Final report-Teratological Evaluation of FDA 71-5 (**Calcium Carragheenate**) in Mice, Rats, Hamsters & Rabbits 5/1/72

Teratological Evaluation of #14
FDA 71-5 (Calcium
carrageenate) in, Mice, Rats
Hamsters and Rabbits

F7

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 May 1, 1972

Laboratory No. 0728 f
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-5 (Calcium carragheenate)

Examination Requested: Teratologic evaluation of FDA 71- 5 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

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

"The administration of the test material in graded dosage levels up to 900 mg/kg (body weight) to pregnant mice for 10 consecutive days caused an apparent increase in the number of resorptions and/or fetal deaths in utero. There was a corresponding decrease in the number of live pups and a reduction in pup weight at delivery, both of which appear to have been dose-dependent. A concurrent retardation in skeletal maturation may be inferred from the increased incidence of missing sternebrae and incomplete skull closure. All other soft and skeletal tissue abnormalities were probably within the accepted limits of variability for the species."

It was concluded that the test material was fetotoxic in the pregnant mouse without exhibiting frank teratogenicity.

(See following page for comment)

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

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

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 31 & 32; 37 through 40

Material: FDA 71-5

Table 1

Fate Summary
(Mice)

Date March 31, 1972

Laboratory No. 0728 f

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
31	Sham	0	27	27	26	26
32	Aspirin*	150	26	24	22	21
37	FDA 71-5	10	25	24	25	24
38	FDA 71-5	45	28	27	26	25
39	FDA 71-5	470	28	23	28	23
40	FDA 71-5	900	40	30	30	25

* Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 31 & 32; 37 through 40

Date March 31, 1972

Material: FDA 71-5

Laboratory No. 0728 f

Table 2
Reproduction Data
(Mice)

Group:	31	32	37	38	39	40
Dose (mg/kg):	Sham	Aspirin**	10	45	470	900
Pregnancies						
Total No.	27	24	24	27	23	30
Died or Aborted (before Day 17)	1	4	0	2	0	10
To term (on Day 17)	26	21	24	25	23	25
Live litters						
Total No. *	26	20	24	25	22	23 ~~23~~ 23+2
Implant sites						
Total No.	306	241	282	299	281	279 ~~279~~
Average/dam *	11.8	11.5	11.8	12.0	12.2	11.7 ~~11.2~~ 11.2
Resorptions						
Total No. *	10	21	11	10	20	35
Dams with 1 or more sites resorbed	4	7	8	6	8	12
Dams with all sites resorbed	0	1	0	0	1	2
Per cent partial resorptions	15.4	33.3	33.3	24.0	34.8	48.0
Per cent complete resorptions	-	4.76	-	-	4.35	8.0
Live fetuses						
Total No.	296	218	268	285	258	244 ~~243~~
Average/dam *	11.4	10.4	11.2	11.4	11.2	9.77 ~~9.72~~
Dead fetuses						
Total No. *	0	2	3	4	3	1
Dams with 1 or more dead	-	2	3	3	2	1
Dams with all dead	-	0	0	0	0	-
Per cent partial dead	-	9.52	12.5	12.0	8.70	4.0
Per cent all dead	-	-	-	-	-	-
Average fetus weight, g	0.96	0.92	1.03	0.92	0.95	0.80

* Includes only those dams examined at term.

** Positive control: 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40 — Laboratory No. 0728 f

Table 3

Material FDA 71-5 — Date March 31, 1972

Summary of Skeletal Findings*

(Mice)

Findings / Group No. / Dose (mg/kg)	31 Sham	32 Aspirin**	37 10	38 45	39 470	40 900
Live Fetuses Examined	193/25	151/20	185/24	197/25	179/22	163/23
Sternebrae						
Incomplete oss.	23/13	44/16	35/13	62/21	31/11	46/16
Scrambled			1/1	1/1		
Bipartite	5/3	11/7	13/6	13/9	8/6	31/10
Fused						
Extra			2/1		1/1	
Missing	4/3	2/2	4/3	18/5	13/4	34/9
Ribs						
Incomplete oss.						
Fused/split			1/1			
Wavy						1/1
Less than 12						
More than 13	16/9	7/5	13/6	16/8	14/7	2/2
Other						
Vertebrae						
Incomplete oss.			1/1	6/2		5/3
Scrambled			5/2			
Fused						
Extra ctrs. oss.	1/1					
Scoliosis			1/1			
Tail defects						
Other						
Skull						
Incomplete closure		2/1	6/4		12/4	8/3
Missing						
Craniostosis						
Other; exencephaly	1/1				1/1	
Extremities						
Incomplete oss.				5/2	3/1	
Missing						
Extra						
Miscellaneous						
Hyoid; reduced	8/5	14/8	9/7	36/19	15/10	15/9
Hyoid; missing	8/7	19/9	10/6	18/11	24/11	38/12

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40 Date March 31, 1972

Material FDA 71-5 Laboratory No. 0728 f

Table 3-a

Summary of Soft Tissue Abnormalities

(Mice)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
32	Aspirin	150	A-8104	1	Fetal monster
				1	Anopia
				1	Mouth and nasal absent

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40

Species Mice

Date March 31, 1972

Laboratory No. 0728 f

Table 4

Average Body Weights

Group	Material	Dose Level	Day 0	6	11	15	17	**
		mg/kg	g					
31	Sham	0	26.6	29.8	34.0	40.2	48.1	(26)
32	Aspirin	150	26.8	30.0	33.0	37.9	43.6	(21)
37	FDA 71-5	10	27.6	30.0	34.8	44.5	49.5	(24)
38	FDA 71-5	45	27.6	29.3	33.8	41.5	48.6	(25)
39	FDA 71-5	470	28.8	31.7	33.4	40.3	47.0	(23)
40	FDA 71-5	900	27.8	29.8	30.2	34.5	39.8	(25)

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

Appendix I

Teratology Study in Mice

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

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 31

Material Sham

Dose 0

Date March 31, 1972

Laboratory No. 0728

Dam No.	Fate *	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
S 8091	P	11	9		2	0.92	
S 8092	P	14		14		----	Died Day 15
S 8093	P	14	14			0.97	
S 8094	P	13	10		3	0.94	
S 8095	P	13	13			0.85	
S 8096	P	14	14			0.93	
S 8097	P	16	16			0.95	
S 8098	P	11	11			0.96	
S 8099	P	13	13			0.97	
S 8100	P	13	13			0.90	
S 8101	P	8	8			0.99	
S 8102	P	12	12			1.11	
S 8103	P	8	8			0.97	
S 8104	P	11	11			0.91	
S 8105	P	10	10			0.95	
S 8106	P	13	13			0.89	
S 8107	P	13	13			0.88	
S 8108	P	11	11			0.92	
S 8109	P	13	12		1	0.99	
S 8110	P	15	15			1.04	
S 8111	P	15	15			1.06	
S 8112	P	9	9			1.02	
S 8113	P	12	12			0.98	
S 8114	P	3	3			1.08	
S 8115	P	13	13			0.87	
S 8116	P	12	8		4	1.04	
S 8117	P	10	10			0.87	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 32

