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

MAY 18 1987

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of teratology study in rabbits with Methoxychlor. EPA ID #41014-5; EPA Record #179906; EPA Accession # 263041 & 263040; Caswell #550; Tox Branch Project 2348.

TO: Laurence Schnaubelt/Dennis Edwards (PM #12)
Insecticide - Rodenticide Branch
Registration Division (TS-767C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/15/87
Pharmacologist, Review Section V
Toxicology Branch/HED (TS-769C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T. Quang Bui 5/18/87
Acting Section Head, Review Section V
and
Theodore M. Farber, Ph.D., D.A.B.T. 5/18/87
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Kincaid Enterprises
Box 671
Nitro, West Virginia 25143

Action Requested: Review teratology study in rabbits.

Recommendations: The teratology study in rabbits with methoxychlor is classified as Core-Supplementary Data. No conclusions can be made relative to the maternal or developmental toxicity in this study due to the total loss of litters in the high dose group and the small number of litters available for evaluation in the mid dose group. The high incidence of lung agenesis noted in fetuses of all dose groups is unusual. Historical control data should be provided by the investigators relative to the incidence of hydrocephaly and lung agenesis as well as other fetal and maternal observations measured in this study. This data should be from animals of the same strain and vendor, treated with the same vehicle. The data should cover studies conducted during a period of 2 years prior to and any studies subsequent to this study. Data should be presented by individual study with the date the study was conducted.

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Primary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/15/87
Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V, Toxicology Branch/HED (TS-769C)

I. Study Type: Acute and Subchronic Oral Toxicity
(Range-Finding Study for Teratology)

Study Title: Acute and Subacute Oral Toxicity Studies in Female Rabbits

EPA Identification Numbers: EPA Identifying No. 41014-5
EPA Record No. 179906
EPA Accession No. 263040
Shaughnessy No.
Caswell No. 550
Tox. Branch Project No. 2348
Document No.

Sponsor: Kincaid Enterprises, Inc.
Box 671
Nitro, West Virginia 25143

Testing Laboratory: Hazelton Laboratories America, Inc.
9200 Leesburg Turnpike
Vienna, Virginia 22180

Study Number: Project No. 2298-101

Study Date: March 20, 1986

Study Author(s): Janet A. Trutter, M.S., D.A.B.T.
Neal G. Phipps, A.A.S.

Test Material: Methoxychlor, Technical Grade
Blend 841209
Purity was assumed to be 100% in this study, from analytical data provided the a.i. is apparently 96.8%.

Vehicle: Tween® 80 (polyoxyethylene [20] sorbitan mono-oleate), Lot No. 730910, from Fisher Scientific Company, Fair Lawn, New Jersey.
Methylcellulose (400 centipoise), Lot No. 14F-0545, from Sigma Chemical Company, St Louis, Missouri.
Polar® Distilled Water, Lot No. 43263, from Polar Water Company, Beltsville, Maryland.

Dosage: For Acute Toxicity: 1000, 2510 and 5010 mg/kg

For Subchronic Toxicity:
50 and 500mg/kg/day for 14 days
1000 mg/kg/day for 7 days

All dosing suspensions were made up in 0.1% Tween 80, 0.5% methylcellulose and distilled water.

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Test Animal: Female, adult New Zealand White Rabbits
Supplier: Hazelton Research Products, Inc.
Received: November 5, 1984
15 animals were used weighing from 3500 to 5127gms.

This study was designed to determined dose levels for a subsequent developmental toxicity study in rabbits.

II. Materials and Methods: A copy of the "Test and Vehicle Materials," "Test Animals" and "Methods" from the investigator's report is attached. The following comments and highlights on the materials and methods are noted:

The method of dosing was not stated in the report, however, the oral route was apparently employed.

The active ingredient concentration of the test substance was not provided in the text. From the analytical data provided the purity is apparently 96.8%. The investigators assumed a purity of 100% for test purposes.

The animals used in this study were selected from a "large pool by a computer randomization procedure." They were kept under standard animal care procedures (see attached materials and methods).

