(5-22-96)

[PARAQUAT] **Developmental Study OPPTS 870.3700 (§83-3(b))**

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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - [Mouse]; OPPTS 870.3700 [§83-3 (b)]

DP BARCODE: D224841
P.C. CODE: 061601
SUBMISSION CODE: S503251
TOX. CHEM. NO.: 634

TEST MATERIAL (PURITY): Paraquat dichloride (38.2% paraquat ion content)

CITATION: Palmer, K. (1992) Y00061/160/001 Oral (gavage) mouse developmental toxicity study. Toxicol Laboratories Limited, Ledbury, Herefordshire, England. CTL Study No. RM0591, CTL Report No. CTL/C/2830, November 1992. MRID 43949902. Unpublished.

SPONSOR: ICI Central Toxicology Laboratory, Alderley Park, Nr. Macclesfield, Cheshire, SK10 4TJ England

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 43949902), paraquat dichloride (38.2% purity as paraquat ion content) was administered to 26 female Crl:CD1 (ICR) BR mice/dose by gavage in water at dose levels of 0, 7.5, 15 or 25 mg paraquat ion/kg/day from days 6 through 15 of gestation.

At 25 mg/kg/day, paraquat is maternally toxic, inducing clinical signs (piloerection, labored respiration, hunched posture, hypothermia, hypoactivity and/or pale extremities and eyes); death; decreases in body weight and body weight gain ($p < 0.01$); dark red lung lobes; increases in lung with trachea and kidney weights and a possible decrease in pregnancy rate. No maternal effects were observed at either 7.5 or 15 mg paraquat ion/kg/day.

At 25 mg/kg/day, significant decreases in mean fetal weights were observed. In addition, skeletal effects were observed which included increases in the number of litters with retarded ossification of the occipital ($p < 0.05$), the number of fetuses and litters with ≤ 6 caudal centra ($p < 0.01$ and < 0.05 for fetuses and litters, respectively), the number of litters with uni- or bilateral extra 14th ribs ($p < 0.05$) and the number of fetuses and litters with non-ossified astragalus in the hindlimb ($p < 0.01$ and < 0.05 for fetuses and litters, respectively). No

other developmental effects were observed at this dose level. No developmental effects were observed at either 7.5 or 15 mg paraquat ion/kg/day.

The maternal LOEL is 25 mg paraquat ion/kg/day, based on clinical signs, death, decreases in body weight and body weight gain, dark red lung lobes, increases in lung with trachea and kidney weights and a possible decrease in pregnancy rate. The maternal NOEL is 15 mg/kg/day.

The developmental LOEL is 25 mg paraquat ion/kg/day, based on decreases in mean fetal weights and retarded ossification of the occipital, increases in the number with ≤ 6 caudal centra, increases in the number with uni- or bilateral extra 14th ribs and increases in the number with non-ossified astragalus in the hindlimb. The developmental NOEL is 15 mg/kg/day.

The developmental toxicity study in the mouse is classified as acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in the mouse.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: paraquat dichloride
   Description: dark brown aqueous liquor
   Batch #: YF6219 ex. No. 9 Product Stock; ICI Central Toxicology Laboratory Y number Y00061/160/001
   Purity: 38.2% paraquat ion content w/v
   CAS #: 1910-42-5

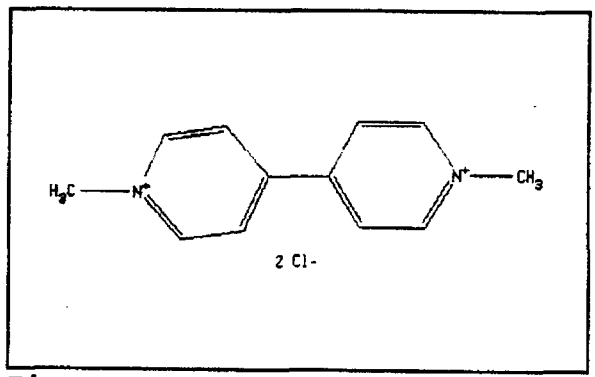

Figure 1 Paraquat

2. Vehicle: purified water (equivalent to single distilled water - produced by reverse osmosis of mains water in an "Elgastat Prima" water purification unit.

