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DATA EVALUATION RECORD

MEVINPHOS

Study Type: 83-4a; A Two-Generation Reproduction Study in Crl:CD BR Sprague-Dawley Rats with Mevinphos

Work Assignment No. 1-01-15F (MRID 42122201)

Prepared for

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Reregistration Branch I, Health Effects Division (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Multi-generation Reproduction Study - Rat
OPPTS Number: 870.3800 OPP Guideline Number: §83-4a

DP BARCODE: D251794 SUBMISSION CODE: S547036
P.C. CODE: 015801 TOX. CHEM. NO.: 160B

TEST MATERIAL (PURITY): Mevinphos (89.57% a.i)

SYNONYMS: MRD-88-331

CITATION: Beyer, B.K. (1991). Multi-Generation Rat Reproduction Study MRD-88-331: Mevinphos. Exxon Biomedical Sciences, Inc. Toxicology Laboratory. East Millstone, New Jersey. Laboratory Project ID 233135, November 26, 1991. MRID 42122201. Unpublished.

SPONSOR: Amvac Chemical Corporation. Los Angeles, CA.

EXECUTIVE SUMMARY: In a 2-generation reproduction toxicity study (MRID 42122201), Mevinphos (89.57% a.i.) as an aqueous formulation was administered continuously, except as noted below, by gavage to 35 Crl:CD BR Sprague-Dawley rats/sex/dose at dose levels of 0, 0.05, 0.1 or 0.5 mg/kg/day. Exposure to P animals began at 7 weeks of age and lasted for 10 weeks prior to mating. F_1 pups selected to produce the F_2 generation were exposed to the same dosage as their parents at post-natal day (PND) 28 and continuously throughout the rest of the study. Treatment was started a week later than specified by the guidelines because of the excessive mortality observed in the range-finding study in which treatment was started at weaning. After approximately 11 weeks of treatment, F_1 offspring were paired to produce the F_2 litters that were necropsied at weaning. Mating to produce a second F_2b generation was not performed.

Treatment-related clinical signs were observed in the high-dose P females following dosing. Signs observed included ataxia (1 occurrence), fine (8 occurrences) or coarse (17 occurrences) tremors, pinpoint pupils (11 occurrences), and oral discharge (8 occurrences). All other P and F_1 groups did not exhibit any treatment-related clinical signs. There were no significant differences in body weight or body weight gain for P generation adults. In the F_1 adults, body weight was

decreased at several intervals during premating, mating and post-mating, although the changes were of relatively low magnitude (6-8% decrease as compared to control values) and therefore of questionable toxicological significance. The high dose P females had decreased body weight gains during Days 0-4 (108%) and Days 0-21 (27%) of lactation; the values were not statistically significant but were toxicologically significant. In the F_1 high-dose males, mean male mating and fertility indices were reduced ↓17% and 22%, respectively, although not significantly. These values were outside of the laboratory's historical control ranges.

Plasma cholinesterase activity was reduced ($p<0.01$) in mid-(↓21%) and high-dose P males (↓44%) and in mid- (↓25%,$p<0.05$) and high-dose P females (↓60%, $p<0.01$). Brain cholinesterase activity was reduced ($p<0.01$) in high-dose males (↓42%) and females (↓49%). Mid-dose female brain cholinesterase activity was also significantly reduced ($p<0.01$), but the difference was small (↓6%) and not of toxicological concern.

F_1 adults had greater reductions in plasma and brain cholinesterase activities than P adults. Plasma cholinesterase activity was reduced 22%, 20%, and 44% ($p<0.01$) in low-, mid-, and high-dose males, respectively. In females, plasma cholinesterase activity was reduced 18% (p=not sign.), 29% ($p<0.01$), and 60% ($p<0.01$) in low-, mid-, and high-dose animals, respectively. Brain cholinesterase activity was reduced in males 6% ($p<0.05$) and 49% ($p<0.01$) in mid- and high-dose males, respectively. Brain cholinesterase activity was reduced ($p<0.01$) and in mid- (8%) and high-dose (51%) females. The reductions in brain cholinesterase activity in the mid-dose animals and plasma cholinesterase activity in low-dose females were too small to be considered of toxicological concern.

There were no treatment-related findings on necropsy of the P adults. In the F_1 males, the high-dose testes+epididymides weight was significantly reduced (↓12%, $p<0.05$). The relative testes+epididymides/body weight ratio was not statistically different from concurrent controls. Relative ovarian weights were decreased in the high-dose F_1 dams (↓17%, $p<0.05$). The F_1 males at 0.5 mg/kg/day had an increase in mutifocal or diffuse unilateral testicular atrophy (3/24 vs 0/13 in controls). The F_1 females at 0.5 mg/kg/day had an increased incidence of animals with decreased number of corpora lutea in the ovaries (11/35 vs 3/35 in controls).

No treatment-related effects on survival indices were observed at any time in the F_1 and F_2 litters. No treatment-related clinical signs were noted in the F_1 or F_2 litters. There were no treatment-related findings at necropsy in the F_1 or F_2 pups.

Body weights were significantly decreased in high-dose male and female F_1 pups from (PND) 4 through 21 (↓10 -16%, $p<0.01$).

The LOAEL for parental toxicity is 0.1 mg/kg/day in females and 0.05 mg/kg/day in males based on inhibition of plasma cholinesterase activity. The parental NOAEL is 0.05 mg/kg/day in females and < 0.05 mg/kg/day (lowest dose tested) in males.
The LOAEL for reproductive/offspring toxicity is 0.5 mg/kg/day based on decreased male mating and fertility indices, decreased absolute weight of testes + epididymides, decreased

relative weight of the ovaries, histological changes in testes and ovaries and decreased pup body weight. The reproductive/offspring NOAEL is 0.1 mg/kg/day.

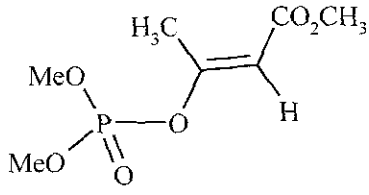
The reproductive study in the rat is determined to be **Acceptable (§83-4)** and does satisfy the guideline requirement for a multi-generational reproductive toxicity study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

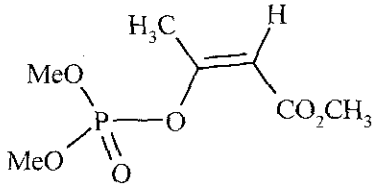
I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Mevinphos
   Description: Colorless liquid
   Lot/Batch #: 810054
   Purity: 89.57% a.i. (74.48% alpha isomer; 15.09% beta isomer)
   Structure:



α-mevinphos



β-mevinphos

2. Vehicle: Reverse osmosis water.

3. Test animals: Species: rat
   Strain: Crl:CD BR (Sprague-Dawley) VAF/Plus
   Age at start of dosing: P - 7 weeks; F_1 - approximately 28 days.
   Weight at start of dosing:
   (P) Males: 229.7-309.8 g Females: 163.2-206.8 g
   (F_1, means) Males: 204.4-231.3 g; Females: 155.5-174.4 g