The animals were allocated to the following groups:

Acute Study Groups	n	Dose (mg/kg)	# Doses
1	3	1000	1
2	3	2510	1
3	3	5010	1
Subchronic Study Groups			
4	2	50	14
5	2	500	14
6	2	1000	7

Test suspensions were prepared fresh on the day of dosing for acute study groups and once every 7 days for the subchronic study groups.

All animals were observed twice daily for mortality and moribundity. Acute study groups were observed for clinical signs of toxicity at 1, 2 and 4 hours post-dosing and then daily observations were conducted for 14 days. Individual body weights were recorded on study days 0, 7 and 14. Subchronic toxicity study groups were observed for clinical signs of toxicity once daily for the duration of their treatment. Individual body weights were recorded on study days 1,7,8 and 14 (day 1 and 7 for study length of 7 days).

Post-mortems were conducted at the end of each study.

No statistical methodology was reported.

No Quality Assurance statement was included.

III. Results:

A. Acute Toxicology Study

1. Mortality

No deaths were reported by the investigators.

2. Clinical Observations

The only reported clinical sign of toxicity was anorexia. This was noted in all acute toxicity study groups (see attached Table 1 from the investigators report).

3. Body Weight Gain

The body weight data provided (attached Table 1) indicate a dose related decrease in body weight gain at study days 0-7 and 7-14 (as well as over the entire observation period).

4. Post-Mortem Examinations

Two animals in the high dose had evidence of hair and food in the stomach (causing impaction) with little chyme in the small intestine. Their gallbladders were also enlarged and filled with a "green fluid".

B. Subchronic Toxicity Study

1. Mortality

No deaths were reported by the investigators.

2. Clinical Observations

The investigators reported anorexia in all dose groups (see attached Table 2 from the investigator's report). Also, in the mid dose (500 mg/kg/day) one animal appeared to be thin and inactive. The other animal in the mid dose presented with swollen eyes and a blue tinge to the anterior chamber and iris along with an apparent sluggish pupillary reaction to light stimuli.

3. Body Weight Gain

An apparent dose-related decrease in body weight gain was noted throughout the study (attached Table 2).

4. Post-Mortem Examinations

Similar findings as noted in the acute study high dose group were noted in all animals used for the subchronic test (involving evidence of hair and food in the stomach [causing impaction] with little chyme in the small intestine and gallbladders enlarged and filled with a "green fluid").

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IV. Conclusions

Doses employed in both phases of this study revealed toxicity of the compound. The No Observed Effect Level could not be established from data available in this study. This study was not adequate to establish a dosing range for a teratology study.

V. Core Classification: Not Applicable

These studies were primarily range finding to establish dosing for a primary teratology study and the submitted data were inadequate to satisfy the intended purpose.

Table 1
Summary of Body Weight Data and Clinical Findings
for Rabbits Receiving a Single Oral Dose of Methoxychlor Technical

Animal Number	Body Weights (g) Day 0	Day 7	Day 14	Body Weight Change (g or %) Days 0 - 7 g	%	7 - 14 g	%	0 - 14 g	%	Clinical Observations Anorexia Days
				Group 1 - 1000 mg/kg						
37593	4356	3970	3701	-386	-9	-269	-7	-655	-15	1-14
37594	4029	3796	4100	-233	-6	304	8	71	2	1-8
37595	3544	3448	3570	-96	-3	122	4	26	1	1-2
Mean	3976	3738	3790	-238	-6	52	2	-186	-4	
S.D.	408.6	265.8	276.1	145.1	3.0	292.8	7.8	406.8	9.5	
				Group 2 - 2510 mg/kg						
37596	3500	3184	3072	-316	-9	-112	-4	-428	-12	1-5, 9-11
37597[a]	4379	3831	3530	-548	-13	-301	-8	-849	-19	1-14
37598	4361	4126	4287	-235	-5	161	4	-74	-2	1-6, 9
Mean	4080	3714	3630	-366	-9	-84	-3	-450	-11	
S.D.	502.4	481.8	613.6	162.5	4.0	232.3	6.1	388.0	8.5	
				Group 3 - 5010 mg/kg						
37599	4727	4058	3680	-669	-14	-378	-9	-1047	-22	1-14
37600	4182	3864	4167	-318	-8	303	8	-15	0	1-3, 7-8
37601	4431	3815	3537	-616	-14	-278	-7	-894	-20	1-14
Mean	4447	3912	3795	-534	-12	-118	-3	-652	-14	
S.D.	272.8	128.5	330.3	189.2	3.5	367.7	9.3	556.9	12.2	

[a] This animal inadvertently was dosed with 44.8 ml instead of 43.8 ml, receiving a dose of approximately 2568 mg/kg.

