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STUDY PROFILE

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700 [§83-3a]; OECD 414.

PC CODE: 128824
DECISION #: 346393

DP BARCODE: 325778
EPA REGISTRATION: 5185-UOO

TEST MATERIAL (PURITY): Belclene 350 (50% a.i.)

SYNONYMS: TK 12 780/2, tri-n-butyltetradeclyphosphonium chloride, tributyl tetradecyl phosphonium chloride

CITATION: Giese P.K. (1983) 83-3 (MUP) Report on Belclene 350 (TK 12 780/2) Teratology Study in Rabbits. CIBA-GEIGY Ltd. (Sisseln, Switzerland). Test No. 82 1227, September, 1983. Accession No. 252019. MRID 00133048. Unpublished;

Giese P.K. (1985) Amendment to 83-3 (MUP) Report on Belclene 350 (TK 12 780/2) Teratology in Rabbits. CIBA-GEIGY Ltd. (Sisseln, Switzerland). Test No. 82 1227, February 21, 1985. MRID 40680705 (006932). Unpublished.

Todhunter, J.A. (2005). Amendment No. 2 to Final Report on Belclene 350 (TK 12 780/2). Teratology Study in Rabbits. Bio-Lab, Inc. P.O. Box 300002, Lawrenceville, GA 30049. Compiled at: SRS International Corporation. Falls Church, VA 22043. MRID 467217-04. Unpublished.

SPONSOR: CIBA GEIGY Ltd.
Plastics and Additives Division
Basle, Switzerland

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 40680705(006932); 00133047), Belclene 350 (50% ai, batch/lot 006) was administered to 20 chinchilla rabbits/dose by gavage at dose levels of 0, 7.5, 22.5, or 45 mg/kg/day from days 6 through 18 of gestation (i.e., gd 6-18). These doses are equivalent to 0, 3.75, 11.25, and 22.5 mg ai/kg/day, respectively, which was confirmed by the registrant.

Treatment-related effects at 11.25 and 22.5 mg ai/kg/day include statistically significant decreased body weight gain during gestational days 6-18 and significantly decreased food

consumption during gestational days 6-11. **The maternal LOAEL is 11.25 mg ai/kg/day, based on significantly decreased body weight gain and food consumption. The maternal NOAEL is 3.75 mg ai/kg/day.**

Developmental findings occurred at 11.25 and 22.5 mg ai/kg/day. Treatment-related effects at 22.5 mg ai/kg/day include statistically decreased fetal weight and an increase compared to the control in the incidence of delayed ossification of the hindlimb phalangeal nuclei. At 11.25 mg ai/kg/day, there was a significant decrease in male fetal weight and an increase compared to the control in the incidence of delayed ossification of the hindlimb phalangeal nuclei. **The developmental LOAEL is 11.25 mg ai/kg/day, based on a significantly increased incidence of delayed ossification of hindlimb phalangeal nuclei, and significantly decreased fetal body weight for males. The developmental NOAEL is 3.75 mg ai/kg/day.**

The study is classified as **ACCEPTABLE-GUIDELINE** and fulfills the guideline requirements of OPPTS 870.3700.

COMPLIANCE: A signed and dated Quality Assurance statement is provided in the original report. Signed and dated GLP, Quality Assurance, and No Data Confidentiality statements are included in the amendment. A Flagging Statement is not included in either report.

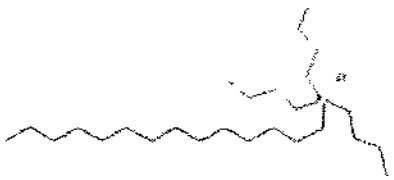
Rabbit
Dev.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Belclene 350

Description:	Liquid stored at room temperature
Lot/Batch #:	006
Purity:	Not reported; according to the registrant and a previous DER prepared by EPA/OPP, Belclene 350 is a manufacturing-use product that contains 50% technical grade active ingredient in water; the active ingredient is tri-n-butyltetradecylphosphonium chloride (94.3% pure).
Compound Stability:	Not reported
CAS #of TGAI:	81741-28-8
Structure[1]:	



