FROM

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

FINAL
January 10, 1975

Teratologic Evaluation of FDA 73-2 (Monosodium phosphate, anhydrous) in Mice and Rats

Final Report-Teratologic Evaluation of FDA 73-2 (Monosodium Phosphate, Anhydrous) in Mice & Rats

025

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: January 10, 1975

Laboratory No. 2123 (4)
Contract No.FDA 223-74-2176

Sample: Fine white powdered material

Marking: FDA 73-2 (Monosodium phosphate, anhydrous)

Examination Requested: Teratologic evaluation of FDA 73-2 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 370 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 RESEARCH LABORATORIES, INC.

Groups: 41 through 46

Material: FDA 73-2

Date: December 6, 1974

Laboratory No.: 2123 (4)

Table 1

Fate Summary
(Mice)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
41	Sham	0.0	25	21	25	21
42	Aspirin*	150.0	27	20	27	20
43	FDA 73-2	3.7	25	22	25	22
44	FDA 73-2	17.2	25	19	25	19
45	FDA 73-2	79.7	25	20	25	20
46	FDA 73-2	370.0	25	22	25	22

* 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 RESEARCH LABORATORIES, INC.

Group : 41 through 46

Material : FDA 73-2

Table 2
Reproduction Data
(Mice)

Date : December 6, 1974

Laboratory No. : 2123 (4)

Group :	41	42	43	44	45	46
Dose (mg/kg) :	Sham	Aspirin**	3.7	17.2	79.7	370.0
Pregnancies						
Total No.	21	20	22	19	20	22
Died or Aborted (before Day 17)	0	0	0	0	0	0
To term (on Day 17)	21	20	22	19	20	22
Corpora Lutea						
Total No.	275	233	255	233	251	279
Average/dam mated	11.0	8.63	10.2	9.32	10.0	11.2
Live Litters						
Total No.*	21	20	22	19	20	22
Implant Sites						
Total No.	259	218	240	224	236	255
Average/dam*	12.3	10.9	10.9	11.8	11.8	11.6
Resorptions						
Total No.*	8	8	5	9	10	13
Dams with 1 or more sites resorbed	8	6	5	4	9	11
Dams with all sites resorbed	--	--	--	--	--	--
Per cent partial resorptions	38.1	30.0	22.7	21.1	45.0	50.0
Per cent complete resorptions	--	--	--	--	--	--
Live Fetuses						
Total No.	248	208	233	215	224	240
Average/dam*	11.8	10.4	10.6	11.3	11.2	10.9
Sex ratio (M/F)	1.04	0.84	0.82	1.01	0.84	1.07
Dead Fetuses						
Total No.*	3	2	2	--	2	2
Dams with 1 or more dead	3	1	2	--	2	2
Dams with all dead	--	--	--	--	--	--
Per cent partial dead	14.3	5.00	9.09	--	10.0	9.09
Per cent all dead	--	--	--	--	--	--
Average Fetus Weight, g	0.80	0.85	0.85	0.92	0.93	0.86

* Includes only those dams examined at term.

** Positive Control : 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 through 46 | Laboratory No. 2123 (4)

Table 3

Material FDA 73-2 | Date December 6, 1974

Summary of Skeletal Findings*
(Mice)

Findings / Group No.:	41	42	43	44	45	46
Dose (mg/kg):	Sham	Aspirin**	3.7	17.2	79.7	370.0
Live Fetuses Examined (at term)	173/21	144/20	165/22	148/19	156/20	167/22
Sternebrae						
Incomplete oss.	60/19	65/19	32/14	51/16	13/5	81/19
Scrambled						
Bipartite		1/1		3/2		3/2
Fused						
Extra						
Missing	39/12	36/11	19/9	13/7	2/2	20/12
Other						
Ribs						
Incomplete oss.						
Fused/split				1/1		
Wavy						
Less than 12						
More than 13	23/10	32/14	23/12	25/10	30/16	25/15
Other						
Vertebrae						
Incomplete oss.	4/2	11/5	4/3	1/1		
Scrambled						
Fused						
Extra ctrs. oss.						
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	2/2					
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.	6/4	15/5	2/2	1/1		1/1
Missing						
Extra						
Miscellaneous						
Hyoid; missing	30/12	60/16	24/12	26/11	27/11	43/15
Hyoid; reduced	26/12	18/13	22/13	26/16	19/10	22/14

