FINAL

DATA EVALUATION REPORT

MK-0244

Study Type: Reproductive Toxicity 9/21/1994

Prepared for:

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031

Principal Reviewer William L McLaben for Date 5/16/94
Sanju Diwan, Ph.D.

Independent Reviewer Pia Lindström Date 5/16/94
Pia Lindström, D.P.H.

QA/QC Manager Date 5/16/94
~~Sharon Segal, Ph.D.~~
Carl A Maczka, Ph.D

Contract Number: 68D10075
Work Assignment Number: 3-25
Clement Number: 84
Project Officer: Caroline Gordon

EPA Reviewer: Myron Ottley, Ph.D.
Review Section IV, Toxicology Branch I/HED

Signature: MOttley
Date: 8/29/94

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I/HED

Signature: Marion Copley
Date: 9/21/94

DATA EVALUATION REPORT

STUDY TYPE: Reproductive Toxicity - Rat (Guideline Series 83-4)

MRID NO.: 428515-11

TOX CHEM. NO.: New chemical

TEST MATERIAL: 4"-Deoxy-4"-epi-methylamino-avermectin B1 (benzoate salt)

SYNONYM: MK-0244; Deoxy avermectin

STUDY NUMBER: TT #91-715-0

SPONSOR: Agricultural Research and Development, Merck and Company Inc., Three Bridges, NJ

TESTING FACILITY: Merck Research Laboratories, Merck and Company Inc., West Point, PA

TITLE OF REPORT: MK-0244: Two-Generation Dietary Reproduction Study in Rats

AUTHOR: G.R. Lankas

DATE REPORT ISSUED: May 12, 1993

CONCLUSIONS:

Dose levels: Administered to Sprague-Dawley rats in the diet, 0, 0.1, 0.6, or 3.6/1.8 mg/kg/day for two generations

Systemic NOEL: 0.6 mg/kg/day
Systemic LOEL: 1.8 mg/kg/day, based on decreased body weight gain and histopathological changes (neuronal degeneration in the brain and spinal cord) in both sexes and generations

Reproductive NOEL: 0.6 mg/kg/day
Reproductive LOEL: 1.8 mg/kg/day based on decreased fecundity and fertility indices and clinical signs (tremors and hind limb extension) in offspring of both generations

Classification: Core Guideline Data

This study satisfies the guideline requirements for a reproductive toxicity study (83-4) in rats.

A. MATERIALS

Test Compound

Purity:	>96%
Description:	None
Lot number:	L-656,748-052S002
Date received:	Not reported
Contaminants:	Not reported
Storage:	Ambient temperature

Test Animals

Species:	Rat
Strain:	Sprague-Dawley [Crl:CD® (SD) BR]
Source:	Charles River Laboratories, Raleigh, NC (females) and Kingston, NY (males)
Age:	Approximately 63 days on study day 0
Weight:	F_0 males--292-405 g on study day 0 F_0 females--179-273 g on study day 0

B. STUDY DESIGN

This study was designed to assess the effects of MK-0244 on the growth and reproductive performance of rats during two successive generations.

Mating Procedure

After approximately 3 weeks of acclimatization followed by 9 weeks of dietary treatment, F_0 females were mated with males from the same group in a ratio of 1:1 for a maximum of 21 days until a copulatory plug was detected or sperm were observed in a vaginal smear. The F_0 generation was mated for a second time approximately 3 weeks following the weaning of the F_{1a} pups. Nonmated animals were paired with fertile animals of the opposite sex from each group for a maximum of 21 days. The day on which mating was confirmed was considered gestational day (GD) 0. F_1 animals were mated in a similar manner avoiding sibling matings.

Animal Husbandry

Rodent diet (Purina Certified Rodent Chow #5002M) and tap water were available ad libitum. The temperature was maintained at 20°-27°C; humidity data were not reported. A 12-hour light/dark cycle was maintained. The study author did not report the number of air changes/hour.

