Final Report

26-Week Capsule Toxicity Study with Ammonium Perfluorooctanoate (APFO) in Cynomolgus Monkeys

> PREPARED FOR: APME Ad-Hoc APFO Toxicology Working Group

> > COVANCE STUDY NUMBER: 6329-231



3M_MN02343342

ł

1

)

)



i

Sponsors:

APME Ad-Hoc APFO Toxicology Working Group

FINAL REPORT

Study Title:

26-Week Capsule Toxicity Study with Ammonium Perfluorooctanoate (APFO) in Cynomolgus Monkeys

Author:

Peter J. Thomford, PhD

Study Completion Date:

December 18, 2001

Testing Facility:

Covance Laboratories Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704-2595

Laboratory Study Identification:

Covance 6329-231

Sponsor Study Identification:

3M T-6889.3

Page 1 of 463

3M_MN02343343

COMPLIANCE STATEMENT

26-Week Capsule Toxicity Study with Ammonium Perfluorooctanoate (APFO) in Cynomolgus Monkeys

All aspects of this study were in accordance with the Environmental Protection Agency Good Laboratory Practice Standards, 40 CFR 792, except that bile acid and palmitoyl CoA oxidase determinations done by the University of Dundee were not done in compliance with GLPs and will be reported separately by the University of Dundee.

Perer J. Thomford, PhD

Study Director Covance Laboratories Inc.

011. Luder Paul Lieder, PhD

Diplomate, ABT Study Monitor 3M

20 December 2001 Date

QUALITY ASSURANCE STATEMENT

This report, with exception of appendices 6, 7, and 8, has been reviewed by the Quality Assurance Unit of Covance Laboratories Inc., in accordance with the Environmental Protection Agency (EPA) Good Laboratory Practice Standards, 40 CFR 792. The following inspections were conducted and findings reported to the study director and study director management.

Inspection Dates			Date Reported to Study Director and
From	То	Phase	Study Director Management
09/24/98	09/24/98	Protocol Review	09/24/98
10/07/98	10/07/98	Analytical Laboratory Inspection	10/07/98
01/05/99	01/05/99	Body Weight	01/05/99
04/01/99	04/01/99	Protocol Amendment Review	04/01/99
05/03/99	05/03/99	Clinical Laboratory Inspection	05/03/99
06/18/99	06/18/99	Data Review	06/23/99
07/29/99	07/29/99	Protocol Amendment Review	07/29/99
08/11/99	08/11/99	Protocol Amendment Review	08/11/99
09/02/99	10/01/99	Data Review	10/01/99
09/13/99	10/01/99	Report Review	10/01/99
11/15/99	11/15/99	Protocol Amendment Review	11/18/99
01/15/01	01/15/01	Protocol Amendment Review	01/15/01
02/26/01	02/27/01	Report Review	03/01/01
12/04/01	12/04/01	Report Review	12/05/01

NAN

Representative Quality Assurance Unit

١

)

)

 \mathcal{N}

Date

in Cynomolgus Monkeys Ammonium Perfluorooctanoate (APFO) **Test Material** APME Ad-Hoc APFO Toxicology **Sponsors** Working Group Paul Lieder, PhD, DABT Study Monitor 3M **Toxicology Services** Building 220-2E-02, 3M Center St. Paul, Minnesota 55144-1000 612.737.2678 John Butenhoff, PhD, DABT Alternate Study Monitor **3M Toxicology Services** Building 220-2E-02, 3M Center St. Paul, Minnesota 55144-1000 612.733.1962 David Farrar, PhD Sponsor's Representative ICI Chemicals & Polymers Limited Occupational Health The Heath, Runcorn, PO Box 13 Cheshire, WA7 4QF 01928.513953 Covance Laboratories Inc. Study Location 3301 Kinsman Boulevard Madison, Wisconsin 53704-2595 Peter J. Thomford, PhD Study Director Covance Laboratories Inc. PO Box 7545 Madison, Wisconsin 53707-7545 608.241.7207

STUDY IDENTIFICATION

26-Week Capsule Toxicity Study with Ammonium Perfluorooctanoate (APFO)

STUDY IDENTIFICATION (Continued)

26-Week Capsule Toxicity Study with Ammonium Perfluorooctanoate (APFO) in Cynomolgus Monkeys

Study Timetable Study Initiation Date In-Life (Experimental) Start Date In-Life Termination Date Experimental Termination Date

September 23, 1998 September 29, 1998 July 2, 1999 December 18, 2001

KEY PERSONNEL

26-Week Capsule Toxicity Study with Ammonium Perfluorooctanoate (APFO) in Cynomolgus Monkeys

Study Director	Peter J. Thomford, PhD
Study Toxicologist	Dale Aldridge, BS
Study Coordinator	Patricia K. McKee Pesik, BS, LAT
Supervisor, Large Animal Toxicology	Meechelle Bordeaux, LAT
Supervisor, Dose Formulation	Dixie Bushee, BS, LATG
Associate Director, Laboratory Animal Medicine	Donna J. Clemons, DVM, MS Diplomate, ACLAM
Clinical Pathologist	Robert L. Hall, DVM, PhD Diplomate, ACVP (Clinical Pathology)
Supervisor, Clinical Pathology	Ronald Markevitch, BS, MT (ASCP)
Anatomic Pathologist	Johnnie J. Eighmy, DVM, MS Diplomate, ACVP Diplomate, ABT
Supervisor, Anatomic Pathology	Kimberly W. Durland, BS, HT
Supervisor, Anatomic Pathology	Laurie J. Schuller, BA, LAT

,

.

,

ł

CONTENTS

	Page
ABSTRACT	11
PURPOSE	15
REGULATORY COMPLIANCE	15
TEST MATERIAL	
Test Material	15
Reserve (Archive) Samples	15
Disposition	15
TEST ANIMALS AND HUSBANDRY	
Animals	16
Identification	
Justification	
Husbandry	16
Acclimation	17
PROCEDURES	17
Group Designations and Dose Level	17
Dosing Procedures	18
Dose Analyses	19
Observation of Animals	19
Blood Hormone Determination	
Serum APFO Level Determination	
Urine and Feces APFO Level Determination	
Clinical Pathology	
Additional Blood Collection	22
Anatomic Pathology	23
Palmitoyl CoA Oxidase Determinations	23
Cell Proliferation Evaluation	23
Bile Acid Determination	
Receptor Level Determination	24
Liver APFO Determination	24
Statistical Analyses	26
Record Retention	27
RESULTS	27
Observation of Animals	
Blood Hormone Determination	30
Clinical Dathalogy	30
Clinical Pathology Cell Proliferation Evaluation	
Anatomic Pathology	
Anatomic Pathology	

,

CONTENTS (Continued)

Pag	e
DISCUSSION AND CONCLUSIONS	2
SIGNATURES	3
REFERENCES	1
OPHTHALMOLOGY REPORT	5
PATHOLOGY REPORT	5
COMMENTS ON THE DATA43	3
CODES, ABBREVIATIONS, AND UNITS	5 7 2 2 4
TABLES	
1 Summary of Clinical Observations	5
2 Summary of Clinical Observations - Recovery	3
3 Summary of Ophthalmic Observations	•
4 Summary of Ophthalmic Observations - Recovery	
5 Summary of Body Weight Data (kg)	
 6 Summary of Body Weight Data (kg) - Recovery	
 7 Summary of Body Weight Change Data (kg)	
9 Summary of Clinical Hematology Data - Day -11	
10 Summary of Clinical Hematology Data - Day 31	
11 Summary of Clinical Hematology Data - Day 63	
12 Summary of Clinical Hematology Data - Day 9181	1
13 Summary of Clinical Hematology Data - Day 18283	3
14 Summary of Clinical Hematology Data - Day 217 (Recovery)	5
15 Summary of Clinical Hematology Data - Day 245 (Recovery)	
16 Summary of Clinical Hematology Data - Day 275 (Recovery)	
17 Summary of Clinical Chemistry Data - Day -11	
18 Summary of Clinical Chemistry Data - Day 31	
 19 Summary of Clinical Chemistry Data - Day 63	
20 Summary of Clinical Chemistry Data - Day 91100 21 Summary of Clinical Chemistry Data - Day 182103	
22 Summary of Clinical Chemistry Data - Day 217 (Recovery)	

÷

CONTENTS (Continued)

Page

TABLES
23 Summary of Clinical Chemistry Data - Day 245 (Recovery)
24 Summary of Clinical Chemistry Data - Day 275 (Recovery)112
25 Summary of Clinical Urinalysis Data - Day -11115
26 Summary of Clinical Urinalysis Data - Day 31116
27 Summary of Clinical Urinalysis Data - Day 63
28 Summary of Clinical Urinalysis Data - Day 91
29 Summary of Clinical Urinalysis Data - Day 182119
30 Summary of Clinical Urinalysis Data - Day 217 (Recovery)
31 Summary of Clinical Urinalysis Data - Day 245 (Recovery)
32 Summary of Clinical Urinalysis Data - Day 275 (Recovery)
33 Summary of Organ Weight Data - Week 27 Sacrifice
34 Summary of Organ Weight Data - Week 40 Recovery Sacrifice
35 Incidence of Macroscopic Observations - Week 27 Sacrifice
36 Incidence of Macroscopic Observations - Week 40 Recovery Sacrifice151
37 Incidence of Microscopic Observations - Week 27 Sacrifice
38 Incidence of Microscopic Observations - Week 40 Recovery Sacrifice
APPENDIX 1
Protocol Deviations
Protocol
Protocol Amendment No. 1
Protocol Amendment No. 2
Material Safety Data Sheet
Certificate of Analysis
APPENDIX 2
Individual Animal Fate Data
Individual Clinical Observations
Individual Ophthalmic Observations
APPENDIX 3
Individual Body Weight Data (kg)
Individual Body Weight Change Data (kg)
APPENDIX 4
Individual Clinical Hematology Data
Individual Clinical Chemistry Data
Individual Clinical Urinalysis Data
APPENDIX 5
Individual Anatomic Pathology Data

CONTENTS (Continued)

Page

APPENDIX 6	
Quality Assurance Statements	
Summary of Hormone Analyses Data	410
Summary of Testosterone Analyses Data (ng/mL)	
Individual Hormone Analyses Data	
Individual Testosterone Analyses Data (ng/mL)	
APPENDIX 7	
Quality Assurance Documentation	
Hormonal Measurements Report (cholecystokinin analyses data)	
APPENDIX 8	
Cell Proliferation Evaluation	

ABSTRACT

The purpose of this study was to assess the effect of the test material, ammonium perfluorooctanoate (APFO), on critical enzyme levels, hormones, and other selected biochemical parameters when administered daily by capsule to cynomolgus monkeys for at least 26 weeks.

Male cynomolgus monkeys were assigned to four groups (six animals/group in Groups 1, 3, and 4, and four animals in Group 2). Animals in Group 1 received empty gelatin capsules. Animals in Groups 2 and 3 received gelatin capsules containing 3 and 10 mg APFO/kg of weight/day (mg/kg/day), respectively. Animals in Group 4 received gelatin capsules containing 30 mg APFO/kg/day on Days 1 through 11; dose administration was discontinued for Days 12 through 21 due to signs of toxicity. Beginning on Day 22 and continuing throughout the remainder of the study, Group 4 males were administered 20 mg APFO/kg/day with the exception that dosing for three animals was discontinued between Days 43 and 81; hereafter, the high dose will be referred to as 30/20 mg/kg/day. Animals were administered APFO daily for at least 26 weeks; two animals in Groups 1 and 3 were treated for 26 weeks, then treatment was discontinued and the animals were observed for reversibility, persistence, or delayed occurrence of toxic effects for 13 weeks posttreatment.

Food was provided once or twice daily. Water was provided *ad libitum*. The animals were observed twice daily (a.m. and p.m.) for mortality and moribundity. At least once daily, animals were examined for abnormalities and signs of toxicity, and food consumption was assessed qualitatively. Ophthalmic examinations were done before initiation of treatment and during Weeks 27 and 40. Body weight data were collected weekly before initiation of treatment, on the first day of treatment, and weekly thereafter. Blood samples for hormone analyses were collected at selected intervals during treatment and recovery. Blood, urine, and fecal samples were collected during Week 2 and every 2 weeks thereafter during treatment and recovery for APFO concentration analyses. Blood and urine samples were collected for clinical hematology, coagulation, clinical chemistry, and urinalysis tests at selected intervals during treatment and recovery. After 26 weeks of treatment, four animals/group in Groups 1 through 3, and all surviving animals in Group 4 were anesthetized, weighed, exsanguinated, and necropsied. After 26 weeks of treatment and 13 weeks without treatment, two animals/group in Groups 1 and 3 were anesthetized, weighed, exsanguinated, and necropsied. At necropsy, macroscopic observations were recorded, selected organs were weighed, and selected

tissues were collected and preserved. In addition, the right lateral lobe of liver was collected from each animal for palmitoyl CoA oxidase activity analyses. Representative samples of liver, right and left testes, and pancreas were collected from each animal for cell proliferation evaluation using proliferation cell nuclear antigen (PCNA). Bile was collected from each animal for bile acid determination. A sample of liver was collected from each animal for APFO concentration analyses. Microscopic examinations were done on tissues from each animal.

One male given 30/20 mg/kg/day and one male given 3 mg/kg/day were sacrificed in moribund condition on Days 29 and 137, respectively. Test material-related observations noted for the male given 30/20 mg/kg/day included hypoactive behavior, entire body cold to the touch, few or no feces, low or no food consumption, and weight loss. Clinical observations noted for the male given 3 mg/kg/day included limited use and paralysis of the hind limbs, ataxic and hypoactive behavior, few feces, and no food consumption.

During Week 1, males given 30 mg/kg/day had observations of few feces, low food consumption, and lost weight. Based on decreased food consumption and body weight loss, the dose level was lowered to 20 mg/kg/day beginning on Day 22. After the dose level was lowered, only two animals tolerated the dose level for remaining 23 weeks of dose administration; one of these animals continued to have test material-related observations of few feces and low food consumption. Dose administration was discontinued for three males given 30/20 mg/kg/day between Days 43 (Week 7) and 81 (Week 12). Test material-related observations noted for these animals included thin appearance, few or no feces, low or no food consumption, and weight loss (17.5 to 23.1%). These animals appeared to recover from the test material-related effects within 3 weeks after dose administration was discontinued.

There were no effects on estrone, estradiol, estriol, thyroid stimulating hormone, or testosterone that were clearly dose-related or consistent in their effects over time. Thyroid hormones in general were decreased beginning on Day 35 in animals administered 10 or 20 mg APFO/kg and in general exhibited recovery in the last 3 months of dosing or during the recovery phase. No alterations in cholecystokinin concentrations were observed at any of the time points.

Administration of APFO at dose levels of 3 or 10 mg/kg/day had no apparent effects on hematology, coagulation, clinical chemistry, or urinalysis results. Of uncertain relationship to administration of APFO at 30/20 mg/kg/day were mildly increased

triglyceride concentration and mildly to moderately decreased absolute neutrophil count, total protein concentration, and albumin concentration. In addition, two animals given APFO at 30/20 mg/kg/day exhibited moderately to markedly increased serum enzyme activities (i.e., aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase, and creatine kinase) and mildly increased serum bile acid concentration prior to the unscheduled sacrifice of one of the animals and the cessation of treatment for the other animal because of poor health. These findings, although not observed for most of the animals given 30/20 mg/kg/day, may also have been caused by the test material.

During recovery, there was no evidence of persistent or delayed toxic effects on clinical pathology test results.

After up to 26 weeks on study, enhanced cell proliferation was not evident in the pancreas or testes of male monkeys, whereas in the liver the findings were equivocal.

Test material-related and statistically significant increases were seen in mean absolute liver weights and mean liver-to-body weight percentages in animals in all dose groups at the terminal sacrifice. In addition, mean liver-to-brain weight significantly increased in animals in the 10 mg/kg/day group; this was also considered test material-related. However, no test material-related macroscopic or microscopic changes were seen in any organs at the terminal sacrifice, including liver, adrenal, spleen, pancreas, and testis.

At the recovery sacrifice, there were no test material-related effects on terminal body weights or on absolute or relative organ weights, indicating that the liver weight increases seen at the termination of dosing were reversible. There were no macroscopic or microscopic findings attributed to test material administration at the recovery sacrifice.

Two animals were sacrificed in a moribund condition during the course of the study, a male given 30/20 mg/kg/day (Day 29) and a male given 3 mg/kg/day (Day 137). The male given 30/20 mg/kg/day had esophageal and gastric lesions indicative of a dosing injury, and liver lesions presumed to be due to the test material. The cause of the moribund condition of the male given 3 mg/kg/day was unclear.

Based on the results of this study in which ammonium perfluorooctanoate (APFO) was administered orally by capsule to cynomolgus monkeys at doses of 0, 3, 10, or 30/20 mg/kg/day for 26 weeks, the no-observable-adverse-effect level (NOAEL) was

10 mg/kg/day. Effects seen in animals administered 10 mg/kg/day were not evident after 13 weeks of recovery.

PURPOSE

The purpose of this study was to assess the effect of the test material, ammonium perfluorooctanoate, on critical enzyme levels, hormones, and other selected biochemical parameters when administered daily by capsule to cynomolgus monkeys for at least 26 weeks.

REGULATORY COMPLIANCE

All aspects of this study were done in accordance with the Environmental Protection Agency Good Laboratory Practice Standards, 40 CFR 792, except that bile acid and palmitoyl CoA oxidase determinations done by the University of Dundee were not done in compliance with GLPs and will be reported separately by the University of Dundee.

TEST MATERIAL

Test Material

The test material, ammonium perfluorooctanoate (APFO), Lot No. 332 (expiration date: December 15, 2001), is a white powder and is 95.2% pure. It was received at Covance on June 10, and October 22, 1998. The test material was stored at room temperature.

Information on synthesis methods, composition, or other characteristics that define the test material is on file with the Sponsor. The Certificate of Analysis is in Appendix 1.

Reserve (Archive) Samples

A reserve sample (1 g) of the test material was taken before initiation of treatment and stored at room temperature. This sample was transferred to the Sponsor on May 2, 2001.

Disposition

The remaining test material was returned on May 2, 2001.

TEST ANIMALS AND HUSBANDRY

Animals

Young adult to adult cynomolgus monkeys were obtained from Covance Research Products Inc. (Denver, Pennsylvania) on August 25, 1998. The animals were approximately 3 to 7 years old and weighed 3.2 to 4.5 kg at initiation of treatment.

Identification

Each animal was assigned a permanent number upon arrival and identified with a collar tag before initiation of treatment. All data for an animal are recorded under this number.

Justification

APFO is a known hepatic peroxisome proliferator (PP) in the rat. When exposed to PP, nonhuman primates (such as the cynomolgus monkey) respond similarly to humans (i.e., low to no hepatic response) and therefore are an appropriate human surrogate species.

Husbandry

Animal Rooms 253 and 227 were used for this study. Recovery animals were transferred to Animal Room 227 on April 15, 1999 (Day 15 of recovery). Environmental controls for the animal rooms were set to maintain 18 to 29°C, a relative humidity of 30 to 70%, and a 12-hour light/12-hour dark cycle. Variations from these conditions are documented in the data and are considered to have had no effect on the outcome of the study.

The animals were housed individually in suspended, stainless-steel cages.

Certified primate diet (#8726C, Harlan Teklad) was provided once or twice daily. The lot numbers are recorded in the data. The diet is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Results of specified nutrient and contaminant analyses are on file with Covance-Madison. Fruits or additional supplements were provided, but did not require analysis. During the study, animals in the high-dose group were offered Gatorade® as well as other supplements to rehydrate and to stimulate food consumption. The lot numbers of the Gatorade® are recorded in the data.

Water was provided *ad libitum*. Samples of the water are analyzed for specified microorganisms and environmental contaminants. The results are on file with Covance-Madison.

There were no known contaminants in the diet or water at levels that would have interfered with this study.

Acclimation

Twenty-four males were received on August 25, 1998, and acclimated in Animal Room 253 for 35 days before initiation of treatment. In general, animals in this shipment appeared healthy. During acclimation, the animals were examined for abnormalities indicative of health problems. In addition, three tuberculosis tests, a physical examination, and a fecal flotation test for parasites were performed on each animal.

PROCEDURES

This study was conducted in accordance with the Protocol dated September 23, 1998, and Protocol Amendment Nos. 1 and 2. The protocol, protocol amendments, and protocol deviations are in Appendix 1.

Group Designations and Dose Level

Selection of animals for the study was based on data collected during acclimation. Animals were assigned to treatment groups using a computerized blocking procedure designed to achieve body weight balance with respect to treatment group.

	Dose Level	
Group	(mg/kg/day)	No. of Males
1 (Control)	O ^a	
2 (Low)	3	4 ^c
3 (Mid)	10	6 ^b
$4 (High)^d$	30/20	6

a The control group (Group 1) received empty gelatin capsules.

b Two animals in Groups 1 and 3 designated as recovery animals were treated for 26 weeks, then treatment was discontinued, and the animals were observed for reversibility, persistence, or delayed occurrence of toxic effects for 13 weeks posttreatment.

c Animal No. I05723 was replaced with Animal No. I05721. Dosing for Animal No. I05721 began on Day 17 (October 15, 1998).

d Dosing for Group 4 was suspended on Day 12 (October 10, 1998) and reinitiated at 20 mg/kg/day on Day 22 (October 20, 1998).

Dosing Procedures

Gelatin capsules (Torpac, Inc., Fairfield, New Jersey), Size No. 2, Lot No. 122932 were used for dose administration. Expiration dates for the empty gelatin capsules are maintained in the raw data.

The test material was dispensed into capsules at least weekly. The dose levels were based on the test material as supplied. For Groups 2 through 4, the specified amount of test material was weighed and transferred into the gelatin capsules. The top and bottom halves of each capsule were joined, and the capsules were placed into the appropriately labeled container. The prepared capsules were stored at room temperature.

Method of Administration. Gelatin capsules were administered orally to compare with previously conducted toxicology studies using the oral route.

The dose preparations were administered orally in gelatin capsules once daily, 7 days/week, for at least 26 weeks (183 days) except that Animal No. 105721 (Group 2 replacement animal) initiated dose administration on Day 17 and the animals in Group 4 were not dosed on Days 12 through 21; dose administration was also discontinued for Animal Nos. 105711, 105722, and 105703 (Group 4) on Days 43 (Week 7), 66 (Week 10), and 81 (Week 10), respectively (see Protocol Deviations for exceptions). Individual daily doses were calculated based on the most recently recorded body weights, with the exception of body weight collection days when the previous body weight was used.

Dose Analyses

Because the test material was not mixed with a vehicle, dose analyses were not required.

Observation of Animals

Clinical Observations. The animals were observed twice daily (a.m. and p.m.) for mortality and moribundity. Animals were observed at least once daily (a.m.) for signs of poor health or abnormal behavior and food consumption was assessed qualitatively; only abnormal findings were recorded. Animals were observed once weekly; abnormal findings or an indication of normal was recorded (see Protocol Deviations for exceptions).

Ophthalmology. Ophthalmic examinations were done on each animal before initiation of treatment and during Weeks 27 and 40 (recovery). The pupils were dilated with 1% Mydriacyl® and the anterior portion of the eye, optic media, and ocular fundus were examined with an indirect ophthalmoscope.

Body Weights. Individual body weight data were recorded weekly before initiation of treatment, on the first day of treatment, and weekly thereafter. An additional body weight was recorded on Day -1 for the Day 1 dose calculations.

Blood Hormone Determination

Blood was collected from a femoral vein of each animal three times before initiation of treatment (Days -18, -8, and -4) and on Days 35, 66, 94, and 183 of treatment and on Days 220, 248, and 276 during recovery. Animals were not fasted before collections. Approximately 6 mL of blood for plasma samples was collected into tubes with potassium EDTA as the anticoagulant. Blood samples for plasma were maintained chilled until plasma was harvested (see Protocol Deviations for exceptions). Approximately 6 mL of blood for serum samples was collected without anticoagulant and allowed to clot. Blood samples for serum were maintained at room temperature until serum was harvested. Serum was divided into two approximately equal aliquots and stored in a freezer, set to maintain -60 to -80°C, until packed on dry ice and shipped to Ani Lytics Inc., for analyses. The serum samples were analyzed for estradiol (E2), estrone (E1), estriol (E3), thyroid stimulating hormone (TSH), total and free

triiodothyronine (T3 and FT3, respectively), total and free thyroxin (T4 and FT4, respectively). Results of these analyses provided by Ani Lytics Inc. are in Appendix 6.

Samples for plasma were centrifuged within 1 hour after collection. Plasma was harvested and stored in a freezer, set to maintain -60 to -80°C, until packed on dry ice and shipped to DuPont for analyses. The plasma samples were analyzed by DuPont for cholecystokinin. Results of these analyses provided by DuPont are in Appendix 7.

Because the decision to analyze blood for testosterone (TESTOS) was made after the terminal sacrifice, an aliquot of plasma from prestudy and Days 35, 66, 94, and 183 collection intervals was transferred from DuPont to Ani Lytics Inc. for analysis of testosterone. In addition, serum samples collected during recovery (Days 220, 248, and 276) were also analyzed for testosterone. Results of these analyses provided by Ani Lytics Inc. are in Appendix 6.

Serum APFO Level Determination

Approximately 2 mL of whole blood were collected from a femoral vein of each animal during Week 2 (after 7 days of treatment) and every 2 weeks thereafter during treatment and recovery. In addition, blood was collected from Animal No. 105724 (Group 4) that was sacrificed in moribund condition. Animals were not fasted before collections. All samples were collected without anticoagulant, maintained at room temperature, and allowed to clot. Samples were centrifuged within 1 hour after collection, serum was harvested and stored in a freezer, set to maintain -10 to -30° C, until packed on dry ice and shipped to 3M for analyses. The samples were analyzed for APFO. Results of the analyses will be reported separately by 3M.

Urine and Feces APFO Level Determination

Samples of urine (at least 2 mL) and feces (at least 5 grams, see Protocol Deviations for exceptions) were collected from each animal during Week 2 (after 7 days of treatment) and every 2 weeks thereafter during treatment and recovery (concurrent with serum APFO sample collection). Animals were not fasted before collections. Urine (collected on wet ice) and feces were collected overnight. Urine and fecal samples were stored in a freezer, set to maintain -10 to -30°C, until packed on dry ice and shipped to 3M for

analyses. The samples were analyzed for APFO. Results of the analyses will be reported separately by 3M.

Clinical Pathology

Blood and urine samples were collected from each animal before initiation of treatment; before the daily dose on Days 31, 63, 91, and 182; and on Days 217, 245, and 275 during recovery. Animals were fasted overnight, and urine was collected on wet ice overnight (approximately 16 hours) before blood sampling; water was provided *ad libitum*. Blood was collected from a femoral vein. Anticoagulants were sodium citrate for coagulation tests and potassium EDTA for hematology tests. Samples for clinical chemistry were collected without anticoagulant. Blood samples were collected from animals sacrificed at an unscheduled interval. Animals were bled in random order. The following were evaluated.

