0	0	0	0	0	0	0
IV	0	0	0	0	0	0	0	0

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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	435.9	452.3	447.3	447.6
		S.D.	31.6	41.1	31.0	37.0
		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
A-L-	3	MEAN	348.8	357.7	357.2	348.0
		S.D.	18.0	27.2	20.4	25.3
		N	30	30	30	30
A-L-	4	MEAN	375.3	384.2	382.3	374.7
		S.D.	22.4	32.8	25.5	27.8
		N	30	30	30	30
A-L-	5	MEAN	401.8	412.1	409.2	405.5
		S.D.	23.1	36.2	28.0	30.1
		N	30	30	30	30
A-L-	6	MEAN	417.1	432.4	426.1	424.5
		S.D.	32.7	38.8	29.2	33.3
		N	30	30	30	30

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

		BODY WEIGHT IN GRAMS			
		MALES			
		DOSE LEVEL: PPM			
STAT	WEEK	0.0000	10.0000	100.0000	1100.0000
SYMBOL:					
A-L-	7	MEAN	435.9	452.3	447.3
		S.D.	31.6	41.1	31.0
		N	30	30	30

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T 2-3
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	258.5	253.4	259.6	253.1
		S.D.	15.8	14.3	20.7	14.2
		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
A-L-	3	MEAN	213.2	209.8	214.4	212.2
		S.D.	12.3	10.5	16.6	12.7
		N	30	30	30	30
A-L-	4	MEAN	225.6	222.0	226.7	225.0
		S.D.	15.3	10.7	17.4	13.1
		N	30	30	30	30
K-J-	5	MEAN	241.6	236.6	241.5	236.4
		S.D.	14.7	10.5	19.4	13.0
		N	30	30	30	30
A-L-	6	MEAN	250.7	247.8	252.1	247.5
		S.D.	15.5	13.8	20.7	13.8
		N	30	30	30	30

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T 2-4
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-		7	MEAN	258.5	253.4	259.6	253.1
			S.D.	15.8	14.3	20.7	14.2
			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

% DIFFERENCE IN BODY WEIGHT MALES DOSE LEVEL: PPM				
WEEK	0.0000	10.0000	100.0000	1100.0000
-1 % DIFF N	0.0 30	3.8 30	2.6 30	2.7 30
0 % DIFF N	0.0 30	1.9 30	1.4 30	0.4 30
1 % DIFF N	0.0 30	1.9 30	1.2 30	-0.8 30
2 % DIFF N	0.0 30	2.5 30	2.4 30	1.3 30
3 % DIFF N	0.0 30	2.6 30	2.4 30	-0.2 30
4 % DIFF N	0.0 30	2.4 30	1.9 30	-0.2 30
5 % DIFF N	0.0 30	2.6 30	1.8 30	0.9 30
6 % DIFF N	0.0 30	3.7 30	2.2 30	1.8 30

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T 3-2
TABLE 3 (CONT.)
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
7 % DIFF	0.0	3.8	2.6	2.7
N	30	30	30	30

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T 3-3
TABLE 3 (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 N	0.0 30	-2.0 30	0.4 30	-2.1 30
0 % DIFF N	0.0 30	0.3 30	-1.1 30	-0.6 30
1 % DIFF N	0.0 30	-1.9 30	0.6 30	-0.7 30
2 % DIFF N	0.0 30	0.5 30	1.4 30	0.4 30
3 % DIFF N	0.0 30	-1.6 30	0.6 30	-0.5 30
4 % DIFF N	0.0 30	-1.6 30	0.5 30	-0.3 30
5 % DIFF N	0.0 30	-2.1 30	0.0 30	-2.2 30
6 % DIFF N	0.0 30	-1.2 30	0.6 30	-1.3 30

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T 3-4
TABLE 3 (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
7 % DIFF	0.0	-2.0	0.4	-2.1
N	30	30	30	30

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TABLE 4

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VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION
AND DEVELOPMENTAL TOXICITY STUDY IN CD RATSFOOD 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-Q	1	MEAN	107.4	104.3	109.2	105.4
		S.D.	5.2	5.4	8.7	6.7
		N	30	28	29	27
K-J	2	MEAN	103.6	103.9	105.9	103.9
		S.D.	10.3	5.5	9.5	8.6
		N	30	30	30	30
A-L-	3	MEAN	94.3	94.7	96.9	96.9
		S.D.	5.2	6.2	5.8	6.5
		N	30	30	30	29
A-L-	4	MEAN	90.3	89.0	92.2	90.6
		S.D.	5.6	4.9	5.9	5.9
		N	30	30	30	30
K-J-	5	MEAN	85.8	87.6	87.6	87.1
		S.D.	4.3	5.6	7.0	7.8
		N	30	30	30	30
A+L-Q+	6	MEAN	79.4	**	**	**
		S.D.	8.4	84.9	84.7	85.0
		N	29	30	30	30
A-L-	7	MEAN	77.6	76.5	76.5	77.7
		S.D.	5.9	5.7	5.0	6.1
		N	30	30	30	30

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TABLE 4 (CONT.)

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VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION
AND DEVELOPMENTAL TOXICITY STUDY IN CD RATSFOOD 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	98.3	98.8	99.5	97.0
		S.D.	4.8	4.0	4.9	4.8
		N	30	30	30	30
A+L-Q+	2	MEAN	86.7	89.3	91.2	89.1
		S.D.	6.3	3.9	4.3	4.7
		N	30	30	30	30
A+L-Q+	3	MEAN	78.5	79.1	82.1	80.3
		S.D.	3.2	3.5	3.8	3.8
		N	30	30	30	30
A-L-	4	MEAN	72.7	72.5	73.3	73.2
		S.D.	3.1	3.9	3.2	3.5
		N	30	30	30	30
AL+	5	MEAN	68.6	69.5	70.3	71.4
		S.D.	2.7	3.5	3.5	3.8
		N	30	29	30	30
AL-Q	6	MEAN	62.6	66.0	65.0	65.6
		S.D.	4.6	3.4	6.0	3.9
		N	30	29	30	30
AL-	7	MEAN	60.2	61.0	62.4	62.3
		S.D.	3.7	2.3	3.5	3.5
		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	
<u>Nonparametric</u>			
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

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