FROM

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

FINAL

February 19, 1975

Teratologic Evaluation of FDA 73-83 (Mustard Flour-Untreated) in Mice and Rats

Final report-Teratologic Evaluation of FDA 73-83 (**Mustard Flour-Untreated**) in Mice & Rats 2/19/75

M I C E

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

Date February 19, 1975

Laboratory No. 2123 (2)
Contract No. FDA 223-74-2176

Sample: Fine gold colored powdered material

Marking: FDA 73-83 (Mustard flour-Untreated)

Examination Requested: Teratologic evaluation of FDA 73-83 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

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

"The administration of up to 490 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.
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Kenneth Morgareidge

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 61 through 66

Material: FDA 73-83-U

Date: January 17, 1975

Laboratory No.: 2123 (2)

Table 1

Fate Summary
(Mice)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
61	Sham	0.0	25	20	25	20
62	Aspirin*	150.0	25	20	25	20
63	FDA 73-83-U	4.9	24	20	24	20
64	FDA 73-83-U	22.7	25	21	25	21
65	FDA 73-83-U	106.0	30	22	30	22
66	FDA 73-83-U	490.0	29	21	29	21

* Positive Control: 150.0 mg/kg

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

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group : 61 through 66

Material : FDA 73-83-U

Table 2
Reproduction Data
(Mice)

Date : January 17, 1975

Laboratory No. : 2123 (2)

Group :	61	62	63	64	65	66
Dose (mg/kg):	Sham	Aspirin**	4.9	22.7	106.0	490.0
Pregnancies						
Total No.	20	20	20	21	22	21
Died or Aborted (before Day 17)	0	0	0	0	0	0
To term (on Day 17)	20	20	20	21	22	21
Corpora Lutea						
Total No.	235	262	252	256	266	266
Average/dam mated	9.40	10.5	10.5	10.2	8.87	9.17
Live Litters						
Total No.*	20	20	20	21	22	21
Implant Sites						
Total No.	218	245	235	235	248	238
Average/dam*	10.9	12.3	11.8	11.2	11.3	11.3
Resorptions						
Total No.*	6	12	7	13	6	15
Dams with 1 or more sites resorbed	6	9	6	8	4	11
Dams with all sites resorbed	--	--	--	--	--	--
Per cent partial resorptions	30.0	45.0	30.0	38.1	18.2	52.4
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	209	232	224	222	241	222
Average/dam*	10.5	11.6	11.2	10.6	11.0	10.6
Sex ratio (M/F)	0.92	0.97	0.85	0.90	0.85	0.95
Dead Fetuses						
Total No.*	3	1	4	--	1	1
Dams with 1 or more dead	3	1	2	--	1	1
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	15.0	5.00	10.0	--	4.55	4.76
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.88	0.83	0.84	0.86	0.88	0.88

* Includes only those dams examined at term.

** Positive Control : 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 | Laboratory No. 2123 (2)

Table 3

Material FDA 73-83-U | Date January 17, 1975

Summary of Skeletal Findings*
(Mice)

Findings / Group No.:	61	62	63	64	65	66
Dose (mg/kg):	Sham	Aspirin**	4.9	22.7	106.0	490.0
Live Fetuses Examined (at term)	144/20	160/20	155/20	155/21	167/22	153/21
Sternebrae						
Incomplete oss.	35/10	81/18	52/18	62/17	49/17	37/12
Scrambled						
Bipartite	1/1	2/2	2/2	3/2	1/1	
Fused						
Extra		1/1				
Missing	26/11	15/9	19/7	31/10	18/9	18/8
Other						
Ribs						
Incomplete oss.						
Fused/split						
Wavy						
Less than 12	2/1					
More than 13	24/12	22/12	14/7	20/13	33/14	14/5
Other						
Vertebrae						
Incomplete oss.	14/7	5/5	8/5	9/3	7/4	7/4
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	1/1	1/1	1/1			
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.	5/2	1/1	2/2	11/4	6/3	4/3
Missing						
Extra						
Miscellaneous						
Hyoid; missing	50/15	33/15	36/13	48/16	29/13	34/14
Hyoid; reduced	19/12	25/13	18/12	20/12	25/14	18/11

