FROM

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

FINAL
March 21, 1975

Teratologic Evaluation of FDA 73-65
(Monopotassium phosphate)
in
Mice and Rats

Final Report-3/21/75-Teratologic Evaluation of FDA 73-65 (Monopotassium phosphate) in Mice & Rats.

M I C E

FOOD AND DRUG Research LABORATORIES, INC.

WAVERLY DIVISION
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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: March 21, 1975

Laboratory No. 2123 (5)
Contract No.FDA 223-74-2176

Sample: Fine white crystalline material

Marking: FDA 73-65 (Monopotassium phosphate)

Examination Requested: Teratologic evaluation of FDA 73-65 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 320 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."

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FOOD AND DRUG RESEA. H LABORATORIES, INC.

Groups: 101 & 102; 97 through 100

Material: FDA 73-65

Table 1

Fate Summary
(Mice)

Date: February 21, 1975

Laboratory No.: 2123(5)

Group	Material	Dose mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
101	Sham	0.0	23	22	23	22
102	Aspirin*	150.0	23	20	23	20
97	FDA 73-65	3.2	21	20	21	20
98	FDA 73-65	14.8	21	20	21	20
99	FDA 73-65	68.9	25	20	25	20
100	FDA 73-65	320.0	20	20	20	20

* Positive Control: 150.0 mg/kg

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

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 101 & 102; 97 through 100

Material: FDA 73-65

Table 2
Reproduction Data
(Mice)

Date: February 21, 1975

Laboratory No.: 2123 (5)

Group:	101	102	97	98	99	100
Dose (mg/kg):	Sham	Aspirin**	3.2	14.8	68.9	320.0
Pregnancies						
Total No.	22	20	20	20	20	20
Died or Aborted (before Day 17)	0	0	0	0	0	0
To term (on Day 17)	22	20	20	20	20	20
Corpora Lutea						
Total No.	265	242	267	244	264	256
Average/dam mated	11.5	10.5	12.7	11.6	10.6	12.8
Live Litters						
Total No.*	22	20	20	20	20	20
Implant Sites						
Total No.	243	217	247	220	241	231
Average/dam*	11.0	10.9	12.4	11.0	12.1	11.6
Resorptions						
Total No.*	11	13	10	7	4	9
Dams with 1 or more sites resorbed	5	8	8	6	4	8
Dams with all sites resorbed	--	--	--	--	--	--
Per cent partial resorptions	25.0	40.0	40.0	30.0	20.0	40.0
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	231	204	237	212	236	221
Average/dam*	10.5	10.2	11.9	10.6	11.8	11.1
Sex ratio (M/F)	0.86	1.13	0.76	0.83	0.79	0.80
Dead Fetuses						
Total No.*	1	--	--	1	1	1
Dams with 1 or more dead	1	--	--	1	1	1
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	4.55	--	--	5.00	5.00	5.00
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.87	0.82	0.86	0.93	0.89	0.95

* Includes only those dams examined at term.

** Positive Control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 101 & 102; 97 through 100 — Laboratory No. 2123 (5)

Table 3

Material FDA 73-65 — Date February 21, 1975

Summary of Skeletal Findings*
(Mice)

Findings / Group No.:	101	102	97	98	99	100
Dose (mg/kg):	Sham	Aspirin**	3.2	14.8	68.9	320.0
Live Fetuses Examined (at term)	165/22	143/20	165/20	146/20	166/20	152/20
Sternebrae						
Incomplete oss.	30/15	67/19	24/10	13/6	26/9	50/15
Scrambled						
Bipartite		1/1				1/1
Fused						
Extra						
Missing	5/5	29/12	11/7	5/3	10/5	10/3
Other						
Ribs						
Incomplete oss.						
Fused/split						
Wavy						
Less than 12						
More than 13	31/10	37/11	33/15	27/13	39/14	26/9
Other						
Vertebrae						
Incomplete oss.	1/1	7/4	5/4	3/2		2/1
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure			1/1	1/1		
Missing			2/1			
Craniostosis						
Other						
Extremities						
Incomplete oss.	1/1	8/5	3/2	1/1		2/1
Missing						
Extra						
Miscellaneous						
Hyoid; missing	19/11	42/15	30/12	13/7	23/10	33/14
Hyoid; reduced	45/16	29/14	19/10	12/7	19/10	29/15