Table 2
Summary of Body Weight Data and Clinical Findings
for Rabbits Receiving Multiple Oral Doses of Methoxychlor Technical

Animal Number	Body Weights (g) Day 1	Day 7	Day 8	Day 14	Body Weight Change (g or %) Days 1 - 7 g	1 - 7 %	7 - 8 g	7 - 8 %	8 - 14 g	8 - 14 %	1 - 14 g	1 - 14 %	Clinical Observations Anorexia Days	Thin and Slightly Depressed Days	Other[a]
Group 4 - 50 mg/kg/day (Dosed Days 1-14)															
37604	4058	3719	3644	3390	-339	-8	-75	-2	-254	-7	-668	-16	3-14		
37651	4062	3708	3675	3385	-354	-9	-33	-1	-290	-8	-677	-17	3-14		
Mean	4060	3714	3660	3388	-347	-9	-54	-2	-272	-8	-673	-17			
S.D.	2.8	7.8	21.9	3.5	10.6	0.7	29.7	0.7	25.5	0.7	6.4	0.7			
Group 5 - 500 mg/kg/day (Dosed Days 1-14)															
37602	4351	3768	3666	3202	-583	-13	-102	-3	-464	-13	-1149	-26	2-14	12-14	
37603	4031	3631	3516	3336	-400	-10	-115	-3	-180	-5	-695	-17	2-14		13-14
Mean	4191	3700	3591	3269	-492	-12	-109	-3	-322	-9	-922	-22			
S.D.	226.3	96.9	106.1	94.8	129.4	2.1	9.2	0.0	200.8	5.7	321.0	6.4			
Group 6 - 1000 mg/kg/day (Dosed Days 1-7)															
37652	5127	4546	-	-	-581	-11	-	-	-	-	-	-	2-7		
37653	4458	3851	-	-	-607	-14	-	-	-	-	-	-	2-7		
Mean	4793	4199			-594	-13									
S.D.	473.1	491.4			18.4	2.1									

[a] Eyes swollen with a bluish tinge to the anterior chamber and iris. Sluggish pupillary reaction to light.

Methoxychlor teratology review

Page _____ is not included in this copy.

Pages 8 through 14 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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Primary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/15/87
Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Action Section Head, Review Section V, Toxicology Branch, HED (TS-769C)

I. Study Type: Teratology Study
Guideline §83-3

Study Title: Rabbit Teratology Study with Methoxychlor, Technical Grade
Final Report

EPA Identification Numbers: EPA Identifying No. 41014-5
EPA Record No. 179906
EPA Accession No. 263041
Shaughnessy No.
Caswell No. 550.
Tox. Branch Project No. 2348
Document No.

Sponsor: Kincaid Enterprises, Inc.
Box 671
Nitro, West Virginia 25143

Testing Laboratory: Hazelton Laboratories America, Inc.
9200 Leesburg Turnpike
Vienna, Virginia 22180

Study Number: Project No. 2298-100

Study Date: May 21, 1986

Study Authors: Janet A. Trutter, M.S., D.A.B.T.
Sharon P. Dyke, B.S.

Test Material: Methoxychlor, Technical Grade
2,2-bis(p-methoxyphenyl)-1,1,1-trichloroethane
Blend No. 841209
Purity was assumed to be 100% in this study, from analytical data provided the a.i. is apparently 96.8%.

Vehicle: Tween® 80, Lot No. 745538 from Fisher Scientific Company, FairLawn, N.J.
Methylcellulose (400 centipoise), Lot No. 14F-0545 from Sigma Chemical Company, St. Louis, Mo.
Polar® Distilled Water, Lot No. 43263 from Polar® Water Company, Beltsville, MD.

Dosage: 0, 5.01, 35.5 and 251.0 mg/kg/day by gavage on days 7 to 19 of gestation.

