Final report-Teratologic Evaluation of FDA 71-12 (**Gum Tragacanth**) in Mice, Rats, Hamsters & Rabbits 8/1/72

FOOD AND DRUG Research LABORATORIES, INC.
MAURICE AVENUE AT 58TH STREET, MASPETH, NEW YORK 11378

#12

FINAL

August 1, 1972

Teratologic Evaluation of FDA 71-12 (Gum tragacanth) in Mice, Rats, Hamsters and Rabbits

M I C E

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INCORPORATED

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FINAL REPORT

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

Date August 1, 1972

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

Sample: Fine light tan powdered material

Marking: FDA 71-12 (Gum tragacanth)

Examination Requested: Teratologic evaluation of FDA 71-12 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 1200 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."

Comment: Attention is called to the fact that this is the seventh 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

Kenneth Morgareidge, Ph.D.
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 61 through 66

Material: FDA 71-12

Date June 15, 1972

Laboratory No. 0893 b

Table 1

Fate Summary
(Mice)

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
61	Sham	0	25	20	23	18
62	Aspirin*	150	22	20	21	19
63	FDA 71-12	12	27	20	25	18
64	FDA 71-12	56	26	20	24	18
65	FDA 71-12	210	30	20	30	20
66	FDA 71-12	1200	29	20	27	18

* 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: 61 through 66

Date June 15, 1972

Material: FDA 71-12

Laboratory No. 0893 b

Table 2
Reproduction Data
(Mice)

Group:	61	62	63	64	65	66
Dose (mg/kg):	Sham	Aspirin **	12	56	210	1200
Pregnancies						
Total No.	20	20	20	20	20	20
Died or aborted (before Day 17)	2	1	1	2	0	2
To term (on Day 17)	18	19	18	18	20	18
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	18	19	18	18	20	18
Implant sites						
Total No. (at term)	198	201	216	199	235	214
Average/dam*	11.0	10.6	12.0	11.1	11.8	11.9
Resorptions						
Total No.*	7	8	16	8	9	22
Dams with 1 or more sites resorbed	7	6	8	6	7	10
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	38.9	31.6	44.4	33.3	35.0	55.5
Per cent complete resorptions	--	--	--	--	--	--
Live fetuses						
Total No. (at term)	188	187	200	187	221	189
Average/dam*	10.4	9.8	11.1	10.4	11.1	10.5
Dead fetuses						
Total No.*	3	6	0	4	5	3
Dams with 1 or more dead	3	4	--	3	3	3
Dams with all dead	0	0	--	0	0	0
Per cent partial dead	16.7	21.1	--	16.7	15.0	16.7
per cent all dead	--	--	--	--	--	--
Average fetus weight, g	0.90	0.91	0.94	0.95	0.93	0.83

* Includes only those dams examined at term.
** Positive control: 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 | Laboratory No. 0893 b

Table 3

Material FDA 71-12 | Date June 15, 1972

Summary of Skeletal Findings
(Mice)

Findings	Group No.	61	62	63	64	65	66
	Dose (mg/kg)	Sham	Aspirin**	12	56	210	1200
Live Fetuses Examined (at term)		131/18	131/19	138/18	131/18	154/20	131/18
Sternebrae							
Incomplete oss.		38/14	57/16	42/13	34/14	40/12	49/14
Scrambled							
Bipartite		4/4	2/2			1/1	4/3
Fused							
Extra							
Missing		16/7	21/9	17/6	8/5	32/9	37/10
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12							
More than 13		29/12	7/4	16/8	16/13	10/6	10/6
Other							
Vertebrae							
Incomplete oss.				1/1			
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis							
Tail defects							
Other							
Skull							
Incomplete closure							
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.				1/1			
Missing							
Extra							
Miscellaneous							
Hyoid; missing		27/10	34/14	37/12	33/13	54/16	43/13
Hyoid; reduced		11/8	12/5	11/8	14/10	11/8	16/10

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 Date June 15, 1972

Material FDA 71-12 Laboratory No. 0893 b

Table 3-a

Summary of Soft Tissue Abnormalities

(Mice)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
65	FDA 71-12	210	B 3090	2	Meningoencephalocele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66

Species Mice

Date June 15, 1972

Laboratory No. 0893 b

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	Day 6	Day 11	Day 15	Day 17**
		mg/kg	g				
61	Sham	0	27.4	29.9	31.6	39.3	45.8 (18)
62	Aspirin***	150	23.3	29.9	33.5	38.6	45.2 (19)
63	FDA 71-12	12	28.7	31.4	33.8	41.9	47.2 (18)
64	FDA 71-12	56	27.9	30.6	34.6	42.5	48.4 (18)
65	FDA 71-12	210	28.1	31.3	33.2	39.3	46.0 (20)
66	FDA 71-12	1200	30.0	32.5	31.9	38.1	43.6 (18)

* 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 61

Material Sham

Dose 0

Appendix II

Reproduction Data in Mice (Individual)

Date June 15, 1972

Laboratory No. 0893

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 3181	NP		0						--	
S 3182	NP		0						--	
S 3183	P		13	12		--	--	1	0.70	
S 3184	P		11	10		--	--	1	0.76	
S 3185	NP		0						--	
S 3186	P		12	11	1	--	--		0.91	
S 3187	P		11	10		--	--	1	0.80	
S 3188	P		10	9		--	--	1	0.84	
S 3189	P		10	10		--	--		0.80	
S 3190	P		12	10	1	--	--	1	0.93	
S 3191	P		10	10		--	--		0.74	
S 3192	NP		0						--	
S 3193	P		12	12		--	--		0.84	
S 3194	P		12	12		--	--		0.82	
S 3195	NP		0						--	
S 3196	P		10	10		--	--		1.31	
S 3197	P		9	9		--	--		--	Aborted Day 14
S 3198	P		11	11		--	--		1.00	
S 3199	P		10	10		2	8		1.05	
S 3200	P		10	9		3	6	1	0.88	
S 3201	P		11	10	1	4	7		0.91	
S 3202	P		9	9		3	6		0.93	
S 3203	P		12	12		6	6		1.04	
S 3204	P		12	11		8	3	1	1.03	
S 3205	P		10	0	10	--	--		--	Died Day 13

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 62 | Appendix II | Date June 15, 1972

