FOOD AND DRUG LABORATORIES, INC.

#17

MAURICE AVENUE AT 59TH STREET, MASPETH, NEW YORK 11378

FINAL

FINAL

July 2, 1973

Teratologic Evaluation of FDA 71-38

(Methyl paraben)

in

Rabbits

Final Report-Teratologic Evaluation of FDA 71-38 (Methyl paraben) in rabbits-4/2/73

FOOD AND DRUG Research LABORATORIES, INC.

Reply to
WAVERLY DIVISION
Route 17
P.O. Box 107
Waverly, New York 14892
(607) 565-2931

July 2, 1973

COPY

Mr. L. C. Appleby, Contracts Officer
Department of Health, Education and Welfare
Food and Drug Administration
Contracts Section CA-272
Contracts and Grants Branch
5600 Fishers Lane
Rockville, Maryland 20852

Subject: Teratologic Studies, Final Report (One Species-Rabbits)
Re: FDA Contract No. 71-260

Dear Mr. Appleby:

We are today forwarding final reports covering teratologic studies on FDA Compounds 71-38 and 71-39 in rabbits. The disposition of the reports is as follows:

Your office	1 copy (via Mr. Carle's office)
Dr. Alan Spiher	2 copies
Dr. Joseph McLaughlin	2 copies

These final copies correspond to drafts dated May 31, 1973.

If you have any further instructions, or questions, please do not hesitate to contact us.

Cordially,

FOOD and DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

KM:smm

cc: Dr. Alan Spiher
Dr. Joseph McLaughlin
Mr. D.A. Carle

JUL 2 10 00 AM '73
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RABBITS

Food and Drug Research Laboratories
INCORPORATED

Maurice Avenue at 58th Street
Maspeth, New York 11378
Telephone: TWining 4-0800
Cable: Foodlabs, New York

FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 2, 1973

Laboratory No. 0904 r
Contract No. FDA 71-260

Sample: Fine white crystalline material

Marking: FDA 71-38 (Methyl paraben)

Examination Requested: Teratologic evaluation of FDA 71-38 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion:

On the basis of the data presented herein, the following conclusion appears to be warranted:

"The administration of up to 300 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

This report is submitted for the exclusive use of the person, partnership, or corporation to whom it is addressed, and neither the report nor the name of these Laboratories nor of any members of its staff, may be used in connection with the advertising or sale of any product or process without written authorization.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 151 through 156

Material: FDA 71-38

Date: May 31, 1973

Laboratory No.: 0904 r

Table 1

Fate Summary
(Rabbits)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
151	Sham	0.0	14	11	13	10
152	6-AN*	2.5	17	10	17	10
153	FDA 71-38	3.0	20	9	19	9
154	FDA 71-38	14.0	20	9	20	9
155	FDA 71-38	65.0	14	10	14	10
156	FDA 71-38	300.0	12	9	9	9

* Positive Control: 6-aminonicotinamide dosed on Day 9
** Administered as a water solution (See Appendix I)
1) Includes all dams examined at term

FOOD AND DRUG RESEAR LABORATORIES, INC.

Group: 151 through 156

Material: FDA 71-38

Table 2
Reproduction Data
(Rabbits)

Date: May 31, 1973

Laboratory No.: 0904 r

Group:	151	152	153	154	155	156
Dose (mg/kg):	Sham	6-AN**	3.0	14.0	65.0	300.0
Pregnancies						
Total No.	11	10	9	9	10	9
Died or Aborted (before Day 29)	1	0	0	0	0	0
To term (on Day 29)	10	10	9	9	10	9
Corpora Lutea						
Total No.	176	207	233	230	178	146
Average/dam mated	12.6	12.9	11.7	11.5	12.7	12.2
Live Litters						
Total No.*	8	10	9	7	9	7
Implant Sites						
Total No.	49	61	58	47	54	42
Average/dam*	4.90	6.10	6.44	5.22	5.40	4.67
Resorptions						
Total No.*	11	22	7	12	11	12
Dams with 1 or more sites resorbed	7	7	4	4	6	6
Dams with all sites resorbed	2	0	0	2	1	2
Per cent partial resorptions	70.0	70.0	44.4	44.4	60.0	66.7
Per cent complete resorptions	20.0	--	--	22.2	10.0	22.2
Live Fetuses						
Total No.	38	39	50	30	43	30
Average/dam*	3.80	3.90	5.56	3.33	4.30	3.33
Sex ratio (M/F)	0.81	0.86	0.79	0.61	0.87	0.76
Dead Fetuses						
Total No.*	--	--	1	5	--	--
Dams with 1 or more dead	--	--	1	1	--	--
Dams with all dead	--	--	0	0	--	--
Per cent partial dead	--	--	11.1	11.1	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	38.6	35.1	39.7	39.5	39.7	39.7

* Includes only those dams examined at term.

** Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 151 through 156 | Laboratory No. 0904 r

Table 3

Material FDA 71-38 | Date May 31, 1973

Summary of Skeletal Findings*
(Rabbits)

Findings / Group No.:	151	152	153	154	155	156
Dose (mg/kg):	Sham	6-AN**	3.0	14.0	65.0	300.0
Live Fetuses Examined (at term)	38/8	39/10	47/9	29/6[a]	43/9	30/7
Sternebrae						
Incomplete oss.		3/2			4/4	
Scrambled						
Bipartite		1/1			2/2	
Fused	1/1	4/4			2/2	1/1
Extra			2/1		4/1	2/1
Missing						
Other						
Ribs						
Incomplete oss.						
Fused/split		2/2				
Wavy						
Less than 12						
More than 13						
Other						
Vertebrae						
Incomplete oss.						
Scrambled		1/1				
Fused						
Extra ctrs. oss.						
Scoliosis		4/3				
Tail defects		22/8				
Other						
Skull						
Incomplete closure		1/1		1/1		
Missing						
Craniostosis					2/1	
Other						
Extremities						
Incomplete oss.						
Missing						
Extra						
Miscellaneous						

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.

** Positive control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

[a] One litter lost in processing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 151 through 156 Date May 31, 1973

Material FDA 71-38 Laboratory No. 0904 r

Table 3-a

Summary of Soft Tissue Abnormalities

(Rabbits)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
152	6-AN*	2.5	Z 4227	1	Fetal monster
				1	Anopia; cleft palate
				1	Anopia; cleft palate; medial rotation of hind limbs; short tail
				1	umbilical hernia

* Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 151 through 156

Date May 31, 1973

Table 4

Species Rabbits

Laboratory No. 0904 r

Average Body Weights*

Group	Material	Dose Level	Day 0	Day 6	Day 12	Day 18	Day 29**
		mg/kg	kg				
151	Sham	0.0	2.46	2.54	2.60	2.62	2.74 (10)
152	6-AN***	2.5	2.39	2.45	2.47	2.51	2.65 (10)
153	FDA 71-38	3.0	2.39	2.50	2.50	2.57	2.72 (9)
154	FDA 71-38	14.0	2.58	2.68	2.76	2.80	2.91 (9)
155	FDA 71-38	65.0	3.04	3.07	3.01	3.02	3.21 (10)
156	FDA 71-38	300.0	2.67	2.77	2.84	2.71	2.88 (9)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 6-aminonicotinamide dosed on Day 9

Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20 x 10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

Dosage (mg/kg)	Dose (ml/kg)	Concentration (mg/ml)
≦ 250	1	≦ 250
251 - 500	2	125 - 250
501 - 750	3	133 - 250
751 - 1000	4	187 - 250
1001 - 1250	5	200 - 250
1251 - 1500	6	208 - 250
1501 - 1600	6.4	235 - 250

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 151

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0904

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 4228 D**	P	11	1					1	----	
S 4229 D	NP	7	0						----	
S 4230 D	P	22	4	2		1	1	2	34.2	One Neonatal Death
S 4231 D	P	16	7	5		4	1	2	42.4	
S 4232 D	P	28	3	2		0	2	1	44.1	
S 4234 D	P	5	3					3	----	
S 4236 D	P	16	9	8		3	5	1	37.8	
S 4237 D	P	10	2	2		--	--		----	Died Day 24 (Accid.)
S 4238 D	P	20	7	7		3	4		37.8	
S 4241 D	P	17	6	6		2	4		42.3	
S 4242 D	P	9	3	3		2	1		35.0	
S 4243 D	NP	3	0						----	
S 4244 D	NP	0	0						----	
S 4245 D	P	12	6	5		2	3	1	35.1	One Neonatal Death

* P = Pregnant; NP = Not Pregnant

** D = Dutch

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 152

Material 6-AN

Dose 2.5 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0904

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Z 4226 D***	P	20	5	2		0	2	3	47.4	
Z 4227 D	P	34	9	3		1	2	6	21.2	
Z 4228 D	NP	9	0						----	
Z 4229 D	NP	4	0						----	
Z 4230 A	P	23	7	6		2	4	1	37.5	
Z 4231 D	P	11	4	2		2	0	2	41.8	
Z 4232 D	NP	6	0						----	
Z 4233 D									----	Not Assigned
Z 4234 A	P	33	11	5		3	2	6	35.7	
Z 4235 D	NP	5	0						----	
Z 4236 D	P	15	4	2		2	0	2	33.2	One Neonatal Death
Z 4237 A	P	13	5	3		1	2	2	36.9	
Z 4238 D	NP	3	0						----	
Z 4239 D	NP	7	0						----	
Z 4240 D	NP	3	0						----	
Z 4241 D	P	11	5	5		3	2		29.8	Three Neonatal Deaths
Z 4242 D	P	--**	5	5		2	3		34.4	One Neonatal Death
Z 4243 D	P	10	6	6		2	4		32.6	

