



Sponsor:

APME Ad-Hoc APFO Toxicology Working Group

FINAL REPORT

Study Title:

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

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Study Completion Date:

December 18, 2001

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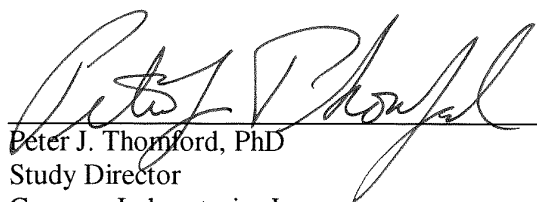
Sponsor Project Identification:

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COMPLIANCE STATEMENT

4-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 (GLPs), 40 CFR 792, except that bile acid determinations done by the University of Dundee were not done in compliance with GLPs.


Peter J. Thomford, PhD
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18 Dec. 2001
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QUALITY ASSURANCE STATEMENT

This report 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		Phase	Date Reported to Study Director and Study Director Management
From	To		
06/07/98	06/07/98	Protocol Review	06/08/98
07/16/98	07/16/98	Clinical Laboratory Inspection	07/16/98
09/22/98	10/01/98	Report Review	10/01/98
10/01/98	10/01/98	Protocol Amendment Review	10/01/98
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06/10/99	06/10/99	Protocol Amendment Review	06/10/99
12/07/99	12/07/99	Protocol Amendment Review	12/07/99
02/23/01	02/23/01	Report Review	02/23/01
11/27/01	11/27/01	Report Review	11/28/01



Representative
Quality Assurance Unit



Date

STUDY IDENTIFICATION

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

Test Material	Ammonium Perfluorooctanoate (APFO)
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Study Timetable	
Study Initiation Date	June 11, 1998
In-Life (Experimental) Start Date	June 17, 1998
In-Life Termination Date	July 16, 1998
Experimental Termination Date	December 18, 2001

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ABSTRACT

The purpose of this study was to provide data for determining an estimated maximum-tolerated dose and lower dose levels to be used in a chronic toxicity study. In addition, the effect on critical enzyme levels, hormones, and other selected biochemical parameters was determined.

Male cynomolgus monkeys were assigned to three groups (two animals in Group 1, three animals each in Groups 2 and 3). Animals in Groups 2 and 3 received gelatin capsules containing 2 and 20 mg Ammonium Perfluorooctanoate (APFO)/kg of body weight/day (mg/kg/day), respectively. Animals in Group 1 received empty gelatin capsules.

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. In addition, animals were observed approximately 30, 60, and 90 minutes postdose for signs of poor health or abnormal behavior. Body weight data were collected before initiation of treatment, on the first day of treatment, and weekly thereafter. Blood samples for hormone analyses [estradiol, estrone, estriol, thyroid stimulating hormone, total and free triiodothyronine (T3), and total and free thyroxine (T4)] were collected before initiation of treatment and on Day 30. Serum was harvested, and the samples were sent to Ani Lytics Inc., for analyses. Blood samples for cholecystokinin analyses were collected before initiation of treatment and on Day 30. Plasma was harvested, and the samples were sent to the DuPont Haskell Company for possible analyses. Blood samples for serum APFO concentration analyses were collected before initiation of treatment and on Day 30. Serum was harvested, and samples were sent to 3M for analyses. Blood samples were collected for hematology and clinical chemistry tests twice before initiation of treatment and on Day 30. In addition, blood for clinical chemistry tests was collected on Day 2. Additional blood was collected at the time of exsanguination, and samples were shipped to 3M for possible future analysis. On Day 30, the animals were anesthetized, weighed, exsanguinated, and necropsied. At necropsy, macroscopic observations were recorded, and selected tissues were collected and preserved. In addition, a sample of liver was collected from each animal for palmitoyl CoA oxidase activity analyses. Representative samples of liver, testes, and pancreas were collected from each animal and sent to Pathology Associates, A Charles River Company for proliferation cell nuclear antigen evaluation. A sample from

the liver and pancreas was collected from each animal and sent to the DuPont Haskell Company for possible receptor level determinations. Bile was collected from each animal and sent to the University of Dundee for bile acid determination. A sample of liver was collected from each animal and sent to 3M for APFO concentration analyses. Microscopic examinations were done on the adrenals, liver, pancreas, spleen, and testes from each animal.

All animals survived to the scheduled sacrifice. There were no apparent test material-related effects on estradiol, estriol, thyroid stimulating hormone, total and free triiodothyronine, and total and free thyroxine. Estrone levels were notably lower for males given 2 and 20 mg/kg/day.

There were no apparent test material-related effects on clinical observations, body weights, food consumption, clinical pathology parameters, or macroscopic or microscopic findings.

There did not appear to be a cell proliferative response to the test material in the liver, testes or pancreas, as determined by proliferating indices which were similar in all animals.

Based on the results of this study, daily capsule administration of Ammonium Perfluorooctanoate to cynomolgus monkeys for 29 days at dose levels of 2 and 20 mg/kg/day was well tolerated and produced no apparent evidence of toxicity.

PURPOSE

The purpose of this study was to provide data for determining an estimated maximum-tolerated dose and lower dose levels to be used in a chronic toxicity study. In addition, the effect on critical enzyme levels, hormones, and other selected biochemical parameters was determined.

REGULATORY COMPLIANCE

All aspects of this study were done in accordance with the Environmental Protection Agency Good Laboratory Practice Standards (GLPs), 40 CFR 792, except that bile acid determinations done by the University of Dundee were not done in compliance with GLPs.

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, 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 SYSTEM

Test Animal

Young adult to adult cynomolgus monkeys were obtained from Covance Research Products Inc. (Denver, Pennsylvania and Alice, Texas), on March 10, 1998. The animals weighed 2.1 to 3.6 kg at initiation of treatment.

Identification

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

Acclimation

Nine males were received on March 10, 1998, transferred from the Covance in-house stock colony on June 3, 1998. All animals were acclimated in Animal Room 2015; animals were acclimated at least 30 days before initiation of treatment (duration includes days animals were in the stock colony). In general, animals in this shipment appeared healthy. During acclimation, the animals were examined for abnormalities indicative of health problems. In addition, tuberculosis tests were done on each animal.

Results of the tuberculosis tests were negative for all animals. One male was eliminated from study consideration because it had the highest body weight. There were eight males in the randomization for assignment to groups (two males in Group 1 and three males each in Groups 2 and 3). The animal not selected for the study was returned to the Covance stock colony.

Housing and Maintenance

Animal Room 2015 was used for this study. Environmental controls for the animal room were set to maintain 18 to 29°C, a relative humidity of 30 to 70%, and a 12-hour light/12-hour dark cycle.

The animals were housed individually in 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. Fruit or additional supplements were provided, but did not require analysis.

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.

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.

PROCEDURES

This study was conducted in accordance with the Protocol dated June 11, 1998, and Protocol Amendment No. 1 through 3. The protocol and protocol amendments are in Appendix 1.

Group Designations and Dose Levels

Selection of animals for the study was based on clinical observations, body weights, and other data as appropriate. Animals were assigned to treatment groups using a computerized blocking procedure designed to achieve body weight balance with respect to treatment group.

Group	Dose Level (mg/kg/day)	Total Material Dose Level (mg/kg/day)	Number of Males
1 (Control)	0 ^a	0 ^a	2
2 (Low-dose)	2	2	3
3 (High-dose)	20	20	3

a The control group (Group 1) received the same size and number of empty gelatin capsules as used for Group 3.

Dose Preparation

Gelatin capsules (Torpac, Inc., Fairfield, New Jersey), Size No. 2, Lot Nos. 122630 (expiration date June 26, 2002) and 122932 (expiration date June 12, 2003), were used for dose administration.

The test material was dispensed into capsules weekly. The dose levels were based on the test material as supplied. For Groups 2 and 3, 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 appropriate container labeled with study number, group number, animal number, and dose level. The prepared capsules were stored at room temperature.

Dose Analyses

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

Method of Administration

Gelatin capsules were used for test material administration 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 29 days. The dosing tubes were flushed with 5 mL of reverse osmosis water. Individual 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. Animals were dosed at approximately the same time each day.

Clinical Observations

The animals were observed twice daily (a.m. and p.m.) for mortality and moribundity. Each animal was observed daily, and food consumption was assessed qualitatively; abnormal findings were recorded. Animals were observed approximately 30, 60, and 90 minutes postdose for signs of poor health or abnormal behavior. Effects were recorded as they were observed. Animals were observed once weekly; abnormal findings or an indication of normal was recorded.

Body Weights

Individual body weight data were recorded 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 before initiation of treatment (Day -8) and on Day 30 (after 29 days of treatment). Blood was collected between 07:00 and 09:00. Animals were fasted overnight before collections. Approximately 3 mL (Day -8) or 6 mL (Day 30) of blood for plasma samples were collected into tubes with potassium EDTA at the anticoagulant. Approximately 5 mL (Day -8) or 6 mL (Day 30) of blood for serum samples were collected without anticoagulant and allowed to clot for serum samples. Blood samples for plasma (Day 30) were maintained chilled until plasma was harvested. Blood samples collected on Day -8 for serum and plasma and blood samples collected on Day 30 for serum were maintained at room temperature until serum and plasma were harvested. Samples for serum were centrifuged within 1 hour after collection, and 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), and total and free thyroxine (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 Haskell Company for possible future analyses. Results of the analyses for cholecystokinin, if any, will be reported separately.

Serum APFO Level Determination

Approximately 2 mL of whole blood were collected from a femoral vein of each animal before initiation of treatment (Day -8) and on Day 30 (after 29 days of treatment). Animals were fasted overnight 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 analyses will be reported separately by 3M.

Clinical Pathology

Blood samples were collected from each animal twice before initiation of treatment (Days -8 and -5) and on Day 30 (after 29 days of treatment) for hematology and clinical chemistry tests. In addition, blood for clinical chemistry tests was collected from each animal on Day 2 (approximately 24 hours after the first dose). Animals were fasted overnight; water was provided *ad libitum*. Blood was collected from a femoral vein. 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 concentration	basophil count
platelet count	blood cell morphology
white blood cell (leukocyte) count	reticulocyte count

Clinical Chemistry

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

Additional Blood Collection

Whole blood (approximately 15 mL) was collected from the vena cava of each animal at the time of exsanguination. Approximately equally sized samples (approximately 5 mL each) of serum (collected without anticoagulant) and whole blood and plasma 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.

Necropsy

On Day 30, animals that were fasted overnight were anesthetized with ketamine and xylazine, weighed, bled for the additional blood collection, exsanguinated, and necropsied. Animals were necropsied in random order.

The necropsy included a macroscopic examination of the external surface of the body; all orifices; the 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.

Palmitoyl CoA Oxidase Determinations

Representative samples of the right lateral lobe of liver were collected from each animal at the scheduled sacrifice. The sample was weighed, flash-frozen in liquid nitrogen, and

stored in a freezer set to maintain -60 to -80°C until analyzed for palmitoyl CoA oxidase activity.

Cell Proliferation Evaluation

Representative samples of the left lateral lobe of the liver, left and right testes, and pancreas were collected and preserved in zinc formalin. 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 7.

Receptor Level Determination

Samples (approximately 2 g) of liver and pancreas was collected from each animal at the scheduled sacrifice, 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 the DuPont Haskell Company for possible analysis. Results of the receptor level determination, if any, will be reported separately.

Bile Acid Determination

Approximately 1.0 to 2.0 mL of bile were collected from each animal at the scheduled sacrifice, 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 the University of Dundee for bile acid determination. Results of the bile acid determination will be reported separately by the University of Dundee.

