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EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX®111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS®CD®(SD)BR PRESUMED PREGNANT RATS

(ARGUS RESEARCH PROJECT 305-001)

FINAL REPORT: APRIL 15, 1985

[redacted]

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Protocol 305-001: Embryo/Fetal Toxicity and Teratogenic Potential Study of SAYTEX®111 Administered Orally via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats.

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CONFIDENTIAL

SUBJECT: Protocol 305-001 - Embryo/Fetal Toxicity and Teratogenic Potential Study of SAYTEX®111 Administered Orally Via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats.

I. SUMMARY AND CONCLUSION

Pregnant Crl:COBS®CD®(SD)BR female rats were given corn oil suspensions of SAYTEX®111 via gavage at dosages of 0(Vehicle), 2.5, 10.0 or 25.0 mg/kg/day (days 6-15 of gestation). The dams were sacrificed on day 20 of gestation, and the fetuses were examined using "state-of-the-art" developmental toxicity methodology. The study was performed in compliance with the EPA guidelines and regulations[1,2].

On the basis of data generated in this study, SAYTEX®111 is more toxic to the conceptus than to the dam. The embryo/fetal no-effect level is 2.5 mg/kg/day. The maternal no-effect level is greater than 25.0 mg/kg/day [the 25.0 mg/kg/day dosage of the test substance resulted in significant ($P \leq 0.01$) effects on maternal body weight gain only after cessation of dosage, an observation inseparable from the significantly increased ($P \leq 0.01$) resorption incidence and significantly decreased ($P \leq 0.01$) fetal body weights observed for litters of these dams, as compared with control values]. In a pilot dosage-range study[a], dosages of 100 mg/kg/day and above inhibited maternal body weight gain, and dosages of 500 mg/kg/day and above were lethal to dams.

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a. See Appendix B of this report for a summary of the pilot evaluation.

As compared with control values, administration of 10.0 and 25.0 mg/kg/day dosages of SAYTEX®111 to the dams resulted in dosage-dependent effects on the conceptuses including reduced average fetal body weights (10.0 and 25.0 mg/kg/day dosage group litters), increased embryo/fetal death (resorption), fetal malformation and delayed skeletal ossification (25.0 mg/kg/day dosage group). These effects were statistically significant ($P \leq 0.01$) only for the high dosage group, as compared with control.

4/11/85

Alan M. Hoberman, Ph.D. Date
Director, Reproductive Toxicology

4-15-85

Elizabeth A. Lochry, Ph.D. Date
Group Leader, Reproductive Toxicology
Study Director

4/15/85

Mildred S. Christian, Ph.D., ATS Date
Director of Research

DESCRIPTION OF TEST PROCEDURES

A. Methodology

1. General Experimental Design and Procedures

SAYTEX®111 was administered via gavage once daily to naturally-bred female rats on days 6 through 15 of presumed gestation. There were 25 presumed pregnant rats assigned to a vehicle control group and to each of three groups given the test substance. Dosages of 0(Vehicle), 2.5, 10.0 or 25.0 mg/kg/day were given using corn oil suspensions of SAYTEX®111 prepared at concentrations of 0.0, 0.5, 2.0 and 5.0 mg/mL, respectively. All dosages were given using a dosage volume of 5 mL/kg/day. The rats were observed for clinical signs of test substance effect, abortion and/or death. Body weight was recorded on day 0 of gestation and daily during the dosage and postdosage periods. The dosages were adjusted daily on the basis of the recorded body weight. On day 20 of presumed gestation, the female rats were sacrificed with carbon dioxide, and the abdomen of each rat was opened and examined for pregnancy, number and placement of implantations, early and late resorptions, live and dead fetuses and number of corpora lutea. Each fetus was weighed, sexed and examined for external variations. Live fetuses were sacrificed, and approximately one-half of the fetuses in each litter were examined for soft tissue anomalies, using a variation of Wilson's sectioning technique[3]. The remaining fetuses in each litter were cleared, stained with Alizarin red-S[4] and examined for skeletal variations.

The acclimation period began on November 13, 1984. The cohabitation period began on the afternoon of December 31, 1984, and ended on the morning of Janaury 5, 1985. Appropriate dosages of the test substance were administered to the female rats on days 6 through 15 of presumed gestation, which occurred on January 7 through January 19, 1985. Day-20 Caesarean-sectioning of the rats was performed on Janaury 21 through January 24, 1985.

2. Conduct of Study

This study was sponsored by the Ethyl Corporation, Toxicology and Industrial Hygiene Department, Ethyl Technical Center, P. O. Box 14799, Baton Rouge, Louisiana 70898. The Study Monitor for the Ethyl Corporation was Michael N. Pinkerton, B.A./B.S. It was conducted by and at Argus Research Laboratories, Inc., 2025 Ridge Road, Perkasie, Pennsylvania 18944. The Study Director was Elizabeth A. Lochry, Ph.D. (Group Leader, Reproductive Toxicology).

Personnel participating in the conduct of the study were Alan M. Hoberman, Ph.D. (Director of Reproductive Toxicology), Elizabeth A. Lochry, Elizabeth L. Feussner, V.M.D., D.A.B.T. (Senior Scientist, Manager Veterinary Care), Eric W. Sica, B.S. (Research Associate), Donna K. Cox-Sica (Research Assistant), Susan J. Armstrong, B.S., Johanna Geiger, B.S., Michelle A. Matula, B.S. and Matthew T. Jardel, B.S. (Laboratory Associates) and Linda A. McKeever, Martin G. McMahon and Nancy Rohs, B.S. (Laboratory Assistants). Animal care was performed by Thomas A. Hance (Animal Care Technician) and Sandra M. LaCava (Animal Care Helper).

Initial visceral and skeletal fetal evaluations were performed by Donna K. Cox-Sica, who also calculated the fetal ossification site averages. Observed gross external, visceral and skeletal fetal variations were confirmed by Alan M. Hoberman and/or Mildred S. Christian, Ph.D., ATS (Director of Research).

Data were reviewed by Elizabeth A. Lochry and/or Alan M. Hoberman. Data were tabulated by Linda L. Stern (Data Coordinator), Kathleen L. Fedorocsko, B.S. (Data Processor/Laboratory Associate) and Roseann E. Gramlich (Data Processor) and were statistically analyzed using programs designed for computer use.

The report was written by Elizabeth A. Lochry and Mildred S. Christian and reviewed by Alan M. Hoberman.

Curricula vitae and training records of personnel involved in the study are on file in the Quality Assurance Office of Argus Research Laboratories, Inc. The study was conducted in compliance with the EPA "Toxic Substances Control; Good Laboratory Practice Standards; Final Rule"(2).

3. Test Substance and Vehicle Identification

SAYTEX®111 (Lot #20-1831-A), a pink powder, was supplied by the Sponsor. Documentation of the methods of synthesis, purity, stability and characterization of the test substance are available in the Sponsor's records. The test substance was stored at room temperature. For the purposes of dosage calculation, the purity of SAYTEX®111 was assumed to be 100%.

The vehicle, corn oil (Mazola Brand®, Lots #JUL 23 85 A and #OCT 11 85 A) was obtained from a local source.

B. Animal Data

1. Test System

The Charles River Crl:COBS®CD®(SD)BR rat was selected for evaluation of SAYTEX®111 because: (1) it is one mammalian species standardly accepted for use in teratogenicity studies; (2) this strain of rat has been demonstrated to be sensitive to teratogens; (3) it has been widely used throughout industry for nonclinical studies of teratogenic potential; (4) historical data and experience exist; and (5) the test substance is pharmacologically active in this species and strain.

On November 13, 1984, 150 Crl:COBS®CD®(SD)BR virgin female rats were received from Charles River Breeding Laboratories, Inc., Kingston, New York. At receipt, the female rats were 66 days old (birthdate of female rats in population used: September 8, 1984) and weighed from 174 to 227 grams[a] each on the day after receipt.

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a. Receipt weights were recorded on the day following arrival, rather than on the day of arrival, in order to obtain a more valid measure of body weight.

On September 11, 1984, 160 male rats of the same strain and source were received for use as breeders. At receipt, the male rats were 73 days old (birthdate of male rats in population used: June 30, 1984) and weighed from 280 to 333 grams[a] on the day after receipt. Just prior to cohabitation, the male breeder rats were 184 days of age and weighed from 471 to 742 grams each.

Following a six-week acclimation period, 130[a] virgin female rats, which were determined to be in good health, were placed in cohabitation with male rats for a maximum of five days (one male was paired with one female rat). Female rats with spermatozoa observed in vaginal smears, or a vaginal plug observed in situ or in the cage pan, were considered to be at day 0 of presumed gestation and assigned to individual housing. The male breeders were removed from the study room at the end of the cohabitation period.

Day 0 of gestation occurred on January 1 to January 4, 1985, for the 100 female rats which were assigned to the study. These female rats weighed from 232 to 320 grams each, on day 0 of presumed gestation, and appeared to be disease-free. The rats were assigned to the four dosage groups using a second computer-generated (weight-ordered) randomization procedure based on day 0 of gestation body weights.

All female rats which either did not mate or were not assigned to study were removed from the study room on Janaury 5, 1985, and sacrificed.

2. Experimental Design and Control of Bias

Upon arrival, the virgin female rats were assigned to individual housing on the basis of a computer-generated randomization procedure. Each female rat was assigned a temporary number (1 through 150) which was used for identification during the acclimation period. Male rats were similarly randomized, upon arrival, and were assigned unique permanent numbers. Each male rat was individually identified with a Monel self-piercing ear tag (Gey Band and Tag Co., Inc., No. MSPT 20101) inscribed with the rat's designated unique number.

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a. On 11/26/84, after the first two weeks of the acclimation period, 20 of the 150 female rats were reassigned to a pilot evaluation (Argus Research Project 305-003P).

Following completion of the five-day cohabitation period, a second computer-generated randomization (weight-ordered) was used to assign those female rats which had mated and appeared to be in good health to the four dosage groups[a]. Each selected female rat was identified with a Monel self-piercing ear tag (Gey Band and Tag Co., Inc., No. MSPT 20101) inscribed with the rat's designated unique permanent number. Dosage group assignment was as follows:

Dosage Group	Dosage (mg/kg/days 6-15 of Presumed Gestation)	Female Rat Numbers	Number of Rats
I	0 (Corn Oil)	[illegible] - 20,425	25
II	[illegible]	[illegible] - 450	25
III	[illegible]	20,451 - 20,475	25
IV	[illegible]	20,476 - 20,500	25

3. Environmental Conditions

The female rats were housed individually in wire-bottomed stainless steel cages suspended above absorbent paper liners, except during cohabitation. During cohabitation (a maximum of five days), male and female rats were placed together, one male per female, in wire-bottomed cages. Upon observation of either spermatozoa in a vaginal smear or a vaginal plug *in situ* or in the cage pan, the female rat was removed from cohabitation and returned to individual housing. Because the dams were terminated prior to the expected day of natural delivery, nesting materials were not supplied.

The study was conducted in Rooms 3 and 6. The rats were housed in Room 3 for the first three weeks of the six-week acclimation period. For the remainder of the in-life phase of the study, the rats were housed in Room 6. These rooms were independently supplied with a minimum of 12 changes per hour of 100% fresh air which had been passed through 99.97% hepa-filters. Rooms 3 and 6 have approximately 166 and 137 square feet of floor space, respectively. The male breeders were placed in the study room prior to cohabitation and removed at the completion of the cohabitation period.

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a. All female rats assigned to study appeared in good health when randomized and assigned to dosage groups on January 5, 1985. Clinical signs were observed for high dosage group dam #20,496 just prior to administration of the first dosage on day 6 of presumed gestation (See Table 11 for adverse clinical signs observed for this rat during the course of the study). Therefore, data for this dam was excluded from all group averages and statistical analyses.

The temperature in the study rooms was maintained at 74°±4°F throughout the study. Humidity in the study rooms was recorded a minimum of once weekly during the study[a] and was documented to range between 35% and 56%.

An automatically-controlled fluorescent light cycle was maintained at 12 hours light:12 hours dark, with each dark cycle beginning at 1900 hours EST.

The rats were given Certified Rodent Chow® #5002 (Ralston Purina) which was available ad libitum throughout the study. Rats were fed from the following lots:

Dates	Lot Numbers
11/13/84 to 11/26/84	SEPT 20 84 1B
11/27/84 to 12/31/84	OCT 10 84 2B
01/01/85 to 01/24/85	NOV 20 84 1B

Analyses are routinely performed by the feed supplier. No contaminants in the feed or deviations from expected nutritional requirements were detected by these analyses. Results of the feed analyses are available in the raw data.

Local water which had been passed through a reverse osmosis membrane was available to the rats ad libitum (individual sipper tubes) from an automatic watering system. The processed water is analyzed annually for possible chemical contamination (Triangle Environmental Laboratories, Inc., Research Triangle Park, NC) and monthly for possible bacterial contamination (Purity-Standard Laboratories, Chalfont, Pennsylvania). Chlorine was added to the processed water as a bacteriostat, and the water contained approximately 0.0 ppm to 0.3 ppm chlorine at the time of analysis. The water was determined to be suitable for consumption. Copies of the results of the water analyses are available in the raw data.

No agent present in either the feed or water was known to interfere with the results of this study.

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a. The weekly humidity recording was inadvertently not performed during two of the ten weeks of the in-life phase.

4. Route of Administration and Dosage Selection

SAYTEX®111 was administered to the rats orally by gavage. The oral route was chosen because: (1) in comparison with the dietary route, the exact dosage can be accurately administered; (2) absorption of the test substance has been demonstrated in previous studies; and (3) the potential route of human exposure is oral.

Dosages were selected by the Sponsor on the basis of previous pilot studies (Argus Research Projects 305-001P and 305-003P). The results of this study are available in Appendices B and C. Once each day, on days 6-15 of gestation, presumed pregnant rats were administered dosages of 0(Vehicle), 2.5, 10.0 or 25.0 mg/kg/day, respectively. All dosages were given at a dosage volume of 5 mL/kg/day, using suspensions of SAYTEX®111 at respective concentrations of 0.0, 0.5, 2.0 or 5.0 mg/mL corn oil.

5. Test Substance Use and Preparation

Suspensions of SAYTEX®111 in corn oil were prepared once per week during the study, at volumes sufficient for seven days of use. The Sponsor evaluated SAYTEX®111 suspensions and found them to be stable for the period of use required by this study (data generated by the Sponsor and available in the Sponsor's records). All of the prepared concentrations were clear golden viscous suspensions. The prepared SAYTEX®111 concentrations and the vehicle were stored at room temperature. Standard safety precautions (use of gloves, safety glasses and a mask) were followed when handling the test substance and prepared suspensions.

The following mg/mL concentrations of SAYTEX®111 were administered to the female rats:

Dosage Group	Dosage (mg/kg/day)	Concentration (mg/mL)	ARGUS Batch Number
I	0(Vehicle)	0.0	B-305-001-A(Month.Day.Year)
II	2.5	0.5	B-305-001-B(Month.Day.Year)
III	10.0	2.0	B-305-001-C(Month.Day.Year)
IV	25.0	5.0	B-305-001-D(Month.Day.Year)

Three[a] 1.0 gram samples of each SAYTEX®111 concentration were taken at five different times during the study: (1) on the first day 6 of presumed gestation; (2) on the first day 9 of presumed gestation; (3) on the first day 12 of presumed gestation; (4) on the first day 15 of presumed gestation; and (5) on the last day 15 of presumed gestation. These samples were shipped to the Sponsor for possible analysis following completion of the study. The results of these analyses, if performed, are available in the Sponsor's records.

Two 0.5 gram samples of SAYTEX®111 were taken, one at the time that the first set of suspensions were prepared, and the other at the end of the dosage period. These samples were shipped to the Sponsor for possible analysis. The results of these analyses, if performed, are available in the Sponsor's records.

A 1.0 gram sample of SAYTEX®111 and a 1.0 gram sample of the corn oil (Mazola Brand®, Lot #JUL 23 85A) were retained at the Test Facility on the first day that SAYTEX®111 concentrations were prepared.

At completion of the all work with SAYTEX®111, all remaining test substance was returned to the Sponsor. All discarded quantities of prepared test substance suspensions were destroyed at the Test Facility.

6. <u>Test Substance Administration</u>

SAYTEX®111 was administered orally via gavage to female rats on days 6 through 15 of presumed gestation. Dosage volumes were adjusted daily for changes in body weight.

Standard safety precautions, use of gloves, safety glasses and mask, were followed when handling and/or administering the test substance.

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a. Each of the three samples were taken as follows: (1) the first 1.0 gram sample was taken prior to intubation of the first rat in the dosage group; (2) the second 1.0 gram sample was taken after approximately half of the rats in that dosage group had been intubated; (3) the third 1.0 gram sample was taken after intubation of the last rat in the dosage group.

Each daily dosage given to the rats was administered as closely as practical to the same time each day, between 1000 and 1130 hours EST, with all rats given the test substance or vehicle approximately 3.0 to 4.5 hours after the beginning of the light interval, at 0700 hours EST.

7. Observations

Throughout the acclimation and study periods, the female rats were observed twice daily for viability. These rats were also observed for clinical signs and/or general appearance several times during the acclimation period and on day 0 of presumed gestation (observations were recorded by exception). Observations for clinical signs of test substance effect, abortion and/or viability were made several times each day of the dosage period (days 6 through 15 of presumed gestation). After completion of the dosage period (days 16 through 20 of presumed gestation), the rats were also observed for clinical signs, abortion and/or natural delivery.

With the exception of one week, body weights of the female rats were recorded at least once weekly prior to mating and then on day 0 and days 6 through 20 of presumed gestation.

On day 20 of presumed gestation, the rats were sacrificed with carbon dioxide. The abdomen of each rat was opened, and the uterus was examined for pregnancy, number and placement of implantations, early and late resorptions and live and dead fetuses. Corpora lutea were counted. An early resorption was defined as one in which it was not grossly evident that organogenesis had occurred, and a late resorption was defined as one in which organogenesis was evident. A live fetus was defined as a term fetus which responded to stimuli. Non-responding term fetuses were considered to be dead. Dead fetuses and late resorptions were differentiated by the degree of autolysis present; marked to extreme autolysis was present in those fetuses considered to be late resorptions. Gross lesions observed in the dams at Caesarean-sectioning were preserved in neutral buffered 10% formalin for possible future evaluation. All other maternal tissues were discarded after evaluation.

Each fetus was removed and placed in an individual container, then weighed, individually identified with a tag and examined to identify sex and gross external variations. Live fetuses were sacrificed. Approximately one-half of the fetuses in each litter were examined for soft tissue anomalies, using a variation of Wilson's sectioning technique[3]. The remaining fetuses in each litter were eviscerated, cleared, stained with alizarin red-S[4] and examined for skeletal variations.

C. Statistical Tests

The following schematic represents the statistical analyses of the data:

Type of Test[a]

- I. Parametric[b]
  - A. Bartlett's[d]
    - Significant at $P \leq 0.05$ → Nonparametric
    - Not Significant → Analysis of Variance
      - Significant at $P \leq 0.05$ → Dunnett's Test
      - Not Significant
  - B. Analysis of Covariance
    - Significant at $P \leq 0.05$ → Covariance Analyses T-test
    - Not Significant
  - C. Variance Test for Homogeneity of the Binomial Distribution[e]
    - Significant at $P \leq 0.05$
    - Not Significant
- II. Nonparametric[c]
  - A. Kruskal-Wallis
    - Significant at $P \leq 0.05$ → Dunn's Test
    - Not Significant

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a. All tests evaluated at $P \leq 0.05$ and $P \leq 0.01$.
b. Used only to analyze data with homogeneity of variance.
c. Proportion data are not included in this category.
d. Test for homogeneity of variance.
e. Test for proportion data.

For all evaluations, the minimum level of statistical significance reported was $P \leq 0.05$.

Maternal physical sign data and incidence data were analyzed using the variance test for homogeneity of the binomial distribution[6].

Maternal body weight data were analyzed on days 0 and 6 through 20 of gestation using Bartlett's test of homogeneity of variances[7] and the Analysis of Variance[8]. If the Analysis of Variance was significant and appropriate, i.e., it passed Bartlett's test, then Dunnett's test[9] was used to identify the statistical significance of individual groups. If the Analysis of Variance was not appropriate, the Kruskal-Wallis test[10] was used; in cases where statistical significance occurred, Dunn's method of multiple comparisons[11] was used to identify the statistical significance of individual groups. Maternal body weight change data were analyzed using the Analysis of Covariance[12]. This analysis was performed using day 0 as the covariate with days 6 and 20, using day 6 as the covariate with days 7 through 16 and 20 and day 16 as the covariate with days 17 through 20.

Count data obtained at Caesarean-sectioning were evaluated using the Kruskal-Wallis test[10]; in cases where statistical significance occurred, Dunn's method of multiple comparisons[11] was used to identify the statistical significance of individual groups.

Litter averages for fetal body weight, ossification site data and percentage incidence per litter data were analyzed using Bartlett's test of homogeneity of variances[7] and the Analysis of Variance[8]. If the Analysis of Variance was significant and appropriate, i.e., it passed Bartlett's test, then Dunnett's test[9] was used to identify the statistical significance of individual groups. If the Analysis of Variance was not appropriate, the Kruskal-Wallis test[10] was used; in cases where statistical significance occurred, Dunn's method of multiple comparisons[11] was used to identify the statistical significance of individual groups. Fetal proportion data were analyzed using the variance test for homogeneity of the binomial distribution[6].

D. Storage

The original report and raw data are retained in the archives of Argus Research Laboratories, Inc., 905 Sheehy Drive, Horsham, Pennsylvania 19044. Preserved maternal and fetal tissues will be returned to the Sponsor upon completion of all work with SAFTEX®111.

III. RESULTS[a]

A. Physical Signs

1. Mortality

No adult rat died during the study.

2. Adverse Clinical Signs (Summary - Table 1; Individual Incidence - Table 11)

Administration of the 25.0 mg/kg/day dosage of the test substance to the rats, as compared with the vehicle, resulted in red or brown vaginal exudate, associated with resorption of conceptuses. The incidence of this clinical sign was significantly increased ($P \leq 0.01$) for the high dosage group dams, as compared with the controls.

No other clinical sign[a] observed was attributed to administration of these dosages of the test substance to the dams. Localized alopecia, soft or liquid feces, urine-stained abdominal fur and a lesion occurred at incidences which were infrequent, not dosage-dependent and/or not significantly increased ($P > 0.05$), as compared with control incidences.

3. Postmortem Physical Signs Observed at Day-20 Caesarean-Sectioning (Table 2)

Necropsy of the rats at Caesarean-sectioning did not reveal any lesions attributed to SAYTEX®111 administration. One high dosage group rat (#20,485) had a white cheese-like substance present in the thoracic cavity, which was considered to be the sequala to intubation injury. All other rats appeared normal at scheduled sacrifice.

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a. All data for Dam #20,496 were excluded from tabulation for this study. This rat had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage, and was thus considered inappropriate for continued use in the study. (Observations for this dam are documented in the appropriate individual tables.) Necropsy of this dam revealed small white foci present on the lobes of the liver and early resorption of its 17 conceptuses. This dam is excluded from all other discussion in this report.

B. Maternal Body Weight Data (Summary - Table 3; Individual Data - Table 12)

With the exception of the first day of dosage, the average maternal body weight gain during the dosage period was comparable and not significantly different (P>0.05) for dams in the four dosage groups. The average maternal body weight gain for days 6-16 of gestation ranged from 40.3 grams to 43.2 grams in the four dosage groups. Administration of the first 10.0 or 25.0 mg/kg/day dosages of SAYTEX®111 to the dams resulted in slight weight loss (-0.1 to -0.3 grams); weight gain was observed for the control (+0.7 grams) and 2.5 mg/kg/day (+0.5 grams) dosage group dams following the initial dosage. This minimal effect on expected body weight gain was not statistically significant (P>0.05).

After completion of the dosage period, days 16 to 20 of gestation, average maternal body weight and body weight gain were significantly less ($P \leq 0.01$) for the 25.0 mg/kg/day dosage group dams (38.8 grams**), as compared with the control values (63.0 grams). Overall average maternal body weight gain during gestation (days 0 to 20 of gestation) was significantly decreased ($P \leq 0.01$) for the high dosage group dams (100.9 grams**), as compared with the control dams (129.9 grams). These observations were interrelated with the high incidence of resorption and small average fetal body weights observed for litters of the high dosage group dams and not indicative of a direct toxic effect of the test substance on the dams.

C. Caesarean-Sectioning Data (Summary - Table 4; Individual Data - Table 13)

Administration of the 25.0 mg/kg/day dosage of SAYTEX®111, to the dams significantly increased ($P \leq 0.01$) resorption (embryo and fetal death) and significantly decreased ($P \leq 0.01$) the interrelated parameter, average live litter size, as compared with control values.

Pregnancy occurred for 25 vehicle control rats and for 24 rats in each of the three groups given the test substance. Two (8.3%) high dosage group rats resorbed all conceptuses; all of the control, 2.5 and 10.0 mg/kg/day dosage group dams had one or more live fetuses. There was an average of 0.6, 1.2*, 0.8

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* Significantly different from the vehicle control ($P \leq 0.05$).
** Significantly different from the vehicle control ($P \leq 0.01$).

and 4.9** resorptions in the control, low, middle and high dosage group litters, respectively. Significantly increased ($P \leq 0.01$) incidences of late resorption and fetal death occurred in high dosage group litters, as compared with control values. There was an average of 14.6, 14.7, 14.0 and 8.9** live fetuses per litter in the control, low, middle and high dosage groups, respectively. One or more resorptions were present for 10(40.0%), 18(75.0%)**, 13(54.2%) and 18(75.0%)** of the dams in these same respective dosage groups.

