FROM

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

020

FINAL
November 27, 1974

Teratologic Evaluation of FDA 73-58

(Monopotassium glutamate)

in

Mice and Rats

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

Date: November 27, 1974

Laboratory No. 2123 (11)
Contract No. FDA 223-74-217

Sample: Fine white crystalline material

Marking: FDA 73-58 (Monopotassium glutamate)

Examination Requested: Teratologic evaluation of FDA 73-58 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 520 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
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Scientific Director

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 21 & 22; 27 through 30

Material: FDA 73-58

Date: October 29, 1974

Laboratory No.: 2123 (11)

Table 1

Fate Summary
(Mice)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
21	Sham	0.0	30	21	30	21
22	Aspirin*	150.0	25	20	25	20
27	FDA 73-58	5.2	30	21	30	21
28	FDA 73-58	24.1	25	21	25	21
29	FDA 73-58	112.0	25	21	25	21
30	FDA 73-58	520.0	24	19	24	19

* Positive Control: 150.0 mg/kg

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

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 21 & 22; 27 through 30

Material: FDA 73-58

Table 2
Reproduction Data
(Mice)

Date: October 29, 1974

Laboratory No.: 2123 (11)

Group:	21	22	27	28	29	30
Dose (mg/kg):	Sham	Aspirin**	5.2	24.1	112.0	520.0
Pregnancies						
Total No.	21	20	21	21	21	19
Died or Aborted (before Day 17)	0	0	0	0	0	0
To term (on Day 17)	21	20	21	21	21	19
Corpora Lutea						
Total No.	277	253	259	244	274	235
Average/dam mated	9.23	10.1	8.63	9.76	11.0	9.79
Live Litters						
Total No.*	21	20	21	21	21	19
Implant Sites						
Total No.	250	220	231	222	253	214
Average/dam*	11.9	11.0	11.0	10.6	12.1	11.3
Resorptions						
Total No.*	9	11	17	15	17	13
Dams with 1 or more sites resorbed	6	8	8	8	9	7
Dams with all sites resorbed	--	--	--	--	--	--
Per cent partial resorptions	28.6	40.0	38.1	38.1	42.9	36.8
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	240	209	212	204	233	201
Average/dam*	11.4	10.5	10.1	9.71	11.1	10.6
Sex ratio (M/F)	0.86	0.99	0.91	0.73	0.81	0.79
Dead Fetuses						
Total No.*	1	--	2	3	3	--
Dams with 1 or more dead	1	--	2	3	3	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	4.76	--	9.52	14.3	14.3	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.90	0.91	0.90	0.84	0.90	0.89

* Includes only those dams examined at term.

** Positive Control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 21 & 22; 27 through 30 — Laboratory No. 2123 (11)

Table 3

Material FDA 73-58 — Date October 29, 1974

Summary of Skeletal Findings*

(Mice)

Findings / Group No.:	21	22	27	28	29	30
Dose (mg/kg):	Sham	Aspirin**	5.2	24.1	112.0	520.0
Live Fetuses Examined (at term)	165/21	146/20	150/21	142/21	162/21	139/19
Sternebrae						
Incomplete oss.	28/9	66/18	55/15	54/16	25/11	29/8
Scrambled						
Bipartite	1/1	3/3	2/2	1/1	1/1	2/2
Fused						
Extra						
Missing	17/7	21/10	19/11	28/13	15/9	22/9
Other						
Ribs						
Incomplete oss.						
Fused/split						
Wavy						
Less than 12						
More than 13	25/13	32/12	24/11	25/9	15/10	15/8
Other						
Vertebrae						
Incomplete oss.	7/6	4/4	2/1	11/5	2/2	13/5
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure						4/2
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.	4/2	5/4	2/1	14/6	1/1	9/2
Missing						
Extra						
Miscellaneous						
Hyoid; missing	32/11	33/14	42/16	32/13	31/11	37/15
Hyoid; reduced	13/8	23/11	23/14	16/9	13/10	15/8

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

** Positive control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 21 & 22; 27 through 30 Date October 29, 1974

Material FDA 73-58 Laboratory No. 2123 (11)

Table 3-a

Summary of Soft Tissue Abnormalities

(Mice)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
21	Sham	0.0	23629	1	Cleft palate
30	FDA 73-58	520.0	23889	2	Hydrocephalus; exophthalmos

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 21 & 22; 27 through 30

Date October 29, 1974

Table 4

Species Rats

Laboratory No. 2123 (11)

