FYI-0794-000973

ARGUS RESEARCH LABORATORIES, INC.

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EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX®115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS®CD®(SD)BR PRESUMED PREGNANT RATS

(ARGUS RESEARCH PROJECT 305-002)

84940000073

DRAFT OF FINAL REPORT: APRIL 1, 1985

FYI-94-000973
INIT: 07/26/94

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CONFIDENTIAL

SUBJECT: Protocol 305-002 - Embryo/Fetal Toxicity and Teratogenic Potential Study of SAYTEX®115 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®115 via gavage at dosages of 0(Vehicle), 10, 100 or 200 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 these data, SAYTEX®115 is not a unique hazard to the conceptus. The maternal no-effect level is 10 mg/kg/day, and the embryo/fetal no-effect level is 100 mg/kg/day. Significant ($P \leq 0.01$) inhibition of maternal body weight gain occurred following administration of 100 or 200 mg/kg/day dosages of SAYTEX®115 to the dams. The higher of these two maternally toxic dosages (200 mg/kg/day) resulted in a slight reduction of average fetal body weights per litter, as compared with control values; this effect was not statistically significant ($P>0.05$). No other adverse effects on the offspring were attributed to administration of these dosages of the test substance to the dams.

Alan M. Hoberman 4/1/85 — Elizabeth A. Lochry 4/1/85

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

Elizabeth A. Lochry, Ph.D. Date
Section Head, Reproductive Toxicology
Study Director

4/1/85

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

II. DESCRIPTION OF TEST PROCEDURES

A. Methodology

1. General Experimental Design and Procedures

SAYTEX®115 was administered via gavage once daily to naturally-bred female rats on days 6 through 15 of presumed gestation. There were 25 rats assigned to a vehicle control group or to each of three groups given the test substance. Dosages of 0(Vehicle), 10, 100 or 200 mg/kg/day were given using corn oil suspensions of SAYTEX®115 prepared at concentrations of 0.0, 2.0, 20.0 and 40.0 mg/mL, respectively. A dosage volume of 5 mL/kg/day was used to administer all dosages. 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 November 26, 1984, and ended on the morning of November 30, 1984. Appropriate dosages of the test substance were administered to the female rats on days 6 through 15 of presumed gestation, which occurred on December 3 through December 15, 1984. Day-20 Caesarean-sectioning of the rats was performed on December 17 through December 20, 1984.

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/Supervisor), 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 and Martin G. McMahon (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 Stern Rohrer (Data Coordinator), Kathleen L. Fedorocsko, B.S. (Data Processor/Laboratory Associate) and Roseann 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®115 (Pentabromodiphenyl Oxide, Lot #5315-61), a brown viscous liquid, 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®115 was assumed to be 100%.

The vehicle, corn oil (Mazola Brand®, Lot # JUL 23 85a), 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®115 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 on the day after receipt weighed from 165 to 220 grams[a] each.

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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 each rat weighed from 280 to 333 grams[a] on the day after receipt. Just prior to cohabitation, the male breeder rats were 149 days of age and weighed from 452 to 670 grams each.

Following a 13-day 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 four 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 November 27 to November 30, 1984, for the 100 female rats which were assigned to the study. These female rats weighed from 217 to 276 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 did not mate were removed from the study on November 30, 1984, and were sacrificed.

2. Experimental Design and Control of Bias

Upon arrival, 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 being acclimatized for two weeks, of the total population of 150 female rats, 130 were assigned to the study, and 20 were reassigned to a pilot study (Argus Research Project 305-003P).

Following completion of the four-day cohabitation period, a second computer-generated randomization (weight-ordered) was used to assign those female rats which had mated and appeared in good health to the four dosage groups. 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	Concentration (mg/mL)	Dosage (mg/kg/days 6-15 of Presumed Gestation)	Female Rat Numbers	Number of Rats
I	0.0	0 (Corn Oil)	18,001 - 18,025	25
II	2.0	10	18,026 - 18,050	25
III	20.0	100	18,051 - 18,075	25
IV	40.0	200	18,076 - 18,100	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 four 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 Room 3. This room was independently supplied with a minimum of 12 changes per hour of 100% fresh air which had been passed through 99.97% hepa-filters. The room has approximately 166 square feet of floor space. The male breeders were placed in the study room prior to cohabitation and removed at the completion of the cohabitation period.

The temperature in the study room was maintained at 74° ± 4°F throughout the study. Humidity in the study room was recorded weekly during the study[a] and was documented to range between 42% and 50%.

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a. The weekly humidity recording was inadvertently not performed once for Room 3 (week of November 26 to December 2, 1984). This period occurred when most rats were in the early stages of gestation, prior to the initiation of the dosage period.

An automatically-controlled fluorescent light cycle was maintained at 12 hours light:12 hours dark, with each dark cycle beginning at 1900 hours EST (2000 EDT).

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 12/20/84	OCT 10 84 2B

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.

4. Route of Administration and Dosage Selection

SAYTEX®115 was administered to the rats orally via 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 a previous study (Argus Research Project, 305-002P). The results of this study are available in Appendix B. Once each day, on days 6-15 of gestation, presumed pregnant rats were administered dosages of 0(Vehicle), 10, 100 or 200 mg/kg/day, respectively. All dosages were given at a dosage volume of 5 mL/kg/day, using suspensions of SAYTEX®115 at respective concentrations of 0.0, 2.0, 20.0 or 40.0 mg/mL corn oil.

5. Test Substance Use and Preparation

Suspensions of SAYTEX®115 in corn oil were prepared once per week during the study, at volumes sufficient for seven days of use. The Sponsor evaluated SAYTEX®115 suspended in the vehicle and found it 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®115 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®115 were administered to the female rats:

Dosage Group	Dosage (mg/kg/day)	Concentration (mg/mL)	ARGUS Batch Number
I	0(Vehicle)	0.0	B-305-002-A(Month.Day.Year)
II	10	2.0	B-305-002-B(Month.Day.Year)
III	100	20.0	B-305-002-C(Month.Day.Year)
IV	200	40.0	B-305-002-D(Month.Day.Year)

Three[a] 1.0 gram samples of each SAYTEX®115 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

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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.

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®115 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®115 and a 1.0 gram sample of the corn oil (Mazola Brand®, Lot #JUL 23 85) were retained at the Test Facility on the first day that SAYTEX®115 concentrations were prepared.

At completion of the all work with SAYTEX®115, all remaining test substance was returned to the Sponsor. All discarded quantities of prepared test substance suspensions were destroyed at the Test Facility.

6. Test Substance Administration

SAYTEX®115 was administered orally via gavage to female rats on days 6 through 15 of presumed gestation[a]. 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.

Each daily dosage given to the rats was administered as closely as practical to the same time each day, between 0817 and 0955 hours EST, with all rats administered the test substance or vehicle approximately 1.25 to 3.00 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

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a. Dam #18,072 was inadvertently not given its first dosage on day 6 of presumed gestation. Data for this dam were excluded from all group averages and statistical evaluations.

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 administration period (days 6 through 15 of presumed gestation). After completion of the dosage period, the rats were also observed for clinical signs, abortion and/or natural delivery on days 16 through 20 of presumed gestation.

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 the criterion for designating a dead fetus as a late resorption. There were no dead fetuses or late resorptions in this study. Gross lesions observed in 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

II. Nonparametric[c]

A. Kruskal-Wallis

- Significant at $P \leq 0.05$ → Dunn'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

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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[5].

Maternal body weight data were analyzed on days 0 and 6 through 20 of gestation using Bartlett's test of homogeneity of variances[6] and the Analysis of Variance[7]. Because average maternal body weights were significantly different ($P \leq 0.05$ to $P \leq 0.01$) among the four dosage groups on day 16 of gestation, these same tests (rather than an analysis of covariance) were used to analyze the average maternal body weight change for days 16 to 17 through 20 of gestation. If the Analysis of Variance was significant and appropriate, i.e., it passed Bartlett's test, then Dunnett's test[8] was used to identify the statistical significance of individual groups. If the Analysis of Variance was not appropriate, the Kruskal-Wallis test[9] was used; in cases where statistical significance occurred, Dunn's method of multiple comparisons[10] was used to identify the statistical significance of individual groups.

Maternal body weight change data for days 0 to 6 and 6 through 16 of gestation were analyzed using the Analysis of Covariance[11]. This analysis was performed using day 0 as the covariate with days 6 and 20 and using day 6 as the covariate with days 7 through 16 and 20.

Count data obtained at Caesarean-sectioning were evaluated using the Kruskal-Wallis test[9]; in cases where statistical significance occurred, Dunn's method of multiple comparisons[10] 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[6] and the Analysis of Variance[7]. If the Analysis of Variance was significant and appropriate, i.e., it passed Bartlett's test, then Dunnett's test[8] was used to identify the statistical significance of

individual groups. If the Analysis of Variance was not appropriate, the Kruskal-Wallis test[9] was used; in cases where statistical significance occurred, Dunn's method of multiple comparisons[10] 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[5].

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 SAYTEX®115.

III. RESULTS

A. Mortality/Clinical Signs (Summary - Table 1; Individual Incidence - Table 10)

No rat died during the conduct of this study, and no clinical sign observed for the dams was considered to be an effect of the test substance. The only clinical observations for rats in this study occurred at incidences which were not dosage-dependent (small areas of alopecia), were not significantly different ($P>0.05$) among the four dosage groups and/or were common observations in the strain of rat (hydronephrosis).

B. Maternal Body Weight Data (Summary - Table 2; Individual Data - Table 11)

Average maternal body weight gain was significantly inhibited ($P\leq0.05$ to $P\leq0.01$) for dams given the 100 or 200 mg/kg/day dosages of SAYTEX®115, as compared with observations for the control dams. The effect was dosage-dependent and increased in severity with continued dosage. A rebound effect on maternal body weight gain occurred during the postdosage period, when middle and high dosage group dams gained significantly ($P\leq0.01$) more weight than the control dams. As a result, average body weights for the middle and high dosage group dams remained less than those for the control dams on day 20 of gestation, but the differences were no longer significant ($P>0.05$), as compared with control values.

Pregnant dams given 0(Vehicle), 10, 100 or 200 mg/kg/day dosages of SAYTEX®115 gained an average of 60.2, 57.4, 48.1** and 42.2** grams, respectively, during days 6-16 of gestation. Average body weight gain for days 6-20 of gestation was 116.8, 114.6, 109.0 and 108.4 grams, for dams in these same respective dosage groups.

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* Significantly different from vehicle control, at $P\leq0.01$.

C. Caesarean-Sectioning Data (Summary - Table 3; Individual Data - Table 12)

Administration of 10, 100 or 200 mg/kg/day dosages of SAYTEX®115 to the dams did not adversely affect pregnancy incidence, implantation or viability of the conceptuses. These parameters had similar incidences among the four dosage groups; no differences were either significant (P>0.05) or dosage-dependent.

Pregnancy occurred for all control and low dosage group rats (25 of 25/group) and for 24 of the 25 rats in each of the middle and high dosage groups. All dams in all dosage groups had one or more live conceptuses. Litter sizes averaged 14.4, 13.9, 14.5 and 15.4 live fetuses for the control, low, middle and high dosage groups, respectively. Resorptions averaged 0.5, 0.7, 0.3 and 0.3 for these same respective dosage groups. There were no dead fetuses, and all resorptions were early.

D. Litter Data (Summary - Table 4; Citation by Litter - Tables 13 and 14)

Administration of the 200 mg/kg/day dosage of SAYTEX®115 to the dams slightly decreased average fetal body weights. The effect was not significant (P>0.05), as compared with control values. In the control, low, middle and high dosage groups litters, respectively, fetal body weights averaged 3.45, 3.50, 3.43 and 3.36 grams, respectively.

Administration of these dosages of the test substance to the dams did not affect either the average percentage of dead or resorbed conceptuses/litter or the average percentage of male fetuses/litter. Values for these parameters were similar among the four dosage groups and not significantly different (P>0.05).

E. Fetal Variations (Summaries - Tables 5, 6, 7 and 8; Citation by Litter - Table 15)

Fetal variations were defined as: 1) malformations (irreversible changes) or 2) developmental changes (reversible acceleration or delay of development).

Administration of 0(Vehicle), 10, 100 or 200 mg/kg/day dosages of the test substance to the dams did not increase either the overall incidence of fetal variation or the incidence of any specific fetal variation, as compared with control incidences. The incidences of fetal variation observed did not demonstrate significant differences (P>0.05) among the four dosage groups, did not remarkably differ from historical control incidences (Appendix B) and did not present a dosage-dependent pattern.

1. Summary of Variations Observed in Fetuses (Table 5; Citation by Litter - Table 15)

Totals of 359, 347, 333[a] and 369 live day-20 Caesarean-delivered fetuses from 25, 25, 23[a] and 24 litters of dams given 0(Vehicle), 10, 100 or 200 mg/kg/day dosages of SAYTEX®115 were evaluated. All of these fetuses were examined for externally visible variations. Soft tissue examination was performed on 173, 166, 161[a] and 178 of these respective fetuses, and 186, 181, 172[a] and 191 of these same respective fetuses were examined for skeletal variations and average number of fetal ossification sites.

2. Gross External Variations Observed (Tables 6 and 15)

One control fetus (#18,018-F9) had a cleft palate. This fetus was assigned to skeletal examination, which confirmed the presence of the cleft palate and additionally revealed that the orbit of the left eye was small and the sphenoid irregularly-shaped.

One low dosage group fetus (#18,043-F9) was edematous and was assigned to skeletal examination. Additional malformations observed for this specimen consisted of hind limbs with shortened, bent fibula and tibia and a "cervical rib" present at the left side of the 7th cervical vertebra. Developmental delays were also observed for this specimen (a small hole in the sphenoid, an unossified centrum of the 1st thoracic vertebra and a bifid centrum of the 10th thoracic vertebrae).

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a. Excludes litter #18,072 which consisted of 13 live fetuses; no variations were revealed by gross external (13 fetuses), soft tissue (six fetuses) and skeletal (seven fetuses) examination of these fetuses. Dam #18,072 was inadvertently not given its first dosage on day 6 of gestation.

One high dosage group fetus (#18,088-F6) had an eye bulge (left eye) which appeared sunken. The fetus was assigned to soft tissue examination, which revealed that the left eye was malformed (microphthalmic). A small delay in kidney development (slight dilation of the pelvis of both kidneys) was its only other variation.

No other gross external variation was observed for any fetus in this study.

3. Soft Tissue Variations Observed (Tables 7 and 15)

a. Fetuses with Malformations

Three fetuses from different control litters had soft tissue malformations. One control fetus (#18,017-F8) had a diaphragmatic hernia. Another control fetus (#18,020-F12) had a malformed lung (agenesis of the right cardiac lobe) and a third control fetus (#18,024-F8) had situs inversus (heart and associated great vessels and the stomach) and small delay in development of the brain (slight dilation of the lateral ventricles).

A malformed lung (agenesis of the lower portion of the left lobe) occurred for one high dosage group fetus (#18,081-F2), and as previously described, one high dosage group fetus (#18,088-F6) had microphthalmia of one eye, initially identified at gross external examination and a small delay in kidney development. No other fetus in this study had malformations revealed by soft tissue examination.

b. Fetuses with Developmental Changes

Small reversible delays in development of the brain (slight to moderate dilation of the lateral and/or third ventricles)[13,14] occurred for two fetuses from different control litters (#18,007-F12, #18,024-F8) and two fetuses from a low dosage group litter (#18,029-F2,F7). One of these control fetuses (#18,024-F8) has been previously described as having situs inversus.

Small reversible delays in kidney development (transient apparent dilation of the renal pelvis of one or both kidneys)[14] occurred for two low dosage group fetuses from different litters (#18,027-F7, #18,029-F2), three middle dosage group fetuses, each from a different litter (#18,063-F2, #18,067-F14 and 18,075-F7) and for two high dosage group fetuses, each from a different litter (#18,078-F8, #18,088-F6). One of these low dosage group fetuses (#18,029-F2) was previously cited as having a slight delay in brain development, and one of these high dosage group fetuses (#18,088-F6) was previously described to have a sunken eye bulge (microphthalmia).

No other variation in soft tissue development was observed for the fetuses in this study.

4. Skeletal Variations Observed (Tables 8 and 15)

a. Fetuses with Malformations

One control fetus (#18,018-F9) was observed to have a cleft palate at gross external examination, as previously described. Skeletal examination of this specimen confirmed the presence of the cleft palate and revealed additional skeletal malformations (the orbit of the left eye was small, and the sphenoid was irregularly-shaped).

One low dosage group fetus (#18,043-F9), observed at gross external examination to be edematous, also had skeletal malformations and developmental delays (hind limbs with bent fibula and tibia, a "cervical rib" present at the left side of the 7th cervical vertebra, a small hole in the sphenoid, an unossified centrum of the 1st thoracic vertebra, and a bifid centrum of the 10th thoracic vertebrae).

All other variations observed at skeletal examination of the fetuses from this study were reversible delays in development[15,16].

b. Fetuses with Developmental Changes

One control fetus (#18,012-F5) had small areas (2-3 mm in diameter) of thickened rib ossification and wavy ribs. A low dosage group fetus (#18,029-F8) had a rib which was hypoplastic.

One control fetus (#18,019-F15) had an enlarged fontanelle, and no apparent ossification of the 1st sternal centrum and the pubes.

The 1st or 2nd sternal centrum was incompletely ossified or not ossified for two other control fetuses (#18,013-F7, #18,018-F11). Incomplete ossification of the 1st sternal centrum also occurred for one low dosage group fetus (#18,040-F3) and for one high dose group fetus (#18,097-F9). The high dosage group fetus (#18,097-F9) also had delayed ossification of the 12th thoracic vertebrae (bifid centrum). One high dosage group fetus (#18,093-F9) had two asymmetric sternal centra. One middle dosage group fetus (#18,053-F1) had a bifid manubrium and multiple small delays in ossification of thoracic vertebrae (unilateral, incomplete or apparent absence of ossification of the centrum).

Delayed ossification of a thoracic vertebra (a bifid centrum) occurred for one control, one low, four middle (three litters) and two high (two litters) dosage group fetuses. These incidences include low (#18,043-F9), middle (#18,053-F1) and high (#18,097-F9) dosage group fetuses which also had the developmental delays which were previously described.