The significant ($P \leq 0.05$) increase in average number of resorptions per litter and significant ($P \leq 0.01$) increase in the incidence of dams with any resorptions present for the low dosage group, as compared with the control values, were not attributed to administration of the 2.5 mg/kg/day dosage of the test substance to the dams. These observations were not dosage-dependent, did not result in decreased average litter sizes, as compared with concurrent control values, and were near the range of the historical values for this parameters[a].

Administration of 2.5, 10.0 and 25.0 mg/kg/day dosages of SAYTEX®111, as compared with the vehicle, did not adversely affect the average numbers of corpora lutea or implantations. These values were respectively equivalent, did not significantly differ ($P > 0.05$) among the four dosage groups and/or were within historical control range[b].

D. <u>Litter Data (Summary - Table 5; Citation by Litter - Tables 14 and 15</u>

As compared with the vehicle, administration of 10.0 and 25.0 mg/kg/day dosages of SAYTEX®111 to the dams decreased average fetal body weights per litter. These data also demonstrated a significant ($P \leq 0.01$) lethal effect on the conceptuses (calculated as the percentage of dead or resorbed conceptuses per litter) resulting from administration of the 25.0 mg/kg/day dosage of the

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** Significantly different from the vehicle control ($P \leq 0.01$).

a. In 13 Segment II studies conducted at this Test Facility between 1983 and 1985, the average number of resorptions per control litter was 0.7 (range of 0.5 to 1.0; total number of litters evaluated was 304), and the incidence of control dams with one or more resorptions ranged from 33.3% to 72.7%.

b. In 13 Segment II studies conducted at this Test Facility between 1983 and 1985, the average number of corpora lutea and implantations per control dam was 15.4 and 13.8 (range of 13.2 to 17.0 and 11.6 to 15.5; total number of dams evaluated was 304), respectively.

test substance to the dams. The increased average percentage of male fetuses per litter observed for the high dosage group litters, as compared with control litters, was not attributed to the test substance because the averages for this parameter were not dosage-dependent and were close to the range of historical control values for this parameter[a].

Fetal body weights averaged 3.38, 3.34, 3.25 and 2.10** grams for the 0(Vehicle), 2.5, 10.0 and 25.0 mg/kg/day dosage group litters, respectively. Male fetuses weighed more than female fetuses in all dosage groups. Control, low, middle and high dosage group male fetuses averaged 3.51, 3.42, 3.32 and 2.14** grams per litter. In these same respective groups, female fetuses averaged 3.26, 3.27, 3.21 and 2.05** grams per litter.

The average percentage of dead or resorbed conceptuses per litter was 4.3, 7.9, 5.6 and 33.2** for the control, low, middle and high dosage groups, respectively.

E. <u>Fetal Variations (Summaries - Tables 6, 7, 8, 9 and 10; Citation by Litter - Tables 16 and 17)</u>

Fetal variations were classified as: 1) malformations (aberrant development), or 2) reversible changes (delays or accelerations) in development.

Administration of the high dosage of SAYTEX®111 to the dams resulted in significant ($P \leq 0.01$) increases in the litter incidences of fetuses with enlarged heart, rear limb malformation (shortened, bent and/or incompletely ossified femur, tibia and/or fibula) and with remarkable delays in ossification of the skull, vertebrae, ribs and pelvis. The fetal incidences of slight dilation of the lateral ventricles of the brain and of malformed and incompletely ossified scapulae were also significantly ($P \leq 0.01$) increased, as were the fetal incidences for all of the previously cited malformations and developmental delays. Significant ($P \leq 0.05$ to $P \leq 0.01$) delays in the average number of ossified sacral and caudal vertebrae, manubrium, sternal and xiphoid centers, metacarpals, metatarsals and both fore- and hindpaw phalanges also occurred for

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** Significantly different from the vehicle control ($P \leq 0.01$).

a. In nine Segment II studies conducted at this Test Facility between 1983 and 1985, the average percentage of male fetuses per control litter was 49.5 (range of 42.2 to 55.3; total number of litters evaluated was 243).

litters of the high dosage group dams, as compared with the vehicle control values.

No fetal variation revealed by gross external, soft tissue or skeletal examination was attributed to administration of the 2.5 or 10.0 mg/kg/day dosages of SAYTEX®111 to the dams. The fetal and litter incidences of all observed variations for these dosage groups were similar to and not significantly increased (P>0.05) from vehicle control incidences.

1. Summary of Variations Observed in Fetuses (Tables 6 and 17)

Totals of 364, 352, 335 and 213 live day-20 Caesarean-delivered fetuses from 25, 24, 24 and 22 litters in the 0(Vehicle), 2.5, 10.0 and 25.0 mg/kg/day dosage groups, respectively, were evaluated for gross external variations. Of these live fetuses, 175, 169, 161 and 99 fetuses were evaluated for soft tissue variations(3), and 189, 183, 174 and 114 fetuses were examined for skeletal variations(4).

In addition to these live specimens, a total of 13 dead fetuses and one late resorption from litters of high dosage group dams were also examined for gross external variations. Five of the 13 dead fetuses were examined for soft tissue variations; the remaining eight dead fetuses and the late resorption were examined for skeletal variations.

Within the limits of evaluation, the dead fetuses and late resorption appeared normal at gross external and soft tissue examination. Skeletal examination of the eight dead fetuses revealed that one of these specimens (#20,489-F11) was malformed (shortened scapulae, bent femur, tibia and fibula of right hindlimb). This specimen also had delayed ossification of the skull, vertebrae, ribs, scapulae and hindlimb(s).

Five of the remaining seven dead fetuses also had delays in ossification of the skull, sternebrae, vertebrae, and/or pelvis, observations expected for specimens of their developmental ages, as did the late resorption which had an enlarged fontanelle and delayed ossification of the vertebrae and pelvis.

Observations for these specimens were excluded from all statistical analyses.

The incidence of fetuses with any variation observed was 4.4%, 1.7%, 3.9% and 18.3%** in the 0(Vehicle), 2.5, 10.0 and 25.0 mg/kg/day dosage groups, respectively. In these same respective dosage groups, 52.0%, 20.8%**, 41.7% and 63.6% of the litters had one or more fetuses with a variation present.

The average incidence of fetuses with any variation per litter was 4.56%, 1.64%, 3.81% and 27.38% in the control, low, middle and high dosage groups, respectively.

2. Gross External Variations Observed (Tables 7 and 16)

No gross external variation observed for the fetuses was attributed to administration of SAYTEX®111 to the dams. The observed incidences were infrequent, non-dosage-dependent and not significantly increased ($P>0.05$), as compared with control values.

3. Soft Tissue Variations Observed (Tables 8 and 16)

Administration of the high dosage of the test substance to the dams resulted in significant increases ($P\leq0.01$) in the fetal and litter incidences of specimens with an enlarged heart. There was also a significant increase ($P\leq0.01$) in the fetal incidence of delayed brain development (slight dilation of the lateral ventricles).

No other variation observed at soft tissue examination was attributed to administration of these dosages of SAYTEX®111 to the dams. The observed incidences were infrequent, non-dosage-dependent and/or not significantly increased ($P>0.05$), as compared with control values.

4. Skeletal Variations Observed (Tables 9 and 16)

Administration of the high dosage of SAYTEX®111 to the dams resulted in significant ($P\leq0.01$) increases in the litter incidences of fetuses with rear limb malformation (shortened, bent and/or incompletely ossified femur, tibia and/or fibula) and with remarkable delays in ossification of the skull,

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** Significantly different from vehicle control ($P\leq0.01$).

vertebrae, ribs and pelvis. The fetal incidence of malformed and incompletely ossified scapulae was also significantly ($P \leq 0.01$) increased, as were the fetal incidences for all of the previously cited malformations and developmental delays.

No other variation revealed by skeletal examination of the fetuses was attributed to administration of these dosages of the test substance to the dams. The incidences for these observations occurred at incidences which were not significantly different ($P > 0.05$) from control values and/or were not dosage-dependent.

5. Fetal Ossification Sites (Table 10)

Fetal ossification site averages were based on 189, 183, 174 and 114 live fetuses which were Caesarean-delivered on day 20 of gestation from 25, 24, 24, and 22 dams in the 0(Vehicle), 2.5, 10.0 and 25.0 mg/kg/day dosage groups, respectively.

Administration of the high dosage of the test substance to the dams significantly ($P \leq 0.05$ to $P \leq 0.01$) retarded ossification of the fetal sacral and caudal vertebrae, manubrium, sternal and xiphoid centers, metacarpals, metatarsals and both fore- and hindpaw phalanges.

Differences in the average numbers of ossified cervical, thoracic and lumbar vertebrae, hyoid, ribs, carpals and tarsals per fetus per litter were within normal range for this strain and/or were not significantly different among the four dosage groups ($P > 0.05$).

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APPENDIX A

REPORT TABLES

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 1 (PAGE 1): SUMMARY OF ADVERSE CLINICAL SIGNS OBSERVED IN RATS

Maximum Incidence: Rats - 25; Days - 15 (Days 6-20 of Presumed Gestation) 25x15=375

Dosage Group (mg/kg/days 6-15 of Presumed Gestation)	Maximum Incidence	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
I - 0(Vehicle)						
	Rats 25	0	6	1	0	1
	Days 375	0	51	3	0	4
II - 2.5						
	Rats 25	0	2	0	0	0
	Days 375	0	11**	0	0	0**
III - 10.0						
	Rats 25	0	5	3	1	0
	Days 375	0	36	17**	7**	0**
IV - 25.0						
	Rats 24[a]	2	3	2	1	0
	Days 360[a]	3**	10**	10	1	0**

[ ] = Code for observed clinical sign.

a. Excludes dam #20,496 which had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).

** Significantly different from vehicle control, at $P \leq 0.01$.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 2 (PAGE 1): POSTMORTEM PHYSICAL SIGNS OBSERVED AT DAY-20 CAESAREAN-SECTIONING[a]

Dosage Group (mg/kg/days 6-15 of Presumed Gestation)	Incidence	Rat Number	Observations
I - 0(Vehicle)	0/25	-	-
II - 2.5	0/25	-	-
III - 10.0	0/25	-	-
IV - 25.0	1/24[b]	20,485	Thoracic Cavity: Filled with a white cheese-like substance. All other gross tissues appeared normal.

a. Signs cited by exception.
b. Excludes dam #20,496 which had adverse clinical signs on day 6 of gestation prior to the first dosage. See Table 11 for individual adverse clinical signs. At scheduled necropsy, small white foci were observed on the lobes of the liver. No other gross lesions were observed.

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'ABLE 3 (PAGE 1): SUMMARY OF MATERNAL BODY WEIGHT DATA

DOSAGE GROUP Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	2.5 MG/KG/DAY	10.0 MG/KG/DAY	25.0 MG/KG/DAY
ANIMALS - TESTED		25	25	25	24a
PREGNANT	N(%)	25(100.0)	24(96.0)	24(96.0)	24(100.0)a
MATERNAL BODY WEIGHT					
DAY 0	MEAN±S.D.	276.0 ± 15.3	276.1 ± 15.4	277.2 ± 13.9	277.3 ± 14.6 [22]
DAY 6	MEAN±S.D.	302.7 ± 17.7	303.7 ± 17.5	301.1 ± 18.7	297.8 ± 17.1 [22]
DAY 7	MEAN±S.D.	303.4 ± 17.0	304.2 ± 16.8	301.0 ± 16.6	297.5 ± 16.8 [22]
DAY 8	MEAN±S.D.	304.5 ± 16.2	306.6 ± 17.5	303.5 ± 16.3	299.4 ± 16.1 [22]
DAY 9	MEAN±S.D.	307.1 ± 16.9	309.4 ± 18.7	307.0 ± 14.9	301.8 ± 16.2 [22]
DAY 10	MEAN±S.D.	313.0 ± 18.3	314.2 ± 18.0	311.6 ± 15.5	308.4 ± 15.6 [22]
DAY 11	MEAN±S.D.	317.8 ± 17.8	319.3 ± 17.7	316.8 ± 15.8	313.1 ± 16.0 [22]
DAY 12	MEAN±S.D.	321.9 ± 18.6	324.2 ± 19.7	319.0 ± 14.4	316.2 ± 15.3 [22]

his table restricted to pregnant animals.
nimals with all implants resorbing excluded from this table.
a. Excludes dam #20,496 which had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).

ALL WEIGHT VALUES IN g
[ ] = NUMBER OF VALUES AVERAGED

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'ABLE 3 (PAGE 2): SUMMARY OF MATERNAL BODY WEIGHT DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	2.5 MG/KG/DAY	10.0 MG/KG/DAY	25.0 MG/KG/DAY
ANIMALS - TESTED		25	25	25	24a
PREGNANT	N(%)	25(100.0)	24(96.0)	24(96.0)	24(100.0)a
MATERNAL BODY WEIGHT					
DAY 13	MEAN±S.D.	324.8 ± 18.3	327.0 ± 18.0	323.1 ± 16.1	319.6 ± 15.9 [22]
DAY 14	MEAN±S.D.	328.9 ± 18.3	331.9 ± 19.5	327.2 ± 15.5	324.8 ± 16.4 [22]
DAY 15	MEAN±S.D.	335.6 ± 19.1	338.1 ± 20.8	333.9 ± 16.0	330.7 ± 15.6 [22]
DAY 16	MEAN±S.D.	343.0 ± 18.2	346.9 ± 21.2	344.2 ± 16.4	339.4 ± 15.7 [22]
DAY 17	MEAN±S.D.	357.2 ± 17.4	360.7 ± 23.2	357.7 ± 17.3	351.6 ± 16.1 [22]
DAY 18	MEAN±S.D.	371.2 ± 17.6	377.7 ± 25.6	372.7 ± 20.0	363.4 ± 17.2 [22]
DAY 19	MEAN±S.D.	386.6 ± 18.8	390.6 ± 25.6	386.4 ± 22.1	370.2 ± 17.2* [22]
DAY 20	MEAN±S.D.	406.0 ± 18.7	409.5 ± 27.8	403.1 ± 23.2	378.2 ± 20.6** [22]

'his table restricted to pregnant animals.
nimals with all implants resorbing excluded from this table.
a. Excludes dam 20,496 which had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).
* Significantly different from vehicle control, at $P \leq 0.05$.
** Significantly different from vehicle control, at $P \leq 0.01$.

ALL WEIGHT VALUES IN g
[ ] = NUMBER OF VALUES AVERAGED

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TABLE 3 (PAGE 3): SUMMARY OF MATERNAL BODY WEIGHT DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	2.5 MG/KG/DAY	10.0 MG/KG/DAY	25.0 MG/KG/DAY
ANIMALS - TESTED		25	25	25	24a
PREGNANT	N(%)	25(100.0)	24(96.0)	24(96.0)	24(100.0)a
MATERNAL BODY WEIGHT CHANGE					
DAYS 0- 6	MEAN±S.D.	+26.6 ± 8.0	+27.6 ± 5.0	+23.9 ± 11.8	+20.5 ± 14.6 [22]
DAYS 6- 7	MEAN±S.D.	+0.7 ± 4.3	+0.5 ± 3.7	-0.1 ± 4.8	-0.3 ± 6.3 [22]
DAYS 6- 8	MEAN±S.D.	+1.8 ± 5.8	+2.9 ± 4.1	+2.4 ± 5.5	+1.6 ± 8.9 [22]
DAYS 6- 9	MEAN±S.D.	+4.4 ± 7.0	+5.8 ± 6.3	+5.9 ± 6.2	+4.0 ± 9.2 [22]
DAYS 6-10	MEAN±S.D.	+10.4 ± 8.7	+10.5 ± 7.0	+10.5 ± 7.2	+10.6 ± 8.0 [22]
DAYS 6-11	MEAN±S.D.	+15.2 ± 8.1	+15.6 ± 7.8	+15.7 ± 7.3	+15.4 ± 8.1 [22]
DAYS 6-12	MEAN±S.D.	+19.2 ± 7.7	+20.5 ± 6.8	+18.0 ± 9.1	+18.4 ± 9.1 [22]
DAYS 6-13	MEAN±S.D.	+22.2 ± 6.8	+23.3 ± 6.6	+22.0 ± 8.8	+21.8 ± 8.4 [22]

This table restricted to pregnant animals.
Animals with all implants resorbing excluded from this table.
a. Excludes dam #20,496 which had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).

ALL WEIGHT VALUES IN g
[ ] = NUMBER OF VALUES AVERAGED

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'ABLE 3 (PAGE 4): SUMMARY OF MATERNAL BODY WEIGHT DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	2.5 MG/KG/DAY	10.0 MG/KG/DAY	25.0 MG/KG/DAY
ANIMALS - TESTED		25	25	25	24a
PREGNANT	N(%)	25(100.0)	24(96.0)	24(96.0)	24(100.0)a
MATERNAL BODY WEIGHT CHANGE					
DAYS 6-14	MEAN±S.D.	+26.2 ± 7.0	+28.2 ± 7.1	+26.1 ± 9.8	+27.0 ± 10.1 [22]
DAYS 6-15	MEAN±S.D.	+33.0 ± 7.5	+34.4 ± 8.0	+32.8 ± 10.0	+33.0 ± 10.2 [22]
DAYS 6-16	MEAN±S.D.	+40.3 ± 9.3	+43.2 ± 8.9	+43.1 ± 10.4	+41.6 ± 11.6 [22]
DAYS 16-17	MEAN±S.D.	+14.2 ± 5.3	+13.8 ± 3.9	+13.5 ± 5.1	+12.2 ± 4.4 [22]
DAYS 16-18	MEAN±S.D.	+28.2 ± 5.6	+30.8 ± 7.3	+28.4 ± 9.1	+24.1 ± 8.2 [22]
DAYS 16-19	MEAN±S.D.	+43.7 ± 8.0	+43.7 ± 7.9	+42.2 ± 9.8	+30.8 ± 9.9** [22]
DAYS 16-20	MEAN±S.D.	+63.0 ± 6.8	+62.7 ± 10.6	+58.9 ± 11.9	+38.8 ± 12.4** [22]
DAYS 6-20	MEAN±S.D.	+103.3 ± 11.4	+105.8 ± 16.0	+102.0 ± 15.2	+80.4 ± 19.6** [22]
DAYS 0-20	MEAN±S.D.	+129.9 ± 13.0	+133.4 ± 18.0	+125.9 ± 19.0	+100.9 ± 22.8** [22]

'his table restricted to pregnant animals.
nimals with all implants resorbing excluded from this table.
a. Excludes dam #20,496 which had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).
** Significantly different from vehicle control, at $P \leq 0.01$.

ALL WEIGHT VALUES IN g
[ ] = NUMBER OF VALUES AVERAGED

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TABLE 4 (PAGE 1): SUMMARY OF CAESAREAN-SECTIONING DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	2.5 MG/KG/DAY	10.0 MG/KG/DAY	25.0 MG/KG/DAY
ANIMALS - TESTED		25	25	25	24a
PREGNANT	N(%)	25(100.0)	24(96.0)	24(96.0)	24(100.0)a
ANIMALS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20	N	25	24	24	24a
CORPORA LUTEA	MEAN±S.D.	17.4 ± 2.0	17.2 ± 2.1	16.4 ± 3.8	17.1 ± 3.8
IMPLANTATIONS	MEAN±S.D.	15.2 ± 1.4	15.9 ± 1.7	14.7 ± 2.8	14.3 ± 3.3
LITTER SIZE	MEAN±S.D.	14.6 ± 1.8	14.7 ± 2.0	14.0 ± 2.9	9.4 ± 6.0**
LIVE FETUSES	N	364	352	335	213
	MEAN±S.D.	14.6 ± 1.8	14.7 ± 2.0	14.0 ± 2.9	8.9 ± 6.2**
DEAD FETUSES	N(%)	0	0	0	13(5.8)**
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 2.0
RESORPTIONS	MEAN±S.D.	0.6 ± 1.0	1.2 ± 1.0*	0.8 ± 0.8	4.9 ± 4.9**
EARLY RESORPTIONS	N	16	30	17	80
	MEAN±S.D.	0.6 ± 1.0	1.2 ± 1.0*	0.7 ± 0.8	3.3 ± 4.4**
LATE RESORPTIONS	N	0	0	1	38
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.2	1.6 ± 2.6**
DAMS WITH ANY RESORPTIONS	N(%)	10(40.0)	18(75.0)**	13(54.2)	18(75.0)**
DAMS WITH ALL IMPLANTATIONS RESORBING	N(%)	0	0	0	2(8.3)
DAMS WITH VIABLE FETUSES	N(%)	25(100.0)	24(100.0)	24(100.0)	22(91.7)

a. Excludes dam #20,496 which had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).
* Significantly different from vehicle control, at $P<0.05$.
** Significantly different from vehicle control, at $P\leq 0.01$.

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TABLE 5 (PAGE 1): SUMMARY OF LITTER DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	2.5 MG/KG/DAY	10.0 MG/KG/DAY	25.0 MG/KG/DAY
LITTERS EXAMINED DAY 20	N	25	24	24	22a
IMPLANTATIONS	MEAN±S.D.	15.2 ± 1.4	15.9 ± 1.7	14.7 ± 2.8	14.4 ± 3.[illegible]
LIVE FETUSES	MEAN±S.D.	14.6 ± 1.8	14.7 ± 2.0	14.0 ± 2.9	9.7 ± 5.8**
LITTERS WITH ONE OR MORE LIVE FETUSES	N	25	24	24	22a
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.38 ± 0.22	3.34 ± 0.27	3.25 ± 0.34	2.10 ± 0.42**
MALE FETUSES	MEAN±S.D.	3.51 ± 0.24	3.42 ± 0.25	3.32 ± 0.36	2.14 ± 0.40**
FEMALE FETUSES	MEAN±S.D.	3.26 ± 0.21	3.27 ± 0.30	3.21 ± 0.36	2.05 ± 0.42** [17]b
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	4.3 ± 6.8	7.9 ± 6.8	5.6 ± 6.5	33.2 ± 35.0**
LIVE FETUSES	N	364	352	335	213
LIVE MALE FETUSES	N	178	178	157	104
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	48.6 ± 14.3	50.2 ± 11.1	46.7 ± 16.6	60.4 ± 24.8

NOTE: - Animals with all implants resorbing excluded from this table.
[ ] = Number of values averaged
a. Excludes dam #20,496 which had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).
b. Excludes litters #20,476, #20,479, #20,481, #20,482 and #20,494 which had no male fetuses.
** Significantly different from vehicle control, at $P \leq 0.01$.

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TABLE 6 (PAGE 1): SUMMARY OF VARIATIONS OBSERVED IN FETUSES

		Dosage (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 2.5	III - 10.0	IV - 25.0
Litters Evaluated	N	25	24	24	22
Fetuses Evaluated	N	364	352	335	227
Live	N	364	352	335	213
Dead	N	0	0	0	13[a]
Late Resorption	N	0	0	0	1[a]
% Fetuses with any Variations/Litter	$\bar{X}$%±S.D.	4.56±6.50	1.64±3.52	3.81±5.35	27.38±34.14
Litters with Fetuses with any Variation Observed	N(%)	13(52.0)	5(20.8)**	10(41.7)	14(63.6)
Fetuses with any Variation Observed	N(%)	16(4.4)	6(1.7)	13(3.9)	39(18.3)**

a. These specimens were excluded from group averages and statistical evaluations. For individual observations, see Table 17.

** Significantly different from vehicle control, at $P \leq 0.01$.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 7 (PAGE 1): SUMMARY OF FETAL GROSS EXTERNAL VARIATIONS

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 2.5	III - 10.0	IV - 25.0
Litters Evaluated	N	25	24	24	22
Fetuses Evaluated	N	364	352	335	227
Live	N	364	352	335	213
Dead	N	0	0	0	13[a]
Late Resorptions	N	0	0	0	1[a]
JAW:					
Micrognathia					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.3)	0	0	0
BODY:					
Edematous					
Litter Incidence	N(%)	1(4.0)	0	0	1(4.5)
Fetal Incidence	N(%)	1(0.3)	0	0	2(0.9)
Umbilical Hernia					
Litter Incidence	N(%)	2(8.0)	0	0	0
Fetal Incidence	N(%)	2(0.5)	0	0	0
TAIL:					
"Thread-like"					
Litter Incidence	N(%)	0	0	1(4.2)	0
Fetal Incidence	N(%)	0	0	1(0.3)	0

a. For observations, see Table 17; these specimens were excluded from calculations.