Hematology

red blood cell (erythrocyte) count	differential blood cell count
hemoglobin	segmented neutrophil count
hematocrit	lymphocyte count
mean corpuscular volume	monocyte count
mean corpuscular hemoglobin	eosinophil count
mean corpuscular hemoglobin	basophil count
concentration	blood cell morphology
platelet count	reticulocyte count
white blood cell (leukocyte) count	

Coagulation

fibrinogen

prothrombin time activated partial thromboplastin time

i

Clinical Chemistry

glucose urea nitrogen creatinine total protein albumin globulin total bilirubin cholesterol triglycerides aspartate aminotransferase alanine aminotransferase alkaline phosphatase gamma glutamyltransferase sorbitol dehydrogenase creatine kinase calcium inorganic phosphorus sodium potassium chloride bile acids amylase lipase pancreatic-specific amylase

Urinalysis

volume (approximately 16 hours) specific gravity pH protein glucose ketones bilirubin blood urobilinogen microscopic examination of sediment appearance

Additional Blood Collection

Whole blood (approximately 19 mL) was collected from the vena cava of each animal at the time of exsanguination (scheduled and unscheduled sacrifices). Approximately equal sized samples of serum [approximately 7 mL (collected without anticoagulant)], whole blood (approximately 5 mL), and plasma (approximately 7 mL) using potassium EDTA as the anticoagulant were transferred into containers and stored in a freezer, set to maintain -60 to -80°C, until packed on dry ice and shipped to 3M for possible future analysis. In addition to the required blood samples, additional whole blood (approximately 40 to 80 mL/animal) was collected from the animals in the control group at the terminal sacrifice using sodium heparin as an anticoagulant. One-half of this sample was transferred into cryotubes and pooled. The remaining half of the sample was centrifuged and the plasma and red blood cells were transferred into cryotubes and pooled. The pooled samples were stored in a freezer, set to maintain -60 to -80°C, until packed on dry ice and shipped to 3M for possible future and pooled. The pooled samples were stored in a freezer, set to maintain -60 to -80°C, until packed on dry ice and shipped to 3M for possible future analysis.

Anatomic Pathology

Necropsy. A necropsy was done on each animal that was sacrificed at an unscheduled interval. After 26 weeks of treatment, four animals/group in Groups 1 through 3 and all surviving animals in Group 4 were fasted overnight, then anesthetized with ketamine and xylazine, weighed, exsanguinated, and necropsied (see Protocol Deviations for exceptions). After 26 weeks of treatment and 13 weeks without treatment, two animals/group in Groups 1 and 3 were fasted overnight, then anesthetized with ketamine and xylazine, weighed, exsanguinated, and necropsied. Animals were necropsied in random order.

The necropsy included a macroscopic examination of the external surface of the body; all orifices; cranial cavity; the brain and spinal cord; the nasal cavity and paranasal sinuses; cervical tissues and organs; and the thoracic, abdominal, and pelvic cavities and viscera.

Organ Weights. At each scheduled and unscheduled sacrifice, the following organs (when present) were weighed; paired organs were weighed separately.

adrenal (2)	liver
brain	pancreas
epididymis (2)	testis (2)
kidney (2)	thyroid (2) with parathyroid

Organ-to-body weight percentages and organ-to-brain weight ratios were calculated.

Palmitoyl CoA Oxidase Determinations

The right lateral lobe of liver was collected from each animal at the scheduled and unscheduled sacrifices. The sample was weighed, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C these samples will be packed on dry ice and shipped to the University of Dundee for palmitoyl CoA oxidase activity analyses. Results of palmitoyl CoA oxidase activity analyses will be reported separately by the University of Dundee.

Cell Proliferation Evaluation

Representative samples of the left lateral lobe of the liver, left and right testes, and pancreas were collected from each animal at the scheduled and unscheduled sacrifices

and preserved in zinc formalin (unscheduled sacrifices and for animals sacrificed during Week 27) or formalin [animals sacrificed during Week 40 (see Protocol Deviations for exceptions)]. After fixation, samples for proliferation cell nuclear antigen (PCNA) evaluation were embedded in paraffin and maintained at ambient temperature (with slides stained with hematoxylin and eosin) until shipped to Pathology Associates, A Charles River Company for PCNA analyses. Results of the evaluation provided by Pathology Associates, A Charles River Company are in Appendix 8.

Bile Acid Determination

All available bile (up to 5 mL) was collected from each animal at the scheduled and unscheduled sacrifices, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C; these samples were packed on dry ice and shipped to the University of Dundee for bile acid determination. Results of the bile acid determination will be reported separately by the University of Dundee.

Receptor Level Determination

Samples (approximately 2 g each) of the liver (left median lobe) and pancreas were collected from each animal at the scheduled and unscheduled sacrifices, flash-frozen in liquid nitrogen, and stored in a freezer, set to maintain -60 to -80°C until packed on dry ice and shipped to DuPont for possible analysis. Results of receptor level determination, if any, will be reported separately.

Liver APFO Determination

)

)

A section of liver (a non-formalin treated liver sample) was collected from each animal at the scheduled sacrifice and unscheduled sacrifices, weighed, flash-frozen in liquid nitrogen, and stored in a freezer, set to maintain -60 to -80°C, until packed on dry ice and shipped to 3M for APFO analyses. Results of the analyses will be reported separately by 3M.

Tissue Preservation. The following tissues (when present) or representative samples were collected and preserved in 10% neutral-buffered formalin, unless otherwise specified.

adrenal (2) aorta brain cecum colon duodenum epididymis (2) esophagus eyes [preserved in Davidson's fixative (2)] femur with bone marrow (articular surface of the distal end) gallbladder heart ileum jejunum kidney (2) lesions liver lung lymph node (mesenteric)

mammary gland pancreas pituitary prostate rectum salivary gland [mandibular (2)] sciatic nerve seminal vesicle (2)skeletal muscle (thigh) skin spinal cord (cervical, thoracic, and lumbar) spleen sternum with bone marrow stomach testis [(2) preserved in Bouin's solution] thymus thyroid (2) with parathyroid trachea urinary bladder

Three samples (approximately 5 g each) of the liver and all remaining pancreas and left and right testes tissue (divided into three approximately equal samples) were collected from each animal at the scheduled and unscheduled sacrifices, weighed, flash-frozen in liquid nitrogen, and stored in a freezer, set to maintain -60 to -80°C, for possible future analysis. In addition, after all other required samples were taken, remaining kidney tissue was collected from the control animals at the terminal sacrifice (Week 27). These tissues were weighed, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C. Testes and kidney tissue samples collected from control animals were packed on dry ice and shipped to 3M for possible future analysis.

Bone marrow smears from the sternum of each animal at the unscheduled and scheduled sacrifices were prepared, stained with Wright's stain, and retained for possible examination.

Histopathology. Tissues (as appropriate) were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically from each animal including the Group 2 male that was replaced, Animal No. 105723 (see Protocol Deviations for exceptions). Pathology findings and histopathology tissue slides from specified animals

in the control, low-, and high-dose groups were transferred to Sierra Biomedical, Inc for a pathology peer review.

Statistical Analyses

Levene's test (Levene, 1960) was done to test for variance homogeneity. In the case of heterogeneity of variance at $p \le 0.05$, transformations were used to stabilize the variance.

One-way analysis of variance [ANOVA (Winer, 1971a)] was used to analyze initial body weights, body weight changes, continuous clinical pathology values, and organ weight data.

ANOVA was done on the homogeneous or transformed data. If the ANOVA was significant, Dunnett's t-test (Dunnett, 1964) was used for control versus treated group comparisons.

One-way analysis of covariance [ANCOVA (Winer, 1971b)] was used to analyze body weights, with initial body weights as the covariate. Although Levene's test for variance homogeneity was done (see above), no transformations were used because covariance adjustment removed extraneous heterogeneity. If the ANCOVA was significant, covariate-adjusted means were used for control versus treated group comparisons.

Groups 2 through 4 were compared with Group 1 (Control). Group comparisons were evaluated at the 5.0%, two-tailed probability level. Only data collected on or after the first day of treatment were analyzed statistically. Data collected before the first day of treatment or during recovery (except for blood hormone analyses data) were not analyzed statistically.

Blood hormone levels, excluding estriol and cholecystokinin, were analyzed by repeated measures analysis of covariance (ANCOVA) procedure with average pretreatment measurements for the parameters as covariates. Treatment effects under ANOVA or ANCOVA procedures were evaluated at p = 0.05 level. All post hoc control-versus-treated-group mean comparisons (including values during recovery) were conducted using Dunnett's many-on-one t procedure. Analyses were carried out with SAS procedure PROC MIXED (SAS, 1996) or BMDP (BMDP, 1992), or both.

Record Retention

All raw data, documentation, records, protocol, and specimens generated as a result of this study will be archived in the storage facilities of Covance-Madison for a period of at least one year. One year after the submission of the final report, the Sponsor will determine the final disposition of the materials. All raw data stored on magnetic media, the protocol, study correspondence, and the original copy of the final report will be retained by Covance-Madison.

Within 1 year after submission of the final report, all of the aforementioned materials from the Sponsor's designees (Ani Lytics Inc., DuPont, 3M E.T. & S, and the University of Dundee) will be sent to the Sponsor (Paul Lieder, PhD, DABT, 3M). Pathology Associates, A Charles River Company (PAI) is responsible for the maintenance of any raw data or specimens produced by PAI.

RESULTS

Observation of Animals

Clinical Observations. Clinical observations are summarized in Tables 1 and 2; individual data are in Appendix 2. Individual animal fate data are also in Appendix 2.

One male (Animal No. I05724) given 30/20 mg/kg/day was sacrificed in moribund condition on Day 29 (Week 5). Test material-related observations noted for Animal No. I05724 included hypoactive behavior, entire body cold to the touch, few or no feces, and low or no food consumption; this animal lost 12.5% (0.5 kg) of its body weight from Week 1 to Week 5. One male given 3 mg/kg/day (Animal No. I05721) was sacrificed in moribund condition on Day 137. Clinical observations noted for Animal No. I05721 on Day 137 (Week 20) included limited use and paralysis of the hind limbs, ataxic and hypoactive behavior, few feces, and no food consumption; this animal lost 9.5% (0.4 kg) of its body weight from Week 19 to Week 20.

During Week 1, all males given 30 mg/kg/day had low food consumption and lost from 3.1 to 7.5% of their body weight; four of the six animals also had observations of few feces. Based on decreased food consumption and body weight loss, the dose level was lowered to 20 mg/kg/day beginning on Day 22. After the dose level was lowered, only two animals (Animal Nos. 105704 and 105713) tolerated the dose level for the remaining 23 weeks of dose administration. After Week 2, test material-related observations noted

for Animal No. 105713 included few feces and low food consumption. After Week 2, there were no clinical observations considered to be test material-related noted for Animal No. 105704.

During the study, dose administration was discontinued for three males given 30/20 mg/kg/day based on test material-related observations. Dose administration for Animal Nos. I05711, I05722, and I05703 was discontinued on Days 43 (Week 7), 66 (Week 10), and 81 (Week 12), respectively. Test material-related observations noted for Animal No. I05711 prior to the suspension of dosing included few or no feces and low or no food consumption; this animal lost 17.5% (0.7 kg) of its body weight from Week 1 to Week 7. Test material-related observations noted for Animal No. I05722 prior to the suspension of dosing included thin appearance, few or no feces, and low or no food consumption; this animal lost 23.1% (0.9 kg) of its body weight from Week 1 to Week 10. Test material-related observations noted for Animal No. I05703 prior to the suspension of dosing included thin appearance, few or no feces, and low or no food consumption; this animal lost 18.7% (0.6 kg) of its body weight from Week 1 to Week 1 to Week 12. These animals appeared to recover from the test material-related effects within 3 weeks after dose administration was discontinued.

During the study, several animals developed physical conditions that required examination by a laboratory animal veterinarian and administration of treatments. On Day 11 (Week 2), Animal No. I05724 (Group 4) had observations of no feces and no food consumption; this animal was treated with Lactated Ringers solution (Abbott Laboratories) on Days 11 through 13. During Weeks 5 and 6, Animal No. I05713 (Group 4) had observations of liquid feces and low food consumption; this animal was treated with erythromycin (Distal Products Co.) on Days 36 through 46. On Day 134 (Week 20), Animal No. I05721 (Group 2) had observations of few feces and low food consumption. Animal No. I05721 was treated with Ensure® (Abbott Laboratories) and Lactated Ringers solution (Abbott Laboratories) on Day 137; however, because the animal had observations of paralysis and limited use of the hind limbs, it was subsequently sacrificed. During Weeks 21 and 26, Animal No. I05719 (Group 3) had liquid feces; this animal was treated with erythromycin (Distal Products Co. or Barre) on Days 143 through 151 and on Days 179 through 183. The condition of these animals improved with treatment except for Animal No. I05721.

Ophthalmology. Ophthalmic observations are summarized in Tables 3 and 4; individual data are in Appendix 2. The Ophthalmology Report contains a discussion of the data.

There were no ophthalmic findings for any animal during the baseline or the Weeks 27 or 40 examinations.

Body Weights. Body weight data are summarized in Tables 5 and 6; individual data are in Appendix 3.

Covariate-adjusted mean body weights were notably lower throughout the study (statistically significant during Weeks 2 through 5 and Week 10) for males given 30/20 mg/kg/day. The lower body weights for the males given 30/20 mg/kg/day were considered test material-related.

All animals maintained body weights during recovery; there were no marked changes in body weight for each individual animal between the treatment and recovery phases. Differences in mean body weights between the mean body weights of the animals given 10 mg/kg/day and those of the controls during recovery can be attributed to biological variation.

Body Weight Changes. Body weight change data are summarized in Tables 7 and 8; individual data are in Appendix 3.

During the first 2 weeks of the study, mean body weight changes were notably lower (significantly lower during Week 2) for males initially given 30 mg/kg/day. After the dose level was lowered to 20 mg/kg/day, mean body weight changes were significantly lower than those of controls during Weeks 7, 9, and 24. Overall mean body weight changes (Weeks 1 through 27) were notably lower for the males given 30/20 mg/kg/day (14.3% of those of the control males).

Food Consumption. Food consumption data are summarized in Tables 1 and 2 (Summary of Clinical Observations); individual data are included in the individual clinical observations in Appendix 2.

There was an increased incidence of low or no food consumption for animals given 30/20 mg/kg/day. The decreased food consumption was considered to be test material-related.

F

Blood Hormone Determination

Summary and individual hormone analyses data provided by Ani Lytics Inc. or DuPont, are in Appendices 6 and 7 (cholecystokinin), respectively.

There were no effects on estrone, estradiol, estriol, thyroid stimulating hormone, or testosterone that were clearly dose-related or consistent in their effects over time. Total triiodothyronine was decreased beginning on Day 35 in animals administered 10 or 30/20 mg APFO/kg/day. While the low number of animals that remained on treatment in the group administered 30/20 mg/kg/day makes interpretation difficult, it appears that the level of triiodothyronine remained depressed through Day 183 in this group. Total thyroxin was decreased beginning on Day 35 in animals administered 10 or 30/20 mg/kg/day. While the low number of animals that remained on treatment in the group administered 30/20 mg/kg/day makes the interpretation difficult, it appears that the effect on thyroxin was most pronounced at Days 35 and 66 in animals administered 10 or 30/20 mg/kg/day, after which the effect began to diminish and there appeared to be recovery by the end of the study. Free triiodothyronine and free thyroxin were decreased beginning on Day 35 in animals administered 10 or 30/20 mg/kg/day. While the low number of animals that remained on treatment in the group administered 30/20 mg/kg/day makes the interpretation difficult, it appears that the level of trijodothyronine remained depressed through Day 183 in animals administered 10 or 30/20 mg/kg/day and that recovery occurred in animals administered 10 mg/kg during the recovery phase.

No alterations in cholecystokinin concentrations were observed at any of the time points.

Clinical Pathology

Hematology, coagulation, clinical chemistry, and urinalysis data are summarized in Tables 9 through 32; individual data are in Appendix 4. The Pathology Report contains a discussion of the data.

Administration of APFO at dose levels of 3 or 10 mg/kg/day had no apparent effects on hematology, coagulation, clinical chemistry, or urinalysis results. Of uncertain relationship to administration of APFO at 30/20 mg/kg/day were mildly increased triglyceride concentration and mildly to moderately decreased absolute neutrophil count, total protein concentration, and albumin concentration. In addition, two animals given APFO at 30/20 mg/kg/day exhibited moderately to markedly increased serum enzyme

activities (i.e., aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase, and creatine kinase) and mildly increased serum bile acid concentration prior to the unscheduled sacrifice of one of the animals and the cessation of treatment for the other animal because of poor health. These findings, although not observed for most of the animals given 30/20 mg/kg/day, may also have been caused by the test material.

During recovery, there was no evidence of persistent or delayed toxic effects on clinical pathology test results.

Cell Proliferation Evaluation

Results of cell proliferation evaluation provided by Pathology Associates, A Charles River Company are in Appendix 8.

After up to 26 weeks on study, enhanced cell proliferation was not evident in the pancreas or testes of male monkeys, whereas in the liver the findings were equivocal.

Anatomic Pathology

Terminal body weight and organ weight data are summarized in Tables 33 and 34; incidences of macroscopic and microscopic observations are summarized in Tables 35 through 38. Individual data are in Appendix 5. The Pathology Report contains a discussion of the data.

Test material-related and statistically significant increases were seen in mean absolute liver weights and mean liver-to-body weight percentages in animals in all dose groups at the terminal sacrifice. In addition, mean liver-to-brain weight significantly increased in animals in the 10 mg/kg/day group; this was also considered test material-related. However, no test material-related macroscopic or microscopic changes were seen in any organs at the terminal sacrifice, including liver, adrenal, spleen, pancreas, and testis.

At the recovery sacrifice, there were no test material-related effects on terminal body weights or on absolute or relative organ weights, indicating that the liver weight increases seen at the termination of dosing were reversible. There were no macroscopic or microscopic findings attributed to test material administration at the recovery sacrifice. Two animals were sacrificed in a moribund condition during the course of the study, a male given 30/20 mg/kg/day (Day 29) and a male given 3 mg/kg/day (Day 137). The male given 30/20 mg/kg/day had esophageal and gastric lesions indicative of a dosing injury and liver lesions presumed to be due to the test material. The cause of the moribund condition of the male given 3 mg/kg/day was unclear.

DISCUSSION AND CONCLUSIONS

Based on the results of this study in which ammonium perfluorooctanoate (APFO) was administered orally by capsule to cynomolgus monkeys at doses of 0, 3, 10, or 30/20 mg/kg/day for 26 weeks, the no-observable-adverse-effect level (NOAEL) was 10 mg/kg/day. Effects seen in animals administered 10 mg/kg/day were not evident after 13 weeks of recovery.

b

SIGNATURES

VINC This

Patricia K. McKee Pesik, BS, LAT Study Coordinator Covance Laboratories Inc.

Peter J. Thornford, PhD Study Director Covance Laboratories Inc.

÷

18 Dec 2001 Date

Dec. 2001 Date

REFERENCES

BMDP, Biomedical Data Processing, BMDP Inc., Los Angeles, California, 1992.

Dunnett, C. W., "New Tables for Multiple Comparisons with a Control," <u>Biometrics</u>, 20:482-491 (1964).

Levene, H., "Robust Tests for Equality of Variances," <u>Contributions to Probability and</u> <u>Statistics</u>, (eds.) I. Olkin et al., Ch. 25, pp. 278-292, Stanford University Press: Stanford, California (1960).

SAS (Statistical Analysis System), SAS Institute, Release 6.12, Cary, North Carolina, 1996.

Winer, B. J., "Design and Analysis of Single-Factor Experiments," <u>Statistical Principles</u> <u>in Experimental Design</u>, Second Ed., Ch. 3, pp. 149-260, McGraw-Hill: New York, New York (1971a).

Winer, B. J., "Analysis of Covariance," <u>Statistical Principles in Experimental Design</u>, Second Ed., Ch. 10, pp. 752-812, McGraw-Hill: New York, New York (1971b).

OPHTHALMOLOGY REPORT

Ophthalmic examinations were done on each animal before initiation of treatment and during Weeks 27 and 40 (recovery). The pupils were dilated with 1% Mydriacyl®, and the anterior portion of the eye, optic media, and ocular fundus were examined with an indirect ophthalmoscope.

There were no ophthalmic findings for any animal during the baseline or the Weeks 27 or 40 examinations.

Donna J. Clemons, DVM, MS Diplomate, ACLAM

I.

Date

PATHOLOGY REPORT

SUMMARY

The purpose of the study was to assess the effect of the test material, ammonium perfluorooctanoate (APFO), on critical enzyme levels, hormones, and other selected biochemical parameters when administered daily by capsule to cynomolgus monkeys for at least 26 weeks. The test material was initially administered at dose levels of 3, 10, and 30 mg/kg/day. Administration of the highest dose was stopped on Day 12 because of signs of toxicity and then resumed on Day 22 at a lower dose level, 20 mg/kg/day.

Administration of APFO at dose levels of 3 or 10 mg/kg/day had no apparent effects on hematology, coagulation, clinical chemistry, or urinalysis results. Of uncertain relationship to administration of APFO at 30/20 mg/kg/day were mildly increased triglyceride concentration and mildly to moderately decreased absolute neutrophil count, total protein concentration, and albumin concentration. In addition, two animals given APFO at 30/20 mg/kg/day exhibited moderately to markedly increased serum enzyme activities (i.e., aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase, and creatine kinase) and mildly increased serum bile acid concentration prior to the unscheduled sacrifice of one of the animals and the cessation of treatment for the other animal because of poor health. These findings, although not observed for most of the animals given 30/20 mg/kg/day, may also have been caused by the test material.

During recovery, there was no evidence of persistent or delayed toxic effects on clinical pathology test results.

Test material-related and statistically significant increases were seen in mean absolute liver weights and mean liver-to-body weight percentages in animals in all dose groups at the terminal sacrifice. In addition, mean liver-to-brain weight significantly increased in animals in the 10 mg/kg/day group; this was also considered test material-related. However, no test material-related macroscopic or microscopic changes were seen in any organs at the terminal sacrifice, including liver, adrenal, spleen, pancreas, and testis.

At the recovery sacrifice, there were no test material-related effects on terminal body weights or on absolute or relative organ weights, indicating that the liver weight increases

seen at the termination of dosing were reversible. There were no macroscopic or microscopic findings attributed to test material administration at the recovery sacrifice.

Two animals were sacrificed in a moribund condition during the course of the study, a male given 30/20 mg/kg/day (Day 29) and a male given 3 mg/kg/day (Day 137). The male given 30/20 mg/kg/day had esophageal and gastric lesions indicative of a dosing injury, and liver lesions presumed to be due to the test material. The reason for the moribund condition of the male given 3 mg/kg/day was unclear.

METHODS

Four groups of male cynomolgus monkeys were administered the test material daily by capsule at a dose level of 0 (control group; received empty capsules), 3, 10, or 30 mg/kg of body weight/day (mg/kg/day). Treatment of the animals given the highest dose level was stopped on Day 12 because of signs of toxicity. The highest dose level was then reduced to 20 mg/kg/day, and treatment of these animals was resumed on Day 22. One animal given 30/20 mg/kg/day was sacrificed on Day 29 because of poor health, and dosing was permanently stopped for three additional animals given 30/20 mg/kg/day, one on each of Days 43, 66, and 81. At study initiation, there were six animals in the control group and the groups given 10 or 30 mg/kg/day; two animals in each of these groups were designated as recovery animals to be observed for approximately 13 weeks posttreatment. Because only two animals were given 30/20 mg/kg/day for the duration of the treatment period (approximately 26 weeks), there were no high-dose recovery animals. There were four animals in the group given 3 mg/kg/day; one of these animals in the group given 3 mg/kg/day; one of these animals. There were four animals in the group given 3 mg/kg/day; one of these animals was sacrificed on Day 137 because of poor health.

Blood and urine were collected for hematology, coagulation, clinical chemistry, and urinalysis tests once before initiation of treatment (Day -11), on Days 31, 63, 91, and 182, and on Days 217, 245, and 275 (recovery animals). Blood for hematology, coagulation, and clinical chemistry tests was also collected from animals prior to unscheduled sacrifices. The terminal and recovery sacrifices occurred on Days 184 and 277, respectively. All animals were necropsied; macroscopic observations were recorded, organ weights were obtained, and tissues were placed in fixative as specified by the protocol. The right lateral lobe of the liver was collected and frozen for analysis of palmitoyl CoA oxidase activity. Samples of pancreas, left and right testes, and the left lateral lobe of the liver were collected and preserved for cell proliferation evaluation

using proliferation cell nuclear antigen. Samples of bile were collected and frozen for bile acid determination. Samples of liver and pancreas were collected and frozen for receptor level determinations. A sample of liver was collected and frozen for APFO determination. Additional samples of the liver and all remaining pancreas and left and right testes tissue were collected and frozen for possible future analysis. Microscopic examinations were done on collected tissues from all animals, including the replaced animal.

Statistically significant differences cited in the Results and Discussion Section are based on comparisons between the control and treated groups.

RESULTS AND DISCUSSION

Mortality

One animal given 30/20 mg/kg/day (Animal No. 105724) was sacrificed on Day 29 because of poor health, and one animal given 3 mg/kg/day (Animal No. 105721) was sacrificed on Day 137 because of poor health. All other animals survived to the respective scheduled sacrifice.

Animal No. 105724, the male given 30/20 mg/kg/day that was sacrificed in a moribund condition on Day 29, had multiple significant microscopic findings. Edema and inflammation of the esophagus and erosions and ulcerations in both the esophagus and stomach suggested that a dosing injury was the immediate cause of the animal's death. However, lesions in the liver, including centrilobular and midzonal hepatocellular degeneration and necrosis, diffuse hepatocellular vacuolation, and hepatocyte basophilia in centrilobular areas (liver regeneration) probably contributed to the animal's moribund condition and were likely to be test material-related. Other important findings included involution of the thymus, a relatively common finding in stressed animals, and degeneration and necrosis in the heart, which were probably agonal changes.

The cause of death for Animal No. 105721, the male given 3 mg/kg/day that was sacrificed in a moribund condition on Day 137, was not apparent. The clinical history suggested that the blood supply to the animal's hind limbs was severely compromised, as the rear limbs were noticeably cold at the time of the final medical examination, and ketamine injected into the thigh muscles apparently failed to reach the systemic circulation (sedation did not occur). However, the macroscopic and microscopic findings

for this animal were minimal and incidental (i.e., evidence for spinal cord injury or impaired blood circulation was not uncovered in the post-life evaluations). Therefore, the role of test material-related toxicity in the animal's declining condition was unclear.

Clinical Pathology

Day -11. Results of clinical pathology tests indicated no obvious group or individual health abnormalities. Animal No. I05721 (Group 2) had a notably high hematocrit (49.7%) and albumin concentration (5.6 g/dL) that may have been an indication of mild dehydration. It also had the lowest absolute neutrophil count of all the animals (1,600/ μ L). Whether these findings were directly or indirectly related to the animal's illness requiring early sacrifice on Day 137 could not be determined.

Days 31, 63, 91, and 182. There were relatively few statistically significant or otherwise notable differences for clinical pathology test results between the control and treated animals, especially those animals given 3 or 10 mg/kg/day. None of the differences were consistent over time. Comparisons with the animals given 30/20 mg/kg/day were compromised by the unscheduled sacrifice of one animal in this group on Day 29 and the cessation of treatment for three others by Day 80. For the clinical pathology testing intervals on Days 91 and 182, there were only two animals in this group still receiving treatment.

Of uncertain relationship to administration of the test material were mildly increased triglyceride concentration and mildly to moderately decreased absolute neutrophil count, total protein concentration, and albumin concentration for animals given 30/20 mg/kg/day. The difference for triglyceride concentration was statistically significant on Days 31 and 91. The other differences were not statistically significant but were relatively consistent over time. Prior to stopping their treatment, absolute neutrophil count and albumin concentration were mildly decreased for each of the three animals given 30/20 mg/kg/day that had their treatment stopped prematurely because of poor health. All of these findings are generally nonspecific and can be associated with poor health for a variety of reasons. Specific mechanisms related to direct actions of the test material were not apparent.

Animal No. 105722, the animal in the high-dose group whose treatment was stopped on Day 66, had moderately high serum activities for aspartate aminotransferase, alanine aminotransferase, and creatine kinase and moderately high serum bile acid concentration

on Day 63. The relationship of these findings to administration of the test material is not known.