Source: Charles River Breeding Laboratory, Stone Ridge, NY.
Housing: Wire-mesh, stainless steel cages during pre-mating (1/cage), mating (1 male and 1 female/cage), and early gestation(1 dam/cage) and in stainless steel cages with solid bottom with bedding during late gestation and lactation (1 dam and litter/cage).
Diet: Purina Certified Rodent Chow #5002, Ralston Purina Co., St. Louis, MO, ad libitum.
Water: Tap water, ad libitum.
Environmental conditions:
Temperature: 68-76°F
Humidity: 40-70%
Air changes: Not reported
Photoperiod: 12 hours light/12 hours dark
Acclimation period (P): 18 days
Study Duration (in life dates): May 7, 1990 - March 1, 1991

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: One male was caged with one female from the same test group overnight for a period of 7 days, or until sperm was observed in a vaginal smear. This day was designated gestation Day (GD) 0. If mating did not occur within 7 days, the male was substituted with an alternate unmated male from the same treatment group for a second 7-day period. The same procedure was followed for a third period, if necessary. Cohabitation lasted no longer than 3 weeks.

2. Study schedule: Starting at 7 weeks of age, P animals were given test article formulations for approximately 10 weeks before they were mated to produce the F_1 litters. At PND 21, F_1 animals were selected to become the F_1 parents of the F_2 generations and were given the same concentration test formulation as their dam starting at PND 28. **Treatment was started one week after weaning because of the excessive mortality observed in the range-finding study in which treatment was started at weaning.** This variation in protocol was approved by the EPA (no documentation was provided). F_1 animals were given test formulations for approximately 11 weeks prior to mating the first time to produce the F_2a litters. Mating to produce an F_2b generation was not performed. Exposure of all animals to the test material was continuous throughout the study except for the one-week interval previously mentioned.

3. Animal assignment: P animals were randomly assigned to test groups (Table 1).

Table 1. Animal assignment[a,b]

Test Group	Dose (mg/kg/day)	Animals/group			
		P Males	P Females	F_1 Males	F_1 Females
Control	0	35	35	35	35
Low-dose	0.05	35	35	35	35
Mid-dose	0.1	35	35	35	35
High-dose	0.5	35	35	35	35

a Formulations were administered from the beginning of the study until sacrifice, except in F_1 animals, which started receiving the formulations at PND 28.
b Data extracted from the study report page 22.

4. Dose selection rationale: The test concentrations were selected based on the results of a range-finding multi-generation reproduction study in rats (EBSI Study 233133), in which 6 groups of Sprague-Dawley rats (10/sex/group) received Mevinphos at 0, 0.005, 0.05, 0.1, 0.5, or 1.0 mg/kg/day. Animals were dosed from 3 weeks prior to mating, throughout mating, during gestation and lactation, and until PND 28, when they were sacrificed.

   Toxicity, manifested as increased mortality and clinical signs and decreased plasma cholinesterase activity, body weights, food consumption and reproductive parameters was apparent at doses of 0.5 mg/kg and above. Pinpoint pupils occurred at all dose levels.

   Apparent treatment-related mortality was observed in the P adults (1 high-dose male; 3 high-dose, 1 high-mid-dose, and 1 low-mid-dose females). Clinical signs were observed post-dosing in males and females. The high-dose males exhibited ataxia (1 treated vs 0 controls), coarse tremors (4 treated vs 0 controls), fine tremors (4 treated vs 0 controls), salivation (7 treated vs 0 controls), and nasal discharge (4 treated vs 1 control). High-mid-dose males exhibited coarse tremors (1), fine tremors (1), and nasal discharge (3). Mid-dose males exhibited nasal discharge (4) and ocular discharge (2). Pinpoint pupils were observed in all treatment groups (6-10 observations/group). Females manifested greater clinical signs than males. High-dose females manifested prostration (9 treated vs 0 controls), ataxia (2 treated vs 0 controls), convulsions (1 treated vs 0 controls), coarse tremors (9 treated vs 0 controls), fine tremors (8 treated vs 0 controls), nasal discharge (3 treated vs 0 controls), oral discharge (3 treated vs 0 controls), salivation (9 treated vs 0 controls), ocular discharge (7 treated vs 0 controls), and rales (3 treated vs 0 controls). Notable observations in high-mid-dose females were fine tremors (5), nasal discharge (1), and ocular discharge (1). Mid-dose females exhibited nasal discharge (2) and ocular discharge (1). Pinpoint pupils were observed in all treated groups (6-9

observations/group) and in controls (3), although the controls were inadvertently dosed with 0.05 mg/kg of the test material at one time point. There were no differences of toxicological significance in mean body weight of either sex during pre-mating or mating. However, the mean body weight of high-dose females during gestation and lactation were slightly lower than controls. Food consumption was not different from concurrent controls during mating, premating, or gestation, but was consistently lower in high-dose females during lactation (↓24% for LD 0-21). There was a dose-dependent decrease in plasma cholinesterase activity, with plasma cholinesterase values being significantly decreased in high-mid-dose groups (↓41-48%, $p<0.01$) and high-dose groups (↓52-59%, $p<0.01$). The high-dose (↓38%, p=not significant.) and high-mid-dose (↓20%, p= not sign.) male fertility indices were reduced, as were the high-dose female fecundity and gestation indices (↓20%, p=not sign.). In the offspring, the Day 1 survival index and lactation index were decreased 20% (p=not sign.). Pup body weights were consistently decreased in high-dose females during lactation (↓7-31%, p=not sign.). Although the majority of deaths in pups after weaning appeared to be due to intubation errors, 8 of the 12 deaths in the high-mid-dose group were not due to intubation error and may be due to toxicity.

Based on the results of these studies, 0.5 mg/kg/day was selected as the high dose for the subsequent reproductive toxicity study in rats. Low- and mid-dose levels chosen were 0.05 and 0.1 mg/kg/day, respectively. The administration of the test formulation to pups was delayed from weaning (PND 21) to PND 28 due to the increased mortality seen at this earlier time in the range-finding study.

5. Dosage preparation and analysis: Formulations were prepared (frequency not reported) by mixing appropriate amounts of the test substance with reverse osmosis water and refrigerating the formulation until use. Adjustments were made for the 89.57% a.i. For homogeneity/concentration analyses, formulations were analyzed weekly for the first month, then monthly thereafter. Each analysis consisted of the mean of 2 aliquots/sample. For stability analyses, 1, 160, and 6000 ppm solutions were refrigerated and analyzed after 3, 6, and 7 days.

   Results -Stability Analysis (% of Day 0): 1 ppm (Day 7) - 88%; 160 ppm (Day 7) - 98%; 6000 ppm (Day 6) - 99%

   Homogeneity/Concentration Analysis (% of nominal ± CV): 10 ppm - 100 ± 2.2%, 20 ppm - 99 ± 2.0%, 100 ppm - 99 ± 2.5%. Mevinphos was not detected in control samples.