Liver APFO Determination

A section of liver (approximately 20 g) was collected from each animal at the scheduled sacrifice, 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 with plasma samples to 3M for APFO analysis. Results of these analysis 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, for possible future microscopic examination:

adrenal (2)	mammary gland
aorta	muscle (thigh)
brain	pancreas
cecum	pituitary
colon	prostate
duodenum	rectum
epididymis (2)	salivary gland [mandibular (2)]
esophagus	sciatic nerve
eyes [preserved in Davidson's fixative(2)]	seminal vesicle (2)
femur with bone marrow (articular surface of the distal end)	skin
gallbladder	spinal cord (cervical, thoracic, and lumbar)
heart	spleen
ileum	sternum with bone marrow
jejunum	stomach
kidney (2)	testis (2)
lesions	thymus
liver	thyroid (2) with parathyroid
lung	trachea
lymph node (mesenteric)	urinary bladder

Histopathology

The adrenals, liver, pancreas, spleen, and testes were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically from each animal.

Statistical Analyses

Only data collected on or after the first day of treatment were analyzed statistically.

One-way analysis of variance [ANOVA (Winer, 1971a)] was used to analyze initial body weights; palmitoyl CoA oxidase activities, and continuous clinical pathology values.

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

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, least squares means t-test was used for control versus treated group comparisons.

Groups 2 and 3 were compared with Group 1 (control). Group comparisons were evaluated at the 5.0%, two-tailed probability level.

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 1 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 and an original copy of the final report will be retained by Covance-Madison.

Within 1 year after submission of the final report, all the aforementioned materials from the Sponsor's designees (Ani Lytics Inc., DuPont Haskell Company, Pathology Associates International, 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 maintenance of any raw data or specimens produced by PAI.

RESULTS

Clinical Observations

Clinical observations are summarized in Tables 1 through 4; individual data are in Appendix 2. Individual animal fate data are also in Appendix 2.

All animals survived to the scheduled sacrifice. There were no test material-related clinical observations.

On Day 23, Animal No. I05419 (Group 2) was observed with a 4-cm laceration on the inner left thigh. The animal was anesthetized with ketamine, and the wound was cleaned and sutured. This condition was not considered to be test material-related.

Body Weights

Body weight data are summarized in Table 5; individual data are in Appendix 3.

There were no test material-related effects on body weights.

Food Consumption

Food consumption data are summarized in Table 1 (Summary of Clinical Observation - A.M./Weekly); individual data are included in the individual clinical observations in Appendix 2.

Low or no food consumption was noted for one animal (Animal No. I05235) given 20 mg/kg/day. For this animal, no food consumption was noted on Day 12, and low food consumption was noted on Days 5, 7, 11, 14, 16, 17, and 24. The decrease in food consumption for this animal may be test material-related.

Blood Hormone Analyses

Summary and individual hormone analyses data are in Appendix 6.

There were no apparent test material-related effects on estradiol, estriol, thyroid stimulating hormone, total and free triiodothyronine, and total and free thyroxine. Estrone levels were notably lower for males given 2 and 20 mg/kg/day.

Clinical Pathology

Hematology and clinical chemistry data are summarized in Tables 6 through 12; individual data are in Appendix 4. The Pathology Report contains a discussion of the data.

Administration of APFO had no 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 7.

Cell proliferation, as determined by measuring the proliferating index, was not increased in the liver, testes or pancreas of monkeys. Thus, there did not appear to be a cell proliferative response to the test material in the liver, testes or pancreas, as determined by proliferating indices which were similar in all animals.

Anatomical Pathology

Incidences of macroscopic and microscopic observations are summarized in Tables 13 and 14. Individual data are in Appendix 5. The Pathology Report contains a discussion of the data.

Administration of APFO had no effects on anatomical pathology test results.

CONCLUSIONS

Based on the results of this study, daily capsule administration of Ammonium Perfluorooctanoate to cynomolgus monkeys for 29 days at dose levels of 2 and 20 mg/kg/day was well tolerated and produced no apparent evidence of toxicity.

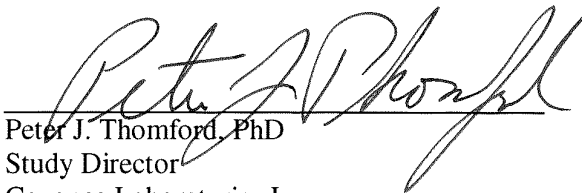
SIGNATURES



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PATHOLOGY REPORT

SUMMARY

The purpose of this study was to provide data for determining an estimated maximum-tolerated dose and lower dose levels to be used in a chronic toxicity study and to assess the effect of the test material, Ammonium Perfluorooctanoate (APFO), on critical enzyme levels, hormones, and other selected biochemical parameters.

Administration of APFO had no effects on clinical or anatomical pathology test results.

METHODS

Three groups of male cynomolgus monkeys were administered the test material orally via capsule at a dose level of 0 (control group; received empty gelatin capsules), 2, or 20 mg/kg of body weight/day (mg/kg/day) for 29 days. There were two animals in the control group and three animals in each of the groups receiving APFO. All animals survived to the scheduled sacrifice.

Blood was collected for hematology and clinical chemistry tests twice before initiation of treatment (Days -8 and -5) and on Day 30. In addition, blood for clinical chemistry tests was collected on Day 2. The animals were sacrificed and necropsied on Day 30; macroscopic observations were recorded, and tissues were preserved in fixative as specified by the protocol. Microscopic examinations were done on adrenals, liver, pancreas, spleen, and testes from all animals. Samples of liver were collected and frozen for determination of hepatic palmitoyl CoA oxidase activity and for determination of APFO content (done by 3M). Samples of liver, testes, and pancreas were collected and preserved in zinc formalin for evaluation of proliferation cell nuclear antigen (PCNA; done by Pathology Associates, a Charles River Company). Samples of liver and pancreas were collected and frozen for possible receptor level determination (done by the DuPont Haskell Company). Samples of bile were collected and frozen for bile acid determination (done by the University of Dundee).

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

RESULTS AND DISCUSSION

Mortality

All animals survived to the scheduled sacrifice.

Clinical Pathology

Individual values for hematology and clinical chemistry tests are in Appendix 4. Mean values and the results of statistical comparisons are in Tables 6 through 12.

Days -8 and -5. Clinical pathology test results indicated no obvious group or individual health abnormalities.

Day 2. Administration of the test material had no effects on clinical chemistry test results at this collection interval.

There were only two statistically significant differences for clinical chemistry results between the control and treated groups; lower glucose for the low-dose group and lower total bilirubin for the high-dose group. These differences were considered incidental because similar differences were present before treatment was initiated. There were no other notable differences for clinical chemistry results between the control and treated groups.

Day 30. Administration of the test material had no effects on hematology or clinical chemistry test results at Day 30.

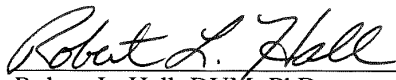
The only statistically significant differences between the control and treated groups was lower glucose for the high-dose males. This difference was considered incidental because a similar difference was present before treatment was initiated. There were no other notable differences for clinical pathology results between the control and treated groups.

Anatomical Pathology

Individual animal pathology data are in Appendix 5. Incidence summaries of the macroscopic and microscopic observations are in Tables 13 and 14, respectively.

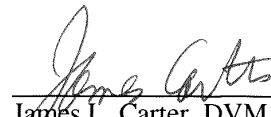
Macroscopic Findings. There were no test material-related gross findings noted at necropsy. A few commonly occurring macroscopic findings frequently observed as spontaneous lesion in monkeys were present.

Microscopic Findings. There were no test material-related microscopic findings. The only microscopic findings were minimal mineralization of the adrenals for one male given 2 mg/kg/day and immature testes for one male given 2 mg/kg/day and one male given 20 mg/kg/day. There were no differences in the appearances of the testes of the other two males given 2 mg/kg/day or the other two males given 20 mg/kg/day.



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18 December 2001
Date



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18 December 2001
Date

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 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 day of initiation of treatment is “Day 1.”

Animal No. I05419 (Group 2) was 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.

CODES, ABBREVIATIONS, AND UNITS

General Codes and Abbreviations

Codes for Clinical Pathology

Abbreviations and Units for Clinical Hematology

Abbreviations and Units for Clinical Chemistry

Codes for Anatomical 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.

General Codes and Abbreviations

WK	Week.
N	Number of measurements in a group.
Mean; MEAN	Arithmetic mean.
CAM	Covariate-adjusted mean.
SD; S.D.; STAND DEV; STANDARD DEV; sd	Standard deviation.
*	Group mean is significantly different from the mean of the control group (Group 1) at $p \leq 0.05$.
-; NA	No value; not applicable; not present.
P	Present.
UNSCHED	Unscheduled.
DISPATCH	Observations transferred from the in-life module of the data collection system to the necropsy module for reference during necropsy. Observations are duplicates of the last in-life observations.
MIN	Minute.
OBS	A.M. daily/weekly observation.
Animal Death Codes:	
T	Terminal sacrifice.

Codes for Clinical Pathology

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
H	Hemolyzed
SL	Slightly lipemic
L	Lipemic
SI	Slightly icteric
I	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

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

Abbreviations and Units for Clinical Hematology

Test	Abbreviation (Units)
Red blood cell count	RBC (E6/UL or $\times 10^6/\mu\text{L}$)
Hemoglobin	HGB (G/DL)
Hematocrit	HCT (%)
Mean corpuscular volume	MCV (FL)
Mean corpuscular hemoglobin	MCH (PG)
Mean corpuscular hemoglobin concentration	MCHC (%)
Platelet count	PLT (E3/UL or $\times 10^3/\mu\text{L}$)
Mean platelet volume	MPV (FL)
Reticulocyte count	RETIC (%)
Absolute reticulocyte count	RETIC (E3/UL or $\times 10^3/\mu\text{L}$)
Heinz body count	HEINZ (%)
Erythrocyte sedimentation rate	ESR (MM/HR)
Prothrombin time	PT (SEC)
Activated partial thromboplastin time	PTT (SEC)
Thrombin time	TT (SEC)
Activated coagulation time	ACT (SEC)
Fibrinogen	FBR (MG/DL)
Fibrin/fibrinogen degradation products	FDP (UG/ML)
Platelet aggregation	
Collagen	PAGG/COL (%)
Adenosine diphosphate	PAGG/ADP (%)
Alpha 2-antiplasmin	ANTIPLAS (%)
Bleeding time	BLE TIME (SEC)
Methemoglobin	METHGB (%)
Plasma hemoglobin	PLA HGB (MG/DL)
Myeloid/erythroid ratio	M/E RATIO
Estimated myeloid/erythroid ratio	EST M/E RATIO
White blood cell count	WBC (E3/UL or $\times 10^3/\mu\text{L}$)
Differential blood cell count	
Nucleated red blood cell count	NRBC (/100 WBC)
Corrected white blood cell count	COR WBC (E3/UL or $\times 10^3/\mu\text{L}$)
Segmented neutrophil count	N-SEG (E3/UL or $\times 10^3/\mu\text{L}$) and %
Band neutrophil count	N-BAND (E3/UL or $\times 10^3/\mu\text{L}$) and %
Lymphocyte count	LYMPH (E3/UL or $\times 10^3/\mu\text{L}$) and %
Monocyte count	MONO (E3/UL or $\times 10^3/\mu\text{L}$) and %
Eosinophil count	EOSIN (E3/UL or $\times 10^3/\mu\text{L}$) and %
Basophil count	BASO (E3/UL or $\times 10^3/\mu\text{L}$) and %
Anisocytosis	ANISO (-,1,2,3)
Polychromasia	POLY (-,1,2,3)

Abbreviations and Units for Clinical Hematology (Continued)

Test	Abbreviation (Units)
Poikilocytosis	POIK (-,1,2,3)
Hypochromasia	HYPO (-,1,2,3)
Howell-Jolly bodies	HJBODY (-,1,2,3,4)
Basophilic stippling	BASTIP (-,1,2,3)
Toxic neutrophils	TOXNEUT (-,1,2,3,4)
Atypical lymphocytes	ATYPLYM (-,1,2,3,4)
Aqueous white blood cell count (right eye)	R EYE (WBC/UL)
Aqueous white blood cell count (left eye)	L EYE (WBC/UL)

