Final report-Teratologic Evaluation of FDA 71-57 (Menthol Natural Brazilian) in Mice, Rats & Hamsters 6/1/73

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FOOD AND DRUG LABORATORIES, INC.

MAURICE AVENUE AT 58TH STREET MASPETH, NEW YORK 11378

FINAL

June 1, 1973

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Teratologic Evaluation of FDA 71-57

(Menthol Natural Brazilian)

in

Mice, Rats, and Hamsters

MICE

NATIONAL
23-280—Colored Tabs
23-281—Clear Tabs
Made in U. S. A.

Food and Drug Research Laboratories
INCORPORATED

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

FINAL REPORT

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

Date June 1, 1973

Laboratory No. 1573 k
Contract No. FDA 71-260

Sample: White needle-like crystalline material

Marking: FDA 71-57 (Menthol Natural Brazilian)

Examination Requested: Teratologic evaluation of FDA 71-57 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion:

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

"The administration of up to 185 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."

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: 251 through 256

Material: FDA 71-57

Date: April 28, 1973

Laboratory No.: 1573 k

Table 1

Fate Summary
(Mice)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
251	Sham	0.0	25	23	25	23
252	Aspirin*	150.0	25	23	25	23
253	FDA 71-57	1.85	28	22	28	22
254	FDA 71-57	8.59	25	22	25	22
255	FDA 71-57	39.9	23	22	23	22
256	FDA 71-57	185.0	25	22	25	22

* Positive Control: 150.0 mg/kg

** Administered as a corn oil solution (See Appendix I); 10 ml per kg of body weight

1) Includes all dams examined at term

FOOD AND DRUG RESEAR LABORATORIES, INC.

Group: 251 through 256

Date: April 28, 1973

Material: FDA 71-57

Laboratory No. 1573 k

Table 2
Reproduction Data
(Mice)

Group:	251	252	253	254	255	256
Dose (mg/kg):	Sham	Aspirin**	1.85	8.59	39.9	185.0
Pregnancies						
Total No.	23	23	22	22	22	22
Died or Aborted (before Day 17)	0	0	0	0	0	0
To term (on Day 17)	23	23	22	22	22	22
Live Litters						
Total No.*	23	23	21	21	22	22
Implant Sites						
Total No.	263	261	241	256	274	260
Average/dam*	11.4	11.4	11.0	11.6	12.5	11.8
Resorptions						
Total No.*	13	7	24	20	7	14
Dams with 1 or more sites resorbed	7	7	11	11	5	6
Dams with all sites resorbed	--	--	1	1	--	--
Per cent partial resorptions	30.4	30.4	50.0	50.0	22.7	27.3
Per cent complete resorptions	--	--	4.55	4.55	--	--
Live Fetuses						
Total No.	247	254	217	231	266	243
Average/dam*	10.7	11.0	9.86	10.5	12.1	11.1
Sex ratio (M/F)	0.93	0.78	0.83	0.72	0.74	0.83
Dead Fetuses						
Total*	3	--	--	5	1	3
Dams with 1 or more dead	3	--	--	4	1	3
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	13.0	--	--	18.2	4.55	13.6
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.94	0.87	0.90	0.89	0.92	0.93

* Includes only those dams examined at term.
** Positive Control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256 | Laboratory No. 1573 k

Table 3

Material FDA 71-57 | Date April 28, 1973

Summary of Skeletal Findings*
(Mice)

Findings / Group No.:	251	252	253	254	255	256
Dose (mg/kg):	Sham	Aspirin**	1.85	8.59	39.9	185.0
Live Fetuses Examined (at term)	169/23	175/23	221/21	159/21	185/22	169/22
Sternebrae						
Incomplete oss.	53/16	101/21	55/15	69/17	58/15	50/17
Scrambled						
Bipartite	1/1	5/5	5/5	1/1	2/2	5/5
Fused						1/1
Extra	2/2	1/1		1/1		4/2
Missing	13/7	42/11	16/8	15/7	12/5	10/5
Other						
Ribs						
Incomplete oss.						
Fused/split		1/1	1/1			
Wavy						
Less than 12						
More than 13	49/16	43/17	33/12	38/10	43/18	44/15
Other						
Vertebrae						
Incomplete oss.		10/5	7/4	5/5	5/3	4/1
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	4/2	9/4	4/4	5/3		
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.	1/1	12/5	7/5	8/4	6/3	4/2
Missing	1/1					
Extra						
Miscellaneous						
Hyoid; missing	24/11	60/13	31/12	43/15	31/13	45/15
Hyoid; reduced	21/12	26/15	16/9	23/13	22/13	16/11

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

** Positive control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256 Date April 28, 1973

Material FDA 71-57 Laboratory No. 1573 k

Table 3-a

Summary of Soft Tissue Abnormalities

(Mice)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
251	Sham	0.0	S 3817	1	Atelocardia
			S 3820	1	Atelocardia
252	Aspirin*	150.0	A 3837	1	Anophthalmia
253	FDA 71-57	1.85	K 3017	1	Anophthalmia
			K 3019	1	Gastroschisis
			K 3022	1	Harelip; anophthalmia; encephalomeningocele
254	FDA 71-57	8.59	K 3049	2	Anophthalmia
255	FDA 71-57	39.9	K 3080	1	Encephalomeningocele

