EXHIBIT S27 TO DECLARATION OF STEPHEN G. SCHWARZ IN SUPPORT OF PLAINTIFFS' MOTION FOR CLASS CERTIFICATION

Oral Teratology Study of FC-95 in Rats

Experiment No.:	0680TR0008
Conducted At:	Safety Evaluation Laboratory Riker Laboratories, Inc. St. Paul, Minnesota
Dosing Period:	July 14, 1980 through July 24, 1980
Study Director:	E. G. Gortner

E. A. Gortner 12/17/80

E. G. Gortner Date
Senior Research Technologist
Animal Reproduction-Teratology
Study Director

Elden G Lamprecht 12/17/80

E. G. Lamprecht Date
Research Veterinary Pathologist

Marvin T Case 12/18/80

M. T. Case, DVM, PhD Date
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

Summary

Oral administration of FC-95 at doses of 10, 5 and 1 mg/kg/day to pregnant Sprague-Dawley rats during days 6 through 15 of gestation (period of organogenesis) resulted in fetuses with teratogenic changes in the lens of the eye. The teratogenic effect was a developmental eye abnormality which appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. The lens abnormality occurred in all FC-95 dose groups, but the proportion of fetuses with the lens changes was significantly higher than the control group only in the 10 mg/kg/day group.

FC-95 administration was maternally toxic only to the 10 mg/kg/day group. At gestation days 12 through 20 their mean maternal body weights were significantly lower than the controls. FC-95 was not maternally toxic to the 5 and 1 mg/kg/day groups.

FC-95 was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The compound did not produce an increase in the number or proportion of abnormal fetal skeleton aberrations.

Introduction

This teratology study[a] of FC-95 in rats was conducted to evaluate the embryotoxic and teratogenic effects of orally administered FC-95. The study was sponsored by 3M Commerical Chemical Division, St. Paul, Minnesota and was conducted by the Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota. The compound administration period was from July 14 through July 24, 1980. The protocol and list of the principal participants and supervisory personnel can be found in Appendices I and II respectively.

All portions of this study were conducted according to the Good Laboratory Practice (GLP) regulations and the Safety Evaluation Laboratory Standard Operating Procedures (see Appendix III for Quality Assurance Unit statement). The storage location for specimens, raw data and a copy of the final report is maintained in the Safety Evaluation Laboratory's record archives.

Methods

Time mated Spraque-Dawley derived rats were obtained from Charles River Breeding Laboratory and assigned cages according to a computer-generated random numbers table. The rats were then divided into four groups of 22 animals weighing 175 to 261 grams. The rats were housed individually in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. Food[b] and water were available ad libitum. The lights were on a 12 hour light/dark cycle.

The animals were observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15 and 20 of gestation and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight. The four groups were dosed with FC-95 (Lot 640) suspended daily in corn oil at 0, 10, 5 or 1 mg/kg/day. FC-95 was administered daily by oral intubation with a syringe equipped with a ball-tipped intubation needle to the rats on days 6 through 15 of gestation (day 0 indicated by sperm-positive vaginal smear). FC-95 analytical characterization (see Appendix IV) was provided by 3M Commercial Chemical Division, St. Paul, Minnesota.

All animals were sacrificed on day 20 by cervical dislocation and the ovaries and uterus, including its contents, were examined immediately to determine the following: number of corpora lutea, number of viable fetuses, number of resorption sites, pup weights and sex, and any gross fetal abnormalities. Approximately one-third of the fetuses were fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine visceral abnormalities. The remaining fetuses were preserved in alcohol for clearing and staining of the skeleton with alizarin red to detect skeletal abnormalities. Selected free-hand sections were processed for histological evaluation.

[a] Riker Experiment No. 0680TRD008
[b] Purina Laboratory Chow, Ralston Purina Company, St. Louis, MO

Results

FC-95 administered during the period of organogenesis was toxic to the high dose group (10 mg/kg/day) maternal rats. The mean body weights of all dose groups were similar at gestation days three through nine (Table 1, Appendix V). At gestation days 12 through 20 the high dose group rats weighed significantly less than controls (0 mg/kg/day). The mean maternal body weights of mid (5 mg/kg/day) and low (1 mg/kg/day) dose groups were not different from the controls throughout the study. Even though FC-95 was maternally toxic at the high dose level, no compound-related clinical signs were observed in any of the dose groups.

FC-95 was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The mean number of male, female, total and dead fetuses; the mean number of resorption sites, implantation sites, corpora lutea and mean fetus weights of the three FC-95 dose groups were not significantly different from the controls (Table 2, Appendix VI). The high dose group did have a lower mean number of viable male, female and total fetuses than the other three groups which resulted from a lower number of embryos at the start of the study. Contributing pieces of evidence to the lower number of high dose embryos are the low mean number of implantation sites, corpora lutea, resorption sites and the absence of dead fetuses.

FC-95 did not cause compound-related abnormal gross fetal findings (Table 3), nor did FC-95 treatment produce an increase in the number or proportion of abnormal fetal skeletal aberrations. Fetal skeleton results of the three compound treated groups were not significantly different from the control group (Table 4). The incidence and proportions of sternebrae nonossified and associated changes of sternebrae assymetrical, sternebrae bipartite and one sternebrae missing were unusually high in all dose groups of this study including the control group.

FC-95 was teratogenic in the rat at all dose levels administered in this study. The teratogenic effect was a developmental eye abnormality which appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. All eye abnormalities were localized to the area of the embryonal lens nucleus although a variety of morphological appearances were present within that location. The range of morphological appearances as observed under the dissecting microscope varied from a slight discoloration of the lens near the anterior margin to a dark colored oval area, often containing a cleft, extending from beneath the lens epithelium to half-way through the lens posteriorly. Histologically the discolorations were due to presence of lens vesicle remnants surrounding the abnormal embryonal lens nucleus. One of the most severly affected eyes had most of the embryonal lens nucleus replaced by sinus spaces containing red blood cells. Also contributing to the discolorations were primary lens fibers which appeared to have not elongated. These lens fibers were tortuous and lacked nuclei in a normal lens bow of nuclei. Secondary lens fiber development progressed normally except immediately surrounding the abnormal embryonal nucleus. Secondary aberrations of secondary lens fibers included the bending of the fibers around the abnormal oval area, the subsequent formation of prominant anterior and posterior Y sutures of the converging fibers and lens vesicle remnants surrounding the embryonal nucleus.

The lens abnormality occurred in all dose groups except the control group. The proportion of fetuses with the lens abnormality in one or both lenses was significantly higher in the high dose group than the control (Table 5). The lens abnormality recorded for one control fetus under the dissecting microscope was an artifact when evaluated by transmission light microscopy. A no-effect dose level for the teratogenic lens abnormality was not established in this study.

Discussion

Optimal visual functional requirements are met during embryonic development by the differentiation of highly specialized populations of cells from undifferentiated precoursers and by the coordinated morphogenesis of the resulting tissues. Both processes are controlled to a remarkable extent by interactions which occur among emerging tissues. Each tissue of the eye is brought to its final state of differentiation, its cell population size and its definitive geometry, not only by intrinsic processes, but also by extrinsic influences exerted by neighboring tissues[1].

The embryonal origin of the lens is undifferentiated ectoderm. The tip of the optic vesicle, presumably the neural retina, plays the final role in inducing lens from overlying ectoderm and in aligning the lens precisely with the rest of the eye. Alternative or sequential action of tissues derived from endoderm (foregut) and mesoderm (heart) on the same target tissue decreases the probability that lens formation would be aborted by accidents during the early phases of induction. While the nature of the inductive influence remains unknown, there are indications that substances may be transferred from the presumptive neural retina to the overlying ectoderm during induction. A prolonged period of inductive interaction not only increases the probabililty that lens induction will occur successfully in the face of interference, but provides a mechanism for continuously adjusting the size, shape, position and orientation of the lens to that of the retina[2].

During the early stages of the inductive process, the ectodermal cells immediately overlying the tip of the optic vesicle elongate prependicularly to the body surface to form a thickened disc (lens placode). The change in cell shape is accomplished without change in cell volume. The number of cells, however, continues to increase during this period. Toward the end of lens placode formation, acidophilic fibrils appear in the apices of the lens placode cells. At about this time, the placode invaginates to form the lens cup. This invagination is independent of the concomitant invagination of the underlying optic vesicle, and is probably due to forces operating within the lens ectoderm. As the lens cup deepens, its opening (lens pore) becomes progressively constricted until its lips meet and fuse, cutting off the lens vesicle internally and re-establishing continuity in the overlying ectoderm. Closure of the lens pore is attended by, and possibly accomplished by, a local and temporaty restricted wave of cell death. Following closure of the lens pore, the cells at the back of the lens vesicle continue to elongate, under the influence of the neural retina, to form the lens fibers. As the fibers grow the cavity of the lens vesicle is obliterated. The lens cells toward the ectoderm, which do not elongate further, form the lens epithelium[2].

The cuboidal lens epithelial cells which face the cornea continue to grow after the lens vesicle forms. As the cells rotate through the equator region, they take their places on the surface of the growing fiber mass. These cells differentiate into secondary lens fibers at the equator and elongate rapidly toward the poles of the lens where they meet with other fibers in planes of junction called sutures. As secondary fibers grow their nuclei become positioned at about the center of the fibers and form a convex lens bow outward. Since the newer fibers are always deposited superficially, the oldest fibers in the lens come to lie centrally and are referred to collectively as the lens nucleus. With time the lens cell nuclei in this region become pycnotic and finally disappear. The cell fibers, however, are not broken down and removed but remain in place. Thus the size and shape of the lens are controlled by factors which control the number, size and shape of lens cells[2].

The teratogenic effect of FC-95 probably occurred during the portion of organogenesis between differentiation of lens tissue from ectoderm and the formation of secondary lens fibers surrounding the embryonal lens nucleus. The exact time of the teratogenic insult and the morphogenesis of the abnormality were not determined in the study. The developmental lens abnormality appears to be unique because it has not been described as a compound-related abnormality[3]. A similar-appearing structural lens abnormality has been reported to occur spontaneously in rat fetuses, but with a very low incidence of 1.2%[4]. The abnormality resembles the Fraser developmental lens abnormality of a mutant mouse strain which results from degenerative primary lens cells[5].

References

1. Coulombre AJ, Coulombre JL: Abnormal Organogenesis of the Eye, in Wilson J., Fraser FC (eds): Handbook of Teratology:2 Mechanisms and Pathogenesis. New York, Plenum Press, 1977, pp 329-341.

2. Coulombre AJ: The Eye, in DeHaan RL, Ursprung H (eds): Organogenesis. New York, Holt Rinehart and Winston, 1965, pp 227-232.

3. Mann I: Development Abnormalities of the Eye, 2nd ed. Philadelphia, JB Lippincott Co., 1957.

4. Weisse I, Niggeschulze A, Stotzer H: Spontaneous congenital cataracts in rats, mice and rabbits. Archiv Fuer Toxikologie 32: pp 199-207, 1974.

5. Hamai Y, Kuwabara T: Early cytologic changes of Fraser cataract. An electron microscopic study. Investigative Ophthalmology 14 (7): pp 517-527, 1975.