Statistically significant differences for other test results were considered incidental and unrelated to administration of the test material. These differences were inconsistent over time, and in some cases, were similar to differences that existed before the initiation of treatment.

Days 217, 245, and 275 (Recovery animals). There was no evidence of persistent or delayed toxic effects on clinical pathology test results.

Unscheduled Sacrifice Animals. Animal No. 105724, an animal in the high-dose group, was sacrificed on Day 29. Its most notable clinical pathology findings were a mild neutrophilia (13,700 neutrophils/ μ L); mild hypoglycemia (glucose = 53 mg/dL); mild azotemia (urea nitrogen = 29 mg/dL); moderate to marked hypoproteinemia (total protein = 5.6 g/dL; albumin = 2.9 g/dL; globulin = 2.7 g/dL); moderate hypocalcemia (calcium = 8.0 mg/dL; likely due to low albumin concentration); marked hypocholesterolemia (cholesterol = 14 mg/dL); marked serum enzyme activities (e.g., aspartate aminotransferase = 1,974 IU/L; alanine aminotransferase = 1,463 IU/L; sorbitol dehydrogenase = 59 IU/L; and creatine kinase = 68,850 IU/L); mild hyperbilirubinemia (total bilirubin = 1.8 mg/dL); mildly increased serum bile acid concentration (49 μ mol/L); and moderate to marked hyponatremia (sodium = 133 mmol/L) and hypochloridemia (89 mmol/L). Although many of these findings are nonspecific and are commonly observed in animals that are very ill, the serum enzyme activities were indicative of substantial liver and muscle injury, and the hypocholesterolemia was unusually severe.

Animal No. 105721, an animal in the low-dose group, was sacrificed on Day 137. Its most notable clinical pathology findings were marked hyperfibrinogenemia (fibrinogen = 702 mg/dL); moderate lymphopenia (1,700 lymphocytes/ μ L); moderate hypoalbuminemia (albumin = 3.3 g/dL); and mild hypocholesterolemia (94 mg/dL). These findings were also nonspecific, and with the exception of low albumin concentration, were not typical of the findings observed in the animals in the high-dose group that had to be withdrawn from treatment. Although the findings for this animal in the low-dose group did not indicate a specific cause for its poor health, they were not considered to be directly related to administration of the test material.

Anatomic Pathology/Terminal Sacrifice (Week 27)

Terminal Body Weights and Organ Weights. Mean absolute liver weights and mean liver-to-body weight percentages were statistically significantly increased in animals that were dosed until Week 27 in the 3, 10, and 30/20 mg/kg/day dose groups. In addition, mean liver-to-brain weight ratio was statistically significantly increased in animals in the 10 mg/kg/day group only. Although no correlative macroscopic or microscopic changes were seen in livers in any of the animals from the terminal sacrifice, the increased liver weights in all dose groups may indicate a test material effect, given the nature of the test material and the liver lesions seen in the male in the high-dose group sacrificed on Day 29.

Absolute left kidney weight was statistically significantly increased in animals in the 30/20 mg/kg/day group, but this was considered an incidental finding because there were no test material-related macroscopic or microscopic findings in the kidney. There were no other statistically significant or toxicologically significant organ weight variations in treated animals.

Macroscopic Findings. There were no test material-related macroscopic findings. All macroscopic findings were of low incidence, were randomly distributed among treated and control animals, and were considered to be spontaneous or incidental changes that were of no toxicological significance.

Microscopic Findings. There were no test material-related microscopic findings in any of the tissues that were examined, including liver, adrenal, spleen, pancreas, and testis. All microscopic findings were considered to be spontaneous or incidental changes and typical of findings seen in monkeys on toxicity studies.

Anatomic Pathology/Recovery Sacrifice (Week 40)

Terminal Body Weights and Organ Weights. There were no test material-related effects on terminal body weights or on absolute or relative organ weights. Absolute organ weights and organ-to-brain weight ratios were consistently higher in the control males, but these elevations were attributed to higher terminal body weights in the control animals (one was even noted as being obese at necropsy). Mean organ-to-body weight percentages, including mean liver-to-body weight, showed only slight variations that were considered unremarkable. These findings indicated that the liver weight increases were reversible.

Macroscopic Findings. There were no test material-related macroscopic findings. In fact, no macroscopic lesions of any kind were seen in one control animal or in either of the 10 mg/kg/day animals. The remaining control male was considered to be obese and had liver adhesions, an incidental change.

Microscopic Findings. There were no test material-related microscopic findings at the recovery sacrifice. All microscopic findings were incidental, occurred randomly in control animals and in animals given 10 mg/kg/day, and were typical of findings seen in cynomolgus monkeys on toxicity studies.

l Hall

Robert L. Hall, DVM, PhD Diplomate, ACVP (Clinical Pathology)

Johnnie J. Eighny, DVM, MS Diplomate, ADVP Diplomate, ABT

18 December 2001 Date

18 December 2001 Date

42

COMMENTS ON THE DATA

Various models of calculators, computers, and computer programs were used to analyze data in this study. Because different models round off or truncate numbers differently, values in some tables (e.g., means, standard deviations, or individual values) may differ slightly from those in other tables, from individually calculated data, or from statistical analysis data. Neither the integrity nor the interpretation of the data was affected by these differences.

Some tabular data were compiled using Excel® Version 7.0 software.

The units for the dose levels on the data collection system (PTS) summary tables are mg/kg/day.

The number of animals listed in the heading of the summary of clinical observations table (Table 1) reflects the number of animals assigned to each group at the start of the study.

The summary tables for clinical observations indicate the number of animals for which a condition was observed without regard to the specific nature, severity, reversibility, number of incidences/animal, or the length of time the condition persisted.

Only observations other than normal are indicated on the summary clinical observations tables.

The level of severity for observations of ataxic and hypoactive behavior was not specified at the time of the observation and is indicated as "UNSPECIFIED" on the summary and individual observations tables.

The specific details for comments in the individual clinical observations tables that are indicated with a "C" can be found at the end of each group for each sex.

The day of initiation of treatment is "Day 1, Week 1." Body weight data are entered at the start of a study week (e.g., a body weight recorded on Day 1 is considered a Week 1 body weight, a body weight recorded on Day 8 is considered a Week 2 body weight). Body weight change data are calculated from the first day of the study week to the first day of the following study week (e.g., Week 1 values are calculated from Day 1 through 7).

Differences in the population size (N) on the summary tables for clinical pathology are explained on the individual data tables.

COMMENTS ON THE DATA (Continued)

Results of clinical pathology samples collected for animals sacrificed at an unscheduled interval appear on the individual clinical pathology tables for the next scheduled interval. These results are not on the summary tables and are not included in the statistical analyses.

Dosing was discontinued for Animal Nos. 105711, 105722, and 105703 (Group 4) on Days 43 (Week 7), 66 (Week 10), and 81 (Week 12). Summary tables do not include data from these animals after dosing was discontinued and this data are not included in the statistical analyses.

Some animals were observed and treated by the laboratory animal veterinary staff, and the data were recorded on the day the examination was done. These data are referenced in the Request for Veterinary Services and are archived with the raw data but do not appear on the summary or individual clinical observations tables.

Data collected for Animal No. 105723 (Group 2) will be maintained in the raw data; this data will not be included in this report. Animal No. 105723 was sacrificed in moribund condition on Day 14; the cause of the moribund condition of this animal was determined to be a bacterial septicemia which was unrelated to the test material. Animal No. 105723 was replaced by Animal No. 105721 on Day 15.

CODES, ABBREVIATIONS, AND UNITS

General Codes and Abbreviations Codes for Clinical Pathology Abbreviations and Units for Clinical Hematology Abbreviations and Units for Clinical Chemistry Abbreviations and Units for Clinical Urinalysis Codes for Anatomic Pathology

Note: The following lists of codes, abbreviations, and units are used by Covance. Some, but not necessarily all, of this information may be needed for this report.

45

ł

)

General Codes and Abbreviations

WK N Mean; MEAN CAM SD; S.D.; STAND DEV;	Week Number of measurements in a group Arithmetic mean Covariate-adjusted mean Standard deviation
STANDARD DEV; sd *	Group mean is significantly different from
	the mean of the control group (Group 1) at $p \le 0.05$
-; NA	No value; not applicable; not present
NVL	No visible lesions
C	Comment found at the end of each group for each sex
UNSCHED	Unscheduled
#	Number
Animal Death Codes:	
Т	Terminal sacrifice
Μ	Moribund
U	First postrecovery sacrifice

Codes for Clinical Pathology

)

k

÷

F

GENERAL CODES

NS	No sample
QS/QNS	Quantity not sufficient
NR	No repeat (sample volume not sufficient for repeat analysis)
FS	Fibrin strands
SC	Sample clotted
SH	Slightly hemolyzed
Н	Hemolyzed
SL	Slightly lipemic
L	Lipemic
SI	Slightly icteric
Ι	Icteric
NF	Animal not fasted
U	Unscheduled/moribund bleed
DT/DOT	Animal died on test
DB	Died during bleeding
TJ	Technician judgment to repeat test
TE	Technical error (instrument or technician error that results in
	unacceptable data, e.g., unacceptable instrument output, sample
	spilled, entry of invalid data)
RE	Recording error (recorded incorrect data, e.g., wrong number,
	spelling error, incorrect date)
EE	Entry error (incorrect keyboard entry)
SE	Sampling error
PC	Platelets clumped
PD	Platelets decreased
PI	Platelets increased
PL	Platelets large
PA	Platelets appear adequate
CO	Color interferes with test
HB	Heinz bodies observed
PLASMO	Plasmodium
NO AGG	No aggregation
FR	Fractious
UTD	Unable to determine
NO COAG	No coagulation
	-

Codes for Clinical Pathology (Continued)

RESULTS NOT INCLUDED IN STATISTICAL ANALYSES

Hemolyzed clinical chemistry or coagulation samples Samples from animals at unscheduled intervals Prothrombin times (PT) greater than 50 seconds Activated partial thromboplastin times (PTT) greater than 110 seconds Bleed times (BLETIME) greater than 30 minutes

)

h

k

CODES FOR BLOOD CELL MORPHOLOGY

The following scale was used to measure the degree of anisocytosis (ANISO), poikilocytosis (POIK), polychromasia (POLY), hypochromasia (HYPO), and toxic neutrophils (TOXNEUT):

Scale	Degree	Presence
-	Normal for the species	Not present
1	Slight	Rare
2	Moderate	Few
3	Marked	Moderate
4	Not applicable	Many

	Color		Clarity	Miscellaneous
A Pale	E Amber	I Black	J Clear	M Debris
B Straw	F Brown	P Blue/green	K Hazy	O Feces
C Yellow	G Red	Q Blue	L Cloudy	
D Dark yellow	H Green	R Orange	•	

URINE APPEARANCE

Codes for Clinical Pathology (Continued)

Urine Gluco	ose	Uri	ne Ketone		Uri	ine Blood
- Negativ	/e	-	Negative		-	Negative
+ 100 mg	/dL	+	5 mg/dL		+	Small
++ 250 mg	/dL	++	15 mg/dL		++	Moderate
+++ 500 mg	/dL	+++	40 mg/dL		+++	Large
++++ 1,000 n	ng/dL	++++	80 mg/dL			
+++++ ≥2,000	mg/dL	╋┿┿╋╋	160 mg/dL			
Urine U	robilinogen	_		Urine	Bilin	ıbin
-	0.2 mg/dL	-		-	Nega	ative
+	1 mg/dL			+	Sma	11
++	2 mg/dL			++	Mod	erate
+++	4 mg/dL			+++	Larg	e
++++	8 mg/dL					

URINE CHEMISTRY MULTISTIX® STRIP

(1 mg = approximately 1 Ehrlich unit)

URINE SEDIMENT

cells, Crystals, Casts, and Comments		Bacteria		
A Amorphous urates	Q	Sperm	0	Not present
B Amorphous phosphates	R	Fecal contamination	1	Few
C Uric acid	S	Pinworm ova found	2	Moderate
D Triple phosphates	Т	Pinworm larvae found	3	Many
E Calcium oxalate	U	Parasite ova found		
F Calcium carbonate				
G Granular casts				
H Hyaline casts	0	Not present		
Cellular casts	1	1-5 per field		
Waxy casts	2	6-10 per field		
K Unknown crystal	3	11-20 per field		
P Mucous threads	4	>20 per field		

Abbreviations and Units for Clinical Hematology

Test Red blood cell count Hemoglobin Hematocrit Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Platelet count Mean platelet volume Reticulocyte count Absolute reticulocyte count Heinz body count Erythrocyte sedimentation rate Prothrombin time Activated partial thromboplastin time Thrombin time Activated coagulation time Fibrinogen Fibrin/fibrinogen degradation products Platelet aggregation Collagen Adenosine diphosphate Alpha 2-antiplasmin **Bleeding** time Methemoglobin Plasma hemoglobin Myeloid/erythroid ratio Estimated myeloid/erythroid ratio White blood cell count Differential blood cell count Nucleated red blood cell count Corrected white blood cell count Segmented neutrophil count Band neutrophil count Lymphocyte count Monocyte count Eosinophil count **Basophil** count Anisocytosis Polychromasia

Abbreviation (Units) RBC (E6/UL or X10⁶/µL) HGB (G/DL) HCT (%) MCV (FL) MCH (PG) MCHC (%) PLT (E3/UL or X10³/ μ L) MPV (FL) RETIC (%) RETIC (E3/UL or X10³/µL) HEINZ(%) ESR (MM/HR) PT (SEC) PTT (SEC) TT (SEC) ACT (SEC) FBR (MG/DL) FDP (UG/ML) PAGG/COL (%) PAGG/ADP (%) ANTIPLAS (%) BLE TIME (SEC) METHGB (%) PLA HGB (MG/DL) M/E RATIO EST M/E RATIO WBC (E3/UL or $X10^3/\mu L$) NRBC (/100 WBC) COR WBC (E3/UL or $X10^3/\mu L$)

N-SEG (E3/UL or X10³/µL) and % N-BAND (E3/UL or X10³/µL) and % LYMPH (E3/UL or X10³/µL) and % MONO (E3/UL or X10³/µL) and % EOSIN (E3/UL or X10³/µL) and % BASO (E3/UL or X10³/µL) and % ANISO (-,1,2,3) POLY (-,1,2,3)

Abbreviations and Units for Clinical Hematology (Continued)

Test

Poikilocytosis Hypochromasia Howell-Jolly bodies Basophilic stippling Toxic neutrophils Atypical lymphocytes Aqueous white blood cell count (right eye) Aqueous white blood cell count (left eye)

Abbreviation (Units)

POIK (-,1,2,3) HYPO (-,1,2,3) HJBODY (-,1,2,3,4) BASTIP (-,1,2,3) TOXNEUT (-,1,2,3,4) ATYPLYM (-,1,2,3,4) R EYE (WBC/UL) L EYE (WBC/UL)

Abbreviations and Units for Clinical Chemistry

Test Glucose Urea nitrogen Urea Creatinine Total protein Albumin Globulin Albumin/globulin ratio Total bilirubin Direct bilirubin Indirect bilirubin Cholesterol Triglyceride Urea nitrogen/creatinine ratio Total lipids **Phospholipids** High-density lipoprotein cholesterol Low-density lipoprotein cholesterol Uric acid Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Gamma glutamyltransferase Sorbitol dehydrogenase Lactate dehydrogenase Creatine kinase Amylase Lipase Pancreatic-specific Amylase Palmitoyl CoA oxidase Calcium Ionized calcium Inorganic phosphorus Sodium Potassium Chloride Magnesium Zinc Strontium Iron

Abbreviation (Units) GLU (MG/DL) UN (MG/DL) UREA (MG/DL) CREAT (MG/DL) T PRO (G/DL) ALB (G/DL) GLOB (G/DL) A/G RATIO T BILI (MG/DL) D BILI (MG/DL) I BILI (MG/DL) CHOL (MG/DL) TRIG (MG/DL) **UN/CREAT (RATIO)** T LIPIDS (MG/DL) P LIPIDS (MG/DL) HDL (MG/DL) LDL (MG/DL) UA (MG/DL) AST/SGOT (IU/L) ALT/SGPT (IU/L) ALK PHOS (IU/L) GGT (IU/L) SDH (IU/L) LDH (IU/L) CK (IU/L) AMYLASE (IU/L) LIPASE (IU/L) P AMYL (U/L) PCOAO (IU/G) CA (MG/DL) ION CA (MG/DL) I PHOS (MG/DL) NA (MMOL/L) K (MMOL/L) CL (MMOL/L) MG (MEQ/L or MG/DL) ZN (MG/L or PPM) SR (MG/L or PPM) FE (UG/DL)

Test Abbreviation (Units) Excess iron EX FE (UG/DL) Total iron binding capacity TIBC (UG/DL) Unbound iron binding capacity UIBC (UG/DL) Percent iron saturation FE %SAT (%) Plasma cholinesterase CHEP (MU/ML) Red blood cell cholinesterase CHER (MU/ML) Brain cholinesterase CHEB (MU/ML) Caudate putamen CAUD PUT (UMOL/G) Hippocampus HIPPOCAM (UMOL/G) Frontal cortex F CORTEX (UMOL/G) Cerebellum CEREBELL (UMOL/G) **Bicarbonate** BICARB (MMOL/L) Serum hemoglobin SER HGB (MG/DL) Serum bile acids SBA (UMOL/L or MG/DL) Fecal bile acids FBA (UG/ML) Average fecal weight FCC WGT (G) Fecal bile acids (calculation) FBA (MG/Day) Osmolality OSMO (MOSM/KG) Electrophoresis Albumin E ALB (G/DL) Alpha-1-globulin E A-1 (G/DL) Alpha-2-globulin E A-2 (G/DL) Beta globulin E BETA (G/DL) Gamma globulin E GAMMA (G/DL) High-density lipoprotein E-HDL (%) Low-density lipoprotein E-LDL (%) Very-low-density lipoprotein E-VLDL (%) Insulin INSULIN (UU/ML) Adrenocorticotropic hormone ACTH (PG/ML) Cortisol CORTISOL (UG/ML) Glucagon GLUCAGON (PG/ML) Creatine kinase isoenzymes BB CK-BB (U/L) MB CK-MB (U/L) MM CK-MM (U/L)

Abbreviations and Units for Clinical Chemistry (Continued)

T = =4	Abbusylistian (Units)
Test	Abbreviation (Units)
Urine volume	U VOL (ML)
8 hour urine volume	8 HR VOL (ML)
Specific gravity	SP GR
Urine osmolality	U OSMO (MOSM/KG)
Quantitative urinary/cerebrospinal	QUAN PRO (MG/DL)
fluid protein	
Urine protein excretion	PRO EXC (MG)
Urine chemistry Multistix® strip	
Urine pH	U PH
Urine protein	U PRO (MG/DL)
Urine glucose	U GLU
Urine ketones	U KET
Urine bilirubin	U BILI
Urine blood	U BLOOD
Urine urobilinogen	UROBILI
Urine reducing substances	U RE SUB
Microscopic examination of urine sediment	
Red blood cells per high-power field	RBC (PER HPF)
White blood cells per high-power field	WBC (PER HPF)
Epithelial cells per high-power field	EPITH (PER HPF)
Bacteria per high-power field	BACT (PER HPF)
Casts per low-power field	CASTS (PER LPF)
Crystals per low-power field	CRYSTALS (PER LPF1 or PER LPF2)
Urine appearance	URINE APP1 or URINE APP2
Comments	COMMENTS

Abbreviations and Units for Clinical Urinalysis

Miscellaneous Codes and Abbreviations for Clinical Pathology

Fecal occult blood	
Fecal parasite detection	
Hemolytic potential	

Not applicable Not applicable Not applicable

Codes for Anatomic Pathology

e Definitio	m
e Definitio)I

ANIMAL DEATH CODES

Т	Terminal sacrifice
U	First postrecovery sacrifice
М	Moribund

MICROSCOPIC CODES

Distribution of Findings
Focal
Diffuse
Multifocal

Grades for Severity or Amount

1	Minimal - the least amount of change that can be observed with the
	light microscope
2	Slight - less than average amount of change, but readily discernible as abnormal
3	Moderate - the average amount of change that is expected for a lesion
4	Moderately severe (marked) - a marked amount of change with possible loss of function of the affected cells or organs
5	Severe - a great amount of change with probable loss of function of the affected cell or organs and frequently involves large areas of the organ

TISSUE ABBREVIATIONS

Abbreviation	Definition
LF	Left
LN	Lymph node
LN, TRACHEOBRON	Tracheobronchial lymph node
RT	Right
STOMACH, GL	Glandular stomach
SALIV GL, MANDIB	Mandibular salivary gland
THYROID/PARA	Thyroid/parathyroid

		H	Table	CO 1	Covance 6329-231 3M T-6889.3
	Summary	of Cl:	[nica]	Summary of Clinical Observations	
26-WEEK CAPSULE TOXICITY (APFO)	TOXICITY (APFO)		HTIW	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 1
	NUMBER	OF AN	IMALS	NUMBER OF ANIMALS AFFECTED	
DAIS 1-104 SEX: GROUF: CATEGORY DOSE:	0	MAL 2 3	MALE4 2 3 10 20	 2.0	
KEYWORD QUALIFIER	9	4	9	٥	
*** TOP OF LIST *** APPEARANCE LIMITED USE LIMITED USE LIMES-HIND	0		0	0	
FARALISIS HIND QUARTERS THIN	00	10	00	2 0	
BEHAVIOR ATAXIC <unspecified></unspecified>	0	-	0	0	
HYPOACTIVE <unspecified></unspecified>	0	ч	0	1	
DISCHARGE VOMITUS CONTAINING FOOD	4	7	ŝ	2	
EXCRETION DISCOLORED URINE BROWN IN COLOR FEW FECES LIQUID FECES NUCOID FECES NO FECES	0 1 7 0 0	04440	00400	10004	
NON-FORMED FECES 1 2 1 2 a Group 4 males were administered 30 mg/kg/day on Days 1 through 11.	Days 1	1 chroug	h 11.	1 Animals were not dosed on Days 12 through 21.	Beginning

,

on Day 22 and continuing throughout the remainder of the study, Group 4 males were administered 20 mg/kg/day, except that dosing for Animal Nos. 105711, 105722, and 105703 was discontinued on Days 43 (week 7), 66 (week 10), and 81 (week 12), respectively.

· ·			Table 1	1	Covance 6329-231 3M T-6889.3
	Summa	ry of (Clinic	Summary of Clinical Observations	
26-WEEK CAPSULE TOXICITY (APFO)	SULE TOXICITY (APFO)		DY WIT	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 2
	INUM	SER OF	ANTMAI	NUMBER OF ANIMALS AFFECTED	
	SEX: GROUP: 1 DOSE: 0		MALE 2 3 3 10		
D			9	0 1	
SKIN & PELAGE		 			
ALOPECIA HEAD-CRANIAL		0	0	0	
LIMB-FRONT-LEFT			000		
LLMB-FRONT - RLGHT LLMBS-FRONT	-11		00	20	
COLD TO TOUCH BODY-ENTIRE	0	000	0	1	
SCAB (S) PERI-ORBITAL-LEFT	0	0	н ,	6.0	
PERT-ORBITAL-RIGHT SCAR TTP (s)	5 0		H (C	
MASS MASS FACE NEXT TO NOSE			C	1 0	
QUALITATIVE FOOD CONSUMPTION	о и ,		H M	s 6	
NONE *** END OF LIST ***	0		0	4	
a Group 4 males were administered 30 mg/kg/day on Days 1 through 11.	ay on Days	1 thro	ugh 11	. Animals were not dosed on Days 12 through 21.	Beginning

on Day 22 and continuing throughout the semainder of the study, Group 4 males were administered 20 mg/kg/day, except that dosing for Animal Nos. 105711, 105722, and 105703 was discontinued on Days 43 (week 7), 66 (week 10), and 81 (week 12), respectively.

57

1812.0058

Covance 6329-231 3M T-6889.3	PAGE: 1			
. Table 2	Summary of Clinical Observations Recovery 26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	DAYS 185-277 NUMBER OF ANIMALS AFFECTED SEX:MALE GROUP: 1 3 GROUP: 1 3 GROUP: 1 3 DOSE: 0 10 KEYWORD NUMBER: 2 2	*** TOP OF LIST *** DISCHARGE VOMITUS CONTAINING FOOD EXCRETION NO FECES 0 1 0 1	QUALITATIVE FOOD CONSUMPTION LOW *** END OF LIST ***

Covance 6329-231 3M T-6889.3		PAGE: 1				
Table 3	Summary of Ophthalmic Observations	6-WEEK CAPSULE TOXICITY STU (APFO) IN		NUMBER: 6 4 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6		
			WEEK -1 CATEGORY KEYWORD	QUALIFIER 		

Covance 6329-231 3M T-6889.3	Surmary of Ophthalmic Observations PAGE: 2	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONUUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	NUMBER OF ANIMALS AFFECTED		. 6 3 6 5	6365	group 4 males were administered 30 mg/kg/day on Days 1 through 11. Animals were not dosed on Days 12 through 21. Beginning on Day 22 and continuing throughout the remainder of the study, Group 4 males were administered 20 mg/kg/day, except that dosing for Animal Nos. 105711, 105722, and 105703 was discontinued on Days 43 (week 7), 66 (week 10), and 81 (week 12), respectively.
	Surmary	26-WEEK CAPSULE TOXICIT' (APPO)	IBBNUN 27	SEX: GROUP: DOSE:	AEYWOKU QUALIFIER 6	*** TOP OF LIST *** NO VISIBLE LESIONS NO VISIBLE LESIONS EYES *** END OF LIST *** 6	a Group 4 males were administered 30 mg/kg/day on Days 1 on Day 22 and continuing throughout the remainder of th dosing for Animal Nos. 105711, 105722, and 105703 was respectively.

Covance 6329-231 3M T-6889.3	PAGE: 1							
Table 4	Summary of Ophthalmic Observations Recovery 26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE	SEX:MALE GROUP: 1 3	DOSE: MBER:	2				
		WEEK 40	CATEGORY KEYWORD QUALIFIER	*** TOP OF LIST *** NO VISIBLE LESIONS NO VISIBLE LESIONS EYES EYES *** END OF LIST ***				

					Summary of Body Weight Data (k	(kg)
1	1 1 1 1 1 1 1 1		26-1	WEEK CAPSULE	26-WEEK CAPSULE TCXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	PERFLUOROOCTANOATE
	<u>د ت</u> رور .		Mare F	Ĺ.		
WEEK	GROUP: DOSE: UNITS:	1 0 MG/KG/DAY	2 3 MG/KG/DAY	3 10 MG/KG/DAY	4ª 20ª MG/KG/DAY	
2	N MEAN S_D_	9 6 7 7 7 7	4 4.0 2.24	6 3.8 .34	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
-1 ^b	N MEAN S.D.	6 50 9.8 0.52	4.0 0.34	6 3.8 0.37	6.10 3.8 0.27	
-1°	N MEAN S.D.	6 3.8 0.54	4 3.9 0.34	6 3.7 0.43	6 0.8 0.29	
-	N MEAN S.D.	6 3.8 0.56	4 4.0 0.36	6 3.8 0.33	6 3.9 0.32	
2	N CAM MEAN S.D.	0.59 0.88 0.93	4 3.9 0.29	6 3.7 0.42	6 3.7 0.29	
m	N CAM MEAN S.D.	00000 00000 00000	4 3.8 0.24 0	6 33.7 0.46	6 3.6 0.29	

(Week 7), 66 (Week 10), and 81 (Week 12), 43 Days was discontinued on I05722, and I05703 dosing for Animal Nos. 105711, pay -ctively. Day -1.