Material Aspirin | Reproduction Data in Mice (Individual) | Laboratory No. 0893

Dose 150 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 3181	NP		0						--	
A 3182	P		11	9		--	--	2	1.29	
A 3183	P		13	12		--	--	1	0.76	
A 3184	P		12	10	1	--	--	1	0.88	
A 3185	P		15	0		--	--	15	--	Died Day 15
A 3186	P		11	11		--	--		0.72	
A 3187	NP		0						--	
A 3188	P		12	10		--	--	2	0.75	
A 3189	P		12	11		--	--	1	0.89	
A 3190	P		3	3		--	--		0.77	
A 3191	P		7	7		--	--		1.31	
A 3192	P		13	13		--	--		0.84	
A 3193	P		13	11	2	--	--		0.75	
A 3194	P		13	13		--	--		0.68	
A 3195	P		11	10	1	--	--		0.84	
A 3196	P		7	7		4	3		0.99	
A 3197	P		9	9		4	5		0.95	
A 3198	P		8	8		2	6		1.01	
A 3199	P		10	10		6	4		0.87	
A 3200	P		9	7	2	2	5		0.84	
A 3201	P		16	15		6	10	1	0.96	
A 3202	P		11	11		6	5		1.11	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 63 | Appendix II | Date June 15, 1972

Material FDA 71-12 | Reproduction Data in Mice (Individual) | Laboratory No. 0893b

Dose 12 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 3001	P		14	14		--	--		0.91	
B 3002	NP		0						--	
B 3003	P		13	0		--	--	13	--	Died Day 12
B 3004	NP		0						--	
B 3005	NP		0						--	
B 3006	P		13	12		--	--	1	0.86	
B 3007	NP		0						--	
B 3008	P		14	14		--	--		0.76	
B 3009	P		14	12		--	--	2	0.71	
B 3010	NP		0						--	
B 3011	P		12	12		--	--		0.81	
B 3012	P		12	12		--	--		0.99	
B 3013	NP		0						--	
B 3014	NP		0						--	
B 3015	P		9	9		--	--		0.96	
B 3016	P		9	7		--	--	2	1.21	
B 3017	P		11	11		--	--		0.99	
B 3018	P		11	11		--	--		0.91	
B 3019	P		11	11		--	--		1.02	
B 3020	P		9	9		3	6		1.13	
B 3021	P		15	0	13	--	--	2	--	Died Day 17
B 3022	P		14	13		10	3	1	0.91	
B 3023	P		12	9		4	5	3	0.91	
B 3024	P		14	12		8	4	2	0.75	
B 3025	P		12	8		3	5	4	0.82	
B 3026	P		13	12		5	7	1	1.18	
B 3027	P		12	12		6	6		1.13	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 64 | Appendix II | Date June 15, 1972

Material FDA 71-12 | Reproduction Data in Mice (Individual) | Laboratory No. 0893b

Dose 56 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 3031	NP		0						--	
B 3032	NP		0						--	
B 3033	P		12	10		--	--	2	0.92	
B 3034	NP		0						--	
B 3035	P		13	12		--	--	1	0.89	
B 3036	P		10	10		--	--		1.01	
B 3037	P		10	8	1	--	--	1	0.88	
B 3038	P		11	10	1	--	--		0.86	
B 3039	P		14	14		--	--		0.85	
B 3040	P		13	13		--	--		0.94	
B 3041	P		9	5	2	--	--	2	0.76	
B 3042	P		12	12		--	--		--	Aborted Day 10
B 3043	NP		0						--	
B 3044	P		12	12		--	--		0.94	
B 3045	P		10	10		--	--		0.99	
B 3046	P		11	10		--	--	1	1.00	
B 3047	P		9	9		--	--		1.10	
B 3048	P		9	9		7	2		1.04	
B 3049	P		9	9		3	6		0.82	
B 3050	P		10	10		4	6		--	Aborted Day 16
B 3051	NP		0						--	
B 3052	P		8	8		5	3		1.12	
B 3053	P		11	11		4	7		1.05	
B 3054	NP		0						--	
B 3055	P		13	13		5	8		1.01	
B 3056	P		15	14		7	7	1	1.00	

* P = Pregnant; NP = Not Pregnant

FOOD A DRUG RESEA H LABORATORI , INC.

Group 65

Material FDA 71-12

Dose 210 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date June 15, 1972

Laboratory No. 0893b

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 3061	NP		0						--	
B 3062	NP		0						--	
B 3063	P		11	10		--	--	1	0.69	
B 3064	P		11	11		--	--		1.05	
B 3065	P		11	11		--	--		1.03	
B 3066	P		13	12		--	--	1	0.67	
B 3067	NP		0						--	
B 3068	P		11	9		--	--	2	0.81	
B 3069	P		14	11	3	--	--		0.74	
B 3070	P		13	13		--	--		0.89	
B 3071	P		12	11		--	--	1	0.86	
B 3072	P		11	11		--	--		0.80	
B 3073	NP		0						--	
B 3074	NP		0						--	
B 3075	NP		0						--	
B 3076	P		8	8		2	6		0.90	
B 3077	NP		0						--	
B 3078	NP		0						--	
B 3079	P		12	12		6	6		0.94	
B 3080	P		9	9		5	4		1.24	
B 3081	P		13	12		6	6	1	0.97	
B 3082	P		12	11	1	7	5		1.09	
B 3083	P		11	11		6	5		1.09	
B 3084	P		10	10		2	8		0.95	
B 3085	P		14	11	1	4	7	2	1.07	
B 3086	P		13	13		8	5		1.17	
B 3087	NP		0						--	
B 3088	P		11	10		5	5	1	0.99	
B 3089	NP		0						--	
B 3090	P		15	15		4	11		0.74	

* P = Pregnant; NP = Not Pregnant

FOOD A DRUG RESEA LABORATORI INC.