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

** Positive control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 through 46 Date December 6, 1974

Material FDA 73-2 Laboratory No. 2123 (4)

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
43	FDA 73-2	3.7	24271	1	Exophthalmos; Encephalomeningocele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 through 46

Species Mice

Date December 6, 1974

Laboratory No. 2123 (4)

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	17**
		mg/kg	g				
41	Sham	0.0	31	34	37	44	50 (21)
42	Aspirin***	150.0	29	33	36	43	49 (20)
43	FDA 73-2	3.7	30	34	37	43	49 (22)
44	FDA 73-2	17.2	31	34	37	46	51 (19)
45	FDA 73-2	79.7	29	33	36	43	51 (20)
46	FDA 73-2	370.0	31	35	37	45	50 (22)

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

Table 5

Groups 41 through 46 | Laboratory No. 2123 (4)

Compound FDA 73-2 | Species: Mice

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1974	a.m.	°F	%
10/6	8:00	76	65
10/7	8:15	75	65
10/8	8:45	70	62
10/9	8:30	70	62
10/10	8:45	74	71
10/11	8:10	72	62
10/12	8:00	74	65
10/13	9:00	74	64
10/14	7:30	76	63
10/15	8:45	76	74
10/16	8:45	71	70
10/17	8:00	76	60
10/18	9:30	76	60
10/19	9:00	74	47
10/20	1:00 p.m.	74	60
10/21	11:00	75	55
10/22	8:00	75	53
10/23	9:00	76	55
10/24	11:00	76	55
10/25	9:00	76	53
10/26	9:00	76	42
10/27	9:00	75	47
10/28	8:30	76	46
10/29	10:30	82	47
10/30	9:00	72	70
10/31	9:30	72	68
11/1	9:00	72	70
11/2	12:30	78	67

Figure 1

(Mice)

Photographs of Grossly Abnormal Fetuses

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 41

Material Sham

Dose 0.0 mg/kg

Date December 6, 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
24201	P	18	14	14		7	7		0.76	
24202	P	12	11	10		5**	4**	1	0.62	
24203	NP	0	0						----	
24204	P	13	12	11		5	6	1	0.76	
24205	P	15	15	14		5	9	1	0.63	
24206	NP	0	0						----	
24207	P	14	14	14		10	4		0.84	
24208	P	15	15	15		10	5		0.88	
24209	P	11	10	10		4	6		0.80	
24210	P	9	9	8		5	3	1	1.00	
24211	P	13	13	12		6	6	1	0.76	
24212	NP	0	0						----	
24213	NP	0	0						----	
24214	P	15	15	14	1	5	9		0.76	
24215	P	16	14	14		7	7		0.88	
24216	P	13	13	13		6	7		1.17	
24217	P	13	12	12		4	8		0.61	
24218	P	12	9	9		5	4		0.74	
24219	P	15	15	14		8	6	1	0.82	
24220	P	11	11	10		6	4	1	0.77	
24221	P	11	11	11		5	6		0.76	
24222	P	10	10	9	1	5	4		0.84	
24223	P	13	12	12		7	5		0.74	
24224	P	12	11	10	1	4	6		0.68	
24225	P	14	13	12		7	5	1	0.90	