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

** Positive control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 Date January 17, 1975

Material FDA 73-83-U Laboratory No. 2123 (2)

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 61 through 66

Date January 17, 1975

Table 4

Species Mice

Laboratory No. 2123 (2)

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	17**
		mg/kg	g				
61	Sham	0.0	28	32	34	43	48 (20)
62	Aspirin***	150.0	29	33	35	42	49 (20)
63	FDA 73-83-U	4.9	28	33	37	44	49 (20)
64	FDA 73-83-U	22.7	29	33	36	43	50 (21)
65	FDA 73-83-U	106.0	28	31	35	43	49 (22)
66	FDA 73-83-U	490.0	27	30	34	41	48 (21)

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

Table 5

Groups 61 through 66
Compound FDA 73-83-U

Laboratory No. 2123 (2)
Species: Mice

Daily Temperature and Humidity Record

Date 1974	Time a.m.	Temp °F	Relative Humidity %
11/2	12:30 p.m.	78	67
11/3	8:00	77	63
11/4	11:00	74	62
11/5	11:00	76	70
11/6	8:00	72	63
11/7	9:00	74	76
11/8	8:00	72	70
11/9	----	--	--
11/10	8:20	74	60
11/11	----	--	--
11/12	8:00	72	60
11/13	8:30	80	60
11/14	8:30	80	58
11/15	8:30	82	50
11/16	10:30	82	54
11/17	2:45 p.m.	82	51
11/18	8:30	80	50
11/19	2:25 p.m.	80	40
11/20	8:30	80	74
11/21	9:00	80	55
11/22	8:30	78	55
11/23	8:00	80	55
11/24	8:00	80	69
11/25	8:30	80	72
11/26	8:30	80	60
11/27	8:30	78	50
11/28	10:00	78	55
11/29	10:00	78	58
11/30	8:00	78	55
12/1	8:00	82	59
12/2	9:15	78	52
12/3	9:00	98	55
12/4	10:00	80	55
12/5	10:30	77	53
12/6	8:30	79	58
12/7	8:00	78	57
12/8	8:00	78	71
12/9	2:30 p.m.	78	70
12/10	8:00	82	50
12/11	11:00	81	50

Figure 1

(Mice)

Photographs of Grossly Abnormal Fetuses

(None Observed in Test Groups)

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 61

Material Sham

Dose 0.0 mg/kg

Date January 17, 1975

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
24801	P	11	11	10	1	4	6		0.74	
24802	P	10	10	9		5	4	1	1.08	
24803	NP	0	0						----	
24804	P	10	10	10		4	6		0.67	
24805	P	9	9	9		4	5		0.87	
24806	P	14	12	12		5	7		0.85	
24807	P	16	14	13	1	5	8		0.83	
24808	P	14	11	10		5	5	1	0.95	
24809	NP	0	0						----	
24810	P	13	13	12	1	7	5		0.91	
24811	P	14	14	13		9	4	1	0.80	
24812	NP	0	0						----	
24813	NP	0	0						----	
24814	P	10	10	9		3	6	1	0.80	
24815	P	13	13	13		10	3		0.83	
24816	P	14	12	12		7	5		0.91	
24817	P	11	11	11		4	7		0.69	
24818	P	12	10	10		5	5		1.04	
24819	P	4	2	2		1	1		0.89	
24820	P	13	13	12		6	6	1	1.03	
24821	NP	0	0						----	
24822	P	10	10	10		3	7		0.71	
24823	P	12	10	9		4	5	1	1.06	
24824	P	13	13	13		5	8		0.89	
24825	P	12	10	10		4	6		0.97	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 62

