Final Report-**Teratologic Evaluation of FDA 73-41 (Calcium Oxide) in Mice & Rats-**
11/15/74

Q6

FROM FDRL

FOOD AND DRUG
Research LABORATORIES, INC.
ROUTE 17C (P.O. BOX 107)
WAVERLY, NEW YORK 14892

FINAL
November 15, 1974

Teratologic Evaluation of FDA 73-41

(Calcium oxide)

in

Mice and Rats

MICE

FOOD AND DRUG Research LABORATORIES, INC.

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

FINAL REPORT

Submitted to: Department of Health, Education and Welfare
Food and Drug Administration
Negotiated Contracts Branch, HFA-510
5600 Fishers Lane
Rockville, Maryland 20852

Date: November 15, 1974

Laboratory No. 2123 (13)
Contract No.FDA 223-74-2176

Sample: Fine white powdered material

Marking: FDA 73-41 (Calcium oxide)

Examination Requested: Teratologic evaluation of FDA 73-41 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 5, Figure 1, and Appendix II

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

"The administration of up to 440 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."

David E. Bailey

David E. Bailey, Ph.D.
Director, Waverly Division

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Scientific Director

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 11 through 16

Material: FDA 73-41

Table 1

Fate Summary
(Mice)

Date: October 17, 1974

Laboratory No.: 2123 (13)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
11	Sham	0.0	22	20	22	20
12	Aspirin*	150.0	22	18	22	18
13	FDA 73-41	4.4	25	20	25	20
14	FDA 73-41	20.4	24	20	24	20
15	FDA 73-41	94.8	25	21	25	21
16	FDA 73-41	440.0	26	17	26	17

* Positive Control: 150.0 mg/kg

** Administered as a water suspension (10 ml per kg of body weight) (See Appendix I)

1) Includes all dams examined at term

FOOD AND DRUG RESEA I LABORATORIES, INC.

Group : 11 through 16

Material : FDA 73-41

Table 2
Reproduction Data
(Mice)

Date : October 17, 1974

Laboratory No. : 2123 (13)

Group :	11	12	13	14	15	16
Dose (mg/kg):	Sham	Aspirin**	4.4	20.4	94.8	440.0
Pregnancies						
Total No.	20	18	20	20	21	17
Died or Aborted (before Day 17)	0	0	0	0	0	0
To term (on Day 17)	20	18	20	20	21	17
Corpora Lutea						
Total No.	226	227	246	225	277	217
Average/dam mated	10.8	10.3	9.84	9.38	11.1	9.43
Live Litters						
Total No.*	20	18	19	20	21	17
Implant Sites						
Total No.	207	204	225	207	249	196
Average/dam*	10.4	11.3	11.3	10.4	11.9	11.5
Resorptions						
Total No.*	9	20	32	14	22	9
Dams with 1 or more sites resorbed	6	9	12	5	10	8
Dams with all sites resorbed	--	--	1	--	--	--
Per cent partial resorptions	30.0	50.0	60.0	25.0	47.6	47.1
Per cent complete resorptions	--	--	5.00	--	--	--
Live Fetuses						
Total No.	198	183	192	191	224	187
Average/dam*	9.90	10.2	9.60	9.55	10.7	11.0
Sex ratio (M/F)	0.87	1.01	0.94	0.86	0.88	0.85
Dead Fetuses						
Total No.*	--	1	1	2	3	--
Dams with 1 or more dead	--	1	1	1	2	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	--	5.56	5.00	5.00	9.52	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.94	0.83	0.84	0.90	0.87	0.85

* Includes only those dams examined at term.