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	17**
		mg/kg	g				
21	Sham	0.0	31	34	37	46	52 (21)
22	Aspirin***	150.0	31	34	38	45	51 (20)
27	FDA 73-58	5.2	30	33	38	45	51 (21)
28	FDA 73-58	24.1	32	35	40	47	52 (21)
29	FDA 73-58	112.0	26	29	34	43	49 (21)
30	FDA 73-58	520.0	29	31	35	43	49 (19)

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

Table 5

Groups 21 & 22; 27 through 30
Compound FDA 73-58

Laboratory No. 2123 (11)
Species: Mice

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1974	a.m.	°F	%
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	74	65
9/20	3:00 p.m.	80	75
9/21	8:10	80	75
9/22	8:00	76	70
9/23	8:15	70	64
9/24	8:00	72	62
9/25	8:30	72	63
9/26	8:10	72	66
9/27	8:20	72	65
9/28	7:30	76	70
9/29	7:15	74	76
9/30	8:30	72	65
10/1	8:30	72	65
10/2	9:30	70	63
10/3	10:00	68	64
10/4	9:00	70	63
10/5	10:30	74	65

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 21

Material Sham

Dose 0.0 mg/kg

Date October 29, 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
23601	P	12	11	11		6	5		0.96	
23602	NP	0	0						----	
23603	NP	0	0						----	
23604	P	12	12	10		6	4	2	0.89	
23605	NP	0	0						----	
23606	P	13	12	10		4	6	2	0.88	
23607	P	14	13	12		4	8	1	1.01	
23608	P	12	12	12		6	6		1.07	
23609	P	12	10	10		3	7		0.95	
23610	P	16	13	13		6	7		0.99	
23611	P	12	11	10	1	2	8		0.94	
23612	P	14	14	14		8	6		0.75	
23613	P	17	14	13		6	7	1	0.99	
23614	NP	0	0						----	
23615	P	12	10	10		6	4		0.67	
23616	P	12	12	12		3	9		1.07	
23617	P	12	12	12		4	8		0.81	
23618	P	12	10	10		6	4		0.71	
23619	NP	0	0						----	
23620	NP	0	0						----	
23621	NP	0	0						----	
23622	P	12	11	11		5	6		0.86	
23623	P	16	14	12		4	8	2	0.76	
23624	P	11	11	10		4	6	1	0.72	
23625	NP	0	0						----	
23626	P	13	12	12		7	5		0.98	
23627	P	20	15	15		7	8		0.80	
23628	P	12	10	10		7	3		1.07	
23629	P	11	11	11		7	4		1.02	
23630	NP	0	0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 22

Material Aspirin

Dose 150.0 mg/kg

Date October 29, 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
23631	P	12	12	9		5	4	3	0.91	
23632	P	12	12	12		7	5		0.94	
23633	P	14	12	12		6	6		0.83	
23634	P	11	9	8		4	4	1	0.94	
23635	P	15	11	11		7	4		0.98	
23636	P	13	10	10		6	4		0.79	
23637	P	14	12	12		5	7		0.89	
23638	P	14	11	11		5	6		0.89	
23639	P	12	11	11		5	6		1.03	
23640	P	13	9	9		3	6		0.92	
23641	P	11	11	11		6	5		1.07	
23642	P	15	12	11		5	6	1	0.85	
23643	P	13	11	9		3	6	2	1.05	
23644	P	15	11	10		5	5	1	0.67	
23645	P	11	10	10		4	6		0.83	
23646	NP	0	0						----	
23647	P	13	12	12		6	6		0.67	
23648	NP	0	0						----	
23649	P	12	12	11		6	5	1	1.31	
23650	P	9	8	7		4	3	1	0.84	
23651	NP	0	0						----	
23652	P	11	11	10		5	5	1	0.88	
23653	P	13	13	13		7	6		0.87	
23654	NP	0	0						----	
23655	NP	0	0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 27

