Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

REPORT TO

3M COMPANY

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

P.O. NO. 7089088

SEPTEMBER 29, 1977

IBT NO. 8532-10654

Industrial **BIO-TEST** *Laboratories, Inc.*
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

September 29, 1977

Dr. J. E. Long
Manager, Toxicology Services
3M Company - 3M Center
St. Paul, Minnesota 55101

Dear Dr. Long:

Re: IBT No. 8532-10654 - 28-Day Oral Toxicity Study with FC-143 (T-1742CoC, Lot No. 269) in Albino Rats - P.O. No. 7089088

We are submitting herewith our laboratory report prepared in connection with the above study.

Very truly yours,

A. J. Frisque
President

AJF/fd

REPORT TO

3M COMPANY

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

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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 rats 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 5 male and 5 female Charles River strain albino rats were fed FC-143 at dietary levels of 0, 30, 100, 300, 1,000, 3,000, 10,000 or 30,000 ppm.

All animals fed 10,000 ppm or more died during the first week of testing. No other mortalities occurred during the study. No unusual behavioral reactions were evident.

Body weight gains among animals fed 1,000 ppm or more were significantly reduced in a dose-related manner. Slight reductions were noted among males (not females) fed 300 ppm while a marginal reduction in body weight gain was noted in rats fed 100 ppm. Body weight gains among animals fed 30 ppm compared favorably to those of the controls.

Food consumption among animals fed up to 300 ppm was similar to that of the controls. Reduced food intake was apparent among rats fed either 1,000 or 3,000 ppm.

The liver weights among males fed 30 ppm or more, and among females fed 300 ppm or more were elevated as a result of treatment. The absolute liver weights among males fed 3,000 ppm only appear to be similar to controls as a result of severe body weight reductions. Female liver weights among lower test groups were similar to those of the controls.

Gross pathologic examination revealed white foci in the cortex and medulla in the kidneys of a 10,000 ppm female. Pelvic dilatation was evident in the kidneys of a control male and a 30,000 ppm female. No other findings were noted.

Treatment-related morphologic changes were observed in the livers among all male and female test animals. The primary lesion consisted of focal to multifocal cytoplasmic enlargement (hypertrophy) of hepatocytes among animals fed 300 ppm or less, and multifocal to diffuse enlargement of hepatocytes among animals fed 1,000 ppm or more. The severity and degree of tissue involvement was slightly more pronounced among male test animals. The other changes described in the liver and kidneys were lesions of naturally occurring diseases or related to the method of sacrifice.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

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fd/cl

III. Procedure

A total of 80 young (28 day old) Charles River CD Albino Rats*, 40 of each sex, was randomly divided into 8 groups of 5 male and 5 female animals each. Animals were allowed a 7 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 rats. Animals that died during the investigation were also examined grossly. At the time of gross examination, a complete set of organs and other tissues was removed and preserved in a formalin solution for future histopathologic examination. The weight of the liver of each sacrificed rat was determined and liver to body weight ratios were calculated. Microscopic examination of the livers from all sacrificed rats was conducted.

Also at sacrifice, 5 ml of sodium heparinized blood and 10 g of whole liver (pooled) from the Control (0 ppm), T-IV (1,000 ppm) and T-V (3,000 ppm) groups was collected and quick frozen. The samples were submitted to 3M Company for analysis.

* Charles River Breeding Laboratories, Wilmington, Mass.
** Purina Rat Chow, Ralston-Purina Company, St. Louis, Missouri.

IV. Results

A. Mortality and Reactions

All animals fed either 10,000 or 30,000 ppm died within the first week of testing. No other deaths occurred during the study. No unusual behavioral reactions were observed during the experiment.

B. Body Weights

Body weight data (Table I) indicate that levels of 30 ppm were well tolerated by the rat. A marginal reduction in body weight gain was seen among rats fed 100 ppm. Males (not females) fed 300 ppm showed slightly reduced body weight gains. Body weight gains among animals fed 1,000 ppm or more were significantly reduced in a dose-related manner.

TABLE I

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Rats

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/rat)
Control	M	88	142	200	244	299	211
(0)	F	76	120	163	186	215	139
T-I	M	89	140	200	247	295	206
(30)	F	76	118	159	183	210	134
T-II	M	88	141	196	234	281	193
(100)	F	76	117	154	175	203	127
T-III	M	88	134	183	225	264	176
(300)	F	76	112	163	186	211	135
T-IV	M	88	112**	147**	174**	201**	113
(1,000)	F	76	115	156	173	196	120
T-V	M	88	90**	105**	119**	138**	50
(3,000)	F	76	93**	126**	153**	171**	95
T-VI	M	88	-	-	-	-	-
(10,000)	F	76	-	-	-	-	-
T-VII	M	88	-	-	-	-	-
(30,000)	F	76	-	-	-	-	-

* Statistically significant difference at the 95% confidence level.
** Statistically significant difference at the 99% confidence level.

\- All animals died during Week 1 of testing.

