CITRIC ACID MAY 16, 1973
Teratologic Evaluation
Mice Rats & Hamsters
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FOOD AND DRUG Research LABORATORIES, INC.

#119

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

FINAL

May 16, 1973

Teratologic Evaluation of FDA 71-54

(Citric Acid)

in

Mice, Rats, and Hamsters

M I C E

E35

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 May 16, 1973

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

Sample: Fine white crystalline material

Marking: FDA 71-54 (Citric acid)

Examination Requested: Teratologic evaluation of FDA 71-54 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 241 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: 241 through 246

Material: FDA 71-54

Date: April 16, 1973

Laboratory No.: 1573 h

Table 1

Fate Summary
(Mice)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
241	Sham	0.0	25	20	25	20
242	Aspirin*	150.0	25	19	25	19
243	FDA 71-54	2.41	28	23	28	23
244	FDA 71-54	11.2	24	22	24	22
245	FDA 71-54	52.0	25	22	25	22
246	FDA 71-54	241.0	25	24	25	24

* Positive Control: 150.0 mg/kg

** Administered as a water solution (10 ml per kg of body weight)

1) Includes all dams examined at term

LABORATORIES, INC.

2
n Data
)

Date: April 16, 1973

Laboratory No. 1573 h

2	243	244	245	24[illegible]
rin**	2.41	11.2	52.0	24[illegible]
	23	22	22	24
	0	0	0	0
	23	22	22	24
	23	22	22	24
	271	259	261	280
.0	11.8	11.8	11.9	11[illegible]
	5	14	11	14
	5	12	8	10
	--	--	--	--
.6	21.7	54.6	36.4	41[illegible]
.26	--	--	--	--
	263	244	249	266
.32	11.4	11.1	11.3	11[illegible]
.99	0.96	1.30	1.06	0[illegible]
	3	1	1	--
	3	1	1	--
	--	--	--	--
.1	13.0	4.55	4.55	--
	--	--	--	--
.83	0.83	0.90	0.94	0[illegible]

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246 | Laboratory No. 1573 h

Table 3

Material FDA 71-54 | Date April 16, 1973

Summary of Skeletal Findings*
(Mice)

Findings / Group No.:	241	242	243	244	245	246
Dose (mg/kg):	Sham	Aspirin**	2.41	11.2	52.0	241.0
Live Fetuses Examined (at term)	154/20	126/18	183/23	171/22	174/22	186/24
Sternebrae						
Incomplete oss.	59/18	47/16	72/20	77/19	28/9	77/16
Scrambled						
Bipartite	5/4		8/7	1/1	6/5	6/6
Fused						
Extra				5/2		
Missing	25/11	39/13	29/11	29/10	7/5	19/10
Other						
Ribs						
Incomplete oss.						
Fused/split						
Wavy		4/3	1/1	1/1		
Less than 12						
More than 13	35/12	13/7	46/16	38/16	43/15	49/16
Other						
Vertebrae						
Incomplete oss.	8/3	3/3	9/6	7/4	1/1	5/1
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	6/1		3/3		1/1	1/1
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.	9/3	5/4	6/4	5/2		4/1
Missing						
Extra						
Miscellaneous						
Hyoid; missing	49/15	57/18	40/15	39/15	24/13	38/16
Hyoid; reduced	18/12	16/8	25/17	24/11	19/12	33/14

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

** Positive control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246 Date April 16, 1973

Material FDA 71-54 Laboratory No. 1573 h

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
245	FDA 71-54	52.0	H 3070	1	Meningoencephalocele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246

Species Mice

Date April 16, 1973

Laboratory No. 1573 n

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	17**
		mg/kg	g				
241	Sham	0.0	30.2	33.8	36.9	43.6	48.9 (20)
242	Aspirin***	150.0	30.9	35.4	36.4	43.1	47.5 (19)
243	FDA 71-54	2.41	28.5	32.7	35.5	41.7	49.0 (23)
244	FDA 71-54	11.2	29.1	33.9	37.0	46.1	51.8 (22)
245	FDA 71-54	52.0	27.4	32.7	35.1	44.7	51.0 (22)
246	FDA 71-54	241.0	31.4	33.6	37.0	45.8	51.7 (24)

* 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 241

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 16, 1973

Laboratory No. 1573

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 3726	NP		0						----	
S 3727	P		12	12		5	7		0.91	
S 3728	NP		0						----	
S 3729	NP		0						----	
S 3730	P		11	10		4	6	1	1.00	
S 3731	P		12	11		5	6	1	0.91	
S 3732	P		13	13		7	6		0.91	
S 3733	P		10	9		6	3	1	0.82	
S 3734	P		13	11		4	7	2	0.92	
S 3735	P		16	14	1	3	11	1	0.76	
S 3736	P		14	14		8	6		0.79	
S 3737	P		12	12		7	5		0.80	
S 3738	P		13	11	1	5	6	1	0.78	
S 3739	NP		0						----	
S 3740	P		13	13		6	7		0.64	
S 3741	P		11	9	1	4	5	1	0.86	
S 3742	P		3	3		2	1		0.88	
S 3743	P		13	13		7	6		0.85	
S 3744	P		13	12		9	3	1	1.06	
S 3745	P		11	9	1	5	4	1	0.75	
S 3746	P		12	12		9	3		0.77	
S 3747	NP		0						----	
S 3748	P		12	12		6	6		0.77	
S 3749	P		11	11		5	6		0.78	
S 3750	P		12	12		5	7		0.88	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 242

Material Aspirin

Dose 150.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 16, 1973

Laboratory No. 1573

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 3726	P		13	11	1	5	6	1	1.05	
S 3727	P		11	10	1	4	6		0.83	
A 3728	P		11	8	2	6	2	1	0.84	
A 3729	NP		0						----	
A 3730	NP		0						----	
A 3731	P		11	11		6	5		0.77	
A 3732	NP		0						----	
A 3733	P		2					2	----	
A 3734	P		9	9		5	4		0.73	
A 3735	P		12	12		6	6		0.82	
A 3736	P		5	5		0	5		0.89	
A 3737	P		14	14		--**	--**		0.85	
A 3738	P		10	7	2	3	4	1	0.72	
A 3739	P		13	13		5	8		0.71	
A 3740	P		9	8		3	5	1	0.78	
A 3741	NP		0						----	
A 3742	P		10	10		4	6		0.90	
A 3743	P		13	13		8	5		0.80	
A 3744	P		2	2		0	2		1.02	
A 3745	P		12	12		6	6		0.87	
A 3746	NP		0						----	
A 3747	P		14	14		8	6		0.83	
A 3748	NP		0						----	
A 3749	P		9	9		9	0		0.84	
A 3750	P		10	9		3	6	1	0.67	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 243

