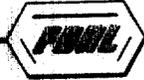


#34
FOOD AND DRUG
Research LABORATORIES, INC.

MAURICE AVENUE AT 58TH STREET, MASPETH, NEW YORK 11378



FINAL

August 31, 1972

Teratologic Evaluation of FDA 71-18

(Propylene glycol alginate)

in

Mice, Rats, Hamsters and Rabbits

Teratologic Evaluation of FDA 71-18 (Propylene Glycol Alginate) in Mice
Rats, Hamsters & Rabbits
NE1772

7-24

M I C E

Food and Drug Research Laboratories
I N C O R P O R A T E D



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

F I N A L
R E P O R T

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

Date August 31, 1972

Laboratory No. 0893 h
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-18 (Propylene glycol alginate)

Examination Requested: Teratologic evaluation of FDA 71-18 in mice.

Procedure: See Appendix I

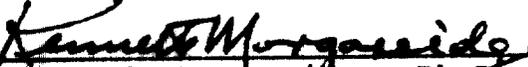
Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 170 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on 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.

In a concurrent group of mice dosed at a level of 780 mg/kg, however, a significant number of maternal deaths occurred (7 out of 32), and there was an increase in the number of resorptions (early fetal death). Surviving dams and fetuses carried to term, however appeared normal in all respects. It is concluded that the test material exhibits maternal toxicity with some loss of embryos in utero. There was no evidence that it is a teratogen for mice under the conditions of the test."

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.
Vice President

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Comment: Attention is called to the fact that this is the tenth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 91 through 96

Date July 31, 1972

Material: FDA 71-18

Table 1
Fate Summary
(Mice)

Laboratory No. 0893 h

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
91	Sham	0	24	21	24	21
92	Aspirin*	150	22	21	22	21
93	FDA 71-18	8	22	20	22	20
94	FDA 71-18	36	24	21	24	21
95	FDA 71-18	170	25	20	24	19
96	FDA 71-18	780	32	20	25	17

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 1 through 96

Date: July 31, 1972

Material: FDA 71-16

Table 2
Reproduction Data
(Mice)

Laboratory No.: 0893 h

Group:	91	92	93	94	95	96
Dose (mg/kg):	Sham	Aspirin**	8	36	170	780
Pregnancies						
Total No.	21	21	20	21	20	20
Died or Aborted (before Day 17)	0	0	0	0	1	7
To term (on Day 17)	21	21	20	21	19	17
Corpora Lutea						
Total No.						
Average/dam mated						
Live Litters						
Total No.*	20	20	20	20	18	13
Implant Sites						
Total No.	243	247	223	245	216	195
Average/dam*	11.6	11.8	11.2	11.7	11.4	11.5
Resorptions						
Total No.*	26	23	12	18	15	52
Dams with 1 or more sites resorbed	11	10	7	8	8	10
Dams with all sites resorbed	1	1	0	1	1	4
Per cent partial resorptions	52.4	47.6	35.0	38.1	42.1	58.8
Per cent complete resorptions	4.76	4.76	--	4.76	5.25	23.5
Live Fetuses						
Total No.	216	222	207	227	198	139
Average/dam*	10.3	10.6	10.4	10.8	10.4	8.18
Sex ratio (M/F)	0.94	1.22	0.87	0.99	0.88	1.02
Dead Fetuses						
Total No.*	1	2	4	0	3	4
Dams with 1 or more dead	1	2	4	--	2	3
Dams with all dead	0	0	0	--	0	0
Per cent partial dead	4.76	9.52	20.0	--	10.5	17.6
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.88	0.84	0.81	0.86	0.87	0.81

*Includes only those dams examined at term.

**Positive Control: 150 mg/kg

Groups 91 through 96

Laboratory No. 0893 h

Table 3

Material FDA 71-18

Date July 31, 1972

Summary of Skeletal Findings *
(Mice)

Findings	Group No. Dose (mg/kg)	91	92	93	94	95	96
		Sham	Aspirin**	8	36	170	780
Live Fetuses Examined (at term)		149/20	155/20	148/20	159/20	140/18	95/13
Sternebrae							
Incomplete oss.		67/17	83/19	71/18	74/17	70/16	54/11
Scrambled							
Bipartite		6/4	8/5	2/2	7/6	5/4	7/5
Fused		2/2					
Extra		1/1			1/1	2/1	
Missing		18/12	35/10	30/7	32/13	31/10	30/7
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12							
More than 13		14/10	7/6	13/6	9/6	6/5	7/4
Other							
Vertebrae							
Incomplete oss.			6/2				4/2
Scrambled					1/1		
Fused							
Extra ctrs. oss.							
Scoliosis						1/1	
Tail defects							
Other							
Skull							
Incomplete closure			3/2				4/1
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.		2/1	16/3	3/2		2/2	6/3
Missing							
Extra							
Miscellaneous							
Hyoid; missing		43/12	54/15	55/14	44/15	35/12	41/10
Hyoid; reduced		25/10	24/11	13/7	15/11	13/10	19/7

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.
** Positive control at 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 91 through 96

Date July 31, 1972

Material FDA 71-18

Laboratory No. 0893 h

Table 3-a
Summary of Soft Tissue Abnormalities
(Mice)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
95	FDA 71-18	170	H3061	1	Meningoencephalocele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 91 through 96

