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K-001711-047

**Huntingdon
Life Sciences**

STUDY NO. 96-4080

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

Developmental Toxicity Study

Final Report

Submitted to: Chemical Manufacturers Association
Chemstar Department
1300 Wilson Boulevard
Arlington, Virginia 22209

Attn: Hasmukh C. Shah, Ph.D.

Date: 30 January 1998

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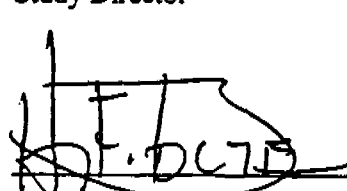
SIGNATURE PAGE

SCIENTIST

The following Scientists were responsible for the overall conduct of this study. Departmental supervisory personnel are listed on the personnel page of this report (Appendix Q).


Raymond E. Schroeder, M.S., DABT
Study Director

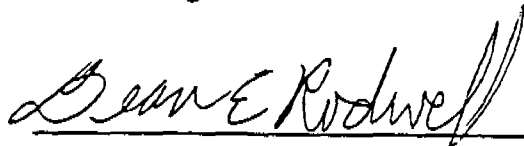
30 Jan 98
Date


Dr. Henry F. Bolte, D.V.M., Ph.D.
Pathologist

January 30, 1998
Date

SCIENTIFIC REVIEW

The following Scientist has reviewed and approved this report.


Dean E. Rodwell, M.S.
Vice President, Toxicology Operations

1/30/98
Date

QUALITY ASSURANCE STATEMENT

Day 21 Lactation Pup Selection and Sacrifice	10 Sep 97	10 Sep 97
Developmental Toxicology Report	26 Jan 98 to 29 Jan 98	29 Jan 98
Developmental Toxicology Analytical Report	29 Jan 98	29 Jan 98



Jane Nelson
Quality Assurance Senior Auditor



Date

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Rule, Federal Register, Volume 56, No. 32, February 15, 1991, pp. 6426-6505 effective March 18, 1991.

2.1.4. FACILITIES MANAGEMENT/ANIMAL HUSBANDRY

Currently acceptable practices of good animal husbandry were followed e.g., Guide for the Care and Use of Laboratory Animals, National Academy Press, 1996. Huntingdon Life Sciences, East Millstone, New Jersey is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

2.2. STUDY MANAGEMENT

2.2.1. SPONSOR

Chemical Manufacturers Association
Chemstar Department
1300 Wilson Boulevard
Arlington, Virginia 22209

2.2.2. SPONSOR REPRESENTATIVE

Hasmukh C. Shah, Ph.D.

2.2.3. TESTING FACILITY

Huntingdon Life Sciences
P.O. Box 2360
Mettlers Road
East Millstone, New Jersey 08875-2360

2.2.4. STUDY DIRECTOR

Raymond E. Schroeder, M.S., DABT

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2.4.5. TERMINATION OF EXPOSURES

10 April 1997

2.4.6. TERMINAL SACRIFICE

2-11 April 1997

2.4.7. STUDY TERMINATION

Date Final Report is signed by the Study Director.

2.5. TEST MATERIAL

Vinyl Chloride

2.5.1. SUPPLIER

The GEON Company
Pedricktown, NJ 08067

2.5.2. LOT NUMBER

1

2.5.3. DATE RECEIVED

28 August 1996

2.5.4. DESCRIPTION

Colorless gas

2.5.5. PURITY

>99.9%

2.5.6. STORAGE

Room temperature

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2.6.4. AGE AT RECEIPT

Females were 57 days in age at receipt.

2.6.5. WEIGHT AT GESTATION DAY 0

Mean: 213 grams

Range: 172-252 grams

2.6.6. JUSTIFICATION FOR ANIMAL SELECTION

The rat is a rodent animal model commonly utilized in reproduction/developmental toxicity studies as recommended in the referenced guidelines. In addition, a historical data base is available at Huntingdon Life Sciences, East Millstone, New Jersey with this strain of rat for comparative evaluations.

2.6.7. ACCLIMATION PERIOD

Approximately two weeks; all animals were observed for viability twice daily. Prior to mating, all animals were examined by the technical staff to ascertain suitability for study.