* P = Pregnant; NP = Not Pregnant

** Not all Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 42

Material Aspirin

Dose 150.0 mg/kg

Date December 6, 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
24231	P	11	10	7		3	4	3	0.65	
23232	NP	0	0						----	
24233	P	13	11	11		6	5		0.74	
24234	NP	0	0						----	
24235	P	13	13	12		6	6	1	0.82	
24236	P	12	11	11		6	5		0.94	
24237	NP	0	0						----	
24238	P	12	10	9		5	4	1	0.96	
24239	P	13	13	12		4	8	1	0.86	
24240	P	13	12	12		7	5		1.00	
24241	NP	0	0						----	
24242	P	15	13	11	2	6	5		0.83	
24243	P	11	11	11		2	9		0.52	
24244	NP	0	0						----	
24245	P	13	12	12		6	6		0.82	
24246	NP	0	0						----	
24247	P	10	9	9		6	3		0.87	
24248	P	10	10	10		5	5		0.98	
24249	NP	0	0						----	
24250	P	14	13	13		7	6		0.81	
24251	P	5	5	5		2	3		0.83	
24252	P	11	10	10		3	7		0.96	
24253	P	10	10	9		3	6	1	0.91	
24254	P	10	9	8		4	4	1	1.17	
24255	P	12	12	12		6	6		0.73	
24256	P	15	15	15		6	9		0.86	
24257	P	10	9	9		2	7		0.70	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 43

Material FDA 73-2

Dose 3.7 mg/kg

Date December 6, 1974

Laboratory No. 2123 (4)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
24261	P	16	15	14	1	8	6		0.85	
24262	P	13	11	11		4	7		0.80	
24263	P	14	14	13		5	8	1	0.78	
24264	NP	0	0						----	
24265	P	15	15	14		6	8	1	0.77	
24266	P	5	2	1		0	1	1	0.97	
24267	P	14	14	14		4	10		0.92	
24268	P	13	13	12		5	7	1	0.89	
24269	P	11	11	11		4	7		1.01	
24270	P	12	12	12		5	7		0.95	
24271	P	15	13	13		7	6		0.88	
24272	P	11	11	11		4	7		0.76	
24273	P	11	11	11		5	6		0.78	
24274	NP	0	0						----	
24275	P	14	14	13		7	6	1	0.89	
24276	NP	0	0						----	
24277	P	8	8	8		5	3		0.78	
24278	P	4	2	2		1	1		0.68	
24279	P	18	16	16		9	7		0.87	
24280	P	13	13	12	1	5	7		0.73	
24281	P	10	10	10		7	3		0.75	
24282	P	11	10	10		4	6		0.85	
24283	P	8	8	8		4	4		0.79	
24284	P	12	11	11		4	7		0.95	
24285	P	7	6	6		2	4		0.95	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 44

Material FDA 73-2

Dose 17.2 mg/kg

Date December 6, 1974

Laboratory No. 2123 (4)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
24291	P	11	11	9		4	5	2	0.85	
24292	P	12	12	12		6	6		0.89	
24293	P	10	10	10		4	6		0.84	
24294	P	10	10	10		9	1		1.15	
24295	P	10	9	9		4	5		0.88	
24296	P	12	12	12		6	6		0.89	
24297	P	17	17	15		8	7	2	0.96	
24298	NP	0	0						----	
24299	P	12	11	10		6	4	1	1.01	
24300	NP	0	0						----	
24301	NP	0	0						----	
24302	P	12	12	8		5	3	4	0.81	
24303	P	16	13	13		6	7		0.97	
24304	P	16	15	15		7	8		0.78	
24305	P	12	12	12		7	5		0.98	
24306	P	13	11	11		8	3		0.78	
24307	NP	0	0						----	
24308	NP	0	0						----	
24309	P	14	14	14		3	11		0.74	
24310	P	9	9	9		3	6		0.79	
24311	P	9	9	9		5	4		0.99	
24312	P	13	12	12		7	5		0.97	
24313	P	14	14	14		3	11		0.97	
24314	P	11	11	11		7	4		1.14	
24315	NP	0	0						----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 45