2. Vehicle and/or positive control: Distilled water; lot/batch and purity not provided.

3. Test animals: Rabbits

Species:	Chinchilla	
Strain:	SPF breeding colony	
Age/weight at study initiation:	4-5 months; 2.8-3.4 kg	
Source:	IVANOVAS Kisslegg, Germany	
Housing:	Females were individually housed in Henkel battery cages, except during mating where one female and one male were placed in breeding cages.	
Diet:	Pelleted, certified standard diet (NAFAG No. 814) was provided *ad libitum*. All batches of diet were assayed for composition and contaminant level by the manufacturer. It is assumed that there were no contaminants that interfered with the study results.	
Water:	Tap water was provided *ad libitum*. Drinking water quality was measured in accordance to the specification of the "Schweizerisches Lebensmittelbuch" and routine chemical examination at the source was conducted periodically by the water authority (Baudepartement des Kantons Aargau, Abteilung Gewaesserschutz). It is assumed that there were no contaminants that interfered with the study results	
Environmental conditions:	**Temperature:**	21±2°C
	Humidity:	55±10%
	Air changes:	Not provided
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	7-14 days	

1 Source: www.chemfinder.com

B. PROCEDURES AND STUDY DESIGN

1. In life dates:
Start: Not reported End: Not reported

2. Mating: One female was placed with one male in special breeding cages. Each dam was mated twice, the second time approximately one hour after the first time on the same day. This day was designated as gestation day (gd) 0.

3. Animal Assignment: Animals were assigned to dose groups as indicated in Table 1. It was not stated whether animals were randomly allocated to their assigned treatment group.

TABLE 1. Animal Assignment

Dose (mg ai/kg/day)	0	3.75	11.25	22.5
# Females	20	20	20	20

4. Dose selection rationale: Doses were selected from a preliminary experiment (Accession No. 252019; Record No. 113212) that was performed on 6 nonpregnant rabbits (3 females per group) at daily doses of 15 and 30 mg/kg body weight/day. The test article was mixed with distilled water and administered orally via intubation for 13 consecutive days (gd 6 through 18). There were no reactions to the treatment for these females.

5. Dosage preparation and analysis: Test formulations were prepared daily by mixing the test material with distilled water. The mixture was then stirred with a magnetic stirrer. Homogeneity, stability, and concentrations analyses do not appear to have been conducted.

Results

Homogeneity Analysis: It was not reported whether the test article was analyzed for homogeneity; because test formulations were true solutions, however, this evaluation is not necessary.

Stability Analysis: It was not reported whether the test article was analyzed for stability; however, a developmental study in rats (MRID 40680704) reported that the compound was stable in vehicle for up to 4 hours at ambient temperature.

Concentration Analysis: It was not reported whether the test article was analyzed for achieved concentration. In a rat developmental study (MRID 40680704), however, the achieved concentrations of 2 and 12 mg/g of test article in vehicle were determined at time 0, 1 hour, 2 hours, and 4 hours. Achieved concentrations were 99.1-102.9% of the nominal concentration.

6. **Dosage administration:** All doses were administered once daily by gavage at a rate of 4 mL/kg body weight. Test formulations were administered from gd 6 to 18. The study report does not indicate whether dosing was adjusted based on body weight determinations.

C. OBSERVATIONS

1. **Maternal Observations and Evaluations:** Dams were checked daily for mortality and clinical signs. Body weight was measured daily. Food consumption was measured on gd 6, 11, 15, 19, 24, and 29. Dams were sacrificed on gd 29 by an intravenous injection of sodium thiopental at a dose-level adapted for euthanasia. The ovaries and uterus (mucosa and contents, including amniotic fluid and placenta) of each dam were assessed for abortions, resorption sites, and the number of corpora lutea.

2. **Fetal Evaluations:** Fetuses were removed, individually weighed, and subjected to a careful external inspection, including an external examination of the skull. An assessment of the body cavities (thorax, abdomen, pelvis) and sex were performed. Examination of the cephalic viscera was performed according to a modified slicing technique of Wilson[2] (1965). Fetal heads were fixed in a mixture of trichloroacetic acid (10 parts) and 30% formaldehyde solution (5 parts). A skeletal assessment of the fetal trunks (including limbs) following clearing in potassium hydroxide and staining with alizarine red S were conducted in accordance to Dawson's[3] technique. To assess the possible occurrence of "wide sutures" of the frontoparietal region of the skull, part of the skin of fetal heads was removed prior to fixation. Abnormalities were classified as anomalies and malformations.

