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A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

Final Report

Submitted to: Chemical Manufacturers Association
2501 M Street N.W.
Washington, DC 20037

Attn: Mr. Henry J. Sauer

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ABSTRACT

This study was conducted for the Chemical Manufacturers Association Hydroquinone Program Panel to evaluate the embryotoxic, fetotoxic and/or teratogenic potential of hydroquinone in the pregnant rabbit. Test article was dissolved in degassed distilled water and administered by gastric intubation to mated New Zealand White rabbits (18 mated females/group) at dose levels of 25, 75 and 150 mg/kg/day during the Day 6-18 gestation period. Included in this study was a vehicle-treated (degassed distilled water) control group (18 mated females).

During gestation, animals were observed twice daily for signs of pharmacologic or toxicologic effects and mortality. Body weights were recorded on Days 0, 6, 9, 12, 16, 18, 24 and 30 of gestation and food consumption was recorded daily throughout gestation (Days 1-29). Additionally, each mated female was given a detailed physical evaluation at regular intervals during the pre-treatment, treatment and post-treatment periods. On Day 30 of gestation, each female was sacrificed, given a gross postmortem evaluation and corpora lutea/uterine implantation data were recorded. Liver and kidney weights were also recorded for each female at Day 30 gestation sacrifice. Fetuses recovered at this time were weighed and evaluated for external and visceral (microdissection procedure) malformations/variations. Subsequently, all fetuses were processed for staining of the skeletal structures with Alizarin Red S and evaluated for skeletal malformations/variations. Animals that delivered prematurely were sacrificed on the day such evidence was observed.

No mortality occurred among the control or treated group females. Pregnancy rates for the control, low-, mid- and high-dose groups were 83.3% (15/18 females), 100% (18/18 females), 100% (18/18 females) and 94.4% (17/18 females), respectively. None of the control or treated females aborted (passing of fetal/placental tissue prior to Day 26 of gestation). The incidences of females delivering prematurely for the control, low-, mid- and high-dose groups were 13.3% (2/15 females), 0% (18 pregnant females), 16.7% (3/18 females) and 11.8% (2/17 females), respectively; and these incidences were comparable between the control and treated groups.

No maternal toxicity, embryotoxicity, fetotoxicity or teratogenicity were seen in the low-dose group (25 mg/kg/day). The incidences of external, visceral and skeletal malformations on a per fetus and per litter basis in the low-dose group did not differ statistically from control data. Likewise, the incidences of low-dose fetuses with external variations or ossification variations were comparable to control data. The incidence of low-dose fetuses with visceral variations (7.0%) was higher than the control incidence (0.9%) and this difference was statistically significant. The visceral variation seen with greatest frequency in the low-dose group was absence of the post-caval lobe of the lung (3.5%). This finding was not seen among the concurrent control fetuses and has not been noted in recent historical control data for our laboratory;

although, published historical control data for this strain of rabbit from other laboratories suggests that this is a common finding in rabbits. In the absence of a dose response-relationship among the treated groups (incidence for the mid- and high-dose groups was 1.3% and 2.4%, respectively), the increased occurrence of this visceral variation (absence of the post-caval lobe of lung) at the low-dose level was not considered indicative of a treatment-related effect. Other visceral variations seen in the low-dose fetuses occurred at low incidence and were not considered indicative of a treatment-related effect.

In the mid-dose group (75 mg/kg/day), no adverse effect of treatment on the maternal animals was evident from weight data, physical observation data, uterine implantation data, liver and kidney weight data or gross postmortem examination data. The only maternal toxic effect seen at the mid-dose level was a reduction in food consumption for the pregnant females during the latter portion of the treatment period (Days 11-14 of gestation); however, only on Days 11 and 12 were these differences from control statistically significant. The mid-dose level was not considered to be embryotoxic, fetotoxic or teratogenic.

In the high-dose group (150 mg/kg/day), maternal toxicity was evident from the following statistically significant differences from control data; lower weights for Days 16 and 18 of gestation; greater magnitude of weight loss over the gestation Day 6-18 treatment interval [the control group also experienced a mean weight loss over this interval (-11 grams versus -282 grams for the high-dose group)]; and reduced food consumption for Days 6-14 and 17 of gestation. No adverse effect of treatment on the high-dose level females was evident from physical observation data, uterine implantation data, liver or kidney weights or gross postmortem examination data. No embryotoxicity was evident from uterine implantation data. Mean fetal weights were comparable to concurrent control data but were outside the low range of recent historical control data for this laboratory.

An increase in incidence of fetuses with external, visceral and skeletal malformations was seen in the high-dose group and the incidence of litters containing affected fetuses was also increased; however, these incidences did not differ statistically from control data and malformations seen were considered to be associated with the maternal toxicity evident at this same dose level. Ocular defects (microphthalmia) and vertebral/rib defects were seen with increased incidence in the high-dose group. Such malformations have been identified in the published literature to be frequently associated with maternal toxicity in rabbit teratology studies. Angulated arch(es) of the hyoid, a minor skeletal malformation, was also seen with increased frequency in high-dose fetuses both in comparison to the concurrent control incidence and recent historical control data for our laboratory. This finding (angulated arch of the hyoid) is a relatively common minor skeletal malformation and was observed in the high-dose group in the absence of an association with other more severe malformations.

The no-observed-effect level (NOEL) for this developmental toxicity study in rabbits with hydroquinone was 25 mg/kg/day. This dose level was without maternal toxic effects and was not considered to be embryotoxic, fetotoxic or teratogenic. At the higher dose levels, maternal toxicity was evident with these effects being most pronounced at the highest dose level evaluated (150 mg/kg/day).

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I. INTRODUCTION:

This study, conducted for the Chemical Manufacturers Association Hydroquinone Program Panel, was designed to meet requirements established by the United States Environmental Protection Agency according to published TSCA protocol guidelines as presented in 40 CFR, Vol. 50, No. 188 (September 27, 1985) #798.4900 and revision in FR Vol. 52 (No. 97), Wednesday, May 20, 1987, Pg. 19077. The conduct of this study was required under the TSCA Hydroquinone Final Test Rule F.R., Vol. 50, No. 250, pages 53145-53151, December 30, 1985.

Uterine implantation data and the examination of fetuses recovered from pregnant rabbits treated during the period of embryonic organogenesis (Days 6-18 of gestation) were used to evaluate the embryotoxic, fetotoxic, and/or teratogenic potential of hydroquinone. Maternal toxicity was also assessed from maternal weight data, food consumption, physical examination data, organ weights and gross postmortem evaluations.

Species and strain of test animal, method and route of test substance administration were established by the sponsor. Dose levels were determined by the sponsor after reviewing data from a pilot study conducted at Bio/dynamics, Inc. (Project No. 87-3218). This study was conducted at Bio/dynamics, Inc., Mettlers Road, East Millstone, New Jersey 08875-2360. All raw data, specimens, the original study protocol, the original final report and a sample of the test material will be stored in the archives of Bio/dynamics, Inc.

II. MATERIALS AND METHODS:

A. Test Substance:

Hydroquinone

Supplier:

Tennessee Eastman Company
P.O. Box 511
Kingsport, Tennessee 37662

II. MATERIALS AND METHODS (cont.):

A. Test Substance (cont.):

Analysis:

The identity, strength, purity and composition; and synthesis, fabrication, and/or derivation of the test substance have been documented by the sponsor. The purity of this lot of test article was determined to be greater than 99% for the duration of the study (see Appendix V).

Lot Number:

71541

Purity:

Considered to be 100% for the purpose of formulating the dosing solutions.

Description:

White crystalline powder.

Date Received:

8 October 1987

Amount Received:

9.81 kg (approximate gross weight).

Storage:

Room temperature in a tightly closed container away from light.

Expiration Date:

8 October 1989 (the test material should be stable for at least 2 years from the date of receipt when stored properly).

Sampling:

An archival sample of approximately 10 grams of the test substance was taken and is stored in the archives of Bio/dynamics, Inc.

B. Vehicle:

Degassed distilled water (see Appendix P for preparation procedure).

II. MATERIALS AND METHODS (cont.):

C. Test Animals:

Species: Rabbit

Strain: New Zealand White

Supplier (Males and Females): Hazleton Research Products, Inc.
Denver, Pennsylvania 17517

Justification for Animal Selection: Generally recognized standard laboratory rabbit. Bio/dynamics, Inc. has historical control data concerning the use of this strain of rabbit in teratology studies and data demonstrating the responsiveness of this strain of rabbit to a known animal teratogen (i.e., 6-aminonicotinamide).

Number of Animals:

Received: 85 females

Placed on Test: 72 females

Date of Receipt:

Females: 18 January 1988

Males: 29 December 1986 and 8 September 1987 (proven breeders used solely for mating purposes; Bio/dynamics in-house breeding colony - a total of 9 males were used for this study).

Age at Receipt:

Females: 4-5 months of age

Males: 7-9 months of age

Acclimation Period (Females):

43 days

Dates of the Acclimation Period (Females):

18 January - 29 February 1988

Weight of Mated Females Used on Test (Day 0):

Mean (gm)	Range (gm)
4174	3385 - 4949

II. MATERIALS AND METHODS (cont.):

D. In-Life:

1. Husbandry:

Housing: Individually, except during mating, in stainless steel suspended cages with wire mesh floors and subcage floor pans.

Food: Feed was withheld on the day of arrival. The following day, each rabbit received one leaf of cabbage; thereafter, Purina Certified Rabbit Chow® No. 5325 (High-Fiber) was fed ad libitum.

Water: Tap water delivered by automatic watering system, ad libitum (Elizabethtown Water Company).

There are no known contaminants present in the food or water capable of interfering with the results of this study.

Batch certification of feed analyses for the lots of diets used during the study as provided by Purina and monthly water analyses provided by Elizabethtown Water Company will be maintained in the archives of Bio/dynamics, Inc.

Environmental Conditions:

Photoperiod: 12 hour light/dark cycle (7 AM to 7 PM) via automatic timer.

Temperature: Recorded twice daily (morning and afternoon).¹

Desired: 60-70°F

Actual (pre-test): 60-72°F, median 67°F

Actual (test): 64-76°F, median 68°F

¹Due to technician error, room environment and animal observations were not done on the afternoon of 29 January 1988 and 2 March 1988.

II. MATERIALS AND METHODS (cont.):

D. In-Life (cont.):

1. Husbandry (cont.):

Environmental
Conditions (cont.):

Relative Humidity:

Recorded once daily (morning).

Desired: 30-70%

Actual (pre-test): 52-86%, median 65%

Actual (test) : 48-87%, median 69%

These deviations in temperature and relative humidity that were outside the desired range specified in the protocol were not considered to have adversely affected the outcome of this study.

2. Identification:

Each mated female rabbit was identified with a metal ear tag bearing its animal number. This individual animal number plus Bio/dynamics' project number comprised a unique identification number.

3. Assignment to Groups:

A sufficient number of female rabbits was received so as to discard unhealthy females prior to initiation of mating.

The population of animals received for study was evaluated for suitability to use on test by the staff veterinarian prior to the initiation of mating.

Females which mated were assigned to the groups daily in such a way as to most nearly equalize the Day 0 mean group body weights.

4. Mating:

Natural mating was used. Each female selected for mating was placed into the male's cage. When coitus was observed, the female was removed and returned to her original cage. Following an interval of one to two hours, the female was placed into the cage of a second, different male. When coitus was observed with the second male, the female was considered mated and returned to her cage. The day on which evidence of mating was observed with both males was defined as Day 0 of gestation.

II. MATERIALS AND METHODS (cont.):

D. In-Life (cont.):

4. Mating (cont.):

Mating was scheduled to provide Day 30 sacrifices during the Monday-to-Friday work week. The number of females mated daily was also controlled to limit the number of mated females sorted into groups on a particular day. In this study, the number of mated females sorted into groups on each day was 6.

Dates of Mating Period:

1, 5-9, 12-16 and 19 March 1988.

5. Experimental Outline:

Group	Dose Level (mg/kg/day)	Dose Volume (ml/kg/day)	Concentration of Dosing Solution (mg/ml)	No. of Females Mated	Treatment Schedule (gestation days)	Fetal Evaluation		
						Proportion of Fetuses Examined/Litter for Malformations/Variations:		
						Soft	External Tissue	Skeletal
I	0 ^a	8	0	18	6-18	A11	A11	A11
II	25	8	3.125	18	6-18	A11	A11	A11
III	75	8	9.375	18	6-18	A11	A11	A11
IV	150	8	18.75	18	6-18	A11	A11	A11

^aDegassed distilled water.

6. Test Substance Administration:

Route:

Gastric intubation

Justification for Route of Administration:

The route of administration of the test substance was determined on the basis of the Hydroquinone Final Test Rule F.R., Vol. 50, No. 250, pages 53145-53151, December 30, 1985.

II. MATERIALS AND METHODS (cont.):

D. In-Life (cont.):

6. Test Substance Administration (cont.):

Dose Volume: 8 ml/kg of body weight/day; dose volumes were derived from Day 6 body weights and were adjusted during the remaining treatment period to the most recent body weights.

Duration: Days 6-18 of gestation.

Dates of Administration: Day 6 of gestation:² 7, 11, 12, 13, 14, 15, 18, 19, 20, 21, 22 and 25 March 1988.

Day 18 of gestation:³ 19, 23, 24, 25, 26, 27, 30 and 31 March and 1, 2, 3 and 6 April 1988.

7. Preparation and Analyses of the Dosing Solutions:

Dosing Solution Preparation: Appropriate amounts of test article were dissolved in degassed distilled water for gastric intubation at a volume of 8 ml/kg of body weight/day. Dosing solutions were prepared fresh daily.

The method of preparation for the dosing solutions is presented in Appendix P.

Stability Analyses: The stability of the test material in the vehicle at the lowest concentration level (i.e., 3.125 mg/ml) over a 6 hour preparation to use interval was determined pre-test. These analyses were conducted at Bio/dynamics, Inc. by the Metabolism and Analytical Chemistry Department and the results of these analyses are presented in Appendix Q of this report.

²Identifies the date that each subgroup of mated females reached their Day 6 of gestation and initiated treatment resulting from the staggered matings.

³Identifies the date that each subgroup of mated females reached their Day 18 of gestation and completed the treatment regimen resulting from the staggered matings.

II. MATERIALS AND METHODS (cont.):

D. In-Life (cont.):

7. Preparation and Analyses of the Dosing Solutions (cont.):

Determination of the Solubility of the Test Article in the Vehicle:

The solubility of a 5% (w/v) aqueous (degassed water) solution of hydroquinone was confirmed pre-test. A 5% solution was prepared and sampled at six locations in the container (two samples were taken from the top level, two from the middle and two from the bottom). The mean \pm S.D. of the analytical results for these six samples was $100\% \pm 2.01$. These analyses were conducted at Bio/dynamics, Inc. by the Metabolism and Analytical Chemistry Department and data regarding these analyses can be found in the data package for the reproductive study (87-3219).

Analytical Confirmation of Dose Level Concentrations:

Samples of the dosing solutions (10 mls) were taken at each dose level for each preparation. These samples were analyzed to confirm concentration on the first day of dosing (mix No. 1), one day each week that dosing solutions were prepared (mix Nos. 8, 15, 18 and 22) and on the last day of dosing (mix No. 31). Analytical confirmation of dose level concentrations was conducted at Bio/dynamics, Inc. by the Metabolism and Analytical Chemistry Department and the results of these analyses are presented in Appendix Q of this report.

Samples taken but not analyzed will be retained frozen at Bio/dynamics, Inc. until the sponsor authorizes their disposition.

III. EVALUATIONS:

A. In-Life:

1. Physical Observations:

(Methodology and References, Appendix A)

Twice daily (morning and afternoon) for signs of pharmacologic or toxicologic effects and mortality. In addition, each female was given a detailed physical examination on Days 0, 6-18, 19, 24 and 30 of gestation. On Days 6-18 of gestation, the detailed physical examinations were conducted after all animals had been dosed for that specific day. The time interval from the initiation of dosing of the Group I females to initiation of the detailed physical observations ranged from a minimum of 8 minutes to a maximum of 144 minutes with a median of 60 minutes. This wide range in time was primarily due to the varied number of animals being dosed on each day.

2. Body Weights:

(Methodology and References, Appendix A)

Recorded on Days 0, 6, 9, 12, 16, 18, 24 and 30 of gestation. Day 30 body weights are presented as actual and corrected (the actual Day 30 body weight minus the weight of the gravid uterus).

3. Food Consumption:

(Methodology and References, Appendix A)

Food consumption was recorded daily throughout gestation (Days 1-29).

