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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

009305

FEB 24 1992

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Developmental Toxicity Study on Dichlorvos (DDVP). EPA ID# 084001. Record # S 400533. MRID # 41915-01

To: Brigid Lowery, PM # 72 Tox Chem No 328
Reregistration Branch Proj No 1-1985
Special Review and Reregistration Division (H7505C)

From: Joycelyn E. Stewart, Ph.D. 2/12/92
Acting Section Head, Section II
Toxicology Branch I
Health Effects Division (H7509C)

Thru: Karl P. Baetcke, Ph.D., Chief,
Toxicology Branch I,
Health Effects Division (H7509C) 2/14/92

Registrant: Amvac Chemical Corporation
Los Angeles, CA 90023

Action Requested: Review developmental toxicity study in rats submitted in response to Registration Standard Data Call-In Notice.

Conclusions: Administration of dichlorvos (DDVP) to pregnant female Sprague-Dawley rats at doses of 0, 0.1, 3.0, and 21 mg/kg/day on gestation days 6 through 15 resulted in maternal toxicity at the highest dose level. The signs of toxicity included tremors, prone positioning, hindleg splay, vocalization, labored respiration, ear shaking, ingesting of urine-marked bedding and decreased water consumption. The NOEL and LOEL were 3 and 21 mg/kg/day. No developmental toxicity was observed in the study. The study is classified core-Minimum.

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DOC 920115

FINAL

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DATA EVALUATION RECORD

DICHLORVOS

Study Type: Developmental Toxicity Study in Rats

Prepared for:

Healths 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 22031-1207

Principal Reviewer Pia Lindstrom Date Jan 12, 1992

Independent Reviewer Sanju Diwan Date 1/17/92

QA/QC Manager Sharon Segal Date 1/17/92

Contract Number: 68D10075
Work Assignment Number: 1-24
Clement Number: 9197
Project Officer: James Scott

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EPA Reviewer
and Section Head: Joycelyn Stewart, Ph.D.
Toxicology Branch I/HED

Signature: Joycelyn Stewart 2/14/92
Date: 2/14/92

DATA EVALUATION REPORT

STUDY TYPE: Developmental toxicity study in rats

EPA IDENTIFICATION NUMBERS

Tox Chem. No.: 323 EPA Registration No. 5481-96

MRID No.: 419515-01

TEST MATERIAL: Dimethyl 2,2-dichlorovinyl phosphate, 96.86% pure; lot number 802097

SYNONYMS: Dichlorvos, DDVP, UDVF, Cekusan, Cypona, Devikol, Duo-Kill, Duravos, Herkol, Marvex, No-Pest, Prentox, Verdican, Verdipor, Verdisol, Ciovap, Ravap, Elastrel

SPONSOR: AMVAC Chemical Corporation, Los Angeles, CA

STUDY NUMBER: 60C-4629-10/20

TESTING FACILITY: Research Triangle Institute, Research Triangle Park, NC

TITLE OF REPORT: Developmental Toxicity Evaluation of DDVP Administered by Gavage to CD (Sprague-Dawley) Rats

AUTHORS: Tyl, R.W., Marr, M.C., Myers, C.B.

REPORT ISSUED: February 22, 1991

CONCLUSIONS: A developmental toxicity study was conducted in which Sprague-Dawley rats were administered dichlorvos via gavage at 0, 0.1, 3, or 21 mg/kg/day during gestational days (GD) 6-15. Maternal toxicity, observed at the highest dose level, was manifested as an increased incidence of clinical signs and decreased body weight, weight gain, and food consumption during the dosing period. Based on these results, the maternal NOEL and LOEL were 3 and 21 mg/kg/day, respectively.

Developmental toxicity was not observed in this study. Consequently, the NOEL for developmental toxicity was 21 mg/kg/day; the LOEL was not determined.

CLASSIFICATION: Core Minimum Data. This study meets the minimum requirements set forth under EPA Guideline §83-3 for a developmental toxicity study in rats.

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A. MATERIALS

Test Compound

Purity:	96.86%
Stability:	Stable under normal use and storage conditions
Density:	1.424 g/mL
Description:	Colorless to amber liquid
Lot number:	802097
Receipt date:	December 29, 1989
Contaminants:	Not reported

Vehicle: Deionized/distilled water

Test Animals

Species:	Rat
Strain:	CD (SD) BR Sprague-Dawley
Source:	Charles River Laboratories Inc., Raleigh, NC
Age:	10 weeks on GD 0
Weight:	206-269 g on GD 0
Males used:	Same strain from the RTI breeding colony originally from the same supplier

B. STUDY DESIGN

This study was designed to assess the potential of dichlorvos to cause developmental toxicity in rats when administered daily via gavage from GD 6 through 15, inclusive.

