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Exhibit
1139
State of Minnesota v. 3M Co.,
Court File No. 27-CV-10-28862

3M_MN01690370

Industrial **BIO-TEST** *Laboratories, Inc.*
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REPORT TO

3M COMPANY

28-DAY ORAL TOXICITY STUDY WITH FC-143 IN ALBINO MICE

IBT NO. 8532-10655

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IBT NO. 8532-10655

I. Introduction

A material identified as FC-143 (T-1742CoC, Lot No. 269) was obtained from 3M Company for the purpose of conducting a 28-day pilot feeding study in albino mice to establish feeding levels for long-term studies in that species. This report presents the results of the experiment.

II. Summary

A 28-day oral toxicity study was conducted in which groups of albino mice were fed dietary concentrations of 0, 30, 100, 300, 1,000, 3,000, 10,000, or 30,000 parts of FC-143 per million parts of diet.

The results obtained during the investigation revealed reduced body weight gains followed by losses in body weight among all test group animals (30, 100, 300 ppm) that were sacrificed after 28 days of testing.

An increase in average food consumption was exhibited by all animals fed FC-143. However, excessive wastage of food from their feeders makes interpretation of this parameter difficult.

All males and females fed 1,000 ppm or more of FC-143 died within the first 9 days of testing. All T-III (300 ppm) mice except 1 male died within 26 days of testing. One animal died in each of the 30 and 100 ppm test groups. No other deaths occurred.

Reactions noted during the investigation included roughed fur and muscular weakness for all animals fed 3,000 ppm or greater after the first 4 days of testing. Animals fed 1,000 ppm (T-IV) of FC-143 exhibited similar reactions and signs of cyanosis after 6 days of testing. All of these reactions were evident in the 300 ppm (T-III) groups after test day 9. Some T-II (100 ppm) animals exhibited slight cyanosis on days 10 and 11 of testing, but appeared normal for the remainder of the study. All 30 ppm (T-I) animals reacted similar to the controls during the 28 days of testing.

Gross pathologic examination of all animals sacrificed after 28 days of testing revealed enlargement and/or discoloration of 1 or more liver lobules. Statistical analyses revealed significant increases in the absolute liver weights from males and females of the remaining 30 ppm (T-I), and 100 ppm (T-II) test groups. Increases were also noted in the liver to body weight ratios for these animals.

Histopathologic examination of all sacrificed mice revealed treatment-related liver findings in the males and females of all test groups examined, 30 ppm (T-I), 100 ppm (T-II), and in two 1,000 ppm (T-IV) animals that died during the study. These findings consisted of diffuse cytoplasmic enlargement (hypertrophy) of hepatocytes throughout the entire liver lobules (panlobular) accompanied by focal to multifocal cytoplasmic lipid vacuoles. There was also degeneration and/or necrosis of hepatocytes and focal bile duct proliferation among animals of all test groups.

The other liver changes observed were those of naturally occurring disease or related to the method of sacrifice.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

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III. Procedure

A total of 80 young (43 day old) Charles River CD albino mice*, 40 of each sex, was randomly divided into 8 groups of 5 male and 5 female animals each. The animals were allowed an 8 day pre-test period to adjust to the caging system. Groups were fed 0 (Control), 30, 100, 300, 1,000, 3,000, 10,000, or 30,000 parts of FC-143 per million parts of diet**.

All animals were individually housed with food and water available ad libitum. Daily observations for behavioral reactions or mortalities were made. Animals were weighed and food consumption calculations were made weekly for a 28-day period.

At the final sacrifice, a complete gross pathologic examination was conducted on all surviving mice. Animals that died during the investigation were also examined grossly. At the time of gross examination, a representative set of organs and other tissues was removed and preserved in neutral buffered formalin for future histopathologic examination. The weight of the liver of each sacrificed mouse was determined and liver to body weight ratios were calculated. Microscopic examination was conducted on the livers from all sacrificed mice.

Also at sacrifice, 5 ml of sodium heparinized blood (when possible) and 10 g of whole liver (pooled) from the Control (0 ppm), T-I (30 ppm), and T-II (100 ppm) groups were collected and quick frozen. The samples were submitted to 3M Company for analyses.

* Charles River Breeding Laboratories, Wilmington, Mass.
** Purina Rat Chow, (dry, pulverized diet), Ralston-Purina Company, St. Louis, Missouri.

IV. Results

A. Body Weights

Mean male and female body weight data collected during the investigation are presented in Table I. All test group animals lost weight. Animals fed 30, 100, or 300 ppm of FC-143 exhibited reductions in body weight gains followed by losses in body weight during the investigation. The body weights were depressed in a dose-related manner.