III. EVALUATIONS (cont.):

B. Postmortem:

1. Maternal Evaluations:

Gross Postmortem
Examinations:

Complete gross postmortem examinations were performed on all mated rabbits. Females showing signs of premature delivery (presence of fetuses/pups at Day 26 of gestation or later) were killed via intravenous injection of sodium pentobarbital in the marginal ear vein on the day such evidence was observed. Reproductive systems were examined. Fetuses/delivered pups recovered during the Day 26-30 gestation interval were evaluated for external malformations, eviscerated (viscera evaluated grossly) and processed for staining of the skeletal structures with Alizarin Red S. These stained specimens were evaluated for skeletal malformations only.

Animals Killed:

Day 30 of gestation.

Method of Sacrifice:

Intravenous injection of Sodium Pentobarbital via the marginal ear vein.

Dates:

31 March and 4-8, 11-15 and 18 April 1988 (for actual dates that specific animals were killed see Appendix B; Animal Termination History).

Tissues/Organs
Preserved:

(Methodology and References, Appendix A)

All gross lesions were saved for all females. Additionally, the following organs were weighed (paired organs were weighed together) and saved for possible histopathological evaluation. All tissues/organs were saved in 10% neutral buffered formalin.

liver
kidneys (both)

III. EVALUATIONS (cont.):

B. Postmortem (cont.):

1. Maternal Evaluations (cont.):

Reproductive System:

The intact uterus (ovaries attached) was removed from the abdominal cavity, weighed and the number and location of the following were recorded for each uterine horn:

live fetuses

dead fetuses (no evidence of tissue degeneration)

late resorptions (recognizable dead fetus undergoing degeneration regardless of size)

early resorptions (evidence of implantation but no recognizable fetus)

implantation sites

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

When no uterine implants were grossly apparent, the uterus was stained with ammonium sulfide (method of Salewski - see Appendix A). When no foci were visualized post-staining, the female was considered not pregnant.

2. Fetal Evaluations:

All fetuses were given a gross examination for external malformations/ variations to include observation for palatal defects. Subsequently, each fetus was weighed and tagged individually for identification.

III. EVALUATIONS (cont.):

B. Postmortem (cont.):

2. Fetal Evaluations (cont.):

Visceral Evaluations: (Methodology and References, Appendix A)

All fetuses were killed (intraperitoneal injection of T-61[®] euthanasia solution) and evaluated for visceral malformations/variatioins using a microdissection procedure similar to that described by Staples. The sex of each fetus was determined during the visceral evaluations by observation of the gonads. Following this procedure, the viscera were removed from the thoracic and abdominal cavities and discarded. The eviscerated fetus was then skinned. As the skin of the head was removed, the eyes were evaluated grossly for obvious malformations. The brain was evaluated by making a transverse cut with a razor blade parallel and just posterior to the frontal-parietal suture in the cranium and through the cerebral hemispheres. The microdissection procedure was performed under a dissecting microscope (10-20X) and magnification lens (2.0X). Eyes and brain observations were performed grossly.

Skeletal Evaluations: (Methodology and References, Appendix A)

The eviscerated/skinned fetal specimens were then processed for staining of the ossified skeletal structures using the Alizarin Red S staining procedure of Crary as modified by Bio/dynamics. Fetal skeletal specimens were evaluated under a 2.0X magnification lens.

Late Resorptions:

Late resorptions were examined grossly for external malformations and discarded.

C. Statistical Analysis:

(Methodology and References, Appendix A)

Data were analyzed between control (Group I) and treated groups (Groups II-IV). Statistically significant differences between the control and treated group data are presented in summary and mean tables of the appendices.

IV. RESULTS AND DISCUSSION:

A. Maternal Data:

1. Mortality (Animal Termination History - Appendix B):

No mortality occurred in the control or treated groups.

2. Pregnancy Rate (Appendix G; page G-1):

Pregnancy rates for the control, low-, mid- and high-dose groups were 83.3% (15/18 females), 100% (18/18 females), 100% (18/18 females) and 94.4% (17/18 females), respectively. These rates were comparable between the control and treated groups.

3. Body Weight Data - Gestation Period:

Mean and individual weights and weight change data during gestation are presented in Appendices C and D, respectively. Mean and individual gravid uterine weights, corrected Day 30 body weights and weight change for the Day 6-30 gestation interval using the corrected Day 30 body weights are presented in Appendix E.

No adverse effect of treatment at the low- or mid-dose levels was evident from body weight data during gestation.

In the high-dose group, mean weights at Days 9, 12, 16 and 18 of gestation were slightly lower than control data and on Days 16 and 18 of gestation these differences in weight data from control were statistically significant. High-dose animals experienced a mean weight loss for each recording interval during the treatment period; however, only for the Day 6-9 interval was this difference from control data statistically significant. Over the entire treatment period (Days 6-18) the high-dose group experienced a considerably greater mean weight loss (-282 grams) than the control group (which also experienced a mean weight loss, i.e., -11 grams) and this difference from control data was statistically significant. During the post-treatment period

IV. RESULTS AND DISCUSSION (cont.):

A. Maternal Data (cont.):

3. Body Weight Data - Gestation Period (cont.):

(Days 18-24, 24-30 and 18-30), high-dose animals were noted with mean weight gains while the control animals experienced slight mean weight losses. The mean weight gains experienced in the high-dose group during the post-treatment period were considered to be reflective of compensatory growth following overt weight loss during the treatment period. Sixteen of 17 pregnant high-dose females lost weight for the Day 6-18 treatment period as compared to seven of 15 control females.

Corrected Day 30 gestation body weights were comparable between the control and treated groups. Using the corrected Day 30 gestation body weights, control and all treated groups experienced a mean weight loss for the Day 6-30 gestation interval and these data were comparable between these same groups.

4. Food Consumption Data - Gestation Period:

Mean and individual food consumption data for each recorded interval during the gestation period are presented in Appendix F.

In the low-dose group, mean food consumption was comparable to control throughout gestation (pre-treatment, treatment and post-treatment intervals).

In the mid-dose group, mean food consumption data were comparable to control data during the pre- and post-treatment intervals. During the treatment period, mean food consumption was slightly lower than control data for Days 6-10 of gestation (these differences from control ranged from -7.3% at Day 9 to -17.8% at Day 10). On Days 11-14 of gestation, mean food consumption for the mid-dose group was markedly lower than control data (differences ranged from -22.6% to -36.1%) and on Days 11 and 12 these differences were statistically

IV. RESULTS AND DISCUSSION (cont.):

A. Maternal Data (cont.):

4. Food Consumption Data - Gestation Period (cont.):

significant. For the remainder of the treatment period (Days 15-18) and for the post-treatment intervals, mean food consumption for the mid-dose group was comparable to or slightly increased in respect to the control data.

In the high-dose group, mean food consumption was comparable to control during the pre-treatment interval. During the treatment period, mean food consumption for the high-dose group was lower than control and these differences were statistically significant for Days 6-14 and Day 17. Mean food consumption for the high-dose group continued to be depressed in comparison to control on Days 19 and 20 of the post-treatment period (-29.2% and -22.2%, respectively) but was higher than control for the remainder of the post-treatment period.

Thus, no adverse effect of treatment was evident from food consumption data at the low-dose level. At the mid- and high-dose levels, reductions in mean food consumption were noted during the treatment period.

IV. RESULTS AND DISCUSSION (cont.):

A. Maternal Data (cont.):

5. Premature Delivery Indices:

Premature delivery prior to scheduled sacrifice was seen for two control females, three mid-dose females and two high-dose females. Premature delivery indices⁴ for the control, mid- and high-dose groups were 13.3% (2/15 females), 16.7% (3/18 females) and 11.8% (2/17 females), respectively; and these incidences were considered comparable between the control and these same treated groups. A low incidence of premature delivery is seen historically in this laboratory (Appendix R) in these types of studies. In the absence of a dose-response relationship in regard to the incidences of females that delivered prematurely among the treated groups, no adverse effect of treatment was indicated.

⁴Premature Delivery Index = No. females that deliver prematurely (Days 26-30)/No. pregnant females X 100.

IV. RESULTS AND DISCUSSION (cont.):

A. Maternal Data (cont.):

5. Premature Delivery Indices (cont.):

The females that delivered prematurely and observations concerning these deliveries are summarized below:

Female No.	Group	Gestation Day	No. of Pups Delivered			Uterine Observations at Necropsy
			Live	Dead	Partially Cannibalized	
1517	I	30	2	3	0	4 fetuses, 1 late resorption and 5 implantation scars found <u>in utero</u> .
1518	I	30	5	4	1 ^a	10 implantation scars found <u>in utero</u> .
3513	III	30	10	1	0	11 implantation scars found <u>in utero</u> .
3515	III	29	5	0	3 ^b	9 implantation scars found <u>in utero</u> .
3518	III	26	0	1	0	7 live fetuses, 5 late resorptions, 1 early resorption and 1 implantation scar found <u>in utero</u> .
4506	IV	27	0	0	0	2 late resorptions found in cage pan and 8 implantation scars found <u>in utero</u> .
4516	IV	27	0	0	0	3 late resorptions and 1 early resorption (attached to placenta) found in cage pan, 1 late resorption found in vagina, 1 late resorption and 8 implantation scars found <u>in utero</u> .

^aAlthough partially cannibalized when first seen, this fetus was viable but could not be evaluated further for visceral or skeletal malformations.

^bSome cannibalization was seen of the ears; specimens were viable when found and were subsequently evaluated for visceral and skeletal malformations.

IV. RESULTS AND DISCUSSION (cont.):

A. Maternal Data (cont.):

6. Physical In-Life Observation Data:

Findings for individual animals as noted during the detailed physical in-life evaluations are presented in Appendix I and these data are summarized on pages I-2 and I-3.

No adverse effect of treatment was evident from physical observation data.

Many of the animals in each of the treated groups were noted to have a dark staining urine on the absorbent paper in the sub-cage floor pan. This was attributed to an excretory product of the test article and not considered indicative of an adverse effect of treatment.

7. Corpora Lutea and Uterine Implantation Data:

Corpora lutea and uterine implantation data for individual females are presented in Appendix G and these data are summarized on page G-1 of this appendix. The identification and distribution of implantations along the uteri of individual females are presented in Appendix H.

The mean number of corpora lutea and uterine implantations per pregnant female was comparable between the control and treated groups. The mean pre-implantation loss indices (summarized on page G-1 of Appendix G) were considered comparable between the control, low- and high-dose groups. In the mid-dose group, the mean pre-implantation loss index was considerably lower than control; however, this change was not considered indicative of an adverse effect of treatment.

IV. RESULTS AND DISCUSSION (cont.):

A. Maternal Data (cont.):

7. Corpora Lutea and Uterine Implantation Data (cont.):

The mean number of viable fetuses was comparable between the control, low- and high-dose groups. In the mid-dose group, the mean number of viable fetuses was higher than control; however, this change was not considered indicative of an adverse effect of treatment. Only one dead fetus was recovered in utero and that was from the litter of high-dose female No. 4515.

The mean number of resorptions per pregnant female was comparable between the control and treated groups. Likewise, the mean resorption/implant ratio and the incidence of females with resorptions among their uterine implants (both parameters summarized on page G-1 of Appendix G) were comparable between the control and treated groups.

Thus, no adverse effect of treatment up to a dose level of 150 mg/kg/day was evident from uterine implantation data.

8. Gross Postmortem Examination Data:

Gross postmortem findings for individual females are presented in Appendix J (Pathology Report).

Accentuated lobular pattern of the liver was seen in some control and treated animals. The incidences of females with this finding for the control, low-, mid- and high-dose groups were 11.1% (2/18), 38.9% (7/18), 38.9% (7/18) and 5.6% (1/18), respectively. The toxicologic significance of this finding in relationship to the test article, particularly in the absence of a dose relationship, remains equivocal on the basis of gross examination only.

Other postmortem findings observed grossly occurred sporadically and were not considered to be related to the test article.

IV. RESULTS AND DISCUSSION (cont.):

A. Maternal Data (cont.):

8. Gross Postmortem Examination Data (cont.):

Four females [two control (No. 1516 and 1518), one low-dose (No. 2516) and one high-dose (No. 4516)] had large "hairballs" in the stomach at gross postmortem evaluation. All of these females experienced extreme weight loss during the later intervals of gestation and reduced food consumption at these same intervals. Two females (No. 1518 and 4516) delivered prematurely prior to scheduled sacrifice. Since the incidence of females with these "hairballs" at gross postmortem evaluation was greatest in the control group, no adverse effect of treatment was indicated from this finding.

9. Organ Weight Data:

Organ weight data for individual animals are presented in Appendix K (pages K-3 to K-6) and summarized by group on page K-2 of this appendix. Organ weight data are presented as absolute values and relative to the corrected Day 30 gestation body weights.

No adverse effect of treatment was evident from kidney or liver weights (absolute or relative to body weight) as these data were comparable between the control and treated groups.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data:

1. Fetal Body Weight Data:

Mean fetal body weights for individual litters are presented in Appendix G and summarized by group on page G-1 of this appendix. Individual fetal weights are presented in Appendix L (Individual Fetal External Examination Data).

Mean fetal weights distinguished by sex and as a composite of both sexes, were comparable between the control and high-dose group. In the low- and mid-dose groups, mean fetal weights were slightly higher than control. Mean fetal weights for both the control and high-dose groups were outside the low range of recent historical control data (Appendix R).⁵ The lower mean fetal weight for the control group was, in part, attributed to low mean fetal weights for two litters; control female No. 1506 had a litter of 12 fetuses and the mean fetal weight was 25.3 grams for male fetuses, 24.9 grams for female fetuses and 25.1 grams for all fetuses (composite of both sexes); and control female No. 1509 had a litter of two fetuses (one fetus of each sex) and the male fetus weighed 19.9 grams and the female fetus weighed 18.4 grams (the mean weight for both fetuses was 19.1 grams).

⁵Historical Control Data (New Zealand White Rabbit - Day 30 fetus) - Bio/dynamics, Inc. (1982-1987). Represents a tabulation of data for 19 control groups (extracted from Appendix R; page R-5).

	<u>Mean</u>	<u>(Range of Values)</u>
Male Fetuses	46.7 grams	(40.0-50.4 grams)
Female Fetuses	45.5 grams	(39.6-48.1 grams)
Both Sexes Combined	46.3 grams	(40.5-49.6 grams)

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

2. Fetal Sex Distribution Data:

The distribution of male and female fetuses within individual litters is presented in Appendix G. The mean number of male and female fetuses per pregnant female and the ratio of viable male/female fetuses per group are summarized on page G-1 of Appendix G.

No adverse effect of treatment up to a dose level of 150 mg/kg/day was evident from fetal sex distribution data.

3. Fetal External Examination Data:

Findings for individual fetuses as noted during the external examinations are presented in Appendix L. The types of malformations seen during the study, the incidence of fetuses with these malformations and the incidence of litters containing fetuses with external malformations are summarized on page L-1 of Appendix L; a similar summary of external variations is presented on page L-2 of this same appendix.

a. External Malformations:

The incidences of fetuses with external malformations for the control, low-, mid- and high-dose groups were 0% (111 fetuses evaluated from 13 litters), 0.7% (1/142 fetuses), 0.6% (1/155 fetuses) and 1.6% (2/125 fetuses), respectively. The incidence of litters containing fetuses with external malformations for the low-, mid- and high-dose groups were 5.6% (1/18 litters), 6.7% (1/15 litters) and 6.7% (1/15 litters), respectively. The incidences of external malformations both on a per fetus and per litter basis did not differ statistically between the control and treated groups.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

3. Fetal External Examination Data (cont.):

a. External Malformations (cont.):

Limb flexure defects were seen in one fetus each from the low- and mid-dose groups. In the low-dose group, one fetus from the litter of female No. 2510 had a flexure defect of the left hindpaw. In the mid-dose group, one fetus from the litter of female No. 3507 had a flexure defect of the left forepaw. In the absence of flexure defects of the fore- or hindlimbs in the high-dose group, the presence of this malformation in two fetuses at lower dose levels was not considered indicative of a treatment-related response.

In the high-dose group, two fetuses from a single litter (female No. 4512) did not have eye bulges, suggestive of ocular malformations and after skinning these specimens in preparation for the Alizarin Red S staining procedure, each fetus was noted to have a small eye (microphthalmia). The remaining three fetuses in this litter were externally unremarkable.

External malformations seen in the treated groups were not considered indicative of a treatment-related effect due to the low incidence at which they occurred.

