Final report-Teratologic evaluation of FDA 71-44 (**Caffine**) in Mice, Rats & Hamsters
1/8/73

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FOOD AND DRUG
LABORATORIES, INC.

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

FINAL

January 8, 1973

Teratologic Evaluation of FDA 71-44

(Caffeine)

in

Mice, Rats, and Hamsters

M I C E

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 January 8, 1973

Laboratory No. 0901 y
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-44 (Caffeine)

Examination Requested: Teratologic evaluation of FDA 71-44 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of additional data in progress, the following is concluded:

"The administration of up to 36 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the eighteenth 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 42 compounds will have been tested in 21 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

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: 171 & 172; 177 through 180

Date: December 8, 1972

Table 1

Laboratory No.: 0901 y

Material: FDA 71-44

Fate Summary
(Mice)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
171	Sham	0.0	26	21	26	21
172	Aspirin*	150.0	27	21	27	21
177	FDA 71-44	0.36	26	21	26	21
178	FDA 71-44	1.7	25	20	25	20
179	FDA 71-44	8.0	25	21	25	21
180	FDA 71-44	36.0	25	21	25	21

* Positive Control: 150.0 mg/kg
** Administered as a water solution;
1) Includes all dams examined at term

(Sham group dosed with anhydrous corn oil)

FOOD AND DRUG RESEA. LABORATORIES, INC.

Group : 171 & 172; 177 through 180

Material : FDA 71-44

Table 2
Reproduction Data
(Mice)

Date : December 8, 1972

Laboratory No. : 0901 y

Group :	171	172	177	178	179	180
Dose (mg/kg) :	Sham	Aspirin**	0.36	1.7	8.0	36.0
Pregnancies						
Total No.	21	21	21	20	21	21
Died or Aborted (before Day 17)	0	0	0	0	0	0
To term (on Day 17)	21	21	21	20	21	21
Corpora Lutea						
Total No.	333	349	357	321	337	358
Average/dam mated	12.8	12.9	13.4	12.4	13.5	14.3
Live Litters						
Total No.*	21	21	21	20	20	21
Implant Sites						
Total No.	236	233	241	228	238	266
Average/dam*	11.2	11.1	11.5	11.4	11.3	12.7
Resorptions						
Total No.*	11	11	4	14	25	16
Dams with 1 or more sites resorbed	8	8	3	7	11	13
Dams with all sites resorbed	--	--	--	--	1	--
Per cent partial resorptions	38.1	38.1	14.3	35.0	52.4	61.9
Per cent complete resorptions	--	--	--	--	4.76	--
Live Fetuses						
Total No.	218	219	231	210	207	245
Average/dam*	10.4	10.4	11.0	10.5	9.86	11.7
Sex ratio (M/F)	0.80	0.67	0.58	0.65	0.72	0.70
Dead Fetuses						
Total No.*	7	3	6	4	6	5
Dams with 1 or more dead	4	3	4	3	3	5
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	19.1	14.3	19.1	15.0	14.3	23.8
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.90	0.84	0.87	0.88	0.83	0.80

* Includes only those dams examined at term.

** Positive Control : 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180 Laboratory No. 0901 y

Table 3

Material FDA 71-44 Date December 8, 1972

Summary of Skeletal Findings*

(Mice)

Findings / Group No.:	171	172	177	178	179	180
Dose (mg/kg):	Sham	Aspirin**	0.36	1.7	8.0	36.0
Live Fetuses Examined (at term)	151/21	140/19[a)]	161/21	147/20	145/20	172/21
Sternebrae						
Incomplete oss.	43/15	48/16	69/17	57/17	39/15	73/20
Scrambled						
Bipartite	9/6	16/10	7/6	3/3	2/2	5/2
Fused						
Extra	1/1			2/2		5/2
Missing	29/12	24/12	19/8	33/9	21/8	53/14
Other						
Ribs						
Incomplete oss.						
Fused/split						
Wavy						
Less than 12	1/1	1/1				1/1
More than 13	26/9	15/7	24/10	15/5	15/5	5/4
Other						
Vertebrae						
Incomplete oss.	3/3	11/8	3/2	2/1	6/3	5/3
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other		19/9				
Skull						
Incomplete closure			1/1	2/2	3/2	1/1
Missing				1/1		
Craniostosis						
Other						
Extremities						
Incomplete oss.	21/9	19/10	15/8	28/10	30/9	26/8
Missing	6/5	4/4				
Extra						
Miscellaneous						
Hyoid; missing	55/17	37/15	45/15	61/16	37/14	49/19
Hyoid; reduced	12/7	15/7	17/11	15/11	20/13	38/18
Hyoid; bipartite						1/1

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

** Positive control: 150.0 mg/kg

a) One litter missing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180 Date December 8, 1972

Material FDA 71-44 Laboratory No. 0901 y

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description

None Observed

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180

Date December 8, 1972

Table 4

Species Mice

Laboratory No. 0901 y

Average Body Weights *

Group	Material	Dose Level	Day 0	6	11	15	17**
		mg/kg	g				
171	Sham	0.0	31.1	32.0	34.6	43.5	49.0 (21)
172	Aspirin***	150.0	30.1	32.1	33.7	42.2	47.7 (21)
177	FDA 71-44	0.36	31.3	33.5	37.1	44.4	51.0 (21)
178	FDA 71-44	1.7	30.9	33.1	35.9	44.3	50.0 (20)
179	FDA 71-44	8.0	29.2	31.6	33.8	41.0	45.8 (21)
180	FDA 71-44	36.0	31.6	33.1	33.9	42.3	47.2 (21)