C. Food Consumption

Normal food consumption data was obtained from animals fed up to 300 ppm FC-143 during the 28-day feeding period (Table II). Reduced food intake was evident among rats fed either 1,000 or 3,000 ppm.

TABLE II

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Rats

Food Consumption Data

Group and Dietary Level (ppm)	Sex	Food Consumption (g/rat/7 days) Week: 1[a]	2[b]	3	4	4-Week Average Food Consumption (g/rat/week)
Control	M	132	133	166	178	152
(0)	F	120	121	142	143	132
T-I	M	135	140	171	176	156
(30)	F	114	119	136	135	126
T-II	M	129	138	163	169	150
(100)	F	108	113	133	130	121
T-III	M	117	129	173	185	151
(300)	F	108	123	145	137	128
T-IV	M	85	105[c]	128	142	115
(1,000)	F	103	114	122	124	116
T-V	M	67	74	92	102	84
(3,000)	F	75	91	117	115	100
T-VI	M	-	-	-	-	-
(10,000)	F	-	-	-	-	-
T-VII	M	-	-	-	-	-
(30,000)	F	-	-	-	-	-

- All animals died.
a = food consumption represents an 8-day interval.
b = food consumption represents a 6-day interval.
c = value represents 4 animals.

D. Pathologic Studies

1. Gross Pathologic Findings

Gross pathologic findings observed at time of the necropsy examination for sacrificed animals and those that died consisted of the following:

Group and Dietary Level (ppm)	Animal Number and Sex	Tissue	Observation
Control (0)	4M	Kidneys	Pelvic dilatation - unilateral
T-VI (10,000)	68F*	Kidneys	Numerous white foci in cortex and medulla - bilateral
T-VII (30,000)	78F*	Kidneys	Pelvic dilatation - bilateral

* Died during the study.

No other findings were noted during gross examination.

2. Organ Weights and Organ to Body Weight Ratios

The results of the statistical analyses conducted on the liver weights and liver to body weight ratios are summarized in Table III. Treatment-related increases were noted in the liver weights among males fed 30 ppm or more, and among females fed 300 ppm or more. The absolute liver weights among males fed 3,000 ppm only appear to be similar to controls as a result of severe body weight reduction.

TABLE III

TEST MATERIAL: FC-143

28-DAY ORAL TOXICITY STUDY - ALBINO RATS

FINAL SACRIFICE

ORGAN WEIGHT AND RATIO DATA

SUMMARY OF MEAN VALUES

ORGAN - LIVER

GROUP	DIETARY LEVEL (PPM)	ORGAN WEIGHT (G) MALES	ORGAN WEIGHT (G) FEMALES	ORGAN/BODY WEIGHT RATIO (G/100 G) MALES	ORGAN/BODY WEIGHT RATIO (G/100 G) FEMALES
CONTROL	0.0	12.978	9.288	4.3475	4.3046
T-I	30.0	17.858*	8.892	6.0434	4.2407
T-II	100.0	16.442	8.398	6.3981	4.1333
T-III	300.0	20.824**	10.448	7.9514	4.9793
T-IV	1,000.0	15.790	11.636*	7.8729	5.9507
T-V	3,000.0	12.240	12.488**	8.8772**	7.3080

* STATISTICALLY SIGNIFICANT INTERGROUP DIFFERENCES AT THE 95% (P<.05) CONFIDENCE LEVEL.
** STATISTICALLY SIGNIFICANT INTERGROUP DIFFERENCES AT THE 99% (P<.01) CONFIDENCE LEVEL.

3. Histopathological Examination

The individual histopathologic liver changes are presented in Table IV. The histopathologic renal changes are presented in Table V. The pathologists' statement is presented on the following page.

IBT No. 8532-10654
3M Company

July 7, 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, T-IV, T-V, T-VI, T-VII) rats of IBT No. 8532-10654. In addition, sections of both kidneys from two female test animals (No. 68, Group T-VI, and No. 78, Group T-VII) were also examined since grossly visible lesions were reported at time of necropsy.

Treatment-related morphologic changes in the liver were observed among all male and female test animals. The primary lesion consisted of focal to multifocal cytoplasmic enlargement (hypertrophy) of hepatocytes among animals in test groups T-I through T-III and multifocal to diffuse enlargement of hepatocytes among animals in test groups T-IV through T-VII. The lobular distribution of the hypertrophy was centrilobular to midzonal among those animals where the lesion was focal to multifocal whereas the same lesion was panlobular where the lesion was diffuse in distribution. The hypertrophy of hepatocytes was accompanied by acidophilic degeneration and/or necrosis of scattered liver cells with no lobular distribution. The severity and degree of tissue involvement of the above lesions are slightly more pronounced among male test animals.

The other changes described in the liver and of the kidneys were lesions of naturally occurring diseases or related to the method of sacrifice.

The individual liver findings are summarized by sex, in Table IV and the renal lesions tabulated in Table V.