Table 1

Oral Teratology Study of FC-95 in Rats
Mean Maternal Body Weights with Standard Deviations

Dose Group		Gestation Day 3	6	9	12	15	20
0 mg/kg/day	MEAN	200	223	247	272	305	300
	STAN. DEV	16.7	17.6	20.9	20.5	24.4	33.8
10 mg/kg/day	MEAN	199	223	243	257[a]	277[a]	343[a]
	STAN. DEV	11.8	13.8	18.2	16.2	18.6	34.6
5 mg/kg/day	MEAN	205	228	249	268	294	373
	STAN. DEV	20.0	16.4	12.6	13.2	17.8	23.8
1 mg/kg/day	MEAN	205	226	252	272	303	379
	STAN. DEV	18.8	19.1	19.7	19.5	24.6	31.8

[a] Significantly lower than the controls (Dunnett's t test $p < 0.05$)

Table 2

Oral Teratology Study of FC-95 in Rats
Mean Litter Data and Pup Weights with
Standard Deviations[a]

Dose Group	No. of Animals	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPORA LUTEA	MEAN WT. FETUS(G)
0 mg/kg/day	20	5.2	4.9	10.0	0.0	0.7	10.8	11.2	4.3
		1.7	2.1	2.3	0.0	0.9	2.5	2.7	0.4
10 mg/kg/day	17	3.8	3.9	7.7	0.0	0.4	8.1	9.2	4.3
		2.8	2.6	4.3	0.0	0.6	4.3	3.1	0.3
5 mg/kg/day	17	5.0	5.5	10.5	0.0	0.7	11.2	11.1	4.2
		1.9	2.0	2.2	0.0	1.0	2.2	2.0	0.3
1 mg/kg/day	19	4.7	5.4	10.1	0.1	0.4	10.6	10.9	4.2
		1.7	2.1	2.8	0.2	0.8	2.7	2.6	0.4

[a] Treatment groups were not significantly different from controls (Dunnett's t test $p < 0.05$)

Table 3

Oral Teratology Study of FC-95 in Rats
Number of Fetuses with Gross Findings[a]

Finding	0 mg/kg/day	10 mg/kg/day	5 mg/kg/day	1 mg/kg/day
No. of fetuses examined	201	131	178	192
Umbilical hernia	1	---	1	---
Runted	---	1	---	1
Total Normal Fetuses	200	130	177	191
Total Abnormal Fetuses	1	1	1	1

[a] Treatment groups were not significantly different from the control (Chi-square $p < 0.05$)

Table 4

Oral Teratology Study of FC-95 in Rats
Number and Percent of Fetuses with Skeleton Findings[a]

Skeleton Finding	0 mg/kg/day	10 mg/kg/day	5 mg/kg/day	1 mg/kg/day
Fontanelle not closed	10 (7)	10 (11)	7 (6)	5 (4)
Frontal nonossified	4 (3)	1 (1)	---	1 (1)
Parietal nonossified	2 (1)	1 (1)	1 (1)	1 (1)
Interparietal nonossified	3 (2)	---	---	1 (1)
Occipital nonossified	1 (1)	1 (1)	---	---
Sternebrae nonossified	114 (81)	77 (85)	100 (81)	107 (81)
Sternebrae asymmetrical	53 (38)	23 (25)	36 (29)	39 (29)
Sternebrae bipartite	7 (5)	4 (4)	5 (4)	6 (5)
One sternebrae missing	30 (21)	13 (14)	26 (21)	26 (20)
Two sternebrae missing	10 (7)	2 (2)	4 (3)	6 (5)
13 ribs	5 (4)	2 (2)	2 (2)	6 (5)
13 ribs spurred	7 (5)	7 (8)	8 (7)	4 (3)
Wavy ribs	1 (1)	2 (2)	---	1 (1)
Protrusion on ribs	6 (4)	9 (10)	3 (2)	8 (6)
One body of the vertebrae bipartite	32 (23)	21 (23)	25 (20)	32 (24)
Two bodies of the vertebrae bipartite	18 (13)	7 (8)	11 (9)	9 (7)
Three bodies of the vertebrae bipartite	4 (3)	1 (1)	1 (1)	3 (4)
Four bodies of the vertebrae bipartite	---	---	---	1 (1)
Total No. Normal Fetuses	7 (5)	3 (3)	10 (8)	10 (8)
Total No. Abnormal Fetuses	133 (95)	88 (97)	113 (92)	123 (92)
Total No. of Fetuses Examined	140	91	123	133

[a] Treatment groups were not significantly different from the control (Chi-square $p < 0.05$)
( ) = percent of total examined

Table 5

Oral Teratology Study of FC-95 in Rats
Number and Percent of Fetuses with Internal Findings

Internal Finding	0 mg/kg/day	10 mg/kg/day	5 mg/kg/day	1 mg/kg/day
Eye abnormality	1[a] (2)	14[b] (35)[c]	4[b] (7)	2[b] (3)
Thoracic cavity full of blood	---	1 (3)	---	---
Enlarged atria	1 (2)	---	---	---
Enlarged renal pelvis area in the kidney	3 (5)	---	---	3 (5)
Abdominal cavity full of blood	4 (7)	2 (5)	5 (9)	2 (3)
Total No. Normal Fetuses	52 (85)	23 (57)	47 (85)	53 (90)
Total No. Abnormal Fetuses	9 (15)	17 (43)	8 (15)	6 (10)
Total No. of Fetuses Examined	61	40	55	59

[a] Eye abnormality was an artifact and was not considered for statistical evaluations
[b] Eye abnormalities were developmental lens abnormalities with secondary lens aberrations
[c] Significantly higher than the control (Chi-square $p < 0.05$)
( ) = percent of total examined

Appendix I

Oral Teratology Study of FC-95 in Rats
Protocol

Objective

A teratology study will be used to evaluate the embryotoxic and teratogenic effects of orally administered FC-95 to pregnant rats during the period of organogenesis. The procedure complies with the general recommendations of the FDA issued in January, 1966 ("Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use"). The study will be conducted according to the 1978 Good Laboratory Practice regulations and Safety Evaluation Laboratory's Standard Operating Procedures.

Sponsor

3M Commercial Chemical Division, St. Paul, Minnesota.

Testing Facility

Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota.

Study Director

E. G. Gortner

Start of Dosing

Mid July, 1980.

Test System

Eighty-eight sexually mature, time mated Sprague-Dawley derived female rats from Charles River Breeding Laboratory will be housed in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. This strain of rats will be used because of historical control data and time mated females are readily available. Purina Laboratory Chow and water will be available ad libitum. The lights will be on a 12 hour light/dark cycle.

Test System Identification

Each animal will be ear tagged and that number will be indicated on the outside of the cage.

Appendix I (Continued)

Randomization

The animals will be assigned cages according to a computer-generated random numbers table.

Control Article

Corn oil.

Test Article

FC-95.

Analytical Specifications

The test article, composition and purity will be determined by the Sponsor (3M Commercial Chemical group) prior to the start of the study and at the end of dosing.

Dosage Levels and Experiment Design

The test article will be suspended in corn oil daily. The test article suspension and control article will be administered by oral intubation to the rats on days 6 through 15 of gestation according to the following:

Dose Group	Dose Level	Group Size
High	10 mg/kg/day	22 ♀
Mid	5 mg/kg/day	22 ♀
Low	1 mg/kg/day	22 ♀
Control	0 mg/kg/day	22 ♀

The oral route of administration will be used because of metabolism studies showed radiolabeled FC-95 was well absorbed. No dietary contaminants are known to interfere with the test article.

The animals will be observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights will be recorded on days 3, 6, 9, 12, 15 and 20 of pregnancy and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight.

The females will be killed on day 20 and the ovaries, uterus and its contents will be examined to determine: number of corpora lutea, number of fetuses (live and dead), number of resorption sites, number of implantation sites, pup weight and gross abnormalities. Approximately one-third of the pups will be fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine any visceral abnormalities using a dissecting

Appendix I (Concluded)

microscope. The remaining approximately two-thirds of the pups will be fixed in ethyl alcohol for subsequent skeletal examination after clearing and staining with alizarin red.

Data Analysis and Final Report

The proposed statistical methods to be used for analysis of the data are: Dunnett's t test for dam and pup weights, number of fetuses, number of resorption sites, number of implantation sites and number of corpora lutea; Chi square for percent abnormalities. The proposed date for the final report is 2-3 months after detailed pup examinations have been completed (approximately fourth quarter, 1980).

Appendix II

Oral Teratology Study of FC-95 in Rats
List of Principal Participating Personnel

NAME	FUNCTION
Edwin G. Gortner	Study Director
Elden G. Lamprecht	Veterinary Pathologist
Cathy E. Ludemann	Coordinator-Histology
Gary C. Pecore	Supervisor-Animal Care
Loren O. Wiseth	Technician

STATEMENT OF QUALITY ASSURANCE

STUDY NUMBER: 06B0TR0008

TITLE: Oral Teratology Study of FC-95 in Rats

Audits and/or inspections were performed by the Riker Quality Assurance Unit for the above titled study, and reported to the study director and to management as follows:

Date Performed	Date Reported
18 July 1980	21 July 1980
28 July 1980	28 July 1980
15 December 1980	17 December 1980
17 December 1980	17 December 1980

J. E. Orterstrom
Laboratory Quality Assurance
Riker Laboratories, Inc.

December 17, 1980
Date

APPENDIX IV

Test and/or Control Article Characterization

for

FC-95, Lot 640

1. The identity strength, uniformity, composition, purity or other pertinent characterizations of the test and/or control substances have been determined and documented as of May 8, 1980.

2. The method of synthesis or origin of the test and control substances, including their amount and the method of bioassay (if applicable) is documented.

yes X no ____

3. The stability of the test and/or control substances have been determined or will be determined as of Completion of Toxicity Testing If Necessary

The above information and documentation are located in the sponsor's records.

D-Rucker 5/21/80

Sponsor Date

Form 19793 PWO

Appendix V

Oral Teratology Study of FC-95 in Rats
Individual Body Weights (g)

Dose Group and Rat No.	Study Day 3	6	9	12	15	20
0 MG/KG/DAY						
N0R 12996	186	212	235	254	287	357
N0R 12997	224	261	239	306	345	424
N0R 12998	216	238	240	277	315	397
N0R 12999	212	232	271	274	302	373
N0R 13000	224	250	245	307	335	435
N0R 13016	182	207	284	255	284	342
N0R 13018	175	201	259	246	277	354
N0R 13019	193	219	237	277	309	378
N0R 13020	194	221	236	277	319	400
N0R 13036	205	228	222	284	322	408
N0R 13040	186	208	233	261	293	381
N0R 13041	195	219	285	258	289	355
N0R 13043	220	239	253	295	340	426
N0R 13044	207	228	284	273	296	359
N0R 13060	230	248	225	310	349	442
N0R 13061	195	212	213	259	297	366
N0R 13062	210	229	222	272	302	362
N0R 13063	185	208	247	257	289	342
N0R 13064	188	211	250	256	289	368
N0R 13080	179	194	258	238	256	321
MEAN	200	223	247	272	305	380
STAN. DEV	16.7	17.6	20.9	20.5	24.4	33.8
NON PREGNANT ANIMALS						
N0R 13017	186	198	243	217	234	253
N0R 13042	188	209	260	247	255	272

Appendix V (Continued)

Oral Teratology Study of FC-95 in Rats
Individual Body Weights (g)

Dose Group and Rat No.	Study Day 3	6	9	12	15	20
10 MG/KG/DAY						
00R 13001	189	222	239	253	281	347
00R 13002	190	217	230	256	283	356
00R 13003	192	222	224	265	290	381
00R 13004	192	212	218	233	255	319
00R 13005	201	225	260	261	285	369
00R 13021	227	257	247	278	293	360
00R 13022	212	244	243	288	311	402
00R 13023	180	206	258	227	245	285
00R 13025	208	237	251	268	297	382
00R 13037	187	214	229	250	274	357
00R 13045	195	216	228	259	289	361
00R 13048	186	205	226	236	248	311
00R 13065	204	223	274	263	279	304
00R 13066	207	226	275	263	262	358
00R 13067	210	234	222	268	278	322
00R 13069	203	228	262	262	283	338
00R 13081	194	209	238	237	251	281
MEAN	199	223	243	257	277	343
STAN. DEV	11.8	13.8	18.2	16.2	18.6	34.6
NON PREGNANT ANIMALS						
00R 13024	195	217	233	230	242	252
00R 13046	187	209	242	228	232	231
00R 13047	184	201	244	221	233	235
00R 13049	213	237	243	250	251	266
00R 13068	216	232	236	239	250	261