Group 66

Appendix II

Date June 15, 1972

Material FDA 71-12

Reproduction Data in Mice (Individual)

Laboratory No. 0893b

Dose 1200 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 3091	P		14	13		--	--	1	0.88	
B 3092	NP		0						--	
B 3093	NP		0						--	
B 3094	P		11	10		--	--	1	0.81	
B 3095	NP		0						--	
B 3096	P		10	8		--	--	2	0.70	
B 3097	P		13	0		--	--	13	--	Died Day 11
B 3098	NP		0						--	
B 3099	P		12	0		--	--	12	--	Aborted Day 16
B 3100	NP		0						--	
B 3101	P		12	10		--	--	2	0.58	
B 3102	NP		0						--	
B 3103	P		9	8		1	7	1	0.59	
B 3104	P		12	12		5	7		0.71	
B 3105	NP		0						--	
B 3106	P		16	13	1	5	9	2	0.83	
B 3107	P		10	5		1	4	5	0.58	
B 3108	P		14	14		3	11		0.83	
B 3109	P		11	10	1	4	6		0.97	
B 3110	P		7	7		3	4		0.88	
B 3111	P		11	11		5	6		1.12	
B 3112	P		14	11		5	6	3	0.83	
B 3113	P		14	12		6	6	2	1.03	
B 3114	NP		0						--	
B 3115	NP		0						--	
B 3116	P		11	8		1	7	3	0.72	
B 3117	P		13	12	1	5	8		0.77	
B 3118	P		15	15		8	7		0.92	
B 3119	P		10	10		4	6		1.11	

* P = Pregnant; NP = Not Pregnant

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FINAL REPORT

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

Date August 1, 1972

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

Sample: Fine light tan powdered material

Marking: FDA 71-12 (Gum tragacanth)

Examination Requested: Teratologic evaluation of FDA 71-12 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 210 mg/kg (body weight) of the test material as a suspension in anhydrous corn oil to pregnant rats for 10 consecutive days had no discernible effect on nidation or on maternal or fetal survival. The number and type of abnormalities seen in fetal soft or skeletal tissues derived from this group of dams did no differ from the number occurring spontaneously in the sham-treated controls. However, in a group of dams dosed at 1200 mg/kg (body weight), significant maternal toxicity ensued with the loss of 6 out of 22 pregnant rats. Death was accompanied by severe diarrhea and urinary incontinence with anorexia for 48 to 72 hours terminally. At autopsy, gross pathological findings were seen other than marked petechial hemorrhage in the mucosa of the small intestine. Rats which survived this high dose and bore living young to term remained outwardly normal and the offspring were likewise normal in all respects. It is concluded that this test substance was not a teratogen in the rat.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

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Comment: Attention is called to the fact that this is the seventh 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: 61 through 66

Material: FDA 71-12

Date June 15, 1972

Laboratory No. 0894 b

Table 1

Fate Summary
(Rats)

Group	Material	Dose ** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
61	Sham	0	27	24	23	21
62	Aspirin*	250	24	20	22	18
63	FDA 71-12	12	24	22	23	21
64	FDA 71-12	56	23	23	22	22
65	FDA 71-12	210	23	22	23	22
66	FDA 71-12	1200	22	20	16	15

* 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: 61 through 66

Date June 15, 1972

Material: FDA 71-12

Laboratory No. 0894 b

Table 2
Reproduction Data
(Rats)

Group:	61	62	63	64	65	66
Dose (mg/kg):	Sham	Aspirin**	12	56	210	1200
Pregnancies						
Total No.	24	20	22	23	22	22
Died or aborted (before Day 20)	4	2	1	1	0	6
To term (on Day 20)	21	18	21	22	22	15
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	21	17	21	22	22	15
Implant sites						
Total No. (at term)	218	194	238	256	225	170
Average/dam*	10.4	10.8	11.3	11.6	10.2	11.3
Resorptions						
Total No.*	5	18	7	5	4	1
Dams with 1 or more sites resorbed	4	7	5	3	3	1
Dams with all sites resorbed	0	1	0	0	0	0
Per cent partial resorptions	19.0	38.9	23.8	13.6	13.6	6.67
Per cent complete resorptions	----	5.55	----	----	----	----
Live fetuses						
Total No. (at term)	213	174	231	251	221	169
Average/dam*	10.1	9.67	11.0	11.4	10.0	11.3
Dead fetuses						
Total No.*	0	2	0	0	0	0
Dams with 1 or more dead	----	1	----	----	----	----
Dams with all dead	----	0	----	----	----	----
Per cent partial dead	----	5.55	----	----	----	----
per cent all dead	----	----	----	----	----	----
Average fetus weight, g	3.97	2.52	3.79	3.95	3.94	3.92

* Includes only those dams examined at term.
** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 | Laboratory No. 0894 b

Table 3

Material FDA 71-12 | Date June 15, 1972

Summary of Skeletal Findings
(Rats)

Findings / Group No. / Dose (mg/kg)	61 Sham	62 Aspirin**	63 12	64 56	65 210	66 1200
Live Fetuses Examined (at term)	148/21	112/17	161/21	172/22	151/22	119/15
Sternebrae						
Incomplete oss.	25/14	60/15	33/18	36/16	45/16	36/10
Scrambled	3/3					
Bipartite		18/9			1/1	2/2
Fused						
Extra		1/1	1/1			
Missing	2/2	74/15	9/4	4/4	14/9	18/6
Other						
Ribs						
Incomplete oss.			1/1		1/1	
Fused/split	1/1	5/3			1/1	
Wavy	6/4	33/11	8/4	6/4	2/2	4/3
Less than 12					2/1	
More than 13	30/14	38/12	17/12		1/1	
Other						
Vertebrae						
Incomplete oss.	9/4	71/16	2/2	10/7	20/8	7/6
Scrambled		6/5				
Fused		2/1				
Extra ctrs. oss.			1/1			
Scoliosis		11/7				
Tail defects						
Other						
Skull						
Incomplete closure	3/2	13/7	17/11	9/8	8/6	11/4
Missing						
Craniostosis						
Other ; exencephally		2/1				
Extremities						
Incomplete oss.		4/3				
Missing						
Extra						
Miscellaneous						
Hyoid; missing	11/8	49/14	21/9	11/4	14/7	20/10
Hyoid; reduced	5/5	10/6	14/11	8/5	11/6	12/5

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 Date June 15, 1972

Material FDA 71-12 Laboratory No. 0894 b

Table 3-a

Summary of Soft Tissue Abnormalities

(Rats)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
62	Aspirin*	250	A 4183	1	Meningoencephalocele
			A 4185	1	Meningoencephalocele
			A 4188	2	Meningoencephalocele, Anopia, Spina bifida
			A 4197	2	Meningoencephalocele, Anopia, Spina bifida
			A 4201	2	Meningoencephalocele Anopia, Spina bifida
			A 4204	4	Meningoencephalocele

*Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66

Species Rats

Date June 15, 1972

Laboratory No. 0894 b

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	20**
		mg/kg	g				
61	Sham	0	213	231	249	272	332 (21)
62	Aspirin***	250	210	229	245	255	305 (18)
63	FDA 71-12	12	219	241	258	280	339 (21)
64	FDA 71-12	56	212	234	251	271	337 (22)
65	FDA 71-12	210	218	240	251	268	330 (22)
66	FDA 71-12	1200	210	239	251	275	332 (15)

* 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 61

Material Sham

Dose 0

Appendix II

Reproduction Data in Rats (Individual)