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

** Positive control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 101 & 102; 97 through 100 Date February 21, 1975

Material FDA 73-65 Laboratory No. 2123 (5)

Table 3-a

Summary of Soft Tissue Abnormalities

(Mice)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
97	FDA 73-65	3.2	25891	1	Gastroschisis
98	FDA 73-65	14.8	25917	1	Encephalomeningocele
			25924	1	Gastroschisis

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 101 &102; 97 through 100

Date February 21, 1975

Table 4

Species Mice

Laboratory No. 2123 (5)

Average Body Weights *

Group	Material	Dose Level	Day 0	6	11	15	17**
		mg/kg	g				
101	Sham	0.0	32	34	38	46	52 (22)
102	Aspirin***	150.0	32	34	37	46	51 (20)
97	FDA 73-65	3.2	33	37	42	50	57 (20)
98	FDA 73-65	14.8	32	36	39	48	54 (20)
99	FDA 73-65	68.9	32	36	40	49	55 (20)
100	FDA 73-65	320.0	30	34	38	47	53 (20)

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

Table 5

Groups 101 & 102; 97 through 100 Laboratory No. 2123 (5)

Compound: FDA 73-65 Species: Mice

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1975	a.m.	°F	%
1/17	8:15	80	
1/18	8:15	80	
1/19	8:15	80	N
1/20	8:15	78	O
1/21	8:15	80	T
1/22	8:15	80	
1/23	8:15	78	
1/24	8:15	78	
1/25	8:15	80	R
1/26	8:15	78	E
1/27	8:15	80	C
1/28	8:15	78	O
1/29	8:15	76	R
1/30	8:15	74	D
1/31	8:15	78	E
2/1	8:15	78	D
2/2	8:15	76	
2/3	8:15	75	
2/4	8:15	78	

Figure 1

(Mice)

Photograph of Grossly Abnormal Fetus

in Test Group

Inadvertently Omitted

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 101

Material Sham

Dose 0.0 mg/kg

Date February 21, 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
26001	P	13	13	13		7	6		0.92	
26002	P	8	7	2		1	1	5	0.98	
26003	P	9	9	8		3	5	1	1.22	
26004	NP	0	0						----	
26005	P	17	14	14		--**	--**		0.88	
26006	P	8	8	8		4	4		0.83	
26007	P	13	12	12		5	7		0.82	
26008	P	9	8	7		4	3	1	0.87	
26009	P	13	12	11		5	6	1	0.87	
26010	P	12	12	12		6	6		0.87	
26011	P	14	14	14		7	7		0.87	
26012	P	13	11	11		5	6		0.86	
26013	P	13	12	12		5	7		0.82	
26014	P	14	12	12		7	5		1.02	
26015	P	14	13	12	1	5	7		0.87	
26016	P	15	14	14		6	8		0.86	
26017	P	8	4	1		0	1	3	0.36	
26018	P	10	10	10		5	5		0.85	
26019	P	10	9	9		4	5		0.92	
26020	P	16	14	14		7	7		0.89	
26021	P	12	11	11		4	7		0.90	
26022	P	13	13	13		5	8		0.82	
26023	P	11	11	11		5	6		0.89	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 102