External examination of delivered pups or fetuses recovered in utero for females that delivered prematurely (Appendix 0) revealed no malformations. A total of 45 pups/fetuses were evaluated [18 control pups/fetuses from two control females (Nos. 1517 and 1518) and 27 mid-dose pups/fetuses from three females (Nos. 3513, 3515 and 3518)]. No term pups/fetuses were recovered from the two high-dose females that delivered prematurely.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

3. Fetal External Examination Data (cont.):

b. External Variations:

Observations noted during the fetal external examination that are not of sufficient severity to constitute malformation, have been identified for this presentation as external variations. No such findings were seen in the 111 control fetuses or 155 mid-dose fetuses. In the low- and high-dose groups, the incidence of fetuses with external variations was 0.7% (1/142 fetuses) and 0.8% (1/125 fetuses), respectively.

External variations seen in the low- and high-dose groups were not considered indicative of an adverse effect of treatment due to the low incidence at which they occurred in these groups.

Thus, no adverse effect of treatment was evident from the fetal external examinations.

4. Fetal Visceral Examination Data:

Findings for individual fetuses as noted during the visceral examinations are presented in Appendix M. The types of malformations seen during the study, the incidence of fetuses with these malformations and the incidence of litters containing fetuses with visceral malformations are presented on page M-1 of Appendix M; a similar summary of visceral variations is presented on page M-2 of this same appendix.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

4. Fetal Visceral Examination Data (cont.):

a. Visceral Malformations:

The incidences of fetuses with visceral malformations for the control, low-, mid- and high-dose groups were 0.9% (1/111 fetuses), 2.8% (4/142 fetuses), 0.6% (1/155 fetuses) and 4.8% (6/125 fetuses), respectively. The incidences of litters containing fetuses with visceral malformations for these same groups were 7.7% (1/13 litters), 16.7% (3/18 litters), 6.7% (1/15 litters) and 20.0% (3/15 litters), respectively. These incidences were statistically comparable between the control and treated groups.

The visceral malformation seen with greatest incidence during the study was absence of the gallbladder. The incidence of this finding for the control, low-, mid- and high-dose groups was 0.9% (1/111 fetuses), 2.1% (3/142 fetuses), 0.6% (1/155 fetuses) and 1.6% (2/125 fetuses), respectively. These incidences were considered similar between the control and treated groups and in the absence of any dose-response relationship, no adverse effect of treatment was indicated from the presence of this malformation among the treated group fetuses. Further, absence of the gallbladder is seen frequently within this laboratory as evident from recent historical control data [overall incidence of fetuses affected was 0.5% (12/2277) with a range of study values from 0.0% to 9.5%; see Appendix R, page R-17].

The only other visceral malformation seen among the low- and mid-dose fetuses was a defect in the lobulation of the left lung seen in one low-dose fetus. The occurrence of this finding in the low-dose group was not considered indicative of a treatment-related effect.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

4. Fetal Visceral Examination Data (cont.):

a. Visceral Malformations (cont.):

In the high-dose group, three fetuses had defects involving small eye (i.e., microphthalmia). This defect, which has not been noted in recent historical control data for this laboratory (Appendix R), was seen in two of six fetuses recovered from female No. 4512 (both of these fetuses were noted with absence of eye bulges at external examinations) and in one of nine fetuses from female No. 4504 [this fetus (No. 8) also had a defect of the aortic arch vessels]. The incidence of fetuses with small eye for the high-dose group was 2.4%. Khera⁶ has identified microphthalmia as a malformation in rabbits that is frequently reported in association with maternal toxicity. In this study the high-dose level (150 mg/kg/day) was maternally toxic as evidenced from the mean weight loss encountered during the treatment period (data were statistically different than control data) and reduced food consumption throughout the treatment period (differences from control data at most of the daily intervals were statistically significant). The slight increase in the small eye (microphthalmia) noted at the high-dose level may be attributable to this maternal toxicity.

Gross evisceration of pups/fetuses recovered from females that delivered prematurely revealed no visceral malformations (18 control and 27 mid-dose pups/fetuses were examined - see Appendix O). No pups or fetuses were recovered from the two high-dose females that delivered prematurely.

⁶Khera, K.S. (1985) "Maternal Toxicity: A Possible Etiological Factor in Embryo-Fetal Deaths and Fetal Malformations of Rodent-Rabbit Species. *Teratology* 31: 129-153.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

4. Fetal Visceral Examination Data (cont.):

b. Visceral Variations:

Visceral variations are findings that involve subtle changes in size, shape or appearance of the visceral organs/tissues. These types of observations are considered to represent transient developmental stages. Such subtle changes are not considered indicative of malformation but an increase in incidence of fetuses with certain visceral variations when seen to occur in a dose-related pattern may be indicative of a fetotoxic response to treatment (i.e., delayed maturation).

The incidences of fetuses with visceral variations for the control, low-, mid- and high-dose groups were 0.9% (1/111 fetuses), 7.0% (10/142 fetuses), 1.3% (2/155 fetuses) and 6.4% (8/125 fetuses), respectively. These incidences were comparable between the control and mid-dose group and were higher than control for the low- and high-dose groups; however, only for the low-dose group was this difference from control data statistically significant. The incidences of litters containing fetuses with visceral variations for the control, low-, mid- and high-dose groups were 7.7% (1/13 litters), 38.9% (7/18 litters), 13.3% (2/15 litters) and 40.0% (6/15 litters), respectively. These incidences were higher than control for the low- and high-dose groups; however, these differences were not statistically significant.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

4. Fetal Visceral Examination Data (cont.):

b. Visceral Variations (cont.):

The visceral variation seen with greatest frequency among the treated groups was absence of the post-caval lobe of the lung. This finding was not seen in the control fetuses and has not been noted in recent historical control data for our laboratory (Appendix R). The incidence of fetuses with this finding (absence of the post-caval lobe of the lung) for the low-, mid- and high-dose groups was 3.5% (5/142), 1.3% (2/155) and 2.4% (3/125), respectively. Stadler⁷ et al. in their review of historical control data for the New Zealand White rabbit over a 10 year period identified post-caval lung agenesis (or absence of the intermediate lung lobe) as one of their three most frequently encountered visceral malformations.⁸ Palmer⁹ in his review of sporadic malformations in the New Zealand White rabbit gives an incidence of 0.58% for agenesis of the intermediate lung lobe. In this study, four of the eight

⁷Stadler, J., M.-J. Kessedjian and J. Perraud (1983). Use of the New Zealand White Rabbit in Teratology: Incidence of Spontaneous and Drug-Induced Malformations. Ed. Chem. Toxic. 21 (5): 631-636.

⁸The authors identify this finding (agenesis of the post-caval lobe of lung) as a minor malformation. The overall incidence of this finding in the report for control animals was 0.8% with 7.7% representing the higher extreme mean value for percentages of fetuses affected/experimental group with the lower value being zero.

⁹Palmer, A.K. (1972). Sporadic Malformations in Laboratory Animals and Their Influence on Drug Testing. Advances in Experimental Medicine and Biology, Vol. 27, pg. 45-60.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

4. Fetal Visceral Examination Data (cont.):

b. Visceral Variations (cont.):

treated group fetuses with absence of the post-caval lobe of the lung [two low-dose (female No. 2502 - fetus Nos. 6 and 7), one mid-dose (female No. 3517 - fetus No. 4) and one high-dose (female No. 4507 - fetus No. 4)] had no other visceral findings (malformations or variations) and did not have external or skeletal malformations. The remaining six fetuses [three low-dose fetuses (female No. 2506 - fetus Nos. 9 and 10 and female No. 2513 - fetus No. 5); one mid-dose fetus (female No. 3506 - fetus No. 2) and two high-dose fetuses (female No. 4511 - fetus No.3 and female No. 4512 - fetus No. 8)] that had absence of the post-caval lobe of the lung also had other visceral or skeletal malformations. In the absence of a dose response relationship, the occurrence of this one visceral variation (absence of the post-caval lobe of the lung) in this study was not considered indicative of a treatment-related response.

Other visceral variations seen among the treated group fetuses occurred at low incidence or with similar frequency as in the control group and were not considered indicative of a treatment-related response.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

5. Fetal Skeletal Examination Data:

Findings (malformations/ossification variations) for individual fetuses noted during the skeletal examinations are presented in Appendix N. The types of skeletal malformations seen, the incidence of fetuses with these malformations and the incidence of litters containing fetuses with malformations are summarized on pages N-1 to N-4 of Appendix N; a similar summary of ossification variations is presented on pages N-5 to N-10 of this same appendix.

a. Skeletal Malformations:

The incidences of fetuses with skeletal malformations for the control, low-, mid- and high-dose groups were 7.2% (8/111), 4.2% (6/142), 3.2% (5/155) and 13.6% (17/125), respectively. The incidences of litters containing fetuses with skeletal malformations for these same groups were 46.2% (6/13), 22.2% (4/18), 26.7% (4/15) and 66.7% (10/15), respectively. The incidences of skeletal malformations on both a per fetus and per litter basis did not differ statistically between the control or treated groups.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

5. Fetal Skeletal Examination Data (cont.):

a. Skeletal Malformations (cont.):

The most frequently seen skeletal malformation was angulated arch(es) of the hyoid. The incidence of fetuses with this malformation for the control, low-, mid- and high-dose groups was 2.7% (3/111), 0.7% (1/142), 0% (155 fetuses evaluated) and 7.2% (9/125), respectively. Angulated arch(es) of the hyoid, a minor malformation, is seen commonly in this laboratory. The overall incidence of fetuses with this malformation from recent historical control data was 1.7% (36/2104) and the range of values for individual studies in this tabulation is 0.0 to 3.7% (page R-13 of Appendix R). The incidences of angulated arch(es) of the hyoid for the control and low-dose group were within the range of recent historical control data. The incidence of fetuses with this finding in the high-dose group (7.2%) is higher than the historical control data. However, this finding (angulated arch of the hyoid) is a relatively common minor malformation and was observed in the high-dose group in the absence of an association with other more severe malformations.

Fused sternbrae, also a minor malformation, was seen in the control and each treated group. The incidence of this finding for the control, low-, mid- and high-dose groups was 3.6% (4/111), 1.4% (2/146), 0.6% (1/155) and 1.6% (2/125), respectively. This finding is seen commonly in this laboratory and the overall historical control incidence is 1.9% (41/2104) with a range of individual study values of 0% to 15.2% (see page R-13 of Appendix R).

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

5. Fetal Skeletal Examination Data (cont.):

a. Skeletal Malformations (cont.):

Excluding those fetuses that had either angulated arch(es) of hyoid or fused sternbrae as their only skeletal malformations, the incidence of fetuses with other types of skeletal malformations for the control, low-, mid- and high-dose groups was 0.9% (1/111), 2.1% (3/142), 2.6% (4/155) and 4.8% (6/125), respectively.

In the low-dose group, three fetuses from a single litter (female No. 2506 - fetus Nos. 1, 9 and 10) had minor defects of the cervical vertebral centra or transverse processes (i.e., misshapen, misaligned) and one of these fetuses also had fused ribs. No other skeletal malformations were seen in the low-dose group. Misshapen/misaligned cervical vertebral elements in association with other skeletal malformations have been seen with low incidence in recent historical control data for this laboratory (Appendix R, page 9). The significance of these minor skeletal malformations seen in three of 11 fetuses from a single low-dose litter was not considered indicative of a treatment-related response. Two of these three fetuses (Nos. 9 and 10) also had dissimilar visceral malformations.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

5. Fetal Skeletal Examination Data (cont.):

a. Skeletal Malformations (cont.):

In the mid-dose group, a minor cervical vertebral defect (i.e., mislocation of third cervical vertebral transverse process) was seen in one fetus (Female No. 3502 - fetus No. 11) and unilateral absence of the third cervical vertebral transverse process was seen in a second fetus from a different litter (female No. 3511 - fetus No. 11). A branched rib was seen in a third mid-dose fetus (female No. 3501 - fetus No. 5) and a fusion of the nasal bones was seen in another mid-dose fetus (female No. 3506 - fetus No. 2). These types of malformations have been noted at low incidence in recent historical control data for this laboratory and the low incidence of their occurrence in this group was not considered indicative of a treatment-related effect.

In the high-dose group, thoracic vertebral defects and/or rib defects (fused, branched or misshapen) were seen in five fetuses from two litters (female No 4504 - fetus Nos. 6 and 8 and female No. 4511 - fetus Nos. 3, 5 and 7). Fused caudal vertebrae were seen in one fetus (No. 7) from the litter of high-dose female No. 4510. Khera in his tabulation of malformation data for completed rabbit teratology studies identified rib malformations as being frequently reported in association with maternal toxicity. The increase in incidence of rib defects in the high-dose group for this study, particularly in the absence of more severe major skeletal malformations within this group, was considered attributable to the maternal toxicity seen at this dose level and was not considered indicative of a teratogenic response.

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

5. Fetal Skeletal Examination Data (cont.):

a. Skeletal Malformations (cont.):

Among the pups/fetuses recovered from control and mid-dose females that delivered prematurely, one fetus (No. 3) from the litter of control female No. 1517 had an angulated arch of the hyoid (right side) and one mid-dose fetus (No. 9) from the litter of female No. 3513 had fused fourth and fifth sternbrae. No other skeletal malformations were seen in the remaining 17 control and 26 mid-dose pups/fetuses evaluated from females that delivered prematurely.

Thus, the overall incidence of skeletal malformations both on a per fetus and per litter basis was comparable between the control, low- and mid-dose groups and, while higher than control in the high-dose group, this difference was not statistically significant. Minor skeletal malformations (i.e., angulated arch(es) of the hyoid, fused sternbrae) were the most frequently seen malformations among all groups. The incidence of fetuses with these minor malformations for the treated groups and control was similar to recent historical control data with the exception of the increased incidence of angulated arch of the hyoid for the high-dose group. The incidence of fetuses in the low- and mid-dose groups with other types of skeletal malformation was low (2.1% and 2.6%, respectively) and considered similar to the control incidence (0.9%). Minor cervical vertebral defects were seen in several low-dose fetuses from a single litter and two mid-dose fetuses; however, in the absence of these types of malformations among the high-dose fetuses, no

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

5. Fetal Skeletal Examination Data (cont.):

a. Skeletal Malformations (cont.):

treatment-related effect was indicated. In the high-dose group, the incidence of fetuses with skeletal malformations exclusive of angulated hyoid arch and fused sternbrae, was 4.8% and the predominant malformation involved rib defects. The increase in rib malformations in the high-dose group was considered related to the maternal toxicity seen at this dose level.

b. Ossification Variations:

Ossification variations may represent delays in the ossification process (retarded ossification) or slight ossification irregularities which may or may not be present in the adult specimen. Ossification variations are not considered representative of malformation but an increase in the incidence of fetuses with ossification variations or an increase in the incidence of fetuses with a particular ossification variation may be suggestive of retardation in ossification which would be regarded as a fetotoxic response to the test material. The types of ossification variations seen during the study and the incidence of fetuses (litters) with these observations are summarized in Appendix N (pages N-5 to N-10).

IV. RESULTS AND DISCUSSION (cont.):

B. Fetal Data (cont.):

5. Fetal Skeletal Examination Data (cont.):

b. Ossification Variations (cont.):

The incidences of fetuses with at least one ossification variation for the control, low-, mid- and high-dose groups were 58.6% (65/111), 59.2% (84/142), 52.9% (82/155) and 59.2% (74/125), respectively. The incidences of litters containing at least one fetus with an ossification variation was 100% for the control, mid- and high-dose groups and 94.4% in the low-dose group. These incidences on a per fetus and per litter basis were comparable between the control and treated groups.

No adverse effect of treatment was evident from ossification variation data.

C. Analytical Results - Dosing Formulations (Appendix Q):

A six-hour stability at room temperature storage was demonstrated for the batch size and concentration level used to prepare the dosing solution for the low-dose group in this study. The solution analyzed had mean nominal values of 99.9% at time zero and 93.8% at the six hour interval.

Periodic analysis of dosing solutions used for the study demonstrated mean nominal values of $100 \pm 2.01\%$, $103 \pm 2.69\%$ and $105 \pm 3.39\%$ for the low-, mid- and high-dose groups, respectively.

IV. RESULTS AND DISCUSSION (cont.):

D. Summary:

Hydroquinone administered by gastric intubation as a solution in degassed water to pregnant rabbits over the Day 6-18 gestation interval was not maternally toxic, embryotoxic, fetotoxic or teratogenic at the 25 mg/kg/day dose level.

At the mid-dose level (75 mg/kg/day), minimal maternal toxicity was evident as a reduction in mean food consumption during the Day 11-14 gestation interval; however, only on Days 11 and 12 were these differences from control data statistically significant. No other maternal toxicity was seen at the mid-dose level and this dose level was not considered to be embryotoxic, fetotoxic or teratogenic.