Date July 31, 1972

Species Mice

Table 4

Laboratory No. 0893 h

Average Body Weights*

Group	Material	Dose Level mg/kg	Day				
			0	6	11	15	17**
91	Sham	0	26.6	29.4	32.2	40.4	46.1 (21)
92	Aspirin***	150	27.2	30.2	34.1	39.6	44.6 (21)
93	FDA 71-18	8	25.4	28.6	31.5	38.6	42.6 (20)
94	FDA 71-18	36	27.1	30.4	33.4	40.9	46.0 (21)
95	FDA 71-18	170	28.3	31.7	33.9	41.8	47.4 (19)
96	FDA 71-18	780	27.3	31.1	29.4	35.3	40.2 (17)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control:



Appendix I

Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were individually housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and 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 17 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 91

Appendix II

Date July 31, 1972

Material Sham

Reproduction Data in Mice (Individual)

Laboratory No. 0893

Dose 0.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 3271	P		11	8		1	7	3	0.82	
S 3272	P		12	12		6	6		0.76	
S 3273	P		12	12		4	8		0.66	
S 3274	NP		0						----	
S 3275	P		13	13		5	8		0.77	
S 3276	P		10	9		5	4	1	0.91	
S 3277	P		11	8		6	2	3	0.80	
S 3278	P		9	9		4	5		0.89	
S 3279	P	13	9	6		3	3	3	0.82	
S 3280	P	19	14	13		7	6	1	0.85	
S 3281	NP	15	0						----	
S 3282	P		11	10		4	6	1	0.90	
S 3283	NP	11	0						----	
S 3284	P	13	11	10		4	6	1	0.87	
S 3285	P	17	10	10		7	3		0.88	
S 3286	P	18	12	12		4	8		0.83	
S 3287	P	19	14	14		6	8		0.87	
S 3288	P	19	13	11		6	5	2	1.02	
S 3289	P	15	11	10		5	5	1	0.89	
S 3290	P	16	9			--	--	9	----	
S 3291	P	16	14	12	1	5	6	1	0.97	
S 3292	P	14	13	13		5	8		1.05	
S 3293	P	15	12	12		9	3		0.96	
S 3294	P	16	12	12		8	4		0.95	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 92

Appendix II

Date July 31, 1972

Material Aspirin

Reproduction Data in Mice (Individual)

Laboratory No. 0893

Dose 150.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 3271	P		12	10		4	6	2	0.87	
A 3272	P		11	0				11	----	
A 3273	P		13	12		5	7	1	0.73	
A 3274	P		14	13	1	8	5		0.84	
A 3275	P		11	10		6	4	1	1.00	
A 3276	P		12	11		5	6	1	0.64	
A 3277	P		10	9		6	3	1	0.81	
A 3278	NP		0						----	
A 3279	P		12	12		4	8		0.77	
A 3280	P		11	10		6	4	1	0.94	
A 3281	P	17	12	12		5	7		0.88	
A 3282	P	13	9	8		6	2	1	0.72	
A 3283	P	14	12	9		8	1	3	0.82	
A 3284	P	12	10	9		6	3	1	0.97	
A 3285	P	17	11	11		8	3		0.95	
A 3286	P	13	12	12		9	3		0.88	
A 3287	P	15	11	11		6	5		0.83	
A 3288	P	7	13	13		4	9		0.96	
A 3289	P	13	12	12		7	5		1.27	
A 3290	P	18	13	12	1	6	6		0.77	
A 3291	P	15	12	12		6	6		0.75	
A 3292	P	21	14	14		7	7		0.53	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 93

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Mice (Individual)

Laboratory No. 0893 h

Dose 8.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 3001	P		12	12		4	8		0.55	
H 3002	NP		0						----	
H 3003	P		11	10	1	5	5		0.84	
H 3004	P		13	13		7	6		0.94	
H 3005	P		13	12		4	8	1	0.89	
H 3006	P		11	10		5	5	1	0.89	
H 3007	P		11	5	1	2	3	5	0.67	
H 3008	P	13	11	11		5	6		0.71	
H 3009	P	11	12	12		9	3		0.79	
H 3010	P	9	8	8		1	7		0.96	
H 3011	P	14	12	11		6	5	1	0.67	
H 3012	P	13	8	8		4	4		0.88	
H 3013	P	13	10	10		5	5		0.98	
H 3014	P	11	11	11		8	3		0.99	
H 3015	P	8	11	11		6	5		0.69	
H 3016	P	16	10	9	1	4	5		0.79	
H 3017	P	14	12	11	1	3	8		0.80	
H 3018	P	15	13	11		4	7	2	0.72	
H 3019	P	14	10	9		1	8	1	0.63	
H 3020	P	16	13	13		7	6		0.82	
H 3021	NP	0	0						----	
H 3022	P	13	11	10		5	5	1	1.03	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 94

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Mice (Individual)