All dosing suspensions were made up in 0.5% methylcellulose, 0.1% Tween 80 and distilled water.

Test Animal: Young adult female New Zealand White Rabbits Received from Hazelton Research Products, Inc., Denver, Pennsylvania on January 21, 1985. 81 animals received, 74 assigned to randomization pool, 68 dams used in study (4 animals kept in reserve, some animals apparently not used). At time of randomization the body weights ranged from 3383 to 4247 gms.

This study was designed to evaluate the developmental toxicity potential of technical grade Methoxychlor when administered to pregnant rabbits from days 7 through 19 of gestation.

II. Materials and Methods: A copy of "Control and Test Materials", "Test Animals and Husbandry" and "Methods" sections from the investigator's report is attached. The following comments and highlights on the materials and methods are noted:

The active ingredient concentration of the test substance was not provided in the text. From the analytical data provided the purity is apparently 96.8%. The investigators assumed a purity of 100% for test purposes.

The animals were quarantined for approximately one month. They were kept under standard animal care conditions (see attached materials and methods).

Animals were randomized by a computerized randomization process which assigned 17 animals each into 3 dose groups and a control (a total of 68 animals). On Gestation Day 0 the animals ranged in weight from 3286 to 4471 grams.

The females were artifically inseminated. The total number of males used was not provided. Insemination procedure is described in attached "materials and methods". The day of insemination was considered as Gestation Day 0 .

The animals were assigned to the following groups:

Group	N	mg/kg/day
1 (Control)	17	0
2 (Low)	17	5.01
3 (Mid)	17	35.5
4 (High)	17	251.0

All animals were dosed from days 7 through 19 of gestation. The procedure for making the test compound suspension is outlined in attached "materials and methods". Dose volume was 2.0 ml/kg. Test suspensions were prepared fresh weekly. Dosing occured between 10:00 am and 2:00 pm with the dose based on individual body weight determined on Gestation Day 7.

Animals were observed twice daily for mortality and moribundity, further they were observed once daily for clinical signs of toxicity. Individual body weights were taken on Gestation Days 0, 7, 10, 14, 20, 24, and 29.

All surviving dams were sacrificed on gestation Day 29. They were subjected to a complete post-mortem examination. Dead offspring were not retained, however, this only constituted 1 control pup and 1 low dose fetus. Each viable fetus was sacrificed and examined externally. Further, each fetus was sexed, examined internally using the Staples' technique. One-half of the fetuses had their heads removed and fixed in Bouin's Solution. The heads were then sectioned by the Wilson's freehand razor-blade technique. All fetuses were then cleared and stained for skeletal examinations.

Statistical analysis methodology was provided (see attached materials and methods).

A Quality Assurance Statement was provided.

III. Results

A. Maternal Observation

1. Mortality

Three animals died. One low dose dam was found dead on Gestation Day 10, this was attributed to gavage error. Two high dose dams were found dead on Gestation Days 27 and 28, respectively. These deaths were attributed by the investigators to compound administration.

2. Clinical Observation Data

The investigators provided summary and individual animal data for clinical observations. Table I presents the findings.

Table I: Clinical Observation Data[a]

Dose(mg/kg/day):	Control	5.01	35.5	251.0
#dams examined	17	17	17	17
#died	0	1	0	2
#aborted	2	0	7	15
Observations for Gestation Days 7-19				
Anorexia	8(2)[†]	19(5)	145(16)	167(16)
Slghty Depressed	-	-	-	11(15)
Discharge (left eye)	5(1)	-	-	-
Observations for Gestation Days 20-29				
Anorexia	83(12)	42(11)	96(14)	104(17)
Cyanotic Appearance	-	-	-	3(1)
Depressed	-	-	-	3(1)
Slightly Depressed	-	-	1(1)	38(9)
Discharge (left eye)	7(1)	-	-	-

[†] = # day observed (# animals)
[a] = Data extracted from Hazelton Project No. 2298-100, Appendix 1.

There is an increase in clinical signs of toxicity at the mid and high dose as exhibited by the number of animals aborted, anorexic and those with a "depressed appearance".