In the high-dose group (150 mg/kg/day), maternal toxicity was evident from the following statistically significant differences from control data; lower weights for Days 16 and 18 of gestation; greater magnitude of weight loss over the gestation Day 6-18 treatment interval [the control group also experienced a mean weight loss over this interval (-11 grams versus -282 grams for the high-dose group)]; and reduced food consumption for Days 6-14 and 17 of gestation. No adverse effect of treatment on the high-dose level females was evident from physical observation data, uterine implantation data, liver or kidney weights or gross postmortem examination data. No embryotoxicity was evident from uterine implantation data. Mean fetal weights were comparable to concurrent control data but were outside the low range of recent historical control data for this laboratory.

IV. RESULTS AND DISCUSSION (cont.):

D. Summary (cont.):

An increase in incidence of fetuses with external, visceral and skeletal malformations was seen in the high-dose group and the incidence of litters containing affected fetuses was also increased; however, these incidences did not differ statistically from control data and malformations seen were considered to be associated with the maternal toxicity evident at this same dose level. Ocular defects (microphthalmia) and vertebral/rib defects were seen with increased incidence in the high-dose group. Such malformations have been identified in the published literature to be frequently associated with maternal toxicity in rabbit teratology studies. Angulated arch(es) of the hyoid, a minor skeletal malformation, was also seen with increased frequency in high-dose fetuses both in comparison to the concurrent control incidence and recent historical control data for our laboratory. This finding (angulated arch of the hyoid) is a relatively common minor malformation and was observed in the high-dose group in the absence of an association with other more severe malformations.

IV. RESULTS AND DISCUSSION (cont.):

D. Summary (cont.):

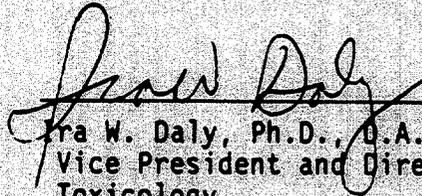
The no-observed-effect level (NOEL) for this developmental toxicity study in rabbits with hydroquinone was 25 mg/kg/day. This dose level was without maternal toxic effects and was not considered to be embryotoxic, fetotoxic or teratogenic. At the higher dose levels, maternal toxicity was evident with these effects being most pronounced at the highest dose level evaluated (150 mg/kg/day).



Raymond E. Schroeder, M.S., D.A.B.T.
Study Director
Manager, Reproduction/Teratology Section

1/9/89

Date



Ira W. Daly, Ph.D., D.A.B.T.
Vice President and Director of
Toxicology

1/9/89

Date



A Developmental Toxicity Study in Rabbits with Hydroquinone

Methodology and References - General

Parameter	Reference or Description
Physical Examination	<p>Behavior: aggressiveness, increased or decreased activity.</p> <p>Respiration: nasal discharge and rales.</p> <p>Ocular: chromodacryorrhea, excessive lacrimation and percent opacity.</p> <p>Appearance: alopecia, ano-genital staining and general condition.</p> <p>Gastrointestinal: abdominal shape and fecal consistency.</p> <p>Palpation for tissue masses.</p> <p>Other: includes any unusual observation not included above.</p>
Body Weight (maternal)	Mettler Balance, Model PE12
Body Weight (fetal)	Mettler Balance, Model PE4000
Food Consumption	<p>Mettler Balance, Model PE12. Feeders were filled (900 grams) and weighed individually just prior to presentation on Days 1-29 (daily) of gestation. Feeders were removed on Days 2-30 (daily) of gestation. The resulting weight at each interval was subtracted from the initial, feeder in weight. Resulting value = grams/day.</p> $\text{g/kg/day} = \frac{\text{grams/day}}{\text{current (first day of the measurement interval) or previous body weight (kg)}}$ <p>Measurement intervals with body weight used to calculate grams of feed per kilogram of body weight per day (g/kg/day) are as follows:</p> <p>Day 1-2 : Day 0 body weight</p> <p>Day 2-3 : Day 0 body weight</p> <p>Day 3-4 : Day 0 body weight</p> <p>Day 4-5 : Day 0 body weight</p> <p>Day 5-6 : Day 0 body weight</p> <p>Day 6-7 : Day 6 body weight</p> <p>Day 7-8 : Day 6 body weight</p> <p>Day 8-9 : Day 6 body weight</p> <p>Day 9-10 : Day 9 body weight</p> <p>Day 10-11 : Day 9 body weight</p> <p>Day 11-12 : Day 9 body weight</p> <p>Day 12-13 : Day 12 body weight</p> <p>Day 13-14 : Day 12 body weight</p>

Appendix A (cont.)
 A Developmental Toxicity Study in Rabbits with Hydroquinone

Methodology and References - General (cont.)

Parameter	Reference or Description
Food Consumption (cont.):	Day 14-15 : Day 12 body weight Day 15-16 : Day 12 body weight Day 16-17 : Day 16 body weight Day 17-18 : Day 16 body weight Day 18-19 : Day 18 body weight Day 19-20 : Day 18 body weight Day 20-21 : Day 18 body weight Day 21-22 : Day 18 body weight Day 22-23 : Day 18 body weight Day 23-24 : Day 18 body weight Day 24-25 : Day 24 body weight Day 25-26 : Day 24 body weight Day 26-27 : Day 24 body weight Day 27-28 : Day 24 body weight Day 28-29 : Day 24 body weight Day 29-30 : Day 24 body weight
Anesthesia/Euthanasia Solution (maternal)	Sleepaway [®] (Euthanasia Solution) Sodium Pentobarbital, Lot No. 471199
Anesthesia/Euthanasia Solution (fetal)	T-61 [®] Euthanasia Solution Lot No. 0450077
Uterine Staining Procedure	Salewski, E. "Farbemethode zum Makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte", <u>Archiv. Path. Exp. Pharmacol.</u> , 247 (1964), 367.

Methodology and References - General (cont.)

Parameter	Reference or Description
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Histological Methods

Fetal Skeletal
Evaluations

Stain -
Alizarin Red S

Crary, D.D. "Modified Benzyl Alcohol Clearing of Alizarin-Stained Specimens without Loss of Flexibility", Stain Technology, 37 (1962), 124-125.

The procedure of Crary was modified by Bio/dynamics, Inc. as follows:

1. Specimens were not air dried but were placed in a 1.0% potassium hydroxide solution immediately following evisceration and skinning;
2. There was a provision for a separate Alizarin Red S staining step;
3. There was a provision for a separate destaining step using a 20% glycerin and 1% potassium hydroxide aqueous solution to remove excess stain from the specimens;
4. Specimens were cleared in a 1:1 mixture of 100% glycerin and 70% ethanol instead of using a solution of glycerin, ethanol and benzyl alcohol; and
5. Specimens were stored in 100% glycerin with a few crystals of thymol added.

Techniques

Fetal Soft Tissue
Evaluations

Microdissection

Staples, R.E. "Detection of Visceral Alteration in Mammalian Fetuses", Teratology, 19 (1974), A37 (Abstract).

Methodology and References - Statistical Analysis

Reference or Description

Statistical Analysis of Data:

Results of analysis by the indicated statistical procedure were reported for the following:

<u>Parameter</u>	<u>Statistical Evaluation</u>
1. Mean body weights - gestation: (Days 0, 6, 9, 12, 16, 18, 24 and 30).	Interval Data (Method A)
2. Mean body weight change - gestation: (Days 0-6, 6-9, 9-12, 12-16, 16-18, 18-24 24-30, 6-18 and 18-30).	Interval Data (Method A)
3. Gravid uterine weight, Day 30 corrected weights and net maternal body weight change - gestation (Days 6-30).	Interval Data (Method A)
4. Mean food consumption - g/kg/day: (Days 1-29 - daily).	Interval Data (Method A)
5. Mean organ weight data - absolute and relative to corrected Day 30 body weights.	Interval Data (Method A)
6. Reproduction Data:	
a. Mean number of corpora lutea	Interval Data (Method A)
b. Mean number of uterine implantation sites	Interval Data (Method A)
c. Mean number of fetuses (live and dead) and mean fetal weight (as a composite for both sexes and when distinguished by sex)	Interval Data (Method A)
d. Mean number of resorptions	Interval Data (Method A)
e. Mean pre-implantation loss ratio	Interval Data (Method A)
f. Mean resorption/implant ratio	Interval Data (Method A)
7. Mortality Rates	Incidence Data (Method B)
8. Pregnancy Rates	Incidence Data (Method B)
9. Incidence of fetuses with malformations/ variations (external, visceral and skeletal) and the incidence of litters containing fetuses with malformations/ variations.	Incidence Data (Method B)
10. Incidence of litters with resorption sites	Incidence Data (Method B)

Appendix A (cont.)
A Developmental Toxicity Study in Rabbits with Hydroquinone

Methodology and References - Statistical Analysis (cont.)

Reference or Description

METHOD A - Methodology and References:

Statistical evaluation of equality of means was made by the appropriate one way analysis of variance technique, followed by a multiple comparison procedure if needed. First, Bartlett's test was performed to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not, nonparametric procedures were used. The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from the control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from control.

A statistical test for trend in the dose levels was also performed. In the parametric case (i.e., equal variance) standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1%, two-sided risk level. All other statistical tests were conducted at the 5% and 1%, two-sided risk level.

References for these techniques are Snedecor, G.W., and Cochran, W.G., Statistical Methods. 6th edition, Iowa State University Press (1967); Hollander, M. and Wolfe, D.A., Nonparametric Statistical Methods. John Wiley and Sons, New York (1973); Dunnett, C.W., J. Am. Sta. Assn. Vol. 50 (1955) and Biometrics. Vol. 20 (1964).

Bartlett's Test	pp. 296-298	S&C
ANOVA	pp. 277-279	S&C
Dunnett's	pp. 1096-1121	D
	pp. 482-491	Bio
Kruskal-Wallis	pp. 114-116	H&W
Summed Rank Test (Dunn)	p. 131	H&W
Regression Analysis		
Trend	pp. 149-152	S&C
Lack of Fit	pp. 456-459	S&C
Jonckheere's Statistic	pp. 120-123	H&W
Arc Sine	pp. 327-329	S&C

Appendix A (cont.)
A Developmental Toxicity Study in Rabbits with Hydroquinone

Methodology and References - Statistical Analysis (cont.)

Reference or Description

Statistical evaluation not performed when the standard deviation for the control group or more than one group is 0.0, due to lack of variance. If the N (number of animals) for the control group is less than or equal to two animals, no statistics are presented due to lack of variance.

METHOD A - Statistical Symbols:

MULTIPLE GROUP ANALYSIS

<u>STAT SYMBOL</u>		<u>STATISTICAL STATEMENT</u>
<u>No Sig</u>	<u>p\leq0.05</u>	<u>p\leq0.01</u>
NT		Not tested due to lack of variance.
<u>Parametric</u>		
A-		No statistical differences among the means (parametric ANOVA).
A	A+	The means differ significantly (parametric ANOVA).
L	L+	The response is linearly related to the dose levels.
Q	Q+	The response shows a lack of fit.
*	**	Significantly different from control (Dunnett's).
<u>Nonparametric</u>		
K-		No statistical differences among the means (Kruskal-Wallis, nonparametric).
K	K+	The means differ significantly (Kruskal-Wallis nonparametric).
J	J+	There is an ordered response to dosage.
*	**	Significantly different from control (Dunn's Rank Sum).

Statistical symbols are presented on the mean and summary tables of the appendices.

Appendix A (cont.)
A Developmental Toxicity Study in Rabbits with Hydroquinone

Methodology and References - Statistical Analysis (cont.)

Reference or Description

METHOD B - Methodology and References:

Statistical analysis of incidence data was performed using contingency tables. First, a standard chi-square analysis was performed to determine if the proportion of incidences differed between the groups tested. Next, each treatment group was compared to the control group using a 2x2 Fisher Exact Test; the significance level was corrected via the Bonferroni inequality to assure an overall test of the stated significance level. Thirdly, Armitage's test for linear trend in the dosage groups was performed. In keeping with standard statistical practice, if any one cell had an expected value less than 5, the chi-square and Armitage's tests were not reported. When this occurred, only the Fisher Exact test (corrected via Bonferroni inequality) was performed and reported.

All test were reported at the 5% and 1% level of significance.

References for the techniques are:

- Chi-square: Snedecor, G.W., and Cochran, W.G., Statistical Methods, 6th ed., Iowa State University Press, Ames, Iowa (1971). pp. 250-253.
- Fisher Exact Test: Bradley, J.V., Distribution Free Statistical Tests. Prentice-Hall, Englewood Cliffs, New Jersey (1968). pp. 195-203.
- Bonferroni Inequality: Miller, R.G., Jr., Simultaneous Statistical Inference. McGraw-Hill Book Co., New York (1966). p. 15.
- Armitage's Test: Armitage, P., "Tests for linear Trends in Proportions and Frequencies", Biometrics. (Sept. 1955). pp. 375-386.

Methodology and References - Statistical Analysis (cont.)

Reference or Description

METHOD B - Statistical Symbols:

<u>SYMBOL</u>			<u>STATISTICAL STATEMENT</u>
<u>No Sig</u>	<u>p≤0.05</u>	<u>p≤0.01</u>	
	C-		No statistical differences among the groups (chi-square).
	C+	C++	The groups differ significantly (chi-square).
	*	**	Significantly different from control (Fisher Exact Test).
	A	A+	The response is linearly related to the dose levels (Armitage's Test).
	F	F+	The response shows a lack of fit.
NS			No statistical differences from control (Fisher Exact Test, when any one cell had an expected value less than 5).
NT			Not tested due to lack of variance.
(FE)			Indicates significance by the Fisher Exact Test when any one cell had an expected value less than 5. An asterisk (*) will appear next to the treated group which is significantly different from the control group.

Statistical symbols are presented on the mean and summary tables of the appendices

B-1
APPENDIX B
A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

ANIMAL TERMINATION HISTORY

AN. NO.	SEX	TYPE OF DEATH	DATE OF DEATH	DAYS ON STUDY	# OF DAYS DOSED
GROUP I					
0 MG/KG					
1501	F	SCHEDULED SACRIFICE	31-MAR-88	30	13 P
1502	F	SCHEDULED SACRIFICE	4-APR-88	30	13 NP
1503	F	SCHEDULED SACRIFICE	4-APR-88	30	13 P
1504	F	SCHEDULED SACRIFICE	5-APR-88	30	13 P
1505	F	SCHEDULED SACRIFICE	5-APR-88	30	13 P
1506	F	SCHEDULED SACRIFICE	6-APR-88	30	13 P
1507	F	SCHEDULED SACRIFICE	7-APR-88	30	13 P
1508	F	SCHEDULED SACRIFICE	8-APR-88	30	13 NP
1509	F	SCHEDULED SACRIFICE	8-APR-88	30	13 P
1510	F	SCHEDULED SACRIFICE	11-APR-88	30	13 P
1511	F	SCHEDULED SACRIFICE	11-APR-88	30	13 P
1512	F	SCHEDULED SACRIFICE	12-APR-88	30	13 NP
1513	F	SCHEDULED SACRIFICE	13-APR-88	30	13 P
1514	F	SCHEDULED SACRIFICE	14-APR-88	30	13 P
1515	F	SCHEDULED SACRIFICE	14-APR-88	30	13 P
1516	F	SCHEDULED SACRIFICE	15-APR-88	30	13 P
1517	F	DELIVERED SACRIFICE	15-APR-88	30	13 P
1518	F	DELIVERED SACRIFICE	18-APR-88	30	13 P
GROUP II					
25 MG/KG					
2501	F	SCHEDULED SACRIFICE	31-MAR-88	30	13 P
2502	F	SCHEDULED SACRIFICE	4-APR-88	30	13 P
2503	F	SCHEDULED SACRIFICE	4-APR-88	30	13 P
2504	F	SCHEDULED SACRIFICE	5-APR-88	30	13 P
2505	F	SCHEDULED SACRIFICE	5-APR-88	30	13 P
2506	F	SCHEDULED SACRIFICE	6-APR-88	30	13 P
2507	F	SCHEDULED SACRIFICE	7-APR-88	30	13 P
2508	F	SCHEDULED SACRIFICE	8-APR-88	30	13 P
2509	F	SCHEDULED SACRIFICE	8-APR-88	30	13 P
2510	F	SCHEDULED SACRIFICE	11-APR-88	30	13 P
2511	F	SCHEDULED SACRIFICE	11-APR-88	30	13 P
2512	F	SCHEDULED SACRIFICE	12-APR-88	30	13 P
2513	F	SCHEDULED SACRIFICE	13-APR-88	30	13 P
2514	F	SCHEDULED SACRIFICE	14-APR-88	30	13 P
2515	F	SCHEDULED SACRIFICE	14-APR-88	30	13 P
2516	F	SCHEDULED SACRIFICE	15-APR-88	30	13 P
2517	F	SCHEDULED SACRIFICE	15-APR-88	30	13 P
2518	F	SCHEDULED SACRIFICE	18-APR-88	30	13 P

P-Pregnant, NP-Not pregnant (No uterine foci visualized after staining).