Appendix V (Continued)

Oral Teratology Study of PC-95 in Rats
Individual Body Weights (g)

Dose Group and Rat No.	Study Day 3	6	9	12	15	20
5 MG/KG/DAY						
P0F 13005	192	218	232	258	272	340
P0F 13007	226	249	272	264	304	398
P0F 13008	197	225	262	262	288	394
P0F 13009	188	212	274	254	283	361
P0F 13010	194	220	245	263	282	343
P0F 13027	212	232	251	269	288	369
P0F 13028	215	235	238	274	294	383
P0F 13029	199	229	241	272	288	366
P0F 13030	176	210	260	270	294	379
P0F 13038	198	219	235	263	288	366
P0F 13050	188	204	239	246	265	333
P0F 13051	222	243	256	283	323	407
P0F 13053	235	248	242	291	325	408
P0F 13054	197	224	238	259	279	349
P0F 13070	254	266	245	297	327	410
P0F 13071	200	223	250	274	304	378
P0F 13072	188	211	260	256	292	363
MEAN	205	228	249	268	294	373
STDN. DEV	20.0	16.4	12.6	13.2	17.8	23.8
NON PREGNANT ANIMALS						
P0F 13026	217	235	294	252	252	261
P0F 13052	218	237	252	248	254	262
P0F 13073	206	231	250	250	244	259
P0F 13074	207	234	244	257	272	287
P0F 13082	195	214	240	225	232	240

Appendix V (Concluded)

Oral Teratology Study of FC-95 in Rats
Individual Body Weights (g)

Dose Group and Rat No.	Study Day 3	6	9	12	15	20
1 MG/KG/DAY						
00R 13011	196	224	250	261	288	367
00R 13012	217	235	248	282	310	386
00R 13013	183	204	230	267	300	379
00R 13014	198	221	224	272	301	376
00R 13015	200	228	253	284	326	413
00R 13031	234	258	241	300	332	411
00R 13032	195	220	246	256	276	322
00R 13033	204	230	244	288	320	407
00R 13034	193	226	254	262	286	355
00R 13035	185	201	236	251	271	352
00R 13039	229	252	302	301	324	416
00R 13055	201	220	232	261	303	379
00R 13056	204	223	259	263	286	371
00R 13057	196	211	236	250	268	333
00R 13059	201	224	264	270	301	375
00R 13075	185	206	283	257	291	362
00R 13077	198	215	263	262	296	363
00R 13078	208	226	243	262	297	374
00R 13082	261	279	278	323	368	459
MEAN	205	226	252	272	303	379
STAN. DEV	18.8	19.1	19.7	19.5	24.6	31.8
NON PREGNANT ANIMALS						
00R 13058	183	205	247	226	238	253
00R 13076	192	213	236	254	278	270
00R 13079	196	218	228	244	255	266

Appendix VI

Oral Teratology Study of FC-95 in Rats
Individual Litter Data with Pup Weights

Dose Group and Rat No.	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPRA LUTEA	MEAN FETUS AVG	WT (G) M	F
0 mg/kg/day										
N0R 12996	5	4	9	0	1	10	9	4.9	5.1	4.7
N0R 12997	4	9	13	0	1	14	16	3.6	3.8	3.5
N0R 12998	7	4	11	0	0	11	12	4.3	4.3	4.2
N0R 12999	7	4	11	0	2	13	13	4.0	4.1	3.9
N0R 13000	7	7	14	0	0	14	17	4.1	4.2	4.0
N0R 13016	4	5	9	0	1	10	9	3.7	3.3	4.0
N0R 13017	NOT PREGNANT									
N0R 13018	7	3	10	0	1	11	11	4.5	4.5	4.3
N0R 13019	6	1	7	0	0	7	6	5.1	5.1	4.9
N0R 13020	4	8	12	0	0	12	12	4.7	4.8	4.7
N0R 13036	5	5	10	0	1	11	8	4.1	4.3	3.9
N0R 13040	6	7	13	0	0	13	12	4.4	4.5	4.2
N0R 13041	6	3	9	0	1	10	12	4.2	4.3	4.1
N0R 13042	NOT PREGNANT									
N0R 13043	4	6	10	0	3	13	15	4.2	4.4	4.1
N0R 13044	5	2	7	0	0	7	11	3.9	3.8	3.9
N0R 13060	8	5	13	0	1	14	12	4.1	4.1	3.9
N0R 13061	4	6	10	0	2	12	11	4.2	4.3	4.1
N0R 13062	3	4	7	0	0	7	9	4.1	4.4	3.8
N0R 13063	1	5	6	0	0	6	9	4.3	4.3	4.3
N0R 13064	5	7	12	0	0	12	12	4.2	4.2	4.2
N0R 13080	6	2	8	0	1	9	9	4.4	4.4	4.2
MEAN	5.2	4.9	10.0	0.0	0.7	10.8	11.2	4.3		
STAN. DEV.	1.7	2.1	2.3	0.0	0.9	2.5	2.7	0.4		

Appendix VI (Continued)

Oral Teratology Study of FC-95 in Rats
Individual Litter Data with Pup Weights

Dose Group and Rat No.	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPRA LUTEA	MEAN FETUS AVG	M	F
10 mg/kg/day										
00R 13001	4	6	10	0	1	11	10	4.5	4.6	4.5
00R 13002	3	6	9	0	2	11	11	3.9	4.1	3.8
00R 13003	4	7	11	0	0	11	12	4.2	4.4	4.1
00R 13004	7	2	9	0	0	9	9	4.2	4.2	4.0
00R 13005	5	7	12	0	0	12	12	4.3	4.3	4.2
00R 13021	1	3	4	0	0	4	7	4.4	4.4	4.4
00R 13022	11	2	13	0	0	13	14	4.2	4.2	3.8
00R 13023	2	0	2	0	0	2	5	4.8	4.8	0.0
00R 13024	NOT PREGNANT									
00R 13025	6	6	12	0	0	12	12	4.4	4.5	4.4
00R 13037	5	5	10	0	0	10	12	4.3	4.4	4.2
00R 13045	4	6	10	0	1	11	11	4.5	4.6	4.4
00R 13046	NOT PREGNANT									
00R 13047	NOT PREGNANT									
00R 13048	5	3	8	0	1	9	8	4.2	4.3	3.9
00R 13049	NOT PREGNANT									
00R 13065	0	1	1	0	0	1	6	4.3	0.0	4.3
00R 13066	4	8	12	0	0	12	11	4.0	4.2	3.9
00R 13067	1	1	2	0	1	3	8	4.6	4.8	4.5
00R 13068	NOT PREGNANT									
00R 13069	2	3	5	0	1	6	6	3.5	3.3	3.7
00R 13081	0	1	1	0	0	1	3	4.1	0.0	4.1
MEAN	3.8	3.9	7.7	0.0	0.4	8.1	9.2	4.3		
STAN. DEV.	2.8	2.6	4.3	0.0	0.6	4.3	3.1	0.3		

Appendix VI (Continued)

Oral Teratology Study of FC-95 in Rats
Individual Litter Data with Pup Weights

Dose Group and Rat No.	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPRA LUTEA	MEAN FETUS WT (G) AVG	M	F
5 mg/kg/day										
P0R 13006	3	3	6	0	3	9	9	4.6	4.8	4.4
P0R 13007	9	3	12	0	0	12	12	4.3	4.4	4.0
P0R 13008	5	7	12	0	0	12	12	3.9	4.0	3.8
P0R 13009	5	4	9	0	0	9	8	3.8	4.1	3.5
P0R 13010	4	7	11	0	0	11	12	3.9	4.0	3.8
P0R 13026	NOT PREGNANT									
P0R 13027	8	3	11	0	2	13	10	4.0	4.1	3.8
P0R 13028	4	8	12	0	0	12	13	4.3	4.4	4.3
P0R 13029	4	3	7	0	0	7	10	4.8	5.2	4.3
P0R 13030	4	9	13	0	1	14	14	4.5	4.5	4.5
P0R 13038	5	5	10	0	0	10	10	4.4	4.7	4.2
P0R 13050	4	5	9	0	1	10	9	4.0	4.2	3.9
P0R 13051	4	7	11	0	2	13	12	4.3	4.4	4.2
P0R 13052	NOT PREGNANT									
P0R 13053	9	5	14	0	0	14	14	3.6	3.7	3.5
P0R 13054	4	6	10	0	0	10	11	4.2	4.3	4.1
P0R 13070	5	8	13	0	2	15	14	4.2	4.2	4.2
P0R 13071	3	6	9	0	1	10	9	4.4	4.7	4.3
P0R 13072	5	4	9	0	0	9	9	4.3	4.4	4.2
P0R 13073	NOT PREGNANT									
P0R 13074	NOT PREGNANT									
P0R 13082	NOT PREGNANT									
MEAN	5.0	5.5	10.5	0.0	0.7	11.2	11.1	4.2		
STAN. DEV.	1.9	2.0	2.2	0.0	1.0	2.2	2.0	0.3		

Appendix VI (Concluded)

Oral Teratology Study of FC-95 in Rats
Individual Litter Data with Pup Weights

Dose Group and Rat No.	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPRA LUTEA	MEAN FETUS AVG	M	F
1 mg/kg/day										
00R 13011	7	3	10	0	0	10	8	4.4	4.5	4.4
00R 13012	5	6	11	0	0	11	12	4.1	4.1	4.0
00R 13013	3	6	9	0	0	9	11	4.4	4.4	4.3
00R 13014	5	7	12	0	0	12	13	3.4	3.8	3.4
00R 13015	4	6	10	0	0	10	9	3.8	3.8	3.8
00R 13021	7	6	13	0	0	13	14	4.0	3.9	4.1
00R 13022	1	1	2	0	0	2	4	3.8	4.3	3.3
00R 13033	4	9	13	0	0	13	14	4.5	4.6	4.5
00R 13034	2	4	6	0	3	9	8	5.0	5.1	4.9
00R 13035	5	5	10	0	1	11	11	4.6	4.7	4.4
00R 13039	6	6	12	0	0	12	12	4.3	4.4	4.2
00R 13055	7	4	11	0	1	12	12	4.3	4.2	4.3
00R 13056	5	6	11	1	1	13	11	4.1	4.3	4.0
00R 13057	4	5	9	0	1	10	12	3.9	3.8	3.9
00R 13058	NOT PREGNANT									
00R 13059	6	4	10	0	0	10	11	4.1	4.3	3.8
00R 13075	6	4	10	0	0	10	11	4.2	4.2	4.1
00R 13076	NOT PREGNANT									
00R 13077	3	5	8	0	1	9	9	4.4	4.4	4.4
00R 13078	5	5	10	0	0	10	10	4.6	4.9	4.4
00R 13079	NOT PREGNANT									
00R 13083	4	11	15	0	0	15	15	4.1	4.2	4.0
MEAN	4.7	5.4	10.1	0.1	0.4	10.6	10.9	4.2		
STAN. DEV.	1.7	2.1	2.8	0.2	0.8	2.7	2.6	0.4		

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Amendment to the Final Report of the Oral
Teratology Study of FC-95 in Rats

Experiment No.: 0680TR0008
Issued: 12/18/80

Please add the amended summary, the amended table 5, and the amendment to the results and discussion sections to the above report. The study conclusions were changed by this amendment to the report.