Material Aspirin

Dose 150.0 mg/kg

Date January 17, 1975

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
24831	P	12	12	11	1	5	6		0.83	
24832	P	14	14	13		6	7	1	0.89	
24833	P	14	13	13		6	7		0.77	
24834	P	7	6	6		4	2		0.93	
24835	P	14	14	12		5	7	2	0.72	
24836	P	12	11	10		5	5	1	0.95	
24837	NP	0	0						----	
24838	P	12	10	10		4	6		0.91	
24839	P	16	16	16		7	9		0.83	
24840	P	13	13	11		6	5	2	0.89	
24841	NP	0	0						----	
24842	NP	0	0						----	
24843	P	11	10	10		6	4		0.85	
24844	P	11	11	10		5	5	1	0.72	
24845	P	15	13	13		5	8		0.82	
24846	P	15	13	11		4	7	2	0.77	
24847	P	14	13	12		8	4	1	0.94	
24848	P	12	11	10		6	4	1	0.77	
24849	P	17	13	13		6	7		0.74	
24850	P	15	15	15		10	5		0.82	
24851	NP	0	0						----	
24852	P	12	11	10		3	7	1	0.82	
24853	NP	0	0						----	
24854	P	12	12	12		6	6		0.78	
24855	P	14	14	14		7	7		0.86	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 63

Material FDA 73-83

Dose 4.9 mg/kg

Date January 17, 1975

Laboratory No. 2123 (2)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
24861	P	11	10	9		3	6	1	0.82	
24862	P	16	16	16		7	9		0.86	
24863	NP	0	0						----	
24864	P	18	18	18		8	10		0.86	
24865	P	18	17	15	2	8	7		1.00	
24866	P	11	10	10		3	7		0.79	
24867	P	13	11	11		6	5		0.88	
24868	P	12	12	12		4	8		0.68	
24869	NP	0	0						----	
24870	P	12	11	11		6	5		0.94	
24871	P	11	9	9		3	6		0.76	
24872	P	10	10	9		5	4	1	0.81	
24873	P	14	13	13		4	9		0.85	
24874	P	13	12	11		6	5	1	0.82	
24875	P	10	9	9		4	5		0.84	
24876	P	10	9	8		3	5	1	0.91	
24877	P	12	12	12		5	7		0.67	
24878	P	15	12	11		6	5	1	0.89	
24879	NP	0	0						----	
24880	P	12	11	9	2	5	4		0.90	
24881	P	12	11	11		5	6		0.82	
24882	NP	0	0						----	
24883	P	10	10	8		5	3	2	0.85	
24884	P	12	12	12		7	5		0.82	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 64

Material FDA 73-83

Dose 22.7 mg/kg

Date January 17, 1975

Laboratory No. 2123(2)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
24891	P	15	14	10		5	5	4	0.78	
24892	P	17	16	15		7	8	1	0.81	
24893	P	12	12	12		4	8		0.79	
24894	P	14	14	13		6	7	1	0.85	
24895	P	12	11	11		6	5		0.77	
24896	P	13	12	12		6	6		1.06	
24897	P	11	11	10		4	6	1	0.91	
24898	P	14	11	10		4	6	1	0.72	
24899	NP	0	0						----	
24900	P	17	16	16		7	9		0.82	
24901	P	8	7	4		2	2	3	0.66	
24902	NP	0	0						----	
24903	P	10	9	9		4	5		0.69	
24904	NP	0	0						----	
24905	P	11	11	11		6	5		0.86	
24906	P	13	11	11		5	6		0.85	
24907	P	7	6	5		3	2	1	0.93	
24908	P	11	9	9		5	4		1.02	
24909	NP	0	0						----	
24910	P	13	12	12		6	6		0.90	
24911	P	13	12	12		7	5		0.96	
24912	P	14	13	12		6	6	1	0.83	
24913	P	13	13	13		6	7		0.89	
24914	P	10	7	7		3	4		0.91	
24915	P	8	8	8		3	5		1.04	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 65