** Positive Control : 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 11 through 16 } Laboratory No. 2123 (13)

Table 3

Material FDA 73-41 Date October 17, 1974

Summary of Skeletal Findings*

(Mice)

Findings / Group No.: / Dose (mg/kg):	11 Sham	12 Aspirin**	13 4.4	14 20.4	15 94.8	16 440.0
Live Fetuses Examined (at term)	140/20	130/18	134/19	133/20	156/21	131/17
Sternebrae						
Incomplete oss.	19/9	34/10	23/10	43/15	23/11	60/17
Scrambled						
Bipartite		1/1				2/2
Fused						
Extra						
Missing	10/3	22/9	32/11	14/7	23/10	41/12
Other						
Ribs						
Incomplete oss.			2/1			
Fused/split		13/4				
Wavy						
Less than 12						
More than 13	21/9	48/15	21/9	35/14	21/12	18/7
Other						
Vertebrae						
Incomplete oss.	4/2	6/3	24/6	3/2	4/4	2/2
Scrambled		2/1				
Fused		6/1				
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure			6/5			
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.	1/1	1/1	17/4	6/4	2/2	5/4
Missing						
Extra						
Miscellaneous						
Hyoid; missing	24/9	24/11	45/14	32/11	46/14	45/14
Hyoid; reduced	14/9	21/11	17/10	17/10	28/14	26/14

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

** Positive control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 11 through 16 Date October 17, 1974

Material FDA 73-41 Laboratory No. 2123 (13)

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
12	Aspirin	150.0	23347	1	Gastroschisis

*Positive Control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 11 through 16

Species Mice

Date October 17, 1974

Laboratory No. 2123 (13)

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	Day 6	Day 11	Day 15	Day 17**
		mg/kg	g				
11	Sham	0.0	29	32	35	42	49 (20)
12	Aspirin***	150.0	32	35	38	45	51 (18)
13	FDA 73-41	4.4	36	38	41	47	54 (20)
14	FDA 73-41	20.4	34	36	40	46	52 (20)
15	FDA 73-41	94.8	29	31	35	42	48 (21)
16	FDA 73-41	440.0	30	32	36	42	47 (17)

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

Table 5

Groups 11 through 16
Blend FDA 73-41

Laboratory No. 2123(13)
Species: Mice

Daily Temperature and Humidity Record

Date 1974	Time a.m.	Temp °F	Relative Humidity %
8/11	11:30	80	73
8/12	8:15	76	67
8/13	9:30	80	70
8/14	8:15	80	70
8/15	8:30	76	68
8/16	9:00	76	68
8/17	8:00	78	74
8/18	8:30	78	70
8/19	8:30	78	78
8/20	8:15	80	75
8/21	8:15	80	73
8/22	8:35	78	67
8/23	8:15	78	78
8/24	7:30	78	75
8/25	7:30	74	70
8/26	8:15	76	64
8/27	8:30	81	75
8/28	8:45	76	78
8/29	8:30	76	74
8/30	8:20	78	76
8/31	1:30 p.m.	80	74
9/1	10:00	79	75
9/2	8:30	75	73
9/3	8:15	76	72
9/4	8:30	75	70
9/5	8:30	75	70
9/6	8:45	75	68
9/7	7:30	78	69
9/8	2:00 p.m.	80	75
9/9	8:15	75	73
9/10	8:20	78	72
9/11	8:45	76	72
9/12	8:25	76	73
9/13	8:15	78	75
9/14	7:40	75	65
9/15	7:30	78	76
9/16	8:30	74	68
9/17	8:45	74	64
9/18	8:45	75	65
9/19	8:50	75	65
9/20	3:00 p.m.	80	75
9/21	8:10	80	75
9/22	8:00	76	70

Figure 1

Grossly Abnormal Fetuses
(Mice)

(None Observed)

Appendix I

Appendix I

Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were gang-housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. (One male was not permitted to impregnate more than one female per group.) 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 with the vehicle at a level equivalent to the group receiving the highest dose.

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. Daily room temperature and humidity were recorded.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the sex, numbers of corpora lutea, 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 the Wilson technique. (Colored photographs were taken of all grossly abnormal

