



DOW CHEMICAL U.S.A.

November 28, 1977

MIDLAND, MICHIGAN 48640

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H. A. Cantor, A. E. Staley Manufacturing Co.
R. B. Jaeder, BASF Wyandotte Corporation
M. N. Johnson, B. F. Goodrich Chemical Co.
A. Konishi, Kureha Chemical Industry Co., Ltd.
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J. M. Smith, Rohm and Haas Company
R. J. Turner, Morton Chemical Company
P. J. Vanderhorst, E.I. duPont de Nemours & Co.
P. L. Wright, Monsanto Company
J. Yamada, Asahi-Dow Limited

Dear Lucille:

A draft copy of the document entitled "The Effect of Maternally Inhaled or Ingested Vinylidene Chloride on Rat and Rabbit Embryonal and Fetal Development" is enclosed for your review. This document will be discussed at the December 7-8, 1977 MCA meeting.

Sincerely,

J. M. Norris
Associate Scientist
Government Registration
Health and Environmental Research

NOV 30 1977

Environmental Affairs

Enclosure

jan



AN OPERATING UNIT OF THE DOW CHEMICAL COMPANY

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THE EFFECT OF MATERNALLY INHALED OR INGESTED
VINYLLIDENE CHLORIDE ON RAT AND RABBIT EMBRYONAL AND
FETAL DEVELOPMENT

BY

F. J. Murray, K. D. Nitschke, J. A. John, J. G. McBride,
M. F. Balmer, A. A. Crawford, J. S. Murray, J. F. Quast,
L. W. Rampy, and B. A. Schwetz

Reviewed by

B. A. Schwetz

DRAFT

November 10, 1977

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THE EFFECT OF MATERNALLY INHALED OR INGESTED VINYLIDENE CHLORIDE
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SUMMARY

The teratogenic potential of inhaled or ingested vinylidene chloride was evaluated in Sprague-Dawley rats and New Zealand rabbits. Both species were exposed to the test material by inhalation for 7 hrs/day at concentrations of 20 (rats only), 80, or 160 ppm. For the ingestion study, rats were maintained on drinking water containing 200 ppm vinylidene chloride. The animals received the test material on days 6-15 (rats) and 6-18 (rabbits) of gestation. A teratogenic effect was not evidenced in rats or rabbits inhaling up to 160 ppm vinylidene chloride for 7 hrs/day or in rats given drinking water containing 200 ppm vinylidene chloride. Toxicity to both the dam and her developing embryo was observed among the rats inhaling 80 or 160 ppm and among the rabbits inhaling 160 ppm. At exposure levels which caused little or no maternal toxicity, 20 ppm in rats and 80 ppm in rabbits, no effect on embryonal or fetal development was discerned. Among the rats given drinking water containing 200 ppm VDC, there was no evidence of toxicity to either the dam or to the developing embryo and fetus.

INTRODUCTION

Vinylidene chloride (1,1-dichloroethylene, VDC, $\text{CH}_2=\text{CCl}_2$) is used in the manufacture of various plastics, including films and coatings for food packaging. Reports on the acute toxicity of vinylidene chloride in laboratory animals have indicated moderate toxicity when given by inhalation or by gavage (Carpenter et al., 1949; Rylova, 1953; Siegel et al., 1971; Jenkins et al., 1972; Jaeger et al., 1973). Repeated inhalation exposure to 100 ppm vinylidene chloride for 6 weeks resulted in some weight loss in rabbits and monkeys, but not in rats, guinea pigs, or dogs (Prendergast, 1967). Rats exposed for up to 4 weeks to 500 ppm vinylidene chloride exhibited nasal irritation, decreased weight gain, and liver cell degeneration; at 200 ppm, only slight nasal irritation was discerned (Gage, 1970).

Balmer et al. (1976), recently reported minimal reversible changes in the liver of rats inhaling 25 or 75 ppm vinylidene chloride for 90 days. Similar hepatic alterations were seen in rats maintained for 90 days on drinking water containing 200 ppm vinylidene chloride, but not among those given water containing 100 ppm or less of vinylidene chloride (Humiston et al., 1975).

Vinylidene chloride has been shown to be a weak mutagen in certain strains of bacteria (McCann et al., 1975; Greim et al., 1975; Bartsch et al., 1975). This effect was seen in bacterial systems only under conditions of activation with microsomal enzymes, implicating a metabolite of vinylidene chloride rather than vinylidene chloride itself as the causative agent.

A review of the scientific literature on vinylidene chloride revealed a lack of information regarding its teratogenic potential. Thus, the studies presented herein were undertaken to evaluate the potential of inhaled and ingested vinylidene chloride to adversely affect embryonal and fetal development in rats and rabbits. For the inhalation studies, both rats and rabbits were exposed to vinylidene chloride at concentrations of up to 160 ppm. The Threshold Limit Value of vinylidene chloride is 10 ppm (ACGIH, 1977). In order to simulate exposure by ingestion, rats were given the test material in the drinking water. The concentration of vinylidene chloride given in the drinking water, 200 ppm, was the upper limit of solubility of the compound in water. These studies were conducted under the auspices of the Manufacturing Chemists Association in the Toxicology Research Laboratory, Health and Environmental Research, The Dow Chemical Company, Midland, Michigan.

MATERIALS AND METHODS

Test Material. The test material used for this study was production grade vinylidene chloride obtained from The Dow Chemical Company, Midland, Michigan. Each sample of the test material had a minimum purity of 99.5% and contained 200-400 ppm monomethylether of hydroquinone (MEHQ) to inhibit polymerization. Since the vinylidene chloride used in various copolymers for food packaging applications is distilled to remove the inhibitor MEHQ, the ingestion portion of the study was conducted on distilled vinylidene chloride having a residual concentration of 1-5 ppm MEHQ. Each sample used for the study was analyzed by gas-liquid chromatography for determination of impurities (Table 1).

Animals. Adult New Zealand white rabbits (Langshaws Rabbitry, Augusta, Michigan), weighing 3.4-4.7 kg, and Sprague-Dawley rats (Spartan Research Animals, Haslett, Michigan), weighing approximately 250 gm, were used. The day on which sperm were found in the vaginal smear of rats was considered day zero of pregnancy; in rabbits, the day of natural mating was designated day zero of pregnancy. The animals were uniquely identified by means of an ear punch (rats) or a metal ear tag (rabbits). Animals were housed individually in wire-bottom cages and maintained on commercially available

laboratory animal chow (Ralston Purina Company, St. Louis, Missouri) and tap water free choice. Animals did not have access to food or water while in the exposure chambers. The food and water consumption of rats was measured at intervals of three days or less during the experimental period.

Experimental Design. In the initial inhalation experiment, groups of 30 bred rats and 18 bred rabbits were exposed to 160 ppm vinylidene chloride for 7 hrs/day on days 6-15 and 6-18 of gestation, respectively. Subsequently, additional groups of 30 bred rats and 22 bred rabbits were exposed to 80 ppm. Because some embryotoxicity was observed in rats exposed to 80 ppm, an additional group of 44 bred rats was exposed to 20 ppm. Groups of 20-47 bred rats and 16 bred rabbits were exposed in chambers to filtered room air to serve as negative controls; there was a separate control group for each level of exposure.

Pregnant animals were exposed in stainless steel and glass Rochester-type chambers of 4.3 cubic meter volume under dynamic airflow conditions. The chamber atmosphere was generated by metering vinylidene chloride at a known rate into a heated vaporization flask and then into the airstream being drawn into the exposure chamber. The concentration of vinylidene chloride in the chamber was analyzed continuously during

exposure using an infrared spectrophotometer. The time-weighted mean analytical concentrations of vinylidene chloride in the chamber for the 20, 80, and 160 ppm exposures were 20 ± 1 , 80 ± 5 , and 158 ± 6 ppm (mean $\pm$ standard deviation), respectively.

For the ingestion study, 26 bred rats were given tap water containing 200 ppm vinylidene chloride on days 6-15 of gestation. A group of 24 bred control rats was given tap water without vinylidene chloride. The water was supplied from 16 ounce wide-mouth glass bottles with plastic screw caps fitted with stainless steel sipper tubes containing stainless steel balls. The bottles were emptied and re-filled daily from freshly prepared stock solutions. In an earlier study, vinylidene chloride was determined to be relatively stable in water for 24 hours.

Maternal and Fetal Observations. Animals were observed daily throughout the experimental period for indications of toxicity from the test material. The maternal body weights of rabbits were recorded on days 6, 12, and 19 of gestation. The body weights of rats were recorded on days 6, 10, and 16 of gestation. In addition, maternal body weight and the weight of the maternal liver were recorded at the time of cesarean section, day 21 in rats and day 29 in rabbits.

On the day of cesarean section, the females were sacrificed by carbon dioxide inhalation; the uterine horns were exteriorized through a mid-line incision in the abdominal wall, and the number and position of live, dead, and resorbed fetuses were noted. The uteri of apparently non-pregnant animals were stained with a 10% solution of sodium sulfide and examined for evidence of early resorption sites (Kopf et al., 1964); this procedure was conducted for the sole purpose of determining the percentage of pregnancy, not the incidence of resorptions. After being weighed, measured (crown-rump length), and sexed, all fetuses were examined for external alterations and cleft palate. One-third of the fetuses of each litter, selected at random, was examined immediately for evidence of soft-tissue alterations by dissection under a low power stereo-microscope (Staples, 1974). The head of each rat fetus which was examined for soft-tissue alterations was placed in Bouin's solution and subsequently examined by the razor section technique of Wilson (1965). All of the fetuses in each litter were eviscerated and placed in 95% ethanol and were cleared and stained with alizarin red-S (Dawson, 1926) to facilitate examination for skeletal alterations.

Statistical Evaluation. The incidences of pregnancy and resorptions were analyzed statistically by the Fisher exact

probability test (Siegel, 1956). The Wilcoxon test as modified by Haseman and Hoel (1974) was used to evaluate the incidence of fetal alterations. Fetal body weights and body measurements, maternal body weights, weights of the maternal livers, and food and water consumption data were analyzed statistically by a one-way analysis of variance (Steel and Torrie, 1960). The level of significance chosen for all cases was $p < 0.05$.

RESULTS

RATS

Maternal Toxicity. No maternal deaths were seen among the rats receiving vinylidene chloride either by inhalation or by ingestion of the compound in the drinking water. Single dams exposed to 80 or 160 ppm vinylidene chloride by inhalation delivered a litter prematurely on days 18 and 21 of gestation, respectively; early deliveries were not seen in any of the other groups of rats. Sialodacryoadenitis, as diagnosed by the presence of swollen salivary glands, was observed in one of the dams inhaling 20 ppm vinylidene chloride, as well as in one concurrent control dam; this disease, presumably of viral origin, was not evident among the other rats.

The mean body weight of the pregnant rats exposed to 20 or 160 ppm vinylidene chloride by inhalation was significantly less than that of the concurrent control rats on day 10 of gestation, (Table 2); at 80 ppm, a significant decrease was observed in maternal body weight on day 16 of gestation. Maternal weight gain on days 6-9 of gestation was decreased in a dose-related manner at 80 and 160 ppm. A significant increase in maternal weight gain was noted during the post-exposure period among the dams exposed to 160 ppm. No significant effect on maternal body weight gain was discerned among the dams inhaling 20 ppm of vinylidene chloride or among those receiving the compound in the drinking water.

Inhalation exposure of the dams to 160 ppm vinylidene chloride resulted in a significant increase in maternal liver weight relative to body weight, but the absolute liver weight was unaffected. The maternal liver weight was not altered by exposure to the lower levels of inhaled vinylidene chloride or by ingestion of drinking water containing vinylidene chloride (Table 2).

The amount of food consumed by the pregnant rats exposed to 160 ppm vinylidene chloride by inhalation was significantly decreased on days 6-8 of gestation and significantly increased on days 12-14 and 18-20 of gestation (Table 3). At 80 ppm,

significant decreases in food consumption were seen between days 6-17 of gestation. Exposure to 20 ppm vinylidene chloride by inhalation or ingestion of drinking water containing 200 ppm vinylidene chloride had no significant effect on the amount of food ingested (Tables 3 and 4).

The amount of water consumed by the pregnant rats exposed to 160 ppm vinylidene chloride was significantly greater than that of its control group throughout days 6-20 of gestation (Table 3). Significant increases in water consumption were also seen in the dams inhaling 80 ppm (days 15-17 of gestation) and 20 ppm (days 12-17 of gestation). Inclusion of vinylidene chloride in the drinking water did not significantly affect the amount of liquid consumed by the dams (Table 4). Based on the amount of water consumed, it was calculated that the dams given vinylidene chloride in their drinking water received an approximate daily dose of 40 mg vinylidene chloride/kg body weight/day.

Embryo- and Fetotoxicity: Observations made at the time of cesarean section of rats are recorded in Table 5. Exposure to vinylidene chloride by inhalation or by ingestion did not significantly affect the incidence of pregnancy. A statistically significant increase in the average number of corpora lutea per dam was discerned among the rats receiving vinylidene

chloride in the drinking water but not among those exposed by inhalation; since the number of corpora lutea is established before day 6 of gestation, this increase was not a compound-related effect. No significant effect on the number of implantations or on the number of live or dead fetuses was discerned among litters of rats given vinylidene chloride by either route of administration. The incidence of resorptions among the litters of rats exposed to 80 ppm vinylidene chloride was significantly greater than among the controls; however, this increase was attributable to a single 80 ppm-exposed litter in which all of its 13 implantations were resorbed. The incidence of resorptions was unaffected among the litters of rats exposed to 20 or 160 ppm vinylidene chloride by inhalation or among those receiving vinylidene chloride in the drinking water. Exposure to vinylidene chloride by either route of administration did not alter the fetal sex ratio or body weight. The mean fetal crown-rump length among the litters of rats receiving drinking water containing vinylidene chloride was significantly greater than that of the controls; this parameter was unaffected among the litters of rats exposed to the compound by inhalation.

The incidence of major malformations, considered individually or collectively, among the litters of rats given vinylidene chloride by inhalation or ingestion was not significantly

different from that of the concurrent control litters (Table 6). No external or soft-tissue alteration occurred significantly more often among the litters of rats receiving vinylidene chloride than among the control litters.

Several minor skeletal alterations occurred significantly more often among the litters of rats exposed to 80 or 160 ppm vinylidene chloride by inhalation (Table 6). At 160 ppm, these included delayed ossification of the interparietal bone of the skull, unfused parietal and interparietal bones of the skull, delayed ossification of centra of cervical vertebrae, and wavy ribs. At 80 ppm, statistically significant increases were observed in the following skeletal alterations: delayed ossification of the parietal and interparietal bones of the skull, lumbar spurs (bilateral), and wavy ribs; in addition, the incidence of unfused parietal and interparietal bones of the skull was significantly decreased compared to the control value. Fetuses with wavy ribs were classified as either type I, those in which only a gentle curve in one or more ribs was observed, or type II, those in which one or more ribs had either a callous or a "U"-shaped bend (Figures 1-3). Among the litters of rats exposed to 160 ppm of vinylidene chloride, the incidence of type II but not type I wavy ribs was significantly increased; in contrast, type I but not type II wavy ribs occurred significantly more often at 80 ppm. No skeletal alteration

occurred among the litters of rats inhaling 20 ppm vinylidene chloride or ingesting water containing 200 ppm vinylidene chloride at an incidence significantly different from that of their respective control groups.

RABBITS

Maternal Toxicity. Single maternal deaths were observed in each of the two control groups and in the 80 ppm-exposed group; two deaths were seen among the rabbits exposed to 160 ppm vinylidene chloride. All of these deaths were associated with pneumonia, enteritis, or perimetritis, and thus did not appear to be compound-related. One dam each from the 80 ppm-exposed group and its concurrent control group delivered a litter on day 28 of gestation, i.e., one day prior to the scheduled day of cesarean section.

The body weight of the dams exposed to 160 ppm vinylidene chloride was not significantly different from that of the controls (Table 7); however, the body weight gain of these dams was significantly decreased on days 6-11 and 12-18 of gestation, (during the period of exposure) and significantly increased on days 19-28 (post-exposure). At the beginning of the experiment (day 6 of gestation), the 80 ppm-exposed dams weighed significantly less than the controls. The maternal weight gain of the 80 ppm-exposed dams was not significantly different from the control value during the

period of exposure, but a significant increase was observed during the post-exposure period.

The liver weight of the dams exposed to 80 ppm was significantly increased on both an absolute and relative basis. No effect on maternal liver weight was discerned among the dams exposed to 160 ppm.

Embryo- and Fetotoxicity. Observations made at the time of cesarean section of rabbits exposed to vinylidene chloride by inhalation are presented in Table 8. The percentage of pregnancy was not significantly altered by exposure to either concentration of vinylidene chloride. No statistically significant effect on the number of corpora lutea, implantations, or live or dead fetuses was noted among the rabbits inhaling vinylidene chloride. The incidence of resorptions among the litters of rabbits exposed to 160 ppm vinylidene chloride was significantly increased compared to that of its control group. Among the dams exposed to 160 ppm vinylidene chloride, four exhibited litters in which all or most of the implantations were resorbed; each of these four dams also showed a greater weight loss than the other dams exposed to 160 ppm, losing an average of approximately 450 gm of body weight during days 6-17 of gestation. Among the litters of dams exposed to 80 ppm vinylidene chloride,

the incidence of resorptions was slightly lower than that of its control group. Exposure to either concentration of vinylidene chloride had no significant effect on fetal body weight, crown-rump length, or sex ratio.

The incidence of major malformations was not significantly affected by exposure to vinylidene chloride (Table 9). No single external alteration occurred at an incidence significantly different from the control incidence among the litters of rabbits inhaling vinylidene chloride. The soft-tissue examination revealed a statistically significant decrease in the occurrence of minor satellite vessels branching off the innominate artery among the litters of rabbits exposed to 160 ppm but not among those exposed to 80 ppm. No other soft-tissue alterations were observed at an incidence that differed significantly from the control incidence. The skeletal examination revealed a significant increase and decrease in the incidence of 13 pairs of ribs and of delayed ossification of the 5th sternbrae, respectively, among the litters of rabbits inhaling 160 ppm vinylidene chloride. At 80 ppm, no skeletal alteration was observed at an incidence significantly different from that of the controls.