D. DATA ANALYSIS

1. **Statistical analyses:** The study report indicates that statistical analyses were performed whenever feasible; specific statistical methods or tests are referenced sporadically in the results section.

2. **Indices:** There were no formulas presented. Preimplantation and postimplantation loss percentages are not presented in the study report.

3. **Historical control data:** Historical control data are provided to allow comparison with concurrent controls (not included in this report). Data include reproductive endpoints and skeletal anomalies and/or malformations.

II. RESULTS

A. MATERNAL TOXICITY

2 Wilson, J.G. 1965. In: Wilson, J.G. and Warkany (eds.). Teratology, Principles and Techniques. The University of Chicago Press: Chicago and London. Pp. 262-277.
3 Dawson, A.B. 1926. Stain Tech. 1:123-124.

1. **Mortality and Clinical Observations:** Two high-dose females (Nos. 362 and 377) spontaneously died on gestation days 18 and 7, respectively. One mid-dose dam (No. 359) died due to an intubation error. In addition, two high-dose females (Nos. 361 and 362) developed diarrhea on gd 17 and 8, respectively.

2. **Body Weight:** Mean body weight and body weight gain values are not presented in the study report; however, mean body weight was presented graphically. According to the Study Report, body weight was decreased in mid- and high-dose dams during the first days of treatment. There were no treatment-related effects observed in low-dose dams.

Mean body weight and body weight gain are calculated and presented in Tables 2 and 3. These data indicate that there were no significant changes in body weight throughout the treatment period. There was a significant decrease in mean body weight gain during gd 6-18 in both the mid- and high-dose dams. Low-dose dams were unaffected by treatment.

TABLE 2. Mean (±SD) Maternal Body Weight (g)[a]

Day	Dose in mg ai/kg/day (# of Dams)			
	0 (17)	3.75 (18)	11.25 (18)	22.5 (17)
Day 0	3.07±0.26	3.23±3.33	3.07±0.28	3.12±0.31
Day 3	3.25±0.23	3.42±0.34	3.25±0.27	3.28±0.33
Day 6	3.32±0.23	3.48±0.34	3.34±0.32	3.37±0.35
Day 9[b]	3.39±0.23	3.52±0.32	3.26±0.29	3.25±0.30
Day 12	3.43±0.25	3.54±0.30	3.36±0.28	3.33±0.34
Day 15[c]	3.48±0.27	3.59±0.29	3.37±0.22	3.41±0.30
Day 18[d]	3.55±0.28	3.65±0.28	3.44±0.26	3.52±0.26
Day 21	3.59±0.27	3.68±0.30	3.51±0.21	3.58±0.26
Day 24	3.66±0.27	3.74±0.31	3.60±0.21	3.66±0.29
Day 27	3.72±0.28	3.78±0.32	3.65±0.19	3.72±0.30
Day 29	3.76±0.29	3.84±0.34	3.71±0.20	3.79±0.28

a Mean body weight was calculated from individual animal data on pages 20-27 in the study report.
b The number of high-dose dams decreased to 16 on gd 7.
c The number of mid-dose dams decreased to 17 on gd 15.
d The number of high-dose dams decreased to 15 on gd 18.