2.7. SELECTION/GROUP ASSIGNMENT

More females than required for the study were purchased and acclimated. Animals considered suitable for study on the basis of pretest physical examinations were included into the mating phase of the study. Females which mated were randomly assigned to groups daily in such a way as to most nearly equalize both the Day 0 gestation mean body weights between groups and the distribution of animals into groups. This was done by ranking the animals by body weight from lightest to heaviest and randomly assigning them to groups in blocks using a random numbers table.

2.8. MATING

Females selected for mating were co-housed with male rats from an in-house breeding colony nightly in a 1:1 ratio. Vaginal smears were taken early in the morning following nightly intervals of co-housing. The females were considered to have mated if sperm was observed microscopically in the vaginal smear and/or a vaginal plug was observed. The day on which evidence of mating was observed was defined as Day 0 of gestation.

2.11.5. MONTHLY WATER ANALYSES

Monthly water analyses, provided by the supplier, are maintained on file at Huntingdon Life Sciences.

2.11.6. BIENNIAL WATER ANALYSES

Biannual chemical and microbiological analyses of water samples collected from representative rooms in this facility were conducted to assure that water met standards specified under EPA National Primary Drinking Water Regulations (40 CFR Part 141). The results of these analyses are being maintained on file at Huntingdon Life Sciences.

2.11.7. CONTAMINANTS

There were no known contaminants in the feed or water which were expected to interfere with the results of this study.

2.11.8. ENVIRONMENTAL CONDITIONS

Light/Dark Cycle

Twelve hour light/dark cycle controlled via an automatic timer.

Temperature

Temperature was monitored and recorded twice daily.

Desired: 20 to 24°C

Actual: 20 to 23°C

Relative Humidity

Relative humidity was monitored and recorded once daily.

Desired: 40 to 70%

Actual: 32 to 76%

equivalent of the limit dose of 1000 mg/kg body weight/day. The high exposure level of 1100 ppm was also expected to produce effects on the liver and other organ systems (ATSDR, 1993). The middle and low exposure levels were selected to provide a dose response for the observed effects and a no-observed effect level, respectively.

2.13. EXPERIMENTAL EVALUATIONS

2.13.1. VIABILITY CHECKS

Animals were observed, at least twice daily in their cages, for mortality, general appearance and signs of severe toxic or pharmacologic effects. Animals in extremely poor health or in a possible moribund condition were identified for further monitoring and possible euthanasia.

2.13.2. PHYSICAL EXAMINATIONS

Animals were removed from their cages and examined on Days 0 and 6-20 of gestation. Examinations included observations of general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia as well as evaluations of respiration. Unusual behavior and physical signs were recorded. During the test period, observations were performed postexposure when animals were being transferred to their home cages.

2.13.3. BODY WEIGHT

Animals were removed from their cages and weighed using a Mettler Balance, Model PE4000 (Mettler Instrument Corporation, Hightstown, New Jersey). Body weights were recorded on Days 0, 6, 9, 12, 15 and 20 of gestation.

2.13.4. FOOD CONSUMPTION

Food was available, without restriction, 7 days/week, except during exposure periods. Animals were presented with weighed feeders on Days 0, 6, 9, 12 and 15 of gestation. Feeders were removed on Days 6, 9, 12, 15 and 20 of gestation and a "feeder-out" weight recorded using a Mettler Balance, Model PE4000 (Mettler Instrument Corporation, Hightstown, New Jersey). The resulting weight was subtracted from the

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Reproductive System

The intact uterus (ovaries attached) was removed from the abdominal cavity and weighed intact (with fetuses and placenta) using a Mettler AK-160 balance (Mettler Instrument Corporation, Hightstown, New Jersey). The uterine weight data was then used to calculate a corrected Day 20 gestation body weight for each animal. The corrected Day 20 gestation weight was determined by subtracting the gravid uterine weight from the terminal Day 20 gestation weight. The uterus was then opened along the antimesometrial border and the number and location of the following were recorded for each uterine horn:

- live fetuses - movement in response to touch.
- dead fetuses - lack of movement in response to touch with no visible degeneration.
- late resorptions - recognizable dead fetus undergoing degeneration regardless of size.
- early resorptions - evidence of implantation but no recognizable fetus.
- implantation sites - total of resorptions and fetuses.