DISCUSSION

The results of these studies, summarized in Table 10, indicate that vinylidene chloride was not teratogenic in rats or rabbits inhaling the compound for 7 hrs/day at concentrations sufficiently high to produce maternal toxicity. In rats, inhalation of 80 or 160 ppm vinylidene chloride produced significant maternal effects including decreased weight gain, decreased food consumption, increased water consumption, and increased liver weight (160 ppm only). At 20 ppm, the only effects noted among the dams were minor changes in body weight and in the amount of water consumed. In comparison, pregnant rabbits inhaling vinylidene chloride exhibited decreased maternal weight gain at 160 ppm but not at 80 ppm. A statistically significant increase in liver weight was noted among the rabbits exposed to 80 ppm vinylidene chloride; because a similar effect was not discerned at 160 ppm, this increase was not interpreted to be related to vinylidene chloride exposure.

No single major malformation occurred among the litters of vinylidene chloride-exposed rats or rabbits at an incidence significantly different from that seen in the control litters. In addition, the incidence of total major malformations, when considered collectively, was not significantly altered by exposure to vinylidene chloride in either species. The

few major malformations which were observed among the vinylidene chloride-exposed litters have been noted to occur among control litters in past studies.

While a teratogenic effect was not observed, some evidence of embryotoxicity and fetotoxicity was noted in both rats and rabbits. In rats, exposure to inhaled vinylidene chloride resulted in a significantly increased incidence of several skeletal alterations at 80 and 160 ppm, which were maternally toxic concentrations. These alterations included wavy ribs and delayed ossification of various bones. In addition, a statistically significant increase in the incidence of resorptions was observed among the rats exposed to 80 ppm vinylidene chloride; however, this increase was not considered to be compound-related because it was attributable to a single litter which was entirely resorbed and because a similar effect was not seen at 160 ppm. At 20 ppm, a concentration which caused little evidence of maternal toxicity, no adverse effect on embryonal or fetal development was discerned.

Rabbits exposed to 160 ppm vinylidene chloride exhibited a marked increase in the incidence of resorptions. The occurrence of resorptions in each litter correlated well with the degree of toxicity observed in the individual dams.

Thus, it is not clear whether the increased incidence of resorptions was due directly to the compound or indirectly to maternal toxicity. Exposure of rabbits to 160 ppm vinylidene chloride also resulted in a significant change in the incidence of several minor fetal alterations, including an increased incidence of 13 pairs of ribs (the normal number is 12 or 13) and decreased incidence of minor satellite vessels and of delayed ossification of the 5th sternbra. At 80 ppm, a level which was not maternally toxic to rabbits, no significant evidence of embryotoxicity or fetotoxicity was observed.

Most of the fetal alterations which occurred at an increased incidence in either species were minor variants, commonly seen in teratologic studies when maternally toxic dose levels of test agents are employed. However, increased occurrences of wavy ribs, as seen among the litters of rats inhaling 80 or 160 ppm vinylidene chloride, are seen less frequently and appear to be more compound-specific. The induction of wavy ribs has been associated with several compounds including insulin (Lichtenstein et al., 1951), clomiphene and other basic phenolic ethers (Diener and Hsu, 1967) and hexachlorophene (Kimmel, 1972). In the present study, the incidence of wavy ribs among the fetuses and

litters of rats exposed to vinylidene chloride was 4 and 33%, respectively, at 80 ppm and 7 and 38%, respectively, at 160 ppm. The frequency of this alteration among the control groups from eight other recent studies involving 2,708 fetuses and 229 litters ranged from 0-2% among fetuses and 0-17% among litters. These figures are consistent with the range of control values in the present study, 0-2% among fetuses and 0-18% among litters.

The severity of the wavy ribs appeared to increase in a dose-related manner. At 160 ppm most of the fetuses with wavy ribs exhibited a callous or even a "U"-shaped bend in the rib, whereas at 80 ppm a gentle wave in the rib was seen more often. The increased occurrence of wavy ribs in rats is regarded to be a manifestation of embryotoxicity but is not generally considered to constitute a teratogenic effect (personal communication, J. G. Wilson¹). In fact, there is some evidence indicating that wavy ribs are a reversible phenomenon (Diener, 1973).

To evaluate the embryotoxic potential of ingested vinylidene chloride, rats were given the compound in their drinking water at a concentration of 200 ppm, the solubility limit of the compound in water. No evidence of maternal toxicity or teratogenicity was discerned among the rats maintained on

¹Childrens Hospital Research Foundation, Elland and Bethesda Avenues, Cincinnati, Ohio.

the vinylidene chloride containing water. The only statistically significant response observed among the litters of rats given the compound in the drinking water was an increase in the average fetal crown-rump length; although this response was statistically significant, it was not considered to be toxicologically significant.

Maintenance of pregnant rats on drinking water containing 200 ppm of vinylidene chloride had less effect on the dam or her offspring than exposure to either 80 or 160 ppm of the test material by inhalation. The average daily dose of vinylidene chloride received by the rats given the compound in their drinking water was calculated to be approximately 40 mg/kg/day. Estimates of the total amount of vinylidene chloride metabolized in rats indicate that a single gavage administration of 40 mg/kg vinylidene chloride is approximately equivalent to a single 7-hr inhalation exposure to 120 ppm of the compound (personal communication, M. J. McKenna²). Thus, the sensitivity of the rat to vinylidene chloride was apparently greater when vinylidene chloride was inhaled than when it was ingested.

Diurnal variation in the metabolism of vinylidene chloride may have been responsible for the apparent route-dependent

²Toxicology Research Laboratory, The Dow Chemical Company, Midland, Michigan.

difference in the sensitivity to vinylidene chloride. A major pathway for the detoxification of vinylidene chloride is conjugation of a reactive metabolite with glutathione (McKenna et al., 1977). Levels of glutathione are known to undergo diurnal variation (Jaeger et al., 1973; Watanabe et al., 1976), rising markedly during the late evening and early morning hours (the period during which the rat normally eats and drinks). Therefore, it is hypothesized that, in the drinking water study, the available levels of glutathione may have been sufficient to prevent toxicity; whereas in the inhalation study, toxicity may have resulted due to the lowered availability of glutathione during the exposure period (approximately 8:30 AM - 3:30 PM).

In these studies, adult rats appeared to be slightly more sensitive than adult rabbits to the toxicity of inhaled vinylidene chloride. However, the susceptibility of the developing embryo to vinylidene chloride appeared to be comparable in the two species since embryotoxicity was observed only at levels of exposure which caused maternal toxicity.

In conclusion, vinylidene chloride was not teratogenic in rats or rabbits inhaling up to 160 ppm of the compound for 7 hrs/day or in rats given water containing 200 ppm of the compound. Some evidence of embryotoxicity or fetotoxicity

was observed in both rats and rabbits exposed to vinylidene chloride by inhalation; these effects were associated with maternally toxic levels of exposure. At concentrations of vinylidene chloride which had little or no effect on the dam, no adverse effect on embryonal or fetal development was discerned in either species.

REFERENCES

1. ACGIH (American Conference of Governmental Industrial Hygienists) Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1977.
2. Balmer, M. F., Rampy, L. W., and Quast, J. F. (1976). 90-Day repeated inhalation toxicity study of vinylidene chloride in rats. Report to the Manufacturing Chemists Association.
3. Bartsch, H., Malaveille, C., Montesano, R., and Tomatis, L. (1975). Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in *Salmonella typhimurium*. *Nature* 255, 641-643.
4. Carpenter, C. P., Smyth, H. F., Jr., and Pozzani, U. C. (1949). The assay of acute vapor toxicity, and the grading and interpretation of results on ninety-six chemical compounds. *J. Ind. Hyg. Toxicol.* 31, 343-346.
5. Dawson, A. B. (1926). A note on the staining of the skeleton of cleared specimens with alizarin red-S. *Stain Tech.* 1, 123-124.
6. Diener, R. M. (1973). The wavy rib syndrome. *The Bulletin of the Society of Pharmacological and Environmental Pathologists.* No. 3, 8-9.
7. Diener, R. M. and Hsu, B.Y.D. (1967). Effects of certain basic phenolic ethers on the rat fetus. *Toxicol. Appl. Pharmacol.* 10, 565-576.
8. Gage, J. C. (1970). Subacute inhalation toxicity of 109 industrial chemicals. *Brit. J. Ind. Med.* 27(1), 1-18.
9. Greim, H., Bonse, G., Radwan, Z., Reichert, D., and Henschler, D. (1975). Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. *Biochem. Pharmacol.* 24, 2013-2017.

10. Haseman, J. K. and Hoel, D. G. (1974). Table of Gehan's generalized Wilcoxon test with fixed point censoring. J. Statist. Comput. Simul. 3, 117-135.
11. Humiston, C. G., McCollister, S. B., and Quast, J. F. (1975). Results of a 90-day study incorporating vinylidene chloride in the drinking water of rats. Report to the Manufacturing Chemists Association.
12. Jaeger, R. J., Conolly, R. B., and Murphy, S. D. (1973). Diurnal variation of hepatic glutathione concentration and its correlation with 1,1-dichloroethylene inhalation toxicity in rats. Res. Commun. Chem. Pathol. Pharmacol. 6, 465-471.
13. Jenkins, L. J., Jr., Trabulus, M. J., and Murphy, S. D. (1972). Biochemical effects of 1,1-dichloroethylene in rats. Comparison with carbon tetrachloride and 1,2-dichloroethylene. Toxicol. Appl. Pharmacol. 23, 501-510.
14. Kimmel, C. A., Moore, W., and Stara, J. F. (1972). Hexachlorophene teratogenicity in rats. Lancet 2, 765.
15. Kopf, R., Lorenz, D., and Salewski, E. (1964). Procedure for staining implantation sites of fresh rat uteri. Naunyn-Schmiedeberg's Arch. Exp. Path. Pharmacol. 247, 121-135.
16. Lichtenstein, H., Guest, G. M., and Warkany, J. (1951). Abnormalities in offspring of white rats given protamin zinc insulin during pregnancy. Proc. Soc. Exp. Biol. Med. 78, 398-402.
17. McCann, J., Choi, E., Yamasaki, E., and Ames, B. N. (1975). Detection of carcinogens in the salmonella microsome test: assay of 300 chemicals. Proc. Natl. Acad. Sci. U.S.A. 72, 5135-5139.
18. McKenna, M. J., Watanabe, P. G., and Gehring, P. J. The pharmacokinetics of vinylidene chloride in the rat. Env. Health Perspectives, in press.

19. Prendergast, J. A., Jones, R. A., Jenkins, L. J., Jr., and Siegel, J. (1967). Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. *Toxicol. Appl. Pharmacol.* 10, 270-289.
20. Rylova, M. L. (1953). Toxicity of 1,1-ethylene dichloride. *Farmakol. i. Toksikol.* 16, 47-50.
21. Siegel, J., Jones, R. A., Coon, R. A., and Lyon, J. P. (1971). Effects on experimental animals of acute, repeated, and continuous inhalation exposures to dichloroacetylene mixtures. *Toxicol. Appl. Pharmacol.* 18, 168-174.
22. Siegel, S. (1956). Non-Parametric Statistics for the Behavioral Sciences. McGraw-Hill Book Company, Inc., New York, New York.
23. Staples, R. E. (1974). Detection of visceral alterations in mammalian fetuses. *Teratology* 9, A-37.
24. Steel, R.G.D. and Torrie, H. H. (1960). Principles and Procedures of Statistics. McGraw-Hill Book Company, Inc., New York, New York.
25. Watanabe, P. G. Hefner, R. E. Jr., and Gehring, P. J. (1976). Vinyl chloride-induced depression of hepatic non-protein sulfhydryl content and effects on bromosulphalein (BSP) clearance in rats. *Toxicology* 6, 1-8.
26. Wilson, J. G. (1965). Teratology: Principles and Techniques. The University of Chicago Press, Chicago, Illinois, 262-277.

TABLE 1

CONCENTRATION OF VARIOUS IMPURITIES IN THE SAMPLES
OF VINYLIDENE CHLORIDE USED FOR THE TERATOLOGY STUDIES

	<u>Sample I</u> ^a	<u>Sample II</u>	<u>Sample III</u>	<u>Sample IV</u>
Concentration in ppm (wt/wt) ^b				
Vinyl chloride	43	66	N.D. ^c	25
Trans 1,2-dichloroethylene	109	340	N.D.	9
Cis 1,2-dichloroethylene	32	47	210	0.6
1,1,1-trichloroethane	2	8	20	N.D.
1,1,2-trichloroethane	<0.2	<0.2	100	N.D.
Monomethylether of hydroquinone (MEHQ)	209	400	220	N.D.

^aSample I was used for the 160 ppm inhalation exposure; Sample II, the 80 ppm inhalation exposure; Sample III, the 20 ppm inhalation exposure; Sample IV, the drinking water study.

^bDetermined by gas-liquid chromatography.

^cN.D. = not detected.

TABLE 2

BODY AND LIVER WEIGHTS OF PREGNANT RATS EXPOSED TO
VINYLIDENE CHLORIDE BY INHALATION OR BY INGESTION

Route of Exposure ppm Vinylidene Chloride	Inhalation ^a						Drinking Water	
	0	20	0	80	0	160	0	200
Number of dams	40	40	20	28	17	26	24	26
Maternal body weight (g) on gestation								
day 6	255±26 ^b	246±27	244±15	242±18	278±21	268±21	290±13	284±30
10	272±28	258±23*	264±15	253±23	292±24	269±20*	309±16	301±22
16	310±29	301±24	307±19	293±24*	329±18	314±24	348±20	342±26
21	390±39	382±30	382±24	366±34	400±48	394±29	421±28	414±35
Maternal weight gain (g) on gestation								
days 6-9	15±12 ^b	12±12	20±8	11±14*	14±13	2±10*	19±7	16±18
10-15	37±17	44±14	43±12	41±18	36±7	44±14	39±6	40±14
16-20	80±18	80±12	75±15	72±16	64±10	80±11*	72±16	72±20
Liver weight on day 21 of gestation								
absolute ^c	15.2±1.9	15.1±1.6	15.9±1.0	15.7±1.7	15.9±1.4	16.7±1.9	15.9±1.7	15.2±1.4
relative ^d	39.0±3.8	39.5±2.9	41.7±2.5	43.1±3.7	39.8±2.2	42.5±3.9*	37.9±3.9	37.0±3.4

^aRats were exposed to 20, 80, or 160 ppm vinylidene chloride for 7 hrs/day or were given drinking water containing 200 ppm of the compound on days 6-15 of gestation.

^bMean ± S.D.

^cg, mean ± S.D.

^dg liver/kg body weight, mean ± S.D.

*Significantly different from the concurrent control value by a one-way analysis of variance, $p < 0.05$.

Individual animal data are presented in Table A-1.

TABLE 3

AMOUNT OF FOOD AND WATER CONSUMED BY PREGNANT RATS EXPOSED TO
VINYLIDENE CHLORIDE BY INHALATION

		ppm Vinylidene Chloride ^a					
		0	20	0	80	0	160
Food consumption (g)							
on gestation days	6-8	20±4 ^b	20±3	22±3	18±4*	22±3	18±6*
	9-11	22±4	22±4	26±5	20±3*	22±4	21±6
	12-14	24±4	25±4	25±2	22±3*	23±6	26±3*
	15-17	27±4	27±3	29±4	27±3*	27±5	29±4
	18-20	29±3	29±4	28±2	27±4	26±4	36±8*
Water consumption (g)							
on gestation days	6-8	42±10 ^b	42±7	34±12	34±10	40±11	53±13*
	9-11	48±8	51±9	50±10	45±12	38±16	60±13*
	12-14	52±10	58±9*	53±6	49±13	40±14	65±10*
	15-17	64±11	69±10*	59±10	66±7*	56±13	76±16*
	18-20	62±9	64±10	58±6	60±8	55±13	74±12*

^aRats were exposed to vinylidene chloride for 7 hrs/day on days
6-15 of gestation.

^bExpressed as grams/rat/day, mean ± S.D.

*Significantly different from the concurrent control value by an analysis
of variance, $p < 0.05$.

TABLE 4

LIQUID AND FOOD CONSUMPTION BY PREGNANT RATS
MAINTAINED ON DRINKING WATER CONTAINING VINYLIDENE CHLORIDE

Days of Gestation	LIQUID			FOOD	
	Control	Vinylidene Chloride ^a		Control	Vinylidene Chloride
6	47±8 ^b	50±9	}	24±2 ^b	23±3
7	49±8	49±6			
8	50±8	51±8	}	24±3	23±3
9	54±12	51±9			
10	53±13	54±12	}	24±2	24±3
11	54±14	59±11			
12	56±14	59±9	}	25±2	25±2
13	58±10	59±7			
14	59±9	59±12	}	27±2	26±4
15	67±9	66±12			
16	64±10	62±19	}	31±8	31±9
17					
18	62±16	64±10	}	25±7	24±8
19					
20	54±11	54±9		24±3	24±4

^a Vinylidene chloride was given in the drinking water at a concentration of 200 ppm on days 6-15 of gestation.

^b g/rat/day, mean ± S.D.

No values differed significantly from control by an analysis of variance, $p < 0.05$.