Material FDA 73-2

Dose 79.7 mg/kg

Date December 6, 1974

Laboratory No. 2123 (4)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
24321	P	12	12	12		6	6		0.85	
24322	P	11	11	10		4	6	1	0.81	
24323	P	12	12	11		4	7	1	0.67	
24324	P	6	6	6		3	3		0.98	
24325	P	13	13	13		6	7		0.80	
24326	P	10	10	10		5	5		1.04	
24327	P	13	11	11		5	6		1.07	
24328	P	14	13	13		6	7		1.04	
24329	NP	0	0						----	
24330	P	14	14	12	1	6	6	1	0.98	
24331	P	14	13	11		6	5	2	0.98	
24332	P	11	10	10		5	5		0.91	
24333	P	11	11	10		6	4	1	0.96	
24334	P	12	11	11		5	6		1.18	
24335	P	15	13	12		6	6	1	0.86	
24336	NP	0	0						----	
24337	P	11	11	10	1	8	2		1.01	
24338	NP	0	0						----	
24339	NP	0	0						----	
24340	P	15	14	13		5	8	1	0.98	
24341	P	13	13	12		3	9	1	0.79	
24342	P	14	13	13		5	8		0.78	
24343	P	14	12	12		5	7		0.99	
24344	NP	0	0						----	
24345	P	16	13	12		3	9	1	0.94	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Mice (Individual)

Group 46

Material FDA 73-2

Dose 370.0 mg/kg

Date December 6, 1974

Laboratory No. 2123 (4)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
24351	P	12	12	11		5	6	1	0.81	
24352	P	13	11	11		5	6		0.85	
24353	P	14	13	12		6	6	1	0.77	
24354	P	18	15	14		8	6	1	0.94	
24355	P	15	13	12		7	5	1	1.02	
24356	P	11	11	10		6	4	1	0.98	
24357	NP	0	0						----	
24358	P	13	11	10		5	5	1	0.84	
24359	P	13	13	11		6	5	2	1.03	
24360	NP	0	0						----	
24361	P	13	12	12		6	6		0.82	
24362	P	15	15	14		7	7	1	0.89	
24363	P	11	9	9		5	4		0.78	
24364	P	7	6	5		3	2	1	0.75	
24365	NP	0	0						----	
24366	P	15	14	12		7	5	2	0.94	
24367	P	11	11	9	1	4	5	1	0.74	
24368	P	13	12	12		7	5		1.00	
24369	P	16	14	14		4	10		0.89	
24370	P	11	10	10		5	5		0.91	
24371	P	15	15	15		8	7		0.75	
24372	P	12	10	10		6	4		0.71	
24373	P	10	9	9		6	3		0.88	
24374	P	13	11	10	1	4	6		0.83	
24375	P	8	8	8		4	4		0.76	

* P = Pregnant; NP = Not Pregnant

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: January 10, 1975

Laboratory No. 2143 (4)
Contract No.FDA 223-74-2170

Sample: Fine white powdered material

Marking: FDA 73-2 (Monosodium phosphate, anhydrous

Examination Requested: Teratologic evaluation of FDA 73-2 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 410 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: 41 through 46

Material: FDA 73-2

Date: December 6, 1974

Laboratory No.: 2143 (4)

Table 1

Fate Summary
(Rats)

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant[1]
41	Sham	0.0	21	20	21	20
42	Aspirin*	250.0	21	20	21	20
43	FDA 73-2	4.1	21	20	21	20
44	FDA 73-2	19.0	21	20	21	20
45	FDA 73-2	88.3	21	20	21	20
46	FDA 73-2	410.0	20	20	20	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 RESEARCH LABORATORIES, INC.