Material FDA 71-54

Dose 2.41 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 16, 1973

Laboratory No. 1573 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 3001	P		10	9	1	4	5		0.70	
H 3002	P		9	9		3	6		0.87	
H 3003	P		12	11		7	4	1	0.89	
H 3004	NP		0						----	
H 3005	P		12	12		9	3		0.92	
H 3006	NP		0						----	
H 3007	P		13	12		6	6	1	0.79	
H 3008	NP		0						----	
H 3009	P		12	12		5	7		0.71	
H 3010	P		13	13		4	9		0.71	
H 3011	P		11	10		4	6	1	0.85	
H 3012	P		12	12		9	3		0.88	
H 3013	P		10	10		5	5		0.88	
H 3014	P		12	12		4	8		0.76	
H 3015	P		12	12		11	1		0.77	
H 3016	NP		0						----	
H 3017	NP		0						----	
H 3018	P		8	8		5	3		0.87	
H 3019	P		13	13		7	6		0.81	
H 3020	P		13	12	1	3	9		0.76	
H 3021	P		12	11		5	6	1	0.82	
H 3022	P		12	10	1	5	5	1	0.82	
H 3023	P		14	14		7	7		0.86	
H 3024	P		9	9		4	5		0.88	
H 3025	P		13	13		5	8		0.79	
H 3026	P		13	13		5	8		0.90	
H 3027	P		14	14		7	7		0.94	
H 3028	P		12	12		5	7		0.87	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 244

Material FDA 71-54

Dose 11.2 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 16, 1973

Laboratory No. 1573 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 3031	P		16	16		8	8		0.89	
H 3032	P		12	11		5	6	1	0.80	
H 3033	P		12	12		6	6		0.84	
H 3034	P		14	13		6	7	1	0.80	
H 3035	P		13	11		7	4	2	1.00	
H 3036	P		13	12		6	6	1	0.73	
H 3037	NP		0						----	
H 3038	P		16	16		8	8		0.78	
H 3039	P		9	8		4	4	1	0.78	
H 3040	P		5	4		2	2	1	0.74	
H 3041	P		12	12		6	6		1.08	
H 3042	P		9	8		5	3	1	0.79	
H 3043	P		13	13		9	4		1.24	
H 3044	P		13	12		5	7	1	0.92	
H 3045	P		11	10		6	4	1	0.87	
H 3046	NP		0						----	
H 3047	P		10	8		6	2	2	1.20	
H 3048	P		12	11		6	5	1	0.93	
H 3049	P		9	8		6	2	1	1.15	
H 3050	P		12	12		5	7		0.78	
H 3051	P		9	9		5	4		0.98	
H 3052	P		13	13		11	2		0.88	
H 3053	P		13	13		10	3		0.82	
H 3054	P		13	12	1	6	6		0.79	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 245

Material FDA 71-54

Dose 52.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 16, 1973

Laboratory No. 1573 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 3061	NP		0						----	
H 3062	P		12	9		6	3	3	1.00	
H 3063	P		8	8		4	4		1.00	
H 3064	P		14	14		7	7		0.99	
H 3065	P		12	11		8	3	1	1.11	
H 3066	P		10	9		5	4	1	0.79	
H 3067	P		10	9		5	4	1	1.01	
H 3068	P		14	14		8	6		0.87	
H 3069	P		13	13		6	7		1.09	
H 3070	P		13	13		5	8		0.87	
H 3071	P		11	11		5	6		0.79	
H 3072	NP		0						----	
H 3073	P		14	14		8	6		0.98	
H 3074	P		12	11		6	5	1	1.33	
H 3075	P		10	10		3	7		0.98	
H 3076	P		11	11		5	6		0.85	
H 3077	NP		0						----	
H 3078	P		9	9		5	4		0.81	
H 3079	P		12	12		4	8		0.91	
H 3080	P		12	12		6	6		0.88	
H 3081	P		10	10		7	3		0.74	
H 3082	P		14	13		5	8	1	0.89	
H 3083	P		13	12		5	7	1	0.97	
H 3084	P		14	13	1	8	5		0.81	
H 3085	P		13	11		7	4	2	0.99	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 246

Material FDA 71-54

Dose 241.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date April 16, 1973

Laboratory No. 1573 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 3091	P		14	13		7	6	1	0.93	
H 3092	P		13	12		6	6	1	0.89	
H 3093	P		13	10		4	6	3	0.81	
H 3094	P		10	10		5	5		0.80	
H 3095	P		13	12		6	6	1	0.82	
H 3096	P		12	12		6	6		0.89	
H 3097	P		9	9		5	4		0.62	
H 3098	P		14	14		6	8		0.75	
H 3099	P		8	8		5	3		0.92	
H 3100	P		11	11		4	7		0.73	
H 3101	P		14	14		6	8		0.87	
H 3102	P		13	13		8	5		0.75	
H 3103	P		11	11		5	6		0.88	
H 3104	P		11	11		7	4		0.84	
H 3105	P		13	12		6	6	1	0.89	
H 3106	NP		0						----	
H 3107	P		13	12		5	7	1	0.95	
H 3108	P		13	11		6	5	2	0.84	
H 3109	P		12	11		9	2	1	0.77	
H 3110	P		12	11		3	8	1	0.79	
H 3111	P		11	11		6	5		1.04	
H 3112	P		13	13		3	10		0.77	
H 3113	P		6	4		2	2	2	0.81	
H 3114	P		10	10		2	8		1.25	
H 3115	P		11	11		8	3		1.16	

* P = Pregnant; NP = Not Pregnant

R A T S

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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 May 16, 1973

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

Sample: Fine white crystalline material

Marking: FDA 71-54 (Citric acid)

Examination Requested: Teratologic evaluation of FDA 71- 54 in rats

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

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

"The administration of up to 295 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: 241 through 246

Material: FDA 71-54

Date: April 16, 1973

Laboratory No.: 1574 h

Table 1

Fate Summary
(Rats)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
241	Sham	0.0	24	21	24	21
242	Aspirin*	250.0	25	24	25	24
243	FDA 71-54	2.95	25	24	25	24
244	FDA 71-54	13.7	25	23	25	23
245	FDA 71-54	63.6	25	19	25	19
246	FDA 71-54	295.0	22	21	22	21

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 241 through 246

Material: FDA 71-54

Date: April 16, 1973

Laboratory No. 1574 h

Table 2
Reproduction Data
(Rats)

Group:	241	242	243	244	245	246
Dose (mg/kg):	Sham	Aspirin**	2.95	13.7	63.6	295.0
Pregnancies						
Total No.	21	24	24	23	19	21
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	21	24	24	23	19	21
Live Litters						
Total No.*	21	24	24	23	19	21
Implant Sites						
Total No.	220	284	283	275	233	246
Average/dam*	10.5	11.8	11.8	12.0	12.3	11.7
Resorptions						
Total No.*	5	14	--	1	5	3
Dams with 1 or more sites resorbed	3	7	--	1	1	3
Dams with all sites resorbed	--	--	--	--	--	--
Per cent partial resorptions	14.3	29.2	--	4.35	5.26	14.3
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	215	267	283	274	227	248
Average/dam*	10.2	11.1	11.8	11.9	12.0	11.6
Sex ratio (M/F)	0.92	0.98	1.10	1.06	1.10	0.85
Dead Fetuses						
Total*	--	3	--	--	1	--
Dams with 1 or more dead	--	2	--	--	1	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	--	8.33	--	--	5.26	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.87	2.80	3.72	3.99	3.96	3.99

* Includes only those dams examined at term.

** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246 | Laboratory No. 1574 h

Table 3

Material FDA 71-54 | Date April 16, 1973

Summary of Skeletal Findings *
(Rats)

Findings / Group No.:	241	242	243	244	245	246
Dose (mg/kg):	Sham	Aspirin**	2.95	13.7	63.6	295.0
Live Fetuses Examined (at term)	153/21	187/24	197/24	191/23	161/19	167/21
Sternebrae						
Incomplete oss.	44/12	144/24	90/22	87/20	56/16	61/17
Scrambled						
Bipartite	1/1	10/8	1/1	1/1	1/1	
Fused						
Extra						
Missing	9/5	143/23	4/3	8/2	6/3	7/5
Other						
Ribs						
Incomplete oss.	2/2	4/4	1/1		2/2	
Fused/split		7/5				
Wavy	19/9	72/22	19/10	18/11	16/10	17/8
Less than 12		8/4				
More than 13		102/23	1/1		1/1	4/2
Other						
Vertebrae						
Incomplete oss.	9/6	118/23	8/8	7/4	5/5	7/5
Scrambled		2/2				
Fused		1/1				
Extra ctrs. oss.						
Scoliosis		4/2				
Tail defects						
Other; wavy		2/1				
Skull						
Incomplete closure	27/9	93/23	23/14	33/13	30/12	56/17
Missing		13/6				
Craniostosis						
Other; facial bones; incomplete		2/1				
Extremities						
Incomplete oss.	2/2	5/3				
Missing			4/1			
Extra						
Miscellaneous						
Hyoid; missing	20/7	115/23	13/7	17/8	22/11	12/8
Hyoid; reduced	20/11	8/7	28/10	35/17	10/6	15/10
Vertebrae; missing		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 241 through 246 Date April 16, 1973

Material FDA 71-54 Laboratory No. 1574 h

Table 3-a

Summary of Soft Tissue Abnormalities

(Rats)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
242	Aspirin*	250.0	A 4729	1	Meningoencephalocele
			A 4730	1	Encephalomyelocele
			A 4731	9	Encephalomyelocele
			A 4739	1	Spina bifida
				2	Encephalomyelocele; umbilical hernia
				1	Encephalomyelocele
			A 4743	1	Encephalomyelocele
			A 4744	1	Encephalomyelocele
			A 4746	2	Encephalomyelocele
			A 4747	1	Encephalomyelocele

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246

Species Rats

Date April 16, 1973

Laboratory No. 1574 h

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	20**
		mg/kg	g				
241	Sham	0.0	212	230	246	267	327 (21)
242	Aspirin***	250.0	216	237	250	270	327 (24)
243	FDA 71-54	2.95	214	237	252	276	338 (24)
244	FDA 71-54	13.7	208	229	247	269	339 (23)
245	FDA 71-54	63.6	212	232	244	272	344 (19)
246	FDA 71-54	295.0	206	227	243	264	335 (21)

* 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 241

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 16, 1973

Laboratory No. 1574

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 4726	P		10	9		5	4	1	4.03	
S 4727	P		10	10		3	7		4.16	
S 4728	P		13	13		7	6		3.85	
S 3729	P		1	1		0	1		4.46	
S 4730	P		12	12		5	7		4.19	
S 4731	P		14	14		4	10		3.58	
S 4732	P		9	6		2	4	3	3.95	
S 4733	NP		0						----	
S 4734	NP		0						----	
S 4735	P		11	11		6	5		4.08	
S 4736	P		14	14		8	6		3.96	
S 4737	P		14	14		6	8		3.65	
S 4738	P		9	9		5	4		3.47	
S 4739										Not Assigned
S 4740	P		10	9		7	2	1	3.84	
S 4741	P		11	11		6	5		3.91	
S 4742	P		13	13		5	8		3.12	
S 4743	P		9	9		4	5		3.86	
S 4744	NP		0						----	
S 4745	P		9	9		2	7		3.82	
S 4746	P		11	11		6	5		4.04	
S 4747	P		11	11		7	4		3.83	
S 4748	P		3	3		0	3		4.10	
S 4749	P		14	14		8	6		3.92	
S 4750	P		12	12		7	5		3.48	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 242

Material Aspirin

Dose 250.0 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 16, 1973

Laboratory No. 1574

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 4726	NP		0						----	
A 4727	P		15	13		6	7	2	2.87	
A 4728	P		14	14		7	7		2.78	
A 4729	P		11	11		5	6		2.37	
A 4730	P		13	13		4	9		3.08	
A 4731	P		13	11		6	5	2	1.88	
A 4732	P		15	14		9	5	1	2.89	
A 4733	P		12	12		7	5		2.89	
A 4734	P		12	10		3	7	2	2.41	
A 4735	P		15	15		1	14		3.33	
A 4736	P		15	14		8	6	1	3.17	
A 4737	P		13	13		8	5		3.09	
A 4738	P		8	5		3	2	3	2.42	
A 4739	P		11	9	2	5	4		3.05	
A 4740	P		9	9		4	5		3.12	
A 4741	P		10	7		3	4	3	2.92	
A 4742	P		14	14		9	5		2.52	
A 4743	P		9	9		5	4		2.66	
A 4744	P		11	10	1	4	6		2.28	
A 4745	P		11	11		5	6		2.71	
A 4746	P		12	12		6	6		2.47	
A 4747	P		12	12		7	5		2.69	
A 4748	P		11	11		7	4		2.94	
A 4749	P		8	8		5	3		3.40	
A 4750	P		10	10		5	5		3.28	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 243