Group Arrangement

F_0 animals were distributed using a randomization procedure based on body weight. The groups were as follows:

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Test Group	Dosage Level (mg/kg/day)	Number of Animals Assigned per Group			
		F_0		F_1	
		Males	Females	Males	Females
Control	0	33	33	33	33
Low dose	0.1	33	33	33	33
Mid dose	0.6	33	33	33	33
High dose*	3.6	33	33	33	33

*The high-dosage level received by the F_0 and F_{1a} females was reduced to 1.8 mg/kg/day on GD 0 following the second cohabitation of F_0 females.

Dosage Administered

Test diets were prepared once or twice weekly by diluting a concentrated premix with untreated diet to achieve appropriate concentrations. Dosages were adjusted to maintain the desired concentration. Diets were stored at room temperature until used. Analyses for concentration, homogeneity, and stability were conducted during weeks 1 and 3 for the F_0 generation and week 7 for the F_{1a} generation.

Dosage Rationale

Dosages were selected based upon the results of a one-generation range-finding reproduction study (TT #90-724-9; MRID No. 427436-33; see Attachment I for a detailed description of the study). Sprague-Dawley female rats (12 dams/group) were administered MK-0243 either by gavage or in the diet on gestational day (GD) 0 through lactational day (LD) 21. The dose levels for the gavage study were 0, 0.1, 0.7, or 5 mg/kg/day, while the diet levels were 0, 1, 7, or 50 ppm (approximately 0, 0.1, 0.7, or 4.6 mg/kg/day).

Maternal toxicity, observed at 5 mg/kg/day in the gavage study and at 50 ppm in the diet study, was manifested as significantly decreased body weight gain on GDs 8-16 for both studies, on LDs 0-8 in the gavage study, and on LDs 8-12 in the diet study. These effects were more pronounced in the gavage study particularly during the first part of the lactation period. Food consumption was also affected more severely in the gavage study during the lactation period. Reproductive toxicity, observed at 5 mg/kg/day in the gavage study and at 50 ppm in the diet study, was manifested as excessive pup mortality during lactation in the gavage study. Also, surviving pups in both studies experienced decreased body weight and tremors during lactation. Histopathology of brain and spinal cord tissues at 50 ppm demonstrated degeneration of these tissues.

Gavage Study: Maternal NOEL = 0.7 mg/kg/day; maternal LOEL = 5 mg/kg/day (decreased body weight gain and food consumption); reproductive NOEL = 0.7 mg/kg/day; reproductive LOEL = 5 mg/kg/day (excessive pup mortality, decreased pup body weight, and increased clinical signs in pups)

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Diet Study: Maternal NOEL = 7 ppm (0.7 mg/kg/day); maternal LOEL = 50 ppm (4.6 mg/kg/day) (decreased body weight gain and food consumption); reproductive NOEL = 7 ppm (0.7 mg/kg/day); reproductive LOEL = 50 ppm (4.6 mg/kg/day) (decreased pup body weight, increased clinical signs [tremors], and histopathological signs [brain and spinal cord degeneration])

Observations

Observations were made once daily for mortality and physical signs. Body weight data were recorded weekly during premating. Body weight data for females were also recorded on GDs 0, 4, 8, 12, 16, 20, and 24 and on lactational days (LDs) 0, 4, 8, 12, 16, 20, and 21; females without live pups were weighed once weekly until sacrifice. Food consumption data were recorded over a 6-day interval during premating; for females it was also recorded over a 4-day interval during GDs and LDs 0-20.

The following data were recorded for each litter:

- Number of live and dead pups, sex, and individual pup weight on LDs 0, 4, 7, 14, and 21
- External anomalies on LDs 0, 4, and 21
- Mortality and physical signs once daily

On day 4, pups were randomly culled to four/sex/litter whenever possible. Pups that died during lactation and 10 pups/sex/litter (randomly selected) were subjected to gross necropsy. Culled pups were examined externally and discarded. Dead pups were fixed in 10% buffered formalin and examined for visceral abnormalities. Twenty-five male and 25 female F_{1a} pups were randomly selected as F_1 parental animals.

Parental males were sacrificed and necropsied at the time of parturition. Parental females were sacrificed and necropsied after weaning of their respective litters between LD 22 and 28. After gross examination, the following tissues were preserved in 10% buffered formalin and processed for histological examination from animals in the control and high-dosage groups.