Reynaldo J. Arceo, M.D.
Staff Pathologist

Reviewed and Approved by:

Donovan E. Gordon, D.V.M., Ph.D.
Diplomate, American College of
Veterinary Pathology

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TABLE IV

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Rats

Individual Histopathologic Liver Changes

Group and Dietary Level (ppm)	Animal Number and Sex	Hepatocellular Hypertrophy			Hepatocellular Degeneration and/or Necrosis			Necrotic Hepatitis	Cytoplasmic Vacuolation		Lymphoid Infiltrations		Bile Duct Proliferation	Extra-medullary Hematopoiesis
		F	M	D	F	M	D	F	Lipid F	Hydrophic F	Periportal F	Sinusoidal F	F	F
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)	11 M		+-++			+-++			+					+
	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 Rats

Individual Histopathologic Liver Changes

Group and Dietary Level (ppm)	Animal Number and Sex	Hepatocellular Hypertrophy			Hepatocellular Degeneration and/or Necrosis			Necrotic Hepatitis	Cytoplasmic Vacuolation		Lymphoid Infiltrations		Bile Duct Proliferation	Extra-medullary Hematopoiesis
									Lipid	Hydrophic	Periportal	Sinusoidal		
		F	M	D	F	M	D	F	F	F	F	F	F	F
T-II (100)	21 M		+-++			++		+						
	22 M		+-++			++				+-++	+	+	+	+
	23 M		+-++			+-++					+	+		+
	24 M		+-++			+-++		+-++				+		
	25 M		+-++			+-++					+	+	+	
	26 F	+				+		+		+				
	27 F	+			+			+						+
	28 F		+		+					+				+
	29 F		+			+								+
	30 F	+			+									+
T-III (300)	31 M		+-++			++								
	32 M		+			++		+						+
	33 M		+			++		+						+-++
	34 M		+-++			+-++								
	35 M		+			++								+
	36 F		+			+-++		+						+
	37 F		+			+					+			+
	38 F		+			+					+			+-++
	39 F	+				+								+
	40 F	+				+-++								+

TABLE IV continued

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Rats

Individual Histopathologic Liver Changes

Group and Dietary Level (ppm)	Animal Number and Sex	Hepatocellular Hepatocellular Hypertrophy F	M	D	Hepatocellular Degeneration and/or Necrosis F	M	D	Necrotic Hepatitis F	Cytoplasmic Vacuolation Lipid F	Hydrophic F	Lymphoid Infiltrations Periportal F	Sinusoidal F	Bile Duct Proliferation F	Extra-medullary Hematopoiesis F
T-IV (1,000)	41 M		+-++		++-+++									
	42 M		+-++		++			+						+
	43 M		+-++		++-+++									
	44 M		+-++		++-+++									
	45 M		+-++		++									+-++
	46 F		+		++									
	47 F	+			++						+			+
	48 F		+		+-++									+-++
	49 F	+-++			+-++									+
	50 F	+			+-++						+			+
T-V (3,000)	51 M		+-++		++-+++				+					
	52 M		+		++-+++									+
	53 M		+-++		+++									+
	54 M		+-++		++-+++									
	55 M		+		++-+++									
	56 F	+-++			++									
	57 F		+-++		++									
	58 F	+-++			++									+
	59 F		+-++		+-++									+-++
	60 F	+-++			+-++									+

TABLE IV continued

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Rats

Individual Histopathologic Liver Changes

Group and Dietary Level (ppm)	Animal Number and Sex	Hepatocellular Hypertrophy			Hepatocellular Degeneration and/or Necrosis			Necrotic Hepatitis	Cytoplasmic Vacuolation		Lymphoid Infiltrations		Bile Duct Proliferation	Extra-medullary Hematopoiesis
		F	M	D	F	M	D	F	Lipid	Hydrophic	Periportal	Sinusoidal	F	F
T-VI (10,000)	61 M*			+	+++					++				
	62 M*			+-++	++									
	63 M*			+-++	++-+++					+-++				
	64 M*			++	++-+++									
	65 M*			+-++	++-+++					+				
	66 F*			+	++-+++					+-++				
	67 F*			+	++						+			
	68 F*			+-++	++									
	69 F*			+-++	+-++					+				
	70 F*			+	++-+++									+
T-VII (30,000)	71 M*			+-++	++-+++			+		++				
	72 M*			+-++	++					+-++	+			
	73 M*			+	++-+++									+
	74 M*			+	+++					++				
	75 M*			+-++	++-+++									
	76 F*			+-++	++-+++					+-++				
	77 F*			+	++-+++									
	78 F*			+	++-+++					+-++				
	79 F*			+-++	++-+++									+
	80 F*			+	++-+++						+			

* Animal found dead.

Grading System and Abbreviations

+ = Minimal in Severity	F = Focal
++ = Mild in Severity	M = Multifocal
+++ = Moderate in Severity	D = Diffuse
++++ = Marked Severity	

TABLE V

TEST MATERIAL: FC-143

28-Day Oral Toxicity Study - Albino Rats

Individual Histopathologic Renal Changes

Group	Animal Number and Sex	Finding	Grade
T-VI	68 F	Pyelonephritis, Acute, Multifocal - Bilateral	2 - 3
T-VII	78 F	Cyst, Cortical - Unilateral	p