fetuses.) The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

Appendix II

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 11

Material Sham

Dose 0.0 mg/kg

Date October 17, 1974

Laboratory No. 2123

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
23301	NP	0	0						----	
23302	P	13	10	10		4	6		0.87	
23303	P	11	9	9		3	6		0.86	
23304	P	11	11	11		3	8		0.79	
23305	P	12	10	10		3	7		0.74	
23306	P	9	8	8		3	5		1.10	
23307	P	12	10	10		5	5		0.84	
23308	P	11	9	9		5	4		0.89	
23309	P	14	12	11		8	3	1	1.01	
23310	P	11	11	10		6	4	1	0.97	
23311	P	15	12	12		6	6		1.02	
23312	P	12	12	12		7	5		0.92	
23313	P	11	11	11		4	7		0.82	
23314	P	14	12	11		8	3	1	0.98	
23315	P	13	11	11		4	7		0.97	
23316	P	9	9	8		5	3	1	0.85	
23317	P	--**	5	1		0	1	4	1.50	
23318	P	14	14	14		5	9		0.99	
23319	NP	0	0						----	
23320	P	13	12	11		4	7	1	0.88	
23321	P	9	7	7		2	5		1.00	
23322	P	12	12	12		7	5		0.87	

* P = Pregnant; NP = Not Pregnant

** Ovaries missing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 12

Material Aspirin

Dose 150.0 mg/kg

Date October 17, 1974

Laboratory No. 2123

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
23332	P	13	12	9		3	6	3	0.68	
23333	P	15	15	15		8	7		0.69	
23335	P	14	12	12		7	5		0.84	
23336	P	9	9	3		1	2	6	0.72	
23339	P	8	5	2		0	2	3	0.92	
23340	NP	0	0						----	
23341	P	16	13	11		6	5	2	0.74	
23342	P	12	11	11		6	5		0.82	
23343	P	13	13	13		5	8		0.85	
23344	P	12	11	10		5	5	1	1.01	
23345	P	19	18	17		7	10	1	0.95	
23346	P	7	6	6		3	3		0.98	
23347	P	12	12	11		6	5	1	0.79	
23348	NP	0	0						----	
23349	NP	0	0						----	
23350	P	13	11	11		5	6		0.86	
23351	P	16	14	13		10	3	1	0.82	
23352	P	13	13	13		7	6		0.92	
23353	P	11	11	11		6	5		0.88	
23354	P	17	14	14		7	7		0.89	
23355	NP	0	0						----	
23356	P	7	4	1	1	0	1	2	0.57	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 13

Material FDA 73-41

Dose 4.4 mg/kg

Date October 17, 1974

Laboratory No. 2123

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
23361	P	11	11	11		4	7		0.86	
23362	NP	0	0						----	
23363	P	11	11	11		8	3		0.95	
23364	P	15	12	12		4	8		0.74	
23365	NP	0	0						----	
23366	P	11	10	8	1	4	4	1	0.89	
23367	P	15	12	12		7	5		0.94	
23368	NP	0	0						----	
23369	P	14	13	12		6	6	1	0.87	
23370	P	11	10	10		5	5		0.66	
23371	P	12	12	12		6	6		0.86	
23372	P	16	16	16		8	8		0.71	
23373	P	15	14	12		7	5	2	0.93	
23374	P	13	11	8		3	5	3	1.05	
23375	P	7	7	5		4	1	2	1.01	
23376	P	7	4	3		0	3	1	0.54	
23377	NP	0	0						----	
23378	P	12	11	11		6	5		0.94	
23379	NP	0	0						----	
23380	P	11	11	9		4	5	2	0.91	
23381	P	18	16	15		7	8	1	1.08	
23382	P	8	7					7	----	
23383	P	12	12	10		5	5	2	0.53	
23384	P	10	10	6		2	4	4	0.61	
23385	P	17	15	9		3	6	6	0.81	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 14

Material FDA 73-41

Dose 20.4 mg/kg

Date October 17, 1974

Laboratory No. 2123

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
23391	P	12	10	10		3	7		0.90	
23393	NP	0	0						----	
23394	P	11	10	10		3	7		0.80	
23395	P	13	12	12		8	4		0.90	
23396	NP	0	0						----	
23397	NP	0	0						----	
23398	P	14	12	12		7	5		0.92	
23399	P	11	10	10		6	4		0.94	
23400	P	11	11	11		5	6		0.97	
23401	NP	0	0						----	
23402	P	14	14	13		6	7	1	0.86	
23403	P	12	10	10		4	6		0.85	
23404	P	11	10	4		2	2	6	0.62	
23405	P	10	6	6		4	1		0.80	
23406	P	11	11	11		1	10		0.79	
23407	P	6	5	5		4	1		1.00	
23408	P	11	11	11		7	4		0.90	
23409	P	11	11	9	2	5	4		0.92	
23410	P	14	14	13		6	7	1	0.94	
23411	P	7	7	7		1	6		0.94	
23412	P	12	12	11		6	5	1	0.96	
23413	P	8	6	1		0	1	5	1.04	
23414	P	13	12	12		6	6		0.92	
23415	P	13	13	13		4	9		0.99	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 15