Material FDA 73-83

Dose 106.0 mg/kg

Date January 17, 1975

Laboratory No. 2123(2)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
24921	P	12	12	12		6	6		0.85	
24922	P	14	13	13		8	5		0.81	
24923	P	5	4	4		2	2		0.85	
24924	NP	0	0						----	
24925	P	14	13	13		6	7		0.73	
24926	NP	0	0						----	
24927	P	14	14	14		8	6		0.92	
24928	P	15	15	15		6	9		0.80	
24929	P	12	10	9		4	5	1	0.82	
24930	NP	0	0						----	
24931	NP	0	0						----	
24932	NP	0	0						----	
24933	P	10	10	10		5	5		0.82	
24934	NP	0	0						----	
24935	P	13	12	12		3	5		0.89	
24936	P	13	10	10		3	7		0.91	
24937	P	14	14	13		5	8	1	0.85	
24938	NP	0	0						----	
24939	P	11	11	11		2	9		0.93	
24940	P	13	13	10		4	6	3	0.75	
24941	P	14	14	13	1	7	6		0.96	
24942	NP	0	0						----	
24943	P	12	12	12		6	6		0.94	
24944	P	12	12	12		6	6		0.89	
24945	P	13	12	12		5	7		0.72	
24946	P	14	11	11		5	6		0.87	
24947	P	6	4	3		2	1	1	1.07	
24948	P	12	11	11		6	5		0.96	
24949	P	13	12	12		6	6		0.93	
24950	P	10	9	9		4	5		1.15	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 66

Material FDA 73-83

Dose 490.0 mg/kg

Date January 17, 1975

Laboratory No. 2123 (2)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
24951	P	10	10	8		5	3	2	1.41	
24952	NP	0	0						----	
24953	P	17	15	15		5	10		0.73	
24954	NP	0	0						----	
24955	NP	0	0						----	
24956	P	13	12	11		5	6	1	0.95	
24957	P	14	13	12	1	8	4		0.77	
24958	NP	0	0						----	
24960	P	13	12	11		2	9	1	0.89	
24961	NP	0	0						----	
24962	P	13	12	12		7	5		0.88	
24963	NP	0	0						----	
24964	P	10	9	9		4	5		0.65	
24965	P	9	8	7		4	3	1	0.78	
24966	P	11	9	9		3	6		0.80	
24967	P	11	10	9		4	5	1	0.84	
24968	NP	0	0						----	
24969	P	13	12	12		6	6		0.77	
24970	P	12	10	10		4	6		0.86	
24971	P	10	10	10		6	4		0.88	
24972	P	13	13	13		6	7		1.04	
24973	P	12	10	8		5	3	2	0.79	
24974	P	13	12	10		7	3	2	0.95	
24975	P	14	13	12		7	5	1	0.74	
24976	NP	0	0						----	
24977	P	15	12	10		5	5	2	0.82	
24978	P	13	11	10		5	5	1	1.25	
24979	P	13	10	9		3	6	1	0.78	
24980	P	17	15	15		7	8		0.84	

* P = Pregnant; NP = Not Pregnant

R A T S

FOOD AND DRUG Research LABORATORIES, INC.

WAVERLY DIVISION
Route 17
P.O. Box 107
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(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: February 19, 1975

Laboratory No. 2143 (2)
Contract No.FDA 223-74-2176

Sample: Fine gold colored powdered material

Marking: FDA 73-83 (Mustard flour-Untreated)

Examination Requested: Teratologic evaluation of FDA 73-83 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 490 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."

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FOOD AND DRUG RESEA. H LABORATORIES, INC.

Groups: 61 through 66

Material: FDA 73-83-U

Date: January 17, 1975

Laboratory No.: 2143 (2)

Table 1

Fate Summary
(Rats)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
61	Sham	0.0	25	23	25	23
62	Aspirin*	250.0	24	21	24	21
63	FDA 73-83-U	4.9	24	21	24	21
64	FDA 73-83-U	22.7	24	20	24	20
65	FDA 73-83-U	105.6	24	20	24	20
66	FDA 73-83-U	490.0	22	19	22	19

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group : 61 through 66

Material : FDA 73-83-U

Table 2
Reproduction Data
(Rats)

Date : January 17, 1975

Laboratory No. : 2143 (2)