ANIMAL TERMINATION HISTORY

AN. NO.	SEX	TYPE OF DEATH	DATE OF DEATH	DAYS ON STUDY	# OF DAYS DOSED
GROUP III		75 MG/KG			
3501	F	SCHEDULED SACRIFICE	31-MAR-88	30	13 P
3502	F	SCHEDULED SACRIFICE	31-MAR-88	30	13 P
3503	F	SCHEDULED SACRIFICE	4-APR-88	30	13 P
3504	F	SCHEDULED SACRIFICE	5-APR-88	30	13 P
3505	F	SCHEDULED SACRIFICE	6-APR-88	30	13 P
3506	F	SCHEDULED SACRIFICE	6-APR-88	30	13 P
3507	F	SCHEDULED SACRIFICE	7-APR-88	30	13 P
3508	F	SCHEDULED SACRIFICE	7-APR-88	30	13 P
3509	F	SCHEDULED SACRIFICE	8-APR-88	30	13 P
3510	F	SCHEDULED SACRIFICE	11-APR-88	30	13 P
3511	F	SCHEDULED SACRIFICE	12-APR-88	30	13 P
3512	F	SCHEDULED SACRIFICE	12-APR-88	30	13 P
3513	F	DELIVERED SACRIFICE	13-APR-88	30	13 P
3514	F	SCHEDULED SACRIFICE	13-APR-88	30	13 P
3515	F	DELIVERED SACRIFICE	13-APR-88	29	13 P
3516	F	SCHEDULED SACRIFICE	15-APR-88	30	13 P
3517	F	SCHEDULED SACRIFICE	18-APR-88	30	13 P
3518	F	DELIVERED SACRIFICE	14-APR-88	26	13 P
GROUP IV		150 MG/KG			
4501	F	SCHEDULED SACRIFICE	31-MAR-88	30	13 P
4502	F	SCHEDULED SACRIFICE	31-MAR-88	30	13 P
4503	F	SCHEDULED SACRIFICE	4-APR-88	30	13 P
4504	F	SCHEDULED SACRIFICE	5-APR-88	30	13 P
4505	F	SCHEDULED SACRIFICE	6-APR-88	30	13 P
4506	F	DELIVERED SACRIFICE	3-APR-88	27	13 P
4507	F	SCHEDULED SACRIFICE	7-APR-88	30	13 P
4508	F	SCHEDULED SACRIFICE	7-APR-88	30	13 P
4509	F	SCHEDULED SACRIFICE	8-APR-88	30	13 P
4510	F	SCHEDULED SACRIFICE	11-APR-88	30	13 P
4511	F	SCHEDULED SACRIFICE	12-APR-88	30	13 P
4512	F	SCHEDULED SACRIFICE	12-APR-88	30	13 P
4513	F	SCHEDULED SACRIFICE	13-APR-88	30	13 P
4514	F	SCHEDULED SACRIFICE	13-APR-88	30	13 NP
4515	F	SCHEDULED SACRIFICE	14-APR-88	30	13 P
4516	F	DELIVERED SACRIFICE	12-APR-88	27	13 P
4517	F	SCHEDULED SACRIFICE	18-APR-88	30	13 P
4518	F	SCHEDULED SACRIFICE	18-APR-88	30	13 P

P-Pregnant, NP-not pregnant (No uterine foci visualized after staining).

C-2
 APPENDIX C (cont.)
 A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

97-3320

INDIVIDUAL MATERNAL BODY WEIGHTS DURING GESTATION - 2F3MS

DOSAGE: 0 MG/KG

FEMALE#	DAY OF GESTATION							
	0	6	9	12	16	18	24	30
1501 P	3385	3365	3509	3559	3653	3673	3741	3736
1502 NP	3817	3939	3897	3878	3846	3772	3867	3955
1503 P	3841	3827	3818	3880	3945	3993	4073	4083
1504 P	4255	4431	4459	4488	4595	4718	4747	4634
1505 P	4573	4573	4532	4608	4562	4602	4569	4700
1506 P	4726	4882	4860	4862	4666	4586	4365	4331
1507 P	3624	4013	3928	3853	3918	3880	3988	4029
1508 NP	3555	3629	3618	3619	3633	3581	3681	3800
1509 P	3822	3867	3792	3711	3613	3646	3753	3527
1510 P	4448	4597	4687	4749	4955	5020	5051	4954
1511 P	4708	4763	4764	4799	4887	4881	4912	5003
1512 NP	4591	4560	4460	4555	4620	4684	4720	4836
1513 P	3839	3902	3939	3935	4007	4000	4057	3962
1514 P	3891	3961	3993	3948	4023	3990	4074	4021
1515 P	4512	4409	4378	4332	4157	4055	4385	4524
1516 P	4366	4319	4338	4310	4322	4212	3854	3594
1517 P	4669	4773	4726	4712	4711	4608	4397	DELIVERED
1518 P	4949	5099	5114	5083	4913	4768	4551	DELIVERED
MEAN	4241	4330	4322	4322	4329	4309	4301	4238
S.D.	472	483	469	478	458	452	411	493
N	15	15	15	15	15	15	15	13

P=PREGNANT NP=NON PREGNANT. BODY WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL BODY WEIGHTS DURING GESTATION - GRAMS

DOSAGE: 25 MG/KG

FEMALE#		DAY OF GESTATION							
		0	6	9	12	16	18	24	30
2501	P	3528	3678	3616	3645	3675	3700	3817	3881
2502	P	3641	3737	3723	3760	3791	3882	3948	3882
2503	P	4024	4136	4123	4176	4332	4371	4424	4395
2504	P	3888	4046	4068	4050	4024	4085	4134	4303
2505	P	4603	4672	4702	4622	4465	4541	4602	4207
2506	P	4456	4516	4529	4510	4599	4573	4626	4598
2507	P	3930	3927	3909	3909	3975	3963	4038	3933
2508	P	3456	3497	3509	3517	3562	3576	3659	3759
2509	P	4340	4339	4374	4349	4286	4366	4070	3870
2510	P	4282	4395	4450	4484	4575	4597	4640	4578
2511	P	4676	4802	4618	4677	4684	4670	4745	4803
2512	P	4287	4380	4320	4344	4384	4258	4247	4351
2513	P	3869	3924	3872	3896	3895	3806	3866	3824
2514	P	3467	3660	3612	3643	3726	3763	3855	3866
2515	P	4583	4601	4546	4532	4415	4340	4505	4708
2516	P	4321	4337	4326	4318	4394	4347	4149	3857
2517	P	4695	4860	4537	4818	4824	4772	4825	4550
2518	P	4637	4682	4629	4673	4766	4749	4862	4860
MEAN		4145	4233	4192	4218	4243	4242	4278	4235
S.D.		434	424	397	408	397	383	382	382
N		16	18	18	18	18	18	18	18

P=PREGNANT NP=NON PREGNANT. BODY WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL BODY WEIGHTS DURING GESTATION - grams

DOSAGE: 75 MG/KG

FEMALE#	DAY OF GESTATION							
	0	6	9	12	16	18	24	30
3501 P	3970	4067	3925	3844	3871	3910	3879	4008
3502 P	4624	4752	4646	4597	4505	4517	4657	4757
3503 P	4085	4120	4166	4205	4276	4314	4304	4168
3504 P	3861	3880	3774	3685	3506	3500	3706	3686
3505 P	3571	3610	3636	3702	3740	3714	3807	3801
3506 P	4234	4301	4372	4385	4455	4414	4365	4252
3507 P	3976	4136	4069	4116	4224	4260	4443	4534
3508 P	4705	4787	4742	4760	4626	4578	4669	4742
3509 P	4350	4498	4505	4487	4638	4630	4632	4552
3510 P	4058	4151	4102	4109	4079	4171	4291	4434
3511 P	3970	4089	4088	4081	4139	4074	4163	4311
3512 P	4101	4312	4224	4220	4477	4559	4496	4808
3513 P	4010	4116	4062	3893	4036	4080	4175	DELIVERED
3514 P	4745	4948	4883	4792	4706	4564	4639	4639
3515 P	4684	4303	4432	4160	4629	4563	4603	DELIVERED
3516 P	4092	4133	4152	4108	3991	3906	3880	3993
3517 P	3738	3918	3929	3912	3934	3975	4049	4208
3518 P	4491	4598	4631	4590	4702	4653	4689	DELIVERED
MEAN	4181	4262	4241	4203	4252	4243	4303	4326
S.D.	346	343	343	338	361	346	329	352
N	18	18	18	18	18	18	18	15

P=PREGNANT NP=NON PREGNANT. BODY WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

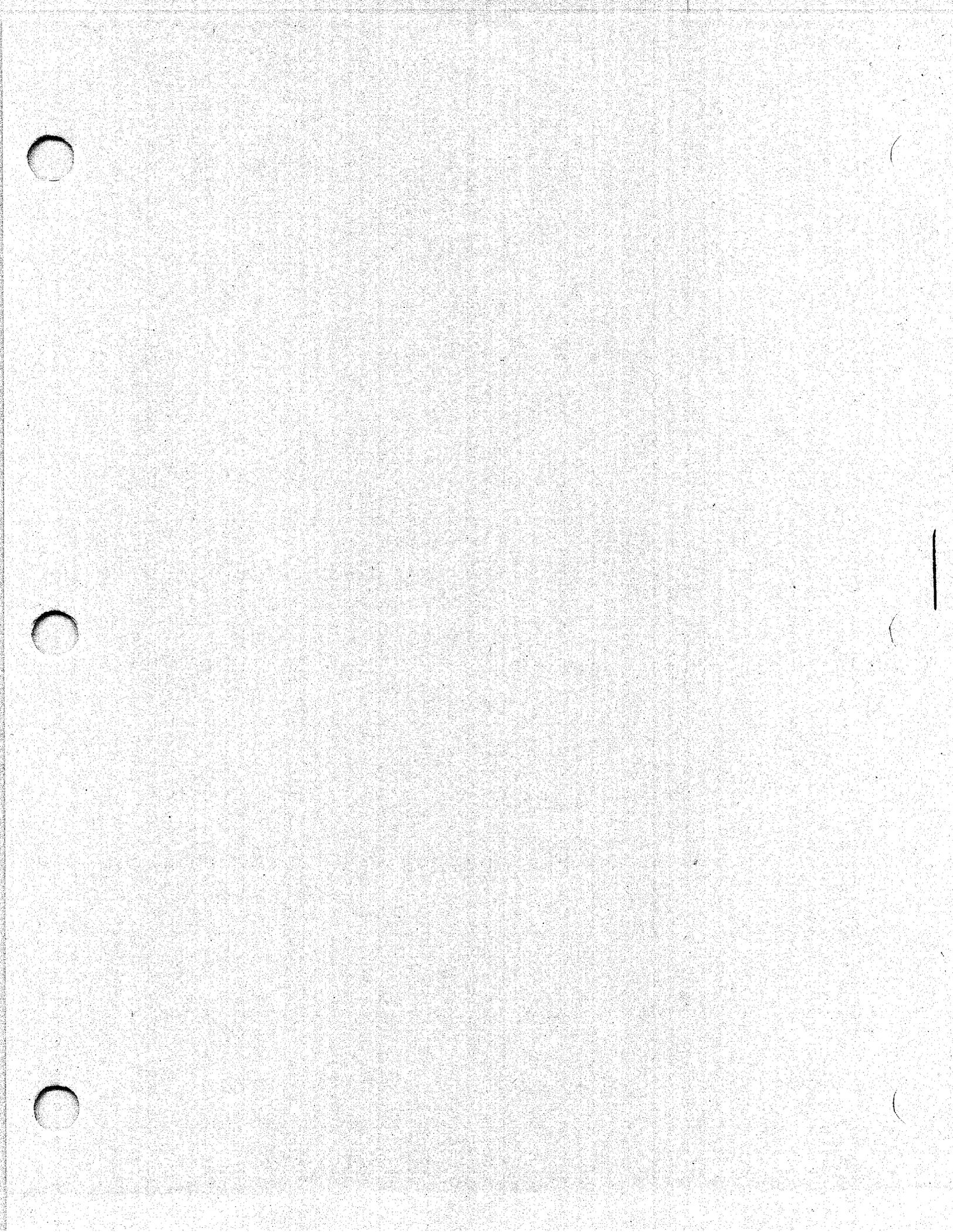
87-3200

INDIVIDUAL MATERNAL BODY WEIGHTS DURING GESTATION - grams

DOSAGE: 150 MG/KG

FEMALE#	DAY OF GESTATION							
	0	5	9	12	16	18	24	30
4501 P	4254	4305	4232	4129	4262	4175	4289	4474
4502 P	4312	4309	4231	4093	3848	3736	3682	3586
4503 P	4371	4388	4219	4056	4184	4056	4330	4415
4504 P	3678	3758	3673	3657	3601	3548	3688	3779
4505 P	3961	4039	4032	3990	3975	3883	4064	4353
4506 P	4187	4223	3967	3690	3775	3751	3728	DELIVERED
4507 P	4132	4273	4154	4198	4287	4373	4444	4393
4508 P	4360	4354	4147	4218	4193	4146	4179	4338
4509 P	4443	4537	4424	4463	4493	4518	4605	4592
4510 P	3938	4112	3996	4035	3923	3902	3427	3802
4511 P	4074	4171	4055	4024	3896	3855	3980	4113
4512 P	4150	4201	4090	3918	3805	3741	3569	3648
4513 P	4132	4081	4039	4051	3919	3877	4061	4186
4514 NP	4541	4618	4534	4412	4361	4205	4472	4489
4515 P	4562	4803	4741	4648	4397	4256	4343	4520
4516 P	4065	4157	3968	3784	3636	3750	3342	DELIVERED
4517 P	3865	3935	3645	3516	3385	3345	3811	3803
4518 P	3953	4019	3915	3920	3970	3944	4135	4408
MEAN	4143	4216	4090	4023	3973	3933	3981	4161
S.D.	327	338	256	280	298	297	369	344
N	17	17	17	17	17	17	17	15

P=PREGNANT NP=NON PREGNANT. BODY WEIGHT NOT INCLUDED IN CALCULATION OF MEAN



[1]
 APPENDIX D
 A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE
 MATERNAL BODY WEIGHT CHANGE DURING GESTATION - grams
 MEAN VALUES

	1	2	3	4	5	6	7	8	9
	1	1	1	2	1	1	2	1	1
	2	6	8	4	6	8	6	8	8
	1	1	1	2	3	1	3	1	3
	6	9	2	6	8	4	6	8	6

STAT SYMBOL:	K-	A+L+	A+L+	A-	A-	K-	A+L+	A+L+	AL
GROUP I - 0 MG/KG/DA									
MEAN	79	3	0	7	-30	-7	-36	-11	-12
S.D.	119	60	51	119	76	174	124	244	250
N	15	15	15	15	15	15	13	15	13
GROUP II - 25 MG/KG/DA									
MEAN	84	-40	26	25	0	36	-43	9	-7
S.D.	60	89	72	78	61	111	161	129	236
N	18	18	18	18	18	18	18	18	18
GROUP III - 75 MG/KG/DA									
MEAN	81	-31	-38	49	-8	59	61	-18	120
S.D.	128	70	82	155	63	78	120	202	147
N	18	18	18	18	18	18	15	18	15
GROUP IV - 150 MG/KG/DA									
MEAN	73	**	-66	-45	-40	48	120	**	*
S.D.	70	-125	106	122	68	231	121	-291	204
N	17	75	17	17	17	17	15	203	209