Laboratory No. 0893 h

Dose 36.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 3031	NP		0						----	
H 3032	P		10	10		6	4		1.00	
H 3033	P		10	10		4	6		0.91	
H 3034	P		12	12		6	6		0.85	
H 3035	P		12	12		4	8		0.93	
H 3036	P		10	9		2	7	1	0.80	
H 3037	P		10	0				10	----	
H 3038	NP		0						----	
H 3039	P		11	11		6	5		0.83	
H 3040	P		10	10		4	6		0.83	
H 3041	P	17	12	12		9	3		0.62	
H 3042	P	14	12	11		6	5	1	0.95	
H 3043	P	16	13	12		5	7	1	0.93	
H 3044	P	17	11	11		7	4		0.84	
H 3045	P	13	11	11		6	5		0.82	
H 3046	NP	9	0						----	
H 3047	P	11	11	10		5	5	1	0.92	
H 3048	P	17	13	11		5	6	2	0.81	
H 3049	P	19	13	13		7	6		0.71	
H 3050	P	20	13	13		6	7		0.92	
H 3051	P	18	12	12		7	5		0.84	
H 3052	P	15	15	14		5	9	1	0.90	
H 3053	P	14	13	13		7	6		0.85	
H 3054	P	13	11	10		6	4	1	0.88	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 95

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Mice (Individual)

Laboratory No. 0893 h

Dose 170.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 3061	P		13	11	2	7	4		0.79	
H 3062	P		7	7		3	4		0.80	
H 3063	P		16	16		7	9		0.98	
H 3064	P		12	12		8	4		0.95	
H 3065	P		16	16		6	10		1.00	
H 3066	P		11	11		6	5		0.84	
H 3067	NP		0						----	
H 3068	P		9	9		3	6		0.80	
H 3069	NP		0						----	
H 3070	NP		0						----	
H 3071	P		10	10		--	--		----	
H 3072	P	15	11	9		5	4	2	0.78	Died Day 12
H 3073	P	12	8	8		4	4		0.75	
H 3074	NP	21	0						----	
H 3075	P	16	10	10		5	5		0.90	
H 3076	P	17	12	11	1	9	2		0.67	
H 3077	P	0	6					6	----	
H 3078	P	14	12	10		5	5	2	0.88	
H 3079	P	19	12	11		2	9	1	0.88	
H 3080	P	15	13	12		4	8	1	0.80	
H 3081	P	14	13	12		3	9	1	0.69	
H 3082	P	18	11	10		6	4	1	1.48	
H 3083	NP	8	0						----	
H 3084	P	15	13	13		5	8		0.68	
H 3085	P	14	11	10		4	6	1	0.90	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 96

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Mice (Individual)

Laboratory No. 0893 h

Dose 780.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 3091	NP		0						----	Died Day 11
H 3092	NP		0						----	
H 3093	P		8	7	1	4	3		0.86	
H 3094	P		10	10		--	--		----	Died Day 6
H 3095	P		11	11		4	7		0.77	
H 3096	NP		0						----	Died Day 8
H 3097	NP		0						----	
H 3098	NP		0						----	
H 3099	NP		0						----	Died Day 10
H 3100	P	15	12	12		5	7		0.86	
H 3101	P	15	11	10		2	8	1	0.66	
H 3102	P	--	11	11		--	--		----	Died Day 10
H 3103	P	16	12	12		9	3		0.89	
H 3104	P	9	14	0				14	----	
H 3105	P	--	9		9				----	Died Day 13
H 3106	P	8	9					9	----	
H 3107	NP	9	0						----	
H 3108	P	15	7	7		5	2		0.81	
H 3109	P	13	13	11		6	5	2	0.80	
H 3110	P	13	16	13		6	7	3	0.75	
H 3111	P	19	9	8		3	5	1	1.57	
H 3112	P	9	7					7	----	
H 3113	NP	2	0						----	Died Day 8
H 3114	P	14	14	11	2	6	5	1	0.51	
H 3115										Not Assigned
H 3116	NP	7	0						----	
H 3117	P	10	12					12	----	

* P = Pregnant; NP = Not Pregnant

Continued on next page.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 96

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Mice (Individual)

Laboratory No. 0893 h

Dose 780.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 3118	NP	6	0						----	
H 3119	P	14	13	13		6	7		0.77	
H 3120	NP	3	0						----	
H 3121	P	15	13	11		7	4	2	0.71	
H 3122	P	15	14	13	1	5	8		0.71	

* P = Pregnant; NP = Not Pregnant

R A T S

Food and **D**rug **R**esearch **L**aboratories
I N C O R P O R A T E D



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F I N A L
R E P O R T

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

Date August 31, 1972

Laboratory No. 0894 h
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-18 (Propylene glycol alginate)

Examination Requested: Teratologic evaluation of FDA 71-18 in rats

Procedure: See Appendix I

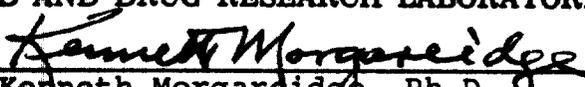
Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 720 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on 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."

Comment: Attention is called to the fact that this is the tenth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.

Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 91 through 96

Date July 31, 1972

Material: FDA 71-18

Table 1
Fate Summary
(Rats)

Laboratory No. 0895 h

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
91	Sham	0	24	23	24	23
92	Aspirin*	250	24	23	24	23
93	FDA 71-18	7	24	23	23	23
94	FDA 71-18	33	24	20	24	20
95	FDA 71-18	155	24	23	24	23
96	FDA 71-18	720	24	23	24	23

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 21 through 96

Date: July 31, 1974

Material: FDA 71-18

Table 2
Reproduction Data
(Rats)