Mating: Following 7 days of acclimation, females were mated 1:1 with males of the same strain and source. Females were checked each morning for the presence of vaginal sperm. The day on which sperm were found was designated day 0 of gestation.

Animal husbandry: Food (#5002 Purina Certified Rodent Chow) and deionized/filtered tap water was available ad libitum throughout the study. A 12:12-hour light/dark cycle was maintained. Temperature and humidity ranges were 68.4-73.1°F and 40.9-60.7%, respectively.

Group arrangement: Animals were allocated to dose groups using a stratified randomization method based on GD 0 body weight as follows.

Test Group	Dose Level (mg/kg/day)	Number Assigned per Group
Control	0	25
Low dose	0.1	25
Mid dose	3	25
High dose	21	25

Dose administered: Doses were administered daily via gavage on GD 6 through 15 in a volume of 5 mL/kg. The most recently recorded body weights were used to calculate the concentration of the doses. The report did not state whether the dosing solutions were adjusted for active ingredient. Doses were prepared twice during the study and refrigerated. Prior to study initiation, homogeneity, stability, and concentration of the test material in the vehicle were determined. Triplicate samples of the dosing solutions were analyzed by high-performance liquid chromatography.

Concentrations of the doses were selected based upon the results of a range-finding study (number 60C-4629-10) conducted in the same strain of eight pregnant rats per group at dose levels of 0, 0.1, 3, 15, or 30 mg/kg/day. Maternal toxicity, evident at 30 mg/kg/day, was manifested as increased mortality and clinical signs; decreased body weight and food consumption; and inhibition of cholinesterase activity. Developmental toxicity, evident at 30 mg/kg/day, was manifested as a slight but nonsignificant decrease in fetal body weight.

Observations: Animals were observed daily for mortality, moribundity, and overt signs of toxicity in addition to twice a day and 1-2 hours postdosing during the dosing period. Body weight was recorded on GD 0, 6, 9, 12, 15, 18, and 20. Food consumption was recorded for the following periods: GD 0-6, 6-9, 9-12, 12-15, 15-18, and 18-20. On GD 20, dams were sacrificed by asphyxiation with CO_2 and litters were delivered by cesarean section. Examination of the dams at sacrifice included the following:

- Gross pathology observations of the abdominal and thoracic cavities;
- Body weights were recorded;
- Gravide uterine weights were recorded;
- Liver weights were recorded and the livers were stored in fixative for possible future evaluation;
- Number of corpora lutea;
- Number of implantation sites; and

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- Numbers of resorptions (early and late) and live and dead fetuses.

Uteri from apparently nonpregnant animals were stained with 10% ammonium sulfide to detect early embryo loss.

Live fetuses were examined in the following manner:

- Individual fetuses were weighed and sexed;

- External anomalies (including cleft palate) were recorded;

- Approximately one-half of the fetuses were examined for visceral anomalies and confirmation of sex using a fresh tissue dissection method (Staples 1974; Stuckhardt and Poppe 1984). Fetal heads were fixed in Bouin's solution and then evaluated using the technique of Wilson (1965); and

- The remaining half of the fetuses were examined for skeletal anomalies (Marr et al. 1988) following evisceration, confirmation of sex, maceration, and staining with Alcain Blue/Alizarin Red S.

Statistical analysis: The following methods were used.

- Maternal body weight and body weight gain, fetal body weight, food consumption, gravid uterus and liver weights, and numbers of corpora lutea, implantation sites, and live fetuses per litter--Bartlett's test for homogeneity, ANOVA, linear trend test, and Dunnett's or William's test for pairwise comparisons;

- Percent preimplantation loss, resorptions, dead fetuses, nonlive and affected implants, males, and fetuses with anomalies per litter--Arcsine square root transformation, Bartlett's test for homogeneity, linear trend test, and ANOVA; and

- Numbers of litters with resorptions, dead fetuses, nonlive or affected implants, and anomalies--Chi Square test and Fisher's Exact test.