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3000

INDIVIDUAL MATERNAL BODY WEIGHT CHANGE DURING GESTATION - grams

DOSAGE: 0 MG/KG

FEMALE#	DAY OF GESTATION									
	0 - 6	6 - 9	9 - 12	12 - 16	16 - 18	18 - 24	24 - 30	6 - 18	18 - 30	
1501 P	-20	144	50	94	20	68	-5	308	63	
1502 NP	122	-42	-19	-32	-74	95	88	-167	183	
1503 P	-14	-9	62	65	48	80	10	166	90	
1504 P	176	28	29	107	123	29	-113	287	-84	
1505 P	-5	-41	76	-46	40	-33	131	29	98	
1506 P	156	-22	2	-196	-80	-221	-34	-296	-255	
1507 P	389	-85	-75	65	-38	108	41	-133	149	
1508 NP	74	-11	1	14	-52	100	119	-48	219	
1509 P	45	-75	-81	-93	28	107	-226	-221	-119	
1510 P	149	90	62	206	65	31	-97	423	-66	
1511 P	75	-19	35	85	-6	31	91	98	122	
1512 NP	-31	-100	95	65	64	36	116	124	152	
1513 P	63	37	-4	72	-7	57	-95	98	-38	
1514 P	70	32	-45	75	-33	84	-53	29	31	
1515 P	-103	-31	-46	-175	-102	330	139	-354	469	
1516 P	-47	19	-28	12	-110	-358	-260	-107	-618	
1517 P	104	-47	-14	-1	-103	-211	DELIVERED	-165		
1518 P	150	15	-31	-170	-145	-217	DELIVERED	-331		
MEAN	79	2	-1	7	-20	-6	-36	-11	-12	
S.D.	119	60	51	119	76	174	124	244	250	
N	15	15	15	15	15	15	13	15	13	

P=PREGNANT NP=NON PREGNANT. BODY WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

D-3
APPENDIX D (cont.)
- DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL BODY WEIGHT CHANGE DURING GESTATION - GRAMS

DOSAGE: 25 MG/KG

FEMALE#	DAY OF GESTATION									
	0 - 6	6 - 9	9 - 12	12 - 16	16 - 18	18 - 24	24 - 30	6 - 18	18 - 30	
2501 P	150	-62	29	30	25	117	64	22	181	
2502 P	96	-14	37	31	91	66	-66	145	0	
2503 P	112	-13	53	156	39	53	-29	235	24	
2504 P	158	22	-18	-26	61	49	169	39	218	
2505 P	69	30	-80	-157	76	61	-395	-131	-334	
2506 P	60	13	-19	89	-26	53	-28	57	25	
2507 P	-3	-18	0	66	-12	75	-105	36	-30	
2508 P	41	12	8	45	14	83	100	79	183	
2509 F	-1	35	-25	-63	80	-296	-200	27	-496	
2510 P	113	55	34	91	22	43	-62	202	-19	
2511 P	126	-184	59	7	-14	75	58	-132	133	
2512 P	93	-60	24	40	-126	-11	104	-122	93	
2513 P	55	-52	24	-1	-89	60	-42	-118	18	
2514 P	193	-48	31	83	37	92	11	103	103	
2515 F	18	-55	-14	-117	-75	165	203	-261	368	
2516 P	16	-11	-5	76	-47	-198	-292	10	-490	
2517 P	165	-323	281	6	-52	53	-275	-88	-222	
2518 P	45	-52	44	92	-17	113	-2	67	111	
MEAN	34	-40	32	35	-1	36	-44	9	-7	
S.D.	60	89	72	78	61	111	161	135	236	
N	12	12	18	18	12	19	12	18	18	

P=PREGNANT NP=NON PREGNANT. BODY WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL BODY WEIGHT CHANGE DURING GESTATION - grams

DOSEAGE: 75 MG/KG

FEMALE#	DAY OF GESTATION									
	0 - 6	6 - 9	9 - 12	12 - 16	16 - 18	18 - 24	24 - 30	6 - 18	18 - 30	
3501 P	97	-142	-81	27	39	-31	129	-157	98	
3502 P	128	-106	-49	-92	12	140	100	-235	240	
3503 F	35	46	39	71	38	-10	-136	194	-146	
3504 P	19	-106	-89	-179	-6	206	-20	-380	186	
3505 P	39	26	66	38	-26	93	-6	104	87	
3506 P	67	71	13	70	-41	-49	-113	113	-162	
3507 F	160	-67	47	106	36	183	91	124	274	
3508 P	82	-45	16	-134	-48	91	73	-209	164	
3509 F	148	7	-18	151	-8	2	-80	132	-78	
3510 P	93	-49	7	-30	92	120	143	20	263	
3511 F	119	-1	-7	58	-65	89	148	-15	237	
3512 P	211	-88	-4	357	82	-63	312	247	249	
3513 P	106	-54	-165	142	44	95	DELIVERED	-36		
3514 P	202	-65	-91	-86	-142	75	0	-384	75	
3515 P	-381	129	-272	469	-66	40	DELIVERED	260		
3516 P	41	19	-44	-117	-85	-26	113	-227	87	
3517 P	180	11	-17	22	41	74	159	57	233	
3518 P	107	33	-41	112	-49	36	DELIVERED	55		
MEAN	81	-21	-38	49	-8	59	61	-19	120	
S.D.	128	70	82	155	62	78	120	202	147	
N	16	18	18	18	18	18	15	18	15	

P=PREGNANT NP=NON PREGNANT. BODY WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

INDIVIDUAL MATERNAL BODY WEIGHT CHANGE DURING GESTATION - grams

DOSAGE: 150 MG/KG

FEMALE#	DAY OF GESTATION									
	0 - 6	6 - 9	9 - 12	12 - 16	16 - 18	18 - 24	24 - 30	6 - 18	18 - 30	
4501 P	51	-73	-103	133	-87	114	185	-130	299	
4502 P	-3	-78	-138	-245	-112	-54	-96	-573	-150	
4503 P	17	-169	-163	128	-128	274	85	-332	359	
4504 P	80	-85	-16	-56	-53	140	91	-210	231	
4505 P	78	-7	-42	-15	-92	181	289	-156	470	
4506 P	36	-256	-277	85	-24	-23	DELIVERED	-472		
4507 P	141	-119	44	89	86	71	-51	100	20	
4508 P	-6	-207	71	-25	-47	33	159	-208	192	
4509 P	94	-113	39	30	25	87	-13	-19	74	
4510 P	174	-116	39	-112	-21	-475	375	-210	-100	
4511 P	97	-116	-31	-128	-41	125	133	-316	258	
4512 P	51	-111	-172	-113	-64	-172	79	-460	-93	
4513 F	-51	-42	12	-132	-42	184	125	-204	309	
4514 NP	77	-84	-122	-51	-156	267	17	-413	284	
4515 F	241	-62	-93	-251	-141	87	177	-547	264	
4516 P	92	-189	-184	-148	114	-408	DELIVERED	-407		
4517 F	70	-290	-129	-131	-40	466	-8	-590	458	
4518 F	66	-104	5	50	-26	191	273	-75	464	
MEAN	72	-106	-67	-49	-41	48	120	-283	204	
S.D.	70	75	100	122	68	331	131	302	309	
N	17	17	17	17	17	17	15	17	15	

DEFINITIONS: NP=NON PREGNANT. BODY WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A Developmental Toxicity Study in Rabbits with Hydroquinone

Gravid Uterine Weight and Net Maternal Body Weight Change
Preface

Key:

UTER. WT = Gravid Uterine Weight.
CORR. B.W. = Corrected Day 30 body weight.
CORR. BWC. = Body weight change from Day 6-30 of gestation using corrected Day 30 body weights.

Note:

On pages E-3 through E-6 (individual values):
CARCASS WEIGHT = Corrected body weight

The actual Day 30 body weight minus the weight of the gravid uterus equals the corrected Day 30 body weight.

APPENDIX E (cont.)

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

GRAVID UTERINE WEIGHT AND NET MATERNAL BODY WEIGHT CHANGE
MEAN VALUES

	U T E R I N E W E I G H T	C O R P O R A L W E I G H T	C O R P O R A L W E I G H T
UNITS	GRAMS	GRAMS	GRAMS
STAT SYMBOL:	A+	A-	A-
GROUP I - 0 MG/KG/DAY			
MEAN	527.9	3710.4	-514.9
S.D.	167.6	376.8	244.4
N	13	13	13
GROUP II - 25 MG/KG/DAY			
MEAN	498.2	3736.5	-496.2
S.D.	101.0	360.8	258.8
N	12	12	18
GROUP III - 75 MG/KG/DAY			
MEAN	663.9	3662.7	-584.0
S.D.	70.7	306.2	217.3
N	15	15	15
GROUP IV - 150 MG/KG/DAY			
MEAN	488.2	3672.4	-546.5
S.D.	123.0	348.8	261.8
N	15	15	15

GRAVID UTERINE WEIGHT AND NET MATERNAL BODY WEIGHT CHANGE IN GRAMS

PREGNANCY STATUS	GRAVID UTERUS	CARCASS WEIGHT	NET BODY CHANGE FROM DAY 6-30	
DAM #	GROUP 1	0 MG/KG		
1501	P	521.2	3214.8	-150.2
1502	NP	14.3	3940.7	1.7
1503	P	526.3	3556.7	-270.3
1504	P	758.2	3875.8	-555.2
1505	P	725.1	3974.9	-598.1
1506	P	465.5	3865.5	-1016.5
1507	P	408.8	3620.2	-392.8
1508	NP	26.7	3773.3	144.3
1509	F	357.7	3269.3	-597.7
1510	F	662.1	4291.9	-305.1
1511	P	621.4	4381.6	-401.4
1512	NP	16.4	4819.6	259.6
1513	P	638.8	3222.2	-578.8
1514	F	472.2	3548.8	-412.2
1515	P	603.2	3920.6	-488.2
1516	F	202.2	3391.8	-927.2
1517	P	DELIVERED		
1518	P	DELIVERED		
MEAN		527.9	3710.4	-514.3
S.D.		167.6	376.8	244.4
N		13	13	13

F-PREGNANT. NP-NONPREGNANT

E-4
 APPENDIX E (cont.)
 A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

GRAVID UTERINE WEIGHT AND NET MATERNAL BODY WEIGHT CHANGE IN GRAMS

PREGNANCY STATUS	GRAVID UTERUS	CARCASS WEIGHT	NET BODY CHANGE FROM DAY 6- 30

DAM #	GROUP II	25 MG/KG	
2501 P	502.1	3378.9	-399.1
2502 P	432.2	3449.8	-287.2
2503 P	662.9	3732.1	-403.9
2504 P	427.3	3875.7	-170.3
2505 P	582.7	3624.3	-1047.7
2506 P	627.2	3970.8	-545.2
2507 P	540.1	3392.9	-534.1
2508 P	453.8	3305.2	-191.8
2509 P	314.4	3555.6	-783.4
2510 P	658.6	3919.4	-475.6
2511 P	498.6	4304.4	-497.6
2512 P	565.4	3785.6	-594.4
2513 P	394.2	3429.8	-494.2
2514 P	507.6	3358.4	-301.6
2515 P	327.7	4380.3	-220.7
2516 P	437.2	3419.8	-917.2
2517 P	540.4	4009.6	-850.4
2518 P	495.8	4364.2	-317.8
MEAN	498.2	3736.5	-496.2
S.D.	101.0	360.8	258.8
n	18	18	18

 P-PREGNANT, NP-NONPREGNANT

GRAVID UTERINE WEIGHT AND NET MATERNAL BODY WEIGHT CHANGE IN GRAMS

PREGNANCY STATUS	GRAVID UTERUS	CARCASS WEIGHT	NET BODY CHANGE FROM DAY 6- 30

DAM #	GROUP III	75 MG/KG	
3501	P 614.2	3393.8	-673.2
3502	P 813.8	3943.2	-808.8
3503	P 616.6	3551.4	-568.6
3504	P 575.0	3111.0	-769.0
3505	P 580.2	3220.8	-389.2
3506	P 638.5	3613.5	-687.5
3507	P 610.4	3923.6	-212.4
3508	P 642.6	4099.4	-687.6
3509	P 726.9	3825.1	-672.9
3510	P 742.9	3691.1	-459.9
3511	P 639.2	3671.8	-417.2
3512	P 777.1	4030.9	-281.1
3513	P DELIVERED		
3514	P 651.6	3987.4	-960.6
3515	P DELIVERED		
3516	P 653.8	3339.2	-793.8
3517	P 669.5	3538.5	-379.5
3518	P DELIVERED		
MEAN	663.5	3662.7	-584.1
S.D.	70.7	306.2	217.3
N	15	15	15

P-PREGNANT. NP-NONPREGNANT

E-6
 APPENDIX E (cont.)
 A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

GRAVID UTERINE WEIGHT AND NET MATERNAL BODY WEIGHT CHANGE IN GRAMS

PREGNANCY STATUS	GRAVID UTERUS	CARCASS WEIGHT	NET BODY CHANGE FROM DAY 6- 30

DAM #	GROUP IV	150 MG/KG	
4501	P 432.0	4042.0	-263.0
4502	P 406.0	3180.0	-1129.0
4503	P 545.9	3869.1	-518.9
4504	P 497.2	3281.8	-476.2
4505	P 722.2	3630.8	-408.2
4506	P DELIVERED		
4507	P 300.4	4092.6	-180.4
4508	P 610.5	3727.5	-626.5
4509	P 417.5	4174.5	-362.5
4510	P 536.5	3265.5	-846.5
4511	P 594.8	3518.2	-652.8
4512	P 274.9	3373.1	-827.9
4513	P 533.7	3652.3	-428.7
4514	NP 31.1	4457.9	-160.1
4515	P 353.4	4166.6	-636.4
4516	P DELIVERED		
4517	P 519.7	3283.3	-651.7
4518	P 578.6	3829.4	-189.6
MEAN	488.2	3672.4	-546.6
S.D.	123.0	348.8	261.8
N	15	15	15

 P-PREGNANT, NP-NONPREGNANT

F-1
APPENDIX F
A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

MATERNAL FOOD CONSUMPTION DURING GESTATION - grams
MEAN VALUES

	D A Y	D A Y	D A Y	D A Y	D A Y	D A Y	D A Y	D A Y	D A Y	D A Y	D A Y	D A Y
	1	2	3	4	5	6	7	8	9	0	1	2
	2	3	4	5	6	7	8	9	0	1	2	3
STAT SYMBOL:	A-	K-	A-	K-	A-	A+L+	K+J+	A+L+	A+L+	A+L+	A+L+	A+L+
GROUP	I - 0 MG/KG/DAY											
MEAN	47	50	48	48	46	47	47	47	41	45	42	36
S.D.	8	6	8	7	6	7	10	7	10	11	11	11
N	14	14	15	14	14	13	13	13	15	13	14	14
GROUP	II - 25 MG/KG/DAY											
MEAN	49	47	48	53	49	46	42	42	45	43	42	35
S.D.	11	8	5	12	8	5	4	7	11	7	7	7
N	18	18	17	16	13	15	13	14	16	16	15	14
GROUP	III - 75 MG/KG/DAY											
MEAN	46	45	48	50	47	40	42	40	38	37	31	23
S.D.	10	13	6	16	7	9	9	10	11	9	14	13
N	17	17	17	18	16	15	15	15	18	18	17	18
GROUP	IV - 150 MG/KG/DAY											
MEAN	45	49	49	48	47	31	25	22	23	20	19	17
S.D.	8	6	6	6	6	12	15	14	13	15	14	17
N	13	15	16	16	14	16	15	16	17	15	16	16

F-2
APPENDIX F (cont.)
A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

MATERNAL FOOD CONSUMPTION DURING GESTATION - grams
MEAN VALUES

	D A Y 1 3 -1 4	D A Y 1 4 -1 5	D A Y 1 5 -1 6	D A Y 1 6 -1 7	D A Y 1 7 -1 8	D A Y 1 8 -1 9	D A Y 1 9 -2 0	D A Y 2 0 -2 1	D A Y 2 1 -2 2	D A Y 2 2 -2 3	D A Y 2 3 -2 4	D A Y 2 4 -2 5
STAT SYMBOL:	A+L+	A+L+	A+L+	A+L+D	A+L+	A	A-	A-	A-	A-	K-	A-
GROUP	I - 0 MG/KG/DAY											
MEAN	31	30	23	20	26	22	24	27	26	23	26	17
S.D.	15	18	19	19	23	19	20	19	18	17	28	16
N	15	15	13	12	15	14	15	14	13	14	15	14
GROUP	II - 25 MG/KG/DAY											
MEAN	32	32	33	33	35	31	33	35	33	30	31	19
S.D.	9	12	21	17	17	14	14	13	14	15	13	15
N	16	17	16	16	16	16	15	15	15	14	15	14
GROUP	III - 75 MG/KG/DAY											
MEAN	24	22	24	24	23	28	29	30	31	30	26	23
S.D.	15	17	16	13	14	12	11	11	11	9	10	10
N	18	17	17	15	15	16	12	13	15	16	15	15
GROUP	IV - 150 MG/KG/DAY											
MEAN	**	**			*	15	17	21	28	29	28	24
S.D.	14	9	10	11	10	15	17	21	28	29	28	24
N	15	13	14	13	11	11	18	18	19	17	17	17
	17	16	17	16	15	15	15	15	17	16	14	13

E-3

APPENDIX E (cont.)