E. G. Gortner 7/26/82
E. G. Gortner Date
Senior Research Technologist
Animal Teratology Reproduction

Elden G Lamprecht 7-26-82
E. G. Lamprecht, DVM, PhD Date
Research Veterinary Pathologist

Maurice T Case 7/27/82
M. T. Case, DVM, PhD Date
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

Amended Summary (p. 1) to the Oral Teratology Study of FC-95 in Rats
Experiment No. 0680TR0008

Oral administration of FC-95 at doses of 10, 5 and 1 mg/kg/day to pregnant Sprague-Dawley rats during days 6 through 15 of gestation (period of organogenesis) was not teratogenic.

FC-95 administration was maternally toxic only to the 10 mg/kg/day group. At gestation days 12 through 20 the maternal body weights of the high dose females were significantly lower than the controls. FC-95 was not maternally toxic to the 5 and 1 mg/kg/day groups.

FC-95 was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The compound did not produce an increase in the number or proportion of fetal skeleton variations.

Amendment to the Results and Discussion Sections (p. 3-5)
of the Oral Teratology Study of FC-95 in Rats

Experiment No. 0680TR0008

(This amendment addresses the last two paragraphs of the results section and the entire discussion section.)

FC-95 was labeled a teratogen of the lens because apparent lens abnormalities were observed at the 10, 5 and 1 mg/kg/day dose levels. Based on subsequent studies, particularly Riker Experiment No. 0681TR0362, the interpretations of these observations have been extensively modified. The lens findings observed under the dissecting microscope are now known to be either freehand sectioning artifacts or a normal area of lens cell degeneration. The fetal rat lens findings were incorrectly interpreted as a teratogenic change in this study.

The gross finding of a lens cleft was an artifact created by freehand sectioning. It represents a separation between the embryonal nucleus lens cells and the lens epithelium. The gross finding of a lens dark streak was a normal observation of the embryonal nucleus. The embryonal nucleus is an area of normal lens cell degeneration in the gestation day 20 fetus.

The gross appearance of the rat lens at day 20 of gestation is determined by the region of the lens which is transected by freehand sectioning. In a subsequent study (Riker Experiment No. 0681TR0362) the compound-related occurance of the lens findings could not be repeated when the fetuses were coded before freehand sectioning and gross evaluation. The range of gross lens observations and the differences among the dose group incidences were due to the manner and frequency in which the lens cleft artifact was created by freehand sectioning and the limitations inherent in visualizing the embryonal nucleus.

In summary, FC-95 <u>in utero</u> exposed fetuses did not have compound-related changes in their lenses.

Amended Table 5 (p. 10)

Oral Teratology Study of FC-95 in Rats
Number and Percent of Fetuses with Internal Findings

Internal Finding	0 mg/kg/day	10 mg/kg/day	5 mg/kg/day	1 mg/kg/day
Lens findings[a]	1 (2)	14 (35)[b]	4 (7)	2 (3)
Thoracic cavity full of blood	---	1 (3)	---	---
Enlarged atria	1 (2)	---	---	---
Enlarged renal pelvis	3 (5)	---	---	3 (5)
Abdominal cavity full of blood	4 (7)	2 (5)	5 (9)	2 (3)
No. of Fetuses Examined	61	40	55	59

[a] The lens findings observed under the dissecting microscope were either freehand sectioning artifacts or a normal area of lens cell degeneration

[b] Significantly higher than the control (chi-square with Yates correction $p < 0.05$)

( ) = percent of total examined

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Amended Appendix VII

STATEMENT OF QUALITY ASSURANCE

STUDY NUMBER: Amendment to 0680TR0008

TITLE: Amendment to the Final Report of the Oral Teratology Study of FC-95 in Rats

Audits and/or inspections were performed by the Riker Compliance Audit unit for the above titled study, and reported to the study director and to management as follows:

Date Performed	Date Reported
July 16 and 19, 1982	July 21, 1982
July 22, 1982	July 23, 1982

Gale E. Van Buskirk
Compliance Audit
Riker Laboratories, Inc.

Date July 23, 1982

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Oral Teratology Study of FM-3422 in Rats T-2253

Experiment No.:	0680TR0010
Conducted At:	Safety Evaluation Laboratory Riker Laboratories, Inc. St. Paul, Minnesota
Inclusive Dosing Period:	August 19 to September 4, 1980
Study Director:	E. G. Gortner

E. G. Gortner 1-22-81

E. G. Gortner Date
Senior Research Technologist
Animal Reproduction-Teratology
Study Director

Elden G Lamprecht 1-22-81

E. G. Lamprecht, DVM, PhD Date
Research Veterinary Pathologist

Marvin T Case 1/23/81

M. T. Case, DVM, PhD Date
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

Summary

Oral administration of FM-3422 at 75, 37.5 and 25 mg/kg/day to pregnant Sprague-Dawley rats during days 6 through 15 of gestation (period of organogenesis) was teratogenic to rat fetuses. Teratogenic changes included a developmental eye abnormality, cleft palate, blood in the kidney parenchyma and sternebrae malformations. The developmental eye abnormality appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. The proportions of fetuses with the lens changes were significantly higher in all FM-3422 groups than in the control group. Cleft palates were produced in the 75 and 37.5 mg/kg/day groups. All three groups receiving compound had fetuses with blood in the kidney parenchyma. The sternebrae changes, although normally considered skeleton aberrations, were viewed as compound-related malformations because of their severity. FM-3422 also produced an increase in other fetal skeleton aberrations.

FM-3422 was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams.

FM-3422 was maternally toxic to the 75 and 37.5 mg/kg/day dose animals in reducing their group mean body weight gain during the dosing interval. Toxic clinical signs and deaths occurred in only the 75 mg/kg/day dose group.

Introduction

This teratology study [a] in rats was conducted to evaluate the embryotoxic and teratogenic effects of orally administered FM-3422. The study was sponsored by 3M Commercial Chemical Division, St. Paul, Minnesota and was conducted by the Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota. Two sets of compound administration groups were dosed between August 19 and September 4, 1980. The protocol and list of the principal participants and supervisory personnel can be found in Appendices I and II respectively.

All portions of this study were conducted according to the Good Laboratory Practice (GLP) regulations and the Safety Evaluation Laboratory Standard Operating Procedures (see Appendix III for Quality Assurance Unit statment). The storage location for specimens, raw data and a copy of the final report is maintained in the Safety Evaluation Laboratory's record archives.

Methods

Time mated Sprague Dawley derived rats were obtained from Charles River - Breeding Laboratory and assigned cages according to a computer-generated random numbers table. The rats were then divided into four groups of 22 animals weighing 140 to 240 grams. The rats were housed individually in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. Food[b] and water were available ad libitum. The lights were on a 12 hour light/dark cycle.

The animals were observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15 and 20 of gestation and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight. The four groups were dosed with FM-3422 (Lot 784) suspended daily in corn oil at 0, 75, 37.5 or 25 mg/kg/day. FM-3422 was administered daily by oral intubation with a syringe equipped with a ball-tipped intubation needle to the rats on days 6 through 15 gestation (day 0 indicated by sperm-positive vaginal smear). FM-3422 analytical characterization (see Appendix IV) was provided by 3M Commercial Chemical Division, St. Paul, Minnesota.

All surviving animals were sacrificed on day 20 by cervical dislocation and the ovaries and uterus, including its contents, were examined immediately to determine the following: number of corpora lutea, number of viable fetuses, number of resorption sites, pup weights and sex, and any gross fetal abnormalities. Approximately one-third of the fetuses were fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine visceral abnormalities. The remaining fetuses were preserved in alcohol for clearing and staining of the skeleton with alizarin red to detect skeletal abnormalities. Selected free-hand sections were processed for histological evaluation.

[a] Riker Experiment No. 0680TR0010
[b] Purina Laboratory Chow, Ralston Purina Company, St. Louis, MO

Results and Discussion

FM-3422 was maternally toxic to the high and mid dose groups (75 and 37.5 mg/kg/day) in reducing their group mean body weight gain during the dosing interval. All groups had lower mean weight gain than the controls at all weighings during the dosing interval of days 6 through 15 of gestation (Table 1). In the case of the high dose group at gestation days 9, 12 and 15 and in the case of the mid dose group at gestation days 9 and 15, the group mean weight gains were significantly lower than the mean weight gains of the control group (0 mg/kg/day). The lower mean weight gains of the high and mid dose groups during the dosing interval were responsible for their significantly lower mean body weights between the end of dosing and the termination of the study (Appendix V). The mean body weights and mean weight gains of the low dose group (25 mg/kg/day) were not significantly different from the control.

Abnormal clinical signs were observed and deaths occurred only in the high dose group. Three rats in the high dose group died. One rat died without clinical signs. Two of the rats that died plus one surviving rat had abnormal compound-related clinical signs which included some of the following: thin, lethargic, ataxic, blood in stool, urinary incontinance and bloody nares. The onset of abnormal clinical signs was on day 11 but the signs disappeared in the surviving rat by day 19 of gestation. The remaining 18 high dose rats and the mid and low dose rats did not have abnormal compound-related clinical signs.

The compound was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The mean number of male, female, total and dead fetuses, the mean number of resorption sites, implantation sites and corpora lutea of the three FM-3422 dose groups were not significantly different from the control (Table 2, Appendix VI).

FM-3422 was not fetal toxic. However, the combination of reduced maternal body weight gain (Table 1) plus higher numbers of fetuses in the treatment groups than the control group (Table 2 Appendix VI) resulted in mean fetus weights of all FM-3422 groups which were significantly lower than the control mean fetus weight. The reduced mean fetus weights were not associated with an increase in runting or other gross fetus findings (Table 3).

FM-3422 administration resulted in malformations in fetal sternebrae. The changes, although normally considered skeleton aberrations, were interpreted as compound-related malformations because of their severity. The severity and often the incidence of sternebrae malformations were greater in the three treatment groups than the control group. These malformations included the following: sternebrae asymmetrical, sternebrae bipartite, sternebrae scrambled, sternebrae enlarged, sternebrae missing and sternebrae misshapen (Table 4). All three FM-3422 dose groups had significantly higher proportions of fetuses with sternebrae asymmetrical than the control group. In addition, the high dose group had a

significantly higher proportion of fetuses with bipartite sternebrae than the control group.

An increase in other skeleton aberrations also occurred as the result of FM-3422 administration. These skeleton aberrations included nonossification changes of the cranial bones and sternebrae plus other sternebrae and rib changes (Table 4). The high dose group had significantly higher proportions of fetuses with all of these skeleton changes than the control group. The mid and low dose groups had significantly higher proportions of fetuses with some of these changes than the control group; notably nonossification of the cranial bones, sternebrae missing and 13 ribs spurred. The skeleton aberrations found are generally considered minor but they are of appreciable significance in this study with FM-3422 because of the high proportion of fetuses with the abnormalities.

The control group had a higher proportion of fetuses with one or two bodies of the vertebrae bipartite than the three treatment groups (Table 4). This difference was significant in all instances except for the finding of one body of the vertebrae bipartite in the low dose group.

FM-3422 administration produced the teratogenic effect of cleft palate in the high and mid dose groups and blood in the kidney parenchyma in all three dose groups. The proportions of fetuses with cleft palate and blood in the kidney parenchyma were sigificantly higher in the high dose group than in the control group (Table 5). No cleft palates were present in control and low dose fetuses examined.

FM-3422 was teratogenic to the eye of the rat at all dose levels administered in this study. The teratogenic effect was a developmental eye abnormality which appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. All eye abnormalities were localized to the area of the embryonal lens nucleus although a variety of morphological appearances were present within that location. The range of morphological appearances as observed under the dissecting microscope varied from a slight discoloration running through the lens to a discoloration of part of the lens and the presence of a cleft beneath the lens epithelium (Table 5). Histologically the discolorations were due to the presence of lens vesicle remnants forming clefts or surrounding the lens nucleus. Also contributing to the discolorations were primary lens fibers which appeared to have not elongated and the possible presence of degenerated epitrichial cells. Secondary lens fiber development progressed normally except immediately surrounding the abnormal embryonal nucleus. Prominant secondary aberrations of secondary lens fibers include V-shaped clefts between the embryonal nucleus and lens epithelium and lens vesicle remnants surrounding the nucleus.