* Positive Control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256

Date April 28, 1973

Table 4

Species Mice

Laboratory No. 1573 k

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	17**
		mg/kg	g				
251	Sham	0.0	29.7	32.7	35.5	43.8	50.0 (23)
252	Aspirin***	150.0	27.0	30.7	33.3	41.3	46.8 (23)
253	FDA 71-57	1.85	28.0	31.3	35.0	41.9	47.2 (22)
254	FDA 71-57	8.59	28.6	31.5	35.3	42.5	48.3 (22)
255	FDA 71-57	39.9	28.5	31.2	35.9	44.2	50.3 (22)
256	FDA 71-57	185.0	29.8	33.2	36.7	44.4	49.1 (22)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 150.0 mg/kg

Appendix I

Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were gang-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 251

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 28, 1973

Laboratory No. 1573

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 3816	P	10	8		6	2	2	0.94	
S 3817	P	10	10		6	4		0.76	
S 3818	P	11	11		7	4		1.02	
S 3819	P	12	12		8	4		1.14	
S 3820	NP	0						----	
S 3821	P	14	13		9	4	1	0.90	
S 3822	P	12	12		7	5		1.10	
S 3823	P	11	7		3	4	4	0.87	
S 3824	P	14	12	1	--**	--**	1	1.07	
S 3825	P	12	12		4	8		0.84	
S 3826	P	11	11		4	7		0.78	
S 3827	P	14	14		5	9		0.98	
S 3828	P	10	9		4	5	1	0.97	
S 3829	P	4	1		1	0	3	1.16	
S 3830	P	11	10	1	4	6		0.78	
S 3831	P	9	9		6	3		1.30	
S 3832	P	13	12		6	6	1	0.81	
S 3833	P	10	10		3	7		0.86	
S 3834	P	13	13		7	6		0.84	
S 3835	P	16	15	1	5	10		0.75	
S 3836	P	10	10		5	5		0.87	
S 3837	P	10	10		3	7		0.94	
S 3838	NP	0						----	
S 3839	P	11	11		3	8		0.81	
S 3840	P	15	15		7	8		1.02	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 252

Material Aspirin

Dose 150.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 28, 1973

Laboratory No. 1573

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 3816	P	10	10		6	4		0.97	
A 3817	P	9	9		4	5		0.92	
A 3818	NP	0						----	
A 3819	NP	0						----	
A 3820	P	9	9		4	5		0.85	
A 3821	P	10	9		5	4	1	0.81	
A 3822	P	11	11		7	4		0.99	
A 3823	P	11	11		5	6		0.80	
A 3824	P	12	12		4	8		0.76	
A 3825	P	9	9		4	5		0.83	
A 3826	P	11	11		4	7		0.79	
A 3827	P	13	13		5	8		0.82	
A 3828	P	11	10		--**	--**	1	0.66	
A 3829	P	12	12		6	6		1.25	
A 3830	P	14	13		5	8	1	0.79	
A 3831	P	11	10		4	6	1	0.77	
A 3832	P	14	13		6	7	1	0.74	
A 3833	P	12	12		5	7		0.82	
A 3834	P	11	10		2	8	1	0.87	
A 3835	P	12	12		7	5		0.89	
A 3836	P	10	10		4	6		0.72	
A 3837	P	10	10		5	5		1.10	
A 3838	P	13	12		5	7	1	0.84	
A 3839	P	15	15		7	8		0.81	
A 3840	P	11	11		3	8		1.22	

* P = Pregnant; NP = Not Pregnant

** Not all recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 253

Material FDA 71-57

Dose 1.85 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 28, 1973

Laboratory No. 1573 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 3001	P	10	9		3	6	1	1.01	
K 3002	P	9	8		4	4	1	1.09	
K 3003	NP	0						----	
K 3004	NP	0						----	
K 3005	NP	0						----	
K 3006	P	12	9		4	5	3	0.79	
K 3007	P	14	14		7	7		0.73	
K 3008	NP	0						----	
K 3009	P	12	12		7	5		0.92	
K 3010	P	14	12		9	3	2	0.90	
K 3011	P	12	11		6	5	1	0.85	
K 3012	P	10	10		3	7		0.85	
K 3013	P	11	10		5	5	1	1.08	
K 3014	P	9	8		5	3	1	0.93	
K 3015	P	10					10	----	
K 3016	P	12	12		5	7		0.93	
K 3017	P	9	7		3	4	2	0.70	
K 3018	NP	0						----	
K 3019	P	12	12		3	9		0.92	
K 3020	P	12	12		5	7		0.88	
K 3021	P	8	8		3	5		0.79	
K 3022	P	12	12		3	9		0.91	
K 3023	P	8	8		4	4		0.87	
K 3024	NP	0						----	
K 3025	P	12	12		4	5		1.01	
K 3026	P	10	9		3	6	1	0.80	
K 3027	P	12	12		6	6		0.94	
K 3028	P	11	10		5	5	1	1.01	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 254