Delayed ossification of the pelvis (one or both pubes not ossified) occurred for a total of three control fetuses (two litters), and for two middle dosage group fetuses (two litters). One or both pubes were incompletely ossified for a total of four fetuses from three other control litters. Two of these fetuses (#18,018-F3, F7) also had incomplete ossification of the ischia. One of these fetuses (#18,019-F15) was previously described as having delayed ossification of the skull and sternum.

No other variation was observed at skeletal examination of the fetuses from this study.

5. Fetal Ossification Site Averages (Table 9)

Evaluation of the average number of ossification sites per fetus did not reveal either significant (P>0.05) or dosage-dependent differences among litters in the four dosage groups.

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APPENDIX A

REPORT TABLES

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX®115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS®CD®(SD)BR PRESUMED PREGNANT RATS

TABLE 1 (PAGE 1): SUMMARY OF PHYSICAL SIGNS OBSERVED IN RATS (INCIDENCE OF RATS OBSERVED/DAYS OBSERVED)

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	Clinical Signs Observed	Postmortem Signs Observed
		Alopecia [03]	Hydronephrosis
I - 0(Vehicle)			
	Rats 25	6	0
	Days 375	80	-
II - 10			
	Rats 25	2**	0
	Days 375	22**	-
III - 100			
	Rats 24[a]	0**	0
	Days 360[a]	0**	-
IV - 200			
	Rats 25	1**	1
	Days 375	8**	-

[ ] = Code for observed physical sign.

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

a. Excludes dam #18,072 which was inadvertently not given its first dosage on day 6 of gestation.

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TABLE 2 (PAGE 1): SUMMARY OF MATERNAL BODY WEIGHT DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY	200 MG/KG/DAY
ANIMALS - TESTED		25	25	24a	25
PREGNANT	N(%)	25(100.0)	25(100.0)	23(95.8)a	24(96.0)
MATERNAL BODY WEIGHT					
DAY 0	MEAN±S.D.	244.4 ± 10.9	245.0 ± 10.1	244.8 ± 10.8	245.2 ± 10.8
DAY 6	MEAN±S.D.	276.3 ± 13.1	277.2 ± 11.7	277.3 ± 11.8	276.8 ± 13.8
DAY 7	MEAN±S.D.	279.3 ± 14.0	278.3 ± 11.2	278.4 ± 12.7	277.5 ± 14.6
DAY 8	MEAN±S.D.	281.8 ± 13.8	282.1 ± 12.3	281.2 ± 13.2	278.9 ± 13.6
DAY 9	MEAN±S.D.	286.7 ± 14.2	286.0 ± 11.9	285.6 ± 13.8	280.8 ± 13.2
DAY 10	MEAN±S.D.	293.6 ± 15.7	292.5 ± 10.9	290.3 ± 14.7	283.5 ± 14.1
DAY 11	MEAN±S.D.	301.4 ± 16.4	300.1 ± 12.0	295.0 ± 15.5	288.2 ± 15.0**
DAY 12	MEAN±S.D.	307.0 ± 17.6	305.4 ± 11.5	300.5 ± 16.5	291.8 ± 15.9**

This table restricted to pregnant animals.
All weight values in grams.
a. Excludes dam #18,072 which was inadvertently not given its first dosage on day 6 of gestation.
** Significantly different from vehicle control, at $P \leq 0.01$.

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TABLE 2 (PAGE 2): SUMMARY OF MATERNAL BODY WEIGHT DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY	200 MG/KG/DAY
ANIMALS - TESTED		25	25	24a	25
PREGNANT	N(%)	25(100.0)	25(100.0)	23(95.8)a	24(96.0)
MATERNAL BODY WEIGHT					
DAY 13	MEAN±S.D.	313.5 ± 18.2	311.6 ± 13.6	305.8 ± 16.1	299.9 ± 15.6**
DAY 14	MEAN±S.D.	318.5 ± 18.6	317.8 ± 14.3	311.3 ± 17.5	302.8 ± 15.6**
DAY 15	MEAN±S.D.	326.9 ± 18.3	324.8 ± 16.5	317.3 ± 17.5	309.5 ± 16.0**
DAY 16	MEAN±S.D.	336.4 ± 18.6	334.6 ± 16.7	325.5 ± 18.3*	319.0 ± 16.7**
DAY 17	MEAN±S.D.	349.1 ± 19.6	347.6 ± 18.2	339.4 ± 19.1	334.9 ± 18.1*
DAY 18	MEAN±S.D.	363.3 ± 21.1	361.8 ± 21.5	355.9 ± 20.8	353.0 ± 20.4
DAY 19	MEAN±S.D.	377.7 ± 22.2	377.4 ± 23.0	370.2 ± 22.0	369.0 ± 20.9
DAY 20	MEAN±S.D.	393.0 ± 23.2	391.8 ± 26.8	386.3 ± 24.5	385.2 ± 23.3

This table restricted to pregnant animals.
All weight values in grams.
a. Excludes dam #18,072 which was inadvertently not given its first dosage on day 6 of gestation.
* Significantly different from vehicle control, at $P \leq 0.05$.
** Significantly different from vehicle control, at $P \leq 0.01$.

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

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY	200 MG/KG/DAY
ANIMALS - TESTED		25	25	24a	25
PREGNANT	N(%)	25(100.0)	25(100.0)	23(95.8)a	24(96.0)
MATERNAL BODY WEIGHT CHANGE					
DAYS 0- 6	MEAN±S.D.	+31.9 ± 6.8	+32.2 ± 5.6	+32.6 ± 7.3	+31.7 ± 7.8
DAYS 6- 7	MEAN±S.D.	+3.0 ± 3.3	+1.1 ± 3.5	+1.0 ± 3.6	+0.7 ± 4.6
DAYS 6- 8	MEAN±S.D.	+5.5 ± 4.0	+4.9 ± 3.9	+3.9 ± 4.6	+2.1 ± 5.1**
DAYS 6- 9	MEAN±S.D.	+10.4 ± 5.5	+8.8 ± 4.5	+8.2 ± 4.9	+4.0 ± 5.1**
DAYS 6-10	MEAN±S.D.	+17.3 ± 4.7	+15.3 ± 4.9	+13.0 ± 5.5**	+6.7 ± 6.0**
DAYS 6-11	MEAN±S.D.	+25.1 ± 5.7	+22.9 ± 6.0	+17.6 ± 6.5**	+11.3 ± 8.1**
DAYS 6-12	MEAN±S.D.	+30.7 ± 7.3	+28.2 ± 6.3	+23.1 ± 7.5**	+14.9 ± 9.0**
DAYS 6-13	MEAN±S.D.	+37.2 ± 8.0	+34.4 ± 8.0	+28.4 ± 6.8**	+23.1 ± 9.3**

This table restricted to pregnant animals.
All weight values in grams.
a. Excludes dam #18,072 which was inadvertently not given its first dosage on day 6 of gestation.
** Significantly different from vehicle control, at $P \leq 0.01$ (Analysis of Covariance).

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TABLE 2 (PAGE 1): SUMMARY OF MATERNAL BODY WEIGHT DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY	200 MG/KG/DAY
ANIMALS - TESTED		25	25	24a	25
PREGNANT	N(%)	25(100.0)	25(100.0)	23(95.8)a	24(96.0)
MATERNAL BODY WEIGHT CHANGE					
DAYS 6-14	MEAN±S.D.	+42.2 ± 8.4	+40.6 ± 9.3	+33.9 ± 8.5**	+25.9 ± 9.6**
DAYS 6-15	MEAN±S.D.	+50.6 ± 8.5	+47.6 ± 10.3	+39.9 ± 9.3**	+32.7 ± 10.7**
DAYS 6-16	MEAN±S.D.	+60.2 ± 9.8	+57.4 ± 11.7	+48.1 ± 12.0**	+42.2 ± 9.9**
DAYS 16-17	MEAN±S.D.	+12.6 ± 4.1	+13.0 ± 4.1	+13.9 ± 3.4	+15.9 ± 3.9**+
DAYS 16-18	MEAN±S.D.	+26.8 ± 5.9	+27.2 ± 7.3	+30.4 ± 5.8	+33.9 ± 6.7**+
DAYS 16-19	MEAN±S.D.	+41.2 ± 8.3	+42.8 ± 9.5	+44.7 ± 7.3	+50.0 ± 7.8**+
DAYS 16-20	MEAN±S.D.	+56.6 ± 10.3	+57.2 ± 13.7	+60.9 ± 10.9	+66.2 ± 9.9**+
DAYS 6-20	MEAN±S.D.	+116.8 ± 15.8	+114.6 ± 23.4	+109.0 ± 18.8	+108.4 ± 15.8
DAYS 0-20	MEAN±S.D.	+148.6 ± 18.9	+146.8 ± 25.6	+141.6 ± 23.7	+140.1 ± 19.4

This table restricted to pregnant animals.
All weight values in grams.
a. Excludes dam #18,072 which was inadvertently not given its first dosage on day 6 of gestation.
** Significantly different from vehicle control, at $P \leq 0.01$ (Analysis of Covariance).
**+ Significantly different from vehicle control, at $P \leq 0.01$ (Analysis of Variance).

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TABLE 3 (PAGE 1): SUMMARY OF CAESAREAN-SECTIONING DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY	200 MG/KG/DAY
ANIMALS - TESTED		25	25	24a	25
PREGNANT	N(%)	25(100.0)	25(100.0)	23(95.8)a	24(96.0)
ANIMALS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20	N	25	25	23 a	24
CORPORA LUTEA	MEAN±S.D.	15.6 ± 2.0	15.7 ± 3.1	15.8 ± 2.8	16.6 ± 2.7
IMPLANTATIONS	MEAN±S.D.	14.8 ± 1.8	14.6 ± 3.1	14.8 ± 3.1	15.7 ± 3.1
LITTER SIZE	MEAN±S.D.	14.4 ± 2.2	13.9 ± 3.9	14.5 ± 3.1	15.4 ± 3.1
LIVE FETUSES	N	359	347	333	369
	MEAN±S.D.	14.4 ± 2.2	13.9 ± 3.9	14.5 ± 3.1	15.4 ± 3.1
DEAD FETUSES	N	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.5 ± 0.8	0.7 ± 1.8	0.3 ± 0.6	0.3 ± 0.6
EARLY RESORPTIONS	N	12	17	7	8
	MEAN±S.D.	0.5 ± 0.8	0.7 ± 1.8	0.3 ± 0.6	0.3 ± 0.6
LATE RESORPTIONS	N	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
DAMS WITH ANY RESORPTIONS	N(%)	8(32.0)	6(24.0)	6(26.1)	6(25.0)
DAMS WITH ALL IMPLANTATIONS RESORBING	N(%)	0	0	0	0
DAMS WITH VIABLE FETUSES	N(%)	25(100.0)	25(100.0)	23(100.0)	24(100.0)

a. Excludes dam #18,072 which was inadvertently not given its first dosage on day 6 of gestation. See Table 12 for individual

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TABLE 4 (PAGE 1): SUMMARY OF LITTER DATA

DOSAGE GROUP (Days 6-15 of Presumed Gestation)		0 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY	200 MG/KG/DAY
LITTERS EXAMINED DAY 20	N	25	25	23 a	24
IMPLANTATIONS	MEAN±S.D.	14.8 ± 1.8	14.6 ± 3.1	14.8 ± 3.1	15.7 ± 3.1
LIVE FETUSES	MEAN±S.D.	14.4 ± 2.2	13.9 ± 3.9	14.5 ± 3.1	15.4 ± 3.1
LITTERS WITH ONE OR MORE LIVE FETUSES	N	25	25	23 a	24
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.45 ± 0.28	3.50 ± 0.23	3.43 ± 0.28	3.36 ± 0.24
MALE FETUSES	MEAN±S.D.	3.54 ± 0.26	3.59 ± 0.24 [24] b	3.52 ± 0.30	3.46 ± 0.26
FEMALE FETUSES	MEAN±S.D.	3.36 ± 0.28	3.41 ± 0.24	3.36 ± 0.28	3.29 ± 0.23
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	3.5 ± 5.7	5.4 ± 15.3	2.1 ± 4.0	2.1 ± 4.3
LIVE FETUSES	N	359	347	333	369
LIVE MALE FETUSES	N	178	173	140	166
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	49.1 ± 13.0	47.2 ± 16.0	42.4 ± 9.9	44.6 ± 11.5

NOTE: - Animals with all implants resorbing excluded from this table.
[ ] = Number of values averaged
a. Excludes litter #18,072; dam was inadvertently not given its first dosage on day 6 of gestation. See Tables 13 and 14 for individual litter data.
b. Litter #18,042 had no male fetuses.

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TABLE 5 (PAGE 1): SUMMARY OF VARIATIONS OBSERVED IN FETUSES

		Dosage (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Evaluated	N	25	25	23[a]	24
Fetuses Evaluated	N	359	347	333[a]	369
Live	N	359	347	333[a]	369
Dead	N	0	0	0	0
Fetuses with any Variations Observed	N(%)	16(4.5)	6(1.7)	9(2.7)	6(1.6)
% Fetuses with any Variations/Litter	$\bar{X}$%±S.D.	4.52±6.54	2.26±7.64	2.70±4.55	1.70±3.07
Litters with Fetuses with any Variation	N(%)	11(44.0)	4(16.0)	7(30.4)	6(25.0)

a. Excludes dam #18,072 which was inadvertently not given its first dosage on day 6 of gestation. See Table 15 for individual fetal variation data.

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TABLE 6 (PAGE 1): SUMMARY OF FETAL GROSS EXTERNAL VARIATIONS

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Evaluated	N	25	25	23[a]	24
Fetuses Evaluated	N	359	347	333[a]	369
Live	N	359	347	333[a]	369
Dead	N	0	0	0	0
EYE(S):					
Left, Bulge, Sunken					
Litter Incidence	N(%)	0	0	0	1(4.2)
Fetal Incidence	N(%)	0	0	0	1(0.3)
BODY:					
Slightly Edematous					
Litter Incidence	N(%)	0	1(4.0)	0	0
Fetal Incidence	N(%)	0	1(0.3)	0	0
PALATE:					
Cleft					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.3)	0	0	0

a. Excludes litter #18,072; dam was inadvertently not given its first dosage on day 6 of gestation. See Table 15 for individual fetal variation data.

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TABLE 7 (PAGE 1): SUMMARY OF FETAL SOFT TISSUE VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Evaluated	N	25	25	23[a]	24
Fetuses Evaluated	N	173	166	161[a]	178
Live	N	173	166	161[a]	178
Dead	N	0	0	0	0
BRAIN:					
Lateral Ventricles and/or Third Ventricle, Slight to Moderate Dilation					
Litter Incidence	N(%)	2(8.0)	1(4.0)	0	0
Fetal Incidence	N(%)	2(1.2)[b]	2(1.2)[c]	0	0
EYES:					
Left, Microphthalmia					
Litter Incidence	N(%)	0	0	0	1(4.2)
Fetal Incidence	N(%)	0	0	0	1(0.6)[d]
HEART:					
Situs Inversus of Heart, Vessels and Stomach					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.6)[b]	0	0	0
LUNG(S):					
Left or Cardiac Lobe, Agenesis					
Litter Incidence	N(%)	1(4.0)	0	0	1(4.2)
Fetal Incidence	N(%)	1(0.6)	0	0	1(0.6)

1. See footnotes on last page of this table.

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TABLE 7 (PAGE 2): SUMMARY OF FETAL SOFT TISSUE VARIATIONS

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Evaluated	N	25	25	23[a]	24
Fetuses Evaluated	N	173	166	161[a]	178
Live	N	173	166	161[a]	178
Dead	N	0	0	0	0
DIAPHRAGM:					
Herniated					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.6)	0	0	0
KIDNEYS:					
Pelvis, Slight to Moderate Dilation					
Litter Incidence	N(%)	0	2(8.0)	3(13.0)	2(8.3)
Fetal Incidence	N(%)	0	2(1.2)[c]	3(1.9)	2(1.1)[d]

a. Excludes litter #18,072; dam was inadvertently not given its first dosage on day 6 of gestation. See Table 15 for individual fetal variation data.
b. Fetus #18,024-F8 had slight dilation of the lateral ventricles of the brain and situs inversus of the heart, vessels and stomach.
c. Fetus #18,029-F2 had slight dilation of the lateral and third ventricles and moderate dilation of the renal pelvis of the kidneys.
d. Fetus #18,088-F6 had microphthalmia and slight dilation of the renal pelves.

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

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Evaluated	N	25	25	23[a]	24
Fetuses Evaluated	N	186	181	172[a]	191
Live	N	186	181	172	191
Dead	N	0	0	0	0
SKULL:					
Eye(s), Left, Orbit Appears Small					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[b]	0	0	0
Palate, Cleft (confirmed)					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[b]	0	0	0
Sphenoid, Irregularly Shaped					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[b]	0	0	0
Sphenoid, Contains a Hole					
Litter Incidence	N(%)	0	1(4.0)	0	0
Fetal Incidence	N(%)	0	1(0.6)[c]	0	0
Fontanelle, Enlarged					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[d]	0	0	0

1. See footnotes on last page of this table.

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TABLE 8 (PAGE 2): SUMMARY OF FETAL SKELETAL VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Evaluated	N	25	25	23[a]	24
Fetuses Evaluated	N	186	181	172[a]	191
Live	N	186	181	172	191
Dead	N	0	0	0	0
VERTEBRAE:					
Thoracic, One or More, Centra, Bifid					
Litter Incidence	N(%)	1(4.0)	1(4.0)	3(13.0)	2(8.3)
Fetal Incidence	N(%)	1(0.5)	1(0.6)[c]	4(2.3)[e]	2(1.0)[f]
Thoracic, One or More, Centra, Not Ossified					
Litter Incidence	N(%)	0	1(4.0)	1(4.3)	0
Fetal Incidence	N(%)	0	1(0.6)[c]	1(0.6)[e]	0
Thoracic, One or More, Centra, Unilateral Ossification					
Litter Incidence	N(%)	0	0	1(4.3)	0
Fetal Incidence	N(%)	0	0	1(0.6)[e]	0

1. See footnotes on last page of this table.

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX® 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS®CD®(SD)BR PRESUMED PREGNANT RATS

TABLE 8 (PAGE 3): SUMMARY OF FETAL SKELETAL VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Evaluated	N	25	25	23[a]	24
Fetuses Evaluated	N	186	181	172[a]	191
Live	N	186	181	172	191
Dead	N	0	0	0	0
RIBS:					
Cervical Rib					
Litter Incidence	N(%)	0	1(4.0)	0	0
Fetal Incidence	N(%)	0	1(0.6)[c]	0	0
One or More, Thickened					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[g]	0	0	0
One or More, Wavy					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[g]	0	0	0
Hypoplastic					
Litter Incidence	N(%)	0	1(4.0)	0	0
Fetal Incidence	N(%)	0	1(0.6)	0	0
MANUBRIUM:					
Bifid					
Litter Incidence	N(%)	0	0	1(4.3)	0
Fetal Incidence	N(%)	0	0	1(0.6)[e]	0

1. See footnotes on last page of this table.

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX® 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS®CD®(SD)BR PRESUMED PREGNANT RATS

TABLE 8 (PAGE 4): SUMMARY OF FETAL SKELETAL VARIATIONS[1]

		Dosage Groups (mg/kg/days 6-15 of Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Evaluated	N	25	25	23[a]	24
Fetuses Evaluated	N	186	181	172[a]	191
Live	N	186	181	172	191
Dead	N	0	0	0	0
STERNEBRAE:					
Incompletely or Not Ossified					
Litter Incidence	N(%)	3(12.0)	1(4.0)	0	1(4.2)
Fetal Incidence	N(%)	3(1.6)[d]	1(0.6)	0	1(0.5)[f]
Asymmetric					
Litter Incidence	N(%)	0	0	0	1(4.2)
Fetal Incidence	N(%)	0	0	0	1(0.5)
PELVIS:					
Ischia and/or Pubes, Incompletely or Not Ossified					
Litter Incidence	N(%)	5(20.0)	0**	2(8.7)*	0**
Fetal Incidence	N(%)	7(3.8)[d]	0**	2(1.2)**	0**
REAR LIMBS:					
Fibula and Tibia, Shortened and Bent					
Litter Incidence	N(%)	0	1(4.0)	0	0
Fetal Incidence	N(%)	0	1(0.6)[c]	0	0

1. See footnotes on last page of this table.

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TABLE 8 (PAGE 5): SUMMARY OF FETAL SKELETAL VARIATIONS

FOOTNOTES

* Significantly different from vehicle control, at $P \leq 0.05$.