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

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

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

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 171

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date December 8, 1972

Laboratory No. 0901

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 1511	P	17	12	12		6	6		1.06	
S 1512	P	13	12	12		6	6		0.89	
S 1513	NP	0	0						----	
S 1514	P	12	4	4		2	2		0.90	
S 1515	P	13	12	9	2	3	6	1	0.90	
S 1516	P	13	9	9		5	4		0.83	
S 1517	P	14	12	10	2	4	6		0.85	
S 1518	NP	11	0						----	
S 1519	P	18	16	15	1	8	7		0.83	
S 1520	P	18	14	14		11	3		0.89	
S 1521	P	22	10	10		3	7		0.92	
S 1522	P	15	15	12	2	5	7	1	0.85	
S 1523	P	16	11	11		4	7		0.84	
S 1524	P	11	5	5		3	2		0.97	
S 1525	P	7	6	2		1	1	4	1.08	
S 1526	P	14	13	12		6	6	1	1.15	
S 1527	P	13	14	13		6	7	1	0.78	
S 1528	P	13	12	11		3	8	1	0.90	
S 1529	P	14	12	12		3	9		0.74	
S 1530	NP	0	0						----	
S 1531	NP	12	0						----	
S 1532	NP	14	0						----	
S 1533	P	10	10	10		3	7		0.88	
S 1534	P	14	13	12		2	10	1	0.89	
S 1535	P	16	13	12		7	5	1	0.82	
S 1536										Not Assigned
S 1537	P	13	11	11		6	5		0.85	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 172

Material Aspirin

Dose 150.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date December 8, 1972

Laboratory No. 0901

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 1511	P	17	12	12		6	6		0.79	
A 1512	NP	5	0						----	
A 1513	P	13	10	9	1	5	4		0.78	
A 1514	NP	8	0						----	
A 1515	P	13	9	9		6	3		0.75	
A 1516	P	16	10	8		3	5	2	0.89	
A 1517	P	11	5	5		2	3		0.80	
A 1518	P	14	12	10	1	5	5	1	0.80	
A 1519	P	13	5	3		1	2	2	0.64	
A 1520	P	13	12	12		6	6		0.88	
A 1521	P	13	14	13		6	7	1	0.81	
A 1522	P	15	12	12		5	7		0.85	
A 1523	P	13	10	10		5	5		0.82	
A 1524	P	13	14	13		4	9	1	0.87	
A 1525	NP	8	0						----	
A 1526	P	14	12	12		4	8		0.79	
A 1527	P	14	14	14		4	10		0.78	
A 1528	P	15	12	10	1	5	5	1	1.12	
A 1529	NP	10	0						----	
A 1530	P	11	10	9		4	5	1	1.05	
A 1531	NP	20	0						----	
A 1532	P	13	11	11		3	8		0.89	
A 1533	P	12	12	10		3	7	2	0.82	
A 1534	P	18	15	15		8	7		0.78	
A 1535										Not Assigned
A 1536	NP	14	0						----	
A 1537	P	13	12	12		2	10		0.89	
A 1538	P	10	10	10		1	9		0.76	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 177

Material FDA 71-44

Dose 0.36 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date December 8, 1972

Laboratory No. 0901 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 1001	P	14	14	14		5	9		0.75	
Y 1002	P	12	12	12		7	5		1.08	
Y 1003	P	16	12	12		5	7		0.83	
Y 1004	P	13	10	10		6	4		0.81	
Y 1005	P	12	7	7		3	4		1.21	
Y 1006	P	17	13	13		3	10		0.83	
Y 1007	NP	10	0						----	
Y 1008	P	12	4	4		3	1		0.90	
Y 1009	P	9	10	7	3	3	4		0.99	
Y 1010	P	14	14	14		7	7		0.78	
Y 1011	P	11	11	11		4	7		0.82	
Y 1012	P	18	15	15		8	7		0.85	
Y 1013	P	16	13	12		6	6	1	0.81	
Y 1014	P	12	10	9	1	1	8		0.67	
Y 1015	NP	19	0						----	
Y 1016	P	14	14	13		1	12	1	0.76	
Y 1017	NP	15	0						----	
Y 1018	NP	7	0						----	
Y 1019	NP	9	0						----	
Y 1020	P	20	16	16		5	11		0.76	
Y 1021	P	14	10	10		1	9		0.94	
Y 1022	P	16	15	14	1	1	13		0.71	
Y 1023	P	8	3	3		2	1		0.99	
Y 1024	P	14	9	9		4	5		0.99	
Y 1025	P	17	15	13		5	8	2	0.82	
Y 1026	P	18	14	13	1	7	6		0.87	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 178

Material FDA 71-44

Dose 1.7 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date December 8, 1972