Laboratory No.: 0895 h

Group:	91	92	93	94	95	96
Dose (mg/kg):	Sham	Aspirin**	7	33	155	720
Pregnancies						
Total No.	23	23	23	20	23	23
Died or Aborted (before Day 20)	0	0	1	0	0	0
To term (on Day 20)	23	23	23	20	23	23
Corpora Lutea						
Total No.	268	270	257	249	270	235
Average/dam mated	11.2	11.3	10.7	10.4	11.3	9.79
Live Litters						
Total No.*	23	15	23	20	23	23
Implant Sites						
Total No.	253	256	245	229	269	235
Average/dam*	11.0	11.1	10.7	11.5	11.7	10.2
Resorptions						
Total No.*	12	106	11	19	8	5
Dams with 1 or more sites resorbed	6	16	8	6	6	5
Dams with all sites resorbed	0	8	0	0	0	0
Per cent partial resorptions	26.1	69.6	34.8	30.0	26.1	21.7
Per cent complete resorptions	--	34.8	--	--	--	--
Live Fetuses						
Total No.	240	150	234	210	261	228
Average/dam*	10.4	6.52	10.2	10.5	11.3	9.91
Sex ratio (M/F)	0.81	0.95	0.83	0.84	0.78	0.78
Dead Fetuses						
Total No.*	1	0	0	0	0	2
Dams with 1 or more dead	1	--	--	--	--	1
Dams with all dead	0	--	--	--	--	0
Per cent partial dead	4.35	--	--	--	--	4.35
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.91	2.63	3.74	3.94	3.58	3.92

*Includes only those dams examined at term.

**Positive Control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 91 through 96

Laboratory No. 0894 h

Table 3

Material FDA 71-18

Date July 31, 1972

Summary of Skeletal Findings*
(Rats)

Findings	Group No. Dose (mg/kg)	91 Sham	92 Aspirin**	93 7	94 33	95 155	96 720
Live Fetuses Examined (at term)		161/23	99/15	155/23	139/20	174/23	156/23
Sternebrae							
Incomplete oss.		15/11	94/16	12/8	14/11	33/12	13/7
Scrambled							
Bipartite			1/1		1/1		
Fused							
Extra							
Missing		2/1	64/14	1/1	1/1	8/3	1/1
Other					1/1		1/1
Ribs							
Incomplete oss.		1/1	12/6				
Fused/split		3/2	4/3				
Wavy		5/2	27/11	7/5	4/4	12/5	16/6
Less than 12			3/3				
More than 13			26/9		1/1		
Other							
Vertebrae							
Incomplete oss.		3/1	75/14	2/1	3/1	11/5	2/1
Scrambled							
Fused			2/2				
Extra ctrs. oss.							
Scoliosis			7/4				
Tail defects							
Other							
Skull							
Incomplete closure		19/11	69/13	6/4	20/11	36/10	25/9
Missing							
Craniosclerosis			1/1				
Other							
Extremities							
Incomplete oss.			6/3				
Missing							
Extra							
Miscellaneous							
Hyoid; missing		9/4	73/15	5/3	15/7	32/11	19/8
Hyoid; reduced		3/2	1/1			1/1	

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
 ** Positive control at 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 91 through 96

Date July 31, 1972

Material FDA 71-18

Laboratory No. 0894 h

Table 3-a
Summary of Soft Tissue Abnormalities
(Rats)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
92	Aspirin*	250	A 4283	3	Acrania, cranioccele
				2	Spina bifida
			A 4284	1	Acrania, cranioccele
			A 4285	1	Subcutaneous edema
			A 4290	2	Acrania, cranioccele, spina bifida
	A 4291	1	Acrania, cranioccele, spina bifida		
96	FDA 71-18	720	H4095	1	Hydrometra; hydrocephalus acrania

* Positive control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 91 through 96

Date July 31, 1972

Species Rats

Table 4
Average Body Weights *

Laboratory No. 0894 h

Group	Material	Dose Level mg/kg	Day				
			0	6	11	15	20**
			g				
91	Sham	0	206	236	260	283	352 (23)
92	Aspirin***	250	214	236	252	270	309 (23)
93	FDA 71-18	7	207	228	250	273	336 (23)
94	FDA 71-18	33	210	228	253	276	341 (20)
95	FDA 71-18	155	218	239	260	276	352 (23)
96	FDA 71-18	720	209	228	246	268	333 (23)

* Of pregnant dams
 ** Number of surviving dams in parentheses (c.f. Table 1)
 *** Positive control:



Appendix I

Teratology Study in Rats

Virgin adult female albino rats (Wistar derived stock) were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and 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 20 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 91

Appendix II

Date July 31, 1972

Material Sham

Reproduction Data in Rats (Individual)

Laboratory No. 0894

Dose 0.0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 4271	P	13	13	12		4	8	1	3.98	
S 4272	P	11	11	11		3	8		3.42	
S 4273	P	12	12	12		5	7		3.37	
S 4274	P	10	10	10		5	5		3.86	
S 4275	P	7	7	3		2	1	4	4.57	
S 4276	P	15	15	14		6	8	1	5.95	
S 4277	P	9	6	6		4	2		3.83	
S 4278	P	13	13	13		7	6		3.93	
S 4279	P	13	13	13		3	10		3.68	
S 4280	P	9	9	8		4	4	1	4.00	
S 4281	P	14	14	14		5	9		3.71	
S 4282	P	11	11	11		8	3		4.12	
S 4283	P	12	12	12		7	5		3.81	
S 4284	P	9	9	9		2	7		3.52	
S 4285	NP	11	0						----	
S 4286	P	13	13	13		5	8		3.89	
S 4287	P	11	11	11		5	6		3.19	
S 4288	P	12	12	12		5	7		3.75	
S 4289	P	13	12	12		5	7		3.29	
S 4290	P	13	13	13		8	5		3.36	
S 4291	P	11	11	10		5	5	1	3.45	
S 4292	P	1	1	1		1	0		5.70	
S 4293	P	11	11	6	1	5	2	4	3.83	
S 4294	P	14	14	14		4	10		3.78	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 92