   The analytical data indicated that the variance between nominal and actual dosage to the study animals was acceptable.

6. Dosage Administration: Formulations were administered by oral gavage, seven days per

week for 10 weeks. Dose volumes (5.0 ml/kg) were based on the most recent body weight. F_1 adults received mevinphos at PND 28 rather than at weaning because of the high mortality observed when administered at the earlier date in the range-finding study.

C. OBSERVATIONS

1. Parental animals: All parental animals were observed daily for morbidity, mortality, and clinical signs. All adult males received a clinical exam prior to selection, on the first day of dosing and weekly thereafter. Females received a clinical exam prior to selection, on the first day of dosing, weekly during mating, on GDs 0, 7, 14, and 21, and on LDs 0, 4, 7, 14, and 21. Males were weighed prior to selection, on the first day of dosing, and weekly until necropsy. Females were weighed prior to selection, on the first day of dosing, weekly during pre-mating, on GDs 0, 7, 14, and 21, and on LDs 0, 4, 7, 14, and 21. Food consumption was measured weekly for both sexes during the premating period. Maternal food consumption was recorded on GDs 0, 7, 14, and 21 and on LDs 0, 4, 7, 14, and 21.

2. Litter observations: Litters were examined twice daily for mortality and unusual conditions. The following litter observations (X) were made (see Table 2):

Table 2. F_1 litter observations[a]

Observation	Time of observation (LD)						
	Day 0	Day 1	Day 4[b]	Day 4[c]	Day 7	Day 14	Day 21
Number of live pups	X	X	X	X	X	X	X
Litter weight	NR	NR	NR	NR	NR	NR	NR
Pup weight	NR	X	X	X	X	X	X
Number of dead pups	X	X	X	X	X	X	X
Sex of each pup	X	X	X	X	X	X	X

a Data extracted from the study report, pages 25 and 26; NR=not reported.
b Before standardization (culling).
c After standardization (culling).

On PND 4, litters were standardized to a maximum of 8 pups/litter with 4/sex/litter, as nearly as possible. Excess pups that appeared normal were sacrificed after gross examination, but tissues were not saved. Abnormal pups were necropsied and tissues were preserved.

Dead pups were examined grossly for abnormalities.

3. Cholinesterase determinations:

P and F_1 males and females were bled from the orbital sinus on the day prior to necropsy for plasma and erythrocyte cholinesterase determinations. Blood samples were taken approximately 3 hours post-dosing. At necropsy, the right hemisphere of the brain was collected for brain cholinesterase determinations.

4. Postmortem observations:

1) Parental animals: P males were sacrificed after delivery of their last F_1 litter sired. P females were sacrificed following weaning. Mated females which did not deliver or lost their litter were euthanized and necropsied. These animals were subjected to a complete external and internal postmortem examination. The animals were weighed, and the following organs or tissues were weighed and preserved (XX), or only preserved (X) in 10% neutral buffered formalin for possible future examination:

XX	Prostate	XX	Testes
XX	Seminal vesicle	XX	Epididymides
XX	Ovaries	X	Pituitary
X	Vagina	X	Uterus
X	Any abnormal tissue		

Slides prepared from these tissues were examined for all high-dose and control adults. Ovaries of the F_1 low- and mid-dose adults were also examined.

Preliminary reproductive indices for the F_1 males suggested possible treatment-related effects in the high-dose groups. Therefore, the testes, epididymides, seminal vesicles, prostate and pituitary from 22 control males and 12 males from each of the treatment groups were collected, weighed, and transferred to Environmental Health Research and Testing, Inc., Lexington Kentucky (EHRT) on the day of necropsy for further evaluation. Organ to body weight ratios were calculated and the data forwarded to EHRT for use in conjunction with the male reproductive assessment.

In addition, the following reproductive endpoints were evaluated: epididymal sperm motility, epididymal sperm count per gram of caudal tissue, and epididymal fluid analysis. The left testis was frozen for evaluation of testicular spermatid head counts,

sperm smears were prepared to determine the incidence of abnormal sperm, and sperm motility was videorecorded for subsequent analysis. Frozen specimen sperm counts, sperm morphology, videorecorded sperm motility, and right testes histopathology sections were evaluated by EHRT.

2) Offspring: Preweaning pups that died were examined for abnormalities. Culled pups which appeared normal were examined externally, but tissues were not saved. Abnormal pups were necropsied, and tissues were preserved for possible examination. At weaning, 5 pups/sex/dose were randomly selected, euthanized and necropsied.

D. DATA ANALYSIS

1. Statistical analyses: All collected data were subjected to routine appropriate statistical procedures.

2. Indices:

Reproductive indices: The following reproductive indices as presented in the study report were calculated for the P and F_1 adults:
female fertility index = # of females confirmed mated/# of females paired x 100%
female fecundity index = # of females pregnant/# of females sperm positive x 100%
male mating index = # of males confirmed mated/total # of males mated x 100%
male fertility index = # of males impregnating females/# of males used for mating x 100%

Offspring viability indices: The following viability indices as presented in the study report were calculated for the F_1 and F_2 litters:

gestation index = # of females with live pups/# of females pregnant x 100%
live birth index = # of live pups alive at birth/total # of pups born x 100%
Day 1 survival index = # of live pups at Day 1/# of live pups at Day 0 x 100%
Day 4 survival index = # of live pups at Day 4(precull)/# of live pups at Day 1 x 100%
Day 7 survival index = # of live pups at Day 7/# of live pups at Day 4 (post-cull) x 100%
Day 14 survival index = # of live pups at Day 14/# of live pups at Day 7) x 100%
Day 21 survival index = # of live pups at Day 21/# of live pups at Day 14 x 100%
lactation index = # live pups at Day 21/# of live pups at Day 4 (post-cull) x 100%
sex ratio = # of males/total # of pups x 100:# of females/total # of pups x 100%

3. Historical control data: Historical control data were provided for comparison with concurrent controls.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: Treatment-related clinical signs were observed in the high-dose P females following dosing. Signs observed included ataxia (1 occurrence), fine (8 occurrences) or coarse (17 occurrences) tremors, pinpoint pupils (11 occurrences), and oral discharge (8 occurrences). All other P and F_1 dose groups did not exhibit any treatment-related clinical signs.

   There were no treatment-related increases in mortality. In the P adult males, 8 (3 control, 2 at 0.1 mg/kg/day and 3 at 0.5 mg/kg/day) died prior to termination; 2 in MDT group and 1 each in control and HDT groups were due to intubation errors. The other deaths were attributed to lymphosarcoma (1 control and 1 high-dose male); renal abnormalities (1 high-dose), or unknown (1 control). In the P females, 5 died prior to termination; 4 (1 each at 0.05 and 0.1 mg/kg/day; 2 at 0.5 mg/kg/day) were due to intubation errors. The other death occurred in a low-dose female; it was attributed to urogenital abnormalities. In the F_1 adults, 3 high-dose males died of unknown causes, reducing survival (↓9%, p=not sign.). This reduction was not considered to be of toxicological concern, due to the lack of associated clinical signs. Three deaths (1 each at 0.05, 0.1 and 0.5 mg/kg/day) were due to intubation errrors. Non-intubation error mortality in the females was limited to 1 high-dose dam (unknown cause) and one control dam (moribund due to necrotic mammary gland mass).