Material FDA 71-54

Dose 2.95 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 16, 1973

Laboratory No. 1574 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 4001	P		9	9		5	4		3.68	
H 4002	P		7	7		3	4		3.26	
H 4003	P		9	9		5	4		3.57	
H 4004	P		12	12		5	7		3.72	
H 4005	P		10	10		10	0		3.35	
H 4006	P		12	12		9	3		3.86	
H 4007	P		17	17		9	8		3.50	
H 4008	P		14	14		4	10		3.91	
H 4009	NP		0						----	
H 4010	P		12	12		8	4		4.19	
H 4011	P		13	13		5	8		3.86	
H 4012	P		13	13		5	8		3.65	
H 4013	P		8	8		3	5		3.93	
H 4014	P		13	13		5	8		3.28	
H 4015	P		13	13		12	1		3.36	
H 4016	P		11	11		3	8		3.83	
H 4017	P		12	12		7	5		3.83	
H 4018	P		11	11		8	3		3.64	
H 4019	P		13	13		10	3		3.67	
H 4020	P		13	13		4	9		3.65	
H 4021	P		16	16		10	6		3.95	
H 4022	P		12	12		6	6		3.84	
H 4023	P		10	10		1	9		3.86	
H 4024	P		12	12		7	5		4.03	
H 4025	P		11	11		4	7		3.96	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 244

Material FDA 71-54

Dose 13.7 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 16, 1973

Laboratory No. 1574 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 4031	P		11	11		5	6		3.52	
H 4032	P		15	15		8	7		3.75	
H 4033	P		11	11		3	8		3.98	
H 4034	P		10	10		4	6		4.09	
H 4035	P		10	10		7	3		5.52	
H 4036	P		10	10		7	3		4.13	
H 4037	P		14	14		3	11		4.28	
H 4038	P		15	15		9	6		4.01	
H 4039	P		12	12		8	4		4.06	
H 4040	P		10	10		6	4		4.12	
H 4041	P		10	10		6	4		3.85	
H 4042	P		13	13		9	4		4.41	
H 4043	NP		0						----	
H 4044	P		14	13		4	9	1	3.97	
H 4045	P		14	14		7	7		3.62	
H 4046	P		15	15		8	7		3.39	
H 4047	P		11	11		5	6		3.70	
H 4048	P		14	14		9	5		3.92	
H 4049	P		10	10		4	6		3.71	
H 4050	P		12	12		4	8		3.93	
H 4051	P		12	12		6	6		4.23	
H 4052	P		10	10		5	5		3.66	
H 4053	P		11	11		7	4		4.07	
H 4054	P		11	11		7	4		3.89	
H 4055	NP		0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 245

Material FDA 71-54

Dose 63.6 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 16, 1973

Laboratory No. 1574 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 4061	P		13	13		6	7		3.87	
H 4062	NP		0						----	
H 4063	P		9	4		2	2	5	4.92	
H 4064	NP		0						----	
H 4065	P		10	10		5	5		3.85	
H 4066	P		11	11		4	7		4.04	
H 4067	P		14	14		8	6		4.41	
H 4068	P		12	12		4	8		3.83	
H 4069	P		14	14		8	6		4.01	
H 4070	NP		0						----	
H 4071	P		11	11		6	5		4.04	
H 4072	P		11	11		5	6		3.92	
H 4073	P		10	10		3	7		3.80	
H 4074	P		14	14		10	4		3.96	
H 4075	P		19	18	1	10	8		3.33	
H 4076	P		14	14		7	7		3.71	
H 4077	P		12	12		9	3		3.97	
H 4078	P		11	11		4	7		4.08	
H 4079	P		13	13		7	6		3.98	
H 4080	NP		0						----	
H 4081	NP		0						----	
H 4082	P		12	12		8	4		3.98	
H 4083	P		14	14		9	5		3.87	
H 4084	P		9	9		4	5		3.73	
H 4085	NP		0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 246

Material FDA 71-54

Dose 295.0 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date April 16, 1973

Laboratory No. 1574 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 4092	P		7	7		5	2		4.18	
H 4093	P		14	14		6	8		3.32	
H 4094	P		11	11		7	4		4.56	
H 4095	P		11	11		6	5		3.66	
H 4096	P		10	9		2	7	1	4.02	
H 4097	P		13	13		4	9		3.98	
H 4098	P		12	12		4	8		3.51	
H 4099										Not Assigned
H 4100	P		15	15		9	6		5.31	
H 4101	P		13	13		6	7		4.34	
H 4102										Not Assigned
H 4103	P		14	14		7	7		3.96	
H 4104	P		9	9		3	6		3.73	
H 4105	P		13	13		7	6		3.53	
H 4106	P		7	6		5	1	1	4.24	
H 4107	P		13	12		1	11	1	4.20	
H 4108	P		15	15		9	6		3.53	
H 4109	P		11	11		5	6		3.98	
H 4110	P		10	10		7	3		4.00	
H 4111	P		12	12		4	8		4.23	
H 4112	P		12	12		5	7		3.78	
H 4113	NP		0						----	
H 4114	P		9	9		2	7		3.81	
H 4115	P		15	15		8	7		3.94	

* P = Pregnant; NP = Not Pregnant

HAMSTERS

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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 May 16, 1973

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

Sample: Fine white crystalline material

Marking: FDA 71-54 (Citric acid)

Examination Requested: Teratologic evaluation of FDA 71- 54 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 272 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: 241 through 246

Material : FDA 71-54

Date: April 16, 1973

Laboratory No. : 1575 h

Table 1

Fate Summary
(Hamsters)

Group	Material	Dose ** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
241	Sham	0.0	29	22	28	21
242 A	Aspirin*	250.0	24	19	24	19
242 B	Aspirin*	300.0	25	24	25	24
242 C	Aspirin*	250.0	25	23	25	23
243	FDA 71-54	2.72	25	22	25	22
244	FDA 71-54	12.6	28	22	28	22
245	FDA 71-54	58.7	25	23	25	23
246	FDA 71-54	272.0	29	23	28	22

* Positive Control : 250.0, 300.0, 350.0 mg/kg
** Administered as a water solution (See Appendix I)
1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 241 through 246

Material: FDA 71-54

Date: April 14, 1973

Laboratory No. 1575 h

Table 2
Reproduction Data
(Hamsters)