Laboratory No. 0901 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 1031	P	13	12	12		6	6		0.94	
Y 1032	P	15	13	13		4	9		0.69	
Y 1033	P	13	10	10		5	5		0.94	
Y 1034	P	16	12	11	1	6	5		1.10	
Y 1035	P	14	10	10		6	4		0.82	
Y 1036	NP	9	0						----	
Y 1037	P	15	13	13		7	6		0.82	
Y 1038	P	17	14	10		4	6	4	1.11	
Y 1039	P	11	10	9	1	3	6		0.93	
Y 1040	P	12	8	8		3	5		0.76	
Y 1041	NP	0	0						----	
Y 1042	P	12	12	11		4	7	1	0.59	
Y 1043	P	11	8	7		2	5	1	0.98	
Y 1044	P	15	11	11		2	9		0.85	
Y 1045	P	15	12	11		4	7	1	0.95	
Y 1046	P	13	13	9		3	6	4	1.00	
Y 1047	P	16	13	11		6	5	2	0.88	
Y 1048	NP	0	0						----	
Y 1049	NP	12	0						----	
Y 1050	P	13	10	10		2	8		0.74	
Y 1051	NP	16	0						----	
Y 1052	P	14	12	12		2	10		0.88	
Y 1053	P	19	13	12		6	6	1	0.92	
Y 1054	P	19	14	14		6	8		0.94	
Y 1055	P	11	8	6	2	2	4		0.66	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 179

Material FDA 71-44

Dose 8.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date December 8, 1972

Laboratory No. 0901 y

Dam No.	Fate*	Corpora Lutea	Implant Sites.	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 1061	P	16	11	11		6	5		0.89	
Y 1062	P	17	10	10		6	4		0.75	
Y 1063	P	17	15	14	1	6	8		0.82	
Y 1064	P	13	11	9		5	4	2	0.89	
Y 1065	P	13	14	12		6	6	2	0.88	
Y 1066	P	17	14	13	1	7	6		0.86	
Y 1067	P	19	9	8		4	4	1	0.81	
Y 1068	P	16	5	5		3	2		0.81	
Y 1069	P	15	15	15		6	9		0.92	
Y 1070	P	10	9	8		1	7	1	0.73	
Y 1071	NP	5	0						----	
Y 1072	P	10	9					9	----	
Y 1073	P	8	10	8		2	6	2	0.81	
Y 1074	P	12	11	6	4	2	4	1	0.46	
Y 1075	NP	14	0						----	
Y 1076	P	11	11	8		3	5	3	1.09	
Y 1077	P	17	13	11		2	9	2	0.63	
Y 1078	P	13	11	10		6	4	1	0.97	
Y 1079	NP	10	0						----	
Y 1080	P	13	10	10		0	10		0.83	
Y 1081	NP	11	0						----	
Y 1082	P	12	11	11		0	11		0.92	
Y 1083	P	15	12	12		6	6		0.89	
Y 1084	P	13	10	9		5	4	1	0.82	
Y 1085	P	20	17	17		6	11		0.77	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 180

Material FDA 71-44

Dose 36.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date December 8, 1972

Laboratory No. 0901 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 1091	P	15	12	11		5	6	1	0.83	
Y 1092	P	18	13	12		5	7	1	0.74	
Y 1093	P	22	14	14		7	7		0.74	
Y 1094	P	14	15	14	1	6	8		0.83	
Y 1095	P	16	9	6		3	3	3	0.81	
Y 1096	P	17	16	14	1	6	8	1	0.95	
Y 1097	P	18	13	13		8	5		0.90	
Y 1098	P	14	14	12	1	4	8	1	0.89	
Y 1099	P	12	10	9		4	5	1	0.82	
Y 1100	P	16	14	14		7	7		0.87	
Y 1101	P	16	14	13		5	8	1	0.67	
Y 1102	P	16	15	14		6	8	1	0.54	
Y 1103	NP	15	0						----	
Y 1104	P	14	13	13		4	9		0.74	
Y 1105	P	12	12	11		2	9	1	0.77	
Y 1106	P	11	11	10		3	7	1	0.75	
Y 1107	P	13	11	11		3	8		0.56	
Y 1108	P	14	12	10	1	4	6	1	0.78	
Y 1109	NP	14	0						----	
Y 1110	P	13	11	10		5	5	1	0.97	
Y 1111	NP	16	0						----	
Y 1112	NP	0	0						----	
Y 1113	P	10	12	9	1	--	--	2	0.80	
Y 1114	P	13	10	10		4	6		0.95	
Y 1115	P	19	15	15		6	9		0.93	

* 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 January 8, 1973

Laboratory No. 0902 y
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-44 (Caffeine)

Examination Requested: Teratologic evaluation of FDA 71-44 in rats

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

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

"The administration of up to 22.5 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the eighteenth 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 42 compounds will have been tested in 21 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

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Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 171 & 172; 177 through 180

Date: December 8, 1972

Table 1

Material: FDA 71-44

Laboratory No.: 0902 y

Fate Summary
(Rats)

Group	Material	Dose ** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
171	Sham	0.0	24	23	24	23
172	Aspirin*	250.0	24	20	24	20
177	FDA 71-44	0.23	24	24	24	24
178	FDA 71-44	0.68	24	19	24	19
179	FDA 71-44	3.2	24	22	24	22
180	FDA 71-44	22.5	28	23	28	23

* Positive Control: 250.0 mg/kg
** Administered as a water solution; (Sham group dosed with anhydrous corn oil)
1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 171 & 172; 177 through 180

Material: FDA 71-44

Table 2
Reproduction Data
(Rats)