Material FDA 73-41

Dose 94.8 mg/kg

Date October 17, 1974

Laboratory No. 2123

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
23421	P	11	11	11		3	8		0.93	
23422	P	16	14	12	2	8	4		0.89	
23423	P	8	8	8		4	4		1.09	
23424	P	14	12	4		0	4	8	0.74	
23425	P	11	9	9		5	4		0.76	
23426	P	15	15	13		7	6	2	0.85	
23427	P	12	12	12		7	5		0.85	
23428	P	12	12	10		5	5	2	0.96	
23429	P	13	12	11		6	5	1	0.77	
23430	P	14	12	10		3	7	2	0.81	
23431	NP	0	0						----	
23432	P	12	12	12		7	5		0.90	
23433	P	14	12	12		6	6		0.71	
23434	NP	0	0						----	
23435	P	14	12	11		6	5	1	0.91	
23436	P	15	11	11		5	6		0.98	
23437	P	14	13	11		3	8	2	0.92	
23438	P	12	10	10		5	5		0.85	
23439	NP	0	0						----	
23440	NP	0	0						----	
23441	P	16	13	13		9	4		0.80	
23442	P	12	12	12		4	8		0.91	
23443	P	13	12	10	1	4	7	1	0.97	
23444	P	16	12	11		4	7	1	0.89	
23445	P	13	13	11		4	7	2	0.86	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 16

Material FDA 73-41

Dose 440.0 mg/kg

Date October 17, 1974

Laboratory No. 2123

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
23451	NP	0	0						----	
23452	P	10	9	9		3	6		0.75	
23453	NP	0	0						----	
23454	P	12	12	12		5	7		0.86	
23456	P	13	11	10		5	5	1	0.83	
23457	P	11	10	10		4	6		0.87	
23458	P	11	8	8		6	2		0.87	
23461	NP	0	0						----	
23462	P	15	14	14		6	8		0.68	
23463	NP	0	0						----	
23464	P	12	9	8		5	3	1	0.89	
23465	P	13	10	8		6	2	2	0.83	
23466	P	12	12	12		3	9		0.73	
23467	NP	0	0						----	
23469	P	8	8	8		3	5		0.92	
23470	NP	0	0						----	
23471	P	15	14	14		9	5		0.86	
23472	P	14	13	12		5	7	1	0.85	
23473	P	14	14	14		6	8		0.92	
23474	P	16	13	12		3	9	1	0.94	
23475	P	16	16	15		5	10	1	0.91	
23476	NP	--**	0						----	
23477	P	13	12	11		6	5	1	1.02	
23478	P	12	11	10		6	4	1	0.79	
23479	NP	--**	0						----	
23480	NP	--**	0						----	

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

R A T S

FOOD AND DRUG Research LABORATORIES, INC.

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

FINAL REPORT

Submitted to: Department of Health, Education and Welfare
Food and Drug Administration
Negotiated Contracts Branch, HFA-510
5600 Fishers Lane
Rockville, Maryland 20852

Date: November 15, 1974

Laboratory No. 2143 (13)
Contract No.FDA 223-74-217

Sample: Fine white powdered material

Marking: FDA 73-41 (Calcium oxide)

Examination Requested: Teratologic evaluation of FDA 73-41 in rats.

Procedure: See Appendix I

Results: See Tables 1 through 5, Figure 1, and Appendix II

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

"The administration of up to 680 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."