Material Aspirin

Dose 150 mg/kg

Date March 31, 1972

Laboratory No. 0728

Dam No.	Fate *	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
A 8091	P	14		13	1	----	Died Day 16
A 8092	P	15		14	1	----	Died Day 16
A 8093	P	12	12			0.69	
A 8094	P	11	11			0.96	
A 8095	P	15			15	----	
A 8096	P	11	10		1	0.95	
A 8097	P	13	12		1	0.91	
A 8098	P	10	10			0.84	
A 8099	P	12	12			0.85	
A 8100	P	14	14			0.85	
A 8101	P	10	9		1	1.22	
A 8102	P	10	10			1.02	
A 8103	P	15	14	1		0.89	
A 8104	P	10	9	1		0.90	
A 8105	NP	0				----	Died Day 13
A 8106	--	--				----	Number not assigned.
A 8107	P	11	10		1	0.88	
A 8108	P	12	12			0.84	
A 8109	P	12	12			1.01	
S 8110	P	12		12		----	Died Day 14
S 8111	P	11	10		1	0.96	
S 8112	P	8	8			0.91	
S 8113	P	10	10			0.92	
S 8114	P	12	12			1.00	
S 8115	P	9	8		1	0.93	
S 8116	NP	0				----	
S 8117	P	13	13			0.93	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 37

Material FDA 71-5

Dose 10 mg/kg

Date March 31, 1972

Laboratory No. 0728 f

Dam No.	Fate *	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 8001	P	11	11			0.89	
F 8002	P	13	13			0.97	
F 8003	P	14	14			1.01	
F 8004	P	11	11			0.93	
F 8005	P	16	16			0.81	
F 8006	P	12	11		1	0.86	
F 8007	P	13	13			0.99	
F 8008	P	10	9		1	1.30	
F 8009	NP	0				----	
F 8010	P	11	10		1	1.01	
F 8011	P	15	14	1		1.04	
F 8012	P	9	7	1	1	1.41	
F 8013	P	11	10		1	1.12	
F 8014	P	7	4		3	0.88	
F 8015	P	12	12			0.86	
F 8016	P	11	11			1.12	
F 8017	P	10	10			1.01	
F 8018	P	11	11			1.27	
F 8019	P	14	14			0.88	
F 8020	P	13	13			1.20	
F 8021	P	10	10			1.28	
F 8022	P	13	12		1	1.28	
F 8023	P	12	12			0.80	
F 8024	P	13	12	1		0.86	
F 8025	P	10	8		2	0.84	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 38 | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Mice (Individual) | Laboratory No. 0728 f

Dose 45 mg/kg

Dam No.	Fate *	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 8031	P	13	11	2		0.95	
F 8032	P	14	14			0.99	
F 8033	P	11	10	1		0.97	
F 8034	P	14		14		----	Died Day 17
F 8035	P	10	10			1.02	
F 8036	P	9			9	----	Died Day 15
F 8037	-	-				----	Number not assigned.
F 8038	P	13	13			0.93	
F 8039	P	9	9			0.80	
F 8040	P	11	10	1		0.76	
F 8041	P	9	9			0.98	
F 8042	P	11	11			0.97	
F 8043	P	9	9			0.98	
F 8044	P	11	10		1	0.94	
F 8045	NP	0				----	
F 8046	P	11	10		1	1.05	
F 8047	P	12	12			1.06	
F 8048	P	10	8		2	1.06	
F 8049	P	12	11		1	0.93	
F 8050	P	18	18			0.85	
F 8051	P	15	15			0.94	
F 8052	P	11	11			0.61	
F 8053	P	12	12			0.98	
F 8054	P	11	11			0.99	
F 8055	P	12	12			0.86	
F 8056	P	11	11			0.93	
F 8057	P	15	15			0.87	
F 8058	P	13	9		4	0.75	
F 8059	P	15	14		1	0.77	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 39

Material FDA 71-5

Dose 470 mg/kg

Date March 31, 1972

Laboratory No. 0728 f

Dam No.	Fate *	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 8061	P	13			13	----	
F 8062	P	15	15			0.95	
F 8063	P	14	14			0.88	
F 8064	P	10	10			0.97	
F 8065	P	13	13			0.93	
F 8066	P	13	13			0.87	
F 8067	P	10	9		1	0.85	
F 8068	NP	--	--			----	
F 8069	P	13	13			0.74	
F 8070	P	12	12			0.94	
F 8071	P	7	6		1	0.91	
F 8072	NP	0	--			----	
F 8073	NP	0	-			----	
F 8074	P	11	11			1.04	
F 8075	P	12	12			0.92	
F 8076	NP	--	--			----	
F 8077	P	12	11		1	1.03	
F 8078	P	12	11		1	0.90	
F 8079	P	17	17			0.85	
F 8080	P	12	10	2		1.09	
F 8081	P	12	12			0.93	
F 8082	P	12	11		1	1.18	
F 8083	NP	0				----	
F 8084	P	13	13			1.20	
F 8085	P	12	12			1.24	
F 8086	P	13	11	1	1	0.55	
F 8087	P	13	12		1	0.78	
F 8088	P	10	10			1.08	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 40

Material FDA 71-5

Dose 900 mg/kg

Date March 31, 1972

Laboratory No. 0728 f

Dam No.	Fate *	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 8091	P	14	14			0.64	
F 8092	P	12	12			0.85	
F 8093	P	11	11			0.68	
F 8094	P	14	14			0.85	
F 8095	P	16	1		15	----	
F 8096	NP	--				----	
F 8097	P	8			8	----	
F 8098	P	11	10		1	0.80	
F 8099	NP	--				----	Died Day 13
F 8100	P	12	11		1	0.62	
F 8101	P	10	9		1	1.05	
F 8102	P	10		10		----	Died Day 12
F 8103	NP	--				----	
F 8104	P	9	8		1	0.96	
F 8105	NP	--				----	Died Day 14
F 8106	NP	--				----	
F 8107	P	10	10			0.97	
F 8108	P	6	6			0.76	
F 8109	NP	--				----	Died Day 12
F 8110	P	12		12		----	Died Day 15
F 8111	P	9	9			0.68	
F 8112	P	10		8	2	----	Died Day 15
F 8113	P	13	12		1	0.85	
F 8114	P	8	8			0.60	
F 8115	P	13	13			0.72	
F 8116	P	7			7	----	Died Day 11
F 8117	P	9	9			----	Aborted Day 16
F 8118	P	11	11			0.79	
F 8119	P	11	10		1	0.61	