Material Aspirin

Dose 150.0 mg/kg

Date February 21, 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
26031	P	10	11	11		6	5		0.79	
26032	P	13	13	13		6	7		0.87	
26033	P	13	12	11		4	7	1	0.80	
26034	P	10	9	9		6	3		0.83	
26035	P	10	9	8		5	3	1	0.77	
26036	NP	0	0						----	
26037	P	10	10	10		7	3		0.89	
26038	P	13	11	10		4	6	1	0.84	
26039	NP	0	0						----	
26040	P	13	13	9		4	5	4	0.90	
26041	P	9	8	8		2	6		0.87	
26042	P	13	11	11		5	6		0.69	
26043	P	12	12	12		8	4		0.82	
26044	P	16	14	12		7	5	2	0.81	
26045	P	14	13	13		7	6		1.05	
26046	P	14	11	10		4	6	1	0.63	
26047	P	6	3	3		1	2		0.73	
26048	P	13	11	10		6	4	1	0.87	
26049	P	17	16	16		10	6		0.82	
26050	P	10	9	7		5	2	2	0.83	
26051	P	14	11	11		5	6		0.80	
26052	P	12	10	10		6	4		0.85	
26053	NP	0	0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 97

Material FDA 73-65

Dose 3.2 mg/kg

Date February 21, 1975

Laboratory No. 2123 (5)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
25881	P	13	13	12		6	6	1	0.84	
25882	P	13	12	11		3	8	1	0.77	
25883	P	9	8	8		4	4		0.85	
25884	P	16	14	14		7	7		0.84	
25885	P	17	16	16		9	7		0.94	
25886	P	10	10	10		4	6		0.97	
25887	P	15	14	14		3	11		0.75	
25888	P	15	14	13		6	7	1	0.92	
25889	P	13	12	12		5	7		0.86	
25890	P	13	12	12		5	7		0.87	
25891	P	15	13	11		4	7	2	0.82	
25892	P	15	14	14		6	8		0.82	
25893	NP	0	0						----	
25894	P	14	13	13		6	7		0.90	
25895	P	11	10	10		5	5		0.88	
25896	P	13	11	11		6	5		0.81	
25897	P	13	13	11		4	7	2	0.89	
25898	P	13	13	12		7	5	1	0.90	
25899	P	15	14	13		5	8	1	1.07	
25900	P	13	12	11		4	7	1	0.85	
25901	P	11	9	9		3	6		0.73	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 98

Material FDA 73-65

Dose 14.8 mg/kg

Date February 21, 1975

Laboratory No. 2123 (5)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
25911	P	19	18	18		10	8		0.91	
25912	P	12	10	10		3	7		0.86	
25913	P	14	13	13		6	7		0.97	
25914	P	9	9	9		2	7		1.07	
25915	P	14	13	12		7	5	1	0.82	
25916	P	16	16	16		5	11		1.00	
25917	P	12	11	11		5	6		1.18	
25919	P	14	12	12		5	7		0.92	
25920	P	3	2	1		0	1	1	0.80	
25921	P	16	15	15		8	7		0.76	
25922	P	7	3	3		2	1		0.99	
25923	P	10	9	9		6	3		1.03	
25924	P	15	14	12		3	9	2	0.82	
25925	P	8	7	6		3	3	1	0.85	
25926	P	13	12	12		5	7		0.79	
25927	P	10	9	9		5	4		0.92	
25928	P	14	13	12		5	7	1	0.87	
25929	NP	0	0						----	
25930	P	13	12	11	1	4	7		1.03	
25931	P	13	12	11		6	5	1	0.86	
25932	P	12	10	10		6	4		1.23	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 99