Group:	241	242 A	242 B	242 C	243	244	245	246
Dose (mg/kg):	Sham	Aspirin**	Aspirin**	Aspirin**	2.72	12.6	58.7	272.0
Pregnancies								
Total No.	22	19	24	23	22	22	23	23
Died or Aborted (before Day 14)	1	0	0	0	0	0	0	1
To term (on Day 14)	21	19	24	23	22	22	23	22
Live Litters								
Total No.*	21	19	24	23	22	22	23	22
Implant Sites								
Total No.	290	277	322	322	295	293	303	291
Average/dam*	13.8	14.6	13.4	14.0	13.4	13.3	13.2	13.2
Resorptions								
Total No.*	8	9	3	7	9	5	9	8
Dams with 1 or more sites resorbed	5	8	3	7	4	4	6	6
Dams with all sites resorbed	--	--	--	--	--	--	--	--
Per cent partial resorptions	23.8	42.1	12.5	30.4	18.2	18.2	26.1	27.3
Per cent complete resorptions	--	--	--	--	--	--	--	--
Live Fetuses								
Total No.	282	267	318	314	286	281	293	283
Average/dam*	13.4	14.1	13.3	13.7	13.0	12.8	12.7	12.9
Sex ratio (M/F)	0.74	0.80	0.57	0.71	0.81	0.75	0.77	0.67
Dead Fetuses								
Total*	--	1	1	1	--	7	1	--
Dams with 1 or more dead	--	1	1	1	--	1	1	--
Dams with all dead	--	--	--	--	--	--	--	--
Per cent partial dead	--	5.26	4.17	4.35	--	4.55	4.35	--
Per cent all dead	--	--	--	--	--	--	--	--
Average Fetus Weight, g	1.78	1.73	1.73	1.72	1.79	1.81	1.78	1.84

* Includes only those dams examined at term.
** Positive Control: 250.0, 300.0, 350.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 241 through 246

Material: FDA 71-54

Table 3

Summary of Skeletal Findings*
(Hamsters)

Laboratory No.: 1575 h

Date: April 16, 1973

Findings	Group No.	241	242 A	242 B	242 C	243	244	245	246
	Dose (mg/kg)	Sham	Aspirin**	Aspirin**	Aspirin**	2.72	12.6	58.7	272.0
Live Fetuses Examined (at term)		194/21	187/19	220/24	218/23	196/22	194/22	203/23	196/22
Sternebrae									
Incomplete oss.		95/21	96/18	124/23	110/23	93/21	66/18	104/22	72/19
Bipartite		11/7	25/15	27/17	25/15	23/13	15/10	22/13	17/10
Extra		1/1	9/3	1/1	5/5	2/2	8/6	2/2	1/1
Missing		30/12	33/10	38/13	26/11	27/15	15/7	21/8	15/9
Ribs									
Incomplete oss.		1/1							
Fused/split		1/1			1/1		1/1		
Wavy		3/3							
Less than 12		2/1							
More than 13		41/15	65/16	53/18	77/20	59/18	57/21	61/17	43/19
Vertebrae									
Incomplete oss.		4/4	3/2	7/5	7/6	6/3	2/2	1/1	2/2
Scrambled			1/1						
Scoliosis		8/5							
Skull									
Incomplete closure						1/1			
Extremities									
Incomplete oss.		5/4	2/2	8/6	7/5	6/4	1/1	1/1	2/2
Miscellaneous									
Hyoid; missing		4/4		3/2	3/3	3/2	1/1		1/1
Hyoid; reduced		4/3	5/4	7/4	9/6	4/3	6/4	4/4	2/2

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

** Positive Control: 250.0, 300.0, 350.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246 Date April 16, 1973

Material FDA 71-54 Laboratory No. 1575 h

Table 3-a

Summary of Soft Tissue Abnormalities

(Hamsters)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
245	FDA 71-54	58.7	H 5066	1	Meningoencephalocele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246

Date April 16, 1973

Species Hamsters

Laboratory No. 1575 h

Table 4

Average Body Weights *

Group	Material	Dose Level	Day 0	6	8	10	14**
		mg/kg	g				
241	Sham	0.0	118.1	121.9	124.7	137.9	160.6 (21)
242 A	Aspirin***	250.0	122.6	125.2	127.7	139.3	163.5 (19)
242 B	Aspirin***	300.0	113.2	114.3	117.8	130.6	154.1 (24)
242 C	Aspirin***	350.0	109.0	113.1	116.9	128.9	154.8 (23)
243	FDA 71-54	2.72	112.5	114.9	119.0	130.6	153.2 (22)
244	FDA 71-54	12.6	113.7	117.1	120.4	132.0	155.7 (22)
245	FDA 71-54	58.7	108.0	111.9	116.3	128.7	150.7 (23)
246	FDA 71-54	272.0	108.6	113.1	116.1	127.6	151.4 (22)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 250.0, 300.0, 350.0 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 241

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 16, 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 5726	NP	0						----	
S 5727	P	15	15		7	8		1.86	
S 5728	P	15	15		6	9		1.59	
S 5729	P	13	12		3	9	1	1.92	
S 5730	P	17	17		8	9		1.65	
S 5731	NP	0						----	
S 5732	P	15	15		7	8		1.53	
S 5733	P	15	15		8	7		1.80	
S 5734	P	13	13		6	7		1.83	
S 5735	NP	0						----	
S 5736	P	13	13		5	8		1.83	
S 5737	NP	0						----	
S 5738	P	11	11		3	8		1.84	
S 5739	P	15	12		4	8	3	1.68	
S 5740	P	14	14		6	8		1.85	
S 5741	P	11	9		4	5	2	1.50	
S 5742	P	15	15		6	9		1.77	
S 5743	P	15	14		5	9	1	1.75	
S 5744	NP	0						----	
S 5745	P	6	5		1	4	1	----	Natural Birth Day 14
S 5746	P	12	12		5	7		1.77	
S 5747	P	12	12		6	6		1.99	
S 5748	P	16	16		8	8		1.61	
S 5749	NP	0						----	
S 5750	NP	0						----	
S 5751	P	13	13		5	8		1.87	
S 5752	P	13	13		6	7		1.89	
S 5753	P	12	11		7	4	1	1.96	
S 5754	P	15	15		5	10		1.96	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 242 A

Material Aspirin

Dose 250.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 16, 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 5726	P	15	14		9	5	1	1.90	
A 5727	P	19	18		12	6	1	1.61	
A 5728	P	13	13		7	6		1.88	
A 5729	P	14	12		5	7	2	1.77	
A 5730	P	12	11		8	3	1	1.86	
A 5731	P	12	11	1	6	5		1.61	
A 5732	P	15	15		7	8		1.53	
A 5733	P	13	13		6	7		1.94	
A 5734	P	15	14		7	7	1	1.94	
A 5735	NP	0						----	
A 5736	NP	0						----	
A 5737	NP	0						----	
A 5738	P	16	16		6	10		1.64	
A 5739	P	14	13		6	7	1	1.75	
A 5740	P	14	14		7	7		1.81	
A 5741	P	18	17		6	11	1	1.72	
A 5742	P	16	15		5	10	1	1.63	
A 5743	NP	0						----	
A 5744	P	16	16		9	7		1.75	
A 5745									Not Assigned
A 5746	P	12	12		0	12		1.69	
A 5747	P	13	13		5	8		1.71	
A 5748	P	16	16		4	12		1.34	
A 5749	P	14	14		4	10		1.87	
A 5750	NP	0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 242 B