Group :	61	62	63	64	65	66
Dose (mg/kg) :	Sham	Aspirin**	4.9	22.7	105.6	490.0
Pregnancies						
Total No.	23	21	21	20	20	19
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	23	21	21	20	20	19
Corpora Lutea						
Total No.	285	260	269	268	254	250
Average/dam mated	11.9	10.8	11.2	11.2	10.6	11.4
Live Litters						
Total No.*	23	15	21	20	20	19
Implant Sites						
Total No.	275	217	243	248	235	238
Average/dam*	12.0	10.3	11.6	12.4	11.8	12.5
Resorptions						
Total No.*	1	57	1	--	--	--
Dams with 1 or more sites resorbed	1	10	1	--	--	--
Dams with all sites resorbed	--	6	--	--	--	--
Per cent partial resorptions	4.35	47.6	4.76	--	--	--
Per cent complete resorptions	--	28.6	--	--	--	--
Live Fetuses						
Total No.	274	160	242	248	235	238
Average/dam*	11.9	7.62	11.5	12.4	11.8	12.5
Sex ratio (M/F)	0.85	0.88	1.35	1.03	1.12	1.18
Dead Fetuses						
Total No.*	--	--	--	--	--	--
Dams with 1 or more dead	--	--	--	--	--	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	--	--	--	--	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.97	2.61	3.99	3.88	3.91	3.90

* Includes only those dams examined at term.

** Positive Control : 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 | Laboratory No. 2143 (2)

Table 3

Material FDA 73-83-U | Date January 17, 1975

Summary of Skeletal Findings*
(Rats)

Findings / Group No.:	61	62	63	64	65	66
Dose (mg/kg):	Sham	Aspirin**	4.9	22.7	105.6	490.0
Live Fetuses Examined (at term)	190/23	111/15	167/21	170/20	164/20	162/19
Sternebrae						
Incomplete oss.	40/15	77/15	48/15	54/18	42/12	57/17
Scrambled						
Bipartite		9/7				1/1
Fused						
Extra		2/1	1/1			
Missing	1/1	57/12	14/6	5/3		15/7
Other						
Ribs						
Incomplete oss.		2/1				
Fused/split						
Wavy	19/8	26/10	14/7	17/10	10/6	25/9
Less than 12						
More than 13		29/10	1/1	2/2		2/2
Other						
Vertebrae						
Incomplete oss.	14/4	53/14	8/4	6/4	7/5	11/6
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	50/13	55/12	20/11	41/14	27/10	35/11
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.		1/1				
Missing						
Extra						
Miscellaneous						
Hyoid; missing	19/9	55/14	18/10	26/11	12/9	31/14
Hyoid; reduced	33/13	11/6	19/8	29/13	23/9	26/12

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66 Date January 17, 1975

Material FDA 73-83-U Laboratory No. 2143 (2)

Table 3-a

Summary of Soft Tissue Abnormalities

(Rats)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
62	Aspirin*	250.0	44832	1	Encephalomeningocele
			44841	1	Encephalomyelocele; Gastroschisis

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 through 66

Date January 17, 1975

Table 4

Species Rats

Laboratory No. 2143 (2)

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	20**
		mg/kg	g				
61	Sham	0.0	222	241	260	280	352 (23)
62	Aspirin***	250.0	230	243	251	265	312 (21)
63	FDA 73-83-U	4.9	237	251	269	292	358 (21)
64	FDA 73-83-U	22.7	234	247	264	286	360 (20)
65	FDA 73-83-U	105.6	225	238	255	277	338 (20)
66	FDA 73-83-U	490.0	223	240	251	266	336 (19)

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

Table 5

Groups 61 through 66
Compound FDA 73-83

Laboratory No. 2143 (2)
Species: Rats

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1974	a.m.	°F	%
11/12	8:00	72	60
11/13	8:30	80	60
11/14	8:30	80	58
11/15	8:30	82	50
11/16	10:30	82	54
11/17	2:45 p.m.	82	51
11/18	8:30	80	50
11/19	2:25 p.m.	80	40
11/20	8:30	80	74
11/21	9:00	80	55
11/22	8:30	78	55
11/23	8:00	80	55
11/24	8:00	80	69
11/25	8:30	80	72
11/26	8:30	80	60
11/27	8:30	78	50
11/28	10:00	78	55
11/29	10:00	78	58
11/30	8:00	78	55
12/1	8:00	82	59
12/2	9:15	78	52
12/3	9:00	98	55
12/4	10:00	80	55
12/5	10:30	77	53
12/6	8:30	79	58
12/7	8:00	78	57
12/8	8:00	78	71
12/9	2:30 p.m.	78	70
12/10	8:00	82	50
12/11	11:00	81	50
12/12	10:00	82	60
12/13	10:00	82	70
12/14	11:00	82	64
12/15	9:00	82	63
12/16	9:00	85	57
12/17	10:00	80	60
12/18	10:00	80	60
12/19	10:00	80	60
12/20	8:00	80	55
12/21	1:30 p.m.	78	65
12/22	10:00	78	65
12/23	9:00	80	50
12/24	9:30	80	60