Material FDA 73-58

Dose 5.2 mg/kg

Date October 29, 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
23781	P	18	17	16		9	7	1	0.98	
23782	NP	0	0						----	
23783	P	9	9	8		4	4	1	0.95	
23784	P	14	11	10		5	5	1	1.04	
23785	P	15	13	13		7	6		0.99	
23786	P	13	11	11		5	6		0.83	
23787	NP	0	0						----	
23788	P	8	3	3		1	2		1.14	
23789	P	12	12	12		4	8		0.97	
23790	P	13	13	13		5	8		0.97	
23791	P	8	7	2	1	2	0	4	0.72	
23792	P	11	8	4		1	3	4	0.87	
23793	P	11	8	4		2	2	4	0.87	
23794	NP	0	0						----	
23795	NP	0	0						----	
23796	NP	0	0						----	
23797	P	19	15	15		6	9		0.93	
23798	P	13	12	11		3	8	1	1.05	
23799	P	14	14	14		6	8		0.84	
23800	NP	0	0						----	
23801	P	10	10	10		5	5		0.78	
23802	NP	0	0						----	
23803	P	13	13	13		7	6		0.76	
23804	P	13	12	12		7	5		0.93	
23805	NP	0	0						----	
23806	P	13	12	12		8	4		0.91	
23807	P	11	11	11		5	6		0.77	
23808	NP	0	0						----	
23809	P	11	11	10		5	5	1	0.80	
23810	P	10	9	8	1	4	4		0.81	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 28

Material FDA 73-58

Dose 24.1 mg/kg

Date October 29, 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
23811	P	14	14	13	1	5	8		0.85	
23812	P	9	5	1		0	1	4	0.74	
23813	P	13	13	9		3	6	4	0.92	
23814	P	5	2	2		0	2		0.63	
23815	NP	0	0						----	
23816	P	16	16	16		5	11		0.84	
23817	P	11	11	11		6	5		0.69	
23818	P	16	16	16		7	9		0.76	
23819	P	8	8	8		4	4		0.90	
23820	P	11	11	9	1	7	2	1	0.95	
23821	P	9	5	3		1	2	2	0.61	
23822	P	11	9	8		3	5	1	0.88	
23823	P	12	12	12		5	7		0.77	
23824	P	9	9	9		2	7		0.98	
23825	NP	0	0						----	
23826	P	13	12	12		4	8		1.03	
23827	P	13	13	12		5	7	1	0.86	
23828	P	12	12	12		4	8		0.86	
23829	NP	0	0						----	
23830	P	13	13	12		5	7	1	0.80	
23831	P	13	10	9		5	4	1	1.12	
23832	P	15	11	11		6	5		0.88	
23833	P	13	13	12	1	5	7		0.75	
23834	NP	0	0						----	
23835	P	8	7	7		4	3		0.77	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 29

Material FDA 73-58

Dose 112.0 mg/kg

Date October 29, 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
23841	P	12	12	12		2	10		0.79	
23842	NP	0	0						----	
23843	P	13	13	11		4	7	2	0.99	
23844	P	17	17	16	1	5	11		0.86	
23845	P	12	12	9		2	7	3	1.03	
23846	P	13	11	11		5	6		0.91	
23847	NP	0	0						----	
23848	P	11	10	8		4	4	2	0.85	
23849	P	14	12	12		3	9		1.01	
23850	P	17	16	16		8	8		0.87	
23851	NP	0	0						----	
23852	P	10	10	9		5	4	1	0.97	
23853	P	13	12	12		6	6		0.94	
23854	P	12	12	12		6	6		0.83	
23855	P	14	11	9		1	8	2	0.85	
23856	P	12	12	10	1	5	5	1	0.94	
23857	NP	0	0						----	
23858	P	13	11	8		6	2	3	0.93	
23859	P	13	12	11		5	6	1	0.88	
23860	P	12	10	8		5	3	2	0.92	
23861	P	10	10	10		7	3		0.94	
23862	P	15	12	12		7	5		0.98	
23863	P	16	14	14		5	9		0.79	
23864	P	13	13	12	1	7	5		0.83	
23865	P	12	11	11		6	5		0.79	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 30

Material FDA 73-58

Dose 520.0 mg/kg

Date October 29, 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
23871	P	14	14	12		6	6	2	0.95	
23872	P	8	2	1		0	1	1	1.15	
23873	P	17	15	15		8	7		0.99	
23874	P	15	13	13		5	8		0.98	
23875	P	12	12	12		3	9		1.10	
23876	NP	0	0						----	
23877	NP	0	0						----	
23878	NP	0	0						----	
23879	P	18	17	17		10	7		0.77	
23880	P	11	11	11		6	5		0.81	
23881	P	11	10	10		7	3		1.02	
23882	P	12	12	10		5	5	2	0.85	
23883	NP	0	0						----	
23884	P	15	12	12		5	7		0.85	
23885	P	10	10	10		4	6		0.91	
23886	P	11	11	11		5	6		1.00	
23887	P	14	11	11		2	9		0.83	
23888	P	13	13	12		4	8	1	0.82	
23889	P	13	11	7		3	4	4	0.57	
23890	P	8	8	6		2	4	2	0.47	
23891	NP	0	0						----	
23893	P	11	11	11		5	6		1.28	
23894	P	12	12	11		5	6	1	0.76	
23895	P	10	9	9		4	5		0.85	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG Research LABORATORIES, INC.