Material Aspirin

Dose 300.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 16, 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 5756	P	13	12		6	6	1	1.76	
A 5757	P	11	11		6	5		1.81	
A 5758	P	13	12		2	10	1	1.87	
A 5759	P	15	15		7	8		1.80	
A 5760	P	15	15		7	8		1.71	
A 5761	P	13	13		6	7		1.61	
A 5762	P	13	12		4	8	1	2.06	
A 5763	P	11	11		4	7		1.84	
A 5764	P	13	13		6	7		1.73	
A 5765	P	13	13		6	7		1.89	
A 5766	P	13	13		4	9		1.82	
A 5767	NP	0						----	
A 5768	P	12	12		5	7		1.78	
A 5769	P	14	14		4	10		1.89	
A 5770	P	15	15		5	10		1.47	
A 5771	P	13	13		4	9		1.54	
A 5772	P	14	14		6	8		1.63	
A 5773	P	18	18		5	13		1.63	
A 5774	P	14	14		3	11		1.65	
A 5775	P	11	11		6	5		1.78	
A 5776	P	13	13		2	11		1.55	
A 5777	P	15	15		5	10		1.47	
A 5778	P	12	12		3	9		1.68	
A 5779	P	15	14	1	5	9		1.79	
A 5780	P	13	13		5	8		1.82	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 242 C

Material Aspirin

Dose 350.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 16, 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 5786	P	10	10		4	6		1.64	
A 5787	NP	0						----	
A 5788	P	11	10		5	5	1	1.88	
A 5789	P	14	14		7	7		1.54	
A 5790	P	15	15		6	9		1.53	
A 5791	P	17	17		9	8		1.55	
A 5792	P	15	15		9	6		1.90	
A 5793	P	14	14		8	6		1.73	
A 5794	P	14	14		7	7		1.78	
A 5795	P	13	13		7	6		2.00	
A 5796	NP	0						----	
A 5797	P	15	14	1	3	11		1.73	
A 5798	P	15	15		6	9		1.79	
A 5799	P	14	13		4	9	1	1.69	
A 5800	P	11	10		5	5	1	1.80	
A 5801	P	16	16		3	13		1.74	
A 5802	P	14	13		6	7	1	1.78	
A 5803	P	15	15		3	12		1.86	
A 5804	P	14	14		3	11		1.73	
A 5805	P	13	12		2	10	1	1.60	
A 5806	P	9	8		3	5	1	1.57	
A 5807	P	19	19		9	10		1.46	
A 5808	P	14	14		6	8		1.74	
A 5809	P	15	14		5	9	1	1.54	
A 5810	P	15	15		10	5		1.87	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 243

Material FDA 71-54

Dose 2.72 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 16, 1973

Laboratory No. 1575 h

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 5001	P	17	17		8	9		1.75	
H 5002	NP	0						----	
H 5003	P	13	12		3	9	1	1.76	
H 5004	P	12	12		5	7		1.83	
H 5005	P	14	14		6	8		1.71	
H 5006	P	12	12		8	4		1.54	
H 5007	P	12	12		6	6		1.61	
H 5008	P	12	12		8	4		1.87	
H 5009	P	12	12		6	6		2.02	
H 5010	P	9	9		4	5		1.89	
H 5011	NP	0						----	
H 5012	P	11	10		4	6	1	1.70	
H 5013	NP	0						----	
H 5014	P	11	5		0	5	6	1.51	
H 5015	P	14	14		5	9		1.91	
H 5016	P	15	15		4	11		1.70	
H 5017	P	12	12		6	6		1.99	
H 5018	P	18	18		7	11		1.81	
H 5019	P	16	16		5	11		1.86	
H 5020	P	18	18		8	10		1.79	
H 5021	P	11	11		4	7		1.62	
H 5022	P	15	15		8	7		1.63	
H 5023	P	12	11		4	7	1	1.84	
H 5024	P	16	16		10	6		1.90	
H 5025	P	13	13		9	4		2.03	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 244

Material FDA 71-54

Dose 12.6 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 16, 1973

Laboratory No. 1575 h

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 5031	P	16	16		8	8		1.83	
H 5032	NP	0						----	
H 5033	P	13	6	7	1	5		1.93	
H 5034	P	17	17		7	10		1.79	
H 5035	P	13	13		5	8		1.67	
H 5036	P	12	12		5	7		1.74	
H 5037	P	14	14		6	8		1.91	
H 5038	P	8	6		3	3	2	1.93	
H 5039	P	16	16		11	5		1.89	
H 5040	P	13	12		5	7	1	1.98	
H 5041	P	16	16		5	11		1.57	
H 5042	NP	0						----	
H 5043	P	9	9		4	5		1.76	
H 5044	P	14	14		6	8		1.62	
H 5045	P	17	17		9	8		1.78	
H 5046	P	12	12		5	7		2.04	
H 5047	NP	0						----	
H 5048	P	11	10		3	7	1	1.71	
H 5049	P	9	9		4	5		1.86	
H 5050	P	11	10		2	8	1	2.02	
H 5051	P	11	11		5	6		1.65	
H 5052	NP	0						----	
H 5053	P	16	16		7	9		1.57	
H 5054	NP	0						----	
H 5055	NP	0						----	
H 5056	P	17	17		7	10		1.91	
H 5057	P	15	15		9	6		1.94	
H 5058	P	13	13		3	10		1.86	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 245

Material FDA 71-54

Dose 58.7 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 16, 1973

Laboratory No. 1575 h

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 5061	P	14	14		7	7		1.90	
H 5062	NP	0						----	
H 5063	P	17	16		4	12	1	1.56	
H 5064	P	11	11		3	8		1.79	
H 5065	P	14	13		4	9	1	1.80	
H 5066	P	14	13	1	7	6		1.71	
H 5067	P	11	11		5	6		1.61	
H 5068	P	14	12		5	7	2	1.72	
H 5069	P	18	18		10	8		1.93	
H 5070	P	10	8		5	3	2	1.94	
H 5071	P	15	15		5	10		1.67	
H 5072	P	15	15		8	7		2.10	
H 5073	P	13	13		6	7		1.51	
H 5074	P	17	17		7	10		1.67	
H 5075	P	9	9		3	6		1.84	
H 5076	P	14	12		5	7	2	1.86	
H 5077	P	14	14		5	9		1.71	
H 5078	P	15	14		5	9	1	1.78	
H 5079	P	11	11		5	6		1.89	
H 5080	P	10	10		8	2		1.79	
H 5081	NP	0						----	
H 5082	P	12	12		5	7		1.81	
H 5083	P	12	12		3	9		1.82	
H 5084	P	12	12		7	5		1.79	
H 5085	P	11	11		5	6		1.71	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 246