Date: December 8, 1972

Laboratory No.: 0902 y

Group:	171	172	177	178	179	180
Dose (mg/kg):	Sham	Aspirin**	0.23	0.68	3.2	22.5
Pregnancies						
Total No.	23	20	24	19	22	23
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	23	20	24	19	22	23
Corpora Lutea						
Total No.	259	244	266	235	276	311
Average/dam mated	10.8	10.2	11.1	9.79	11.5	11.1
Live Litters						
Total No.*	23	19	24	19	22	23
Implant Sites						
Total No.	235	209	255	216	250	243
Average/dam*	10.2	10.5	10.6	11.4	11.4	10.6
Resorptions						
Total No.*	4	24	3	4	6	5
Dams with 1 or more sites resorbed	2	5	2	3	4	5
Dams with all sites resorbed	--	1	--	--	--	--
Per cent partial resorptions	8.70	25.0	8.33	15.8	18.2	21.7
Per cent complete resorptions	--	5.00	--	--	--	--
Live Fetuses						
Total No.	230	185	252	212	244	237
Average/dam*	10.0	9.25	10.5	11.2	11.1	10.3
Sex ratio (M/F)	0.98	0.80	0.98	0.77	0.85	0.88
Dead Fetuses						
Total No.*	1	--	--	--	--	1
Dams with 1 or more dead	1	--	--	--	--	1
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	4.35	--	--	--	--	4.35
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.84	2.76	3.71	3.57	3.86	3.94

* Includes only those dams examined at term.

** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180 Laboratory No. 0902 y

Table 3

Material FDA 71-44 Date December 8, 1972

Summary of Skeletal Findings*

(Rats)

Findings / Group No.:	171	172	177	178	179	180
Dose (mg/kg):	Sham	Aspirin**	0.23	0.68	3.2	22.5
Live Fetuses Examined (at term)	162/23	127/19	179/24	149/19	170/22	166/23
Sternebrae						
Incomplete oss.	33/14	83/19	48/17	53/16	21/10	37/14
Scrambled						
Bipartite		6/4		3/2		
Fused						
Extra						
Missing	17/9	104/17	22/8	26/7	11/8	7/4
Other						
Ribs						
Incomplete oss.		2/2				
Fused/split		1/1				
Wavy	1/1	40/12	17/10	8/4	13/9	5/5
Less than 12		2/1	1/1			
More than 13	1/1	91/18		1/1	1/1	2/2
Other						
Vertebrae						
Incomplete oss.	2/2	90/17	27/11	47/14	20/9	10/8
Scrambled		1/1				
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	17/10	63/17	2/2	12/9	4/4	15/6
Missing		5/2				
Craniostosis						
Other			1/1		1/1	
Extremities						
Incomplete oss.		4/3	2/1	2/1		
Missing		2/1	2/2	4/3	2/2	
Extra						
Miscellaneous						
Hyoid; missing	19/10	68/17	30/18	25/12	19/9	26/11
Hyoid; reduced	28/13	17/11	24/14	48/15	22/15	26/11

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180 Date December 8, 1972

Material FDA 71-44 Laboratory No. 0902 y

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
172	Aspirin*	250.0	A 2511	1	Exencephaly
			A 2525	1	Exencephaly
			A 2534	3	Exencephaly
178	FDA 71-44	0.68	Y 2035	1	Short Tail

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180

Date December 8, 1972

Table 4

Species Rats

Laboratory No. 0902 y

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	20**
		mg/kg	g				
171	Sham	0.0	206	225	241	257	319 (23)
172	Aspirin***	250.0	211	230	239	252	307 (20)
177	FDA 71-44	0.23	201	221	237	253	315 (24)
178	FDA 71-44	0.68	211	228	243	253	324 (19)
179	FDA 71-44	3.2	199	217	231	250	313 (22)
180	FDA 71-44	22.5	207	227	236	247	303 (23)

* 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 intubation; the controls were sham treated.

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

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

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 171

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date December 8, 1972

Laboratory No. 0902

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 2511	P	14	13	13		8	5		4.08	
S 2512	P	14	13	13		6	7		3.75	
S 2513	P	13	13	13		5	8		4.11	
S 2514	P	10	10	10		5	5		4.15	
S 2515	P	13	13	13		8	5		3.14	
S 2516	P	12	13	10		5	5	3	3.92	
S 2517	P	10	10	10		5	5		3.82	
S 2518	P	11	11	11		2	9		3.77	
S 2519	P	14	14	14		7	7		3.35	
S 2520	P	9	9	8		5	3	1	3.69	
S 2521	P	13	9	9		3	6		3.54	
S 2522	P	7	7	7		3	4		3.72	
S 2523	P	10	10	10		7	3		3.43	
S 2524	P	11	11	11		7	4		3.77	
S 2525	P	8	7	7		2	5		3.11	
S 2526	P	12	11	10	1	7	3		3.80	
S 2527	NP	5	0						----	
S 2528	P	12	11	11		4	7		3.89	
S 2529	P	12	12	12		8	4		3.88	
S 2530	P	8	2	2		1	1		5.28	
S 2531	P	14	14	14		6	8		3.65	
S 2532	P	5	1	1		0	1		4.74	
S 2533	P	11	11	11		5	6		3.97	
S 2534	P	11	10	10		5	5		3.84	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 172

Material Aspirin

Dose 250.0 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date December 8, 1972