TABLE 3. Mean (±SD) Maternal Body Weight Gain (g)[a]

Interval	Dose in mg ai/kg/day (# of Dams)			
	0 (17)	3.75 (18)	11.25 (18)	22.5 (17)
Pretreatment: Days 0-6	0.25±0.07	0.25±0.08	0.28±0.22	0.26±0.09
Treatment: Days 6-18[b, c, d]	0.23±0.14	0.17±0.12	0.09±0.23*	0.11±0.15*
Posttreatment: Days 18-29	0.21±0.09	0.19±0.11	0.27±0.14	0.27±0.13
Entire Study Days 0-29	0.69±0.22	0.61±0.18	0.64±0.20	0.64±0.18
Corrected BW Gain	-0.2±4.2	-1.1±5.1	-1.5±3.8	-1.1±7.3

a Mean body weight gain was calculated from individual animal data on pages 20-27 in the study report; mean corrected body weight gain was obtained from pages 28-31 in the study report.
b The number of high-dose dams decreased to 16 on gd 7.
c The number of mid-dose dams decreased to 17 on gd 15.
d The number of high-dose dams decreased to 15 on gd 18.
* Statistically different ($p<0.05$) from the control.

3. **Food Consumption:** Average food consumption values were not presented in the study; however, this information was presented graphically. According to the study report, decreases in food consumption corresponding to body weight loss were observed during the first days of treatment in mid- and high-dose dams. There were no treatment-related effects observed in low-dose dams.

Mean maternal food consumption are calculated and presented in Table 4. These data indicate that there was a significant decrease in food consumption during gd 6-11 in both the mid- and high-dose dams. There were no treatment-related effects observed in low-dose dams.

Table 4. Mean (±SD) Maternal Food Consumption (g animal/day)[a]

Interval	Dose in mg ai/kg/day(# of Dams)			
	0 (17)	3.75 (18)	11.25 (18)	22.5 (17)
Day 0-6	189.02±17.17	198.61±25.75	185.74±48.95	190.88±39.37
Day 6-11[b]	195.29±27.55	182.56±26.27	138.22±67.31**	117.63±65.00**
Day 11-15[c, d]	172.79±41.87	170.00±41.24	152.06±50.47	146.67±62.47
Day 15-19	177.06±37.17	179.44±31.18	153.97±45.24	170.83±34.42
Day 19-24[e, f]	168.12±26.99	172.12±27.17	184.88±30.27	183.07±49.41
Day 24-29[g, h]	144.00±34.33	149.06±25.42	161.20±31.70	164.27±47.19

a Mean food consumption was calculated from individual animal data on pages 32-35 in the study report.
b The number of high-dose dams decreased to 16 on gd 11due to mortality.
c The number of mid-dose dams decreased to 17 on gd 15 due to mortality.
d The number of high-dose dams decreased to 15 on gd 15due to illegible data and mortality.
e The number of low-dose dams decreased to 17 on gd 24 due to missing data.
f The number of mid-dose dams decreased to 16 on gd 24 due to missing data.
g The number of controls decreased to 14 on gd 29 due to missing/illegible data.
h The number of mid-dose dams decreased to 15 on gd 29 due to missing data.
** Statistically different ($p<0.01$) from the control.

4. Gross Pathology: Gross pathology data were not presented in the study report, except for the two high-dose dams (Nos. 362 and 377, respectively) that spontaneously died prior to scheduled necropsy. These dams exhibited abscess of the lungs and bronchopneumonia.

5. Cesarean Section Data: Data are summarized in Table 5. There were no treatment-related effects on the mean number of corpora lutea, implantation sites, or live fetuses per dam.

The number of resorptions (denoted in the study as embryonal deaths [i.e., early resorptions] and fetal deaths [i.e., late resorptions are calculated]). There appears to be an increase in the occurrence of early resorptions in mid-dose dams. It is believe that this increase is incidental and due to dam No. 354, whose litter was completely resorbed.

TABLE 5. Cesarean Section Observations[a]