Group: 41 through 46

Material: FDA 73-2

Table 2
Reproduction Data
(Rats)

Date: December 6, 1974

Laboratory No.: 2143 (4)

Group:	41	42	43	44	45	46
Dose (mg/kg):	Sham	Aspirin**	4.1	19.0	88.3	410.0
Pregnancies						
Total No.	20	20	20	20	20	20
Died or Aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	20	20	20	20	20	20
Corpora Lutea						
Total No.	267	263	263	252	264	267
Average/dam mated	12.7	12.5	12.5	12.0	12.6	13.4
Live Litters						
Total No.*	20	19	20	20	20	20
Implant Sites						
Total No.	262	238	240	251	239	244
Average/dam*	13.1	11.9	12.0	12.6	12.0	12.2
Resorptions						
Total No.*	--	35	1	5	1	2
Dams with 1 or more sites resorbed	--	7	1	3	1	1
Dams with all sites resorbed	--	1	--	--	--	--
Per cent partial resorptions	--	35.0	5.00	15.0	5.00	5.00
Per cent complete resorptions	--	5.00	--	--	--	--
Live Fetuses						
Total No.	262	203	239	246	238	242
Average/dam*	13.1	10.2	12.0	12.3	11.9	12.1
Sex ratio (M/F)	1.06	0.92	1.03	0.95	1.00	1.12
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	3.93	2.92	3.84	3.91	4.00	3.85

* Includes only those dams examined at term.

** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 through 46 | Laboratory No. 2143 (4)

Table 3

Material FDA 73-2 | Date December 6, 1974

Summary of Skeletal Findings*
(Rats)

Findings / Group No.:	41	42	43	44	45	46
Dose (mg/kg):	Sham	Aspirin**	4.1	19.0	88.3	410.0
Live Fetuses Examined (at term)	179/20	143/19	166/20	171/20	168/20	170/20
Sternebrae						
Incomplete oss.	37/16	89/19	42/17	82/18	49/15	45/11
Scrambled						
Bipartite		8/6	1/1			1/1
Fused						
Extra						
Missing	3/3	70/15	4/3	10/7		7/6
Other						
Ribs						
Incomplete oss.	2/2	15/8	7/2			1/1
Fused/split		5/2				
Wavy	23/8	60/17	19/8	23/11	11/6	13/5
Less than 12						
More than 13	2/2	59/15		4/4		1/1
Other						
Vertebrae						
Incomplete oss.	4/4	68/18	2/1	1/1	9/6	10/4
Scrambled						
Fused						
Extra ctrs. oss.		1/1				
Scoliosis						
Tail defects						
Other						
Skull						
Incomplete closure	38/13	88/19	33/14	30/12	37/11	40/11
Missing						
Craniostosis						
Other						
Extremities						
Incomplete oss.		3/3				
Missing						
Extra						
Miscellaneous						
Hyoid; missing	21/10	54/16	21/12	19/10	12/8	20/11
Hyoid; reduced	26/13	21/10	33/14	28/11	41/14	47/14

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

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 through 46 Date December 6, 1974

Material FDA 73-2 Laboratory No. 2143 (4)

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

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
42	Aspirin*	250.0	44235	1	Hydrocephalus
			44240	1	Hydrocephalus; Encephalomeningocele
			44246	2	Hydrocephalus
			44252	1	Spina bifida; Encephalomeningocele
			44255	1	Hydrocephalus
45	FDA 73-2	88.3	44337	1	Umbilical hernia

*Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 41 through 46

Species Rats

Date December 6, 1974

Laboratory No. 2143 (4)

Table 4

Average Body Weights*

Group	Material	Dose Level	Day 0	6	11	15	20**
		mg/kg	g				
41	Sham	0.0	226	248	263	286	359 (20)
42	Aspirin***	250.0	234	243	255	276	333 (20)
43	FDA 73-2	4.1	227	246	262	284	345 (20)
44	FDA 73-2	19.0	223	242	257	280	352 (20)
45	FDA 73-2	88.3	233	249	264	285	356 (20)
46	FDA 73-2	410.0	237	260	274	293	364 (20)