TABLE 5

OBSERVATIONS MADE AT THE TIME OF CESAREAN SECTION OF RATS EXPOSED TO VINYLIDENE CHLORIDE BY INHALATION OR BY INGESTION

Route of Exposure ppm Vinylidene Chloride	Inhalation ^a						Drinking Water	
	0	20	0	80	0	160	0	200
No. of bred females	47	44	21	30	18	30	27	26
No. deaths	0	0	0	0	0	0	0	0
Percent Pregnant ^b	85(40/47)	91(40/44)	95(20/21)	97(29/30) ^c	94(17/18)	90(27/30) ^c	89(24/27)	100(26/26)
Pregnancies detected by stain ^d	0	1	1	1	0	0	0	0
Percent pregnant, total ^e	85(40/47)	93(41/44)	100(21/21)	100(30/30)	94(17/18)	90(27/30)	89(24/27)	100(26/26)
Number of litters	40	40	20	27	17	26	24	26
Corpora lutea/dam ^f	13±2	14±3	12±2	12±2	14±2	13±2	12±2	14±3
Implantation sites/dam ^f	12±3	12±2	12±2	11±3	13±2	12±2	11±3	12±4
Pregnancy wastage ^f	1±2	2±2	1±2	1±2	1±1	1±2	2±2	3±3
Live fetuses/litter ^f	12±3	12±2	12±2	10±4	12±2	11±2	10±3	11±4
Resorptions/litter ^{f,g}	0.2±0.5	0.4±0.7	0.4±0.9	0.8±2.4	0.4±0.7	0.5±0.7	0.3±0.5	0.4±0.8
% Implantations resorbed ^g	2(9/479)	3(16/478)	3(8/238)	8(24/316)*	3(7/216)	4(14/305)	3(8/238)	4(11/301)
% Litters with resorptions ^g	18(7/40)	28(11/40)	25(5/20)	39(11/28)	29(5/17)	42(11/26)	33(8/24)	27(7/26)
% Litters totally resorbed ^g	0(0/40)	0(0/40)	0(0/20)	4(1/28)	0(0/17)	0(0/26)	0(0/24)	4(1/26)
Resorptions/litters with resorptions ^g	1.3(9/7)	1.5(16/11)	1.6(8/5)	2.2(24/11)	1.4(7/5)	1.3(14/11)	1.0(8/8)	1.6(11/7)
% Dead fetuses	(0/479)	(0/478)	(0/230)	(0/292)	(0/209)	(0/291)	(0/250)	(0/290)
Fetal sex ratio, M:F	50:50	53:47	43:57	50:50	48:52	51:49	49:51	50:50
Fetal body weight, g ^h	5.60±0.40	5.61±0.28	5.54±0.26	5.72±0.45	5.52±0.26	5.47±0.82	5.79±0.44	5.70±0.30
Fetal crown-rump length, mm ^h	43.9±1.1	44.0±0.9	44.4±1.0	45.1±1.3	43.8±0.8	43.6±2.6	46.6±2.4	47.8±1.3**

^aBred rats were exposed to 20, 80, or 160 ppm vinylidene chloride for 7 hrs/day or were given drinking water containing 200 ppm of the compound on days 6-15 of gestation.

^bNo. of females with visible implantation sites at the time of cesarean section/total no. of bred females.

^cOne dam at the intermediate and high dose levels delivered a litter on days 18 and 21 of gestation, respectively; these dams were included in the calculation of the pregnancy rates. Their litters were not examined for fetal alterations.

^dNo. of females with implantation sites detected only after staining the uterus with sodium sulfide stain.

^eNo. of females with implantation sites as observed either visually at the time of cesarean section or necropsy or after staining the uterus with sodium sulfide stain/total no. of bred females.

^fMean ± S.D.

^gResorptions detected only by sodium sulfide staining were not included in these calculations.

^hMean of the litter means ± S.D.

*Significantly different from the concurrent control value by Fishers exact probability test, p<0.05.

**Significantly different from the concurrent control value by a one-way analysis of variance, p<0.05.

Individual litter data are presented in Table A-2.

TABLE 6

INCIDENCE OF FETAL ALTERATIONS AMONG LITTERS OF RATS EXPOSED TO
VINYLIDENE CHLORIDE BY INHALATION OR BY INGESTION

Route of Exposure ^a		Inhalation						Drinking Water	
ppm Vinylidene Chloride		0	20	0	80	0	160	0	200
No. Fetuses/No. Litters Examined									
EXTERNAL AND SKELETAL EXAMINATION		470/40	462/40	230/20	292/27	209/17	291/26	250/24	290/25
SOFT TISSUE EXAMINATION		162/40	158/40	77/20	103/27	70/17	100/26	86/24	100/25
SKULL BONE EXAMINATION		303/39	304/39	153/20	189/26	139/17	191/26	164/23	190/24
% Affected (No. Affected)									
<u>Total Major Malformations^b</u>	F ^c	0.4(2)	0	0.4(1)	0.7(2)	2(4)	5(14)	0	0
	L	5(2)	0	5(1)	7(2)	12(2)	15(4)	0	0
<u>External Examination</u>									
Short trunk and multiple defects*	F	0.2(1) ^d	0	0	0	0.4(1) ^e	0	0	0
	L	2(1)	0	0	0	6(1)	0	0	0
Subcutaneous edema	F	0	0.2(1)	0	0	0	0	0	0
	L	0	2(1)	0	0	0	0	0	0
Omphalocele*	F	0	0	0	0.3(1)	0	0	0	0
	L	0	0	0	4(1)	0	0	0	0
Narrow head, pointed snout*	F	0	0	0	0.3(1)	0	0	0	0
	L	0	0	0	4(1)	0	0	0	0
Subcutaneous hemorrhage - head, neck, or back	F	0.6(3)	0.4(2)	0	0.3(1)	0	0	0.4(1)	1(4)
	L	8(3)	2(1)	0	4(1)	0	0	4(1)	8(2)
<u>Soft Tissue Examination</u>									
Diaphragmatic hernia*	F	0	0	1(1)	0	0	0	0	0
	L	0	0	5(1)	0	0	0	0	0
Yellow-colored focus on liver	F	0	0	0	0	1(1)	0	0	0
	L	0	0	0	0	6(1)	0	0	0
Hemorrhage, liver	F	0	0.6(1)	0	1(1)	0	0	1(1)	0
	L	0	2(1)	0	4(1)	0	0	4(1)	0
Hydroureters	F	0	0	0	0	0	4(4)	1(1)	3(3)
	L	0	0	0	0	0	11(3)	4(1)	12(3)
Dilated renal pelvis	F	0	0	0	0	1(1)	0	0	0
	L	0	0	0	0	6(1)	0	0	0
Ectopic ovaries*	F	1.2(1)	0	0	0	1(1)	0	0	0
	L	5(2)	0	0	0	6(1)	0	0	0
Head - subcutaneous hemorrhage ^f	F	0.6(1)	0	2(2)	2(2)	1(1)	0	3(3)	3(3)
	L	2(1)	0	10(2)	4(1)	6(1)	0	12(3)	12(3)
Head - thickened dermal and subcutaneous tissue in ocular region	F	0	2(3)	0	0	0	0	0	0
	L	0	8(3)	0	0	0	0	0	0

TABLE 6 (Continued)

Route of Exposure ^a ppm Vinylidene Chloride		Inhalation						Drinking Water	
		0	20	0	80	0	160	0	200
<u>Skeletal Examination</u>									
Skull - delayed ossification of parietal bone	F	3(8)	1(3)	1(2)	6(11)**	4(6)	7(13)	2(3)	3(5)
	L	13(5)	8(3)	10(2)	27(7)	12(2)	27(7)	9(2)	12(3)
-delayed ossification of interparietal bone	F	14(42)	12(36)	8(13)	20(38)**	17(24)	30(57)**	12(19)	17(32)
	L	44(17)	46(18)	35(7)	50(13)	47(8)	77(20)	43(10)	46(11)
-delayed ossification of any skull bone	F	14(42)	12(36)	8(13)	20(38)**	17(24)	31(59)**	12(19)	17(32)
	L	44(17)	46(18)	35(7)	50(13)	47(8)	77(20)	43(10)	46(11)
-unfused parietal and interparietal	F	0.3(1)	0.3(1)	11(17)	4(8)**	4(6)	17(33)**	57(93)	55(104)
	L	3(1)	3(1)	45(9)	19(5)	24(4)	54(14)	87(20)	83(20)
-bone island, interparietal	F	0	0.3(1)	1(1)	0	0	2(3)	0(0)	1(2)
	L	0	2(1)	5(1)	0	0	8(3)	0(0)	8(2)
-misshapen parietal and interparietal	F	0	0	1(1)	0	0	0	0	0
	L	0	0	5(1)	0	0	0	0	0
-extra site of ossification between skull bones	F	0	0	0	0.5(1)	0	0	1(1)	0
	L	0	0	0	4(1)	0	0	4(1)	0
-delayed ossification of zygomatic arch	F	0	0	0	1(2)	0	0	0	0
	L	0	0	0	8(2)	0	0	0	0
Vertebrae - delayed ossification of atlas	F	0	0	0	0	0	0.3(1)	0	0
	L	0	0	0	0	0	4(1)	0	0
-delayed ossification of cervical centra	F	7(34)	13(58)	10(24)	16(47)	14(30)	37(107)**	18(46)	14(42)
	L	42(17)	48(19)	70(14)	63(17)	77(13)	77(20)	67(16)	72(18)
-delayed ossification of thoracic centrum	F	0	0	0	0.3(1)	0	0	0	0
	L	0	0	0	4(1)	0	0	0	0
-unfused cervical centrum	F	0	0	0	0.3(1)	0	0.3(1)	0	0
	L	0	0	0	4(1)	0	4(1)	0	0
-unfused thoracic centrum	F	0.2(1)	0.2(1)	0.4(1)	1(2)	0	0.3(1)	1(2)	0.3(1)
	L	2(1)	2(1)	5(1)	7(2)	0	4(1)	8(2)	4(1)
-missing some thoracic, all lumbar and all sacral vertebrae* ⁸	F	0.2(1)	0	0	0	0.5(1)	0	0	0
	L	2(1)	0	0	0	6(1)	0	0	0
-missing one thoracic vertebra and one lumbar vertebra*	F	0	0	0	0	1(2)	5(14)	0	0
	L	0	0	0	0	6(1)	15(4)	0	0
-any missing vertebra*	F	0.2(1)	0	0	0	1(3)	5(14)	0	0
	L	2(1)	0	0	0	6(1)	15(4)	0	0
-fused vertebrae, thoracic region*	F	0	0	0	0	0.5(1)	0	0	0
	L	0	0	0	0	6(1)	0	0	0
-extra thoracic vertebra and pair of ribs*	F	0	0	0	0	0.5(1)	0	0	0
	L	0	0	0	0	6(1)	0	0	0

TABLE 6 (Continued)

Route of Exposure ^a ppm Vinylidene Chloride		Inhalation						Drinking Water	
		0	20	0	80	0	160	0	200
Ribs - unilateral spur on 1st lumbar	F	13(59)	12(56)	12(28)	13(38)	13(28)	16(45)	13(32)	16(46)
	L	65(26)	65(26)	65(13)	67(18)	71(12)	73(19)	79(19)	84(21)
-bilateral spurs on 1st lumbar	F	8(40)	5(25)	5(11)	10(30)**	8(16)	10(30)	6(14)	7(19)
	L	50(20)	35(14)	35(7)	63(17)	59(10)	62(16)	33(8)	40(10)
-any spurs on 1st lumbar	F	21(99)	18(81)	17(39)	23(68)	21(44)	26(75)	18(46)	22(65)
	L	78(31)	75(30)	75(15)	85(23)	82(14)	85(22)	88(21)	84(21)
-unilateral wavy ribs	F	1(5)	1(4)	0	1(4)	1(2)	1(3)	0.4(1)	0.3(1)
	L	12(5)	10(4)	0	15(4)	6(1)	8(2)	4(1)	4(1)
-bilateral wavy ribs	F	1(4)	2(9)	0	2(7)**	0.5(1)	7(19)**	0	1(2)
	L	10(4)	12(5)	0	26(7)	6(1)	35(9)	0	4(1)
-any wavy ribs	F	2(9)	3(13)	0	4(11)**	1(3)	8(22)**	0.4(1)	1(3)
	L	18(7)	18(7)	0	33(9)	6(1)	38(10)	4(1)	8(2)
-Class I wavy ribs ^h	F	1(5)	2(10)	0	3(9)**	1(2)	3(9)	0	1(3)
	L	12(5)	18(7)	0	30(8)	6(1)	19(5)	0	8(2)
-Class II wavy ribs ^h	F	1(4)	1(3)	0	1(2)	0.5(1)	4(13)**	0.4(1)	0
	L	10(4)	5(2)	0	7(2)	6(1)	35(9)	4(1)	0
-any shortened 12th rib ⁱ	F	0	0	0	0	1(2)	4(11)	0	0
	L	0	0	0	0	6(1)	15(4)	0	0
-missing 12th rib - unilateral ⁱ	F	0	0	0	0	0.5(1)	1(4)	0	0
	L	0	0	0	0	6(1)	8(2)	0	0
-missing 13th pair of ribs only** ^d	F	0	0	0	0	1(2)	5(14)	0	0
	L	0	0	0	0	6(1)	15(4)	0	0
-missing ribs - multiple ribs** ^g	F	0.2(1)	0	0	0	0.5(1)	0	0	0
	L	2(1)	0	0	0	6(1)	0	0	0
-any missing ribs	F	0.2(1)	0	0	0	1(3)	5(15)	0	0
	L	2(1)	0	0	0	6(1)	15(4)	0	0
-extra ribs	F	1(6)	0.2(1)	0.4(1)	1(2)	2(4)	2(6)	4(1)	0
	L	8(3)	2(1)	5(1)	7(2)	12(2)	19(5)	4(1)	0
Sternebrae - delayed ossification of sternebrae	F	4(21)	4(20)	5(12)	3(10)	4(9)	5(15)	5(13)	3(9)
	L	32(13)	30(12)	30(6)	30(8)	41(7)	31(8)	42(10)	24(6)
-unossified sternebrae	F	0	0	0	0	0	1(4) ^e	0.4(1)	0
	L	0	0	0	0	0	4(1)	4(1)	0
-unfused sternebrae	F	1(5)	1(3)	0	1(2)	0.5(1)	0.3(1)	1(2)	0
	L	12(5)	8(3)	0	4(1)	6(1)	4(1)	8(2)	0
-fused sternebrae ^g	F	0.2(1)	0	0	0	0	0	0	0
	L	2(1)	0	0	0	0	0	0	0
Limbs and Digits - delayed ossification of metacarpels or metatarsals	F	0	0	0	0	0	4(13)	0	0
	L	0	0	0	0	0	12(3)	0	0

^aPregnant rats were exposed to 20, 80, or 160 ppm vinylidene chloride for 7 hrs/day or were given drinking water containing 200 ppm of the compound on days 6-15 of gestation.

^bTotal major malformations detected by external, soft tissue, or skeletal examination.

^cF = fetuses; L = litters.

^dIn addition to short trunk, this fetus exhibited hypoplastic tail, inward rotation of the hindlimbs, ectopic ovaries, missing 4-13th thoracic vertebrae, missing all lumbar and all sacral vertebrae, and missing 4-13th pairs of ribs.

^eThis fetus demonstrated short trunk, acaudia, anteriorly displaced ovaries and uterine horns, missing 3-13th thoracic vertebrae, missing all lumbar and sacral vertebrae, and missing 2-13th ribs.

^fThis alteration was observed during the examination of the heads fixed in Bouin's solution.

^gThis alteration was observed only among fetuses exhibiting a short trunk in the external examination.

^hType I = gentle wave; Type II = callous or "U"-shaped bend in rib.

ⁱThis alteration occurred only in fetuses missing one thoracic and one lumbar vertebrae.

*This alteration was considered to be a major malformation.

**Significantly different from control value by a modified Wilcoxon test, $p < 0.05$.

Individual litter data are presented in Table A-3.

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TABLE 7

BODY AND LIVER WEIGHTS OF PREGNANT RABBITS EXPOSED TO
VINYLIDENE CHLORIDE BY INHALATION

	ppm Vinylidene Chloride ^a			
	0	80	0	160
Number of dams	14	18	13	15
Maternal body weight on gestation				
day 6	4.33±0.32 ^b	4.04±0.34*	4.03±0.27	4.07±0.38
12	4.28±0.34	4.02±0.30*	4.01±0.27	3.90±0.37
19	4.34±0.33	4.00±0.44*	4.12±0.29	3.86±0.40
29	4.42±0.29	4.22±0.35	4.19±0.32	4.07±0.40
Maternal weight gain (kg) on gestation				
days 6-11	-0.05±0.06 ^b	-0.03±0.11	-0.02±0.09	-0.17±0.14*
12-18	0.06±0.07	-0.02±0.22	0.12±0.08	-0.04±0.14*
19-28	0.07±0.10	0.23±0.15*	0.07±0.22	0.21±0.13*
Liver weight on day 29 of gestation				
absolute ^c	99±14	107±12*	104±16	109±19
relative ^d	22.3±2.9	25.3±3.0*	24.8±4.0	26.5±3.6

^aPregnant rabbits were exposed to 80 or 160 ppm vinylidene chloride for 7 hrs/day on days 6-18 of gestation.

^bMean ± S.D.

^cg, mean ± S.D.

^dg liver/kg body weight, mean ± S.D.

*Significantly different from the concurrent control value by a one-way analysis of variance, $p < 0.05$.

Individual animal data are presented in Table A-4.

TABLE 8

OBSERVATIONS MADE AT THE TIME OF CESAREAN SECTION OF RABBITS INHALING VINYLIDENE CHLORIDE

	ppm Vinylidene Chloride ^a			
	0	80	0	160
No. of bred females	16	22	16	18
No. deaths	1	1	1	2
Percent pregnant ^b	100(16/16) ^c	91(20/22) ^c	88(14/16)	94(17/18) ^d
Pregnancies detected by stain ^e	0	1	0	0
Percent pregnant, total ^f	100(16/16)	96(21/22)	88(14/16)	94(17/18)
Number of litters	14	18	13	15
Corpora lutea/dam ^g	9±2	9±2	9±2	8±3
Implantation sites/dam ^g	9±2	9±1	9±3	9±2
Pregnancy wastage ^g	0.1±0.4	0.3±0.8	1.0±1.8	0.6±0.8
Live fetuses/litter ^g	8±2	9±1	8±3	6±4
Resorptions/litter ^{g,h}	0.8±1.2	0.7±0.9	0.3±0.6	2.7±3.9*
% Implantations resorbed ^h	9(12/128)	7(13/168)	3(4/115)	31(41/132)**
% Litters with resorptions ^h	43(6/14)	50(9/18)	23(3/13)	53(8/15)
% Litters totally resorbed ^h	(0/14)	(0/18)	(0/13)	20(3/15)
Resorptions/litters with resorptions	1.5(9/6)	0.8(7/9)	1.3(4/3)	5.1(41/8)
% Dead fetuses	(0/116)	(0/155)	(0/111)	1(1/91)
Fetal sex ratio, M:F	52:48	56:44	52:48	53:47
Fetal body weight, g ⁱ	36.8±3.7	36.9±5.0	37.4±7.6	36.0±4.2
Fetal crown-rump length, mm ⁱ	94.6±2.8	93.4±4.1	93.4±6.2	92.9±4.7

^aBred rabbits were exposed to 80 or 160 ppm vinylidene chloride for 7 hrs/day on days 6-18 of gestation.