2. Body weight, body weight gains, and food consumption: Selected mean body weight, body weight gain, and food consumption data are presented in Table 3a through 3d. There were no significant differences in body weight or body weight gains in P males or females during the premating, mating, lactation or gestation (Table 3a). The mean weight gain for Days 0-4 of lactation for the HDT females was decreased (-0.5 vs. 6.1 for control), however the change was not statistically significant and is not considered toxicologically significant (Table 3c). For Days 0-21, body weight gain was reduced 27%; the change was not statistically significant.

   In the F_1 adults (Table 3b), body weights were reduced in the high-dose males on Days 7, 14, and 112 (↓6-8%, $p<0.05$). These reductions were minor and are not considered to be of toxicological concern. There were no significant differences in body weight in females during mating, premating, gestation, or lactation. Body weight gains were not analyzed for F_1 adults during premating. Body weight gains in F_1 females were not significantly different from concurrent controls during gestation or lactation.

   No toxicologically significant differences in food consumption occurred in the P or F_1 adults. Food consumption was increased in P females during week 8 of premating (↑7%,

$p<0.05$) and decreased during the LD 4-7 interval (↓11%, $p<0.05$). The isolated increase in food consumption was not considered to be of toxicological significance. The decrease in food consumption for the LD 4-7 period was accompanied by non-significant decreases (↓2-8%) at the other time periods. Although by themselves these decreases are not considered to be of toxicological concern, they may have contributed to the decreased pup weights observed in the F_1 offspring. Significant differences in food consumption did occur in the F_1 adults, but these were sporadic and minor and are not considered to be of toxicological concern.

Table 3a. Selected mean body weights (g), body weight gains (g), and food consumption (g/animal/day) - P generation, males during premating, mating, and postmating and females during premating.[a]

Observation/Study Days	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
P Generation Males - Premating, Mating, and Postmating[b]				
Mean body weight/Day 0	271.8	271.1	270.5	270.0
Mean body weight/Day 70	551.4	549.9	540.7	551.7
Mean body weight/Day 126	621.9	636.3	619.9	633.7
Mean weight gain/Day 0-126[c]	350.1	365.2	349.4	363.7
Mean food consumption/Week 1	202.4	200.3	200.6	200.4
Mean food consumption/Week 10	209.4	214.8	205.7	205.6
Mean food consumption/Week 18	213.0	214.5	208.9	209.2
P Generation Females - Premating only				
Mean body weight/Day 0	184.8	186.3	183.2	183.9
Mean body weight/Day 35	265.2	264.2	263.4	268.3
Mean body weight/Day 70	299.6	300.8	303.3	308.8
Mean weight gain/Day 0-70[c]	114.8	114.5	120.1	124.9
Mean food consumption/Week 1	134.9	136.0	134.6	137.1
Mean food consumption/Week 5	146.3	148.3	147.3	148.1
Mean food consumption/Week 10	144.7	148.0	151.8	149.8

a Data extracted from the study report Tables 6 and 9, pages 71, 72, 75, and 76.

b The premating interval extended from Day 0 to Day 70. The mating and post-mating interval extended from Day 70 to Day 126.

c Calculated by the reviewers.

Table 3b. Selected mean body weights (g), body weight gains (g), and food consumption (g/animal/day) - F_1 generation males during premating, mating, and postmating and females during premating.[a]

Observation/Study Days	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
F_1 Generation Males - Premating, Mating, and Postmating[b]				
Mean body weight/Day 0	221.8	231.3	226.4	204.4
Mean body weight/Day 7	287.9	297.2	289.9	264.3* (8)[d]
Mean body weight/Day 14	343.8	355.0	349.2	321.3* (7)
Mean body weight/Day 112	635.8	628.5	632.4	598.0* (6)
Mean body weight/Day 147	672.9	657.1	688.7	648.4
Mean weight gain/Day 0-147[c]	451.1	425.8	462.3	444
Mean food consumption/Week 1	205.8	213.6	207.1	190.0* (8)
Mean food consumption/Week 11	209.4	218.4	212.8	206.8
F_1 Generation Females - Premating only				
Mean body weight/Day 0	166.5	174.4	173.2	155.5
Mean body weight/Day 77	310.2	319.6	326.3	315.2
Mean weight gain/Day 0-77[c]	143.7	145.2	153.1	159.7
Mean food consumption/Week 1	144.7	152.6	151.9	141.5
Mean food consumption/Week 11	143.5	154.4	148.2	145.0

a Data extracted from the study report Tables 26 and 29, pages 115, 116, and 119.
b The premating interval extended from weaning (Day 0) to Day 70. The mating and post-mating interval extended from Day 70 to Day 147.
c Calculated by the reviewers.
d (Percentage decrease from control value) calculated by the reviewer
* Significantly different from controls at $p<0.05$.

Table 3c. Selected mean body weights (g), body weight gains (g), and food consumption (g/animal/day) - P generation females during F_1 gestation and lactation.[a]

Observation/Study Day	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
P Generation Females - F_1 Gestation				
Mean body weight/Day 0	293.4	297.2	304.8	303.3
Mean body weight/Day 7	325.9	330.2	336.0	334.7
Mean body weight/Day 14	361.0	360.1	368.3	366.9
Mean body weight/Day 21	442.0	446.6	449.7	450.9
Mean weight gain/Day 0-7	32.5	33.0	31.2	31.5
Mean weight gain/Day 0-21	147.6	149.4	144.9	147.6
Mean food consumption/Days 0-7	172.9	178.9	176.1	176.4
Mean food consumption/Days 7-14	191.9	193.9	193.3	201.4
Mean food consumption/Days 14-21	201.1	202.8	199.8	201.9
Mean food consumption/Days 0-21	566.7	575.6	569.2	575.4
P Generation Females - F_1 Lactation				
Mean body weight/Day 0	335.0	332.3	341.8	343.4
Mean body weight/Day 4	341.2	338.1	349.8	342.8
Mean body weight/Day 7	345.2	345.1	352.3	346.3
Mean body weight/Day 14	361.5	363.6	369.0	367.3
Mean body weight/Day 21	349.1	345.8	351.9	354.6
Mean weight gain/Day 0-4	6.1	5.8	8.0	-0.5 (108)[b]
Mean weight gain/Day 0-21	14.4	13.5	10.1	10.5 (27)
Mean food consumption/Days 0-4	118.4	110.8	123.0	116.5
Mean food consumption/Days 4-7	121.6	116.5	120.2	108.4* (11)
Mean food consumption/Days 7-14	384.3	378.8	395.4	360.3 (6)
Mean food consumption/Days 14-21	486.0	464.7	480.0	448.4 (8)
Mean food consumption/Days 0-21	1110.3	1071.0	1123.9	1047.4

a Data extracted from the study report Tables 7, 8, 10, and 11 , pages 73, 74, 77, and 78.
b (Percent decrease from control value) calculated by the reviewer
* Significantly different from controls at $p<0.05$.