Uteri without grossly visible implantations were stained according to the procedure of Salewski (1964) to identify the presence of sites of early resorption. If no stained sites were present, the female was considered not pregnant.

Ovaries

The ovaries were dissected free from the uterus and evaluated for the presence and number of corpora lutea.

2.14.3. FETAL EVALUATIONS

External Evaluations

Each fetus was individually weighed using a Mettler Balance, Model PE4000, sexed externally (ano-genital distance) and examined for external malformations/variations to include observation for palatal defects.

2.15. STATISTICAL ANALYSIS

The following items were analyzed statistically in the final report:

2.15.1. CONTINUOUS DATA:

Body weights (all recorded intervals)^a

Body weight change (between all recorded intervals to include Days 6-20 of gestation using the actual and corrected Day 20 gestation weights)^a

Food consumption values (all recorded intervals)^a

Organ weight data absolute and relative to the Day 20 gestation weight^a

Number of corpora lutea^a

Uterine implantation data (fetuses^a, resorptions^b, implantations^a)

Pre-implantation loss^b

Post-implantation loss^b

Mean percent male and female fetuses per litter^a

Fetal weight distinguished by sex and as a composite for both sexes (litter as experimental unit)^a

2.15.2. CONTINUOUS DATA - MULTIPLE GROUP ANALYSIS:

Employed when data for more than one treated group are compared to control. All statistical tests were conducted at the 5% and 1%, two-sided risk levels.

^aStatistical evaluation of equality of means was made by the appropriate one way analysis of variance (ANOVA) technique, followed by a multiple comparison procedure, if needed. If ANOVA showed no difference, no additional comparisons were made. If ANOVA was significant, Dunnett's test was used to determine which data, if any, differed from the control.

References for these techniques are as follows:

Dunlap, W.P. and J.A. Duffy (1975) "Fortran IV functions for calculating exact probabilities associated with Z, Chi-square, T and F values." Behav. Res. Methods and Instrumentations, 7:59-60.

Dunlap, W.P., M.S. Marx and G.J. Agamy (1981) "Fortran IV functions for calculating probabilities associated with Dunnett's Test", Behav. Res. Methods and Instrumentations, 13:363-366.

^bThe Kruskal-Wallis test (2 X n) was used to test equality of means. If no

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Archives of Huntingdon Life Sciences for a period of ten years after submission of the signed final report. The Sponsor will be contacted in order to determine the final disposition of these materials.

2.17. PROTOCOL DEVIATIONS

The following protocol deviations occurred during the study but were not considered to have compromised the validity or integrity of the study:

Relative humidity in the animal quarters was out of the protocol specified range on several occasions.

The protocol states that detailed physical examinations were to be performed on Days 0 and 6-20 (daily) during gestation; however, one animal (Group IV female No. 4625) was not observed on Day 0 due to technician error; the initial observations for this animal were recorded on Day 3 of gestation.

3.2.2. PREGNANCY RATES

(Table 1; Appendix F)

Pregnancy rates were comparable between the control and vinyl chloride-treated groups. Pregnancy rates for the control, 10, 100 and 1100 ppm treated groups were 92%, 96%, 88% and 96%, respectively.

3.2.3. PHYSICAL OBSERVATION DATA

(Table 2; Appendix A)

No adverse effect of treatment with vinyl chloride was indicated from clinical findings noted during the detailed physical examinations. There was a slight increase in the incidence of females with alopecia of the extremities and/or snout in the 100 ppm group but in the absence of a similar increase in the 1100 ppm group, this was not considered treatment-related. Other clinical findings seen in the treated groups occurred at low incidence or with similar frequency as control and were not considered treatment-related.

3.2.4. BODY WEIGHT DATA - GESTATION PERIOD

(Tables 3, 4 and 8; Appendices B, C and G)

Mean body weights were comparable for the control and treated groups throughout the treatment period. Mean body weight gains for the treated groups were comparable to control data during the pretreatment period (Days 0-6) and early in the treatment period (Days 6-9, 9-12, 12-15). However, for Days 15-20 of gestation, mean body weight gains for all three treated groups were significantly lower than control. Since these differences were slight (less than 10% in comparison to control data in the 100 and 1100 ppm groups and 12% in the 10 ppm group) and were not dose-response related, and in the absence of an effect of treatment on food consumption, the reduction in weight gains in these groups was considered related to the slight reduction in litter size seen in the treated groups (about one fetus/litter) and the slightly lower gravid uterine weights (Table 8). The mean body weight gains for all treated groups over the Day 6 to 20 gestation interval using the corrected Day 20 gestation weights (actual Day 20 gestation weight minus the weight of the gravid uterus) were comparable to control data. Thus, these slight changes in body weight gain are not likely to be treatment-related.