- Brain
- Spinal cord
- Sciatic nerve
- Uterus
- Vagina
- Gross lesions
- Ovaries
- Testes
- Epididymides
- Seminal vesicles
- Prostate

In addition, brain, spinal cord, and sciatic nerve tissues from animals in the 0.6-mg/kg/day group and the sciatic nerve tissue from animals in the 0.1-mg/kg/day group were processed for histopathological examination.

Statistical Analysis

The following analyses were conducted:

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- Parental and pup body weight/weight gain; food consumption; length of gestation; time to mating; mating, fertility, and fecundity indices; and numbers of implantation sites and live and dead pups--Analysis of variance or covariance followed by a trend test and rankit transformation (for continuous variables) or Mantel-Haenszel test (for discrete variables)

- Infertility--NOSTASOT, Mantel-Haenszel test, and/or Chi-Square test

Compliance

The following statements were provided:

- A signed Statement of No Data Confidentiality Claims, dated June 3, 1993

- A signed Statement of Compliance with EPA GLPs dated May 5, and June 2 and 3, 1993

- A signed Quality Assurance Statement, dated May 5, 1993

C. RESULTS

Test Material Analysis

Results of concentration analyses for two separate batches revealed values ranging from 82% to 106% of target (with two exceptions) for all three dosage levels. Homogeneity, also analyzed at all dosage levels on three separate batches, revealed values ranging from 82% to 108% of target. The results of stability analyses revealed values ranging from 80% to 100%.

Parental Toxicity

Mortality

No compound-related mortalities were observed at any exposure level in either sex or generation. In the F_0 generation, three males were found dead (one each at 0.1, 0.6, and 3.6 mg/kg/day during weeks 18, 7, and 20, respectively). Four F_0 females were found dead (one at 0.1 mg/kg/day, one at 0.6 mg/kg/day, and two at 3.6/1.8 mg/kg/day during weeks 21, 15, and 22-24, respectively). No treatment-related gross findings were observed at necropsy.

In the F_1 generation, three males were sacrificed moribund (one each at 0, 0.1, and 3.6 mg/kg/day during weeks 13, 13 and 12, respectively); necropsy did not reveal the cause of death. Among F_1 females, one animal from the control group was found dead at week 19. In addition, four animals were sacrificed moribund (one at 0.1 mg/kg/day, two at 0.6 mg/kg/day, and one at 3.6/1.8 mg/kg/day during weeks 19, 2, and 1, respectively). No treatment-related gross findings were observed at necropsy.

Clinical Observations

No compound-related clinical signs were observed at any exposure level in either sex or generation.

Body Weight

Compound-related effects in body weight gain were observed at 3.6/1.8 mg/kg/day for both sexes and generations. Summaries of body weight/weight gain data for selected intervals are presented in Tables 1 and 2. Detailed results are discussed below.

In the F_0 generation among males, a significantly decreasing trend with increasing dosage was observed with regard to body weight gain (Table 1) for the entire premating period (weeks -1 to 8). Body weights in these males (data not shown) decreased slightly at 3.6 mg/kg/day throughout the same period. For F_0 females during the premating period, a significantly increasing trend with increasing dosage was observed with regard to body weight gain (Table 1), while body weights increased slightly above control (data not shown). During the first gestation period, a significantly decreasing trend with increasing dosage was observed with regard to body weight gain (Table 2). Body weight during the first gestation period (data not shown) was comparable among all dose groups. No treatment-related effects on body weight or weight gain were seen during the second gestation period and first and second lactation periods (data not shown).

In the F_1 generation among males, a significantly decreasing trend with increasing dosage was observed with regard to body weight gain (Table 1) for the entire premating period (weeks -1 to 15). Body weight in these males decreased below control throughout the study at 3.6 mg/kg/day (data not shown). For F_1 females during the premating period, a significantly decreasing trend with increasing dosage was also observed with regard to body weight gain (Table 1), while body weight decreased below control at 1.8 mg/kg/day. During the gestation period, a significantly decreasing trend with increasing dosage was observed with regard to body weight gain (Table 2) on GDs 0-20, while body weight (data not shown) was consistently lower than control. No treatment-related effects on body weight or weight gain were seen during lactation (data not shown).