Table 3d. Selected mean body weights (g), body weight gains (g), and food consumption (g/animal/day) - F_1 generation females during F_2 gestation and lactation.[a]

Observation/Study Day	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
F_1 Generation Females - F_2 Gestation				
Mean body weight/Day 0	312.6	308.2	319.2	314.5
Mean body weight/Day 7	347.1	342.3	358.8	348.7
Mean body weight/Day 14	378.3	370.7	391.0	380.5
Mean body weight/Day 21	463.4	449.0	483.4	462.8
Mean weight gain/Day 0-7	34.4	34.0	39.7	34.3
Mean weight gain/Day 0-21	150.8	140.8	164.3	148.3
Mean food consumption/Days 0-7	173.9	174.5	181.4	171.8
Mean food consumption/Days 7-14	189.2	193.9	194.5	198.0
Mean food consumption/Days 14-21	198.5	194.2	199.8	200.9
Mean food consumption/Days 0-21	565.7	560.3	573.0	570.6
F_1 Generation Females - F_2 Lactation				
Mean body weight/Day 0	358.6	353.6	363.5	360.1
Mean body weight/Day 4	361.1	356.9	367.5	355.2
Mean body weight/Day 7	365.3	355.6	368.7	360.2
Mean body weight/Day 14	379.7	373.2	382.5	376.5
Mean body weight/Day 21	369.3	367.8	365.1	365.4
Mean weight gain/Day 0-4	2.5	4.0	4.0	1.7
Mean weight gain/Day 0-21	11.7	14.9	1.7	11.9
Mean food consumption/Days 0-4	125.8	114.7	121.3	121.8
Mean food consumption/Days 4-7	123.7	114.1	117.4	115.2
Mean food consumption/Days 7-14	399.4	356.5	377.9	368.1
Mean food consumption/Days 14-21	498.3	475.3	489.9	463.0
Mean food consumption/Days 0-21	1155.0	1059.3	1106.5	1065.2

a Data extracted from the study report Tables 27, 28, 30, and 31, pages 117, 118, 121, and 122.

3. Reproductive function:

   a. Estrous cycle length and periodicity: No data were presented pertaining to the estrous cycle length and periodicity in this study.
   b. Sperm and male reproductive organ measures in special study of F_1 males (see page 9): There were no differences of toxicological concern in terminal body weights, epididymal, testicular, prostate, seminal vesicle or pituitary weights. There were no differences of toxicological concern in epididymal sperm count per gram of caudal

tissue, the relative incidence of abnormal sperm, average spermatid head count, spermatid heads per testis, and spermatid heads per gram of testis. No unexpected cell types were detected in the epididymal fluid. There were no differences of toxicological concern in sperm motility, both by automated analysis or manual determination. Mid-dose males showed increased left caudal epididymal weights and decreased epididymal sperm motility versus concurrent controls. Due to the lack of a dose-response, these findings are not considered to be of toxicological concern.

c. Sexual maturation (F_1): No observations were made pertaining to the sexual maturation rates of the F_1 litters.

4. Reproductive performance: Reproductive performance results are presented in Tables 4a and b. There were no treatment-related differences in reproductive performance in P dams. P sires had a slightly reduced fertility index (↓11%), but the difference was not significant and not considered to be of toxicological concern.

In the F_1 high-dose males, mean male mating and fertility indices were reduced ↓17% and 22%, respectively, although not significantly. The mid-dose male fertility index (67.6%) was also reduced (↓16%), although it was within historical control ranges (66.7-93.1%) and therefore not considered to be of toxicological concern. High-dose F_1 dams had reduced fertility (80.0%, ↓15%), although the reductions were not statistically significant and were within historical control ranges (80.0-96.6%) and are thus not considered to be of toxicological concern. A negative dose response was seen in the gestation index, but was due to a non-significant reduction (↓9%) in the high-dose group and is not considered of toxicological concern. The gestation index of all other groups was 100%.

Table 4a. Reproductive performance of P sires and dams.[a]

Observation	Dose Group (mg/kg/day)				
	0	0.05	0.1	0.5	Historical control ranges (%)
P Generation - Litter F_1					
Female Fertility Index-%	91.4	100.0	97.1	85.3	80.0-96.6
Female Fecundity Index-%	87.5	94.1	88.2	79.3	82.1-92.9
Male Mating Index-%	91.4	100.0	100.0	85.3	80.0-96.6
Male Fertility Index-%	82.9	94.1	87.9	73.5	66.7-93.1
Gestation Index-%	100.0	96.9	96.8	100.0	
Gestation Length (days)	22.3	22.2	22.2	22.2	
Number of Litters	29	31	30	25	

a Data extracted from the study report Table 16, page 87 and Appendix P, pages 313 through 317.

Table 4b. Reproductive performance of F_1 sires and dams.[a]

Observation	Dose Group (mg/kg/day)				
	0	0.05	0.1	0.5	Historical control ranges (%)
F_1 Generation - Litter F_2a					
Female Fertility Index-%	94.3	85.7	88.6	80.0	80.0-96.6
Female Fecundity Index-%	81.8	83.3	74.2	78.6	82.1-92.9
Male Mating Index-%	94.3	85.3	88.2	78.1	80.0-96.6
Male Fertility Index-%	80.0	76.5	67.6	62.5	66.7-93.1
Gestation Index-% (++)	100.0	100.0	100.0	90.9	
Gestation Length (days)	22.7	22.6	22.6	22.8	
Number of Litters	28	27	23	20	

a Data extracted from the study report Table 36, pages 128, and Appendix KK, pages 786-790.
(++) Positive dose-response by Armitage Test with $p<0.01$.

5. Cholinesterase evaluation: **P adults** manifested reduced plasma and brain cholinesterase activities (Table 5). **Plasma cholinesterase** activity was reduced ($p<0.01$) in mid- (↓21%) and high-dose males (↓44%) and in mid- (↓25%,$p<0.05$) and high-dose females (↓60%, $p<0.01$). **Brain cholinesterase** activity was reduced ($p<0.01$) in high-dose males (↓42%) and females (↓49%). Mid-dose female brain cholinesterase activity was also significantly reduced ($p<0.01$), but the difference was small (↓6%) and not of toxicological concern. **Erythrocyte cholinesterase** activity was not significantly different from concurrent controls.