Material FDA 71-57

Dose 8.59 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 28, 1973

Laboratory No. 1573 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 3031	P	13	12		3	9	1	0.88	
K 3032	P	13	13		7	6		0.90	
K 3033	P	10	9		4	5	1	0.94	
K 3034	P	13	12	1	5	7		0.99	
K 3035	P	14	14		9	5		0.98	
K 3036	P	12	12		4	8		0.92	
K 3037	P	12	12		4	8		0.81	
K 3038	P	3					3	----	
K 3039	P	11	9	1	3	6	1	0.82	
K 3040	P	11	7		4	3	4	1.02	
K 3041	P	12	10		5	5	2	0.79	
K 3042	NP	0						----	
K 3043	P	11	10		5	5	1	0.95	
K 3044	P	12	12		5	7		0.84	
K 3045	P	11	10		5	5	1	0.94	
K 3046	P	10	10		4	6		0.90	
K 3047	P	13	10		2	8	3	0.87	
K 3048	P	9	9		3	6		0.88	
K 3049	P	12	10	2	5	5		0.85	
K 3050	NP	0						----	
K 3051	NP	0						----	
K 3052	P	13	12	1	3	9		0.71	
K 3053	P	12	12		5	7		0.80	
K 3054	P	15	14		7	7	1	0.96	
K 3055	P	14	12		5	7	2	0.89	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 255

Material FDA 71-57

Dose 39.9 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 28, 1973

Laboratory No. 1573 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 3061	P	14	13		4	9	1	0.85	
K 3062	P	13	13		4	9		0.98	
K 3063									Not Assigned
K 3064	P	10	10		4	6		0.93	
K 3065									Not Assigned
K 3066	P	12	11	1	5	6		0.75	
K 3067	P	12	12		5	7		0.85	
K 3068	P	14	14		10	4		1.21	
K 3069	P	14	14		8	6		0.95	
K 3070	P	14	13		7	6	1	0.95	
K 3071	P	13	12		6	6	1	0.83	
K 3072	P	13	13		4	9		0.76	
K 3073	P	12	12		4	8		0.83	
K 3074	P	13	13		4	9		0.69	
K 3075	P	13	13		6	7		0.76	
K 3076	P	8	8		3	5		1.03	
K 3077	P	13	13		4	9		0.86	
K 3078	P	14	13		5	8	1	0.91	
K 3079	P	12	9		4	5	3	1.14	
K 3080	P	12	12		6	6		0.92	
K 3081	P	14	14		6	8		0.95	
K 3082	P	14	14		6	8		0.98	
K 3083	P	10	10		4	6		0.98	
K 3084	P	10	10		4	6		1.07	
K 3085	NP	0						----	

* P = Pregnant; NP = Not Pregnant

RATS

Food and Drug Research Laboratories
INCORPORATED

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

FINAL REPORT

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

Date June 1, 1973

Laboratory No. 1574 k
Contract No. FDA 71-260

Sample: White needle-like crystalline material

Marking: FDA 71-57 (Menthol Natural Brazilian)

Examination Requested: Teratologic evaluation of FDA 71-57 in rats

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion:

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

"The administration of up to 218 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."

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: 251 through 256

Date: April 28, 1973

Material: FDA 71-57

Laboratory No.: 1574 k

Table 1

Fate Summary
(Rats)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
251	Sham	0.0	25	25	25	25
252	Aspirin*	250.0	25	23	25	23
253	FDA 71-57	2.18	25	22	25	22
254	FDA 71-57	10.15	25	23	25	23
255	FDA 71-57	47.05	25	23	25	23
256	FDA 71-57	218.0	25	22	25	22

* Positive Control: 250.0 mg/kg
** Administered as a corn oil solution (See Appendix I)
1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 251 through 256

Material: FDA 71-57

Date: April 28, 1973

Laboratory No. 1574 k

Table 2
Reproduction Data
(Rats)

Group:	251	252	253	254	255	256
Dose (mg/kg):	Sham	Aspirin**	2.18	10.15	47.05	218.0
Pregnancies						
Total No.	25	23	22	23	23	22
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	25	23	22	23	23	22
Live Litters						
Total No.*	25	19	22	23	23	22
Implant Sites						
Total No.	241	262	256	266	275	250
Average/dam*	9.64	11.4	11.6	11.6	12.0	11.4
Resorptions						
Total No.*	5	79	8	--	2	4
Dams with 1 or more sites resorbed	4	12	3	--	2	4
Dams with all sites resorbed	--	4	--	--	--	--
Per cent partial resorptions	16.0	52.2	13.6	--	8.70	18.2
Per cent complete resorptions	--	17.4	--	--	--	--
Live Fetuses						
Total No.	236	180	248	266	273	246
Average/dam*	9.44	7.83	11.3	11.6	11.9	11.2
Sex ratio (M/F)	0.79	0.87	1.07	0.72	0.82	0.85
Dead Fetuses						
Total*	--	3	--	--	--	--
Dams with 1 or more dead	--	2	--	--	--	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	--	8.70	--	--	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.82	2.49	3.82	3.82	3.85	3.88