Abbreviations and Units for Clinical Chemistry

Test	Abbreviation (Units)
Glucose	GLU (MG/DL)
Urea nitrogen	UN (MG/DL)
Urea	UREA (MG/DL)
Creatinine	CREAT (MG/DL)
Total protein	T PRO (G/DL)
Albumin	ALB (G/DL)
Globulin	GLOB (G/DL)
Albumin/globulin ratio	A/G RATIO
Total bilirubin	T BILI (MG/DL)
Direct bilirubin	D BILI (MG/DL)
Indirect bilirubin	I BILI (MG/DL)
Cholesterol	CHOL (MG/DL)
Triglyceride	TRIG (MG/DL)
Urea nitrogen/creatinine ratio	UN/CREAT (RATIO)
Total lipids	T LIPIDS (MG/DL)
Phospholipids	P LIPIDS (MG/DL)
High-density lipoprotein cholesterol	HDL (MG/DL)
Low-density lipoprotein cholesterol	LDL (MG/DL)
Uric acid	UA (MG/DL)
Aspartate aminotransferase	AST/SGOT (IU/L)
Alanine aminotransferase	ALT/SGPT (IU/L)
Alkaline phosphatase	ALK PHOS (IU/L)
Gamma glutamyl transferase	GGT (IU/L)
Sorbitol dehydrogenase	SDH (IU/L)
Lactate dehydrogenase	LDH (IU/L)
Creatine kinase	CK (IU/L)
Amylase	AMYLASE (IU/L)
Lipase	LIPASE (IU/L)
Palmitoyl CoA oxidase	PCOAO (IU/G)
Calcium	CA (MG/DL)
Ionized calcium	ION CA (MG/DL)
Inorganic phosphorus	I PHOS (MG/DL)
Sodium	NA (MMOL/L)
Potassium	K (MMOL/L)
Chloride	CL (MMOL/L)
Magnesium	MG (MEQ/L or MG/DL)
Zinc	ZN (MG/L or PPM)
Strontium	SR (MG/L or PPM)
Iron	FE (UG/DL)

Abbreviations and Units for Clinical Chemistry (Continued)

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)
Adrenocorticotrophic 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)
Pancreatic-specific amylase	P AMYL (U/L)

Codes for Anatomical Pathology

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
STOMACH, GL	Glandular stomach

Table 1

Summary of Clinical Observations
A.M./Weekly

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

PAGE: 1

NUMBER OF ANIMALS AFFECTED				
DAYS 1-30	SEX:	-----MALE-----		
CATEGORY	GROUP:	1	2	3
KEYWORD	DOSE:	0	2	20
QUALIFIER	NUMBER:	2	3	3
*** TOP OF LIST ***				
EXCRETION				
NO FECES		0	0	1
SKIN & PELAGE				
BROKEN SKIN				
THIGH-LEFT		0	1	0
SCAB(S)				
LIMB-HIND-LEFT		0	1	0
QUALITATIVE FOOD CONSUMPTION				
LOW		1	1	1
NONE		0	0	1
*** END OF LIST ***				

Table 2

Summary of Clinical Observations
30 Minutes Postdose

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

PAGE: 1

DAYS 1-29		NUMBER OF ANIMALS AFFECTED		
CATEGORY	SEX:	-----MALE-----		
KEYWORD	GROUP:	1	2	3
QUALIFIER	DOSE:	0	2	20
	NUMBER:	2	3	3
*** TOP OF LIST ***				
SKIN & PELAGE				
BROKEN SKIN				
DIGIT(S)-HIND-RIGHT				
THIGH-LEFT				
SCAB(S)				
LIMB-HIND-LEFT				
*** END OF LIST ***				

Table 3

Summary of Clinical Observations
60 Minutes Postdose

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

PAGE: 1

NUMBER OF ANIMALS AFFECTED				
DAYS 1-29	SEX:	-----MALE----		
	GROUP:	1 2 3		
CATEGORY	DOSE:	0 2 20		
KEYWORD				
QUALIFIER	NUMBER:	2 3 3		

*** TOP OF LIST ***				
SKIN & PELAGE				
BROKEN SKIN				
DIGIT(S)-HIND-RIGHT				
THIGH-LEFT				
SCAB(S)				
LIMB-HIND-LEFT				
*** END OF LIST ***				

Table 4

Summary of Clinical Observations
90 Minutes Postdose

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

PAGE: 1

NUMBER OF ANIMALS AFFECTED				
DAYS 1-29	SEX:	-----MALE----		
	GROUP:	1 2 3		
	DOSE:	0 2 20		
CATEGORY	NUMBER:	2 3 3		
KEYWORD				
QUALIFIER				

*** TOP OF LIST ***				
APPEARANCE				
UNDER EFFECTS OF ANESTHESIA		0 1 0		
SKIN & PELAGE				
BROKEN SKIN				
DIGIT(S)-HIND-RIGHT		1 0 0		
THIGH-LEFT		0 1 0		
SCAB(S)				
LIMB-HIND-LEFT		0 1 0		
*** END OF LIST ***				

Table 5

Summary of Body Weight Data (kg)

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

PAGE: 1

WEEK	SEX:	MALE		
	GROUP:	1	2	3
	DOSE:	0	2	20
	UNITS:	MG/KG/DAY	MG/KG/DAY	MG/KG/DAY
-2	N	2	3	3
	MEAN	3.0	2.8	2.7
	S.D.	0.71	0.70	0.50
-1 ^a	N	2	3	3
	MEAN	3.0	2.9	2.8
	S.D.	0.71	0.75	0.50
-1 ^b	N	2	3	3
	MEAN	3.1	2.8	2.8
	S.D.	0.78	0.75	0.50
1	N	2	3	3
	MEAN	3.1	2.9	2.8
	S.D.	0.71	0.75	0.55
2	N	2	3	3
	CAM	2.9	2.9	2.9
	MEAN	3.1	2.9	2.8
	S.D.	0.57	0.70	0.56
3	N	2	3	3
	CAM	2.9	3.0	2.9
	MEAN	3.2	2.9	2.8
	S.D.	0.64	0.70	0.56
4	N	2	3	3
	CAM	2.9	2.9	2.9
	MEAN	3.1	2.9	2.8
	S.D.	0.64	0.70	0.50
5	N	2	3	3
	CAM	2.9	3.0	3.0
	MEAN	3.2	3.0	2.9
	S.D.	0.64	0.75	0.56

a Day -7.

b Day -1.

Table 6
Summary of Clinical Hematology Data

Males Day -8

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

DOSE mg/kg/day		RBC X10 ⁶ /μL	HGB G/DL	HCT %	MCV FL	MCH PG	MCHC %	PLT X10 ³ /μL	RETIC %	RETIC X10 ³ /μL
0	MEAN	5.96	12.6	40.5	70.4	22.2	31.3	430	.4	19
	S.D.	2.157	.92	6.65	14.28	6.43	2.83	75.7	.42	17.0
	N	2	2	2	2	2	2	2	2	2
2	MEAN	6.85	13.6	44.2	65.8	20.3	30.7	422	.6	34
	S.D.	1.196	.57	1.21	11.04	4.63	1.80	41.1	.57	30.0
	N	3	3	3	3	3	3	3	3	3
20	MEAN	6.39	13.3	42.3	67.2	21.2	31.4	522	.3	20
	S.D.	.925	.96	.72	10.84	4.78	2.22	131.7	.23	10.7
	N	3	3	3	3	3	3	3	3	3

Table 6
Summary of Clinical Hematology Data

Males Day -8

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

DOSE mg/kg/day		WBC X10 ³ /μL	N-SEG X10 ³ /μL	LYMPH X10 ³ /μL	MONO X10 ³ /μL	EOSIN X10 ³ /μL	BASO X10 ³ /μL	N-SEG%	LYMPH%	MONO%	EOSIN%	BASO%
0	MEAN	10.4	1.8	7.4	.6	.6	.0	17	72	6	6	0
	S.D.	1.63	1.13	.64	.28	.71	.00	8.5	17.0	2.1	6.4	.0
	N	2	2	2	2	2	2	2	2	2	2	2
2	MEAN	9.4	2.6	5.9	.9	.1	.0	27	63	9	1	0
	S.D.	1.01	1.51	1.40	.42	.06	.00	15.5	18.1	3.2	.6	.0
	N	3	3	3	3	3	3	3	3	3	3	3
20	MEAN	9.6	2.8	6.0	.5	.3	.0	28	63	6	2	0
	S.D.	1.10	1.83	1.38	.15	.15	.06	16.6	18.1	1.2	1.5	.6
	N	3	3	3	3	3	3	3	3	3	3	3

Table 7
Summary of Clinical Hematology Data

Males Day -5

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

DOSE mg/kg/day		RBC X10 ⁶ /μL	HGB G/DL	HCT %	MCV FL	MCH PG	MCHC %	PLT X10 ³ /μL	RETIC %	RETIC X10 ³ /μL
0	MEAN	5.47	11.5	37.3	70.6	22.0	31.0	404	.6	26
	S.D.	1.711	.35	4.45	14.00	6.29	2.83	61.5	.85	36.1
	N	2	2	2	2	2	2	2	2	2
2	MEAN	5.91	11.8	38.4	66.3	20.6	30.8	395	.9	51
	S.D.	1.061	.49	1.17	10.81	4.93	2.22	22.1	.61	24.5
	N	3	3	3	3	3	3	3	3	3
20	MEAN	5.75	11.9	37.9	67.3	21.2	31.4	500	.2	9
	S.D.	1.057	.42	1.48	10.68	4.83	2.20	101.4	.12	4.4
	N	3	3	3	3	3	3	3	3	3

Table 7
Summary of Clinical Hematology Data

Males Day -5

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

DOSE mg/kg/day		WBC X10 ³ /μL	N-SEG X10 ³ /μL	LYMPH X10 ³ /μL	MONO X10 ³ /μL	EOSIN X10 ³ /μL	BASO X10 ³ /μL	N-SEG%	LYMPH%	MONO%	EOSIN%	BASO%
0	MEAN	11.1	2.0	7.8	.7	.6	.0	18	72	6	4	0
	S.D.	1.56	1.13	.49	.14	.64	.07	7.8	14.1	.7	4.9	.7
	N	2	2	2	2	2	2	2	2	2	2	2
2	MEAN	10.7	4.3	5.6	.7	.2	.0	40	52	6	2	0
	S.D.	3.18	1.81	1.76	.12	.10	.00	12.1	12.6	.6	.6	.0
	N	3	3	3	3	3	3	3	3	3	3	3
20	MEAN	10.5	4.1	5.4	.6	.2	.0	38	54	5	2	0
	S.D.	3.10	1.89	.76	.32	.21	.00	9.0	12.7	2.1	1.7	.0
	N	3	3	3	3	3	3	3	3	3	3	3

Table 8
Summary of Clinical Hematology Data

Males Day 30

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

DOSE mg/kg/day		RBC X10 ⁶ /μL	HGB G/DL	HCT %	MCV FL	MCH PG	MCHC %	PLT X10 ³ /μL	RETIC %	RETIC X10 ³ /μL
0	MEAN	5.96	12.4	40.8	70.1	21.6	30.5	461	.2	14
	S.D.	1.457	.14	2.26	13.44	5.52	2.05	66.5	.21	9.2
	N	2	2	2	2	2	2	2	2	2
2	MEAN	6.74	13.6	44.3	66.5	20.5	30.6	407	.2	10
	S.D.	.824	1.19	1.51	11.02	4.52	1.63	4.2	.21	11.8
	N	3	3	3	3	3	3	3	3	3
20	MEAN	6.24	13.0	41.9	68.1	21.3	31.1	489	.2	14
	S.D.	.814	1.11	1.31	10.91	4.78	2.25	116.0	.21	12.1
	N	3	3	3	3	3	3	3	3	3