Material FDA 73-65

Dose 68.9 mg/kg

Date February 21, 1975

Laboratory No. 2123 (5)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
25941	NP	0	0						----	
25942	P	14	13	13		4	9		0.85	
25943	P	11	10	10		3	7		0.83	
25944	P	15	14	14		9	5		0.93	
25945	P	13	13	13		7	6		0.87	
25946	P	14	11	10		4	6	1	1.18	
25947	P	12	11	10		5	5	1	1.32	
25948	P	13	12	12		6	6		0.76	
25949	P	16	13	13		5	8		0.97	
25950	P	8	6	5		2	3	1	0.80	
25951	P	16	15	14	1	4	10		0.80	
25952	P	15	14	14		8	6		0.85	
25953	NP	0	0						----	
25954	NP	0	0						----	
25955	NP	0	0						----	
25956	P	15	14	14		5	9		0.90	
25957	P	15	14	14		7	7		0.93	
25958	NP	0	0						----	
25959	P	12	11	11		5	6		0.85	
25960	P	9	9	9		4	5		0.77	
25961	P	15	14	13		5	8	1	0.78	
25962	P	13	11	11		6	5		0.88	
25963	P	10	8	8		3	5		0.86	
25964	P	14	14	14		6	8		0.86	
25965	P	14	14	14		6	8		0.80	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 100

Material FDA 73-65

Dose 320.0 mg/kg

Appendix II

Reproduction Data in Mice (Individual)

Date February 21, 1975

Laboratory No. 2123 (5)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
25971	P	14	13	13		6	7		0.93	
25972	P	13	13	12		4	8		0.95	
25973	P	14	11	11		4	7		0.87	
25974	P	11	10	10		3	7		0.73	
25975	P	13	12	12		6	6		1.33	
25976	P	13	12	10		5	5	2	1.16	
25977	P	11	10	9		4	5	1	1.09	
25978	P	12	11	11		6	5		1.05	
25979	P	14	13	12		5	7	1	0.92	
25981	P	11	11	11		5	6		0.96	
25982	P	16	15	14		6	8	1	0.94	
25983	P	14	13	12		5	7	1	0.86	
25984	P	13	13	12		6	6	1	0.86	
25985	P	12	10	9		4	5	1	0.92	
25986	P	13	12	12		7	5		1.16	
25987	P	14	13	13		4	9		0.80	
25988	P	12	11	11		5	6		0.90	
25989	P	13	9	9		4	5		0.96	
25990	P	14	13	12		6	6	1	0.79	
25991	P	9	6	6		3	3		0.87	

* P = Pregnant; NP = Not Pregnant

R A T S

FOOD AND DRUG Research LABORATORIES, INC.

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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: March 21, 1975

Laboratory No. 2143 (5)
Contract No.FDA 223-74-2176

Sample: Fine white crystalline material

Marking: FDA 73-65 (Monopotassium phosphate)

Examination Requested: Teratologic evaluation of FDA 73-65 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 282 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effects 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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FOOD AND DRUG RESEA. H LABORATORIES, INC.

Groups: 101 & 102; 97 through 100

Material: FDA 73-65

Table 1

Fate Summary
(Rats)

Date: February 21, 1975

Laboratory No.: 2143 (5)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
101	Sham	0.0	28	25	28	25
102	Aspirin*	250.0	25	22	25	22
97	FDA 73-65	2.82	21	20	21	20
98	FDA 73-65	13.1	22	20	22	20
99	FDA 73-65	60.7	21	20	21	20
100	FDA 73-65	282.0	22	20	22	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 : 101 & 102; 97 through 100

Material : FDA 73-65

Table 2
Reproduction Data
(Rats)

Date : February 21, 1975

Laboratory No. : 2143 (5)

Group :	101	102	97	98	99	100
Dose (mg/kg) :	Sham	Aspirin**	2.82	13.1	60.7	282.0
Pregnancies						
Total No.	25	22	20	20	20	20
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	25	22	20	20	20	20
Corpora Lutea						
Total No.	334	298	260	249	241	253
Average/dam mated	11.9	11.9	12.4	11.3	11.5	11.5
Live Litters						
Total No.*	25	17	20	20	20	20
Implant Sites						
Total No.	284	256	236	213	222	229
Average/dam*	11.4	11.6	11.8	10.7	11.1	11.5
Resorptions						
Total No.*	4	105	2	3	6	8
Dams with 1 or more sites resorbed	3	14	2	1	4	5
Dams with all sites resorbed	--	5	--	--	--	--
Per cent partial resorptions	12.0	63.6	10.0	5.00	20.0	25.0
Per cent complete resorptions	--	22.7	--	--	--	--
Live Fetuses						
Total No.	280	149	234	210	216	221
Average/dam*	11.2	6.77	11.7	10.5	10.8	11.1
Sex ratio (M/F)	1.17	0.86	1.09	1.19	0.80	0.92
Dead Fetuses						
Total No.*	--	2	--	--	--	--
Dams with 1 or more dead	--	1	--	--	--	--
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	--	4.55	--	--	--	--
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	3.91	2.74	3.85	3.89	3.84	3.94