Figure 1

(Rats)

Photographs of Grossly Abnormal Fetuses

(None Observed in Test Groups)

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 61

Material Sham

Dose 0.0 mg/kg

Date January 17, 1975

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
44801	P	14	14	14		6	8		3.37	
44802	P	13	12	12		5	7		3.46	
44803	P	17	16	16		7	9		5.18	
44804	P	15	13	13		8	5		3.82	
44805	P	14	14	14		7	7		3.83	
44806	P	13	13	13		4	9		3.85	
44807	P	15	15	15		6	9		3.68	
44808	NP	0	0						----	
44809	P	13	13	13		8	5		3.75	
44810	P	14	12	12		8	4		3.76	
44811	P	10	9	9		2	7		3.88	
44812	P	7	6	6		3	3		4.54	
44813	P	14	14	14		7	7		4.01	
44814	P	11	10	10		4	6		4.13	
44815	P	13	10	10		7	3		4.06	
44816	P	12	12	12		4	8		3.45	
44817	P	12	11	11		3	8		4.09	
44818	P	11	10	9		4	5	1	3.69	
44819	P	12	11	11		6	5		5.74	
44820	NP	0	0						----	
44821	P	14	11	11		4	7		4.20	
44822	P	12	9	9		4	5		3.99	
44823	P	13	13	13		6	7		3.65	
44824	P	--**	13	13		6	7		3.45	
44825	P	16	14	14		7	7		3.72	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 62

Material Aspirin

Dose 250.0 mg/kg

Date January 17, 1975

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
44831	P	14	10	10		4	6		2.63	
44832	P	9	7	7		5	2		2.32	
44834	P	12	10	8		3	5	2	2.92	
44835	P	15	10					10	----	
44836	NP	0	0						----	
44837	P	13	5					5	----	
44838	NP	0	0						----	
44839	P	9	6					6	----	
44840	P	14	13	13		8	5		2.99	
44841	P	13	13	13		6	7		2.37	
44842	P	15	15	15		7	8		3.16	
44843	P	9	9					9	----	
44844	P	14	14	14		6	8		2.93	
44845	P	12	10	7		5	2	3	1.99	
44846	P	12	5	5		3	2		2.37	
44847	P	11	10					10	----	
44848	P	14	10					10	----	
44849	P	13	12	11		2	9	1	2.23	
44850	NP	0	0						----	
44851	P	11	11	11		4	7		3.00	
44852	P	14	13	13		6	7		2.48	
44853	P	12	10	9		6	3	1	2.31	
44854	P	12	12	12		6	6		2.55	
44855	P	12	12	12		4	8		2.96	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 63

Material FDA 73-83

Dose 4.9 mg/kg

Date January 17, 1975

Laboratory No. 2143 (2)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
44861	P	11	7	7		6	1		4.05	
44862	NP	0	0						----	
44863	P	13	12	12		6	6		3.59	
44864	P	14	12	12		6	6		5.52	
44865	P	14	13	13		10	3		3.73	
44866	P	14	14	14		7	7		3.81	
44867	NP	0	0						----	
44868	P	13	11	11		6	5		3.81	
44869	NP	0	0						----	
44870	P	14	12	12		5	7		3.85	
44871	P	14	14	14		7	7		3.88	
44872	P	13	12	12		7	5		3.91	
44873	P	9	6	6		3	3		4.30	
44874	P	13	11	11		6	5		5.45	
44875	P	13	12	12		9	3		3.77	
44876	P	13	13	13		7	6		3.41	
44877	P	15	15	15		11	4		3.16	
44878	P	8	7	7		5	2		3.93	
44879	P	12	12	12		9	3		3.78	
44880	P	13	12	12		4	8		4.08	
44881	P	13	12	12		8	4		3.97	
44882	P	14	14	13		4	9	1	3.81	
44883	P	13	10	10		8	2		4.18	
44884	P	13	12	12		5	7		3.79	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 64