Material FDA 71-54

Dose 272.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date April 16, 1973

Laboratory No. 1575 h

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 5091	P	13	11		7	4	2	1.86	
H 5092	NP	0						----	
H 5093	NP	0						----	
H 5094	P	14	14		3	11		1.76	
H 5095	P	16	16		6	10		1.95	
H 5096	P	14	14		5	9		1.73	
H 5097	P	18	18		13	5		1.69	
H 5098	P	13	12		5	7	1	1.84	
H 5099	P	10	9		3	6	1	1.94	
H 5100	P	13	11		4	7	2	1.66	
H 5101	NP	0						----	
H 5102	P	15	15		7	8		1.78	
H 5103	P	12	12		5	7		1.87	
H 5104	P	10	10		4	6		1.89	
H 5105	P	17	17		9	8		1.99	
H 5106	P	10	9		2	7	1	1.97	
H 5107	NP	0						----	
H 5108	P	10	10		4	6		1.95	
H 5109	P	16	16		6	10		1.72	
H 5110	P	11	11		4	7		1.82	
H 5111	P	12	12		4	8		1.78	
H 5112	NP	0						----	
H 5113	P	11	11					----	Natural Birth Day 14
H 5114	NP	0						----	
H 5115	P	11	11		5	6		1.89	
H 5116	P	16	15		4	11	1	2.00	
H 5117	P	15	15		8	7		1.81	
H 5118	P	12	12		3	9		2.13	
H 5119	P	13	13		3	10		1.48	

* P = Pregnant; NP = Not Pregnant

RABBITS

FOOD AND DRUG
Research LABORATORIES, INC.

FINAL REPORT

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

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

Date August 9, 1973

Laboratory No. 1576 h
Contract No. FDA 71-260

Sample: Fine white crystalline material

Marking: FDA 71-54 (Citric acid)

Examination Requested: Teratologic evaluation of FDA 71-54 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion:

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

"The administration of up to 425 mg/kg (body weight) of the test material to pregnant rabbits for 13 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

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 241 through 246

Material: FDA 71-54

Date: July 9, 1973

Laboratory No.: 1576 h

Table 1

Fate Summary
(Rabbits)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
241	Sham	0.0	13	9	13	9
242	6-AN*	2.5	15	10	15	10
243	FDA 71-54	4.25	18	14	13	11
244	FDA 71-54	19.75	14	10	13	10
245	FDA 71-54	91.7	15	9	14	9
246	FDA 71-54	425.0	15	14	15	14

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

** Administered as a water solution (See Appendix I)

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 241 through 246

Material: FDA 71-54

Table 2
Reproduction Data
(Rabbits)

Date: July 9, 1973

Laboratory No.: 1576 h

Group:	241	242	243	244	245	246
Dose (mg/kg):	Sham	6-AN**	4.25	19.75	91.7	425.0
Pregnancies						
Total No.	9	10	14	10	9	14
Died or Aborted (before Day 29)	0	0	3	0	0	0
To term (on Day 29)	9	10	11	10	9	14
Corpora Lutea						
Total No.	136	153	211	173	122	201
Average/dam mated	15.1	15.3	13.2	14.4	11.1	14.4
Live Litters						
Total No.*	8	10	10	10	9	13
Implant Sites						
Total No.	49	67	67	63	47	67
Average/dam*	5.44	6.70	6.09	6.30	5.22	4.79
Resorptions						
Total No.*	6	9	13	2	--	4
Dams with 1 or more sites resorbed	6	7	4	2	--	3
Dams with all sites resorbed	1	--	1	--	--	1
Per cent partial resorptions	66.7	70.0	36.4	20.0	--	21.4
Per cent complete resorptions	11.1	--	9.09	--	--	7.14
Live Fetuses						
Total No.	43	58	54	60	47	61
Average/dam*	4.78	5.80	4.91	6.00	5.22	4.36
Sex ratio (M/F)	0.95	1.00	0.93	1.07	1.04	0.91
Dead Fetuses						
Total No.*	--	--	--	1	--	2
Dams with 1 or more dead	--	--	--	1	--	2
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	--	--	--	10.0	--	14.3
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	37.9	32.3	36.6	36.7	37.6	35.0

* Includes only those dams examined at term.

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246 | Laboratory No. 1576 h

Table 3

Material FDA 71-54 | Date July 9, 1973

Summary of Skeletal Findings*
(Rabbits)

Findings / Group No.:	241	242	243	244	245	246
Dose (mg/kg):	Sham	6-AN**	4.25	19.75	91.7	425.0
Live Fetuses Examined (at term)	43/8	58/10	54/10	51/9[a]	47/9	54/12[a]
Sternebrae						
Incomplete oss.	1/1	5/3	2/2	4/3	2/2	5/3
Scrambled						
Bipartite			1/1	1/1	1/1	
Fused		4/3	4/3			
Extra		3/2	3/2		3/3	2/2
Missing		6/5		7/2	3/1	
Other						
Ribs						
Incomplete oss.						
Fused/split		15/8				
Wavy						
Less than 12						
More than 13						
Other						
Vertebrae						
Incomplete oss.						
Scrambled		13/9				
Fused						
Extra ctrs. oss.						
Scoliosis		8/5				
Tail defects		53/10				
Other						
Skull						
Incomplete closure		1/1				
Missing		1/1				
Craniostosis		3/2				
Other						
Extremities						
Incomplete oss.						
Missing						
Extra						
Miscellaneous						

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

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

[a] One litter lost in processing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246 Date July 9, 1973

Material FDA 71-54 Laboratory No. 1576 h

Table 3-a

Summary of Soft Tissue Abnormalities
(Rabbits)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
242	6-AN*	2.5	Z 6392	8	Anopia
			Z 6394	7	Anopia; medial rotation of hind limbs; club feet
			Z 6396	1	Anopia; medial rotation of hind limbs
				1	Anopia
			Z 6397	6	Anopia
			Z 6398	6	Anopia
			Z 6401	4	Anopia
			Z 6402	7	Anopia
			Z 6404	6	Anopia
				1	Anopia; medial rotation of hind limbs