* Includes only those dams examined at term.

** Positive Control : 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 101 & 102; 97 through 100 — Laboratory No. 2143 (5)

Table 3

Material FDA 73-65 — Date February 21, 1975

Summary of Skeletal Findings*

(Rats)

Findings / Group No.:	101	102	97	98	99	100
Dose (mg/kg):	Sham	Aspirin**	2.82	13.1	60.7	282.0
Live Fetuses Examined (at term)	197/25	107/17	163/20	146/20	151/20	155/20
Sternebrae						
Incomplete oss.	64/18	58/12	45/13	32/14	36/14	39/17
Scrambled						
Bipartite		5/3				1/1
Fused						
Extra		1/1				
Missing	16/6	58/11		11/7	1/1	11/3
Other						
Ribs						
Incomplete oss.		13/5				
Fused/split		4/2				
Wavy	28/12	35/10	12/8	15/8	6/5	11/8
Less than 12						
More than 13		82/17	1/1	2/2		1/1
Other						
Vertebrae						
Incomplete oss.	8/6	66/15	6/5	1/1	7/4	5/3
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	24/9	48/10	23/11	14/6	21/11	25/7
Missing		6/3				
Craniostosis						
Other						
Extremities						
Incomplete oss.		19/7				
Missing						
Extra						
Miscellaneous						
Hyoid; missing	37/14	66/14	11/9	13/7	4/2	27/9
Hyoid; reduced	15/9	15/7	32/13	21/9	27/13	29/11

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 101 & 102; 97 through 100 Date February 21, 1975

Material FDA 73-65 Laboratory No. 2143 (5)

Table 3-a

Summary of Soft Tissue Abnormalities
(Rats)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
102	Aspirin*	250.0	88038	1	Gastroschisis
			88049	4	Encephalomeningocele
			88055	2	Gastroschisis
			88057	1	Gastroschisis
98	FDA 73-65	13.1	45925	1	Gastroschisis

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 101 & 102; 97 through 100

Date February 21, 1975

Table 4

Species Rats

Laboratory No. 2143 (5)

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	14	20**
		mg/kg	g				
101	Sham	0.0	245	256	272	288	359 (25)
102	Aspirin***	250.0	239	253	259	273	318 (22)
97	FDA 73-65	2.82	218	232	247	271	334 (20)
98	FDA 73-65	13.1	219	232	246	270	333 (20)
99	FDA 73-65	60.7	224	238	252	270	340 (20)
100	FDA 73-65	282.0	221	233	249	278	339 (20)

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

Table 5

Groups 101 & 102; 97 through 100 Laboratory No. 2143 (5)

Compound: FDA 73-65 Species: Rats

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1975	a.m.	°F	%
1/12	8:15	78	
1/13	8:15	78	
1/14	8:15	80	
1/15	8:15	78	N
1/16	8:15	78	O
1/17	8:15	80	T
1/18	8:15	80	
1/19	8:15	80	
1/20	8:15	78	R
1/21	8:15	80	E
1/22	8:15	80	C
1/23	8:15	78	O
1/24	8:15	78	R
1/25	8:15	80	D
1/26	8:15	78	E
1/27	8:15	80	D
1/28	8:15	78	
1/29	8:15	76	
1/30	8:15	74	
1/31	8:15	78	
2/1	8:15	78	
2/2	8:15	76	
2/3	8:15	75	
2/4	8:15	78	
2/5	8:15	76	
2/6	8:15	75	