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TABLE 8 (PAGE 1): SUMMARY OF FETAL SOFT TISSUE VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0 (Vehicle)	II - 2.5	III - 10.0	IV - 25.0
Litters Evaluated	N	25	24	24	17[a]
Fetuses Evaluated	N	175	169	161	104
Live	N	175	169	161	99
Dead	N	0	0	0	5[b]
Late Resorptions	N	0	0	0	0
JAW:					
Micrognathia					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.6)	0	0	0
PALATE:					
Shortened					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.6)	0	0	0
TONGUE:					
Agenesis					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.6)	0	0	0
BRAIN:					
Lateral Ventricles, Slight Dilation					
Litter Incidence	N(%)	0	0	1(4.2)	1(5.9)
Fetal Incidence	N(%)	0	0	1(0.6)	3(3.0)**

1. See footnotes on the last page of this table.

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TABLE 8 (PAGE 2): SUMMARY OF FETAL SOFT TISSUE VARIATIONS

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0 (Vehicle)	II - 2.5	III - 10.0	IV - 25.0
Litters Evaluated	N	25	24	24	17[a]
Fetuses Evaluated	N	175	169	161	104
Live	N	175	169	161	99
Dead	N	0	0	0	5[b]
Late Resorptions	N	0	0	0	0
HEART:					
Enlarged					
Litter Incidence	N(%)	0	0	0	3(17.6)**
Fetal Incidence	N(%)	0	0	0	6(6.1)**
KIDNEYS:					
Pelves, Slight to Marked Dilation					
Litter Incidence	N(%)	2(8.0)	1(4.2)	0	0
Fetal Incidence	N(%)	2(1.1)	1(0.6)	0	0
INTESTINES:					
Protrude from Abdominal Cavity					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.6)	0	0	0

** Significantly different from vehicle control, at $P<0.01$.

a. Excludes litters #20,476, #20,479, #20,481, #20,482 and #20,494 which each had only one live fetus which was assigned to skeletal evaluation.

b. Litter #20,476 had five dead fetuses which were evaluated for visceral variations. For observations, see Table 17; these specimens were excluded from calculations.

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TABLE 9 (PAGE 1): SUMMARY OF FETAL SKELETAL VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0 (Vehicle)	II - 2.5	III - 10.0	IV - 25.0
Litters Evaluated	N	25	24	24	22
Fetuses Evaluated	N	189	183	174	123
Live	N	189	183	174	114
Dead	N	0	0	0	8[a]
Late Resorptions	N	0	0	0	1[a]
MALFORMATIONS					
SCAPULAE:					
Shortened and/or Incompletely Ossified					
Litter Incidence	N(%)	0	0	0	1(4.5)
Fetal Incidence	N(%)	0	0	0	2(1.8)**
REAR LIMB(S):					
Femur, Tibia and/or Fibula: Shortened, Bent and/or Incompletely Ossified					
Litter Incidence	N(%)	0	0	0	4(18.2)**
Fetal Incidence	N(%)	0	0	0	7(6.1)**
VERTEBRAE:					
Caudal, Only One Present					
Litter Incidence	N(%)	0	0	1(4.2)	0
Fetal Incidence	N(%)	0	0	1(0.6)	0

1. See footnotes on last page of this table.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 9 (PAGE 2): SUMMARY OF FETAL SKELETAL VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 2.5	III - 10.0	IV - 25.0
Litters Evaluated	N	25	24	24	22
Fetuses Evaluated	N	189	183	174	123
Live	N	189	183	174	114
Dead	N	0	0	0	8[a]
Late Resorptions	N	0	0	0	1[a]
DEVELOPMENTAL CHANGES (DELAYED OR ACCELERATED DEVELOPMENT)					
SKULL:					
Delayed Ossification of Skull (Enlarged Fontanelle, Supra-occipital, Inter-parietal, Sphenoid and/or Exoccipital: Incompletely or Not Ossified					
Litter Incidence	N(%)	0	0	1(4.2)	8(36.4)**
Fetal Incidence	N(%)	0	0	1(0.6)	16(14.0)**
Sphenoid, Contains a Hole					
Litter Incidence	N(%)	0	0	1(4.2)	7(31.8)**
Fetal Incidence	N(%)	0	0	1(0.6)	10(8.8)**
VERTEBRAE:					
Delayed Ossification of Thoracic Centra[b]					
Litter Incidence	N(%)	4(16.0)	1(4.2)	5(20.8)	11(50.0)**
Fetal Incidence	N(%)	4(2.1)	1(0.5)	5(2.9)	21(13.4)**

1. See footnotes on last page of this table.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™ CD™ (SD) BR PRESUMED PREGNANT RATS

TABLE 9 (PAGE 3): SUMMARY OF FETAL SKELETAL VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0 (Vehicle)	II - 2.5	III - 10.0	IV - 25.0
Litters Evaluated	N	25	24	24	22
Fetuses Evaluated	N	189	183	174	123
Live	N	189	183	174	114
Dead	N	0	0	0	8[a]
Late Resorptions	N	0	0	0	1[a]
VERTEBRAE (CONTINUED):					
Thoracic, Arches, One or More, Fused					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)	0	0	0
Delayed Ossification of Lumbar Centra and/or Arches[c]					
Litter Incidence	N(%)	0	0	0	10(45.4)**
Fetal Incidence	N(%)	0	0	0	19(16.7)**
Delayed Ossification of Sacral Arches[d]					
Litter Incidence	N(%)	0	0	0	4(18.2)**
Fetal Incidence	N(%)	0	0	0	5(4.4)**
RIBS:					
One or More, Hypoplastic and/or Wavy					
Litter Incidence	N(%)	1(4.0)	0	0	9(40.9)**
Fetal Incidence	N(%)	1(0.5)	0	0	15(13.2)**

1. See footnotes on last page of this table.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 9 (PAGE 4): SUMMARY OF FETAL SKELETAL VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 2.5	III - 10.0	IV - 25.0
Litters Evaluated	N	25	24	24	22
Fetuses Evaluated	N	189	183	174	123
Live	N	189	183	174	114
Dead	N	0	0	0	8[a]
Late Resorptions	N	0	0	0	1[a]
RIBS (CONTINUED):					
One or More, Fused					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)	0	0	0
MANUBRIUM:					
Incompletely Ossified					
Litter Incidence	N(%)	0	0	0	1(4.5)
Fetal Incidence	N(%)	0	0	0	1(0.9)
STERNEBRAE:					
Incompletely or Not Ossified					
Litter Incidence	N(%)	5(20.0)	4(16.7)	6(25.0)	5(22.7)
Fetal Incidence	N(%)	7(3.7)	4(2.2)	6(3.4)	5(4.4)
PELVIS:					
Ischia and/or Pubes, Incompletely or Not Ossified					
Litter Incidence	N(%)	1(4.0)	0	3(12.5)	7(31.8)**
Fetal Incidence	N(%)	1(0.[illegible])	0	3(1.7)	19(16.7)**

1. See footnotes on last page of this table.

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TABLE 9 (PAGE 5): SUMMARY OF FETAL SKELETAL VARIATIONS

FOOTNOTES

** Significantly different from vehicle control, at $P \leq 0.01$.

a. For observations, see Table 17; these specimens were excluded from calculations.

b. Includes incompletely ossified, unilaterally ossified, unossified and/or bifid thoracic centra.

c. Includes incompletely ossified and/or unossified lumbar centra and/or arches.

d. Includes incompletely ossified sacral arches.

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TABLE 10 (PAGE 1): FETAL OSSIFICATION SITES (LIVE FETUSES - DAY 20)

		Dosage Group - (mg/kg/days 6-15 of Presumed Gestation)			
		I - 0(Vehicle)	II - 2.5	III - 10.0	IV - 2..0
Litters Examined	N	25	24	24	22
Fetuses Examined	N	189	183	174	114
Ossification Sites[a]					
Hyoid	$\bar{X}$±S.D.	0.90 ± 0.15	0.89 ± 0.17	0.94 ± 0.08	0.84 ± 0.28
Cervical (VERTEBRAE)	$\bar{X}$±S.D.	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00
Thoracic (VERTEBRAE)	$\bar{X}$±S.D.	13.02 ± 0.04	13.00 ± 0.00	13.00 ± 0.00	13.00 ± 0.00
Lumbar (VERTEBRAE)	$\bar{X}$±S.D.	5.98 ± 0.05	6.00 ± 0.00	6.00 ± 0.00	5.97 ± 0.13
Sacral (VERTEBRAE)	$\bar{X}$±S.D.	3.00 ± 0.00	2.99 ± 0.04	3.00 ± 0.00	2.65 ± 0.60**
Caudal (VERTEBRAE)	$\bar{X}$±S.D.	4.72 ± 0.40	4.72 ± 0.54	4.60 ± 0.39	2.64 ± 1.61**
Ribs	$\bar{X}$±S.D.	13.02 ± 0.04	13.00 ± 0.00	13.00 ± 0.00	13.00 ± 0.00
Manubrium	$\bar{X}$±S.D.	1.00 ± 0.00	1.00 ± 0.02	1.00 ± 0.00	0.95 ± 0.10*
Sternal	$\bar{X}$±S.D.	3.60 ± 0.32	3.59 ± 0.30	3.57 ± 0.29	2.62 ± 1.09**
Xiphoid	$\bar{X}$±S.D.	1.00 ± 0.02	0.98 ± 0.06	1.00 ± 0.00	0.64 ± 0.50**
Forepaws					
Carpals	$\bar{X}$±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Metacarpals	$\bar{X}$±S.D.	3.40 ± 0.34	3.39 ± 0.30	3.42 ± 0.36	3.06 ± 0.21**
Phalanges	$\bar{X}$±S.D.	4.98 ± 0.18	4.95 ± 0.26	4.97 ± 0.36	2.75 ± 2.12**
Hindpaws					
Tarsals	$\bar{X}$±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Metatarsals	$\bar{X}$±S.D.	4.00 ± 0.00	3.98 ± 0.08	3.99 ± 0.04	3.76 ± 0.34**
Phalanges	$\bar{X}$±S.D.	4.84 ± 0.30	4.84 ± 0.38	4.80 ± 0.39	2.03 ± 2.22**

a. Per fetus per litter.
* Significantly different from vehicle control, at $P<0.05$.
** Significantly different from vehicle control, at $P\leq 0.01$.

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TABLE 11 (PAGE 1): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: I 0(Vehicle) mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,401	-	14,15,16,17,18,19, 20	-	-	-
20,402	-	-	-	-	-
20,403	-	-	-	-	-
20,404	-	-	-	-	-
20,405	-	-	-	-	-
20,406	-	-	-	-	-
20,407	-	-	-	-	-
20,408	-	-	-	-	-
20,409	-	6,7,8,9,10,11,12, 13,14,15,16,17,18, 19,20	-	-	-
20,410	-	-	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 2): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: I 0(Vehicle) mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,411	-	-	-	-	-
20,412	-	-	-	-	-
20,413	-	-	-	-	-
20,414	-	-	-	-	-
20,415	-	-	-	-	-
20,416	-	-	-	-	17,18,19,20
20,417	-	17,18	-	-	-
20,418	-	-	-	-	-
20,419	-	6,7,8,9,10,11,12, 13,14,15,16,17,18, 19,20	12,13,14	-	-
20,420	-	-	-	-	-
20,421	-	-	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.

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TABLE 11 (PAGE 3): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: I 0(Vehicle) mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,422	-	15,16,17,18,19,20	-	-	-
20,423	-	-	-	-	-
20,424	-	-	-	-	-
20,425	-	15,16,17,18,19,20	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.

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TABLE 11 (PAGE 4): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: II 2.5 mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,426	-	-	-	-	-
20,427	-	-	-	-	-
20,428	-	-	-	-	-
20,429	-	-	-	-	-
20,430	-	-	-	-	-
20,431[b]	-	-	-	-	-
20,432	-	15,16,17,18,19,20	-	-	-
20,433	-	-	-	-	-
20,434	-	-	-	-	-
20,435	-	-	-	-	-
20,436	-	-	-	-	-
20,437	-	-	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.
b. Not pregnant.

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TABLE 11 (PAGE 5): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: II 2.5 mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,438	-	-	-	-	-
20,439	-	-	-	-	-
20,440	-	-	-	-	-
20,441	-	-	-	-	-
20,442	-	-	-	-	-
20,443	-	-	-	-	-
20,444	-	-	-	-	-
20,445	-	-	-	-	-
20,446	-	-	-	-	-
20,447	-	-	-	-	-
20,448	-	-	-	-	-
20,449	-	-	-	-	-
20,450	-	16,17,18,19,20	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.

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TABLE 11 (PAGE 6): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: III 10.0 mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,451	-	-	-	-	-
20,452	-	-	-	-	-
20,453	-	-	-	-	-
20,454	-	13,14,15,16,17,18, 19,20	-	-	-
20,455	-	18,19,20	-	-	-
20,456	-	-	-	-	-
20,457	-	-	-	-	-
20,458	-	-	-	-	-
20,459	-	-	-	-	-
20,460	-	-	-	-	-
20,461	-	11,12,13,14,15,16, 17,18,19,20	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 7): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: III 10.0 mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,462	-	-	-	-	-
20,463	-	12,13,14,15,16,17, 18,19,20	-	-	-
20,464	-	-	-	-	-
20,465	-	-	-	-	-
20,466	-	-	11,12,13,14,15,16, 17	14,15,16,17,18,19, 20	-
20,467	-	-	17	-	-
20,468	-	15,16,17,18,19,20	-	-	-
20,469[b]	-	-	-	-	-
20,470	-	-	-	-	-
20,471	-	-	11,12,13,14,15,16, 17,18,19	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.
b. Not pregnant.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 8): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: III 10.0 mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,472	-	-	-	-	-
20,473	-	-	-	-	-
20,474	-	-	-	-	-
20,475	-	-	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 9): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,476	-	-	-	-	-
20,477	-	-	-	-	-
20,478	-	-	-	-	-
20,479	-	-	-	8	-
20,480	18	-	-	-	-
20,481	-	-	-	-	-
20,482	-	-	-	-	-
20,483	-	-	-	-	-
20,484	-	-	-	-	-
20,485	-	-	-	-	-
20,486[b]	15,16	17,18,19,20	-	-	-
20,487	-	-	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.
b. All conceptuses were resorbed.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 11): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation				
	Observation/Day of Presumed Gestation				
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]
20,497	-	15	-	-	-
20,498	-	-	16	-	-
20,499	-	-	-	-	-
20,500	-	-	-	-	-

[ ] = Code for observed clinical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 10): ADVERSE CLINICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation									
	Observation/Day of Presumed Gestation									
	Red or Brown Exudate from Vagina [07]	Localized Alopecia [03]	Soft or Liquid Feces [30]	Urine-Stained Abdominal Fur [36]	Lesion [05]	Thin Appearance [32]	Ungroomed Coat [35]	Chromorrhinorrhea [13]	Hypersensitivity [23]	Decreased Motor Activity [15]
20,488	-	-	-	-	-	-	-	-	-	-
20,489	-	-	-	-	-	-	-	-	-	-
20,490[b]	-	16,17,18, 19,20	-	-	-	-	-	-	-	-
20,491	-	-	-	-	-	-	-	-	-	-
20,492	-	-	-	-	-	-	-	-	-	-
20,493	-	-	-	-	-	-	-	-	-	-
20,494	-	-	-	-	-	-	-	-	-	-
20,495	-	-	11,12,13, 14,15,16, 17,18,19	-	-	-	-	-	-	-
20,496[b]	-	-	(10,11,12, 13,14,15, 16)	(6[c],7,8,9, 10,11,12, 13,14,15, 16,17,18, 19,20)	-	(6[c],7,8,9, 10,11,12, 13,14,15, 16,17,18, 19,20)	(6[c],7,8,9, 10,11,12, 13,14,15, 16,17,18, 19,20)	(13,14,15, 16,17,18, 19,20)	(20)	(20)

[ ] = Code for observed clinical sign. ( ) = Excluded from summary table.

a. Cited by exception from day 6 to day 20 of presumed gestation.

b. All conceptuses were resorbed.

c. Observed both prior to and following dosage on day 6 of gestation.

ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY
VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 12 (PAGE 1): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 0	6	7	8	9	10	11	12	13	14	15	16	17
DAM #	DOSAGE GROUP I VEHICLE CONTROL 0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION												
20401 P	284.	313.	313.	316.	319.	330.	329.	338.	337.	340.	345.	353.	362.
20402 P	320.	356.	357.	352.	359.	370.	377.	384.	384.	389.	393.	398.	410.
20403 P	275.	313.	316.	316.	314.	322.	332.	325.	332.	334.	344.	350.	358.
20404 P	269.	298.	299.	301.	303.	306.	313.	318.	324.	328.	334.	344.	354.
20405 P	288.	312.	307.	311.	310.	316.	318.	325.	328.	332.	338.	344.	354.
20406 P	259.	278.	283.	285.	289.	292.	302.	304.	304.	309.	314.	324.	334.
20407 P	267.	306.	308.	307.	312.	319.	324.	329.	332.	335.	341.	349.	360.
20408 P	274.	301.	295.	302.	305.	315.	318.	324.	321.	327.	332.	340.	352.
20409 P	265.	293.	290.	294.	295.	299.	305.	310.	312.	316.	321.	331.	345.
20410 P	245.	269.	267.	268.	269.	278.	281.	284.	283.	287.	290.	298.	319.
20411 P	262.	287.	288.	284.	298.	296.	302.	304.	307.	311.	314.	324.	337.
20412 P	265.	283.	290.	290.	302.	302.	311.	321.	319.	327.	332.	342.	361.
20413 P	274.	307.	313.	317.	319.	330.	319.	329.	334.	333.	342.	353.	362.
20414 P	269.	301.	299.	307.	305.	313.	315.	322.	327.	332.	342.	350.	362.
20415 P	278.	309.	310.	308.	314.	326.	328.	331.	336.	339.	349.	360.	368.
20416 P	289.	312.	316.	314.	318.	323.	330.	335.	338.	343.	354.	335.	344.
20417 P	270.	292.	296.	294.	298.	305.	314.	314.	318.	316.	327.	336.	347.
20418 P	281.	324.	321.	317.	324.	327.	336.	335.	341.	342.	350.	358.	372.
20419 P	285.	317.	314.	313.	316.	320.	321.	327.	331.	340.	347.	357.	380.
20420 P	273.	298.	305.	310.	314.	316.	321.	326.	327.	330.	338.	348.	367.
20421 P	277.	293.	293.	290.	290.	305.	308.	304.	313.	322.	326.	334.	353.
20422 P	298.	317.	316.	320.	322.	327.	334.	337.	337.	343.	352.	357.	375.
20423 P	292.	299.	296.	294.	298.	300.	304.	304.	308.	312.	317.	323.	346.
20424 P	287.	310.	304.	305.	294.	289.	299.	315.	318.	322.	329.	333.	359.
20425 P	255.	279.	289.	297.	290.	300.	305.	303.	310.	314.	320.	333.	349.

=Pregnant NP=Not Pregnant (Values excluded from averages)
ll weights in g DAY = Day of presumed gestation

PROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 12 (PAGE 3): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 0	6	7	8	9	10	11	12	13	14	15	16	17
DAM #	DOSAGE GROUP II LOW DOSE				2.5 MG/KG/DAYS 6-15 OF PRESUMED GESTATION								
20426 P	232.	253.	259.	261.	259.	266.	276.	273.	284.	283.	291.	293.	301.
20427 P	267.	292.	285.	287.	289.	294.	302.	303.	309.	312.	318.	327.	333.
20428 P	263.	300.	306.	307.	305.	312.	324.	324.	331.	335.	337.	355.	370.
20429 P	275.	311.	310.	312.	310.	322.	328.	333.	340.	351.	357.	365.	378.
20430 P	271.	300.	299.	300.	305.	304.	310.	314.	320.	319.	330.	338.	354.
20431 NP	255.	289.	290.	289.	291.	293.	292.	294.	301.	302.	292.	283.	288.
20432 P	279.	306.	313.	310.	314.	323.	328.	332.	331.	332.	341.	347.	363.
20433 P	285.	314.	318.	317.	328.	328.	336.	340.	348.	350.	358.	372.	383.
20434 P	258.	290.	284.	287.	294.	299.	306.	307.	308.	314.	314.	322.	331.
20435 P	274.	302.	306.	308.	309.	311.	319.	324.	326.	331.	338.	348.	357.
20436 P	274.	306.	306.	310.	315.	316.	321.	328.	327.	332.	335.	341.	359.
20437 P	298.	326.	325.	322.	315.	312.	312.	328.	337.	344.	349.	354.	376.
20438 P	288.	315.	316.	316.	318.	326.	325.	332.	332.	340.	352.	354.	366.
20439 P	303.	329.	328.	339.	344.	344.	350.	363.	359.	361.	376.	382.	400.
20440 P	276.	299.	300.	299.	302.	309.	315.	318.	317.	324.	332.	341.	354.
20441 P	283.	317.	317.	326.	338.	339.	344.	352.	352.	366.	372.	380.	398.
20442 P	290.	320.	315.	325.	323.	325.	337.	340.	338.	342.	344.	362.	370.
20443 P	302.	335.	333.	332.	338.	347.	351.	355.	354.	360.	369.	375.	392.
20444 P	262.	280.	282.	283.	283.	290.	294.	294.	297.	302.	305.	310.	322.
20445 P	286.	318.	318.	322.	324.	332.	334.	338.	341.	347.	354.	358.	372.
20446 P	269.	293.	297.	301.	307.	314.	314.	320.	327.	328.	330.	344.	358.
20447 P	282.	302.	300.	303.	306.	314.	317.	319.	323.	331.	337.	348.	364.
20448 P	268.	291.	289.	293.	298.	301.	303.	314.	313.	316.	321.	334.	351.
20449 P	266.	290.	294.	294.	297.	305.	307.	310.	316.	321.	326.	336.	352.
20450 P	275.	300.	301.	305.	306.	308.	311.	320.	318.	324.	328.	339.	353.

P=Pregnant NP=Not Pregnant (Values excluded from averages)
All weights in g DAY = Day of presumed gestation

'ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

'ABLE 12 (PAGE 4): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 18	19	20
DAM #	DOSAGE GROUP II LOW DOSE		2.5 MG/KG/DAYS 6-15 OF PRESUMED GESTATION
20426 P	319.	331.	352.
20427 P	348.	355.	371.
20428 P	384.	398.	416.
20429 P	397.	414.	432.
20430 P	373.	389.	409.
20431 NP	292.	286.	286.
20432 P	381.	398.	418.
20433 P	405.	422.	437.
20434 P	340.	354.	365.
20435 P	370.	387.	402.
20436 P	380.	390.	408.
20437 P	397.	405.	424.
20438 P	383.	386.	416.
20439 P	420.	426.	455.
20440 P	373.	386.	420.
20441 P	424.	431.	460.
20442 P	392.	413.	428.
20443 P	411.	426.	445.
20444 P	339.	348.	366.
20445 P	384.	393.	408.
20446 P	380.	387.	411.
20447 P	375.	393.	404.
20448 P	370.	393.	408.
20449 P	351.	370.	380.
20450 P	368.	379.	394.

'=Pregnant NP=Not Pregnant (Values excluded from averages)
ll weights in g DAY = Day of presumed gestation

PROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 12 (PAGE 5): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 0	6	7	8	9	10	11	12	13	14	15	16	17
DAM #	DOSAGE GROUP III MID DOSE				10.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION								
20451 P	267.	296.	298.	302.	308.	311.	316.	322.	330.	332.	339.	348.	360.
20452 P	296.	315.	314.	318.	318.	320.	329.	333.	341.	346.	350.	360.	366.
20453 P	263.	252.	266.	272.	278.	285.	291.	300.	300.	308.	313.	326.	334.
20454 P	300.	329.	324.	330.	333.	342.	347.	346.	350.	351.	358.	369.	373.
20455 P	258.	279.	277.	278.	288.	292.	303.	303.	307.	314.	319.	328.	341.
20456 P	270.	305.	300.	297.	301.	311.	317.	316.	322.	327.	333.	340.	361.
20457 P	274.	298.	302.	305.	311.	320.	324.	328.	332.	337.	346.	352.	362.
20458 P	288.	333.	331.	334.	332.	342.	341.	339.	351.	350.	354.	367.	387.
20459 P	281.	309.	312.	309.	305.	310.	314.	320.	323.	328.	340.	352.	369.
20460 P	272.	282.	278.	284.	287.	287.	290.	291.	296.	298.	304.	315.	326.
20461 P	266.	296.	291.	301.	302.	314.	319.	321.	323.	325.	336.	346.	363.
20462 P	280.	320.	320.	326.	326.	332.	332.	334.	338.	347.	354.	363.	374.
20463 P	268.	306.	299.	308.	308.	309.	316.	316.	318.	321.	330.	342.	362.
20464 P	276.	309.	314.	313.	312.	320.	329.	329.	331.	334.	340.	350.	366.
20465 P	256.	284.	286.	284.	293.	296.	299.	303.	311.	311.	319.	332.	348.
20466 P	286.	313.	313.	312.	315.	315.	320.	324.	325.	333.	339.	347.	357.
20467 P	282.	303.	302.	299.	306.	315.	314.	315.	309.	318.	323.	334.	351.
20468 P	261.	270.	271.	278.	280.	286.	285.	290.	291.	296.	303.	310.	326.
20469 NP	252.	275.	274.	278.	282.	281.	283.	286.	278.	269.	274.	268.	266.
20470 P	274.	302.	304.	306.	311.	311.	317.	321.	327.	335.	343.	359.	372.
20471 P	315.	325.	317.	320.	326.	326.	340.	329.	341.	336.	344.	355.	379.
20472 P	284.	301.	304.	308.	310.	310.	315.	319.	320.	324.	332.	338.	346.
20473 P	288.	310.	304.	307.	317.	317.	323.	332.	337.	345.	351.	364.	378.
20474 P	275.	300.	304.	301.	307.	308.	317.	320.	323.	327.	334.	344.	358.
20475 P	272.	289.	292.	292.	294.	300.	304.	306.	308.	310.	309.	320.	326.