3. Test animals: Species: mice
Strain: Crl:CD-1(ICR)BR

Age: 8 wks at receipt, 9 weeks, 4 days at mating

Weight: 25-29 g at receipt; mean range of 27.9 - 28.4 g on day 0 of gestation

Source: Charles River (UK) Limited, Margate, England

Housing: grid bottomed polypropylene cages over paper-lined trays during acclimatization and mating; males housed individually and females in groups of up to 5, except when paired for mating. Mated females were individually housed in solid bottomed polypropylene cages, with wood sawdust (grade 4/4 Lignocel) provided as bedding.

Diet: pelleted rodent diet (SQCk Rat and Mouse No. 3 Breeder, expanded) ad libitum

Water: tap water ad libitum

Environmental conditions:
Temperature: 16-25 °C
Humidity: 39-68 %
Air changes: 16/hr
Photoperiod: 12 hrs dark/ 12 hrs light
Acclimation period (P): 11 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - start: 6/3/92 end: 6/19/92 (necropsy completed)

2. Mating: The females were paired 1:1 overnight (from midnight) for mating with sexually mature male mice of the same source and strain. Matings were confirmed the following morning by the presence of a copulation plug either in situ in the vagina or in the cage tray. The day on which a copulation plug was observed was designated day 0 of pregnancy. The animals for this study were mated over 4 consecutive days.

3. Animal Assignment: Animals were assigned to dose groups as indicated in Table 1. Assignment was random based on bodyweight.

TABLE 1 Animal Assignment

Test Group	Paraquat ion* (mg/kg/day)	Number of Mated Females
Control	0	26
Low (LDT)	7.5	26
Mid (MDT)	15	26
High (HDT)	25	26

* The test material was supplied as paraquat dichloride with a stated ion (purity) content. Dose levels were expressed as the ion content. Dosing was done by gavage.

4. Dose selection rationale: The dose levels were selected on the basis of results from a preliminary study performed at Toxicol Laboratories (Toxicol study number ICL/18/R).

5. Dosage preparation and analysis: Dosing was prepared once for the study and divided into appropriate aliquot portions. The test material was weighed and dissolved in the appropriate volume of vehicle. The report stated that "separate solutions were prepared, corrected for paraquat ion (purity) content, for each dose level. The aliquots were stored at room temperature protected from light, until required for dosing." Samples from each dosing solution were analyzed for paraquat. Samples of each solution prepared were analyzed before and after completion of the study.

Results:

Stability Analysis: The analysis of the samples taken after completion of the study indicated that the dosing solutions were stable for a period of one month. The percent recovery ranged from 101.2 to 108.9% of the nominal concentrations.

Concentration Analysis: The analysis of the samples indicated that the actual concentrations were within a reasonable range of the nominal concentrations.

The percent of the nominal concentrations ranged from 96.4 to 129.5%. The 129.5% value was originally calculated to be 91.3%. The report stated that "on checking the data a calculation error was discovered and the correct value was 129.5%. As the data check was conducted at a later date and the initial value was within acceptable limits, the sample was not re-analyzed. It was considered that an error during the preparation of the group 3 sample (the 129.5% sample) for analysis led to the high observed concentration. This is supported by the stability data which found group 3 formulation to be within 2-7% of the nominal and groups 2 and 4 formulation to be stable under the storage conditions used."

6. Dosage administration: All doses were administered once daily by gavage, on gestation days 6 through 15, in a volume of 10 ml/kg of body weight/day. Dosing was based on the body weight on the most recent body weight determination.

C. OBSERVATIONS

1. Maternal Observations and Evaluations: The animals were checked daily for mortality or clinical signs. Body weights were recorded on gestation days 0, 6-15 and 18. Food consumption was measured over the following periods: days 0-6, 6-9, 9-12, 12-15 and 15-18. Dams were sacrificed on day 18 of gestation. The report stated that "the thoracic and abdominal cavities were opened by a ventral mid-line incision and the major organs were examined. The lungs with trachea and kidneys were removed, weighed and fixed in buffered formal saline." The following observations were also conducted: pregnancy status, weight of the gravid uterus, number and distribution of implantations in uterine horns classified as early and late resorptions and/or dead and live fetuses and fetal weights.