дυ

 \mathfrak{G}

Summary of Body Weight Data (kg) Data (kg) 26-WEEK Carbon Prevention Correcting Subserves 26-WEEK Carbon Prevention Correcting Subserves 26-WEEK Carbon Prevention Correcting Subserves 260000 200000 20000						Ë	таble 5 т-6889.3
And the second constrained of the second consecond constrained of the second constrained of the sec						0 f	Data
SEX:				26-1	WEEK CAPSULE	TOXICITY (APFO)	PAGE:
N 6 4 6 4 6 3.9 6 5 6	WEEK	SEX: GROUP: DOSE: UNITS:	1 1 MG/KG/DAY	L C C L	E3 3 MG/XG/DAY	20 ⁴ MG/ XG/ DAY	
N CAM 6 4 6 4 S.D. 0.63 0.53 0.245 S.D. 0.63 0.245 0.45 N CAM 6 6 4 0.24 N CAM 4.0 4.0 3.9 S.D. 0.53 0.21 0.53 N MEAN 4.1 3.9 4.0 N MEAN 4.1 0.13 0.53 N CAM 4.0 4.0 4.1 3.9 N MEAN 4.0 4.1 0.57 N MEAN 4.0 4.1 0.57 N MEAN 4.0 4.1 0.57 N MEAN 4.0 4.1 0.57 N MEAN 4.0 4.1 0.55 S.D. 0.55 0.05 N MEAN 4.0 4.0 4.0 4.0 S.D. 0.55 0.05 N MEAN 4.0 4.0 4.0 0.57 N MEAN 4.0 0.55 0.05	4	N CAM MEAN S.D.	6 4.0 0.57	4 3.9 0.22 22	6 3.9 3.48 0.44	6 3.7 0.27	
N 6 4 6 4 6 4 6 6 4 8 6 6 8 4 0 8 EAN 4.0 4.0 4.1 3.9 5.5 0.21 0.53 0.21 0.53 0.21 0.53 0.21 0.53 0.21 0.53 0.21 0.53 0.21 0.53 0.21 0.21 0.21 0.53 0.57 0.21 0.21 0.21 0.23 0.57 0.52 0.25 0.25 0.25 0.25 0.25 0.25 0.25	2 2	N CAM MEAN S.D.	6 4.0 0.53	4 033 0.8 .24	6 3.8 0.45 0.45	8.7 * 3.7 * 0.30	
N 6 4 4.1 3.9 6 7 4.0 8 8 8 8 1 3.9 6 7 8 1 3.9 8 1 3.	9	N CAM MEAN S.D.	6 446 0.0 33	4 4.0 0.21 221	0 . 9 0 . 9 0 . 9	3.7 3.7 0.30	
N 6 4 6 4 6 6 4 10 6 6 6 10 14 0.52 8.D. 0.51 0.14 0.52 9.52 8.D. 0.51 0.14 0.52 0.52 0.52 8.D. 0.55 0.05 0.05 0.05 0.05 0.05 0.05 0	7	N CAM MEAN S.D.	6 4.1 0.62	4 3.9 4.1 0.13	6 4.0 0.57	3.7 3.7 0.42	
N 6 4 6 6 CAM 4.0 4.0 6 MEAN 4.0 4.0 4.0 S.D. 0.55 0.05 0.60	ω	N CAM MEAN S.D.	4.0 51	4 4.0 4.1 0.14	6 3.9 0.52	4 3.6 0.42	
	<i>م</i>	N CAM MEAN S.D.	6 4.0 55	4 4 0.05 0.05	6 4.0 0.60	4 33.6 0.46 0.44	

- 21 dosing for Anirespectively.

			PAGE: 3
	26-WEEK CAPSULE	TOXICITY STUDY W1TH AMMONIUM PERFLUOROOCTANOATE (AFFO) IN CYNOMOLGUS MONKEYS	
SEX:MALE GROUP: 1 2 DOSE: 0 3 UNITS: MG/KG/DAY MG/KG/DAY MG		20 ⁴ 20 ³ MG/XG/DAY	
N 6 4 CAM 4.0 4.0 MEAN 4.0 4.1 S.D. 0.54 0.10	6 4.0 0.58	لم 3.55 × 0.45 ×	
N 6 4 CAM 6.1 4.0 MEAN 4.1 4.0 S.D. 0.58 0.05	6 4.1 0.59 0.59	3 3.6 0.60	
N 6 4 CAM 4.1 4.0 MEAN 4.1 4.2 S.D. 0.53 0.06	6 4.0 0.60	3 3.5 3.4 0.76	
N 6 4 CAM 4.1 4.1 MEAN 4.1 4.2 S.D. 0.53 0.10	6 4.1 0.58	2 3.8 0.35	
N 6 4 CAM 4.1 4.1 MEAN 4.1 4.2 S.D. 0.55 0.05	6 4.1 0.59	2 3.9 0.35	
N 6 4 CAM 4.2 4.2 MEAN 4.2 4.3 S.D. 0.53 0.06	6 4.1 0.59	2 3.7 3.8 0.49	

(Week 12), ;; . 5 24 respectively.

6 6329-231 I T-6889.3	-							ទ័ព
Covance 3M PAGE: 4								. Beginni: cept that ck 12),
Table 5 of Body Weight Data (kg) stupy WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS								Group 4 males were administered 30 mg/kg/day on Days 1 through 11. Animals were not dosed on Days 12 through 21. Beginning on Day 22 and continuing throughout the remainder of the study, Group 4 males were administered 20 mg/kg/day, except that dosing for Animal Nos. I05711, I05722, and I05703 was discontinued on Days 43 (Week 7), 66 (Week 10), and 81 (Week 12), respectively.
T Summary of Boo TOXICITY STUDY (APFO) IN CY	4 4 MG/KG/DAY	2 3.7 0.49	2 3.8 0.42	2.9 4.0 .42	2.84.0 0.49	2.33.7 0.64	2 3.7 0.64	Days 1 throug er of the stud 03 was discont
26-WEEK CAPSULE	6 3 10 MG/KG/DAY	6.2 4.1 0.56	0446 .56 .56	44.6 44.3 0.58	6 4.3 0.60	6 4.3 0.58 0.58	6446.3 0.58 0.58	mg/kg/day on the remaind 722, and I057
26 - 1 	MALE 2 3 MG/KG/DAY	4.1 4.2 0.05	444 0.32 08	4 44.3 0.10	4 4-3 0-13	4 4.2 0.32	44.3 0.06	inistered 30 ng throughout 105711, 1057
	1 0 MG/KG/DAY	4.2 4.2 0.53	6 44.2 0.53 0.53	6 4.3 0.57	6 44.3 0.58 0.58	44 44 04 0 0 0 0 0	6 4.3 0.59	les were admi and continuir Animal Nos. LY.
	SEX: - GROUP: DOSE: UNITS:	N CAM MEAN S.D.	N CAM MEAN S.D.	N CAM MEAN S.D.	N CAM MEAN S.D.	N CAM MEAN S.D.	N CAM MEAN S.D.	Group 4 males on Day 22 and dosing for An respectively.
	WEEK 	16	17	18	19	20	21	r Gor R

					Table 5	Covance 6329-231 3M T-6889.3
					Summary of Body Weight Data (kg)	
				26-WEEK CAPSULE TOXICITY (APFO)	E TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	PAGE: 5
	- SEX: -	 	MALE	i		
WEEK 	DOSE: DOSE: UNLTS:	MG/KG/DAY	Z 3 MG/KG/DAY	10 MG/KG/DAY	20 ⁴ MG/KG/DAY	
22	N CAM MEAN S.D.	6444.3 0.59 0.59	0443 066	6 44.3 0.58 0.58	2 3.7 3.9 0.64	
23	N CAM MEAN S.D.	6 4.4 0.60	6449 6444 056	6 44 0.56 0.56	2 3.9 4.0 0.57	
24	N CAM MEAN S.D.	44.4 0.59 0.59	44 44 0000 0000	6 4.4 0.58	2 4.0 4.1 0.57	
25	N CAM MEAN S.D.	446 444 0.59	0.00 0.00	6 4.4 4.3 0.60	2 3.9 3.6 0.64	
26	N CAM MEAN S.D.	6 4.5 0.60	44.6 44.6 0.06	6 4.5 0.62	2 3.9 4.0 0.71	
27	N CAM MEAN S.D.	6 4.5 64 64	3.06 0.06	6 4.5 0.60	2 44.0 4.1 0.71	
й Gon K gon G	oup 4 mal Day 22 a sing for	es were adm nd continuir Animal Nos.	inistered 30 ng throughout 105711, 1057	mg/kg/day on the remaind 722, and I057	Group 4 males were administered 30 mg/kg/day on Days 1 through 11. Animals were not dosed on Days 12 through 21. Beginn on Day 22 and continuing throughout the remainder of the study, Group 4 males were administered 20 mg/kg/day, except that dosing for Animal Nos. 105711, 105722, and 105703 was discontinued on Days 43 (Week 7), 66 (Week 10), and 81 (Week 12),	Beginning ept that 1k 12),

)

(Week IZ), È, 2 - Ņ. respectively.

Covance 6329-231 3M T-6889.3		PAGE: 1									
Table 6	Summary of Body Weight Data (kg) Recovery	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	MALE	3.8 0.07	2 3.8 0.00						
		 	1 1 MG/KG/D	5.1 0.28	2 5.2 0.28	2 5.2 0.21	2 5.2 0.21	2 5.3 0.28	2 5.3 0.42	2 5.5 0.28	
			SEX: GROUP: UNITS:	N MEAN S.D.							
		1	WEEK	28	29 ,	30	31	32	33	34	

)

3M_MN02343409

Covance 6329-231 3M T-6889.3		PAGE: 2									
Table 6	Summary of Body Weight Data (kg) Recovery	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROUCTANOATE (APFO) IN CYNOMOLGUS MONKEYS									
		26-WEE	3 3 10 MG/KG/DAY	2 3.8 0.14	2 3.8 0.14	2 3.8 0,14	2 3.8 0.14	2 3.8 0.21	2 3.8 0.21		
			MALE	2 5.5 0.28	2 5.6 0.35	2 5.6 0.28	2 5.6 0.28	2 5.7 0.28	2 5.7 0.28		
			SEX: - GROUP: DOSE: UNITS:	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.		
			WEEK	35	36	37	8 M	6 M	40		

6329-231 Т-6889.3											La .
Covance 6329-231 3M T-6889.3		PAGE: 1									1 21. Beginning
Table 7	Summary of Body Weight Change Data (kg)	OXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APPO) IN CYNOMOLGUS NONTEYS	20 ⁴ MG/KG/DAY	6 -0.2 0.08	6 -0.1 * 0.17	6 0.2 0.08	6 -0.1 0.08	5 0.0 0.07	5 0.0 0.15	4 -0.3 * 0.10	Group 4 males were administered 30 mg/kg/day on Days 1 through 11. Animals were not dosed on Days 12 through 21. on Day 22 and continuing throughout the remainder of the study. Group 4 males were administered 30 mc/redser even
	uttri:S	26-WEEK CAPSULE TOXICITY (APFO)	3 10 MG/KG/DAY	6 -0.1 0.12	6 0.0 0.05	6 0.1 0.05	6 -0.1 0.05	6 0.1 0.10	6 0.0 0.10	6 0.0 0.09	ıg∕kg∕day on the remainde
		26-WI	MALE- 2 3 MG/KG/DAY	4 0.0 0.08	4 0.0 0.05	4 0.0 0.06	4 -0.1 0.08	4 0.2 0.05	4 0.0 0.08	4 0.0 0.10	listered 30 m r throughout
			1 0 MG/KG/DAY	6 -0.1 0.05	6 0.1 0.06	6 0.1 0.04	6 0.0 0.10	6 0.0 0.10	6 0.1 0.10	6 -0.1 0.12	ns were admin d continuing
			SEX: GROUP: DOSE: UNTTS:	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	up 4 male Dav 22 an
			WEEKS	1-2	2-3	3-4	4-5	5-6	6-7	7-8	a On On

3M_MN02343411

69

1812.0070

						Covance 6329-231 3M T-6889.3	6329-231 T-6889.3
				Sw	mmary of Bod	Summary of Body Weight Change Data (kg)	
1			26-1-22	26-WEEK CAPSULE TOXICITY (APFO)		STUDY WITH AMMONIUM PERFLUCKOOCTANOATE IN CYNOMOLGUS MONKEYS	
	CEV.		1 4 M	ũ			
WEEKS	GROUP: DOSE: UNITS:	1 0 MG/KG/DAY		10 3 MG/KG/DAY			
8 6	N MEAN S.D.	6 0.0 0.13	4 0.1 0.13	6 0.1 0.08	4 0.0 0.08		
9-10	N MEAN S.D.	6 0.0 0.05	4 0.0 0.06	6 0.0 0.08	4 -0.1 * 0.13		
10-11	N MEAN S.D.	6 0.0 0.05	4 0.0 0.06	6 0.10 0.10	3 0.0		
11-12	N MEAN S.D.	6 0.0 0.06	4 0.0 0.05	6 0.0 0.05	3 -0.1 0.17		
12-13	N MEAN S.D.	6 0.0 0.05	4 0.1 0.05	6 0.1 0.06	2 0.1 0.00		
13-14	N MEAN S.D.	6 0.0 0.04	4 -0.1 0.10	6 -0.1 0.05	$^{2}_{0.00}$		
14-15	N MEAN S.D.	6 0.1 0.05	4 0.1 0.05	6 0.1 0.08	2 0.0 0.14		
a Gro on dos	up 4 ma. Day 22 ; inc for	les were adm: and continuir	inistered 30 ig throughout	ng/kg/day or t the remaind	n Days 1 thr der of the s	Group 4 males were administered 30 mg/kg/day on Days 1 through 11. Animals were not dosed on Days 12 through 21. Beginning on Day 22 and continuing throughout the remainder of the study, Group 4 males were administered 20 mg/kg/day, except that	£

)

dosing for Animal Nos. 105711, 105722, and 105703 was discontinued on Days 43 (Week 7), 66 (Week 10), and 81 (Week 12), respectively.

Covance 6329-231 3M T-6889.3	ata (kg) PERFLUOROOCTANOATE VS									Group 4 males were administered 30 mg/kg/day on Days 1 through 11. Animals were not dosed on Days 12 through 21. Beginning on Day 22 and continuing throughout the remainder of the study, Group 4 males were administered 20 mg/kg/day, except that dosing for Animal Nos. I05711, I05722, and I05703 was discontinued on Days 43 (Week 7), 66 (Week 10), and 81 (Meek 12),
Table 7	sody stud znud znud	4 20 ^a MC/KG/DAY	2 0.00 0.00	2 0.0 0.07	2 0.1 0.00	2 0.0 0.07	2 -0.1 0.14	2 0.0 0.00	2 0.0 0.0	Days 1 through 11. Animals er of the study, Group 4 male 03 was discontinued on Days 4
	Summary of F 26-WEEK CAPSULE TOXICITY (APFO)		6 0.0 0.05	6 0.0 0.05	6 0.0 0.05	6 0.0 0.08	6 0.0 0.04	6 0.0 0.00	6 0.0 0.04	mg/kg/đay on the remaind 22, and I0570
	26-W	2 2 MG/KG/DAY	4 0.0 0.05	4 0.1 0.05	4 0.1 0.13	4 0.0 0.10	4 -0.1 0.20	3 0.0 0.06	3 0.0 0.00	nistered 30 : g throughout I05711, I057.
		1 0 MG/KG/DAY	6 0.06 0.06	6 0.0 0.00	6 0.1 0.05	6 0.0 0.06	6 0.0 0.05	6 0.0 0.04	6 0.0 0.00	es were admi ind continuin Animal Nos.
		SEX: - GROUP: DOSE: WEEKS UNTTS:	15-16 N MEAN S.D.	16-17 N MEAN S.D.	17-18 N MEAN S.D.	18-19 N MEAN S.D.	19-20 N MEAN S.D.	20-21 N MEAN S.D.	21-22 N MEAN S.D.	a Group 4 males on Day 22 and dosing for An

)

)

ł

3M_MN02343413

				Table 7	Covance (3M 1	ance 6329-231 3M T-6889.3
			Sun	Summary of Body Weight Change Data (kg)		
		26-1	WEEK CAPSULE	26-WEEK CAPSULE TOXICITY STUDY WITH AMMCNIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	PAGE:	4
. 2002			r			
GROUP: GROUP: DOSE: WEEKS UNITS:	1 0 MG/KG/DAY		3 3 10 MG/KG/DAY	4 20 ⁴ MG/KG/DAY		
22-23 N MEAN S.D.	6 0.1 0.05	3 0.1 0.06	6 0.0 0.05	2 0.1 0.07		
23-24 N MEAN S.D.	6 0.0 0.06	3 0.1 0.06	6 0.1 0.05	2 0.1 0.00		
24-25 N MEAN S.D.	6 0.0 0.05	3 0.06 0.06	6 0.0 0.05	2 -0.2 * 0.07		
25-26 N MEAN S.D.	6 0.1 0.04	3 0.1 0.00	6 0.1 0.04	2 0.1 0.07		-
26-27 N MEAN S.D.	6 0.0 0.05	3 0.0 0.06	6 0.0 0.06	2 0.1 0.00		
1-27 N MEAN S.D.	6 0.7 0.33	3 0.7 0.35	6 0.6 0.34	2 0.1 0.71		
a Group 4 mai on Day 22 d dosing for	les were adm and continui: Animal Nos.	inistered 30 ng throughout 105711, 1057	mg/kg/day or the remaind '22, and 1057	Days 1 through 11. Animals were n er Of the study, Group 4 males were 13 was discontinued on Days 43 (wee	Group 4 males were administered 30 mg/kg/day on Days 1 through 11. Animals were not dosed on Days 12 through 21. Beginn on Day 22 and continuing throughout the remainder of the study. Group 4 males were administered 20 mg/kg/day. except that dosing for Animal Nos. 105711, 105722, and 105703 was discontinued on Days 43 (Meek 71, 66 (Meek 70) and 81 (Mee	Beginning ot that

ł

1

dosing for Animal Nos. 105711, 105722, and 105703 was discontinued on Days 43 (Week 7), 66 (Week 10), and 81 (Week 12), respectively.

COVANCE 6329-231 3M T-6889.3		T :: 7984									
Table 8	Summary of Body Weight Change Data (kg) Recovery	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS									·
		26-WEE		2 -0.1 0.07	2 0.1 0.07	2 -0.2 0.07	2 0.1 0.07	2 0.0 0.07	2 0.0 0.07	2 0.0 0.00	
			MG/KG/DAY MG/KG/DAY	-0.1 0.07	2 0.1 0.00	2 0.0	2 0.0 0.0	2 0.2 0.07	2 0.0 0.14	2 0.2 0.14	
			SEX: - GROUP: DOSE: WEEKS UNITS:	27-28 N MEAN S.D.			30-31 N MEAN S.D.			33-34 N MEAN S.D.	

Covance 6329-231 3M T-6889.3		PAGE: 2										
Table 8	Summary of Body Weight Change Data (kg) Recovery	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (AFFO) IN CYNOMOLGUS MONKEYS		/DAY		00	00	0	, 0	7		
			- - -	- 3 10 MG/KG/1		0.00	0.00	000	2 0.0 0.00	000 000	0.0	0.2
				1 0 MG/KG/DAY	·····	0.00	$\begin{array}{c} 2\\ 0.1\\ 0.07 \end{array}$	2 0.0 0.07	2 0.00 0.00	2 0.1 0.00	2 0.0 0.00	2.5 0.07
			CEX.	GROUP: DOSE: UNITS:		MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.	N MEAN S.D.
		 		WEEKS U	1 56 - 17 6	ר ר ו	35-36	36-37	37-38	38-39	39-40	27-40

þ

•

)

Þ

)

ł

3M_MN02343416

74

1812.0075

)

)

J

þ

)

)

÷

Table 9

Summary of Clinical Hematology Data

Day -11 Males

000 MITIN D MAKE L 7.4 T FCFACE 26-WEEK CAPSULE

(AZFU)	
OCTANUALE	
LEAF BUCK	0
MOTINOMER	IS MONKEVS
	TIP TOMORY
	~
1	

FBR MG/DL	286 32.2 6	345 52.3 4	315 22.2 6	304 44.9 6
PTT	18.2 1.23	20.5 5.03 4	18.3 1.59 6	20.0 3.76 6
PT SEC	9.7 .32	9.6 .10	9.6 .18 6	9.8 • 36
RETIC X10 ³ /µБ	45 26.3	48 29,9	43 24.7 6	49 16.9 6
RETIC 8	.36 .36	. 4 4 4	9.0 8.0	.22
РГТ X10 ³ /µГ	513 155.0 6	562 109.5 4	515 98.3 6	547 90.6 6
MCHC &	29.5 1.03	29.4 .22 4	30.0 .48 .6	29.6 .58 6
MCH PG	18.9 1.21 6	18.8 .95 4	18.1 1.02 6	17.8 .89 6
MCV FL	63.9 3.05 6	63.8 3.80 4	60.4 3.78 6	60.2 2.63 6
ا ۲۰۰۶ ۴۰۰۲ ۴۰۰۲ ۴۰	42.1 .85	43.9 4.51 4	40.4 1.92 6	41.2 2.68 6
HGB G/DL	12.4 .26	12.9 1.23 4	12.1 .56	12.2 .83 .6
RBC X10 ⁶ /µL	6.60 .405 6	6.88 .433 4	6.70 .268 6	6.84 .302 6
DOSE mg/kg/ĉay 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

)

¥.

ļ

Table 9

Summary of Clinical Hematology Data

Day -11 Males

26-WEEK CAFSULE TOXICITY STUDY WITH AMMONIUM PERFLUCROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

SE WBC N-SEG LYMPH MONO BASO N-SEG LYMPH MONO EOSTIN EOSTIN EASO N-SEG LYMPH MONO EOSTIN EOSTIN EASO N-SEG LYMPH MONO EOSTIN EOSTIN <theostin< th=""> <theostin< th=""> <theostin< <="" th=""><th>BASO⁸</th><th>0 6.4</th><th>4 0 4</th><th>0 6.4</th><th>0.4 6.4</th></theostin<></theostin<></theostin<>	BASO ⁸	0 6.4	4 0 4	0 6.4	0.4 6.4
SE /kg/day WWBC x10 ³ /μL N-EEG x10 ³ /μL LYWPH x10 ³ /μL MONO BASO x10 ³ /μL N-SEG ³ LYMPH ⁴ MONO ⁴ MEAN 12.7 6.0 5.5 1.0 20 47 43 8 MEAN 12.7 6.0 5.5 1.0 2.2 0.5 47 43 8 MEAN 10.7 4.6 5.2 1.0 2.3 10 47 43 8 MEAN 10.7 4.6 5.2 1.0 39 11 4 5 5 5	1	و [.] 5	4.0	.0 6.2	6.8 6.8
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1				
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	I				
SE WBC N-SEG LYMPH MONO BOSTN /kg/day x10 ³ /µL x10 ³ /µL <t< td=""><td>,</td><td>.0 6 5</td><td>.05 .05</td><td>.0 .05</td><td>0.089</td></t<>	,	.0 6 5	.05 .05	.0 .05	0.089
SE WBC N-SEG LYNPH MONO /kg/day X10 ³ /μL X10	- 1	6 12 6 6	4.12 4.12	.13 .13	6.14 6.14
SE /kg/day x10 ³ /μL x10					
SE /day X10 ³ /µL ² /kg/day X10 ³ /µL ² MEAN 12.7 S.D. 4.5 MEAN 10.7 S.D. 3.62 N ^{12.4} S.D. 3.62 N ^{11.4} S.D. 3.63 N ^{11.4} S.D. 3.03 N ^{13.3} S.D. 13.3 N ^{13.3} S.D. ^{13.3} S.D. ^{13.3} S.D. ^{13.3} S.D. ^{13.3}	тхмрн х10 ³ /µг				
SE /kg/day X1 /kg/day X1 MEAN S.D. MEAN S.D. S.D. S.D. S.D. N S.D. N N	N-SEG X10 ³ /μL	6.0 6.2 61	4.6 2.84 4	5.7 2.66 6	7.3 1.57 6
Ngyday Ngyday Mean S.D. MEan S.D. MEan S.D. MEAN S.D. N.	WBC X10 ³ /µL	12.7 4.36	10.7 3.62 4	11.4 3.03 6	13.3 2.25 6
30,10 30,10 30,10	DOSE mg/kg/day 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

)

)

)

)

)

)

ł

٢

Table 10

Summary of Clinical Hematology Data

Males Day 31

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

	FBR MG/DL	369 187.4	334 24.0 4	291 38.8 6	475 250.9 5
	FTT SEC N	10.8 130.6 1.26	21.9 4.98 4	20-0 2.02 6	24.0 4.22 5
	PT SEC	10.0 66	9.8 .29	10.1 .34 6	10.0 .47 5
	RETIC X10 ³ /µL	21 8.4	13 10.4 4	11 5.2 6	23 19.1 5
	RETIC % X		.2 44	6 8 6 8 6 8	5. 56
	РГТ X10 ³ /µГ	428 87.8 6	499 98.7 4	446 107.9 6	516 159.7 5
	WCHC	29.3 1.23 6	30.0 .45	29.6 .46	29.6 1.56
	MCH PG	19.0 1.12 6	19.2 1.06	18.4 1.09 6	18.2 .54 .5
	MCV FL	64.7 3.01	64.0 3.43	62.2 3.73 6	61.6 3.23 5
	HCT %	44.0 1.88 6	41.3 1.76	41.8 2.11 6	40.9 3.06 5
	HGB G/DL	12.9 .80	12.4 .57	12.3 .51	12.1 .99
	RBC X10 ⁶ /μL	6.81 .415 6	6.47 .378 4	6.73 .387 6	6.63 .396 5
	DOSE mg/kg/čay 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

3M_MN02343419

F

)

)

)

ł

t

Table 10

Summary of Clinical Hematology Data

Day 31 Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

	BASO&	0 ⁻ 0	4°2	0.0	5.4
	E SNINS	6, 1 6	4.4 4.4	2 6.12	5. ⁹
	MONO\$ E0	6.1 6.1	4.38 4.38	6 2.4	13 * 5.6
	 М	40 15.0 6	56 11.1 4	38 11.9 6.	42 7.1
	N-SEG% L	54 14.1 6	34 45.3 4.3	53 6.6	44 5.0
CITYMON C	в а so N X10 ³ /µі	000	.02 455	.0 .04	.00
	EOSIN X10 ³ /µL X1 			-10 -10	
N-T	ΜΟΝΟ X10 ³ /μι			.23 6	
	ТУМРН X10 ³ /μL			3.9 6.88 6.88	
	N-SEG X10 ³ /μL	7.3 4.05 6	2.8 1.76 4	6.0 3.45 6	4.0 .98 5
	WBC X10 ³ /µL	12.8 4.48 6	7.8 2.34 4	10.7 3.51 6	9.2 1.84 5
	DOSE WBC ng/kg/day X10 ³ /µL	0 MEAN S.D. N		10 MEAN S.D. N	30/20 MEAN S.D. N
		J	1*1	1	(*)

3M_MN02343420

78

1812.0079

)

ł

I

.