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FINAL REPORT

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

"The administration of up to 450 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 RESEARCH LABORATORIES, INC.

Groups: 21 & 22; 27 through 30

Material: FDA 73-58

Date: October 29, 1974

Laboratory No.: 2143 (11)

Table 1

Fate Summary
(Rats)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
21	Sham	0.0	25	20	25	20
22	Aspirin*	250.0	25	19	25	19
27	FDA 73-58	4.5	25	20	25	20
28	FDA 73-58	20.9	25	20	25	20
29	FDA 73-58	97.0	23	20	23	20
30	FDA 73-58	450.0	25	20	25	20

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

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 21 & 22; 27 through 30

Material: FDA 73-58

Table 2
Reproduction Data
(Rats)

Date: October 29, 1974

Laboratory No.: 2143 (11)

Group:	21	22	27	28	29	30
Dose (mg/kg):	Sham	Aspirin**	4.5	20.9	97.0	450.0
Pregnancies						
Total No.	20	19	20	20	20	20
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	20	19	20	20	20	20
Corpora Lutea						
Total No.	244	258	249	263	247	261
Average/dam mated	9.76	10.3	9.96	10.5	10.7	10.4
Live Litters						
Total No.*	20	19	20	20	20	20
Implant Sites						
Total No.	228	225	230	241	217	248
Average/dam*	11.4	11.8	11.5	12.1	10.9	12.4
Resorptions						
Total No.*	4	17	2	3	6	1
Dams with 1 or more sites resorbed	2	8	2	3	3	1
Dams with all sites resorbed	--	--	--	--	--	--
Per cent partial resorptions	10.0	42.1	10.0	15.0	15.0	5.00
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	224	208	228	238	211	247
Average/dam*	11.2	11.0	11.4	11.9	10.6	12.4
Sex ratio (M/F)	0.96	1.04	1.00	1.16	1.03	0.99
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	3.90	2.97	3.96	4.02	4.02	4.00

* Includes only those dams examined at term.

** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 21 & 22; 27 through 30 — Laboratory No. 2143 (11)

Table 3

Material FDA 73-58 — Date October 29, 1974

Summary of Skeletal Findings*
(Rats)

Findings / Group No.:	21	22	27	28	29	30
Dose (mg/kg):	Sham	Aspirin**	4.5	20.9	97.0	450.0
Live Fetuses Examined (at term)	156/20	145/19	156/20	166/20	148/20	173/20
Sternebrae						
Incomplete oss.	20/12	86/18	47/19	14/8	48/16	16/9
Scrambled						
Bipartite		3/2				1/1
Fused						
Extra						
Missing	2/2	117/19	8/6	6/4	17/8	1/1
Other						
Ribs						
Incomplete oss.	3/2			1/1		
Fused/split		1/1				
Wavy	21/9	55/16	27/13	11/7	19/9	21/10
Less than 12						
More than 13		110/17		1/1		1/1
Other						
Vertebrae						
Incomplete oss.	6/4	64/17	6/5	3/2	7/5	
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	32/12	48/14	17/9	15/9	20/8	27/14
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.	1/1	4/3				
Missing						
Extra						
Miscellaneous						
Hyoid; missing	16/8	45/15	12/7	8/7	13/8	4/2
Hyoid; reduced	29/14	9/6	29/12	22/11	17/10	22/10

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 21 & 22; 27 through 30 Date October 29, 1974

Material FDA 73-58 Laboratory No. 2143(11)

Table 3-a

Summary of Soft Tissue Abnormalities

(Rats)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
22	Aspirin*	250.0	43634	1	Encephalomeningocele; encephalomyelocele
			43639	1	Gastroschisis
			43645	1	Hydrocephalus
			43654	4	Encephalomyelocele
			43655	1	Encephalomyelocele

*Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 21 & 22; 27 through 30

Species Rats

Date October 29, 1974

Laboratory No. 2143 (11)