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Kidney weights, absolute and relative to the Day 20 gestation weights, were comparable to control in the 10 ppm group. In the 100 and 1100 ppm groups, absolute kidney weights were comparable to control data but relative weights were slightly higher. These latter differences were statistically significant and considered indicative of a treatment-related response.

3.3. FETAL DATA

3.3.1. FETAL BODY WEIGHT DATA

(Table 7; Appendices F and H)

No adverse effect of treatment with vinyl chloride at a concentration level up to and inclusive of 1100 ppm was seen from fetal body weight data. Mean fetal body weights distinguished by sex and for both sexes combined were comparable between the control and treated groups.

3.3.2. FETAL SEX DISTRIBUTION DATA

(Table 7; Appendix F)

No adverse effect of treatment with vinyl chloride at a concentration level up to and inclusive of 1100 ppm was seen from fetal sex distribution data. The mean percentage of male and female fetuses per litter was comparable between the control and treated groups.

3.3.3. FETAL EXTERNAL EXAMINATION DATA

(Tables 11 and 12; Appendix K)

No malformations were seen in the external examination of the 318 control fetuses from 23 litters, 297 Group II (10 ppm) fetuses from 24 litters or 283 Group III (100 ppm) fetuses from 22 litters. In the 1100 ppm group, craniorachischisis, a severe malformation involving the cranium and spinal cord, was seen in one fetus from the litter of female No. 4622. No other external malformations were seen in the remaining 304 fetuses examined in the 1100 ppm group from 24 litters. Though not seen in recent historical control data for this laboratory (Appendix P, page P-7), a low incidence of craniorachischisis has been noted in the recently published MARTA/MTA compilation of historical control data for the Crl:CD® BR rat (average fetal and litter occurrences were

No adverse effect of treatment was evident from fetal ossification variation data. The litter incidences for the various ossification variations seen during the study were generally comparable between the control and treated groups. In the 1100 ppm group, the incidence of litters containing at least one fetus with reduced ossification of the cervical vertebral arches was significantly lower than control. This was not considered to represent an adverse effect of treatment.

4. CONCLUSION

In this study, vinyl chloride was administered via whole body inhalation (6 hours/day) to pregnant rats at targeted concentration levels of 0, 10, 100 and 1100 ppm during Days 6-19 of gestation. No maternal or developmental toxicity was seen at the 10 ppm exposure level. At the 100 ppm exposure level, the only maternal toxicity seen was an increase in the kidney weight relative to the Day 20 gestation weight. At the 1100 ppm exposure level, the only maternal toxicity observed was an increase in kidney and liver weights relative to the Day 20 gestation weights. No developmental toxicity was seen at either the 100 or 1100 ppm exposure levels. Thus, the no-observed-effect level (NOEL) for maternal toxicity with vinyl chloride in the pregnant rat was 10 ppm and the NOEL for developmental toxicity was 1100 ppm.

REFERENCES AND CALCULATIONS

CALCULATIONS

Preimplantation Loss:

no. of corpora lutea - no. of implantation sites

Percent Preimplantation Loss:

no. of corpora lutea - no. of implantation sites/no. of corpora lutea

Postimplantation Loss:

total no. of early and late resorptions and dead fetuses

Percent Postimplantation Loss:

no. of early and late resorptions and dead fetuses/no. of implantation sites

TABLE 1

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

SUMMARY OF SURVIVAL AND PREGNANCY

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
No. of females mated	N	25	25	25	25
Pregnant	N	23	24	22	24
- Died/sacrificed moribund	N	0	0	0	0
- Elective sacrifice	N	0	0	0	0
Nonpregnant	N	2	1	3	1
- Died/sacrificed moribund	N	0	0	0	0
- Elective sacrifice	N	0	0	0	0
Total no. of females died/ sacrificed moribund	N %	0 0.0	0 0.0	0 0.0	0 0.0
Examined at scheduled c-section	N	25	25	25	25
- Nonpregnant	N	2	1	3	1
- With total implant loss	N %	0 0.0	0 0.0	0 0.0	0 0.0
- With viable fetuses	N %	23 92.0	24 96.0	22 88.0	24 96.0