* P= Pregnant; NP= Not Pregnant

(continued on following page)

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 40 (concluded) | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Mice (Individual) | Laboratory No. 0728 f

Dose 900 mg/kg

Dam No.	Fate *	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 8120	P	2			2	----	
F 8121	P	9	8	1		0.94	
F 8122	NP	--				----	
F 8123	P	12	11		1	0.92	
F 8124	P	15	13		2	0.88	
F 8125	P	14	14			0.73	
F 8126	NP	--				----	Died Day 12.
F 8127	NP	--				----	
F 8128	P	13	12		1	0.94	
F 8129	NP	--				----	Died Day 12
F 8130	P	16	16			0.80	
		327	252				
		48	9				
		279	243				

* 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 May 1, 1972

Laboratory No. 0729 f
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-5 (Calcium carragheenate)

Examination Requested: Teratologic evaluation of FDA 71- 5 in rats

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

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

"The administration of the test material in graded dosage levels up to 600 mg/kg (body weight) to pregnant rats for 10 consecutive days caused an apparent increase in the number of resorption sites observed with or without a corresponding decrease in the number of live pups delivered. At the highest dose level, there may have been a decrease in the birth weight of the pups. A concurrent retardation in skeletal maturation was indicated by a dose-dependent increase in missing sternebrae. There were no other findings in either soft or skeletal tissues which appeared to be treatment-related.

It was concluded that the test material depressed fetal development in the pregnant rat and caused an increase in early fetal deaths (resorptions). There was no evidence of frank teratogenicity.

(See following page for comment)

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

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

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 31 & 32; 37 through 40

Material: FDA 71-5

Table 1

Fate Summary
(Rats)

Date March 31, 1972

Laboratory No. 0729 f

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
31	Sham	0	25	23	25	23
32	Aspirin*	250	29	27	25	24
37	FDA 71-5	40	24	23	23	22
38	FDA 71-5	100	24	22	24	22
39	FDA 71-5	240	25	22	22	20
40	FDA 71-5	600	28	21	24	19

* Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 31 & 32: 37 through 40

Material: FDA 71-5

Table 2
Reproduction Data
(Rats)

Date March 31, 1972

Laboratory No. 0729 f

Group:	31	32	37	38	39	40
Dose (mg/kg):	Sham	Aspirin**	40	100	240	600
Pregnancies						
Total No.	23	27	23	22	22	21
Died or Aborted (before Day 20)	0	4	1	0	3	4
To term (on Day 20)	23	24	22	22	20	19
Live litters						
Total No. *	23	18	22	22	20	19
Implant sites						
Total No.	252	267	233	246	233	184
Average/dam *	11.0	11.1	10.6	11.2	11.7	9.68
Resorptions						
Total No. *	7	110	9	4	6	21
Dams with 1 or more sites resorbed	5	15	6	4	6	8
Dams with all sites resorbed	0	5	0	0	0	0
Per cent partial resorptions	21.7	62.5	27.3	16.0	30.0	42.1
Per cent complete resorptions	-	20.8	-	-	-	-
Live fetuses						
Total No.	245	156	224	241	226	162
Average/dam *	10.7	6.50	10.2	11.0	11.3	8.53
Dead fetuses						
Total No. *	0	1	0	1	1	1
Dams with 1 or more dead	-	1	-	1	1	1
Dams with all dead	-	0	-	0	0	0
Per cent partial dead	-	4.17	-	4.55	5.00	5.26
Per cent all dead	-	0	-	-	-	-
Average fetus weight, g	3.75	2.47	3.99	3.91	3.70	3.43

* Includes only those dams examined at term.

** Positive control: 250 mg/kg.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40 — Laboratory No. 0729 f

Table 3

Material FDA 71-5 — Date March 31, 1972

Summary of Skeletal Findings*

(Rats)

Findings / Group No. / Dose (mg/kg)	31 Sham	32 Aspirin**	37 40	38 100	39 240	40 600
Live Fetuses Examined	171/23	103/17	155/22	168/22	157/22	112/19
Sternebrae						
Incomplete oss.	93/23	41/15	73/20	149/22	104/19	81/20
Scrambled	18/11	16/6	16/11	62/21	41/19	31/14
Bipartite	16/10	27/10	7/7		21/10	4/4
Fused						
Extra					3/1	
Missing	23/10	91/17	30/10	8/6	28/8	45/12
Other						
Ribs						
Incomplete oss.		2/2				
Fused/split		3/3			1/1	
Wavy	1/1	18/8		4/3		9/5
Less than 12					1/1	
More than 13	2/2	19/7	1/1			
Other						
Vertebrae						
Incomplete oss.		9/5			2/1	
Scrambled		15/7			6/3	
Fused					1/1	
Extra ctrs. oss.						
Scoliosis		1/1			1/1	3/3
Tail defects						
Other						
Skull						
Incomplete closure	19/12	10/3	43/17	5/5	19/7	10/6
Missing					2/1	
Craniostosis	2/1					
Other						
Extremities						
Incomplete oss.		1/1				
Missing		1/1				
Extra						
Miscellaneous						
Hyoid; reduced	12/7	28/6	14/8	23/10	18/13	10/7
Hyoid; missing	11/6	51/13	17/11	7/5	13/10	23/10

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

** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40 Date March 31, 1972

Material FDA 71-5 Laboratory No. 0729 f

Table 3-a

Summary of Soft Tissue Abnormalities

(Rats)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
32	Aspirin	250	A-9091	1	Meningoencephalocele
32	Aspirin	250	A-9104	6	Anopia
				5	Club feet
				6	Hydrocephalus
				6	Umbilical hernia
				5	Cleft palate
				6	Meningoencephalocele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40