Laboratory No. 0902

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 2511	P	9	9	9		6	3		2.60	
A 2512	P	10	9					9	----	
A 2513	P	5	10	2		1	1	8	2.01	
A 2514	P	10	10	10		6	4		3.36	
A 2515	P	13	13	13		6	7		2.76	
A 2516	P	15	12	12		3	9		2.22	
A 2517	NP	0	0						----	
A 2518	P	8	5	5		1	4		2.51	
A 2519	P	9	7	6		2	4	1	2.87	
A 2520	NP	21	0						----	
A 2521	P	11	10	10		4	6		2.64	
A 2522	NP	1	0						----	
A 2523	P	11	11	11		5	6		2.37	
A 2524	P	12	10	6		1	5	4	2.11	
A 2525	P	11	11	11		5	6		2.36	
A 2526	P	13	13	13		6	7		2.85	
A 2527	P	14	14	14		5	9		2.89	
A 2528	P	11	10	10		6	4		2.27	
A 2529	P	10	10	10		4	6		4.55	
A 2530	P	11	11	11		5	6		4.07	
A 2531	P	12	9	9		4	5		2.79	
A 2532	P	11	12	10		7	3	2	3.02	
A 2533	NP	3	0						----	
A 2534	P	13	13	13		5	8		2.23	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 177

Material FDA 71-44

Dose 0.23 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date December 8, 1972

Laboratory No. 0902 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 2001	P	11	11	11		5	6		3.98	
Y 2002	P	10	10	8		5	3	2	3.91	
Y 2003	P	11	11	11		6	5		3.78	
Y 2004	P	10	10	10		5	5		4.43	
Y 2005	P	11	11	11		8	3		3.87	
Y 2006	P	9	9	9		3	6		3.59	
Y 2007	P	14	12	12		6	6		3.75	
Y 2008	P	14	13	13		6	7		5.43	
Y 2009	P	12	11	11		4	7		3.92	
Y 2010	P	14	14	14		3	11		3.75	
Y 2011	P	12	12	12		8	4		3.50	
Y 2012	P	8	8	8		5	3		3.83	
Y 2013	P	8	8	8		6	2		2.32	
Y 2014	P	7	7	7		3	4		2.79	
Y 2015	P	8	8	8		3	5		2.52	
Y 2016	P	12	12	12		7	5		3.52	
Y 2017	P	14	14	14		5	9		3.82	
Y 2018	P	15	14	14		7	7		3.85	
Y 2019	P	12	8	8		4	4		3.73	
Y 2020	P	9	6	6		3	3		4.14	
Y 2021	P	10	10	10		6	4		3.63	
Y 2022	P	10	10	10		5	5		3.55	
Y 2023	P	13	14	13		7	6	1	3.81	
Y 2024	P	12	12	12		5	7		3.71	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 178

Material FDA 71-44

Dose 0.68 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date December 8, 1972

Laboratory No. 0902 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 2031	P	10	10	10		6	4		3.81	
Y 2032	NP	1	0						----	
Y 2033	P	11	11	11		10	1		4.11	
Y 2034	P	9	9	9		4	5		4.02	
Y 2035	P	10	10	10		2	8		4.12	
Y 2036	P	8	8	8		2	6		3.56	
Y 2037	P	17	16	16		5	11		3.57	
Y 2038	P	9	8	7		5	2	1	3.85	
Y 2039	P	11	11	11		3	8		3.96	
Y 2040	P	12	12	12		6	6		3.87	
Y 2041	P	14	14	14		5	9		3.89	
Y 2042	P	12	11	11		4	7		3.53	
Y 2043	P	10	10	9		4	5	1	2.22	
Y 2044	P	10	10	10		4	6		2.51	
Y 2045	P	9	8	8		4	4		2.89	
Y 2046	NP	0	0						----	
Y 2047	NP	0	0						----	
Y 2048	NP	5	0						----	
Y 2049	NP	9	0						----	
Y 2050	P	16	17	15		7	8	2	3.63	
Y 2051	P	16	15	15		5	10		3.82	
Y 2052	P	11	11	11		7	4		3.07	
Y 2053	P	12	12	12		4	8		3.55	
Y 2054	P	13	13	13		5	8		3.88	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 179

Material FDA 71-44

Dose 3.2 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date December 8, 1972

Laboratory No. 0902 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 2061	P	14	14	14		6	8		3.49	
Y 2062	P	11	11	11		3	8		3.69	
Y 2063	P	15	15	15		8	7		3.73	
Y 2064	NP	5	0						----	
Y 2065	P	13	13	13		8	5		4.07	
Y 2066	P	14	13	12		4	8	1	3.95	
Y 2067	P	9	10	8		4	4	2	3.46	
Y 2068	P	13	12	12		5	7		3.75	
Y 2069	P	12	8	8		2	6		3.84	
Y 2070	P	13	11	11		6	5		5.01	
Y 2071	P	12	11	11		4	7		3.81	
Y 2072	P	10	10	10		6	4		3.70	
Y 2073	P	13	7	7		2	5		4.01	
Y 2074	P	11	11	11		7	4		5.07	
Y 2065	P	12	12	12		5	7		3.52	
Y 2076	NP	3	0						----	
Y 2077	P	12	11	11		5	6		3.98	
Y 2078	P	10	9	9		8	1		3.80	
Y 2079	P	12	12	10		6	4	2	3.79	
Y 2080	P	14	14	14		4	10		3.54	
Y 2081	P	13	13	12		5	7	1	3.71	
Y 2082	P	14	13	13		6	7		3.52	
Y 2083	P	10	10	10		3	7		4.00	
Y 2084	P	11	10	10		5	5		3.49	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 180