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	20**
		mg/kg	g				
21	Sham	0.0	218	238	256	278	342 (20)
22	Aspirin***	250.0	221	238	252	274	335 (19)
27	FDA 73-58	4.5	215	232	253	275	340 (20)
28	FDA 73-58	20.9	217	235	256	278	345 (20)
29	FDA 73-58	97.0	215	233	252	274	331 (20)
30	FDA 73-58	450.0	222	239	262	283	356 (20)

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

Table 5

Groups 21 & 22; 27 through 30 — Laboratory No. 2143 (11)

Compound FDA 73-58 — Species: Rats

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1974	a.m.	°F	%
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	74	65
9/20	3:00 p.m.	80	75
9/21	8:10	80	75
9/22	8:00	76	70
9/23	8:15	70	64
9/24	8:00	72	62
9/25	8:30	72	63
9/26	8:10	72	66
9/27	8:20	72	65
9/28	7:30	76	70
9/29	7:15	74	76
9/30	8:30	72	65
10/1	8:30	72	65
10/2	9:30	70	63

Figure 1

Original Photographs in First Copy of Report 2143 (8)

Figure 1

Grossly Abnormal Fetuses
(Rats)

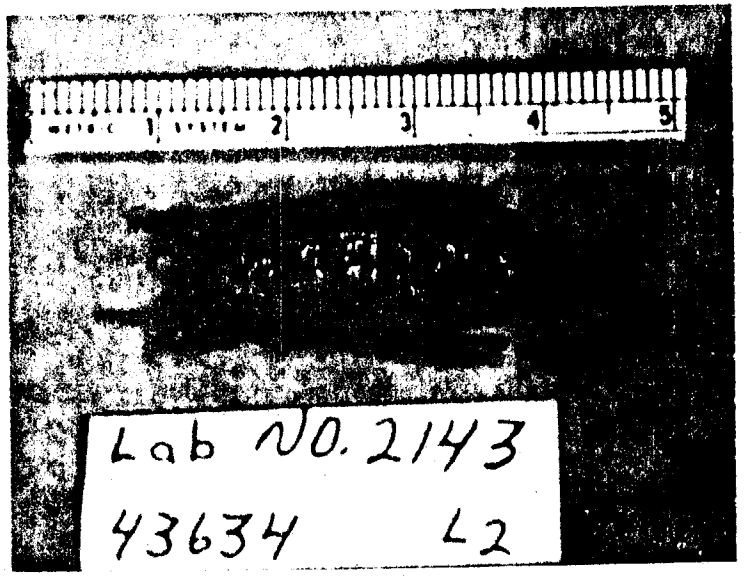
Group: 22

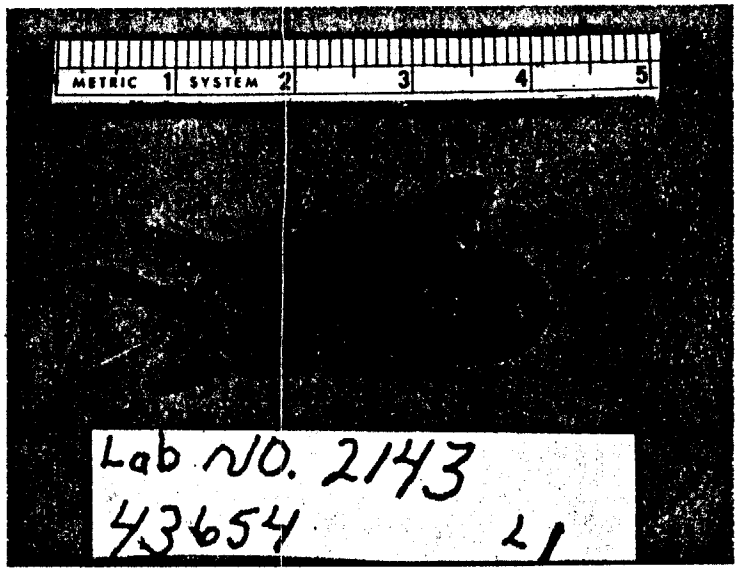
Material: Aspirin

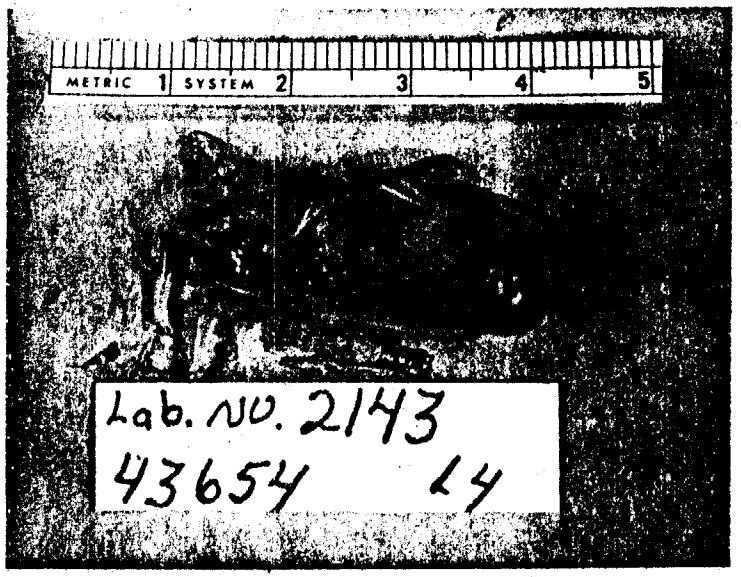
Dose: 250.0 mg/kg

Date: October 29, 1974

Lab. No. 2143







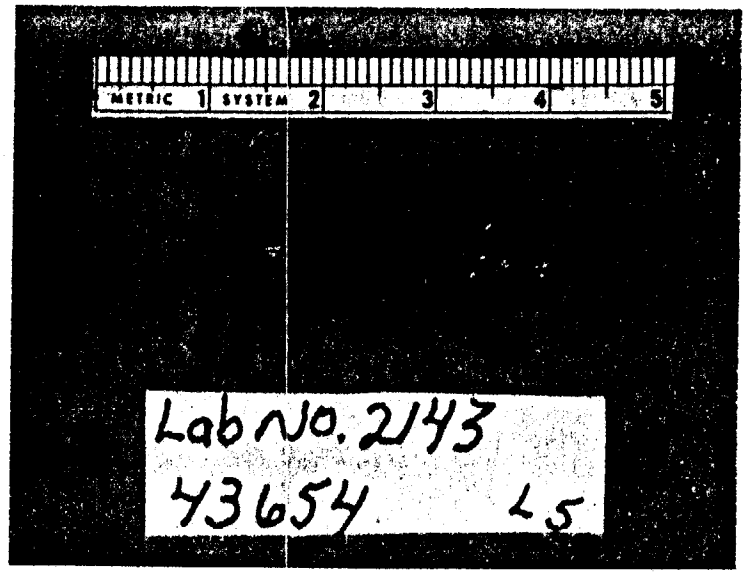


Figure 1

Grossly Abnormal Fetuses
(Rats)