2. Fetal Evaluations: The report stated that the fetuses were examined in the following manner: "live fetuses were briefly fixed in ethanol (70% Industrial Methylated Spirit) and then subjected to an external examination and the sex recorded. One half of the live fetuses were then fixed in Bouin's fluid and subsequently examined for visceral abnormalities using a combined sectioning/dissection technique. The remaining fetuses were replaced in the 70% alcohol and were subsequently eviscerated. The viscera were examined. These fetuses were

subsequently cleared in potassium hydroxide, stained with alizarin red S and were examined for skeletal variants and abnormalities."

D. DATA ANALYSIS:

1. Statistical analyses: Maternal bodyweight, bodyweight gain, food consumption and absolute and relative organ weights; numbers of implantations and live fetuses/female; percentage post-implantation loss; percentage male fetuses and litter weight and mean fetal weight were all analyzed by analysis of variance. Fetal data were analyzed on a litter basis and percentages were transformed before analysis using the double arcsine transformation. Each treated group was compared to the control group using the Student's t-test, based on the error mean square from the analysis of variance. The tests were two-sided and statistical significance was set at $p < 0.05$ and 0.01. Fisher's exact probability test was used to compare each treated group with the control group for both the proportion of fetuses with each individual defect and the proportion of litters with each individual defect. The tests were one-sided and statistical significance was set at $p < 0.05$ and 0.01.

2. Indices: The following indices were calculated from cesarean section records of animals in the study: mean post-implantation loss (%) was calculated but it was not defined as to how it was calculated.

3. Historical control data: Historical control data from February 1991 to June 1992 were provided to allow comparison with concurrent controls.

II. **RESULTS**

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: In the high dose group, one dam was found dead on day 16 of gestation. Prior to her death, she had had no clinical signs of toxicity. Four other dams were sacrificed prematurely, due to poor clinical condition on days 15-17 of gestation. Clinical signs of toxicity for these dams included piloerection, labored respiration, hunched posture, hypothermia, hypoactivity and/or had pale extremities and eyes. Clinical signs of toxicity were not observed in any of the other treated dams.

2. Body Weight: Statistically significant decreases in mean body weight and body weight gain were observed in the high dose group when compared to the control group. Decreases in mean body weight gain were observed for days 12-15, 15-18, 6-15 and 0-18. When adjusted for gravid uterine weight, there were still decreases in body weight gain, but they were not statistically significant. Mean bodyweight was statistically significantly less than the control group on day 15 ($p<0.05$) and day 18 ($p<0.01$) of gestation. No treatment-related differences in mean body weights or body weight gains were observed in any of the other treated groups. Body weight gain data are summarized in Table 2 and as follows:

TABLE 2 Maternal Mean Body Weight Gain (g)[a]

Interval	Dose in mg/kg/day			
	0	7.5	15	25
Pretreatment: Days 0 - 6	3.1	2.9	3.0	3.3
Treatment: Days 6 - 15	16.9	15.9	16.1	13.1**
Posttreatment: Days 15 - 18	11.3 (23)	11.4	11.5	8.0** (14)
Gestation Period: Days 0 - 18	31.3 (23)	30.2	30.5	25.4** (14)
Days 0-18 Adjusted for gravid uterine weight	7.1 (21)	6.4 (19)	7.2 (21)	5.8 (13)

[a] Data extracted from Table 2 of report
[b] () = N where differs from original
**Significantly different from control, $p<0.01$

3. Food Consumption: Mean food consumption was reduced in the high dose group from days 12-15, although not statistically significant. No treatment-related differences in food consumption were observed between the treated groups and the control group.

4. Gross Pathology: Of the 5 females that were either found dead or were sacrificed in extremis, 3 had no food present in the stomach, the 1 that was found

dead had stomach and intestines distended with gas and all five had dark red lung lobes. All were pregnant and had live fetuses in utero at the time of death. Dark red lung lobes were observed at the scheduled necropsy on day 18 of pregnancy for 4 other females in the high dose group. There were no treatment-related abnormalities in any of the females from the other treated groups or in the control group. In the high dose group, the mean absolute and relative lung with trachea weights were significantly greater than the control group ($p<0.01$). Relative kidney weights were also slightly increased although absolute kidney weights were slightly reduced. No treatment-related differences in organs weights were observed for any of the other treated groups.