Food Consumption

No compound-related effects on food consumption (g/animal/day) were observed in either sex or generation. For F_0 lactating females, a decrease in food consumption was noted at 3.6/1.8 mg/kg/day on LDs 4, 8, and 12, and at all three dosage levels on LDs 16 and 20. These decreases were not seen for F_1 females, and therefore, they were considered to be incidental.

Histopathology

Compound-related effects in histopathology were observed in both sexes and generations at 3.6/1.8 mg/kg/day. In the F_0 generation, neuronal degeneration in the brain and/or spinal cord was observed in males (29/33 and 31/33, respectively) and females (23/33 and 5/33, respectively); slight degeneration of the sciatic nerve was observed in 4 of 33 males.

In the F_1 generation, neuronal degeneration in the brain and/or spinal cord was also noted in males (23/25 and 23/25, respectively) and females (18/27 and 7/27, respectively); no degeneration of sciatic nerves was observed in males at 3.6/1.8 mg/kg/day.

Reproductive Toxicity

Compound-related reproductive effects were observed at 3.6/1.8 mg/kg/day in both generations. Summaries of reproductive parameters are presented in Tables 3, 4, 5 and 6. Detailed results are discussed below.

In the F_0 generation (Table 3) during the first mating period, nonsignificant decreases in the fertility index were observed at 0.1, 0.6, and 3.6 mg/kg/day as a result of decreases in the fecundity index. During the second mating period in the F_0 generation (Table 4) and in the F_1 generation (Table 5), similar decreases in fecundity and fertility indices were observed only at 3.6/1.8 mg/kg/day.

In the F_0 generation (Table 3), a significant trend towards decreasing number of live pups/litter with increasing dosage was observed for the first mating. However, all incidents were within the range of historical controls, and therefore, this finding was considered to be incidental. In addition, similar trends were not seen in the F_0 second mating and F_1 mating.

In F_{1a} and F_{1b} litters (Table 6) prior to weaning, the following clinical signs were observed at 3.6/1.8 mg/kg/day: intermittent head tremors and/or whole body tremors, hind limb extension and its limited use, and/or hind limb splay. Some signs in F_{1a} pups (hind limb splay in 25/25 males and 27/27 females and whole body tremors in 10/25 males and 13/27 females) persisted during the post-weaning period (data not shown). In F_2 litters (Table 6), on the contrary, only 1 of 11 litters at 3.6/1.8 mg/kg/day exhibited clinical signs consisting of whole body tremors and hind limb extension from LD 14 to LD 21. Thus, lowering the high-dosage level from 3.6 to 1.8 mg/kg/day beginning on GD 0 reduced the incidence of treatment-related signs in F_{1b} and F_2 pups.

Among F_{1a} pups (Table 3), a significantly decreasing trend with increasing dosage was observed on body weight for both sexes on LDs 14 and 21. For F_2 offspring (Table 5), a significantly decreasing trend with increasing dosage was observed with regard to body weight for male pups on LD 4 and for male and female pups on LDs 14 and 21. The decreases in pup body weight during late lactation may have been associated with the physical inability of the pups to reach the feeder as a consequence of tremors and hind limb immobility.

D. REVIEWERS' DISCUSSION/CONCLUSIONS

Test Material Analyses

The purity, homogeneity, and stability of the test compound were confirmed. With the exception of a few occasions, the concentration analyses revealed values within ±20% of target.

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Parental Toxicity

Compound-related parental toxicity was observed at 3.6/1.8 mg/kg/day. It was manifested as decreased body weight gain in F_0 and F_1 males and females during premating, and in F_0 and F_1 females during gestation. In addition, histopathological changes, including neuronal degeneration in the brain and spinal cord, were observed in both generations and sexes. Based on these results, the NOEL and LOEL for parental toxicity were 0.6 and 1.8 mg/kg/day, respectively.