Observation	Dose (mg ai/kg/day)			
	0	3.75	11.25	22.5
# Animals Assigned (Mated)	20	20	20	20
# Animals Pregnant	17	18	18	17
Pregnancy Rate (%)	85	90	90	85
# Nonpregnant	3	2	2	3
Maternal Wastage				
# Died	0	0	1	2
# Died Pregnant	0	0	1	2
# Died Nonpregnant	0	0	0	0
# Aborted	0	0	0	0
# Premature Delivery	0	0	0	0
Total # Corpora Lutea	NA	NA	NA	NA
Corpora Lutea/Dam	10.7±2.8	10.7±3.8	10.5±3.8	10.3±3.0
Total # Implantations	137	132	154	130
Implantations/Dam	8.1±2.9	7.3±4.0	9.1±2.2	8.7±3.2
Total # Litters	17	18	17	15
Total # Live Fetuses	132	125	139	122
Live Fetuses/Dam	7.76±2.82	6.94±4.01	8.18±2.92	8.13±3.34
Total # Dead Fetuses	0	0	0	0
Dead Fetuses/Dam	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Total # Resorptions				
Total	5	7	15	8
Early	4	6	13	6
Late	1	1	2	2
Resorptions/Dam				
Total	0.29±0.47	0.41±1.06	0.88±2.15	0.53±0.64
Early	0.24±0.44	0.35±0.86	0.76±2.17	0.38±0.62
Late	0.06±0.24	0.06±0.24	0.12±0.33	0.13±0.34
Litters with Total Resorptions	0	0	1	0
Mean Fetal Weight (g)				
Males	38.9±6.6	40.9±NA	36.4±5.6**	35.6±6.1**
Females	38.9±5.5	37.6±7.2	36.9±5.8	34.7±6.9**
Sex Ratio (% Male)	53.8	44.8	50.4	50.0
Preimplantation Loss (%)	NA	NA	NA	NA
Postimplantation Loss (%)[b]	5.21±12.28	5.21±16.10	9.42±23.87	8.63±13.67

a Data obtained from pages 11 and 36-43 in the study report.
b Postimplantation loss (defined as [(the number of implantations – the number of live fetuses)/the number of implantations] X 100) was calculated by Versar. A statistical analysis was not performed on the data.
** Statistically different ($p<0.01$) from the control.

B. DEVELOPMENTAL TOXICITY

1. External Examination: There were no treatment-related effects on the sex distribution of fetuses (Chi^2 test, Yates' correction, $p>0.05$). High-dose fetuses exhibited a treatment-related, significant reduction in body weight (males and females; Student's t test, one-tailed, $p<0.01$). Additionally, male fetuses from mid-dose dams exhibited a slight, but significant decrease in mean body weight (Student's t test, one-tailed, $p<0.01$). There were no treatment-related effects observed at the low dose. There were no treatment-related external malformations or anomalies.

2. Visceral Examination: There were no treatment-related visceral malformations or anomalies. Findings were limited to unilateral agenesis of the kidney and ureter in one low-dose fetus and encephalocele in one high-dose fetus.

3. Skeletal Examination: There were no treatment-related skeletal malformations or anomalies observed at any dose level. Findings consisted of irregular ossification of the ribs in one low-dose fetus (partial fusion and partial hyperplasia), two mid-dose fetuses (partial fusion and absence), and two high-dose fetuses (partial and total fusion). Both of the high-dose fetuses and one of the mid-dose fetuses with irregular ossification of the ribs also exhibited irregularities in ossification of the vertebral column.

Data on developmental delays in skeletal maturation are presented in Table 6 and Appendices 1 to 5. There was an increased incidence of delayed ossification of the hindlimb phalangeal nuclei in mid- and high-dose fetuses.

Table 6. Developmental Delays in Skeletal Maturation Analyzed by Litter Incidence*,+

Observations[b]	Dose (mg ai/kg/day)			
	0	3.75	11.25	22.5
Total Litters examined	17	18	17	15
Phalangeal nuclei : left forelimb, ossification still absent in phalanges II, digit 5	12/17 70.1%	16/18 88.9%	13/17 76.5%	14/15 93.0%
Phalangeal nuclei : left hindlimb, ossification still absent in phalanges II, digit 5	3/17 17.6%	3/18 16.7%	7/17 41.1%	8/15 53.3%
5[th] Sternebra, ossification still absent	7/17 41.1%	9/18 50.0%	7/17 41.1%	3/15 20.0.0%

*From Appendices 1 to 5 and Table 5.
+ Number of Abnormal litters/Total number of litters.