Compliance

- A signed Statement of No Data Confidentiality Claim, dated October 24, 1990, was provided;

- A signed Statement of Compliance with EPA, FDA, and Japanese MAFF GLPs, dated February 4, 1991, was provided; and

- A signed Quality Assurance Statement, dated January 9, 1991, was provided.

C. RESULTS

1. Test Material Analysis

Purity of the test compound was determined by chromatography to be approximately 97%. Analyses conducted on dosing solutions for

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concentration revealed a range of 92-107% of nominal values. Homogeneity analysis, conducted on low and high dosing solutions, were within a range of 3%. Stability of the dosing solutions for seven days in refrigerated storage revealed values of 102-104% of target.

2. Maternal Toxicity

Mortality: No mortality was noted.

Abortion: No abortions were noted.

Clinical observations: Compound-related clinical signs were observed at 21 mg/kg/day; all dams at this dose level exhibited tremors at some time during the dosing period. Other anti-cholinesterase-related activities, also exhibited during dosing at the highest dose level, included prone positioning, hindlimb splay, circling, vocalization, excitability, hypoactivity, labored respiration, ear shaking, coprophagia, ingestion of urine-marked bedding, lower jaw movement, pica, rooting in bedding, and decreased water consumption. Additional incidental clinical signs were noted at all dose levels.

Body weight: A summary of maternal body weight gain for selected intervals is presented in Table 1. Compound-related decreases in body weight and weight gain were observed at 21 mg/kg/day. During the dosing period (GD 6-15), body weight gain was significantly decreased by 28%. Significant decreasing trends in weight gain during dosing as well as corrected weight gain were observed. Weight gain during the entire gestation (GD 0-20) and corrected weight gain were decreased (nonsignificantly) by 8% and 12%, respectively.

Maternal body weight (data not shown) was significantly decreased on GD 9 (4%; $p<0.05$), GD 12 (6%; $p<0.01$), and GD 15 (5%; $p<0.05$). In addition, for these same days, significant ($p<0.001$) decreasing trends were observed in body weight.

Food consumption: A summary of food consumption (g/kg/day) is presented in Table 2. A compound-related decrease in food consumption (g/day or g/kg/day) was observed at 21 mg/kg/day. Significant ($p<0.01$) decreases were observed in food efficiency for the following periods: GD 6-9 (16%), GD 9-12 (11%), GD 6-15 (12%), and GD 0-20 (6%). For these same periods, significant ($p<0.001$) decreasing trends were observed.

When calculated as g/animal/day (data not shown), food consumption at 21 mg/kg/day was significantly ($p<0.01$) decreased for the following periods: GD 6-9 (18%), GD 9-12 (16%), GD 12-15 (12%), GD 6-15 (15%), and GD 0-20 (8%). For these same periods, significant ($p<0.001$ or $p<0.01$) decreasing trends were observed.

Gross pathology observations: No compound-related gross pathology findings were noted at any dose level. At 0.1 mg/kg/day, one dam exhibited reddened areas on all lung lobes.

No compound-related effects were noted in maternal absolute and relative liver weights or in gravid uterine weight at any dose level.

Cesarean section observations: A summary of cesarean section data is presented in Table 3. No compound-related effects were noted for any parameter at any dose level.

3. Developmental Toxicity

Incidences of external, visceral, and skeletal anomalies are presented in Tables 4, 5, 6, and 7. No compound-related anomalies were noted at any dose level. A significant ($p<0.05$) trend in increasing number of any variation per litter was observed with increased dose in males. Since this trend was not noted in females or when the sexes were combined, nor were pairwise comparisons significant, this was not considered to be a compound-related effect.

External examinations: Cleft palate was observed in one fetus at 3 mg/kg/day (Table 4). A kinked tail (variation) was seen in one fetus at 21 mg/kg/day.

Visceral examinations: The following incidental visceral malformations were observed (Table 5): extra lateral ventricle (one control fetus and one low-dose fetus); hydronephrosis (two control fetuses and one high-dose fetus); and extra kidney vessel (one mid-dose fetus and one high-dose fetus). Variations (Tables 5 and 7) were noted in all dose groups and included the lateral ventricle, kidney, ureter, liver, and uterine horn.

Skeletal examinations: Skeletal malformations included cleft sternum (observed in 11 control, 3 low-dose, 8 mid-dose, and 4 high-dose fetuses) and fused ribs (observed in 1 high-dose fetus). Variations were noted in all dose groups and included ribs and ossification centers.