No statistically significant differences

N = number of animals

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TABLE 2

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

SUMMARY OF CLINICAL OBSERVATIONS DURING GESTATION (frequency/animals)

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
DAY 0 to 20					
TERMINAL SACRIFICE		25/25	25/25	25/25	25/25
General Appearance					
RED EXUDATE FROM ANO-GENITAL AREA		0/ 0	1/ 1	0/ 0	0/ 0
Dermal-General					
ALOPECIA - EXTREMITIES/SNOUT		10/ 2	11/ 1	45/ 6	32/ 3
ALOPECIA - GENERAL		4/ 1	0/ 0	0/ 0	0/ 0
Ocular					
CHROMODACRYORRHEA - UNILATERAL		6/ 1	4/ 2	0/ 0	0/ 0
LACRIMATION - UNILATERAL		2/ 1	0/ 0	0/ 0	0/ 0
Oral/Buccal					
INCISORS BROKEN/MISSING		0/ 0	11/ 1	0/ 0	0/ 0
INCISORS MALOCCLUDED		9/ 1	8/ 2	0/ 0	0/ 0

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TABLE 3

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

SUMMARY OF GESTATION BODY WEIGHTS (GRAMS)

Concentration		Group (ppm)	I 0	II 10	III 100	IV 1100
DAY 0	MEAN		214	214	210	214
	S.D.		13.7	12.3	12.9	10.5
	N		23	24	22	24
DAY 6	MEAN		243	240	240	242
	S.D.		14.8	13.3	13.7	10.8
	N		23	24	22	24
DAY 9	MEAN		254	250	251	250
	S.D.		16.0	13.8	13.2	10.2
	N		23	24	22	24
DAY 12	MEAN		270	266	266	266
	S.D.		15.8	16.7	13.2	11.4
	N		23	24	22	24
DAY 15	MEAN		287	282	282	282
	S.D.		19.0	15.8	14.5	11.6
	N		23	24	22	24
DAY 20	MEAN		353	340	341	342
	S.D.		25.3	19.2	23.6	15.6
	N		23	24	22	24

No statistically significant differences

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Developmental Toxicity Study

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TABLE 4

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

SUMMARY OF GESTATION BODY WEIGHT GAIN (GRAMS)

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
DAYS 0 TO 6	MEAN	29	26	30	28
	S.D.	5.6	5.8	8.9	10.3
	N	23	24	22	24
DAYS 6 TO 9	MEAN	10	10	10	8
	S.D.	5.8	5.7	4.6	3.6
	N	23	24	22	24
DAYS 9 TO 12	MEAN	16	16	16	15
	S.D.	3.5	5.7	3.9	4.8
	N	23	24	22	24
DAYS 12 TO 15	MEAN	17	16	15	16
	S.D.	4.3	4.0	4.8	3.9
	N	23	24	22	24
DAYS 15 TO 20	MEAN	66	58*	60*	60*
	S.D.	8.7	8.2	12.7	7.8
	N	23	24	22	24
DAYS 6 TO 20	MEAN	110	100*	101*	99*
	S.D.	13.5	13.8	14.0	10.4
	N	23	24	22	24

Statistical key: * = p<0.05

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Developmental Toxicity Study

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TABLE 5

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

SUMMARY OF GESTATION FOOD CONSUMPTION (GRAMS/ANIMAL/DAY)

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
DAYS 0 TO 6	MEAN	19	19	19	19
	S.D.	2.5	1.7	1.7	1.7
	N	23	24	22	22
DAYS 6 TO 9	MEAN	18	19	19	18
	S.D.	1.6	1.9	2.0	1.4
	N	23	24	22	22
DAYS 9 TO 12	MEAN	20	20	20	20
	S.D.	1.7	2.6	1.7	1.3
	N	23	24	22	22
DAYS 12 TO 15	MEAN	21	22	22	22
	S.D.	2.0	1.7	2.2	1.6
	N	22	24	22	22
DAYS 15 TO 20	MEAN	24	23	23	24
	S.D.	1.9	1.9	2.2	2.3
	N	23	24	22	22