3. Maternal Body Weight

The investigators provided mean animal body weights, mean body weight changes and individual animal data. The attached Table 3 from the investigators report presents the "Mean Maternal Body Weight Changes During Gestation" in grams. It can be noted that the mid and high dose group animals gained significantly less weight during the dosing period when compared to the contol group.

4. Cesarean Section Observations

Post-mortems conducted on animals who aborted revealed pale and mottled livers. Of those sacrificed early or at Gestation Day 29 the only observation not seen in controls was the presence of hair in the stomach of the mid and high dose animals. The investigators provided summary as well as individual animal data for post-mortem observations and reproduction data. The attached Table 6A from the investigator's report presents the "Summary of Female Reproduction Data." The findings of note are a dose related decrease in mean percent live males and a slight dose related decrease in mean fetal body weight. No data was available for the high dose due to the total loss of litters. The investigators included historical control data for some of the measured parameters as a comparison. There was high pre-implantation loss in all dose groups (control=47%; low dose = 35%; mid dose = 42%; no data available for the high dose).

Table 3
Mean Maternal Body Weight Changes During Gestation (grams)
Rabbit Teratology Study with Methoxychlor, Technical Grade

Maternal Body Weight Change Mean ± S.D.	Group 1 0 mg/kg	Group 2 5.01 mg/kg	Group 3 35.5 mg/kg	Group 4 251.0 mg/kg
No. animals treated	17	17	17	17
No. pregnant	16	16	14	17
Percent pregnant	94.1	94.1	82.4	100.0
Days 0-7	66 ± 66.4	63 ± 101.7	66 ± 40.8	88 ± 66.8
Days 7-10^{R}	50 ± 50.4	26 ± 67.5	-72* ± 101.9 [.0004]	-222* ± 109.2 [.0000]
Days 7-20^{R}	35 ± 120.1	7 ± 158.8 (15)	-447* ± 247.2 [.0000]	-737* ± 190.7 [.0000]
Days 0-29	79 ± 215.8 (14)	127 ± 193.8 (15)	-13 ± 438.7 (7)	-
Days 7-29	17 ± 221.7 (14)	64 ± 244.1 (15)	-81 ± 411.9 (7)	-

NOTES: Sample size = Number pregnant as shown above.
( ) = Number of values averaged when the sample size changed due to death or abortion.
* = Statistically significant difference from control. Probability level is shown in brackets.
R = Data analyzed following rank-transformation.

B. Fetal Observations

1. External Examinations

The investigators provided summary and individual animal data for external examinations. Table II below presents the external anomaly findings (no data available for high dose group).

Table II: External Anomaly Observations[a]

Dose (mg/kg/day):	Control	5.01	35.5
#Fetuses Examined	85	109	47
#Litters Examined	13	15	7
Observations:			
Malformed right ear	1(1)/1(8)[†]	-	-
Cranioschisis and exencepholy	-	1(1)/1(7)	-
Domed head	-	-	2(2)/4(29)
Hyperflexion:			
forepaw	1(1)/1(8)	-	-
hindlimb	-	2(1)/2(7)	1(1)/2(14)
hindpaw	-	-	3*(1)/6(14)
Wart-like protrusion, left lower lip	-	-	1(1)/2(14)

[†] = # fetus(# litters)/% fetuses(% litters)
* = "statistically significant difference from control."
[a] = Data extrated from Hazelton Project No. 2298-100, Table 8.

There was an increase in external observations in the mid dose observations consisting of domed head and hyperflexion of the hindlimbs and paws.

2. Visceral Examinations

The investigators provided summary and individual animal data for visceral examinations. Table III presents the visceral anomaly findings (no data available for the high dose group).

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Table III: Visceral Anomaly Observations[a]

Dose (mg/kg/day):	Control	5.01	35.5
#Fetuses Examined	85	109	47
#Fetal Heads Examined	40	50	22
#Litters Examined	13	15	7
Observations:			
Folded/detached retina	1(1)/3(8)[†]	1(1)/2(7	1(1)/5(14)
Small Nasal Septum-nares	-	1(1)/2(7)	-
Small or irregularly Shaped olfactory lobes	2(1)/5(8)	1(1)/2(7)	1(1)/5(14)
Exencephaly	-	1(1)/2(7)	-
Hydrocephaly	-	-	2(2)/9(29)
Small Heart	1(1)/1(8)	-	-
Cyst-gallbladder	-	1(1)/1(7)	-
Small & pale spleen	-	-	1(1)/1(14)
Ectopic Kidney	-	-	1(1)/1(14)
Lung agenesis: intermediate lobe	14(8)/17(62)	20(8)/18(53)	5(4)/11(57)
Small Intermediate Lung Lobe	-	2(1)/2(7)	-

[†] = # fetus(# litters)/% fetuses(% litters)
[a] = Date extracted from Hazelton Project 2298-100, Table 9.