TABLE I

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Mice

Body Weight Data

Summary of Mean Values

Group and Dietary Level (ppm)	Sex	Body Weight Week: 0	1	2	3	4	4-Week Total Weight Change (g/mouse)
Control	M	33	34	37	35	40	+ 7
(0)	F	23	24	25	24	28	+ 5
T-I	M	33	33	34	32	32	- 1
(30)	F	23	24	25	22	21**	- 2
T-II	M	33	28*	25**	23**	25**	- 8
(100)	F	23	21	18**	16**	17**	- 6
T-III	M	33	23**	23**	21**	20**	-13
(300)	F	23	17**	17**	17*	-	-
T-IV	M	33	21**	-	-	-	-
(1,000)	F	23	14**	-	-	-	-
T-V	M	33	-	-	-	-	-
(3,000)	F	23	-	-	-	-	-
T-VI	M	33	-	-	-	-	-
(10,000)	F	23	-	-	-	-	-
T-VII	M	33	-	-	-	-	-
(30,000)	F	23	-	-	-	-	-

* Statistically significant intergroup difference at the 95 percent ($P < 0.05$) confidence level.

** Statistically significant intergroup difference at the 99 percent ($P < 0.01$) confidence level.

- = All animals died.

B. Food Consumption

Mean weekly food consumption data collected during the investigation are presented in Table II. All surviving test group animals exhibited an increase in the average food consumption when compared to controls. However, in each of the groups fed FC-143, excessive food wastage was observed during the study.

TABLE II

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Mice

Food Consumption Data

Group and Dietary Level (ppm)	Sex	Food Consumption (g/mouse/7 days) Week: 1	2	3	4	Average Food Consumption (g/mouse/7 days)
Control	M	NA	40	110	54	68
(0)	F	NA	42	52	57	50
T-I	M	NA	84	118	89	97
(30)	F	NA	87	57	76	73
T-II	M	NA	56	136	76	89
(100)	F	NA	63	77	77	72
T-III	M	NA	121	143	101	122
(300)	F	NA	133	96	-	-
T-IV	M	NA	-	-	-	-
(1,000)	F	NA	-	-	-	-
T-V	M	-	-	-	-	-
(3,000)	F	-	-	-	-	-
T-VI	M	-	-	-	-	-
(10,000)	F	-	-	-	-	-
T-VII	M	-	-	-	-	-
(30,000)	F	-	-	-	-	-

- = All animals died.
NA = Data not available. Food consumption inadvertently collected as a mean per group for males and females together.

C. Mortality and Reactions

All animals in the T-IV (1,000 ppm), T-V (3,000 ppm), T-VI (10,000 ppm), and T-VII (30,000 ppm) groups died within the first 9 days of testing. All mice, but 1 T-III (300 ppm) animal (male No. 31), died within 26 days of testing. One animal died in each of the 30 and 100 ppm test groups during the 28 day feeding period. No other deaths occurred during the study.

Reactions noted during the study included roughed fur and muscular weakness for all animals fed 3,000 ppm or more after the first 4 days of testing. Animals fed 1,000 ppm (T-IV) of FC-143 exhibited similar reactions and signs of cyanosis after 6 days of testing. All of these reactions were evident in the 300 ppm (T-III) group after 9 days of testing. Some 100 ppm (T-II) animals exhibited slight signs of cyanosis on days 10 and 11, but appeared normal for the remainder of the study. All 30 ppm (T-I) animals appeared similar to those of the controls. No other unusual behavioral reactions were noted.

D. Pathologic Studies

1. Gross Pathologic Findings

Gross pathologic examination of animals sacrificed after 28 days of testing revealed enlargement and/or discoloration of 1 or more lobes of the livers of all test group males and females. No other gross pathologic differences between the test and control animals were noted.

2. Liver Weight and Liver to Body Weight Ratio Data

The results of the statistical analyses conducted on the absolute liver weights and liver to body weight ratios are summarized in Table III. Significant differences between a test group and a control group are designated by asterisks. Statistically significant increases were noted in the absolute liver weights among the males and females of the remaining test groups (30 and 100 ppm). The increased liver to body weight ratios for these animals can be attributed to the reduced body weights after 28 days of feeding.