* Includes only those dams examined at term.
** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256 | Laboratory No. 1574 k

Table 3

Material FDA 71-57 | Date April 28, 1973

Summary of Skeletal Findings*
(Rats)

Findings / Group No.:	251	252	253	254	255	256
Dose (mg/kg):	Sham	Aspirin**	2.18	10.15	47.05	218.0
Live Fetuses Examined (at term)	167/25	127/19	175/22	183/23	190/23	173/22
Sternebrae						
Incomplete oss.	80/22	94/18	92/20	93/22	101/19	92/19
Scrambled						
Bipartite	1/1	7/6		2/2		1/1
Fused						
Extra						
Missing	14/6	114/19	11/8	17/5	11/4	
Other						
Ribs						
Incomplete oss.		1/1		1/1		
Fused/split		4/3				
Wavy	25/10	64/16	33/13	19/10	21/10	16/8
Less than 12		2/2				
More than 13	3/3	89/18	5/3	2/2	2/2	3/3
Other						
Vertebrae						
Incomplete oss.	9/5	107/19	11/6	12/7	14/7	10/7
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis		1/1				
Tail defects						
Other						
Skull						
Incomplete closure	41/16	114/19	46/15	63/16	67/20	49/17
Missing		1/1				
Craniostosis						
Other						
Extremities						
Incomplete oss.		10/3				
Missing	1/1	1/1				
Extra						
Miscellaneous						
Hyoid; missing	18/13	66/18	18/8	27/12	22/13	15/9
Hyoid; reduced	13/10	10/7	25/11	16/10	20/10	19/7

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256 Date April 28, 1973

Material FDA 71-57 Laboratory No. 1574 k

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
252	Aspirin*	250.0	A 4820	1	Meningoencephalocele; spina bifida
				1	Meningoencephalocele; spina bifida; exophthalmos
			A 4828	1	Meningoencephalocele; spina bifida
			A 4835	1	Meningoencephalocele; spina bifida
			A 4836	2	Meningoencephalocele; spina bifida
			A 4838	1	Meningoencephalocele; spina bifida
254	FDA 71-57	10.15	K 4044	1	Petechiae
			K 4053	1	Anophthalmia
255	FDA 71-57	47.05	K 4064	1	Hydrocephalus; lobster claw
			K 4066	1	Anophthalmia
			K 4072	1	Anophthalmia
			K 4075	1	Gastroschisis
			K 4084	1	Gastroschisis

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256

Date April 28, 1973

Table 4

Species Rats

Laboratory No. 1574 k

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	20**
		mg/kg	g				
251	Sham	0.0	204	225	240	261	316 (25)
252	Aspirin***	250.0	214	238	248	268	298 (23)
253	FDA 71-57	2.18	213	238	257	272	338 (22)
254	FDA 71-57	10.15	223	246	259	278	348 (23)
255	FDA 71-57	47.05	214	236	251	276	348 (23)
256	FDA 71-57	218.0	226	248	261	281	343 (22)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 250.0 mg/kg

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 intubations. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

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

Body weights were recorded on Days 0, 6, 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 251

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 28, 1973

Laboratory No. 1574

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 4816	P	9	9		3	6		3.67	
S 4817	P	8	8		4	4		4.21	
S 4818	P	14	13		4	9	1	3.56	
S 4819	P	12	11		6	5	1	3.86	
S 4820	P	7	7		3	4		3.76	
S 4821	P	13	13		6	7		3.88	
S 4822	P	6	6		2	4		3.91	
S 4823	P	3	3		2	1		4.19	
S 4824	P	12	12		6	6		3.71	
S 4825	P	12	12		7	5		3.99	
S 4826	P	9	9		5	4		3.79	
S 4827	P	8	8		3	5		4.01	
S 4828	P	9	9		2	7		3.37	
S 4829	P	10	10		1	9		3.87	
S 4830	P	7	7		3	4		3.50	
S 4831	P	4	4		2	2		3.48	
S 4832	P	10	8		5	3	2	4.19	
S 4833	P	12	12		5	7		3.47	
S 4834	P	12	12		4	8		3.73	
S 4835	P	9	8		5	3	1	4.29	
S 4836	P	11	11		3	8		3.81	
S 4837	P	14	14		6	8		3.90	
S 4838	P	7	7		4	3		4.16	
S 4839	P	11	11		7	4		3.46	
S 4840	P	12	12		6	6		3.81	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 252