D. DISCUSSION/CONCLUSIONS

1. Acceptance Criteria

The reviewers have completed an Acceptance Criteria check list (Attachment I) to be included with the evaluation of the study. Criterion 12 (corpora lutea) was fulfilled; however, individual animal data were not submitted. All other criteria were satisfied.

2. Test Material Analyses

Purity of the test material as well as homogeneity and stability of the test material in the vehicle were confirmed. Concentrations of the dosing solutions were within ±10% of target.

3. Maternal Toxicity

Compound-related maternal toxicity was only observed at the highest dose level and was manifested as an increased incidence of clinical signs and decreased body weight, weight gain, and food consumption.

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Based on these results, the maternal NOEL and LOEL were 3 and 21 mg/kg/day, respectively.

4. Developmental Toxicity

a. Deaths/resorptions: No compound-related effects were noted at any dose level in the number (or %) of dead or resorbed fetuses overall or per litter.

b. Altered growth: No compound-related effects were noted at any dose level in fetal (male, female, or combined) body weight or in delayed ossification.

c. Developmental anomalies: No compound-related fetal malformations were noted at any dose level.

"A possibly increased incidence of slightly enlarged lateral ventricles of the forebrain" was evaluated separately to determine whether or not this variation was an effect caused by the test compound (Table 7). While unilateral enlargement of the ventricle occurred at similar incidences in all dose groups, there was a slight increase at 21 mg/kg/day in the number of fetuses exhibiting enlarged bilateral ventricles. The reviewers agree with the study authors that since no significance was noted either on a per litter or fetal basis and no other signs of developmental toxicity were present, this finding was unrelated to the test compound.

Based on these results, the developmental NOEL was 21 mg/kg/day; the highest dose tested was not determined.

E. STUDY/REPORTING DEFICIENCIES

Individual animal data for numbers of corpora lutea were not submitted. Because of this reporting deficiency, the total number of corpora lutea for each dose level could not be determined by the reviewers, and the number of corpora lutea per litter could not be confirmed.

Historical control data were not submitted; however, they were not needed to determine the maternal and developmental NOELs and LOELs.

F. CORE CLASSIFICATION: Core Minimum Data

Maternal NOEL = 3 mg/kg/day
Maternal LOEL = 21 mg/kg/day
Developmental Toxicity NOEL = 21 mg/kg/day
Developmental Toxicity LOEL = Not determined

F. RISK ASSESSMENT: Not applicable

TABLE 1. Mean Body Weight Gain (g ± S.E.M.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-6)[b]	Dosing Period (GD 6-15)	Gestation Period (GD 0-20)	Corrected Body Weight Change[c]
0	42.0 ± 1.6	60.0 ± 2.4***	171.7 ± 4.0	79.4 ± 3.3*
0.1	39.8 ± 1.4	56.8 ± 3.6	161.6 ± 7.5	77.9 ± 3.4
3	40.0 ± 1.8	57.3 ± 2.8	167.3 ± 4.2	79.2 ± 2.3
21	44.6 ± 2.1	43.0 ± 1.8**	157.3 ± 4.7	70.0 ± 4.0

[a]Data were extracted from Study No. 60C-4629-10/20, Table 2.
[b]Calculated by the reviewers.
[c]Weight gain during gestation minus gravid uterine weight.

*Significant decreasing trend ($p<0.05$).
**Significantly different from control ($p<0.01$).
***Significant decreasing trend ($p<0.001$).

TABLE 2. Mean Food Consumption (g/kg/day ± S.E.M.)[a]

Dose Group (mg/kg/day)	Prior to Dosing Period (GD 0-6)	Dosing Period (GD 6-15)	Post Dosing Period (GD 15-20)	Gestation Period (GD 0-20)
0	100.6 ± 1.2	88.5 ± 0.9***	78.2 ± 0.9	84.9 ± 0.7***
0.1	100.9 ± 1.8	87.4 ± 1.2	79.7 ± 2.0	85.0 ± 1.1
3	101.2 ± 1.2	87.5 ± 1.4	79.6 ± 0.9	85.1 ± 0.9
21	100.3 ± 1.5	78.1 ± 1.6**	76.4 ± 1.1	80.4 ± 1.0**

[a]Data were extracted from study number 60C-4629-10/20, Table 4.