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

Table 5

Groups 41 through 46
Compound FDA 73-2

Laboratory No. 2143 (4)
Species: Rats

Daily Temperature and Humidity Record

Date	Time	Temp	Relative Humidity
1974	a.m.	°F	%
9/27	8:20	72	65
9/28	8:30	76	70
9/29	8:15	74	76
9/30	8:20	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
10/6	8:00	76	65
10/7	8:15	75	65
10/8	8:45	70	62
10/9	8:30	70	62
10/10	8:45	74	71
10/11	8:10	72	62
10/12	8:00	74	65
10/13	9:00	74	64
10/14	7:30	76	63
10/15	8:45	76	74
10/16	8:45	71	70
10/17	8:00	76	60
10/18	9:30	76	60
10/19	9:00	74	47
10/20	1:00 p.m.	74	60
10/21	11:00	75	55
10/22	8:00	75	53
10/23	9:00	76	55
10/24	11:00	76	55
10/25	9:00	76	53
10/26	9:00	76	42
10/27	9:00	75	47
10/28	8:30	76	46
10/29	10:30	82	47

Figure 1

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 41

Material Sham

Dose 0.0 mg/kg

Date December 6, 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
44201	P	15	15	15		9	6		4.03	
44202	P	15	15	15		9	6		3.81	
44203	P	6**	12	12		6	6		3.91	
44204	P	15	15	15		6	9		3.80	
44205	P	14	13	13		8	5		3.94	
44206	P	12	11	11		6	5		3.93	
44207	P	15	15	15		7	8		3.88	
44208	P	15	15	15		7	8		4.12	
44209	P	17	16	16		9	7		3.87	
44210	P	10	10	10		5	5		3.72	
44211	P	12	12	12		9	3		3.65	
44212	P	15	13	13		10	3		3.75	
44213	P	13	13	13		6	7		4.03	
44214	P	11	10	10		4	6		4.15	
44215	P	11	10	10		5	5		3.77	
44216	P	16	16	16		6	10		4.12	
44217	P	15	13	13		7	6		4.30	
44218	P	14	12	12		6	6		4.05	
44219	NP	0	0						----	
44220	P	14	14	14		6	8		4.08	
44221	P	12	12	12		4	8		3.73	

* P = Pregnant; NP = Not Pregnant

** One Ovary Missing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 42

Material Aspirin

Dose 250.0 mg/kg

Date December 6, 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
44231	P	15	14	14		9	5		2.97	
44232	P	13	13	13		7	6		3.63	
44233	P	10	10					10	----	
44234	P	13	11	10		2	8	1	2.91	
44235	P	15	14	10		5	5	4	2.57	
44236	P	11	10	10		5	5		3.12	
44237	P	11	9	4		2	2	5	2.97	
44238	P	14	13	13		5	8		2.82	
44239	P	14	14	14		6	8		2.96	
44240	P	16	15	15		5	10		2.90	
44241	P	15	14	14		7	7		2.74	
44242	P	14	14	14		7	7		3.20	
44243	NP	0	0						----	
44244	P	15	12	12		4	8		3.35	
44245	P	14	13	13		7	6		4.50	
44246	P	14	7	6		3	3	1	3.35	
44247	P	15	14	1		0	1	13	1.90	
44248	P	12	11	11		8	3		2.41	
44249	P	12	11	10		4	6	1	2.41	
44251	P	9	8	8		5	3		2.56	
44252	P	11	11	11		6	5		2.15	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 43

Material FDA 73-2

Dose 4.1 mg/kg

Date December 6, 1974

Laboratory No. 2143 (4)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
44261	P	16	14	14		5	9		3.88	
44262	P	11	11	10		4	6	1	3.49	
44263	P	11	9	9		3	6		3.88	
44264	P	14	14	14		11	3		3.84	
44265	P	15	14	14		8	6		3.51	
44266	P	14	13	13		6	7		3.81	
44267	P	13	13	13		7	6		3.63	
44268	P	12	10	10		3	7		3.69	
44269	P	15	14	14		10	4		3.79	
44270	NP	0	0						----	
44271	P	10	9	9		3	6		3.99	
44272	P	14	14	14		4	10		4.12	
44273	P	10	10	10		4	6		3.56	
44274	P	11	11	11		6	5		3.88	
44275	P	13	12	12		8	4		4.14	
44276	P	15	13	13		6	7		4.29	
44277	P	15	15	15		8	7		3.90	
44278	P	16	14	14		9	5		3.83	
44279	P	10	6	6		4	2		3.87	
44280	P	13	9	9		6	3		3.91	
44281	P	15	15	15		6	9		3.69	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 44