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

a. Excludes litter #18,072; dam was inadvertently not given its first dosage on day 6 of gestation. See Table 15 for individual fetal variation data.

b. Fetus #18,018-F9 had an eye with a small orbit, a cleft palate and an irregularly-shaped sphenoid.

c. Fetus #18,043-F9 had a sphenoid which contained a hole, a thoracic vertebra with a bifid centrum, a thoracic vertebra with an unossified centrum, a cervical rib, and shortened and bent fibula and tibia in the rear limbs.

d. Fetus #18,019-F15 had an enlarged fontanelle, an unossified sternebra and unossified pubes.

e. Fetus #18,053-F1 had a bifid manubrium and thoracic vertebral centra which were unossified, unilaterally ossified or bifid.

f. Fetus #18,097-F9 had a thoracic vertebra with a bifid centrum and an unossified sternebra.

g. Fetus #18,012-F5 had wavy and medially thickened ribs.

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TABLE 9 (PAGE 1): FETAL OSSIFICATION SITES (LIVE FETUSES - DAY 20)

		Dosage Group - (mg/kg/days 6-15 of Presumed Gestation)			
		I - 0(Vehicle)	II - 10	III - 100	IV - 200
Litters Examined	N	25	25	23[b]	24
Fetuses Examined	N	186	181	172[b]	191
Ossification Sites[a]					
Hyoid	$\bar{X}$±S.D.	0.88 ± 0.17	0.92 ± 0.13	0.93 ± 0.14	0.94 ± 0.15
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.	13.00 ± 0.00	13.00 ± 0.04	13.02 ± 0.05	13.00 ± 0.00
Lumbar (VERTEBRAE)	$\bar{X}$±S.D.	6.00 ± 0.00	6.00 ± 0.02	5.97 ± 0.06	6.00 ± 0.00
Sacral (VERTEBRAE)	$\bar{X}$±S.D.	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00
Caudal (VERTEBRAE)	$\bar{X}$±S.D.	4.74 ± 0.45	4.89 ± 0.47	4.75 ± 0.58	4.73 ± 0.58
Ribs	$\bar{X}$±S.D.	13.00 ± 0.02	13.00 ± 0.04	13.02 ± 0.05	13.00 ± 0.00
Manubrium	$\bar{X}$±S.D.	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Sternal	$\bar{X}$±S.D.	3.58 ± 0.33	3.58 ± 0.30	3.53 ± 0.33	3.57 ± 0.30
Xiphoid	$\bar{X}$±S.D.	0.97 ± 0.09	1.00 ± 0.00	0.98 ± 0.06	1.00 ± 0.00
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.	3.56 ± 0.35	3.57 ± 0.36	3.55 ± 0.33	3.51 ± 0.36
Phalanges	$\bar{X}$±S.D.	4.67 ± 0.88	4.78 ± 0.59	4.98 ± 0.86	5.14 ± 0.57
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.	3.98 ± 0.06	3.99 ± 0.06	4.00 ± 0.02	4.00 ± 0.00
Phalanges	$\bar{X}$±S.D.	4.19 ± 1.19	4.50 ± 0.65	4.37 ± 1.19	4.58 ± 0.96

a. Per fetus per litter.
b. Excludes dam #18,072 which was inadvertently not given its first dosage on day 6 of gestation.

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TABLE 10 (PAGE 1): PHYSICAL 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	
	Clinical Signs Observed	Postmortem Signs Observed
	Alopecia [03]	Hydronephrosis
18,001	-	-
18,002	-	-
18,003	-	-
18,004	6,7,8,9,10,11,12,13,14,15,16,17,18,19,20	-
18,005	-	-
18,006	-	-
18,007	6,7,8,9,10,11,12,13,14,15,16,17,18,19,20	-
18,008	-	-
18,009	-	-
18,010	-	-
18,011	-	-
18,012	7,8,9,10,11,12,13,14,15,16,17,18,19,20	-

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

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TABLE 10 (PAGE 2): PHYSICAL 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	
	Clinical Signs Observed	Postmortem Signs Observed
	Alopecia [03]	Hydronephrosis
18,013	-	-
18,014	-	-
18,015	8,9,10,11,12,13,14,15,16,17,18,19,20	-
18,016	-	-
18,017	-	-
18,018	-	-
18,019	-	-
18,020	12,13,14,15,16,17,18,19,20	-
18,021	-	-
18,022	7,8,9,10,11,12,13,14,15,16,17,18,19,20	-
18,023	-	-
18,024	-	-
18,025	-	-

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

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TABLE 10 (PAGE 3): PHYSICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: II 10 mg/kg/days 6-15 of Presumed Gestation	
	Observation/Day of Presumed Gestation	
	Clinical Signs Observed	Postmortem Signs Observed
	Alopecia [03]	Hydronephrosis
18,026	-	-
18,027	-	-
18,028	-	-
18,029	-	-
18,030	-	-
18,031	-	-
18,032	-	-
18,033	-	-
18,034	-	-
18,035	-	-
18,036	-	-
18,037	-	-

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

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TABLE 10 (PAGE 4): PHYSICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: II 10 mg/kg/days 6-15 of Presumed Gestation	
	Observation/Day of Presumed Gestation	
	Clinical Signs Observed	Postmortem Signs Observed
	Alopecia [03]	Hydronephrosis
18,038	13,14,15,16,17,18,19,20	-
18,039	-	-
18,040	-	-
18,041	-	-
18,042	-	-
18,043	-	-
18,044	-	-
18,045	-	-
18,046	7,8,9,10,11,12,13,14,15,16,17,18,19,20	-
18,047	-	-
18,048	-	-
18,049	-	-
18,050	-	-

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

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TABLE 10 (PAGE 5): PHYSICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: III 100 mg/kg/days 6-15 of Presumed Gestation	
	Observation/Day of Presumed Gestation	
	Clinical Signs Observed	Postmortem Signs Observed
	Alopecia [03]	Hydronephrosis
18,051	-	-
18,052[b]	-	-
18,053	-	-
18,054	-	-
18,055	-	-
18,056	-	-
18,057	-	-
18,058	-	-
18,059	-	-
18,060	-	-
18,061	-	-
18,062	-	-

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

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TABLE 10 (PAGE 6): PHYSICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: III 100 mg/kg/days 6-15 of Presumed Gestation	
	Observation/Day of Presumed Gestation	
	Clinical Signs Observed	Postmortem Signs Observed
	Alopecia [03]	Hydronephrosis
18,063	-	-
18,064	-	-
18,065	-	-
18,066	-	-
18,067	-	-
18,068	-	-
18,069	-	-
18,070	-	-
18,071	-	-
18,072[b]	-	-
18,073	-	-
18,074	-	-
18,075	-	-

[ ] = Code for observed physical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.
b. Data for dam #18,072 were excluded from all group averages and statistical evaluations. This dam was inadvertently not given its first dosage on day 6 of gestation.

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TABLE 10 (PAGE 7): PHYSICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: IV 200 mg/kg/days 6-15 of Presumed Gestation	
	Observation/Day of Presumed Gestation	
	Clinical Signs Observed	Postmortem Signs Observed
	Alopecia [03]	Hydronephrosis
18,076	-	-
18,077	-	-
18,078	-	-
18,079	-	-
18,080	-	-
18,081	-	-
18,082	-	-
18,083	-	-
18,084	13,14,15,16,17,18,19,20	-
18,085	-	-
18,086[b]	-	-
18,087	-	-

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

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TABLE 10 (PAGE 8): PHYSICAL SIGNS OBSERVED IN INDIVIDUAL RATS[a]

Rat Number	Dosage Group: IV 200 mg/kg/days 6-15 of Presumed Gestation	
	Observation/Day of Presumed Gestation	
	Clinical Signs Observed	Postmortem Signs Observed
	Alopecia [03]	Hydronephrosis
18,088	-	-
18,089	-	-
18,090	-	1[b]
18,091	-	-
18,092	-	-
18,093	-	-
18,094	-	-
18,095	-	-
18,096	-	-
18,097	-	-
18,098	-	-
18,099	-	-
18,100	-	-

[ ] = Code for observed physical sign.
a. Cited by exception from day 6 to day 20 of presumed gestation.
b. Dam #18,090 had marked dilation of both kidneys which were filled with clear fluid.

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TABLE 11 (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												
18001 P	233.	275.	273.	275.	280.	286.	293.	297.	298.	302.	310.	313.	327.
18002 P	254.	284.	286.	290.	299.	305.	311.	318.	326.	326.	340.	351.	363.
18003 P	245.	279.	278.	282.	283.	296.	297.	315.	323.	331.	336.	343.	357.
18004 P	229.	262.	261.	266.	268.	274.	279.	277.	291.	302.	313.	323.	332.
18005 P	246.	276.	280.	285.	287.	294.	300.	304.	308.	313.	317.	326.	339.
18006 P	240.	280.	287.	294.	303.	304.	311.	319.	329.	323.	341.	357.	362.
18007 P	263.	296.	303.	307.	314.	318.	328.	329.	336.	349.	353.	357.	365.
18008 P	251.	274.	279.	280.	285.	293.	303.	302.	308.	320.	328.	340.	352.
18009 P	256.	284.	285.	286.	282.	299.	302.	304.	312.	314.	318.	328.	334.
18010 P	245.	269.	273.	272.	276.	285.	293.	296.	306.	309.	319.	329.	333.
18011 P	238.	274.	281.	283.	290.	298.	311.	319.	325.	333.	338.	348.	365.
18012 P	240.	266.	269.	271.	277.	287.	295.	299.	304.	310.	315.	329.	339.
18013 P	246.	270.	272.	273.	281.	284.	293.	296.	297.	304.	314.	324.	340.
18014 P	236.	273.	274.	277.	284.	287.	300.	310.	315.	315.	327.	338.	355.
18015 P	256.	299.	304.	298.	305.	314.	322.	334.	339.	347.	359.	370.	384.
18016 P	238.	274.	280.	278.	285.	290.	301.	304.	317.	323.	329.	341.	353.
18017 P	249.	283.	284.	288.	292.	298.	307.	313.	318.	325.	334.	341.	353.
18018 P	249.	284.	293.	299.	301.	315.	319.	327.	329.	336.	345.	354.	372.
18019 P	234.	255.	255.	256.	262.	265.	271.	273.	275.	279.	290.	299.	308.
18020 P	250.	280.	285.	287.	286.	298.	304.	307.	314.	317.	325.	328.	345.
18021 P	242.	273.	276.	278.	282.	290.	292.	308.	311.	315.	324.	330.	349.
18022 P	269.	298.	295.	300.	304.	316.	328.	332.	340.	341.	346.	359.	377.
18023 P	243.	290.	297.	295.	307.	308.	320.	327.	338.	343.	350.	357.	372.
18024 P	241.	270.	269.	279.	280.	285.	296.	299.	308.	312.	319.	334.	346.
18025 P	217.	239.	244.	246.	255.	251.	259.	266.	270.	273.	282.	292.	305.

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

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 2): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 18	19	20
DAM #	DOSAGE GROUP I	VEHICLE CONTROL	0 MG/KG/DAYS 6-15 OF PRESUMED GESTATION
18001 P	330.	347.	361.
18002 P	375.	393.	414.
18003 P	365.	378.	392.
18004 P	348.	352.	376.
18005 P	347.	361.	371.
18006 P	387.	401.	405.
18007 P	377.	390.	400.
18008 P	367.	378.	390.
18009 P	350.	359.	372.
18010 P	346.	364.	375.
18011 P	373.	391.	408.
18012 P	349.	366.	379.
18013 P	358.	379.	397.
18014 P	368.	391.	408.
18015 P	398.	411.	428.
18016 P	373.	390.	406.
18017 P	369.	370.	387.
18018 P	387.	405.	424.
18019 P	324.	341.	354.
18020 P	358.	371.	390.
18021 P	370.	387.	407.
18022 P	394.	414.	431.
18023 P	391.	401.	419.
18024 P	361.	375.	392.
18025 P	317.	327.	340.

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

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (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				10 MG/KG/DAYS 6-15 OF PRESUMED GESTATION								
18026 P	258.	303.	300.	306.	310.	319.	325.	331.	347.	347.	364.	369.	382.
18027 P	234.	269.	267.	270.	277.	281.	293.	298.	307.	312.	321.	335.	349.
18028 P	244.	269.	272.	277.	282.	286.	295.	298.	306.	315.	318.	331.	343.
18029 P	250.	288.	289.	298.	304.	306.	320.	324.	332.	342.	349.	359.	373.
18030 P	238.	278.	273.	280.	284.	291.	298.	302.	311.	317.	329.	338.	349.
18031 P	235.	268.	268.	270.	275.	281.	284.	288.	295.	300.	304.	313.	331.
18032 P	240.	280.	281.	290.	293.	301.	306.	307.	316.	326.	330.	344.	355.
18033 P	254.	280.	286.	290.	292.	295.	307.	311.	319.	327.	333.	348.	360.
18034 P	242.	282.	281.	288.	294.	300.	306.	312.	320.	328.	338.	344.	357.
18035 P	241.	266.	268.	270.	269.	277.	284.	285.	288.	286.	292.	298.	301.
18036 P	237.	270.	270.	270.	276.	284.	290.	300.	301.	309.	316.	325.	338.
18037 P	247.	276.	278.	284.	288.	295.	305.	307.	314.	317.	328.	333.	344.
18038 P	245.	274.	275.	278.	288.	290.	305.	306.	314.	326.	328.	343.	358.
18039 P	239.	267.	263.	264.	269.	279.	279.	292.	293.	301.	308.	318.	334.
18040 P	243.	281.	282.	292.	292.	297.	310.	315.	322.	329.	337.	351.	367.
18041 P	241.	267.	271.	278.	276.	288.	297.	301.	312.	317.	326.	334.	350.
18042 P	246.	281.	279.	279.	284.	289.	294.	301.	298.	306.	308.	313.	318.
18043 P	247.	279.	276.	282.	288.	294.	300.	305.	313.	320.	325.	337.	344.
18044 P	272.	304.	307.	307.	312.	316.	324.	327.	332.	341.	354.	362.	380.
18045 P	260.	290.	288.	295.	297.	302.	309.	320.	327.	331.	338.	348.	361.
18046 P	251.	285.	290.	290.	292.	300.	302.	310.	310.	315.	326.	332.	346.
18047 P	250.	275.	279.	281.	283.	291.	298.	301.	308.	312.	311.	323.	338.
18048 P	224.	256.	259.	263.	269.	283.	287.	301.	301.	308.	311.	324.	345.
18049 P	232.	258.	269.	264.	274.	281.	287.	293.	299.	306.	314.	324.	332.
18050 P	254.	284.	286.	286.	282.	287.	297.	300.	304.	306.	311.	319.	336.

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

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 4): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 18	19	20
DAM #	DOSAGE GROUP II	LOW DOSE	10 MG/KG/DAYS 6-15 OF PRESUMED GESTATION
18026 P	402.	417.	437.
18027 P	363.	381.	404.
18028 P	356.	372.	388.
18029 P	384.	400.	409.
18030 P	365.	377.	396.
18031 P	342.	362.	383.
18032 P	373.	390.	408.
18033 P	373.	393.	411.
18034 P	371.	388.	407.
18035 P	302.	309.	314.
18036 P	355.	373.	389.
18037 P	359.	374.	384.
18038 P	372.	390.	409.
18039 P	346.	367.	380.
18040 P	387.	402.	419.
18041 P	370.	385.	404.
18042 P	324.	334.	338.
18043 P	359.	374.	386.
18044 P	398.	417.	435.
18045 P	377.	390.	402.
18046 P	360.	371.	384.
18047 P	346.	359.	368.
18048 P	362.	374.	394.
18049 P	350.	368.	377.
18050 P	350.	368.	369.