Date June 15, 1972

Laboratory No. 0894

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 4181	P		11	11		--	--		3.81	
S 4182	P		12	12		--	--		3.98	
S 4183	P		10	10		--	--		3.69	
S 4184	P		10	10		--	--		3.72	
S 4185	P		13	13		--	--		4.31	
S 4186	P		9	9		--	--		3.84	
S 4187	P		10	10		7	3		5.34	
S 4188	P		10	9		6	3	1	4.08	
S 4189	P		11	11		7	4		3.84	
S 4190	P		13	13		7	6		3.93	
S 4191	P		10	10		--	--		----	Died Day 15
S 4192	P		9	7		3	4	2	3.44	
S 4193	P		10	10		--	--		----	Died Day 14
S 4194	P		15	0		--	--	15	----	Died Day 17
S 4195	P		9	9		5	4		3.84	
S 4196	NP		0						----	Died Day 13
S 4197	P		12	12		4	8		3.87	
S 4198	P		12	12		6	6		3.90	
S 4199	NP		0						----	
S 4200	NP		0						----	
S 4201	P		10	10		6	4		3.49	
S 4202	P		9	9		5	4		3.74	
S 4203	P		9	9		7	2		4.20	
S 4204	P		13	13		4	9		4.00	
S 4205	P		8	8		5	3		4.12	
S 4206	P		6	5		3	2	1	4.08	
S 4207	P		12	11		5	6	1	4.13	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 62 | Appendix II | Date June 15, 1972

Material Aspirin | Reproduction Data in Rats (Individual) | Laboratory No. 0894

Dose 250 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 4181	P		13	13		--	--		2.43	
A 4182	P		12	12		--	--		2.98	
A 4183	P		10	8		--	--	2	2.17	
A 4184	P		11	11		--	--		2.95	
A 4185	P		10	10		--	--		2.46	
A 4186	P		6	6		--	--		1.96	
A 4187	NP		0						----	
A 4188	P		12	10		5	5	2	1.97	
A 4189	P		14	14		--	--		----	Died Day 18
A 4190	P		13	13		9	4		2.12	
A 4191	P		9			--	--	9	----	
A 4192	P		15	15		8	7		3.21	
A 4193	P		12	12		7	5		3.07	
A 4194	P		10	10		4	6		3.39	
A 4195	P		15	15		--	--		----	Died Day 10
A 4196	P		9	8		5	3	1	2.82	
A 4197	P		10	9		4	5	1	1.98	
A 4198	NP		0						----	
A 4199	NP		0						----	
A 4200	NP		0						----	
A 4201	P		11	7	2	3	4	2	1.92	
A 4202	P		13	13		7	6		2.58	
A 4203	P		5	4		1	3	1	2.56	
A 4204	P		13	13		5	8		2.34	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 63 | Appendix II | Date June 15, 1972

Material FDA 71-12 | Reproduction Data in Rats (Individual) | Laboratory No. 0894 b

Dose 12 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 4001	P		11	11		--	--		3.80	
B 4002	NP		0						----	
B 4003	P		13	13		--	--		4.02	
B 4004	P		5	5		--	--		3.59	
B 4005	P		10	10		--	--		3.76	
B 4006	P		10	10		--	--		4.02	
B 4007	P		8	8		3	5		3.88	
B 4008	P		15	15		9	6		3.81	
B 4009	P		10	10		6	4		3.87	
B 4010	NP		0						----	
B 4011	P		13	13		5	8		3.81	
B 4012	P		6	6		--	--		----	Died Day 15
B 4013	P		12	12		4	8		4.40	
B 4014	P		10	9		5	4	1	3.74	
B 4015	P		9	7		6	1	2	3.72	
B 4016	P		13	13		9	4		3.86	
B 4017	P		11	11		6	5		3.70	
B 4018	P		13	13		5	8		3.73	
B 4019	P		15	15		8	7		2.43	
B 4020	P		11	11		10	1		3.73	
B 4021	P		11	10		3	7	1	3.78	
B 4022	P		10	9		3	6	1	3.70	
B 4023	P		14	12		5	7	2	4.01	
B 4024	P		14	14		5	9		4.14	

* P = Pregnant; NP = Not Pregnant

FOOD A DRUG RESEARCH LABORATORIES, INC.

Group 64

Appendix II

Date June 15, 1972

Material FDA 71-12

Reproduction Data in Rats (Individual)

Laboratory No. 0894 b

Dose 56 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 4031	P		13	11		--	--	2	3.58	
B 4032	P		15	15		--	--		3.75	
B 4033	P		12	12		--	--		3.94	
B 4034	P		10	10		6	4		4.09	
B 4035	P		12	12		6	6		4.16	
B 4036	P		8	8		4	4		3.85	
B 4037	P		11	11		5	6		3.77	
B 4038	P		10	10		6	4		4.06	
B 4039	P		12	12		5	7		5.69	
B 4040	P		8	8		3	5		4.22	
B 4041	P		13	13		9	4		4.01	
B 4042	P		10	10		4	6		3.66	
B 4043	P		14	14		4	10		3.76	
B 4044	P		14	14		8	6		3.80	
B 4045	P		10	8		5	3	2	4.02	
B 4046	P		11	11		3	8		3.75	
B 4047	P		12	12		6	6		3.47	
B 4048	P		12	12		7	5		3.64	
B 4049	P		14			--	--	14	----	Died Day 15
B 4050	P		11	10		--	--	1	3.67	
B 4051	P		12	12		7	5		3.74	
B 4052	P		13	13		8	5		4.29	
B 4053	P		13	13		5	8		3.87	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 65 | Appendix II | Date June 15, 1972

Material FDA 71-12 | Reproduction Data in Rats (Individual) | Laboratory No. 0894 b

Dose 210 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 4061	P		11	10		--	--	1	3.73	
B 4062	P		7	6		--	--	1	4.09	
B 4063	P		13	13		7	6		4.44	
B 4064	P		11	11		9	2		4.41	
B 4065	NP		0						----	
B 4066	P		12	12		6	6		3.89	
B 4067	P		12	12		3	9		3.32	
B 4068	P		9	9		5	4		4.07	
B 4069	P		9	9		3	6		5.95	
B 4070	P		11	11		3	8		3.63	
B 4071	P		9	9		5	4		4.02	
B 4072	P		11	9		3	6	2	3.95	
B 4073	P		12	12		6	6		3.94	
B 4074	P		10	10		2	8		3.91	
B 4075	P		9	9		2	7		3.73	
B 4076	P		5	5		1	4		3.23	
B 4077	P		13	13		8	5		3.54	
B 4078	P		12	12		6	6		3.84	
B 4079	P		8	8		3	5		3.71	
B 4080	P		9	9		6	3		4.29	
B 4081	P		13	13		8	5		3.73	
B 4082	P		10	10		3	7		3.81	
B 4083	P		9	9		4	5		3.42	

* P = Pregnant; NP = Not Pregnant

FOOD A DRUG RESEARCH LABORATORIES, INC.