III. DISCUSSION and CONCLUSIONS

A. The maternal NOAEL is 3.75 mg ai/kg/day, and the LOAEL is 11.25 mg ai/kg/day, based on decreased body weight and food consumption. The developmental LOAEL is 11.25 mg ai/kg/day, based on an increased incidence of delayed ossification of the hindlimb phalangeal nuclei, and

significantly decreased fetal body weight for males. The developmental NOAEL is 3.75 mg ai/kg/day.

1. **Maternal toxicity:** Treatment-related effects at 11.25 and 22.5 mg ai/kg/day included decreased body weight and food consumption.

2. **Developmental toxicity:**

a. Deaths/Resorptions: There appears to be an increase in the occurrence of early resorptions in mid-dose dams. This increase is likely incidental and due to dam No. 354, whose litter was completely resorbed.

b. Altered Growth: There was a decrease in mean fetal weight at 11.25 (male only) and 22.5 (male and female) mg ai/kg/day. There was a dose-related trend of increased incidence of delayed ossification of the hindlimb phalangeal nuclei across all treated groups. The mid-dose and high-dose group exhibited a significant increase when compared to the control group.

c. Developmental Variations: There were no treatment-related external, visceral, or skeletal variations.

d. Malformations: There were no treatment-related external, visceral, or skeletal malformations.

C. **STUDY DEFICIENCIES:** The following study deficiencies were noted by Versar:

- It was not reported whether dosing was based on the most recent body weight determination.
- The animals were treated only until gd 18. According to guidelines, the test substance should be administered daily from implantation to the day before cesarean section on the day prior to the expected day of parturition. Versar does not expect this deficiency to affect the outcome of the study.
- The total numbers of corpora lutea per treatment group were not provided.
- Mean maternal body weight, body weight gain, and food consumption values were not presented in the study report; however, these values were calculated statistical analyses performed on them.
- Individual fetal and/or litter data for external and visceral malformation or anomalies was not presented.
- Page number 64 from the amendment is missing.

D. **STUDY CLASSIFICATION:** This study is classified as **ACCEPTABLE-GUIDELINE**, and fulfills the guideline requirements of OPPTS 870.3700.

APPENDICES

Appendix 1. Litter Incidence of Skeletal Fetal Effects in Rabbits at 0 mg/kg/day

Appendix 2. Litter Incidence of Skeletal Fetal Effects in Rabbits at 7.5 mg/kg/day

Appendix 3. Litter Incidence of Skeletal Fetal Effects in Rabbits at 11.25 mg/kg/day

Appendix 4. Litter Incidence of Skeletal Fetal Effects in Rabbits at 22.5 mg/kg/day

Appendix 5. Summary of Fetal and Litter Effects in the Rabbit

Ref: Todhunter, J.A. (2005). Amendment No. 2 to Final Report on Belclene 350 (TK 12 780/2). Teratology Study in Rabbits. Bio-Lab, Inc. P.O. Box 300002, Lawrenceville, GA 30049. Compiled at: SRS International Corporation. Falls Church, VA 22043. MRID 467217-04. Unpublished.

Appendix 1. Litter Incidence of Skeletal Fetal Effects at 0 mg/kg/day

Female #	Live Male Fetuses	Live Female Fetuses	% Live Fetuses Male	Embryonic Deaths (resorptions)	Fetal Deaths (resorptions)	Phalangeal Nuclei (b). Left Fore-Limb	Phalangeal Nuclei (b). Right Fore-Limb	Phalangeal Nuclei (b) Left Hind-Limb	Phalangeal Nuclei (b) Right Hind-Limb	5th Sternebra (c)	Skeletal Anomalies	Other Anomalies
301 (a)	0	0	n/a	0	0	0	0	0	0	0	0	0
302	5	3	62.5	0	0	[illegible]	[illegible]	[illegible]	0	[illegible]	0	0
303	2	0	100	0	0	[illegible]	[illegible]	[illegible]	0	0	0	0
304	6	3	66.7	[illegible]	0	8	[illegible]	[illegible]	[illegible]	[illegible]	0	0
305	6	5	[illegible]	0	1	6	[illegible]	0	0	1	0	0
306	[illegible]	4	64	[illegible]	0	[illegible]	3	0	0	[illegible]	0	0
307	[illegible]	[illegible]	[illegible]	1	0	[illegible]	3	0	[illegible]	0	[illegible]	0
308	2	6	[illegible]	0	0	[illegible]	[illegible]	[illegible]	[illegible]	0	0	0
309	1	4	[illegible]	1	0	2	2	[illegible]	0	0	0	0
310	[illegible]	[illegible]	[illegible]	0	0	0	[illegible]	[illegible]	[illegible]	[illegible]	0	0
311 (a)	0	0	n/a	0	0	0	0	0	0	0	0	0
312	6	3	66.7	0	0	0	0	0	0	1	0	0
313	4	4	50	0	0	8	7	3	2	0	0	0
314	3	3	50	0	0	0	0	0	0	0	0	0
315	3	2	60	0	0	0	0	0	0	0	0	0
316 (a)	0	0	n/a	0	0	0	0	0	0	0	0	0
317	3	6	33.4	0	0	0	0	0	0	0	0	0
318	4	6	40	0	0	6	5	1	2	4	0	0