David E. Bailey
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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 11 through 16

Material: FDA 73-41

Date: October 17, 1974

Laboratory No.: 2143 (13)

Table 1

Fate Summary
(Rats)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
11	Sham	0.0	25	19	25	19
12	Aspirin*	250.0	21	21	21	21
13	FDA 73-41	6.8	22	20	22	20
14	FDA 73-41	31.5	21	19	21	19
15	FDA 73-41	146.5	21	20	21	20
16	FDA 73-41	680.0	22	20	22	20

* Positive Control: 250.0 mg/kg

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

1) Includes all dams examined at term

FOOD AND DRUG RESEA LABORATORIES, INC.

Group: 11 through 16

Material: FDA 73-41

Table 2
Reproduction Data
(Rats)

Date: October 17, 1974

Laboratory No.: 2143 (13)

Group:	11	12	13	14	15	16
Dose (mg/kg):	Sham	Aspirin**	6.8	31.5	146.5	680.0
Pregnancies						
Total No.	19	21	20	19	20	20
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	19	21	20	19	20	20
Corpora Lutea						
Total No.	242	241	254	232	268	246
Average/dam mated	9.68	11.5	11.6	11.1	12.8	11.2
Live Litters						
Total No.*	19	19	20	19	20	19
Implant Sites						
Total No.	218	212	221	209	246	221
Average/dam*	11.5	10.1	11.1	11.0	12.3	11.1
Resorptions						
Total No.*	3	48	2	5	--	19
Dams with 1 or more sites resorbed	3	12	1	2	--	5
Dams with all sites resorbed	--	2	--	--	--	1
Per cent partial resorptions	15.8	57.1	5.00	10.5	--	25.0
Per cent complete resorptions	--	9.52	--	--	--	5.00
Live Fetuses						
Total No.	215	163	219	204	246	202
Average/dam*	11.3	8.58	11.0	10.7	12.3	10.1
Sex ratio (M/F)	0.94	0.99	1.23	0.98	1.02	1.04
Dead Fetuses						
Total No.*	--	1	--	--	--	--
Dams with 1 or more dead	--	1	--	--	--	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	--	4.76	--	--	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.82	2.64	3.80	3.81	3.83	3.75

* Includes only those dams examined at term.

** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 11 through 16 | Laboratory No. 2143 (13)

Table 3

Material FDA 73-41 | Date October 17, 1974

Summary of Skeletal Findings*
(Rats)

Findings / Group No.:	11	12	13	14	15	16
Dose (mg/kg):	Sham	Aspirin**	6.8	31.5	146.5	680.0
Live Fetuses Examined (at term)	151/19	114/19	150/20	142/19	171/20	136/19
Sternebrae						
Incomplete oss.	28/12	73/18	32/14	21/9	46/14	23/10
Scrambled						
Bipartite	1/1	12/7	4/4	2/2		2/2
Fused						
Extra						
Missing	2/2	72/19	5/4	7/4	1/1	8/3
Other						
Ribs						
Incomplete oss.		17/11	4/1	4/3	2/1	3/1
Fused/split		7/4				
Wavy	30/9	45/15	26/10	26/12	27/14	17/6
Less than 12		1/1				
More than 13		79/18		1/1	1/1	
Other						
Vertebrae						
Incomplete oss.	4/4	54/6	5/5	6/3	5/4	4/1
Scrambled						
Fused		1/1				
Extra ctrs. oss.		1/1				
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	32/8	44/14	25/10	27/10	35/13	10/6
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.		3/3				3/1
Missing						
Extra						
Miscellaneous						
Hyoid; missing	15/8	38/16	11/7	11/7	16/6	7/4
Hyoid; reduced	28/12	7/3	17/7	23/11	17/9	9/5

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 11 through 16 Date October 17, 1974

Material FDA 73-41 Laboratory No. 2143 (13)

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
11	Sham	0.0	43323	1	Encephalomeningocele; anopia; micromeglia
12	Aspirin*	250.0	43336	1	Gastroschisis
			43345	1	Gastroschisis
			43346	1	Encephalomeningocele
13	FDA 73-41	6.8	43361	1	Gastroschisis
			43382	1	Gastroschisis
14	FDA 73-41	31.5	43409	1	Cleft palate; gastroschisis

*Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 11 through 16

Species Rats

Date October 17, 1974

Laboratory No. 2143 (13)