Table 11

Summary of Clinical Hematology Data

Males Day 63

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

FBR MG/DL	343 100.1 6	318 33.9 4	257 46.5 6	194 × 85.7
PTT SEC MG	19.2 1.59 6		20.0 2.47 6	
PT SEC	10.1 .41 6	10.0 .30	10.2 .27 6	10.8 .95
RETIC X10 ³ /µL	18 4.4 6	28 10.4 4	13 6.6	12 5.6
RETIC AP	605 605	4 17	2 111 6	40 10 10
РЦТ X10 ³ /µL	458 187.7 6	467 104.0 4	436 87.3 6	433 131.4 4
MCHC &	29.7 .97	30.0 .83	30.1 .53	29.6 .59
MCH PG	18.8 1.03 6	19.2 1.27	18.3 1.05 6	17.8 .54
MCV FL	63.3 3.24 6	63.9 4.66 4	60.9 2.86 6	60.0 2.31
ا اللہ اللہ اللہ اللہ اللہ اللہ اللہ الل	42.1 3.75	43.0 2.45 4	41.2 1.17 6	40.6 4.58 4
HGB G/DL	12.5 1.10 6	13.0 .90	12.4 .37	12.0 1.28 4
квс X10 ⁶ /µL	6.66 .641 6	6.75 .485 4	6.78 .323 6	6.77 .600 4
DOSE mg/kg/čaY 	0 Mean S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

<u>7</u>9

þ

J

ł

k

ł

,

Table 11

Summary of Clinical Hematology Data

Day 63 Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

	æ !	0 6.4	0.4	6.5 6.5	4.6 4.6
	BASO&				
	EOSIN&	¢.5	0.4	¢. 5	400
	MONO% EC	6.5 6.5	4.0 4	7 6.0	9 6 6 4 7 . 7
	i	41 6.8	42 12.3 4	37 10.9 6	54 7.0 4
	сся LYMPH%		50 13.5 4		
CIEVA	N-SEG%		0. 4		
ייישי מחפתה	вазо х10 ³ /µL		455		
	EOGIN X10 ³ /µL				
7	MONO X10 ³ /µL		.6 .17		
	тумрн X10 ³ /μь		4.1 .76		
	N-SEG X10 ³ /μL	1.83 1.83	2.5 .91	5.6 1.93 6	2.7 1.44 4
	WBC X10 ³ /μL	11.1 1.78 6		10.1 1.60 6	7.7 1.96 4
	DOSE mg/kg/day X. 	MEAN S.D. N	MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N
	ăĕ	0	m	T	ň

80

.

1

3

)

)

J

)

1

ł

Table 12

Summary of Clinical Hematology Data

Males Day 91

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

 $\begin{array}{c} 311\\ 49.0\\ 4\end{array}$ 278 15.2 6 262 36.2 6 244 57.3 2 FBR MG/DL 18.1 1.31 6 19.6 2.73 4 $\begin{array}{c} \mathbf{19.2} \\ \mathbf{1.64} \\ \mathbf{1.64} \\ \mathbf{6} \end{array}$ 22.5 2.05 2 PTT SEC 10.2 .19 6 10.3 .22 10.4 .34 .6 10.4 .49 .2 SEC PT 10 3.5 2.5 21 8.2 6.2 22 4.4 20 14.3 6 RETIC X10³/µL ω.5.4 .11 6 . 3 6 . 3 2.07 RETIC % 435 145.1 6 504 129.5 4 406 70.7 2 $\substack{421\\42.1\\6\end{cases}$ PLT X10³/µL 29.1 1.18 6 30.0 .81 4 30.1 .75 .6 29.8 .92 2 MCHC % 18.8 1.35 6 19.1.98 .4 18.4 1.10 6 17.2 .64 .2 PG $64.4 \\ 3.88 \\ 6 \\ 6$ 63.8 4.08 4 61.1 3.41 6 57.6 .42 .2 MCV 42.1 3.30 4 41.6 1.12 6 44.2 2.83 6 37.2 * 2.97 22 HCT % 12.9 .84 6 12.6 .91 12.5 .32 .6 11.1 .57 .2 HGB G/DL 6.61 .455 .4 6.87 .372 6 6.82 .374 6 6.46 .559 2 RBC X10⁶/µL DOSE mg/kg/day MEAN S.D. N MEAN S.D. N MEAN S.D. N MEAN S. D. N 30/20 10 0 m

3M_MN02343423

ł

)

ł

)

Table 12

Summary of Clinical Hematology Data

Males Day 91

1

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANDATE (APFO) IN CYNOMOLGUS MONKEYS

BASO&	6.4 6.4	4.0	0 • 4	2.7
EOSIN%	و. 8 8	5 4.1	2 1.5	2.7
MONO\$ EO	6.3 9	4.9 4.9	8 3.1	248
 ТАМРН%	52 6.4	46 10.1 4	40 10.4 6	49 149 2
л і 	40 9.4 6	42 15.4 4	50 14.0 6	40 19.8 2
BASO N X10 ³ /µL			.05 655	
EOSIN X10 ³ /µL X3			.18 6	
момо X10 ³ /µll			. 33 6	
лтин 10 ³ /µг			4.0 * .88 6	
N-SEG X10 ³ /µL		4.3 1.91 4	5.4 2.42 6	3.4 2.69 2
WBC X10 ³ /µL	10.8 1.68 6	10.2 2.73	10.4 2.58 6	7.7 2.97 2
DOSE mg/kg/day X1 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

)

)

)

÷

I.

Table 13

Summary of Clinical Hematology Data

Day 182 Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

FBR MG/DL	272 30.2 6	294 7.5 3	278 66.9 6	224 69.3 2
PTT SEC 1	17.9 1.53	20.6 4.98 3	19.6 1.74 6	25.5 7.00 2
PT	10.2 .43 .6	10.1 .45	10.3 .23 6	10.3 .07 2
RETIC X10 ³ /µL	42 27.0 6	60 11.7 3	35 25.5 6	8 12.0 2
RETIC RETIC	.41 641	6. 90.	5. 541 0	231
ргт X10 ³ /µг	408 133.8 6	516 132.3 3	416 103.5 6	378 180.3 2
MCHC &	31.1 .98	31.2 1.21 3	31.5 .67	31.4 .85 .2
MCH PG	19.0 1.17 6	18.5 1.01 3	18.3 1.14 6	17.2 .49 .2
MCV FL	60.8 3.33 6	59.4 2.56 3	58.1 4.19 6	55.0 .21
HCH HCH	40.6 .82 6	40.9 4.41 3	39.1 2.19 6	33.9 4.45 2
HGB G/DL	12.6 .55	12.7 1.04 3	12.3 .57	10.6 * 1.13 2
RBC X10 ⁶ /µL	6,69 .263	6.91 .928 3	6.76 .470 6	6.18 .841 2
DOSE mg/kg/đay 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

ί,

)

Ţ

i

)

Т

Table 13

Summary of Clinical Hematology Data

Day 182 Males 26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

BAS0%	 ی ف' ک	3.6 3.6
\$NISO5	 6 ⁻⁵	4.6 3.4.6
MONO% E	 9.6 9.6	10 35 0
гумрня	 45 9.9	49 11.4 3
N-SEG& LY	 45 7.3	37 20.7 3
	. 0 65	.1 .06
IN BASO /μι X10 ³ /μι	د. 13	.5 94
μι X10 ³ /μι	8 84.0 8	1.3 .85 3
МОМО . X10 ³ /µL	4.8 1.40 6	6.3 2.35 3
ГУМРН X10 ³ /µL		
N-SEG X10 ³ /µL	5.0 0.0 0.0	4.3 2.06 3
WBC X10 ³ /µL	10.9 3.43 6	12.5 1.75 3
⊃OSE mg/kg/đay	0 MEAN S.D. N	3 MEAN S.D. N

2.7

.1 0.7 0.7

11 2.0

54 12.7 2

30 10.6 2

500.1

0.220

538

4.1 .28 .2

5.2 1.2 1.2

7.8 2.19 2

MEAN S.D. N

30/20

1 6.4

3 6.6

9 6.8

43 11.2 6

45 12.5 6

.04 64

61.9

6.23 6

4.1 1.53 6

4.4 1.84 64

9.7 2.93 6

MEAN S.D. N

10

Covance 6329-231 3M T-6889.3					FBR MG/DL	305 53.7 2	214 14.8 2
Covance 3M					PTT I	17.9 .92 .2	20.2 1.34 2
					PT SEC	9. 255 255	10.2 .21 .2
				g (APFO)	RETIC X10 ³ /µL	46 6.4 2	20 19.1 2
				OCTANOATI	RETIC \$ X1	.6 207 2	288.2
		Summary of Clinical Hematology Data	covery)	STUDY WITH AMMONIUM PERFLUOROOCTANOATE (AFFO) IN CYNOMOLGUS MONKEYS	ргт X10 ³ /µг	492 247.5 2	390 78.5 2
	Table 14	iical Hemat	Day 217 (Recovery)	ITH AMMONI	MCHC &	30.6 .2	31.0 .71 .2
	H	ary of Clir	Males D	TY STUDY W IN CYNON	PG	19.6 .28	17.5 .07 .2
		Summe	ž	JEEK CAPSULE TOXICITY	MCV FL	64.0 1.84 2	56.5 1.70 2
					НСТ %	44.8 .00	39.8 .99 .2
				26-1	HGB G/DL	13.7 .14	12.3 .64 .2
					RBC X10 ⁶ /μL	7.00 .191 2	7.04 .389 2
					DOSE mg/kg/day 	0 MEAN S.D. N	10 MEAN S.D. N

3M_MN02343427

Table 14

Summary of Clinical Hematology Data

Males Day 217 (Recovery)

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

BASO&	 Ч	5.0	0 .7
EOSIN& B	en -	1.4	2.5 2.9
MONO\$ EO	 10	2.9	10 3.5 2.5
LYMPH&	49	5.2 8.2	43 9.9 2.9
N-SEG\$	36	14.8 2	42 17.7 2
BASO N X10 ³ /µL	5	.07	214
EOSIN X10 ³ /µl X1	. ۲ د	- 00	. 4 2 2 2 2
MONO X10 ³ /µL	1.7	500	1.1 .57
ТҮМРН Х10 ³ /µГ		207	4.9 1.56 2
N-SEG X10 ³ /µL	7.4	75. 0	4.6 1.48 2
WBC X10 ³ /µL	18.7	8.00 8	11.1 1.13 2
DOSE mg/kg/day	0 MEAN	n N N	10 MEAN S.D. N

Table 15

ı.

I.

Summary of Clinical Hematology Data

Males Day 245 (Recovery)

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

FBR MG/DL	 323 4.2 2.2	227 14.1 2
PTT SEC MG	18.0 1.77 2.2	19.2 .21 2
PT SEC		10.2 .07 2
RETIC X10 ³ /µL	24.9	10 14.8 2
RETIC 8 2		2122
PLT X10 ³ /μL	529 190.9 2	421 97.6 2
MCHC &	30.5 30.5 2	31.2 1.34 2
PG PG	19.6 2	17.5 .14 .2
MCV FL	64.1 1.56 1.2	56.3 1.98 2
HCT %	44 44 2 2	40.8 .85 2
HGB G/DL	13.6 13.6 21 21	12.7 .85 .2
RBC X10 ⁶ /µL	6.92 6.92 28	7.25 .410 2
DOSE mg/kg/day	0 NEAN S.D. N	10 MEAN S.D. N

Summary of Clinical Hematology Data

Day 245 (Recovery) Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM FERFLUCECOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

80	5 ⁻¹	2.7
BAS0%		
EOSIN&	0.1 0.1	212
*ONOM	0.00 0.00	10_7 7
T	52 25.7	44 7.8 2
N-SEG\$ LY	35 11.3 2	44 8.5 2
	8. .02	0.02
I BASO L X10 ³ /μL	550 80	5.58 5.58
EOSIN X10 ³ /µL		
момо x10 ³ /µг.	1.4	1.0 .35
ТҮМРН Х10 ³ /µГ	8.2 .49	4.9 3.11 2
N-SEG X10 ³ /µL	5.7 2.83	4.4 1.34 2
WBC X10 ³ /µL	15.8 2.90 2	10.7 5.09 2
DOSE mg/kg/day	MEAN S.D. N	MEAN S.D. N
O DEL	0	10

6329-231	6889.
Covance	ЗM

Summary of Clinical Hematology Data

Day 275 (Recovery) Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOHOOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

RBC HGB HCT MCV MCH PLT RETIC RETIC PTT PTT PTT X10 ⁵ /µL G/DL % FL PG % X10 ⁵ /µL % X10 ⁵ /µL % X10 ⁵ /µL % </th <th></th> <th></th> <th></th>			
RBC HGB HGT MCV MCH MCHC PLT RETTIC RETTIC PTT PTT X10 ⁵ /µL G/DL % FL PG % X10 ⁵ /µL % X10 ⁵ /µL SEC SEC SEC <td>FBR MG/DL</td> <td>530 530 173.2</td> <td>300 26.2 2</td>	FBR MG/DL	530 530 173.2	300 26.2 2
RBC HGB HGT MCV MCH PLT RETIC RETIC PT PT X10 ⁵ /µL G/DL % FL PG % X10 ⁵ /µL % X10 ⁵ /µL %		17.6 .49 .2	18.3 .71 .2
RBC HGB HCT MCV MCH MCHC PLT RETIC RETIC		9.8 9.8 .57	10.2 .21 .2
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		10 10 2.2	24 34.6 2
RBC HGB HCT MCV MCH MCHC PLT x10 ⁵ /µL G/DL % FL PG % x10 ³ /µL S/DL % FL PG % x10 ³ /µL PG % 31.6 \$84 6.96 13.8 43.6 62.5 19.8 31.6 \$84 7.714 1.20 3.89 6.85 .35 21.4 244.0 7.20 12.8 41.1 57.2 17.7 31.0 446 7.205 12.8 41.1 57.2 17.7 31.0 446		.07	49 249
RBC HGB HCT MCV MCH MCH x10 ⁵ /µL G/DL % FL PG % % FL PG % 8 9 3 % % % 6 96 13.8 43.6 62.5 19.8 31.6 7.14 1.20 3.89 63.5 19.8 31.6 7.20 12.8 41.1 57.2 17.7 31.0 7.20 12.8 41.1 57.2 17.7 31.0	_	584 244.0 2	446 53.7 2
RBC HGB HCT MCV MCH x10 ⁶ /µL G/DL % FL PG % FL PG PG PG PG PG PG PG 6'96 13.8 43.5 62.5 19.8 6'714 1.20 3.89 685 .35 7.20 12.8 41.1 57.2 .35 7.325 .49 .54 1.63 .17.7		31.6 31.6 2	31.0 .64 .2
RBC HGB HCT MCV x10 ⁵ /μL G/DL % FL g/DL % 62.5 6:96 13.8 43.6 62.5 .714 1.20 3.89 63.5 7.20 12.8 41.1 57.2 .325 .49 .64 1.63		19.8 .35 .25	17.7 .14 .2
RBC HGB HCT & HCT X10 ⁵ /µL G/DL & HCT & 1200000000000000000000000000000000000		62.5 285 2	57.2 1.63 2
RBC HGB X10 ⁵ /µL G/DL G/DL 6.96 13.8 6.96 13.8 7.20 12.8 .325 .49		43.6	41.1 .64 .2
RBC X10 ⁶ /µL 6.96 .714 .72 .325		13.8 1.20	12.8 .49 .2
I	RBC \$10 ⁶ /µL	4	7.20 .325 .25
		- MEAN S.D.) MEAN S.D.
	D D D D D D D D D D D D D D D D D D D	0	10

89

.

Table 16

Summary of Clinical Hematology Data

Day 275 (Recovery) Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

	÷		
BASO%		5. ¹	5.0
EOSIN\$		2.7	0 .7
MONO% E(12 2.8	8 2.1
1 %HAR		38 2.7	38 20.5 2
N-SEG\$		49 2.8	54 23.3 2
		. 1 200	200
EOSIN BASO X10 ³ /µl X10 ³ /µl		80.0 	1002
MONO E(X10 ³ /µl X1		1.6 .07 .2	1.3 200
гүмрн м х10 ³ /µс х1		5.6 1.77 2	5.6 1.77 2
N-SEG L X10 ³ /µL X1		7.4 2.55 2	9.1 5.94 2
WBC N. X10 ³ /µL X1		15.0 4.31 2	16.2 4.17 2
pose mg/kg/đay X1	I	MEAN S.D. N	MEAN S.D. N
DOSE DOSE		0	10

Table 17

Summary of Clinical Chemistry Data

Day -11 Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGHIS MONIER'S

	TRIG MG/DL	39 11.3 6	50 10.2 4	61 18.0 6	56 13.2 6
	CHOL MG/DL	147 44.3 6	174 53.7 4	145 22.0 6	140 26.3 6
	SBA UMOL/L M	62.0 6.0	10 4.6	9 6.7	8 4.7 6
	T BILI MG/DL (.0 655	4.1 4.1 .1	.23	.2 6 6
E K N	GLOB T G/DL 1 	4.6 .56	4.2 .63	4.3 .63	4.4 .70 6
DLGUS MONK.	ALB G/DL	4.8 .40 6	с. 2.29 6.4	4.8 .21 6	4.8 .20
IN CYNOM	T PRO G/DL	9.4 .58 .6	9.4 .87	9.1 .68 .6	9.1 .77 6
	CREAT MG/DL	1.2 .15	1.1 .15 .45	1.2 .05	1.1 .21 6
	MG/DL N	16 5.6	14 4-6	16 1.6 6	15 2.0 6
	GLU MG/DL M	92 15.3	88 11.7 4	92 21.5 6	81 4.6 6
	DOSE mg/kg/đay h	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 Mean S.d. N

Т

1

)

Summary of Clinical Chemistry Data

Day -11 Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

	8	4	.9	0
P AMYL U/L		183 30.4 4		
LIPASE IU/L		38 27.3 4		
AMYLASE IU/L	516 214.2 6	377 41.6 4	369 98.5 6	380 89.3 6
СЖ IU/L	145 77.2 6	142 19.1 4	128 45.0 6	142 56.6 6
HDS LU/L	ی. م. 8	5.7 4.7	5 6.1	9 6.4
GGT IU/L 	126 32.4 6	135 24.3 4	120 38.0 6	117 49.1 6
ALK PHOS IU/L	455 202.2 6	556 180.3 4	604 173.8 6	521 231.6 6
ALT/SGPT AL IU/L	58 58.8 6.8	42 8.1	77 52.6 6	66 41.8 6
AST/SGOT ALT IU/L	35 9.6 3	40 3.9	40 6.3	39 8.3 6.3
DOSE AS' mg/kg/day	MEAN S.D. N	3 MEAN S.D. N	MEAN S.D. N	20 MEAN S.D. N
/Som	0	m.	10	30/

ł

ŧ

Summary of Clinical Chemistry Data

Males Day -11

26-WEEK CAFSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

CL MMOL/L	114 1.6 6	110 1.7 4	112 1.5 6	112 2.2 6
K MMOL/L	5.8 .50	5.9 .78	5.4 .48 6	5.6 .56
NA MMOL/L	163 2.9 6	162 5.7 4	158 2.4 6	159 4.2 6
TC/DM TO/DM	5.8 .69	6.7 .53	6.3 1.37 6	6.1 .96
CA MG/DL	11.4 .45	11.4 .70	10.9 .45 6	10.7 .57 6
DOSE mg/kg/day 	0 MEAN S.D. N	3 MEAN S.D.	10 MEAN S.D. N	30/20 MEAN S.D. N

Table 18

ł

ł

Summary of Clinical Chemistry Data

Males Day 31

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)

•		
	IN CYNONOLGUS MONKEYS	

TRIG MG/DL	44 22.9 6	51 24.1 4	76 26.6 6	108 * 57.3 5
сног мG/DL	146 19.1 6	151 60.4 4	142 25.9 6	158 20.8 5
SBA UMOL/L	8 6.9	1.4	10 3.3 6	5.9 5.9
T BILI MG/DL	.2 .12 6	.14 .14		.1 509
GLOB T G/DL	4.6 .56	3.7 .45	4.1 .55	4.3 .37 5
ALB G/DL	4.7 .42 6	4.9 .24	4.8 .27 6	4.5 .38 5
T PRO G/DL	9.2 .58	8.6 .37	8.9 .75	8.8 .49 5
CREAT MG/DL	1.3 .17 6	1.2 .17	1.3 .15 6	1.3 .13
UN UN	15 2.4 6	16 4.4	17 1.5 6	16 2.4 5.4
GLU	78 22.9 6	78 9.3 4	72 8.5 6.5	75 9.3
DOSE mg/kg/day M	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

Table 18

Þ

1

Summary of Clinical Chemistry Data

Males Day 31

26-WEEK CAFSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

P AMYL U/L		181 33.5 4		
LIPASE IU/L		46 21.0 4		
AMYLASE IU/L		396 58.3 4		
CK IU/L		157 88.3 4		
SDH IU/L	4 6.6 6	4.23 4	2 6.4	5.1 5.3
GGT IU/L	121 29.3 6	107 24,5 4	107 29.6 6	98 34,1 5
ALK PHOS IU/L		629 193.9 4		
ALT/SGPT A IU/L		29 6.4 4		
AST/SGOT A IU/L		39 10.9 4		
DOSE mg/kg/day	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

3M_MN02343437

Table 18

ł

Summary of Clinical Chemistry Data

Males Day 31

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUORDOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

CL MMOL/L	113 2.8 6	111 1.3 4	110 2.1 6	112 3.7
K MMOL/L	5.8 .37 6	5.3 .22 4	5.0 .55	0 .90 .90
NA MMOL/L	158 3.3 6.	152 2.5 4	153 5.1 6	157 6.2 5
TC/5W SOH4 I	5.9 1.12 6	5 • 8 4	5.9 .75 .6	4.9 .63
CA MG/DL	11.0 .45	10.1 .14 4	10.4 .34 6	10.7 .81 .5
DOSE mg/kg/day 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

Table 19

)

Summary of Clinical Chemistry Data

Males Day 63

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANDATE (APFO)

26-WEEK CARSULE TOALCITE STUDY MITH ANNOUND FART DOCTOR CONTRACT AND A CARLON	
J NOTNOWWY UITM ICOLS	IN CYNOMOLGUS MONKEYS
CAPSULE TUALUTE	
20-WUUK	

TRIG MG/DL	43 13.5 6	59 20.4 4	76 27.4 6	66 39.0 4
CHOL MG/DL	151 36.9 6	161 61.3 4	158 46.2 6	146 12.2 4
SBA UMOL/L	3.7 6.7	9 4.1	9 6.2	22 4.8
r BILI MG/DL	4. 8 8	.3 48.08	.2 6	.3 41
GLOB G/DL			4.0 .54 .6	
ALB G/DL			4.6 .35 6	
T PRO G/DL			8.6 .67	
CREAT MG/DL	1.2 .19	1.1 .10	1.2 .16	1.2 .13 .4
UN MG/DL	17 3.8 6	18 4.3	17 1.5 6	20 5.0 4
GLU GLU			71 10.7 6	
DOSE mg/kg/day	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 Mean S.D. N

ļ

)

Summary of Clinical Chemistry Data

Day 63 Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

P AMYL U/L	262 81.8 6	220 45.4 4	211 83.4 6	、204 49.5 4
LIPASE P IU/L	28 16.2 6	86 81.3 4	13 12.2 6	13.6 4.6
AMYLASE L IU/L	481 147.1 6	396 58.5 4	347 106.2 6	352 71.3 4
CK A IU/L	139 78.9 6	131 16.2 4	143 65.6 6	379 496.0 4
SDH LU/L	4 6.9	2 4.0	3 6.5	9 4.89
GGT IU/L	123 31.2 6	121 15.9 4	114 29.7 6	110 55.7 4
ALK PHOS IU/L	582 193.3 6	612 169.9 4	668 190.3 6	484 159.5 4
ALT/SGPT ALK IU/L	62 63.9	45 46.7 4	53 19.4	192 269.7 4
AST/SGOT ALT IU/L	36 8.0 6.	35 10.4 4	36 9.9 9.9	141 187.4 4
DOSE AS mg/kg/day 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

Table 19

ł

Summary of Clinical Chemistry Data

Males Day 63

26-WEEK CAPSULE TOXICLTY STUDY WITH ANMONIUM PERFLUCROOCTANOATE (AFFO) IN CYNOMOLGUS MONKEYS

CL MMOL/L	111 2.9 6.	111 2.2 4	110 2.6 6	111 2.6 4
 ММОТ/Т К	5.1 .31	5.0 .13	4.6 .45 .6	5 • 9 4
NA MMOL/L	156 3.4 6	154 3.9 4.	150 * 1.8 6	152 3.9 4
I PHOS	5.9 .44	6.2 1.07 4	5.7 .69	4.9 .48
CA MG/DL	10.6 .32 6	10.6 .33	10.4 .38 6	9.9 9.93
DOSE mg/kg/đay 	0 MEAN S.D. N	3 MEAN S.D. N	1) MEAN S.D. N	30/20 MEAN S.D. N

Summary of Clinical Chemistry Data

Day 91 Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUORDOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

	TRIG MG/DL	40 8.5 6	56 25.2 4	88 36.8 6	99 55.2 2
	CHOL	167 45.3 6	157 51.3 4	155 30.6 6	142 9.2 2
	SBA UMOL/L P	11 4.5 6	12 4.0	11 5.2 6	13 5.7 2
	T BILL MG/DL	.2 6		.12 6	2.14 2.14
2	GLOB G/DL 	4.6 .27 6	4.0 .17 .4	4.3 .53	4.6 .49 2
	ALB G/DL	4.9 .33	4.9 .19 4	4.7 .33 6	4.4 .64 .2
	T PRO G/DL	9.5 .52	8.9 .12	9.1 .70	9.0 1.13 2
	CREAT MG/DL	1.3 .23 6	1.2 .14 4	1.3 .12 6	1.0 .21 2
	UN MG/DL	19 6.8	18 4.5	20 6.9	17 1.4 2
	MG/DL DLD DLD		78 9.8		
	DOSE mg/kg/đay 	MEAN S.D.	3 MEAN S.D. N	.0 MEAN S.D. N	80/20 Mean S.D. N
	08 I	0	m	Ч	(1)

ł

Summary of Clinical Chemistry Data

Males Day 91

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

P AMYL U/L	270 66.1	207 47.2 4	219 77.0 6	184 62.9 2
LIPASE I IU/L	20 17.4 6	50 32.0 4	9 12.6 6	11 15.6 2
AMYLASE 1 IU/L	515 148.7 6	378 63.6 4	367 100.7 6	318 67.9 2
СК 1 IU/L	143 55.8 6	126 35.3 4	133 34.4 6	156 31.8 2
TU/L HUS	10 3.7 6	10 1.0 4.0	11 2.9	10 2_0
GGT IU/L	128 31.4 6	118 22.5 4	113 30.8 6	120 88.4 2
ALK PHOS IU/L	529 240.3 6	585 177.6 4	656 208.6 6	432 306.2 2
ALT/SGPT AL. IU/L	63 22.7 6	47 25.2 4	53 15.5 6	48 17.7 2
AST/SGOT AL' IU/L		40 6.7 4		
DOSE mg/kg/day 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

Summary of Clinical Chemistry Data

Males Day 91

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

ł	CL MMOL/L	
	K MMOL/L	
	NA MMOL/L	
	I PHOS MG/DL	
	CA MG/DL	
	DOSE mg/kg/day	

	117 2.7 6	118 1.7 4	117 1.9 6	114 3.5 2
	5.3 5.3 5.3	5.1 .46	4.8 .37 6	5.4 .85 .2
	167 3.0 6	162 2.5 4	160 * 3.7 6	158 × 2.8
	6.4 .60	6.3 1.10 4	6.1 .80 6	5.0 .42 2
	11.3 .20	10.8 * .44	10.8 * .34 .6	10.1 * .71 2
	MEAN S.D. N	MEAN S.D. N	MEAN S.D. N	20 MEAN S.D. N
- Ann	0	m	10	30/20