Material Aspirin

Dose 250.0 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 28, 1973

Laboratory No. 1574

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 4816	P	12	12		6	6		3.21	
A 4817	P	17	17		8	9		2.99	
A 4818	NP	0						----	
A 4819	P	12					12	----	
A 4820	P	13	13		5	8		2.05	
A 4821	P	8	2		1	1	6	1.87	
A 4822	P	7					7	----	
A 4823	P	10	9		7	2	1	3.31	
A 4824	P	9	9		6	3		2.96	
A 4825	P	12	11		6	5	1	2.15	
A 4826	P	7					7	----	
A 4827	P	11	11		10	1		2.91	
A 4828	P	10	7		1	6	3	2.06	
A 4829	P	16	16		4	12		3.29	
A 4830	P	8	7		1	6	1	2.16	
A 4831	P	15					15	----	
A 4832	NP	0						----	
A 4833	P	12	4		2	2	8	1.83	
A 4834	P	15	6		2	4	9	2.43	
A 4835	P	10	10		5	5		2.68	
A 4836	P	13	12	1	--**	--**		2.38	
A 4837	P	13	11	2	4	7		2.79	
A 4838	P	11	11		7	4		1.93	
A 4839	P	10	1		0	1	9	1.78	
A 4840	P	11	11		3	8		2.58	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 253

Material FDA 71-57

Dose 2.18 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 28, 1973

Laboratory No. 1574 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 4001	P	12	12		9	3		4.04	
K 4002	P	13	13		4	9		3.57	
K 4003	P	11	5		2	3	6	3.93	
K 4004	P	14	14		6	8		3.65	
K 4005	NP	0						----	
K 4006	P	8	8		5	3		3.83	
K 4007	P	8	8		6	2		4.35	
K 4008	P	12	12		5	7		3.76	
K 4009	P	11	11		6	5		3.78	
K 4010	P	10	10		6	4		3.61	
K 4011	P	9	8		4	4	1	3.49	
K 4012	P	13	12		6	6	1	3.63	
K 4013	NP	0						----	
K 4014	P	13	13		4	9		3.68	
K 4015	P	7	7		2	5		4.19	
K 4016	P	11	11		4	7		3.07	
K 4017	P	10	10		5	5		3.66	
K 4018	P	16	16		9	7		3.83	
K 4019	P	14	14		10	4		4.04	
K 4020	NP	0						----	
K 4021	P	11	11		6	5		4.02	
K 4022	P	13	13		7	6		3.91	
K 4023	P	13	13		9	4		3.78	
K 4024	P	17	17		6	11		3.87	
K 4025	P	10	10		7	3		4.40	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 254

Material FDA 71-57

Dose 10.15 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 28, 1973

Laboratory No. 1574 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 4031	P	12	12		2	10		4.14	
K 4032	P	16	16		8	8		3.95	
K 4033	P	12	12		5	7		3.96	
K 4034	NP	0						----	
K 4035	P	12	12		5	7		3.63	
K 4036	P	8	8		5	3		3.78	
K 4037	P	9	9		3	6		4.22	
K 4038	P	12	12		7	5		3.63	
K 4039	P	12	12		4	8		3.83	
K 4040	NP	0						----	
K 4041	P	12	12		4	8		3.42	
K 4042	P	11	11		4	7		3.65	
K 4043	P	11	11		4	7		3.88	
K 4044	P	10	10		2	8		3.90	
K 4045	P	13	13		3	10		4.16	
K 4046	P	11	11		5	6		3.58	
K 4047	P	14	14		5	9		4.11	
K 4048	P	9	9		2	7		3.87	
K 4049	P	15	15		9	6		4.20	
K 4050	P	13	13		6	7		3.88	
K 4051	P	15	15		7	8		3.22	
K 4052	P	9	9		3	6		3.82	
K 4053	P	13	13		8	5		3.65	
K 4054	P	6	6		3	3		4.02	
K 4055	P	11	11		7	4		3.29	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 255

Material FDA 71-57

Dose 47.05 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 28, 1973

Laboratory No. 1574 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 4061	P	12	12		8	4		3.81	
K 4062	P	11	11		4	7		3.85	
K 4063	P	11	11		5	6		3.42	
K 4064	P	13	13		3	10		3.21	
K 4065	P	13	13		7	6		3.87	
K 4066	P	11	11		3	8		3.87	
K 4067	P	14	14		4	10		4.02	
K 4068	P	12	12		3	9		3.61	
K 4069	P	14	14		7	7		4.13	
K 4070	P	11	11		7	4		3.85	
K 4071	P	11	10		4	6	1	3.82	
K 4072	P	14	14		8	6		4.05	
K 4073	P	12	12		3	9		3.94	
K 4074	P	11	11		4	7		3.74	
K 4075	P	9	8		4	4	1	4.60	
K 4076	NP	0						----	
K 4077	P	12	12		7	5		4.09	
K 4078	P	9	9		3	6		4.37	
K 4079	P	10	10		4	6		3.93	
K 4080	P	12	12		7	5		3.44	
K 4081	P	13	13		9	4		3.70	
K 4082	NP	0						----	
K 4083	P	14	14		4	10		3.66	
K 4084	P	14	14		8	6		4.02	
K 4085	P	12	12		7	5		3.55	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 256