Material FDA 71-44

Dose 22.5 mg/kg

Appendix II

Reproduction Data in Rats (Individual)

Date December 8, 1972

Laboratory No. 0902 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 2091	P	10	7	7		2	5		3.93	
Y 2092	P	9	9	9		4	5		3.89	
Y 2093	NP	20	0						----	
Y 2094	NP	17	0						----	
Y 2095	NP	5	0						----	
Y 2096	NP	8	0						----	
Y 2097	P	11	9	9		7	2		3.76	
Y 2098	P	13	12	12		3	9		3.82	
Y 2099	P	14	13	13		6	7		3.86	
Y 2100	P	11	10	9		5	4	1	3.96	
Y 2101	P	10	9	9		5	4		4.12	
Y 2102	P	9	8	8		3	5		3.93	
Y 2103	P	9	9	9		4	5		6.06	
Y 2104	P	13	12	12		6	6		5.17	
Y 2105	P	9	9	8		4	4	1	3.76	
Y 2106	P	13	11	10		7	3	1	3.81	
Y 2107	NP	2	0						----	
Y 2108	P	13	13	13		7	6		3.61	
Y 2109	P	11	11	11		6	5		3.64	
Y 2110	P	12	11	11		4	7		3.79	
Y 2111	P	14	14	14		6	8		3.55	
Y 2112	P	11	13	12		8	4	1	3.83	
Y 2113	P	9	7	6		2	4	1	3.42	
Y 2114	P	14	13	13		6	7		4.17	
Y 2115	P	14	14	14		6	8		3.63	
Y 2116	P	10	9	9		2	7		3.61	
Y 2117	P	9	10	9	1	3	6		3.33	
Y 2118	P	11	10	10		5	5		4.00	

* P = Pregnant; NP = Not Pregnant

HAMSTERS

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INCORPORATED

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FINAL REPORT

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

Date January 8, 1973

Laboratory No. 0903 v
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-44 (Caffeine)

Examination Requested: Teratologic evaluation of FDA 71-44 in hamsters

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

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

"The administration of up to 30 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the eighteenth 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 42 compounds will have been tested in 21 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 171 & 172; 177 through 180

Material: FDA 71-44

Date: December 8, 1972

Laboratory No.: 0903 y

Table 1

Fate Summary
(Hamsters)

Group	Material	Dose ** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
171	Sham	0.0	24	21	24	21
172	Aspirin*	250.0	22	20	22	20
177	FDA 71-44	0.3	22	21	22	21
178	FDA 71-44	1.4	22	21	21	20
179	FDA 71-44	6.5	26	20	26	20
180	FDA 71-44	30.0	27	20	27	20

* Positive Control: 250.0 mg/kg
** Administered as a water solution; (sham group dosed with anhydrous corn oil)
1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 171 & 172; 177 through 180

Material: FDA 71-44

Table 2
Reproduction Data
(Hamsters)

Date: December 8, 1972

Laboratory No.: 0903 y

Group:	171	172	177	178	179	180
Dose (mg/kg):	Sham	Aspirin**	0.3	1.4	6.5	30.0
Pregnancies						
Total No.	21	20	21	21	20	20
Died or Aborted (before Day 14)	0	0	0	1	0	0
To term (on Day 14)	21	20	21	20	20	20
Corpora Lutea						
Total No.	289	280	265	250	283	291
Average/dam mated	12.0	12.7	12.0	11.4	10.9	10.8
Live Litters						
Total No.*	20	20	21	20	20	20
Implant Sites						
Total No.	262	248	258	223	237	220
Average/dam*	12.5	12.4	12.3	11.2	11.9	11.0
Resorptions						
Total No.*	10	3	2	1	0	6
Dams with 1 or more sites resorbed	4	3	1	1	--	5
Dams with all sites resorbed	--	--	--	--	--	--
Per cent partial resorptions	19.0	15.0	4.76	5.00	--	25.0
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	232	243	254	222	232	213
Average/dam*	11.0	12.2	12.1	11.1	11.6	10.7
Sex ratio (M/F)	0.73	0.71	0.79	0.73	0.61	0.76
Dead Fetuses						
Total No.*	20	2	2	--	5	1
Dams with 1 or more dead	2	2	2	--	4	1
Dams with all dead	1	--	--	--	--	--
Per cent partial dead	9.52	10.0	9.52	--	20.0	5.00
Per cent all dead	4.76	--	--	--	--	--
Average Fetus Weight, g	1.71	1.71	1.73	1.84	1.82	1.79

* Includes only those dams examined at term.

** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180 Laboratory No. 0903 y

Table 3

Material FDA 71-44 Date December 8, 1972

Summary of Skeletal Findings*

(Hamsters)

Findings / Group No.:	171	172	177	178	179	180
Dose (mg/kg):	Sham	Aspirin**	0.3	1.4	6.5	30.0
Live Fetuses Examined (at term)	162/20	170/20	177/21	155/20	163/20	148/20
Sternebrae						
Incomplete oss.	96/20	95/20	76/19	64/20	81/17	50/19
Scrambled						
Bipartite	16/11	23/11	29/16	15/10	23/11	13/9
Fused					1/1	
Extra	1/1				4/2	
Missing	26/13	39/13	41/15	10/8	13/7	12/7
Other						
Ribs						
Incomplete oss.						
Fused/split			1/1			
Wavy			1/1			
Less than 12			1/1			
More than 13	6/5	11/8	19/10	12/5	29/10	13/8
Other						
Vertebrae						
Incomplete oss.		6/1	22/6		8/2	4/3
Scrambled			1/1			
Fused			1/1			
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure			2/2			1/1
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.		1/1	17/7	6/4	1/1	8/5
Missing				1/1		
Extra						
Miscellaneous						
Hyoid; missing		9/1	14/4	1/1		1/1
Hyoid; reduced	1/1	1/1	14/10	1/1	19/6	3/2

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180 Date December 8, 1972

Material FDA 71-44 Laboratory No. 0903 y

Table 3-a

Summary of Soft Tissue Abnormalities

(Hamsters)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
172	Aspirin*	250.0	A 3514	1	Club foot
			A 3520	1	Meningoencephalocele
177	FDA 71-44	0.3	Y 3003	2	Club foot

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 171 & 172; 177 through 180

Date December 8, 1972

Table 4

Species Hamsters

Laboratory No. 0903 y

Average Body Weights*

Group	Material	Dose Level	Day 0	6	8	10	14**
		mg/kg	g				
171	Sham	0.0	103.4	109.9	113.7	123.5	146.8 (21)
172	Aspirin***	250.0	107.3	117.7	118.4	132.5	152.4 (20)
177	FDA 71-44	0.3	109.2	118.5	120.5	131.0	152.2 (21)
178	FDA 71-44	1.4	96.0	105.1	108.2	118.6	136.7 (20)
179	FDA 71-44	6.5	97.5	103.9	111.1	121.9	144.4 (20)
180	FDA 71-44	30.0	95.2	103.1	107.6	116.9	136.4 (20)

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

Appendix I

Teratology Study in Hamsters

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

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 171

Material Sham

Dose 0.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date December 8, 1972

Laboratory No. 0903

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
S 3511	P	10	11	10		6	4	1	1.63	
S 3512	P	9	11	9		3	6	2	1.61	
S 3513	P	10	10	10		5	5		2.01	
S 3514	P	21	17		17				----	
S 3515	NP	3	0						----	
S 3516	P	14	14	14		6	8		1.71	
S 3517	P	12	12	12		6	6		1.72	
S 3518	P	10	9	9		3	6		1.81	
S 3519	P	12	11	11		6	5		1.85	
S 3520	P	17	15	15		4	11		1.82	
S 3521	P	15	15	15		7	8		1.63	
S 3522	P	12	13	7		3	4	6	1.35	
S 3523	P	13	13	12		3	9	1	1.38	
S 3524	P	14	14	14		2	12		1.50	
S 3525	NP	12	0						----	
S 3526	P	11	10	10		7	3		1.71	
S 3527	P	10	10	10		6	4		1.89	
S 3528	P	11	11	11		4	7		1.90	
S 3529	P	14	14	11	3	6	5		1.75	
S 3530	NP	4	0						----	
S 3531	P	14	14	14		6	8		1.74	
S 3532	P	14	14	14		5	9		1.79	
S 3533	P	13	11	11		6	5		1.79	
S 3534	P	14	13	13		4	9		1.69	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Hamsters (Individual)

Group 172

Material Aspirin

Dose 250.0 mg/kg

Date December 8, 1972

Laboratory No. 0903

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
A 3511	P	10	10	10		4	6		1.76	
A 3512	P	9	9	8		2	6	1	1.75	
A 3513	P	18	18	18		7	11		1.59	
A 3514	P	14	14	14		5	9		0.96	
A 3515	P	16	13	13		4	9		1.79	
A 3516	P	14	11	11		5	6		1.89	
A 3517	P	19	14	13		6	7	1	1.77	
A 3518	NP	7	0						----	
A 3519	P	10	10	10		5	5		1.83	
A 3520	P	11	8	7	1	3	4		1.88	
A 3521	P	18	18	18		8	10		1.53	
A 3522	P	18	17	16	1	6	10		1.72	
A 3523	P	10	10	10		2	8		1.85	
A 3524	NP	0	0						----	
A 3525	P	14	14	14		8	6		1.49	
A 3526	P	11	10	10		5	5		1.75	
A 3527	P	11	11	10		3	7	1	1.49	
A 3528	P	15	11	11		5	6		1.79	
A 3529	P	13	13	13		4	9		1.61	
A 3530	P	16	12	12		8	4		1.86	
A 3531	P	13	13	13		4	9		1.73	
A 3532	P	13	12	12		6	6		2.09	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 177

Material FDA 71-44

Dose 0.3 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date December 8, 1972