The proportion of fetuses with the lens abnormality in one or both lenses was significantly higher in all groups than in the control group (Table 5).

No lens abnormalities occurred in the control group. A no-effect dose level for the teratogenic abnormality was not established in this study.

Further Discussion on Lens Embryology

Lens structural and functional requirements are met during embryonic development by the differentiation of highly specialized populations of cells from undifferentiated procursers and by the coordinated morphogenesis of the resulting tissues. Both processes are controlled to a remarkable extent by interactions which occur among emerging tissues. Each tissue of the eye is brought to its final state of differentiation, its cell population, size and its definitive geometry, not only by intrinsic processes, but also by extrinsic influences exerted by neighboring tissues[1].

The embryonal origin of the lens is undifferentiated ectoderm. The tip of the optic vesicle, presumably the neural retina, plays the final role in inducing lens from overlying ectoderm and in aligning the lens precisely with the rest of the eye. Additional action of tissues derived from endoderm (foregut) and mesoderm (heart) on the same target tissue decreases the probability that lens formation would be aborted by accidents during the early phases of induction. While the nature of the inductive influence remains unknown, there are indications that substances may be transferred from the presumptive neural retina to the overlying ectoderm during induction. A prolonged period of inductive interaction not only increases the probability that lens induction will occur successfully in the face of interference, but provides a mechanism for continuously adjusting the size, shape, position and orientation of the lens to that of the retina[2].

During the early stages of the inductive process, the ectodermal cells immediately overlying the tip of the optic vesicle elongate perpendicularly to the body surface to form a thickened disc (lens placode). The change in cell shape is accomplished without change in cell volume. The number of cells, however, continues to increase during this period. Toward the end of lens placode formation, acidophilic fibrils appear in the apices of the lens placode cells. At about this time, the placode invaginates to form the lens cup. This invagination is independent of the concomitant invagination of the underlying optic vesicle, and is probably due to forces operating within the lens ectoderm. As the lens cup deepens, its opening (lens pore) becomes progressively constricted until its lips meet and fuse, cutting off the lens vesicle internally and re-establishing continuity in the overlying ectoderm. Closure of the lens pore is attended by, and possibly accomplished by, a local and temporary restricted wave of cell death. Following closure of the lens pore, the cells at the back of the lens vesicle continue to elongate, under the influence of the neural retina, to form the lens fibers. As the fibers grow the cavity of the lens vesicle is obliterated. The lens cells toward the ectoderm, which do not elongate further, form the lens epithelium[2].

The cuboidal lens epithelial cells which face the cornea continue to grow

after the lens vesicle forms. As the cells rotate through the equator region, they take their places on the surface of the growing fiber mass. These cells differentiate into secondary lens fibers at the equator and elongate rapidly toward the poles of the lens where they meet with other fibers in planes of junction called sutures. As secondary fibers grow their nuclei become positioned at about the center of the fibers and form a convex lens bow outward. Since the newer fibers are always deposited superficially, the oldest fibers in the lens come to lie centrally and are referred to collectively as the lens nucleus. With time the lens cell nuclei in this region become pycnotic and finally disappear. The cell fibers, however, are not broken down and removed but remain in place. Thus the size and shape of the lens are controlled by factors which control the number, size and shape of the lens cells[2].

The teratogenic lens effect of FM-3422 probably occurred during the portion of organogenesis between differentiation of lens tissue from ectoderm and the formation of secondary lens fibers surrounding the embryonal lens nucleus. The exact time of the teratogenic insult and the morphogenesis of the abnormality were not determined in the study. The developmental lens abnormality appears to be unique because it has not been described as a compound-related abnormality[3]. A similar-appearing structural lens abnormality has been reported to occur spontaneously in rat fetuses but with a very low incidence of 1.2%[4]. The abnormality resembles the Fraser developmental lens abnormality of a mutant mouse strain which results from degenerative primary lens cells[5].

References

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Table 1

Oral Teratology Study of FM-3422 in Rats
Mean Body Weight Gains of Pregnant Rats Between Weighings
with Standard Deviations

Dose Group		Gestation Day 6	9	12	15	20
0 mg/kg/day	MEAN	28	17	26	29	71
	STAN. DEV	5.5	7.5	5.8	4.9	12.1
75 mg/kg/day	MEAN	30	0[a]	6[a]	2[a]	69
	STAN. DEV	14.2	14.6	19.8	17.0	15.1
37.5 mg/kg/day	MEAN	28	6[a]	17	14[a]	69
	STAN. DEV	5.4	10.9	9.8	10.4	15.8
25 mg/kg/day	MEAN	27	11	20	22	73
	STAN. DEV	11.9	15.3	8.9	5.4	11.6

[a] Significantly lower than the control (Dunnett's t test $p < 0.05$)

Table 2

Oral Teratology Study of FM-3422 in Rats
Mean Litter Data with Fetus Weights and Standard Deviations

Dose Group	No. of Animals	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPORA LUTEA	MEAN WT. FETUS(G)
0 mg/kg/day	18	3.6	5.4	8.9	0.0	0.7	9.6	9.9	4.4
		1.6	1.8	2.6	0.0	1.0	2.5	2.1	0.5
75 mg/kg/day	17	5.1	4.7	9.8	0.1	0.5	10.4	10.5	3.7[a]
		2.1	2.3	2.1	0.2	0.6	1.9	2.2	0.5
37.5 mg/kg/day	20	4.4	5.4	9.7	0.0	0.7	10.4	10.5	4.0[a]
		2.1	2.1	1.9	0.0	0.9	1.6	1.7	0.3
25 mg/kg/day	21	4.3	5.8	10.1	0.0	0.5	10.7	11.3	4.0[a]
		1.6	1.9	1.9	0.0	0.5	2.0	1.9	0.3

[a] Significantly lower than the control (Dunnett's t test $p < 0.05$)

Table 3

Oral Teratology Study of FM-3422 in Rats
Number of Fetuses with Gross Findings[a]

Finding	0 mg/kg/day	75 mg/kg/day	37.5 mg/kg/day	25 mg/kg/day
Total Fetuses Examined	161	167	195	213
Runted	---	2	---	2
Umbilical hernia	1	---	---	2
Total Normal Fetuses	160	165	195	209
Total Abnormal Fetuses	1	2	0	4

[a] Treatment groups were not significantly different from control (Chi-square $p < 0.05$)

Table 4

Oral Teratology Study of FM-3422 in Rats
Number and Percent of Fetuses with Skeleton Findings

Skeleton Finding	0 mg/kg/day		75 mg/kg/day		37.5 mg/kg/day		25 mg/kg/day	
Fontanelle not closed	27	(24)	26	(22)	25	(18)	28	(19)
Holes in parietal	1	(1)	1	(1)				
Parietal scalloped	1	(1)						
Frontal nonossified	21	(19)	62	(53)[a]	70	(51)[a]	75	(50)[a]
Parietal nonossified	21	(19)	62	(53)[a]	70	(51)[a]	74	(50)[a]
Interparietal nonossified	14	(12)	54	(47)[a]	46	(33)[a]	59	(40)[a]
Occipital nonossified			1	(1)				
Sternebrae nonossified	80	(71)	100	(86)[a]	102	(74)	111	(75)
Sternebrae asymmetrical	10	(9)	42	(36)[a]	34	(25)[a]	36	(24)[a]
Sternebrae bipartite	2	(2)	37	(32)[a]	6	(4)	5	(3)
Sternebrae scrambled			1	(1)	1	(1)		
Sternebrae enlarged			1	(1)				
Sternebrae misshapen					1	(1)		
One sternebrae missing	23	(20)	32	(28)	31	(22)	33	(22)
Two sternebrae missing	2	(2)	16	(14)[a]	9	(7)	16	(11)[a]
Three sternebrae missing			1	(1)				
One body vertebrae missing			1	(1)				
13 ribs	1	(1)	3	(3)	3	(2)	5	(3)
13 ribs spurred	3	(3)	32	(28)[a]	28	(20)[a]	9	(6)
Wavy ribs	5	(4)	8	(7)	4	(3)	2	(1)
Protrusion on ribs	8	(7)	12	(10)	5	(4)	7	(5)
One body of the vertebrae bipartite	29	(26)	15	(13)[b]	21	(15)[b]	30	(20)
Two bodies of the vertebrae bipartite	17	(15)	4	(3)[b]	5	(4)[b]	3	(2)[b]
Three bodies of the vertebrae bipartite					1	(1)	2	(1)
Four bodies of the vertebrae bipartite							1	(1)
Five bodies of the vertebrae bipartite							1	(1)
Total Normal Fetuses	9	(8)	2	(2)	6	(4)	7	(5)
Total Abnormal Fetuses	104	(92)	114	(98)	132	(96)	142	(95)
Total Fetuses Examined	113		116		138		149	

[a] Significantly higher than the control (Chi-square $p < 0.05$)
[b] Significantly lower than the control (Chi-square $p < 0.05$)
( ) = percent of total examined

Table 5

Oral Teratology Study of FM-3422 in Rats
Number and Percent of Fetuses with Internal Findings

Internal Finding	0 mg/kg/day		75 mg/kg/day		37.5 mg/kg/day		25 mg/kg/day	
Fetuses with eye abnormalities	0		35	(69)[a]	29	(51)[a]	27	(42)[a]
Discoloration running through the lens of one eye			7	(13)	2	(4)	1	(2)
Discoloration running through the lens of both eyes							1	(2)
Discoloration running 1/2 to 3/4 through the lens of one eye			16	(31)[a]	13	(23)[a]	10	(16)[a]
Discoloration running 1/2 to 3/4 through the lens of both eyes			5	(10)	1	(2)	5	(8)
Discoloration in back of lens							2	(3)
Bubble on outside of lens and discoloration running through the lens of one eye			1	(2)				
Cleft in the lens and discoloration running through the lens of one eye			5	(10)	7	(12)[a]	4	(6)
Cleft in the lens and discoloration running through the lens of both eyes					1	(2)		
Bubble on outside of lens cleft in the lens of one eye					1	(2)	1	(2)
Cleft in the lens of one eye			1	(2)	5	(9)	3	(5)
Open space in the rear of the lens of one eye							1	(2)
Small eyes			1	(2)				
Cleft palate			7	(14)[a]	3	(5)		
Enlarged atriums							2	(3)
Enlarged renal pelvis area in the kidney	5	(10)	1	(2)				
Blood in the kidney parenchyma			11	(22)[a]	3	(5)	3	(5)
Abdominal cavity full of blood	1	(2)	3	(6)			1	(2)
Total Normal Fetuses	42	(87.5)	8	(16)	25	(44)	32	(50)
Total Abnormal Fetuses	6	(12.5)	43	(84)	32	(56)	32	(50)
Total Fetuses Examined	48		51		57		64	

[a] Significantly different from the control (Chi-square $p < 0.05$)

CONFIDENTIAL

REPORT NO. 1610

DATE: 2/18/81

Oral Teratology Study of FM-3422 in Rats

Experiment No.:	0680TR0010
Conducted At:	Safety Evaluation Laboratory Riker Laboratories, Inc. St. Paul, Minnesota
Inclusive Dosing Period:	August 19 to September 4, 1980
Study Director:	E. G. Gortner

E. G. Gortner 1-22-81

E. G. Gortner Date
Senior Research Technologist
Animal Reproduction-Teratology
Study Director

Eldon G. Lamprecht 1-22-81

E. G. Lamprecht, DVM, PhD Date
Research Veterinary Pathologist

Maurice T Case 1/23/81

M. T. Case, DVM, PhD Date
Manager, Pathology-Toxicology
Safety Evaluation Laboratory

Exhibit
1251
State of Minnesota v. 3M Co.,
Court File No. 27-CV-10-28862

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Summary

Oral administration of FM-3422 at 75, 37.5 and 25 mg/kg/day to pregnant Sprague-Dawley rats during days 6 through 15 of gestation (period of organogenesis) was teratogenic to rat fetuses. Teratogenic changes included a developmental eye abnormality, cleft palate, blood in the kidney parenchyma and sternebrae malformations. The developmental eye abnormality appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. The proportions of fetuses with the lens changes were significantly higher in all FM-3422 groups than in the control group. Cleft palates were produced in the 75 and 37.5 mg/kg/day groups. All three groups receiving compound had fetuses with blood in the kidney parenchyma. The sternebrae changes, although normally considered skeleton aberrations, were viewed as compound-related malformations because of their severity. FM-3422 also produced an increase in other fetal skeleton aberrations.