Species Rats

Table 4

Average Body Weights *

Date March 31, 1972

Laboratory No. 0729 f

Group	Material	Dose Level	Day 0	6	11	15	20	**
		mg/kg	g					
31	Sham	0	216	236	250	270	322	(23)
32	Aspirin	250	230	247	254	269	308	(24)
37	FDA 71-5	40	211	228	243	263	322	(22)
38	FDA 71-5	100	221	238	252	271	337	(22)
39	FDA 71-5	240	215	238	251	265	330	(20)
40	FDA 71-5	600	212	234	236	243	301	(19)

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

Appendix I

Teratology Study in Rats

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

Body weights were recorded on Days 0, 6, 11, 15, and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 20 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 31

Material Sham

Dose 0

Date March 31, 1972

Laboratory No. 0729

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
S 9091	P	11	11			4.09	
S 9092	P	11	11			3.84	
S 9093	P	9	9			4.13	
S 9094	P	12	12			3.70	
S 9095	P	12	12			3.36	
S 9096	P	11	11			3.64	
S 9097	P	6	4		2	4.17	
S 9098	P	9	9			3.71	
S 9099	NP	0				----	
S 9100	P	14	14			3.44	
S 9101	P	14	13		1	3.88	
S 9102	P	7	7			4.13	
S 9103	P	11	11			3.93	
S 9104	P	10	8		2	3.32	
S 9105	P	8	8			3.43	
S 9106	P	12	12			4.02	
S 9107	P	10	10			4.12	
S 9108	NP	0				----	
S 9109	P	12	12			3.95	
S 9110	P	10	9		1	3.98	
S 9111	P	8	8			3.92	
S 9112	P	12	12			3.90	
S 9113	P	14	14			3.83	
S 9114	P	11	11			3.44	
S 9115	P	18	17		1	2.32	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 32

Material Aspirin

Dose 250 mg/kg

Date March 31, 1972

Laboratory No. 0729

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
A 9091	P	13	8		5	2.15	
A 9092	P	12			12	----	
A 9093	P	11		11		----	Died Day 7.
A 9094	P	13	1		12	1.79	
A 9095	P	11	2		9	1.76	
A 9096	P	14	14			3.12	
A 9097	P	14	14			3.07	
A 9098	P	12			12	----	
A 9099	NP	0				----	
A 9100	P	13	13			2.58	
A 9101	P	13			13	----	
A 9102	P	12	10		2	2.20	
A 9103	P	7	1		6	1.70	
A 9104	P	10	8		2	1.75	
A 9105	P	11		1	10	----	
A 9106	P	15	10		5	2.36	
A 9107	P	9	9			2.60	
A 9108	P	10	10			2.49	
A 9109	P	11	11			2.55	
A 9110	P	6			6	----	
A 9111	P	11	11			3.86	
A 9112	NP	0				----	Died Day 8.
A 9113	P	11	8		3	2.83	
A 9114	P	12		12		----	
A 9115	P	11	11			2.66	
A 9116	P	9	9			2.49	
A 9117	P	14			14	----	
A 9118	P	8	6		2	2.51	
A 9120	P	11			11	----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 37

Material FDA 71-5

Dose 40 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date March 31, 1972

Laboratory No. 0729 f

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 9001	P	11	11			3.87	
F 9002	P	10	10			3.74	
F 9003	P	10	10			3.88	
F 9004	P	13	12		1	4.28	
F 9005	P	10	10			3.41	
F 9006	NP	0				----	
F 9007	P	5	5			3.76	
F 9008	P	14	12		2	3.43	
F 9009	P	8	8			3.84	
F 9010	P	11	11			3.79	
F 9011	P	13	13			4.05	
F 9012	P	14	12		2	3.99	
F 9013	P	10	10			4.02	
F 9014	P	12	11		1	3.91	
F 9015	P	6	6			4.34	
F 9016	P	11	11			4.35	
F 9017	P	9	9			5.66	
F 9018	P	10		10		----	Died Day 20.
F 9019	P	11	11			3.92	
F 9020	P	11	11			3.84	
F 9021	P	9	9			4.17	
F 9022	P	9	9			4.13	
F 9023							Number not assigned
F 9024							Number not assigned
F 9025	P	13	12		1	4.08	
F 9026	P	13	11		2	3.25	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 38

Material FDA 71-5

Dose 100 mg/kg

Date March 31, 1972

Laboratory No. 0729 f

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 9031	P	9	9			3.70	
F 9032	P	11	11			3.79	
F 9033	P	13	12		1	4.16	
F 9034	P	14	14			3.58	
F 9035	P	13	13			4.17	
F 9036	P	8	8			3.77	
F 9037	P	11	10	1		3.89	
F 9038	NP	0				----	
F 9039	P	13	13			3.87	
F 9040	P	10	10			4.09	
F 9041	P	10	10			3.70	
F 9042	P	13	13			4.01	
F 9043	P	11	10		1	3.94	
F 9044	P	9	8		1	3.73	
F 9045	P	12	12			4.02	
F 9046	P	10	10			3.94	
F 9047	P	10	9		1	4.07	
F 9048	P	13	13			4.03	
F 9049	P	8	8			3.99	
F 9050	P	9	9			4.21	
F 9051	NP	0				----	
F 9052	P	15	15			3.71	
F 9053	P	14	14			3.85	
F 9054	P	10	10			3.81	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 39

Material FDA 71-5

Dose 240 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date March 31, 1972

Laboratory No. 0729 f

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 9061	P	11	11			4.35	
F 9062	P	12	12			4.28	
F 9063	P	14	13		1	3.78	
F 9064	P	13	13			3.93	
F 9065	P	9	8		1	2.71	
F 9066	P	13	13			3.55	
F 9067	P	11	10		1	3.37	
F 9068	P	11	10	1		3.15	
F 9069	P	12	12			3.18	
F 9070	P	10	10			3.75	
F 9071	NP	0				----	
F 9072	P	14	14			3.73	
F 9073	P	10	9		1	4.23	
F 9074	P	15	15			3.49	
F 9075	NP	0				----	
F 9076	P	12	12			3.89	
F 9077	P	9			9	----	Died Day 20.
F 9078	P	12	12			3.74	
F 9079	P	10	10			3.80	
F 9080	P	11	10		1	4.13	
F 9081	P	12		12		----	Died Day 20.
F 9082	P	11	11			3.99	
F 9083	P	13	13			3.85	
F 9084	P	9	8		1	3.03	
F 9085	NP	0				----	Died Day 15.