   F_1 adults had greater reductions in plasma and brain cholinesterase activities than P adults. **Plasma cholinesterase** activity was reduced 22%, 20%, and 44% ($p<0.01$) in low-, mid-, and high-dose males, respectively. In females, plasma cholinesterase activity was reduced 18% (p=not sign.), 29% ($p<0.01$), and 60% ($p<0.01$) in low-, mid-, and high-dose animals, respectively. **Brain cholinesterase** activity was reduced in males 6% ($p<0.05$) and 45% ($p<0.01$) in mid- and high-dose males, respectively. Brain cholinesterase activity was reduced ($p<0.01$) and in mid- (8%) and high-dose (51%) females. The reductions in brain cholinesterase activity in the mid-dose animals and plasma cholinesterase activity in low-dose females were equivocal results. The erythrocyte cholinesterase activity between treated and control groups was comparable.

Table 5. Mean cholinesterase values (IU/L) - P and F_1 generation animals.[a]

Tissue	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
P Generation				
Male				
Plasma Cholinesterase	502	428	398** (21)	280** (44)[b]
Erythrocyte Cholinesterase	8638	8451	8606	8269
Brain Cholinesterase	11872	11769	11440	6828** (42)
Females				
Plasma Cholinesterase	2016	1835	1505* (25)	802** (60)
Erythrocyte Cholinesterase	7717	7864	7218	7465
Brain Cholinesterase	11438	11299	10765** (6)	5872** (49)
F_1 Generation				
Male				
Plasma Cholinesterase	567	443** (22)	451** (20)	316** (44)
Erythrocyte Cholinesterase	8649	7978* (8)	7509	7289** (16)
Brain Cholinesterase	12048	11706	11365* (6)	6595** (45)
Females				
Plasma Cholinesterase	2485	2031 (18)	1770** (29)	995** (60)
Erythrocyte Cholinesterase	8114	7673	7585	7448
Brain Cholinesterase	12041	11867	11126** (8)	5848** (51)

a Data extracted from the study report Tables 12 and 32, pages 80 and 123.
b (Percent decrease from control value) calculated by the reviewer
* and ** Significantly different from controls at $p<0.05$ or 0.01.

6. Parental postmortem results

a) Gross Pathology: There were no treatment-related trends in the necropsy findings for the P or F_1 generation.

b) Organ Weights: There were no significant differences in absolute or relative organ weights in the P adults (Tables 6a and b).

In the F_1 males, the high-dose testes+epididymides weight was significantly reduced (↓12%, $p<0.05$) (Table 6a). The relative testes+epididymides/body weight ratio was not statistically different from concurrent controls. Because the male sexual organ weights are generally maintained despite decreases in body weight, the reduced testes+epididymides weight is considered to be of toxicological concern. Relative

ovarian weights were decreased in the high-dose F_1 dams (↓17%, $p<0.05$) (Table 6b), but the absolute mean ovary weight in the high dose F_1 dams was comparable to the controls. The increase in relative ovary weight could be the result of a slight increase in mean body weight of the high dose F_1 dams.

Table 6a. Mean absolute organ weights - P and F_1 generation animals.[a]

Tissue	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
P Generation				
Male				
Total Body Weight	617.3	620.5	609.8	624.9
Testes+Epididymides	6.25	6.17	6.00	6.31
Prostate+Seminal Vesicles	3.861	3.829	3.958	3.891
Females				
Total Body Weight	327.4	328.7	332.4	341.8
Ovaries	0.111	0.119	0.119	0.110
F_1 Generation				
Male				
Total Body Weight	672.7	657.2	660.6	628.6
Testes+Epididymides	6.10	5.65	5.59	5.36*
Prostate+Seminal Vesicles	4.056	3.821	4.205	3.756
Females				
Total Body Weight	348.3	353.9	372.7	365.3
Ovaries	0.105	0.112	0.105	0.091

a Data extracted from the study report Tables 13 and 33, pages 82 and 124.
* Significantly different from controls at $p<0.05$

Table 6b. Mean relative organ weights - P and F_1 generation animals.[a]

Tissue	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
P Generation				
Male				
Testes+Epididymides/Body weight	0.0102	0.0102	0.0099	0.0102
Prostate+Seminal Vesicles/Body weight	0.00632	0.00633	0.00651	0.00630
Females				
Ovaries/Body weight	0.00034	0.00036	0.00036	0.00032
F_1 Generation				
Male				
Testes+Epididymides/Body weight	0.0092	0.0086	0.0088	0.0088
Prostate+Seminal Vesicles/Body weight	0.00611	0.00585	0.00656	0.00608
Females				
Ovaries/Body weight	0.00030	0.00032	0.00028	0.00025*

a Data extracted from the study report Tables 14 and 34, pages 83 and 125.
* Significantly different from controls at $p<0.05$.

b) Histopathology: There were no treatment-related histopathology findings for the P or F_1 generation. High-dose F_1 males had non-significantly increased multifocal or diffuse unilateral testicular atrophy (3/24 treated vs 0/13 controls). The study report states that this is a common finding in rats of this age and strain and is not considered of toxicological concern. High-dose F_1 females had decreased numbers of corpora lutea in the ovaries (11/35 treated vs 3/35 controls), but the incidence was not statistically significant. Low- (2/35) and mid-dose groups (5/35) were similar to controls. The ovaries were either devoid of corpora lutea or contained remnants of corpora lutea and were comprised predominantly of immature follicles in various stages of development. The ovarian morphology was otherwise histologically normal.

B. OFFSPRING

1. Viability and clinical signs: Mean litter size was not analyzed. No treatment-related effects on survival indices were observed at any time in the F_1 and F_2 litters (Tables 7a and b). Survival indices were sporadically decreased in the high-dose and low-dose F_1 litters (↓2-4%, $p<0.05$-0.01). The high-dose lactation index was also slightly decreased (↓6%, $p<0.01$). F_2 litters had sporadically different survival indices (↑1-↓5%, $p<0.01$). However, these deviations were small and are therefore not of toxicological concern. No treatment-related clinical signs were noted in the F_1 or F_2 litters.

Table 7a. F_1 generation mean litter size and survival.[a]

Observation	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
Number of Litters	29	31	30	25
Mean litter size				
Day 0	13.5	14.7	13.4	13.3
Day 1[d]	13.1	13.9	13.3	12.4
Day 4[bd]	13.1	13.7	13.3	12.0
Day 4[cd]	7.6	7.6	7.7	7.5
Day 7[d]	7.6	7.6	7.6	7.2
Day 14[d]	7.6	7.6	7.6	6.9
Day 21[d]	7.5	7.6	7.6	6.9
Number live pups				
Day 0	383	447	404	321
Day 1	381	431	398	311
Day 4[b]	379	425	398	301
Day 4[c]	220	237	230	187
Day 7	219	236	229	180
Day 14	219	236	228	173
Day 21	217	236	228	173
Number missing[d]				
Days 0-4[b]	3	26	14	13
Days 5-21	1	0	1	10
Number deaths[d]				
Days 0-4[b]	7	18	14	16
Days 5-21	2	1	1	4
Survival indices (%)				
Livebirth	97.7	95.1	97.1	96.7
Survival (Day 1)	99.5	96.4**	98.5	97.2*
Survival (Day 4)[b]	99.5	98.6	100.0	96.8*
Survival (Day 7)	99.5	99.6	99.6	96.3
Survival (Day 14)	100.0	100.0	99.6	96.1*
Survival (Day 21)	99.1	100.0	100.0	100.0
Lactation	98.6	99.6	99.1	92.5**
Sex ratio (% male)	51.7	49.0	51.0	45.5

a Data extracted from the study report Tables 16, 17 and 18, pages 87 through 93, and Appendix R, pages 548 through 551.
b Before standardization (culling).
c After standardization (culling).
d Calculated by the reviewers.
*, ** Significantly different from controls at $p<0.05$ or 0.01, respectively.