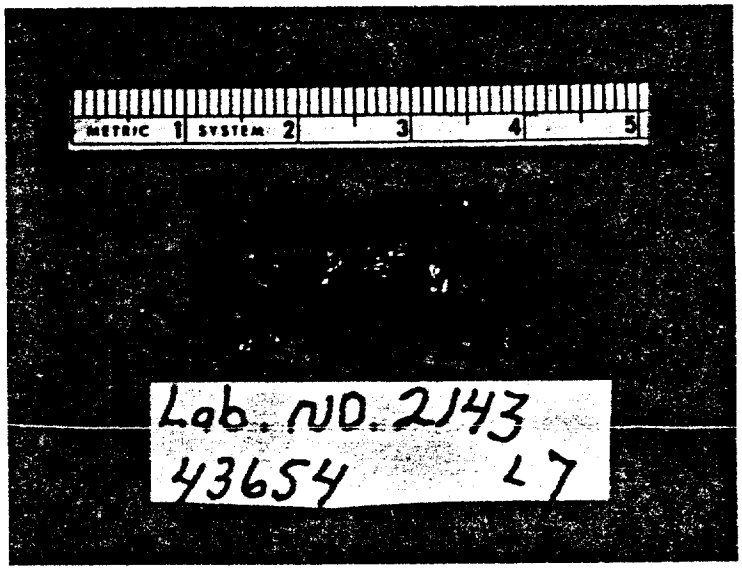
Group: 22

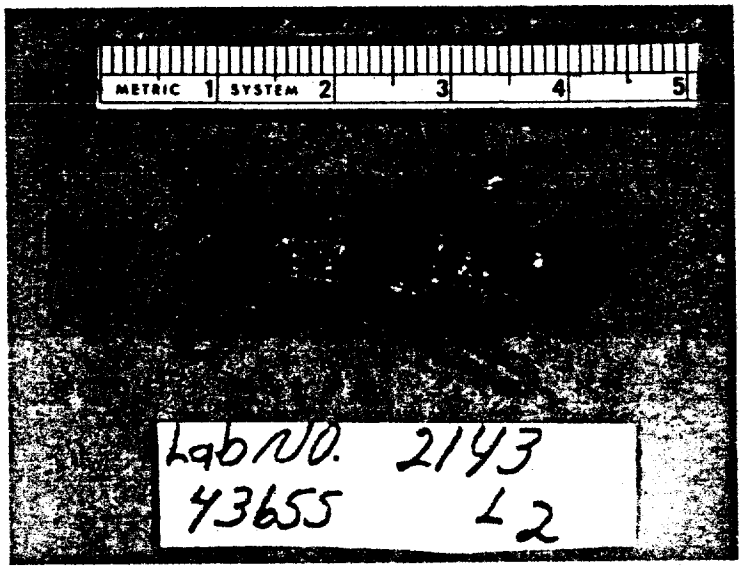
Material: Aspirin

Dose: 250.0 mg/kg

Date: October 29, 1974

Lab. No. 2143





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 21

Material Sham

Dose 0.0 mg/kg

Date October 29, 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
43601	P	10	10	10		3	7		4.23	
43602	NP	0	0						----	
43603	P	12	12	12		5	7		3.73	
43604	NP	0	0						----	
43605	P	12	11	11		7	4		4.10	
43606	P	14	13	13		3	10		4.26	
43607	P	13	11	11		5	6		3.41	
43608	P	12	12	12		6	6		3.63	
43609	P	11	11	11		3	8		4.13	
43610	P	16	8	6		1	5	2	3.70	
43611	P	14	14	14		10	4		4.23	
43612	NP	0	0						----	
43613	P	13	13	13		9	4		4.03	
43614	P	15	14	14		10	4		3.79	
43615	NP	0	0						----	
43616	P	11	11	11		3	8		3.56	
43617	P	15	15	15		8	7		4.40	
43618	P	10	10	10		7	3		4.23	
43619	P	9	6	6		2	4		3.82	
43620	P	13	13	13		3	10		3.69	
43621	P	12	12	12		6	6		3.92	
43622	P	12	12	10		8	2	2	3.58	
43623	P	10	10	10		5	5		3.59	
43624	P	10	10	10		6	4		3.89	
43625	NP	0	0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 22

Material Aspirin

Dose 250.0 mg/kg

Date October 29, 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
43631	P	15	15	15		8	7		3.26	
43632	P	13	12	11		8	3	1	3.76	
43633	P	16	15	14		7	7	1	3.32	
43634	P	13	13	13		8	5		2.72	
43635	P	15	14	14		6	8		2.89	
43636	NP	0	0						----	
43637	P	14	7	7		1	6		3.03	
43638	P	13	13	13		5	8		3.04	
43639	P	14	13	13		7	6		3.28	
43640	NP	0	0						----	
43641	P	13	9	9		5	4		2.89	
43642	P	13	7	6		2	4	1	3.06	
43643	P	14	11	10		7	3	1	3.42	
43644	P	14	12	11		6	5	1	3.17	
43645	P	13	13	4		2	2	9	2.01	
43646	P	14	13	13		8	5		2.57	
43647	P	13	12	12		4	8		3.13	
43648	P	13	12	10		6	4	2	2.32	
43649	P	15	14	14		7	7		3.23	
43650	NP	0	0						----	
43651	NP	0	0						----	
43652	NP	0	0						----	
43653	NP	0	0						----	
43654	P	12	10	10		5	5		2.46	
43655	P	11	10	9		4	5	1	2.79	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 27

Material FDA 73-58

Dose 4.5 mg/kg

Date October 29, 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
43781	P	10	5	5		2	3		4.63	
43782	NP	0	0						----	
43783	P	15	15	15		9	6		3.99	
43784	P	16	12	12		7	5		4.05	
43785	P	15	15	15		7	8		4.01	
43786	P	14	13	13		7	6		3.77	
43787	P	11	10	10		4	6		3.99	
43788	P	10**	13	13		9	4		4.32	
43789	P	13	12	11		5	6	1	3.99	
43790	NP	0	0						----	
43791	P	13	13	12		4	8	1	3.99	
43792	P	15	12	12		5	7		4.04	
43793	P	13	13	13		6	7		3.73	
43794	P	12	11	11		2	9		4.06	
43795	P	12	12	12		11	1		3.76	
43796	P	9	9	9		4	5		3.83	
43797	NP	0	0						----	
43798	NP	0	0						----	
43799	P	12	12	12		7	5		3.86	
43800	P	13	11	11		4	7		4.03	
43801	P	14	10	10		7	3		4.16	
43802	P	12	12	12		6	6		3.69	
43803	NP	0	0						----	
43804	P	11	11	11		4	7		3.72	
43805	P	9	9	9		4	5		3.51	