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 40

Material FDA 71-5

Dose 600 mg/kg

Date March 31, 1972

Laboratory No. 0729 f

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 9091	P	9	9			4.29	
F 9092	P	11	11			3.66	
F 9093	P	13	13			3.72	
F 9094	NP	0				----	Died Day 8.
F 9095	NP	0				----	
F 9096	P	2	2			3.78	
F 9097	P	9	8		1	3.71	
F 9098	NP	0				----	
F 9099	P	10	9		1	4.07	
F 9100	NP	0				----	
F 9101	P	7		7		----	Died Day 19.
F 9102	NP	0				----	
F 9103	P	12	8		4	2.42	
F 9104	P	4	4			3.96	
F 9105	P	9	9			2.54	
F 9106	P	7	7			3.07	
F 9107	P	6	6			3.84	
F 9108	P	10	10			4.18	
F 9109	NP	0				----	
F 9110	P	11	10		1	3.63	
F 9111	P	10	3		7	1.99	
F 9112	P	9	8		1	3.77	
F 9113	P	11		11		----	Died Day 14.
F 9114	P	14	14			3.75	
F 9115	P	13	13			3.19	
F 9116	P	11	5	1	5	2.41	
F 9117	NP	0				----	Died Day 7.
F 9118	P	14	13		1	3.14	

* 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 May 1, 1972

Laboratory No. 0730 f
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-5 (Calcium carragheenate)

Examination Requested: Teratologic evaluation of FDA 71- 5 in hamsters

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

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

"The administration of the test material in graded dosage levels to pregnant hamsters for 5 consecutive days had no clearly significant effect on nidation or on maternal or fetal survival. There was some evidence of delayed skeletal maturation (missing or incomplete centers of ossification) which was dose dependent. The number of malformations (terata?) seen were within the range of normal variation for the species, except for the occurrence of extra ribs. The conclusion is less clear than in the case of the sodium salt of carragheenin in the same species.

(See following page for comment)

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

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

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 31 & 32; 37 through 40

Material: FDA 71-5

Table 1

Fate Summary
(Hamsters)

Date March 31, 1972

Laboratory No. 0730 f

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
31	Sham	0	30	30	29	29
32	Aspirin*	250	30	27	29	26
37	FDA 71-5	40	26	23	26	23
38	FDA 71-5	100	26	25	26	25
39	FDA 71-5	240	27	24	26	23
40	FDA 71-5	600	30	30	29	29

* Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 31 & 32; 37 through 40

Date March 31, 1972

Material: FDA 71-5

Laboratory No. 0730 f

Table 2
Reproduction Data
(Hamsters)

Group:	31	32	37	38	39	40
Dose (mg/kg):	Sham	Aspirin**	40	100	240	600
Pregnancies						
Total No.	30	27	23	25	24	29
Died or Aborted (before Day 14)	1	1	0	0	1	1
To term (on Day 14)	29	26	23	25	23	29
Live litters						
Total No. *	29	24	23	25	21	28
Implant sites						
Total No.	340	327	278	324	290	361
Average/dam *	11.7	12.6	12.1	13.0	12.6	12.4
Resorptions						
Total No. *	15	31	10	12	16	20
Dams with 1 or more sites resorbed	8	12	7	8	6	12
Dams with all sites resorbed	0	2	0	0	1	1
Per cent partial resorptions	27.6	46.2	30.4	32.0	26.1	41.4
Per cent complete resorptions	-	7.69	-	-	4.35	3.45
Live fetuses						
Total No.	322	296	268	312	260	341
Average/dam *	11.1	11.4	11.7	12.5	11.3	11.8
Dead fetuses						
Total No. *	3	-	-	-	14	0
Dams with 1 or more dead	3	-	-	-	2	-
Dams with all dead	0	-	-	-	1	-
Per cent partial dead	10.3	-	-	-	8.70	-
Per cent all dead	-	-	-	-	4.35	-
Average fetus weight, g	1.86	1.78	1.78	1.78	1.82	1.77

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40 — Table 3 — Laboratory No. 0730 f

Material FDA 71-5 — Date March 31, 1972

Summary of Skeletal Findings *
(Hamsters)

Findings	Group No.	31	32	37	38	39	40
	Dose (mg/kg)	Sham	Aspirin**	40	100	240	600
Live Fetuses Examined (at term)		220/29	206/24	185/23	210/24[a]	181/21	235/28
Sternebrae							
Incomplete oss.		75/27	92/24	81/21	60/21	41/14	44/18
Scrambled		1/1					
Bipartite		30/19	26/19	6/5	32/16	25/15	61/24
Fused						1/1	
Extra							
Missing		17/12	25/10	51/17	37/14	12/8	32/14
Other							
Ribs							
Incomplete oss.							
Fused/split		2/2		3/1	2/2		
Wavy			1/1				1/1
Less than 12							
More than 13		19/10	11/6	22/11	22/11	49/16	49/18
Other, extra							1/1
Vertebrae							
Incomplete oss.		2/2	2/2	6/2	4/4	11/3	1/1
Scrambled							
Fused							
Extra ctrs. oss.		23/14	12/8	3/3	4/4		8/3
Scoliosis		4/4	4/4	3/3			
Tail defects							
Other							
Skull							
Incomplete closure		1/1					
Missing							
Craniostosis			1/1				
Other; Occip./Parietals/ Facials; inc.		3/3	2/2		1/1	11/4	9/3
Extremities							
Incomplete oss.		36/14	55/17	64/14	73/18	36/13	78/19
Missing							
Extra							
Miscellaneous							
Pubis/Ilium/ischium; inc.		3/3	2/2				1/1
Hind leg left rotation			1/1				
Hyoid; missing			1/1		2/2		
Club foot						1/1	

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
** Positive control: 250 mg/kg.
a) 1 litter lost.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40

Species Hamsters

Date March 31, 1972

Laboratory No. 0730 f

Table 4

Average Body Weights *

Group	Material	Dose Level	Day 0	6	8	10	14	**
		mg/kg	g					
31	Sham	0	97.4	103	104	116	137	(29)
32	Aspirin	250	99.7	104	105	117	135	(26)
37	FDA 71-5	40	97.0	101	104	115	137	(23)
38	FDA 71-5	100	102	105	108	119	142	(25)
39	FDA 71-5	240	101	106	108	117	136	(23)
40	FDA 71-5	600	98.9	103	104	115	137	(29)

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

Appendix I

Teratology Study in Hamsters

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

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

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

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 31 | Appendix II | Date March 31, 1972