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 101

Material Sham

Dose 0.0 mg/kg

Date February 21, 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
88001	P	13	10	10		9	1		5.28	
88002	P	11	10	10		6	4		4.90	
88003	P	14	12	12		6	6		3.95	
88004	P	10	8	8		4	4		3.83	
88005	P	14	12	12		6	6		3.64	
88006	NP	0	0						----	
88007	P	16	15	15		7	8		3.90	
88008	P	14	13	13		6	7		3.91	
88009	P	12	12	10		6	4	2	3.70	
88010	P	16	10	10		5	5		5.39	
88011	NP	0	0						----	
88012	P	16	2	2		2	0		4.03	
88013	P	15	14	14		7	7		3.30	
88014	P	13	11	11		7	4		3.59	
88015	P	16	14	14		10	4		3.27	
88016	P	18	18	18		9	9		3.34	
88017	P	12	11	11		5	6		3.97	
88018	P	12	8	8		4	4		3.99	
88019	P	11	8	8		5	3		4.08	
88020	P	14	14	14		8	6		4.31	
88021	P	11	11	11		6	5		3.72	
88022	P	13	12	12		4	8		3.14	
88023	P	15	12	12		5	7		3.41	
88024	P	11	11	10		6	4	1	4.02	
88025	P	12	12	12		5	7		3.75	
88026	P	13	13	13		9	4		3.69	
88027	P	12	11	10		4	6	1	3.70	
88028	NP	0	0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 102

Material Aspirin

Dose 250.0 mg/kg

Date February 21, 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
88032	P	17	15	15		9	6		2.64	
88033	P	12	10	10		3	7		4.75	
88034	NP	0	0						----	
88035	P	13	12	12		7	5		3.41	
88036	NP	0	0						----	
88037	P	13	13	13		5	8		3.90	
88038	P	11	5	5		3	2		2.93	
88039	P	13	13					13	----	
88040	P	15	14	14		4	10		1.93	
88041	P	13	12					12	----	
88042	P	12	9	9		3	6		5.06	
88043	P	14	14	10	2	5	5	2	2.05	
88044	P	14	12	2		1	1	10	1.63	
88046	P	13	10	1		0	1	9	1.75	
88047	P	16	9	5		1	4	4	2.30	
88049	P	14	8	6		3	3	2	2.20	
88050	P	12	11					11	----	
88051	P	14	12					12	----	
88052	P	13	13	13		6	7		2.40	
88053	P	15	14					14	----	
88054	P	16	13	11		5	6	2	3.24	
88055	P	13	12	11		8	3	1	2.11	
88056	NP	0	0						----	
88057	P	11	11	1		0	1	10	1.70	
88058	P	14	14	11		6	5	3	2.57	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 97

Material FDA 73-65

Dose 2.82 mg/kg

Date February 21, 1975

Laboratory No. 2143 (5)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
45881	P	12	10	10		6	4		4.14	
45882	P	13	11	11		6	5		4.04	
45883	P	10	10	10		2	8		3.67	
45884	P	16	14	14		7	7		3.65	
45885	P	11	10	10		5	5		3.46	
45886	P	12	12	12		7	5		4.65	
45887	P	12	10	10		5	5		3.68	
45888	P	14	12	12		8	4		4.02	
45889	P	14	12	12		6	6		3.77	
45890	P	14	13	13		6	7		3.92	
45891	P	13	13	13		4	9		3.28	
45892	P	14	12	12		7	5		4.17	
45893	P	14	13	13		8	5		3.79	
45894	P	12	11	11		6	5		3.74	
45895	P	15	14	13		7	6	1	4.12	
45896	P	11	11	10		5	5	1	4.29	
45897	P	13	12	12		7	5		3.64	
45898	NP	0	0						----	
45899	P	13	13	13		6	7		3.68	
45900	P	13	12	12		10	2		3.79	
45901	P	14	11	11		4	7		3.44	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 98