Table 8
Summary of Clinical Hematology Data

Males Day 30

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

DOSE mg/kg/day		WBC X10 ³ /μL	N-SEG X10 ³ /μL	LYMPH X10 ³ /μL	MONO X10 ³ /μL	EOSIN X10 ³ /μL	BASO X10 ³ /μL	N-SEG%	LYMPH%	MONO%	EOSIN%	BASO%
0	MEAN	9.8	1.6	7.2	.6	.4	.0	16	74	6	4	0
	S.D.	.07	.64	.78	.21	.35	.07	7.1	7.8	2.1	3.5	.7
	N	2	2	2	2	2	2	2	2	2	2	2
2	MEAN	8.0	2.2	5.4	.3	.0	.0	27	67	5	1	0
	S.D.	2.29	.79	1.60	.15	.06	.00	4.6	6.6	2.9	.0	.0
	N	3	3	3	3	3	3	3	3	3	3	3
20	MEAN	8.3	3.1	4.4	.6	.1	.0	38	53	7	2	1
	S.D.	.85	1.11	1.31	.10	.12	.00	12.7	14.6	1.5	.6	.6
	N	3	3	3	3	3	3	3	3	3	3	3

Table 9
Summary of Clinical Chemistry Data

Males Day -8

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

DOSE mg/kg/day		GLU MG/DL	UN MG/DL	CREAT MG/DL	T PRO G/DL	ALB G/DL	GLOB G/DL	T BILI MG/DL	SBA umol/L	CHOL MG/DL	TRIG MG/DL
0	MEAN	74	22	1.0	8.7	5.2	3.5	.4	9	146	34
	S.D.	20.5	7.8	.21	2.40	1.13	1.27	.14	5.7	9.2	7.8
	N	2	2	2	2	2	2	2	2	2	2
2	MEAN	76	18	1.1	8.4	5.1	3.3	.3	9	174	36
	S.D.	14.2	2.0	.26	1.30	.30	1.00	.12	2.5	19.9	6.7
	N	3	3	3	3	3	3	3	3	3	3
20	MEAN	64	23	1.2	8.0	4.8	3.3	.2	12	141	31
	S.D.	5.1	2.3	.25	.55	.21	.75	.06	.6	12.7	6.7
	N	3	3	3	3	3	3	3	3	3	3

Table 9
Summary of Clinical Chemistry Data

Males Day -8

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

DOSE mg/kg/day		AST/SGOT IU/L	ALT/SGPT IU/L	ALK PHOS IU/L	GGT IU/L	SDH IU/L	CK IU/L	AMYLASE IU/L	LIPASE IU/L	P AMYL U/L
0	MEAN	41	45	847	122	2	348	492	43	252
	S.D.	1.4	9.9	420.0	11.3	.0	244.0	70.0	1.4	33.2
	N	2	2	2	2	2	2	2	2	2
2	MEAN	48	53	1013	159	5	369	522	46	250
	S.D.	14.7	22.2	106.1	45.1	4.4	159.3	174.5	23.4	41.7
	N	3	3	3	3	3	3	3	3	3
20	MEAN	52	59	948	136	5	195	496	43	239
	S.D.	6.7	26.7	65.5	35.5	1.2	40.3	32.0	8.5	37.3
	N	3	3	3	3	3	3	3	3	3

Table 9
Summary of Clinical Chemistry Data
Males Day -8
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)
IN CYNOMOLGUS MONKEYS

DOSE mg/kg/day		CA MG/DL	I PHOS MG/DL	NA MMOL/L	K MMOL/L	CL MMOL/L
-----		-----	-----	-----	-----	-----
0	MEAN	11.4	7.2	158	6.6	112
	S.D.	1.70	.99	11.3	.71	1.4
	N	2	2	2	2	2
2	MEAN	11.0	7.5	158	5.6	108
	S.D.	.35	1.11	4.6	.35	1.2
	N	3	3	3	3	3
20	MEAN	10.9	7.0	154	6.1	108
	S.D.	.53	.29	1.5	.40	.6
	N	3	3	3	3	3

Table 10
Summary of Clinical Chemistry Data

Males Day -5

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

DOSE mg/kg/day		GLU MG/DL	UN MG/DL	CREAT MG/DL	T PRO G/DL	ALB G/DL	GLOB G/DL	T BILI MG/DL	SBA umol/L	CHOL MG/DL	TRIG MG/DL
0	MEAN	84	18	1.2	8.4	5.0	3.4	.6	4	138	28
	S.D.	41.0	9.2	.14	1.70	.78	.92	.07	2.1	26.2	.7
	N	2	2	2	2	2	2	2	2	2	2
2	MEAN	66	15	1.1	8.0	4.8	3.2	.3	5	155	34
	S.D.	6.5	1.0	.21	.85	.10	.90	.17	4.0	12.3	3.8
	N	3	3	3	3	3	3	3	3	3	3
20	MEAN	67	20	1.1	8.0	4.7	3.4	.4	1	141	39
	S.D.	14.4	5.1	.15	.57	.25	.75	.31	1.0	13.5	11.0
	N	3	3	3	3	3	3	3	3	3	3

Table 10
Summary of Clinical Chemistry Data

Males Day -5

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

DOSE mg/kg/day		AST/SGOT IU/L	ALT/SGPT IU/L	ALK. PHOS IU/L	GGT IU/L	SDH IU/L	CK IU/L	AMYLASE IU/L	LIPASE IU/L	P AMYL U/L
0	MEAN	38	43	788	112	3	494	495	40	252
	S.D.	4.9	12.7	393.9	6.4	.0	478.7	76.4	2.8	26.2
	N	2	2	2	2	2	2	2	2	2
2	MEAN	39	49	930	137	3	279	520	56	252
	S.D.	13.3	15.2	83.5	39.7	1.0	227.6	174.8	9.2	37.2
	N	3	3	3	3	3	3	3	3	3
20	MEAN	48	51	896	121	3	171	466	57	229
	S.D.	9.8	14.5	54.7	38.2	1.0	29.3	15.0	13.5	18.4
	N	3	3	3	3	3	3	3	3	3

Table 10
Summary of Clinical Chemistry Data
Males Day -5
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)
IN CYNOMOLGUS MONKEYS

DOSE mg/kg/day		CA MG/DL	I PHOS MG/DL	NA MMOL/L	K MMOL/L	CL MMOL/L
-----		-----	-----	-----	-----	-----
0	MEAN	10.9	6.8	156	5.4	108
	S.D.	1.27	1.27	9.2	.92	2.1
	N	2	2	2	2	2
2	MEAN	10.4	6.4	155	5.2	110
	S.D.	.61	1.04	3.5	.75	2.6
	N	3	3	3	3	3
20	MEAN	10.4	6.2	152	5.0	107
	S.D.	.51	.17	2.6	.58	1.7
	N	3	3	3	3	3

Table 11
Summary of Clinical Chemistry Data

Males Day 2

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

DOSE mg/kg/day		GLU MG/DL	UN MG/DL	CREAT MG/DL	T PRO G/DL	ALB G/DL	GLOB G/DL	T BILI MG/DL	SBA umol/L	CHOL MG/DL	TRIG MG/DL
0	MEAN	76	21	1.0	9.0	5.2	3.9	.4	10	152	28
	S.D.	4.2	7.1	.21	2.19	.92	1.27	.21	4.9	7.8	7.8
	N	2	2	2	2	2	2	2	2	2	2
2	MEAN	65 *	20	1.0	8.4	4.9	3.5	.3	9	169	52
	S.D.	4.2	4.9	.21	.65	.10	.75	.06	3.0	22.3	8.3
	N	3	3	3	3	3	3	3	3	3	3
20	MEAN	68	23	1.0	8.3	4.8	3.5	.1 *	14	132	45
	S.D.	2.0	1.0	.12	.51	.21	.70	.06	4.4	10.0	11.1
	N	3	3	3	3	3	3	3	3	3	3

Table 11
Summary of Clinical Chemistry Data

Males Day 2

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

DOSE mg/kg/day		AST/SGOT IU/L	ALT/SGPT IU/L	ALK PHOS IU/L	GGT IU/L	SDH IU/L	CK IU/L	AMYLASE IU/L	LIPASE IU/L	P AMYL U/L
0	MEAN	47	53	872	125	1	225	477	29	249
	S.D.	2.8	25.5	355.7	5.7	.0	62.2	59.4	1.4	29.7
	N	2	2	2	2	2	2	2	2	2
2	MEAN	53	52	1029	148	2	794	483	44	244
	S.D.	32.7	26.8	113.3	44.9	1.5	1173.2	144.3	7.5	42.7
	N	3	3	3	3	3	3	3	3	3
20	MEAN	55	56	921	126	1	165	479	33	234
	S.D.	4.9	22.4	124.2	39.1	1.0	44.4	40.1	12.2	32.5
	N	3	3	3	3	3	3	3	3	3

Table 11
Summary of Clinical Chemistry Data
Males Day 2
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)
IN CYNOMOLGUS MONKEYS

DOSE mg/kg/day		CA MG/DL	I PHOS MG/DL	NA MMOL/L	K MMOL/L	CL MMOL/L
-----		-----	-----	-----	-----	-----
0	MEAN	11.6	8.8	162	6.2	110
	S.D.	1.63	.28	12.0	.99	4.9
	N	2	2	2	2	2
2	MEAN	10.5	8.0	155	5.3	109
	S.D.	.57	1.30	2.5	.44	3.8
	N	3	3	3	3	3
20	MEAN	10.7	7.4	156	5.5	109
	S.D.	.83	.90	4.2	.67	1.5
	N	3	3	3	3	3

Table 12
Summary of Clinical Chemistry Data

Males Day 30

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

DOSE mg/kg/day		GLU MG/DL	UN MG/DL	CREAT MG/DL	T PRO G/DL	ALB G/DL	GLOB G/DL	T BILI MG/DL	SBA umol/L	CHOL MG/DL	TRIG MG/DL
0	MEAN	84	19	1.0	8.6	5.1	3.4	.5	4	150	32
	S.D.	9.2	5.7	.07	1.77	.71	1.06	.28	3.5	31.8	.7
	N	2	2	2	2	2	2	2	2	2	2
2	MEAN	76	17	1.1	8.3	5.0	3.3	.1	4	147	43
	S.D.	3.2	2.1	.06	.60	.17	.75	.06	1.5	9.2	3.2
	N	3	3	3	3	3	3	3	3	3	3
20	MEAN	65 *	20	1.2	7.8	4.5	3.3	.1	6	138	52
	S.D.	2.1	3.5	.35	.47	.23	.70	.15	4.5	31.5	10.6
	N	3	3	3	3	3	3	3	3	3	3

Table 12
Summary of Clinical Chemistry Data

Males Day 30

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

DOSE mg/kg/day		AST/SGOT IU/L	ALT/SGPT IU/L	ALK PHOS IU/L	GGT IU/L	SDH IU/L	CK IU/L	AMYLASE IU/L	LIPASE IU/L	P AMYL U/L	PCOA0 IU/G
0	MEAN	52	59	917	110	2	511	471	42	242	2
	S.D.	.7	.0	.2	.3	.4	.9	.3	.3	.4	.7
	N	2	2	2	2	2	2	2	2	2	2
2	MEAN	50	75	1111	136	2	324	500	38	244	1
	S.D.	19.7	33.3	88.9	35.8	1.0	220.4	155.0	7.8	49.9	1.7
	N	3	3	3	3	3	3	3	3	3	3
20	MEAN	55	83	704	101	2	207	441	39	218	6
	S.D.	11.5	50.0	87.8	33.2	1.5	9.0	71.8	11.6	52.8	3.1
	N	3	3	3	3	3	3	3	3	3	3