Table 7b. F_2 generation mean litter size and survival.[a]

Observation	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
Number of Litters♪	28	27	23	20
Mean litter size				
Day 0	13.2	11.6	15.1	13.0
Day 1[d]	13.0	11.9	14.8	12.8
Day 4[bd]	12.8	11.7	14.1	12.6
Day 4[cd]	7.2	7.2	7.7	7.5
Day 7[d]	7.2	7.2	7.6	7.4
Day 14[d]	7.7	7.1	7.5	7.3
Day 21[d]	7.7	7.0	7.5	7.2
Number live pups				
Day 0	364	307	342	264
Day 1	350	297	340	255
Day 4[b]	345	293	325	240
Day 4[c]	195	181	178	142
Day 7	194	179	175	140
Day 14	192	177	173	138
Day 21	192	176	172	130
Number missing[d]				
Days 0-4[b]	7	7	5	6
Days 5-21	0	3	1	2
Number deaths[d]				
Days 0-4[b]	16	11	13	25
Days 5-21	3	2	3	2
Survival indices (%)				
Livebirth	98.4	98.4	98.6	96.7
Survival (Day 1)	96.2	96.7	99.4**	96.6
Survival (Day 4)[b]	98.6	98.7	96.8	94.1**
Survival (Day 7)	99.5	98.9	98.3	98.6
Survival (Day 14)	99.0	98.9	98.9	98.6
Survival (Day 21)	100.0	99.4	99.4	100.0
Lactation	98.5	97.2	96.6	97.0
Sex ratio (% male)	51.1	51.5	45.6	46.2

a Data extracted from the study report Tables 36, 37, and 38, pages 128 through 133, and Appendix MM, pages 983 through 986,

b Before standardization (culling).

c After standardization (culling).

d Calculated by the reviewers.

♪ The number of litters decreased in the control, 0.05 and 0.5 mg/kg/day groups from Day 0 to 27 due to loss of all fetuses.

** Significantly different from controls at $p<0.01$.

2. Body weight: There were treatment-related decreases in F_1 and F_2 pup body weights (Table 8). Body weights in the F_1 high-dose were decreased from PND 4 through 21 (↓10 -16%, $p<0.01$). Low dose animals showed sporadic decreases (↓6-7%, $p<0.05$); these differences were small, not dose-dependent, and therefore not of toxicological concern. In the F_2 pups, body weights were only significantly decreased in high dose males at PND 4, 14, and 21 (↓9-10%, $p<0.05$). There were no significant differences in body weights in the F_2 females.

Table 8. Mean F_1 and F_2 pup weights (g).[a]

Lactation Day	Dose Group (mg/kg/day)			
	0	0.05	0.1	0.5
F_1 litters				
Males				
Day 1	7.12	6.82	7.19	6.85
Day 4[b]	9.98	9.34* (6)[c]	9.87	8.80** (12)
Day 7	15.99	14.96	15.93	13.38** (16)
Day 14	32.80	31.04	32.72	28.26** (14)
Day 21	53.26	49.36*	52.73	45.47** (15)
Females				
Day 1	6.71	6.45	6.82	6.44
Day 4[b]	9.36	8.87	9.42	8.43** (10)
Day 7	15.08	14.40	15.13	12.89** (15)
Day 14	31.52	29.95	31.50	27.32** (13)
Day 21	50.86	47.23* (7)	50.40	43.40** (15)
F_2 litters				
Males				
Day 1	7.14	6.81	7.10	6.93
Day 4[b]	9.99	9.54	9.76	9.10* (9)
Day 7	15.77	15.34	15.70	14.20
Day 14	33.32	30.93	32.42	30.19* (9)
Day 21	54.57	50.77	53.67	48.95* (10)
Females				
Day 1	6.72	6.49	6.85	6.69
Day 4[b]	9.37	9.15	9.55	9.11
Day 7	14.60	14.88	15.41	13.73
Day 14	31.43	30.48	32.07	29.24
Day 21	50.74	49.23	52.22	47.20

a Data extracted from the study report Tables 19 and 39, pages 94 and 134.
b Before standardization (culling).
c (Percent decrease from control value) calculated by the reviewer
* and ** Significantly different from control group at $p<0.05$ and 0.01.

3. Offspring postmortem results:

a) Organ weights: Organs were not weighed for any of the pups in this study.

b) Pathology

1) Macroscopic examination: There were no treatment-related findings at necropsy in the F_1 or F_2 pups.

2) Microscopic examination: Histopathology was not performed on any of the F_1 or F_2 pups.

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS: Parental toxicity was apparent at the high-dose (0.5 mg/kg/day), manifested as postdose clinical signs in P dams and reductions in ovarian weight in F_1 dams. Significant plasma cholinesterase inhibition was observed in F_1 males at all dose levels and significant brain cholinesterase inhibition was observed in both sexes of both generations in the high-dose groups. Based on these results, the parental NOAEL is 0.1 mg/kg, with the exception of plasma cholinesterase inhibition. Based on the reductions in F_1 male mating and fertility indices, the reproductive NOAEL is 0.1 mg/kg. Based on the observed reductions in male and female high-dose pup body weights, the developmental NOAEL is 0.1 mg/kg. Therefore, offspring do not appear to be more sensitive than their parents to Mevinphos under the conditions of this study.

B. REVIEWER'S DISCUSSION: In this 2-generation reproduction study, mevinphos was administered continuously by gavage to Crl:CD BR Sprague-Dawley rats (35/sex/dose) at dose levels of 0, 0.05, 0.1 or 0.5 mg/kg/day. Exposure to P animals began at 7 weeks of age and lasted for 10 weeks prior to mating. F_1 pups selected to produce the F_2 generation were exposed to the same dosage as their parents at PND 28 and continuously throughout the rest of the study. Treatment was started a week later than specified by the guidelines because of the excessive mortality observed in the range-finding study in which treatment was started at weaning. F_1 animals were administered the test article for approximately 11 weeks prior to mating to produce the F_2 litters. Mating to produce a second F_2b generation was not performed.

The analytical data indicated that the variance between nominal and actual dosage to the study animals and formulation stability were acceptable.

1. Parental Toxicity: There was no evidence of a treatment-related increase in mortality. Treatment-related clinical signs were observed in the high-dose P females following dosing. Signs observed included ataxia (1 occurrence), fine (8 occurrences) or coarse (17 occurrences) tremors, pinpoint pupils (11 occurrences), and oral discharge (8 occurrences).