No statistically significant differences

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29-JAN-1975 12:15

Huntingdon Life Sciences 96-4080D
Developmental Toxicity Study

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TABLE 6

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

SUMMARY OF GESTATION FOOD CONSUMPTION (GRAMS/KG/DAY)

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
DAYS 0 TO 6	MEAN	90	89	93	89
	S.D.	10.2	8.5	10.7	8.4
	N	23	24	22	22
DAYS 6 TO 9	MEAN	76	77	77	73
	S.D.	5.2	6.7	8.0	5.3
	N	23	24	22	22
DAYS 9 TO 12	MEAN	79	81	81	79
	S.D.	6.3	8.0	5.6	3.9
	N	23	24	22	22
DAYS 12 TO 15	MEAN	79	81	81	82
	S.D.	4.8	5.3	7.3	4.9
	N	22	24	22	22
DAYS 15 TO 20	MEAN	84	83	82	84
	S.D.	4.2	5.9	4.7	8.2
	N	23	24	22	22

No statistically significant differences

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TABLE 7

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

SUMMARY OF CESAREAN SECTION DATA

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
Pregnant	N	23	24	22	24
Dams with no Viable Fetuses	N	0	0	0	0
Dams with Viable Fetuses	N	23	24	22	24
Corpora Luta	TOTAL	351	355	337	363
No. per animal	MEAN	15.3	14.8	15.3	15.1
	S.D.	1.45	3.41	4.31	2.68
Implantation Sites	TOTAL	327	309	289	320
No. per animal	MEAN	14.2	12.9	13.1	13.3
	S.D.	1.38	1.80	2.55	2.30
Preimplantation Loss	TOTAL	24	46	48	43
No. per animal	MEAN	1.0	1.9	2.2	1.8
	S.D.	1.19	2.75	3.02	1.61
% per animal	MEAN%	6.6	11.1	11.8	11.6
	S.D.	7.22	11.21	12.68	9.99
Live Fetuses	TOTAL	318	297	283	305
No. per animal	MEAN	13.8	12.4	12.9	12.7
	S.D.	1.64	1.84	2.57	2.27
Males	TOTAL	149	149	133	151
	MEAN%	46.7	50.7	46.5	50.1
	S.D.	14.39	16.50	12.41	10.36
Females	TOTAL	169	148	150	154
	MEAN%	53.3	49.3	53.5	49.9
	S.D.	14.39	16.50	12.41	10.36

No statistically significant differences

N = number of animals

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TABLE 7

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

SUMMARY OF CESAREAN SECTION DATA

Concentration		Group (ppm)	I 0	II 10	III 100	IV 1100
Fetal Body Weight (g)	MEAN		3.4	3.4	3.4	3.3
	S.D.		0.17	0.17	0.22	0.22
	N		23	24	22	24
Male Fetuses	MEAN		3.5	3.5	3.5	3.4
	S.D.		0.22	0.19	0.24	0.21
Female Fetuses	MEAN		3.3	3.3	3.3	3.2
	S.D.		0.18	0.18	0.22	0.23

No statistically significant differences

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TABLE 8

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

SUMMARY OF GRAVID UTERINE WEIGHT AND NET BODY WEIGHT CHANGE (GRAMS)

Concentration		Group (ppm)	I 0	II 10	III 100	IV 1100
NET BODY WT. CHANGE	MEAN		110	100*	101*	99*
	S.D.		13.5	13.8	14.0	10.4
	N		23	24	22	24
GRAVID UTERINE WT.	MEAN		75	69	70	69
	S.D.		9.7	10.0	12.0	10.4
	N		23	24	22	24
NET WEIGHT CHANGE MINUS UTERINE WT.	MEAN		35	31	31	30
	S.D.		8.5	9.1	9.0	7.6
	N		23	24	22	24

Statistical k y: * = $p < 0.05$

NET BODY WT. CHANGE = TERMINAL BODY WT. MINUS DAY 6 BODY WEIGHT
NET WEIGHT CHANGE = NET BODY WT. CHANGE MINUS UTERINE WEIGHT