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	20**
		mg/kg	g				
11	Sham	0.0	215	235	251	275	344 (19)
12	Aspirin***	250.0	211	228	241	261	309 (21)
13	FDA 73-41	6.8	214	232	249	272	340 (20)
14	FDA 73-41	31.5	213	230	249	268	338 (19)
15	FDA 73-41	146.5	223	243	262	288	360 (20)
16	FDA 73-41	680.0	202	220	233	248	306 (20)

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

Table 5

Groups 11 through 16 Laboratory No. 2143 (13)

Blend FDA 73-41 Species: Rats

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1974	a.m.	°F	%
8/7	8:35	80	76
8/8	8:25	78	70
8/9	2:50 p.m.	78	78
8/10	8:00	80	--
8/11	11:30	80	73
8/12	8:15	76	67
8/13	9:30	80	70
8/14	8:15	80	70
8/15	8:15	76	68
8/16	9:00	76	68
8/17	8:00	78	74
8/18	8:30	78	70
8/19	8:30	78	78
8/20	8:15	80	75
8/21	8:15	80	73
8/22	8:35	78	67
8/23	8:30	78	78
8/24	7:30	78	75
8/25	7:30	74	70
8/26	8:15	76	64
8/27	8:30	81	75
8/28	8:45	76	78
8/29	8:30	76	74
8/30	8:20	78	76
8/31	1:30 p.m.	80	74
9/1	10:00	79	75
9/2	8:30	75	73
9/3	8:15	76	72
9/4	8:30	75	70
9/5	8:30	75	70
9/6	8:45	75	68
9/7	7:30	78	69
9/8	2:00	80	75
9/9	8:45	75	72
9/10	8:45	78	75

Figure 1

Original Photographs in First Copy of Report 2143 (13)

Figure 1

Grossly Abnormal Fetuses
(Rats)

Group: 11

Material: Sham

Dose: 0.0 mg/kg

Date: October 17, 1974

Lab. No. 2143 (13) (19)

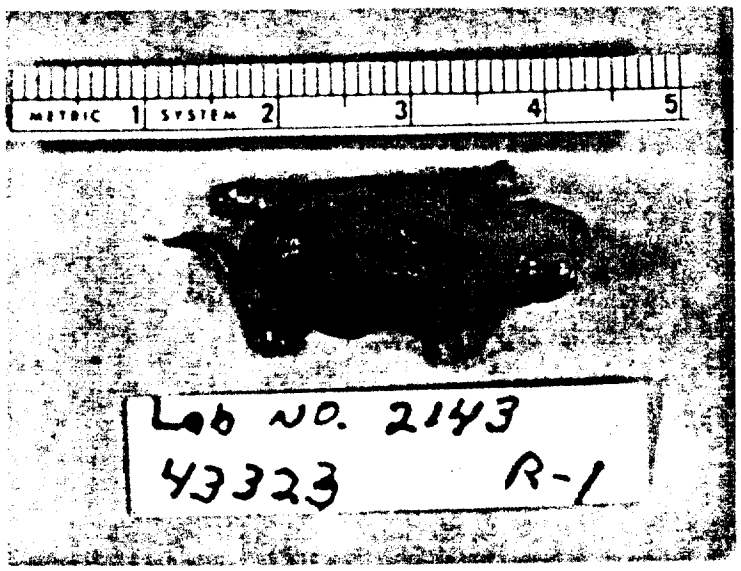


Figure 1

Grossly Abnormal Fetuses
(Rats)