3M_MN02343444

Ì

Summary of Clinical Chemistry Data

Day 182 Males

26-WEEK CAPSULE TOXICLTY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

DOSE mg/kg/day CLU MG/DL M		TRIG MG/DL	44 8.7 6	51 24.4 3.6	72 24.5 6	92 40.3 2
CLU UNIV CREAT T PRO ALL GIOB T BILL SBA MG/DL MG/DL MG/DL G/DL G/DL G/DL MG/DL UNOL/L 14 14 14 14 <td></td> <td>i</td> <td>156 35.0 6</td> <td>142 47.4 3</td> <td>154 30.6 6</td> <td>150 15.6 2</td>		i	156 35.0 6	142 47.4 3	154 30.6 6	150 15.6 2
CLU UN CREAT T PRO ALB GLOB T BLLT MG/DL MG/DL CREAT T PRO ALB GLOB T BLLT MG/DL MG/DL G/DL G/DL GLOB T BLLT 14.5 3.1 1.1 8.6 4.7 3.9 .3 14.5 5.0 1.1 8.6 4.7 3.9 .3 14.5 5.0 1.1 8.6 4.7 3.9 .3 63 22.8 1.1 8.4 4.9 3.5 .3 8.1 5.8 1.1 8.4 4.9 3.5 .3 19.7 6.6 1.1 8.4 4.6 6 6 19.7 2.4 1.19 8.4 4.6 6 6 6 27.6 1.6 2 2		i	18 3.6 6	17 2.5 3	16 1.4 6	18 .7
GLU UNV CREAT T PRO ALB G GG/DL MG/DL MG/DL CREAT T PRO ALB G 71 MG/DL MG/DL G/DL G/DL G/DL G 71 14.5 6.1 1.1 8.6 4.7 14.5 5.1 1.1 8.6 4.7 63 22.8 1.1 8.6 4.9 8.1 5.8 1.25 51 .32 65 20.4 1.1 8.4 4.6 19.7 6.4 1.1 8.4 4.6 19.7 6. 1.1 8.3 4.2 27.6 2 2 2 2 2		i				
CLU UNV CREAT T PRO GLU UNV CREAT T PRO AG/DL MG/DL G/DL G/DL G 14.5 50.1 1.1 8.6 63 2.1 1.1 8.6 63 2.2 1.1 8.4 66 20 1.1 8.4 19.7 2.4 1.19 8.4 19.7 2.4 1.19 8.4 8.3 33 80 16 .9 8.3 27.6 16 .9 8.3	C I T U	GLOB G/DL				
GLU UN CREAT T MG/DL MG/DL G 14.5 MG/DL MG/DL G 14.5 3.1 1.1 14.5 5.8 1.15 8.1 22.8 1.1 66 20 1.1 19.7 2.4 1.19 19.7 2.4 1.19 19.7 2.4 1.19 80 169 80 169		ALB G/DL				
GLU UN GR MG/DL MG/DL MG 71 MG/DL MG 71 20 14.5 30.1 63 22.8 8.1 22.8 80.16 19.7 20.4 10.7 20.4 80 16 27.6 10 27.6 20		T PRO G/DL				
GLU MG/DL MG MG/DL MG 71 63 8.1 65 19.7 19.7 22.6 27.6		CREAT MG/DL	1.1 .17	1.1 .25 .3	1.1 .19 .6	.9 .14 2
			20 3.1 6	22 9.8 9.8	20 2.4 6	16 2.7
DOSE mg/kg/day 		 GLU GLU				
		l l	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

)

Summary of Clinical Chemistry Data

Males Day 182

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

P AMYL U/L		313 72.0 3		
LIPASE 1 IU/L	29 0.0	106 63.8 3	11 9.1 6	8 12.0 2
AMYLASE IU/L	500 144.3 6	457 105.5 3	362 114.7 6	305 55.2 2
CK IU/II	140 28.8 6	139 37.6 3	922 1902.1 6	169 58.0 2
SDH IU/L	5.3 6.3	3.0 3.0	2.2	2.7
GGT IU/L	124 30.5 6	130 39.2 3	110 24.1 6	122 95.5 2
ALK PHOS IU/L	444 190.8 6	574 290.4 3	544 181.0 6	384 260.9 2
ALT/SGPT ALL IU/L	68 15.7 6	4 9 9 8	53 26.7 6	48 7.8 2
AST/SGOT ALT IU/L		46 31.5 3		
DOSE mg/kg/đay 	0 Mean S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 Mean S.D. N

ł

ł

Summary of Clinical Chemistry Data

Males Day 182

26-WEEK CAPSULE TOXICLTY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APPO) IN CYNOMOLGUS MONKEYS

CL MMOL/L	106 1.3 6	109 1.7 3	106 2.3 6	108 1.4 2
К ММОL/L	4.9 6.3 6	4.9 .96	4.3 .57	5.0 1.20 2
NA MMOL/L	152 6	154 10.4 3	148 3.9 6	150 2.8 2
JUC/DM SOH4 I	5.8 .44	6.0 2.12 3	5.8 1.16 6	4.8 .00 2
CA MG/DL	-0.0 -23	10.3 1.29 3	9.7 .52	9.2 .21
DOSE mg/kg/đay 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

105

.

Summary of Clinical Chemistry Data

Day 217 (Recovery) Males

26-WEEK CAFSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

TRIG MG/DL		40 2	80 43.8 2
CHOL MG/DL	-	194 48.8 2	159 39.6 2
SBA UMOL/L		ъ.0 6	2.0
T BILI MG/DL		.07 .2	.07 207
GLOB G/DL		4.4 .07 .2	3.3 .42 2
ALB G/DL		4.8 .35	4.6 .21 2
T PRO G/DL	-	9.2 .28	8.0 .21 2
CREAT MG/DL		1.4 .07 .2	1.4 .14 2
UN MG/DF		17 2.0	21 1.4 2
GLU GLU		101 36.8 2	61 67 67
DOSE mg/kg/day		0 MEAN S.D. N	10 MEAN S.D. N

Table 22

Summary of Clinical Chemistry Data

Males Day 217 (Recovery)

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUORUOCTANDATE (APFU) IN CYNOMOLGUS MONKEYS

TN CINORODO MONVEIS

P AMYL U/L	415	192.3 2	392 133.6 2
LIPASE IU/L	20	13.4 2	22 7.1 2
AMYLASE IU/L	612	221.3	477 94.8 2
CK IU/L		14.1 2	140 3.5 2
SDH IU/L	י ט ו ו	1.4	1.4
GGT IU/L	140	51.6	120 31.1 2
ALK PHOS IU/L	247	18.4	548 196.6 2
ALT/SGPT A. IU/L	42	17.0	18 8.5
AST/SGOT A. IU/L	34	2.8	50 57.8 57.8
DOSE mg/kg/đay	 0 MEAN	s.D. N	MEAN S.D. N

Table 22

1

Summary of Clinical Chemistry Data

Day 217 (Recovery) Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUURUOCTANDATE (AFFO) IN CYNOMOLGUS MONKEYS

CL CL CL	108 3.5 2	108 2.7
К ММОL/L	5.8 .35 .2	4.6 .14 2
NA MMOL/L	156 2.2 2.2	146 1.4 2
TC /9W SOHA I	6. 28 28	6.2 1.41 2
CA MG/DL	10.9 .00	6.6 00.2
DOSE mg/kg/đay	0 MEAN S.D. N	10 MEAN S.D. N

Table 23

Summary of Clinical Chemistry Data

Day 245 (Recovery) Males

	TRIG MG/DL	49 2.8 2.8	92 64.3 2
	CHOL MG/DL	203 67.9 2	164 30.4 2
NTE (APFO)	S3A UMOL/L	 4 2.0	51.4 7.4
ROOCTANOAT	T BILI MG/DL	 .07 207	207
UM PERFLUO (EYS	GLOB GLDL	 4.2 .35 2	3.2 .35 .35
STUDY WITH AMMONIUM	ALB G/DL	4.8 .35	4.8 .21
TY STUDY WI IN CYNOMO	T PRO G/DL	9.1 -00 2	8.1 14 2
CAPSULE TOXICITY	CREAT MG/DL	1.3 .14 2	1.3 .14 2
26-WEEK CAPSI	UN MG/DL	15 2.0	20 2.8 2.8
-92	GLU GLU	 95 2.4	80 2.1
	DOSE mg/kg/đay 1	 0 MEAN S.D. N	10 MEAN S.D. N

Table 23

Summary of Clinical Chemistry Data

Males Day 245 (Recovery)

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

		~	51
P AMYL U/L		420 186.0 2	394 112.4 2
LIPASE IU/L	-	46 2.1 2	56 13.4 2
AMYLASE I IU/L		604 219.2 2	490 70.0 2
CK AI IU/L		508 559.3 2	164 53.0 2
SDH SDH		4.2.7	2.7
GGT IU/L		134 65.8 2	120 32.5 2
ALK PHOS IU/L		245 58.0 2	635 206.5 2
ALT/SGPT ALI IU/L		44 1.4 2	44 2.2
AST/SGOT AL		35 7.1 2	28 3.5 2
DOSE AST mg/kg/day		MEAN S.D. N	MEAN S.D. N
SOU SOU	1	0	10

)

•

)

)

ŧ

1

Table 23

Summary of Clinical Chemistry Data

Day 245 (Recovery) Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

CL CL	110.7	2 114 2.7
K K	5.6	5.2 2.42 2.42
NA MMOL/L	 158 .0	2 153 2.8 2.8
על/DW SOH4 I	6.8 .21	2 6.4 1.06
CA MG/DL	10.7 .00	10.3 2 .00 .2
DOSE mg/kg/đay	0 MEAN S.D.	N 10 MEAN S.D. N

111

,

ł

ī

Table 24

Summary of Clinical Chemistry Data

Males Day 275 (Recovery)

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM FERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

TRIG MG/DL		38 12.0 2	48 36.8 2
CHOL MG/DL		194 88.4 2	150 39.6 2
SBA UMOL/L		10 2.7	8.7
T BILI MG/DL		ы. 4 2	۳.00 000
GLOB G/DL	-	4.5 .28	3.3 .42
ALB G/DL		4.7 .85	4.9 .42 .22
T PRO G/DL		9.2 .57	8.2 .00 .20
CREAT MG/DL		1.2 .42 .2	1. 3 200
UN UN		18 2.1	21 2.0
GLU GLU		84 12.0 2	90 4.2 2
DOSE mg/kg/day		0 MEAN S.D. N	10 MEAN S.D. N

÷

ł

÷

Table 24

Summary of Clinical Chemistry Data

Males Day 275 (Recovery)

26-WEEX CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

P AMYL U/L	 574 168 3	2	903 787.7 2
LIPASE P IU/L	 164 61 5	2	357 422.8 2
AMYLASE I IU/L	 826 224 2	7	1074 813.2 2
CK A IU/L	 1024 533.9	2	1524 563.6 2
IU/L SDH	 2 10	0	2 2.4
GGT IU/L	 112 21.2	7	116 31.1 2
ALK PHOS IU/L	 270	5	603 210.7 2
ALT/SGPT AL IU/L	108 63.6	7	76 7.8 2
AST/SGOT AL IU/L	 60 6.4	77	50 4.9 2.9
DOSE AS mg/kg/day	 0 MEAN S.D.	N 10	MEAN S.D. N

)

)

)

ł

Table 24

Summary of Clinical Chemistry Data

Males Day 275 (Recovery)

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUCROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

CL MMOL/L	107 2.2	103 2.0
K MMOT./F.	6.0 .78 .2	4.4 .00 2
NA MMOL/L	154	150 2.8 2
IC/DM SOH4 I		5.2 1.91 2
CA MG/DL	10.9	10.2 .00 2
DOSE mg/kg/đay	MEAN S. D.	.C MEAN S.D. N
	1 0	-

)

÷

)

Table 25

Summary of Clinical Urinalysis Data

Males Day -11

26-WEEX CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

Hả N	8.2 .41 6	7.9 .25	8.2 .41 6	8.2 .42
SP GR	1.016 .0073 6	1.010 .0086 4	1.014 .0060 6	1.014 .0081
U VOL	136.8 131.02 6	231.0 220.83	141.0 157.36 6	88.3 66.52 6
DOSE mg/kg/đay 	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

)

)

Ł

Table 26

Summary of Clinical Urinalysis Data

Males Day 31

26-WEEX CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

Нd	1	7.9 .38 6	7.8 .50	8.1 .20	7.5 .50
D					
SP GR	-	1.015 .0066 6	1.010 .0092	1.014 .0067 6	L.007 .0056
ß	ļ				
NL VOL		166.5 158.98 6	241.8 141.01	155.3 111.19	223.2 99.35 5
D			77		10
/day	Т	MEAN S.D. N	MEAN S.D. N	MEAN S.D. N	MEAN S.D. N
DOSE mg/kg/đay				0	30/20
18	1 0	>	m	Ч	ŝ

Table 27

Summary of Clinical Urinalysis Data

Males Day 63

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

H4 U	8.1 .20	7.5 * .41 .4	8.2 .26	7.5 .58 4
SP GR	1.013 .0078 6	1.010 .0097 4	1.012 .0057 6	1.016 .0048 4
U VOL ML	189.0 191.82 6	253.0 145.45 4	190.0 188.04 6	83.0 22.89 4
DOSE mg/kg/day	0 MEAN S.D.	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

)

)

)

)

ł

1

Table 28

Summary of Clinical Urinalysis Data

Males Day 91

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

H4 N	8 .27 .27	7.8 .29 4	7.9 .20	
SP GR	1,017 .0083 .06	1.012 .0088	1.012 .0054 6	
U VOL	186.0 182.11	272.0 218.99	222.0 174.10 6	c t
DOSE mg/kg/đa <u>v</u>	MEAN S.D. N	MEAN S.D. N	MEAN S.D. N	0
DOSE mg/kg	0	m	10	30/20

8.2 8.3 8

1.020.0000 2

 $71.0 \\ 9.90 \\ 2$

MEAN S.D. N

)

•

)

)

I

1

ŀ

1

Table 29

Summary of Clinical Urinalysis Data

Males Day 182

26-WEEK CAPSULE TOXICITY STUDY WITH ANMONIUM PERFLUOROCCTANOATE (APFU) IN CYNOMOLGUS MONKEYS

Hd D	7.7 .41	7.8 .29	7.2 .27	7.8 .35
SP GR	1.015 .0063 6	1.016 .0060 3	1.013 .0067 6	1.014 .0113 2
U VOL	159.5 67.63	172.3 71.07 3	208.5 159.04 6	197.0 154.15 2
DOSE mg/kg/day	0 MEAN S.D. N	3 MEAN S.D. N	10 MEAN S.D. N	30/20 MEAN S.D. N

)

•

ł

)

Table 30

Summary of Clinical Urinalysis Data

Day 217 (Recovery) Males

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

H4 D	8 .00 2	7.8 .35 .2
SP GR	1.008 .0071 2	1.006 .0035 2
U VOL.	392.5 215.67	290.0 233.35 2
DOSE mg/kg/åav 	0 MEAN S.D. N	10 MEAN S.D.

i

Table 31

Summary of Clinical Urinalysis Data

Males Day 245 (Recovery)

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

H4 N	 8.0 .00 2	7.5 .00 2
SP GR	1.013 .0099 2	1.005 .0028 2
U VOL ML	 196.0 166.88 2	341.5 246.78 2
DOSE mg/kg/đay	 0 MEAN S.D. N	10 MEAN S.D. N

J

)

١

)

ī

Table 32

Summary of Clinical Urinalysis Data

Males Day 275 (Recovery)

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUCROCTANOATE (APFO) IN CYNOMOLGUS MONKEYS

H4 N	7.0 .00	8.0 .00 2
SP GR	1.018 .0042 2	1.012 .0028 2
U VOL ML	115.0 60.81 2	135.5 61.52 2
DOSE mg/kg/đay	0 MEAN S.D. N	10 MEAN S.D. N

26-WEEK CAPSULLE TOXICITY 26-WEEK CAPSULLE TOXICITY (APFO) (APF	26-WEEK CAPSULLE TOXICITY 26-WEEK CAPSULLE TOXICITY (APFO) 0RGAN ORGAN-TO- 0RGAN WEIGHT BODY WT BRAIN (g) (%) RATI (g) (%) 0.00 0.0462 0.0003 0.0	26-WEEK CAPSULLE TOXICLITY 26-WEEK CAPSULLE TOXICLITY (APFC) 0RGAN ORGAN-TD- ORCAN WELGHT BODY WT BRAIN (g) (%) TATT 60.0078 0.0 0.0460 0.0003 0.0 0.0460 0.0010 0.0 0.0083 0.0 0.0069 0.0	26-WEEK CAPSUI	Week 27 Sacrifice
26-WEEK CAPSULE TOXICITY (APFO) (APFO) ORGAN 0RGAN-TO- 0RGAN WEIGHT BODY WT BRAIN (G) (%) **********************************	26-WEEK CAPSULLE TOXICITY (AFFO) ORGAN ORGAN-TO- ORGAN WEIGHT BODY WT BRAIN (g) (%) WT BRAIN (g) 0.0078 0.00 0.0462 0.0003 0.0	26-WEEK CAPSULLE TOXICITY (APFO) ORGAN ORGAN-TO- ORGAN WELGHT DOCAN WT BRAIN (g) (%) T BAIN (g) 0.0078 0.0 0.0460 0.00078 0.0 0.0460 0.0003 0.0 0.0460 0.00010 0.0 0.0460 0.00010 0.0	26-WEEK CAPSUI	
ORGAN ORGAN-TO- ORGAN WEIGHT BODY WT BRAIN (g) (%) RATI (g) (%) 4 4	ORGAN ORGAN-TO- ORGAN WEIGHT BODY WT BRAIN (g) (%) T BRAIN (g) 0.0078 0.0 0.0462 0.0003 0.0 3 3720 0.0010 0.0	ORGAN ORGAN-TO- ORGAN WEIGHT BODY WT BRAIN (g) (%) FATI (%) FATI (%) 0.0078 0.0 0.0462 0.0078 0.0 0.0460 0.0003 0.0 0.0460 0.0010 0.0		
ORGAN ORGAN-TO- ORGAN ORGAN-TO- WEIGHT BODY WT (\$) (\$) (\$) (\$) (\$) (\$) (\$) (\$) (\$) (\$)	TERMINAL ORGAN ORGAN ORGAN ORGAN BODY WT WEIGHT BODY WT BODY WT (g) (g) (g) (g) 3947.5 0.3855 0.0003 591.1 0.0462 0.0003 333 330.6 0.0460 0.0010	TERMINAL ORGAN ORGAN ORGAN TCO BODY WT WT BODY WT BODY WT G(\$) (\$) (G) (G) (G) (G) (\$) (\$) 3947.5 0.3085 0.0078 0.0078 591.1 0.3085 0.0003 0.0003 33.3 3.0.6 0.3720 0.0003 30.6 0.3720 0.0010 0.0010 4465.7 0.3720 0.0010 0.0010 4447.5 0.3030 0.0024 0.0024	TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;SUBSET=ALL	LF ADREWAL
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	4 4 4 0.3085 0.0078 0.30462 0.0078 0.3720 0.00083 0.3720 0.0083 0.3720 0.0083 0.0460 0.0024 0.0940 0.0024	HINAL ORGAN WEIGHT (9) (9)	1
$\begin{array}{cccc} & 4 & 4 \\ 0.3085 & 0.0078 \\ 0.0462 & 0.0003 \end{array}$	3947.5 0.3085 0.0078 591.1 0.0462 0.0003 	3947.5 0.3085 0.0078 591.1 0.0462 0.0003 591.1 0.0462 0.0003 1486.7 0.3720 0.0083 30.6 0.0460 0.0010 1447.5 0.3030 0.0024 498.5 0.0940 0.0024		
		0.0940 0.0024	4 0.3085 0.0462	
		0.0940 0.0024		, 1 1
3 3 3 3 4486.7 0.3720 0.0083 30.6 0.0460 0.0010				• • 1
4486.7 0.3720 0.0083 30.6 0.0460 0.0010 4447.5 0.0940 0.0024 498.5 0.0940 0.0024	4 0.3030 4 0.0069 0.0940 0.0024		3925.0 0.3320 0.0087 583.0 0.0311 0.0006	

J

)

λ

•

)

ł

)

3M_MN02343465

			SUI	TABLE 33 Summary of Organ Weight Data		Covance 6329-231 3M T-6889.3
				Week 27 Sacrifice	Sacrifice	
		26-WEE1	K CAPSULE TO	KICITY STUDY WI	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APPO) IN CYNOMOLGUS MONKEYS	PAGE: 2
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;SUBSET=ALL	ALL;WEEKS=ALL =ALL	-		RT ADRENAL	ЯАТ.	
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	DRGAN-TO- ORGAN-TO- BODY WT (\$)	ORGAN-TO- ORGAN-TO- BRAIN WT RATIO		
 MBER STA				1		
10		-				
MBER IN GRO ME STANDARD D	67 1	3 0.3573 0.0492	- m 0 0 0			
10						
NUMBER IN GROUP: MEAN: STANDARD DEV:	4447.5 4447.5 498.5	4 0.2328 0.0512	4 0.0054 0.0016	- $ 0.0036$ 0.0009		
4						
	3925.0 583.0	2 2620 0.2620 0.0891				

, j

)

ŀ

>

)

3M_MN02343466

26-WEEK CAPSULE TOXICITY STUDY W 26-WEEK CAPSULE TOXICITY STUDY W 0RAI 0RGAN 0REAN 1.6471 1.6803 <th>ABLE INCLUDES: SEX-ALL; GROUPEST = ALL; MEEKS=ALL DEATH=T; SUBSET = ALL DEATH=T; SUBSET = ALL GROUP (9) (1) (1) (1) (1) (1) (1) (1) (1) (1) (1</th> <th></th> <th></th> <th></th> <th>Su</th> <th>Summary of Organ Weight Data Week 27 Sacrifice</th> <th></th> <th>3M T-6839.3</th>	ABLE INCLUDES: SEX-ALL; GROUPEST = ALL; MEEKS=ALL DEATH=T; SUBSET = ALL DEATH=T; SUBSET = ALL GROUP (9) (1) (1) (1) (1) (1) (1) (1) (1) (1) (1				Su	Summary of Organ Weight Data Week 27 Sacrifice		3M T-6839.3
	ORGAN ORGAN-TO ORGAN-TO WEIGHT DODY WT BRAIN WT (g) (%) RATIO (g) (%) RATIO (g) (%) 1.0000 7.6823 0.1763 0.0000 7.6823 0.1763 0.0000 64.5708 1.6471 1.0000 63.5134 1.4622 1.0000 64.2590 0.0614 0.0000 64.2590 0.2194 1.0000 74.2590 0.2194 0.0000 3.6416 0.2309 0.2309 0.0000			26-WEE	K CAPSULE TO	XICITY STUDY WI (APFO) IN CYNOM	11TH AMMONLUM FERFLUOROOCTANOATE MOLGUS MONKEYS	
TERMINAL OFCAN ORCAN TO- BODY WT (G) (F) WT (G) (G) (F) (F) (F) (F) (F) (F) (F) (F) (F) (F	TERMINAL OFCAN ORCAN TO- BODY WT (G) (G) (F) WT (G) (G) (G) (F) (F) (F) (G) (G) (G) (G) (G) (G) (G) (G) (G) (G	TABLE INCLUDES: SEX=ALL;GROUP=A DEATH=T;SUBSET=	LL; WEEKS=AI Ань	11		BRAIN	R	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$				 ORGAN-TO- BODY WT (%)			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$							
4485.7 5.5134 1.4827 4486.7 5.5134 1.4827 30.66.2.3695 0.0614 447.5 64.2743 1.4622 428.5 4.2590 0.2194 	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	NUMBER IN GROUP: MEAN: MEAN: STANDARD DEV:	 3947.5 591.1		- $ -$			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2				-		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	NUMBER IN GROUP: MEAN: STANDARD DEV:						
4447.5 64.2743 4.4622 498.5 64.2743 1.4622 4.2590 0.2194 3925.0 74.2460 1.9603 583.0 3.6416 0.2309	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3			- i			
	$ \begin{array}{ccccccccccccccccccccccccccccccccccc$	JUMBER IN GROUP: MEAN: MEAN: STANDARD DEV:	4447.5 498.5		- $ -$	4 1.0000 0.0000		
	3925.0 74.2460 1.9603 583.0 3.6416 0.2309	4		 				
						- $ -$		
	125					12	5	

I

3M_MN02343467

1812.0126

				E	Covance 3M	ce 6329-231 3M T-6889.3
			SU	ummary of Or	Summary of Organ Weight Data	
				Week 27	27 Sacrifice	
		26-WEE	26-WEEK CAPSULE TOXICITY (APFO)		PAGE: 4 IN CYNOMOLGUS MONIUN PERFLUORGOCTANOATE	
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;SUBSET=ALL	ALL ; WEEKS=ALI =ALL	н		LF EP	LF EPIDIDYMIS	
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO- BODY WT (%)			
M 1 		$\frac{1}{4}$	4 0.0410 0.0112	4 0.0256 0.0955		
2						
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:						
3						
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:				4 0.0268 0.0094		
M 4			1			
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:	325.0 583.0			2 0.0257 0.058		

T

Ł

			3	Week 27 Sacrifice	acrifice
		26-WEEI	26-WEEK CAPSULE TOXICITY (APFO)		PAGE: 5 STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS
TABLE INCLUDES: TABLE INCLUDES: SEX=ALL;GROUP=ALL; DEATH=T;SUBSET=ALL	LL;WEEKS=ALL		 	RT EPIDIDYMIS	SIWX
SEX DOSE	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO- BODY WT (%)	RATIO	
M 1		i i		1 1	
NUMBER IN GROUP: NEAN: STANDARD DEV:		4 1.7750 0.4542			
 M 2	1				
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:					
М 3	i.				
NUMBER IN GROUP: MEAN: STANDARD DEV:	4447.5 498.5	4 1.6640 0.5738		$4 \\ 0.0261 \\ 0.091$	
NUMBER IN GROUP: MEAN: STANDARD DEV:		2 2 1.7740 0.2489			

PAGE: 5

I

ķ

TABLE 33

Summary of Organ Weight Data

				Τ	TABLE 33	Covance 6329-231
			Su	mmary of Org	Summary of Organ Weight Data	3M T-6889.3
				Week 2	Week 27 Sacrifice	
		26-WEE.	26-WEEK CAPSULE TOXICITY (APFO)	XICITY STUDY (APFO) IN CY	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 6
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;SUBSET=ALL	all;WEEKS=All =All	. 7		LF X	LF KIDNEY	
	TERMINAL BODY WT (G)	DECAN WEIGHT (g)	CRGAN-TO- BODY WT (%)	ORGAN-TO BRAIN WT RATIO		
MBER STAN	3947.5 591.1	4 6.5898 0.9070	4			
M 2		-				
NUMBER IN GROUP: MEAN: STANDARD DEV:				- $ -$		
3						
NUMBER IN GROUP: MEAN: STANDARD DEV:		4 4 8.0508 0.6366	- $ -$	4 0.1260 0.0168		
M 4						
NUMBER IN GROUP: MEAN: STANDARD DEV:	3925.0 583.0	2 9.1090 * 1.0041				

3M_MN02343470

			πs	T/ Summary of Org	TABLE 33 Organ Weight Data	Covance 6329-231 3M T-6889.3
				Week	Week 27 Sacrifice	
		26-WEE	26-WEEK CAPSULE TOXICITY (APFO)		STUDY WITH AMMONIUM FERFLUOROOCTANOATE IN CYNONOLGUS MONKEYS	PAGE: 7
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;SUBSET=ALL	ALL; WEEKS=ALL =ALL			RT 1	RT KIDNEY	
SEX DOSE GROUP M 1	TERMINAL BODY WT (G)	ORGAN WEIGHT (g)				
NUMBER IN GROUP: MEAN: STANDARD DEV: M 2	3947.5 3947.5 591.1	4.5520 6.5520 1.0155		4 0.0092		
3				 		
			4	4		
4						
NUMBER IN GROUP: MEAN: STANJARD DEV:	3925.0 583.0 583.0	2		2		
		 		9 1 1 1 1 2 1 2 1 1 1		

F

t

)