* P = Pregnant; NP = Not Pregnant

** Ovaries missing

*** D = Dutch; A = Albino

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 153

Material FDA 71-38

Dose 3.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0904 r

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
R 4002 D**	NP	4	0						----	
R 4005 D	P	14	4	4		1	3		41.4	
R 4008 D	P	17	9	6		2	4	3	40.1	
R 4009 D	NP	3	0						----	
R 4011 A	NP	3	0						----	
R 4012 A	P	27	6	6		2	4		42.3	
R 4014 A	P	20	7	5		3	2	2	36.3	One Neonatal Death
R 4015 D	NP	13	0						----	
R 4062 A	NP	7	0						----	
R 4063 A	NP	7	0						----	
R 4064 D	P	17	7	7		3	4		42.9	Three Neonatal Deaths
R 4069 D	NP	6	0						----	
R 4070 D	NP	6	0						----	
R 4071 D	P	12	6	4	1	3	1	1	33.1	
R 4072 D	NP	7	0						----	
R 4077 D	NP	14	0						----	
R 4078 D	P	19	8	8		2	6		36.4	
R 4079 D	P	9	3	3		2	1		35.5	
R 4081 D	P	22	8	7		4	3	1	49.2	
R 4082 D	NP	6	0						----	Died Day 25

* P = Pregnant; NP = Not Pregnant

** D = Dutch; A = Albino

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 154

Material FDA 71-38

Dose 14.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0904 r

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
R 4016 D**	P	21	5	5		1	4		40.4	
R 4018 A	NP	5	0						----	
R 4019 A	P	22	9	8		2	6	1	41.6	
R 4020 D	P	6	3					3	----	
R 4021 D	NP	5	0						----	
R 4022 D	NP	4	0						----	
R 4024 A	P	14	5	5		2	3		42.0	
R 4025 A	NP	6	0						----	
R 4026 D	NP	14	0						----	
R 4027 D	NP	7	0						----	
R 4030 A	P	17	3	2		1	1	1	42.6	
R 4065 D	NP	7	0						----	
R 4066 D	P	29	6	6		3	2		43.9	
R 4067 D	NP	4	0						----	
R 4068 D	P	14	3	3		2	1		41.3	
R 4074 D	NP	7	0						----	
R 4075 D	NP	0	0						----	
R 4083 D	P	24	6	1	5	0	1		24.8	
R 4084 D	NP	7	0						----	
R 4085 D	P	17	7					7	----	

* P = Pregnant; NP = Not Pregnant

** D = Dutch; A = Albino

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 155

Material FDA 71-38

Dose 65.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0904 r

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
R 4032 A**	P	21	9	8		2	6	1	41.2	
R 4033 D	P	11	2	2		0	2		34.2	
R 4034 D	P	13	8	6		3	3	2	35.7	
R 4035 D	NP	7	0						----	
R 4036 D	NP	2	0						----	
R 4037 A	P	25	8	7		4	3	1	34.8	
R 4038 A	P	23	7	5		2	3	2	40.0	
R 4039 D	P	19	6	6		3	3		41.4	
R 4040 D	P	16	3	3		3	0		37.4	
R 4041 A	P	12	2	2		2	0		46.5	
R 4042 D	NP	5	0						----	
R 4043 D	NP	0	0						----	
R 4044 A	P	12	5	4		1	3	1	45.7	
R 4045 A	P	12	4					4	----	

* P = Pregnant; NP = Not Pregnant

** D = Dutch; A = Albino

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 156

Material FDA 71-38

Dose 300.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date May 31, 1973

Laboratory No. 0904 r

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
R 4046 D**	P	20	10	5		2	3	5	41.5	
R 4047 D	P	9	3	2		1	1	1	31.9	
R 4048 D	NP	12	0						----	
R 4051 D	P	7	4	3		1	2	1	42.9	
R 4052 D	NP	2	0						----	
R 4053 D	P	6	2					2	----	
R 4054 D	P	17	5	5		1	4		40.9	
R 4055 A	P	21	6	6		4	2		33.3	One Neonatal Death
R 4057 A	P	13	4	4		2	2		40.1	
R 4059 D	P	20	6	5		2	3	1	47.1	One Neonatal Death
R 4060 A	P	11	2					2	----	
R 4088 A	NP	8	0						----	Died Day 20

* P = Pregnant; NP = Not Pregnant

** D = Dutch; A = Albino