319	5	4	55 6	0	0	2	2	0	0	0	0	0
320	8	3	73	1	0	3	2	0	0	1	0	0
Abnormal Fetuses/Litte r	70 (16)	61 (16)	53.8	4 (4)	1(1)	50 (12)	44 (12)	5 (3)	5 (3)	17 (7)	0 (0)	0 (0)

(a) No implantations
(b) Ossification still absent in phalanges II, digit 5
(c) Ossification still absent
1 Page 20 (Female #310) is missing from copy of study MRID 406807-05 "Amendment 1 to "Belclene 350 (TK 12780/2) Teratology Study in Rabbits"
() Number of litters having affected fetuses

Appendix 2. Litter Incidence of Skeletal Fetal Effects at 3.75 mg/kg/day

Female #	Live Male Fetuses	Live Female Fetuses	% Live Fetuses Male	Embryonic Deaths (resorptions)	Fetal Deaths (resorptions)	Phalangeal Nuclei (b): Left Fore-Limb	Phalangeal Nuclei (b): Right Fore-Limb	Phalangeal Nuclei (b) Left Hind-Limb	Phalangeal Nuclei (b) Right Hind-Limb	5th Sternebra (c)	Skeletal Anomalies	Other Anomalies
323	1	[illegible]	25	1	0	1	1	0	0	0	0	0
322	1	[illegible]	50	2	0	5	5	0	0	0	0	0
329	[illegible]	[illegible]	62.5	0	0	1	1	0	0	[illegible]	0	0
321	0	[illegible]	0	0	0	0	0	0	0	[illegible]	0	0
323	4	6	40	0	0	4	1	1	1	0	0	0
326(a)	0	0	n/a	0	0	0	0	0	0	0	0	0
324	[illegible]	5	50	0	0	0	0	0	0	2	0	0
328	1	0	100	[illegible]	0	1	1	0	0	0	0	0
[illegible]	[illegible]	5	50	0	0	4	4	0	0	3	0	0
[illegible]	6	2	75	0	0	7	1	0	0	4	0	0
[illegible]	2	0	100	0	0	2	2	0	0	2	0	0
[illegible]	5	3	50	0	0	6	[illegible]	0	0	0	0	0
151	1	1	50	0	0	1	1	0	0	0	0	0
314	2	2	50	0	0	2	1	0	0	0	0	0
[illegible]	1	2	33	0	0	3	2	1	2	0	0	0
[illegible]	2	1	29	0	0	1	3	2	2	1	1(d)	1(e)
137(a)	0	0	n/a	0	0	0	0	0	0	0	0	0
319	1	[illegible]	[illegible]	3	1	2	1	0	0	0	0	0

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[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Abnormal Fetuses/Litter	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

(b) Ossifications still absent in phalanges II digit 5 (c) Ossifications still absent

(d) Ribs 1 - 2 with hypoplasia of distal ends (ventral) 3 rib 2 distally fused with rib 3 or additional (e) Agenesis of kidney and ureter unilateral