^bNo. of females with visible implantation sites at the time of cesarean section or necropsy/total no. of bred females.

^cOne 80 ppm-exposed dam and one dam from its control group which both delivered litters on day 28 of gestation were included in the calculation of the pregnancy rates. Their litters were not examined for fetal alterations.

^dThe single non-pregnant rabbit exhibited a purulent inflammation of the ovaries.

^eNo. of females with implantation sites detected only after staining the uterus with sodium sulfide stain.

^fNo. of females with implantation sites as observed either visually at the time of cesarean section or necropsy or after staining the uterus with sodium sulfide stain/total no. of bred females.

^gMean ± S.D.

^hResorptions detected only by sodium sulfide staining of the uterus were not included in these calculations.

ⁱMean of litter means ± S.D.

*Significantly different from the control mean by a one-way analysis of variance, $p < 0.05$.

**Significantly different from the control value by Fishers exact probability test, $p < 0.05$.

Individual litter data are presented in Table A-5.

TABLE 9

INCIDENCE OF FETAL ALTERATIONS AMONG LITTERS OF RABBITS EXPOSED TO
VINYLIDENE CHLORIDE BY INHALATION

		ppm Vinylidene Chloride ^a			
		0	80	0	160
		No. Fetuses/No. Litters Examined			
EXTERNAL AND SKELETAL EXAMINATION		116/14	155/18	111/13	91/12
SOFT TISSUE EXAMINATION		44/14	56/18	42/13	37/12
		% Affected (No. Affected)			
<u>Total Major Malformations</u> ^b	F ^c	0	2(3)	2(2)	2(2)
	L	0	17(3)	15(2)	16(2)
<u>External Examination</u>					
Edema - neck and abdominal region	F	0	0	0	1(1)
	L	0	0	0	8(1)
<u>Soft Tissue Examination</u>					
Dilated cerebral ventricles*	F	0	2(1)	0	0
	L	0	5(1)	0	0
Heart - thinning of right ventricular wall*	F	0	0	0	3(1)
	L	0	0	0	8(1)
Satellite vessel off aorta	F	0	0	10(4)	0
	L	0	0	15(2)	0
Satellite vessels off innominate artery	F	9(4)	20(11)	31(13)	8(3)**
	L	21(3)	44(8)	62(8)	17(2)
Fused left carotid and innominate arteries	F	71(31)	55(31)	60(25)	78(29)
	L	93(13)	72(13)	77(10)	100(12)
Kidney - cortical indentation, unilateral	F	0	2(1)	0	0
	L	0	5(1)	0	0
<u>Skeletal Examination</u>					
Skull - delayed ossification	F	0	0	2(2)	2(2)
	L	0	0	8(1)	17(2)
-frontal ridge*	F	0	1(1)	0	0
	L	0	5(1)	0	0
-foramen, frontal bone	F	0	0	2(2)	0
	L	0	0	8(1)	0
-foramen, parietal bone	F	0	1(2)	2(2)	0
	L	0	11(2)	15(2)	0
-extra suture lines, parietal bone	F	0	1(1)	0	1(1)
	L	0	5(1)	0	8(1)
-bone island, parietal bone	F	0	1(1)	0	1(1)
	L	0	5(1)	0	8(1)
-extra site of ossification between occipital condyles and atlas	F	0	0	0	1(1)
	L	0	0	0	8(1)
Ribs - 13th rib - bilateral	F	48(56)	45(70)	31(34)	50(45)**
	L	93(13)	89(16)	69(9)	100(12)
-13th rib - unilateral	F	16(19)	8(12)	10(11)	11(10)
	L	71(10)	56(10)	54(7)	58(7)
-lumbar spurs	F	7(8)	2(3)	6(7)	3(3)
	L	29(4)	17(3)	31(4)	25(3)
-shortened first thoracic	F	1(1)	0	0	0
	L	7(1)	0	0	0
-11 ribs on left and 12 ribs on right*	F	0	0	1(1)	0
	L	0	0	8(1)	0

TABLE 9 (Continued)

		ppm Vinylidene Chloride ^a			
		0	80	0	160
Vertebrae - extra cervical	F	0	1(1)	0	0
vertebrae*	L	0	5(1)	0	0
-extra and misshapen lumbar	F	0	0	1(1)	0
vertebrae*	L	0	0	8(1)	0
-hemivertebrae in thoracic					
region fused or forked rib	F	0	1(1)	0	1(1)
& misshapen centra*	L	0	5(1)	0	8(1)
Sternebrae - delayed ossifica-	F	3(3)	1(1)	0	2(2)
tion of 2nd sternebra	L	21(3)	5(1)	0	17(2)
-delayed ossification of	F	41(48)	27(42)	40(44)	21(19)**
5th sternebra	L	86(12)	67(12)	85(11)	58(7)
-delayed ossification of	F	33(38)	20(31)	21(23)	23(21)
6th sternebra	L	79(11)	67(12)	69(9)	58(7)
-unfused	F	1(1)	0	0	1(1)
	L	7(1)	0	0	8(1)
-fused	F	1(1)	2(3)	0	2(2)
	L	7(1)	11(2)	0	17(2)
-extra site of ossification					
between 5th and 6th	F	0	0	0	1(1)
sternebrae	L	0	0	0	8(1)
Limbs and Digits - delayed					
ossification of phalanges in	F	1(1)	0	0	0
first digit, bilateral	L	7(1)	0	0	0

^aRabbits were exposed to 80 or 160 ppm vinylidene chloride for 7 hrs/day on days 6-18 of gestation.

^bTotal major malformations detected by external, soft tissue, or skeletal examination.

^cF = fetuses; L = litters.

*This alteration was considered to be a major malformation.

**Significantly different from the concurrent control value by a modified Wilcoxon test, $p < 0.05$.

Individual litter data are presented in Table A-6.

TABLE 10

SUMMARY - VINYLIDENE CHLORIDE TERATOLOGIC STUDIES

ppm Vinylidene Chloride	Rats				Rabbits	
	Inhalation			Drinking Water	Inhalation	
	20	80	160	200	80	160
<u>Maternal Toxicity</u>						
Altered appearance and demeanor	no ^a	no	no	no	no	no
Body weight gain	--	dec	dec	--	--	dec
Food consumption	--	dec	dec	--	ND	ND
Water consumption	inc	inc	inc	--	ND	ND
Liver weight -						
absolute	--	--	--	--	inc	--
relative	--	--	inc	--	inc	--
<u>Embryo- and Fetotoxicity</u>						
Resorptions	--	inc	--	--	--	inc
Fetal body weight	--	--	--	--	--	--
Fetal crown-rump length	--	--	--	inc	--	--
External alterations	--	--	--	--	--	--
Soft tissue alterations	--	--	--	--	--	dec ^b
Skeletal alterations	--	inc	inc	--	--	yes ^c
Major malformations	--	--	--	--	--	--

^a(--) = not significantly different from the concurrent control value; dec = decreased; inc = increased; ND = no data.

^bDecreased incidence of minor satellite vessels off innominate artery.

^cDecreased incidence of delayed ossification of the 5th sternebra and increased incidence of 13 pairs of ribs.

TABLE A-1

INDIVIDUAL BODY AND LIVER WEIGHTS OF PREGNANT RATS EXPOSED TO
VINYLIDENE CHLORIDE BY INHALATION OR INGESTION

Route: Inhalation - Exposure Level: 0 ppm (Concurrent Controls for 20 ppm)

Animal Number	Maternal Body Weight (g)				Maternal Body Weight Gain (g)			Maternal Liver Weight (Day 21)	
	Day(s) of Gestation							Absolute (g)	Relative (g/kg Body Weight)
	6	10	16	21	6-9	10-15	16-20		
44-7746	225	249	273	328	24	24	55	13.61	41.49
7747	242	262	300	372	20	38	72	13.17	35.40
7748	226	243	289	377	17	46	88	15.47	41.03
7749	229	242	292	367	13	50	75	13.86	37.76
7751	254	270	317	390	16	47	73	14.88	38.15
7752	267	284	294	367	17	10	73	14.75	40.19
7753	244	265	309	382	21	44	73	16.18	42.36
7754	236	242	302	360	6	60	58	14.41	40.02
7755	240	252	288	351	12	36	63	16.03	45.67
7756	287	296	345	440	9	49	95	17.61	40.02
7758	227	223	232	309	-4	9	77	11.80	38.19
7759	217	217	273	332	0	56	59	11.67	35.15
7760	280	268	273	364	-12	5	91	15.60	42.86
7761	284	279	330	393	-5	51	63	13.76	35.01
7763B	252	279	315	410	27	36	95	15.69	38.27
7764B	ND	311	351	435	ND	40	84	19.67	45.22
7765B	224	248	305	385	24	57	80	17.23	44.75
7766B	270	285	315	385	15	30	70	16.43	42.68
7767B	255	281	320	405	26	39	85	17.00	41.98
7768B	212	233	277	351	21	44	74	14.48	41.25
7769B	ND	295	331	443	ND	36	112	19.28	43.52
7770B	227	257	266	355	30	9	89	14.77	41.60
7779	275	295	325	406	20	30	81	14.22	35.02
7780	252	277	316	400	25	39	84	13.67	34.18
7781	297	307	309	435	10	2	126	13.89	31.93
7782	277	310	358	451	33	48	93	18.30	40.58
7783	267	285	321	426	18	36	105	16.45	38.62
7784	314	325	334	380	11	9	46	16.77	44.13
7795	291	294 ^a	340	380	3 ^a	46 ^a	40	16.25	42.76
7796	231	321 ^a	307	394	90 ^a	-14 ^a	87	15.22	38.63
7797	280	261 ^a	328	421	-19 ^a	67 ^a	93	15.88	37.72
7798	207	284 ^a	247	286	77 ^a	-37 ^a	39	12.46	43.57
7799	270	295 ^a	318	415	25 ^a	23 ^a	97	16.01	38.58
7800	271	242 ^a	342	431	-29 ^a	100 ^a	89	15.46	35.87
7801	274	306 ^a	310	399	32 ^a	4 ^a	89	13.52	33.88
7802	227	266 ^a	308	384	39 ^a	42 ^a	76	13.27	34.56
7810	276	314	365	465	38	51	100	16.80	36.13
7813	271	283	343	434	12	60	91	14.37	33.11
7815	252	270	312	390	18	42	78	13.81	35.41
7816	253	244	308	387	-9	64	79	12.80	33.07
MEAN±SD	255±26	272±28	310±29	390±39	15±12	37±17	80±18	15.16±1.86	39.01±3.79

TABLE A-1 (Continued)

Route: Inhalation - Exposure Level: 20 ppm

Animal Number	Maternal Body Weight (g)				Maternal Body Weight Gain (g)			Maternal Liver Weight (Day 21)	
	Day(s) of Gestation							Absolute (g)	Relative (g/kg Body Weight)
	6	10	16	21	6-9	10-15	16-20		
44-7762A	251	258	293	340	7	35	47	15.00	44.12
7763A	240	252	268	364	12	16	96	14.22	39.06
7764A	235	227	285	351	-8	58	66	14.95	42.59
7765A	208	222	277	355	14	55	78	11.50	32.39
7766A	225	230	282	355	5	52	73	14.95	42.11
7767A	285	277	333	429	-8	56	96	16.79	39.14
7768A	231	240	285	364	9	45	79	13.78	37.86
7769A	230	237	281	365	7	44	84	14.15	38.77
7771	248	253	302	382	5	49	80	13.77	36.05
7774	222	237	289	369	15	52	80	15.37	41.65
7775	224	247	298	385	23	51	87	16.07	41.74
7776	254	290	331	421	36	41	90	16.60	39.43
7777	229	250	300	390	21	50	90	13.95	35.77
7778	262	287	330	407	25	43	77	17.74	43.59
7788	280	286	325	411	6	39	77	16.48	40.10
7789	295	296	316	399	1	20	83	15.59	39.07
7790	249	259	301	386	10	42	85	15.34	39.74
7791	233	257	297	364	24	40	67	13.98	38.41
7792	279	287	323	415	8	36	92	15.50	37.35
7793	272	283	337	419	11	54	82	17.97	42.89
7794	257	270	315	388	13	45	73	15.21	39.20
7803	268	290	290	354	22	0	64	13.24	37.40
7804	281	270	336	424	-11	66	88	17.54	41.37
7805	245	260	294	376	15	34	82	12.34	32.82
7807	239	226	295	382	-13	69	87	15.68	41.05
7808	223	241	278	360	18	37	82	12.78	35.50
7817A	290	295	326	408	5	31	82	14.84	36.37
7818A	265	255	297	341	-10	42	44	15.16	44.46
7821A	310	302	359	466	-8	57	107	18.29	39.25
7822A	214	243	306	396	29	63	90	16.54	41.77
7823A	250	266	303	375	16	37	72	15.20	40.53
7824A	262	274	315	390	12	41	75	14.04	36.00
7818A	207	231	264	347	24	33	83	13.10	37.75
7819B	221	232	277	358	11	45	81	14.82	41.40
7821B	210	229	267	329	19	38	62	14.40	43.77
7822B	236	245	304	384	9	59	80	15.94	41.51
7823B	261	287	337	426	26	50	89	16.41	38.52
7824B	240	255	306	396	15	51	90	14.89	37.60
7825B	200	224	250	327	24	26	77	12.64	38.65
7826B	220	244	285	366	22	41	81	15.50	42.35
MEAN±SD	246±27	258±23*	301±24	382±30	12±12	44±14	80±12	15.06±1.55	39.48±2.90

SL 083323

TABLE A-1 (Continued)

Rouge: Inhalation - Exposure Level: 0 ppm (Concurrent Controls for 80 ppm)

Animal Number	Maternal Body Weight (g)				Maternal Body Weight Gain (g)			Maternal Liver Weight (Day 21)	
	Day(s) of Gestation							Absolute (g)	Relative (g/kg Body Weight)
	6	10	16	21	6-9	10-15	16-20		
33-6439	262	272	307	355	10	35	48	15.85	44.65
6440	254	272	317	386	18	45	69	14.91	38.63
6441	223	232	285	354	9	53	69	13.57	38.33
6442	244	257	314	391	13	57	77	15.28	39.08
6443	260	273	323	400	13	50	77	16.27	40.68
6444	240	268	306	383	28	38	79	16.76	43.76
6445	262	267	318	402	5	51	84	16.87	41.96
6446	257	273	299	352	16	26	53	14.65	41.62
6453	258	284	336	402	26	52	66	16.14	40.15
6454	215	243	299	367	28	56	68	16.23	44.22
6455	265	287	332	401	22	45	69	16.39	40.87
6456	220	241	277	337	21	36	60	15.16	44.98
6457	245	266	274	383	21	8	109	17.90	46.74
6458	235	251	294	351	16	43	57	14.40	41.02
6459	248	268	311	405	20	43	94	15.92	39.31
6459A	245	267	349	430	42	62	81	17.20	40.00
6461	237	257	303	382	20	46	79	17.26	45.18
6463	256	275	312	409	19	37	97	15.72	38.44
6464	230	258	296	382	28	38	86	16.21	42.43
6465	232	249	291	374	17	42	83	15.95	42.65
MEAN±SD	244±15	264±15	307±19	382±24	20±8	43±12	75±15	15.93±1.05	41.74±2.52

TABLE A-1 (Continued)

Route: Inhalation - Exposure Level: 80 ppm

Animal Number	Maternal Body Weight (g)				Maternal Body Weight Gain (g)			Maternal Liver Weight (Day 21)	
	Day(s) of Gestation							Absolute (g)	Relative (g/kg Body Weight)
	6	10	16	21	6-9	10-15	16-20		
33-6371	234	256	290	378	22	34	88	16.12	42.65
6372	227	245	254	282	18	9	28	12.97	45.99
6373	240	254	296	363	14	42	67	16.20	44.63
6374	270	288	315	398	18	27	83	17.59	44.20
6375	263	278	322	415	15	44	93	18.52	44.63
6376	227	242	275	361	15	33	86	13.22	36.62
6377	229	244	270	315	15	26	45	13.90	44.13
6378	288	298	335	406	10	37	71	17.13	42.19
6379	260	275	317	399	15	42	82	15.39	38.57
6380	257	267	309	378	10	42	69	15.68	41.48
6381	244	240	267	299	-4	27	32	13.02	43.55
6382	259	268	318	399	9	50	81	14.36	35.99
6391	251	249	279	353	-2	30	74	16.93	47.96
6392	228	187	251	336	-41	64	85	16.39	48.78
6393	230	229	279	338	-1	50	59	15.25	45.12
6394	207	217	303	378	10	86	75	16.64	44.02
6395	260	261	313	389	1	52	76	18.78	48.28
6396	260	270	303	370	10	33	67	16.35	44.19
6397	236	239	287	353	3	48	66	16.72	47.37
6398	237	240	277	361	3	37	84	16.98	47.04
6400	220	250	296	378	30	46	82	16.99	44.95
6401	220	228	265	354	8	37	89	15.71	44.38
6402	219	233	265	334	14	32	69	14.86	44.49
6404	244	271	267	329	27	-4	62	11.58	35.20
6405	237	275	306	379	38	31	73	14.59	38.50
6406	248	262	321	415	14	59	94	18.10	43.61
6407	239	253	314	398	14	61	84	15.33	38.52
6408	246	257	319	382	11	62	63	15.32	40.10
MEAN±SD	242±18	253±23	293±24*	366±34	11±14*	41±18	72±16	15.74±1.74	43.11±3.73

SL 083325

TABLE A-1 (Continued)

Rouge: Inhalation - Exposure Level: 0 ppm (Concurrent Controls for 160 ppm)