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

MATERNAL FOOD CONSUMPTION DURING GESTATION - grams
MEAN VALUES

	D A Y 2 5 - 2 6	D A Y 2 6 - 2 7	D A Y 2 7 - 2 8	D A Y 2 8 - 2 9	D A Y 2 9 - 3 0
STAT SYMBOL:	A-	A-	A-	A-	AL
GROUP	I - 0 MG/KG/DAY				
MEAN	15	13	15	15	16
S.D.	14	12	14	14	14
N	15	15	15	15	13
GROUP	II - 25 MG/KG/DAY				
MEAN	16	16	17	18	20
S.D.	13	14	14	15	16
N	15	15	17	17	17
GROUP	III - 75 MG/KG/DAY				
MEAN	20	19	21	22	22
S.D.	13	13	12	14	11
N	17	16	16	15	14
GROUP	IV - 150 MG/KG/DAY				
MEAN	27	21	28	28	32
S.D.	21	16	14	13	13
N	14	14	13	12	13

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		DAY 1 - 2	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13
DAM #	GROUP I	O MG/KG											
1501	P	54.	56.	65.	52.	54.	53.	64.	58.	52.	67.	66.	55.
1502	NP	52.	47.	48.	47.	49.	43.	40.	43.	38.	38.	41.	35.
1503	P	55.	43.	41.	43.	46.	SPILLED	37.	SPILLED	40.	45.	45.	32.
1504	P	31.	59.	58.	62.	61.	51.	67.	54.	60.	58.	53.	52.
1505	P	38.	40.	43.	42.	42.	40.	42.	36.	39.	SPILLED	34.	26.
1506	P	52.	50.	54.	54.	50.	47.	47.	45.	43.	40.	40.	33.
1507	P	48.	53.	55.	42.	41.	63.	44.	55.	38.	36.	27.	17.
1508	NP	41.	46.	41.	51.	46.	44.	47.	38.	42.	42.	41.	45.
1509	P	49.	SPILLED	37.	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	18.	SPILLED	SPILLED	SPILLED
1510	P	SPILLED	56.	54.	57.	58.	54.	57.	57.	55.	56.	52.	51.
1511	P	51.	50.	46.	53.	45.	46.	42.	40.	43.	45.	43.	36.
1512	NP	44.	45.	48.	39.	44.	36.	4.	39.	49.	43.	44.	48.
1513	P	51.	53.	42.	51.	50.	46.	SPILLED	49.	47.	46.	45.	41.
1514	P	51.	44.	50.	40.	46.	43.	45.	44.	38.	44.	36.	32.
1515	P	43.	44.	49.	41.	42.	39.	46.	38.	40.	38.	25.	19.
1516	P	50.	52.	46.	46.	44.	47.	45.	47.	42.	46.	41.	35.
1517	P	34.	47.	37.	43.	45.	38.	35.	43.	30.	31.	30.	36.
1518	P	48.	46.	49.	46.	45.	44.	40.	45.	28.	29.	43.	38.
MEAN		47.	50.	48.	48.	48.	47.	47.	47.	41.	45.	42.	36.
S.D.		8.	6.	8.	7.	6.	7.	10.	7.	10.	11.	11.	11.
N		14	14	15	14	14	13	13	13	15	13	14	14

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		STATUS DAY											
		1 - 2	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13
DAM #	GROUP II	35 MG/KG											
2501 P	55.	55.	59.	58.	70.	38.	43.	49.	46.	49.	46.	42.	
2502 P	24.	43.	56.	51.	56.	57.	47.	58.	50.	52.	53.	42.	
2503 P	45.	43.	48.	46.	50.	49.	44.	SPILLED	47.	49.	56.	38.	
2504 P	47.	55.	52.	55.	45.	44.	SPILLED	43.	49.	55.	44.	43.	
2505 P	46.	48.	51.	63.	SPILLED	52.	44.	44.	51.	41.	33.	36.	
2506 P	36.	35.	43.	49.	39.	44.	39.	41.	44.	38.	40.	37.	
2507 P	50.	57.	SPILLED	SPILLED	SPILLED	43.	SPILLED	SPILLED	34.	45.	SPILLED	SPILLED	
2508 P	57.	31.	37.	60.	SPILLED	SPILLED	SPILLED	SPILLED	79.	SPILLED	SPILLED	SPILLED	
2509 P	50.	48.	44.	53.	49.	46.	47.	43.	36.	32.	32.	21.	
2510 P	57.	40.	45.	SPILLED	SPILLED	47.	48.	45.	48.	46.	45.	37.	
2511 P	58.	49.	48.	52.	50.	52.	37.	28.	44.	42.	42.	34.	
2512 P	43.	46.	43.	41.	45.	41.	38.	36.	31.	40.	36.	25.	
2513 P	78.	63.	46.	91.	SPILLED								
2514 P	55.	42.	50.	41.	47.	44.	47.	39.	44.	46.	47.	42.	
2515 P	48.	50.	53.	48.	45.	41.	SPILLED	47.	SPILLED	31.	47.	SPILLED	
2516 P	45.	59.	52.	52.	49.	50.	44.	42.	35.	42.	38.	36.	
2517 P	47.	46.	50.	51.	50.	SPILLED	44.	43.	47.	41.	33.	20	
2518 P	38.	41.	47.	41.	41.	42.	40.	33.	41.	38.	35.		
MEAN	49.	47.	48.	53.	49.	46.	43.	42.	45.	43.	42.	35.	
S.D.	11.	8.	5.	12.	8.	5.	4.	7.	11.	7.	7.	7.	
N	18	18	17	16	13	15	13	14	16	16	15	14	

P=PREGNANT NP=NON PREGNANT, FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		STATUS DAY 1 - 2 2 - 3 3 - 4 4 - 5 5 - 6 6 - 7 7 - 8 8 - 9 9 - 10 10 - 11 11 - 12 12 - 13											
DAM #	GROUP III	75 MG/KG											
3501	P	35.	37.	43.	45.	47.	35.	35.	29.	28.	30.	19.	11.
3502	P	46.	47.	48.	46.	52.	29.	39.	34.	36.	34.	23.	22.
3503	P	40.	47.	48.	48.	46.	SPILLED	SPILLED	SPILLED	45.	44.	47.	29.
3504	P	44.	42.	46.	46.	46.	22.	25.	18.	3.	14.	10.	5.
3505	P	60.	49.	54.	55.	52.	60.	48.	52.	49.	47.	57.	48.
3506	P	52.	49.	45.	95.	SPILLED	SPILLED	62.	52.	46.	46.	50.	40.
3507	P	47.	0.	54.	43.	51.	37.	41.	42.	37.	40.	30.	32.
3508	P	41.	42.	45.	38.	46.	38.	SPILLED	39.	34.	38.	31.	20.
3509	P	50.	51.	51.	59.	52.	49.	51.	46.	51.	44.	43.	42.
3510	P	54.	45.	47.	49.	48.	47.	41.	30.	41.	39.	25.	10.
3511	P	18.	43.	51.	42.	44.	29.	38.	39.	40.	33.	29.	21.
3512	P	52.	60.	57.	52.	47.	SPILLED	34.	SPILLED	44.	46.	SPILLED	28.
3513	P	56.	59.	53.	61.	52.	42.	41.	43.	43.	46.	38.	31.
3514	P	SPILLED	SPILLED	SPILLED	62.	SPILLED	44.	SPILLED	SPILLED	42.	24.	19.	8.
3515	P	45.	40.	32.	11.	22.	33.	45.	53.	51.	25.	3.	0.
3516	P	45.	51.	49.	45.	46.	38.	34.	41.	30.	37.	30.	28.
3517	P	52.	48.	53.	59.	54.	47.	48.	43.	35.	36.	30.	14.
3518	P	45.	46.	49.	42.	46.	45.	46.	40.	36.	39.	36.	31.
MEAN		46.	45.	48.	50.	47.	40.	42.	40.	38.	37.	31.	23.
S.D.		10.	13.	6.	16.	7.	9.	9.	10.	11.	9.	14.	12.
N		17	17	17	18	16	15	15	15	18	18	17	18

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		DAY 1 - 2	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13
DAM #	GROUP IV	150 MG/KG											
4501 P	52.	55.	56.	56.	55.	30.	55.	49.	41.	30.	17.	43.	
4502 P	23.	SPILLED	56.	46.	51.	21.	39.	31.	33.	30.	13.	4.	
4503 P	44.	39.	45.	42.	43.	30.	12.	11.	8.	3.	1.	2.	
4504 P	50.	59.	52.	53.	SPILLED	30.	38.	26.	29.	33.	30.	29.	
4505 P	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	23.	15.	23.	SPILLED	
4506 P	48.	41.	43.	45.	37.	18.	6.	2.	0.	0.	1.	1.	
4507 P	49.	47.	44.	42.	52.	40.	35.	29.	32.	40.	37.	28.	
4508 P	SPILLED	51.	50.	36.	50.	20.	1.	9.	27.	44.	38.	28.	
4509 P	46.	50.	43.	51.	44.	33.	35.	32.	39.	38.	37.	35.	
4510 P	SPILLED	52.	56.	58.	SPILLED	63.	SPILLED	32.	38.	SPILLED	SPILLED	46.	
4511 P	51.	55.	53.	50.	52.	32.	26.	27.	18.	15.	17.	0.	
4512 P	SPILLED	49.	47.	46.	50.	47.	25.	19.	16.	5.	7.	0.	
4513 P	36.	38.	42.	47.	34.	28.	19.	25.	18.	24.	31.	30.	
4514 NP	47.	48.	SPILLED	46.	39.	SPILLED	23.	27.	21.	SPILLED	24.	30.	
4515 P	54.	55.	57.	52.	53.	41.	40.	37.	34.	14.	15.	3.	
4516 P	45.	50.	48.	51.	47.	16.	8.	0.	6.	0.	1.		
4517 P	48.	47.	53.	45.	46.	19.	11.	5.	5.	4.	5.		
4518 P	40.	43.	40.	45.	48.	33.	28.	18.	29.	SPILLED	33.	...	
MEAN	45.	49.	49.	48.	47.	31.	25.	22.	23.	20.	19.	17.	
S.D.	8.	6.	6.	6.	6.	12.	15.	14.	13.	15.	14.	17.	
N	13	15	16	16	14	16	15	16	17	15	16	16	

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

F-8
APPENDIX F (cont.)
A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		STATUS											
		DAY13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25
DAM #	GROUP I	O MG/KG											
1501	P	54.	49.	SPILLED	SPILLED	64.	SPILLED	60.	54.	SPILLED	SPILLED	110.	53.
1502	NP	44.	42.	44.	27.	15.	36.	47.	43.	43.	39.	58.	40.
1503	P	44.	42.	43.	46.	49.	44.	44.	42.	39.	36.	38.	SPILLED
1504	P	49.	52.	55.	SPILLED	48.	47.	45.	49.	40.	35.	29.	13.
1505	P	19.	13.	12.	12.	24.	18.	24.	25.	25.	25.	21.	31.
1506	P	20.	7.	0.	0.	0.	5.	0.	0.	2.	6.	4.	0.
1507	P	27.	36.	33.	34.	36.	31.	21.	37.	37.	43.	38.	34.
1508	NP	51.	47.	44.	27.	38.	32.	35.	39.	42.	40.	49.	45.
1509	P	10.	0.	2.	3.	1.	1.	1.	SPILLED	SPILLED	3.	1.	6.
1510	P	49.	52.	49.	52.	49.	42.	32.	36.	48.	39.	38.	25.
1511	P	37.	37.	24.	30.	32.	27.	34.	32.	32.	35.	29.	27.
1512	NP	48.	41.	49.	43.	47.	44.	43.	44.	45.	48.	40.	41.
1513	P	35.	37.	SPILLED	SPILLED	43.	48.	45.	43.	42.	35.	24.	11.
1514	P	33.	33.	27.	24.	30.	37.	33.	31.	32.	26.	15.	8.
1515	P	1.	1.	1.	3.	2.	4.	16.	26.	40.	38.	41.	28.
1516	P	42.	42.	34.	34.	5.	1.	0.	1.	0.	0.	0.	2.
1517	P	24.	28.	15.	3.	1.	1.	2.	0.	0.	0.	0.	0.
1518	P	27.	21.	1.	0.	0.	0.	1.	0.	0.	0.	0.	1.
MEAN		31.	30.	23.	20.	26.	22.	24.	27.	26.	23.	26.	17.
S.D.		15.	18.	19.	19.	23.	19.	20.	19.	18.	17.	28.	16.
N		15	15	13	12	15	14	15	14	13	14	15	14

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

F-9
APPENDIX F (cont.)
A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		STATUS DAY											
		13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25
DAM #	GROUP II	25 MG/KG											
2501 P		40.	43.	SPILLED	38.	76.	45.	48.	51.	49.	48.	41.	35.
2502 P		47.	46.	45.	49.	51.	34.	44.	44.	51.	43.	44.	SPILLED
2503 P		40.	45.	49.	42.	42.	32.	37.	38.	20.	19.	21.	11.
2504 P		30.	29.	35.	50.	46.	51.	51.	48.	41.	49.	45.	38.
2505 P		8.	4.	7.	19.	29.	33.	32.	33.	28.	24.	18.	3.
2506 P		37.	38.	45.	38.	37.	26.	28.	29.	35.	31.	27.	11.
2507 P	SPILLED	27.	37.	39.	32.	39.	SPILLED	40.	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED
2508 P	SPILLED	SPILLED	90.	63.	SPILLED								
2509 P		27.	11.	8.	1.	2.	0.	0.	0.	0.	0.	3.	5.
2510 P		37.	41.	39.	SPILLED	38.	36.	38.	40.	35.	26.	19.	6.
2511 P		29.	35.	31.	35.	40.	39.	40.	40.	42.	38.	33.	28.
2512 P		27.	27.	7.	17.	14.	19.	23.	24.	22.	23.	19.	14.
2513 P		41.	43.	SPILLED	SPILLED	17.	SPILLED						
2514 P		31.	44.	47.	46.	50.	46.	44.	49.	48.	37.	32.	10.
2515 P		22.	21.	6.	4.	SPILLED	4.	8.	26.	41.	48.	52.	47.
2516 P		28.	32.	32.	32.	37.	36.	38.	24.	19.	3.	42.	0
2517 P		32.	28.	22.	26.	22.	24.	28.	32.	31.	31.	28.	
2518 P		37.	33.	33.	32.	34.	29.	32.	SPILLED	40.	SPILLED	35.	
MEAN		32.	32.	33.	33.	35.	31.	33.	35.	33.	30.	31.	19.
S.D.		9.	12.	21.	17.	17.	14.	14.	13.	14.	15.	13.	15.
N		16	17	16	16	16	16	15	15	15	14	15	14

P=PREGNANT NP=NON PREGNANT, FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		STATUS DAY13 - 14 14 - 15 15 - 16 16 - 17 17 - 18 18 - 19 19 - 20 20 - 21 21 - 22 22 - 23 23 - 24 24 - 25											
DAM #	GROUP III	75 MG/KG											
3501 P		2.	11.	16.	24.	17.	28.	27.	25.	20.	14.	13.	20.
3502 P		10.	3.	12.	17.	13.	SPILLED	SPILLED	18.	25.	22.	27.	21.
3503 P		49.	SPILLED	37.	SPILLED	SPILLED	42.	SPILLED	SPILLED	45.	30.	20.	15.
3504 P		1.	0.	1.	7.	7.	20.	45.	53.	42.	39.	27.	25.
3505 P		44.	41.	39.	38.	38.	39.	43.	37.	34.	34.	31.	24.
3506 P		40.	40.	47.	32.	35.	31.	35.	26.	27.	23.	10.	13.
3507 P		39.	48.	50.	44.	46.	47.	38.	48.	43.	43.	42.	35.
3508 P		14.	12.	14.	29.	8.	9.	15.	17.	19.	26.	22.	21.
3509 P		41.	28.	38.	38.	38.	30.	34.	35.	39.	35.	32.	26.
3510 P		16.	2.	13.	30.	27.	17.	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED
3511 P		26.	26.	23.	7.	15.	35.	23.	27.	24.	30.	25.	31.
3512 P		30.	28.	35.	SPILLED	SPILLED	27.	SPILLED	SPILLED	SPILLED	39.	SPILLED	SPILLED
3513 P		18.	20.	27.	30.	36.	38.	34.	32.	38.	33.	28.	24.
3514 P		5.	1.	3.	4.	6.	4.	9.	17.	13.	21.	23.	7.
3515 P		26.	53.	SPILLED									
3516 P		18.	13.	5.	8.	6.	11.	16.	20.	17.	17.	16.	13.
3517 P		18.	21.	16.	20.	31.	37.	SPILLED	SPILLED	50.	43.	46.	44.
3518 P		37.	33.	33.	32.	25.	28.	30.	35.	32.	27.	24.	7.
MEAN		24.	22.	24.	24.	23.	28.	29.	30.	21.	30.	26.	22.
S.D.		15.	17.	16.	13.	14.	12.	11.	11.	11.	9.	10.	10.
N		18	17	17	15	15	16	12	13	15	16	15	15