FM-3422 was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams.

FM-3422 was maternally toxic to the 75 and 37.5 mg/kg/day dose animals in reducing their group mean body weight gain during the dosing interval. Toxic clinical signs and deaths occurred in only the 75 mg/kg/day dose group.

significantly higher proportion of fetuses with bipartite sternebrae than the control group.

An increase in other skeleton aberrations also occurred as the result of FM-3422 administration. These skeleton aberrations included nonossification changes of the cranial bones and sternebrae plus other sternebrae and rib changes (Table 4). The high dose group had significantly higher proportions of fetuses with all of these skeleton changes than the control group. The mid and low dose groups had significantly higher proportions of fetuses with some of these changes than the control group; notably nonossification of the cranial bones, sternebrae missing and 13 ribs spurred. The skeleton aberrations found are generally considered minor but they are of appreciable significance in this study with FM-3422 because of the high proportion of fetuses with the abnormalities.

The control group had a higher proportion of fetuses with one or two bodies of the vertebrae bipartite than the three treatment groups (Table 4). This difference was significant in all instances except for the finding of one body of the vertebrae bipartite in the low dose group.

FM-3422 administration produced the teratogenic effect of cleft palate in the high and mid dose groups and blood in the kidney parenchyma in all three dose groups. The proportions of fetuses with cleft palate and blood in the kidney parenchyma were significantly higher in the high dose group than in the control group (Table 5). No cleft palates were present in control and low dose fetuses examined.

FM-3422 was teratogenic to the eye of the rat at all dose levels administered in this study. The teratogenic effect was a developmental eye abnormality which appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. All eye abnormalities were localized to the area of the embryonal lens nucleus although a variety of morphological appearances were present within that location. The range of morphological appearances as observed under the dissecting microscope varied from a slight discoloration running through the lens to a discolorstion of part of the lens and the presence of a cleft beneath the lens epithelium (Table 5). Histologically the discolorations were due to the presence of lens vesicle remnants forming clefts or surrounding the lens nucleus. Also contributing to the discolorations were primary lens fibers which appeared to have not elongated and the possible presence of degenerated epitrichial cells. Secondary lens fiber development progressed normally except immediately surrounding the abnormal embryonal nucleus. Prominant secondary aberrations of secondary lens fibers include V-shaped clefts between the embryonal nucleus and lens epithelium and lens vesicle remnants surrounding the nucleus.

The proportion of fetuses with the lens abnormality in one or both lenses was significantly higher in all groups than in the control group (Table 5).

Results and Discussion

FM-3422 was maternally toxic to the high and mid dose groups (75 and 37.5 mg/kg/day) in reducing their group mean body weight gain during the dosing interval. All groups had lower mean weight gain than the controls at all weighings during the dosing interval of days 6 through 15 of gestation (Table 1). In the case of the high dose group at gestation days 9, 12 and 15 and in the case of the mid dose group at gestation days 9 and 15, the group mean weight gains were significantly lower than the mean weight gains of the control group (0 mg/kg/day). The lower mean weight gains of the high and mid dose groups during the dosing interval were responsible for their significantly lower mean body weights between the end of dosing and the termination of the study (Appendix V). The mean body weights and mean weight gains of the low dose group (25 mg/kg/day) were not significantly different from the control.

Abnormal clinical signs were observed and deaths occurred only in the high dose group. Three rats in the high dose group died. One rat died without clinical signs. Two of the rats that died plus one surviving rat had abnormal compound-related clinical signs which included some of the following: thin, lethargic, ataxic, blood in stool, urinary incontinance and bloody nares. The onset of abnormal clinical signs was on day 11 but the signs disappeared in the surviving rat by day 19 of gestation. The remaining 18 high dose rats and the mid and low dose rats did not have abnormal compound-related clinical signs.

The compound was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. The mean number of male, female, total and dead fetuses, the mean number of resorption sites, implantation sites and corpora lutea of the three FM-3422 dose groups were not significantly different from the control (Table 2, Appendix VI).

FM-3422 was not fetal toxic. However, the combination of reduced maternal body weight gain (Table 1) plus higher numbers of fetuses in the treatment groups than the control group (Table 2 Appendix VI) resulted in mean fetus weights of all FM-3422 groups which were significantly lower than the control mean fetus weight. The reduced mean fetus weights were not associated with an increase in runting or other gross fetus findings (Table 3).

FM-3422 administration resulted in malformations in fetal sternebrae. The changes, although normally considered skeleton aberrations, were interpreted as compound-related malformations because of their severity. The severity and often the incidence of sternebrae malformations were greater in the three treatment groups than the control group. These malformations included the following: sternebrae asymmetrical, sternebrae bipartite, sternebrae scrambled, sternebrae enlarged, sternebrae missing and sternebrae misshapen (Table 4). All three FM-3422 dose groups had significantly higher proportions of fetuses with sternebrae asymmetrical than the control group. In addition, the high dose group had a

Introduction

This teratology study [a] in rats was conducted to evaluate the embryotoxic and teratogenic effects of orally administered FM-3422. The study was sponsored by 3M Commercial Chemical Division, St. Paul, Minnesota and was conducted by the Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota. Two sets of compound administration groups were dosed between August 19 and September 4, 1980. The protocol and list of the principal participants and supervisory personnel can be found in Appendices I and II respectively.

All portions of this study were conducted according to the Good Laboratory Practice (GLP) regulations and the Safety Evaluation Laboratory Standard Operating Procedures (see Appendix III for Quality Assurance Unit statment). The storage location for specimens, raw data and a copy of the final report is maintained in the Safety Evaluation Laboratory's record archives.

Methods

Time mated Sprague Dawley derived rats were obtained from Charles River Breeding Laboratory and assigned cages according to a computer-generated random numbers table. The rats were then divided into four groups of 22 animals weighing 140 to 240 grams. The rats were housed individually in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. Food[b] and water were available ad libitum. The lights were on a 12 hour light/dark cycle.

The animals were observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights were recorded on days 3, 6, 9, 12, 15 and 20 of gestation and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight. The four groups were dosed with FM-3422 (Lot 784) suspended daily in corn oil at 0, 75, 37.5 or 25 mg/kg/day. FM-3422 was administered daily by oral intubation with a syringe equipped with a ball-tipped intubation needle to the rats on days 6 through 15 gestation (day 0 indicated by sperm-positive vaginal smear). FM-3422 analytical characterization (see Appendix IV) was provided by 3M Commercial Chemical Division, St. Paul, Minnesota.

All surviving animals were sacrificed on day 20 by cervical dislocation and the ovaries and uterus, including its contents, were examined immediately to determine the following: number of corpora lutea, number of viable fetuses, number of resorption sites, pup weights and sex, and any gross fetal abnormalities. Approximately one-third of the fetuses were fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine visceral abnormalities. The remaining fetuses were preserved in alcohol for clearing and staining of the skeleton with alizarin red to detect skeletal abnormalities. Selected free-hand sections were processed for histological evaluation.

[a] Riker Experiment No. 0680TR0010
[b] Purina Laboratory Chow, Ralston Purina Company, St. Louis, MO

No lens abnormalities occurred in the control group. A no-effect dose level for the teratogenic abnormality was not established in this study.

Further Discussion on Lens Embryology

Lens structural and functional requirements are met during embryonic development by the differentiation of highly specialized populations of cells from undifferentiated procursers and by the coordinated morphogenesis of the resulting tissues. Both processes are controlled to a remarkable extent by interactions which occur among emerging tissues. Each tissue of the eye is brought to its final state of differentiation, its cell population, size and its definitive geometry, not only by intrinsic processes, but also by extrinsic influences exerted by neighboring tissues[1].

The embryonal origin of the lens is undifferentiated ectoderm. The tip of the optic vesicle, presumably the neural retina, plays the final role in inducing lens from overlying ectoderm and in aligning the lens precisely with the rest of the eye. Additional action of tissues derived from endoderm (foregut) and mesoderm (heart) on the same target tissue decreases the probability that lens formation would be aborted by accidents during the early phases of induction. While the nature of the inductive influence remains unknown, there are indications that substances may be transferred from the presumptive neural retina to the overlying ectoderm during induction. A prolonged period of inductive interaction not only increases the probability that lens induction will occur successfully in the face of interference, but provides a mechanism for continuously adjusting the size, shape, position and orientation of the lens to that of the retina[2].

During the early stages of the inductive process, the ectodermal cells immediately overlying the tip of the optic vesicle elongate perpendicularly to the body surface to form a thickened disc (lens placode). The change in cell shape is accomplished without change in cell volume. The number of cells, however, continues to increase during this period. Toward the end of lens placode formation, acidophilic fibrils appear in the apices of the lens placode cells. At about this time, the placode invaginates to form the lens cup. This invagination is independent of the concomitant invagination of the underlying optic vesicle, and is probably due to forces operating within the lens ectoderm. As the lens cup deepens, its opening (lens pore) becomes progressively constricted until its lips meet and fuse, cutting off the lens vesicle internally and re-establishing continuity in the overlying ectoderm. Closure of the lens pore is attended by, and possibly accomplished by, a local and temporary restricted wave of cell death. Following closure of the lens pore, the cells at the back of the lens vesicle continue to elongate, under the influence of the neural retina, to form the lens fibers. As the fibers grow the cavity of the lens vesicle is obliterated. The lens cells toward the ectoderm, which do not elongate further, form the lens epithelium[2].

The cuboidal lens epithelial cells which face the cornea continue to grow

after the lens vesicle forms. As the cells rotate through the equator region, they take their places on the surface of the growing fiber mass. These cells differentiate into secondary lens fibers at the equator and elongate rapidly toward the poles of the lens where they meet with other fibers in planes of junction called sutures. As secondary fibers grow their nuclei become positioned at about the center of the fibers and form a convex lens bow outward. Since the newer fibers are always deposited superficially, the oldest fibers in the lens come to lie centrally and are referred to collectively as the lens nucleus. With time the lens cell nuclei in this region become pycnotic and finally disappear. The cell fibers, however, are not broken down and removed but remain in place. Thus the size and shape of the lens are controlled by factors which control the number, size and shape of the lens cells[2].

The teratogenic lens effect of FM-3422 probably occurred during the portion of organogenesis between differentiation of lens tissue from ectoderm and the formation of secondary lens fibers surrounding the embryonal lens nucleus. The exact time of the teratogenic insult and the morphogenesis of the abnormality were not determined in the study. The developmental lens abnormality appears to be unique because it has not been described as a compound-related abnormality[3]. A similar-appearing structural lens abnormality has been reported to occur spontaneously in rat fetuses but with a very low incidence of 1.2%[4]. The abnormality resembles the Fraser developmental lens abnormality of a mutant mouse strain which results from degenerative primary lens cells[5].