There is an apparent increase in observations involving head anomalies in the mid dose group especially the increased fetal and litter incidence of hydrocephaly. There was no indication provided for the lung agenesis if it was partial or complete. The high incidence noted in all groups is unusual. Historical control data should be provided by the investigators relating to the incidence of hydrocephaly and lung agenesis.

3. Skeletal Examination

The investigators supplied summary and individual animal data for skeletal examinations. Table IV presents the skeletal anomaly findings (no data available for the high dose group).

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Table IV: Skeletal Anomaly Observations[a]

Dose (mg/kg/day):	Control	5.01	35.5
# Fetuses Examined	85	109	47
# Fetal Heads Examined	45	59	25
# Litters Examined	13	15	7
Observations:			
Fused Parietal(s)	-	-	1(1)/4(14)[†]
Irregularly Shaped Parietal(s)	-	1(1)/2(7)	3*(2)/12(29)
Parietal-i.o[††]	1(1)/2(8)	1(1)/2(7)	-
Irregular Shaped Fronital(s)	-	-	1(1)/4(14)
Vertebral anomaly w/wo[†††] rib anomaly	2(2)/2(15)	2(2)/2(13)	-
Less than 15 ossified caudal vertebrae	-	2(1)/2(7)	1(1)/2(14)
Fused sternebrae	-	1(1)/1(7)	1(1)/2(14)
Less than 5 ossified sternebrae	2(1)/2(8)	2(2)/2(13	5(4)*/11(57)
Malaligned sternebrae	-	1(1)/1(7)	-
13th bilateral rib(s):			
rudimentary	9(5)/11(39)	3*(3)/3(20)	2(2)/4(29)
full	5(4)/6(31)	18*(9)/17(60)	13*(5)/28(71)
either rud.or full	14(6)/14(46)	21(10)/19(67)	15*(6)/32(86)
one rud., one full	7(6)/8(46)	5(2)/5(13)	-
rud. and/or full	21(10)/25(77)	26(10)/24(67)	15(6)/32(86)
13th unilateral rib(s):			
rudimentary	5(5)/6(39)	10(7)/9(47)	4(4)/9(57)
full	4(4)/5(31)	1(1)/1(7)	4(2)/9(29)
rud. or full	9(7)/11(54)	11(8)/10(53)	8(4)/17(57)
rud. and/or full	30(12)/35(92)	37(13)/34(87)	23(7)/49(100)
12th unilateral rib: full	-	1(1)/1(7)	-
12th bilateral ribs:			
one rud., one full	-	1(1)/1(7)	-
Less than 19 Metacarpals & phalanges ossified per limb	5(4)/6(31)	6(4)/6(27)	7(2)/15(29)
Less than 16 Metatarsals & phalanges ossified per limb	1(1)/1(8)	-	-

† = # fetuses(# litters)/% fetuses(% litters)
†† = i.o. = incompletely ossified
††† = w/wo = with or without
* = "statistically significant differences from control."
a = Data extracted from Hazelton Project No. 2298-100, Table 10.

The mid dose group presented with an increase in the number of fetuses and litters with skull bone anomalies, reduced ossification of the sternebrae, 13th bilateral ribs (either rudementary or full) and the number of fetuses with less than 19 metacarpals and phalanges ossified per limb.

IV. Conclusions

No conclusions can be made relative to the maternal or developmental toxicity in this study due to the total loss of litters in the high dose group and the small number of litters available for evaluation in the mid dose group. The high incidence of lung agenesis noted in fetuses of all dose groups is unusual. Historical control data should be provided by the investigators relative to the incidence of hydrocephaly and lung agenesis as well as other fetal and maternal observations measured in this study. This data should be from animals of the same strain and vendor, treated with the same vehicle. The data should cover studies conducted during a period of 2 years prior to and any studies subsequent to this study. Data should be presented by individual study with the date the study was conducted.