Material FDA 73-65

Dose 13.1 mg/kg

Date February 21, 1975

Laboratory No. 2143 (5)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
45911	P	12	7	7		5	2		3.66	
45912	P	17	16	16		10	6		3.89	
45913	NP	0	0						----	
45914	P	13	6	6		4	2		4.08	
45915	P	12	11	11		8	3		3.80	
45916	P	14	14	14		5	9		4.21	
45917	P	10	9	9		3	6		3.62	
45918	P	11	9	9		5	4		4.09	
45919	P	12	12	12		6	6		3.90	
45920	P	14	13	10		5	5	3	3.83	
45921	P	12	11	11		6	5		4.01	
45922	P	15	15	15		9	6		3.98	
45923	NP	0	0						----	
45924	P	10	10	10		5	5		4.21	
45925	P	14	9	9		5	4		3.94	
45926	P	10	9	9		4	5		3.45	
45927	P	13	10	10		5	5		3.89	
45928	P	9	9	9		5	4		3.80	
45929	P	14	12	12		7	5		3.86	
45930	P	15	13	13		9	4		3.56	
45931	P	10	10	10		3	7		4.00	
45932	P	12	8	8		5	3		4.02	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 99

Material FDA 73-65

Dose 60.7 mg/kg

Date February 21, 1975

Laboratory No. 2143(5)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
45941	P	15	13	13		9	4		4.06	
45942	P	10	10	7		3	4	3	3.81	
45943	P	15	15	15		5	10		3.66	
45944	P	12	12	12		6	6		4.10	
45945	P	13	12	12		5	7		3.36	
45946	P	11	11	11		5	6		3.92	
45947	P	13	11	11		6	5		3.83	
45948	P	13	11	10		4	6	1	4.01	
45949	P	13	13	12		5	7	1	3.86	
45950	P	12	12	12		5	7		3.87	
45951	NP	0	0						----	
45952	P	11	11	11		5	6		3.76	
45953	P	13	13	13		10	3		4.34	
45954	P	14	14	13		7	6	1	4.12	
45955	P	11	10	10		5	5		3.90	
45956	P	10	10	10		5	5		3.76	
45957	P	10	5	5		1	4		3.59	
45958	P	14	13	13		3	10		3.88	
45959	P	10	7	7		1	6		3.62	
45960	P	6	5	5		1	4		3.72	
45961	P	15	14	14		5	9		3.58	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 100

Material FDA 73-65

Dose 282.0 mg/kg

Date February 21, 1975

Laboratory No. 2143(5)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
45971	P	9	6	5		0	5	1	3.34	
45972	P	11	10	10		4	6		3.91	
45973	P	11	10	10		5	5		3.57	
45974	P	13	12	12		5	7		3.45	
45975	P	15	15	15		8	7		3.50	
45976	P	13	7	7		3	4		4.13	
45977	P	13	13	13		4	9		4.40	
45978	P	10	7	5		3	2	2	4.02	
45979	P	12	11	10		4	6	1	3.68	
45980	P	14	14	14		7	7		3.65	
45981	P	12	10	7		5	2	3	3.67	
45982	P	14	14	13		7	6	1	4.05	
45983	P	11	11	11		5	6		4.30	
45984	P	14	13	13		9	4		4.20	
45985	NP	0	0						----	
45986	P	12	11	11		6	5		5.58	
45987	P	11	10	10		5	5		3.83	
45988	P	15	15	15		7	8		4.07	
45989	P	18	17	17		8	9		4.00	
45990	NP	0	0						----	
45991	P	11	10	10		5	5		3.52	
45992	P	14	13	13		6	7		3.94	

* P = Pregnant; NP = Not Pregnant