Animal Number	Maternal Body Weight (g)				Maternal Body Weight Gain (g)			Maternal Liver Weight (Day 21)	
	Day(s) of Gestation							Absolute	Relative
	6	10	16	21	6-9	10-15	16-20	(g)	(g/kg Body Weight)
33-6268	278	292	332	382	14	40	50	15.39	40.29
6269	293	311	352	431	18	41	79	17.51	40.63
6270	303	312	343	402	9	31	59	16.20	40.30
6272	262	285	313	377	23	28	64	15.26	40.48
6273	262	272	302	354	10	30	52	15.62	44.12
6274	258	285	312	373	27	27	61	13.53	36.27
6276	294	303	343	418	9	40	75	16.98	40.62
6277	274	286	333	403	12	47	70	15.63	38.78
6282	274	285	ND	423	11	ND	ND	16.80	39.72
6283	272	284	ND	374	12	ND	ND	14.94	39.95
6284	254	262	ND	372	8	ND	ND	14.83	39.86
6286	324	348	ND	496	24	ND	ND	19.17	38.65
6287	303	324	ND	412	21	ND	ND	14.41	34.98
6288	289	277	ND	422	-12	ND	ND	17.00	40.28
6289	260	247	ND	329	-13	ND	ND	14.27	43.37
6290	247	286	ND	401	39	ND	ND	15.07	37.58
6291	282	310	ND	429	28	ND	ND	17.48	40.74
MEAN±SD	278±21	292±24	329±18	400±38	14±13	36±7	64±10	15.89±1.44	39.80±2.20

SL 083326

TABLE A-1 (Continued)

Route: Inhalation - Exposure Level: 160 ppm

Animal Number	Maternal Body Weight (g)				Maternal Body Weight Gain (g)			Maternal Liver Weight (Day 21)	
	Day(s) of Gestation							Absolute	Relative
	6	10	16	21	6-9	10-15	16-20	(g)	(g/kg Body Weight)
33-6200	280	285	323	401	5	38	78	18.89	47.11
6201	281	283	326	426	2	43	100	18.09	42.46
6202	240	234	279	357	-6	45	78	17.05	47.76
6203	274	283	321	404	9	38	83	17.69	43.79
6204	256	256	307	393	0	51	86	16.35	41.60
6205	272	274	316	392	2	42	76	15.57	39.72
6206	286	297	356	434	11	59	78	18.84	43.41
6207	261	253	298	362	-8	45	64	13.88	38.34
6208	303	308	348	440	5	40	92	17.33	39.39
6209	259	263	287	342	4	25	55	15.45	45.18
6210	251	262	336	423	11	74	87	17.27	40.83
6212	228	255	256	341	27	1	85	13.41	39.32
6213	292	300	343	452	8	43	109	19.43	42.99
6214	247	245	299	377	-2	54	78	12.66	33.58
6215	263	272	322	397	9	50	75	15.31	38.56
6216	250	245	285	368	-5	40	83	16.40	44.56
6217	266	272	305	366	6	33	61	17.83	48.72
6218	285	287	319	398	2	32	79	18.52	46.53
6219	291	274	314	395	-17	40	81	14.85	37.59
6221	250	253	297	384	3	44	87	16.70	43.49
6222	273	275	324	406	2	49	82	19.00	46.80
6223	300	301	350	432	1	49	82	18.31	42.38
6224	295	265	334	410	-30	69	76	19.75	48.17
6225	225	235	295	368	10	60	73	16.45	44.70
6227	259	255	300	376	-4	45	76	16.12	42.87
6229	276	270	318	388	-6	48	70	13.91	35.85
MEAN±SD	268±21	269±20*	314±24	394±29	2±10*	44±14	80±11*	16.73±1.94	42.53±3.93*

SL 083327

TABLE A-1 (Continued)

Route: Drinking Water - Concentration: 0 ppm

Animal Number	Maternal Body Weight (g)				Maternal Body Weight Gain (g)			Maternal Liver Weight (Day 21)	
	Day(s) of Gestation							Absolute	Relative
	6	10	16	21	6-9	10-15	16-20	(g)	(g/kg Body Weight)
33-5950	288	312	351	418	24	39	67	13.37	31.98
5951	305	340	386	476	35	46	90	17.93	37.67
5952	290	315	358	445	25	43	87	14.15	31.80
5953	300	321	360	432	21	39	72	17.84	41.30
5954	287	309	346	380	22	37	40	14.99	38.83
5955	283	309	349	422	26	40	73	14.03	33.25
5963	309	327	381	461	16	54	80	16.36	35.49
5964	283	313	354	430	30	41	76	16.19	37.65
5965	260	283	319	391	23	36	72	14.15	36.19
5966	293	306	342	405	13	36	63	15.64	38.62
5967	275	295	331	408	20	36	77	15.78	38.68
5968	302	323	352	390	21	29	38	14.43	37.00
5977	280	298	341	409	18	43	68	17.14	41.91
5978	302	320	364	443	18	44	79	17.55	39.62
5979	294	304	331	365	10	27	34	18.64	51.07
5981	308	336	383	478	28	47	95	19.64	41.09
5983	292	304	348	407	12	44	59	14.88	36.56
5994	285	299	337	424	14	38	87	16.41	38.70
5995	269	289	330	409	20	41	79	14.80	36.23
5996	294	312	347	443	18	35	96	17.10	38.60
5997	266	266	303	386	0	37	77	13.24	34.30
5998	287	303	335	412	16	32	77	15.15	36.77
5999	307	325	366	434	18	41	68	15.73	36.24
6000	296	312	349	422	16	37	73	17.17	40.69
MEAN±SD	290±13	309±16	348±20	421±28	19±7	39±6	72±16	15.93±1.70	37.93±3.90

SL 083328

TABLE A-1 (Continued)

Route: Drinking Water - Concentration: 200 ppm

Animal Number	Maternal Body Weight (g)				Maternal Body Weight Gain (g)			Maternal Liver Weight (Day 21)	
	Day(s) of Gestation							Absolute	Relative
	6	10	16	21	6-9	10-15	16-20	(g)	(g/kg Body Weight)
33-5956	315	335	371	454	20	36	83	16.59	36.54
5957	273	291	326	393	18	35	67	15.06	38.32
5958	270	293	297	390	23	4	93	14.02	35.95
5959	235	303	345	437	68	42	92	17.41	39.84
5960	260	268	313	393	8	45	80	15.14	38.52
5961	307	324	361	407	17	37	46	14.17	34.82
5962	235	267	300	362	32	33	62	14.43	39.86
5970	325	305	386	471	-20	81	85	15.04	31.93
5971	289	307	347	415	18	40	68	14.26	34.36
5972	289	303	337	392	14	34	55	12.88	32.86
5973	318	334	375	448	16	41	73	14.52	32.41
5974	276	296	340	421	20	44	81	13.64	32.40
5975	323	331	351	361	8	20	10	14.60	40.44
5976	314	326	382	461	12	56	79	17.29	37.50
5984	310	320	ND	441	10	ND	ND	17.43	39.52
5985	310	317	ND	457	7	ND	ND	17.97	39.32
5986	250	272	ND	334	22	ND	ND	14.74	44.13
5987	304	304	ND	433	0	ND	ND	14.74	34.04
5988	295	284	ND	431	-11	ND	ND	14.18	32.90
5989	258	267	ND	381	9	ND	ND	13.09	34.36
6001	274	295	330	415	21	35	85	16.97	40.89
6002	275	275	323	385	0	48	62	14.79	38.42
6003	301	320	355	410	19	35	55	17.40	42.44
6004	300	317	365	458	17	48	93	15.84	34.58
6005	210	275	319	392	65	44	73	15.18	38.72
6006	274	292	326	422	18	34	96	15.24	36.11
MEAN±SD	284±30	301±22	342±26	414±35	16±18	40±14	72±20	15.25±1.43	36.97±3.36

^aExcluded from the calculations due to a likely scale error on day 10 of gestation.

ND = No data available.

*Significantly different from the control value by a one-way analysis of variance, $p < 0.05$.

TABLE A-2

INDIVIDUAL LITTER SUMMARY OF OBSERVATIONS MADE AT THE TIME OF CESAREAN SECTION OF RATS
EXPOSED TO VINYLIDENE CHLORIDE BY INHALATION OR BY INGESTION

Route: Inhalation - Exposure Level: 0 ppm (Concurrent Controls for 20 ppm)

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
44-7746	10	10	0	0	10	5:5	5.48	43.2
7747	15	13	2	0	13	8:5	5.40	42.7
7748	14	14	0	0	14	6:8	5.68	44.0
7749	15	12	3	0	12	7:5	5.78	44.2
7750	Non-pregnant							
7751	13	12	1	1	11	4:7	5.36	42.6
7752	11	10	1	0	10	5:5	5.45	43.6
7753	14	12	2	0	12	6:6	5.32	43.6
7754	10	10	0	0	10	1:9	5.99	43.5
7755	11	12	0	0	12	5:7	5.17	43.1
7756	15	15	0	1	14	8:6	5.36	43.4
7757	Non-pregnant							
7758	12	13	0	0	13	4:9	5.06	41.8
7759	8	8	0	0	8	2:6	6.69	46.3
7760	14	14	0	1	13	7:6	5.17	42.5
7761	12	11	1	1	10	3:7	5.96	44.6
7763B	12	12	0	0	12	5:7	5.67	44.7
7764B	13	14	0	0	14	8:6	5.22	42.9
7765B	11	14	0	0	14	4:10	4.99	42.2
7766B	15	11	4	0	11	5:6	5.22	43.2
7767B	13	12	1	0	12	7:5	5.38	43.5
7768B	11	12	0	0	12	4:8	5.17	42.0
7769B	16	15	1	0	15	10:5	5.30	45.8
7770B	13	13	0	0	13	7:6	5.16	42.9
7779	15	12	3	0	12	9:3	4.96	44.2
7780	13	13	0	0	13	8:5	5.93	43.1
7781	15	16	0	0	16	8:8	5.61	43.4
7782	13	15	0	1	14	5:9	5.52	45.5
7783	14	14	0	0	14	11:3	5.66	43.3
7784	12	1	11	0	1	1:0	7.01	45.8
7785	Non-pregnant							
7786	Non-pregnant							
7795	14	6	8	2	4	2:2	5.88	45.0
7796	13	11	2	0	11	7:4	5.56	43.6
7797	14	12	2	0	12	8:4	5.68	44.4
7798	10	6	4	2	4	2:2	5.87	44.7
7799	13	12	1	0	12	6:6	5.62	44.4
7800	18	14	4	0	14	8:6	5.42	43.2
7801	13	11	2	0	11	7:4	5.69	44.2
7802	16	14	2	0	14	5:9	5.70	44.6
7810	14	14	0	0	14	5:8	5.66	45.5
7811	Non-pregnant							
7812	Non-pregnant							
7813	16	15	1	0	15	6:9	6.07	45.4
7814	Non-pregnant							
7815	12	12	0	0	12	6:6	5.61	44.7
7816	13	12	1	0	12	7:5	5.71	44.6
MEAN±SD	13±2	12±3	1±2	0.2±0.5	12±3	233:237	5.60±0.40	43.9±1.1

TABLE A-2 (Continued)

Route: Inhalation - Exposure Level: 20 ppm

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
44-7762A	14	9	5	0	9	5:4	5.74	43.7
7763A	12	12	0	0	12	10:2	5.38	42.5
7764A	12	11	1	0	11	5:6	5.28	43.1
7765A	14	12	2	1	11	4:7	5.74	44.0
7766A	10	10	0	0	10	5:5	5.83	45.3
7767A	14	14	0	0	14	9:5	5.81	44.5
7768A	12	12	0	0	12	6:6	5.42	43.4
7769A	15	11	4	0	11	6:5	5.07	42.5
7771	22	13	9	1	12	6:6	6.22	45.8
7772	Removed from study due to dehydration resulting from mechanical failure of watering system.							
7773	Removed from study due to dehydration resulting from mechanical failure of watering system.							
7774	12	12	0	1	11	6:5	5.70	43.8
7775	15	11	4	0	11	6:5	5.44	43.6
7776	14	14	0	0	14	6:8	5.71	44.3
7777	14	14	0	1	13	5:8	6.04	45.2
7778	14	12	2	0	12	7:5	5.66	43.9
7787	Removed from study due to dehydration resulting from mechanical failure of watering system.							
7788	13	13	0	2	11	6:5	5.57	43.3
7789	15	14	1	0	14	7:7	5.16	42.5
7790	15	13	2	0	13	9:4	5.67	44.0
7791	17	12	5	1	11	7:4	5.60	43.6
7792	16	16	0	1	15	10:5	5.26	43.2
7793	19	13	6	1	12	4:8	5.58	43.7
7794	15	12	3	0	12	4:8	5.68	44.0
7803	11	11	0	3	8	4:4	5.65	44.3
7804	14	9	5	0	9	5:4	5.73	44.9
7805	17	12	5	0	12	7:5	5.78	44.8
7806	Implantation sites detected only after sodium sulfide staining.							
7807	13	11	2	0	11	5:6	5.58	44.3
7808	11	11	0	0	11	7:4	5.66	44.1
7809	Non-pregnant							
7817A	14	14	0	1	13	10:3	5.41	43.7
7818A	12	3	9	0	3	1:2	6.26	46.1
7819A	Non-pregnant							
7820A	Non-pregnant							
7821A	21	16	5	1	15	5:10	5.51	43.9
7822A	17	14	3	0	14	5:9	5.32	42.2
7823A	12	11	1	2	9	3:6	5.70	44.7
7824A	15	13	2	0	13	4:9	5.61	44.0
7818B	15	13	2	0	13	11:2	5.35	43.9
7819B	14	13	1	0	13	8:5	5.53	44.2
7820B	Removed from study due to dehydration resulting from mechanical failure of watering system.							
7821B	10	9	1	0	9	7:2	6.07	45.7
7822B	14	12	2	0	12	5:7	5.12	43.2
7823B	14	13	1	0	13	7:6	5.78	45.2
7824B	14	11	3	0	11	9:2	5.94	45.4
7825B	15	11	4	0	11	5:6	5.49	43.9
7826B	10	11	0	0	11	6:5	5.21	43.6
MEAN±SD	14±3	12±2	2±2	0.4±0.7	12±2	247:215	5.61±0.28	44.0±0.9

TABLE A-2 (Continued)

Route: Inhalation - Exposure Level: 0 ppm (Concurrent Controls for 80 ppm)

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-6439	10	11	0	4	7	3:4	5.30	43.8
6440	12	12	0	0	12	4:8	5.29	43.7
6441	11	11	0	0	11	2:9	5.30	44.0
6442	11	11	0	0	11	2:9	5.95	45.9
6443	11	12	0	0	12	6:6	5.69	45.5
6444	13	13	0	0	13	7:6	4.18	43.2
6445	10	11	0	0	11	6:5	5.57	45.0
6446	9	9	0	1	8	3:5	5.63	45.0
6453	14	14	0	1	13	6:7	5.08	42.9
6454	15	13	2	0	13	6:7	5.62	43.5
6455	10	8	2	0	8	2:6	5.70	44.0
6456	12	10	2	1	9	4:5	5.74	45.7
6457	15	14	1	0	14	4:10	5.14	42.7
6458	10	10	0	0	10	5:5	5.72	44.3
6459	15	15	0	0	15	8:7	5.56	43.8
6459A	20	13	7	0	13	4:9	5.51	44.5
6460	Implantation sites detected only after sodium sulfide staining.							
6461	14	13	1	1	12	5:7	5.68	45.2
6462	Removed from study due to dehydration resulting from mechanical failure of watering system.							
6463	13	13	0	0	13	7:6	5.96	45.4
6464	13	13	0	0	13	7:6	5.37	44.1
6465	13	12	1	0	12	7:5	5.79	45.5
MEAN±SD	12±2	12±2	1±2	0.4±0.9	12±2	98:132	5.54±0.26	44.4±1.0

TABLE A-2 (Continued)

Route: Inhalation - Exposure Level: 80 ppm

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-6371	14	14	0	1	13	7:6	5.44	44.3
6372	5	1	4	0	1	0:1	7.42	49.6
6373	11	11	0	0	11	7:4	5.61	44.5
6374	13	13	0	1	12	9:3	5.42	44.3
6375	14	15	0	0	15	10:5	5.49	44.7
6376	15	14	1	0	14	5:9	5.50	44.7
6377	11	5	6	0	5	3:2	5.75	46.0
6378	14	14	0	2	12	5:7	5.72	45.4
6379	14	14	0	0	14	5:9	5.52	45.0
6380	12	12	0	0	12	4:8	5.46	44.2
6381	15	13	2	13	0	0:0	-	-
6382	16	15	1	1	14	7:7	5.74	45.8
6391	12	9	3	0	9	6:3	5.88	45.5
6392	14	12	2	1	11	4:7	5.30	43.5
6393	11	8	3	0	8	4:4	5.59	44.7
6394	11	11	0	0	11	2:9	5.58	44.5
6395	13	12	1	1	11	5:6	5.39	44.4
6396	10	7	3	0	7	4:3	6.06	46.5
6397	10	9	1	1	8	4:4	5.94	46.2
6398	13	9	4	0	9	4:5	5.89	46.2
6399	Delivered on day 18 of gestation							
6400	12	11	1	1	10	3:7	5.74	46.0
6401	11	11	0	0	11	6:5	5.54	44.8
6402	9	9	0	0	9	5:4	5.52	44.3
6403	Implantation sites detected only after sodium sulfide staining.							
6404	9	10	0	0	10	8:2	6.77	47.1
6405	13	13	0	1	12	8:4	5.84	44.8
6406	15	15	0	0	15	8:7	5.35	43.1
6407	15	14	1	0	14	8:6	5.59	43.6
6408	15	15	0	1	14	4:10	5.36	43.6
MEAN±SD	12±2	11±3	1±2	0.8±2.4	10±4	145:147	5.72±0.45	45.1±1.3

TABLE A-2 (Continued)

Route: Inhalation - Exposure Level: 0 ppm (Concurrent Controls for 160 ppm)

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-6268	18	15	3	0	15	8:7	4.96	42.8
6269	13	12	1	0	12	7:5	5.51	43.7
6270	13	13	0	0	13	4:9	5.50	43.8
6271	Non-pregnant							
6272	15	11	4	0	11	5:6	5.62	44.2
6273	12	9	3	0	9	3:6	5.38	43.6
6274	15	13	2	1	12	5:7	5.56	44.0
6275	Removed from study due to dehydration resulting from mechanical failure of watering system.							
6276	15	12	3	0	12	7:5	6.18	45.9
6277	16	14	2	0	14	7:7	5.43	44.5
6282	15	15	0	0	15	9:6	5.45	44.0
6283	11	11	0	2	9	5:4	5.37	43.6
6284	16	13	3	1	12	2:10	5.41	43.8
6285	Removed from study due to dehydration resulting from mechanical failure of watering system.							
6286	14	14	0	0	14	6:8	5.65	44.1
6287	14	14	0	0	14	8:6	5.56	42.5
6288	14	14	0	2	12	4:8	5.63	44.1
6289	12	11	1	1	10	5:5	5.30	43.0
6290	12	12	0	0	12	8:4	5.90	43.8
6291	14	13	1	0	13	7:6	5.36	43.1
MEAN±SD	14±2	13±2	1±1	0.4±0.7	12±2	100:109	5.52±0.26	43.8±0.8