**Significantly different from control ($p<0.01$).

***Significant decreasing trend ($p<0.001$).

TABLE 3. Cesarean Section Observations[a]

Parameter	Dose Level (mg/kg/day) 0	0.1	3	21
No. animals assigned	25	25	25	25
No. animals mated	25	25	25	25
No. animals pregnant	19	23	22	23
Pregnancy rate (%)	76	92	88	92
Maternal wastage				
No. died/nonpregnant	0	0	0	0
No. died/pregnant	0	0	0	0
No. nonpregnant	6	2	3	2
No. aborted	0	0	0	0
No. premature delivery	0	0	0	0
Total corpora lutea	-[b]	-	-	-
Corpora lutea/dam	17.7 ± 0.7[c]	17.0 ± 1.2	17.0 ± 0.5	16.8 ± 0.3
Total implantations[d]	308	336	350	361
Implantations/dam	16.2 ± 0.3	14.6 ± 1.0	15.9 ± 0.5	15.7 ± 0.6
Total live fetuses[d]	300	327	332	345
Live fetuses/dam	15.8 ± 0.3	14.9 ± 0.8*	15.1 ± 0.6	15.0 ± 0.8
Total resorptions[d]	7	8	16	14
Early	6	8	14	13
Middle	1	0	2	1
Late	0	0	0	0
Resorptions/dam	0.4 ± 0.2	0.3 ± 0.1	0.7 ± 0.3	0.6 ± 0.3
Total dead fetuses	0	1	0	0
Dead fetuses/dam	0	0.04 ± 0.04	0	0
Fetal weight/litter (g)	3.72 ± 0.06	3.77 ± 0.07	3.68 ± 0.06	3.83 ± 0.12
Preimplantation loss (%)	7.7	13.0	7.2	7.6
Postimplantation loss (%)[d]	2.4	7.6	4.8	5.3
Sex ratio (% male)[d]	51.6	52.3	57.1	52.4

[a]Data were extracted from Study No. 60C-4629-10/20, Table 5 and Appendix II.

[b]Individual animal data not reported; therefore total No. cannot be calculated.

[c]Mean ± S.E.M.

[d]Calculated by the reviewers.

*One litter excluded from calculation due to no live fetuses.

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TABLE 4. Incidences of Fetal External Malformations and Variations[a]

Findings[b]	Dose Level (mg/kg/day) 0	0.1	3	21
No. fetuses (litters) examined	300 (19)	327 (22)	333 (22)	346 (23)
Malformations				
Cleft palate	0	0	1	0
Total No. fetuses (litters) with external malformations	0	0	1	0
Total % fetuses (litters) with external malformations	0	0	0.3 (4.5)	0
Variations				
Kinked tail	0	0	0	1
Total No. fetuses (litters) with external variations	0	0	0	1
Total % fetuses (litters) with external variations	0	0	0	0.3 (4.3)

[a]Data were extracted from Study No. 60C-4629-10/20, Tables 6 and 7 and Appendix II.

[b]More than one type of anomaly may be found in one fetus.

TABLE 5. Incidences of Fetal Visceral Malformations and Variations[a]

Findings[b]	Dose Level (mg/kg/day) 0	0.1	3	21
No. fetuses (litters) examined	152 (19)	163 (22)	167 (22)	173 (23)
Malformations				
Extra lateral ventricle, bilateral	1	1	0	0
Extra vessel, anterior right kidney	0	0	1	1
Hydronephrosis, bilateral	1	0	0	0
right	1	0	0	1
Total No. fetuses (litters) with visceral malformations	2 (2)	1	1	2 (2)
Total % fetuses (litters) with visceral malformations	1.3 (10.5)	0.6 (4.5)	0.6 (4.5)	1.2 (8.7)
Variations				
Enlarged lateral ventricle, bilateral, slight	9 (5)	10 (8)	11 (6)	18 (8)
bilateral	0	0	1	0
left, slight	6 (5)	5 (3)	6 (4)	5 (4)
Small vessel, right kidney	0	0	1	0
Blood filled kidney capsule, left	1	0	0	0
right	0	0	1	0
Distended ureter, bilateral	7 (3)	4 (4)	1	2 (2)
left	4 (3)	2 (2)	4 (4)	7 (2)
right	1	0	1	0
Red foci left lateral liver lobe	0	0	0	1
Small left uterine horn	0	0	0	1
Total No. fetuses (litters) with visceral variations	26 (11)	21 (12)	25 (12)	32 (16)
Total % fetuses (litters) with visceral variations	17.1 (57.9)	12.9 (54.5)	15 (54.5)	18.5 (69.6)

[a]Data were extracted from Study No. 60C-4629-10/20, Tables 6 and 7 and Appendix II.