Laboratory No. 0903 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 3001	P	11	12	10		5	5	2	1.71	
Y 3002	P	10	9	9		3	6		1.76	
Y 3003	P	15	15	15		6	9		0.92	
Y 3004	P	16	16	16		8	8		1.76	
Y 3005	P	13	13	13		6	7		1.79	
Y 3006	P	12	12	12		6	6		1.84	
Y 3007	P	12	12	12		7	5		1.86	
Y 3008	P	12	13	13		7	6		1.68	
Y 3009	P	12	11	11		5	6		1.80	
Y 3010	P	16	16	15	1	11	4		1.64	
Y 3011	NP	3	0						----	
Y 3012	P	9	9	9		1	8		1.66	
Y 3013	P	15	14	14		6	8		1.80	
Y 3014	P	12	11	11		2	9		1.79	
Y 3015	P	11	11	11		4	7		1.91	
Y 3016	P	12	12	12		3	9		1.92	
Y 3017	P	12	11	11		6	5		1.64	
Y 3018	P	14	14	14		8	6		1.98	
Y 3019	P	14	14	13	1	5	8		1.55	
Y 3020	P	12	12	12		6	6		1.67	
Y 3021	P	12	12	12		3	9		1.72	
Y 3022	P	10	9	9		4	5		1.84	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 178

Material FDA 71-44

Dose 1.4 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date December 8, 1972

Laboratory No. 0903 y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 3031	P	12	12	12		3	9		----	Aborted Day 14
Y 3032	P	13	13	13		7	6		1.98	
Y 3033	NP	0	0						----	
Y 3034	P	13	13	13		7	6		1.75	
Y 3035	P	12	12	12		5	7		2.03	
Y 3036	P	11	9	9		4	5		1.88	
Y 3037	P	10	10	10		3	7		1.92	
Y 3038	P	9	7	7		3	4		1.93	
Y 3039	P	10	10	10		4	6		2.08	
Y 3040	P	15	15	15		7	8		1.81	
Y 3041	P	13	11	11		5	6		1.72	
Y 3042	P	18	15	15		7	8		1.78	
Y 3043	P	10	9	8		5	3	1	1.55	
Y 3044	P	10	10	10		5	5		2.10	
Y 3045	P	13	12	12		3	9		1.79	
Y 3046	P	11	11	11		4	7		1.75	
Y 3047	P	13	10	10		4	6		1.66	
Y 3048	P	12	11	11		4	7		1.79	
Y 3049	P	13	13	13		5	8		1.72	
Y 3050	P	10	10	10		4	6		1.87	
Y 3051	P	12	12	12		4	8		1.68	
Y 3052	P	10	10	10		4	6		1.96	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 179

Material FDA 71-44

Dose 6.5 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date December 8, 1972

Laboratory No. 0903 Y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 3061	P	10	10	8	2	4	5		1.54	
Y 3062	P	12	12	11	1	3	8		1.99	
Y 3063	P	19	18	18		8	10		1.67	
Y 3064	P	12	11	11		5	6		2.08	
Y 3065	P	12	12	12		4	8		1.91	
Y 3066	P	11	10	10		4	6		2.06	
Y 3067	NP	3	0						----	
Y 3068	NP	5	0						----	
Y 3069	P	15	14	14		6	8		1.97	
Y 3070	P	10	9	9		5	4		2.01	
Y 3071	P	16	16	16		4	12		1.83	
Y 3072	NP	7	0						----	
Y 3073	P	11	9	9		4	5		1.71	
Y 3074	P	9	9	9		4	5		1.67	
Y 3075	P	12	11	11		5	6		1.85	
Y 3076	P	12	12	12		5	7		1.87	
Y 3077	P	14	13	13		5	8		1.81	
Y 3078	NP	11	0						----	
Y 3079	NP	3	0						----	
Y 3080	P	13	12	11	1	3	8		1.76	
Y 3081	P	12	12	12		5	7		1.96	
Y 3082	P	14	14	13	1	4	9		1.86	
Y 3083	P	13	9	9		2	7		1.51	
Y 3084	P	11	11	11		4	7		1.70	
Y 3085	NP	2	0						----	
Y 3086	P	14	13	13		4	9		1.56	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 180

Material FDA 71-44

Dose 30.0 mg/kg

Appendix II

Reproduction Data in Hamsters (Individual)

Date December 8, 1972

Laboratory No. 0903 Y

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
Y 3091	P	8	9	8		5	3	1	1.71	
Y 3092	P	12	12	12		4	8		1.71	
Y 3093	P	16	10	9		6	3	1	1.55	
Y 3094	NP	8	0						----	
Y 3095	P	10	10	10		6	4		1.93	
Y 3096	P	10	10	10		5	5		1.69	
Y 3097	P	13	13	12		5	7	1	1.87	
Y 3098	NP	9	0						----	
Y 3099	P	12	12	12		6	6		1.86	
Y 3100	P	10	2	2		1	1		2.18	
Y 3101	P	12	11	11		5	6		1.79	
Y 3102	P	14	13	13		7	6		1.73	
Y 3103	NP	8	0						----	
Y 3104	P	10	10	10		3	7		1.67	
Y 3105	P	10	11	8	1	3	5	2	1.73	
Y 3106	P	10	10	10		6	4		1.91	
Y 3107	NP	2	0						----	
Y 3108	NP	3	0						----	
Y 3109	P	13	12	12		2	10		1.75	
Y 3110	NP	11	0						----	
Y 3111	P	14	12	12		3	9		1.80	
Y 3112	P	13	13	13		3	10		1.84	
Y 3113	P	14	14	13		4	9	1	1.67	
Y 3114	P	12	10	10		4	6		1.87	
Y 3115	NP	4	0						----	
Y 3116	P	18	13	13		8	5		1.78	
Y 3117	P	15	13	13		6	7		1.72	

* P = Pregnant; NP = Not Pregnant