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		STATUS DAY											
		13 - 14	14 - 15	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25
DAM #	GROUP IV	150 MG/KG											
4501 P	34.	37.	47.	36.	31.	27.	37.	43.	46.	45.	45.	43.	
4502 P	5.	0.	0.	0.	1.	1.	1.	3.	1.	0.	0.	5.	
4503 P	2.	1.	6.	7.	27.	33.	50.	43.	50.	45.	43.	38.	
4504 P	25.	12.	8.	17.	5.	14.	8.	25.	32.	34.	33.	33.	
4505 P	9.	1.	7.	2.	3.	8.	36.	SPILLED	44.	SPILLED	SPILLED	SPILLED	
4506 P	1.	1.	0.	0.	0.	2.	0.	12.	21.	35.	46.	45.	
4507 P	38.	35.	35.	39.	20.	33.	37.	41.	43.	40.	39.	30.	
4508 P	9.	10.	15.	20.	18.	18.	16.	26.	29.	28.	32.	41.	
4509 P	37.	26.	29.	24.	29.	28.	34.	37.	35.	38.	39.	8.	
4510 P	43.	SPILLED	9.	14.	SPILLED	9.	1.	0.	1.	2.	2.	0.	
4511 P	7.	4.	7.	7.	3.	8.	5.	8.	20.	32.	SPILLED	SPILLED	
4512 P	1.	0.	2.	0.	0.	SPILLED	3.	3.	5.	9.	12.	9.	
4513 P	7.	2.	2.	2.	7.	19.	26.	32.	35.	37.	32.	35.	
4514 NP	25.	26.	25.	6.	7.	20.	36.	47.	47.	48.	49.	45.	
4515 P	0.	0.	0.	0.	5.	4.	2.	0.	13.	24.	28.	29.	
4516 P	0.	0.	1.	0.	2.	2.	0.	0.	0.	0.	0.		
4517 P	5.	3.	2.	4.	2.	22.	SPILLED	43.	46.	35.	41.	SP	
4518 P	11.	6.	7.	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	57.	53.	SPILLED	SPILLED	
MEAN	14.	9.	10.	11.	10.	15.	17.	21.	28.	29.	28.	24.	
S.D.	15.	13.	14.	13.	11.	11.	18.	18.	19.	17.	17.	17.	
N	17	16	17	16	15	15	15	15	17	16	14	13	

P=PREGNANT NP=NON PREGNANT, FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

F-12
 APPENDIX F (cont.)
 A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY
 STATUS DAY25 - 26 26 - 27 27 - 28 28 - 29 29 - 30

DAM #	GROUP I				
1501	P	24.	26.	32.	29.
1502	NP	42.	38.	45.	40.
1503	P	25.	17.	16.	16.
1504	P	13.	12.	13.	8.
1505	P	24.	26.	22.	24.
1506	P	4.	2.	0.	0.
1507	P	29.	30.	38.	34.
1508	NP	41.	42.	48.	46.
1509	P	0.	0.	0.	2.
1510	P	17.	19.	12.	16.
1511	P	27.	26.	29.	29.
1512	NP	44.	50.	47.	44.
1513	P	6.	1.	28.	16.
1514	P	5.	9.	7.	11.
1515	P	46.	20.	26.	39.
1516	P	0.	0.	1.	0.
1517	P	0.	0.	0.	0. DELIVERED
1518	P	0.	0.	0.	0. DELIVERED
MEAN		15.	13.	15.	15.
S.D.		14.	12.	14.	14.
N		15	15	15	13

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

F-13
APPENDIX F (cont.)
A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY		STATUS				
		DAY 25 - 26	26 - 27	27 - 28	28 - 29	29 - 30
DAM #	GROUP II	25 MG/KG				
2501 P	29.	31.	31.	30.	31.	
2502 P	SPILLED	23.	16.	11.	13.	
2503 P	7.	10.	11.	3.	16.	
2504 P	22.	30.	36.	40.	48.	
2505 P	2.	0.	0.	1.	1.	
2506 P	10.	2.	11.	13.	18.	
2507 P	SPILLED	SPILLED	4.	17.	17.	
2508 P	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	
2509 P	0.	0.	0.	0.	1.	
2510 P	0.	16.	12.	9.	16.	
2511 P	21.	23.	29.	30.	34.	
2512 P	16.	18.	22.	22.	20.	
2513 P	12.	6.	10.	26.	29.	
2514 P	11.	SPILLED	30.	26.	32.	
2515 P	40.	44.	45.	50.	52.	
2516 P	0.	0.	0.	0.	0.	
2517 P	30.	7.	0.	0.	0.	
2518 P	32.	30.	27.	24.	17.	
MEAN		16.	16.	17.	18.	20.
S.D.		13.	14.	14.	15.	16.
N		15	15	17	17	17

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY

STATUS DAY25 - 26 26 - 27 27 - 28 28 - 29 29 - 30

DAM #	GROUP III	75 MG/KG				
3501 P	26.	26.	35.	26.	22.	
3502 P	25.	18.	27.	32.	20.	
3503 P	7.	8.	13.	9.	11.	
3504 P	28.	32.	26.	SPILLED	22.	
3505 P	20.	18.	25.	27.	26.	
3506 P	17.	10.	10.	10.	11.	
3507 P	23.	23.	24.	29.	30.	
3508 P	23.	21.	22.	16.	17.	
3509 P	22.	15.	18.	17.	4.	
3510 P	39.	41.	32.	45.	36.	
3511 P	35.	27.	35.	38.	36.	
3512 P	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED	
3513 P	10.	0.	1.	1.	DELIVERED	
3514 P	2.	2.	13.	15.	14.	
3515 P	0.	0.	1.	0.	DELIVERED	
3516 P	11.	16.	17.	20.	14.	
3517 P	46.	40.	49.	39.	41.	
3518 P	0.	DELIVERED				
MEAN	30.	19.	21.	22.	22.	
S.D.	13.	13.	12.	14.	11.	
N	17	16	16	15	14	

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

E-15
 APPENDIX F (cont.)
 A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL MATERNAL FOOD CONSUMPTION DURING GESTATION - g/kg/day

PREGNANCY
 STATUS DAY25 - 26 26 - 27 27 - 28 28 - 29 29 - 30

DAM #	GROUP	IV	150 MG/KG			
4501	P	46.	SPILLED	43.	40.	41.
4502	P	0.	0.	2.	0.	0.
4503	P	38.	30.	36.	30.	33.
4504	P	27.	32.	31.	28.	31.
4505	P	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED
4506	P	49.	43.	DELIVERED		
4507	P	23.	29.	25.	29.	33.
4508	P	74.	26.	32.	32.	27.
4509	P	25.	9.	24.	33.	31.
4510	P	1.	15.	38.	25.	42.
4511	P	SPILLED	26.	26.	SPILLED	42.
4512	P	9.	3.	0.	15.	25.
4513	P	18.	3.	28.	41.	36.
4514	NP	31.	7.	37.	54.	49.
4515	P	34.	46.	50.	49.	54.
4516	P	0.	0.	DELIVERED		
4517	P	28.	28.	25.	20.	22.
4518	P	SPILLED	SPILLED	SPILLED	SPILLED	SPILLED
MEAN		27.	21.	28.	28.	32.
S.D.		21.	16.	14.	13.	13.
N		14	14	13	12	13

P=PREGNANT NP=NON PREGNANT. FOOD WEIGHT NOT INCLUDED IN CALCULATION OF MEAN

A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

SUMMARY OF REPRODUCTION DATA

DOSE GROUP	0 MG/KG	25 MG/KG	75 MG/KG	150 MG/KG	STAT SYMBOL
#Females Mated	18	18	18	18	
#Prenant (Z)	15 (83.3)	18 (100.0)	18 (100.0)	17 (94.4)	NS
#Pregnancies Aborted	0	0	0	0	NT
#Premature Births	2	0	3	2	NS
#Litters with Viable Fetuses	13	18	15	15	NS
#Litters with all resorptions	0	0	0	0	NT
Female Mortality # (Z)	0	0	0	0	NT
#Corpora Lutea	146	182	174	164	
Mean ± S.D.	11.2 ± 2.9	10.1 ± 1.6	11.6 ± 1.6	10.9 ± 2.5	A-
#Implantation sites	124	154	167	147	
Mean ± S.D.	9.5 ± 3.4	8.6 ± 1.8	11.1 ± 1.5	9.8 ± 2.4	A
Preimplantation Loss					
Mean ± S.D.	0.161 ± 0.188	0.148 ± 0.155	0.036 ± 0.073 ^a	0.101 ± 0.101	A
Viable Fetuses	111	142	155	124	K+
Dead Fetuses	0	0	0	1	NT
Mean Litter Size ± S.D.	8.5 ± 3.4	7.9 ± 1.9	10.3 ± 1.0	8.3 ± 2.5	K+
Mean # Males ± S.D.	4.0 ± 2.0	4.1 ± 1.8	5.4 ± 1.5	4.3 ± 2.3	A-
Mean # Females ± S.D.	4.5 ± 2.0	3.8 ± 2.1	4.9 ± 2.1	3.9 ± 1.7	A-
#Resorptions	13	12	12	22	
Mean ± S.D.	1.0 ± 1.4	0.7 ± 0.9	0.8 ± 1.3	1.5 ± 3.3	K-
Resorptions / Implants					
Mean ± S.D.	0.111 ± 0.190	0.077 ± 0.112	0.063 ± 0.103	0.124 ± 0.212	A-
#Litters with Resorptions (Z)	6 (46.2)	8 (44.4)	5 (33.3)	8 (53.3)	C-
Mean Body Weight (g) of Viable Fetuses ± S.D.	39.74 ± 9.68	43.78 ± 8.09	43.71 ± 4.13	38.88 ± 6.66	A-
Male Fetuses	40.54 ± 10.07	44.68 ± 7.93	44.21 ± 3.71	37.54 ± 6.45	KJ
Female Fetuses	38.91 ± 9.59	42.09 ± 8.35	42.88 ± 6.04	39.25 ± 6.90	A-
Ratio of Viable Fetuses Total males / Total females	0.9	1.1	1.1	1.1	

NOTE: Preimplantation Loss = Corpora lutea - implant

Corpora lutea



A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL FEMALE REPRODUCTION DATA AND MEAN FETAL WEIGHT DATA

DOSAGE: 0 MG/KG

FEMALE#	CORPORA LUTEA	IMPLANT SITES	RESORPTIONS			FETUSES			SEX		AVERAGE FETAL BODY WEIGHT (GM)		
			EARLY	LATE	TOTAL	LIVE	DEAD	TOTAL	MALE	FEMALE	MALE	FEMALE	BOTH
1501	9	9	0	0	0	9	0	9	5	4	43.5	40.9	42.3
1502	NOT PREGNANT												
1503	9	8	0	0	0	8	0	8	5	3	50.5	46.3	48.9
1504	17	16	0	3	3	13	0	13	7	6	34.9	38.7	36.7
1505	11	10	0	0	0	10	0	10	4	6	46.5	51.6	49.5
1506	15	13	0	1	1	12	0	12	6	6	25.3	24.9	25.1
1507	10	6	1	0	1	5	0	5	1	4	52.6	52.0	52.1
1508	NOT PREGNANT												
1509	7	6	0	4	4	2	0	2	1	1	19.9	18.4	19.1
1510	11	11	0	3	3	8	0	8	4	4	48.8	41.7	45.2
1511	15	13	0	1	1	12	0	12	5	7	34.2	33.5	33.8
1512	NOT PREGNANT												
1513	11	11	0	0	0	11	0	11	6	5	38.6	42.4	40.3
1514	10	9	0	0	0	9	0	9	2	7	39.2	35.7	36.5
1515	12	9	0	0	0	9	0	9	4	5	51.6	44.2	47.5
1516	9	3	0	0	0	3	0	3	2	1	41.5	35.5	39.5
1517	DELIVERED												
1518	DELIVERED												
MEAN	11.2	9.5	0.1	0.9	1.0	8.5	0.0	8.5	4.0	4.5	40.5	38.9	39.7
S.D.	2.9	3.4	0.3	1.4	1.4	3.4	0.0	3.4	2.0	2.0	10.1	9.6	9.7
N	13	13	13	13	13	13	13	13	13	13	13	13	13

NOT PREGNANT - NO UTERINE FOCI VISUALIZED AFTER STAINING.

INDIVIDUAL FEMALE REPRODUCTION DATA AND MEAN FETAL WEIGHT DATA

DOSAGE: 150 MG/KG

FEMALE#	CORPORA LUTEA	IMPLANT SITES	RESORPTIONS			FETUSES			SEX		AVERAGE FETAL BODY WEIGHT (GM)		
			EARLY	LATE	TOTAL	LIVE	DEAD	TOTAL	MALE	FEMALE	MALE	FEMALE	BOTH
4501	7	6	0	0	0	6	0	6	0	6	-	46.9	46.9
4502	10	10	1	0	1	9	0	9	5	4	26.5	28.2	27.3
4503	10	10	0	1	1	9	0	9	7	2	38.3	43.4	39.4
4504	10	9	0	0	0	9	0	9	8	1	38.5	38.1	38.4
4505	14	12	0	0	0	12	0	12	6	6	42.2	40.6	41.4
4506	DELIVERED												
4507	10	7	1	1	2	5	0	5	2	3	38.1	37.4	37.7
4508	13	11	0	0	0	11	0	11	5	6	38.0	39.6	38.9
4509	13	9	0	1	1	8	0	8	5	3	34.1	32.1	33.4
4510	12	11	0	0	0	11	0	11	6	5	33.1	34.6	33.8
4511	12	12	0	1	1	11	0	11	6	5	34.3	37.8	35.9
4512	9	8	2	0	2	6	0	6	4	2	27.8	26.0	27.2
4513	9	9	0	0	0	9	0	9	3	6	42.9	42.3	42.5
4514	NOT PREGNANT												
4515	17	16	13	0	13	2	1	3	0	2	-	44.9	44.9
4516	DELIVERED												
4517	9	8	0	0	0	8	0	8	4	4	45.8	47.1	46.4
4518	9	9	1	0	1	8	0	8	4	4	48.6	49.7	49.2
MEAN	10.9	9.8	1.2	0.3	1.5	8.3	0.1	8.3	4.3	3.9	37.5	39.2	38.9
S.D.	2.5	2.4	3.3	0.5	3.3	2.7	0.3	2.5	2.3	1.7	6.5	6.9	6.7
N	15	15	15	15	15	15	15	15	15	15	13	15	15

NOT PREGNANT - NO UTERINE FOCI VISUALIZED AFTER STAINING.

H-1
 APPENDIX H
 A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH HYDROQUINONE

87-3220

INDIVIDUAL FETAL STATUS AND UTERINE LOCATION

DOSAGE: 0 MG/KG

FEMALE#	IMPLANT #																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1501	MA	EA	EA	MA	EA	MA / MA	EA	MA															
1503	EA	MA	MA / MA	EA	MA	EA	MA																
1504	MA	EA	EA	MA	L	L	EA	MA	MA	MA	MA / EA	L	EA	EA	MA								
1505	EA	EA	EA	MA	MA / EA	MA	EA	MA	EA														
1506	MA	EA	MA	MA	MA	EA / EA	EA	L	EA	MA	MA	EA											
1507	MA / EA	EA	EA	E	EA																		
1509	L	L	EA / L	MA	L																		
1510	MA	EA	L / EA	EA	MA	MA	MA	L	EA	L													
1511	EA	MA	EA	MA	EA	EA / EA	EA	MA	EA	MA	L	MA											
1513	EA	MA	MA	MA	MA	EA / MA	MA	EA	EA	EA													
1514	EA	MA	EA	EA	EA / MA	EA	EA	EA															
1515	EA	MA	MA	MA	EA	EA	EA / MA	EA															
1516	MA	MA	EA /																				

M MALE F FEMALE A ALIVE E EARLY RESORPTION L LATE RESORPTION D DEAD FETUS / DENOTES POSITION OF CERVIX