V. Core Classification: Core-Supplementary Data

Key to Table 6A

Pregnancy Rate (percent) = (number of pregnant rabbits/number of rabbits inseminated) x 100

Mortality Rate (percent) = (number of pregnant rabbits found dead/number of pregnant rabbits) x 100

Abortion Rate (percent) = (number of pregnant rabbits classified as aborting their litter/number of pregnant rabbits) x 100.

Cesarean Section Rate (percent) = (number of remaining pregnant rabbits surviving to Day 29 cesarean section and providing litter data/number of pregnant rabbits) x 100.

Mean Implantation Efficiency (percent) = group mean of ([implantations per litter/corpora lutea per litter] x 100).

Mean Incidence of Resorptions (percent)[a] = group mean of ([resorptions per litter/implantations per litter] x 100).

Mean Incidence of Fetal Viability (percent) = group mean of ([live fetuses per litter/implantations per litter] x 100).

Mean Incidence of Fetal Losses (percent) = group mean of ([dead and resorbing fetuses and empty implantations per litter/implantations per litter] x 100).

Mean Percent Males = group mean of ([male fetuses per litter/total live fetuses per litter] x 100).

(%) = Percent

[a] Values calculated separately for early, late, and total resorptions.

NOTES: *Statistically significant difference from control.
**Statistically significant trend noted.
Probability level is shown in brackets.

Table 6A
Summary of Female Reproduction Data
Rabbit Teratology Study with Methoxychlor, Technical Grade

Table 6A
Summary of Female Reproduction Data
Rabbit Teratology Study with Methoxychlor, Technical Grade

Observation	Group 1 0 mg/kg	Group 2 5.01 mg/kg	Group 3 35.5 mg/kg	Group 4 251.0 mg/kg
No. of females	17	17	17	17
No. of pregnant females	16	16	14	17
Pregnancy rate (%)	94.1	94.1	82.4	100.0
No. of pregnant females which died	0	1[a]	0	2
Mortality rate (%)	0.0	6.3	0.0	11.8
No. of pregnant females which aborted	2	0	7	15
Abortion rate (%)**	12.5	0.0	50.0*	88.2*
[.0000]			[.0323]	[.0000]
No. of remaining pregnant females	14	15	7	0
Cesarean section rate (%)	87.5	93.8	50.0	0.0
Mean number of:				
Corpora lutea	13.6	12.9	13.7	-
Implantations	7.2	8.4	8.0	-
Early resorptions	0.9	1.1	0.7	-
Late resorptions	0.1	0.0	0.6	-
Total resorptions	1.1	1.1	1.3	-
Indices calculated on a per litter basis:				
Mean implantation efficiency (%)	54.8	65.5	62.5	-
Mean incidence of early resorptions (%)	18.6	12.2	8.4	-
Mean incidence of late resorptions (%)	1.5	0.0	7.3	-
Mean incidence of total resorptions (%)	20.2	12.2	15.6	-
Mean number of:				
Fetuses - dead	0.0	0.1	0.0	-
- live	6.1	7.3	6.7	-

[a] This death was due to an apparent gavage error and was not compound related.

Table 6A - Continued
Summary of Female Reproduction Data
Rabbit Teratology Study with Methoxychlor, Technical Grade

Observation	Group 1 0 mg/kg	Group 2 5.01 mg/kg	Group 3 35.5 mg/kg	Group 4 251.0 mg/kg
Indices calculated on a per litter basis:				
Mean incidence of fetal viability (%)	78.8	87.1	84.4	-
Mean incidence of fetal losses (%)	21.2	12.9	15.6	-
Mean percent live males:** [.0124]	57.6	48.4	35.5	-
Live fetuses:				
Mean body weight (grams)				
Males - unadjusted	44.4	41.7	39.4	-
- covariate adjusted	44.0	42.3	39.2	-
Females - unadjusted	41.9	41.9	37.9	-
- covariate adjusted	41.6	42.6	37.4	-

Methoxychlor teratology review

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