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Dose Group		Gestation Day 6	9	12	15	20
0 mg/kg/day	MEAN	28	17	26	29	71
	STAN. DEV	5.5	7.5	5.8	4.9	12.1
75 mg/kg/day	MEAN	30	0[a]	6[a]	2[a]	69
	STAN. DEV	14.2	14.6	19.8	17.0	15.1
37.5 mg/kg/day	MEAN	28	6[a]	17	14[a]	69
	STAN. DEV	5.4	10.9	9.8	10.4	15.8
25 mg/kg/day	MEAN	27	11	20	22	72
	STAN. DEV	11.9	15.3	8.9	5.4	11.6

[a] Significantly lower than the control (Dunnett's t test $p < 0.05$)

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Table 2

Oral Teratology Study of FM-3422 in Rats
Mean Litter Data with Fetus Weights and Standard Deviations

Dose Group	No. of Animals	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPORA LUTEA	MEAN WT. FETUS(G)
0 mg/kg/day	18	3.6	5.4	8.9	0.0	0.7	9.6	9.9	4.4
		1.6	1.8	2.6	0.0	1.0	2.5	2.1	0.5
75 mg/kg/day	17	5.1	4.7	9.8	0.1	0.5	10.4	10.5	3.7[a]
		2.1	2.3	2.1	0.2	0.6	1.9	2.2	0.5
37.5 mg/kg/day	20	4.4	5.4	9.7	0.0	0.7	10.4	10.5	4.0[a]
		2.1	2.1	1.9	0.0	0.9	1.6	1.7	0.3
25 mg/kg/day	21	4.3	5.8	10.1	0.0	0.5	10.7	11.2	4.0[a]
		1.6	1.9	1.9	0.0	0.5	2.0	1.9	0.3

[a] Significantly lower than the control (Dunnett's t test $p < 0.05$)

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Table 3

Oral Teratology Study of FM-3422 in Rats
Number of Fetuses with Gross Findings[a]

Finding	0 mg/kg/day	75 mg/kg/day	37.5 mg/kg/day	25 mg/kg/day
Total Fetuses Examined	161	167	195	213
Runted	---	2	---	2
Umbilical hernia	1	---	---	2
Total Normal Fetuses	160	165	195	209
Total Abnormal Fetuses	1	2	0	4

[a] Treatment groups were not significantly different from control (Chi-square $p < 0.05$)

Table 4

Oral Teratology Study of PM-3422 in Rats
Number and Percent of Fetuses with Skeleton Findings

Skeleton Finding	0 mg/kg/day		75 mg/kg/day		37.5 mg/kg/day		25 mg/kg/day	
Fontanelle not closed	27	(24)	26	(22)	25	(18)	28	(19)
Holes in parietal	1	(1)	1	(1)				
Parietal scalloped	1	(1)						
Frontal nonossified	21	(19)	62	(53)[a]	70	(51)[a]	75	(50)[a]
Parietal nonossified	21	(19)	62	(53)[a]	70	(51)[a]	74	(50)[a]
Interparietal nonossified	14	(12)	54	(47)[a]	46	(33)[a]	59	(40)[a]
Occipital nonossified			1	(1)				
Sternebrae nonossified	80	(71)	100	(86)[a]	102	(74)	111	(75)
Sternebrae asymmetrical	10	(9)	42	(36)[a]	34	(25)[a]	36	(24)[a]
Sternebrae bipartite	2	(2)	37	(32)[a]	6	(4)	5	(3)
Sternebrae scrambled			1	(1)	1	(1)		
Sternebrae enlarged			1	(1)				
Sternebrae misshapen					1	(1)		
One sternebrae missing	23	(20)	32	(28)	31	(22)	33	(22)
Two sternebrae missing	2	(2)	16	(14)[a]	9	(7)	16	(11)[a]
Three sternebrae missing			1	(1)				
One body vertebrae missing			1	(1)				
13 ribs	1	(1)	3	(3)	3	(2)	5	(3)
13 ribs spurred	3	(3)	32	(28)[a]	28	(20)[a]	9	(6)
Wavy ribs	5	(4)	8	(7)	4	(3)	2	(1)
Protrusion on ribs	8	(7)	12	(10)	5	(4)	7	(5)
One body of the vertebrae bipartite	29	(26)	15	(13)[b]	21	(15)[b]	30	(20)
Two bodies of the vertebrae bipartite	17	(15)	4	(3)[b]	5	(4)[b]	3	(2)[b]
Three bodies of the vertebrae bipartite					1	(1)	2	(1)
Four bodies of the vertebrae bipartite							1	(1)
Five bodies of the vertebrae bipartite							1	(1)
Total Normal Fetuses	9	(8)	2	(2)	6	(4)	7	(5)
Total Abnormal Fetuses	104	(92)	114	(98)	132	(96)	142	(95)
Total Fetuses Examined	113		116		138		149	

[a] Significantly higher than the control (Chi-square $p < 0.05$)
[b] Significantly lower than the control (Chi-square $p < 0.05$)
( ) = percent of total examined

Table 5

Oral Teratology Study of FM-3422 in Rats
Number and Percent of Fetuses with Internal Findings

Internal Finding	0 mg/kg/day		75 mg/kg/day		37.5 mg/kg/day		25 mg/kg/day	
Fetuses with eye abnormalities	0		35	(69)[a]	29	(51)[a]	27	(42)[a]
Discoloration running through the lens of one eye			7	(13)	2	(4)	1	(2)
Discoloration running through the lens of both eyes							1	(2)
Discoloration running 1/2 to 3/4 through the lens of one eye			16	(31)[a]	13	(23)[a]	10	(16)[a]
Discoloration running 1/2 to 3/4 through the lens of both eyes			5	(10)	1	(2)	5	(8)
Discoloration in back of lens							2	(3)
Bubble on outside of lens and discoloration running through the lens of one eye			1	(2)				
Cleft in the lens and discoloration running through the lens of one eye			5	(10)	7	(12)[a]	4	(6)
Cleft in the lens and discoloration running through the lens of both eyes					1	(2)		
Bubble on outside of lens cleft in the lens of one eye					1	(2)	1	(2)
Cleft in the lens of one eye			1	(2)	5	(9)	3	(5)
Open space in the rear of the lens of one eye							1	(2)
Small eyes			1	(2)				
Cleft palate			7	(14)[a]	3	(5)		
Enlarged atriums							2	(3)
Enlarged renal pelvis area in the kidney	5	(10)	1	(2)				
Blood in the kidney parenchyma			11	(22)[a]	3	(5)	3	(5)
Abdominal cavity full of blood	1	(2)	3	(6)			1	(2)
Total Normal Fetuses	42	(87.5)	8	(16)	25	(44)	32	(50)
Total Abnormal Fetuses	6	(12.5)	43	(84)	32	(56)	32	(50)
Total Fetuses Examined	48		51		57		64	

[a] Significantly different from the control (Chi-square $p < 0.05$)

Appendix I

Oral Teratology Study of FM-3422 in Rats
Protocol

Objective

A teratology study will be used to evaluate the embryotoxic and teratogenic effects of orally administered FM-3422 to pregnant rats during the period of organogenesis. The procedure complies with the general recommendations of the FDA issued in January, 1966 ("Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use"). The study will be conducted according to the 1978 Good Laboratory Practice regulations and Safety Evaluation Laboratory's Standard Operating Procedures.

Sponsor

3M Commercial Chemical Division, St. Paul, Minnesota.

Testing Facility

Safety Evaluation Laboratory, Riker Laboratories, Inc., St. Paul, Minnesota.

Study Director

E. G. Gortner

Start of Dosing

Mid August, 1980.

Test System

Eighty-eight sexually mature, time mated Sprague-Dawley derived female rats from Charles River Breeding Laboratory will be housed in hanging stainless steel cages with wire mesh floors and fronts in a temperature and humidity controlled room. This strain of rats will be used because of historical control data and time mated females are readily avilable. Purina Laboratory Chow and water will be available ad litibum. The lights will be on a 12 hour light/dark cycle.

Test System Identification

Each animal will be ear tagged and that number will be indicated on the outside of the cage.

Randomization

The animals will be assigned cages according to a computer-generated random numbers table.

Appendix I (Concluded)

Control Article

Corn oil.

Test Article

FM-3422.

Analytical Specifications

The test article, composition and purity will be determined by the Sponsor (3M Commercial Chemical group) prior to the start of the study and at the end of dosing.

Dosage Levels and Experiment Design

The test article will be suspended in corn oil daily. The test article suspension and control article will be administered by oral intubation to the rats on days 6 through 15 of gestation according to the following:

Dose Group	Dose Level	Group Size
High	75 mg/kg/day	22 ♀
Mid	37.5 mg/kg/day	22 ♀
Low	25 mg/kg/day	22 ♀
Control	0 mg/kg/day	22 ♀

The oral route of administration will be used because toxicity has been defined by this route in a rangefinder study. No dietary contaminants are known to interfere with the test article.

The animals will be observed daily from day 3 through day 20 of gestation for abnormal clinical signs. Body weights will be recorded on days 3, 6, 9, 12, 15 and 20 or pregnancy and the rats dosed accordingly using a constant dose volume of 5 ml/kg of body weight.

The females will be killed on day 20 and the ovaries, uterus and its contents will be examined to determine: number of corpora lutea, number of fetuses (live and dead), number of resorption sites, number of implantation sites, pup weight and gross abnormalities. Approximately one-third of the pups will be fixed in Bouin's solution for subsequent free-hand sectioning by the Wilson technique to determine any visceral abnormalities using a dissecting microscope. The remaining approximately two-thirds of the pups will be fixed in ethyl alcohol for subsequent skeletal examination after clearing and staining with alizarin red.

Data Analysis and Final Report

The proposed statistical methods to be used for analysis of the data are: Dunnett's t test for dam and pup weights, number of fetuses, number of resorption sites, number of implantation sites and number of corpora lutea; chi-square for percent abnormalities. The proposed date for the final report is 2-3 months after detailed pup examinations have been completed (approximately first quarter, 1981).

Appendix II

Oral Teratology Study of FM-3422 in Rats
List of Principal Participating Personnel

NAME	FUNCTION
Edwin G. Gortner	Study Director
Elden G. Lamprecht	Veterinary Pathologist
Cathy E. Ludemann	Coordinator-Histology
Gary C. Pecore	Supervisor-Animal Care
Loren O. Wiseth	Technician

Appendix III
STATEMENT OF QUALITY ASSURANCE

STUDY NUMBER: 0680TR0010

TITLE: Oral Teratology Study of FM-3422 in Rats

Audits and/or inspections were performed by the Riker Quality Assurance Unit for the above titled study, and reported to the study director and to management as follows:

Date Performed	Date Reported
20 August 1980	21 August 1980
2 September 1980	4 September 1980
20 and 21 January 1981	22 January 1981
22 January 1981	22 Janaury 1981

J.E. Orterstrom
Laboratory Quality Assurance
Riker Laboratories, Inc.

January 22, 1981
Date

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Appendix IV

Test and/or Control Article Characterization

for

FM-3422 LOT 784

1. The identity strength, uniformity, composition, purity or other pertinent characterizations of the test and/or control substances have been determined and documented as of May 8, 1980.

2. The method of synthesis or origin of the test and control substances, including their amount and the method of bioassay (if applicable) is documented.

yes X no ____

3. The stability of the test and/or control substances have been determined or will be determined as of Completion of Tox Testing If Necessary

The above information and documentation are located in the sponsor's records.