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 241 through 246

Date July 9, 1973

Species Rabbits

Laboratory No. 1576 h

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	Day 6	Day 12	Day 18	Day 29**
		mg/kg	kg				
241	Sham	0.0	2.21	2.26	2.34	2.41	2.48 (9)
242	6-AN***	2.5	2.22	2.38	2.57	2.47	2.56 (10)
243	FDA 71-54	4.25	2.33	2.45	2.47	2.45	2.57 (11)
244	FDA 71-54	19.75	2.07	2.26	2.31	2.38	2.57 (10)
245	FDA 71-54	91.9	1.96	2.00	2.10	2.19	2.24 (9)
246	FDA 71-54	425.0	2.07	2.13	2.13	2.18	2.20 (14)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

Appendix I

Teratology Study in Rabbits

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

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

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

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 241

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date July 9, 1973

Laboratory No. 1576

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 6391	P	15	7	7		4	3		35.4	
S 6392	NP	--**	0						----	
S 6393	P	14	8	7		3	4	1	43.3	One Neonatal Death
S 6394	NP	--**	0						----	
S 6395	P	5	1					1	----	
S 6396	P	10	4	4		2	2		36.2	
S 6397	P	11	5	5		4	1		36.2	
S 6398	NP	--**	0						----	
S 6399	NP	--**	0						----	
S 6400	P	25	7	6		2	4	1	33.7	
S 6401	P	20	6	5		4	1	1	42.8	
S 6402	P	22	6	5		0	5	1	40.4	
S 6409	P	14	5	4		2	2	1	35.5	

* P = Pregnant; NP = Not Pregnant
** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 242

Material 6-AN

Dose 2.5 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date July 9, 1973

Laboratory No. 1576

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Z 6391	P	13	5	5		2	3		37.8	One Neonatal Death
Z 6392	P	17	9	8		4	4	1	32.9	One Neonatal Death
Z 6393	NP	--**	0						----	
Z 6394	P	15	7	6		3	3	1	25.9	Four Neonatal Deaths
Z 6395	NP	--**	0						----	
Z 6396	P	9	2	2		0	2		26.0	Two Neonatal Deaths
Z 6397	P	11	7	6		3	3	1	30.4	Five Neonatal Deaths
Z 6398	P	10	6	6		2	4		28.6	Six Neonatal Deaths
Z 6399	NP	--**	0						----	
Z 6400	NP	--**	0						----	
Z 6401	P	27	5	4		2	2	1	38.6	
Z 6402	P	20	10	7		5	2	3	36.1	Three Neonatal Deaths
Z 6403	P	21	8	7		4	3	1	35.8	Two Neonatal Deaths
Z 6404	P	10	8	7		4	3	1	30.9	One Neonatal Death
Z 6405	NP	--**	0						----	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 243

Material FDA 71-54

Dose 4.25 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date July 9, 1973

Laboratory No. 1576 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 6001	P	9	6	6		2	4		34.0	
H 6002	P	11	7	6		2	4	1	37.1	
H 6003	P	7	2	2		0	2		41.8	
H 6004	NP	12	0						----	Died Day 25
H 6005	P	28	13	--		--	--		----	Died Day 23
H 6006	P	13	5	5		1	4		39.4	
H 6007	P	11	9	6		3	3	3	37.7	
H 6008	P	8	4	3		3	0	1	43.5	
H 6009	P	15	5	5		2	3		35.4	
H 6010	P	11	2	--		--	--		----	Died Day 16
H 6011	NP	0	0						----	Died Day 17
H 6012	P	14	8					8	----	
H 6013	P	19	6	6		2	4		21.8	One Neonatal Death
H 6014	P	22	10	--		--	--		----	Died Day 7
H 6015	NP	--**	0						----	
H 6017	P	10	8	8		6	2		30.9	One Neonatal Death
H 6019	P	21	7	7		5	2		43.9	
H 6018	NP	--**	0						----	

* P = Pregnant; NP = Not Pregnant
** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 244

Material FDA 71-54

Dose 19.75 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date July 9, 1973

Laboratory No. 1576 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 6021	NP	--**	0						----	
H 6022	NP	--**	0						----	
H 6023	P	12	6	6		3	3		35.7	
H 6024	NP	12	0						----	
H 6025	P	19	11	11		6	5		40.5	One Neonatal Death
H 6026	P	12	5	5		3	2		43.2	
H 6027	P	10	5	5		0	5		34.8	
H 6028	P	13	3	3		2	1		33.5	
H 6029	P	14	6	6		4	2		38.8	
H 6030	P	17	7	6		2	4	1	30.2	One Neonatal Death
H 6032	NP	0	0						----	Died Day 19
H 6033	P	19	9	9		6	3		34.6	
H 6034	P	12	8	7	1	5	2		29.8	
H 6035	P	23	3	2		0	2	1	45.7	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 245

Material FDA 71-54

Dose 91.70 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date July 9, 1973

Laboratory No. 1576 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 6041	P	17	5	5		2	3		42.7	
H 6043	P	12	5	5		2	3		41.8	
H 6045	NP	4	0						----	
H 6046	NP	--**	0						----	
H 6047	P	7	3	3		2	1		47.5	
H 6048	P	12	5	5		3	2		38.9	
H 6049	P	8	6	6		2	4		35.7	
H 6050	P	14	6	6		2	4		33.2	
H 6051	P	9	4	4		2	2		27.7	
H 6052	P	14	1	1		1	0		36.4	
H 6053	NP	5	0						----	Died Day 23
H 6060	P	20	12	12		8	4		34.6	
H 6056	NP	--**	0						----	
H 6059	NP	--**	0						----	
H 6061	NP	--**	0						----	

* P = Pregnant; NP = Not Pregnant
** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 246

Material FDA 71-54

Dose 425.0 mg/kg

Appendix II

Reproduction Data in Rabbits (Individual)

Date July 9, 1973

Laboratory No. 1576 h

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
H 6061	P	16	6	6		4	2		40.5	
H 6062	P	17	6	5		1	4	1	40.1	One Neonatal Death
H 6063	P	13	7	7		5	2		36.3	
H 6064	P	18	6	5	1	1	4		20.8	Three Neonatal Deaths
H 6065	P	11	7	7		3	4		34.2	One Neonatal Death
H 6066	P	16	4	4		2	2		38.0	
H 6067	P	13	5	5		2	3		41.4	
H 6068	P	10	2	2		1	1		33.8	
H 6069	P	11	5	5		3	2		42.2	
H 6070	P	15	7	7		3	4		32.8	
H 6072	P	13	2					2	----	
H 6073	P	19	4	4		2	2		44.2	
H 6074	NP	--**	0						----	
H 6075	P	12	3	2	1	1	1		33.9	Two Neonatal Deaths
H 6076	P	17	3	2		1	1	1	51.9	

* P = Pregnant; NP = Not Pregnant
** Not Recorded