(g) Number of Litters having affected fetuses

Appendix 3. Litter Incidence of Skeletal Feral Effects at 11.25 mg/kg/day

Dam#	Live Male Fetuses	Live Female Fetuses	% Live Fetuses Male	Embryonic Deaths (resorptions)	Fetal Deaths (stillborn)	Phalangeal Nodes (b) Left Fore-Limb	Phalangeal Nodes (b) Right Fore-Limb	Phalangeal Nodes (b) Left Hind-Limb	Phalangeal Nodes (b) Right Hind-Limb	Sternebra (c)	Skeletal Anomalies	Other Anomalies
[illegible]	[illegible]	4	55	[illegible]	1	[illegible]	[illegible]	6	5	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	43 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Ster. fill	[illegible]
[illegible]	[illegible]	[illegible]	29	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	33	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	64	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	50	[illegible]	[illegible]	[illegible]	[illegible]	2	0	0	0	0
349	6	4	60	1	0	10	10	3	3	1	0	0
350	6	6	50	0	0	0	0	0	0	0	0	0
351	7	2	78	0	0	2	1	0	0	0	0	0
352	2	5	29	1	0	2	1	0	1	4	0	0
353	6	3	66.7	0	0	0	0	0	0	0	0	0
354	0	0	n/a	9	0	0	0	0	0	0	0	0
355 (a)	0	0	n/a	0	0	0	0	0	0	0	0	0
356	5	2	71.4	0	0	6	7	0	0	0	0	0
357	5	3	62.5	0	0	0	0	0	0	3	0	0
358 (a)	0	0	n/a	0	0	0	0	0	0	0	0	0

359 (b)	0	0	n/a	0	0	0	0	0	0	0	0	0
360	1	8	11.1	0	0	8	7	0	0	7	0	0
Abnormal Fetuses/Litte r	70 (16)	69 (16)	50.4	13 (5)	2 (2)	72 (13)	61 (12)	17 (7)	14 (6)	20 (7)	2 (1)	0 (0)

(Number is obscured
(a) No implantations
(b) Death because of intubation error, (c) Ossification still absent in phalanges II, digit 5
(d) Ossification still absent, (e) Basal fusion of ribs 10 + 11 (unilateral
(f) Absence of 9th rib and vertebral arch (unilateral, malposition of corresponding centers 9+10).
(i) Number of litters having affected fetuses

Appendix 4. Litter Incidence of Skeletal Fetal Effects at 22.5 mg/kg/day

Female #	Live Male Fetuses	Live Female Fetuses	% Live Fetuses Male	Embryonic Deaths (resorptions)	Fetal Deaths (resorptions)	Phalangeal Nuclei (b): Left Fore-Limb	Phalangeal Nuclei (c): Right Fore-Limb	Phalangeal Nuclei (c): Left Hind-Limb	Phalangeal Nuclei (c): Right Hind-Limb	5th Sternebra (c)	Skeletal Anomalies (e)	Other Anomalies
361(a)	0	0	n/a	0	0	0	0	0	0	0	0	0
362(d)	0	0	n/a	0	0	0	0	0	0	0	0	0
363	2	1	40	0	0	0	1	0	0	0	0	0
364	1	4	50	1	0	7	7	3	5	0	1(e)	0
365	0	1	0	1	5	2	1	0	0	0	0	0
366	5	9	36	0	0	4	6	3	1	6	0	0
367	6	4	60	0	1	1	5	0	0	2	0	0
368	4	3	57	0	0	3	1	0	0	0	0	0
369	1	7	36	0	0	5	8	2	2	0	0	0
370(a)	0	0	n/a	0	0	0	0	0	0	0	0	0
371	4	2	66.7	7	0	0	0	2	2	0	0	0
372	6	1	66.7	1	0	1	3	0	0	0	0	0
373	4	6	40	0	0	1	3	1	1	1	0	0
374	4	5	100	0	0	4	3	0	0	0	1 1(f)	0
375	7	1	63	0	0	4	4	1	1	0	0	0
376(a)	0	0	n/a	0	0	0	0	0	0	0	0	0
377(b)	0	0	n/a	0	0	0	0	0	0	0	0	0
378	3	3	44	0	2	9	9	5	5	0	0	1
379	1	2	50	1	0	4	5	1	1	0	1(g)	0

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