TABLE A-2 (Continued)

Route: Inhalation - Exposure Level: 160 ppm

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-6200	13	10	3	2	8	1:7	5.91	45.1
6201	14	14	0	0	14	9:5	5.37	44.5
6202	14	12	2	1	11	9:2	3.93	39.5
6203	14	11	3	1	10	7:3	5.74	44.2
6204	16	14	2	0	14	8:6	5.66	43.5
6205	14	11	3	0	11	5:6	6.04	45.9
6206	15	15	0	1	14	7:10	5.64	44.2
6207	11	10	1	0	10	4:6	5.92	44.9
6208	14	14	0	0	14	6:8	5.69	44.5
6209	8	6	2	0	6	2:4	2.81	35.2
6210	13	12	1	1	11	6:5	3.92	39.1
6211	Non-pregnant							
6212	11	11	0	1	10	5:5	5.79	44.0
6213	16	14	2	2	12	7:5	5.66	43.8
6214	13	13	0	0	13	9:4	5.92	44.7
6215	13	13	0	0	13	7:6	5.67	44.3
6216	12	13	0	0	13	5:8	5.26	42.1
6217	15	6	9	0	6	4:2	5.17	42.9
6218	11	10	1	0	10	6:4	5.92	44.5
6219	12	11	1	0	11	7:4	6.64	46.9
6220	Delivered on morning of day 21 of gestation							
6221	12	14	0	1	13	7:6	5.68	44.2
6222	14	14	0	2	12	4:8	5.49	44.0
6223	14	12	2	0	12	4:8	5.67	44.4
6224	12	9	3	1	8	2:6	4.95	41.6
6225	12	12	0	1	11	10:1	5.72	45.2
6226	Non-pregnant							
6227	13	13	0	0	13	7:6	5.42	43.9
6228	Non-pregnant							
6229	10	11	0	0	11	2:9	6.72	48.0
MEAN±SD	13±2	12±2	1±2	0.5±0.7	11±2	147:144	5.47±0.82	43.6±2.6

TABLE A-2 (Continued)

Route: Drinking Water - Concentration: 0 ppm

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-5950	12	11	1	1	10	7:3	6.38	45.9
5951	13	13	0	0	13	6:7	5.98	44.6
5952	15	14	1	0	14	8:6	5.63	47.1
5953	13	12	1	0	12	6:6	5.60	42.6
5954	12	5	7	0	5	3:2	6.18	43.9
5955	11	11	0	1	10	2:8	5.64	43.0
5963	11	11	0	0	11	3:8	6.02	47.5
5964	12	12	0	0	12	6:6	5.81	45.7
5965	10	10	0	0	10	3:7	5.67	46.6
5966	11	9	2	1	8	5:3	5.68	46.8
5967	13	11	2	0	11	5:6	5.67	45.5
5968	13	4	9	0	4	2:2	6.28	48.4
5969	Non-pregnant							
5977	12	12	0	0	12	6:6	5.15	42.6
5978	13	12	1	0	12	5:7	5.63	43.4
5979	8	1	7	0	1	1:0	7.29	53.2
5980	Non-pregnant							
5981	16	14	2	0	14	11:3	5.44	46.9
5982	Non-pregnant							
5983	12	11	1	1	10	6:4	5.84	49.2
5994	14	13	1	1	12	6:6	5.62	47.2
5995	16	14	2	1	13	6:7	5.41	47.3
5996	13	13	0	1	12	3:9	5.55	47.7
5997	13	13	0	0	13	8:5	5.36	47.4
5998	10	10	0	0	10	3:7	5.80	48.3
5999	9	9	0	0	9	6:3	6.01	49.5
6000	15	13	2	1	12	5:7	5.41	47.5
MEAN±SD	12±2	11±3	2±2	0.3±0.5	10±3	122:128	5.79±0.44	46.6±2.4

SL 083336

TABLE A-2 (Continued)

Route: Drinking Water - Concentration: 200 ppm

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-5956	15	14	1	0	14	8:6	5.57	46.7
5957	19	9	10	0	9	5:4	5.90	47.9
5958	12	11	1	0	11	9:2	5.56	46.8
5959	12	14	0	0	14	4:10	5.30	45.9
5960	13	12	1	0	12	5:7	5.47	46.7
5961	10	8	2	0	8	3:5	6.27	50.6
5962	14	12	2	2	10	6:4	5.88	48.2
5970	15	13	2	0	13	8:5	5.79	47.4
5971	13	13	0	0	13	5:8	5.16	45.7
5972	13	9	4	0	9	5:4	5.94	48.7
5973	13	13	0	0	13	5:8	5.66	48.1
5974	14	14	0	0	14	5:9	5.64	48.5
5975	7	1	6	1	0	0:0	-	-
5976	16	16	0	0	16	3:13	5.42	47.8
5984	17	11	6	0	11	4:7	5.70	48.0
5985	19	15	4	1	14	12:2	5.69	48.0
5986	13	6	7	3	3	3:0	6.51	49.7
5987	14	13	1	0	13	8:5	5.46	47.2
5988	16	14	2	0	14	10:4	5.76	47.3
5989	17	15	2	0	15	6:9	5.21	44.8
6001	15	15	0	2	13	5:8	5.60	47.8
6002	12	10	2	1	9	5:4	5.89	49.0
6003	12	5	7	0	5	2:3	5.92	48.6
6004	16	14	2	0	14	7:7	5.76	48.6
6005	21	12	9	1	11	7:4	5.57	47.5
6006	13	12	1	0	12	6:6	5.84	49.5
MEAN±SD	14±3*	12±4	3±3	0.4±0.8	11±4	146:144	5.70±0.30	47.8±1.3*

*Significantly different from concurrent control values by a one-way analysis of variance, $p < 0.05$.

INDIVIDUAL LITTER SIGNANT OF FETAL ALTERATIONS

[illegible]

TABLE A-3 (Continued)

Route: Inhalation - Exposure Level: 20 ppm

Animal Number:	44-7762, 63, 64, 65, 66, 67, 68, 69, 71, 74, 75, 76, 77, 78, 80, 89, 90, 91, 92, 93, 94, 903, 04, 05, 07, 08, 17A, 18A, 21A, 22A, 23A, 24A, 18B, 19B, 21B, 22B, 23B, 24B, 25B, 26B	Total Exposure	Total Litters	
		Number of Animals Examined	Number of Animals Affected	
EXTERNAL EXAMINATION	9 12 11 11 10 14 12 11 12 11 11 14 13 12 11 14 13 11 15 12 12	8 9 12 11 11 13 3 13 14 9 13 12 12 9 12 12 11 11 11	462	46
SOFT TISSUE EXAMINATION	3 1 4 4 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	136	40
SKULL BONE EXAMINATION	9 12 11 11 10 14 12 11 12 11 11 14 13 12 11 14 13 11 15 12 12	8 9 12 11 11 13 3 13 14 9 13 12 12 9 12 12 11 11 11	462	40
SKULL BONE EXAMINATION	4 8 7 7 7 10 8 7 8 7 7 9 8 7 8 7 8 7 8 7 7	9 8 10 9 6 9 9 9 9 9 9 7 7 7 7 7 7 7 7 7 7	308	39
		Number of Animals Affected		
Total Major Alterations	0 0	0 0	0	0
Internal Examination				
Short trunk and other defects	0 0	0 0	0	0
Subcutaneous edema	0 0	0 0	1	1
Ophthalmia	0 0	0 0	0	0
Narrow head, pointed snout	0 0	0 0	0	0
Subcutaneous hemorrhage - neck, head, and back	0 0	0 0	1	1
Soft Tissue Examination				
Diaphragmatic hernia	0 0	0 0	0	0
Tumor-colored focus on liver	0 0	0 0	1	1
Hemorrhage, liver	0 0	0 0	0	0
Hydrothorax	0 0	0 0	0	0
Dilated renal pelvis	0 0	0 0	0	0
Uterine ovaries	0 0	0 0	0	0
Head - subcutaneous hemorrhage	0 0	0 0	0	0
Head - thickened skull and subcutaneous tissue in occipital region	0 0	0 0	1	1
Skeletal Examination				
Skull - delayed ossification of parietal bone	0 0	0 0	3	3
-delayed ossification of interparietal bone	2 0	1 0	36	18
-delayed ossification of any skull bone	2 0	1 0	36	18
-unfused parietal and interparietal bone island - interparietal	0 0	0 0	1	1
-unfused parietal and interparietal bone site of ossification	0 0	0 0	0	0
-delayed ossification of symphysis arch	0 0	0 0	0	0
Vertebrae - delayed ossification of spine	0 0	0 0	0	0
-delayed ossification of thoracic vertebra	0 0	0 0	0	0
-unfused cervical vertebra	0 0	0 0	0	0
-unfused thoracic vertebra	0 0	0 0	1	1
-delayed ossification of cervical vertebra	0 1 0 3 0 0 2 4 0 0 1 0 0 0 1 0 7 8 0 6 5 1 8 0 0 0 2 4 0 2 1 0 0 2 0 3 1 4	0 0	30	19
-missing one thoracic vertebra and one lumbar vertebra	0 0	0 0	0	0
-missing all lumbar and sacral vertebra	0 0	0 0	0	0
-ray missing vertebra	0 0	0 0	0	0
-fused vertebrae - thoracic region	0 0	0 0	0	0
-extra thoracic vertebra and pair of ribs	0 0	0 0	0	0
Ribs - unilateral spur on 1st lumbar	1 3 0 3 2 4 0 0 1 0 1 4 4 2 1 0 0 0 1 0 3 0 2 3 1 0 1 2 4 2 3 2 3 1 0 0 0 0	0 0	36	26
-bilateral spur on 1st lumbar	0 0 0 2 0 5 2 1 0 1 0 4 0 0 1 0 0 0 0 2 0 0 0 1 0 0 1 1 2 0 0 1 0 0 0 0 0 0	0 0	29	14
-any spur on 1st lumbar	1 3 0 3 2 4 0 0 1 0 1 4 4 2 1 0 0 0 1 0 3 0 2 3 1 0 1 2 4 2 3 2 3 1 0 0 0 0	0 0	81	30
-unilateral 11th rib	0 0	0 0	4	4
-bilateral 11th rib	0 0	0 0	1	1
-any 11th rib	0 0	0 0	13	7
-Close 11th rib	0 0	0 0	10	7
-any shortened 11th rib	0 0	0 0	0	0
-missing 12th rib - unilateral	0 0	0 0	0	0
-missing 12th pair of ribs only	0 0	0 0	0	0
-missing ribs - multiple ribs	0 0	0 0	0	0
-any missing ribs	0 0	0 0	0	0
-extra ribs	0 1 0	0 0	1	1
Stomach - delayed ossification of stomach	0 0 0 2 1 0 0 1 1 0 1 0	0 0	20	12
-unfused stomach	0 0	0 0	0	0
-fused stomach	0 0	0 0	0	0
Lungs & Diaphragm - delayed ossification of diaphragm	0 0	0 0	0	0
-delayed ossification of diaphragm	0 0	0 0	0	0

SL 083339

Route: Inhalation - Exposure Level: 80 ppm

SL 083340

TABLE A-3 (Continued)

Route: Inhalation - Exposure Level: 0 ppm (Concurrent Controls for 80 ppm)

Animal Numbers:	33-6439, 40, 41, 42, 43, 44, 45, 46, 53, 54, 55, 56, 57, 58, 59, 59A, 61, 63, 64, 65																				Total Fetuses	Total Litters
	Number of Fetuses Examined																					
EXTERNAL EXAMINATION	7	12	11	11	12	13	11	8	13	13	8	9	14	10	15	13	12	13	13	12	230	20
SOFT TISSUE EXAMINATION	3	4	4	4	4	4	4	3	4	4	3	3	5	3	5	4	4	4	4	4	77	20
SKELETAL EXAMINATION	7	12	11	11	12	13	11	8	13	13	8	9	14	10	15	13	12	13	13	12	230	20
SKULL BONE EXAMINATION	4	8	7	7	8	9	7	5	9	9	5	6	9	7	10	9	8	9	9	8	153	20
	Number of Fetuses Affected																					
<u>Total Major Malformations</u>	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1
<u>External Examination</u>																						
Short trunk and other defects	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Subcutaneous edema	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Omphalocele	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Narrow head, pointed snout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Subcutaneous hemorrhage - neck, head, and back	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<u>Soft Tissue Examination</u>																						
Diaphragmatic hernia	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1
Yellow-colored focus on liver	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage, liver	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hydronephrosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dilated renal pelvis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ectopic ovaries	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Head - subcutaneous hemorrhage	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	2	2
Head - thickened dermal and subcutaneous tissue in occular region	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<u>Skeletal Examination</u>																						
Skull - delayed ossification of parietal bone	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	2	2
-delayed ossification of interparietal bone	0	0	0	1	0	3	0	0	1	0	0	0	0	1	0	3	1	3	0	0	13	7
-delayed ossification of any skull bone	0	0	0	1	0	3	0	0	1	0	0	0	0	1	0	3	1	3	0	0	13	7
-unfused parietal and interparietal bone island - interparietal	0	0	0	0	1	0	1	0	3	0	0	0	1	1	1	2	0	3	0	4	17	9
-misshapen parietal and interparietal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
-extra site of ossification between skull bone	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-delayed ossification of zygomatic arch	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vertebrae - delayed ossification of atlas	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-delayed ossification of thoracic centrum	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-unfused cervical centrum	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-unfused thoracic centrum	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
-delayed ossification of cervical centrum	0	1	1	1	1	3	2	3	2	2	1	0	4	0	1	1	0	0	1	0	24	14
-missing one thoracic vertebra and one lumbar vertebra	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-missing all lumbar and sacral vertebrae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-any missing vertebra	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-fused vertebrae - thoracic region	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra thoracic vertebrae & pair of ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ribs - unilateral spur on 1st lumbar	4	2	2	3	0	0	0	0	2	2	1	0	1	3	2	2	0	2	2	0	28	13
-bilateral spurs on 1st lumbar	0	4	0	1	0	1	0	0	1	2	0	0	0	0	0	1	1	0	0	0	11	7
-any spurs on 1st lumbar	4	6	2	4	0	1	0	0	3	4	1	0	1	3	2	3	1	2	2	0	39	15
-unilateral wavy ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-bilateral wavy ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-any wavy ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Class I wavy ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-Class II wavy ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-any shortened 12th rib	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-missing 12th rib - unilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-missing 13th pair of ribs only	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-missing ribs - multiple ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-any missing ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra ribs	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1
<u>Sternebrae - delayed ossification of sternebrae</u>																						
-unossified sternebrae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-unfused sternebrae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-fused sternebrae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<u>Limbs & Digits - delayed ossification of metacarpals</u>																						
-delayed ossification of metatarsals	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SL 083341

TABLE A-3 (continued)