Material Sham | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730

Dose 0

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
S 0091	P	12	11	1	0	2.04	
S 0092	P	11	11	0	0	1.75	
S 0093	P	12	12	0	0	2.03	
S 0094	P	9	9	0	0	1.85	
S 0095	P	11	11	0	0	1.81	
S 0096	P	14	12	0	2	1.72	
S 0097	P	12	12	0	0	1.94	
S 0098	P	11	7	0	4	1.58	
S 0099	P	11	11	0	0	1.71	
S 0100	P	14	14	0	0	1.69	
S 0101	P	11	10	0	1	1.77	
S 0102	P	13	13	0	0	1.90	
S 0103	P	13	13	0	0	1.85	
S 0104	P	10	10	0	0	1.79	
S 0105	P	12	12	0	0	1.97	
S 0106	P	13	11	0	2	1.94	
S 0107	P	14	13	1	0	1.74	
S 0108	P	10	9	0	1	1.63	
S 0109	P	12	0	12	0	--	Died Day 14.
S 0110	P	12	9	0	3	1.91	
S 0111	P	11	9	1	1	2.16	
S 0112	P	11	11	0	0	1.64	
S 0113	P	11	11	0	0	1.84	
S 0114	P	12	12	0	0	1.64	
S 0115	P	8	8	0	0	2.20	
S 0116	P	12	11	0	1	1.82	
S 0117	P	14	14	0	0	1.82	
S 0118	P	13	13	0	0	2.11	
S 0119	P	11	11	0	0	2.03	
S 0120	P	12	12	0	0	2.11	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 32 | Appendix II | Date March 31, 1972

Material Aspirin | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730

Dose 250 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
A 0091	P	9	9	0	0	1.78	
A 0092	P	14	14	0	0	1.88	
A 0093	P	11	11	0	0	1.76	
A 0094	P	12	10	0	2	2.08	
A 0095	NP	0				--	
A 0096	P	15	14	0	1	1.81	
A 0097	P	13	13	0	0	1.83	
A 0098	NP	0				--	
A 0099	P	13	11	0	2	1.82	
A 0100	P	10	10	0	0	1.90	
A 0101	P	12	12	0	0	1.56	
A 0102	P	15	14	0	1	1.83	
A 0103	P	16	15	0	1	1.50	
A 0104	P	9	8	0	1	1.97	
A 0105	P	11	11	0	0	1.96	
A 0106	P	19	18	0	1	1.57	
A 0107	P	13	11	0	2	1.82	
A 0108	P	12	12	0	0	1.60	
A 0109	P	9	0	0	9	--	
A 0110	P	14	14	0	0	1.65	
A 0111	P	13	13	0	0	1.70	
A 0112	P	15	0	15	0	--	Dam Died Day 8.
A 0113	NP	0				--	
A 0114	P	12	12	0	0	1.65	
A 0115	P	12	11	0	1	1.91	
A 0116	P	9	0	0	9	--	
A 0117	P	15	15	0	0	1.72	
A 0118	P	15	14	0	1	1.69	
A 0119	P	11	11	0	0	1.91	
A 0120	P	13	13	0	0	1.80	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 37 | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730 f

Dose 40 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 0001	P	13	13	0	0	1.86	
F 0002	P	11	11	0	0	1.89	
F 0003	NP	0				--	
F 0004	P	10	10	0	0	1.54	
F 0005	P	13	13	0	0	1.96	
F 0006	P	13	12	0	1	1.84	
F 0007	P	15	15	0	0	1.71	
F 0008	P	12	12	0	0	1.59	
F 0009	P	14	14	0	0	1.51	
F 0010	0	9	8	0	1	1.97	
F 0011	P	12	11	0	1	1.47	
F 0012	NP	0				--	
F 0013	P	13	10	0	3	1.69	
F 0014	P	12	12	0	0	1.94	
F 0015	P	14	14	0	0	1.77	
F 0016	P	12	10	0	2	2.05	
F 0017	P	12	12	0	0	2.00	
F 0018	NP	0				--	
F 0019	P	11	10	0	1	1.84	
F 0020	P	7	7	0	0	1.59	
F 0021	P	14	14	0	0	1.89	
F 0022	P	13	13	0	0	1.91	
F 0023	P	12	11	0	1	1.63	
F 0024	P	12	12	0	0	1.84	
F 0025	P	12	12	0	0	1.68	
F 0026	P	12	12	0	0	1.69	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 38 | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730 f

Dose 100 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 0031	P	11	10	0	1	1.93	
F 0032	P	14	14	0	0	1.73	
F 0033	P	11	11	0	0	1.92	
F 0034	P	11	11	0	0	1.94	
F 0035	P	12	12	0	0	1.65	
F 0036	P	15	15	0	0	1.68	
F 0037	P	12	12	0	0	1.70	
F 0038	P	13	13	0	0	1.84	
F 0039	P	13	13	0	0	1.71	
F 0040	P	13	10	0	3	1.72	
F 0041	P	17	17	0	0	1.90	
F 0042	P	12	11	0	1	1.55	
F 0043	NP	0				--	
F 0044	P	12	12	0	0	2.12	
F 0045	P	14	14	0	0	1.34	
F 0046	P	11	10	0	1	1.35	
F 0047	P	13	13	0	0	1.56	
F 0048	P	15	15	0	0	1.92	
F 0049	P	12	10	0	2	2.00	
F 0050	P	15	14	0	1	1.90	
F 0051	P	13	13	0	0	1.69	
F 0052	P	11	9	0	2	1.95	
F 0053	P	14	14	0	0	1.84	
F 0054	P	11	10	0	1	1.69	
F 0055	P	16	16	0	0	1.95	
F 0056	P	13	13	0	0	1.96	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 39 | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730 f

Dose 240 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 0061	P	11	10	0	1	1.83	
F 0062	P	14	14	0	0	1.82	
F 0063	P	13	13	0	0	1.81	
F 0064	P	13	13	0	0	1.92	
F 0065	P	15	15	0	0	1.90	
F 0066	P	12	12	0	0	1.93	
F 0067	P	14	13	0	1	1.81	
F 0068	P	10	10	0	0	1.97	
F 0069	P	15	15	0	0	1.67	
F 0070	NP	0				--	
F 0071	NP	0				--	
F 0072	P	14	14	0	0	1.72	
F 0073	P	13	12	1	0	1.93	
F 0074	P	13	13	0	0	1.77	
F 0075	P	14	14	0	0	1.87	
F 0076	P	13	13	0	0	1.95	
F 0077	P	13	13	0	0	1.98	
F 0078	P	14	12	0	2	1.71	
F 0079	P	13	0	13	0	--	Dam Died Day 8.
F 0080	P	10	0	0	10	--	
F 0081	P	13	12	0	1	1.67	
F 0082	P	12	12	0	0	1.72	
F 0083	P	13	0	13	0	--	
F 0084	P	10	9	0	1	1.63	
F 0085	P	10	10	0	0	1.66	
F 0086	P	11	11	0	0	2.02	
F 0087	NP	0				--	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 40 | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730 f