Reproductive Toxicity

Compound-related reproductive toxicity was observed at 3.6/1.8 mg/kg/day. It was manifested in both generations as decreases in the fecundity and fertility indices. The number of infertile F_0 females increased at 1.8 mg/kg/day (21% versus 3% in the control) when animals that did not produce a pregnancy in the first mating were paired during the second mating with known fertile animals. The number of infertile males, however, was comparable across all groups. This observation suggests that the treatment specifically affected the females. Clinical signs of toxicity were seen in pups from both generations. Incidences of clinical signs decreased in F_2 litters receiving lower dosage levels (1.8 mg/kg/day). Based on these results, the NOEL and LOEL for reproductive toxicity were 0.6 and 1.8 mg/kg/day, respectively.

E. CORE CLASSIFICATION

Core Guideline Data. This study satisfies the guideline requirements for a reproductive toxicity study (83-4) in rats.

Systemic NOEL = 0.6 mg/kg/day
Systemic LOEL = 1.8 mg/kg/day based on decreased body weight gain and histopathological changes in neural tissue of both sexes and generations

Reproductive NOEL = 0.6 mg/kg/day
Reproductive LOEL = 1.8 mg/kg/day based on decreased fecundity and fertility and clinical signs in pups of both generations

F. RISK ASSESSMENT: Not applicable

TABLE 1. Body Weight and Weight Gain (g) During the Premating Period for Rats Exposed to MK-0244 for Two Successive Generations[a,b]

Week of Treatment	Exposure Level (mg/kg/day) 0	0.1	0.6	3.6/1.8[c]
F_0 males				
-1	350	348	347	346
1	393	388	389	392
4	501	493	495	494
8	583	576	583	565
-1 to 8	233	227	235	219*
F_0 females				
-1	230	229	228	232
1	243	244	244	244
4	288	291	289	293
8	317	323	322	332
-1 to 8	87	95	93	101*
F_1 males				
-1	82	81	81	59
1	134	132	133	100
4	324	316	317	261
8	496	489	492	437
12	571	570	579	508
14	606	599	608	545
-1 to 14	536	530	542	500*
F_1 females				
-1	85	87	86	67
1	130	136	133	108
4	227	231	230	200
8	295	295	298	262
12	326	325	330	297
14	342	338	347	316
-1 to 14	257	254	261	249*

[a]Data were extracted from Study No. TT #91-715-0, Tables A-8, A-9, A-46, and A-47.

[b]Standard deviations were not provided.

[c]The high-dosage received by the F_0 and F_{1a} females was reduced to 1.8 mg/kg/day on GD 0 following the second cohabitation of F_0 females.

*Significant trend through indicated dosage ($p<0.05$)

TABLE 2. Body Weight Gain (g ± S.D.) During Gestation for Rats Exposed to MK-0244 for Two Successive Generations[a,b]

Gestation Day	Exposure Level (mg/kg/day) 0	0.1	0.6	3.6/1.8[c]
F_0 generation-F_{1a} litters				
0–12	59	62	61	61
12–16	20	19	16	11
16–20	63	63	64	63
0–20	142	144	142	136*
F_1 generation-F_2 litters				
0–12	54	60	59	42
12–16	25	25	28	31
16–20	54	51	57	53
0–20	133	135	145	126*

[a]Data were extracted from Study No. TT #91-715-0, Tables A-13 and A-51.

[b]Standard deviations were not provided.

[c]The high-dosage received by the F_0 and F_{1a} females was reduced to 1.8 mg/kg/day on GD 0 following the second cohabitation of F_0 females.

*Significant trend through indicated dosage ($p<0.05$)

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TABLE 3. Effects of Exposure to MK-0244 on F_0 Reproductive Parameters and F_{1a} Offspring Survival and Body Weight[a]