5. Cesarean Section Data: Statistically significant decreases in mean fetal weights (males and/or females) were observed in the high dose group. There were no other statistically significant differences between the treated and control groups. However, it should be noted that in the high dose group there were numerical decreases in the pregnancy rate, implantations/dam and in the number of live fetuses/dam. It is also noted here that the number of corpora lutea were not counted and that there was no explanation as to why. This makes it more difficult to assess the possible differences listed above. In the historical control data, the range of percent pregnancy incidences were from 90.0 to 100.0% with a mean of 96.6%. None of the treated groups were in that range. For implantations/dam, the historical range for group means is 12.4 - 13.7. The high dose group value is just 1/10 points below the historical control range. Finally, for the number of live fetuses/dam, the historical range for group means is 11.8-12.8. Again, the high dose group value is just 1/10 points below the historical control range. Based on the above data, a case can be made that the numerical decreases in the mean number of implantations/dam and the mean number of live fetuses/dam in the high dose group when compared to the control group may not be biologically significant. However, it is more difficult to argue the case for percent pregnancy. Although the high dose value was not statistically significantly decreased from the control value, the numerical decrease is well below the historical mean range (73% versus 90%, the values for the other two treated groups were between 80 and 85%). Therefore, at least for the high dose group, this may be an

effect of the test chemical. It should be noted that this possible effect does not show up in either the previous mouse study or in the rat reproduction study. These studies were conducted at lower dose levels. The following table summarizes the results.

TABLE 3 Cesarean Section Observations[a]

Observation	Dose (mg/kg/day)			
	0	7.5	15	25
# Animals Assigned (Mated)	26	26	26	26
# Animals Pregnant (%)	24 (92)	21 (81)	22 (85)	19 (73)
# Nonpregnant	2	5	4	7
# Dams Died	0	0	0	5[b]
# Dams Died Pregnant	0	0	0	5[b]
# Dams Died Nonpregnant	0	0	0	0
# Dams That Aborted	0	0	0	0
# Dams Prematurely Delivered	0	0	0	0
# Corpora Lutea/Dam	Corpora lutea not counted in this study.			
Total # Implantations	329	284	306	173
Implantations/Dam	13.7	13.5	13.9	12.3
Total # Litters	24	21	22	14
Total # Live Fetuses	312	267	287	165
Live Fetuses/Dam	13.0	12.7	13.0	11.7
Total # Dead Fetuses	0	5	2	2
Dead Fetuses/Dam	0.0	0.24	0.09	0.14
Total # Resorptions	17	12	17	7
Early	11	12	15	7
Late	6	0	2	0
Resorptions/Dam	0.71	0.57	0.77	0.50
Early	0.46	0.57	0.68	0.50
Late	0.25	0	0.09	0.0
Litters with Total Resorptions	0	0	0	0
Mean Fetal Weight (g)	1.41	1.38	1.37	1.28**
Males	1.44	1.40	1.39	1.30**
Females	1.38	1.36	1.34	1.26**
Sex Ratio (% Male)	55	48	48	5
Preimplantation Loss (%)	Not determined - no corpora lutea			
Postimplantation Loss (%)	5.5	6.2	6.3	5.0

a Data extracted from Table 5 and Appendix 6
b Includes dams that were prematurely killed in extremis.
**Significantly different from control, $p<0.01$, Student's t-test

B. DEVELOPMENTAL TOXICITY

1. General Summary of Major and Minor Abnormalities: Significant increases in the total number of minor external and/or visceral abnormalities were observed in the low and mid-dose fetuses and in the low dose litters. No other significant differences were observed, including in the high dose group and including the skeletal examinations. Since there was no dose-response, these increases are not considered to be biologically significant (see Table 4).

2. External Examination: No significant differences were observed in the external examinations in the treated groups when compared to the control groups (see table 5).

3. Visceral Examination: Significant increases in the number of fetuses with uni- or bilateral increased pelvic cavitation were observed in the low and mid-dose groups. Significant increases were not observed in the number of litters affected nor in the high dose group. Therefore, these increases are not considered to be biologically significant (see Table 5).