Appendix II

Date July 31, 1972

Material Aspirin

Reproduction Data in Rats (Individual)

Laboratory No. 0894

Dose 250.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 4271	P	9	9					9	----	
A 4272	NP	9	0						----	
A 4273	P	13	13					13	----	
A 4274	P	13	13					13	----	
A 4275	P	5	5					5	----	
A 4276	P	14	12					12	----	
A 4277	P	7	7					7	----	
A 4278	P	13	13					13	----	
A 4279	P	15	15	12		5	7	3	2.19	
A 4280	P	10	10					10	----	
A 4281	P	15	15	10		6	4	5	2.24	
A 4282	P	10	10	8		4	4	2	2.49	
A 4283	P	10	10	8		5	3	2	2.00	
A 4284	P	13	13	6		4	2	7	2.12	
A 4285	P	8	8	8		6	2		3.24	
A 4286	P	11	11	10		7	3	1	2.35	
A 4287	P	18	18	18		8	10		2.68	
A 4288	P	9	6	6		3	3		3.33	
A 4289	P	11	11	11		5	6		3.27	
A 4290	P	12	12	12		7	5		2.57	
A 4291	P	12	12	12		6	6		2.58	
A 4292	P	12	12	10		4	6	2	2.87	
A 4293	P	11	11	11		2	9		2.84	
A 4294	P	10	10	8		1	7	2	2.61	

* P. = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 93

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Rats (Individual)

Laboratory No. 0894 h

Dose 7.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 4001	P	10	10	9		5	4	1	3.29	
H 4002	P	12	12	10		4	6	2	3.79	
H 4003	P	10	10	10		5	5		5.38	
H 4004	P	10	10	10		4	6		3.83	
H 4005	P	12	12	12		7	5		3.38	
H 4006	P	10	10	10		4	6		3.97	
H 4007	P	16	16	16		6	10		3.76	
H 4008	P	11	11	11		4	7		3.68	
H 4009	P	9	9	9		5	4		3.61	
H 4010	P	7	7	6		2	4	1	4.20	
H 4011	P	14	14	14		6	8		3.91	
H 4012	P	9	9	7		4	3	2	3.97	
H 4013	P	9	9	9		6	3		3.10	
H 4014	P	10	10	10		5	5		3.86	
H 4015	P	11	11	10		4	6	1	3.75	
H 4016	P	14	14	14		9	5		3.01	
H 4017	P	11	11	9		5	4	2	3.66	
H 4018	P	9	9	9		4	5		3.61	
H 4019	P	13	13	13		3	10		3.58	
H 4020	NP	12	0						----	Died Day 11
H 4021	P	11	11	11		6	5		3.66	
H 4022	P	9	9	9		3	6		3.40	
H 4023	P	8	8	7		3	4	1	3.94	
H 4024	P	10	10	9		2	7	1	3.68	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 94

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Rats (Individual)

Laboratory No. 0894 h

Dose 33.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 4031	P	11	11	11		7	4		3.67	
H 4032	P	11	11	11		4	7		3.50	
H 4033	P	13	12	11		8	3	1	3.87	
H 4034	P	7	7	4		3	1	3	5.75	
H 4035	P	11	11	11		8	3		3.78	
H 4036	P	14	13	13		2	11		3.35	
H 4037	NP	0	0						----	
H 4038	NP	9	0						----	
H 4039	P	10	10	10		5	5		3.90	
H 4040	NP	9	0						----	
H 4041	P	13	13	12		5	7	1	4.03	
H 4042	P	11	11	11		8	3		3.88	
H 4043	NP	0	0						----	
H 4044	P	13	13	13		6	7		3.76	
H 4045	P	13	13	13		5	8		3.90	
H 4046	P	12	12	12		4	8		5.07	
H 4047	P	14	14	14		6	8		3.44	
H 4048	P	11	11	11		6	5		3.89	
H 4049	P	9	9	9		1	8		3.87	
H 4050	P	11	11	11		3	8		3.95	
H 4051	P	12	12	11		8	3	1	3.67	
H 4052	P	11	11	11		3	8		3.62	
H 4053	P	11	11	1		0	1	10	3.90	
H 4054	P	13	13	10		4	6	3	3.95	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 95

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Rats (Individual)