Group 66 | Appendix II | Date June 15, 1972

Material FDA 71-12 | Reproduction Data in Rats (Individual) | Laboratory No. 0894 b

Dose 1200 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks **
B 4091	P		12	12		--	--		----	Died Day 9
B 4092	P		15	14		--	--	1	3.51	
B 4093	NP		0						----	
B 4094	P		10	10		6	4		4.14	
B 4095	NP		0						----	Died Day 8
B 4096	P		11	11		7	4		3.84	
B 4097	P		12	12		7	5		4.31	
B 4098	P		13	13		5	8		4.02	
B 4099	P		12	12		--	--		----	Died Day 11
B 4100	P		9	9		4	5		3.83	
B 4101	P		8	8		5	3		4.03	
B 4102	P		11	11		--	--		----	Died Day 14
B 4103	P		12	12		--	--		----	Died Day 11
B 4104	P		13	13		7	6		3.13	
B 4105	P		12	12		3	9		3.71	
B 4106	P		8	8		4	4		3.57	
B 4107	P		13	13		9	4		3.76	
B 4108	P		10	10		5	5		3.79	
B 4109	P		11	11		7	4		4.02	
B 4110	P		11	11		5	6		5.14	
B 4111	P		14	14		8	6		4.02	
B 4112	P		11	11		--	--		----	Died Day 3

* P = Pregnant; NP = Not Pregnant
** Toxic death (see page 1)

HAMSTERS

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INCORPORATED

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FINAL REPORT

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

Date August 1, 1972

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

Sample: Fine light tan powdered material

Marking: FDA 71-12 (Gum tragacanth)

Examination Requested: Teratologic evaluation of FDA 71-12 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 900 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernable 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 seventh of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at leat 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

Kenneth Morgareidge, Ph.D.
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 61 through 66

Material: FDA 71-12

Date June 15, 1972

Laboratory No. 0895 b

Table 1

Fate Summary
(Hamsters)

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
61	Sham	0	21	20	20	19
62	Aspirin*	250	21	20	20	19
63	FDA 71-12	9	22	20	22	20
64	FDA 71-12	42	21	20	21	20
65	FDA 71-12	185	22	20	22	20
66	FDA 71-12	900	22	20	22	20

* 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: 61 through 66

Date June 15, 1972

Material: FDA 71-12

Laboratory No. 0895 b

Table 2
Reproduction Data
(Hamsters)

Group:	61	62	63	64	65	66
Dose (mg/kg):	Sham	Aspirin**	9	42	185	900
Pregnancies						
Total No.	20	20	20	20	20	20
Died or aborted (before Day 14)	1	1	0	0	0	0
To term (on Day 14)	19	19	20	20	20	20
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	19	19	20	20	20	20
Implant sites						
Total No. (at term)	242	238	256	240	273	260
Average/dam*	12.7	12.5	12.8	12.0	13.7	13.0
Resorptions						
Total No.*	5	11	5	8	4	14
Dams with 1 or more sites resorbed	3	9	4	4	3	8
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	15.8	47.4	20.0	20.0	15.0	40.0
Per cent complete resorptions	----	----	----	----	----	----
Live fetuses						
Total No. (at term)	236	226	249	230	269	246
Average/dam*	12.4	11.9	12.5	11.5	13.5	12.3
Dead fetuses						
Total No.*	1	1	2	2	0	0
Dams with 1 or more dead	1	1	2	2	----	----
Dams with all dead	0	0	0	0	----	----
Per cent partial dead	5.26	5.26	10.0	10.0	----	----
per cent all dead	----	----	----	----	----	----
Average fetus weight, g	1.83	1.84	1.84	1.84	1.85	1.81

* Includes only those dams examined at term.
** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 | Laboratory No. 0895 b

Table 3.

Material FDA 71-12 | Date June 15, 1972

Summary of Skeletal Findings*
(Hamsters)

Findings	Group No.	61	62	63	64	65	66
	Dose (mg/kg)	Sham	Aspirin**	9	42	185	900
Live Fetuses Examined (at term)		161/19	156/19	172/20	160/20	184/20	167/20
Sternebrae							
Incomplete oss.		71/17	65/15	74/17	56/19	66/18	45/18
Scrambled							
Bipartite		33/14	25/15	27/13	22/10	28/15	20/12
Fused							
Extra			7/2	9/4		20/7	2/2
Missing		59/14	26/12	18/6	13/8	9/4	14/8
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy			1/1				
Less than 12							
More than 13		19/10	43/12	47/18	23/11	67/18	35/15
Other							
Vertebrae							
Incomplete oss.							
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis			6/3				2/2
Tail defects							
Other							
Skull							
Incomplete closure			2/2				
Missing							
Craniostosis							
Other; exencephally					1/1		
Extremities							
Incomplete oss.			1/1			2/1	
Missing							
Extra							
Miscellaneous							
Hyoid; missing		3/2	2/1			1/1	
Hyoid; reduced		3/3	4/3	2/2		2/2	2/2

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 Date June 15, 1972

Material FDA 71-12 Laboratory No. 0895 b

Table 3-a

Summary of Soft Tissue Abnormalities

(Hamsters)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
62	Aspirin*	250	A 5188	1	Thoracic Subcutaneous Hematoma
63	FDA 71-12	9	B 5014	15	Meningoencephalocele
64	FDA 71-12	42	B 5045	3	Meningoencephalocele
65	FDA 71-12	185	B 5068	1	Cranial Subcutaneous Hematoma
66	FDA 71-12	900	B 5094	1	Cranial Subcutaneous Hematoma

*Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66

Species Hamsters

Date June 15, 1972

Laboratory No. 0895 b

Table 4

Average Body Weights *

Group	Material	Dose Level mg/kg	Day 0 (g)	6	8	10	14**
61	Sham	0	104.6	109.1	111.2	123.2	148.2 (19)[a]
62	Aspirin***	250	109.3	110.5	110.0	121.2	145.8 (19)[a]
63	FDA 71-12	9	110.0	111.4	114.3	124.5	148.3 (20)
64	FDA 71-12	42	107.8	110.0	114.0	124.7	146.6 (20)
65	FDA 71-12	185	112.5	112.6	115.6	127.8	152.2 (20)
66	FDA 71-12	900	111.6	112.8	115.9	125.3	148.2 (20)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive Control
[a] Average based on weights of 18 dams only