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

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (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				100 MG/KG/DAYS 6-15 OF PRESUMED GESTATION								
18051 P	265.	297.	301.	302.	309.	315.	322.	323.	330.	339.	342.	348.	362.
18052 NP	248.	274.	281.	284.	286.	287.	287.	288.	295.	299.	294.	289.	290.
18053 P	242.	266.	266.	263.	271.	273.	281.	288.	296.	301.	308.	324.	331.
18054 P	234.	280.	277.	279.	282.	291.	298.	304.	313.	319.	329.	340.	354.
18055 P	231.	272.	276.	271.	281.	286.	297.	303.	300.	307.	318.	332.	344.
18056 P	241.	277.	272.	279.	280.	284.	293.	303.	307.	308.	315.	312.	334.
18057 P	255.	292.	298.	300.	309.	316.	318.	325.	329.	335.	336.	329.	346.
18058 P	238.	270.	275.	277.	288.	289.	289.	302.	308.	314.	322.	332.	345.
18059 P	246.	272.	275.	278.	282.	288.	288.	288.	295.	302.	306.	320.	333.
18060 P	246.	266.	264.	274.	274.	280.	281.	284.	288.	291.	298.	301.	318.
18061 P	241.	271.	280.	280.	278.	288.	294.	296.	303.	302.	310.	323.	339.
18062 P	237.	275.	276.	280.	284.	291.	296.	300.	305.	315.	318.	327.	339.
18063 P	238.	271.	265.	267.	273.	274.	283.	289.	291.	299.	303.	313.	330.
18064 P	239.	270.	271.	270.	273.	280.	284.	285.	291.	297.	299.	310.	319.
18065 P	251.	283.	280.	281.	284.	290.	295.	292.	303.	307.	315.	324.	338.
18066 P	246.	290.	293.	301.	299.	306.	318.	324.	326.	339.	350.	365.	383.
18067 P	254.	276.	278.	280.	286.	290.	283.	296.	300.	308.	316.	325.	335.
18068 P	235.	261.	264.	273.	275.	278.	287.	289.	296.	300.	307.	313.	327.
18069 P	258.	291.	293.	291.	304.	304.	308.	318.	323.	332.	336.	343.	358.
18070 P	250.	284.	285.	287.	288.	292.	297.	307.	315.	313.	320.	324.	338.
18071 P	249.	273.	274.	275.	277.	276.	277.	280.	286.	284.	288.	289.	297.
18072[a]P	[244.]	a	[276.]	[282.]	[281.]	[287.]	[295.]	[293.]	[302.]	[308.]	[318.]	[324.]	[338.]
18073 P	222.	265.	262.	273.	277.	280.	282.	284.	292.	296.	305.	313.	328.
18074 P	269.	309.	309.	318.	322.	330.	335.	344.	347.	353.	357.	366.	380.
18075 P	243.	268.	269.	269.	272.	277.	279.	287.	289.	298.	299.	313.	328.

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

[ ] = Excluded from tabulation.

a. Data for dam #18,072 were excluded from all group averages and statistical evaluations. This dam was inadvertently not given its first dosage on day 6 of gestation.

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 6): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 18	19	20
DAM #	DOSAGE GROUP III MID DOSE		100 MG/KG/DAYS 6-15 OF PRESUMED GESTATION
18051 P	380.	387.	409.
18052 NP	290.	290.	288.
18053 P	342.	356.	366.
18054 P	370.	389.	406.
18055 P	359.	372.	392.
18056 P	354.	362.	389.
18057 P	370.	386.	401.
18058 P	359.	375.	393.
18059 P	351.	369.	385.
18060 P	328.	345.	359.
18061 P	355.	374.	388.
18062 P	356.	370.	389.
18063 P	344.	359.	380.
18064 P	333.	344.	355.
18065 P	354.	369.	390.
18066 P	402.	424.	447.
18067 P	353.	372.	385.
18068 P	342.	359.	371.
18069 P	384.	396.	411.
18070 P	357.	370.	388.
18071 P	311.	318.	322.
18072[a] P	[358.]	[371.]	[392.]
18073 P	346.	359.	376.
18074 P	394.	405.	414.
18075 P	342.	354.	370.

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

[ ] = Excluded from tabulation.

a. Data for dam #18,072 were excluded from all group averages and statistical evaluations. This dam was inadvertently not given its first dosage on day 6 of gestation.

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (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				200 MG/KG/DAYS 6-15 OF PRESUMED GESTATION								
18076 P	228.	263.	268.	268.	274.	274.	289.	291.	300.	302.	311.	320.	337.
18077 P	229.	264.	255.	259.	255.	253.	251.	250.	269.	270.	286.	292.	306.
18078 P	249.	283.	289.	289.	290.	289.	300.	297.	306.	304.	319.	333.	351.
18079 P	254.	281.	286.	289.	285.	285.	292.	293.	292.	298.	299.	314.	323.
18080 P	234.	274.	270.	267.	273.	274.	273.	279.	298.	296.	309.	317.	334.
18081 P	245.	269.	270.	273.	273.	274.	281.	286.	291.	294.	301.	312.	321.
18082 P	246.	293.	290.	291.	290.	295.	301.	304.	304.	315.	316.	329.	344.
18083 P	263.	299.	296.	294.	299.	306.	308.	314.	326.	333.	336.	354.	367.
18084 P	237.	254.	255.	255.	257.	259.	256.	257.	264.	268.	264.	279.	294.
18085 P	239.	264.	267.	269.	274.	277.	284.	292.	295.	300.	307.	315.	330.
18086 NP	250.	280.	282.	280.	282.	276.	278.	277.	279.	273.	268.	260.	261.
18087 P	252.	288.	280.	279.	291.	293.	296.	305.	317.	314.	322.	330.	348.
18088 P	240.	271.	271.	274.	278.	280.	284.	290.	297.	303.	311.	315.	327.
18089 P	236.	257.	264.	267.	269.	273.	280.	280.	286.	290.	296.	304.	324.
18090 P	276.	308.	312.	314.	309.	315.	320.	317.	327.	328.	336.	344.	366.
18091 P	248.	283.	289.	284.	287.	286.	296.	296.	302.	302.	306.	316.	334.
18092 P	242.	261.	264.	268.	272.	277.	283.	285.	296.	306.	312.	316.	329.
18093 P	240.	280.	279.	279.	280.	285.	291.	301.	312.	311.	326.	333.	347.
18094 P	245.	264.	257.	265.	264.	273.	277.	279.	289.	293.	297.	304.	326.
18095 P	246.	275.	276.	278.	285.	292.	288.	294.	312.	312.	320.	328.	346.
18096 P	238.	269.	267.	274.	272.	272.	282.	284.	288.	287.	297.	300.	313.
18097 P	242.	284.	289.	283.	283.	288.	299.	296.	296.	300.	312.	318.	337.
18098 P	255.	286.	285.	288.	293.	288.	290.	294.	297.	300.	300.	312.	323.
18099 P	242.	281.	285.	291.	289.	293.	294.	306.	314.	316.	320.	334.	349.
18100 P	258.	293.	297.	296.	297.	303.	301.	312.	320.	324.	325.	338.	362.

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

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 11 (PAGE 8): BODY WEIGHT OBSERVATIONS - INDIVIDUAL RATS

PREGNANCY STATUS	DAY 18	19	20
DAM #	DOSAGE GROUP IV	HIGH DOSE	200 MG/KG/DAYS 6-15 OF PRESUMED GESTATION
18076 P	355.	372.	393.
18077 P	322.	338.	353.
18078 P	364.	387.	404.
18079 P	333.	346.	357.
18080 P	351.	375.	392.
18081 P	339.	350.	366.
18082 P	369.	379.	400.
18083 P	386.	405.	428.
18084 P	304.	327.	339.
18085 P	349.	371.	384.
18086 NP	264.	265.	271.
18087 P	367.	388.	404.
18088 P	337.	354.	368.
18089 P	337.	351.	362.
18090 P	387.	405.	426.
18091 P	352.	362.	372.
18092 P	347.	364.	380.
18093 P	370.	384.	402.
18094 P	346.	358.	372.
18095 P	369.	390.	408.
18096 P	329.	342.	360.
18097 P	364.	381.	398.
18098 P	347.	358.	375.
18099 P	367.	378.	391.
18100 P	380.	392.	412.

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

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 12 (PAGE 1): CAESAREAN-SECTIONING DATA - INDIVIDUAL ANIMALS

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																		
18001	9	4	5	8	13	0	0	0	2	0	2	0	0	0	7	8	15	7	8	15
18002	9	7	10	6	16	0	0	0	0	0	0	0	0	0	10	6	16	10	6	16
18003	5	7	4	8	12	0	0	0	1	1	2	0	0	0	5	9	14	5	9	14
18004	7	5	4	8	12	0	0	0	0	0	0	0	0	0	4	8	12	4	9	13
18005	4	7	5	6	11	0	0	0	1	1	2	0	0	0	6	7	13	7	7	14
18006	5	10	7	8	15	0	0	0	1	0	1	0	0	0	8	8	16	8	9	17
18007	3	7	2	8	10	0	0	0	2	0	2	0	0	0	4	8	12	4	8	12
18008	5	8	9	4	13	0	0	0	0	1	1	0	0	0	9	5	14	9	6	15
18009	7	6	6	7	13	0	0	0	1	0	1	0	0	0	7	7	14	8	8	16
18010	8	6	7	7	14	0	0	0	0	0	0	0	0	0	7	7	14	7	8	15
18011	5	9	8	6	14	0	0	0	0	0	0	0	0	0	8	6	14	9	7	16
18012	5	7	6	6	12	0	0	0	1	0	1	0	0	0	7	6	13	7	7	14
18013	11	4	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	7	8	15
18014	9	7	6	10	16	0	0	0	0	0	0	0	0	0	6	10	16	7	10	17
18015	7	6	4	9	13	0	0	0	0	0	0	0	0	0	4	9	13	5	9	14
18016	8	9	9	8	17	0	0	0	0	0	0	0	0	0	9	8	17	10	8	18
18017	5	9	6	8	14	0	0	0	0	0	0	0	0	0	6	8	14	6	8	14
18018	10	5	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	6	15
18019	3	12	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	8	7	15
18020	8	8	7	9	16	0	0	0	0	0	0	0	0	0	7	9	16	7	9	16
18021	10	7	10	7	17	0	0	0	0	0	0	0	0	0	10	7	17	11	8	19
18022	9	11	11	9	20	0	0	0	0	0	0	0	0	0	11	9	20	12	10	22
18023	10	7	6	11	17	0	0	0	0	0	0	0	0	0	6	11	17	6	11	17
18024	8	7	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	9	8	17
18025	8	6	6	8	14	0	0	0	0	0	0	0	0	0	6	8	14	7	8	15

M=MALE, F=FEMALE

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 12 (PAGE 2): CAESAREAN-SECTIONING DATA - INDIVIDUAL ANIMALS

DOSAGE GROUP II LOW DOSE 10 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																		
18026	9	9	10	8	18	0	0	0	0	0	0	0	0	0	10	8	18	10	8	18
18027	12	5	6	11	17	0	0	0	1	0	1	0	0	0	7	11	18	7	11	18
18028	8	7	6	9	15	0	0	0	0	0	0	0	0	0	6	9	15	6	9	15
18029	2	6	4	4	8	0	0	0	0	1	1	0	0	0	4	5	9	5	5	10
18030	6	8	7	7	14	0	0	0	0	0	0	0	0	0	7	7	14	8	7	15
18031	8	8	8	8	16	0	0	0	0	0	0	0	0	0	8	8	16	8	9	17
18032	7	9	10	6	16	0	0	0	0	0	0	0	0	0	10	6	16	11	6	17
18033	6	9	10	5	15	0	0	0	0	0	0	0	0	0	10	5	15	11	5	16
18034	9	8	10	7	17	0	0	0	0	0	0	0	0	0	10	7	17	10	7	17
18035	1	2	1	2	3	0	0	0	2	6	8	0	0	0	3	8	11	4	8	12
18036	7	7	7	7	14	0	0	0	0	0	0	0	0	0	7	7	14	8	7	15
18037	7	5	5	7	12	0	0	0	0	0	0	0	0	0	5	7	12	5	8	13
18038	8	7	12	3	15	0	0	0	0	1	1	0	0	0	12	4	16	13	4	17
18039	9	6	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	8	9	17
18040	9	10	8	11	19	0	0	0	0	0	0	0	0	0	8	11	19	9	11	20
18041	13	3	8	8	16	0	0	0	0	0	0	0	0	0	8	8	16	8	9	17
18042	0	4	2	2	4	0	0	0	0	0	0	0	0	0	2	2	4	2	3	5
18043	5	8	6	7	13	0	0	0	0	0	0	0	0	0	6	7	13	7	8	15
18044	9	8	11	6	17	0	0	0	0	0	0	0	0	0	11	6	17	11	8	19
18045	3	10	10	3	13	0	0	0	0	2	2	0	0	0	10	5	15	10	7	17
18046	8	5	7	6	13	0	0	0	0	0	0	0	0	0	7	6	13	9	7	16
18047	6	5	5	6	11	0	0	0	1	3	4	0	0	0	6	9	15	7	9	16
18048	7	8	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	8	8	16
18049	6	9	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	10	7	17
18050	8	8	8	8	16	0	0	0	0	0	0	0	0	0	8	8	16	8	9	17

M=MALE, F=FEMALE

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 12 (PAGE 3): CAESAREAN-SECTIONING DATA - INDIVIDUAL ANIMALS

DOSAGE GROUP III MID DOSE 100 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																		
18051	4	8	8	4	12	0	0	0	1	0	1	0	0	0	9	4	13	10	4	14
18052	NOT PREGNANT																			
18053	5	7	7	5	12	0	0	0	0	0	0	0	0	0	7	5	12	8	6	14
18054	9	10	7	12	19	0	0	0	0	0	0	0	0	0	7	12	19	7	12	19
18055	4	10	5	9	14	0	0	0	0	0	0	0	0	0	5	9	14	6	9	15
18056	4	11	6	9	15	0	0	0	0	0	0	0	0	0	6	9	15	6	9	15
18057	8	7	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	9	7	16
18058	7	11	6	12	18	0	0	0	1	0	1	0	0	0	7	12	19	7	12	19
18059	6	8	5	9	14	0	0	0	1	0	1	0	0	0	6	9	15	6	9	15
18060	5	7	6	6	12	0	0	0	0	0	0	0	0	0	6	6	12	6	7	13
18061	8	9	10	7	17	0	0	0	0	0	0	0	0	0	10	7	17	11	8	19
18062	7	7	8	6	14	0	0	0	1	0	1	0	0	0	9	6	15	9	7	16
18063	8	7	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	8	8	16
18064	6	5	5	6	11	0	0	0	1	1	2	0	0	0	6	7	13	8	7	15
18065	6	10	11	5	16	0	0	0	0	0	0	0	0	0	11	5	16	12	6	18
18066	8	11	9	10	19	0	0	0	0	0	0	0	0	0	9	10	19	9	11	20
18067	5	11	9	7	16	0	0	0	0	0	0	0	0	0	9	7	16	10	7	17
18068	5	10	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	6	15
18069	5	12	11	6	17	0	0	0	0	0	0	0	0	0	11	6	17	11	6	17
18070	7	7	5	9	14	0	0	0	0	0	0	0	0	0	5	9	14	6	10	16
18071	2	2	1	3	4	0	0	0	0	0	0	0	0	0	1	3	4	2	4	6
18072[a]	[7]	[6]	[10]	[3]	[13]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[10]	[3]	[13]	[11]	[4]	[15]
18073	9	6	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	8	8	16
18074	4	10	6	8	14	0	0	0	0	0	0	0	0	0	6	8	14	7	9	16
18075	8	7	4	11	15	0	0	0	1	0	1	0	0	0	5	11	16	6	11	17

M=MALE, F=FEMALE

[ ] = Excluded from tabulation.

a. Data for dam #18,072 were excluded from all group averages and statistical evaluations. This dam was inadvertently not given its first dosage on day 6 of gestation.

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 12 (PAGE 4): CAESAREAN-SECTIONING DATA - INDIVIDUAL ANIMALS

DOSAGE GROUP IV HIGH DOSE 200 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
18076	9	8	8	9	17	0	0	0	0	0	0	0	0	0	8	9	17	9	9	18
18077	3	11	8	6	14	0	0	0	0	0	0	0	0	0	8	6	14	8	6	14
18078	9	8	6	11	17	0	0	0	0	0	0	0	0	0	6	11	17	6	11	17
18079	3	3	0	6	6	0	0	0	0	0	0	0	0	0	0	6	6	2	7	9
18080	10	9	8	11	19	0	0	0	0	0	0	0	0	0	8	11	19	9	12	21
18081	7	8	7	8	15	0	0	0	0	0	0	0	0	0	7	8	15	8	8	16
18082	7	8	10	5	15	0	0	0	0	0	0	0	0	0	10	5	15	10	5	15
18083	9	8	8	9	17	0	0	0	0	0	0	0	0	0	8	9	17	9	9	18
18084	5	10	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	10	7	17
18085	9	7	10	6	16	0	0	0	0	1	1	0	0	0	10	7	17	11	7	18
18086	NOT PREGNANT																			
18087	8	11	9	10	19	0	0	0	0	0	0	0	0	0	9	10	19	9	10	19
18088	5	6	7	4	11	0	0	0	1	1	2	0	0	0	8	5	13	8	5	13
18089	5	10	9	6	15	0	0	0	0	0	0	0	0	0	9	6	15	9	6	15
18090	8	12	10	10	20	0	0	0	0	0	0	0	0	0	10	10	20	10	10	20
18091	2	10	6	6	12	0	0	0	0	0	0	0	0	0	6	6	12	6	7	13
18092	7	10	8	9	17	0	0	0	0	0	0	0	0	0	8	9	17	9	9	18
18093	8	7	8	7	15	0	0	0	0	0	0	0	0	0	8	7	15	9	8	17
18094	8	6	9	5	14	0	0	0	1	1	2	0	0	0	10	6	16	10	7	17
18095	7	11	9	9	18	0	0	0	0	1	1	0	0	0	9	10	19	10	10	20
18096	6	8	6	8	14	0	0	0	0	0	0	0	0	0	6	8	14	7	8	15
18097	9	10	7	12	19	0	0	0	0	0	0	0	0	0	7	12	19	7	12	19
18098	7	5	5	7	12	0	0	0	0	0	0	0	0	0	5	7	12	6	8	14
18099	4	10	8	6	14	0	0	0	0	1	1	0	0	0	8	7	15	8	8	16
18100	11	7	12	6	18	0	0	0	0	1	1	0	0	0	12	7	19	12	7	19