P=Pregnant NP=Not Pregnant (Values excluded from averages)
All weights in g DAY = Day of presumed gestation

'ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

'ABLE 12 (PAGE 6): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 18	19	20
DAM #	DOSAGE GROUP III MID DOSE		10.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION
20451 P	372.	386.	400.
20452 P	382.	402.	418.
20453 P	350.	368.	382.
20454 P	393.	412.	425.
20455 P	361.	376.	391.
20456 P	375.	388.	403.
20457 P	378.	393.	410.
20458 P	408.	431.	447.
20459 P	392.	403.	419.
20460 P	344.	344.	370.
20461 P	390.	401.	427.
20462 P	390.	401.	422.
20463 P	382.	392.	405.
20464 P	382.	396.	408.
20465 P	365.	374.	398.
20466 P	375.	379.	405.
20467 P	368.	370.	392.
20468 P	332.	352.	365.
20469 NP	258.	267.	270.
20470 P	376.	392.	402.
20471 P	396.	416.	437.
20472 P	358.	373.	388.
20473 P	386.	408.	425.
20474 P	361.	375.	387.
20475 P	328.	343.	348.

=Pregnant NP=Not Pregnant (Values excluded from averages)
ll weights in g DAY = Day of presumed gestation

PROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 12 (PAGE 7): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 0	6	7	8	9	10	11	12	13	14	15	16	17
DAM #	DOSAGE GROUP IV HIGH DOSE				25.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION								
20476 P	289.	321.	320.	319.	323.	326.	329.	331.	338.	345.	346.	354.	365.
20477 P	286.	256.	261.	270.	272.	284.	290.	300.	302.	313.	315.	320.	332.
20478 P	260.	268.	264.	269.	274.	276.	278.	282.	287.	292.	298.	312.	320.
20479 P	317.	312.	294.	286.	289.	307.	318.	324.	329.	335.	341.	348.	351.
20480 P	270.	284.	287.	291.	294.	306.	310.	307.	307.	314.	316.	323.	341.
20481 P	298.	320.	322.	325.	330.	329.	338.	337.	341.	342.	342.	344.	350.
20482 P	266.	278.	279.	283.	287.	287.	296.	295.	296.	300.	307.	312.	321.
20483 P	272.	306.	307.	308.	313.	320.	321.	330.	328.	328.	339.	346.	359.
20484 P	274.	299.	295.	290.	293.	304.	302.	311.	311.	320.	326.	343.	350.
20485 P	292.	319.	301.	302.	303.	316.	321.	320.	326.	329.	336.	339.	358.
20486aP	[261.]	[295.]	[297.]	[305.]	[313.]	[310.]	[314.]	[324.]	[326.]	[327.]	[329.]	[333.]	[336.]
20487 P	268.	292.	293.	296.	300.	307.	313.	324.	325.	336.	346.	364.	384.
20488 P	284.	307.	308.	312.	311.	318.	322.	325.	328.	330.	330.	343.	357.
20489 P	263.	291.	294.	297.	301.	310.	312.	314.	319.	321.	334.	341.	352.
20490aP	[268.]	[284.]	[284.]	[290.]	[290.]	[295.]	[298.]	[302.]	[306.]	[311.]	[314.]	[323.]	[326.]
20491 P	273.	303.	306.	310.	313.	314.	321.	325.	331.	337.	341.	351.	365.
20492 P	288.	314.	319.	324.	330.	335.	336.	337.	342.	350.	353.	364.	374.
20493 P	278.	308.	313.	315.	315.	324.	329.	333.	334.	338.	346.	357.	371.
20494 P	284.	306.	310.	312.	316.	324.	330.	328.	334.	343.	349.	351.	359.
20495 P	276.	299.	303.	304.	302.	307.	312.	315.	317.	324.	330.	335.	347.
20496bP	[282.]	[266.]	[266.]	[267.]	[272.]	[275.]	[272.]	[268.]	[273.]	[274.]	[272.]	[261.]	[260.]
20497 P	274.	302.	306.	304.	302.	308.	319.	318.	324.	328.	336.	346.	358.
20498 P	255.	276.	274.	277.	279.	284.	286.	291.	292.	291.	303.	316.	332.
20499 P	278.	298.	299.	302.	300.	299.	301.	302.	307.	318.	326.	331.	347.
20500 P	255.	292.	290.	291.	293.	300.	305.	307.	313.	312.	316.	326.	342.

=Pregnant NP=Not Pregnant (Values excluded from averages)
ll weights in g DAY = Day of presumed gestation [ ] = Excluded from tabulation.
. Dam resorbed all conceptuses.
. Data for dam #20,496 were excluded from all group averages and statistical evaluations. This dam had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).

ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 12 (PAGE 8): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 18	19	20
DAM #	DOSAGE GROUP IV HIGH DOSE		25.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION
20476 P	373.	380.	389.
20477 P	346.	357.	369.
20478 P	338.	346.	351.
20479 P	355.	364.	370.
20480 P	354.	371.	367.
20481 P	356.	367.	370.
20482 P	330.	327.	337.
20483 P	374.	383.	396.
20484 P	370.	369.	379.
20485 P	376.	378.	404.
20486aP	[347.]	[338.]	[352.]
20487 P	403.	414.	430.
20488 P	367.	365.	376.
20489 P	366.	365.	376.
20490aP	[331.]	[331.]	[343.]
20491 P	378.	377.	394.
20492 P	390.	385.	391.
20493 P	384.	396.	410.
20494 P	361.	374.	376.
20495 P	349.	362.	365.
20496bP	[249.]	[247.]	[245.]
20497 P	367.	376.	380.
20498 P	348.	362.	365.
20499 P	353.	364.	368.
20500 P	358.	362.	357.

=Pregnant NP=Not Pregnant (Values excluded from averages)
11 weights in g DAY = Day of presumed gestation [ ] = Excluded from tabulation.
. Dam resorbed all conceptuses.
. Data for dam #20,496 were excluded from all group averages and statistical evaluations. This dam had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).

PROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 13 (PAGE 1): CAESAREAN-SECTIONING DATA - INDIVIDUAL RATS

DOSAGE GROUP I VEHICLE CONTROL 0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT HORN	LEFT HORN	TOTAL	RIGHT OVARY	LEFT OVARY	TOTAL
DAM#	M	F																		
20401	4	10	9	5	14	0	0	0	1	0	1	0	0	0	10	5	15	10	6	16
20402	10	6	8	8	16	0	0	0	1	0	1	0	0	0	9	8	17	10	10	20
20403	4	9	8	5	13	0	0	0	1	1	2	0	0	0	9	6	15	10	6	16
20404	7	8	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	8	9	17
20405	8	5	10	3	13	0	0	0	0	0	0	0	0	0	10	3	13	12	6	18
20406	6	9	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	9	11	20
20407	6	5	5	6	11	0	0	0	1	1	2	0	0	0	6	7	13	7	7	14
20408	5	7	5	7	12	0	0	0	0	0	0	0	0	0	5	7	12	5	9	14
20409	6	8	8	6	14	0	0	0	1	0	1	0	0	0	9	6	15	10	7	17
20410	5	9	4	10	14	0	0	0	0	0	0	0	0	0	4	10	14	5	10	15
20411	4	11	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	8	9	17
20412	6	10	8	8	16	0	0	0	0	0	0	0	0	0	8	8	16	11	11	22
20413	6	5	4	7	11	0	0	0	0	4	4	0	0	0	4	11	15	6	11	17
20414	7	7	7	7	14	0	0	0	0	1	1	0	0	0	7	8	15	9	11	20
20415	11	6	7	10	17	0	0	0	0	0	0	0	0	0	7	10	17	8	10	18
20416	12	4	9	7	16	0	0	0	1	0	1	0	0	0	10	7	17	12	8	20
20417	8	7	4	11	15	0	0	0	0	0	0	0	0	0	4	11	15	5	13	18
20418	6	6	8	4	12	0	0	0	0	2	2	0	0	0	8	6	14	8	10	18
20419	8	8	6	10	16	0	0	0	0	1	1	0	0	0	6	11	17	8	11	19
20420	9	6	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	8	7	15
20421	13	4	7	10	17	0	0	0	0	0	0	0	0	0	7	10	17	7	10	17
20422	10	5	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	9	8	17
20423	5	9	7	7	14	0	0	0	0	0	0	0	0	0	7	7	14	8	8	16
20424	7	10	8	9	17	0	0	0	0	0	0	0	0	0	8	9	17	8	9	17
20425	5	12	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	9	8	17

M=MALE, F=FEMALE

PROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 13 (PAGE 2): CAESAREAN-SECTIONING DATA - INDIVIDUAL RATS

DOSAGE GROUP II LOW DOSE 2.5 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT	
DAM#	M	F	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	OVARY	OVARY	TOTAL
20426	8	6	6	8	14	0	0	0	0	0	0	0	0	0	6	8	14	10	10	20
20427	7	6	6	7	13	0	0	0	0	2	2	0	0	0	6	9	15	6	9	15
20428	10	4	6	8	14	0	0	0	0	2	2	0	0	0	6	10	16	6	11	17
20429	11	4	6	9	15	0	0	0	1	0	1	0	0	0	7	9	16	7	9	16
20430	11	6	6	11	17	0	0	0	0	1	1	0	0	0	6	12	18	9	12	21
20431	NOT PREGNANT																			
20432	9	6	11	4	15	0	0	0	0	1	1	0	0	0	11	5	16	11	5	16
20433	8	8	8	8	16	0	0	0	0	0	0	0	0	0	8	8	16	8	8	16
20434	3	7	3	7	10	0	0	0	1	3	4	0	0	0	4	10	14	4	10	14
20435	5	8	7	6	13	0	0	0	1	1	2	0	0	0	8	7	15	8	7	15
20436	6	8	4	10	14	0	0	0	1	1	2	0	0	0	5	11	16	9	11	20
20437	9	6	4	11	15	0	0	0	0	2	2	0	0	0	4	13	17	5	15	20
20438	7	9	9	7	16	0	0	0	1	0	1	0	0	0	10	7	17	10	7	17
20439	8	7	6	9	15	0	0	0	0	2	2	0	0	0	6	11	17	8	12	20
20440	10	8	10	8	18	0	0	0	0	0	0	0	0	0	10	8	18	11	8	19
20441	8	9	9	8	17	0	0	0	0	1	1	0	0	0	9	9	18	9	9	18
20442	8	9	9	8	17	0	0	0	0	1	1	0	0	0	9	9	18	9	9	18
20443	7	8	10	5	15	0	0	0	1	1	2	0	0	0	11	6	17	11	7	18
20444	7	6	8	5	13	0	0	0	0	0	0	0	0	0	8	5	13	10	6	16
20445	5	6	7	4	11	0	0	0	0	1	1	0	0	0	7	5	12	8	6	14
20446	7	11	9	9	18	0	0	0	0	0	0	0	0	0	9	9	18	9	9	18
20447	5	9	6	8	14	0	0	0	0	1	1	0	0	0	6	9	15	8	9	17
20448	7	7	7	7	14	0	0	0	0	3	3	0	0	0	7	10	17	8	11	19
20449	7	6	4	9	13	0	0	0	1	0	1	0	0	0	5	9	14	5	9	14
20450	5	10	11	4	15	0	0	0	0	0	0	0	0	0	11	4	15	12	4	16

M=MALE, F=FEMALE

ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 13 (PAGE 3): CAESAREAN-SECTIONING DATA - INDIVIDUAL RATS

DOSAGE GROUP III MID DOSE 10.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT	
DAM#	M	F	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	OVARY	OVARY	TOTAL
20451	12	4	10	6	16	0	0	0	0	0	0	0	0	0	10	6	16	11	9	20
20452	5	10	9	6	15	0	0	0	1	0	1	0	0	0	10	6	16	11	6	17
20453	3	11	6	8	14	0	0	0	1	1	2	0	0	0	7	9	16	7	9	16
20454	5	11	7	9	16	0	0	0	1	1	2	0	0	0	8	10	18	8	10	18
20455	7	6	6	7	13	0	0	0	0	0	0	0	0	0	6	7	13	7	7	14
20456	4	11	6	9	15	0	0	0	1	0	1	0	0	0	7	9	16	7	9	16
20457	5	10	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	8	17
20458	7	11	10	8	18	0	0	0	1	0	1	0	0	0	11	8	19	11	9	20
20459	11	2	7	6	13	0	0	0	0	2	2	0	0	0	7	8	15	8	10	18
20460	5	7	10	2	12	0	0	0	0	1	1	0	0	0	10	3	13	10	3	13
20461	7	10	8	9	17	0	0	0	0	0	0	0	0	0	8	9	17	8	10	18
20462	11	4	6	9	15	0	0	0	0	0	0	0	1	1	6	10	16	6	11	17
20463	5	11	9	7	16	0	0	0	0	0	0	0	0	0	9	7	16	9	10	19
20464	7	6	3	10	13	0	0	0	0	2	2	0	0	0	3	12	15	4	13	17
20465	5	7	7	5	12	0	0	0	1	0	1	0	0	0	8	5	13	8	7	15
20466	7	7	7	7	14	0	0	0	1	1	2	0	0	0	8	8	16	13	11	24
20467	5	10	6	9	15	0	0	0	0	0	0	0	0	0	6	9	15	10	12	22
20468	9	4	5	8	13	0	0	0	0	0	0	0	0	0	5	8	13	5	8	13
20469	NOT PREGNANT																			
20470	10	6	9	7	16	0	0	0	0	0	0	0	0	0	9	7	16	9	8	17
20471	6	8	5	9	14	0	0	0	0	0	0	0	0	0	5	9	14	5	9	14
20472	5	6	7	4	11	0	0	0	0	1	1	0	0	0	7	5	12	8	5	13
20473	9	7	9	7	16	0	0	0	0	0	0	0	0	0	9	7	16	11	7	18
20474	6	7	4	9	13	0	0	0	0	0	0	0	0	0	4	9	13	4	10	14
20475	1	2	3	0	3	0	0	0	1	0	1	0	0	0	4	0	4	4	0	4

M=MALE, F=FEMALE

ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 13 (PAGE 4): CAESAREAN-SECTIONING DATA - INDIVIDUAL RATS

DOSAGE GROUP IV HIGH DOSE 25.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT	
DAM#	M	F	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	HORN	HORN	TOTAL	OVARY	OVARY	TOTAL
20476	5	6	1	0	1	3	7	10	2	1	3	0	0	0	6	8	14	7	11	18
20477	5	9	8	6	14	0	0	0	1	0	1	0	1	1	9	7	16	10	8	18
20478	8	7	10	5	15	0	0	0	0	0	0	0	0	0	10	5	15	10	6	16
20479	1	0	1	0	1	0	0	0	7	6	13	0	0	0	8	6	14	8	8	16
20480	6	4	7	3	10	0	0	0	0	0	0	4	0	4	11	3	14	11	6	17
20481	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	2	2
20482	1	0	1	0	1	0	0	0	2	6	8	4	1	5	7	7	14	7	9	16
20483	4	8	3	9	12	0	0	0	1	2	3	0	0	0	4	11	15	10	11	21
20484	7	6	7	5	12	1	0	1	1	1	2	0	0	0	9	6	15	9	7	16
20485	7	6	7	6	13	0	0	0	0	1	1	1	0	1	8	7	15	9	8	17
20486	0	0	0	0	0	0	0	0	10	5	15	0	0	0	10	5	15	10	8	18
20487	8	9	10	7	17	0	0	0	0	0	0	0	0	0	10	7	17	12	9	21
20488	4	9	7	6	13	0	0	0	0	1	1	0	0	0	7	7	14	7	8	15
20489	5	9	8	5	13	1	0	1	2	2	4	0	1	1	11	8	19	12	11	23
20490	0	0	0	0	0	0	0	0	7	4	11	0	0	0	7	4	11	8	10	18
20491	5	7	5	7	12	0	0	0	1	1	2	0	2	2	6	10	16	8	11	19
20492	8	3	3	8	11	0	0	0	1	1	2	1	2	3	5	11	16	7	12	19
20493	5	10	6	9	15	0	0	0	0	0	0	0	0	0	6	9	15	8	12	20
20494	1	0	0	1	1	0	0	0	3	5	8	2	0	2	5	6	11	6	9	15
20495	7	2	5	4	9	0	0	0	2	0	2	3	0	3	10	4	14	11	5	16
20496a	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[10]	[7]	[17]	[0]	[0]	[0]	[10]	[7]	[17]	[20]	[11]	[21]
20497	4	5	6	2	8	1	0	1	1	1	2	2	3	5	10	6	16	12	7	19
20498	8	9	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	9	8	17
20499	8	7	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	8	17
20500	1	1	2	0	2	0	0	0	2	0	2	4	7	11	8	7	15	8	8	16

M=MALE, F=FEMALE

[ ] = Excluded from tabulation.

a. Data for dam #20,496 were excluded from all group averages and statistical evaluations. This dam had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).

ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 14 (PAGE 1): LITTER DATA - INDIVIDUAL INCIDENCE

DOSAGE GROUP I VEHICLE CONTROL 0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (g)			--- IMPLANTATIONS ----- DEAD OR RESORBED		
DAM#	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL	N	N	%
20401	4	10	14	3.44	3.14	3.23	15	1	6.7
20402	10	6	16	3.41	3.39	3.40	17	1	5.9
20403	4	9	13	3.27	2.90	3.01	15	2	13.3
20404	7	8	15	3.60	3.41	3.50	15	0	0.0
20405	8	5	13	3.39	3.28	3.35	13	0	0.0
20406	6	9	15	3.45	3.52	3.49	15	0	0.0
20407	6	5	11	3.61	3.27	3.46	13	2	15.4
20408	5	7	12	3.51	3.08	3.26	12	0	0.0
20409	6	8	14	3.79	3.48	3.61	15	1	6.7
20410	5	9	14	3.06	2.92	2.97	14	0	0.0
20411	4	11	15	3.16	3.16	3.16	15	0	0.0
20412	6	10	16	3.62	3.38	3.47	16	0	0.0
20413	6	5	11	3.19	2.79	3.01	15	4	26.7
20414	7	7	14	3.40	3.30	3.35	15	1	6.7
20415	11	6	17	3.62	3.24	3.49	17	0	0.0
20416	12	4	16	3.22	3.13	3.19	17	1	5.9
20417	8	7	15	3.62	3.59	3.60	15	0	0.0
20418	6	6	12	3.17	2.97	3.07	14	2	14.3
20419	8	8	16	3.66	3.24	3.45	17	1	5.9
20420	9	6	15	3.46	3.38	3.43	15	0	0.0
20421	13	4	17	3.73	3.34	3.64	17	0	0.0
20422	10	5	15	3.96	3.34	3.75	15	0	0.0
20423	5	9	14	3.67	3.30	3.43	14	0	0.0
20424	7	10	17	3.85	3.51	3.65	17	0	0.0
20425	5	12	17	3.85	3.58	3.66	17	0	0.0

ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 14 (PAGE 2): LITTER DATA - INDIVIDUAL INCIDENCE

DOSAGE GROUP II LOW DOSE 2.5 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (g)			--- IMPLANTATIONS ----- DEAD OR RESORBED		
DAM#	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL	N	N	%
20426	8	6	14	3.20	2.94	3.09	14	0	0.0
20427	7	6	13	3.29	3.12	3.21	15	2	13.3
20428	10	4	14	4.02	3.98	4.01	16	2	12.5
20429	11	4	15	3.56	3.47	3.53	16	1	6.2
20430	11	6	17	3.37	3.27	3.34	18	1	5.6
20431	NOT PREGNANT								
20432	9	6	15	3.54	3.57	3.55	16	1	6.2
20433	8	8	16	3.27	3.20	3.23	16	0	0.0
20434	3	7	10	3.06	2.83	2.90	14	4	28.6
20435	5	8	13	3.05	2.78	2.88	15	2	13.3
20436	6	8	14	3.44	3.18	3.29	16	2	12.5
20437	9	6	15	2.99	2.72	2.88	17	2	11.8
20438	7	9	16	3.26	3.08	3.16	17	1	5.9
20439	8	7	15	3.23	3.11	3.17	17	2	11.8
20440	10	8	18	3.64	3.34	3.50	18	0	0.0
20441	8	9	17	3.64	3.48	3.55	18	1	5.6
20442	8	9	17	3.03	3.03	3.03	18	1	5.6
20443	7	8	15	3.63	3.49	3.55	17	2	11.8
20444	7	6	13	3.57	3.65	3.61	13	0	0.0
20445	5	6	11	3.63	3.20	3.39	12	1	8.3
20446	7	11	18	3.62	3.44	3.51	18	0	0.0
20447	5	9	14	3.30	3.34	3.35	15	1	6.7
20448	7	7	14	3.63	3.54	3.59	17	3	17.6
20449	7	6	13	3.39	3.23	3.32	14	1	7.1
20450	5	10	15	3.61	3.47	3.51	15	0	0.0

ROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 14 (PAGE 3): LITTER DATA - INDIVIDUAL INCIDENCE

DOSAGE GROUP III MID DOSE 10.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (g)			--- IMPLANTATIONS ----- DEAD OR RESORBED		
DAM#	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL	N	N	%
20451	12	4	16	2.70	2.76	2.72	16	0	0.0
20452	5	10	15	3.01	3.01	3.01	16	1	6.2
20453	3	11	14	3.10	3.03	3.04	16	2	12.5
20454	5	11	16	2.94	2.74	2.80	18	2	11.1
20455	7	6	13	3.76	3.62	3.69	13	0	0.0
20456	4	11	15	3.58	3.32	3.39	16	1	6.2
20457	5	10	15	3.24	3.12	3.16	15	0	0.0
20458	7	11	18	3.25	3.06	3.13	19	1	5.3
20459	11	2	13	3.48	3.24	3.44	15	2	13.3
20460	5	7	12	3.75	3.51	3.60	13	1	7.7
20461	7	10	17	3.36	3.24	3.29	17	0	0.0
20462	11	4	15	2.91	3.04	2.94	16	1	6.2
20463	5	11	16	3.01	2.93	2.95	16	0	0.0
20464	7	6	13	3.18	3.06	3.13	15	2	13.3
20465	5	7	12	3.70	3.63	3.66	13	1	7.7
20466	7	7	14	3.58	3.40	3.49	16	2	12.5
20467	5	10	15	3.16	2.91	2.99	15	0	0.0
20468	9	4	13	3.49	3.60	3.52	13	0	0.0
20469	NOT PREGNANT								
20470	10	6	16	2.88	2.30	2.66	16	0	0.0
20471	6	8	14	3.67	3.42	3.53	14	0	0.0
20472	5	6	11	3.07	3.35	3.22	12	1	8.3
20473	9	7	16	3.81	3.64	3.74	16	0	0.0
20474	6	7	13	2.92	3.18	3.06	13	0	0.0
20475	1	2	3	4.01	3.91	3.94	4	1	25.0

PROTOCOL 305-001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (PAGE 4): LITTER DATA - INDIVIDUAL INCIDENCE

DOSAGE GROUP IV HIGH DOSE 25.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (g)			--- IMPLANTATIONS ----- DEAD OR RESORBED		
DAM#	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL	N	N	%
20476	1	0	1	1.69	-	1.69	14	13	92.8
20477	5	9	14	1.81	1.71a	1.75	16	2	12.5
20478	8	7	15	2.21	1.95	2.09	15	0	0.0
20479	1	0	1	1.77	-	1.77	14	13	92.8
20480	6	4	10	1.92	1.79	1.87	14	4	28.6
20481	1	0	1	3.14	-	3.14	1	0	0.0
20482	1	0	1	2.01	-	2.01	14	13	92.8
20483	4	8	12	2.28	2.23	2.24	15	3	20.0
20484	6	6	12	2.36	2.32	2.34	15	3	20.0
20485	7	6	13	2.89	2.81	2.85	15	2	13.3
20486	0	0	0	-	-	-	15	15	100.0
20487	8	9	17	2.36	2.55	2.46	17	0	0.0
20488	4	9	13	2.14	1.78	1.89	14	1	7.1
20489	5	8	13	1.90	1.78	1.82	19	6	31.6
20490	0	0	0	-	-	-	11	11	100.0
20491	5	7	12	1.77	1.75	1.76	16	4	25.0
20492	8	3	11	1.72	1.61	1.69	16	5	31.2
20493	5	10	15	2.27	2.27	2.27	15	0	0.0
20494	1	0	1	1.91	-	1.91	11	10	90.9
20495	7	2	9	2.00	2.14	2.04	14	5	35.7
20496b	[0]	[0]	[0]	[-]	[-]	[-]	[17]	[17]	[100.0]
20497	4	4	8	1.74	1.80	1.77	16	8	50.0
20498	8	9	17	2.92	2.98	2.95	17	0	0.0
20499	8	7	15	2.06	1.80	1.94	15	0	0.0
20500	1	1	2	2.19	1.65	1.92	15	13	86.7

a. Excludes one female fetus (F9) which was inadvertently not weighed.

[ ] = Excluded from tabulation.

b. Data for dam #20,946 were excluded from all group averages and statistical evaluations. This dam had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).