Table 12
Summary of Clinical Chemistry Data
Males Day 30
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)
IN CYNOMOLGUS MONKEYS

DOSE mg/kg/day		CA MG/DL	I PHOS MG/DL	NA MMOL/L	K MMOL/L	CL MMOL/L
-----		-----	-----	-----	-----	-----
0	MEAN	10.7	7.2	153	5.4	106
	S.D.	.71	1.77	5.7	.49	2.8
	N	2	2	2	2	2
2	MEAN	10.8	6.7	155	5.2	109
	S.D.	.53	1.06	2.1	.90	2.9
	N	3	3	3	3	3
20	MEAN	10.2	5.5	151	5.2	109
	S.D.	.70	.31	5.1	.66	2.1
	N	3	3	3	3	3

TABLE 13
Incidence of Macroscopic Observations

Covance 6329-230
3M T-6889.2

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

PAGE: 1

--- 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: -----MALE-----		
SEX=ALL;GROUP=ALL;WEEKS=ALL	GROUP: -1- -2- -3-		
DEATH=ALL;SUBSET=ALL	NUMBER: 2 3 3		
ORGAN AND KEYWORD(S) OR PHRASE	-----		
** TOP OF LIST **	-- -- --		
GENERAL COMMENT (GC)	NUMBER EXAMINED:	2	3
EYES - DAVIDSONS		2	3
NO MACROSCOPIC LESIONS		0	3
KIDNEY (KD)	NUMBER EXAMINED:	2	3
	NOT REMARKABLE:	1	3
LIGHT FOCUS(I)/AREA(S)		1	0
LUNG (LU)	NUMBER EXAMINED:	2	3
	NOT REMARKABLE:	2	3
ADHESION(S)		0	0
STOMACH, GL (ST)	NUMBER EXAMINED:	2	3
	NOT REMARKABLE:	1	3
RED FOCUS(I)/AREA(S)		1	0
** END OF LIST **			2

TABLE 14
Incidence of Microscopic Observations

Covance 6329-230
3M T-6889.2

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

PAGE: 1

TABLE INCLUDES:				
SEX=ALL;GROUP=ALL;WEEKS=ALL				
DEATH=ALL;FIND=ALL;SUBSET=ALL				
--- N U M B E R - O F - A N I M A L S - A F F E C T E D				
SEX: -----MALE-----				
GROUP: -1- -2- -3-				
ORGAN AND FINDING DESCRIPTION	NUMBER:	2	3	3

** TOP OF LIST **				
LIVER (LI)	NUMBER EXAMINED:	2	3	3
	NOT REMARKABLE:	2	3	3
SPLEEN (SP)	NUMBER EXAMINED:	2	3	3
	NOT REMARKABLE:	2	3	3
PANCREAS (PA)	NUMBER EXAMINED:	2	3	3
	NOT REMARKABLE:	2	3	3
TESTIS (TE)	NUMBER EXAMINED:	2	3	3
	NOT REMARKABLE:	2	2	2
--IMMATURE		0	1	1
ADRENAL (AD)	NUMBER EXAMINED:	2	3	3
	NOT REMARKABLE:	2	2	3
--MINERALIZATION		0	1	0
** END OF LIST **				

APPENDIX 1

Protocol
Protocol Amendment No. 1
Protocol Amendment No. 2
Protocol Amendment No. 3
Material Safety Data Sheet
Certificate of Analysis



Sponsors:

APME Ad-Hoc APFO Toxicology Working Group

PROTOCOL

Study Title:

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

Date:

June 11, 1998

Performing Laboratory:

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

Laboratory Study Identification:

Proposal No. w6806a

Covance 6329-230

Study

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

Purpose

To provide data for determining an estimated maximum-tolerated dose and lower dose levels to be used in a chronic toxicity study. In addition, the effect on critical enzyme levels, hormones, and other selected biochemical parameters will be determined.

Sponsors

APME Ad-Hoc APFO Toxicology Working Group

Study Monitor

Paul Lieder, PhD, DABT

3M

Toxicology Services

Building 220-2E-02, 3M Center

St. Paul, Minnesota, 55144-1000

Telephone No.: 612.737.2678

Facsimile No.: 612.733.1773

Alternate Study Monitor

John Butenhoff, PhD, DABT

3M

Toxicology Services

Building 220-2E-02, 3M Center

St. Paul, Minnesota, 55144-1000

Telephone No.: 612.733.1962

Facsimile No.: 612.733.1733

Study Location

Covance Laboratories Inc.

3301 Kinsman Boulevard

Madison, Wisconsin 53704-2595

Mailing Address: PO Box 7545
Madison, Wisconsin 53707-7454

Study Director

Peter J. Thomford, PhD
Covance Laboratories Inc.
Telephone No.: 608.241.7207
Facsimile No.: 608.242.2736

Toxicologist

Dale Aldridge, BS
Covance Laboratories Inc.

Proposed Study Timetable

Study Initiation Date: June 11, 1998
In-Life (Experimental) Start Date: June 17, 1998
In-Life Termination Date: July 17, 1998
Experimental Termination Date: To be determined
Audited Draft Report Date: November 3, 1998

Regulatory Compliance

This study will be conducted in compliance with the Environmental Protection Agency Good Laboratory Practice Regulations as set forth in Title 40 of the US Code of Federal Regulations, Part 792, issued November 29, 1983 (effective December 29, 1983), and with any applicable amendments.

Animal Care and Use Statement

All procedures in this protocol are in compliance with the Animal Welfare Act Regulations, 9 CFR 1-4. In the opinion of the Sponsor and study director, the study does not unnecessarily duplicate any previous work.

Quality Assurance

The protocol, study conduct, and final report will be audited by the Covance Quality Assurance Unit (QAU). The proliferation cell nuclear antigen evaluation data and report will be audited by the QAU of Pathology Associates International. The serum and liver APFO analysis and report will be audited by the QAU of 3M Environmental Laboratories. The blood hormone determinations and report will be audited by the QAUs of Ani Lytics Inc and DuPont, as appropriate. The receptor level determinations and report will be audited by the QAU of the University of Dundee.

Test Material**Identification**

Ammonium Perfluorooctanoate (APFO)

Lot Number

The lot number will be maintained in the raw data.

Purity

Responsibility of the Sponsor

Stability

Responsibility of the Sponsor

Storage Conditions

At room temperature

Characteristics

Information on synthesis methods, composition, or other characteristics that define the test material is on file with the Sponsor.

Gelatin Capsules

Capsules (Size No. 2) obtained from Torpac, Inc. (Fairfield, New Jersey); lot number will be supplied by the manufacturer. Gelatin capsules will be stored at room temperature. A copy of the Certificate of Analysis provided by the manufacturer will be maintained in the data.

Reserve (Archive) Samples

A reserve sample (1 g each) of each lot of test material will be taken and stored at room temperature. These samples will be transferred to the Sponsor after completion of the in-life phase.

Disposition of Test Material

Any remaining test material will be returned after authorization from the Sponsor.

Animals**Species**

Cynomolgus monkey

Source

Covance Research Products Inc.

Age at Initiation of Treatment

Young adult/adult

Weight at Initiation of Treatment

2 to 4 kg

Number and Sex

Eight males

Identification

Collar tag

Husbandry**Housing**

Individual. Animals will be housed in suspended, stainless steel cages.

Diet

Certified primate diet (#8726C, Harlan Teklad) once or twice daily. The diet is routinely analyzed by the manufacturer for nutritional components and environmental contaminants. Results of specified nutrient and contaminant analyses are on file at Covance-Madison. Fruit, vegetables, or other supplements may be provided but will not require analysis.

Water

Ad libitum. Samples of the water are routinely analyzed for specified microorganisms and environmental contaminants. The results are on file at Covance-Madison.

Contaminants

There are no known contaminants in the diet or water at levels that might interfere with this study.

Environment

Environmental controls for the animal room will be set to maintain 18 to 29°C, a relative humidity of 30 to 70%, and a 12-hour light/12-hour dark cycle.

Acclimation

Minimum of 4 weeks

Randomization

Animals will be weighed, stratified by body weight, and allocated to the number of blocks equal to the number of animals to be selected for each group. Animals in each block will then be assigned to groups using computer-generated random numbers.

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.

Group Designations and Dose Levels

Group	Dose Level (mg/kg/day)	Total Material Dose Level (mg/kg/day)	Number of Males
1 (control)	0 ^a	0 ^a	2
2 (low-dose)	2	2	3
3 (high-dose)	20	20	3

a The control group (Group 1) will receive empty gelatin capsules

Dosing Procedures**Method of Administration**

Orally by gelatin capsules, daily for at least 28 days

Reason for Dosing Route

To compare with previously conducted toxicology studies using the oral route, which is the route of most likely exposure.

Dose Preparation

Capsules will be prepared at least weekly. The size and number of capsules will depend on the physical characteristics of the test material, the dose level, and the weight of the monkey. Individual daily doses will be based on the most recent individual body weights, with the exception of body weight collection days when the previous body weight will be used. Dose levels will be based on the test material as supplied. All dose preparations will be stored at room temperature until dosed.

Dose Analysis

Because the test material is not being mixed with a vehicle, dose analyses are not required.

Observation of Animals**Clinical Observations**

Each animal will be observed twice daily (a.m. and p.m.) for mortality and moribundity; findings will be recorded as they are observed.

Each animal will be observed daily, and food consumption will be assessed qualitatively; abnormal findings will be recorded. Once weekly, each animal will be observed; abnormal findings, or an indication of normal will be recorded. During treatment, each animal will be observed for signs of poor health or abnormal behavior approximately 30, 60, and 90 minutes postdose.

Additional findings will be recorded as they are observed.

Body Weights

Weekly before initiation of treatment, Day -1 (for the Day 1 dose calculations), on the first day of treatment, and weekly thereafter.

Clinical Pathology**Frequency****Unscheduled Collections**

When possible, blood will be collected for clinical pathology tests from animals sacrificed at unscheduled intervals

Scheduled Collections

Hematology and clinical chemistry will be done twice before initiation of treatment and after at least 28 days of treatment; clinical chemistry will also be done on Day 2 (approximately 24 hours after the first dose).

Method of Collection

Animals will be fasted overnight; blood will be collected from a femoral vein (an alternative vein may be used if necessary). Anticoagulant will be potassium EDTA for hematology tests. No anticoagulant is used for clinical chemistry tests.

Tests**Hematology**

red blood cell (erythrocyte) count	platelet count
hemoglobin	white blood cell (leukocyte) count
hematocrit	differential blood cell count
mean corpuscular volume	blood cell morphology
mean corpuscular hemoglobin	reticulocyte count
mean corpuscular hemoglobin concentration	

Clinical Chemistry

glucose	aspartate aminotransferase
urea nitrogen	gamma glutamyltransferase
creatinine	sorbitol dehydrogenase
total protein	creatine kinase
albumin	calcium
globulin	inorganic phosphorus
total bilirubin	sodium
direct bilirubin (if total bilirubin is greater than 2.0 mg/dL)	potassium
cholesterol	chloride
triglycerides	bile acids
alanine aminotransferase	amylase
alkaline phosphatase	lipase
	pancreatic-specific amylase

Blood Hormone Determination**Frequency**

Before initiation of treatment and after 28 days of treatment; blood will be collected between 7:00 a.m. and 9:00 a.m.

Number of Animals

All

Method of Collection

Animals will be fasted overnight; blood will be collected from a femoral vein (an alternative vein may be used if necessary). Approximately 5 mL of blood for plasma samples will be collected with EDTA as anticoagulant. Approximately 5 mL of blood for serum samples will be collected without anticoagulant and allowed to clot.