TABLE III

TEST MATERIAL - FC-143

28-DAY ORAL TOXICITY STUDY - ALBINO MICE

FINAL SACRIFICE

ORGAN WEIGHT AND RATIO DATA

SUMMARY OF MEAN VALUES

ORGAN - LIVER

GROUP	DIETARY LEVEL (PPM)	ORGAN WEIGHT (G)		ORGAN/BODY WEIGHT RATIO (G/100 G)		ORGAN/BRAIN WEIGHT RATIO (G/G)	
		MALES	FEMALES	MALES	FEMALES	MALES	FEMALES
CONTROL	0.0	2.128	1.272	5.2448	4.6066	********	********
T-I	30.0	5.767**	3.838**	17.9530	18.1703*	********	********
T-II	100.0	4.658**	2.930**	18.4746*	17.2457	********	********
T-III	300.0	3.230[a]	********	16.1500[a]	********	********	********

* STATISTICALLY SIGNIFICANT INTERGROUP DIFFERENCES AT THE 95% (P<.05) CONFIDENCE LEVEL.
** STATISTICALLY SIGNIFICANT INTERGROUP DIFFERENCES AT THE 99% (P<.01) CONFIDENCE LEVEL.
**** DATA NOT AVAILABLE

[a] VALUES FOR 1 REMAINING ANIMAL AFTER 28 DAYS.

3. Histopathologic Findings

Histopathologic examination was conducted on sections of livers taken from all mice sacrificed after 28 days of testing and from 2 T-IV (1,000 ppm) animals that died during the investigation. Treatment-related liver findings were noted among the males and females from all test groups examined. These findings are presented in Table IV. The key for the grading system and abbreviations used is shown below:

\+ = minimal in severity
++ = mild in severity
+++ = moderate in severity
++++ = marked in severity
F = focal
M = multifocal
D = diffuse

The pathologist's statement follows on the next page.

IBT No. 8532-10655
3M Company

June 9, 1977

I have completed a histopathological examination of H&E stained sections of liver from control and test (Groups T-I, T-II, T-III) mice of IBT No. 8532-10655. In addition, sections of liver from two animals of test group T-IV that died during the study were also examined.

Treatment-related morphologic changes were present among both male and female animals of all test groups. The lesions consisted of diffuse cytoplasmic enlargement (hypertrophy) of the hepatocytes situated throughout the entire liver lobules (panlobular) accompanied by focal to multifocal cytoplasmic lipid vacuoles of variable size which were random in distribution. There was also degeneration and/or necrosis of hepatocytes and focal bile duct proliferation among animals of all test groups.

The other liver changes observed were lesions of naturally occurring diseases or related to the method of sacrifice. All findings are tabulated in Table IV.

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Reviewed and Approved:

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TABLE IV

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Mice

Individual Histopathologic Liver Changes

Group and Dietary Level (ppm)	Animal Number and Sex	Hepatocellular Hypertrophy			Hepatocellular Degeneration and/or Necrosis			Cytoplasmic Vacuoles - Lipid			Bile Duct Proliferation			Lymphoid Infiltrations Periportal			Cytoplasmic Vacuoles - Hydrophic		
		F	M	D	F	M	D	F	M	D	F	M	D	F	M	D	F	M	D
Control (0)	1-M																		
	2-M																		
	3-M																+		
	4-M																		
	5-M																		
	6-F													+					
	7-F																		
	8-F																		
	9-F																		
	10-F																+		
T-1 (30)	12-M			++-+++	+-++			+-++			+								
	13-M			++-+++	+-++				++										
	14-M			+++	+			+-++			+								
	15-M			++-+++		++		+-++			+								
	16-F			++	+-++									+			+		
	17-F			++-+++	+-++			+-++											
	18-F			++-+++		++		+-++											
	19-F			++-+++		++		+			+								
	20-F			++-+++		++		+-++											

TABLE IV continued

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Mice

Individual Histopathologic Liver Changes

Group and Dietary Level (ppm)	Animal Number and Sex	Hepatocellular Hypertrophy F	M	D	Hepatocellular Degeneration and/or Necrosis F	M	D	Cytoplasmic Vacuoles - Lipid F	M	D	Bile Duct Proliferation F	M	D	Lymphoid Infiltrations Periportal F	M	D	Cytoplasmic Vacuoles - Hydrophic F	M	D
T-II (100)	21-M			+++	++			+-++			+								
	22-M			++-+++	++			++									+		
	23-M			++-+++	++			++			+								
	24-M			+++		+++		++			+-++								
	25-M			++-+++	++	-+++		++	-+++		+								
	26-F			++-+++	++	-+++		++	-+++		+						+		
	27-F			++-+++	++			++											
	28-F			++-+++	++			+-++											
	30-F			++-+++	++														
T-III (300)	31-M			+++	++			++	-+++		+						+		
T-IV (1,000)	45-M*			++-+++	++	-+++		++	-+++										
	50-F*			++-+++	++			++									+-++		

* Animal found dead.