3M_MN02343471

				TABLE 33 Summarv of Orcan Weicht Data	a ta	Covance 6329-231 3M T-6889.3
			5	Week 27 Sacrifice	area a	
		26-WEE	26-WEEK CAPSULE TOXICITY (APFO)	XICITY STUDY WITH AMMON (APFO) IN CYNOMOLGUS MOI	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 8
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;SUBSET=ALL	ALL; WEEKS=AL	Ţ		LIVER		
- 10 - 10 - 10	TERMINAL BODY WT (g)	versen versen versen (g)	ORGAN-TO- BODY WT (%)	C.C.A.NT.O. BRAIN WT RATIO		
M L 		- $ -$	- $ -$	4 0.3344 0.0736		
2						
NUMBER IN GROUP: MEAN: STANDARD DEV:	4486.7 4486.7 30.6	- $ -$				
NUMBER IN GROUP: MEAN: STANDARD DEV:		- $ -$	4			
4						
				2		
				130		

ł

t

1

3M_MN02343472

				TABLE 33		Covance 6329-231
			Su	Summary of Organ Weight Data	it Data	3M T-6889.3
				Week 27 Sacrifice	ice	
	, , , , , , , , , , , , , , , , , , ,	26-WEE	26-WEEK CAPSULE TOXICITY (APFO)	KICITY STUDY WITH AMM (APFO) IN CYNOMOLGUS	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 9
TABLE INCIUDES: SEX=ALL; GROUP=ALL; WEEKS=ALL DEATH=T; SUBSET=ALL	ALL;WEEKS=AL	L		PANCREAS		
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	DRGAN-TO- BODY WT (%)	ORGAN-TO- ORGAN-TO- BRATIN WT RATIO		
M 1 						
2						
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:	4486.7 4486.7 30.6		 3 0.1359 0.0262			
M 3						
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:	4447.5 4447.5 498.5		4 0.1194 0.0281			
4						
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:				2		

				TABLE 3	33 Cova	Covance 6329-231
			Su	Summary of Organ Weight Data		С. 2080-Т. M.C
				Week 27 Sacr	Sacrifice	
		26-WEE	26-WEEK CAPSULE TOXICITY (APFO)		PAGE: STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	GE: 10
TABLE INCLUDES; SEX=ALL; (SUOUP=ALL; WEEKS=ALL DEATH=T; SUBSET=ALL	ALL;WEEKS=AL	L		LF TESTIS		
- <u>- 16</u>	TERMINAL BODY WT (G)	0RGAN WEIGHT (g)		ORGAN-TO- BRAIN WT RATIO		
-1						
ST BE		66	- 251 098	40		
2						
NUMBER IN GROUP: MEAN: STANDARD DEV:						
3						
NUMBER IN GROUP: MEAN: STANDARD DEV:			4 0.2728 0.1022	- $ 0.1915$ 0.0740		
4				-		
NUMBER IN GROUP: MEAN: STANDARD DEV:		2		 0.1396 0.0360		
			1 1 1 1 1 1 1 1 1 1			

J

)

÷

ł

				TABLE 33		Covance 6329-231
			Su	Summary of Organ Weight Data	Data	C. 2000-I MC
				Week 27 Sacrifice	0	
		26-W3EI	26-WEEK CAPSULE TOXICITY (APFO)	KICITY STUDY WITH AMMON (APFO) IN CYNOMOLGUS MO	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 11
ABLE INCLUDES SEX=ALL; GRO DEATH=T; SUB	ALL;WEEKS=ALI =ALL			RT TESTIS		
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO- BODY WT (%)	ORGAN-TO- ORGAN-TO- BRAIN WT FATIO		
215 1			- $ -$			
M						
NUMBER IN GROUP: MEAN: STANDARD DEV:	3 4485.7 30.6	3 16.1067 4.2181	3 0.3588 0.0930	3 0.2425 0.0641		
IN GRO ME NDARD D	4447.5 498.5	- 1 1 - 1	021	4 0.1810 0.0633		
M 4						
IBER IN G STANDARD	3925.0 583.0	2 9.8880 2.0633	2 0.266 0.098	2		

ì

1

i

3M_MN02343475

				TAE	TABLE 33 COVA	Covance 6329-231
			Su	mmary of Orga	Summary of Organ Weight Data	U-0005. MC
				Week 27	7 Sacrifice	
		26-WEE1	K CAPSULE TO	XICITY STUDY (APFO) IN CYN	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	PAGE: 12
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;SUBSET=ALL	all; WEEKS=All =All	. "		LF THYRC	LF THYROID/PARA	·
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	CRGAN-TO- BODY WT (%)			
M 1 		4 0.2205 0.0617				
NUMBER IN GROUP: MEAN: STANDARD DEV:						
				1		
NUMBER IN GROUP: MEAN: STANJARD DEV:		4 0.3340 0.1502	4 0.0074 0.0028	- $ 0.0053$ 0.0025		
4						
NUMBER IN GROUP: NEAN: STANDARD DEV:				2		

)

÷

ł

			ć	ί.Ι. ·		Covance 6329-231 3M T-6889.3
			SU	mmary of Orc	Summary of Organ Weight Data	
				Week 2	Week 27 Sacrifice	
		26-WEE	26-WEEK CAPSULE TOXICITY (APFO)	XICITY STUDY (APFO) IN CY	STUDY WITH AMMONIUM PERFLUCKOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 13
TABLE INCUUDES: SEX=ALL;GROUP=ALL;WEEXS=ALL DEATE=T;SUBSET=ALL	ALL;WEEKS=ALI FALL	.7		КТ ТНҮБ	RT THYROID/PARA) 1 1 1 1 1 1 1 1 1 1 1 1 1
	TERMINAL BODY WT (g)	DRGAN ORGAN WEIGHT (g)	ORGAN-TO- BODY WT (%)	ORGAN-TO BRAIN WT BRAIN WT RATIO		
M 1 NUMBER IN GROUP: STANDARD DEV:		4.0.2225 0.0654	- $ -$	- $ -$		
2						
М 3			1			
NUMBER IN GROUP: MEAN: STANDARD DEV:			- $ -$	4		
NUMBER IN GROUP: MEAN: STANDARD DFV:						

)

)

ł

3M_MN02343477

				TABLE 34	Covance 632	6329-231
				Summary of Organ Weight Data	3M T-68	5.9880
				Week 40 Recovery Sacrifice		
		26-WEE	26-WEEK CAPSULE TOXICITY (APFO)	XICITY STUDY WITH AMMONIUM PERFLUOROCCTANOATE (AFPO) IN CYNOMOLGUS MONKEYS	PAGE: 1	
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=U;SUBSBT=ALL	ALL;WEEKS=ALL =ALL	_		LF ADRENAL		
SEX DOSE GROUP	TERMINAL BODY WT (9)	ORGAN WEIGHT (g)	ORGAN-TO- DORY WT (%)	 CRGAN-TO- BRAIN WT RATIO		
М 1						
NUMBER IN GROUP: REAN: STANDARD DEV:	5410.0 240.4	2		2		
E M		1				
IBER IN GRC ME STANDARD D	2 3932.5 618.7	0.0	0.0	0.00041 0.00041		

)

)

)

)

)

T

				TABLE 34 Summary of Organ Weight Data	Covance 6329-231 3M T-6889.3
				Week 40 Recovery Sacrifice	
		26-WEE	K CAPSULE TO	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLHOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	PAGE: 2
TABLE INCLUDES: SEX=ALL,GROUP=ALL;WEEXS=ALL DEATH=U;SUBSET=ALL	⊧ALL;WEEKS=ALL ;=ALL			RT ADRENAL	
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO- BODY WT (%)	ORGAN-TO- ORGAN-TO- BRAIN WT RATIO	
м 1					
NUMBER IN GROUP: MEAN: STANDARD DEV:				- 5 0.003 - 0.003	
3	1		1		
UMBER IN GROUP: MEAN: STANDARD DEV:		2 0.1920 0.0382	2	0.000	

				Summary of Organ Weight Data	JM T-0889.3
				Week 40 Recovery Sacrifice	
		26-WEEK	26-WEEK CAPSULE TOXICITY (APFO)	XICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APPO) IN CYNOMOLGUS MONKEYS	PAGE: 3
TABLE INCLUDES: SEX=MLL;GROUP=ALL;WEEKS=ALL DEATH=U;SUBSET=ALL	JEEKS=ALL			BRAIN	
EX DOSE		ORGAN WEIGHT (g)		CORGAN-TO- ORGAN-TO- BRAIN WT RATIO	
NUMBER IN GROUP: 5 STANJARD DEV: 5					
3					
			$\begin{array}{c} - & - & - & - \\ 2 \\ 1.7330 \\ 0.4292 \end{array}$		

)

÷

ŧ

138

3M_MN02343480

				TABLE 3	34 Covance	Covance 6329-231
				Summary of Organ Weight Data		3M T-6889.3
				Week 40 Recovery Sacrifice	y Sacrifice	
			K CAPSULE TO	XICITY STUDY WITH AMMONIUM PI (APPO) IN CYNOMOLGUS MONKEYS	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUORCOCTANOATE (APPO) IN CYNOMOLGUS MONKEYS	4
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATF=U;SUBSET=ALL	all; ALL;			LF EPIDIDYMIS	SIM	
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO- BODY WT (\$)	ORGAN-TO- ORGAN-TO- BRAIN WT RATIO		
ч						
NUMBER IN GROUP: MEAN: STANDARD DEV:	5410.0 240.4	2	$\begin{bmatrix} -2 & -2 & -2 \\ 2 & 0.0481 \\ 0.0033 \end{bmatrix}$	2 0.0397 0.0001		
i i m		i –	1	{		
NUMBER IN GROWP: MEAN: STANDARD DEV:		 2 1.6595 0.0955	$\begin{bmatrix} 2 & - & - & - \\ 2 & 0.425 \\ 0.0043 \end{bmatrix}$			

į.

3M_MN02343481

				TABLE 34	4 Altore Toto	Covance 6329-231 3M T-6889.3
					Vergint Data	
				Week 40 Recovery Sacrifice	Sacrifice	
			26-WEEK CAPSULE TOXICITY (APFO)	ICITY STUDY WITH AN APFO) IN CYNOMOLGUS	IN CYNOMOLGUS MONKEYS IN CYNOMOLGUS MONKEYS	PAGE: 5
TABLE INCLUDES: SEX-ALL; GROUP=ALL; MEEKS=ALL DEATH=U; SUBSET=ALL	ыь; WEEKS=Aлл Алг			RT EPIDIDYMIS	ß	
x DOSE			DRGAN-TO- DRGAN-TO- BODY WT (%)	 ORGAN-TO- BRAIN WT RATIO		
M 1		1	t i	 		
		2				
M 3						
		, , ,				

				TABLE 34		Covance 6329-231
				Summary of Organ Weight Data	ď	U-0000 T. MC
				Week 40 Recovery Sacrifice		
		26-WEEK	26-WEEK CAPSULE TOXICITY (AFFO)	XICITY SFUDY WITH AMMONIUM PERFLUOROOCTANOATE (AFFO) IN CYNOMOLGUS MONKEYS	PERFLUOROOCTANOATE	PAGE: 6
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=U;SUBSET=ALL	EEKS=ALL			LF KIDNEY		
z	TERMINAL BODY WT (G)	ORGAN WEIGHT (g)				
NUMBER IN GROUP: 5. STANDARD DEV: 5.	2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 -					
MBER IN GROUP: MEAN: MEAN: STANDARD DEV:						

)

)

)

÷

				TABLE 34		Covance 6329-231 3M m_6880 3
				Summary of Organ Weight Data		
				Week 40 Recovery Sacrifice		
		26-WEE!	K CAPSULE TO.	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APPO) IN CYNOMOLGUS MONKEYS	UROOCTANOATER	PAGE: 7
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=U;SUBSET=ALL	ALL;WEEKS=ALL			RT KIDNEY		
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN ORGAN WEIGHT (g)	CRGAN-TO- CRGAN-TO- BODY WT (%)	CRGAN-TO- BRAIN WT RATIO		
А						
NUMBER IN GROUP: MEAN: STANDARD DEV:	5410.0 240.4 240.4	2 8.8620 0.9730				
M 3		1				
NUMBER IN GROUP: MEAN: STANDARD DEV:		 2 5.6370 0.6449				

3M_MN02343484

				TABLE 34		Covance 6329-231
				Summary of Organ Weight Data	: Data	C. 2000-T. MC
				Week 40 Recovery Sacrifice	fice	
		26-WEER	CAPSULE TOX	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APPO) IN CYNOMOLGUS MONKEYS	LUM PERFLUOROOCTANOATE NKEYS	PAGE: 8
TABLE INCLUDES: SEX=ALL;GROUP=ALL;MEEKS=ALL DEATH=U;SUBSET=ALL	LL;WEEKS=ALL ALL			LIVER		
SEX DOSE	 TERMINAL BODY WT (g)		ORGAN-TO- ORGAN-TO- BODY WT (%)	 ORGAN-TO- BRAIN WT RATIO		
M 1		F 				
NUMBER IN GROUP: MEAN: STANDARD DEV:						
3						
NUMBER IN GROUP: MEAN: STANDARD DEV:			2			

				T2	TABLE 34	Covance 6329-231
				Summary of	Summary of Organ Weight Data	2. 4889-1 MC
				Week 40 Re	Recovery Sacrifice	
		26-WEE1	26-WEEK CAPSULE TOXICITY (AFFO)		STUDY WITH AMMCNIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 9
TABLE INCLUDES; SEX-ALL;GROUP=ALL;WEEKS=ALL DEATH=U;SUBSET=ALL	all, weeks=all			PANC	PANCREAS	
SEX DOSE GROUP	 TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO- BODY WT (%)	AN-T AN-T TN W TIO W		
UNBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:	5410.0 240.4	2	2 0.1570 0.0060	2 0.0037		
3						
		2		2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 -		

)

)

)

)

)

)

)

)

3M_MN02343486

				TABLE 34	COVANCE 6329-231
				Summary of Organ Weight Data	3M T-6889.3
				Week 40 Recovery Sacrifice	
		26-W3E.	26-WEEK CAPSULE TOXICITY (APFO)	KICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	PAGE: 10 IANOATE
TABLE INCLUDES: SEX=ALL;GOUP=ALL;WEEKS=ALL DEATH=U;SUBSET=ALL	ЧLL;WEEKS=ALL =Аыь			LF TESTIS	
SEX DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO- BCDY WT (%)		
Ħ					
NUMBER IN GROUP: MEAN: STANDARD DEV:	5410.0 240.4	2 2 16.0235 2.4600	22975 0.2975 0.0587		
3					
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:					

)

•

)

•

)

)

3M_MN02343487

				TA	TABLE 34 Covance 6329-231	39-231
				Summary of (3M T-681 Summary of Organ Weight Data	5889.3
				Week 40 Red	Week 40 Recovery Sacrifice	
		26-WEEI	26-WEEK CAPSULE TOXICITY (APFO)		STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=U;SUBSET=ALL	ALL; WEEKS=ALL	_	1	RT T	RT TESTIS	
SEX DOSE GROUP	 TERMINAL BODY WT (G)	ORGAN WEIGHT (G)		 ORGAN-TO- BRAIN WT RATIO		
NUMBER IN GROUP: NUMBER IN GROUP: MEAN: STANDARD DEV:	5410.0 240.4 240.4	2 $ -$				
NUMBER IN GROUP: MEAN: STANDARD DEV:		2				

;

)

÷

÷

3M_MN02343488

				TABLE Summary of Orce	TABLE 34 of Orran Weidth Dara	Covance 6329-231 3M T-6889.3
				Summary UL Orga	AII WEIGIL DALA	
				Week 40 Recovery Sacrifice	ery Sacrifice	
		26-W3EF	26-WEEK CAPSULE TOXICITY (APPO)	XICITY STUDY WIT (AFFO) IN CYNOMO	STUDY WITH AMMONIUM PERFJUOROOCTANOATE	PAGE: 12
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=U;SUBSET=ALL	ALL; WEEKS=ALL :ALL			LF THYROID/PARA)/PARA	
SEX DOSE GROUP		 RGAN IGHT g)		 ORGAN-TO- BRAIN WT RATIO		
ц						
	5410.0 240.4 240.4		2 0.0047 0.0005			
			i –			
NUMBER IN GROUP: MEAN: STANDARD DEV:		2 2 0.3165 0.1732		2		

F

6

1

•

)

Ŧ

ı,

Summary of Organ Weight Data Beek 40 RECOVERY Sacrifice Medication The answer of the transmertain of the t					AUAAT.
Meek 40 Recovery Sacrifice 26-WEEK CAPSULE TOXICITY STUDY WITH AMONIUM FERFLUOROCCTANOATE 26-WEEK CAPSULE TOXICITY STUDY WITH AMONIUM FERFLUOROCCTANOATE 7000000000000000000000000000000000000					Summary of C
26-WEEK CAPSULE TOXICITY STUDY WITH AMONION PERFLUOROOCTANDATE (APPO) IN YUNOSUGUS MONIEYS R.T THYROID/PARA R.T THYROID/PARA R.T THYROID/PARA R.T THYROID/PARA R.T THYROID/PARA R.T THYROID/PARA (G) (R) (R) (R) (R) (G) (R) (G) (R) (R) (G) (R) (G) (R) (G) (R) (R) (R)					Week 40 Rec
ORGAN ORGAN TO ORGAN TO ORGAN ORGAN ORGAN TO ORGAN (g) (%) HA (g) (%) (%) A (g)			26-WEER	CAPSULE TO	KICITY STUDY (APFO) IN CYI
TERMINAL OKGAN ORGAN TRANTO EODY WT WEIGHT BODY WT (g) (g) (g) (k) (g) 0.0127 0.0004 240.4 0.0127 0.0004 3932.5 0.3000 0.0081 618.7 0.1937 0.0062	E INCLUDES: EX=ALL;GROUP= EATH=U;SUBSET	ALL;WEEKS=ALL =ALL			КТ ТНҮК
5410.0 0.2570 0.0048 5410.0 0.2570 0.00048 240.4 0.0127 0.00048 3932.5 0.3000 0.0081 618.7 0.1937 0.0062	1 1 1	 TERMINAL BODY WT (g)	1	 ORGAN-TO- BODY WT (%)	
5410.0 0.2570 2 5410.0 0.2570 0.0048 240.4 0.0127 0.00048 332.5 0.3000 0.0081 618.7 0.1937 0.0062	1				
	REAN: REAN: MEAN: RANDARD DEV:		$\begin{bmatrix} 2 \\ 2 \\ 0.2570 \\ 0.0127 \end{bmatrix}$		
3932.5 2.3000 0.0081 618.7 0.1937 0.0062					
	R IN GROUP:	1			
	MEAN: FANDARD DEV:	2 3932.5 618.7		2 0.0081 0.0062	•
	MEAN: PANDARD DEV:	3932.5 618.7	,	20081	· · ·

J

5

1

 \rightarrow

i

T

3M_MN02343490

26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROCCTANOATE ATBLE INCLUDES: TABLE INCLUDES: TABLE INCLUDES: SEXTH=T; SUBSET=ALL DEATH=T; SUBSET=ALL CROUP: CROUP: DEATH=T; SUBSET AND REVERAL COMMENT CROUP: CORMANATINEDONS NOM REREAL COMMENT BONE MARROW SNEAR TAKEN ENERAL COMMENT MARRONSONS NOM REREAL COMMENT BONE MARROW SNEAR TAKEN ANTIMAL OBSEE NOM REREAL MARKABELIC: ANTIMER EXAMINED: ANTIMER EXAMINED: ANTIMER EXAMINED: ANTIMER EXAMINED: ANTIMER EXAMINED: ANTIMER EXAMINED:	MUTINO MUTUM	Дам 		PAGE: 1 OCTANOATE - 0 F - A N I M A L S - A F F E C T E D -1- -1- -1- -1- -1- -1- -1-
MOTTLED RED FOCUS(I)/AREA(S)	00	04	-0	0.0

)

k

ł

t,

TABLE 35 Incidence of Macroscopic Observations

Week 27 Sacrifice

3M_MN02343491

3M T-6889.3		PAGE: 2	MALS-AFFECTED													
70		STUDY W1TH AMMONIUM PERFLUOROOCTANOATE	BER-OF-ANIN		-34-	-==- -=-	44 w 57 J	1 0	4 4 ເບ ເບ	0 0	4 د ت	1 0	4 რ იი ი	1 0	4 4 Ω 4	0 1
ations		M PERI EYS	M U M	WALF	-2-	ι 1	ςς κα	0	ΜŊ	Ч	ΜM	0	ŝ	0	ოო	0
bserv	ice	MONTU			4	-=-	やや	0	4 M	Ħ	44	0	44	0	44	0
Incidence of Macroscopic Observations	Week 27 Sacrifice			SEX:	GROUP:	NUMBER:	NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:	
Incidence		26-WEEK CAPSULE TOXICITY (APFO)	TABLE INCLUDES:	SEX=ALL, GROUP=ALL, WEEKS=ALL DEATH=T, SUBSET=ALL		ORGAN AND KEYWORD(S) OR PHRASE	PARATHYROID (PT)	CYST (S)	CECUM (CE)	RED FOCUS(I)/AREA(S)	SKIN (SK)	CRUSTED AREA(S)	LN, TRACHEOBRON (TE)	DIFFUSELY DARK	LN, MANDIBULAR (MN)	LARGE ** END OF LIST

ŧ

¥

)

Ņ

ł

TABLE 35

TABLE 36			Covance 6329-231
Incidence of Macroscopic Observations	obser	rvations	C. COOU-I MC
Week 40 Recovery Sacrifice	acrifi	Ce	
26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUORCOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	MONIUN :	I PERFLUOROOCTANOATE SYS	PAGE: 1
		N U M B E R - O F - A N I M A L S - A	FFCTED
WEEKS=ALL	SEX:MALE		
DEATH=U;SUBSET=ALL	1-	-3 -	
ORGAN AND KEYWORD(S) OR PHRASE		N	
** TOP OF LIST ** GENERAL COMMENT (GC)	N	- 7	
BONE MARROW SMEAR TAKEN EYES - DAVIDSONS NO MACROSCOPIC LESIONS ANIMAL OBESE	11111	0000	
LIVER (LI)	110	0.0	
APHESION(S) ** END OF LIST	Ч	0	

i

ł

ł

k

3M_MN02343493

Incidence of Microscopic Observations	Observ	ation	Ω)	3M T-0889.3
Week 27 Sacrifice	e G			
26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APPO) IN CYNOMOLGUS MONKEYS	ON TUM MONKEY	PERFL	UOROC	PAGE: 1
TABLE INCLUDES:	N	а м Л	ы 14	- 0 F - A N I M A L S - A F F E C T E D
P-AUL; WEEKS-ALL 		MALE		
GROUP :	- - - -	-2-	- 3 -	-4-
ORGAN AND FINDING DESCRIPTION				ſſ
** TOP CF LIST ** Adrenal, cortex (AC)	1 41 M	' ∥ 	- - - - - - - - - - - - - - - - - - -	 ມີ ເບີຍ
CORTICAL TISSUE, EXTRACAPSULAR ECTOPIC ZONA GLOMERUIOSA-LIKE CELLS, ZONA FASCICULATA HYPERTROPHY, CORTICAL CELL MINERALIZATION	нонн	1040	- 00 0	1440
ADRENAL, MEDULLA (MA)	ব ক	m m	やや	
LIVER (LI)	77	n ⊢	40	50
INFILTRATE, LYMPHOHISTIOCYTIC PIGMENT, HEPATOCELLULAR PIGMENT, KUPFFER CELL	moo	0HH	400	
SPLEEN (SP) NUMBER EXAMINED: NOT REMARKABLE:	44	ς Γ	44	ŭΩ
PANCREAS (PA)	44	ოო	4 M	טי טי
INFILTRATE, LYMPHOHISTIOCYTIC	0	0	ч	٥

J

ł

ł

ì

TABLE 37

Þ

•

ł

Ì

T

TABLE 37

3M_MN02343495

7 Covance 6329-231 3M T-6889.3 .c Observations	eek 27 Sacrifice PAGE: 3 STUDY WITH AMMONIUM PERFLUOROOCTANOATE	NUMBER - OF - ANIMALS - AFFECTED SEX:MALE	GROUD: -1- ~234-	3ER: 4 3 4 5 ====-	EED: 4 3 4 5 3LE: 4 3 4 3	0 0 0 1 0 0 1	BED: 4 3 4 5 3LE: 2 2 1 2	0 0 0 1 1 1 0 1 2 0 3 2 2	JED: 4 3 4 5 3LR: 0 0 0 0	01014 0000 00004 00100	NED: 4 3 4 5 SLE: 4 2 2 4	0 1 2 1
TABLE 37 Incidence of Microscopic Observations	3		DEATH=T; FIND=ALL; SUBSET=ALL GROI	ORGAN AND FINDING DESCRIPTION	BRAIN (BR) NUMBER EXAMINED: NOT REMARKABLE:	INFILTRATE, LYMPHOHISTIOCYTIC MINERALIZATION	KIDNEY (KD) NUMBER EXAMINED: NOT REMARKABLE:	CYST INFTLFRATE, LYMPHOHISTIOCVTIC KINERALIZATION, TUBULAR	LUNG (LU) NUMBER EXAMINED: NOT REMARKABLE:	CONGESTION INFILTRATE, EOSINOPHILIC INFILTRATE, MACROPHAGE, ALVEOLAR MINERALIZATION, ALVEOLAR PIGMENT	HEART (HT) NUMBER EXAMINED: NOT REMARKABLE:	INFILTRATE, LYMPHOHISTIOCYTIC

Covance 6329-231 3M T-6889.3	PAGE: 4	ТМА Ь S-АFFEСТЕD									
suoj	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	UMBER-OF-AN 	234-	3 4 5 ==-	3 4 4 5 3	3 4 2 2 5 5	1 2 0	33 4 3 35 2	00001	3344 4475	۲۵ ۲۹ ۳۹
servati	NIUM E		-12.	-==-	ት ት	44	0	4 W	ਜਜਜ	4	4
TABLE 37 Incidence of Microscopic Observations Week 27 Sacrifice		SEX.		NUMBER:	NUMBER EXAMINED: NOT REMARKABLE:	NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:	NUMBER EXAMINED: NOT REMARKABLE:
Incidence	26-WEEK CAPSULE TOXICITY (APFO)	TARLE INCLUDES; SEX=ALL;GROUP=ALL;WEEKS=ALL	DEATH=T;FIND=ALL;SUBSET=ALL	ORGAN AND FINDING DESCRIPTION	GALLBLADDER (GB)	тихиис (нт) странати (нт) с	INVOLUTION	LN, MESENTERIC (MS)	INFILTRATE, EOSINOPHILIC INFLAMMATION, GRANULOMATOUS PARASITISM PIGMENT	ТКАСНЕА (ТК)	ESOPHAGUS (ES)

ł

ł

)