Laboratory No. 0894 h

Dose 155.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 4061	P	12	10	10		4	6		3.74	
H 4062	P	13	13	13		8	5		3.09	
H 4063	P	14	15	14		7	7	1	3.73	
H 4064	NP	0	0						----	
H 4065	P	11	11	11		5	6		3.63	
H 4066	P	14	14	14		4	10		3.66	
H 4067	P	9	9	9		7	2		3.66	
H 4068	P	12	12	12		7	5		3.48	
H 4069	P	9	9	8		3	5	1	3.53	
H 4070	P	12	12	12		4	8		3.42	
H 4071	P	13	13	13		8	5		3.33	
H 4072	P	10	10	10		4	6		3.67	
H 4073	P	14	14	13		2	11	1	3.53	
H 4074	P	13	13	13		6	7		3.41	
H 4075	P	9	9	8		3	5	1	3.78	
H 4076	P	9	9	9		3	6		3.79	
H 4077	P	10	10	8		6	2	2	3.38	
H 4078	P	12	12	12		5	7		3.68	
H 4079	P	13	13	13		5	8		3.91	
H 4080	P	14	14	14		4	10		3.70	
H 4081	P	10	10	10		6	4		2.97	
H 4082	P	13	13	13		7	6		3.78	
H 4083	P	13	13	11		2	9	2	3.58	
H 4084	P	11	11	11		4	7		3.87	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 96

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Rats (Individual)

Laboratory No. 0894 b

Dose 720.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 4091	P	10	10	9		3	6	1	3.59	
H 4092	P	10	10	10		3	7		4.02	
H 4093	P	13	13	13		6	7		3.60	
H 4094	P	9	9	9		5	4		3.88	
H 4095	P	2	1	1		1	0		6.20	
H 4096	P	11	11	11		8	3		3.93	
H 4097	P	10	10	10		3	7		3.59	
H 4098	P	13	13	13		7	6		3.08	
H 4099	P	11	11	10		2	8	1	3.50	
H 4100	P	10	10	10		7	3		3.68	
H 4101	P	11	11	10		7	3	1	3.80	
H 4102	P	10	10	10		1	9		3.87	
H 4103	P	11	13	12		3	9	1	3.49	
H 4104	P	10	9	9		6	3		3.82	
H 4105	P	12	12	12		6	6		3.96	
H 4106	P	13	13	11	2	1	10		2.69	
H 4107	P	10	10	10		6	4		3.29	
H 4108	P	12	12	12		5	7		3.58	
H 4109	P	13	13	13		4	9		3.82	
H 4110	P	10	10	9		3	6	1	3.69	
H 4111	P	9	9	9		5	4		5.78	
H 4112	NP	0	0						----	
H 4113	P	6	6	6		4	2		5.10	
H 4114	P	9	9	9		4	5		4.10	

* P = Pregnant; NP = Not Pregnant

HAMSTERS

Food and Drug Research Laboratories
I N C O R P O R A T E D



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**F I N A L
R E P O R T**

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

Date August 31, 1972

Laboratory No. 0895 h
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-18 (Propylene glycol alginate)

Examination Requested: Teratologic evaluation of FDA 71-18 in hamsters

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 700 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on 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."

Comment: Attention is called to the fact that this is the tenth of a series of reports which will be issues in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.

Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 91 through 96

Date July 31, 1972

Material: FDA 71-18

Table 1
Fate Summary
(Hamsters)

Laboratory No. 0895 h

Group	Material	Dose ** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
91	Sham	0	20	20	17	17
92	Aspirin	250	20	20	20	20
93	FDA 71-18	7	20	20	20	20
94	FDA 71-18	33	23	21	23	21
95	FDA 71-18	150	23	21	23	21
96	FDA 71-18	700	20	20	20	20

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

FOOD AND DRUG RESEAF) LABORATORIES, INC.

Group: 91 through 96

Date: July 31, 1972

Material: FDA 71-18

Table 2
Reproduction Data
(Hamsters)

Laboratory No.: 0895 h

Group:	91	92	93	94	95	96
Dose (mg/kg):	Sham	Aspirin**	7	33	150	700
Pregnancies						
Total No.	20	20	20	21	21	20
Died or Aborted (before Day 14)	3	0	0	0	0	0
To term (on Day 14)	17	20	20	21	21	20
Corpora Lutea						
Total No.	321	328	321	349	348	321
Average/dam mated	16.1	16.4	16.1	15.2	15.1	16.1
Live Litters						
Total No.*	17	20	20	21	21	20
Implant Sites						
Total No.	208	243	246	265	260	244
Average/dam*	12.2	12.2	12.3	12.6	12.4	12.2
Resorptions						
Total No.*	10	19	18	18	11	16
Dams with 1 or more sites resorbed	8	9	8	11	7	7
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	47.1	45.0	40.0	52.4	33.3	35.0
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	198	223	227	238	249	228
Average/dam*	11.6	11.2	11.4	11.3	11.9	11.4
Sex ratio (M/F)	0.48	0.58	0.64	0.54	0.77	0.61
Dead Fetuses						
Total No.*	0	1	1	9	0	0
Dams with 1 or more dead	--	1	1	2	--	--
Dams with all dead	--	0	0	0	--	--
Per cent partial dead	--	5.00	5.00	9.52	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	1.79	1.81	1.77	1.75	1.86	1.82

*Includes only those dams examined at term.