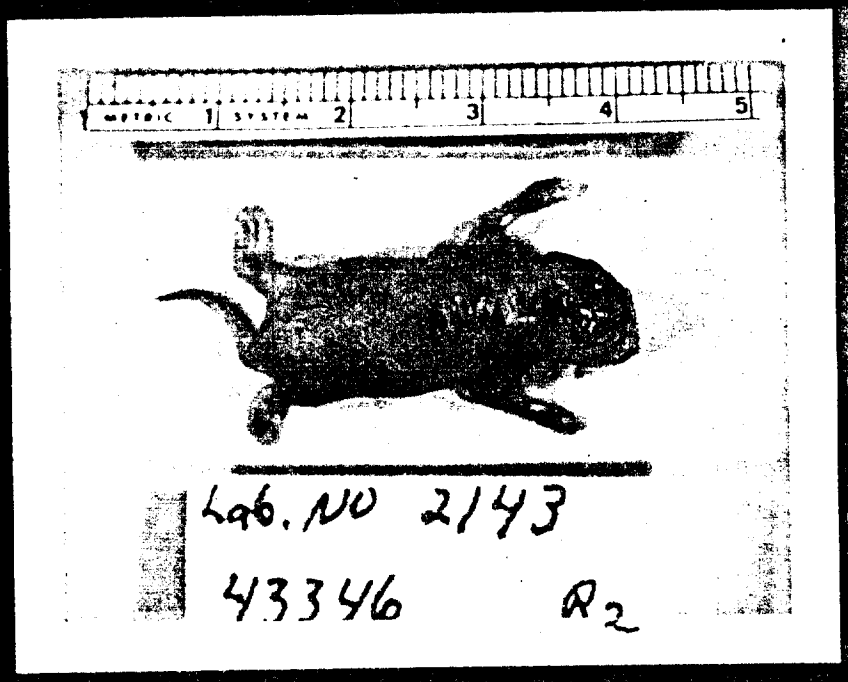
Group: 12

Material: Aspirin

Dose: 250.0 mg/kg

Date: October 17, 1974

Lab. No. 2143 (13) (19)



Appendix I

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. (One male was not permitted to impregnate more than one female per group.) Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubations. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

Dosage (mg/kg)	Dose (ml/kg)	Concentration (mg/ml)
≦ 250	1	≦ 250
251-500	2	125-250
501-750	3	133-250
751-1000	4	187-250
1001-1600	5	200-250

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

On Day 20 all dams were subjected to Caesarean Section under surgical anesthesia, and the sex, numbers of corpora lutea, 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 the Wilson technique. (Colored photographs were taken of all grossly abnormal fetuses.) The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

Appendix II

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 11

Material Sham

Dose 0.0 mg/kg

Date October 17, 1974

Laboratory No. 2143

Dam No.	Rate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
43301	P	16	16	16		7	9		3.83	
43302	P	16	16	16		6	10		3.79	
43303	NP	0	0						----	
43304	P	11	11	11		4	7		3.57	
43305	P	14	13	13		5	8		3.59	
43306	P	14	14	14		6	8		4.13	
43307	P	15	15	15		8	7		3.71	
43308	NP	0	0						----	
43309	P	11	7	7		5	2		4.08	
43310	P	14	13	13		8	5		3.92	
43311	P	13	13	13		6	7		3.81	
43312	NP	0	0						----	
43313	P	9	8	8		4	4		4.01	
43314	P	9	8	7		3	4	1	3.89	
43315	P	12	8	8		2	6		3.88	
43316	NP	0	0						----	
43317	P	12	12	12		5	7		3.64	
43318	P	13	13	13		10	3		3.84	
43319	NP	0	0						----	
43320	P	16	16	16		8	8		3.72	
43321	P	10	6	5		4	1	1	3.89	
43322	P	14	13	12		6	6	1	4.11	
43323	P	12	11	11		6	5		3.73	
43324	NP	0	0						----	
43325	P	11	5	5		1	4		3.42	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 12

Material Aspirin

Dose 250.0 mg/kg

Date October 17, 1974

Laboratory No. 2143

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
43331	P	10	10	10		3	7		2.52	
43332	P	10	9	9		3	6		2.51	
43333	P	11	9	9		4	5		2.97	
43334	P	13	12	7	1	1	6	4	1.81	
43335	P	12	11	11		8	3		3.13	
43336	P	12	11	7		4	3	4	2.54	
43337	P	10	10	10		3	7		3.09	
43338	P	10	7	7		3	4		3.19	
43339	P	12	11	11		6	5		3.28	
43340	P	11	10	2		1	1	8	2.18	
43341	P	11	11					11	----	
43342	P	10	10	9		6	3	1	2.09	
43343	P	13	9	9		4	5		3.11	
43344	P	11	7	3		1	2	4	2.71	
43345	P	10	8	8		7	1		3.00	
43346	P	13	12	11		6	5	1	2.21	
43347	P	9	8	7		5	2	1	2.02	
43348	P	14	9					9	----	
43349	P	12	12	10		6	4	2	2.37	
43350	P	15	15	14		6	8	1	2.80	
43351	P	12	11	9		4	5	2	2.59	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 13