ROTOCOL 305001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 15 (Page 1): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP I VEHICLE CONTROL 0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

DAM #	CL'S	FETUS # 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
20401		MA	FA	FA	FA	FA	MA	FA	MA	E	MA / FA		FA	FA	FA	FA								
	10/ 6	3.47	3.18	3.20	3.30	3.13	3.44	2.72	3.37		3.48	3.03	2.91	3.17	3.45	3.32								
20402		MA	MA	FA	E	MA	MA	MA	FA	FA / MA		FA	MA	FA	FA	MA	MA	MA						
	10/10	2.83	3.27	3.28		3.78	3.41	3.35	3.51	3.44	3.26	3.37	3.47	3.20	3.56	3.54	3.58	3.63						
20403		FA	MA	FA	E	FA	MA	FA	MA	FA / MA		E	FA	FA	FA	FA								
	10/ 6	3.03	3.32	2.95		2.98	3.33	2.80	3.58	3.17	2.85		2.94	2.15	2.82	3.27								
20404		FA	FA	MA	MA	MA	FA	MA / FA		MA	MA	FA	FA	FA	MA	FA								
	8/ 9	3.30	3.45	3.58	3.74	3.89	3.47	3.58	3.34	3.43	3.18	3.26	3.33	3.43	3.83	3.71								
20405		MA	MA	FA	MA	MA	FA	FA	MA	MA	FA / MA		FA	MA										
	12/ 6	2.87	3.52	3.24	3.43	3.61	3.41	3.14	3.01	3.53	3.13	3.35	3.48	3.82										
20406		FA	FA	FA	MA	FA	FA	FA / MA		MA	FA	MA	MA	MA	FA	FA								
	9/11	3.35	3.63	3.46	3.71	4.03	3.32	3.91	2.52	3.72	3.58	3.41	3.81	3.52	3.22	3.22								
20407		FA	MA	MA	E	FA	FA / MA		FA	E	MA	MA	MA	FA										
	7/ 7	3.15	3.47	3.85		3.12	3.52	3.33	3.05		3.65	3.70	3.68	3.52										
20408		MA	FA	FA	FA	FA / FA		FA	FA	MA	MA	MA	MA											
	5/ 9	3.49	3.21	3.24	2.92	3.44	2.57	3.07	3.08	3.22	3.65	3.67	3.53											
20409		E	MA	FA	MA	MA	FA	FA	FA	FA / MA		FA	MA	FA	FA	MA								
	10/ 7		3.85	3.49	3.96	3.68	3.54	3.36	3.55	3.71	3.61	3.32	3.57	3.48	3.39	4.05								
20410		MA	FA	FA	FA / FA		MA	FA	MA	FA	FA	FA	MA	FA	MA									
	5/10	3.17	2.91	2.85	2.71	2.87	2.86	3.21	3.03	2.92	3.03	2.83	2.97	2.94	3.29									
20411		FA	FA	FA	FA	FA	FA	FA	FA / MA		MA	MA	MA	FA	FA	FA								
	8/ 9	3.14	3.12	3.33	2.97	3.06	3.15	3.27	3.14	2.97	3.23	3.25	3.20	3.02	3.19	3.37								
20412		FA	MA	FA	MA	MA	FA	FA	FA / FA		MA	FA	FA	FA	FA	MA	MA							
	11/11	2.87	3.57	3.58	3.66	3.61	3.57	3.14	3.27	3.50	3.45	3.21	3.66	3.45	3.55	3.65	3.77							
20413		MA	MA	MA	MA / MA		E	FA	FA	FA	E	FA	E	FA	E	MA								
	6/11	3.24	3.40	3.05	3.32	2.90		2.32	3.20	2.44		3.03		2.96		3.24								

M=Male, F=Female, A=Alive, D=Dead, E=Early Resorption, L=Late Resorption, '/' Denotes Position of Cervix.
CL'S=Corpora Lutea/Ovary. Fetal body weights in grams.
NOTE - This table excludes data for animals that aborted or delivered litters.

ROTOCOL 305001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 15 (Page 2): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP I VEHICLE CONTROL 0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DAM # CL'S																							
20414	MA	FA	MA	FA	MA	MA	FA / FA		MA	E	FA	MA	MA	FA	FA								
9/11	3.32	3.47	3.37	3.23	3.67	3.50	3.37	3.13	3.31		3.20	3.41	3.25	3.36	3.36								
20415	MA	MA	MA	MA	MA	MA	MA / FA		FA	FA	MA	FA	MA	FA	FA	MA	MA						
8/10	3.96	3.60	3.73	3.71	3.66	3.77	3.70	3.32	2.96	3.22	3.32	3.49	3.23	3.21	3.22	3.44	3.76						
20416	MA	FA	MA	FA	MA	MA	MA	MA	MA	E / MA		MA	FA	MA	FA	MA	MA						
12/ 8	2.91	3.16	3.13	3.13	3.21	3.26	3.03	3.21	3.16		3.15	3.07	3.11	3.58	3.12	3.37	3.51						
20417	FA	MA	MA	FA / FA		MA	FA	FA	MA	MA	FA	FA	MA	MA	MA								
5/13	3.76	3.89	3.89	3.65	3.60	3.60	3.52	3.65	3.62	3.55	3.59	3.35	3.61	3.21	3.56								
20418	MA	FA	MA	MA	FA	FA	FA	MA / MA		MA	FA	FA	E	E									
8/10	3.12	2.91	2.96	2.91	2.72	3.36	2.24	3.44	3.41	3.18	2.95	3.63											
20419	FA	MA	MA	FA	MA	FA / FA		MA	MA	FA	FA	FA	MA	FA	MA	E	MA						
8/11	3.34	3.21	3.77	3.13	3.88	3.52	3.08	3.34	3.85	3.33	3.05	3.21	3.47	3.29	3.88		3.86						
20420	MA	MA	FA	FA	MA	FA	MA	FA / FA		MA	MA	MA	MA	MA	FA								
8/ 7	3.56	3.59	3.19	3.86	3.29	3.30	3.63	3.27	3.21	3.59	3.35	3.49	3.27	3.41	3.45								
20421	MA	FA	MA	MA	MA	MA	MA / FA		FA	MA	MA	MA	MA	MA	FA	MA	MA						
7/10	3.41	3.54	3.67	3.66	3.64	3.96	3.75	3.19	3.30	3.86	3.91	3.95	3.53	3.69	3.32	3.64	3.78						
20422	MA	MA	MA	MA	MA	FA	FA	FA / MA		MA	MA	FA	MA	MA	FA								
9/ 8	4.02	4.16	4.18	3.99	3.78	3.28	3.64	3.28	3.80	4.02	3.70	2.42	4.05	3.88	4.06								
20423	FA	FA	MA	MA	MA	MA	MA / FA		FA	FA	FA	FA	FA	FA									
8/ 8	3.43	3.22	3.74	3.57	3.61	3.76	3.66	3.49	3.32	3.31	3.33	3.46	3.25	2.92									
20424	FA	FA	FA	FA	MA	MA	MA	FA / FA		MA	FA	MA	FA	FA	MA	FA	MA						
8/ 9	3.61	3.59	3.46	3.68	3.88	3.78	3.78	3.88	3.58	3.65	3.63	3.99	2.78	3.43	3.88	3.45	4.02						
20425	FA	FA	FA	FA	FA	FA	FA	MA	MA / MA		FA	MA	FA	FA	MA	FA	FA						
9/ 8	3.47	3.74	3.08	3.83	4.07	3.78	3.29	4.07	3.49	4.24	3.81	4.23	3.46	3.39	3.21	3.43	3.66						

M=Male, F=Female, A=Alive, D=Dead, E=Early Resorption, L=Late Resorption, '/' Denotes Position of Cervix.
CL'S=Corpora Lutea/Ovary. Fetal body weights in grams.
NOTE - This table excludes data for animals that aborted or delivered litters.

ROTOCOL 305001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 15 (Page 3): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP II LOW DOSE 2.5 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DAM # CL'S																							
20426	MA	MA	MA	MA	MA	EA / MA		EA	EA	MA	EA	EA	EA	MA									
10/10	3.05	3.25	3.32	3.21	3.27	2.88	2.98	2.95	2.98	3.37	3.05	2.96	2.85	3.15									
20427	MA	MA	EA	EA	EA	MA / MA		E	MA	EA	E	MA	MA	EA	EA								
6/ 9	3.13	3.40	3.01	2.93	3.11	3.45	3.10		3.16	3.03		3.28	3.49	3.49	3.15								
20428	MA	MA	MA	MA	MA	EA / MA		EA	E	MA	MA	EA	MA	MA	E	EA							
6/11	3.92	4.13	3.82	4.09	4.10	3.91	3.91	4.02		3.98	4.24	3.96	4.00	4.03		4.03							
20429	MA	EA	MA	EA	E	MA	MA / MA		MA	EA	MA	MA	MA	EA	MA	MA							
7/ 9	3.78	3.44	3.24	3.42		3.66	3.33	3.45	3.73	3.55	3.90	3.76	3.30	3.46	3.52	3.47							
20430	MA	EA	MA	MA	EA	EA / EA		MA	EA	MA	MA	MA	MA	EA	MA	MA	MA	E					
9/12	3.32	3.58	3.44	3.12	3.07	3.22	3.16	3.42	3.20	3.46	3.74	3.57	3.20	3.37	3.11	3.36	3.38						
20431	NOT PREGNANT																						
20432	MA	EA	MA	MA	MA	MA	EA	MA	EA	EA	MA / MA		MA	EA	E	EA							
11/ 5	3.19	3.57	3.61	3.46	3.58	3.75	3.63	3.73	3.45	3.63	3.64	3.47	3.41	3.64		3.50							
20433	MA	EA	EA	MA	MA	EA	MA	MA / MA		EA	MA	EA	MA	EA	EA	EA							
8/ 8	3.50	3.23	3.18	3.32	3.46	3.08	3.82	2.40	3.02	3.39	3.35	3.16	3.26	3.03	3.23	3.21							
20434	EA	EA	E	EA /	E	MA	E	MA	EA	EA	EA	EA	MA	E									
4/10	2.64	2.86		3.25		3.00		3.14	2.88	2.81	2.46	2.91	3.04										
20435	MA	EA	MA	EA	EA	EA	E	MA /	E	EA	EA	EA	EA	MA	MA								
8/ 7	2.58	2.59	3.12	2.60	2.74	3.26		3.23		2.81	2.52	2.69	3.01	3.13	3.17								
20436	EA	EA	MA	E	MA / MA		EA	EA	MA	EA	EA	MA	EA	E	EA	MA							
9/11	3.14	3.16	3.41		3.34	3.11	3.24	3.14	3.43	3.15	3.06	3.37	3.32		3.25	3.97							
20437	MA	MA	EA	MA / EA		E	EA	MA	MA	MA	MA	EA	E	MA	MA	EA	EA						
5/15	2.90	3.25	3.01	3.10	2.70		2.81	2.69	3.15	3.01	2.91	2.68		3.12	2.79	3.03	2.10						
20438	MA	EA	MA	EA	MA	MA	EA	EA	MA	E / EA		EA	MA	EA	MA	EA	EA						
10/ 7	3.21	3.03	3.34	3.13	3.24	3.55	3.18	3.00	3.12		2.80	3.25	3.04	3.04	3.29	2.97	3.29						

M=Male, F=Female, A=Alive, D=Dead, E=Early Resorption, L=Late Resorption, '/' Denotes Position of Cervix.
CL'S=Corpora Lutea/Ovary. Fetal body weights in grams.
NOTE - This table excludes data for animals that aborted or delivered litters.

ROTOCOL 305001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

ABLE 15 (Page 4): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP II LOW DOSE 2.5 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DAM # CL'S																							
20439	MA	EA	MA	MA	EA	EA / MA		MA	E	MA	MA	MA	EA	EA	EA	EA	E						
8/12	2.99	2.76	3.17	3.26	3.17	2.76	3.27	3.44		3.18	3.23	3.29	3.02	3.54	3.22	3.30							
20440	EA	EA	EA	EA	MA	MA	MA	EA	EA	MA / MA		MA	MA	MA	MA	EA	MA	EA					
11/ 8	3.18	3.51	3.48	3.28	3.93	3.67	3.68	3.38	2.75	3.86	3.25	3.70	3.80	3.43	3.54	3.60	3.52	3.51					
20441	MA	EA	EA	EA	MA	MA	MA	EA	EA / EA		MA	EA	E	MA	MA	MA	EA	EA					
9/ 9	4.00	3.76	3.45	3.16	3.27	3.84	3.19	3.37	3.67	3.20	3.54	3.65		3.58	3.82	3.85	3.56	3.51					
20442	MA	EA	EA	MA	EA	MA	MA	MA	EA / EA		MA	EA	EA	MA	EA	MA	E	EA					
9/ 9	1.64	3.01	2.75	3.47	3.28	3.30	3.35	3.46	3.06	2.82	3.33	3.02	3.08	2.21	3.08	3.46		3.15					
20443	EA	EA	EA	MA	EA	MA	MA	MA	EA	MA	E / MA		MA	EA	E	EA	EA						
11/ 7	3.52	3.51	3.27	3.33	3.29	3.74	4.01	3.49	3.79	3.87		3.41	3.55	3.65		3.46	3.43						
20444	MA	MA	EA	MA	MA	MA	MA	MA / EA		EA	EA	EA	EA										
10/ 6	3.68	3.77	3.45	4.06	3.76	3.68	2.82	3.25	3.64	3.73	3.54	3.76	3.78										
20445	EA	EA	MA	EA	EA	MA	EA / MA		MA	E	EA	MA											
8/ 6	2.91	3.33	3.65	2.86	3.19	3.53	3.38	3.75	3.62		3.50	3.62											
20446	MA	EA	EA	EA	MA	EA	EA	EA	MA / EA		EA	MA	MA	EA	EA	EA	MA	MA					
9/ 9	3.36	3.51	3.49	3.45	3.76	3.60	3.73	2.94	3.91	3.52	3.34	3.60	3.57	3.49	3.27	3.49	3.30	3.84					
20447	EA	EA	MA	EA	MA	EA / MA		EA	MA	EA	EA	MA	E	EA	EA								
8/ 9	3.15	3.15	3.67	3.28	3.66	3.38	2.83	3.24	3.55	3.33	3.52	3.22		3.32	3.65								
20448	MA	MA	EA	EA	EA	MA	MA / MA		E	MA	MA	EA	EA	EA	E	EA	E						
8/11	3.16	3.71	3.56	3.15	3.57	3.61	3.85	3.61		3.54	3.96	3.60	3.33	3.50		4.06							
20449	MA	E	MA	EA	EA / EA		MA	MA	EA	MA	EA	MA	EA	MA									
5/ 9	3.46		3.75	3.08	2.85	3.59	3.60	3.29	3.08	3.05	3.43	3.24	3.37	3.36									
20450	MA	EA	EA	MA	MA	EA	EA	EA	EA	EA	EA / MA		EA	EA	MA								
12/ 4	3.57	3.35	3.46	3.85	3.18	3.20	3.34	3.42	3.20	3.53	3.60	3.52	3.61	3.96	3.92								

M=Male, F=Female, A=Alive, D=Dead, E=Early Resorption, L=Late Resorption, '/' Denotes Position of Cervix,
CL'S=Corpora Lutea/Ovary. Fetal body weights in grams.
NOTE - This table excludes data for animals that aborted or delivered litters.

PROTOCOL 305001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (Page 5): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP III MID DOSE 10.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

DAM #	CL'S	FETUS # 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
20451		MA	FA	MA	MA	MA	MA	MA	MA	MA	FA / MA		FA	MA	MA	FA	MA							
	11/ 9	2.66	2.59	2.17	2.88	2.69	2.59	2.84	2.92	2.86	2.64	2.99	2.96	2.71	2.43	2.87	2.73							
20452		FA	E	FA	MA	MA	MA	FA	FA	FA	FA / FA		FA	MA	FA	MA	FA							
	11/ 6	2.60		2.76	2.42	3.24	3.17	2.86	3.20	2.60	3.34	3.31	3.03	2.89	3.02	3.33	3.38							
20453		FA	FA	MA	E	FA	FA	FA /	E	FA	MA	FA	FA	FA	MA	FA	FA							
	7/ 9	3.35	3.16	3.23		3.47	3.19	2.54		3.33	3.26	3.37	3.15	1.82	2.80	2.95	2.98							
20454		FA	FA	MA	FA	E	MA	FA	MA /	E	FA	FA	FA	MA	FA	MA	FA	FA	FA					
	8/10	2.67	2.73	2.82	3.05		3.21	2.72	2.81		2.07	2.65	2.70	2.81	2.66	3.05	3.07	2.74	3.04					
20455		MA	MA	FA	MA	FA	MA /	FA	MA	MA	FA	MA	FA	FA										
	7/ 7	3.72	3.57	3.64	3.87	3.68	3.85	3.69	3.96	3.51	3.56	3.85	3.46	3.67										
20456		E	FA	FA	FA	MA	MA	FA /	FA	FA	FA	FA	FA	FA	MA	FA	MA							
	7/ 9		3.35	3.36	3.33	3.78	3.38	3.37	3.30	3.33	3.06	3.32	3.68	3.02	3.65	3.37	3.51							
20457		FA	MA	FA	FA	FA	FA	FA	MA	MA /		FA	FA	MA	FA	FA								
	9/ 8	2.88	3.50	3.42	2.96	3.09	3.11	3.35	3.11	3.51	2.[illegible]	2.86	3.43	3.29	3.15	3.00								
20458		MA	MA	FA	FA	FA	FA	MA	FA	FA	E	MA / MA		FA	FA	FA	FA	MA	FA	MA				
	11/ 9	3.20	3.17	3.02	3.06	3.19	2.83	3.47	3.16	2.83		3.31	2.97	3.00	2.98	3.10	3.24	3.30	3.20	3.32				
20459		MA	MA	MA	MA	FA	FA	MA /	MA	MA	MA	E	MA	MA	MA	E								
	8/10	3.63	3.37	3.60	3.52	3.31	3.17	3.46	3.10	3.48	3.46		3.54	3.50	3.61									
20460		FA	FA	MA	FA	FA	FA	MA	MA	MA	FA / MA		FA	E										
	10/ 3	3.27	3.57	3.89	3.61	3.69	3.66	3.79	3.67		3.48	3.65	3.31											
20461		MA	MA	MA	MA	FA	FA	MA	MA /	FA	FA	FA	FA	FA	FA	MA	FA	FA						
	8/10	3.02	3.42	3.41	3.18	3.23	3.07	3.54	3.33	3.23	3.14	3.11	3.42	3.07	3.46	3.66	3.27	3.42						
20462		MA	MA	MA	MA	MA	MA /	MA	L	FA	MA	MA	FA	MA	FA	FA	MA							
	6/11	2.60	2.99	3.71	2.92	3.05	1.98	2.47		2.99	3.13	3.16	2.99	3.17	2.98	3.22	2.80							
20463		FA	MA	FA	FA	MA	FA	FA	MA	FA / FA		MA	FA	FA	MA	FA	FA							
	9/10	2.87	2.94	2.95	2.83	2.90	2.86	2.93	3.22	2.98	2.84	2.98	3.13	3.12	2.99	2.94	2.78							

M=Male, F=Female, A=Alive, D=Dead, E=Early Resorption, L=Late Resorption, '/' Denotes Position of Cervix,
CL'S=Corpora Lutea/Ovary. Fetal body weights in grams.
NOTE - This table excludes data for animals that aborted or delivered litters.

PROTOCOL 305001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (Page 6): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP III MID DOSE 10.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

DAM #	CL'S	FETUS # 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
20464		MA	EA	MA / MA		MA	EA	E	MA	E	EA	EA	EA	EA	MA	MA								
	4/13	3.25	3.18	3.53	2.92	2.90	2.94		3.07		2.96	3.00	3.19	3.10	3.48	3.12								
20465		EA	EA	E	EA	MA	EA	EA	EA / EA		MA	MA	MA	MA										
	8/ 7	3.58	3.84		3.90	3.27	3.68	3.33	3.53	3.53	3.59	3.85	3.75	4.02										
20466		EA	MA	MA	EA	MA	E	MA	EA / EA		EA	MA	MA	E	EA	EA	MA							
	13/11	3.14	3.44	3.49	3.38	3.44		3.51	3.19	3.67	3.46	3.54	3.66		3.50	3.43	4.01							
20467		EA	EA	EA	EA	MA	EA / EA		MA	EA	MA	EA	EA	MA	EA	MA								
	10/12	3.07	3.11	2.93	2.07	2.90	3.23	3.17	3.02	2.86	2.98	2.88	2.67	3.21	3.11	3.71								
20468		MA	EA	MA	EA	MA / MA		MA	MA	MA	EA	MA	MA	EA										
	5/ 8	3.54	3.57	3.56	3.40	3.48	3.48	3.43	3.40	3.55	3.68	3.59	3.36	3.73										
20469		NOT PREGNANT																						
20470		MA	MA	MA	MA	MA	MA	MA	MA	EA / MA		MA	EA	EA	EA	EA	EA							
	9/ 8	3.10	2.54	3.38	2.85	3.60	3.31	3.20	2.36	3.05	2.62	1.88	2.20	1.85	1.76	1.84	3.11							
20471		MA	MA	EA	MA	MA / EA		MA	EA	MA	EA	EA	EA	EA	EA									
	5/ 9	3.55	3.49	3.52	3.47	4.08	3.09	3.57	3.31	3.86	3.38	3.25	3.58	3.57	3.65									
20472		MA	MA	MA	EA	EA	EA	EA / E		EA	MA	MA	EA											
	8/ 5	2.34	3.62	2.99	3.68	3.03	3.36	3.64		3.33	3.48	2.94	3.05											
20473		MA	EA	MA	EA	MA	EA	EA	MA	EA / EA		MA	EA	MA	MA	MA	MA							
	11/ 7	3.69	3.41	3.79	3.79	4.13	3.74	3.83	3.77	3.45	3.60	3.61	3.65	3.87	3.95	3.79	3.72							
20474		EA	EA	EA	EA / MA		EA	EA	EA	MA	MA	MA	MA	MA										
	4/10	3.03	3.05	3.55	3.52	3.35	3.36	3.27	2.47	2.64	3.47	2.56	2.20	3.30										
20475		E	EA	EA	MA /																			
	4/ 0		3.91	3.91	4.01																			

M=Male, F=Female, A=Alive, D=Dead, E=Early Resorption, L=Late Resorption, '/' Denotes Position of Cervix.
CL'S=Corpora Lutea/Ovary. Fetal body weights in grams.
NOTE - This table excludes data for animals that aborted or delivered litters.

PROTOCOL 305001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (Page 7): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP IV HIGH DOSE 25.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

DAM #	CL'S	FETUS # 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
20476	7/11	MA 1.69	E	E	ED	FD	FD / MD		E	MD	MD	ED	ED	FD	MD									
20477	10/ 8	MA 1.51	MA 1.65	E	FA 1.76	FA 1.55	FA 2.05	MA 1.95	FA 1.73	FA / a	L	FA 1.44	FA 1.50	FA 1.60	FA 2.07	MA 2.31	MA 1.63							
20478	10/ 6	MA 2.68	MA 1.83	MA 2.84	MA 2.01	FA 1.83	MA 2.24	FA 2.00	MA 1.88	FA 2.01	FA / 1.57	FA 1.75	MA 1.87	FA 2.33	MA 2.31	FA 2.17								
20479	8/ 8	E	E	E	E	E	MA 1.77	E	E /	E	E	E	E	E	E									
20480	11/ 6	MA 1.81	L	FA 1.65	L	L	MA 2.31	MA 2.03	L	FA 2.53	FA 1.45	FA / 1.53	MA 1.60	MA 1.92	MA 1.84									
20481	0/ 2	/ MA 3.14																						
20482	7/ 9	E	L	E	L	MA 2.01	L	L /	E	E	E	L	E	E	E									
20483	10/11	FA 2.41	FA 1.22	E	MA / 2.04	E	MA 2.18	MA 2.15	FA 2.43	FA 2.33	MA 2.73	FA 2.57	FA 2.55	FA 1.96	FA 2.37	E								
20484	9/ 7	MD	MA 3.05	E	MA 2.07	FA 2.25	FA 2.50	FA 2.31	MA 2.56	FA / 2.08	MA 2.23	FA 2.63	E	FA 2.14	MA 2.24	MA 2.02								
20485	9/ 8	L	MA 2.66	MA 2.93	FA 3.16	MA 3.25	FA 2.66	FA 2.67	FA / 2.49	MA 2.80	MA 2.98	MA 2.92	MA 2.67	FA 2.90	FA 2.98	E								
20486	10/ 8	E	E	E	E	E	E	E	E	E	E /	E	E	E	E	E								
20487	12/ 9	FA 3.03	FA 2.15	MA 2.19	MA 2.36	FA 2.79	MA 2.11	MA 2.42	FA 2.63	FA 2.20	FA / 2.43	MA 2.48	MA 2.71	FA 2.15	MA 2.49	FA 2.83	FA 2.73	MA 2.08						
20488	7/ 8	FA 1.74	FA 1.60	FA 1.96	MA 2.57	MA 1.80	FA 2.08	FA / 1.43	FA 2.05	FA 1.54	MA 2.13	FA 1.79	MA 2.07	E	FA 1.84									

M=Male, F=Female, A=Alive, D=Dead, E=Early Resorption, L=Late Resorption, '/' Denotes Position of Cervix.
CL'S=Corpora Lutea/Ovary. Fetal body weights in grams.
NOTE - This table excludes data for animals that aborted or delivered litters.
a. The weight for fetus #20,477-F9 was inadvertently not recorded.