M=MALE, F=FEMALE

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 13 (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	%
18001	9	4	13	3.23	3.02	3.17	15	2	13.3
18002	9	7	16	3.67	3.48	3.59	16	0	0.0
18003	5	7	12	3.85	3.73	3.78	14	2	14.3
18004	7	5	12	3.95	3.67	3.83	12	0	0.0
18005	4	7	11	3.71	3.40	3.51	13	2	15.4
18006	5	10	15	3.35	3.12	3.20	16	1	6.2
18007	3	7	10	3.40	3.41	3.41	12	2	16.7
18008	5	8	13	3.39	3.27	3.32	14	1	7.1
18009	7	6	13	3.46	3.26	3.37	14	1	7.1
18010	8	6	14	3.34	3.34	3.34	14	0	0.0
18011	5	9	14	3.79	3.85	3.83	14	0	0.0
18012	5	7	12	3.53	3.29	3.39	13	1	7.7
18013	11	4	15	3.94	3.55	3.83	15	0	0.0
18014	9	7	16	3.64	3.64	3.64	16	0	0.0
18015	7	6	13	3.47	3.34	3.41	13	0	0.0
18016	8	9	17	3.25	3.05	3.14	17	0	0.0
18017	5	9	14	3.59	3.39	3.46	14	0	0.0
18018	10	5	15	3.47	3.35	3.43	15	0	0.0
18019	3	12	15	2.87	2.56	2.62	15	0	0.0
18020	8	8	16	3.53	3.37	3.45	16	0	0.0
18021	10	7	17	3.85	3.65	3.77	17	0	0.0
18022	9	11	20	3.85	3.68	3.76	20	0	0.0
18023	10	7	17	3.54	3.33	3.45	17	0	0.0
18024	8	7	15	3.24	3.02	3.14	15	0	0.0
18025	8	6	14	3.50	3.26	3.40	14	0	0.0

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 13 (PAGE 2): LITTER DATA - INDIVIDUAL INCIDENCE

DOSAGE GROUP II LOW DOSE 10 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	%
18026	9	9	18	3.58	3.39	3.49	18	0	0.0
18027	12	5	17	3.48	3.32	3.43	18	1	5.6
18028	8	7	15	3.49	3.29	3.40	15	0	0.0
18029	2	6	8	3.12	3.03	3.05	9	1	11.1
18030	6	8	14	3.78	3.54	3.64	14	0	0.0
18031	8	8	16	3.56	3.30	3.43	16	0	0.0
18032	7	9	16	3.58	3.41	3.48	16	0	0.0
18033	6	9	15	3.81	3.34	3.53	15	0	0.0
18034	9	8	17	3.68	3.56	3.62	17	0	0.0
18035	1	2	3	4.03	3.96	3.98	11	8	72.7
18036	7	7	14	3.74	3.61	3.67	14	0	0.0
18037	7	5	12	3.46	3.05	3.29	12	0	0.0
18038	8	7	15	4.01	3.78	3.90	16	1	6.2
18039	9	6	15	3.07	3.11	3.08	15	0	0.0
18040	9	10	19	3.32	3.21	3.26	19	0	0.0
18041	13	3	16	3.77	3.63	3.74	16	0	0.0
18042	0	4	4	-	3.73	3.73	4	0	0.0
18043	5	8	13	3.85	3.60	3.69	13	0	0.0
18044	9	8	17	3.68	3.32	3.51	17	0	0.0
18045	3	10	13	3.71	3.58	3.61	15	2	13.3
18046	8	5	13	3.71	3.54	3.64	13	0	0.0
18047	6	5	11	3.39	3.32	3.36	15	4	26.7
18048	7	8	15	3.45	3.30	3.37	15	0	0.0
18049	6	9	15	3.49	3.37	3.42	15	0	0.0
18050	8	8	16	3.36	2.97	3.17	16	0	0.0

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 13 (PAGE 3): LITTER DATA - INDIVIDUAL INCIDENCE

DOSAGE GROUP III MID DOSE 100 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	%
18051	4	8	12	3.72	3.41	3.51	13	1	7.7
18052	NOT PREGNANT								
18053	5	7	12	3.35	3.46	3.41	12	0	0.0
18054	9	10	19	3.20	3.03	3.11	19	0	0.0
18055	4	10	14	3.92	3.75	3.80	14	0	0.0
18056	4	11	15	3.59	3.47	3.50	15	0	0.0
18057	8	7	15	3.31	3.24	3.28	15	0	0.0
18058	7	11	18	3.23	3.16	3.19	19	1	5.3
18059	6	8	14	3.91	3.84	3.87	15	1	6.7
18060	5	7	12	3.06	3.16	3.12	12	0	0.0
18061	8	9	17	3.43	3.27	3.35	17	0	0.0
18062	7	7	14	4.06	3.86	3.96	15	1	6.7
18063	8	7	15	3.72	3.12	3.44	15	0	0.0
18064	6	5	11	3.40	3.29	3.35	13	2	15.4
18065	6	10	16	3.88	3.81	3.83	16	0	0.0
18066	8	11	19	3.58	3.39	3.47	19	0	0.0
18067	5	11	16	3.33	3.10	3.17	16	0	0.0
18068	5	10	15	3.47	3.10	3.22	15	0	0.0
18069	5	12	17	3.37	3.32	3.33	17	0	0.0
18070	7	7	14	3.69	3.26	3.48	14	0	0.0
18071	2	2	4	3.80	3.68	3.74	4	0	0.0
18072[a]	[7]	[6]	[13]	[3.79]	[3.74]	[3.77]	[13]	[0]	[0.0]
18073	9	6	15	3.53	3.36	3.46	15	0	0.0
18074	4	10	14	3.58	3.48	3.50	14	0	0.0
18075	8	7	15	2.83	2.73	2.79	16	1	6.2

a. Data for dam #18,072 were excluded from all group averages and statistical evaluations. This dam was inadvertently not given its first dosage on day 6 of gestation.

[ ] = Excluded from tabulation.

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 13 (PAGE 4): LITTER DATA - INDIVIDUAL INCIDENCE

DOSAGE GROUP IV HIGH DOSE 200 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	%
18076	9	8	17	3.27	3.10	3.19	17	0	0.0
18077	3	11	14	3.14	3.00	3.03	14	0	0.0
18078	9	8	17	3.50	3.29	3.40	17	0	0.0
18079	3	3	6	3.79	3.48	3.64	6	0	0.0
18080	10	9	19	3.14	2.86	3.01	19	0	0.0
18081	7	8	15	3.50	3.28	3.38	15	0	0.0
18082	7	8	15	3.57	3.50	3.53	15	0	0.0
18083	9	8	17	3.30	3.23	3.26	17	0	0.0
18084	5	10	15	3.18	3.21	3.20	15	0	0.0
18085	9	7	16	3.46	3.24	3.36	17	1	5.9
18086	NOT PREGNANT								
18087	8	11	19	3.34	3.19	3.25	19	0	0.0
18088	5	6	11	3.71	3.35	3.52	13	2	15.4
18089	5	10	15	3.48	3.26	3.33	15	0	0.0
18090	8	12	20	3.08	3.04	3.05	20	0	0.0
18091	2	10	12	3.66	3.34	3.39	12	0	0.0
18092	7	10	17	3.46	3.35	3.40	17	0	0.0
18093	8	7	15	3.71	3.50	3.61	15	0	0.0
18094	8	6	14	3.46	3.39	3.43	16	2	12.5
18095	7	11	18	3.94	3.74	3.82	19	1	5.3
18096	6	8	14	3.28	3.16	3.21	14	0	0.0
18097	9	10	19	3.58	3.30	3.43	19	0	0.0
18098	7	5	12	4.00	3.94	3.98	12	0	0.0
18099	4	10	14	3.23	3.15	3.17	15	1	6.7
18100	11	7	18	3.15	3.02	3.10	19	1	5.3

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (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
18001		MA	MA	FA	MA	E	E	FA / MA		MA	FA	MA	MA	MA	MA	FA								
	7/ 8	3.05	3.26	2.52	3.34			3.10	3.18	3.22	3.30	3.20	3.38	3.34	3.14	3.14								
18002		FA	MA	FA	FA	MA	MA	MA	MA	MA	FA / FA		MA	FA	MA	MA	FA							
	10/ 6	3.08	3.36	3.56	3.62	3.71	3.77	3.83	3.50	3.48	3.45	3.51	3.65	3.63	3.69	4.06	3.49							
18003		FA	E	MA	FA	MA / FA		MA	MA	FA	FA	FA	FA	MA	E									
	5/ 9	3.78		3.90	3.76	3.61	3.78	3.62	3.70	3.79	3.76	3.76	3.48	4.41										
18004		FA	MA	FA	MA / FA		MA	MA	FA	MA	MA	MA	FA											
	4/ 9	3.72	3.92	3.62	3.92	3.70	4.15	4.08	3.65	3.94	3.89	3.73	3.68											
18005		FA	FA	E	MA	FA	FA / MA		E	FA	FA	FA	MA	MA										
	7/ 7	3.43	3.38		3.76	3.30	3.42	3.75		3.06	3.82	3.38	3.60	3.74										
18006		FA	E	FA	MA	FA	FA	FA	FA / FA		MA	FA	MA	FA	MA	MA	FA							
	8/ 9	2.52		3.08	3.27	3.45	3.39	2.95	3.23	3.38	3.52	3.26	3.32	2.86	3.40	3.23	3.12							
18007		FA	E	E	FA / FA		FA	FA	MA	FA	FA	MA	MA											
	4/ 8	3.53			3.66	3.45	3.16	3.06	3.92	3.44	3.58	4.10	2.17											
18008		MA	FA	FA	FA	FA	FA	MA	MA	FA /	E	MA	FA	MA	FA									
	9/ 6	3.31	3.28	3.08	3.50	3.47	3.30	3.36	3.40	2.99		3.44	3.40	3.46	3.17									
18009		E	FA	MA	MA	MA	MA	FA / MA		MA	FA	FA	MA	FA	FA									
	8/ 8		3.06	3.59	3.77	3.25	3.22	3.13	3.32	3.51	3.37	3.54	3.59	3.43	3.01									
18010		MA	MA	MA	FA	FA	FA	MA / MA		MA	MA	FA	FA	MA	FA									
	7/ 8	2.26	3.45	3.48	3.58	2.93	3.37	3.58	3.13	3.67	3.56	3.35	3.42	3.63	3.42									
18011		FA	FA	MA	MA	FA	MA	MA	MA / FA		FA	FA	FA	FA	FA									
	9/ 7	3.72	3.91	3.95	3.78	3.99	3.11	4.18	3.93	3.74	3.86	3.82	3.88	3.86	3.86									
18012		FA	FA	FA	FA	MA	MA	E / MA		MA	FA	FA	FA	MA										
	7/ 7	3.12	3.26	3.07	3.52	3.64	3.43		3.32	3.53	3.25	3.29	3.50	3.71										
18013		MA	MA	FA	MA	MA	MA	FA / MA		MA	FA	MA	MA	MA	MA	FA								
	7/ 8	3.99	4.13	3.80	3.97	3.61	3.84	2.69	3.98	4.20	3.72	3.83	3.75	3.97	4.03	3.98								

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 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (PAGE 2): 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
18014		MA	FA	MA	FA	MA	FA / MA	FA	MA	FA	MA	MA	MA	FA	MA	FA								
	7/10	3.84	3.74	3.16	3.77	3.48	3.70	3.77	3.55	3.93	3.51	3.23	4.11	3.54	3.84	3.70	3.40							
18015		MA	MA	FA	FA / FA	MA	FA	MA	MA	MA	MA	FA	FA											
	5/ 9	3.50	3.59	3.66	3.41	3.28	3.58	3.17	3.40	3.42	3.36	3.42	3.17	3.34										
18016		MA	FA	FA	MA	FA	FA	MA	MA	MA / MA	MA	FA	FA	FA	FA	MA	FA							
	10/ 8	2.90	2.74	2.96	3.32	3.05	2.43	3.41	3.32	3.43	3.16	3.38	3.45	3.07	3.31	3.11	3.05	3.34						
18017		MA	FA	FA	FA	FA	MA / FA	FA	FA	MA	FA	MA	FA	MA										
	6/ 8	3.33	3.35	3.53	3.51	3.32	3.64	3.41	3.35	3.37	3.48	3.32	3.79	3.36	3.72									
18018		FA	FA	MA	MA	MA	FA	MA	MA	MA / FA	MA	MA	MA	FA	MA									
	9/ 6	3.25	3.59	3.26	3.14	3.66	3.33	3.50	3.18	3.52	3.11	3.35	3.68	3.55	3.45	3.89								
18019		MA	FA	FA	FA	FA	FA	MA	MA / FA	FA	FA	FA	FA	FA	FA									
	8/ 7	2.53	2.96	2.52	2.37	2.31	2.40	3.09	3.00	2.63	3.00	2.98	2.01	2.76	2.86	1.94								
18020		MA	FA	MA	FA	FA	MA	FA / MA	FA	MA	MA	MA	FA	FA	MA	FA								
	7/ 9	3.56	3.54	3.79	3.43	3.35	3.50	3.08	3.40	3.48	3.40	3.67	3.49	3.24	3.25	3.41	3.58							
18021		MA	FA	MA	FA	FA	FA	MA	MA	FA	MA / FA	MA	MA	MA	MA	FA	MA							
	11/ 8	3.52	3.41	3.73	3.66	3.74	3.60	3.96	3.76	3.67	3.98	3.56	3.69	3.96	3.97	3.72	3.92	4.18						
18022		FA	FA	MA	MA	MA	MA	FA	MA	FA	FA	MA / FA	FA	MA	MA	FA	FA	MA	FA	FA				
	12/10	3.43	3.77	3.61	3.86	3.75	3.89	3.75	3.94	3.56	3.70	4.05	3.76	3.48	3.79	3.87	3.70	3.72	3.89	3.79	3.84			
18023		MA	MA	MA	FA	MA	MA / FA	MA	MA	FA	FA	MA	MA	MA	FA	FA	FA							
	6/11	3.57	3.48	3.54	3.10	3.53	3.80	3.28	3.78	3.32	3.39	3.10	3.48	3.50	3.36	3.45	3.56	3.45						
18024		FA	FA	MA	MA	FA	MA	MA	MA / FA	MA	FA	FA	MA	FA	MA									
	9/ 8	2.72	2.95	3.18	3.58	2.86	3.26	2.99	2.71	3.42	3.47	3.31	2.78	3.18	3.13	3.53								
18025		FA	MA	MA	FA	MA	MA / MA	MA	FA	FA	FA	FA	MA	MA										
	7/ 8	3.07	3.52	3.43	3.48	3.57	3.44	3.69	3.83	3.34	3.11	3.47	3.10	3.30	3.19									

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 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (PAGE 3): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP II LOW DOSE 10 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
18026		MA	FA	MA	FA	FA	MA	FA	MA	FA	MA /	FA	FA	MA	FA	MA	FA	MA	MA					
	10/ 8	3.53	3.23	3.78	3.48	3.54	3.94	3.24	3.64	3.35	3.50	3.62	3.25	3.42	3.43	3.09	3.38	3.54	3.83					
18027		MA	MA	E	FA	MA	FA	MA /	MA	MA	MA	MA	MA	MA	FA	MA	FA	FA	MA					
	7/11	3.56	3.12		3.13	3.55	3.48	4.06	3.21	3.22	3.65	3.35	3.60	3.54	3.43	3.44	3.21	3.33	3.47					
18028		FA	FA	MA	MA	FA	FA /	FA	MA	MA	FA	FA	MA	MA	MA	MA								
	6/ 9	3.23	3.20	3.53	3.62	3.26	3.38	3.44	3.09	3.33	3.09	3.45	3.56	3.63	3.39	3.80								
18029		FA	FA	FA	FA /	MA	E	FA	MA	FA														
	5/ 5	2.76	3.13	3.07	3.32	3.21		2.40	3.04	3.49														
18030		MA	FA	FA	FA	FA	MA	MA /	FA	MA	FA	FA	MA	MA	FA									
	8/ 7	3.46	3.29	3.36	3.57	3.61	3.75	3.55	3.64	4.03	3.66	3.42	3.88	4.03	3.77									
18031		FA	FA	MA	MA	FA	MA	FA	FA /	FA	MA	MA	MA	MA	FA	FA	MA							
	8/ 9	3.00	3.28	3.56	3.53	3.37	3.50	3.22	3.53	3.28	3.70	3.61	3.35	3.57	3.42	3.32	3.69							
18032		MA	MA	FA	FA	MA	MA	MA	FA	FA	FA /	MA	MA	FA	FA	FA	FA							
	11/ 6	3.54	3.45	3.51	3.31	3.53	3.70	3.67	3.33	3.40	3.36	3.52	3.63	3.30	3.58	3.48	3.44							
18033		FA	FA	FA	FA	MA	FA	MA	FA	FA	FA /	MA	MA	MA	MA	FA								
	11/ 5	3.39	3.52	3.24	3.32	3.61	3.45	3.47	3.36	3.14	3.36	3.85	3.93	4.04	3.96	3.32								
18034		FA	MA	MA	MA	MA	FA	MA	FA	MA	FA /	FA	MA	MA	FA	MA	FA	FA						
	10/ 7	3.65	3.48	3.64	3.65	3.79	3.48	3.76	3.50	3.52	3.34	3.60	3.79	3.78	3.70	3.72	3.64	3.54						
18035		E	E	MA /	E	E	FA	E	E	FA	E	E												
	4/ 8			4.03			4.00			3.92														
18036		FA	FA	MA	FA	MA	FA	MA /	MA	MA	FA	FA	MA	FA	MA									
	8/ 7	3.56	3.63	3.77	3.83	3.82	3.59	3.66	3.77	3.61	3.49	3.52	3.95	3.64	3.60									
18037		FA	MA	MA	MA	FA /	FA	MA	FA	MA	MA	MA	FA											
	5/ 8	3.18	3.31	3.19	3.57	3.33	2.59	3.53	2.87	3.60	3.50	3.55	3.29											
18038		FA	MA	MA	FA	MA	MA	MA	FA	FA	MA	MA	FA /	E	FA	FA	MA							
	13/ 4	3.45	4.29	4.09	3.67	4.04	4.05	3.90	4.01	3.81	3.79	3.81	3.71		3.70	4.13	4.08							