ŧ

÷

ł

)

t

ł

T

ł

26-WIEK CAPBULE TOXICITY STUDY WITH AMOUTH PERTUCHOCOCAMONATIN PAGE: 5 AREO: IN CONDUCTS: CAPPO IN CONDUCTS: SEXFALL; GROUP-ALL; SEXFALL; GROUP-ALL; SEXFALL; GROUP-ALL; SEXFALL; GROUP-ALL; SEXFALL;	Incidence o	Incidence of Microscopic Observations Week 27 Sacrifice	ervati	suo		3M T-6889.3
DES: NUMBER SEX: MALE FIND=ALL, SUBSER-ALL SEX: MALE FIND=ALL, SUBSER-ALL GROUP	26-WEEK CAPSULE TOXICI (APP		NTUM NONKEY	PERFI S	UOROC	PAGE:
Distribution SEX: SEX: SEX: SEX: FIND=ALL; SUBSET=ALL GROUP: -1- -2- -3- FIND=ALL; SUBSET=ALL GROUP: -1- -2- -3- FIND=ALL; SUBSET=ALL GROUP: -1- -2- -3- CENTRUE NUMBER EXAMINED: -4 3 4 Y) NOT REMARKABLE: 3 3 0 TATE, LYMPHOHISTICCYTIC NUMBER EXAMINED: 3 3 4 YNDIE UNDER EXAMINED: NUMBER EXAMINED: 3 3 4 (PT) NUMBER EXAMINED: 3 3 4 4 3 4 (PT) NUMBER EXAMINED: NUMBER EXAMINED: 3 3 4 4 3 4 (PT) NUMBER EXAMINED: NUMBER EXAMINED: 3 3 4 4 3 4 (PT) NUMBER EXAMINED: NUMBER EXAMINED: 4 3 4 4 3 4 4 4 4 3 4 4 4 4 4 4 4		I	z	Σ	щ	ОЕ - АИІМАГЅ - АЕЕСТЕD
INDERGE EXAMPLY CODERFIEND GROUP: -1- -2- -2- -3- INDERGE DESCRIPTION NUMBER:	NCLUDES: The structures = ALL;WEEKS=ALL			MALF		
INDING DESCRIPTION Y) NUMBER EXAMINED: 3 3 4 Y) NOT REMARKABLE: 3 3 4 IC THYNUS NOT REMARKABLE: 3 3 4 IC THYNUS NOT REMARKABLE: 3 3 4 THYROGLOSSAL NUMBER EXAMINED: 0 0 0 1 THYROGLOSSAL NUMBER EXAMINED: 3 3 4 (PT) NOT REMARKABLE: 3 3 4 (PT) NOT REMARKABLE: 4 3 4 (PT)	TTY=L					-4-
Y) NUMBER EXAMINED: 4 3 4 IC THYNUS NOT REMARKABLE: 3 3 0 TRATE, LYMPHOHLSTIOCYTIC NUMBER EXAMINED: 1 0 0 2 THYROGLOSSAL NUMBER EXAMINED: NUMBER EXAMINED: 3 3 4 (PT) NUT REMARKABLE: 3 3 4 (PT) NUT REMARKABLE: 4 3 4 (PT) NUT REMARKABLE: 3 4 3 (PT) NUT REMARKABLE: 4 3 4 (PT) NUT REMARKABLE: 3 4 3	ND FINDING DESCRIPTION					ری – ۱
IC THYNUS 0 0 0 2 IMATE, LYWFHOHLSTICCYTIC 0 0 0 2 XAMINED THYROGLOSSAL 0 0 1 0 1 THYROGLOSSAL NUMBER EXAMINED: 3 3 4 (PT) NOT REMARKABLE: 3 3 4 (PT) NOT REMARKABLE: 4 3 4 (PT) NOT REMARKABLE: 4 3 4 (PT) NOT REMARKABLE: 4 3 4 (PI) NOT REMARKABLE: 4 3 4 MOT REMARKABLE: 1 0 1 1 1 (PI) NUMBER EXAMINED: 4 3 4 4 3 4 MOT REMARKABLE: 1 0 1 1 0 1 </td <td>•••••••••••••••••••••••••••••••••••••••</td> <td>UMBER EXAMINED: NOT REMARKABLE:</td> <td>4 M</td> <td>mm</td> <td>40</td> <td>10 Q</td>	•••••••••••••••••••••••••••••••••••••••	UMBER EXAMINED: NOT REMARKABLE:	4 M	mm	40	10 Q
(PT) NUMBER EXAMINED: 3 3 4 CLANDULAR NOT REMARKABLE: 3 2 3 4 CLANDULAR NUMBER EXAMINED: 0 1 1 1 NUMBER EXAMINED: 4 3 4	ECTOPIC THYMUS INFILTRATE, LYMPHOHISTIOCYTIC ONE EXAMINED CYST, THYROGLOSSAL		0040	0000	H 0 N N	00112
GLANDULAR 0 1 1		UMBER EXAMINED: NOT REMARKABLE:	ოო	ΜQ	4 0	o N
(PI) NUMBER EXAMINED: 4 3 4 (PI) NOT REMARKABLE: 3 4 3 4 (PI) NUMBER EXAMINED: 3 3 4 (PI) NUMBER EXAMINED: 4 3 4 ANDIB (SC) NUMBER EXAMINED: 4 3 4	ZST, GLANDULAR		0	Ч	Ч	0
(PI) NUMBER EXAMINED: 4 3 4 NOT REMARKABLE: 3 3 4 Image: Second		UMBER EXAMINED: NOT REMARKABLE:	44	ωω	44	υΩ
1 0 0 (SG) NUMBER EXAMINED: 4 3 4 NOT REMARKABLE: 2 2 3 . LYMPHOHISTIOCYTIC 2 1 1		UMBER EXAMINED: NOT REMARKABLE:	4 00	~ ~	44	υΩ
(SG)	КЗТ		4	0	0	0
TIC 2 1	(SG)	UMBER EXAMINED: NOT REMARKABLE:	40	79 M	4 ω	10 4
	WFILTRATE, LYMPHOHISTIOCYTIC		69	ч	1	1

TABLE 37

T

3M_MN02343498

Incidence of Incidence of 26-WEEK CAPSULE TOXICITY (APPO) TABLE INCLUDES: SIX=ALL;0ROUP=ALL;WEEKS=ALL DEATH=T;FIND=ALL;SUBSET=ALL ORGAN AND FINDING DESCRIPTION	Microscopic Ob Week 27 Sacrifi STUDY WITH ANNM IN CYNOMOLGUS IN CYNOMOLGUS SEX: SEX: GROUP: NUMBER:	Servatio cce Contum PE MONTEYS MONTEYS M M -12- -12-	tions PERFLUO YS U M B E MALE -23- 3 4	Б	раде: 6 остамоате
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED: NOT REMARKABLE:	। 1 4*7* ≝	ເ ແ ແ	∥ ∥	1
DEGENERATION/NECROSIS INFLAMMATION, ACUTE		00	00	ल ल	0.0
SPINAL CORD (SC)	NUMBER EXAMINED: NOT REMARKABLE:	ヤヤ	mm	やや	υn
NERVE, SCIATIC (SN)	NUMBER EXAMINED: NOT REMARKABLE:	4	n n	ተ	ហល
STOMACE, GL (ST)	NUMBER EXAMINED: NOT REMARKABLE:	44	mm	হু হ	10 4 ,
INFLAMMATION, GRANULOMATOUS PARASITISM		00	00	00	1
DUODENUM (DU) (DU)	NUMBER EXAMINED: NOT REMARKABLE:	44	mm	4 M	υΩ
PARASITISM		0	0	Ч	0
JEJUNUM (JE)	NUMBER EXAMINED: NOT REMARKABLE:	44	n n	ት 4	ហហ

TABLE 37

3M_MN02343499

And and an analysis of a second or and a second a second or and a second a second and a second a seco		TABLE 37				0	Covance 6329-231 3M T-6889.3
Week 27 Sacrifice S6-WEEK CAPSULE TOXICITY STUPY WITH AMONITH PERFLUCENCOCTANOATE PAGE: 7 S6-WEEK CAPSULE TOXICITY STUPY WITH AMONITH PERFLUCENCOCTANOATE INTENDESTING CONTINUES TO TOXICITY STUPY WITH AMONITH PERFLUCENCOCTANOATE INTENDESTING CONTINUES SEX: NUMBER: SEX:	Incidence	of Microscopic Obs	servat	ions			
36-WERK CAPSULE POLICITY AND MATHIN AND MATHIN AND AND AND AND AND AND AND AND AND AN		Week 27 Sacrific	e				
BEKS-ALL SEX: MUNER: SEX: MUNER: SEX: MUNER: SEX: MUNER: SEX: MUNER: SEX: MUNER: SEX: SEX:	26-WEEK CAPSULE TOXICI (APF		NI UM IONKEY	PERFL S	UOROC	OCTANOATE	7
EEKS=ALL SEX: MALEMALE				×	Ē	OF-ANIMALS-A	
GROUP: -1- -2- -2- -3- RIPTION NUMBER: NOPHILIC NUMBER: NOPHILIC NUMBER: NOPHILIC NUMBER: EXAMINED: 4 3 4 NOPHILIC NUMBER: EXAMINED: 4 3 4 NOPHILIC NUMBER: EXAMINED: 4 3 4 ANULOMATOUS NUMBER: EXAMINED: 4 3 4 RONIC NUMBER: EXAMINED: 3 <td>uoudas: Ligenoutra alui, Mereks=alui mientenenenenenenenenenenenenenenenenenen</td> <td></td> <td></td> <td>-MALE</td> <td></td> <td>-</td> <td></td>	uoudas: Ligenoutra alui, Mereks=alui mientenenenenenenenenenenenenenenenenenen			-MALE		-	
RIPTION NUMBER A A NOPHILIC NUMBER 4 3 4 NOPHILIC NUMBER A 3 3 3 NOPHILIC NUMBER NUMBER 4 3 4 NOPHILIC NUMBER NUMBER 2 4 3 4 ANULOMATOUS NUMBER NUMBER 2 3 3 4 RONIC NUMBER NUMBER 3 3 3 4 RONIC			1			-4	
NOPHILLC 4 3 4 NOPHILLC 0 0 0 1 ANULOMATOUS NUMBER EXAMINED: 4 3 4 RONIC NUMBER EXAMINED: 4 3 4 ANULOMATOUS NUMBER EXAMINED: 4 3 4 RONIC NOT REMARKABLE: 3 3 4 RONIC NOT REMARKABLE: 3 3 4 RONIC NOT REMARKABLE: 3 3 4 RONIC NOT REMARKABLE: <	FINDING DESCRIPTION					± - 5 ± - 1	
NOFHILIC NOFHILIC NUTREALABLE: 3 3 4 AUULOMATOUS NUTREMARKABLE: 3 3 4 1 0 1 NUTREMARKABLE: 3 3 4 NUTREMARKABLE: 4 3 4 NUTREMARKABLE: 3 3 3 4 NUTREMARKABLE: 3 3 3 4 NUTREMARKABLE: 3 3 1 NUTREMARKABLE: 3 1 1 NUMBER EXAMINED: 4 3 4 NUTREMARKABLE: 3 3 1 NUTREMARKABLE: 3 1 1 NUMBER EXAMINED: 3 1 1 NUTREMARKABLE: 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	ъ)	NUMBER EXAMINED: NOT REMARKABLE:	ቲ ቲ	m m	4 M	ហាបា	
NUMBER EXAMINED: 4 3 4 ANULOMATOUS 1 0 1 0 1 ANULOMATOUS 1 0 1 0 1 ANULOMATOUS 1 0 1 0 1 ANULOMATOUS NUMBER EXAMINED: 4 3 4 RONIC NOT REMARKABLE: 3 4 3 4 RONIC NUMBER EXAMINED: 4 3 4 3 4 RONIC NUMBER EXAMINED: 1 0 0 1 0 0 1 RONIC NUMBER EXAMINED: 3 3 4 3 4 3 4 RONIC NUMBER EXAMINED: 1 0 0 1 0 1 RONIC NUMBER EXAMINED: 3 3 3 4 3 4 RONIC NOT REMARKABELE: 3 3 3 3 4 RONIC NOT REMARKABELE: 3 3 3 4 3 4 RONIC NOT REMARKABE	ILTRATE, EOSINOPHILIC		0	0	1	0	
ANULOMATOUS 1 0 1 ANULOMATOUS 1 0 0 Image: State in the state i		NUMBER EXAMINED: NOT REMARKABLE:	ሳኮ	тm	ቅ	ហហ	
NUMBER EXAMINED: 4 3 4 RONIC NOT REMARKABLE: 3 3 4 RONIC NUMBER EXAMINED: 4 3 4 ANULOMATOUS NUMBER EXAMINED: 4 3 4 ANULOMATOUS NOT REMARKABLE: 3 3 4 RONIC NUMBER EXAMINED: 3 3 3 ANULOMATOUS NOT REMARKABLE: 3 3 4 RONIC NUMBER EXAMINED: 3 3 4	LAMMATION, GRANULOMATOUS ASITISM			00	10	00	
1 0 0 1 0 0 1 0 1 1 0 1 1 0 0 1 0 0 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1 1 0 1	(c	NUMBER EXAMINED: NOT REMARKABLE:	4 M	ოო	ヤマ	nu	
NUMBER EXAMINED: 4 3 4 NOT REMARKABLE: 4 3 3 3 US 0 0 1 0 1 UNMBER EXAMINED: 3 3 3 4 NUMBER EXAMINED: 3 3 3 4 NOT REMARKABLE: 3 3 3 3 NOT REMARKABLE: 3 3 3 3	LAMMATION, CHRONIC		Ч	0	0	0	
MATOUS 	RE)	NUMBER EXAMINED: NOT REMARKABLE:	4	ოო	4 M	u U U	
NOT REWARKABLE: 3 3 4 NOT REWARKABLE: 3 3 3 3 0 1	LAMMATION, GRANULOMATOUS		0	0	ч	0	
		JUMBER EXAMINED: NOT REMARKABLE:	ოო	ოო	4 M	សស	
	UTHOSIS LAMMATION, CHRONIC		00	00	⊢ 1 ⊢1	00	

,

÷

Ŧ

)

)

ŧ

)

ŧ

÷

Covance 6329-231	JM T-0889.3		PAGE: 8	MALS-AFFECTED											·	
			OOCTANOATE	R - OF - ANI		-4	ر ۱۱ ۱۱	വവ	1 -1	0 7	2 2	щŌ	ى م <u>ا</u>	0	ب ة 7	1
	15		RFLUOR	E E	ALE		4	ოო	4.4	0 m	77	9 11	40	7	4	0
	vatio		UM PEI KEYS	D N	MALE	-2-	€ 	ოო	м N	64	β	01	mm	0	ΜM	0
	Obser	Sacrifice	NOM S			:-1-			4.0	5	40	00	77	0	4.0	1
TABLE 37	Incidence of Microscopic Observations	Week 27 Sacı	ULE TOXICITY STUDY MITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS		SEX:	GROUP:	NUMBER:	NUMBER EXAMINED: NOT REMARKABLE:	NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:		NUMBER EXAMINED: NOT REMARKABLE:	
	Г		26-WEEK CAPSULE TOXICITY (AFFO)	artinec.	JANDEL INCLOUDES. SEX=ALL; GROUP=ALL;WEEKS=ALL DEATH-T:FIND=ALL;SURSET=ALL		ORGAN AND FINDING DESCRIPTION	MAMMARY, MALE (MM)	URINARY BLADDER (UB)	INFILTRATE, EOSINOPHILIC INFILTRATE, LYMPHOHISTIOCYTIC	PROSTATE (PR)	INFILTRATE, LYMPHOHISTIOCYTIC INFLAMMATION, SUBACUTE	SEMINAL VESICLES (SV)	MINERALIZATION	EPIDIDYMIDES (EP)	INFILTRATE, LYMPHOHISTIOCYTIC

Covance 6329-231 3M T-6889.3		PAGE: 9	MALS-AFFECTED						
TABLE 37 Incidence of Microscopic Observations	Week 27 Sacrifice	26-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS	NUMBER - OF - ANI	TABLE INCLUDES: SEXEALL;GROUP=ALL;WEEKS=ALL SEXEALL;GROUP=ALL;WEEKS=ALL	DEATH=T;FLND=ALLL;SUBSET=ALL	ORGAN AND FINDING DESCRIPTION	LN, MANDIBULAR (MN)	LN, TRÀCHEOBRON (TB)	PIGMENT 0 0 1 0

--PIGMENT ** END OF LIST

	TABLE 38			Covance 6329-231
Incidenc	Incidence of Microscopic Observations	Obser	vations	C.2000-1 MC
Wei	Week 40 Recovery Sacrifice	rific	ψ	
26-WEEK CAPSULE TOXICITY (APPO)		NULUM MULUM	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	PAGE: 1
		N	U M B E R - O F - A N I M A L S	- AFFECTED
TABLE INCLOUES: SEX=All, GROUP=1,3;WEEKS=All Sexment: PTTND-DTT - CTDACEM_ST	SEX: -	MALE	M	
DEATH=0, FIND=ALL, SOBSET=ALL	GROUP: -	1	-3 -	
ORGAN AND FINDING DESCRIPTION	NUMBER :		3	
** TOP OF LIST ** ADRENAL, CORTEX (AC)	NUMBER EXAMINED: NOT RENARKABLE:	- 01	- NO 	
CORTICAL TISSUE, EXTRACAPSULAR		ч	8	
ADRENAL, MEDULLA (MA)	NUMBER EXAMINED: NOT REMARKABLE:	00	0.0	
LIVER (LI)	NUMBER EXAMINED: NOT REMARKABLE:	00	1 2	
FIEROSIS, CAPSULAR/SUBCAPSULAR INFILTRATE, LYMPHOHISTIOCYTIC PIGMENT, HEPATOCELLULAR		н о н	040	
SPLEEN (SP)	NUMBER EXAMINED: NOT REMARKABLE:	00	201	
PANCREAS (PA)	NUMBER EXAMINED: NOT REMARKABLE:	20	0.01	
TESTIS (TE)	NUMBER EXAMINED: NOT REMARKABLE:	00	8 2	

TABI	TABLE 38			Covance 6329-231 3M m-6880 3
Incidence of Microscopic Observations	opic Obser	vati	ons	C. 2000-1 MC
Week 40 Recovery Sacrifice	very Sacri	fice		
26-WEEK CAPSULE TOXICITY STUDY W (AFFO) IN CYNC	STUDY WITH AMMONIUM PI IN CYNOMOLGUS MONKEYS	NKEY	STUDY WITH AMMONIUM PERFLUOROCCTANOATE IN CYNOMOLGUS MONKEYS	
- Definitions		N	U M B E R - O F - A N I M A L S - A	А F E C T E D
TABLE INCLODES: SEX=ALL(GROUP=1,3;WEEKS=ALL DEARL-11:ETAND-2T. OTDERMA_ALL	SEX:	MALE	1	
הנאדוירט לה הארק-המניס (מתפקים אין אין הארקים הארקים אין	GROUP: -1-		-3-	
ORGAN AND FINDING DESCRIPTION	NUMBER: 2		N	
BONE, FEMUR (FE)			NQ	
MARROW, FEMUR (FM) NUMBER EXAMINED: NOT REMARKABLE:		0 0	0.03	
MARROW, STERNUM (SE)		22	0.0	
BONE, STERNUM (SB)		2 2	0.0	
EVE (EY) NUMBER EXAMINED: NOT REMARKABLE:		0 0	2	
INFILTRATE, LYMPHOHISTIOCYTIC, CHOROIDAL		2	٥	
BRAIN (BR) NUMBER EXAMINED: NOT REMARKABLE:		00	1 2	
INFILTRAFE, LYMPHOHISTIOCYTIC MINERALLZATION		17	10	

	TABLE 38		Cove	Covance 6329-231
Incidence	Incidence of Microscopic Observations	ervations	20	JM T-6889.3
We	Week 40 Recovery Sacrifice	ifice		
26-WEEK CAPSULE TOXICITY (APPO)	LITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE PPO) IN CYNOMOLGUS MONKEYS	NIUM PERF NNKEYS		PAGE: 4
			BER-OF-ANIMALS-AFF	ECTED
TABLE INCLUDES: SEXEALL; GROUPE1, 3;WEEKS=ALL PARAMILT: ATTINGTAN STIT	:XHX	MALE		
	GROUP: -1	13-		
ORGAN AND FINDING DESCRIPTION	NUMBER:	-=- 2 -=-		
LN, MESENTERIC (MS)	NUMBER EXAMINED: NOT REMARKABLE:	00		
PIGMENT		2 0		
TRACHEA (TR)	NUMBER EXAMINED: NOT REMARKABLE:	1 2 2		
INFLAMMATION, ACUTE		1		
ESOPHAGUS (ES)	NUMBER EXAMINED: NOT REMARKABLE:	0 0 0 0		
THYROID (TY)	NUMBER EXAMINED: NOT REMARKABLE:	2 2 2		
CYST, GLANDULAR		0 1		
PARATHYROID (PT)	NUMBER EXAMINED: NOT REMARKABLE:	ы. С. Ц.		
INFILTRATE, LYMPHOHISTIOCYTIC		0 1		
AORTA (AO)	NUMBER EXAMINED: NOT REMARKABLE:	5 7 5 7		
THICKENING, INTIMAL		0		

	TABLE 38			Covance 6329-231
Incidence of	Incidence of Microscopic Observations	servat	tions	C. 6000-1 MC
Week	40 Recovery Sacrifice	rifice	ð	
26-WEEK CAPSULE TOXICITY (APFO)		ON TUM	STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	FAGE: 5
		M U N	U M B E R - O F - A N I M A	L S - A F F E C T E D
TABLE INCLUDES: SEX=ALL; GROUP=1,3;WEEKS=ALL	SEX: -	MALE		
DEATH=U;FIND=ALL;SUBSET=ALL	GROUP: -	-1-	- 3 -	
ORGAN AND FINDING DESCRIPTION	NUMBER:	- 7		
PITUITARY (PI)NU	NUMBER EXAMINED: NOT REMARKABLE:	7 7	2.2	
SALIV GL, MANDIB (SG) NU	NUMBER EXAMINED: NOT REMARKABLE:	00	20	
INFILTRATE, LYMPHOHISTIOCYTIC		2	2	
MUSCLE, SKELETAL (SM) NU	NUMBER EXAMINED: NOT REMARKABLE:	00	2	
FARASITISM		0	1	
SPINAL CORD (SC) NU	NUMBER EXAMINED: NOT REMARKABLE:	77	2 2	
NERVE, SCIATIC (SN) NU	NUMBER EXAMINED: NOT REMARKABLE:	75	20	
FIBROSIS INFILTRATE, LYMPHOHISTIOCYTIC			00	
STOMACE, GL (ST) NU	NUMBER EXAMINED: NOT REMARKABLE:	77	12	
INFLAMMATION, CHRONIC		0	1	

÷

	TABLE 38		Covance 6 3M T	6329-231 T-6889.3
Incidence of	Incidence of Microscopic Observations	ervat	tions	
Week	40 Recovery Sacrifice	lfice	21	
26-WEEK CAPSULE TOXICITY (APFO)		NIUM	PAGE: 7 STUDY WITH AMMONIUM PERFLUOROOCTANOATE IN CYNOMOLGUS MONKEYS	
		N	NUMBER-OF-ANIMALS-AFFECT	Ξ D
TABLE INCLUDES: SEX=ALL;GROUP=1,3;WEEKS=ALL	SEX: -	MALE-		
DEATH=U;FIND=ALL;SUBSET=ALL	GROUP: -	-1-	-3-	
ORGAN AND FINDING DESCRIPTION	NUMBER:		2	
RECTUM (RE) NU	NUMBER EXAMINED: NOT REMARKABLE:	00	0.0	
NUN (SK) (SK)	NUMBER EXAMINED: NOT REMARKABLE:	0 0	0.01	
MAMMARY, MALE (MM) NU	NUMBER EXAMINED: NOT REMARKABLE:	20	20.02	
URINARY BLADDER (UB)NU	NUMBER EXAMINED: NOT REMARKABLE:	00	80	
INFILTRATE, LYMPHOHISTIOCYTIC		2	3	
ркоsтате (рк) Nu	NUMBER EXAMINED: NOT REMARKABLE:	0 0	0 0	
INFILTRATE, LYMPHOHISTIOCYTIC		7	2	
SEMINAL VESICLES (SV) N	NUMBER EXAMINED: NOT REMARKABLE:	N N	2.2	
EPIDIDYMIDES (EP) N	NUMBER EXAMINED: NOT REMARKABLE:	20		
** END OF LIST				

÷

3M_MN02343509

APPENDIX 1

Protocol Deviations Protocol Protocol Amendment No. 1 Protocol Amendment No. 2 Material Safety Data Sheet Certificate of Analysis

Protocol Deviations

F

ł

Protocol. Husbandry. Diet. "Certified primate diet (#8726C, Harlan Teklad) once or twice daily."

Actual Procedure. All animals were fasted beginning in the afternoon on November 15, 1998 (Day 48); animals were provided with food in the morning on November 16, 1998 (Day 49).

Protocol. Dosing Procedures. Method of Administration. "Orally by gelatin capsules, daily (7 days/week) for at least 26 weeks."

Actual Procedure. There were several occasions when the test material was not administered to animals due to the condition of the animal or at the recommendation of a laboratory animal veterinarian. Dose administration was discontinued for Animal No. I05724 (Group 4) on Day 28; this animal was subsequently sacrificed in moribund condition on Day 29. Dose administration was discontinued for Animal Nos. I05722, and I05703 (Group 4) on Days 43 (Week 7), 66 (Week 10), and 81 (Week 12), respectively. Dose administration was discontinued for Animal No. I05721 (Group 2) for Days 135 and 136; this animal was subsequently sacrificed in moribund condition on Day 137.

On Day 44, Animal No. 105703 (Group 4) did not receive its amount of dose preparation because the capsule broke during dose administration procedures.

Protocol. Observation of Animals. Clinical Observations. "Once weekly, each animal will be observed; abnormal findings, or an indication that the animal is normal will be recorded."

Protocol Deviations (Continued)

١

Actual Procedure. The following animals did not have a weekly observation recorded on the following days: Animal No. I05714 (Group 1) on Days 1 and 22; Animal No. I05725 (Group 1) on Day 1; Animal No. I05717 (Group 2) on Day 57; Animal No. I05719 (Group 3) on Days 1 and 29; Animal No. I05703 (Group 4) on Days 8 and 15; Animal No. I05704 (Group 4) on Day 15; Animal No. I05711 (Group 4) on Days 8 and 15; Animal No. I05713 (Group 4) on Days 15, 43, and 64; and Animal No. I05724 (Group 4) on Day 8.

Protocol. Blood Hormone Determination. Method of Collection. "Blood samples will be maintained chilled until plasma is harvested."

Actual Procedure. Blood samples collected for blood hormone determination on Days 35, 66, and 94 were stored at room temperature during harvesting.

Protocol. Urine and Feces APFO Level Determination. Sample Handling. "Samples of urine (at least 2 mL) and feces (at least 5 grams) will be stored in a freezer set to maintain -10 to -30°C."

Actual Procedure. Approximately 3 grams of feces were collected from Animal Nos. 105711 and 105724 (Group 4) during Week 2 for feces APFO level Determination.

Protocol. Termination. Scheduled Sacrifices. "After at least 26 weeks of treatment, four animals/sex/group will be fasted overnight, then anesthetized with ketamine and xylazine, weighed, exsanguinated, and necropsied."

Actual Procedure. Animal No. 105709 (Group 1) was weighed incorrectly at the terminal sacrifice (Week 27, Day 184). The body weight collected for this animal on Day 183 was entered into the computer system for organ-to-body weight weight percentage calculations.

Protocol Deviations (Continued)

Protocol. Termination. Postmortem Procedures. Cell Proliferation Evaluation. "Representative samples of the left lateral lobe of the liver, left and right testes, and pancreas will be collected from each animal at the scheduled and unscheduled sacrifices and preserved in formalin."

Actual Procedure. The fixative used for the tissue samples collected from the left lateral lobe of the liver, left and right testes, and pancreas of the recovery animals for cell proliferation evaluation was documented incorrectly.

Protocol. Experimental Design. Postmortem Procedures. Histopathology. "Tissues from each animal (including Animal No. 105723) will be embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically."

Actual Procedure. Some tissues, required by the protocol, were not available for histopathologic examination. Missing tissues or insufficient tissue samples are listed with appropriate comments in the pathology data sheets for individual animals. Summary tables do not include them as having been examined.

These deviations are not expected to have affected the results of the study.