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 sketal abnormalities.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 61

Appendix II

Date June 15, 1972

Material Sham

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895

Dose 0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M**	Sex F**	Resorption Sites	Average Fetus Weight (g)	Remarks
S 5181	P		12	12					2.25	
S 5182	P		19	17				2	1.76	
S 5183	P		9	9					1.85	
S 5184	P		11	11					2.09	Aborted Day 13
S 5185	P		13	13					1.84	
S 5186	P		13	11				2	1.90	
S 5187	P		14	14					1.73	
S 5188	P		14	13				1	2.08	
S 5189	P		13	13					1.86	
S 5190	P		11	11					1.95	
S 5191	P		10	10					1.91	
S 5192	P		13	13					2.12	
S 5193	P		13	12	1				1.51	
S 5194	NP		0						--	
S 5195	P		9	9					2.00	
S 5196	P		15	15					1.54	
S 5197	P		12	12					1.95	
S 5198	P		12	12					1.63	
S 5199	P		12	12					1.66	
S 5200	P		12	12					1.52	
S 5201	P		16	16					1.79	

* P = Pregnant; NP = Not Pregnant

** Not recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 62

Appendix II

Date June 15, 1972

Material Aspirin

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895

Dose 250 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M**	Sex F**	Resorption Sites	Average Fetus Weight (g)	Remarks
A 5181	P		11	11					2.29	
A 5182	P		14	14					2.10	
A 5183	P		16	15				1	1.77	
A 5184	P		15	15					1.60	
A 5185	P		15	13				2	1.85	
A 5186	P		12	12						Aborted Day 13
A 5187	P		13	13					1.73	
A 5188	P		12	12					1.74	
A 5189	P		13	13					1.76	
A 5190	P		13	12				1	2.06	
A 5191	P		12	11				1	2.06	
A 5192	P		10	9				1	1.73	
A 5193	P		10	9				1	1.54	
A 5194	P		14	13	1				1.82	
A 5195	P		11	10				1	1.65	
A 5196	P		10	10					2.03	
A 5197	P		16	15				1	1.77	
A 5198	P		10	10					1.94	
A 5199	NP		0						--	
A 5200	P		13	13					1.94	
A 5201	P		10	8				2	1.59	

* P = Pregnant; NP = Not Pregnant

** Not recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 63 | Appendix II | Date June 15, 1972

Material FDA 71-12 | Reproduction Data in Hamsters (Individual) | Laboratory No. 0895b

Dose 9 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M**	Sex F**	Resorption Sites	Average Fetus Weight (g)	Remarks
B 5001	P		7	7					2.66	
B 5002	NP		0						--	
B 5003	P		12	12					1.58	
B 5004	P		13	13					1.92	
B 5005	P		12	10				2	2.17	
B 5006	P		11	11					1.85	
B 5007	P		15	15					1.89	
B 5008	P		13	12	1				1.91	
B 5009	P		12	12					1.54	
B 5010	P		14	14					1.73	
B 5011	P		14	14					1.72	
B 5012	P		14	12	1			1	1.62	
B 5013	P		13	13					1.55	
B 5014	P		15	15					1.64	
B 5015	P		9	9					2.32	
B 5016	P		14	14					1.55	
B 5017	P		14	14					1.73	
B 5018	P		14	13				1	1.85	
B 5019	P		14	14					1.80	
B 5020	P		17	17					1.98	
B 5021	NP		0						--	
B 5022	P		9	8				1	1.83	

* P = Pregnant; NP = Not Pregnant
** Not recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 64

Appendix II

Date June 15, 1972

Material FDA 71-12

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895b

Dose 42 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M**	Sex F**	Resorption Sites	Average Fetus Weight (g)	Remarks
B 5031	P		12	12					1.93	
B 5032	P		11	11					1.91	
B 5033	P		14	13	1				1.79	
B 5034	NP		0						--	
B 5035	P		13	13					2.00	
B 5036	P		11	11					2.00	
B 5037	P		13	13					2.00	
B 5038	P		12	10				2	2.08	
B 5039	P		8	8					1.91	
B 5040	P		10	9				1	1.83	
B 5041	P		13	12	1				1.71	
B 5042	P		11	9				2	1.61	
B 5043	P		13	13					1.69	
B 5044	P		14	14					1.65	
B 5045	P		10	7				3	1.41	
B 5046	P		11	11					2.02	
B 5047	P		14	14					1.75	
B 5048	P		11	11					1.65	
B 5049	P		13	13					1.87	
B 5050	P		12	12					2.10	
B 5051	P		14	14					1.84	

* P = Pregnant; NP = Not Pregnant

** Not recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 65

Appendix II

Date June 15, 1972

Material FDA 71-12

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895b

Dose 185 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M**	Sex F**	Resorption Sites	Average Fetus Weight (g)	Remarks
B 5061	P		12	11				1	1.75	
B 5062	P		12	12					1.49	
B 5063	NP		0						--	
B 5064	P		11	9				2	2.17	
B 5065	P		14	14					1.89	
B 5066	P		14	14					1.93	
B 5067	P		13	13					2.10	
B 5068	P		12	12					2.15	
B 5069	P		14	14					1.61	
B 5070	P		14	14					1.81	
B 5071	P		15	15					1.89	
B 5072	NP		0						--	
B 5073	P		14	13				1	1.41	
B 5074	P		14	14					1.76	
B 5075	P		11	11					1.95	
B 5076	P		14	14					1.86	
B 5077	P		15	15					2.11	
B 5078	P		15	15					1.84	
B 5079	P		14	14					1.74	
B 5080	P		15	15					1.78	
B 5081	P		12	12					1.80	
B 5082	P		18	18					2.03	

* P = Pregnant; NP = Not Pregnant
** Not recorded

FOOD A. DRUG RESEA. H LABORATORI, INC.