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 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (PAGE 4): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP II LOW DOSE 10 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																							
18039	MA	MA	FA	FA	MA	MA	MA / FA		FA	MA	MA	MA	FA	MA	FA								
8/ 9	2.90	3.23	3.30	3.52	2.89	3.22	3.45	2.92	3.04	3.12	2.91	2.90	2.86	2.98	3.01								
18040	MA	MA	MA	FA	MA	FA	FA	MA / MA		FA	FA	FA	FA	MA	FA	FA	MA	FA	MA				
9/11	3.27	3.41	3.35	3.21	3.52	3.21	3.33	3.32	3.56	3.17	3.30	3.18	3.37	3.16	3.07	2.91	3.44	3.36	2.84				
18041	MA	MA	FA	MA	MA	FA	MA	MA / MA		MA	MA	MA	MA	MA	FA	MA							
8/ 9	3.73	3.80	3.75	3.66	3.56	3.53	3.87	3.70	3.61	3.83	3.82	3.72	4.05	3.96	3.61	3.71							
18042	FA	FA / FA		FA																			
2/ 3	3.75	3.56	3.86	3.74																			
18043	FA	FA	FA	MA	MA	MA / FA		MA	FA	FA	FA	MA	FA										
7/ 8	3.79	3.78	3.73	3.94	3.74	3.71	3.67	3.86	2.61	3.89	3.82	4.00	3.19										
18044	MA	MA	FA	FA	MA	FA	FA	MA	FA	MA	MA / FA		MA	MA	MA	FA	FA						
11/ 8	3.69	3.64	3.23	3.12	3.52	3.21	3.53	3.51	3.12	3.87	3.66	3.48	4.00	3.69	3.56	3.30	3.55						
18045	FA	FA	FA	FA	FA	MA	FA	FA	MA	FA /	E	MA	FA	FA	E								
10/ 7	3.40	3.70	3.64	3.43	3.59	3.78	3.62	3.56	3.72	3.56		3.62	3.45	3.89									
18046	FA	MA	MA	MA	FA	MA	MA / MA		FA	MA	MA	FA	FA										
9/ 7	3.53	3.82	3.63	3.71	3.75	3.77	3.71	3.61	3.20	3.75	3.68	3.58	3.64										
18047	FA	MA	MA	MA	FA	E /	E	FA	FA	MA	MA	E	FA	E	MA								
7/ 9	3.41	3.34	3.54	3.40	3.43			3.29	3.29	3.33	3.37		3.20		3.37								
18048	FA	MA	FA	FA	FA	MA	FA	FA / FA		MA	FA	MA	MA	MA	MA								
8/ 8	2.95	3.36	3.22	3.42	3.31	3.17	3.19	3.58	3.35	3.59	3.42	3.51	3.78	3.35	3.40								
18049	MA	FA	FA	FA	FA	FA	MA	MA / MA		MA	FA	FA	MA	FA	FA								
10/ 7	3.48	3.30	3.36	3.31	3.37	3.22	3.43	3.48	3.61	3.33	3.62	3.39	3.63	3.64	3.15								
18050	FA	MA	FA	MA	MA	MA	FA	MA / FA		MA	MA	FA	FA	FA	FA	MA							
8/ 9	2.69	3.20	3.14	3.59	2.93	3.28	3.06	3.65	3.16	3.32	3.38	2.95	3.00	2.81	2.97	3.53							

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 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CDBS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (PAGE 5): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP III MID DOSE 100 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																							
18051	FA	FA	MA	FA	MA	FA	FA	FA	E / FA		FA	MA	MA										
10/ 4	3.11	3.26	3.93	3.44	3.33	3.53	3.62	3.64		2.90	3.76	3.58	4.05										
18052	NOT PREGNANT																						
18053	MA	MA	FA	FA	FA	MA	MA / FA		FA	FA	FA	MA											
8/ 6	2.34	3.49	3.12	3.66	3.53	3.80	3.47	3.32	3.69	3.39	3.48	3.67											
18054	MA	FA	FA	FA	MA	MA	MA / MA		FA	FA	FA	MA	MA	FA	MA	FA	FA	MA	FA				
7/12	3.14	3.09	2.86	3.18	3.47	3.54	3.39	2.35	3.08	2.84	2.79	3.11	3.20	2.99	3.10	3.24	3.25	3.49	3.00				
18055	FA	FA	FA	MA	FA / MA		FA	MA	FA	FA	FA	MA	FA	FA									
6/ 9	3.85	3.54	3.69	3.71	4.01	3.87	3.68	4.09	3.89	3.62	3.73	4.02	3.47	4.03									
18056	FA	FA	FA	FA	MA	FA / MA		MA	FA	FA	FA	FA	MA	FA	FA								
6/ 9	3.30	3.59	3.48	3.43	3.28	3.63	3.53	3.87	3.53	3.33	3.49	3.24	3.69	3.58	3.53								
18057	MA	MA	FA	FA	MA	MA	MA	MA / FA		FA	FA	MA	MA	FA	FA								
9/ 7	3.20	3.31	3.11	3.20	3.39	3.30	2.84	3.60	3.36	3.02	3.32	3.43	3.43	3.25	3.45								
18058	MA	MA	E	MA	MA	FA	MA / FA		FA	FA	FA	MA	FA	FA	MA	FA	FA	FA	FA				
7/12	2.89	3.43		3.24	3.27	3.60	3.49	2.88	3.14	3.07	3.10	3.14	3.15	3.29	3.17	2.95	2.98	3.37	3.29				
18059	E	FA	FA	FA	MA	MA / MA		FA	FA	FA	FA	MA	FA	MA	MA								
6/ 9		3.97	3.74	3.77	3.81	3.91	3.93	3.85	3.94	3.76	3.97	4.09	3.68	3.84	3.87								
18060	MA	MA	FA	MA	FA	MA / FA		FA	FA	FA	FA	MA											
6/ 7	3.04	3.34	2.96	2.66	3.17	3.02	2.81	3.24	3.29	3.31	3.33	3.25											
18061	MA	MA	MA	FA	FA	MA	MA	MA	FA	FA / FA		FA	MA	MA	FA	FA	FA						
11/ 8	3.52	3.56	3.21	3.44	3.29	3.38	3.34	3.50	3.11	2.99	3.24	3.26	3.43	3.53	3.33	3.45	3.35						
18062	E	MA	MA	MA	MA	FA	FA	FA	MA / FA		MA	FA	FA	MA	FA								
9/ 7		3.93	3.58	4.13	4.16	4.07	3.76	3.98	4.11	3.55	4.02	4.01	3.82	4.53	3.81								
18063	FA	FA	FA	MA	MA	MA	MA / MA		FA	MA	FA	FA	MA	FA	MA								
8/ 8	2.88	2.11	3.08	3.70	3.97	3.45	3.58	3.79	3.23	3.70	3.58	3.58	3.63	3.41	3.93								

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 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (PAGE 6): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP III MID DOSE 100 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																							
18064	MA	MA	FA	MA	E	MA / MA		FA	FA	MA	FA	FA	E										
8/ 7	3.25	3.39	3.59	3.75		3.42	3.31	3.34	3.13	3.30	3.23	3.18											
18065	MA	MA	FA	FA	FA	FA	FA	FA	FA	MA	MA / MA		FA	MA	FA	FA							
12/ 6	3.51	3.92	3.68	3.74	3.84	3.85	3.83	4.06	3.86	3.81	4.20	3.96	3.99	3.87	3.93	3.30							
18066	MA	FA	MA	MA	FA	FA	FA	MA	MA / FA		FA	FA	MA	MA	MA	FA	FA	FA	FA				
9/11	3.23	3.53	3.43	3.57	3.46	3.33	3.39	3.81	3.76	3.57	3.07	3.57	3.79	3.54	3.49	3.54	3.21	3.18	3.47				
18067	FA	MA	MA	FA	MA	FA	FA	FA	MA / FA		FA	FA	FA	FA	MA	FA							
10/ 7	2.85	3.05	3.15	3.18	3.50	2.97	3.20	3.22	3.32	2.83	3.03	3.24	2.93	3.09	3.65	3.53							
18068	FA	MA	MA	MA	MA	FA	FA	FA	FA / MA		FA	FA	FA	FA	FA								
9/ 6	3.29	3.48	3.58	3.17	3.63	3.11	2.72	2.90	3.16	3.47	3.08	3.27	3.08	3.15	3.20								
18069	FA	FA	MA	FA	FA	FA	FA	FA	MA	MA	MA / FA		FA	MA	FA	FA	FA						
11/ 6	3.12	3.25	3.35	3.43	3.16	3.35	3.30	3.24	3.16	3.20	3.52	3.46	3.30	3.62	3.58	3.21	3.41						
18070	MA	FA	MA	FA	FA / FA		FA	MA	MA	MA	FA	MA	FA	MA									
6/10	3.74	3.43	3.90	3.16	3.31	2.71	3.08	3.89	3.49	3.48	3.57	3.84	3.56	3.50									
18071	MA / FA		MA	FA																			
2/ 4	3.60	3.85	3.99	3.50																			
18072[a]	[MA	FA	FA	MA	FA	MA	FA	FA	MA	FA / MA		MA	MA]										
[11/ 4]	[3.63	3.86	3.85	3.94	3.84	3.77	3.56	3.50	3.77	3.84	3.87	3.87	3.71]										
18073	FA	MA	FA	FA	MA	MA	MA / MA		MA	FA	MA	FA	MA	FA	MA								
8/ 8	3.48	3.80	3.34	3.24	3.69	3.46	3.77	3.38	3.43	3.12	3.38	3.50	3.32	3.48	3.58								
18074	MA	FA	FA	MA	FA	FA / FA		FA	MA	MA	FA	FA	FA	FA									
7/ 9	3.27	3.50	3.70	3.63	3.35	3.50	3.10	3.47	3.58	3.82	3.54	3.49	3.52	3.61									
18075	E	MA	MA	MA	MA / MA		FA	MA	FA	MA	FA	FA	MA	FA	FA	FA							
6/11		3.04	2.89	3.04	3.05	2.08	2.08	2.96	3.01	2.81	2.92	2.83	2.80	2.61	2.83	2.84							

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. Data for dam #18,072 were excluded from all group averages and statistical evaluations. This dam was inadvertently not given its first dosage on day 6 of gestation.

[ ] = Excluded from tabulation.

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (PAGE 7): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP IV HIGH DOSE 200 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																							
18076	MA	MA	MA	FA	FA	FA	FA	MA /	MA	FA	MA	MA	FA	MA	MA	FA	FA						
9/ 9	3.05	3.27	3.32	3.23	3.26	3.22	2.93	3.13	3.26	3.16	3.30	3.49	3.09	3.11	3.18	3.04	2.85						
18077	MA	FA	MA	FA	FA	FA	FA	FA /	FA	FA	FA	FA	MA	FA									
8/ 6	2.89	2.63	3.08	3.11	3.28	2.72	2.96	2.96	3.23	3.03	2.96	3.12	3.45	3.02									
18078	MA	FA	MA	FA	MA	FA /	MA	FA	FA	FA	FA	MA	MA	MA	MA	FA	MA						
6/11	3.38	3.19	3.60	3.62	3.44	3.45	3.09	3.44	3.31	3.08	3.25	3.63	3.63	3.32	3.64	3.00	3.74						
18079	/ FA	MA	FA	MA	FA	MA																	
2/ 7	3.30	3.65	3.71	3.90	3.44	3.82																	
18080	FA	FA	FA	FA	MA	MA	FA	MA /	FA	FA	MA	MA	MA	MA	MA	FA	FA	MA	MA				
9/12	3.00	2.75	2.82	3.16	3.47	3.03	2.91	3.28	2.61	3.02	2.91	2.99	3.16	3.18	3.00	2.74	2.76	3.03	3.33				
18081	MA	MA	MA	MA	FA	FA	FA /	MA	FA	MA	FA	FA	FA	FA	MA								
8/ 8	3.37	3.39	3.64	3.81	3.42	3.14	3.04	2.88	3.33	3.55	3.20	3.61	3.03	3.43	3.87								
18082	FA	FA	MA	FA	MA	MA	MA	FA	FA	MA /	FA	FA	MA	MA	FA								
10/ 5	3.31	3.23	3.47	3.41	3.81	2.73	3.45	3.55	3.68	3.77	3.43	3.72	3.86	3.91	3.65								
18083	FA	MA	MA	FA	MA	FA	FA	MA /	MA	MA	FA	FA	FA	FA	MA	MA	MA						
9/ 9	3.12	3.24	3.67	3.74	3.18	3.37	3.31	3.77	2.92	3.21	3.11	3.22	2.91	3.06	3.52	3.29	2.88						
18084	MA	MA	FA	FA	MA	FA	FA	FA	FA /	FA	MA	FA	MA	FA	FA								
10/ 7	3.30	3.44	3.37	3.06	2.64	3.34	3.20	3.04	2.96	3.41	3.27	2.77	3.25	3.50	3.41								
18085	MA	FA	MA	MA	MA	FA	MA	FA	FA	MA /	MA	E	MA	FA	MA	FA	FA						
11/ 7	3.58	3.28	3.51	3.39	3.51	3.32	3.45	2.97	3.23	3.21	3.26		3.60	3.34	3.61	3.24	3.34						
18086	NOT PREGNANT																						
18087	MA	FA	FA	MA	FA	FA	FA	FA	FA /	MA	MA	MA	MA	MA	MA	FA	FA	FA	FA				
9/10	3.50	2.97	3.10	3.51	3.21	3.47	3.50	3.29	3.24	3.15	3.52	2.96	3.07	3.58	3.43	2.90	3.19	3.10	3.15				
18088	FA	MA	MA	MA	MA	FA	FA	E /	E	MA	FA	FA	FA										
8/ 5	3.39	3.52	3.74	3.71	3.61	2.45	3.50			3.99	3.58	3.66	3.54										

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 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX(TM) 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:CORS(TM)CD(TM)(SD)BR PRESUMED PREGNANT RATS

TABLE 14 (PAGE 8): INDIVIDUAL FETAL SEX, STATUS AND WEIGHT DATA

DOSAGE GROUP IV HIGH DOSE 200 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
18089		FA	FA	FA	MA	FA	FA	FA	FA	FA / MA		FA	FA	MA	MA	MA								
	9/ 6	3.09	3.23	3.26	3.35	3.33	3.12	3.24	3.23	3.41	3.07	3.28	3.37	3.60	3.42	3.94								
18090		MA	FA	MA	MA	MA	MA	FA	FA	FA	MA / FA		FA	FA	MA	FA	FA	FA	FA	MA	FA			
	10/10	2.91	3.08	2.93	2.97	3.42	3.25	2.96	3.12	2.93	3.16	3.15	3.16	3.27	3.40	2.95	3.22	2.66	2.64	2.62	3.29			
18091		FA	FA	FA	FA	FA	MA / MA		FA	FA	FA	FA	FA											
	6/ 7	3.39	3.55	3.11	3.20	3.28	3.67	3.64	3.31	3.35	3.41	3.47	3.29											
18092		FA	MA	FA	MA	FA	FA	MA	FA / FA		FA	FA	MA	FA	MA	FA	MA	MA						
	9/ 9	3.26	3.32	3.36	3.52	3.19	3.41	3.55	3.27	3.27	3.37	3.62	3.48	3.63	3.60	3.11	3.25	3.52						
18093		MA	FA	FA	MA	MA	MA	MA	MA / MA		FA	FA	MA	FA	FA	FA								
	9/ 8	3.60	3.32	2.90	3.75	3.95	4.05	3.87	3.31	3.46	3.72	3.28	3.69	3.91	3.68	3.72								
18094		MA	FA	FA	E	MA	FA	FA	MA	MA	MA / MA		MA	E	MA	FA	FA							
	10/ 7	3.52	3.29	2.31		3.46	3.46	3.87	3.55	3.32	3.58	3.14	3.36		3.76	3.66	3.74							
18095		MA	FA	FA	FA	MA	FA	FA	MA	FA / MA		FA	MA	E	MA	FA	FA	MA	FA	FA				
	10/10	4.12	3.77	3.99	3.89	4.13	4.03	3.50	3.68	3.39	4.01	3.73	3.84		3.90	3.48	3.98	3.90	3.90	3.50				
18096		FA	MA	FA	MA	FA	MA / FA		MA	FA	MA	MA	FA	FA	FA									
	7/ 8	3.20	3.38	3.16	3.29	3.06	3.14	3.03	3.05	3.06	3.36	3.48	3.51	3.09	3.14									
18097		MA	MA	MA	FA	FA	FA	FA / FA		FA	MA	FA	FA	MA	MA	MA	MA	FA	MA	FA				
	7/12	3.50	3.46	3.53	3.49	3.40	3.50	3.37	2.34	3.49	3.77	3.22	3.63	3.63	3.70	3.73	3.45	2.93	3.41	3.59				
18098		MA	FA	FA	FA	MA / MA		MA	FA	MA	MA	MA	FA											
	6/ 8	3.75	3.95	4.24	3.74	4.12	3.85	4.32	3.91	3.94	3.76	4.30	3.88											
18099		FA	MA	FA	MA	FA	FA	FA	FA / E		MA	FA	FA	FA	FA	MA								
	8/ 8	3.20	3.09	3.03	3.23	3.25	3.16	3.27	2.96		3.19	3.20	2.99	3.24	3.21	3.40								
18100		MA	MA	MA	FA	MA	MA	FA	MA	FA	FA	MA	MA / E		MA	MA	FA	MA	FA	FA				
	12/ 7	2.94	2.98	3.28	3.12	3.16	3.13	2.94	3.18	3.06	2.87	2.93	3.13		3.43	3.09	2.85	3.38	3.24	3.09				

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 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 1): FETAL ANOMALY DATA - LITTER INCIDENCE

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
18,001	0	13	0	-	6	0	-	7	0	-
18,002	0	16	0	-	8	0	-	8	0	-
18,003	0	12	0	-	6	0	-	6	0	-
18,004	0	12	0	-	6	0	-	6	0	-
18,005	0	11	0	-	5	0	-	6	0	-
18,006	0	15	0	-	7	0	-	8	0	-
18,007	1(10.0)	10	0	-	5	1	Brain: Lateral ventricles, moderately dilated-F12	5	0	-
18,008	1(7.7)	13	0	-	6	0	-	7	1	Pelvis: Pubes, incompletely ossified-F1
18,009	0	13	0	-	6	0	-	7	0	-
18,010	0	14	0	-	7	0	-	7	0	-
18,011	1(7.1)	14	0	-	7	0	-	7	1	Vertebrae: Thoracic, centrum, 13th, bifid-F5
18,012	1(8.3)	12	0	-	6	0	-	6	1	Ribs: Right, 6-8, thickened, medially; 10-12, wavy-F5

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 2): FETAL ANOMALY DATA - LITTER INCIDENCE