4. Skeletal Examination: Table 6 shows statistically significant differences in the mid- and high dose group fetuses for a number of skeletal changes when compared to the control group. In addition, there were significant decreases in the number of fetuses with 13 normal pairs of ribs and increases in the number of fetuses with uni- or bilateral vestigial 14th ribs in all dose groups except the mid-dose group in the latter case. For most of these cases, however, there were no differences in the number of litters with these changes. Therefore, the biological significance of these differences is questionable. For litters, significant increases in the number of litters with a particular effect were observed for retarded ossification of the occipital (high dose group), number with ≤ 6 caudal centra (all dose groups), number with uni- or bilateral extra 14th ribs (mid- and high dose group) and for non-ossified astragalus in the hindlimb (high dose group). The number of fetuses with the number of caudal central vertebrae ≤ 6 was statistically significant only at the high dose level. The same was true for non-ossified astragalus. The report stated that the number of high dose litters affected with retarded ossification of the occipital,

astragalus not ossified and six or less caudal centra were considered to be a result of the lower fetal weights. In addition, the report stated that the incidence of fetuses with the variant of 6 or less caudal centra ossified was unusually low in the control group. The incidences in the low and mid-dose groups were high, but were within the historical control range (9.0-22.5% versus 7.0, 13.4, 12.6 and 47.0% in the control, low mid and high dose groups, respectively). The historical control data is of limited value because differences in the number of litters affected is more important than the number of fetuses affected. The historical control data for litters were not provided. In examining the individual animal data for each litter, for percent fetuses affected with either 6 or less caudal centra ossified or for those with uni- or bilateral extra 14th ribs, there was an obvious effect at the high dose for the first parameter. For the percent of fetuses affected with either 6 or less caudal centra, the range of the percentages of the number of fetuses affected were as follows: 14-50, 11-67, 14-83 (with 9/11 litters between 14-20%) and 33-100% for the control, low, mid- and high dose groups, respectively. For the percent of fetuses affected with uni- and bilateral extra 14th ribs, the range of the percentages of the number of fetuses affected were as follows: 13-83, 14-83, 14-57 and 17-43% for the control, low, mid- and high dose groups, respectively. The effects at the mid- and low doses were borderline and were not considered to be biologically significant. Therefore, for the skeletal examinations, effects were observed at the high dose level, which included increases in the number of litters with retarded ossification of the occipital, the number of fetuses and litters with ≤ 6 caudal centra, the number of litters with uni- or bilateral extra 14th ribs and the number of fetuses and litters with non-ossified astragalus in the hindlimb.

TABLE 4 Fetal Examinations: General Group Mean Summary Data

Dose Levels (mg/kg/day)	0		7.5		15		25	
Parameter	Fetuses	Litters	Fetuses	Litters	Fetuses	Litters	Fetuses	Litters
External and Visceral Examination								
Total number examined	312	24	267	21	287	22	165	14
Number with minor abnormalities only	2	2	14**	9++	9*	6	5	4
Number with major abnormalities	0	0	1	1	2	2	0	0
Skeletal Examination								
Total number examined	157	24	134	21	143	22	83	14
Number with minor abnormalities only	8	4	8	6	7	6	4	3
Number with major abnormalities	0	0	1	1	0	0	0	0
Combined Examination								
Number with any major abnormality	0	0	1	1	2	2	0	0

++ = Significantly different from control litter incidence: $p < 0.01$: Fisher's test
* = Significantly different from control fetal incidence: $p < 0.05$: Fisher's test
** = Significantly different from control fetal incidence: $p < 0.01$: Fisher's test

TABLE 5 Fetal External and Visceral Examinations: Group Mean Summary Data

Dose Levels (mg/kg/day)		0		7.5		15		25	
Findings	Type	Fetuses	Litters	Fetuses	Litters	Fetuses	Litters	Fetuses	Litters
Cleft palate	major	0	0	0	0	1	1	0	0
Innominate artery absent. Right common carotid and right subclavian arteries arising directly from the aortic arch	minor	0	0	1	1	0	0	0	0
Kidney - uni or bilateral: agenesis	major	0	0	0	0	1	1	0	0
Kidney - uni or bilateral: increased pelvic cavitation	minor	2	2	11**	6	10*	6	5	4
Ureter - uni or bilateral: kinked	minor	0	0	1	1	0	0	0	0
Spina bifida	major	0	0	1	1	0	0	0	0
Head: hematoma	minor	0	0	1	1	0	0	0	0
Number of fetuses examined by sectioning/dissection technique		155		133		144		82	
Total number of fetuses examined		312		267		287		165	
Total number of litters examined		24		21		22		14	

†† = Mean percent calculation based on fetuses examined by sectioning/dissection technique
* = Significantly different from control fetal incidence: $p < 0.05$: Fisher's test
** = Significantly different from control fetal incidence: $p < 0.01$: Fisher's test