[b]More than one type of anomaly may be found in one fetus.

TABLE 6. Incidences of Fetal Skeletal Malformations and Variations[a]

Findings[b]	Dose Level (mg/kg/day) 0	0.1	3	21
No. fetuses (litters) examined	147 (19)	164 (22)	166 (22)	170 (23)
Malformations				
Cleft sternum	11 (6)	3 (2)	8 (7)	3 (3)
Fused ribs	0	0	0	1
Total No. fetuses (litters) with skeletal malformations	11 (6)	3 (2)	8 (7)	4 (4)
Total % fetuses (litters) with skeletal malformations	7.5 (31.6)	1.8 (9.1)	4.8 (31.8)	2.4 (17.4)
Variations				
Rib on lumbar I				
Bilateral full	0	0	1	0
Left full	0	0	2	0
Right rudimentary	0	1	0	0
Bipartite ossification center				
Lumbar centrum	0	0	0	1
Thoracic centrum	1	0	0	0
Unilateral ossification center				
Thoracic centrum	0	0	0	1
Total No. fetuses (litters) with skeletal variations	1	1	3 (3)	1
Total % fetuses (litters) with skeletal variations	0.7 (5.3)	0.6 (4.5)	1.8 (13.6)	0.6 (4.3)

[a]Data were extracted from Study No. 60C-4629-10/20, Tables 6 and 7 and Appendix II.

[b]More than one type of anomaly may be found in one fetus.

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TABLE 7. Incidences of Enlarged Lateral Ventricle[a]

Findings[b]		Dose Level (mg/kg/day) 0	0.1	3	21
No. fetuses (litters) examined		152 (19)	163 (22)	167 (22)	173 (23)
Variation					
Slightly enlarged lateral ventricle					
Bilateral:	Total no. fetuses	9 (5)	10 (8)	12 (7)	18 (8)
	Total % fetuses	5.9 (26.3)	6.1 (36.4)	7.2 (31.8)	10.4 (34.8)
	No. fetuses per litter	0.5	0.5	0.5	0.8
	% fetuses per litter	5.9	5.5	7.5	10.4
Left:	Total no. fetuses	6 (5)	5 (3)	6 (4)	5 (4)
	Total % fetuses	3.9 (26.3)	3.1 (13.6)	3.6 (18.2)	2.9 (17.4)
	No. fetuses per litter	0.3	0.2	0.3	0.2
	% fetuses per litter	3.8	3.2	3.9	2.7
Bilateral or left:	Total no. fetuses	15 (7)	15 (10)	18 (9)	23 (10)
	Total % fetuses	9.8 (36.8)	9.2 (45.5)	10.8 (40.9)	13.3 (43.5)
	No. fetuses per litter	0.8	0.7	0.8	1.0
	% fetuses per litter	9.7	8.8	11.4	13.1

[a]Data were extracted from Study No. 60C-4629-10/20, Tables 6 and 7 and Appendix II.

[b]More than one type of anomaly may be found in one fetus.

ATTACHMENT I

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.	YES	Technical form of the active ingredient tested.
2.	YES	At least 20 pregnant animals/dose group for mice, rats, or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3.	YES	At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.*	YES	At the low dose, no developmental toxicity is reported.
5.	YES	Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.*	YES	Analysis for test material stability, homogeneity, and concentration in dosing medium.
7.	YES	Individual daily observations.
8.	YES	Individual body weights.
9.	YES	Individual food consumption.
10.	YES	Necropsy on all animals.
11.	YES	Individual uterine examination, including numbers of fetal deaths, early and late resorptions, and viable fetuses per sex.
12.	Y/N	All ovaries examined to determine number of corpora lutea.
13.	YES	Individual litter weights and/or individual fetal weights/sex/litter.
14.	YES	Individual fetal external examination.
15.	YES	Individual fetal skeletal examination for 1/3 to 1/2 of each litter for rodents and all for rabbits.
16.	YES	Individual fetal soft tissue examination.

Criteria marked with a * are supplemental, may not be required for every study.

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