Material FDA 71-57

Dose 218.0 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 28, 1973

Laboratory No. 1574 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 4091	NP	0						----	
K 4092	NP	0						----	
K 4093	P	6	5		1	4	1	3.49	
K 4094	P	8	8		2	6		3.91	
K 4095	P	13	13		7	6		3.96	
K 4096	P	10	10		5	5		4.06	
K 4097	P	10	10		4	6		3.88	
K 4098	P	15	15		5	10		3.71	
K 4099	P	13	13		5	8		4.05	
K 4100	P	14	14		9	5		3.74	
K 4101	P	11	11		6	5		3.55	
K 4102	P	10	9		3	6	1	3.66	
K 4103	P	13	13		4	9		4.14	
K 4104	P	12	11		5	6	1	4.32	
K 4105	P	9	9		8	1		4.41	
K 4106	P	14	13		5	8	1	3.37	
K 4107	P	13	13		6	7		4.27	
K 4108	P	11	11		5	6		3.76	
K 4109	P	14	14		7	7		3.77	
K 4110	P	7	7		1	6		3.87	
K 4111	P	15	15		8	7		3.93	
K 4112	P	8	8		6	2		4.04	
K 4113	P	10	10		5	5		3.68	
K 4114	NP	0						----	
K 4115	P	14	14		6	8		3.74	

* P = Pregnant; NP = Not Pregnant

Food and Drug Research Laboratories
INCORPORATED

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

FINAL REPORT

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

Date June 1, 1973

Laboratory No. 1575 k
Contract No. FDA 71-260

Sample: White needle-like crystalline material

Marking: FDA 71-57 (Menthol Natural Brazilian)

Examination Requested: Teratologic evaluation of FDA 71-57 in hamsters

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion:

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

"The administration of up to 405 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."

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: 251 through 256

Material: FDA 71-57

Date: April 28, 1973

Laboratory No.: 1575 k

Table 1

Fate Summary
(Hamsters)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
251	Sham	0.0	25	22	25	22
252	Aspirin*	250.0	25	22	25	22
253	FDA 71-57	4.05	24	22	22	20
254	FDA 71-57	21.15	25	23	24	22
255	FDA 71-57	98.2	25	21	24	20
256	FDA 71-57	405.0	25	21	24	20

* Positive Control: 250.0 mg/kg
** Administered as a corn oil solution (See Appendix I)
1) Includes all dams examined at term

FOOD AND DRUG RESEAR LABORATORIES, INC.

Group: 251 through 256

Material: FDA 71-57

Date: April 28, 1973

Laboratory No. 1575 k

Table 2
Reproduction Data
(Hamsters)

Group:	251	252	253	254	255	256
Dose (mg/kg):	Sham	Aspirin**	4.05	21.15	98.2	405.0
Pregnancies						
Total No.	22	22	22	23	21	21
Died or Aborted (before Day 14)	0	0	2	1	1	1
To term (on Day 14)	22	22	20	22	20	20
Live Litters						
Total No.*	22	21	20	22	20	20
Implant Sites						
Total No.	289	311	283	313	264	272
Average/dam*	13.1	14.1	14.2	14.2	13.2	13.6
Resorptions						
Total No.*	5	4	3	5	3	3
Dams with 1 or more sites resorbed	4	4	3	4	3	2
Dams with all sites resorbed	--	--	--	--	--	--
Per cent partial resorptions	18.2	18.2	15.0	18.2	15.0	10.0
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	283	289	279	307	261	269
Average/dam*	12.9	13.1	14.0	14.0	13.1	13.5
Sex ratio (M/F)	0.70	0.74	0.64	0.80	0.66	0.64
Dead Fetuses						
Total*	1	18	1	1	--	--
Dams with 1 or more dead	1	4	1	1	--	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	4.55	18.2	5.00	4.55	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	1.83	1.85	1.90	1.79	1.82	1.90

* Includes only those dams examined at term.
** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256 | Laboratory No. 1575 k

Table 3

Material FDA 71-57 | Date April 28, 1973

Summary of Skeletal Findings*
(Hamsters)

Findings / Group No.:	251	252	253	254	255	256
Dose (mg/kg):	Sham	Aspirin**	4.05	21.15	98.2	405.0
Live Fetuses Examined (at term)	197/22	201/21	195/20	212/22	181/20	184/20
Sternebrae						
Incomplete oss.	84/21	79/21	56/18	112/21	74/18	62/18
Scrambled						
Bipartite	16/12	19/11	22/13	26/13	19/12	16/11
Fused			1/1			
Extra			19/9	1/1	7/4	9/5
Missing	31/13		8/6	36/14	24/9	2/2
Other						
Ribs						
Incomplete oss.			1/1			
Fused/split						
Wavy						
Less than 12						
More than 13	40/18	62/18	74/17	56/16	38/13	44/15
Other						
Vertebrae						
Incomplete oss.	1/1			7/5	5/5	
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure						
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.			2/2	5/3	3/3	1/1
Missing						
Extra						
Miscellaneous						
Hyoid; missing	2/1			4/2		1/1
Hyoid; reduced	3/1	1/1	2/2	8/6	9/5	2/2