All other P and F_1 groups did not exhibit any treatment-related clinical signs.

Mean body weight gain was decreased in P females at 0.5 mg/kg/day for Days 0-4 of lactation (108%) and Days 0-21of lactation (27%); neither was statistically significant. Food consumption was decreased in P dams during the LD 4-7 interval (↓11%, $p<0.05$). This decrease in food consumption was accompanied by non-significant decreases (↓2-8%) at the other time periods. Food consumption in the F_1 adults was similar for the majority of the study.

P adults manifested reduced plasma and brain cholinesterase activities. Erythrocyte cholinesterase activity was not significantly different from concurrent controls. Plasma cholinesterase was reduced ($p<0.01$) in mid-(↓21%) and high-dose males (↓44%) and in mid-(↓25%,$p<0.05$) and high-dose females (↓60%, $p<0.01$). Brain cholinesterase was reduced ($p<0.01$) in high-dose males (↓42%) and females (↓49%). Mid-dose female brain cholinesterase was also significantly reduced ($p<0.01$), but the difference was small (↓6%) and not of toxicological concern.

F_1 adults had greater reductions in plasma and brain cholinesterase than P adults. Plasma cholinesterase was reduced 22%, 20% and 44% ($p<0.01$) in low, mid-, and high-dose males, respectively. In females, plasma cholinesterase was reduced 18% ($p>0.05$), 29% ($p<0.01$), and 60% ($p<0.01$) in low-, mid-, and high-dose animals, respectively. Brain cholinesterase activity was reduced in high-dose males 45% ($p<0.01$). In females, brain cholinesterase activity was reduced ($p<0.01$) 51% in high-dose animals.

The LOAEL for parental toxicity is 0.1 mg/kg/day in females and 0.05 mg/kg/day in males based on inhibition of plasma cholinesterase activity. The parental NOAEL is 0.05 mg/kg/day in females and ≤ 0.05 mg/kg/day (lowest dose tested) in males.

2. Reproductive Toxicity: There were no treatment-related differences in reproductive performance in P dams. High-dose P sires had a slightly reduced fertility index (↓11%), but the difference was not significant and not considered to be of toxicological concern.

In the F_1 high-dose males, mean male mating and fertility indices were reduced ↓17% and 22%, respectively, although not statistically significantly. The mid-dose male fertility index (67.6%) was also reduced (↓16%), although it was within historical control ranges (66.7-93.1%) and therefore not considered to be of toxicological concern. Several other findings pertaining to the male sexual reproduction system corroborate the decreased fertility and mating indices. There were dose responses of reduced terminal body weight and testes/epididymides weight and the high-dose testes/epididymides weight was significantly reduced (↓12%, $p<0.05$). High-dose F_1 males had non-significantly increased multifocal or diffuse unilateral testicular atrophy (3/24 treated vs 0/13 controls). The study report states that this is a common finding in rats of this age and strain and was not considered of toxicological concern. Tubular atrophy is common in aging rats, however it has been reported in males older than in this study. In Sprague-Dawley rats, up to 7% of animals maintained

for 52 weeks showed spermatogenesis not proceeding beyond the spermatocyte stage; 20% of rats maintained for 104 weeks developed atrophy of the seminiferous epithelium.[1] Treatment of F_1 males in this reproduction study began when the animals were 28 days old and continued for 10 weeks until they were mated. Cohabitation lasted a maximum of 3 weeks. The males were euthanized after delivery of the last litter sired, an additional 6 weeks for gestation and lactation. Therefore, the animals were approximately 23 weeks old when they were sacrificed. Upon determining that F_1 males had reduced mating and fertility indices, they were given a reproductive assessment battery. In these tests, mid-dose F_1 males showed increased left caudal epididymal weights and decreased epididymal sperm motility. However, due to the lack of a dose-response, these findings were not considered to be of toxicological concern. There were no differences of toxicological concern in terminal body weights, epididymal, testicular, prostate, seminal vesicle or pituitary weights. There were no significant differences in epididymal sperm count per gram of caudal tissue, the relative incidence of abnormal sperm, average spermatid head count, spermatid heads per testis, and spermatid heads per gram of testis. No unexpected cell types were detected in the epididymal fluid. There were no significant differences in sperm motility, both by automated analysis or manual determination.

High-dose F_1 dams had reduced fertility (80.0%, ↓15%), although the reductions were not statistically significant and were within historical control ranges (80.0-96.6%) and are thus not considered to be of toxicological concern. However, several related findings indicated causes for the reduced fertility. Relative ovarian weights were decreased in the high-dose F_1 dams (↓17%, $p<0.05$). High-dose F_1 females had decreased numbers of corpora lutea in the ovaries (11/35 treated vs 3/35 controls), but the incidence was not statistically significant. Low- (2/35) and mid-dose groups (5/35) were similar to controls. The ovaries were either devoid of corpora lutea or contained remnants of corpora lutea and were comprised predominantly of immature follicles in various stages of development. The ovarian morphology was otherwise histologically normal. No data were presented pertaining to the estrous cycle length and periodicity or sexual maturation rates of the F_1 litters in this study.

Mean litter size was not analyzed. No treatment-related effects on survival indices were observed at any time in the F_1 and F_2 litters. No treatment-related clinical signs were noted in the F_1 or F_2 litters.

Body weights were significantly decreased in high-dose male and female F_1 pups from PND 4 through 21 (↓10 -16%, $p<0.01$). Low dose males and females showed sporadic decreases ($p<0.05$) at PND 4 (↓6%, males only) and 21 (↓7%, males and females), but these differences were small, not dose-dependent, and therefore not of toxicological concern. In the F_2 pups, body weights were only significantly decreased in males at PND 4, 14, and 21 (↓9-10%, $p<0.05$). There were no significant differences in body weights in the females.

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[1] Tahahaski M, Kazutashi S, Hayashi Y. Nonneoplastic Changes in the Testis. In Mohr U, Dungworth DL, Capen CC (eds) Pathobiology of the Aging Rat, Volume 1. ILSI, Washington, D.C., pp 407-411.

Organs were not weighed for any of the pups in this study. There were no treatment-related findings at necropsy in the F_1 or F_2 pups. Histopathology was not performed on any of the F_1 or F_2 pups

The LOAEL for reproductive/offspring toxicity is 0.5 mg/kg/day based on decreased male mating and fertility indices, decreased absolute weight of testes + epididymides, decreased relative weight of the ovaries, histological changes in testes and ovaries and decreased pup body weight. The reproductive/offspring NOAEL is 0.1 mg/kg/day.

The reproductive study in the rat is determined to be **Acceptable/guideline (§83-4)** and does satisfy the guideline requirement for a multi-generational reproductive toxicity study in rats.

C. STUDY DEFICIENCIES: Treatment of the F_1 generation began on PND 28, rather than at weaning (PND 21), as required in the OPPTS 870.3800 guidelines.