* P = Pregnant; NP = Not Pregnant

** One Ovary Missing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 28

Material FDA 73-58

Dose 20.9 mg/kg

Date October 29, 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
43811	P	13	13	13		9	4		4.07	
43812	P	13	13	13		7	6		3.73	
43813	P	14	14	14		5	9		3.90	
43814	P	10	9	9		5	4		3.82	
43815	NP	0	0						----	
43816	P	16	13	13		5	8		4.07	
43817	P	15	14	14		7	7		4.18	
43818	P	13	11	10		4	6	1	3.88	
43819	P	15	15	14		7	7	1	4.11	
43820	P	15	15	15		7	8		4.01	
43821	P	14	6	6		1	5		4.32	
43822	P	14	13	13		7	6		4.10	
43823	P	14	14	14		7	7		4.07	
43824	P	11	11	10		8	2	1	3.90	
43825	P	12	12	12		8	4		4.07	
43826	P	11	11	11		8	3		3.94	
43827	NP	0	0						----	
43828	NP	0	0						----	
43829	NP	0	0						----	
43830	P	13	12	12		8	4		3.94	
43831	P	16	14	14		6	8		4.08	
43832	P	11	11	11		5	6		4.02	
43833	P	11	11	11		8	3		4.12	
43834	NP	0	0						----	
43835	P	12	9	9		6	3		4.13	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 29

Material FDA 73-58

Dose 97.0 mg/kg

Date October 29, 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
43841	P	14	10	10		7	3		5.83	
43842	P	12	12	12		8	4		4.05	
43843	P	14	12	12		7	5		3.83	
43844	P	12	11	10		5	5	1	3.97	
43845	P	13	12	12		6	6		3.74	
43846	P	14	7	7		5	2		4.40	
43847	NP	0	0						----	
43848	P	11	11	10		4	6	1	3.63	
43849	P	15	13	13		6	7		4.03	
43850	P	14	14	14		8	6		3.81	
43851	P	13	13	13		7	6		3.91	
43852	P	11	11	11		5	6		4.24	
43853	P	13	13	13		4	9		4.00	
43854	P	12	11	11		8	3		3.50	
43855	P	10	9	9		4	5		3.69	
43856	P	13	13	13		6	7		3.91	
43857	NP	0	0						----	
43858	P	12	10	10		5	5		4.03	
43859	P	11	11	11		5	6		4.07	
43860	P	9	7	3		0	3	4	3.86	
43861	P	12	9	9		3	6		3.90	
43862	NP	0	0						----	
43863	P	12	8	8		4	4		3.93	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 30

Material FDA 73-58

Dose 450.0 mg/kg

Date October 29, 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
43871	P	14	14	14		6	8		4.39	
43872	NP	0	0						----	
43873	P	13	13	13		6	7		3.59	
43874	P	14	14	14		7	7		3.84	
43875	P	12	10	10		7	3		4.18	
43876	NP	0	0						----	
43877	P	12	12	12		8	4		3.98	
43878	P	13	13	13		5	8		3.87	
43879	P	10	9	9		2	7		4.39	
43880	P	13	13	13		5	8		3.98	
43881	P	14	11	11		6	5		4.03	
43882	P	14	13	13		6	7		4.27	
43883	P	11	11	11		5	6		3.83	
43884	P	15	15	15		11	4		3.85	
43885	NP	0	0						----	
43886	P	10	10	10		3	7		4.09	
43887	P	13	13	13		8	5		4.10	
43888	P	13	13	13		6	7		3.94	
43889	NP	0	0						----	
43890	P	14	10	10		3	7		4.12	
43891	P	15	14	14		6	8		4.07	
43892	P	17	17	17		10	7		3.88	
43893	NP	0	0						----	
43894	P	13	12	11		6	5	1	4.00	
43895	P	11	11	11		7	4		3.53	

* P = Pregnant; NP = Not Pregnant