Serum Sample Handling

Samples for serum will be centrifuged within 1 hour after collection, and serum will be harvested. Serum will be 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:

Dr. Saroj Das
Ani Lytics Inc.
200 Girard Street, Suite 200
Gaithersburg, Maryland 20877
Telephone No.: 301.921.0168
Facsimile No.: 301.977.0433

Ani Lytics Inc. will be notified regarding shipment of samples.

Serum Tests

Samples will be analyzed by Ani Lytics Inc., for estradiol, estrone, estriol, thyroid stimulating hormone, triiodothyronine (T3), and thyroxin (T4). Results will be provided for inclusion in the final report.

Plasma Sample Handling

Samples for plasma will be centrifuged within 1 hour after collection. Plasma will be harvested and stored in a freezer set to maintain -60 to -80°C until packed on dry ice and shipped to:

Jon C. Cook, PhD, DABT
E. I. du Pont de Nemours & Company, Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Building 14
Elkton Road
Newark, Delaware 19714-0500
Telephone No.: 302.366.5495
Facsimile No.: 302.366.5003

DuPont will be notified regarding shipment of samples.

Plasma Analysis

Samples will be analyzed by DuPont Haskell Company for cholecystokinin. Results will be provided for inclusion in the final report.

Serum APFO Level Determination**Frequency**

Once before initiation of treatment and after at least 28 days of treatment

Number of Animals

All

Method of Collection

Animals will be fasted overnight; blood (approximately 2 mL) will be collected from a femoral vein (an alternative vein may be used if necessary) without an anticoagulant.

Sample Handling

Samples will be centrifuged within 1 hour after collection, and serum will be harvested. Serum samples will be stored in a freezer set to maintain -10 to -30°C.

Sample Shipping

Serum samples will be packed on dry ice and shipped to:

Kris J. Hansen, PhD
3M E.T. & S
Bldg. 2-3E-09
935 Bush Avenue
St. Paul, Minnesota 55106

Kris J. Hansen, PhD or her designee will be notified regarding the shipment of the samples. Results will be provided for inclusion in the final report.

Additional Blood Collection

At scheduled and unscheduled necropsies, blood (as much as possible, up to 20 mL) will be collected from animals at the time of exsanguination. Blood from each animal will be transferred into containers (approximately 5 mL each) and stored in a freezer set to maintain -60 to -80°C until shipped to the Sponsor for possible future analysis.

Termination

Unscheduled Sacrifices and Deaths

Necropsies will be done. Animals to be sacrificed will be anesthetized with ketamine and xylazine, weighed, bled for the additional blood collection, and exsanguinated.

Scheduled Sacrifice

After at least 4 weeks of treatment, all surviving animals will be fasted overnight, then anesthetized with ketamine and xylazine, weighed, bled for the additional blood collection, exsanguinated, and necropsied.

Postmortem Procedures

Necropsy

The necropsy will include examination of:

- all orifices
- cranial cavity
- external surface of the brain; the external surface of the spinal cord and cut surfaces of the brain and spinal cord will be examined whenever tissue trimming is performed

cervical tissues and organs
thoracic, abdominal, and pelvic cavities and viscera
external surface of the body
nasal cavity and paranasal sinuses

Palmitoyl CoA Oxidase Determinations

Representative samples of the right lateral lobe of liver will be collected from each animal at the scheduled sacrifice, weighed, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C until analyzed for palmitoyl CoA oxidase activity.

Cell Proliferation Evaluation

Representative samples of the left lateral lobe of the liver, left and right testes, and pancreas will be collected and preserved in zinc formalin.

After fixation, samples for proliferation cell nuclear antigen (PCNA) evaluation will be embedded in paraffin and shipped to:

Sandra R. Eldridge, PhD
Pathology Associates International
15 Worman's Mill Court
Suite I
Frederick, Maryland 21701
Telephone No.: 301.663.1644 ext. 2201
Facsimile No: 301.663.8994

Pathology Associates International will be notified regarding shipment of samples. Results of PCNA analyses will be provided for inclusion in the final report.

Receptor Level Determination

All available bile (up to 5 mL) will be collected from each animal at the scheduled sacrifice, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C. Samples (approximately 2 g) of liver and pancreas will be collected from each animal at the scheduled sacrifice, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C. Bile, liver, and pancreas samples will be packed on dry ice and shipped to:

Dr. Cliff Elcombe
Biomedical Research Center
University of Dundee
Dundee, Scotland
Telephone No.: 011 44 1382 632641
Facsimile No.: 011 44 1382 668278

Results of analyses will be provided for inclusion in the final report.

Liver APFO Determination

A section (approximately 20 g) of liver will be collected from each animal at the scheduled sacrifice, weighed, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C until shipped with plasma samples to 3M (Kris Hansen) for analysis. Results will be provided for inclusion in the final report.

Tissue Preservation

The following tissues (when present) from each animal will be preserved in 10% neutral-buffered formalin, unless otherwise specified, for possible future microscopic examination:

adrenal (2)	mesenteric lymph node
aorta	pancreas
brain	pituitary
cecum	prostate
colon	rectum
duodenum	salivary gland [mandibular (2)]
epididymis (2)	sciatic nerve
esophagus	seminal vesicle (2)
eye [to be preserved in Davidson's fixative for sacrificed animals only (2)]	skeletal muscle (thigh)
femur with bone marrow (articular surface of the distal end)	skin
gallbladder	spinal cord (cervical, thoracic, and lumbar)
heart	spleen
ileum	sternum with bone marrow
jejunum	stomach
kidney (2)	testis (2)
lesions	thymus
liver	thyroid (2) with parathyroid
lung	trachea
mammary gland	urinary bladder

Histopathology

The pancreas, liver, adrenals, spleen, and testes from each animal will be embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically.

Reports

A draft report that includes the following information will be prepared and submitted:

Experimental Design and Methods**Results**

mortality

clinical observations

body weights

food consumption

clinical pathology results

palmitoyl CoA oxidase activities

hormone analyses (provided by Ani Lytics and DuPont Haskell Company)

receptor determination (provided by the Sponsor's designee)

serum and liver APFO levels (provided by 3M)

macroscopic observations

microscopic observations

cell proliferation evaluations (provided by the Sponsor's designee)

Statistical Evaluation

Levene's test will be done to test for variance homogeneity. In the case of heterogeneity of variance at $p \leq 0.05$, transformations will be used to stabilize the variance. Comparison tests will take variance heterogeneity into consideration.

One-way analysis of variance (ANOVA) will be used (if applicable) to analyze initial body weights, continuous clinical pathology values, and palmitoyl CoA oxidase activities. If the ANOVA is significant, Dunnett's t-test will be used for control versus treated group comparisons.

One-way analysis of covariance (ANCOVA) will be used to analyze body weights, with initial body weights as the covariate. If the ANCOVA is significant, covariate-adjusted means will be used for control versus treated group comparisons.

Group comparisons (Groups 2 and 3 versus Group 1) will be evaluated at the 5.0% two-tailed probability level. Only data collected on or after the first day of treatment will be analyzed statistically.

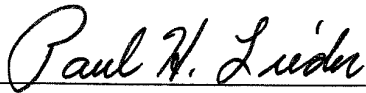
At the end of 1 year after issuance of the audited draft report, if no requested revisions or instructions to finalize have been communicated by the Sponsor, then the audited draft report will be considered 'final' and issued as the final report, signed by the study director, and submitted to the Sponsor.

Any modifications or changes to the audited draft report requested 1 year after issuance will be performed at additional cost to the Sponsor.

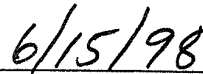
Record Retention

All raw data, documentation, records, protocol, specimens, and final report generated as a result of this study will be archived in the storage facilities of Covance-Madison for a period of 1 year following submission of the final report to the Sponsor. One year after submission of the final report, all of the aforementioned materials will be sent to the Sponsor, and a return fee will be charged. The Sponsor may elect to have the materials retained in the Covance archives for an additional period of time, and Covance will charge a storage fee. If the Sponsor chooses to have Covance dispose of the materials, a disposal fee will be charged. All raw data stored on magnetic media will be retained by Covance.

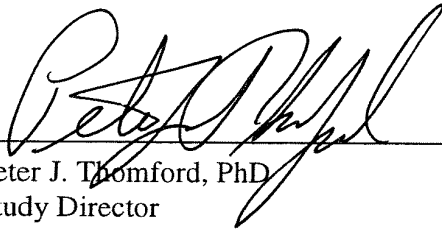
PROTOCOL APPROVAL



Paul Lieder, PhD
Diplomate, ABT
Study Monitor
3M



Date



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



Date



PROTOCOL AMENDMENT NO. 1

Covance 6329-230

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

Sponsor:	APME Ad-Hoc APFO Toxicology Working Group
Study Monitor:	Paul Lieder, PhD, DABT
Testing Facility:	Covance Laboratories Inc., Madison, Wisconsin
Study Director:	Peter J. Thomford, PhD

This amendment modifies the following portions of the protocol:

Effective June 11, 1998

1. **Page 1, Study Title and all other occurrences of the name of test material in the protocol.** To correct the spelling of the test material, delete the name of the test material and replace with the following:

Ammonium Perfluorooctanoate (APFO)

2. **Page 3, Regulatory Compliance.** Because bile acid determinations done by the University of Dundee will not be in compliance with GLPs, delete the text in this section and replace with the following:

This study will be conducted in compliance with the Environmental Protection Agency Good Laboratory Practice Regulations as set forth in Title 40 of the US Code of Federal Regulations, Part 792, issued November 29, 1983 (effective December 29, 1983), and with any applicable amendments except that bile acid determinations done by University of Dundee will not be done in compliance with GLPs.

3. **Page 4, Quality Assurance, Sentence 5.** Because receptor level analysis will be done by DuPont Haskell Company, delete this sentence and replace with the following:

The receptor level determinations and report will be audited by the QAU of the DuPont Haskell Company. Bile acid determinations done by the University of Dundee will not be audited.

4. **Page 7, Dosing Procedures, Reason for Dosing Route.** To correct the reason for the dosing route, delete the text in this section and replace with the following:

To compare with previously conducted toxicology studies using the oral route

5. **Page 10, Blood Hormone Determination, Method of Collection.** To increase the volume of the blood collected for serum and plasma samples, to specify the use of serum separation tubes, and to specify the storage conditions of blood samples before serum or plasma samples are prepared, delete the text in this section and replace with the following:

Animals will be fasted overnight; blood will be collected from a femoral vein (an alternative vein may be used if necessary). Approximately 6 mL of blood for plasma samples will be collected into tubes with potassium EDTA as the anticoagulant. Approximately 6 mL of blood for serum samples will be collected without anticoagulant and allowed to clot. Blood samples will be maintained at room temperature until serum is harvested. Blood samples will be maintained chilled until plasma is harvested.

6. **Page 10, Blood Hormone Determination, Serum Tests, Sentence 1.** To specify total and free triiodothyronine (T3) and total and free thyroxine (T4) tests that will be done, delete this sentence and replace with the following:

Samples will be analyzed by Ani Lytics Inc., for estradiol, estrone, estriol, thyroid stimulating hormone, total and free triiodothyronine (T3), and total and free thyroxine (T4).

7. **Page 11, Blood Hormone Determination, Plasma Sample Handling, Paragraph 2.** To correct the shipping address, delete this paragraph and replace with the following:

Jon C. Cook, PhD, DABT
E. I. du Pont de Nemours & Company, Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Building 11 Room 1325
1090 Elkton Road
Newark, Delaware 19711-0500
Telephone No.: 302.366.5495
Facsimile No.: 302.366.5003

8. **Page 12, Additional Blood Collection, Sentence 2.** To clarify the processing and disposition of the additional blood samples, delete this sentence and replace with the following:

Approximately equally sized samples of serum (collected without anticoagulant) and whole blood and plasma (both collected using potassium EDTA as the anticoagulant) from each animal will be transferred into containers (approximately 5 mL each). Whole blood, serum, and plasma samples will be stored in a freezer set to maintain -60 to -80°C until shipped to the Sponsor for possible future analysis.