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256 Date April 28, 1973

Material FDA 71-57 Laboratory No. 1575 k

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
251	Sham	0.0	S 5816	1	Cardiomegaly; apulmonism
252	Aspirin*	250.0	A 5816	1	Moderate hydrocephalus
253	FDA 71-57	4.05	K 5016	1	Abdominal hernia
			K 5023	1	Gastroschisis
254	FDA 71-57	21.15	K 5049	2	Cardiomegaly; apulmonism
				1	Atelocardia
			K 5068	1	Atelocardia

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 251 through 256

Species Hamsters

Date April 28, 1973

Laboratory No. 1575 k

Table 4

Average Body Weights *

Group	Material	Dose Level	Day 0	6	8	10	14**
		mg/kg	g				
251	Sham	0.0	101.8	110.1	112.3	124.3	149.1 (22)
252	Aspirin***	250.0	108.2	116.0	119.4	130.9	154.5 (22)
253	FDA 71-57	4.05	104.4	114.6	119.8	132.5	159.1 (20)
254	FDA 71-57	21.15	107.5	117.1	122.8	135.4	159.3 (22)
255	FDA 71-57	98.2	106.0	114.8	120.1	132.3	157.4 (20)
256	FDA 71-57	405.0	101.5	111.2	116.1	128.6	154.6 (20)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 250.0 mg/kg

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 with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

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

Body weights were recorded on Days 0, 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 251

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 28, 1973

Laboratory No. 1575

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 5816	P	16	15	1	5	10		1.83	
S 5817	P	13	13		2	11		----**	
S 5818	NP	0						----	
S 5819	NP	0						----	
S 5820	P	11	11		5	6		1.99	
S 5821	P	12	12		4	8		1.65	
S 5822	P	13	13		7	6		1.65	
S 5823	P	7	6		2	4	1	2.12	
S 5824	P	16	16		5	11		1.73	
S 5825	P	17	17		9	8		1.70	
S 5826	P	15	15		7	8		1.90	
S 5827	P	13	13		5	8		1.59	
S 5828	P	12	11		5	6	1	2.05	
S 5829	P	13	13		6	7		1.80	
S 5830	NP	0						----	
S 5831	P	17	17		7	10		1.69	
S 5832	P	14	13		3	10	1	1.79	
S 5833	P	10	10		4	6		1.78	
S 5834	P	10	10		4	6		2.03	
S 5835	P	14	14		7	7		1.94	
S 5836	P	13	11		5	6	2	1.97	
S 5837	P	14	14		5	9		1.78	
S 5838	P	12	12		8	4		1.97	
S 5839	P	12	12		7	5		1.65	
S 5840	P	15	15		5	10		1.86	

* P = Pregnant; NP = Not Pregnant

** Weights not recorded.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 252

Material Aspirin

Dose 250.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 28, 1973

Laboratory No. 1575

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 5816	P	13	13		6	7		1.86	
A 5817	NP	0						----	
A 5818	P	14	13		6	7	1	1.85	
A 5819	P	12	12		5	7		1.91	
A 5820	P	12	11	1	2	9		1.63	
A 5821	NP	0						----	
A 5822	P	10	9		2	7	1	1.79	
A 5823	P	16		15			1	----	
A 5824	P	15	15		6	9		1.91	
A 5825	P	14	14		5	9		1.83	
A 5826	P	13	13		7	6		1.79	
A 5827	P	19	19		11	8		1.82	
A 5828	P	13	12	1	4	8		1.87	
A 5829	P	16	16		9	7		1.77	
A 5830	P	15	14	1	5	9		1.61	
A 5831	P	15	14		6	8	1	1.91	
A 5832	P	13	13		4	9		1.96	
A 5833	P	13	13		6	7		2.11	
A 5834	P	17	17		8	9		1.90	
A 5835	P	14	14		5	9		1.96	
A 5836	P	15	15		6	9		1.84	
A 5837	P	17	17		8	9		1.70	
A 5838	NP	0						----	
A 5839	P	11	11		7	4		1.91	
A 5840	P	14	14		5	9		1.88	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 253