Dose 600 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 0091	P	11	11	0	0	1.83	
F 0092	P	6	4	0	2	1.90	
F 0093	P	13	13	0	0	1.86	
F 0094	P	14	14	0	0	1.56	
F 0095	P	12	12	0	0	1.88	
F 0096	P	14	13	0	1	1.76	
F 0097	P	14	13	0	1	1.73	
F 0098	P	13	12	0	1	1.73	
F 0099	P	14	13	0	1	1.74	
F 0100	P	6	0	0	6	--	
F 0101	P	14	14	0	0	1.57	
F 0102	P	12	10	0	2	1.57	
F 0103	P	15	15	0	0	1.71	
F 0104	P	11	11	0	0	1.70	
F 0105	P	13	13	0	0	1.66	
F 0106	P	11	11	0	0	2.01	
F 0107	P	12	11	0	1	2.05	
F 0108	P	15	13	0	2	1.85	
F 0109	P	10	10	0	0	2.00	
F 0110	P	11	11	0	0	2.33	Aborted Day 14.
F 0111	P	12	12	0	0	1.59	
F 0112	P	14	14	0	0	2.01	
F 0113	P	11	11	0	0	2.01	
F 0114	P	15	15	0	0	1.75	
F 0115	P	13	12	0	1	1.88	
F 0116	P	12	12	0	0	2.01	
F 0117	P	16	15	0	1	1.55	
F 0118	P	11	11	0	0	1.70	
F 0119	P	15	15	0	0	1.50	
F 0120	P	12	11	0	1	1.56	

* 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 May 1, 1972

Laboratory No. 0731 f
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-5 (Calcium carragheenate)

Examination Requested: Teratologic evaluation of FDA 71- 5 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

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

For these reasons, the conclusion stated below is regarded as provisional and subject to reexamination in the light of later findings:

"The administration of up to 260 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: 31 & 32; 37 through 40

Material: FDA 71-5

Date March 31, 1972

Laboratory No. 0731 f

Table 1

Fate Summary
(Rabbits)

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
31	Sham	0	15	13	11	9
32	6-AN*	2.5	15	13	15	13
37	FDA 71-5	3.0	15	12	14	12
38	FDA 71-5	10	15	11	14	10
39	FDA 71-5	60	15	13	15	13
40	FDA 71-5	260	15	14	14	13

* Positive Control: 6-amino nicotinamide dosed on Day 9.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 31 & 32; 37 through 40 Date March 31, 1972

Material: FDA 71-5 Laboratory No. 0731 f

Table 2
Reproduction Data
(Rabbits)

Group:	31	32	37	38	39	40
Dose (mg/kg):	Sham	6-AN**	3	10	60	260
Pregnancies						
Total No.	13	13	12	15	13	14
Died or aborted (before Day 29)	4	0	1	2	0	1
To term (on Day 29)	9	13	12	10	13	13
Corpora lutea						
Total No.	243	235	207	201	172	187
Average/dam mated	16.2	15.7	13.8	13.4	11.5	12.5
Live litters						
Total No.*	9	10	10	9	12	9
Implant sites						
Total No. (at term)	39	59	59	51	70	56
Average/dam*	4.33	4.54	4.92	5.10	5.38	4.31
Resorptions						
Total No.*	5	15	9	13	6	7
Dams with 1 or more sites resorbed	3	8	5	4	6	5
Dams with all sites resorbed	0	2	2	1	0	4
Per cent partial resorptions	33.3	61.5	41.7	40.0	46.2	38.5
Per cent complete resorptions	--	15.4	16.7	10.0	--	30.8
Live fetuses						
Total No. (at term)	34	43	50	38	64	49
Average/dam*	3.78	3.31	4.17	3.80	4.92	3.08
Dead fetuses						
Total No.*	0	1	0	0	0	0
Dams with 1 or more dead	-	1	-	-	-	-
Dams with all dead	-	0	-	-	-	-
Per cent partial dead	-	-	-	-	-	-
per cent all dead	-	7.69	-	-	-	-
Average fetus weight, g	37.3	31.0	42.0	38.9	37.2	37.1

* Includes only those dams examined at term.

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40 — Laboratory No. 0731 f

Table 3

Material FDA 71-5 — Date March 31, 1972

Summary of Skeletal Findings *

(Rabbits)

Findings	Group No.	31	32	37	38	39	40
	Dose (mg/kg)	Sham	6-AN**	3	10	60	260
Live Fetuses Examined		32/9	42/10	50/10	33/9	64/12	57/10
Sternebrae							
Incomplete oss.		7/5	16/7	8/7	7/4	15/6	16/8
Scrambled							
Bipartite			8/6		2/1		
Fused		2/1	12/6		1/1	1/1	1/1
Extra			3/3	5/5	2/2	4/2	1/1
Missing			1/1	1/1	1/1		1/1
Other							
Ribs							
Incomplete oss.			2/2				
Fused/split			7/6		2/1		
Wavy							
Less than 12				4/1	1/1	1/1	1/1
More than 13		1/1	1/1		3/3	9/4	12/4
Other							
Vertebrae							
Incomplete oss.							
Scrambled			1/1				
Fused							
Extra ctrs. oss.							
Scoliosis			1/1				
Tail defects			23/7	2/1			
Other; Scrambled tail					1/1		
Skull							
Incomplete closure						1/1	
Missing							
Craniostosis		1/1	8/2	3/3	6/4	7/3	9/4
Other: Eyes; incomplete			8/2				
Extremities							
Incomplete oss.							
Missing							
Extra							
Miscellaneous							
Club feet			5/3				

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.
** Positive control: 6- amino nicotinamide dosed on Day 9.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40 Date March 31, 1972