Material FDA 73-41

Dose 6.8 mg/kg

Date October 17, 1974

Laboratory No. 2143

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
43361	P	15	13	13		4	9		3.83	
43362	P	11	11	11		6	5		4.19	
43363	P	12	11	11		6	5		3.77	
43364	P	13	13	13		9	4		3.62	
43365	P	13	12	12		7	5		3.68	
43366	P	13	8	8		2	6		4.17	
43367	P	13	10	10		6	4		3.90	
43368	P	11	10	10		5	5		3.84	
43369	NP	0	0						----	
43370	P	13	12	12		5	7		3.78	
43371	P	15	6	6		3	3		3.41	
43372	NP	0	0						----	
43373	P	11	11	11		7	4		3.89	
43374	P	12	12	12		9	3		3.84	
43375	P	12	10	10		9	1		4.27	
43376	P	12	11	11		7	4		3.79	
43377	P	13	12	12		5	7		3.50	
43378	P	17	14	12		7	5	2	3.75	
43379	P	10	10	10		5	5		3.51	
43380	P	10	9	9		3	6		3.86	
43381	P	14	14	14		9	5		3.55	
43382	P	14	12	12		7	5		3.86	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 14

Material FDA 73-41

Dose 31.5 mg/kg

Date October 17, 1974

Laboratory No. 2143

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
43391	P	11	11	11		5	6		4.11	
43392	P	9	9	9		7	2		3.74	
43393	P	12	11	11		3	8		3.94	
43394	P	13	13	13		7	6		3.73	
43395	P	14	14	14		8	6		3.95	
43396										Not Assigned
43397	NP	0	0						----	
43398										Not Assigned
43399	P	16	14	14		--**	--**		3.95	
43400	P	10	10	10		6	4		4.08	
43401	P	12	12	12		7	5		4.10	
43402	P	9	8	8		4	4		4.12	
43403	P	12	10	10		3	7		3.71	
43404	P	11	11	11		6	5		4.02	
43405	P	12	12	12		6	6		4.19	
43406	P	12	7	6		1	5	1	4.23	
43407	P	12	12	12		4	8		3.47	
43408										Not Assigned
43409	P	11	8	8		5	3		3.24	
43410	P	14	12	12		7	5		3.78	
43411	NP	0	0						----	
43412	P	14	13	13		7	6		3.91	
43413	P	14	13	13		6	7		3.46	
43414	P	14	9	5		2	3	4	2.58	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 15

Material FDA 73-41

Dose 146.5 mg/kg

Date October 17, 1974

Laboratory No. 2143

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
43421	P	12	12	12		7	5		4.18	
43422										Not Assigned
43423	P	12	10	10		6	4		3.50	
43424	P	13	13	13		6	7		3.30	
43425	P	16	13	13		7	6		3.96	
43426	P	16	14	14		7	7		4.33	
43427	P	18	16	16		10	6		3.94	
43428										Not Assigned
43429	NP	0	0						----	
43430	P	17	14	14		5	9		3.66	
43431	P	13	12	12		5	7		4.05	
43432	P	11	8	8		3	5		4.29	
43433	P	15	15	15		11	4		4.06	
43434	P	11	11	11		2	9		3.66	
43435	P	12	11	11		6	5		4.09	
43436	P	11	11	11		5	6		3.97	
43437	P	12	11	11		7	4		3.67	
43438	P	14	13	13		7	6		3.71	
43439	P	12	12	12		6	6		3.69	
43440	P	14	13	13		7	6		3.64	
43441	P	10	10	10		5	5		3.57	
43442	P	16	15	15		8	7		3.50	
43443	P	13	12	12		4	8		3.76	

* P = Pregnant; NP = Not Pregnant