Route: Inhalation - Exposure Level: 160 ppm

Animal Numbers:	33-6200, 01, 02, 03, 04, 05, 06, 07, 08, 09, 10, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 27, 29	Total Fetuses	Total Litters
Number of Fetuses Examined			
EXTERNAL EXAMINATION	8 14 11 10 14 11 14 10 14 6 11 10 12 13 13 13 6 10 11 13 12 12 8 11 13 11	291	26
SOFT TISSUE EXAMINATION	3 3 4 3 5 4 5 3 5 3 4 3 4 4 4 4 3 3 4 4 4 4 3 4 4 4	100	26
SKELETAL EXAMINATION	8 14 11 10 14 11 14 10 14 6 11 10 12 13 13 13 6 10 11 13 12 12 8 11 13 11	291	26
SKULL BONE EXAMINATION	5 9 7 7 9 7 9 7 9 3 7 8 9 9 9 9 3 7 7 9 8 8 5 7 9 7	191	26
Number of Fetuses Affected			
Total Major Malformations	0 0 0 0 9 0 1 0 0 1 0 0 3 0 0 0 0 0 0 0 0 0 0 0 0 0	14	4
<u>External Examination</u>			
Short trunk and other defects	0 0	0	0
Subcutaneous edema	0 0	0	0
Omphalocele	0 0	0	0
Narrow head, pointed snout	0 0	0	0
Subcutaneous hemorrhage - head, neck, and back	0 0	0	0
<u>Soft Tissue Examination</u>			
Diaphragmatic hernia	0 0	0	0
Yellow-colored focus on liver	0 0	0	0
Hemorrhage, liver	0 0	0	0
Hydronephrosis	0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	4	3
Dilated renal pelvis	0 0	0	0
Ectopic ovaries	0 0	0	0
Head - subcutaneous hemorrhage	0 0	0	0
Head - thickened dermal and subcutaneous tissue in occular region	0 0	0	0
<u>Skeletal Examination</u>			
Skull - delayed ossification of parietal bone	0 0 1 0 0 0 0 0 1 2 1 4 3 0 0 0 0 0 0 0 0 0 0 0 0 0	13	7
-delayed ossification of interparietal bone	0 1 1 0 2 2 2 1 3 3 2 4 6 2 4 4 0 3 3 0 2 0 0 4 3 1	57	20
-delayed ossification of any skull bone	0 1 1 0 2 2 2 1 5 3 4 4 6 2 4 4 0 3 3 0 2 0 0 4 3 1	59	20
-unfused parietal and interparietal	0 0 0 0 0 2 3 1 1 2 1 3 2 5 6 1 0 1 0 0 4 0 0 0 0 1	33	14
-bone island - interparietal	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 0	3	3
-misshapen parietal and interparietal	0 0	0	0
-extra site of ossification between skull bone	0 0	0	0
-delayed ossification of zygomatic arch	0 0	0	0
Vertebrae - delayed ossification of atlas	0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	1	1
-delayed ossification of thoracic centrum	0 0	0	0
-unfused cervical centrum	0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	1	1
-unfused thoracic centrum	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0	1	1
-delayed ossification of cervical centrum	0 10 11 7 12 2 11 0 0 6 11 0 5 8 1 6 2 1 0 1 2 2 3 3 1 0	107	20
-missing one thoracic vertebra and one lumbar vertebra	0 0 0 0 9 0 1 0 0 1 0 0 3 0 0 0 0 0 0 0 0 0 0 0 0 0	14	4
-missing all lumbar and sacral vertebrae	0 0	0	0
-any missing vertebra	0 0 0 0 9 0 1 0 0 1 0 0 3 0 0 0 0 0 0 0 0 0 0 0 0 0	14	4
-fused vertebrae - thoracic region	0 0	0	0
-extra thoracic vertebra & pair of ribs	0 0	0	0
Ribs - unilateral spur on 1st lumbar	2 2 3 1 1 2 2 3 2 3 1 0 0 0 0 5 1 1 0 0 5 3 3 3 0 2 0	45	19
-bilateral spurs on 1st lumbar	2 3 1 2 0 3 2 3 0 1 2 0 0 0 2 1 1 0 0 0 0 0 0 1 4 1 1	30	16
-any spurs on 1st lumbar	4 5 4 3 1 5 4 6 2 4 3 0 0 0 2 6 2 1 0 0 5 3 3 4 4 3 1	75	22
-unilateral wavy ribs	0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 2 0 0	3	2
-bilateral wavy ribs	2 1 0 0 0 0 0 0 0 1 1 0 0 3 0 0 0 0 0 0 0 0 0 5 2 1	19	9
-any wavy ribs	2 1 0 0 1 0 0 0 1 1 0 0 3 0 0 0 0 0 0 0 0 0 0 5 4 1	22	10
-Class I wavy ribs	0 0 0 0 1 0 0 0 0 0 0 0 2 0 0 0 0 0 0 0 0 0 0 3 3 0	9	5
-Class II wavy ribs	2 0 0 0 0 0 0 0 0 1 1 0 0 1 0 0 0 0 0 0 0 0 0 2 1 1	13	9
-any shortened 12th rib	0 0 0 0 6 0 1 0 0 1 0 0 3 0 0 0 0 0 0 0 0 0 0 0 0 0	11	4
-missing 12th rib - unilateral	0 0 0 0 1 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	4	2
-missing 12th pair of ribs only	0 0 0 0 9 0 1 0 0 1 0 0 3 0 0 0 0 0 0 0 0 0 0 0 0 0	14	4
-missing ribs - multiple ribs	0 0	0	0
-any missing ribs	0 0 0 0 9 0 2 0 0 1 0 0 3 0 0 0 0 0 0 0 0 0 0 0 0 0	15	4
-extra ribs	0 0 2 0 0 0 1 1 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	6	3
Sternum - delayed ossification of sternbrae	0 0 4 0 0 0 2 0 0 2 2 0 2 0 0 0 0 0 0 0 0 0 1 0 1 1	15	8
-unossified sternbrae	0 0 0 0 0 0 0 0 0 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	4	1
-unfused sternbrae	0 0 0 0 1 0	1	1
-fused sternbrae	0 0	0	0
Limbs & Digits - delayed ossification of metacarpals	0 0 1 0 0 0 0 0 0 2 11 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	13	3
-delayed ossification of metatarsals	0 0	0	0

SL 083342

TABLE A-3 (Continued)

Route: Drinking Water - Exposure Level: 0 ppm

Animal Numbers:	33-5950, 51, 52, 53, 54, 55, 63, 64, 65, 66, 67, 68, 77, 78, 79, 81, 83, 94, 95, 96, 97, 98, 99, 00	Total Fetuses	Total Litters																								
	Number of Fetuses Examined																										
EXTERNAL EXAMINATION	10	13	14	12	5	10	11	12	10	8	11	4	12	12	1	14	10	12	13	12	13	10	9	12	250	24	
SOFT TISSUE EXAMINATION	3	4	5	4	3	3	4	4	3	3	4	3	4	4	1	5	3	4	4	4	4	3	3	4	86	24	
SKELTAL EXAMINATION	10	13	14	12	5	10	11	12	10	8	11	4	12	12	1	14	10	12	13	12	13	10	9	12	250	24	
SKULL BONE EXAMINATION	7	9	9	8	2	7	7	8	7	5	7	1	8	8	0	9	7	8	9	8	9	7	6	8	164	23	
	Number of Fetuses Affected																										
Total Major Malformations	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>External Examination</u>																											
Subcutaneous hemorrhage - head, neck, and back	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	
<u>Soft Tissue Examination</u>																											
Hydrothoraxes	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	
Hemorrhage, liver	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	
Head - subcutaneous hemorrhage	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	3	3	
<u>Skeletal Examination</u>																											
Skull - delayed ossification of parietal bone	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	0	0	0	3	2	
-delayed ossification of interparietal bone	0	0	2	0	1	1	1	1	0	1	0	0	0	6	0	1	0	1	0	0	4	0	0	0	19	10	
-delayed ossification of any skull bone	0	0	2	0	1	1	1	1	0	1	0	0	0	6	0	1	0	1	0	0	4	0	0	0	19	10	
-unfused parietal and interparietal	7	7	4	1	2	2	4	7	6	5	7	0	6	8	0	7	7	2	0	3	0	4	1	3	93	20	
-bone island - interparietal	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	
-misshapen parietal and interparietal	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	
-extra site of ossification between skull bones	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	
-delayed ossification of zygomatic arch	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	
Vertebrae - delayed ossification of atlas	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	
-delayed ossification of cervical centra	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	
-delayed ossification of thoracic centrum	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	
-unfused cervical centrum	0	2	7	1	0	1	0	1	0	1	0	1	2	0	5	0	4	7	8	1	2	1	2	2	46	16	
-unfused thoracic centrum	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	2	2	
-missing one thoracic vertebra and one lumbar vertebra	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	
-missing some thoracic, all lumbar and all sacral vertebrae	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	
-any missing vertebra	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	
-fused vertebrae, thoracic region	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	
-extra thoracic vertebra & pair of ribs	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	
Ribs - unilateral spur on 1st lumbar	4	2	0	1	0	1	5	2	1	1	0	1	1	3	1	1	2	0	1	1	0	1	2	1	32	19	
-bilateral spurs on 1st lumbar	1	0	2	0	0	0	3	2	0	0	0	0	0	2	0	0	0	1	0	2	0	1	0	0	14	8	
-any spurs on 1st lumbar	5	2	2	1	0	1	8	4	1	1	0	1	5	1	1	2	1	1	3	0	2	2	1	46	21	1	
-unilateral wavy ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	
-bilateral wavy ribs	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	
-any wavy ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	
-Class I wavy ribs	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	
-Class II wavy ribs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	
-any shortened 12th rib	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	
-missing 12th rib - unilateral	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	
-missing 12th pair of ribs only	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	
-missing ribs - multiple ribs	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	
-any missing ribs	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	
-extra ribs	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	
<u>Sternum - delayed ossification of sternum</u>																											
-unossified sternum	0	0	0	0	0	0	1	1	2	0	0	0	0	1	0	0	2	0	1	1	2	1	0	1	0	13	10
-unfused sternum	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	
-fused sternum	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	2	2	
-fused sternum	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>Limbs & Digits - delayed ossification of metacarpals</u>																											
-delayed ossification of metacarpals	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
-delayed ossification of metatarsals	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 A-3 (Continued)

Route: Drinking Water - Exposure Level: 200 ppm

Animal Numbers:	33-5956, 57, 58, 59, 60, 61, 62, 70, 71, 72, 73, 74, 76, 84, 85, 86, 87, 88, 89, 01, 02, 03, 04, 05, 06	Total Fetuses	Total Litters
	Number of Fetuses Examined		
EXTERNAL EXAMINATION	14 9 11 14 12 8 10 13 13 9 13 14 16 11 14 3 13 14 15 13 9 5 14 11 12	290	25
SOFT TISSUE EXAMINATION	5 3 4 5 4 3 3 4 4 3 4 5 4 4 5 3 4 5 5 4 3 3 5 4 4	100	25
SKELETAL EXAMINATION	14 9 11 14 12 8 10 13 13 9 13 14 16 11 14 3 13 14 15 13 9 5 14 11 12	290	25
SKULL BONE EXAMINATION	9 6 7 9 8 5 7 9 9 6 9 9 12 7 9 0 9 9 10 9 6 2 9 7 8	190	24
	Number of Fetuses Affected		
Total Major Malformations	0 0	0	0
External Examination			
Subcutaneous hemorrhage - head, neck, and back	0 0 0 0 0 2 0 0 0 0 0 0 0 2 0 0 0 0 0 0 0 0 0 0	4	2
Soft Tissue Examination			
Hydrothorax	0 0 0 1 0 0 0 0 0 1 0 0 0 0 0 0 0 0 1 0 0 0 0 0	3	3
Hemorrhage, liver	0 0	0	0
Head - subcutaneous hemorrhage	0 0 0 1 0 0 0 0 0 0 0 0 0 1 0 0 0 0 1 0 0 0 0 0	3	3
Skeletal Examination			
Skull - delayed ossification of parietal bone	0 0 0 0 0 0 2 0 0 0 0 0 2 0 0 0 0 1 0 0 0 0 0 0	5	3
-delayed ossification of interparietal bone	1 0 1 0 1 0 4 0 0 0 0 0 8 1 0 0 4 5 0 3 0 0 3 1 0	32	11
-delayed ossification of any skull bone	1 0 1 0 1 0 4 0 0 0 0 0 8 1 0 0 4 5 0 3 0 0 3 1 0	32	11
-unfused parietal and interparietal bone island, interparietal	3 3 3 5 5 0 1 6 7 6 9 8 10 4 7 0 8 6 0 5 1 0 4 1 0	104	20
-malshaped parietal and interparietal	0 0 0 0 0 0 1 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0	2	2
-extra site of ossification between skull bones	0 0	0	0
-delayed ossification of zygomatic arch	0 0	0	0
Vertebrae - delayed ossification of atlas	0 0	0	0
-delayed ossification of cervical centra	3 0 0 3 0 0 1 1 1 1 1 2 2 3 3 0 4 1 3 7 1 0 0 2 3	42	18
-delayed ossification of thoracic centrum	0 0	0	0
-unfused cervical centrum	0 0	0	0
-unfused thoracic centrum	0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0	1	1
-missing one thoracic vertebra and one lumbar vertebra	0 0	0	0
-missing some thoracic, all lumbar, and all sacral vertebrae	0 0	0	0
-any missing vertebrae	0 0	0	0
-fused vertebrae - thoracic region	0 0	0	0
-extra thoracic vertebra & pair of ribs	0 0	0	0
Ribs - unilateral spurs on 1st lumbar	2 4 0 2 2 2 0 4 1 1 2 3 3 1 1 0 2 0 4 1 1 5 1 2	46	21
-bilateral spurs on 1st lumbar	0 0 0 1 0 2 0 5 0 1 0 0 0 0 0 0 0 0 0 0 1 1 3 0 1	19	10
-any spurs on 1st lumbar	2 4 0 3 2 4 0 9 1 2 2 3 3 1 4 0 2 0 4 2 2 6 1 3	65	21
-unilateral wavy ribs	0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	1	1
-bilateral wavy ribs	0 0	2	1
-any wavy ribs	0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	3	2
-Class I wavy ribs	0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-Class II wavy ribs	0 0	0	0
-any shortened 12th rib	0 0	0	0
-missing 12th rib - unilateral	0 0	0	0
-missing 12th pair of ribs only	0 0	0	0
-missing ribs - multiple ribs	0 0	0	0
-any missing ribs	0 0	0	0
-extra ribs	0 0	0	0
Sternum - delayed ossification of sternum	0 0 0 2 0 0 1 0 0 0 0 0 0 1 0 0 2 2 0 0 0 0 0 1	9	6
-unossified sternum	0 0	0	0
-unfused sternum	0 0	0	0
-fused sternum	0 0	0	0
Limbs & Digits - delayed ossification of metacarpals	0 0	0	0
-delayed ossification of metatarsals	0 0	0	0

SL 083344

TABLE A-4

INDIVIDUAL BODY AND LIVER WEIGHTS OF PREGNANT RABBITS EXPOSED TO VINYLIDENE CHLORIDE BY INHALATION

Exposure Level: 0 ppm (Concurrent Controls for 80 ppm)

Animal Number	Maternal Body Weight (kg)				Maternal Body Weight Gain (kg)			Maternal Liver Weight (Day 29)	
	Day(s) of Gestation				6-11	12-18	19-28	Absolute	Relative
	6	12	19	29				(g)	(g/kg Body Weight)
33-6431	4.17	4.07	4.13	4.35	-0.10	0.06	0.22	112	25.75
-6432	4.51	4.60	4.65	4.75	0.09	0.05	0.10	100	21.05
-6433	4.75	4.74	4.73	4.81	-0.01	-0.01	0.08	122	25.36
-6434	4.51	4.47	4.62	4.68	-0.04	0.15	0.06	102	21.79
-6435	4.39	4.26	4.34	4.39	-0.13	0.08	0.05	113	25.76
-6436	3.91	3.84	3.79	4.00	-0.07	-0.05	0.21	79	19.75
-6437	4.52	4.47	4.55	4.56	-0.05	0.08	0.01	90	19.74
-6447	3.58	3.52	3.60	3.82	-0.06	0.08	0.12	95	24.87
-6448	4.48	4.40	4.49	4.46	-0.08	0.09	-0.03	95	21.30
-6449	4.64	4.53	4.48	4.47	-0.11	-0.05	-0.01	93	20.81
-6451	4.19	4.16	4.30	4.51	-0.03	0.14	0.21	119	26.39
-6452	4.51	4.51	4.59	4.65	0.00	0.08	0.06	92	19.78
-6466	4.46	4.45	4.40	4.35	-0.01	-0.05	-0.05	99	22.76
-6467	3.98	3.93	4.05	4.05	-0.05	0.12	0.00	70	17.28
MEAN±SD	4.33±0.32	4.28±0.34	4.34±0.33	4.42±0.29	-0.05±0.06	0.06±0.07	0.07±0.10	99±14	22.31±2.86

SL 083345

TABLE A-4 (Continued)

Exposure Level: 80 ppm

Animal Number	Maternal Body Weight (kg)				Maternal Body Weight Gain (kg)			Maternal Liver Weight (Day 29)	
	Day(s) of Gestation							Absolute (g)	Relative (g/kg Body Weight)
	6	12	19	29	6-11	12-18	19-28		
33-6409	3.98	4.12	4.25	4.45	0.14	0.13	0.20	125	28.09
6410	3.94	4.12	4.24	4.37	0.18	0.12	0.13	105	24.03
6411	4.10	4.08	4.18	4.38	-0.02	0.10	0.20	106	24.20
6412	3.43	3.41	3.14	3.38	-0.02	-0.27	0.24	94	27.81
6413	3.89	3.89	3.89	4.19	0.00	0.00	0.30	93	22.20
6414	4.10	4.17	4.02	4.25	0.07	-0.15	0.23	116	27.29
6415	4.15	4.11	3.84	4.04	-0.04	-0.27	0.20	115	28.47
6417	4.19	4.11	3.94	4.22	-0.08	-0.17	0.28	127	30.09
6419	4.30	4.32	4.97	4.72	0.02	0.55	-0.15	97	20.55
6420	3.93	3.91	3.76	4.18	-0.02	-0.15	0.42	112	26.79
6421	4.38	4.29	3.94	4.41	-0.09	-0.35	0.47	112	25.40
6422	3.50	3.56	3.58	3.84	0.06	0.02	0.26	112	29.17
6423	4.14	4.10	4.17	4.54	-0.04	0.07	0.37	105	23.13
6424	4.03	3.94	3.64	3.95	-0.09	-0.30	0.31	117	29.62
6425	3.97	3.85	3.84	3.93	-0.12	-0.01	0.09	98	24.94
6427	4.55	4.46	4.53	4.69	-0.09	0.07	0.16	112	23.88
6428	4.73	4.41	4.60	4.62	-0.32	0.19	0.02	98	21.21
6430	3.51	3.43	3.40	3.77	-0.08	-0.03	0.37	83	22.02
MEAN±SD	4.04±0.34*	4.02±0.30*	4.00±0.44*	4.22±0.35	-0.03±0.11	-0.02±0.22	0.23±0.15*	107±12*	25.33±2.97*

SL 083346

TABLE A-4 (Continued)

Exposure Level: 160 ppm

Animal Number	Maternal Body Weight (kg)				Maternal Body Weight Gain (kg)			Maternal Liver Weight (Day 29)	
	Day(s) of Gestation							Absolute	Relative
	6	12	19	29	6-11	12-18	19-28	(g)	(g/kg Body Weight)
33-6241	4.61	4.19	4.00	4.40	-0.42	-0.19	0.40	116	26.36
6242	4.06	3.98	3.87	4.20	-0.08	-0.11	0.33	87	20.71
6244	3.73	3.71	3.74	4.05	-0.02	0.03	0.31	111	27.41
6245	3.97	3.85	3.72	3.99	-0.12	-0.13	0.27	101	25.31
6246	4.47	4.47	4.61	4.69	0.00	0.14	0.08	116	24.73
6248	3.92	3.85	3.85	4.05	-0.07	0.00	0.20	110	27.16
6249	3.36	3.18	3.16	3.19	-0.18	-0.02	0.03	73	22.88
6250	4.12	4.03	4.07	4.24	-0.09	0.04	0.17	142	33.49
6251	4.11	3.63	3.32	3.78	-0.48	-0.31	0.46	113	29.88
6252	4.82	4.68	4.59	4.80	-0.14	-0.09	0.21	133	27.71
6253	3.85	3.58	3.52	3.63	-0.27	-0.06	0.11	ND	ND
6254	4.30	4.00	3.80	4.10	-0.30	-0.20	0.30	133	32.44
6255	3.86	3.74	4.00	4.01	-0.12	0.36	0.01	91	22.69
6256	3.70	3.62	3.63	3.73	-0.08	0.01	0.10	90	24.13
6257	4.21	4.06	4.05	4.23	-0.15	-0.01	0.18	112	26.48
MEAN±SD	4.07±0.38	3.90±0.37	3.86±0.40	4.07±0.40	-0.17±0.14*	-0.04±0.14*	0.21±0.13*	109±19	26.53±3.61

ND = no data available.

See Table for summary data.