Material FDA 71-5 Laboratory No. 0731 f

Table 3-a

Summary of Soft Tissue Abnormalities

(Rabbits)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
31	Sham	0	S-1051	2	Euryopia
				1	Hair lip
32	6-AN*	2.5	Z-1046	5	Anopia
				3	Club feet
32	6-AN		Z-1047	7	Anopia
				3	Cleft palate
				2	Hair lip
32	6-AN		Z-1049	6	Anopia
				4	Club feet
				3	Cleft palate
				3	Hair lip
32	6-AN		Z-1052	1	Anopia
				2	Missing digits
				1	Dysgnathia
32	6-AN		Z-1053	2	Anopia
				3	Club feet
32	6-AN		Z-1054	3	Club feet
				1	Anopia
				1	Hair lip
32	6-AN		Z-1055	7	Anopia
				5	Club feet
32	6-AN		Z-1059	5	Anopia
				3	Club feet
				3	Cleft palate

* 6 - amino nicotinamide dosed on Day 9.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 31 & 32; 37 through 40

Species Rabbits

Table 4

Average Body Weights

Date March 31, 1972

Laboratory No. 0731 f

Group	Material	Dose Level	Day 0	6	12	18	29	**
		mg/kg	kg					
31	Sham	0	2.34	2.35	2.38	2.36	2.41	(9)
32	6-AN***	2.5	2.21	2.18	2.27	2.27	2.36	(13)
37	FDA 71-5	3.0	2.35	2.39	2.44	2.51	2.55	(12)
38	FDA 71-5	10	2.50	2.57	2.54	2.66	2.63	(10)
39	FDA 71-5	60	2.25	2.28	2.32	2.37	2.47	(13)
40	FDA 71-5	260	2.28	2.28	2.28	2.29	2.42	(13)

* Of pregnant dams.
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 6-amino nicotinamide 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 20×10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

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

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of

each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 31

Material Sham

Dose 0

Appendix II

Reproduction Data in Rabbits (Individual)

Date March 31, 1972

Laboratory No. 0731

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
S 1046	P	13	4		4		----	Died Day 14
S 1047	P	19	1	1			36.4	
S 1048	NP	12	0				----	
S 1049	P	19	5	5			36.9	
S 1050	P	25	5	3		2	43.6	
S 1051	P	15	6	5		1	17.7	
S 1052	P	8	6	6			42.7	
S 1053	P	16	6	6			32.8	
S 1054	P	20	3	3			38.4	
S 1055	P	19	1	1			46.1	
S 1056	NP	2	0				----	
S 1057	P	13	4		4		----	Died Day 10
S 1058	P	23	6	4		2	40.7	
S 1059	P	20	5		5		----	Died Day 10
S 1060	P	19	2		2		----	Died Day 11

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rabbits (Individual)

Group 32

Material 6 - AN

Dose 2.5 mg/kg

Date March 31, 1972

Laboratory No. 0731

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
Z 1046	P	21	6	6			28.8	
Z 1047	P	18	7	7			27.0	
Z 1048	NP	8	0				----	
Z 1049	P	21	6	5		1	29.2	
Z 1050	P	11	1			1	----	
Z 1051	P	8	2			2	----	
Z 1052	P	9	4	1		3	21.6	
Z 1053	P	11	4	3		1	29.7	
Z 1054	P	39	6	3		3	29.0	
Z 1055	P	25	8	7	1		27.6	
Z 1056	P	15	5	4		1	34.0	
Z 1057	P	8	2	2			43.0	
Z 1058	P	14	3			3	----	
Z 1059	P	23	5	5			40.3	
Z 1060	NP	4	0				----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rabbits (Individual)

Group 37

Material FDA 71-5

Dose 3 mg/kg

Date March 31, 1972

Laboratory No. 0731 f

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 1001	P	20	7	7			30.4	
F 1002	P	16	5	4		1	45.6	
F 1003	P	11	4	1		3	49.0	
F 1004	NP	9	0				----	
F 1005	P	22	9	9			38.8	
F 1006	NP	1	0				----	
F 1007	P	4	2	0		2	----	
F 1008	P	14	4	4			43.4	
F 1009	NP	11	0				----	Died Day 23.
F 1010	P	33	6	6			34.1	
F 1011	P	12	2	2			51.3	
F 1012	P	18	2			2	----	
F 1013	P	6	3	2		1	54.1	
F 1014	P	8	4	4			37.2	
F 1015	P	22	11	11			36.9	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 38 | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Rabbits (Individual) | Laboratory No. 0731 f

Dose 10 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 1016	P	25	7	7			36.2	
F 1017	P	23	1	1			39.6	
F 1018	NP	7	0				----	
F 1019	NP	3	0				----	
F 1020	P	30	2	2			39.0	
F 1021	P	22	10	8		2	38.5	
F 1022	NP	0	0				----	
F 1023	P	9	8			8	----	
F 1024	P	19	7	7			39.4	
F 1025	P	13	2	2			42.7	
F 1026	P	10	4	4			43.2	
F 1027	P	11	6	4		2	35.3	
F 1028	P	13	4	3		1	36.8	
F 1029	NP	0	0				----	
F 1030	P	16	8		8		----	Died Day 25.

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 39 | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Rabbits (Individual) | Laboratory No. 0731 f

Dose 60 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 1031	P	25	7	6		1	39.5	
F 1032	P	4	1			1	----	
F 1033	P	20	9	8		1	37.6	
F 1034	P	11	4	4			36.9	
F 1035	P	27	8	8			32.9	
F 1036	P	6	6	6			38.5	
F 1037	P	8	5	5			36.5	
F 1038	NP	3	0				----	
F 1039	P	8	4	3		1	38.7	
F 1040	P	13	8	7		1	39.6	
F 1041	P	11	4	3		1	37.0	
F 1042	P	9	5	5			28.0	
F 1043	P	11	6	6			38.1	
F 1044	NP	2	0				----	
F 1045	P	14	3	3			44.2	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 40 | Appendix II | Date March 31, 1972

Material FDA 71-5 | Reproduction Data in Rabbits (Individual) | Laboratory No. 0731 f

Dose 260 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Resorption Sites	Average Fetus Weight (g)	Remarks
F 1046	NP	7	0				----	
F 1047	P	31	4	4			39.9	
F 1048	P	30	8	8			36.7	
F 1049	P	11	1			1	----	
F 1050	P	14	5	5			33.4	
F 1051	P	15	7	7			33.7	
F 1052	P	11	3	3			42.6	
F 1053	P	6	3			3	----	
F 1054	P	7	4	4			----	Aborted Day 20
F 1055	P	7	6	6			37.2	
F 1056	P	5	1			1	----	
F 1057	P	9	5	5			36.4	
F 1058	P	7	1			1	----	
F 1059	P	14	8	7		1	34.3	
F 1060	P	13	4	4			40.3	

* P = Pregnant; NP = Not Pregnant