Group 66

Material FDA 71-12

Dose 900 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date June 15, 1972

Laboratory No. 0895b

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M**	Sex F**	Resorption Sites	Average Fetus Weight (g)	Remarks
B 5091	P		6	3				3	1.99	
B 5092	P		10	10					1.92	
B 5093	P		14	13				1	1.73	
B 5094	P		14	13				1	1.83	
B 5095	P		12	12					1.95	
B 5096	P		13	13					2.07	
B 5097	P		15	15					1.73	
B 5098	P		11	10				1	2.11	
B 5099	P		12	11				1	1.82	
B 5100	P		11	11					1.77	
B 5101	P		16	15				1	1.85	
B 5102	P		13	13					1.75	
B 5103	P		15	10				5	1.72	
B 5104	P		15	15					1.54	
B 5105	P		13	13					1.70	
B 5106	P		13	13					1.77	
B 5107	NP		0						--	
B 5108	P		16	16					1.83	
B 5109	NP		0						--	
B 5110	P		14	14					1.82	
B 5111	P		15	14				1	1.75	
B 5112	P		12	12					1.46	

* P = Pregnant; NP = Not Pregnant
** Not recorded

RABBITS

Food and Drug Research Laboratories
INCORPORATED

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FINAL REPORT

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

Date August 1, 1972

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

Sample: Fine light tan powdered material

Marking: FDA 71-12 (Gum tragacanth)

Examination Requested: Teratologic evaluation of FDA 71-12 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination of the data, it is tentatively concluded that:

"The administration of up to 33 mg/kg (body weight) of the test material as a suspension in anhydrous corn oil to pregnant rabbits for 13 consecutive days had no discernable effect on nidation or on maternal or fetal survival. The number and type of abnormalities seen in fetal soft or skeletal tissues derived from this group of does did not differ from the number occurring spontaneously in the sham-treated controls. However, in 2 groups of dams dosed at 150 and 700 mg/kg (body weight), significant maternal toxicity ensued with the loss of a majority of the animals. Death was preceded by severe bloody diarrhea and urinary incontinence with anorexia for 48 to 72 hours terminally. At autopsy, no gross pathological findings were seen other than marked hemorrhage in the mucosa of the small intestine. Does which survived this high dose and bore living young to term remained outwardly normal and the offspring were likewise normal in all respects. It is concluded that this test substance was not a teratogen in the rabbit.

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.

Comment: Attention is called to the fact that this is the seventh 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: 61 through 66

Material: FDA 71-12

Date June 15, 1972

Laboratory No. 0896 b

Table 1

Fate Summary
(Rabbits)

Group	Material	Dose ** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
61	Sham	0	15	13	12	10
62	6-AN	2.5	15	10	14	9
63	FDA 71-12	7.0	15	13	14	12
64	FDA 71-12	33.0	15	10	12	9
65	FDA 71-12	150.0	15	10	9	7
66	FDA 71-12	700.0	15	12	6	5

* Positive Control: 6-amino nicotinamide dosed on Day 9
** Administered as a suspension in anhydrous corn oil; 1.o ml per kg of body weight

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 61 through 66

Date June 15, 1972

Material: FDA 71-12

Laboratory No. 0896 b

Table 2
Reproduction Data
(Rabbits)

Group:	61	62	63	64	65	66
Dose (mg/kg):	Sham	6-AN**	7.0	33	150	700
Pregnancies						
Total No.	13	10	13	10	10	10
Died or aborted (before Day 29)	3	1	1	1	6	9
To term (on Day 29)	10	9	12	9	7	5
Corpora lutea						
Total No.	161	154	196	166	167	157
Average/dam mated	10.7	10.3	13.1	11.1	11.1	10.5
Live litters						
Total No.*	10	8	12	9	7	5
Implant sites						
Total No. (at term)	47	49	61	50	48	27
Average/dam*	4.70	5.44	5.08	5.55	6.86	5.40
Resorptions						
Total No.*	7	17	6	17	3	3
Dams with 1 or more sites resorbed	3	8	4	5	1	2
Dams with all sites resorbed	0	1	0	0	0	0
Per cent partial resorptions	30.0	88.9	33.3	55.6	14.3	40.0
Per cent complete resorptions	----	11.1	----	----	----	----
Live fetuses						
Total No. (at term)	40	31	55	33	45	24
Average/dam*	4.00	3.44	4.58	3.67	6.43	4.80
Dead fetuses						
Total No.*	0	1	0	0	0	0
Dams with 1 or more dead	----	1	----	----	----	----
Dams with all dead	----	0	----	----	----	----
Per cent partial dead	----	11.1	----	----	----	----
per cent all dead	----	----	----	----	----	----
Average fetus weight, g	36.1	32.4	37.5	41.6	38.2	33.8

* Includes only those dams examined at term.

** Positive control: 2.5 mg/kg 6-amino nicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 | Laboratory No. 0896 b

Table 3

Material FDA 71-12 | Date June 15, 1972

Summary of Skeletal Findings *
(Rabbits)

Findings	Group No.	61	62	63	64	65	66
	Dose (mg/kg)	Sham	6-AN**	7.0	33.0	150.0	700.0
Live Fetuses Examined (at term)		40/10	29/8	51/12	33/9	45/7	24/5
Sternebrae							
Incomplete oss.		3/1	4/3	2/2	2/2	2/1	
Scrambled			1/1				
Bipartite		3/3	5/5	2/2			
Fused		3/2	6/6	6/4	4/2	2/2	
Extra			1/1	1/1	1/1	1/1	
Missing							
Other							
Ribs							
Incomplete oss.							
Fused/split			2/2				
Wavy			3/1				
Less than 12							
More than 13							
Other							
Vertebrae							
Incomplete oss.							
Scrambled			9/5				
Fused							
Extra ctrs. oss.							
Scoliosis			7/4	1/1			
Tail defects			21/5				
Other							
Skull							
Incomplete closure							1/1
Missing							
Craniostosis			1/1				
Other							
Extremities							
Incomplete oss.							
Missing							
Extra							
Miscellaneous							

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
** Positive control at 2.5 mg/kg 6 amino nicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 Date June 15, 1972

Material FDA 71-12 Laboratory No. 0896 b

Table 3-a

Summary of Soft Tissue Abnormalities

(Rabbit)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
62	6-AN*	2.5	Z 6092	8	Anopia
				4	Club feet
			Z 6094	4	Anopia Club feet
			Z 6097	3	Anopia, club feet, cleft palate, hair lip
			Z 6100	4	Anopia Club feet
			Z 6101	1	Anopia

*6-amino nicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66

Species Rabbits

Date June 15, 1972

Laboratory No., 0896 b

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	Day 6	Day 12	Day 18	Day 29**
		mg/kg	kg				
61	Sham	0.0	2.23	2.26	2.31	2.35	2.44 (10)
62	6-AN**	2.5	2.40	2.42	2.37	2.45	2.51 (9)
63	FDA 71-12	7.0	2.41	2.47	2.48	2.51	2.59 (12)[a]
64	FDA 71-12	33.0	2.37	2.39	2.42	2.49	2.62 (9)
65	FDA 71-12	150.0	2.25	2.33	2.35	2.41	2.55 (7)
66	FDA 71-12	700.0	2.12	2.17	2.12	2.12	2.46 (5)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive Control: 6-amino nicotinamide dosed on Day 9
a) Average based on weights of 11 does only

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.