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
18,013	1(6.7)	15	0	-	7	0	-	8	1	Sternebrae: 1st, not ossified-F7
18,014	0	16	0	-	8	0	-	8	0	-
18,015	0	13	0	-	6	0	-	7	0	-
18,016	1(5.9)	17	0	-	8	0	-	9	1	Pelvis: Pubes, not ossified-F1
18,017	2(14.3)	14	0	-	7	1	Diaphragm: Herniated-F8	7	1	Pelvis: Pubis, left, incompletely ossified-F1
18,018	4(26.7)	15	1	Palate: Cleft-F9	7	0	-	8	4	Skull: Eye(s), left, orbit appears small-F9; Palate, cleft-F9; Sphenoid, irregularly shaped-F9 Sternebrae: 2nd, incompletely ossified-F11 Pelvis: Ischia and pubes, incompletely ossified-F3,F7
18,019	2(13.3)	15	0	-	7	0	-	8	2	Skull: Fontanelle, enlarged-F15 Sternebrae: 1st, not ossified-F15 Pelvis: Pubes, not ossified-F5,F15

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 3): FETAL ANOMALY DATA - LITTER INCIDENCE

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
18,020	1(6.2)	16	0	-	8	1	Lungs: Right cardiac lobe, agenesis-F12	8	0	-
18,021	0	17	0	-	8	0	-	9	0	-
18,022	0	20	0	-	10	0	-	10	0	-
18,023	0	17	0	-	8	0	-	9	0	-
18,024	1(6.7)	15	0	-	7	1	Brain: Lateral ventricles, slightly dilated-F8 Heart: Situs inversus-heart, vessels and stomach-F8	8	0	-
18,025	0	14	0	-	7	0	-	7	0	-

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 4): FETAL ANOMALY DATA - LITTER INCIDENCE

Dosage Group: II 10 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
18,026	0	18	0	-	9	0	-	9	0	-
18,027	1(5.9)	17	0	-	8	1	Kidney(s): Right pelvis, slightly dilated-F7	9	0	-
18,028	0	15	0	-	7	0	-	8	0	-
18,029	3(37.5)	8	0	-	4	2	Brain: Lateral ventricles and third ventricle, slightly dilated-F2,F7 Kidney(s): Bilateral, pelvis, moderately dilated-F2	4	1	Ribs: Left, 13th, in two segments (hypoplastic)-F8
18,030	0	14	0	-	7	0	-	7	0	-
18,031	0	16	0	-	8	0	-	8	0	-
18,032	0	16	0	-	8	0	-	8	0	-
18,033	0	15	0	-	7	0	-	8	0	-
18,034	0	17	0	-	8	0	-	9	0	-
18,035	0	3	0	-	1	0	-	2	0	-
18,036	0	14	0	-	7	0	-	7	0	-
18,037	0	12	0	-	6	0	-	6	0	-
18,038	0	15	0	-	7	0	-	8	0	-

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 5): FETAL ANOMALY DATA - LITTER INCIDENCE

Dosage Group: II 10 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
18,039	0	15	0	-	7	0	-	8	0	-
18,040	1(5.3)	19	0	-	9	0	-	10	1	Sternebrae: 1st, incompletely ossified-F3
18,041	0	16	0	-	8	0	-	8	0	-
18,042	0	4	0	-	2	0	-	2	0	-
18,043	1(7.7)	13	1	Body: Slightly edematous-F9	6	0	-	7	1	Skull: Sphenoid, contains a hole-F9 Vertebrae: Thoracic, 10th, centrum, bifid-F9; Thoracic, 1st, centrum, not ossified-F9 Ribs: Left, "Cervical rib" present-F9 Rear Limbs: Bilateral, fibula and tibia, shortened and bent-F9
18,044	0	17	0	-	8	0	-	9	0	-
18,045	0	13	0	-	6	0	-	7	0	-
18,046	0	13	0	-	6	0	-	7	0	-
18,047	0	11	0	-	5	0	-	6	0	-

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 6): FETAL ANOMALY DATA - LITTER INCIDENCE

Dosage Group: II 10 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
18,048	0	15	0	-	7	0	-	8	0	-
18,049	0	15	0	-	7	0	-	8	0	-
18,050	0	16	0	-	8	0	-	8	0	-

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 7): FETAL ANOMALY DATA - LITTER INCIDENCE

Dosage Group: III 100 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
18,051	0	12	0	-	6	0	-	6	0	-
18,052	NOT PREGNANT	-	-	-	-	-	-	-	-	-
18,053	1(8.3)	12	0	-	6	0	-	6	1	Vertebrae: Thoracic, centra, 1st and 2nd, not ossified-F1; Thoracic, centra, 9th and 13th, right, unilateral ossification-F1; Thoracic, centra, 12th and 14th, left, unilateral ossification-F1; Thoracic, centra, 4th, 8th and 11th, bifid-F1 Manubrium: Bifid-F1
18,054	0	19	0	-	9	0	-	10	0	-
18,055	0	14	0	-	7	0	-	7	0	-
18,056	1(6.7)	15	0	-	7	0	-	8	1	Vertebrae: Thoracic, centrum, 11th, bifid-F9
18,057	1(6.7)	15	0	-	7	0	-	8	1	Pelvis: Pubes, not ossified-F3

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 8): FETAL ANOMALY DATA - LITTER INCIDENCE

Dosage Group: III 100 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
18,058	0	18	0	-	9	0	-	9	0	-
18,059	0	14	0	-	7	0	-	7	0	-
18,060	0.	12	0	-	6	0	-	6	0	-
18,061	0	17	0	-	8	0	-	9	0	-
18,062	0	14	0	-	7	0	-	7	0	-
18,063	1(6.7)	15	0	-	7	1	Kidney(s): Right, pelvis, slightly dilated-F2	8	0	-
18,064	0	11	0	-	5	0	-	6	0	-
18,065	0	16	0	-	8	0	-	8	0	-
18,066	0	19	0	-	9	0	-	10	0	-
18,067	1(6.2)	16	0	-	8	1	Kidney(s): Right, pelvis, slightly dilated-F14	8	0	-
18,068	0	15	0	-	7	0	-	8	0	-
18,069	0	17	0	-	8	0	-	9	0	-
18,070	2(14.3)	14	0	-	7	0	-	7	2	Vertebrae: Thoracic, centrum, 12th, bifid-F7,F9
18,071	0	4	0	-	2	0	-	2	0	-

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 9): FETAL ANOMALY DATA - LITTER INCIDENCE

Dosage Group: III 100 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
18,072[a]	0	13	0	-	6	0	-	7	0	-
18,073	0	15	0	-	7	0	-	8	0	-
18,074	0	14	0	-	7	0	-	7	0	-
18,075	2(13.3)	15	0	-	7	1	Kidney(s): Left, pelvis, slightly dilated-F7	8	1	Pelvis: Pubis, right, not ossified-F6

a. Data for dam #18,072 were excluded from all group averages and statistical evaluations. This dam was inadvertently not given its first dosage on day 6 of gestation.

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 10): FETAL ANOMALY DATA - LITTER INCIDENCE

Dosage Group: IV 200 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
18,076	0	17	0	-	8	0	-	9	0	-
18,077	1(7.1)	14	0	-	7	0	-	7	1	Vertebrae: Thoracic; centrum, 11th, bifid-F13
18,078	1(5.9)	17	0	-	8	1	Kidney(s): Right pelvis, moderately dilated-F8	9	0	-
18,079	0	6	0	-	3	0	-	3	0	-
18,080	0	19	0	-	9	0	-	10	0	-
18,081	1(6.7)	15	0	-	7	1	Lung(s): Lower portion of left lobe, agenesis-F2	8	0	-
18,082	0	15	0	-	7	0	-	8	0	-
18,083	0	17	0	-	8	0	-	9	0	-
18,084	0	15	0	-	7	0	-	8	0	-
18,085	0	16	0	-	8	0	-	8	0	-
18,086	NOT PREGNANT	-	-	-	-	-	-	-	-	-
18,087	0	19	0	-	9	0	-	10	0	-
18,088	1(9.1)	11	1	Eye(s): Left, bulge, sunken-F6	5	1	Eye(s): Left, microphthalmia-F6 Kidney(s): Bilateral pelvis, slightly dilated-F6	6	0	-

F = Fetus

PROTOCOL 305-002: EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL STUDY OF SAYTEX™ 115 ADMINISTERED ORALLY VIA GAVAGE TO Crl:COBS™CD™(SD)BR PRESUMED PREGNANT RATS

TABLE 15 (PAGE 11): FETAL ANOMALY DATA - LITTER INCIDENCE

Dosage Group: IV 200 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
18,089	0	15	0	-	7	0	-	8	0	-
18,090	0	20	0	-	10	0	-	10	0	-
18,091	0	12	0	-	6	0	-	6	0	-
18,092	0	17	0	-	8	0	-	9	0	-
18,093	1(6.7)	15	0	-	7	0	-	8	1	Sternebrae: 2nd and 3rd, asymmetric-F9
18,094	0	14	0	-	7	0	-	7	0	-
18,095	0	18	0	-	9	0	-	9	0	-
18,096	0	14	0	-	7	0	-	7	0	-
18,097	1(5.3)	19	0	-	9	0	-	10	1	Vertebrae: Thoracic, centrum, 12th, bifid-F9 Sternebrae: 1st, not ossified-F9
18,098	0	12	0	-	6	0	-	6	0	-
18,099	0	14	0	-	7	0	-	7	0	-
18,100	0	18	0	-	9	0	-	9	0	-

F = Fetus

APPENDIX B

SUMMARY OF PILOT REPORT - 305-002P

Protocol 305-002P: Dosage-Range Embryo/Fetal Toxicity and Teratogenic Potential of SAYTEX®115 Administered Orally Via Gavage to Crl:COBS®CD®(SD)BR Presumed Pregnant Rats (Pilot Study).

SAYTEX®115 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®115 at dosages of 0(Vehicle), 100, 500, 2500 or 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.

The body weights of the rats were recorded on days 0 and 6 through 20 of presumed gestation. All rats were sacrificed with carbon dioxide on day 20 of presumed gestation. 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 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, 4(50.0%), 8(100%) and 8(100%) rats died during the study. All (100%) 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.

Death produced by 500 mg/kg/day dosages of SAYTEX®115 occurred after completion of the dosage period on days 16 to 19 of gestation. These rats had been given the full complement of ten daily dosages. Deaths in the 2500 mg/kg/day dosage group occurred on days 12 to 17 of gestation, following 6 to 10 daily dosages. Death occurred on days 10 to 16 of gestation, following 4 to 10 dosages, for the 5000 mg/kg/day dosage group rats.

Three of the four 500 mg/kg/day dosage group rats which died had 13 to 16 embryos or fetuses *in utero*, all of which were normally developed for the day of gestation on which maternal death occurred; these rats had no resorptions. Autolysis precluded determination of developmental status of the 13 conceptuses present *in utero* in the remaining dam in this dosage group.

Of the eight 2500 mg/kg/day dosage group rats which died, four had 12 to 14 normally developed conceptuses present *in utero* and no resorptions. Three dams in this same dosage group resorbed all implantations. Severe autolysis precluded determination of the developmental status of the nine conceptuses present *in utero* in the remaining 2500 mg/kg/day dosage group dam.

Four of the eight rats administered the 5000 mg/kg/day dosage of SAYTEX®115 had 13 to 15 conceptuses present *in utero*, all of which were normally developed for the day of gestation on which maternal death occurred; these dams had no resorptions. The remaining four dams in this dosage group resorbed all implantations.

Agent-related postmortem signs revealed by necropsy of the rats which died included lesions of the gastrointestinal tract (stomach ulcerated, thin-walled or containing dark brown to black liquid and/or particles) and liver (enlarged and/or mottled). Other postmortem observations noted for the rats which died included lung (bright red) and kidney (unilateral or bilateral slight dilation) lesions; these signs were not considered related to SAYTEX®115 as the incidences were neither frequent nor dosage-dependent.

As compared with the vehicle, administration of the test substance produced dosage-dependent thin appearance, ungroomed coat, urine-stained abdominal fur, soft or liquid feces, red vaginal exudate, ptosis (500, 2500 and 5000 mg/kg/day), tremors, exudate from mouth (2500 and 5000 mg/kg/day), ataxia, rales and labored breathing (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 (lesion, cloudy eye, chromodacryorrhea, excess salivation, alopecia) and/or were related to the moribund condition of the one of the 500 mg/kg/day dosage group rats which died (decreased motor activity, loss of righting reflex, catalepsy).

All female rats which survived to scheduled Caesarean-sectioning on day 20 of presumed gestation appeared normal. No gross lesions were noted in these rats.

Dosage-dependent weight loss and/or inhibited body weight gain occurred throughout the dosage period for all surviving dams in the SAYTEX®115 dosage groups, as compared with control levels. Following the first dosage, weight loss occurred for all SAYTEX®115 dosage groups. Although the low dosage group (100 mg/kg/day) had gained weight by day 9 of gestation, weight gain remained until the end of the dosage period, as compared with control levels. At dosages of 500 mg/kg/day and above, weight loss persisted throughout the dosage period for surviving rats.

During the postadministration period (days 16 to 20 of gestation), agent-related rebound in weight gain occurred for the 500 mg/kg/day dosage group rats, as compared with control levels. This rebound effect was not sufficient to mask the inhibited weight gain which occurred during the dosage period. Overall weight gain during gestation (days 0 to 20) reflected the dosage-dependent pattern of inhibition which characterized the dosage period for the surviving rats in the SAYTEX®115 dosage groups.

Pregnancy occurred for 7(87.5%), 8(100%), 7(87.5%), 8(100%) and 8(100%) 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 7, 8, and 3 pregnant rats which survived to scheduled sacrifice on day 20 of gestation in the 0(Vehicle), 100 and 500 mg/kg/day dosage groups, respectively. No 2500 or 5000 mg/kg/day dosage group dams survived beyond day 17 of gestation.

As compared with the vehicle, administration of the 100 and 500 mg/kg/day dosages of SAYTEX®115 did not affect the average numbers of corpora lutea, implantations, resorptions or litter sizes. Similarly, the incidences of early resorptions, late resorptions, live fetuses, dams with resorptions and dams with viable fetuses were not affected by administration of the test substance, as compared with the vehicle. As the average number of corpora lutea was slightly decreased for dams in the 500 mg/kg/day dosage group, as compared with control

levels, the average numbers of implantations, litter size and live fetuses per litter were also slightly decreased; this decrease was possibly related to slightly impaired implantation efficiency.

Average fetal body weight per litter, percentage of dead or resorbed conceptuses per litter and percentage of male fetuses per litter were equivalent for the 0(Vehicle), 100 and 500 mg/kg/day dosage groups.

Administration of the test substance, as compared with the vehicle, did not produce fetal gross external variations. One low dosage group fetus (100 mg/kg/day) had sunken eyes. All other fetuses appeared normal at gross external observation.

CONCLUSION

Administration of the 500, 2500 and 5000 mg/kg/day dosages of SAYTEX®115 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 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. With the exception of a possible slight effect on implantation efficiency at the 500 mg/kg/day dosage, there were no adverse effects on the development of the conceptuses of dams which survived.

On the basis of these data, dosages of 0(Vehicle), 50, 100 and 250 mg/kg/day are suggested for use in the definitive embryo/fetal toxicity-teratogenic potential study of SAYTEX®115.

3/26/85 3/26/85

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Protocol 305-002P - Dosage-Range Embryo/Fetal Toxicity and Teratogenic Potential of SAYTEX\115 Administered Orally Via Gavage to Crl:COBS\CD\(SD)BR Presumed Pregnant Rats.

Table 1 (Page 1): Mortality - Female Rats

Dosage (mg/kg/day)	Rat Number	Dosages	Observations
0 (Vehicle)	-	-	-
100	-	-	-
500	18,269	10	Found dead day 16 of gestation. Uterine Contents: 14 implantation sites. 14 fetuses (normally developed). Stomach: Fundic and pyloric region, thin-walled. Liver: Enlarged and mottled. All other tissues appeared normal.
	18,270	10	Found dead day 19 of gestation. Uterine Contents: 16 implantation sites. 16 fetuses (marked autolysis). Stomach: Filled with dark brown viscous fluid. Pyloric region, several black areas (0.5 mm in diameter). All other tissues appeared normal.
	18,272	10	Found dead day 15 of gestation. Uterine Contents: 13 implantation sites. 13 fetuses (normally developed). Stomach: Fundic and pyloric region, thin-walled. Pyloric region, numerous ulcerated areas (0.2 mm to 0.5 mm in diameter). Liver: Mottled. All other tissues appeared normal.
	18,274	10	Found dead day 17 of gestation. Uterine Contents: 13 implantation sites. (autolytic state of the implantation sites precludes determination of developmental status). Stomach: Filled with dark red viscous fluid. Fundic and pyloric regions, numerous black areas (approximately 0.5 mm in diameter). Kidneys: slight dilation, bilateral. All other tissues appeared normal.

Protocol 305-002P - Dosage-Range Embryo/Fetal Toxicity and Teratogenic Potential of SAYTEX\115 Administered Orally Via Gavage to Crl:COBS\CD\(SD)BR Presumed Pregnant Rats.

Table 1 (Page 2): Mortality - Female Rats

Dosage (mg/kg/day)	Rat Number	Dosages	Observations
2500	18,275	6	Found dead day 12 of gestation. Uterine Contents: 13 implantation sites. 13 fetuses (normally developed). Stomach: Fundic region thin-walled with numerous ulcerated areas (0.2 to 0.5 cm in diameter). Liver: Mottled. All other tissues appeared normal.
	18,276	10	Found dead day 16 of gestation. Uterine Contents: 10 implantation sites. 10 resorptions. Stomach: Fundic and pyloric regions, thin-walled. Liver: Mottled. All other tissues appeared normal.
	18,277	7	Found dead day 12 of gestation. Uterine Contents: 14 implantation sites 14 fetuses (normally developed). Stomach: Fundic region, thin-walled. Fundic and pyloric region, ulcerated areas (0.2 cm to 0.5 cm in diameter). Liver: Mottled All other tissues appeared normal.
	18,278	7	Found dead day 12 of gestation. Uterine Contents: 12 implantation sites. 12 fetuses (normally developed). Stomach: Fundic and pyloric regions, thin-walled. Liver: Mottled. All other tissues appeared normal.
	18,279	9	Found dead day 15 of gestation. Uterine Contents: 12 implantation sites. 12 resorptions. Stomach: Filled with black viscous fluid. Fundic and pyloric regions, numerous ulcerated areas (0.5 to 1.0 mm in diameter). Liver: Mottled. All other tissues appeared normal.