Parameter	Observation at Each Exposure Level (mg/kg/day)			
	0	0.1	0.6	3.6
No. paired females	33	33	33	33
No. matings	33	31	33	31
Mating index (%)[b,c]	100	94	100	94
No. pregnant females	30	22	25	22
Fertility index (%)[d]	91	67	76	67
Fecundity index (%)[e]	91	71	76	71
Gestation index (%)[f]	100	100	100	100
Gestation length (days)	22.5	22.4	22.7	22.5
No. females with liveborn pups	30	22	25	22
Total no. live pups				
Day 0	424	331	367	287
Day 4, precull[b]	406	319	355	278
Day 21[b]	228	173	191	161
Mean no. live pups/litter[g]				
Day 0	14.1 (30)	15.0 (22)	14.7 (25)	13.0* (22)
Day 4, precull[b]	13.5 (30)	14.5 (22)	14.2 (25)	12.6 (22)
Day 21[b]	7.9 (29)	7.9 (22)	7.9 (24)	7.6 (21)
Live birth index (%)[b,h]	94	99	97	96
Viability index (%)[b,i]	96	96	97	97
Lactation index (%)[b,j]	99	99	99	99
Mean pup body weight (g), males				
Day 0	6.6	6.6	6.7	6.7
Day 7	18.1	17.7	18.3	18.2
Day 21	59.8	59.2	60.8	40.2*
Mean pup body weight (g), females				
Day 0	6.3	6.3	6.4	6.4
Day 7	17.2	17.5	17.3	17.4
Day 21	56.9	57.8	58.9	40.4*
Sex ratio (% males day 0)[b]	47	53	47	49

[a]Data were extracted from Study No. TT #91-715-0, Tables A-32, A-33, and A-98.

[b]Calculated (but not analyzed) by the reviewers using individual animal data

[c]Mating index: No. of mated females expressed as % of no. of paired females

[d]Fertility index: No. of pregnant females expressed % of no. of paired females

[e]Fecundity index: No. of pregnant females expressed % of no. of mated females

[f]Gestation index: No. of females delivering a live litter expressed as % of no. of pregnant females

[g]Numbers in parenthesis are the numbers of litters included in the calculation.

[h]Live birth index: Percentage of pups born alive based on no. of total pups born

[i]Viability index: Percentage of pups surviving 4 days based on no. of pups born alive

[j]Lactation index: Percentage of pups surviving 21 days based on no. of live pups on day 4 postcull

*Significant trend through indicated dosage ($p<0.05$)

TABLE 4. Effects of Exposure to MK-0244 on F_0 Reproductive Parameters and F_{1b} Offspring Survival and Body Weight[a]

Parameter	Observation at Each Exposure Level (mg/kg/day) 0	0.1	0.6	3.6/1.8
No. paired females	33	33	32	33
No. matings	32	32	31	31
Mating index (%)[b,c]	97	97	97	94
No. pregnant females	28	28	26	23
Fertility index (%)[d]	85	85	81	70
Fecundity index (%)[e]	88	88	84	74
Gestation index (%)[f]	100	96	100	100
Gestation length (days)	22.2	22.4	22.4	22.4
No. females with liveborn pups	28	27	26	23
Total no. live pups				
Day 0	416	391	419	347
Day 4, precull[b]	393	377	407	336
Day 21[b]	214	206	202	163
Mean no. live pups/litter[g]				
Day 0	14.9 (28)	14.5 (27)	16.1 (26)	15.1 (23)
Day 4, precull[b]	14.0 (28)	14.0 (27)	15.7 (26)	14.6 (23)
Day 21[b]	7.6 (28)	7.6 (27)	7.8 (26)	7.4 (22)
Live birth index (%)[b,h]	95	99	99	98
Viability index (%)[b,i]	94	96	97	97
Lactation index (%)[b,j]	99	97	99	95
Mean pup body weight (g), males				
Day 0	6.5	6.7	6.7	6.8
Day 7	16.6	16.9	17.4	17.8
Day 21	57.9	59.4	61.5	60.2
Mean pup body weight (g), females				
Day 0	6.1	6.4	6.3	6.4
Day 7	15.3	16.0	16.3	16.3
Day 21	54.4	56.9	57.8	56.3
Sex ratio (% males day 0)[b]	50	51	51	49

[a]Data were extracted from Study No. TT #91-715-0, Tables A-34, A-35, and A-99.

[b]Calculated (but not analyzed) by the reviewers using individual animal data

[c]Mating index: No. of mated females expressed as % of no. of paired females

[d]Fertility index: No. of pregnant females expressed % of no. of paired females

[e]Fecundity index: No. of pregnant females expressed % of no. of mated females

[f]Gestation index: No. of females delivering a live litter expressed as % of no. of pregnant females

[g]Numbers in parenthesis are the numbers of litters included in the calculation.