PROTOCOL 305001 : EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (Page 8): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP IV HIGH DOSE 25.0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DAM # CL'S																							
20489	E	FA	FA	FA	E	MA	MA	MA	MA	FA	FD /	FA	E	FA	FA	MA	FA	E	L				
12/11		1.85	1.60	1.75		1.77	1.86	2.13	1.67	1.74		1.73		1.75	1.84	2.06	1.94						
20490	E	E	E	E	E	E	E /	E	E	E	E												
8/10																							
20491	E	MA	FA	MA	FA	FA /	MA	FA	L	L	MA	E	FA	FA	MA	FA							
8/11		1.80	1.61	1.81	1.89	1.81	1.86	1.71			1.83		1.77	1.62	1.56	1.85							
20492	L	MA	MA	FA	E /	MA	MA	FA	L	FA	MA	L	MA	MA	MA	E							
7/12		1.83	1.90	1.73		1.62	1.65	1.61		1.49	1.70		1.71	1.58	1.74								
20493	FA	MA	MA	FA	FA	MA /	MA	FA	FA	MA	FA	FA	FA	FA	FA								
8/12	2.23	2.13	2.22	1.97	2.49	2.28	2.35	2.68	2.23	2.38	2.27	1.92	2.46	2.17	2.26								
20494	L	E	L	E	E /	MA	E	E	E	E	E												
6/ 9						1.91																	
20495	L	MA	MA	E	L	E	MA	MA	MA	L /	MA	MA	FA	FA									
11/ 5		2.01	1.91				2.04	1.93	1.90		2.28	1.97	2.14	2.15									
20496a	[E	E	E	E	E	E	E	E	E	E /	E	E	E	E	E	E	E]						
[10/11]																							
20497	MA	FA	E	L	MA	FA	MA	L	FD	FA /	L	L	L	MA	E	FA							
12/ 7	1.70	1.54			1.65	1.85	1.72			1.73				1.88		2.08							
20498	FA	FA	MA	FA	FA	MA	FA	FA	MA /	MA	MA	FA	MA	FA	MA	MA	FA						
9/ 8	2.90	2.64	2.72	3.41	3.21	3.23	3.11	3.38	1.96	3.19	3.16	3.01	3.32	2.86	3.01	2.77	2.27						
20499	FA	MA	FA	FA	MA	MA	MA	MA	FA /	FA	MA	FA	FA	MA	MA								
9/ 8	1.66	2.18	1.72	1.99	2.03	2.07	2.38	2.02	1.86	1.46	1.90	1.91	1.99	1.84	2.07								
20500	L	MA	E	E	L	L	L	FA /	L	L	L	L	L	L	L								
8/ 8		2.19						1.65															

M=Male, F=Female, A=Alive, D=Dead, E=Early Resorption, L=Late Resorption, '/' Denotes Position of Cervix,
CL'S=Corpora Lutea/Ovary. Fetal body weights in grams. [ ] = Excluded from tabulation.
NOTE - This table excludes data for animals that aborted or delivered litters.

1. Data for dam #20,946 were excluded from all group averages and statistical evaluations. This dam had adverse clinical signs observed on day 6 of gestation, prior to administration of its first dosage (see Table 11 for adverse clinical signs observed for this rat during the course of the study).

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 16 (PAGE 1): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: I 0(Vehicle) mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,401	0	14	0	-	7	0	-	7	0	-
20,402	1(6.2)	16	0	-	8	0	-	8	1	FETUS 1 Sternebrae: 1st, not ossified
20,403	4(30.8)	13	2	FETUS 6 Body: Edematous[a] FETUS 13 Body: Umbilical hernia	6	0	-	7	3	FETUS 1 Sternebrae: 1st, not ossified FETUS 10 Sternebrae: 1st, not ossified FETUS 13 Vertebrae: Thoracic, centra, 1st, 4th and 10th, not ossified; 5th, 8th, 9th and 13th, right, unilateral ossification; 6th and 7th, left, unilateral ossification; 11th and 12th, bifid; Thoracic, arches, left, 3rd and 4th, fused Ribs: Left, 2nd and 3rd, fused, distally

a. Assigned to skeletal examination; no other variation was observed.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 16 (PAGE 2): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: I 0(Vehicle) mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,403 (Cont.)										4th and 5th, fused at base; 9-11, fused, medially; 10th and 11th, fused medially to distally Sternebrae: 1st, not ossified
20,404	1(6.7)	15	0	-	7	0	-	8	1	FETUS 7 Vertebrae: Thoracic, centrum, 10th, bifid
20,405	0	13	0	-	6	0	-	7	0	-
20,406	0	15	0	-	7	0	-	8	0	-
20,407	0	11	0	-	5	0	-	6	0	-
20,408	0	12	0	-	6	0	-	6	0	-
20,409	1(7.1)	14	0	-	7	1	FETUS 7 Kidney: Right, pelvis, marked dilation	7	0	-
20,410	1(7.1)	14	0	-	7	0	-	7	1	FETUS 11 Vertebrae: Thoracic, centrum, 4th, bifid Sternebrae: 1st, incompletely ossified

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TABLE 16 (PAGE 3): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: I 0(Vehicle) mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,411	0	15	0	-	7	0	-	8	0	-
20,412	1(6.2)	16	0	-	8	0	-	8	1	FETUS 15 Sternebrae: 1st, incompletely ossified
20,413	1(9.1)	11	1	FETUS 7 Jaw: Micrognathia	5	1	FETUS 7 Jaw: Micrognathia (confirmed) Palate: Shortened Tongue: Agenesis	6	0	-
20,414	1(7.1)	14	1	FETUS 4 Body: Umbilical hernia	7	1	FETUS 4 Intestines: Protrude from abdominal cavity	7	0	-
20,415	0	17	0	-	8	0	-	9	0	-
20,416	1(6.2)	16	0	-	8	0	-	8	1	FETUS 7 Vertebrae: Thoracic, centrum, 10th, bifid
20,417	0	15	0	-	7	0	-	8	0	-
20,418	1(8.3)	12	0	-	6	0	-	6	1	FETUS 7 Sternebrae: 1st, incompletely ossified
20,419	0	16	0	-	8	0	-	8	0	-

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 16 (PAGE 4): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: I 0(Vehicle) mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,420	1(6.7)	15	0	-	7	0	-	8	1	FETUS 1 Ribs: Right, 8-12, wavy
20,421	0	17	0	-	8	0	-	9	0	-
20,422	1(6.7)	15	0	-	7	1	FETUS 14 Kidney: Right, pelvis, slight dilation	8	0	-
20,423	0	14	0	-	7	0	-	7	0	-
20,424	1(5.9)	17	0	-	8	0	-	9	1	FETUS 13 Pelvis: Pubes, not ossified
20,425	0	17	0	-	8	0	-	9	0	-

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 16 (PAGE 5): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: II 2.5 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,426	0	14	0	-	7	0	-	7	0	-
20,427	1(7.7)	13	0	-	6	1	FETUS 6 Kidney: Right, pelvis, moderate dilation	7	0	-
20,428	0	14	0	-	7	0	-	7	0	-
20,429	0	15	0	-	7	0	-	8	0	-
20,430	1(5.9)	17	0	-	8	0	-	9	1	FETUS 7 Sternebrae: 1st, not ossified
20,431	NOT PREGNANT	-	-	-	-	-	-	-	-	-
20,432	1(6.7)	15	0	-	7	0	-	8	1	FETUS 11 Sternebrae: 1st, incompletely ossified
20,433	0	16	0	-	8	0	-	8	0	-
20,434	0	10	0	-	5	0	-	5	0	-
20,435	0	13	0	-	6	0	-	7	0	-
20,436	0	14	0	-	7	0	-	7	0	-
20,437	2(13.3)	15	0	-	7	0	-	8	2	FETUS 15 Vertebrae: Thoracic, centrum, 5th, bifid

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TABLE 16 (PAGE 6): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: II 2.5 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,437 (Cont.)										FETUS 17 Sternebrae: 1st, not ossified
20,438	0	16	0	-	8	0	-	8	0	-
20,439	0	15	0	-	7	0	-	8	0	-
20,440	0	18	0	-	9	0	-	9	0	-
20,441	1(5.9)	17	0	-	8	0	-	9	1	FETUS 14 Sternebrae: 1st, incompletely ossified
20,442	0	17	0	-	3	0	-	9	0	-
20,443	0	15	0	-	7	0	-	8	0	-
20,444	0	13	0	-	6	0	-	7	0	-
20,445	0	11	0	-	5	0	-	6	0	-
20,446	0	18	0	-	9	0	-	9	0	-
20,447	0	14	0	-	7	0	-	7	0	-
20,448	0	14	0	-	7	0	-	7	0	-
20,449	0	13	0	-	6	0	-	7	0	-
20,450	0	15	0	-	7	0	-	8	0	-

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TABLE 16 (PAGE 7): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: III 10.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,451	0	16	0	-	8	0	-	8	0	-
20,452	3(20.0)	15	1	FETUS 14 Tail: "Thread-like"	7	0	-	8	2	FETUS 4 Vertebrae: Thoracic, centrum, 13th, bifid FETUS 14 Vertebrae: Caudal, only one present FETUS 16 Pelvis: Ischia, incompletely ossified; Pubes, not ossified
20,453	1(7.1)	14	0	-	7	0	-	7	1	FETUS 13 Skull: Supraoccipital, not ossified; Sphenoid, contains a hole Vertebrae: Thoracic, centrum, 11th, bifid Sternebrae: 1st, not ossified Pelvis: Pubes, not ossified
20,454	0	16	0	-	8	0	-	8	0	-
20,455	1(7.7)	13	0	-	6	0	-	7	1	FETUS 1 Vertebrae: Thoracic, centrum, 12th, bifid

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TABLE 16 (PAGE 8): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: III 10.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,456	0	15	0	-	7	0	-	8	0	-
20,457	0	15	0	-	7	0	-	8	0	-
20,458	1(5.6)	18	0	-	9	0	-	9	1	FETUS 1 Sternebrae: 1st, not ossified; 2nd, incompletely ossified
20,459	0	13	0	-	6	0	-	7	0	-
20,460	0	12	0	-	6	0	-	6	0	-
20,461	0	17	0	-	8	0	-	9	0	-
20,462	2(13.3)	15	0	-	7	1	FETUS 6 Brain: Lateral ventricles, slight dilation	8	1	FETUS 16 Sternebrae: 1st, not ossified Pelvis: Ischium, left, incompletely ossified; Pubes, not ossified
20,463	1(6.2)	16	0	-	8	0	-	8	1	FETUS 5 Vertebrae: Thoracic, centrum, 12th, bifid
20,464	1(7.7)	13	0	-	6	0	-	7	1	FETUS 3 Sternebrae: 1st, incompletely ossified

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TABLE 16 (PAGE 9): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: III 10.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,465	0	12	0	-	6	0	-	6	0	-
20,466	0	14	0	-	7	0	-	7	0	-
	0	15	0	-	7	0	-	8	0	-
20,468	0	13	0	-	6	0	-	7	0	-
20,469	NOT PREGNANT	-	-	-	-	-	-	-	-	-
20,470	0	16	0	-	8	0	-	8	0	-
20,471	1(7.1)	14	0	-	7	0	-	7	1	FETUS 11 Sternebrae: 1st, incompletely ossified
20,472	1(9.1)	11	0	-	5	0	-	6	1	FETUS 1 Sternebrae: 1st, incompletely ossified
20,473	0	16	0	-	8	0	-	8	0	-
20,474	1(7.7)	13	0	-	6	0	-	7	1	FETUS 7 Vertebrae: Thoracic, centrum, 12th, bifid
20,475	0	3	0	-	1	0	-	2	0	-

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TABLE 16 (PAGE 10): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,476	0	1[a]	0	-	0[a]	0	-	1[a]	0	-
20,477	8(57.1)	14[b]	2	FETUS 1 Body: Slightly edematous FETUS 9 Body: Moderately edematous	7	3	FETUS 2 Brain: Lateral ventricles, slight dilation Heart: Appears enlarged FETUS 5 Brain: Lateral ventricles, slight dilation Heart: Appears enlarged FETUS 9 Brain: Lateral ventricles, slight dilation Heart: Appears enlarged	7[b]	5	FETUS 1 Skull: Fontanelle, enlarged; Interparietals and supraoccipital, not ossified; Sphenoid, not ossified Vertebrae: Thoracic, centra, 1-3 and 10-13, not ossified; Lumbar, 6th, arches and centrum, not ossified; 1-5, centra, not ossified Pelvis: Ischia and pubes, not ossified FETUS 4 Skull: Fontanelle, enlarged; Interparietals and supraoccipital, not ossified; Sphenoid, not ossified Vertebrae: Thoracic, centra, 1st, not ossified; 5-9 and

a. Excludes 10 dead fetuses; see Table 17 for observations for these specimens.
b. Excludes one late resorption; see Table 17 for observations for this specimen.

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TABLE 16 (PAGE 11): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,477 (Cont.)										11+12, incompletely ossified; 10+13, bifid; Lumbar, arches, right, 3rd and bilateral 4-6, incompletely ossified; Centra, 1-6, incompletely ossified Ribs: Right, 4-13, left, 5-13, wavy; Right, 4-13, left, 1 and 5-13, incompletely ossified (hypoplastic) Pelvis: Ischia and pubes, not ossified Rear Limb(s): Fibula, bilateral, incompletely ossified; Femur, left, shortened FETUS 8 Skull: Supraoccipital, not ossified; Sphenoid, contains a hole Vertebrae: Thoracic, centra, 9-13, not ossified; Lumbar, centra, 1-6, not ossified

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TABLE 16 (PAGE 12): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,477 (Cont.)										Pelvis: Ischia and pubes, not ossified FETUS 12 Pelvis: Ischia and pubes, not ossified FETUS 16 Skull: Fontanelle, enlarged; Supraoccipital, not ossified Vertebrae: Thoracic, centra, 1 and 4-13, not ossified; Lumbar, centra, 1-6, not ossified; Left, arch, 6th, incompletely ossified Ribs: Right, 5-13, left, 4-13, wavy; Right, 8-13, left, 8 and 10-13, incompletely ossified (hypoplastic) Pelvis: Ischia and pubes, not ossified Rear Limb(s): Femur and fibula, bilateral, bent, incompletely ossified and shortened

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TABLE 16 (PAGE 13): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,478	0	15	0	-	7	0	-	8	0	-
20,479	1(100.0)	1	0	-	0[a]	0	-	1	1	FETUS 6 Skull: Fontanelle, enlarged; Supraoccipital, not ossified; Sphenoid, contains a hole Vertebrae: Thoracic, centra, 12th and 13th, incompletely ossified; Lumbar, centra, 1-6, incompletely ossified; Sacral, 2nd, left, arch, incompletely ossified Sternebrae: 1st, not ossified
20,480	3(30.0)	10	0	-	5	2	FETUS 3 Heart: Appears enlarged FETUS 7 Heart: Appears enlarged	5	1	FETUS 11 Skull: Fontanelle, enlarged; Interparietals and supraoccipital, not ossified Vertebrae: Thoracic, centra, 1st and 10-13, not ossified

a. Dam #20,479 had only one fetus which was assigned to skeletal evaluation.

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TABLE 16 (PAGE 14): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,480 (Cont.)										Lumbar, centra, 1-6, not ossified; Arches, right, 4th, bilateral, 5th, right, 6th, incompletely ossified Pelvis: Ischia and pubes, not ossified
20,481	0	1	0	-	0[a]	0	-	1	0	-
20,482	1(100.0)	1	0	-	0[a]	0	-	1	1	FETUS 5 Ribs: Right; 4-11, wavy; Left, 4-12, wavy
20,483	0	12	0	-	6	0	-	6	0	-
20,484	0	12[b]	0	-	6	0	-	6[b]	0	-
20,485	1(7.7)	13	0	-	6	0	-	7	1	FETUS 10 Vertebrae: Thoracic, centrum, 11th, bifid
20,486	ALL CONCEPTUSES WERE RESORBED		-	-	-	-	-	-	-	-
20,487	0	17	0	-	8	0	-	9	0	-

a. Dams #20,481 and #20,482 each had only one fetus which was assigned to skeletal evaluation.
b. Excludes one dead fetus; see Table 17 for observations for this specimen.

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TABLE 16 (PAGE 15): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,488	3(23.1)	13	0	-	6	0	-	7	3	FETUS 7 Skull: Fontanelle, enlarged; Sphenoid, contai[illegible] Vertebrae: Thoracic, cent[illegible], 1st and 13th, not ossified; Lumbar, centra, 1-6, not ossified Pelvis: Ischia and pubes, incompletely ossified FETUS 9 Skull: Fontanelle, enlarged; Supraoccipital not ossified; Sphenoid, not ossified Vertebrae: Thoracic, centra, 5+6 and 8-13, not ossified; Lumbar, centra, 1-6, not ossified; Arches, bilateral, 4-6, incompletely ossified Ribs: Bilateral, 4-13, wavy and incompletely ossified (hypoplastic)

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TABLE 16 (PAGE 16): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Dam Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,488 (Cont.)										**Pelvis**: Ischia and pubes, not ossified FETUS 14 **Vertebrae**: Thoracic, centrum, 12th, bifid **Sternebrae**: 1st, incompletely ossified
20,489	5(38.5)	13[a]	0	-	7	0	-	6[a]	5	FETUS 2 **Skull**: Sphenoid, contains a hole **Rear Limb(s)**: Femur, right, bent FETUS 4 **Skull**: Supraoccipital, not ossified; Sphenoid, not ossified **Vertebrae**: Thoracic, centra, 1st and 10-13, not ossified; 7-9, incompletely ossified; Lumbar, centra, 1 and 5+6, not ossified; 2-4, incompletely ossified; Arches, bilateral, 5+6, incompletely ossified

a. Excludes one dead fetus; see Table 17 for observations for this specimen.

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TABLE 16 (PAGE 18): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation										
		External Examination			Soft Tissue Examination			Skeletal Examination		
Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,489 (Cont.)										Sphenoid, not ossified Vertebrae: Thoracic, centra, 1, 4 and 6-13, not ossified; 2+5, incompletely ossified; Lumbar, centra, 1-6, not ossified Ribs: Right, 4-13, wavy and incompletely ossified (hypoplastic) Scapulae: Shortened and incompletely ossified Pelvis: Ischia, incompletely ossified; Pubes, not ossified Rear Limb(s): Femur, tibia and fibula, shortened, bent and incompletely ossified FETUS 14 Skull: Supraoccipital not ossified; Sphenoid, incompletely ossified; Exoccipital, incompletely ossified

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TABLE 16 (PAGE 17): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,489 (Cont.)										Sacral, arches, 1+2, bilateral, incompletely ossified Pelvis: Ischia and pubes, incompletely ossified FETUS 7 Skull: Supraoccipital, not ossified; Sphenoid, contains a hole Vertebrae: Thoracic, centra. 12+13, incompletely ossified; Lumbar, centra, 1-6, incompletely ossified Ribs: Right, 5-12, left, 4-12, wavy; Left, 11+12, incompletely ossified (hypoplastic) Pelvis: Ischia and pubes, incompletely ossified FETUS 9 Skull: Fontanelle, enlarged; Exoccipital, incompletely ossified;

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TABLE 16 (PAGE 19): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,489 (Cont.)										Vertebrae: Thoracic, centra, 1st, not ossified; 6-13, incompletely ossified; Lumbar, centra, 1-4, incompletely ossified; 5+6, not ossified; Arches, 3,5+6, bilateral, incompletely ossified Ribs: Right, 3-13, left, 4-13, wavy and incompletely ossified (hypoplastic) Scapulae: Shortened Pelvis: Ischia and pubes, not ossified Rear Limb(s): Femur, tibia and fibula, bilateral, bent; Fibula, bilateral, incompletely ossified
20,490	ALL CONCEPTUSES WERE RESORBED	-		-	-	-	-	-	-	-

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TABLE 16 (PAGE 20): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,491	3(25.0)	12	0	-	5	0	-	7	3	FETUS 4 Vertebrae: Sacral, arches, 2-3, incompletely ossified FETUS 6 Vertebrae: Lumbar, centra, 1-6, incompletely ossified Sacral, arches, 3rd, incompletely ossified Ribs: Right, 4-12, left, 4-6 and 11+12, wavy FETUS 8 Ribs: Right, 5-13, left, 4-13, wavy
20,492	3(27.3)	11	0	-	5	1	FETUS 14 Heart: Appears enlarged	6	1	FETUS 7 Skull: Sphenoid, contains a hole Sternebrae: 1st, not ossified FETUS 10 Skull: Supraoccipital, not ossified; Sphenoid, contains a hole

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TABLE 16 (PAGE 21): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,492 (Cont.)										Vertebrae: Thoracic, centra, 5-13, incompletely ossified; Lumbar, centra, 1-6, incompletely ossified Ribs: Bilateral, 4-13, wavy and incompletely ossified Rear Limb(s): Femur, right, bent; Fibula, right, incompletely ossified
20,493	0	15	0	-	7	0	-	8	0	-
20,494	1(100.0)	1	0	-	0[a]	0	-	1	1	FETUS 6 Skull: Fontanelle, enlarged; Sphenoid, contains a hole Vertebrae: Thoracic, centra, 1st, not ossified; 4-13, incompletely ossified; Lumbar, centra, 1-6, incompletely ossified; Arches, right, 1-3, left, 3+4, incompletely

a. Dam #20,494 had only one fetus which was assigned to skeletal evaluation.

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TABLE 16 (PAGE 22): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,494 (Cont.)										ossified; Sacral, arch, 1st, right, incompletely ossified Ribs: Right, 3-13, left, 4-12, wavy and incompletely ossified (hypoplastic) Pelvis: Ischia and pubes, incompletely ossified Rear Limb(s): Femur and fibula, bilateral, bent
20,495	1(11.1)	9	0	-	4	0	-	5	1	FETUS 9 Sternebrae: 1st, not ossified
20,496	ALL CONCEPTUSES WERE RESORBED	-		-	-	-	-	-	-	-
20,497	4(50.0)	8[a]		-	4	0	-	4[a]	4	FETUS 1 Skull: Sphenoid, contains a hole Vertebrae: Thoracic, centra, 1 and 8-13, not ossified; 5-7, incompletely ossified; Lumbar, centra, 1-6, not ossified Ribs: Right, 8-13, wavy

a. Excludes one dead fetus; see Table 17 for observations for this specimen.

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 16 (PAGE 23): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,497 (Cont.)										Pelvis: Ischia, incompletely ossified FETUS 5 Skull: Exoccipital, incompletely ossified; Sphenoid, not ossified Vertebrae: Thoracic, centra, 1 and 3-13, not ossified; Lumbar, centra, 1-6, not ossified Ribs: Right, 5-13, left 5+6, wavy Pelvis: Ischia and pubes, not ossified FETUS 7 Skull: Supraoccipital, not ossified; Sphenoid, contains a hole Vertebrae: Thoracic, centra, 1+2, 9-13, not ossified; Lumbar, centra, 1-6, not ossified Ribs: Right, 6+7 and 10-12, wavy

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 16 (PAGE 24): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,497 (Cont.)										Pelvis: Ischia and pubes, incompletely ossified FETUS 14 Manubrium: Incompletely ossified Pelvis: Pubes, not ossified
20,498	1(5.9)	17	0	-	8	0	-	9	1	FETUS 17 Vertebrae: Thoracic, centrum, 12th, bifid
20,499	4(26.7)	15	0	-	7	0	-	8	4	FETUS 1 Sternebrae: 1st, not ossified FETUS 5 Pelvis: Ischium, right, incompletely ossified FETUS 11 Vertebrae: Thoracic, centra, 6-13, incompletely ossified; Lumbar, centra, 1-5, incompletely ossified

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 16 (PAGE 25): FETAL ANOMALY DATA - LITTER INCIDENCE (LIVE FETUSES - DAY 20)

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,499 (Cont.)										Pelvis: Ischia, incompletely ossified FETUS 13 Ribs: Right, 3-12, left, 4-10, wavy
20,500	0	2	0	-	1	0	-	1	0	-

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 17 (PAGE 1): FETAL ANOMALY DATA - DEAD CONCEPTUSES

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,476	3(30.0)	10(D)	0	-	5(D)	0	-	5(D)	3	FETUS 10 Skull: Sphenoid, contains a hole FETUS 12 Skull: Sphenoid, contains a hole FETUS 14 Sternebrae: 1st, incompletely ossified
20,477	1(100.0)	1(LR)	0	-	0	0	-	1(LR)	1	FETUS 10 Skull: Fontanelle, enlarged Vertebrae: Thoracic, centra, 1-3, not ossified; 10th, right, unilateral ossification; 11th, left, unilateral ossification; 12th, bifid Pelvis: Pubes, not ossified
20,484	1(100.0)	1(D)	0	-	0	0	-	1(D)	1	FETUS 1 Vertebrae: Lumbar, centra, 5+6, not ossified Sternebrae: 1st and 2nd, incompletely ossified Pelvis: Ischia, incompletely ossified

D = Dead
LR = Late Resorption

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 17 (PAGE 2): FETAL ANOMALY DATA - DEAD CONCEPTUSES

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,489	1(100.0)	1(D)	0	-	0	0	-	1(D)	1	FETUS 11 Skull: Supraoccipital, not ossified; Exoccipital, incompletely ossified; Sphenoid, not ossified Vertebrae: Thoracic, centra, 1+2 and 8-13, not ossified; 3-7, incompletely ossified; Lumbar, centra, 1-6, not ossified; Arch, left, 6th, incompletely ossified Ribs: Right, 5-11, left, 5-12, wavy and incompletely ossified (hypoplastic) Scapulae: Shortened and incompletely ossified Rear Limb(s): Femur, tibia and fibula, right, bent and incompletely ossified; Fibula, left, incompletely ossified

D = Dead

PROTOCOL 305-001: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™111 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 17 (PAGE 3): FETAL ANOMALY DATA - DEAD CONCEPTUSES

Dosage Group: IV 25.0 mg/kg/days 6-15 of Presumed Gestation

Rat Number	Fetuses with Gross External, Soft Tissue or Skeletal Variations N(%)	External Examination			Soft Tissue Examination			Skeletal Examination		
		Total N	Affected N	Description	Total N	Affected N	Description	Total N	Affected N	Description
20,497	1(100.0)	1(D)	0	-	0	0	-	1(D)	1	FETUS 9 Skull: Sphenoid, not ossified Vertebrae: Thoracic, centra, 1-3 and 6-13, not ossified; Lumbar, centra, 1-6, not ossified; Arches, bilateral, 4-6, incompletely ossified Pelvis: Ischia and pubes, incompletely ossified

D = Dead

APPENDIX B

SUMMARY OF THE PILOT EVALUATION - 305-001P

APPENDIX B

SUMMARY OF THE RESULTS OF THE PILOT EVALUATION

RE: Protocol 305-001P: Dosage-Range Embryo/Fetal Toxicity and Teratogenic Potential Study of SAYTEX®111 Administered Orally Via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats (Pilot Study).