*Significantly different from the concurrent control value by a one-way analysis of variance, $p < 0.05$.

SL 083347

TABLE A-5

INDIVIDUAL LITTER SUMMARY OF OBSERVATIONS MADE AT THE TIME OF
CESAREAN SECTION OF RABBITS INHALING VINYLIDENE CHLORIDE

Exposure Level: 0 ppm (Concurrent Controls for 80 ppm)

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-6431	9	9	0	0	9	1:8	42.5	98.3
6432	10	10	0	0	10	4:6	34.4	94.1
6433	10	11	0	3	8	3:5	37.0	95.9
6434	12	12	0	1	11	5:6	33.4	91.2
6435	5	4	1	2	2	2:0	44.4	99.2
6436	9	8	0	0	8	4:4	36.2	94.0
6437	9	9	0	0	9	2:7	34.0	89.0
6438	Delivered on day 28 of gestation.							
6447	8	8	0	0	8	6:2	38.1	96.4
6448	9	9	0	0	9	7:2	38.6	96.4
6449	8	8	0	2	6	3:3	32.4	91.8
6450	Dead on day 16 of gestation; pneumonia-related.							
6451	11	11	0	0	11	6:5	36.7	94.5
6452	10	10	0	1	9	7:2	40.9	97.5
6466	11	10	1	3	7	5:2	32.7	93.2
6467	9	9	0	0	9	5:4	34.4	93.5
MEAN±SD	9±2	9±2	0.1±0.4	0.8±1.2	8±2	60:56	36.8±3.7	94.6±2.8

SL 083348

TABLE A-5 (Continued)

Exposure Level: 80 ppm

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-6409	10	10	0	1	9	5:4	40.2	93.2
6410	12	11	1	1	10	6:4	36.7	91.8
6411	9	9	0	1	8	7:1	41.4	94.4
6412	7	7	0	0	7	3:4	34.5	91.3
6413	9	9	0	0	9	3:6	39.54	94.2
6414	14	11	3	1	10	5:5	33.6	90.2
6415	9	9	0	2	7	5:2	30.6	87.4
6416	Delivered on day 28 of gestation.							
6417	12	12	0	1	11	6:5	33.7	93.8
6418	Dead on day 23 of gestation; enteritis-related; pregnant.							
6419	7	9	0	2	7	4:3	47.0	98.2
6420	9	9	0	0	9	5:4	40.3	99.8
6421	12	11	1	3	8	6:2	34.2	91.6
6422	8	8	0	0	8	6:2	32.1	91.3
6423	9	9	0	1	8	4:4	42.6	97.7
6424	7	8	0	0	8	6:2	29.6	85.9
6425	10	11	0	0	11	2:0	29.4	87.9
6426	Non-pregnant.							
6427	7	8	0	0	8	4:4	38.4	97.3
6428	9	9	0	0	9	4:5	38.1	96.3
6429	Implantation sites detected only after sodium sulfide staining.							
6430	8	8	0	0	8	6:2	42.6	99.3
MEAN±SD	9±2	9±1	0.3±0.8	0.7±0.9	9±1	87:68	36.9±5.0	93.4±4.1

TABLE A-5 (Continued)

Exposure Level: 0 ppm (Concurrent Controls for 160 ppm)

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-6298	9	5	4	0	5	3:2	36.6	91.9
6299	8	5	3	0	5	2:3	43.3	93.8
6300	8	8	0	0	8	4:4	36.6	95.6
6301	Non-pregnant.							
6302	Non-pregnant.							
6303	9	9	0	2	7	4:3	45.1	101.0
6304	12	12	0	1	11	8:3	28.3	88.2
6305	9	9	0	0	9	4:5	40.1	99.8
6318	12	11	1	0	11	7:4	30.7	87.4
6319	Dead on day 25 of gestation; pneumonia-related; pregnant.							
6320	10	14	0	0	14	6:8	25.6	80.8
6321	6	8	0	0	8	7:1	32.2	89.3
6322	11	11	0	0	11	5:6	33.3	89.8
6323	8	9	0	0	9	2:7	39.4	98.8
6324	12	12	0	0	12	5:7	42.3	95.9
6325	7	2	5	1	1	1:0	53.3	101.7
MEAN±SD	9±2	9±3	1.0±1.8	0.3±0.6	8±3	58:53	37.4±7.6	93.4±6.2

SL 083350

TABLE A-5 (Continued)

Exposure Level: 160 ppm

Animal Number	Corpora Lutea	Implantations	Pregnancy Wastage	Resorptions	Litter Size	Sex Ratio M:F	Fetal Body Weight (g)	Crown-Rump Length (mm)
33-6241	12	12	0	9	3	1:2	32.6	85.8
6242	10	8	2	0	8	6:2	40.3	96.5
6243	Dead on day 22 of gestation; perimetritis-related; pregnant. ^a							
6244	12	11	1	1	10 ^a	8:2	35.4	95.4
6245	10	10	0	0	10	5:5	36.4	93.6
6246	9	9	0	1	8	3:5	34.2	90.6
6247	Non-pregnant; purulent inflammation of the ovaries.							
6248	11	11	0	0	11	5:6	25.2	82.6
6249	7	6	1	0	6	4:2	38.24	91.6
6250	9	9	0	2	7	3:4	34.5	93.2
6251	8	6	2	6	0			
6252	10	8	2	2	6	5:1	40.6	96.0
6253	0	9	0	9	0			
6254	7	11	0	11	0			
6255	8	8	0	0	8	3:5	38.4	97.6
6256	8	7	1	0	7	2:5	38.9	97.7
6257	7	7	0	0	7	3:4	37.1	94.6
6258	Dead on day 28 of gestation; pneumonia-related; pregnant.							
MEAN±SD	8±3	9±2	0.6±0.8	2.7±3.9 *	6±4	48:43	36.0±4.2	92.9±4.7

^aOne male fetus from litter No. 33-6244 was noted to be dead at the time of cesarean section.

*Significantly different from the concurrent control value by a one-way analysis of variance, $p < 0.05$.

TABLE A-6

INDIVIDUAL LITTER SUMMARY OF FETAL ALTERATIONS AMONG LITTERS OF RABBITS
EXPOSED TO VINYLIDENE CHLORIDE BY INHALATION

Exposure Level: 0 ppm (Concurrent Control for 80 ppm)

Animal Numbers:	33-6431, 32, 33, 34, 35, 36, 37, 47, 48, 49, 51, 52, 66, 67	Total Fetuses	Total Litters
Number of Fetuses Examined			
EXTERNAL EXAMINATION	9 10 8 11 2 8 9 8 9 6 11 9 7 9	116	14
SOFT TISSUE EXAMINATION	3 3 3 4 2 3 3 3 3 3 4 3 3 4	44	14
SKELLETAL EXAMINATION	9 10 8 11 2 8 9 8 9 6 11 9 7 9	116	14
Number of Fetuses Affected			
<u>Total Major Malformations</u>	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
<u>External Examination</u>			
Edema - neck and abdominal region	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
<u>Soft Tissue Examination</u>			
Dilated cerebral ventricles	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
Heart - thinning of right ventricular wall	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
Satellite vessel off aorta	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
Satellite vessel off innominate artery	2 0 0 0 1 1 0 0 0 0 0 0 0 0	4	3
Fused left carotid and innominate artery	3 1 3 4 1 3 1 1 3 2 4 1 0 4	31	13
Kidney - cortical indentation unilateral	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
<u>Skeletal Examination</u>			
Skull - delayed ossification	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-frontal ridge	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-foramen, frontal	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-foramen, parietal	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-extra suture lines, parietal	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-bone island, parietal	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-extra site of ossification	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-between occipital condyles and atlas	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
Vertebrae - hemivertebrae thoracic region with corresponding fused or forked rib & misshapen centra	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-extra and misshapen left vertebrae	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-extra cervical vertebrae	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
Ribs - 11 ribs on left & 12 ribs on right	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
-shortened 1st thoracic rib	0 0 0 0 0 1 0 0 0 0 0 0 0 0	1	1
-13th ribs - bilateral	1 4 1 9 2 3 5 0 7 1 5 9 5 4	56	13
-13th rib - unilateral	1 2 4 1 0 4 1 0 0 1 2 0 2 1	19	10
-lumbar spurs	3 0 0 0 0 1 0 0 0 0 3 0 0 1	8	4
Sternebrae - delayed ossification of 2nd sternebra	0 1 0 0 0 1 0 0 0 0 1 0 0 0	3	3
-delayed ossification of 5th	5 8 5 2 0 1 4 7 0 2 5 4 3 2	48	12
-delayed ossification of 6th	1 5 0 5 0 1 0 4 4 2 1 6 7 2	38	11
-unfused	0 0 0 0 0 0 0 0 0 0 0 1 0 0	1	1
-fused	0 0 0 0 1 0 0 0 0 0 0 0 0 0	1	1
-extra site of ossification between 5th & 6th	0 0 0 0 0 0 0 0 0 0 0 0 0 0	0	0
Limbs - delayed ossification of phalanges in first digit, bilateral	1 0 0 0 0 0 0 0 0 0 0 0 0 0	1	1

SL 083352

TABLE A-6 (Continued)

Exposure Level: 80 ppm

Animal Numbers:	33-6409, 10, 11, 12, 13, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 27, 28, 30																		Total Fetuses	Total Litters
Number of Fetuses Examined																				
EXTERNAL EXAMINATION	9	10	8	7	9	10	7	11	7	9	8	8	8	8	11	8	9	8	155	18
SOFT TISSUE EXAMINATION	3	3	3	3	3	3	3	4	3	3	3	3	3	3	4	3	3	3	56	18
SKELETAL EXAMINATION	9	10	8	7	9	10	7	11	7	9	8	8	8	8	11	8	9	8	155	18
Number of Fetuses Affected																				
<u>Total Major Malformations</u>	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	3	3
<u>External Examination</u>																				
Edema - neck and abdominal region	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<u>Soft Tissue Examination</u>																				
Dilated cerebral ventricles	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
Heart - thinning of right ventricular wall	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Satellite vessel off aorta	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Satellite vessel off innominate artery	0	1	0	0	0	1	0	0	3	2	0	1	1	0	0	1	0	1	11	8
Fused left carotid and innominate arteries	3	2	0	0	3	2	0	4	2	3	0	2	1	2	0	2	2	3	31	13
Kidney - carotid indentation unilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
<u>Skeletal Examination</u>																				
Skull - delayed ossification	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-frontal ridge	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
-foramen, frontal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-foramen, parietal	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	2	2
-extra suture lines, parietal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
-bone island, parietal	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
-extra site of ossification between occipital condyles and atlas	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vertebrae - hemivertebrae thoracic region with corresponding fused or forked rib and misshapen centra	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
-extra and misshapen lumbar vertebrae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra cervical vertebrae	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1
Ribs - 11 ribs on left & 12 ribs on right	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-shortened 1st thoracic rib	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-13th rib - bilateral	2	4	0	3	2	5	1	6	3	4	6	6	6	6	10	5	5	2	70	16
-13th rib - unilateral	1	1	1	2	1	0	0	0	0	2	1	0	1	0	0	1	1	0	12	10
-lumbar spurs	0	0	1	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	3	3
Sternebrae - delayed ossification of 2nd sternebra	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1
-delayed ossification of 5th	7	2	8	0	4	5	2	0	0	0	3	0	2	3	2	2	0	2	42	12
-delayed ossification of 6th	0	1	7	6	0	2	4	2	0	0	1	1	3	0	1	2	0	1	31	12
-unfused	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-fused	0	0	0	0	0	0	0	1	0	0	0	0	0	2	0	0	0	0	3	2
-extra site of ossification between 5th & 6th	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Limbs - delayed ossification of phalanges in first digit, bilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SL 083353

TABLE A-6 (Continued)

Exposure Level: 160 ppm

Animal Numbers:	33-6241, 42, 44, 45, 46, 48, 49, 50, 52, 55, 56, 57, 58													Total Fetuses	Total Litters
	Number of Fetuses Examined														
EXTERNAL EXAMINATION	3	8	10	10	8	11	6	7	6	8	7	7	0	91	12
SOFT TISSUE EXAMINATION	3	3	3	3	3	4	3	3	3	3	3	3	0	37	12
SKELETAL EXAMINATION	3	8	10	10	8	11	6	7	6	8	7	7	0	91	12
	Number of Fetuses Affected														
<u>Total Major Malformations</u>	1	0	0	1	0	0	0	0	0	0	0	0	0	2	2
<u>External Examination</u>															
Edema - neck and abdominal region	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1
<u>Soft Tissue Examination</u>															
Dilated cerebral ventricles	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Heart - thinning of right ventricular wall	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Satellite vessel off aorta	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Satellite vessel off innominate artery	0	0	0	0	0	0	1	0	2	0	0	0	0	3	2
Fused left carotid and innominate arteries	3	1	3	2	3	4	3	1	3	3	1	2	0	29	12
Kidney - cortical indentation unilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<u>Skeletal Examination</u>															
Skull - delayed ossification	0	1	0	0	0	1	0	0	0	0	0	0	0	2	2
-frontal ridge	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-foramen, frontal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-foramen, parietal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra suture lines, parietal	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1
-bone island, parietal	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1
-extra site of ossification between occipital condyles and atlas	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1
Vertebrae - hemivertebrae thoracic region with corresponding fused or forked rib and misshapen centra	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1
-lumbar vertebrae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra cervical vertebrae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ribs - 11 ribs on left & 12 ribs on right	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-shortened 1st thoracic rib	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-13th ribs - bilateral	3	8	2	3	2	1	5	5	1	6	5	4	0	45	12
-13th ribs - unilateral	0	0	2	1	0	2	0	1	0	1	1	2	0	10	7
-lumbar spurs	0	0	0	0	1	1	0	0	0	1	0	0	0	3	3
Sternebrae - delayed ossification of 2nd sternebra	0	0	0	0	0	1	0	0	1	0	0	0	0	2	2
-delayed ossification of 5th sternebrae	0	0	0	4	4	2	0	1	1	1	0	6	0	19	7
-delayed ossification of 6th sternebrae	0	5	2	7	0	1	0	0	3	1	0	2	0	21	7
-unfused	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1
-fused	1	0	0	0	1	0	0	0	0	0	0	0	0	2	2
-extra site of ossification between 5th & 6th	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1
Limbs - delayed ossification of phalanges in first digit, bilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

*Significantly different from the concurrent control value by a one-way analysis of variance, $p < 0.05$.

SL 083354

TABLE A-6 (Continued)

Exposure Level: 0 ppm (Concurrent Control for 160 ppm)

Animal Numbers:	33-6298, 99, 300, 03, 04, 05, 18, 20, 21, 22, 23, 24, 25													Total Fetuses	Total Litters
	Number of Fetuses Examined														
EXTERNAL EXAMINATION	5	5	8	7	11	9	11	14	8	11	9	12	1	111	13
SOFT TISSUE EXAMINATION	3	3	3	3	4	3	4	5	3	4	3	4	1	43	13
SKELETAL EXAMINATION	5	5	8	7	11	9	11	14	8	11	9	12	1	111	13
	Number of Fetuses Affected														
<u>Total Major Malformations</u>	0	0	0	0	0	0	0	1	1	0	0	0	0	2	2
<u>External Examination</u>															
Edema - neck and abdominal region	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<u>Soft Tissue Examination</u>															
Dilated cerebral ventricles	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Heart - thinning of right ventricular wall	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Satellite vessel off aorta	0	0	0	0	1	0	3	0	0	0	0	0	0	4	2
Satellite vessel off innominate artery	1	1	0	2	0	1	3	1	3	0	0	1	0	13	8
Fused left carotid and innominate arteries	1	2	0	3	1	2	4	2	3	4	3	0	0	25	10
Kidney - cortical indentation unilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<u>Skeletal Examination</u>															
Skull - delayed ossification	0	0	0	0	0	0	0	2	0	0	0	0	0	2	1
-frontal ridge	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-foramen, frontal	0	0	0	0	0	0	0	2	0	0	0	0	0	2	1
-foramen, parietal	0	0	0	0	1	0	0	0	0	0	1	0	0	2	2
-extra suture lines, parietal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-bone island, parietal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra site of ossification between occipital condyles and atlas	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vertebrae - hemivertebrae thoracic region with corresponding fused or forked rib & misshapen centra	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra and misshapen lumbar vertebrae	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1
-extra cervical vertebrae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ribs - 11 ribs on left & 12 ribs on right	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1
-shortened 1st thoracic rib	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-13th ribs - bilateral	0	4	0	1	2	5	2	6	0	3	5	6	0	34	9
-13th ribs - unilateral	0	0	1	0	3	2	0	2	0	1	1	1	0	11	7
-lumbar spurs	0	0	0	0	3	1	0	0	0	2	0	1	0	7	4
Sternebrae - delayed ossification of 2nd sternebra															
-delayed ossification of 5th sternebrae	5	4	4	5	9	0	4	1	4	2	3	3	0	44	11
-delayed ossification of 6th sternebrae	1	2	0	3	1	0	5	3	3	1	4	0	0	23	9
-unfused	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-fused	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-extra site of ossification between 5th & 6th	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Limbs - delayed ossification of phalanges in first digit, bilateral	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SL 083355

On the day of cesarean section, the females were sacrificed by carbon dioxide inhalation; the uterine horns were exteriorized through a mid-line incision in the abdominal wall, and the number and position of live, dead, and resorbed fetuses were noted. The uteri of apparently non-pregnant animals were stained with a 10% solution of sodium sulfide and examined for evidence of early resorption sites (Kopf et al., 1964); this procedure was conducted for the sole purpose of determining the percentage of pregnancy, not the incidence of resorptions. After being weighed, measured (crown-rump length), and sexed, all fetuses were examined for external alterations and cleft palate. One-third of the fetuses of each litter, selected at random, was examined immediately for evidence of soft-tissue alterations by dissection under a low power stereo-microscope (Staples, 1974). The head of each rat fetus which was examined for soft-tissue alterations was placed in Bouin's solution and subsequently examined by the razor section technique of Wilson (1965). All of the fetuses in each litter were eviscerated and placed in 95% ethanol and were cleared and stained with alizarin red-S (Dawson, 1926) to facilitate examination for skeletal alterations.

Statistical Evaluation. The incidences of pregnancy and resorptions were analyzed statistically by the Fisher exact