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Table 1 (Page 3): Mortality - Female Rats

Dosage (mg/kg/day)	Rat Number	Dosages	Observations
2500 (contd)	18,280	10	Found dead day 17 of gestation. Uterine Contents: 13 implantation sites. 13 fetuses. (normally developed). Stomach: Numerous hemorrhages (up to 1.0 mm in diameter). All other tissues appeared normal.
	18,281	7	Found dead day 13 of gestation. Uterine Contents: 11 implantation sites. 11 resorptions. Stomach: Fundic region, three ulcerated areas (each 1.0 mm in diameter) Liver: Enlarged and mottled (discolored light tan to dark red). Kidneys: Left, slight dilation. All other tissues appeared normal.
	18,282	10	Found dead day 15 of gestation. Uterine Contents: 9 implantation sites. (autolytic state of the implantation sites precludes determination of developmental status). Stomach: Fundic region contains numerous hemmorrhages (1.0 mm in diameter). All other tissues appeared normal.
5000	18,283	4	Found dead day 10 of gestation. Uterine Contents: 15 implantation sites, 15 fetuses (normally developed). Stomach: Pyloric and fundic regions, thin-walled. Lungs: Bright red All other tissues appeared normal.
5000	18,284	10	Found dead day 16 of gestation. Uterine Contents: 13 implantation sites, 13 resorptions. Stomach: Fundic pyloric region, thin-walled. Pyloric region, black free floating particles. All other tissues appeared normal.

Protocol 305-002P - Dosage-Range Embryo/Fetal Toxicity and Teratogenic Potential of SAYTEX\115 Administered Orally Via Gavage to Crl:COBS\CD\(SD)BR Presumed Pregnant Rats.

Table 1 (Page 4): Mortality - Female Rats

Dosage (mg/kg/day)	Rat Number	Dosages	Observations
5000 (contd)	18,285	8	Found dead day 14 of gestation. Uterine Contents: 15 implantation sites, 15 fetuses (normally developed). Stomach: Pyloric and fundic regions, thin-walled. Liver: Mottled. All other tissues appeared normal.
	18,286	6	Found dead day 12 of gestation. Uterine Contents: 13 implantation sites, 13 fetuses (normally developed). Stomach: Pyloric and fundic regions, thin-walled with numerous ulcerated areas (0.02 to 0.5 cm in diameter) Liver: Mottled. All other tissues appeared normal.
	18,287	9	Found dead day 15 of gestation. Uterine Contents: 14 implantation sites, 14 fetuses (normally developed). Stomach: Pyloric and fundic regions, numerous ulcerated areas (0.5 to to 1.0 mm in diameter) Liver: Mottled. All other tissues appeared normal.
	18,288	9	Found dead day 15 of gestation. Uterine Contents: 13 implantation sites, 13 resorptions. Stomach: Fundic and pyloric region, thin-walled with numerous ulcerated areas (0.2 mm to 0.5 mm in diameter). Liver: Mottled. All other tissues appeared normal.
	18,289	7	Found dead day 12 of gestation. Uterine Contents: 10 implantation sites. 10 resorptions. Stomach: Fundic region, numerous ulcerated areas (1 mm to 3 mm in diameter). Liver: Enlarged, mottled and discolored (tan to dark red). All other tissues appeared normal.

Protocol 305-002P - Dosage-Range Embryo/Fetal Toxicity and Teratogenic Potential of SAYTEX\115 Administered Orally Via Gavage to Crl:COBS\CD\(SD)BR Presumed Pregnant Rats.

Table 1 (Page 5): Mortality - Female Rats

Dosage (mg/kg/day)	Rat Number	Dosages	Observations
5000 (contd)	18,290	8	Found dead day 14 of gestation. Uterine Contents: 9 implantation sites 9 resorptions. Stomach: Fundic and pyloric regions, numerous ulcerated areas (1.0 mm to 1.5 mm in diameter). Liver: Enlarged, mottled and discolored (light tan to dark red). All other tissues appeared normal.

PROTOCOL 305002P : DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 115 ADMINISTERED ORALLY VIA GAVAGE TO RATS

TABLE 2 PAGE 1 : PHYSICAL SIGN INCIDENCE -- SUMMARY

TABLE RANGE: 102984-111584

FEMALES / DOSE GROUP	1	2	3	4	5
APPEARS NORMAL					
NO SIGNIFICANT CLINICAL OBSERVATIONS	120/ 8	99/ 7	40/ 7	12/ 6	17/ 8
DEAD					
FOUND DEAD	0/ 0	0/ 0	4/ 4	8/ 8	8/ 8
SCHEDULED SACRIFICE	8/ 8	8/ 8	4/ 4	0/ 0	0/ 0
MASS / LESION					
LESION	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
DEPRESSION					
ATAXIA	0/ 0	0/ 0	1/ 1	0/ 0	1/ 1
DECREASED MOTOR ACTIVITY	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
LOSS OF RIGHTING REFLEX	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
CATALEPSY	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
EXCITATION					
TREMORS	0/ 0	0/ 0	0/ 0	10/ 6	15/ 6
EYES / NOSE					
PTOSIS	0/ 0	0/ 0	4/ 2	1/ 1	2/ 2
CLOUDY	0/ 0	0/ 0	0/ 0	2/ 2	0/ 0
CHROMODACRYORRHEA	0/ 0	0/ 0	9/ 2	1/ 1	4/ 2
MISCELLANEOUS					
RED EXUDATE	0/ 0	0/ 0	9/ 3	11/ 6	11/ 6
THIN	0/ 0	0/ 0	25/ 6	21/ 7	15/ 7
ORAL-BUCCAL					
EXUDATE	0/ 0	0/ 0	2/ 1	1/ 1	7/ 3
SALIVATION	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
RESPIRATION					
HYPERPNEA	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
LABORED BREATHING	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
RALES	0/ 0	0/ 0	0/ 0	0/ 0	2/ 1
SKIN/FUR					
ALOPECIA	0/ 0	22/ 2	33/ 3	13/ 2	0/ 0

PROTOCOL 305002P : DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 115 ADMINISTERED ORALLY VIA GAVAGE TO RATS

TABLE 2 PAGE 2 : PHYSICAL SIGN INCIDENCE -- SUMMARY

TABLE RANGE: 110784-111584

FEMALES	DOSE GROUP 1	2	3	4	5
UNGROOMED COAT	0/ 0	0/ 0	15/ 4	37/ 8	30/ 8
URINE STAINED ABDOMINAL FUR	0/ 0	0/ 0	39/ 7	40/ 8	42/ 7
STOOL/URINE					
SOFT OR LIQUID FECES	0/ 0	0/ 0	14/ 6	27/ 6	27/ 7
MAXIMUM INCIDENCE/# EXAMINED	120/ 8	120/ 8	107/ 8	72/ 8	68/ 8

PROTOCOL 305002P : DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 115 ADMINISTERED ORALLY VIA GAVAGE TO RATS

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/
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	7(87.5)	8(100.0)	7(87.5)	8(100.0)	8(100.0)
MATERNAL BODY WEIGHT						
DAY 0	MEAN±S.D.	260.8 ± 10.8	261.1 ± 16.4	262.1 ± 13.0	261.2 ± 10.3	262.4 ± 11
DAY 6	MEAN±S.D.	276.0 ± 14.2	278.5 ± 16.8	276.8 ± 15.8	280.1 ± 9.9	283.1 ± 16
DAY 7	MEAN±S.D.	278.3 ± 15.6	277.0 ± 17.3	276.7 ± 17.2	277.0 ± 8.9	279.9 ± 11
DAY 8	MEAN±S.D.	280.6 ± 14.4	278.5 ± 16.5	275.3 ± 16.1	266.2 ± 10.6	270.5 ± 14
DAY 9	MEAN±S.D.	281.8 ± 15.7	281.8 ± 18.9	272.0 ± 18.0	263.8 ± 12.6	260.6 ± 17
DAY 10	MEAN±S.D.	286.1 ± 15.1	285.6 ± 18.2	270.0 ± 19.2	251.2 ± 17.0	252.8 ± 13 [7]
DAY 11	MEAN±S.D.	292.7 ± 15.1	290.1 ± 17.0	266.8 ± 22.6	237.0 ± 16.9	239.4 ± 13 [7]
DAY 12	MEAN±S.D.	298.4 ± 15.2	293.2 ± 21.1	262.1 ± 23.9	229.0 ± 19.2 [6]	223.8 ± 14 [6]
DAY 13	MEAN±S.D.	303.1 ± 13.9	299.2 ± 20.4	255.7 ± 26.8	224.2 ± 20.5 [4]	212.8 ± 6 [5]
DAY 14	MEAN±S.D.	310.1 ± 15.6	304.8 ± 18.3	246.4 ± 30.2	210.8 ± 20.6 [4]	200.7 ± 9 [3]
DAY 15	MEAN±S.D.	317.6 ± 14.6	309.4 ± 18.8	238.6 ± 34.0	206.0 ± 21.2 [2]	189.0 ± 0 [1]
DAY 16	MEAN±S.D.	328.6 ± 14.4	323.1 ± 16.8	238.3 ± 36.3 [6]	208.0 ± 0.0 [1]	-
DAY 18	MEAN±S.D.	362.7 ± 17.4	351.4 ± 18.2	291.2 ± 60.7 [4]	-	-
DAY 20	MEAN±S.D.	390.6 ± 15.1	386.2 ± 19.5	359.0 ± 25.5 [3]	-	-

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

PROTOCOL 305002P : DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 115 ADMINISTERED ORALLY VIA GAVAGE TO RATS

TABLE 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/DA
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	7(87.5)	8(100.0)	7(87.5)	8(100.0)	8(100.0)
MATERNAL BODY WEIGHT CHANGE						
DAYS 0- 6	MEAN±S.D.	+15.1 ± 7.2	+17.4 ± 6.5	+14.7 ± 8.4	+18.9 ± 2.4	+20.8 ± 7.4
DAYS 6- 7	MEAN±S.D.	+2.3 ± 3.5	-1.5 ± 4.2	-0.1 ± 2.1	-3.1 ± 4.2	-3.2 ± 5.7
DAYS 6- 8	MEAN±S.D.	+4.6 ± 2.8	+0.0 ± 3.5	-1.5 ± 4.4	-13.8 ± 5.1	-12.6 ± 4.0
DAYS 6- 9	MEAN±S.D.	+5.8 ± 4.2	+3.2 ± 4.3	-4.8 ± 7.7	-16.3 ± 9.2	-22.5 ± 11.4
DAYS 6-10	MEAN±S.D.	+10.1 ± 4.3	+7.1 ± 5.4	-6.8 ± 10.8	-28.8 ± 13.4	-32.8 ± 12.0 [7]
DAYS 6-11	MEAN±S.D.	+16.7 ± 6.0	+11.6 ± 6.1	-10.0 ± 13.7	-43.1 ± 14.7	-46.2 ± 13.6 [7]
DAYS 6-12	MEAN±S.D.	+22.4 ± 4.0	+14.8 ± 8.1	-14.7 ± 16.8	-52.3 ± 18.4 [6]	-59.1 ± 15.4 [6]
DAYS 6-13	MEAN±S.D.	+27.1 ± 3.9	+20.8 ± 8.7	-21.1 ± 21.6	-56.2 ± 20.8 [4]	-73.4 ± 17.5 [5]
DAYS 6-14	MEAN±S.D.	+34.1 ± 5.4	+26.2 ± 10.5	-30.4 ± 24.9	-69.7 ± 20.8 [4]	-78.6 ± 8.3 [3]
DAYS 6-15	MEAN±S.D.	+41.6 ± 4.8	+30.9 ± 8.6	-38.2 ± 29.6	-73.0 ± 22.6 [2]	-90.0 ± 0.0 [1]
DAYS 6-16	MEAN±S.D.	+52.6 ± 6.0	+44.6 ± 7.6	-36.1 ± 29.7 [6]	-70.0 ± 0.0 [1]	-
DAYS 16-18	MEAN±S.D.	+34.1 ± 4.6	+28.2 ± 5.7	+34.0 ± 35.7 [4]	-	-
DAYS 16-20	MEAN±S.D.	+62.0 ± 5.4	+63.1 ± 7.2	+90.0 ± 12.0 [3]	-	-
DAYS 6-20	MEAN±S.D.	+114.6 ± 9.8	+107.8 ± 10.6	+76.3 ± 24.8 [3]	-	-
DAYS 0-20	MEAN±S.D.	+129.7 ± 9.6	+125.1 ± 7.0	+89.3 ± 30.5 [3]	-	-

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

PROTOCOL 305002P : DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 115 ADMINISTERED ORALLY VIA GAVAGE TO RATS

TABLE 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/D
ANIMALS - TREATED		8	8	8	8	8
PREGNANT	N(%)	7(87.5)	8(100.0)	7(87.5)	8(100.0)	8(100.0)
ABORTED	N	0	0	0	0	0
DIED	N	0	0	4	8	8
DELIVERED NATURALLY	N	0	0	0	0	0
ANIMALS PREGNANT AND DELIVERED BY CAESAREAN-SECTIONING ON DAY 20	N	7	8	3	0	0
CORPORA LUTEA	MEAN±S.D.	16.8 ± 1.8	16.8 ± 1.5	15.0 ± 0.0	-	-
IMPLANTATIONS	MEAN±S.D.	14.6 ± 1.4	14.4 ± 1.5	12.3 ± 3.8	-	-
LITTER SIZE	MEAN±S.D.	13.8 ± 1.8	14.1 ± 1.2	11.7 ± 4.2	-	-
LIVE FETUSES	N	97	113	35	0	0
	MEAN±S.D.	13.8 ± 1.8	14.1 ± 1.2	11.7 ± 4.2	-	-
DEAD FETUSES	N	0	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	-	-
RESORPTIONS	MEAN±S.D.	0.7 ± 0.8	0.2 ± 0.5	0.7 ± 0.6	-	-
EARLY RESORPTIONS	N	5	2	2	0	0
	MEAN±S.D.	0.7 ± 0.8	0.2 ± 0.5	0.7 ± 0.6	-	-
LATE RESORPTIONS	N	0	0	0	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	-	-
DAMS WITH ANY RESORPTIONS	N(%)	4(57.1)	2(25.0)	2(66.7)		
DAMS WITH ALL IMPLANTATIONS RESORBING	N(%)	0	0	0		
DAMS WITH VIABLE FETUSES	N(%)	7(100.0)	8(100.0)	3(100.0)		

PROTOCOL 305002P : DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 115 ADMINISTERED ORALLY VIA GAVAGE TO RATS

TABLE 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/D
LITTERS EXAMINED DAY 20	N	7	8	3	0	0
IMPLANTATIONS	MEAN±S.D.	14.6 ± 1.4	14.4 ± 1.5	12.3 ± 3.8	-	-
LIVE FETUSES	MEAN±S.D.	13.8 ± 1.8	14.1 ± 1.2	11.7 ± 4.2	-	-
LITTERS WITH ONE OR MORE LIVE FETUSES	N	7	8	3	0	0
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.42 ± 0.14	3.29 ± 0.20	3.40 ± 0.18	-	-
MALE FETUSES	MEAN±S.D.	3.48 ± 0.14	3.37 ± 0.20	3.56 ± 0.26	-	-
FEMALE FETUSES	MEAN±S.D.	3.34 ± 0.20	3.24 ± 0.18	3.29 ± 0.18	-	-
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	5.0 ± 5.4	1.6 ± 2.9	6.5 ± 6.3	-	-
LIVE FETUSES	N	97	113	35	0	0
LIVE MALE FETUSES	N	57	53	14	0	0
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	60.0 ± 20.2	46.7 ± 17.1	45.2 ± 22.8	-	-

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

PROTOCOL 305002P : DOSAGE-RANGE EMBRYO/FETAL TOXICITY AND TERATOGENIC POTENTIAL OF SAYTEX 115 ADMINISTERED ORALLY VIA GAVAGE TO RATS

ABLE 7 (PAGE 1): EXTERNAL FETAL OBSERVATIONS -- SUMMARY

DOSE GROUP		0 MG/KG/DAY	100 MG/KG/DAY	500 MG/KG/DAY	2500 MG/KG/DAY	5000 MG/KG/
LITTERS EVALUATED	N	7	8	3	0	0
FETUSES EVALUATED	N	97	113	35	0	0
LIVE	N	97	113	35	0	0
DEAD	N	0	0	0	0	0
EYE: SUNKEN						
LITTER INCIDENCE	N(%)	0	1(12.5)	0		
FETAL INCIDENCE	N(%)	0	1(0.9)	0		

APPENDIX C

STUDY DIRECTOR'S STATEMENT

ARGUS RESEARCH LABORATORIES, INC.

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

APPENDIX C

Protocol 305-002: Embryo/Fetal Toxicity and Teratogenic Potential Study of SAYTEX®115 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 4-1-85

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

APPENDIX D

QUALITY ASSURANCE STATEMENT

ARGUS RESEARCH LABORATORIES, INC.

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

April 1, 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 305-002: Embryo/Fetal Toxicity and Teratogenic Potential Study of SAYTEX®115 Administered Orally via Gavage to Crl:CDBS®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 November 26, 1984.

The study was also inspected three times during its conduct. The first inspection occurred on November 29, 1984 and included:

1. Observation of cohabitation procedures.
2. Observation of raw data recording procedures.
3. An audit of room records.

The results of this inspection were reported to the Study Director and to Management on December 12, 1984.

The second inspection occurred on December 7, 1984 and included:

1. Observation of test article preparation.
2. Verification of concentration calculations.
3. Observation of test article administration to study animals.
4. Observation of raw data recording procedures.

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

The results of this inspection were reported to the Study Director and to Management on December 7, 1984.

The third inspection occurred on December 18, 1984 and included:

1. Observation of the Caesarean-sectioning of study animals.
2. Verification of study animal unique identification.
3. An audit of the balance log book.
4. Observation of gross external examination, sexing and weighing of fetuses.

The results of this inspection were reported to the Study Director and to Management on December 19, 1984.

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 March 26, 1985 and April 1, 1985.

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

Jane E. Goeke 04/01/85

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

Elizabeth L. Feussner 4/1/85

Elizabeth L. Feussner, V.M.D., D.A.B.T. Date
Principal Auditor and Senior Scientist