Material FDA 71-57

Dose 4.05 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 28, 1973

Laboratory No. 1575 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 5001	P	15	15		6	9		1.80	
K 5002	P	17	17		--	--		----	Natural Birth Day 14
K 5003	P	15	15		--	--		----	Natural Birth Day 14
K 5004	P	11	11		5	6		1.87	
K 5005	P	14	14		8	6		2.11	
K 5006	P	13	13		5	8		2.23	
K 5007	P	14	14		2	12		1.78	
K 5008	NP	0						----	
K 5009	P	17	17		5	12		1.99	
K 5010	P	16	16		3	13		1.93	
K 5011	P	15	14		6	8	1	1.90	
K 5012	NP	0						----	
K 5013	P	11	11		5	6		1.87	
K 5014	P	15	14		6	8	1	1.62	
K 5015	P	12	11		4	7	1	1.81	
K 5016	P	15	15		6	9		1.70	
K 5017	P	14	14		6	8		2.02	
K 5018	P	12	11	1	3	8		1.81	
K 5019	P	12	12		4	8		1.95	
K 5020	P	16	16		5	11		2.02	
K 5021	P	16	16		6	10		2.03	
K 5022	P	15	15		8	7		1.89	
K 5023	P	16	16		10	6		1.98	
K 5024									Not Assigned
K 5025	P	14	14		6	8		1.77	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 254

Material FDA 71-57

Dose 21.15 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 28, 1973

Laboratory No. 1575 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 5031	P	15	15		7	8		1.78	
K 5032	P	14	14		7	7		1.67	
K 5033	P	11	11		7	4		1.95	
K 5034	P	15	15		8	7		1.90	
K 5035	P	15	15		8	7		1.84	
K 5036	P	13	11		1	10	2	1.48	
K 5037	P	14	14		5	9		1.72	
K 5038	P	14	14		5	9		1.75	
K 5039	P	14	14		3	11		1.79	
K 5040	NP	0						----	
K 5041	P	15	15		8	7		1.48	
K 5042	P	19	19		9	10		1.78	
K 5043	NP	0						----	
K 5044	P	12	12		6	6		1.75	
K 5045	P	16	16		6	10		1.72	
K 5046	P	17	17		--	--		----	Natural Birth Day 14
K 5047	P	15	14		4	10	1	1.95	
K 5048	P	12	11		6	5	1	2.07	
K 5049	P	15	15		7	8		1.88	
K 5050	P	14	14		6	8		2.10	
K 5051	P	12	12		7	5		2.07	
K 5052	P	16	14	1	7	7	1	1.79	
K 5053	P	15	15		8	7		1.59	
K 5054	P	15	15		7	8		1.77	
K 5055	P	12	12		4	8		1.58	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 255

Material FDA 71-57

Dose 98.2 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 28, 1973

Laboratory No. 1575 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 5061	P	12	12		7	5		1.98	
K 5062	NP	0						----	
K 5063	P	11	11		--	--		----	Natural Birth Day 14
K 5064	P	14	14		--**	--**		1.67	
K 5065	P	13	13		8	5		1.86	
K 5066	NP	0						----	
K 5067	P	13	13		4	9		1.69	
K 5068	P	13	12		2	10	1	1.80	
K 5069	P	14	14		5	9		1.82	
K 5070	P	17	17		6	11		1.82	
K 5071	P	12	12		5	7		1.86	
K 5072	NP	0						----	
K 5073	P	13	13		6	7		1.91	
K 5074	P	12	12		5	7		1.88	
K 5075	P	12	11		3	8	1	1.63	
K 5076	P	15	15		5	10		1.42	
K 5077	NP	0						----	
K 5078	P	13	13		5	8		1.81	
K 5079	P	12	12		4	8		1.88	
K 5080	P	11	11		5	6		1.85	
K 5081	P	14	14		6	8		1.85	
K 5082	P	11	11		5	6		1.95	
K 5083	P	14	14		8	6		1.96	
K 5084	P	14	13		5	8	1	1.91	
K 5085	P	15	15		4	11		1.88	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 256

Material FDA 71-57

Dose 405.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 28, 1973

Laboratory No. 1575 k

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
K 5091	P	15	15		10	5		2.03	
K 5092	P	12	12		5	7		1.91	
K 5093	P	15	15		7	8		2.16	
K 5094	P	9	9		--	--		----	Natural Birth Day 14
K 5095	P	11	11		3	8		1.80	
K 5096	P	12	12		1	11		1.96	
K 5097	P	13	12		7	5	1	1.93	
K 5098	P	14	14		5	9		1.77	
K 5099	P	15	15		6	9		1.70	
K 5100	P	14	12		4	8	2	1.93	
K 5101	P	19	19		6	13		1.66	
K 5102	P	12	12		5	7		2.17	
K 5103	P	10	10		3	7		2.03	
K 5104	NP	0						----	
K 5105	P	11	11		3	8		1.78	
K 5106	NP	0						----	
K 5107	P	12	12		5	7		1.86	
K 5108	P	15	15		5	10		1.98	
K 5109	NP	0						----	
K 5110	NP	0						----	
K 5111	P	12	12		4	8		1.99	
K 5112	P	14	14		6	8		1.95	
K 5113	P	16	16		7	9		1.60	
K 5114	P	16	16		7	9		1.87	
K 5115	P	14	14		6	8		1.96	

* P = Pregnant; NP = Not Pregnant