Material FDA 73-2

Dose 19.0 mg/kg

Date December 6, 1974

Laboratory No. 2143 (4)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
44291	P	6**	14	14		8	6		3.69	
44292	P	12	12	12		6	6		3.71	
44293	P	14	14	13		6	7	1	3.88	
44294	P	14	13	13		4	9		3.71	
44295	P	10	10	10		5	5		4.06	
44296	P	10	10	10		5	5		3.81	
44297	P	13	13	13		8	5		3.66	
44298	P	12	9	9		5	4		3.98	
44299	P	14	14	14		3	11		3.93	
44300	P	8**	14	14		8	6		3.95	
44301	P	17	13	10		4	6	3	3.52	
44302	P	15	15	15		6	9		3.83	
44303	NP	0	0						----	
44304	P	14	14	14		8	6		4.10	
44305	P	13	7	6		3	3	1	3.52	
44306	P	15	15	15		9	6		3.77	
44307	P	14	14	14		7	7		3.76	
44309	P	13	13	13		8	5		3.90	
44310	P	13	12	12		6	6		5.81	
44311	P	12	12	12		4	8		3.86	
44312	P	13	13	13		7	6		3.68	

* P = Pregnant; NP = Not Pregnant

** One Ovary Missing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 45

Material FDA 73-2

Dose 88.3 mg/kg

Date December 6, 1974

Laboratory No. 2143 (4)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
44321	P	13	4	4		3	1		4.20	
44322	P	12	12	12		6	6		3.41	
44323	P	14	14	14		10	4		3.57	
44324	P	13	13	12		8	4	1	3.91	
44325	P	14	14	14		7	7		3.93	
44326	P	14	14	14		8	6		4.19	
44327	P	15	14	14		8	6		3.57	
44328	P	15	12	12		3	9		3.61	
44329	P	14	14	14		7	7		3.99	
44330	P	11	11	11		3	8		3.78	
44331	P	12	11	11		4	7		3.71	
44332	P	12	9	9		5	4		4.19	
44333	P	11	10	10		5	5		4.32	
44334	P	12	12	12		6	6		4.47	
44335	P	13	12	12		5	7		4.02	
44336	P	19	17	17		7	10		3.96	
44337	P	13	13	13		5	8		4.15	
44338	NP	0	0						----	
44339	P	9	6	6		4	2		4.78	
44340	P	17	16	16		9	7		4.10	
44341	P	11	11	11		6	5		4.17	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Reproduction Data in Rats (Individual)

Group 46

Material FDA 73-2

Dose 410.0 mg/kg

Date December 6, 1974

Laboratory No. 2143 (4)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses Alive	Fetuses Dead	Sex M	Sex F	Resorption Sites	Average Fetus Weight (g)	Remarks
44351	P	11	6	6		3	3		4.33	
44352	P	12	11	11		8	3		3.80	
44353	P	14	13	13		7	6		3.83	
44354	P	13	13	13		5	8		3.73	
44355	P	13	14	14		8	6		3.73	
44356	P	13	11	9		4	5	2	3.92	
44357	P	14	11	11		7	4		3.63	
44358	P	13	12	12		5	7		3.50	
44359	P	14	12	12		7	5		4.03	
44360	P	17	16	16		10	6		3.41	
44361	P	14	14	14		6	8		3.89	
44362	P	14	14	14		9	5		3.88	
44363	P	14	14	14		6	8		4.11	
44364	P	14	14	14		6	8		3.70	
44365	P	15	14	14		7	7		3.59	
44366	P	10	9	9		6	3		4.36	
44367	P	13	11	11		8	3		4.12	
44368	P	14	14	14		6	8		4.08	
44369	P	11	8	8		4	4		3.56	
44370	P	14	13	13		6	7		3.71	

* P = Pregnant; NP = Not Pregnant