Material FDA 73-83

Dose 22.7 mg/kg

Date January 17, 1975

Laboratory No. 2143(2)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
44891	P	13	9	9		4	5		3.64	
44892	P	13	12	12		4	8		4.23	
44893	P	13	12	12		4	8		3.74	
44894	NP	0	0						----	
44895	P	15	14	14		8	6		3.66	
44896	NP	0	0						----	
44897	NP	0	0						----	
44899	P	13	12	12		7	5		3.83	
44900	P	14	13	13		9	4		3.57	
44901	P	13	13	13		7	6		3.96	
44902	P	18	18	18		7	11		3.60	
44903	P	12	11	11		6	5		4.18	
44904	P	14	10	10		7	3		3.68	
44905	P	14	12	12		7	5		3.82	
44906	P	14	13	13		5	8		3.94	
44907	P	15	14	14		7	7		3.47	
44908	NP	0	0						----	
44909	P	8	8	8		5	3		3.55	
44910	P	10	10	10		5	5		3.99	
44911	P	14	14	14		6	8		3.83	
44912	P	15	15	15		9	6		4.09	
44913	P	13	13	13		7	6		3.87	
44914	P	13	12	12		4	8		5.19	
44915	P	14	13	13		8	5		3.67	

*P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 65

Material FDA 73-83

Dose 105.6 mg/kg

Date January 17, 1975

Laboratory No. 2143 (2)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
44921	P	13	12	12		7	5		3.56	
44922	P	12	10	10		9	1		4.15	
44923	P	14	13	13		6	7		3.91	
44924	P	12	8	8		5	3		4.43	
44925	NP	0	0						----	
44926	P	14	14	14		8	6		4.05	
44927	NP	0	0						----	
44928	P	11	11	11		4	7		3.34	
44929	P	8**	16	16		11	5		3.91	
44930	P	11	10	10		2	8		4.25	
44931	NP	0	0						----	
44932	P	14	13	13		7	6		4.07	
44933	P	14	14	14		7	7		3.87	
44934	P	16	16	16		11	5		5.15	
44935	P	15	9	9		3	6		3.77	
44936	P	14	13	13		9	4		3.55	
44937	P	14	12	12		4	8		3.66	
44938	NP	0	0						----	
44939	P	8	8	8		3	5		3.97	
44940	P	14	13	13		4	9		3.92	
44941	P	11	10	10		4	6		3.95	
44942	P	12	7	7		4	3		3.57	
44943	P	15	14	14		9	5		3.95	
44944	P	12	12	12		7	5		3.21	

* P = Pregnant; NP = Not Pregnant

** One Ovary Missing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 66

Material FDA 73-83

Dose 490.0 mg/kg

Date January 17, 1975

Laboratory No. 2143(2)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
44951	P	12	12	12		5	7		3.35	
44952	P	12	12	12		7	5		4.03	
44953	P	15	15	15		8	7		3.97	
44954	P	15	15	15		8	7		3.48	
44955	NP	0	0						----	
44956	NP	0	0						----	
44957	P	13	13	13		5	8		5.83	
44959	P	12	12	12		9	3		3.51	
44960	P	12	10	10		5	5		4.04	
44961	NP	0	0						----	
44963	P	12	12	12		6	6		3.61	
44964	P	14	13	13		6	7		3.62	
44965	P	13	13	13		7	6		3.49	
44966	P	15	14	14		8	6		4.15	
44967	P	14	12	12		7	5		3.95	
44968	P	11	11	11		6	5		4.05	
44970	P	13	13	13		4	9		3.80	
44971	P	15	12	12		7	5		3.64	
44972	P	14	14	14		11	3		3.95	
44973	P	12	11	11		4	7		3.76	
44974	P	14	12	12		8	4		4.01	
44975	P	12	12	12		8	4		3.77	

* P = Pregnant; NP = Not Pregnant