SAYTEX®111 was administered orally via gavage to naturally-bred Crl:COBS®CD®(SD)BR rats on days 6 through 15 of presumed gestation. Presumed pregnant rats were assigned to one of four groups administered the test substance (eight rats per group) or to one group administered the vehicle (eight rats). These rats were given suspensions of SAYTEX®111 at dosages of 0(Vehicle), 100, 500, 2500 and 5000 mg/kg/day. All test substance suspensions were administered at a dosage volume of 5 mL/kg, using respective concentrations of 20, 100, 500 and 1000 mg/mL. The volume administered to each rat was adjusted each day on the basis of the observed body weight.

Body weights of the rats were observed and recorded on days 0 and 6 through 20 of presumed gestation. Rats were sacrificed with carbon dioxide on day 20 of presumed gestation. The abdomen of each was opened and examined for pregnancy, number and placement of implantations, early and late resorptions, live and dead fetuses and corpora lutea. Each fetus was weighed, sexed and examined for external variations.

Deaths attributed to the test substance occurred for rats in the 500, 2500 and 5000 mg/kg/day dosage groups. Of the eight rats in each of these respective groups, 2(25.0%), 4(50.0%) and 5(62.5%) rats died during the study; three of the five high dosage group rats which died had injuries related to intubation accidents. With the exception of one rat in each of the 2500 and 5000 mg/kg/day dosage groups, all of the rats which died were pregnant. No rats in the control or 100 mg/kg/day dosage groups died during the course of the study.

The two 500 mg/kg/day dosage group deaths, occurred on days 14 and 18 of gestation, following 9 and 10 dosages, respectively. All four of the 2500 mg/kg/day dosage group rats which died had been given the full complement of ten daily dosages; these deaths occurred on days 15 to 17 of gestation. Death occurred on days 12 to 17 of gestation, following 7 to 10 dosages, for the 5000 mg/kg/day dosage group rats.

One of the two 500 mg/kg/day dosage group rats which died had 13 embryos in utero, all of which were normally developed for the day of gestation on which maternal death occurred, and no resorptions. Autolysis precluded determination of the developmental status of the 14 conceptuses present in utero in the remaining dam which died in this dosage group.

Of the four 2500 mg/kg/day dosage group rats which died, one was not pregnant, and three had 13 to 15 implantation sites present in utero. Severe autolysis precluded determination of the developmental status of the conceptuses present in utero in all three pregnant 2500 mg/kg/day dosage group rats.

Of the five 5000 mg/kg/day dosage group rats which died, one was not pregnant and four had 12 to 18 conceptuses present in utero. Of these four pregnant dams in this dosage group, one resorbed all implantations, two had embryos which appeared normally developed for the day of gestation on which maternal death occurred and one had severe autolysis which precluded determination of the developmental status of the conceptuses.

Agent-related postmortem signs revealed by necropsy of the rats which died included lesions of the gastrointestinal tract (stomach ulcerated, thin-walled or contained dark red to black viscous fluid or substance; perforated small intestine) and liver (mottled).

Three of the five high dosage group rats which died had injuries which were attributed to intubation accidents. These injuries included lesions of the lungs (bright red), thoracic cavity (filled with white substance) and esophagus (perforated). One of these rats also had moderate dilation of the right kidney.

No other postmortem observations were noted for the rats which died.

As compared with the vehicle, administration of the test substance produced dosage-dependent chromodacryorrhea, thin appearance, urine-stained abdominal fur, ungroomed coat, soft or liquid feces, red vaginal exudate (500, 2500 and 5000 mg/kg/day), excess salivation and rales (2500 and 5000 mg/kg/day). No other clinical signs were observed which were attributable to administration of these dosages of the test substance to the dams, as the incidences of these signs were not dosage-dependent and/or were related to the moribund condition of the rats which died (alopecia, vocalization, cloudy eye, ptosis, decreased motor activity, black exudate from mouth).

Agent-related postmortem signs observed for 500, 2500 and 5000 mg/kg/day dosage group rats which survived to day 20 Caesarean-sectioning included gastrointestinal and liver lesions. One of six 500 mg/kg/day dosage group female rats had pitted areas in the fundic region of the stomach. Two of the four surviving 2500 mg/kg/day dosage group dams had a mottled liver, discolored kidneys or a dark green-black substance in the cecum and colon. One of three high dosage group female rats had a thick-walled fundic region which appeared pitted. All other rats which survived to day 20 Caesarean-sectioning appeared normal at scheduled sacrifice.

Weight loss and/or inhibited body weight gain occurred throughout the dosage period for all dams in the SAYTEX®111 dosage groups, as compared with control values. Following the first dosage, weight loss occurred for the 500, 2500 and 5000 mg/kg/day dosage groups. Weight loss continued for rats in these three dosage groups throughout the dosage period. Average weight gain during the postadministration period (days 16 to 20 of gestation) was inhibited for these three dosage groups, as compared with control values. Weight gain during the dosage (days 6 to 15) and the postdosage (days 16 to 20) periods was inhibited for the 100 mg/kg/day dosage group rats, as compared with controls.

Pregnancy occurred for 8(100%), 8(100%), 7(87.5%), 7(87.5%) and 7(87.5%) of the eight female rats in the 0(Vehicle), 100, 500, 2500 and 5000 mg/kg/day dosage groups, respectively. Caesarean-sectioning observations were based on the 8, 8, 5, 4 and 2 pregnant rats which survived to scheduled sacrifice on

day 20 of gestation in the 0(Vehicle), 100, 500, 2500 and 5000 mg/kg/day dosage groups, respectively.

None of the surviving dams in any of the SAYTEX®111 dosage groups had viable fetuses. All (100%) of the dams in these dosage groups resorbed all implantations. The eight pregnant control dams averaged 14.6 live fetuses per litter and 0.5 resorptions per litter.

As compared with the vehicle, administration of the 100, 500, 2500 and 5000 mg/kg/day dosages of SAYTEX®111 did not affect the average numbers of corpora lutea or implantations (11.5 to 16.0 per litter).

CONCLUSION

Administration of the 100, 500, 2500 and 5000 mg/kg/day dosages of SAYTEX®111 was embryo-lethal. None of the surviving dams in any of the SAYTEX®111 dosage groups had viable fetuses. All (100%) of the dams in these dosage groups resorbed implantations.

Administration of the 500, 2500 and 5000 mg/kg/day dosages of SAYTEX®111 was maternally lethal. Moderate to severe inhibitory effects on average maternal body weight gain were produced by dosages of 100 to 5000 mg/kg/day. Agent-related clinical signs and postmortem observations were produced by dosages of 500 to 5000 mg/kg/day. There were no other apparent toxic effects of the test substance on the female rats which survived to Caesarean-sectioning on day 20 of gestation.

On the basis of these data, the pilot dosage-range evaluation of SAYTEX®111 should be repeated using a lower range of dosages, as there was not sufficient information available to select dosages for definitive embryo/fetal toxicity-teratogenic potential study of this test substance in the current evaluation. Dosages of 0(Vehicle), 5, 25, 50 and 100 mg/kg/day are suggested for use in the repeat dosage-range pilot evaluation of SAYTEX®111.

4/11/85 — 4/15/85

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Director, Reproductive Toxicology

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4-15-85

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Protocol 305-001P - SAYTEX®111

TABLE 1 (PAGE 1)

Mortality

Dosage (mg/kg/day)	Rat Number	Dosages	Observations
0(Vehicle)	-	-	-
100	-	-	-
500	18,982	10	Found dead day 18 of gestation. Uterine Contents: 14 implantation sites. (autolytic state of the implantation sites precludes determination of developmental status). Stomach: Filled with a dark red viscous fluid. Fundic region, several ulcerated areas (approximately 1.0 mm in diameter). All other tissues appeared normal.
	18,984	9	Found dead day 14 of gestation. Uterine Contents: 13 implantation sites. 13 embryos (normally developed). Stomach: Contained a black viscous substance. Fundic and pyloric regions, thin-walled. Pyloric region, numerous ulcerated areas (0.5 mm to 0.8 mm in diameter). Liver: Mottled. All other tissues appeared normal.

TABLE 1 (PAGE 2)

Dosage (mg/kg/day)	Rat Number	Dosages	Observations
2500	18,987	10	Found dead day 15 of presumed gestation. Not pregnant. Stomach: Fundic and pyloric region, thin-walled. Liver: Mottled. All other tissues appeared normal.
	18,988	10	Found dead day 17 of gestation. Uterine Contents: 13 implantation sites. (autolytic state of the implantation sites precludes determination of developmental status). With the exception of autolysis, all tissues appeared normal.
	18,989	10	Found dead day 16 of gestation. Uterine Contents: 15 implantation sites. (autolytic state of the implantation sites precludes determination of developmental status). Intestines: Small, perforated. With the exception of autolysis, all other tissues appeared normal.
	18,992	10	Found dead day 17 of gestation. Uterine Contents: 14 implantation sites. (autolytic state of the implantation sites precludes determination of developmental status). Stomach: Filled with dark red-black viscous fluid. Fundic region, numerous black areas (approximately 0.5 to 1.0 mm in diameter). With the exception of autolysis, all other tissues appeared normal.

TABLE 1 (PAGE 3)

Dosage (mg/kg/day)	Rat Number	Dosages	Observations
5000	18,993	10	Found dead day 15 of gestation. Uterine Contents: 13 implantation sites. 13 embryos (normally developed). Thoracic cavity: Filled with white substance. Esophagus: Perforated. All other tissues appeared normal. (Presumed intubation injury)
	18,994	7	Found dead day 12 of presumed gestation. Not pregnant. Lungs: Bright red. Esophagus: Perforated. Kidneys: Right, moderate dilation, clear fluid. All other tissues appeared normal. (Presumed intubation injury)
	18,995	10	Found dead day 16 of gestation. Uterine Contents: 12 implantation sites. 12 embryos (normally developed). Stomach: Filled with black viscous substance. Fundic and pyloric regions, thin-walled. Fundic region, numerous ulcerated areas (0.2 mm to 0.3 mm in diameter). All other tissues appeared normal.
	18,997	10	Found dead day 17 of gestation. Uterine Contents: 10 implantation sites. 10 resorptions (9 early resorptions and 1 late resorption). With the exception of autolysis, all tissues appeared normal.
	19,000	10	Found dead day 16 of gestation. Uterine Contents: 18 implantation sites. (autolytic state of the implantation sites precludes determination of developmental status). Thoracic cavity: Filled with white substance. Esophagus: Perforated. With the exception of autolysis, all other tissues appeared normal. (Presumed intubation injury)

PROTOCOL 305001P : DOSAGE-RANGE FINDING EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX 111 ADMINISTERED ORALLY TO RATS

LE 2 PAGE 1 : PHYSICAL SIGN INCIDENCE -- SUMMARY

TABLE RANGE: 102904-111504

FEMALES / DOSE GROUP	1	2	3	4	5
APPEARS NORMAL					
NO SIGNIFICANT CLINICAL OBSERVATIONS	105/ 7	118/ 8	47/ 8	35/ 7	49/ 8
DEAD					
FOUND DEAD	0/ 0	0/ 0	2/ 2	4/ 4	5/ 5
SCHEDULED SACRIFICE	8/ 8	8/ 8	6/ 6	4/ 4	3/ 3
DEPRESSION					
DECREASED MOTOR ACTIVITY	0/ 0	0/ 0	1/ 1	3/ 3	0/ 0
EXCITATION					
VOCALIZATION	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
EYES / NOSE					
CHROMODACRYORRHEA	0/ 0	0/ 0	4/ 2	7/ 2	2/ 2
PTOSIS	0/ 0	0/ 0	1/ 1	1/ 1	1/ 1
CLOUDY	0/ 0	0/ 0	1/ 1	5/ 3	0/ 0
MISCELLANEOUS					
THIN	0/ 0	0/ 0	13/ 3	27/ 4	31/ 6
FOUND DEAD	0/ 0	0/ 0	1/ 1	4/ 4	4/ 4
RED EXUDATE	0/ 0	0/ 0	5/ 4	6/ 4	4/ 3
ORAL-BUCCAL					
SALIVATION	0/ 0	0/ 0	0/ 0	1/ 1	2/ 1
EXUDATE	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
RESPIRATION					
RALES	1/ 1	0/ 0	0/ 0	3/ 3	7/ 4
SKIN/FUR					
ALOPECIA	15/ 1	2/ 2	34/ 4	42/ 4	0/ 0
URINE STAINED ABDOMINAL FUR	0/ 0	0/ 0	24/ 3	34/ 8	15/ 5
UNGROOMED COAT	0/ 0	0/ 0	17/ 3	29/ 6	15/ 3
STOOL/URINE					
SOFT OR LIQUID FECES	0/ 0	0/ 0	12/ 4	36/ 7	22/ 6
MAXIMUM INCIDENCE/# EXAMINED	120/ 8	120/ 8	110/ 8	105/ 8	96/ 8

TABLE 3 (PAGE 1): SUMMARY OF MATERNAL BODY WEIGHTS (GESTATION PERIOD)

	DOSAGE GROUP	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	2500 MG/KG/DAY	5000 MG/KG/DAY
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	7(87.5)	7(87.5)	7(87.5)
MATERNAL BODY WEIGHT						
DAY 0	MEAN±S.D.	293.9 ± 24.3	294.9 ± 22.6	298.4 ± 18.6	287.3 ± 23.6	290.6 ± 16.8
DAY 6	MEAN±S.D.	315.6 ± 28.6	312.0 ± 25.3	319.8 ± 23.5	306.1 ± 21.0	306.8 ± 22.7
DAY 7	MEAN±S.D.	315.6 ± 28.8	313.4 ± 25.0	315.8 ± 27.5	303.3 ± 18.8	301.0 ± 26.2
DAY 8	MEAN±S.D.	319.5 ± 29.4	313.6 ± 20.9	311.0 ± 27.5	299.0 ± 17.2	293.6 ± 23.2
DAY 9	MEAN±S.D.	321.1 ± 29.4	313.9 ± 18.5	305.4 ± 30.1	291.3 ± 20.4	287.7 ± 21.6
DAY 10	MEAN±S.D.	323.2 ± 31.9	317.4 ± 20.3	302.6 ± 29.6	285.6 ± 22.7	287.3 ± 24.8
DAY 11	MEAN±S.D.	327.0 ± 33.9	318.1 ± 18.9	300.0 ± 30.8	279.0 ± 23.9	289.3 ± 36.4
DAY 12	MEAN±S.D.	329.8 ± 30.3	319.1 ± 17.8	296.1 ± 31.0	270.0 ± 24.9	272.8 ± 27.4
DAY 13	MEAN±S.D.	336.9 ± 31.9	323.9 ± 18.7	293.4 ± 32.4	262.4 ± 21.6	271.0 ± 26.9 [6]
DAY 14	MEAN±S.D.	341.9 ± 32.0	329.9 ± 17.9	289.7 ± 33.9	252.1 ± 21.2	257.0 ± 27.3 [6]
DAY 15	MEAN±S.D.	352.4 ± 33.4	329.0 ± 19.8	285.3 ± 39.6 [6]	244.1 ± 20.7	258.5 ± 28.9 [6]
DAY 16	MEAN±S.D.	361.6 ± 34.3	332.0 ± 20.5	287.3 ± 42.9 [6]	232.7 ± 20.0 [6]	278.0 ± 26.9 [3]
DAY 18	MEAN±S.D.	392.2 ± 36.1	351.4 ± 20.3	318.4 ± 31.4 [5]	217.5 ± 31.6 [4]	299.0 ± 29.7 [2]
DAY 20	MEAN±S.D.	427.5 ± 36.8	359.5 ± 25.6	331.6 ± 28.6 [5]	227.2 ± 45.8 [4]	331.0 ± 14.1 [2]

This table restricted to pregnant animals.
ALL WEIGHT VALUES IN g
[ ] NUMBER OF VALUES AVERAGED

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4 - (PAGE 1): SUMMARY OF MATERNAL GESTATION MEAN BODY WEIGHT CHANGES

	DOSAGE GROUP	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	2500 MG/KG/DAY	5000 MG/KG/DAY
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	7(87.5)	7(87.5)	7(87.5)
MATERNAL BODY WEIGHT CHANGE						
DAYS 0- 6	MEAN±S.D.	+21.8 ± 8.5	+17.1 ± 11.5	+21.4 ± 13.1	+18.8 ± 13.2	+16.3 ± 12.8
DAYS 6- 7	MEAN±S.D.	+0.0 ± 1.8	+1.4 ± 3.5	-4.0 ± 8.4	-2.8 ± 4.5	-5.8 ± 4.7
DAYS 6- 8	MEAN±S.D.	+3.9 ± 2.7	+1.6 ± 6.2	-8.8 ± 10.3	-7.1 ± 5.2	-13.3 ± 5.1
DAYS 6- 9	MEAN±S.D.	+5.5 ± 4.8	+1.9 ± 9.3	-14.4 ± 12.1	-14.8 ± 9.2	-19.1 ± 8.0
DAYS 6-10	MEAN±S.D.	+7.6 ± 8.9	+5.4 ± 9.4	-17.2 ± 14.3	-20.5 ± 10.2	-24.5 ± 7.9
DAYS 6-11	MEAN±S.D.	+11.4 ± 10.4	+6.1 ± 12.0	-19.8 ± 17.1	-27.1 ± 13.4	-17.5 ± 22.9
DAYS 6-12	MEAN±S.D.	+14.1 ± 11.3	+7.1 ± 17.7	-23.7 ± 21.8	-36.1 ± 14.2	-34.0 ± 8.5
DAYS 6-13	MEAN±S.D.	+21.2 ± 9.3	+11.9 ± 17.5	-26.4 ± 26.7	-43.7 ± 10.3	-40.8 ± 14.1 [6]
DAYS 6-14	MEAN±S.D.	+26.2 ± 8.2	+17.9 ± 15.8	-30.1 ± 29.1	-54.0 ± 11.9	-54.8 ± 18.7 [6]
DAYS 6-15	MEAN±S.D.	+36.8 ± 8.3	+17.0 ± 17.7	-32.5 ± 33.0 [4]	-62.0 ± 11.4	-53.3 ± 18.8 [6]
DAYS 6-16	MEAN±S.D.	+46.0 ± 7.7	+20.0 ± 16.9	-30.5 ± 33.3 [4]	-71.5 ± 11.9 [6]	-47.0 ± 21.9 [3]
DAYS 16-18	MEAN±S.D.	+30.6 ± 4.8	+19.4 ± 5.4	+19.2 ± 7.6 [5]	-13.2 ± 6.8 [4]	+28.0 ± 4.2 [2]
DAYS 16-20	MEAN±S.D.	+65.9 ± 6.5	+27.5 ± 9.0	+32.4 ± 11.7 [5]	-3.5 ± 32.2 [4]	+60.0 ± 19.8 [2]
DAYS 6-20	MEAN±S.D.	+111.9 ± 8.9	+47.5 ± 13.2	+10.2 ± 17.8 [5]	-75.0 ± 20.5 [4]	+15.5 ± 10.6 [2]
DAYS 0-20	MEAN±S.D.	+133.6 ± 15.4	+64.6 ± 13.8	+37.2 ± 13.3 [5]	-52.2 ± 30.5 [4]	+35.5 ± 26.2 [2]

This table restricted to pregnant animals.
WEIGHT VALUES IN g
[ ] NUMBER OF VALUES AVERAGED

PROTOCOL 305001P : DOSAGE-RANGE FINDING EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX 111 ADMINISTERED ORALLY TO RATS

E 5 (PAGE 1): CAESAREAN-SECTIONING DATA - SUMMARY

	DOSAGE GROUP	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	2500 MG/KG/DAY	5000 MG/KG/DAY
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	7(87.5)	7(87.5)	7(87.5)
ABORTED	N	0	0	0	0	0
DIED	N	0	0	2	3	5
DELIVERED NATURALLY	N	0	0	0	0	0
ANIMALS PREGNANT AND DELIVERED BY CAESAREAN-SECTIONING ON DAY 20	N	8	8	5	4	2
CORPORA LUTEA	MEAN±S.D.	15.6 ± 1.4	15.8 ± 2.2	16.2 ± 1.3	13.5 ± 4.1	15.0 ± 2.8
IMPLANTATIONS	MEAN±S.D.	15.1 ± 1.1	15.0 ± 1.8	16.0 ± 1.2	11.5 ± 7.1	14.0 ± 1.4
LITTER SIZE	MEAN±S.D.	14.6 ± 1.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
LIVE FETUSES	N	117	0	0	0	0
	MEAN±S.D.	14.6 ± 1.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
DEAD FETUSES	N	0	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.5 ± 0.5	15.0 ± 1.8	16.0 ± 1.2	11.5 ± 7.1	14.0 ± 1.4
EARLY RESORPTIONS	N	4	120	80	46	28
	MEAN±S.D.	0.5 ± 0.5	15.0 ± 1.8	16.0 ± 1.2	11.5 ± 7.1	14.0 ± 1.4
LATE RESORPTIONS	N	0	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
DAMS WITH ANY RESORPTIONS	N(%)	4(50.0)	8(100.0)	5(100.0)	4(100.0)	2(100.0)
DAMS WITH ALL IMPLANTATIONS RESORBING	N(%)	0	8(100.0)	5(100.0)	4(100.0)	2(100.0)
DAMS WITH VIABLE FETUSES	N(%)	8(100.0)	0	0	0	0

PROTOCOL 305001P : DOSAGE-RANGE FINDING EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX 111 ADMINISTERED ORALLY TO RATS

E 6 (PAGE 1): FETAL LITTER DATA - SUMMARY

	DOSE GROUP	0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	2500 MG/KG/DAY	5000 MG/KG/DAY
LITTERS EXAMINED DAY 20	N	8	0	0	0	0
IMPLANTATIONS	MEAN±S.D.	15.1 ± 1.1	-	-	-	-
LIVE FETUSES	MEAN±S.D.	14.6 ± 1.3	-	-	-	-
LITTERS WITH ONE OR MORE LIVE FETUSES	N	8	0	0	0	0
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.44 ± 0.17	-	-	-	-
MALE FETUSES	MEAN±S.D.	3.56 ± 0.17	-	-	-	-
FEMALE FETUSES	MEAN±S.D.	3.34 ± 0.16	-	-	-	-
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	3.3 ± 3.6	-	-	-	-
LIVE FETUSES	N	117	0	0	0	0
IVE MALE FETUSES	N	53	0	0	0	0
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	45.0 ± 13.1	-	-	-	-

NOTE: - Animals with all implants resorbing excluded from this table.

APPENDIX C

SUMMARY OF THE PILOT EVALUATION - 305-003P

APPENDIX C

SUMMARY OF THE RESULTS OF THE PILOT EVALUATION

RE: Protocol 305-003P: Dosage-Range Embryo/Fetal Toxicity and Teratogenic Potential of SAYTEX®111 Administered Orally Via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats (Pilot Study)

Saytex® 111 was administered orally via gavage to mated female rats (Crl:COBS®CD®(SD)BR) on days 6 through 15 of presumed gestation. Eight rats were assigned to each dosage group. Dosages of 0(vehicle), 5, 25, 50 or 75 mg/kg/day were given once daily; the dosage was adjusted each day on the basis of the observed body weight. All dosages were given at a volume of 5 mL/kg.

Clinical signs and body weights of the rats were recorded daily during the administration and postadministration periods. Dams were examined for signs of abortion and delivery. On day 20 of presumed gestation, all rats were sacrificed with carbon dioxide. The thorax and abdomen of each rat was opened and examined for gross lesions. The ovaries and uterus were excised, and the number of corpora lutea were counted. The uterus was examined for pregnancy and numbers of live and dead fetuses and of early and late resorptions. Live fetuses were examined for gross external variations and weighed.

As shown in Table 1, no adult female rat died during the course of the study. Seven or eight of the eight female rats in each dosage group were pregnant (uteri were stained with ammonium sulfide when no implants were initially evident).

Red or brown exudate around the vagina, associated with resorption of conceptuses, occurred for five high dosage group dams (75 mg/kg/day) and for one mid dosage group dam (25 mg/kg/day). This was the only clinical sign attributed to the test substance. All other signs occurred at incidences which were not dosage-dependent [lesion, alopecia (small areas), soft or liquid feces] and/or occurred in only one rat (thin appearance). The incidences for clinical observations are presented in Table 1.

No gross lesions attributed to Saytex® 111 were revealed by necropsy of the dams when Caesarean-sectioned. One 25 mg/kg/day dosage group dam had hydronephrosis, and one 75 mg/kg/day dosage group dam had a cystic ovary. No other gross lesion was revealed by necropsy of the dams.

As shown in Tables 2 and 3, average body weight gain was decreased for dams given dosages of 25 mg/kg/day and above. In dams given the 25 and 50 mg/kg/day dosages, this effect probably reflects the resorption of conceptuses, rather than a direct effect of the test substance on the dams. Both indirect effects on body weight (resorption of conceptuses) and direct effects on maternal body weight gain were evident for the 75 mg/kg/day dosage group dams.