[h]Live birth index: Percentage of pups born alive based on no. of total pups born

[i]Viability index: Percentage of pups surviving 4 days based on no. of pups born alive

[j]Lactation index: Percentage of pups surviving 21 days based on no. of live pups on day 4 postcull

TABLE 5. Effects of Exposure to MK-0244 on F_1 Reproductive Parameters and F_2 Offspring Survival and Body Weight[a]

Parameter	Observation at Each Exposure Level (mg/kg/day)			
	0	0.1	0.6	3.6/1.8
No. paired females	25	25	25	25
No. matings	25	23	22	23
Mating index (%)[b,c]	100	92	88	92
No. pregnant females	20	20	21	12
Fertility index (%)[d]	80	80	84	48*
Fecundity index (%)[e]	80	87	95	52*
Gestation index (%)[f]	95	100	95	92
Gestation length (days)	22.4	22.3	22.4	22.5
No. females with liveborn pups	19	20	20	11
Total no. live pups				
Day 0	265	271	307	162
Day 4, precull[b]	252	263	287	157
Day 21[b]	129	137	131	83
Mean no. live pups/litter[g]				
Day 0	13.9 (19)	13.6 (20)	15.4 (20)	14.7 (11)
Day 4, precull[b]	13.3 (19)	13.2 (20)	14.4 (20)	14.3 (11)
Day 21[b]	6.8 (19)	7.2 (19)	7.7 (20)	7.5 (11)
Live birth index (%)[b,h]	98	99	97	99
Viability index (%)[b,i]	95	97	93	97
Lactation index (%)[b,j]	88	94	86	94
Mean pup body weight (g), males				
Day 0	6.7	6.4	6.4	6.4
Day 7	16.6	17.1	16.5	15.2
Day 21	58.0	58.4	59.7	52.7*
Mean pup body weight (g), females				
Day 0	6.3	6.2	6.1	6.1
Day 7	15.4	16.6	15.4	14.8
Day 21	54.8	57.5	57.4	51.0*
Sex ratio (% males day 0)[b]	49	51	50	50

[a]Data were extracted from Study No. TT #91-715-0, Tables A-62, A-63, and A-126.

[b]Calculated (but not analyzed) by the reviewers using individual animal data

[c]Mating index: No. of mated females expressed as % of no. of paired females

[d]Fertility index: No. of pregnant females expressed % of no. of paired females

[e]Fecundity index: No. of pregnant females expressed % of no. of mated females

[f]Gestation index: No. of females delivering a live litter expressed as % of no. of pregnant females

[g]Numbers in parenthesis are the numbers of litters included in the calculation.

[h]Live birth index: Percentage of pups born alive based on no. of total pups born

[i]Viability index: Percentage of pups surviving 4 days based on no. of pups born alive

[j]Lactation index: Percentage of pups surviving 21 days based on no. of live pups on day 4 postcull

*Significant trend through indicated dosage ($p<0.05$)

TABLE 6. Physical Signs During Preweaning Period Exhibited By F_{1a}, F_{1b}, and F_2 Litters Exposed to MK-0244[a]

Parameter	Observation at Each Exposure Level (mg/kg/day)			
	0	0.1	0.6	3.6/1.8
F_{1a} litters				
Number of litters examined	30	22	25	22
Hind limb extension	0	0	0	21
Hind limb splay	0	0	0	18
Intermittent head tremors	0	0	0	20
Limited use of hind limb(s)	0	0	0	21
Whole body tremors	0	0	0	21
F_{1b} litters				
Number of litters examined	28	27	26	23
Hind limb extension	0	0	0	5
Hind limb splay	0	1	0	0
Intermittent head tremors	0	0	0	0
Limited use of hind limb(s)	0	0	0	5
Whole body tremors	0	0	0	7
F_2 litters				
Number of litters examined	19	19	19	11
Hind limb extension	0	0	0	1
Hind limb splay	0	0	0	0
Intermittent head tremors	0	0	0	0
Limited use of hind limb(s)	0	0	0	0
Whole body tremors	0	0	0	1

[a]Data were extracted from Study No. TT #91-715-0, Tables A-36, A-37, and A-64.

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