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TABLE 9

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

SUMMARY OF MATERNAL NECROPSY OBSERVATIONS

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
DAMS	N	25	25	25	25
GROSS EXAM	N	1	0	0	1
ALOPECIA	N %	1 4.0	0 0.0	0 0.0	1 4.0
KIDNEY	N	0	1	0	0
KIDNEY DISTENDED	N %	0 0.0	1 4.0	0 0.0	0 0.0
BLADDER	N	0	0	0	1
BLADDER FLUID FILLED; MODERATE (THICK WHITE)	N %	0 0.0	0 0.0	0 0.0	1 4.0
UTERUS	N	0	0	0	1
UTERUS DISTENDED	N %	0 0.0	0 0.0	0 0.0	1 4.0

No statistically significant differences

N = Number of animals

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TABLE 10
Vinyl Chloride Combined Inhalation Two-Generation
Reproduction and Developmental Toxicity Study in CD Rats
ABSOLUTE ORGAN WEIGHTS

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Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
FINAL BODY WEIGHT g	MEAN	353	340	341	342
	S.D.	25.3	19.2	23.6	15.6
	N	23	24	22	24
LIVER g	MEAN	14.418	14.022	14.267	14.610
	S.D.	0.9598	1.0870	1.4462	1.0688
	N	23	24	22	24
KIDNEYS g	MEAN	1.871	1.849	1.944	1.924
	S.D.	0.1256	0.1388	0.1322	0.1496
	N	23	24	22	24

MEAN INCLUDES ONLY DAMS WITH VIABLE FETUSES AT TERMINATION

No statistically significant differences

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TABLE 11

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TABLE 12

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TABLE 12

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

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
SQUAMOSAL(S) REDUCED OSSIFICATION					
Fetal Incidence		6	18	15	6
Litter Incidence		3	10	10	5
MAXILLA(E) REDUCED OSSIFICATION					
Fetal Incidence		4	8	2	3
Litter Incidence		2	6	2	3
MALAR(S) REDUCED OSSIFICATION					
Fetal Incidence		4	13	15	3
Litter Incidence		3	7	10	3
PARIETAL(S) REDUCED OSSIFICATION					
Fetal Incidence		7	11	9	5
Litter Incidence		4	6	6	4
FRONTAL(S) REDUCED OSSIFICATION					
Fetal Incidence		3	1	0	0
Litter Incidence		1	1	0	0
PRESPHENOID REDUCED OSSIFICATION					
Fetal Incidence		1	0	0	0
Litter Incidence		1	0	0	0
MALAR UNOSSIFIED					
Fetal Incidence		0	0	1	0
Litter Incidence		0	0	1	0
SUPRAOCCIPITAL UNOSSIFIED					
Fetal Incidence		0	0	1	0
Litter Incidence		0	0	1	0

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No statistically significant differences

TABLE 12

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

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

Concentration	Group (ppm)	I 0	II 10	III 100	IV 1100
CAUDAL ARCH(ES) UNOSSIFIED					
Fetal Incidence		32	37	35	27
Litter Incidence		12	14	14	12
CAUDAL CENTRUM(A) UNOSSIFIED					
Fetal Incidence		0	0	3	1
Litter Incidence		0	0	1	1
STERNEBRA(E) 5 AND/OR 6 UNOSSIFIED					
Fetal Incidence		110	89	94	111
Litter Incidence		23	23	21	24
STERNEBRA(E) 1,2,3 AND/OR 4 UNOSSIFIED					
Fetal Incidence		2	3	6	6
Litter Incidence		2	3	4	6
STERNEBRA(E) 1,3 AND/OR 4 REDUCED OSSIFICATION					
Fetal Incidence		0	2	6	3
Litter Incidence		0	2	3	3
RIB(S) 13TH RUDIMENTARY					
Fetal Incidence		2	2	2	4
Litter Incidence		2	1	2	4
RIB(S) BENT					
Fetal Incidence		0	1	0	0
Litter Incidence		0	1	0	0
RIB(S) REDUCED OSSIFICATION					
Fetal Incidence		2	1	0	0
Litter Incidence		1	1	0	0

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No statistically significant differences