Inhibition of average maternal body weight gain was first evident for the 25 mg/kg/day dosage group dams after the dosage period (day 18 of gestation), and for the 50 mg/kg/day dosage group dams on the last day of the dosage period (day 15 of gestation). This effect was first observed for the 75 mg/kg/day dosage group dams after the first two dosages of the test substance had been given. These data correlate well with the incidences of early and late resorptions in the 25 mg/kg/day dosage group dams, and with the incidence of early resorption in the 50 and 75 mg/kg/day dosage group dams.

When only dams with one or more live Caesarean-delivered fetuses were evaluated (Tables 4 and 5), a small inhibitory effect on maternal body weight gain was evident for the 25 mg/kg/day dosage group dams. As previously noted, this effect could not be separated from the increased resorption incidence present in litters of this dosage group. The seven pregnant rats in each of the 50 and 75 mg/kg/day dosage groups could not be evaluated using this criterion; each of these rats resorbed all conceptuses and had no live fetuses.

The Caesarean-sectioning data (Table 6) demonstrate that administration of dosages of 25 mg/kg/day of Saytex® 111 and above resulted in a decreased litter size (live fetuses), reflecting resorption (death) of conceptuses. The incidences of early (embryo) and late (fetal) resorption were increased for the 25 mg/kg/day dosage group litters, as compared with the control litters. The 50 and 75 mg/kg/day dosages of the test substance resulted in the death of all conceptuses (early resorption) prior to their attaining the fetal stage.

The incidence of pregnancy and the average numbers of corpora lutea and implantations were unaffected by administration of these dosages of the test substance to the dams.

As shown in Table 7, as compared with the control values, average fetal body weight of the 25 mg/kg/day dosage group litters was decreased by administration of this dosage to the dams. All fetuses appeared normal at gross external examination (Table 8). Because all conceptuses of dams given the 50 or 75 mg/kg/day dosages of the test substance died , no term day-20 fetuses were available for gross external examination or body weight evaluation.

CONCLUSION

On the basis of these data, administation of the 25 mg/kg/day dosage of Saytex® 111 to the dams resulted in increased incidences of embryo and/or fetal death and in reduced fetal body weights per litter, as compared with control values. Administration of the 50 and 75 mg/kg/day dosages of the test substance to the dams resulted in the death of all conceptuses prior to completion of the period of embryogenesis (early resorption).

Average maternal body weight gain was reduced for the 25 mg/kg/day dosage group dams only during the fetal period. This period occurs after the completion of the dosage period (days 6 through 15 of gestation), and the effect reflected the death of the conceptuses (resorption). Maternal body weight gain was not affected during the period of embryogenesis, the developmental period during which the dams were given the 25 mg/kg/day dosage of the test substance. The effect of the 50 mg/kg/day dosage on maternal body weight also appeared to be related to resorption of conceptuses, rather than a direct effect on the dams. In these dams, inhibition of maternal body weight gain also was not

clearly evident until after completion of the dosage period. Only the 75 mg/kg/day dosage of the test substance resulted in effects which were considered to be direct signs of maternal toxicity. That is, only this dosage resulted in inhibition of maternal body weight gain which was not secondary to embryo/fetal resorption.

RECOMMENDATION

Dosages of 0(vehicle), 5, 25 and 75 mg/kg/day of Saytex® 111 are recommended for use in the definitive developmental toxicity study (305-003) of this test substance, which is to be performed in rats.

It is expected that the 5 mg/kg/day dosage will provide a no-effect level. The 25 mg/kg/day dosage is expected to result in increased resorption (early and late) of conceptuses and decreased fetal body weights in surviving fetuses. The high dosage (75 mg/kg/day) is expected to produce a high incidence of resorption and few, if any, surviving fetuses. This high dosage should be tested because it is the only one which is expected to demonstrate toxic effects in the dam, a necessary requirement for EPA-regulated studies.

Since the dosage required for demonstration of maternal toxicity is higher than the dosage required for demonstration of embryo-fetal toxicity, safety assessment should be based on the more sensitive embryo-fetal dosage level.

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PROTOCOL 305-003P: DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 111 ADMINISTERED ORALLY TO PRESUMED PREGNANT RATS - PILOT

TABLE 1 (PAGE 1): PHYSICAL SIGN INCIDENCE -- SUMMARY

FEMALES / DOSE GROUP	1	2	3	4	5
APPEARS NORMAL					
NO SIGNIFICANT CLINICAL OBSERVATIONS	106/ 8	75/ 5	94/ 8	120/ 8	83/ 8
HEAD					
SCHEDULED SACRIFICE	8/ 8	8/ 8	8/ 8	8/ 8	8/ 8
MASS / LESION					
LESION	8/ 1	0/ 0	0/ 0	0/ 0	0/ 0
MISCELLANEOUS					
BROWN EXUDATE - VAGINA	0/ 0	0/ 0	2/ 1	0/ 0	2/ 2
THIN	0/ 0	0/ 0	0/ 0	0/ 0	3/ 1
SKIN/FUR					
ALOPECIA	6/ 1	45/ 3	22/ 2	0/ 0	25/ 3
STOOL/URINE					
SOFT OR LIQUID FECES	0/ 0	0/ 0	2/ 1	2/ 1	4/ 1
	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
[illegible] EXUDATE - VAGINA	0/ 0	0/ 0	0/ 0	0/ 0	6/ 4
MAXIMUM INCIDENCE/# EXAMINED	120/ 8	120/ 8	120/ 8	120/ 8	120/ 8

1 = 0(Vehicle)
2 = 5 mg/kg/day
3 = 25 mg/kg/day
4 = 50 mg/kg/day
5 = 75 mg/kg/day

PROTOCOL 305-003P: DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 111 ADMINISTERED ORALLY TO PRESUMED PREGNANT RATS - PILOT

TABLE 2 (PAGE 1): SUMMARY OF MATERNAL BODY WEIGHTS (GESTATION PERIOD)

	DOSAGE GROUP	0 MG/KG/DAY	5 MG/KG/DAY	25 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	8(100.0)	7(87.5)	7(87.5)
MATERNAL BODY WEIGHT						
DAY 0	MEAN+S.D.	245.4 ± 15.5	244.5 ± 9.6	245.6 ± 12.2	242.1 ± 11.0	245.8 ± 12.7
DAY 6	MEAN+S.D.	275.0 ± 14.5	275.6 ± 12.0	275.6 ± 15.7	271.3 ± 12.7	269.3 ± 19.2
DAY 7	MEAN+S.D.	276.1 ± 14.9	275.5 ± 11.4	275.4 ± 17.5	271.6 ± 12.2	270.3 ± 18.0
DAY 8	MEAN+S.D.	280.5 ± 15.7	280.2 ± 12.2	278.9 ± 17.3	275.6 ± 14.9	271.0 ± 17.6
DAY 9	MEAN+S.D.	288.4 ± 18.5	285.0 ± 12.4	283.5 ± 18.8	277.4 ± 13.6	277.1 ± 20.7
DAY 10	MEAN+S.D.	291.1 ± 16.9	290.1 ± 14.0	288.1 ± 19.2	287.6 ± 15.2	281.1 ± 20.6
DAY 11	MEAN+S.D.	295.4 ± 16.6	296.6 ± 14.2	296.5 ± 18.2	294.1 ± 15.0	285.4 ± 21.4
DAY 12	MEAN+S.D.	302.1 ± 18.6	301.6 ± 16.0	303.4 ± 20.2	299.1 ± 14.2	292.8 ± 24.3
DAY 13	MEAN+S.D.	306.0 ± 15.5	307.2 ± 16.2	307.1 ± 19.5	306.6 ± 14.4	297.7 ± 26.6
DAY 14	MEAN+S.D.	310.5 ± 17.1	312.5 ± 15.9	313.1 ± 21.4	311.6 ± 17.3	298.4 ± 25.5
DAY 15	MEAN+S.D.	318.8 ± 19.1	320.2 ± 19.6	319.1 ± 23.7	312.0 ± 16.1	296.0 ± 25.0
DAY 16	MEAN+S.D.	327.2 ± 18.2	330.9 ± 20.0	327.1 ± 28.2	313.6 ± 15.0	294.7 ± 27.6
DAY 18	MEAN+S.D.	355.6 ± 21.6	360.8 ± 23.4	345.4 ± 30.5	323.4 ± 15.1	308.0 ± 29.6
DAY 20	MEAN+S.D.	389.8 ± 20.8	395.5 ± 29.3	359.1 ± 31.0	328.6 ± 17.1	306.8 ± 35.7

This table restricted to pregnant animals.
ALL WEIGHT VALUES IN g

PROTOCOL 305-003P: DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 111 ADMINISTERED ORALLY TO PRESUMED PREGNANT RATS - PILOT

TABLE 3 (PAGE 1): SUMMARY OF MATERNAL GESTATION MEAN BODY WEIGHT CHANGES

	DOSAGE GROUP	0 MG/KG/DAY	5 MG/KG/DAY	25 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	8(100.0)	7(87.5)	7(87.5)
MATERNAL BODY WEIGHT CHANGE						
DAYS 0- 6	MEAN+S.D.	+29.6 ± 5.5	+31.1 ± 5.1	+30.0 ± 6.6	+29.1 ± 5.0	+23.4 ± 10.2
DAYS 6- 7	MEAN+S.D.	+1.1 ± 4.1	-0.1 ± 3.2	-0.2 ± 3.7	+0.3 ± 4.4	+1.0 ± 2.2
DAYS 6- 8	MEAN+S.D.	+5.5 ± 4.2	+4.6 ± 4.6	+3.2 ± 2.4	+4.3 ± 4.4	+1.7 ± 5.5
DAYS 6- 9	MEAN+S.D.	+13.4 ± 10.4	+9.4 ± 5.2	+7.9 ± 5.5	+6.1 ± 5.9	+7.8 ± 5.8
DAYS 6-10	MEAN+S.D.	+16.1 ± 5.3	+14.5 ± 7.4	+12.5 ± 6.5	+16.3 ± 7.4	+11.8 ± 4.6
DAYS 6-11	MEAN+S.D.	+20.4 ± 7.0	+21.0 ± 7.5	+20.9 ± 4.7	+22.8 ± 5.1	+16.1 ± 5.3
DAYS 6-12	MEAN+S.D.	+27.1 ± 7.2	+26.0 ± 7.1	+27.8 ± 5.9	+27.8 ± 6.0	+23.6 ± 7.5
DAYS 6-13	MEAN+S.D.	+31.0 + 6.0	+31.6 ± 9.3	+31.5 ± 6.2	+35.3 ± 7.2	+28.4 ± 8.6
DAYS 6-14	MEAN+S.D.	+35.5 ± 5.2	+36.9 ± 7.4	+37.5 ± 7.5	+40.3 ± 10.5	+29.1 ± 7.0
DAYS 6-15	MEAN+S.D.	+43.8 ± 8.2	+44.6 ± 11.2	+43.5 ± 9.4	+40.7 ± 9.9	+26.7 ± 6.4
DAYS 6-16	MEAN+S.D.	+52.2 ± 7.2	+55.2 ± 10.5	+51.5 ± 13.7	+42.3 ± 8.8	+25.4 ± 9.4
DAYS 6-18	MEAN+S.D.	+80.6 ± 9.0	+85.1 ± 15.3	+69.8 ± 17.8	+52.1 ± 9.2	+38.7 ± 11.6
DAYS 6-20	MEAN+S.D.	+114.8 ± 9.3	+119.9 ± 21.8	+83.5 ± 18.3	+57.3 ± 10.5	+37.6 ± 20.6
DAYS 16-20	MEAN+S.D.	+62.5 ± 4.5	+64.6 ± 13.3	+32.0 ± 6.5	+15.0 ± 5.4	+12.1 ± 20.0
DAYS 0-20	MEAN+S.D.	+144.4 ± 11.0	+151.0 ± 24.4	+113.5 ± 22.8	+86.4 ± 12.7	+61.0 ± 21.8

This table restricted to pregnant animals.
ALL WEIGHT VALUES IN g

PROTOCOL 305-003P: DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 111 ADMINISTERED ORALLY TO PRESUMED PREGNANT RATS - PILOT

TABLE 4 (PAGE 1): SUMMARY OF MATERNAL BODY WEIGHTS (GESTATION PERIOD)

	DOSAGE GROUP	0 MG/KG/DAY	5 MG/KG/DAY	25 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	8(100.0)	7(87.5)	7(87.5)
MATERNAL BODY WEIGHT						
DAY 0	MEAN+S.D.	245.4 ± 15.5	244.5 ± 9.6	245.8 ± 13.2 [7]	-	-
DAY 5	MEAN+S.D.	275.0 ± 14.5	275.6 ± 12.0	276.0 ± 15.9 [7]		-
DAY 7	MEAN+S.D.	276.1 ± 14.9	275.5 ± 11.4	276.3 ± 18.7 [7]		-
DAY 8	MEAN+S.D.	280.5 ± 15.7	280.2 ± 12.2	279.6 ± 18.5 [7]		-
DAY 9	MEAN+S.D.	288.4 ± 18.5	285.0 ± 12.4	284.6 ± 20.0 [7]	-	-
DAY 10	MEAN+S.D.	291.1 ± 16.9	290.1 ± 14.0	289.3 ± 20.4 [7]	-	-
DAY 11	MEAN+S.D.	295.4 ± 16.6	296.6 ± 14.2	297.3 ± 19.5 [7]	-	-
DAY 12	MEAN+S.D.	302.1 ± 18.6	301.6 ± 16.0	304.1 ± 21.7 [7]	-	-
DAY 13	MEAN+S.D.	306.0 ± 15.5	307.2 ± 16.2	308.4 ± 20.7 [7]	-	-
DAY 14	MEAN+S.D.	310.5 ± 17.1	312.5 ± 15.9	313.7 ± 23.0 [7]	-	-
DAY 15	MEAN+S.D.	318.8 ± 19.1	320.2 ± 19.6	320.6 ± 25.2 [7]	-	-
DAY 16	MEAN+S.D.	327.2 ± 18.2	330.9 ± 20.0	330.0 ± 29.1 [7]	-	-
DAY 18	MEAN+S.D.	355.6 ± 21.6	360.8 ± 23.4	350.1 ± 29.5 [7]	-	-
DAY 20	MEAN+S.D.	389.8 ± 20.8	395.5 ± 29.3	364.0 ± 29.9 [7]	-	-

This table restricted to pregnant animals.
Animals with all implants resorbing excluded from this table.
ALL WEIGHT VALUES IN g
[ ] NUMBER OF VALUES AVERAGED

PROTOCOL 305-003P: DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 111 ADMINISTERED ORALLY TO PRESUMED PREGNANT RATS - PILOT

TABLE 5 (PAGE 1): SUMMARY OF MATERNAL GESTATION MEAN BODY WEIGHT CHANGES

	DOSAGE GROUP	0 MG/KG/DAY	5 MG/KG/DAY	25 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	8(100.0)	7(87.5)	7(87.5)
MATERNAL BODY WEIGHT CHANGE						
DAYS 0- 6	MEAN±S.D.	+29.6 ± 5.5	+31.1 ± 5.1	+30.1 ± 7.1 [7]	-	-
DAYS 6- 7	MEAN±S.D.	+1.1 ± 4.1	-0.1 ± 3.2	+0.3 ± 3.7 [7]	-	-
DAYS 6- 8	MEAN±S.D.	+5.5 ± 4.2	+4.6 ± 4.6	+3.6 ± 2.4 [7]	-	-
DAYS 6- 9	MEAN±S.D.	+13.4 ± 10.4	+9.4 ± 5.2	+8.6 ± 5.6 [7]	-	-
DAYS 6-10	MEAN±S.D.	+16.1 ± 5.3	+14.5 ± 7.4	+13.3 ± 6.6 [7]	-	-
DAYS 6-11	MEAN±S.D.	+20.4 ± 7.0	+21.0 ± 7.5	+21.3 ± 4.9 [7]	-	-
DAYS 6-12	MEAN±S.D.	+27.1 ± 7.2	+26.0 ± 7.1	+28.1 ± 6.3 [7]	-	-
DAYS 6-13	MEAN±S.D.	+31.0 ± 6.0	+31.6 ± 9.3	+32.4 ± 6.1 [7]	-	-
DAYS 6-14	MEAN±S.D.	+35.5 ± 5.2	+36.9 ± 7.4	+37.7 ± 8.1 [7]	-	-
DAYS 6-15	MEAN±S.D.	+43.8 ± 8.2	+44.6 ± 11.2	+44.6 ± 9.6 [7]	-	-
DAYS 6-16	MEAN±S.D.	+52.2 ± 7.2	+55.2 ± 10.5	+54.0 ± 12.7 [7]	-	-
DAYS 6-18	MEAN±S.D.	+80.6 ± 9.0	+85.1 ± 15.3	+74.1 ± 13.8 [7]	-	-
DAYS 6-20	MEAN±S.D.	+114.3 ± 9.3	+119.9 ± 21.8	+88.[illegible] ± 14.2 [7]	-	-
DAYS 16-20	MEAN±S.D.	+62.5 ± 4.5	+64.6 ± 13.3	+34.0 ± 3.4 [7]	-	-
DAYS 0-20	MEAN±S.D.	+144.4 ± 11.0	+151.0 ± 24.4	+118.1 ± 20.1 [7]	-	-

This table restricted to pregnant animals.
Animals with all implants resorbing excluded from this table.

ALL WEIGHT VALUES IN g
[ ] NUMBER OF VALUES AVERAGED

PROTOCOL 305-003P: DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 111 ADMINISTERED ORALLY TO PRESUMED PREGNANT RATS - PILOT

TABLE 6 (PAGE 1): CAESAREAN-SECTIONING DATA - SUMMARY

	DOSAGE GROUP	0 MG/KG/DAY	5 MG/KG/DAY	25 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	8(100.0)	8(100.0)	8(100.0)	7(87.5)	7(87.5)
ABORTED	N	0	0	0	0	0
DIED	N	0	0	0	0	0
DELIVERED NATURALLY	N	0	0	0	0	0
ANIMALS PREGNANT AND DELIVERED BY CAESAREAN-SECTIONING ON DAY 20	N	8	8	8	7	7
CORPORA LUTEA	MEAN±S.D.	15.8 ± 1.5	16.2 ± 2.6	16.1 ± 2.4	16.1 ± 1.1	15.3 ± 1.4
IMPLANTATIONS	MEAN±S.D.	15.0 ± 1.3	15.2 ± 2.9	15.1 ± 2.8	15.4 ± 1.3	14.6 ± 1.0
LITTER SIZE	MEAN±S.D.	14.4 ± 1.9	15.1 ± 2.9	10.0 ± 5.6	0.0 ± 0.0	0.0 ± 0.0
LIVE FETUSES	N	115	121	80	0	0
	MEAN±S.D.	14.4 ± 1.9	15.1 ± 2.9	10.0 ± 5.6	0.0 ± 0.0	0.0 ± 0.0
DEAD FETUSES	N	0	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.6 ± 0.7	0.1 ± 0.4	5.1 ± 4.4	15.4 ± 1.3	14.6 ± 1.0
EARLY RESORPTIONS	N	4	1	29	108	102
	MEAN±S.D.	0.5 ± 0.8	0.1 ± 0.4	3.6 ± 5.1	15.4 ± 1.3	14.6 ± 1.0
LATE RESORPTIONS	N	1	0	12	0	0
	MEAN±S.D.	0.1 ± 0.4	0.0 ± 0.0	1.5 ± 1.7	0.0 ± 0.0	0.0 ± 0.0
DAMS WITH ANY RESORPTIONS	N(%)	4(50.0)	1(12.5)	8(100.0)	7(100.0)	7(100.0)
DAMS WITH ALL IMPLANTATIONS RESORBING	N(%)	0	0	1(12.5)	7(100.0)	7(100.0)
DAMS WITH VIABLE FETUSES	N(%)	8(100.0)	8(100.0)	7(87.5)	0	0

PROTOCOL 305-003P: DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 111 ADMINISTERED ORALLY TO PRESUMED PREGNANT RATS - PILOT

TABLE 7 (PAGE 1): FETAL LITTER DATA - SUMMARY

	DOSE GROUP	0 MG/KG/DAY	5 MG/KG/DAY	25 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY
LITTERS EXAMINED DAY 20	N	8	8	7	0	0
IMPLANTATIONS	MEAN+S.D.	15.0 ± 1.3	15.2 ± 2.9	15.3 ± 3.0	-	-
LIVE FETUSES	MEAN+S.D.	14.4 ± 1.9	15.1 ± 2.9	11.4 ± 4.2	-	-
LITTERS WITH ONE OR MORE LIVE FETUSES	N	8	8	7	0	0
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN+S.D.	3.46 ± 0.30	3.60 ± 0.17	1.86 ± 0.20		-
MALE FETUSES	MEAN+S.D.	3.55 ± 0.31	3.70 ± 0.15	1.88 ± 0.18	-	-
FEMALE FETUSES	MEAN+S.D.	3.38 ± 0.31	3.51 ± 0.24	1.87 ± 0.22		-
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN+S.D.	4.5 ± 5.6	0.8 ± 2.2	26.8 ± 21.3		-
LIVE FETUSES	N	115	121	80	0	0
MALE FETUSES	N	70	56	36	0	0
% LIVE MALE FETUSES/LITTER	MEAN+S.D.	59.7 ± 18.1	47.6 ± 14.6	47.2 ± 16.9	-	-

NOTE: - Animals with all implants resorbing excluded from this table.

PROTOCOL 305-003P: DOSE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 111 ADMINISTERED ORALLY TO PRESUMED PREGNANT RATS - PILOT

TABLE B (PAGE 1): EXTERNAL FETAL OBSERVATIONS — SUMMARY

	DOSE GROUP	0 MG/KG/DAY	5 MG/KG/DAY	25 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY
LITTERS EVALUATED	N	8	8	7	0	0
FETUSES EVALUATED	N	115	121	80	0	0
LIVE	N	115	121	80	0	0
DEAD	N	0	0	0	0	0

APPENDIX D

STUDY DIRECTOR'S STATEMENT

ARGUS RESEARCH LABORATORIES, INC.

935 Horsham Road
Horsham, Pennsylvania 19044
(215) 443-8710

APPENDIX D

Protocol 305-001: Embryo/Fetal Toxicity and Teratogenic Potential Study of SAYTEX®111 Administered Orally via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats.

STATEMENT OF THE STUDY DIRECTOR

This final report accurately reflects the raw data obtained during the performance of the study. No significant deviations from the EPA "Toxic Substances Control; Good Laboratory Practice Standards; Final Rule"[2] which affected the quality or integrity of the study occurred.

Elizabeth A. Lochry 4/15/85

Elizabeth A. Lochry, Ph.D. Date
Group Leader, Reproductive Toxicology
Study Director

APPENDIX E

QUALITY ASSURANCE STATEMENT

ARGUS RESEARCH LABORATORIES, INC.

935 Horsham Road
Horsham, Pennsylvania 19044
(215) 443-8710

April 15, 1985

QUALITY ASSURANCE UNIT FINAL REPORT STATEMENT

Study Director: Elizabeth A Lochry, Ph.D.

Director of Research: Mildred S. Christian, Ph.D., ATS

Argus Project 305-001: Embryo/Fetal Toxicity and Teratogenic Potential Study of SAYTEX®111 Administered Orally via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats.

The protocol for the above listed study was audited for adherence to EPA "Toxic Substances Control; Good Laboratory Practice Standards; Final Rule,"(2) on January 7, 1985.

The study was also inspected four times during its conduct. The first inspection occurred on January 4, 1985 and included:

1. Observation of cohabitation procedures.
2. Observation of technician adherence to protocol and to safety requirements.
3. An audit of room records.

The results of this inspection were reported to the Study Director and to Management on January 7, 1985.

The second inspection occurred on January 11, 1984 and included:

1. Observation of test article preparation.
2. Observation of the administration of the test article to study animals.
3. Verification of study animal unique identification.

4. An audit of raw data recording procedures.
5. An audit of the balance log book.
6. An audit of room records.
7. Observation of technician adherence to protocol and safety requirements.

The results of this inspection were reported to the Study Director and to Management on January 5, 1985.

The third inspection occurred on January 22, 1985 and included:

1. Observation of the Caesarean-sectioning of study animals.
2. Observation of the gross external examination of fetuses.
3. An audit of the balance log book.
4. Observation of raw data recording procedures.

The results of this inspection were reported to the Study Director and to Management on January 24, 1985.

The fourth inspection occurred on January 29, 1985 and included:

An audit of the following raw data records:

a. Test article receipt preparation and use.
b. Randomization.
c. Cohabitation.
d. Body weight.
e. In-life transaction.
f. Animal receipt.
g. General comments.
h. Necropsy.
i. Protocol.
j. Packing list.
k. Acclimation.
l. Caesarean-sectioning.
m. Edit request.

The results of this inspection were reported to the Study Director and to Management on February 1, 1985.

The final report and raw data for this study were compared and audited for accuracy, for adherence to protocol requirements and for adherence to EPA "Toxic Substances Control: Good Laboratory Practice Standards; Final Rule,"[2] between April 2, 1985 and April 15, 1985.

This study was conducted according to EPA "Toxic Substances Control: Good Laboratory Practice Standards; Final Rule"[2].

04/15/85

Jane E. Goeke, Ph.D. Date
Director of Quality Assurance

AMTEK CORP.

CERTIFICATE OF AUTHENTICITY

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