D. Rucker 5/21/80
Sponsor Date

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Appendix V

Oral Teratology Study of FM-3422 in Rats
Individual and Mean Body Weights of Rats
With Standard Deviations

Dose Group and Rat No.	Study Day 3	6	9	12	15	20
0 MG/KG/DAY						
N0R 14756	204	230	248	276	304	350
N0R 14757	196	214	242	278	304	371
N0R 14760	213	250	257	286	310	358
N0R 14776	184	209	222	243	278	334
N0R 14777	232	262	274	307	341	426
N0R 14778	186	219	232	264	297	377
N0R 14780	226	255	271	300	325	396
N0R 14796	190	220	232	254	280	341
N0R 15385	197	211	251	271	301	384
N0R 15387	188	216	238	264	292	376
N0R 15388	196	228	254	286	322	406
N0R 15389	193	222	242	269	293	346
N0R 15405	184	209	219	235	260	310
N0R 15406	195	220	240	261	299	371
N0R 15407	238	267	272	287	312	390
N0R 15408	239	258	278	306	331	401
N0R 15409	193	218	240	263	297	379
N0R 15425	154	171	206	232	255	313
MEAN	200	229	245	271	300	371
STAN. DEV	21.8	23.4	20.0	22.1	22.6	30.7
NON PREGNANT ANIMALS						
N0R 14758	212	244	259	273	268	293
N0R 14759	210	223	226	242	249	264
N0R 14779	194	222	227	255	243	250
N0R 15386	192	225	243	244	252	280

Appendix V (Continued)

Oral Teratology Study of FM-3422 in Rats
Individual and Mean Body Weights of Rats
With Standard Deviations

Dose Group and Rat No.	Study Day 3	6	9	12	15	20
75 MG/KG/DAY						
00R 14761	215	247	238	255	252	307
00R 14762	224	252	218	217	243	321
00R 14763	188	211	208	230	246	320
00R 14764	193	220	220	245	250	309
00R 14765	230	260	267	292	303	384
00R 14782	202	232	209	204	210	267
00R 14783	207	245	237	264	262	317
00R 14785	208	246	249	281	282	370
00R 14797	188	214	210	237	225	291
00R 15390	176	209	222	226	186	231
00R 15391	204	238	228	191	168	0[a]
00R 15392	212	225	233	232	225	285
00R 15393	234	252	251	263	265	311
00R 15394	194	222	227	237	240	309
00R 15410	185	211	215	185	182	260
00R 15411	140	221	231	216	237	313
00R 15414	219	240	261	255	259	351
00R 15426	195	216	243	243	276	358
MEAN	201	231	232	237[b]	240[b]	311[b]
STAN. DEV	22.1	16.6	17.6	28.8	35.7	40.2
NON PREGNANT ANIMALS						
00R 14781	208	243	208	165	0	0[a]
00R 14784	195	221	194	177	204	239
00R 15412	224	245	229	179	149	0[a]
00R 15413	223	241	248	240	242	258

[a] Rat died
[b] Significantly lower than the control (Dunnett's t test $p < 0.05$)

Appendix V (Continued)

Oral Teratology Study of FM-3422 in Rats
Individual and Mean Body Weights of Rats
With Standard Deviations

Dose Group and Rat No.	Study Day 3	6	9	12	15	20
37.5 MG/KG/D						
P0R 14766	183	214	218	237	254	301
P0R 14767	209	250	240	269	261	315
P0R 14768	208	234	238	264	287	368
P0R 14769	218	245	249	273	294	362
P0R 14770	212	242	251	286	299	377
P0R 14787	187	215	223	250	267	314
P0R 14788	176	204	209	226	245	309
P0R 14789	197	222	212	234	246	303
P0R 14790	192	221	225	251	278	314
P0R 14798	196	228	210	236	256	303
P0R 15395	182	204	227	240	262	332
P0R 15396	191	212	233	235	243	316
P0R 15397	217	245	266	282	307	382
P0R 15398	231	249	256	269	279	360
P0R 15399	189	217	225	237	245	303
P0R 15415	205	239	246	269	292	374
P0R 15416	210	243	254	270	295	371
P0R 15417	222	244	245	257	262	340
P0R 15418	196	231	252	267	287	355
P0R 15419	240	263	257	246	237	340
P0R 15427	192	216	231	238	245	268
MEAN	203	230	237	254[b]	268[b]	337[b]
STAN. DEV	16.8	16.7	16.9	17.3	22.7	31.3
NON PREGNANT ANIMALS						
P0R 14786	188	206	213	214	222	226

[b] Significantly lower than the control (Dunnett's t test $p < 0.05$)

Appendix V (Concluded)

Oral Teratology Study of FM-3422 in Rats
Individual and Mean Body Weights of Rats
With Standard Deviations[c]

Dose Group and Rat No.	Study Day -3	6	9	12	15	20
25 MG/KG/DAY						
Q0R 14771	232	261	265	282	295	376
Q0R 14772	212	240	247	263	273	347
Q0R 14773	192	223	226	251	270	322
Q0R 14774	182	210	215	236	256	326
Q0R 14775	202	238	241	269	289	344
Q0R 14791	217	251	261	291	315	389
Q0R 14792	201	229	242	270	291	371
Q0R 14793	221	254	251	281	300	375
Q0R 14794	216	248	264	291	311	376
Q0R 14795	193	223	223	250	276	345
Q0R 14799	187	212	207	236	250	340
Q0R 15400	153	131	201	214	242	317
Q0R 15401	191	217	233	245	269	346
Q0R 15402	206	238	255	269	297	394
Q0R 15403	179	212	220	229	247	311
Q0R 15404	192	229	254	274	308	392
Q0R 15420	214	241	250	262	291	367
Q0R 15421	183	207	219	234	255	324
Q0R 15422	185	216	231	260	280	361
Q0R 15423	228	253	262	257	282	365
Q0R 15424	227	257	259	280	302	376
MEAN	201	228	240	259	281	355
STAN. DEV	19.8	28.0	19.9	21.3	21.6	27.1
NON PREGNANT ANIMALS						
Q0R 15428	196	225	231	234	236	271

[c] Means not significantly different from control (Dunnett's t test $p < 0.05$)

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Appendix VI

Oral Teratology Study of FM-3422 in Rats
Individual Litter Data With Mean Fetus Weights

Dose Group and Rat No.	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESORPTION SITES	IMPLANTATION SITES	CORPORA LUTEA	MEAN FETUS WT (G) AVG	M	F
0 mg/kg/day										
0MF 15385	4	7	11	0	0	11	7	3.3	3.3	3.4
0MF 15386	NOT PREGNANT									
0MF 15387	4	8	12	0	0	12	11	3.7	3.8	3.6
0MF 15388	3	8	11	0	1	12	10	4.5	4.8	4.4
0MF 15389	1	3	4	0	0	4	6	4.4	4.5	4.4
0MF 15405	3	3	6	0	4	10	8	4.1	4.5	3.8
0MF 15406	3	6	9	0	2	11	10	4.5	4.4	4.5
0MF 15407	3	6	9	0	0	9	11	4.1	4.2	4.1
0MF 15408	4	5	9	0	0	9	12	4.8	4.7	4.9
0MF 15409	3	7	10	0	0	10	10	4.2	4.3	4.2
0MF 15425	3	4	7	0	0	7	7	4.9	5.0	4.9
0MF 14756	4	7	11	0	0	11	11	4.2	4.5	4.0
0MF 14757	2	6	8	0	1	9	9	4.4	4.4	4.4
0MF 14758	NOT PREGNANT									
0MF 14759	NOT PREGNANT									
0MF 14760	1	2	3	0	1	4	8	4.7	4.5	4.7
0MF 14776	3	7	10	0	0	10	12	4.2	4.3	4.1
0MF 14777	7	6	13	0	1	14	14	4.0	4.0	3.9
0MF 14778	7	4	11	0	0	11	11	5.1	5.2	4.8
0MF 14779	NOT PREGNANT									
0MF 14780	4	4	8	0	1	9	11	5.5	5.7	5.3
0MF 14796	5	4	9	0	1	10	11	3.9	3.8	3.9

Appendix VI (Continued)

Oral Teratology Study of FM-3422 in Rats

Individual Litter Data With Mean Fetus Weights

Dose Group and Rat No.	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESOR PTION SITES	IMPLAN TATION SITES	CORPRA LUTEA	MEAN FETUS AVG	M	F
0 mg/kg/day										
HDR 15390	4	3	7	0	2	9	9	2.8	2.9	2.6
HDR 15391	DEAD									
HDR 15392	6	3	9	0	1	10	9	3.5	3.4	3.5
HDR 15393	2	4	6	0	1	7	6	3.6	3.5	2.6
HDR 15394	4	5	9	0	1	10	9	3.6	3.7	3.4
HDR 15410	5	3	8	0	0	8	8	3.1	2.5	3.0
HDR 15411	4	7	11	0	0	11	12	3.4	3.7	3.3
HDR 15412	DEAD									
HDR 15413	NOT PREGNANT									
HDR 15414	2	11	13	1	0	14	14	4.1	3.9	4.1
HDR 15426	5	7	12	0	0	12	12	4.2	4.4	4.1
HDR 14761	8	2	10	0	0	10	12	3.4	3.4	3.3
HDR 14762	8	4	12	0	0	12	11	3.3	3.3	3.3
HDR 14763	8	2	10	0	1	11	11	3.7	3.6	3.1
HDR 14764	5	4	9	0	0	9	9	3.6	3.5	3.6
HDR 14765	7	4	11	0	1	12	13	4.1	4.1	4.1
HDR 14781	DEAD									
HDR 14782	6	5	11	0	0	11	11	3.3	3.5	3.1
HDR 14783	1	5	6	0	1	7	8	4.7	5.3	4.6
HDR 14784	NOT PREGNANT									
HDR 14785	7	4	11	0	1	12	13	4.4	4.3	4.5
HDR 14797	5	7	12	0	0	12	11	3.8	3.9	3.8

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Appendix VI (Continued)

Oral Teratology Study of FM-3422 in Rats

Individual Litter Data With Mean Fetus Weights

Dose Group and Rat No.	VIABLE FETUSES M	F	TOTAL	DEAD FETUSES	RESOR PTION SITES	IMPLAN TATION SITES	CORPRA LUTEA	MEAN FETUS WT (G) AVG	M	F
37.5 mg/kg/day										
FOR 15395	4	5	9	0	0	9	9	3.7	3.9	3.5
FOR 15396	3	5	8	0	0	8	9	3.6	3.8	3.5
FOR 15397	5	6	11	0	0	11	10	4.3	4.5	4.2
FOR 15398	3	8	11	0	1	12	11	4.1	4.4	3.9
FOR 15399	3	5	8	0	2	10	8	4.0	4.3	3.8
FOR 15415	6	6	12	0	1	13	13	3.9	4.0	3.8
FOR 15416	9	3	12	0	0	12	11	3.8	3.8	3.8
FOR 15417	8	3	11	0	0	11	11	4.2	4.3	4.1
FOR 15418	2	8	10	0	1	11	12	4.7	5.0	4.6
FOR 15419	6	8	14	0	0	14	14	3.9	4.1	3.6
FOR 14766	5	3	8	0	3	11	13	3.7	3.8	3.5
FOR 14767	4	2	6	0	2	8	8	4.0	4.1	3.9
FOR 14768	3	8	11	0	0	11	11	3.8	3.9	3.7
FOR 14769	5	4	9	0	0	9	9	4.0	4.0	3.9
FOR 14770	5	4	9	0	1	10	10	4.1	4.3	3.9
FOR 14786	NOT PREGNANT									
FOR 14787	4	5	9	0	0	9	10	4.1	4.2	4.1
FOR 14788	4	7	11	0	1	12	12	4.4	4.3	4.4
FOR 14789	1	8	9	0	1	10	11	3.6	3.8	3.5
FOR 14790	1	7	8	0	1	9	11	4.4	4.1	4.5
FOR 14798	7	2	9	0	0	9	8	4.3	4.3	4.0

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