FOOD A DRUG RESEARCH LABORATORIES, INC.

Group 61

Material Sham

Dose 0.0

Appendix II

Reproduction Data in Rabbits (Individual)

Date June 15, 1972

Laboratory No. 0896

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 6091	P	15	8	8		2	6		36.4	
S 6092	NP	7	0						----	
S 6093	P	6	1	1		--	--		----	Died Day 13
S 6094	P	20	6	6		2	4		37.1	
S 6095	P	9	3	1		0	1	2	36.8	
S 6096	P	9	4	4		1	3		38.5	
S 6097	P	13	5	3		1	2	2	34.7	
S 6098	NP	3	0						----	
S 6099	P	13	6	6		2	4		39.2	
S 6100	P	8	3	3		0	3		24.0	
S 6101	P	12	5	2		1	1	3	36.7	
S 6102	P	14	6	6		--	--		----	Died Day 14
S 6103	P	14	4	4		1	3		36.4	
S 6104	P	9	4	4		--	--		----	Died Day 13
S 6105	P	9	3	3		1	2		40.9	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 62

Appendix II

Date June 15, 1972

Material 6-AN

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896

Dose 2.5 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Z 6091	NP	4	0						----	
Z 6092	P	21	9	8		3	5	1	33.8	
Z 6093	P	14	5	5		--	--		----	Died Day 22
Z 6094	P	20	10	8	1	2	6	1	26.8	
Z 6095	P	8	2			--	--	2	----	
Z 6096	NP	7	0						----	
Z 6097	P	11	6	3		1	2	3	27.1	
Z 6098	NP	5	0						----	
Z 6099	NP	6	0						----	
Z 6100	P	13	8	4		1	3	4	33.8	
Z 6101	P	12	5	1		0	1	4	32.1	
Z 6102	P	8	3	2		1	1	1	36.4	
Z 6103	P	7	4	3		-	1-	1	37.8	
Z 6104	NP	8	0						----	
Z 6105	P	10	2	2		1	1		31.6	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 63

Material FDA 71-12

Dose 7.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date June 15, 1972

Laboratory No. 0896 b

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 6001	P	10	1	1		0	1		37.5	
B 6002	NP	1	0						----	
B 6003	P	15	6	6		1	5		39.8	
B 6004	P	11	5	5		2	3		35.8	
B 6005	P	25	10	10		2	8		34.5	
B 6006	P	10	5	4		1	3	1	30.9	
B 6007	P	14	4	3		1	2	1	40.5	
B 6008	P	17	9	9		3	6		32.5	
B 6009	P	26	4	4					----	Aborted Day 20
B 6010	P	13	8	8		2	6		38.4	
B 6011	P	15	2	2		2	0		40.5	
B 6012	NP	9	0						----	
B 6013	P	10	5	4		0	4	1	37.4	
B 6014	P	11	2	2		1	1		40.6	
B 6015	P	9	4	1		1	0	3	41.8	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 64

Appendix II

Date June 15, 1972

Material FDA 71-12

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 b

Dose 33.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
B 6016	P	8	3	3		--	--		----	Died Day 14
B 6017	NP	15	0						----	
B 6018	P	12	3	3		1	2		41.6	
B 6019	NP	10	0						----	Died Day 10
B 6020	P	12	5	5		2	3		42.5	
B 6021	P	15	7	2		0	2	5	42.8	
B 6022	NP	13	0						----	
B 6023	P	16	7	7		1	6		40.5	
B 6024	P	13	8	8		3	5		32.9	
B 6025	P	10	6	2		0	2	4	53.4	
B 6026	NP	7	0						----	
B 6027	P	9	3	2		1	1	1	34.6	
B 6028	P	12	7	1		0	1	6	43.7	
B 6029	NP	3	0						----	Died Day 17
B 6030	P	11	4	3		2	1	1	42.6	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES INC.

Group 65

Appendix II

Date June 15, 1972

Material FDA 71-12

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 b

Dose 150.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks**
B 6031	P	12	7	7		2	5		37.7	
B 6032	NP	5	0						----	
B 6033	NP	3	0						----	
B 6034	NP	4	0						----	Died Day 29
B 6035	P	7	5			--	--	5	----	Aborted Day 16
B 6036	P	14	10	10		4	6		41.7	
B 6037	P	21	9	9		--	--		----	Died Day 10
B 6038	P	12	6	6		1	5		39.4	
B 6039	P	13	8	8		4	4		34.4	
B 6040	NP	11	0						----	Died Day 15
B 6041	P	13	5	5		--	--		----	Died Day 11
B 6042	P	17	5	5		2	3		41.6	
B 6043	P	20	8	8		4	4		35.1	
B 6044	NP	7	0						----	Died Day 27
B 6045	P	8	4	1		0	1	3	37.5	

* P = Pregnant; NP = Not Pregnant

** Toxic death (See Page 1)

FOOD AND DRUG RESEARCH LABORATORIES INC.

Group 66

Appendix II

Date June 15, 1972

Material FDA 71-12

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 b

Dose 700.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks**
B 6046	NP	8	0						----	Died Day 19
B 6047	P	13	8	8		2	6		26.8	
B 6048	P	16	2	2		--	--		----	Died Day 19
B 6049	NP	13	0						----	Died Day 11
B 6050	NP	5	0						----	
B 6051	P	12	4	4		3	1		32.4	
B 6052	P	10	5	5		--	--		----	Died Day 9
B 6053	P	10	3	3		--	--		----	Died Day 12
B 6054	P	8	4	4		--	--		----	Died Day 12
B 6055	P	10	7	7		--	--		----	Died Day 16
B 6056	P	14	5	5		--	--		----	Died Day 18
B 6057	P	12	3	3		--	--		----	Died Day 9
B 6058	P	14	5	4		2	2	1	44.9	
B 6059	P	14	7	7		4	3		36.6	
B 6060	P	8	3	1		0	1	2	28.2	

* P = Pregnant; NP = Not Pregnant

** Toxic death (See Page 1)