Summary of Skeletal Findings*
(Hamsters)

Findings	Group No.	91	92	93	94	95	96
	Dose (mg/kg)	Sham	Aspirin**	7	33	150	700
Live Fetuses Examined (at term)		138/17	152/20	155/20	164/21	173/21	158/20
Sternebrae							
Incomplete oss.		73/17	95/19	67/18	78/19	83/21	69/19
Scrambled							
Bipartite		13/9	22/13	18/12	18/10	18/11	12/10
Fused							1/1
Extra		3/2		1/1			2/2
Missing		13/6	33/16	17/7	9/8	15/10	18/9
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12							
More than 13		22/12	18/8	19/10	27/15	46/14	27/9
Other							
Vertebrae							
Incomplete oss.							
Scrambled							
Fused							
Extra ctrs. oss.		2/2					
Scoliosis							
Tail defects							
Other							
Skull							
Incomplete closure							
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.			3/2			5/3	
Missing							
Extra							
Miscellaneous							
Hyoid; missing			4/3			1/1	
Hyoid; reduced		1/1	8/7	1/1	1/1	9/5	1/1

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
 ** Positive control at 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 91 through 96

Date July 31, 1972

Material FDA 71-18

Laboratory No. 0895 h

Table 3-a
Summary of Soft Tissue Abnormalities
(Hamsters)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
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None Observed

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 91 through 96

Date July 31, 1972

Species Hamsters

Table 4

Laboratory No. 0895 h

Average Body Weights*

Group	Material	Dose Level mg/kg	Day				
			0	6	8	10	14**
91	Sham	0	96.5	105.1	103.8	115.1	138.0 (17)
92	Aspirin***	250	97.7	105.8	109.4	120.1	141.0 (20)
93	FDA 71-18	7	93.6	99.9	103.7	113.9	135.7 (20)
94	FDA 71-18	33	97.1	105.2	110.2	120.8	142.4 (21)
95	FDA 71-18	150	96.3	102.6	106.9	118.4	139.3 (21)
96	FDA 71-18	700	95.7	103.5	105.6	114.9	136.1 (20)

* Of pregnant dams
 ** Number of surviving dams in parentheses (c.f. Table 1)
 *** Positive control:



Appendix I

Teratology Study in Hamsters

Virgin adult female golden hamsters from an outbred strain were individually housed in mesh bottom cages in temperature and humidity controlled quarters with free access to food and fresh tap water at all times. They were mated (1 to 1) with mature males and the appearance of motile sperm in the vaginal smear was considered as Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, the indicated dose levels of the test material were administered by oral intubation; the controls were sham-treated.

Body weights were recorded on Days 0, 8, 10, and 14 of the gestation period. All animals were observed daily for appearance and behavior with particular attention to food consumption in order to better recognize any abnormalities resulting from anorexic effects in the pregnant animal.

On Day 14, all animals were subjected to Caesarian section under deep anesthesia and the numbers of implantation sites, resorption sites, live and dead fetuses were recorded. All live pups were weighed and the genital tract of each dam was examined for any anatomical abnormalities.

All fetuses were examined grossly for the presence of external congenital defects and one-third of each litter underwent detailed visceral examination under 10X magnification. The remaining two-thirds of the pups were cleared in potassium hydroxide, stained with alizarin red dye, and examined for the presence of skeletal abnormalities.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 91

Appendix II

Date July 31, 1972

Material Sham

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895

Dose 0.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 5271	P	16	11	11		4	7		2.19	
S 5272	P	17	12	11		4	7	1	1.83	
S 5273	P	15	13	13		3	10		1.82	
S 5274	P	11	9	9		3	6		----	Aborted Day 13
S 5275	P	14	12	12		3	9		1.66	
S 5276	P	16	12	12		4	8		1.59	
S 5277	P	16	15	14		2	12	1	1.71	
S 5278	P	16	14	13		4	9	1	1.80	
S 5279	P	15	10	9		2	7	1	1.92	
S 5280	P	15	13	12		3	9	1	1.67	
S 5281	P	19	12	12		3	9		1.72	
S 5282	P	17	13	13		5	8		1.80	
S 5283	P	20	11	8		3	5	3	2.04	
S 5284	P	21	12	11		3	8	1	1.76	
S 5285	P	16	12	12		5	7		1.95	
S 5286	P	15	10	10		4	6		1.73	
S 5287	P	12	15					15	----	Died Day 14
S 5288	P	15	13	12		6	6	1	1.77	
S 5289	P	16	12	12		1	11		----	Aborted Day 13
S 5290	P	19	13	13		7	6		1.71	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Date July 31, 1972

Group 92

Material Aspirin

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895

Dose 250.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 5271	P	17	9	8		3	5	1	1.91	
A 5272	P	15	10	10		4	6		1.76	
A 5273	P	17	9	9		5	4		1.82	
A 5274	P	17	12	11	1	1	10		1.76	
A 5275	P	18	13	8		5	3	5	1.77	
A 5276	P	14	10	9		2	7	1	1.82	
A 5277	P	16	12	12		4	8		1.76	
A 5278	P	15	12	11		2	9	1	2.08	
A 5279	P	18	12	12		5	7		1.68	
A 5280	P	11	12	7		2	5	5	1.70	
A 5281	P	17	12	12		3	9		1.58	
A 5282	P	17	11	11		3	8		1.80	
A 5283	P	18	14	14		0	14		1.96	
A 5284	P	20	12	12		6	6		1.88	
A 5285	P	15	13	12		4	8	1	1.92	
A 5286	P	19	16	16		8	8		1.68	
A 5287	P	17	15	14		5	9	1	1.75	
A 5288	P	18	14	13		8	5	1	1.94	
A 5289	P	15	12	9		5	4	3	1.77	
A 5290	P	14	12	12		7	5		1.82	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 93