TABLE 6 Fetal Skeletal Examinations: Group Mean Summary Data

Dose Levels (mg/kg/day)		0		7.5		15		25	
Findings	Type	Fetuses	Litters	Fetuses	Litters	Fetuses	Litters	Fetuses	Litters
Skull									
Occipital : retarded ossification	variant	6	2	6	5	6	3	8	6+
Vertebrae									
No. of thoracic: 13	usual	135	24	107	21	108*	21	61*	14
14	variant	22	9	27	11	35*	14	22*	9
No. of lumbar: 5	variant	21	9	27	11	34*	13	22*	9
6	usual	136	24	107	21	109*	21	61*	14
No. of caudal centra: ≤ 6	variant	11	5	18	11+	18	11+	39**	8+
≥ 7	usual	146	24	116	21	125	22	44**	13
No. of caudal neural arches: ≥ 4	usual	155	24	129	21	142	22	76**	14
Ribs									
13 normal pairs	usual	115	23	75**	20	74**	18	38**	12
Uni or bilateral: vestigial 14th	variant	17	12	29**	13	24	12	19*	10
Extra 14th with vestigial 14th	variant	4	3	4	3	11*	6	7*	4
Uni or bilateral: extra 14th	variant	18	7	23	10	24	14+	15	9+
Hindlimbs									
Astragalus: not ossified	variant	14	5	18	8	13	7	30**	8+
Total number of fetuses examined		157		134		143		83	
Total number of litters examined		24		21		22		14	

* = Significantly different from control fetal incidence: $p < 0.05$: Fisher's test
** = Significantly different from control fetal incidence: $p < 0.01$: Fisher's test
\+ = Significantly different from control litter incidence: $p < 0.05$: Fisher's test
++ = Significantly different from control litter incidence: $p < 0.01$: Fisher's test

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS: The investigators stated that "oral administration of paraquat ion to the pregnant mouse during days 6 to 15 of pregnancy (organogenesis) at 25 mg/kg/day, elicited maternal toxicity and embryonic/fetal growth retardation. There was no evidence of increased embryolethality or teratogenicity at this dose level. The no-observed effect level (NOEL) for maternal and developmental toxicity was 15 mg paraquat ion/kg/day."

B. REVIEWER'S DISCUSSION: The Agency reviewer agrees with the assessment provided by the authors of the study report. The NOEL for maternal and developmental toxicity is 15 mg paraquat ion/kg/day and the LOEL is 25 mg paraquat ion/kg/day.

1. MATERNAL TOXICITY: Paraquat is maternally toxic at 25 mg/kg/day inducing clinical signs (piloerection, labored respiration, hunched posture, hypothermia, hypoactivity and/or pale extremities and eyes); death; decreases in body weight and body weight gain ($p < 0.01$); dark red lung lobes; increases in lung with trachea and kidney weights and a possible decrease in pregnancy rate. No maternally toxic effects were observed at either 15 or 7.5 mg paraquat ion/kg/day.

2. DEVELOPMENTAL TOXICITY: At 25 mg/kg/day, significant decreases in mean fetal weights were observed. In addition, skeletal effects were observed which included increases in the number of litters with retarded ossification of the occipital ($p < 0.05$), the number of fetuses and litters with $\leq$ 6 caudal centra ($p < 0.01$ and < 0.05 for fetuses and litters, respectively), the number of litters with uni- or bilateral extra 14th ribs ($p < 0.05$) and the number of fetuses and litters with non-ossified astragalus in the hindlimb ($p < 0.01$ and < 0.05 for fetuses and litters, respectively). No other developmental effects were observed at this dose level. No developmental effects were observed at either 7.5 or 15 mg/kg/day.

C. STUDY DEFICIENCIES: Several items need to be mentioned because it was more difficult to review the study without them. The first item was that the number of corpora lutea was not counted. This made it difficult to assess the numerical decreases observed in the implantations/dam and in the number of live fetuses/dam. The second item was that the total number

of resorptions and the number of resorptions/dam were not summarized. The Agency reviewer had to count them from the individual animal data. Finally, the historical control data had only fetal data and not litter data, which is more appropriate. These omissions did not compromise the data to a sufficient extent that the study should be rejected. The study is acceptable for regulatory purposes.