9. **Page 13, Receptor Level Determination.** To correct and clarify the process, delete this section and replace with the following:

Receptor Level Determination

Samples (approximately 2 g) of liver and pancreas will be collected from each animal at the scheduled sacrifice, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C. Liver and pancreas samples will be packed on dry ice and shipped to:

Jon C. Cook, PhD, DABT
E. I. du Pont de Nemours & Company, Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Building 11 Room 1325
1090 Elkton Road
Newark, Delaware 19711-0500
Telephone No.: 302.366.5495
Facsimile No.: 302.366.5003

Results of receptor level determinations will be provided for inclusion in the final report.

Bile Acid Determination

All available bile (up to 5 mL) will be collected from each animal at the scheduled sacrifice, flash-frozen in liquid nitrogen, and stored in a freezer set to maintain -60 to -80°C. Bile samples will be packed on dry ice and shipped to:

Biomedical Research Centre
Level 5
Ninewells Hospital and Medical School
University of Dundee
Dundee DD1 9SY
UK
Dr Cliff Elcombe
Biomedical Research Centre
Ninewells Hospital and Medical School
University of Dundee
Dundee DD1 9SY, UK
Telephone: +44 (0)1382-632641
Fax: +44 (0)1382-425586

Results of bile acid determinations will be provided for inclusion in the final report.

10. **Page 15, Reports, Results.** To include bile acid determinations in the list of items to be reported, add the following:

Bile Acid Determinations (provided by the University of Dundee)

11. **Page 16, Record Retention.** To clarify the record retention requirements for the Sponsor's designees, add the following:

Within 1 year after submission of the final report, all of the aforementioned materials from the Sponsor's designees (Ani Lytics Inc., E. I. du Pont de Nemours & Company, Inc., 3M E.T. & S, Pathology Associates International, and the University of Dundee) will be sent to the Sponsor (Paul Lieder, PhD, DABT, 3M).

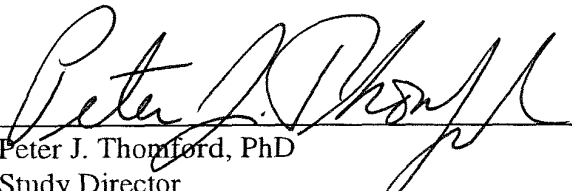
AMENDMENT APPROVAL



Paul Lieder, PhD
Diplomate, ABT
Study Monitor
3M

9/25/98

Date



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

9/23/98

Date



PROTOCOL AMENDMENT NO. 2

Covance 6329-230

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

Sponsor:	APME Ad-Hoc APFO Toxicology Working Group
Study Monitor:	Paul Lieder, PhD, DABT
Testing Facility:	Covance Laboratories Inc., Madison, Wisconsin
Study Director:	Peter J. Thomford, PhD

This amendment modifies the following portions of the protocol.

Effective December 15, 1998

1. **Page 13, Postmortem Procedures, Cell Proliferation Evaluation, Paragraph 3, Sentence 2.** To include evaluation of slides stained with hematoxylin and eosin in the PCNA evaluation, delete this sentence and replace with the following.

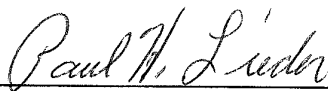
PCNA evaluation (including examination of slides stained with hematoxylin and eosin) will be done on the samples and results will be provided for inclusion in the final report.

Effective April 8, 1999

2. **Page 16, Record Retention, Paragraph 2.** To modify the record retention requirements for Pathology Associates International, delete this paragraph and replace with the following.

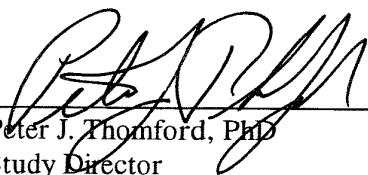
Within 1 year after submission of the final report, all of the aforementioned materials from the Sponsor's designees (Ani Lytics Inc., E. I. du Pont de Nemours & Company, Inc., 3M E.T. & S, and the University of Dundee) will be sent to the Sponsor (Paul Lieder, PhD, DABT, 3M). Pathology Associates International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

AMENDMENT APPROVAL



Paul Lieder, PhD
Diplomate, ABT
Study Monitor
3M

24 June 1999
Date



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

18 June 1999
Date

PROTOCOL AMENDMENT NO. 3

Covance 6329-230

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

Sponsor:	APME Ad-Hoc APFO Toxicology Working Group
Study Monitor:	Paul Lieder, PhD, DABT
Testing Facility:	Covance Laboratories Inc., Madison, Wisconsin
Study Director:	Peter J. Thomford, PhD

This amendment modifies the following portions of the protocol.

Effective October 21, 1999

- Page 11, Blood Hormone Determination, Plasma Analysis.** To reflect the Sponsor's decision to retain these samples for possible future analysis, delete the text in this section and replace with the following.

Plasma samples for cholecystokinin determination will be stored in a freezer set to maintain -60 to -80°C for possible future analysis.
- Page 11, Serum APFO Level Determination, Sample Shipping, Paragraph 2, Sentence 2.** To reflect the Sponsor's decision to report the results of specified analyses separately, delete this sentence and replace with the following.

Results will be reported separately.
- Page 13, Postmortem Procedures, Receptor Level Determination, Paragraph 2, Sentence 1.** To reflect the Sponsor's decision to retain these samples for possible future analysis, delete this sentence and replace with the following.

Liver and pancreas samples for receptor level determination will be stored in a freezer set to maintain -60 to -80°C for possible future analysis.

4. **Page 14, Postmortem Procedures, Bile Acid Determination, Paragraph 2, Sentence 1.** To reflect the Sponsor's decision to report the results of specified analyses separately, delete this sentence and replace with the following.

Results will be reported separately.

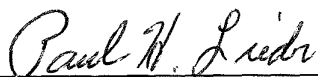
5. **Page 14, Postmortem Procedures, Liver APFO Determination, Sentence 2.** To reflect the Sponsor's decision to report the results of specified analyses separately, delete this sentence and replace with the following.

Results will be reported separately.

6. **Page 15, Report, Results.** To reflect the Sponsor's decision to report the results of specified analyses separately, delete this sentence and replace with the following.

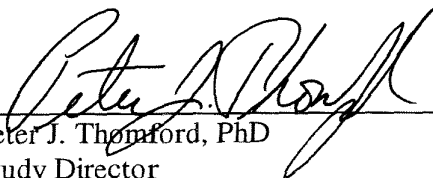
mortality
clinical observations
body weights
food consumption
clinical pathology results
palmitoyl CoA oxidase activities
hormone analyses (provided by Ani Lytics)
macroscopic observations
microscopic observations
cell proliferation evaluations (provided by the Sponsor's designee)

AMENDMENT APPROVAL



Paul Lieder, PhD
Diplomate, ABT
Study Monitor
3M

14 June 2000
Date



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

09 June 2000
Date

MATERIAL SAFETY DATA SHEET
3M
3M Center
St. Paul, Minnesota
55144-1000
1-800-364-3577 or (612) 737-6501 (24 hours)

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DIVISION: 3M CHEMICALS

TRADE NAME:

FC-143 FLUORAD Brand Fluorochemical Surfactant

ID NUMBER/U.P.C.:

98-0211-0008-0 00-51135-09138-8 98-0211-0891-9 00-51135-09365-8
98-0211-5489-7 00-51135-02941-1 98-0211-6581-0 00-51135-10405-7
98-0211-7394-7 00-51135-10762-1 ZF-0002-0378-4 - - -

ISSUED: January 29, 1998

SUPERSEDES: November 05, 1997

DOCUMENT: 10-3808-2

INGREDIENT	C.A.S. NO.	PERCENT
AMMONIUM PERFLUOROOCTANOATE.....	3825-26-1	93 - 97
AMMONIUM PERFLUOROHEPTANOATE.....	6130-43-4	1 - 3
AMMONIUM PERFLUOROPENTANOATE.....	68259-11-0	1 - 3
AMMONIUM PERFLUOROHXANOATE.....	21615-47-4	0.1 - 1

2. PHYSICAL DATA

BOILING POINT:..... N/A
VAPOR PRESSURE:..... N/A
VAPOR DENSITY:..... N/A
EVAPORATION RATE:..... N/A
SOLUBILITY IN WATER:..... apprec.
SPECIFIC GRAVITY:..... 0.4 - 0.5 Water=1
(Bulk)
PERCENT VOLATILE:..... N/A
pH:..... ca. 5
(0.5% Aqueous)
VISCOSITY:..... N/D
MELTING POINT:..... N/A

PEARANCE AND ODOR:

light colored powder; slight odor.

MSDS: FC-143 FLUORAD Brand Fluorochemical Surfactant
January 29, 1998

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3. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT:..... Non-flammable
FLAMMABLE LIMITS - LEL:..... N/A
FLAMMABLE LIMITS - UEL:..... N/A
AUTOIGNITION TEMPERATURE:..... N/A

EXTINGUISHING MEDIA:

Water, Carbon dioxide, Dry chemical, Foam

SPECIAL FIRE FIGHTING PROCEDURES:

Wear full protective clothing, including helmet, self-contained, positive pressure or pressure demand breathing apparatus, bunker coat and pants, bands around arms, waist and legs, face mask, and protective covering for exposed areas of the head.

UNUSUAL FIRE AND EXPLOSION HAZARDS:

See Hazardous Decomposition section for products of combustion.

4. REACTIVITY DATA

STABILITY: Stable

INCOMPATIBILITY - MATERIALS/CONDITIONS TO AVOID:

Not Applicable

HAZARDOUS POLYMERIZATION: Hazardous polymerization will not occur.

HAZARDOUS DECOMPOSITION PRODUCTS:

Carbon Monoxide and Carbon Dioxide, Oxides of Nitrogen, Hydrogen Fluoride, Ammonia.

5. ENVIRONMENTAL INFORMATION

SPILL RESPONSE:

Observe precautions from other sections. Collect spilled material. Use wet sweeping compound or water to avoid dusting. Clean up residue. Place in a closed container.

RECOMMENDED DISPOSAL:

Incinerate in an industrial or commercial facility in the presence of a combustible material. Combustion products will include HF. Disposal alternative: Dispose of waste product in a facility permitted to accept chemical waste.

FC-143 FLUORAD Brand Fluorochemical Surfactant
January 29, 1998

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5. ENVIRONMENTAL INFORMATION (continued)

ENVIRONMENTAL DATA:
SUPPORTING DATA:

BIODEGRADATION:

Theoretical Oxygen Demand (ThOD): 0.320 g/g
Chemical Oxygen Demand (COD): 0.0007 g/g
20-Day Biochemical Oxygen Demand (BOD20): Nil

AQUATIC TOXICITY:

Fathead minnow (*Pimephales promelas*) 96-hr LC50: 766 mg/L
Water flea (*Daphnia magna*) 48-hr EC50: 632 mg/L
Bluegill sunfish (*Lepomis macrochirus*) 96-hr EC50: 569 mg/L
Green Algae (*Selenastrum capricornutum*) 14-Day EC50:
>1000 mg/L
Microtox (*Photobacterium phosphoreum*) 30-min EC50: 730 mg/L

BIOCONCENTRATION:

BCF = 1.8

REGULATORY INFORMATION:

Volatile Organic Compounds: N/A.
VOC Less H2O & Exempt Solvents: N/A.

Since regulations vary, consult applicable regulations or authorities before disposal. U.S. EPA Hazardous Waste Number = None (Not U.S. EPA Hazardous).

The components of this product are in compliance with the chemical registration requirements of TSCA, EINECS, CDSL, AICS, MITI and KTCCL.

OTHER ENVIRONMENTAL INFORMATION:

This substance did not degrade significantly in a ready biodegradation test.