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 h

Dose 7.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 5001	P	12	10	10		3	7		1.89	
H 5002	P	16	14	14		8	6		1.55	
H 5003	P	16	14	14		5	9		1.91	
H 5004	P	14	13	10		6	4	3	1.79	
H 5005	P	16	12	11		2	9	1	1.58	
H 5006	P	18	9	9		2	7		1.94	
H 5007	P	18	12	9		6	3	3	1.89	
H 5008	P	16	12	10		2	8	2	1.73	
H 5009	P	14	11	11		3	8		1.42	
H 5010	P	16	15	14		4	10	1	1.89	
H 5011	P	16	13	13		4	9		1.87	
H 5012	P	15	11	9		3	6	2	1.64	
H 5013	P	20	12	12		7	5		1.90	
H 5014	P	18	16	16		7	9		1.53	
H 5015	P	18	13	13		4	9		1.77	
H 5016	P	20	11	6		2	4	5	1.91	
H 5017	P	16	12	11	1	7	4		1.98	
H 5018	P	12	12	12		3	9		1.75	
H 5019	P	17	14	14		7	7		1.88	
H 5020	P	13	10	9		4	5	1	1.71	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 94

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 h

Dose 33.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 5031	NP	0	0						----	
H 5032	P	15	13	13		4	9		1.86	
H 5033	P	15	12	12		3	9		1.53	
H 5034	P	14	12	12		4	8		1.87	
H 5035	P	16	7	4		1	3	3	1.96	
H 5036	P	14	10	10		3	7		1.70	
H 5037	NP	0	0						----	
H 5038	P	15	11	10		4	6	1	1.41	
H 5039	P	17	9	8		2	6	1	1.86	
H 5040	P	15	13	11		2	9	2	1.75	
H 5041	P	15	15	15		4	11		1.74	
H 5042	P	18	14	9	2	4	5	3	1.58	
H 5043	P	17	11	10		3	7	1	1.69	
H 5044	P	17	15	14		8	6	1	1.93	
H 5045	P	19	15	15		5	10		1.91	
H 5046	P	16	14	12		5	7	2	1.96	
H 5047	P	18	14	14		5	9		1.68	
H 5048	P	18	11	10		3	7	1	1.87	
H 5049	P	19	12	11		3	8	1	2.01	
H 5050	P	18	13	13		6	7		1.80	
H 5051	P	18	12	5	7	1	4		1.58	
H 5052	P	19	18	18		8	10		1.76	
H 5053	P	16	12	10		4	6	2	1.77	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 95

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 h

Dose 150.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 5061	P	14	9	8		4	4	1	1.81	
H 5062	P	12	10	10		3	7		1.76	
H 5063	P	15	13	12		9	3	1	1.96	
H 5064	P	18	12	12		3	9		1.82	
H 5065	P	13	10	7		2	5	3	1.87	
H 5066	P	16	13	13		6	7		1.94	
H 5067	P	16	11	10		3	7	1	1.99	
H 5068	P	20	14	14		9	5		1.78	
H 5069	P	15	12	12		5	7		1.77	
H 5070	NP	8	0						----	
H 5071	P	14	12	12		2	10		1.98	
H 5072	P	20	15	15		9	6		1.95	
H 5073	P	19	15	15		8	7		1.75	
H 5074	P	19	15	13		5	8	2	1.91	
H 5075	P	19	11	11		5	6		2.02	
H 5076	P	18	14	14		6	8		1.80	
H 5077	P	20	14	14		7	7		1.87	
H 5078	P	15	12	11		6	5	1	1.85	
H 5079	P	13	11	11		5	6		1.77	
H 5080	NP	0	0						----	
H 5081	P	14	11	9		4	5	2	1.79	
H 5082	P	16	14	14		7	7		1.88	
H 5083	P	14	13	13		1	12		1.71	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 96

Appendix II

Date July 31, 1972

Material FDA 71-18

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 h

Dose 700.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
H 5091	P	15	11	11		2	9		1.97	
H 5092	P	15	13	11		4	7	2	1.86	
H 5093	P	18	12	12		6	6		1.64	
H 5094	P	13	10	10		2	8		1.94	
H 5095	P	12	10	10		5	5		1.64	
H 5096	P	14	11	11		1	10		1.81	
H 5097	P	18	13	12		7	5	1	1.94	
H 5098	P	15	11	11		3	8		1.86	
H 5099	P	16	12	12		5	7		1.75	
H 5100	P	16	11	10		2	8	1	1.72	
H 5101	P	17	15	15		5	10		1.84	
H 5102	P	16	14	14		6	8		1.86	
H 5103	P	16	13	13		8	5		2.05	
H 5104	P	20	15	7		3	4	8	1.35	
H 5105	P	15	10	9		3	6	1	1.75	
H 5106	P	17	12	11		5	6	1	2.00	
H 5107	P	14	14	14		6	8		1.81	
H 5108	P	21	14	14		6	8		1.72	
H 5109	P	17	11	11		2	9		1.76	
H 5110	P	16	12	10		6	4	2	1.89	

* P = Pregnant; NP = Not Pregnant

RABBITS

Food and Drug Research Laboratories
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F I N A L
R E P O R T

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

Date August 31, 1972

Laboratory No. 0896 h
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-18 (Propylene glycol alginate)

Examination Requested: Teratologic evaluation of FDA 71-18 in rabbits

Procedure: (See Appendix I)

Results: (To Follow)

Conclusion:

(This test has been deferred due to unavailability of suitable rabbits.)

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge
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Vice President

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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 20×10^6 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.

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.