This compound is completely fluorinated (perfluorinated), or it contains perfluorinated portions. Perfluoroalkyl groups resist degradation in most natural environments.

This substance has minimal toxicity to aquatic organisms (100 mg/L < Lowest LC50, EC50, or IC50 < or = 1000 mg/L).

No data are available on the toxicity effects of this substance on wastewater treatment system organisms.

This substance has been found to not bioconcentrate or accumulate significantly in one or more living organisms.

EPCRA HAZARD CLASS:

FIRE HAZARD: No PRESSURE: No REACTIVITY: No ACUTE: Yes CHRONIC: Yes

MSDS: FC-143 FLUORAD Brand Fluorochemical Surfactant
January 29, 1998

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6. SUGGESTED FIRST AID

EYE CONTACT:

Immediately flush eyes with large amounts of water for at least 15 minutes. Get immediate medical attention.

SKIN CONTACT:

Flush skin with large amounts of water. If irritation persists, get medical attention.

INHALATION:

If signs/symptoms occur, remove person to fresh air. If signs/symptoms continue, call a physician.

IF SWALLOWED:

Do not induce vomiting. Drink two glasses of water. Call a physician.

7. PRECAUTIONARY INFORMATION

PERSONAL PROTECTION:

Avoid eye contact. Wear vented goggles.

SKIN PROTECTION:

Avoid skin contact. Wear appropriate gloves when handling this material. A pair of gloves made from the following material(s) are recommended: butyl rubber. Use one or more of the following personal protection items as necessary to prevent skin contact: head covering, coveralls. Protective garments (other than gloves) should be made of either of the following materials: polyethylene/polyvinylidene chloride (Saranex).

RECOMMENDED VENTILATION:

Use with appropriate local exhaust ventilation. Provide sufficient ventilation to maintain emissions below recommended exposure limits. If exhaust ventilation is not adequate, use appropriate respiratory protection.

RESPIRATORY PROTECTION:

Avoid breathing of airborne material. Select one of the following NIOSH approved respirators based on airborne concentration of contaminants and in accordance with OSHA regulations: full-face high-efficiency filter respirator, full-face supplied air respirator.

PREVENTION OF ACCIDENTAL INGESTION:

Do not eat, drink or smoke when using this product. Wash exposed areas thoroughly with soap and water. Wash hands after handling and before eating.

FC-143 FLUORAD Brand Fluorochemical Surfactant
January 29, 1998

PAGE 5

7. PRECAUTIONARY INFORMATION (continued)

RECOMMENDED STORAGE:

Do not store containers on their sides. Store at room temperature.
Keep container dry. Keep container closed when not in use.

****PREVENT MOISTURE CONTAMINATION TO KEEP POWDER FREE FLOWING.****

FIRE AND EXPLOSION AVOIDANCE:

Keep container tightly closed. No smoking while handling this material.

HMIS HAZARD RATINGS: HEALTH: 3 FLAMMABILITY: 0 REACTIVITY: 0
PERSONAL PROTECTION: X (See precautions, section 7.)

EXPOSURE LIMITS

INGREDIENT	VALUE	UNIT	TYPE	AUTH	SKIN*
AMMONIUM PERFLUOROOCTANOATE.....	0.01	MG/M3	TWA	ACGIH	Y
AMMONIUM PERFLUOROHEPTANOATE.....	0.1	MG/M3	TWA	3M	Y
AMMONIUM PERFLUOROPENTANOATE.....	0.1	MG/M3	TWA	3M	Y
AMMONIUM PERFLUOROHXANOATE.....	0.1	MG/M3	TWA	3M	Y

* SKIN NOTATION: Listed substances indicated with 'Y' under SKIN refer to the potential contribution to the overall exposure by the cutaneous route including mucous membrane and eye, either by airborne or, more particularly, by direct contact with the substance. Vehicles can alter skin absorption.

SOURCE OF EXPOSURE LIMIT DATA:

- ACGIH: American Conference of Governmental Industrial Hygienists
- 3M: 3M Recommended Exposure Guidelines

8. HEALTH HAZARD DATA

EYE CONTACT:

Moderate Eye Irritation: signs/symptoms can include redness, swelling, pain, tearing, and hazy vision.

Airborne product may cause eye injury consisting of corneal opacity.

SKIN CONTACT:

Product is not expected to be irritating to the skin.

Mild Skin Irritation (after prolonged or repeated contact): signs/symptoms can include redness, swelling, and itching.

Product may be absorbed through the skin and persist in the body for an extended time.

MSDS: FC-143 FLUORAD Brand Fluorochemical Surfactant
January 29, 1998

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8. HEALTH HAZARD DATA (continued)

INHALATION:

Illness requiring medical attention may result from a single exposure by inhalation to moderate quantities of this material.

May be absorbed by inhalation and persist in the body for an extended time.

Single overexposure, above recommended guidelines, may cause:

Irritation (upper respiratory): signs/symptoms can include soreness of the nose and throat, coughing and sneezing.

Prolonged or repeated overexposure, above recommended guidelines, may cause:

Liver Effects: signs/symptoms can include yellow skin(jaundice) and tenderness of upper abdomen.

Repeated inhalation of airborne product above the exposure guideline can result in elevated organofluoride levels in the blood.

IF SWALLOWED:

Ingestion is not a likely route of exposure to this product.

Illness may result from a single swallowing of a moderate quantity of this material.

CANCER:

A mixture of ammonium perfluorooctanoate, ammonium perfluoroheptanoate, ammonium perfluoropentanoate and ammonium perfluorohexanoate, that was 93 to 97% AMMONIUM PERFLUOROOCTANOATE (3825-26-1) was fed to albino rats for 2 years, no compound induced carcinogenicity was found in the study. There were statistically significant compound related benign testicular tumors. In a second two-year study there were statistically significant compound related benign tumors in the liver, pancreas, and testis when compared to ad libitum and pair-fed controls. Based on the current knowledge, these findings have no human health implications. (3825-26-1) (1983 and 1993 studies conducted jointly by 3M and DuPont).

MUTAGENICITY:

Not mutagenic in invitro mutagenicity assays. Did not cause cell transformation in a mammalian cell transformation assay.

REPRODUCTIVE/DEVELOPMENTAL TOXINS:

Not teratogenic in rabbits by oral administration. Not teratogenic to rats by gavage or inhalation exposures.

FC-143 FLUORAD Brand Fluorochemical Surfactant
January 29, 1998

PAGE 7

8. HEALTH HAZARD DATA (continued)

OTHER HEALTH HAZARD INFORMATION:

This product is not known to contain any substances regulated under California Proposition 65.

A Product Toxicity Summary Sheet is available.

SECTION CHANGE DATES

HEADING	SECTION CHANGED SINCE November 05, 1997	ISSUE
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Abbreviations: N/D - Not Determined N/A - Not Applicable CA - Approximately

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Centre Analytical Laboratories, Inc.

3048 Research Drive

State College, PA 16801

Phone: (814) 231-8032

Fax: (814) 231-1253 or (814) 231-1580

INTERIM CERTIFICATE OF ANALYSIS

Centre Analytical Laboratories COA Reference #: 023-033

3M Product: Ammonium Perfluorooctanoate

Test Control Reference #: TCR-99131-37, Lot #: 332

Purity: 95.2%

Test Name	Specifications	Result
Purity ¹		95.2%
Appearance	White, crystalline solid	Conforms
Identification NMR		Positive
Metals (ICP/MS)		
1. Calcium		1. 0.001 wt./wt.%
2. Magnesium		2. <0.001 wt./wt.%
3. Sodium		3. 0.005 wt./wt.%
4. Potassium		4. <0.001 wt./wt.%
5. Nickel		5. <0.001 wt./wt.%
6. Iron		6. <0.001 wt./wt.%
7. Manganese		7. <0.001 wt./wt.%
Total % Impurity (NMR)		0.34 wt./wt.%
Total % Impurity (LC/MS)		4.49 wt./wt.%
Total % Impurity (GC/MS)		None Quantified
Residual Solvents (TGA)		None Detected
Purity by DSC		99.7%
Inorganic Anions (IC)		
1. Chloride		1. <0.015 wt./wt.%
2. Fluoride		2. <0.005 wt./wt.%
3. Bromide		3. <0.040 wt./wt.%
4. Nitrate		4. <0.009 wt./wt.%
5. Nitrite		5. <0.006 wt./wt.%
6. Phosphate		6. <0.006 wt./wt.%
7. Sulfate		7. <0.040 wt./wt.%
Organic Acids ² (IC)		
1. TFA		1. <0.1 wt./wt.%
2. PFPA		2. <0.1 wt./wt.%
3. HFBA		3. <0.1 wt./wt.%
4. NFPA		4. <0.25 wt./wt.%
Elemental Analysis ³ :		
1. Carbon	Theoretical Value = 22.3%	1. 18.9 wt./wt.%
2. Hydrogen	Theoretical Value = 0.935%	2. 1.31 wt./wt.%
3. Nitrogen	Theoretical Value = 3.25%	3. 3.75 wt./wt.%
4. Sulfur	Theoretical Value = 0%	4. 4.34 wt./wt.%
5. Fluorine	Theoretical Value = 66.1%	5. 63.2 wt./wt.%
Ammonium Analysis ³ Ion Selective Electrode	Theoretical Value = 4.18%	3.49 wt./wt. %



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INTERIM CERTIFICATE OF ANALYSIS

Centre Analytical Laboratories COA Reference #: 023-033

3M Product: Ammonium Perfluorooctanoate

Test Control Reference #: TCR-99131-37, Lot #: 332

Date of Last Analysis: 12/15/00

Expiration Date: 12/15/01

Storage Conditions: < -10 °C

Re-assessment Date: 12/15/01

¹Purity = 100% - (Total Metal impurities, 0.006% + Total NMR impurities, 0.34% + Total LC/MS impurities, 4.49%)

Total impurity from all tests = 4.84%

Purity = 100% - 4.84% = 95.2%

² TFA Trifluoroacetic acid
HFBA Heptafluorobutyric acid
NFPA Nonafluoropentanoic acid
PFPA Pentafluoropropanoic acid

³Theoretical value calculations based on the empirical formula, C₈F₁₅O₂⁽⁻⁾NH₄⁽⁺⁾
(MW=431.1)

LC/MS Purity Profile:

Peak #	Retention Time (min)	Mass(s)	Identity	Area	% Area
1	12.140	269	C ₆	167596	0.73
2	13.504	331, 319	C ₇ homologue/F ₁₃	860991	3.76
3	14.099	369	PFOA	21861700	-
Total	-	-	-	22890287	4.49

This work was conducted under EPA Good Laboratory Practice Standards (40 CFR 160).

Prepared By: David S. Bell
David S. Bell
Scientist, Centre Analytical Laboratories

01/09/01
Date

Reviewed By: John M. Flaherty
John Flaherty
Laboratory Manager, Centre Analytical Laboratories

1/9/01
Date

APPENDIX 2

Individual Animal Fate Data
Individual Clinical Observations

APPENDIX 2
Individual Animal Fate Data

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

PAGE: 1

ANIMAL NUMBER	DOSE GROUP	SEX	DEATH CODE	TYPE OF DEATH	DESCRIPTION OF DEATH	DATE OF DEATH	DAY OF STUDY	WEEK OF STUDY
I05353	1	MALE	T	SCHEDULED	TERMINAL SACRIFICE	07/16/98	30	5
I05417	1	MALE	T	SCHEDULED	TERMINAL SACRIFICE	07/16/98	30	5
I05231	2	MALE	T	SCHEDULED	TERMINAL SACRIFICE	07/16/98	30	5
I05352	2	MALE	T	SCHEDULED	TERMINAL SACRIFICE	07/16/98	30	5
I05419	2	MALE	T	SCHEDULED	TERMINAL SACRIFICE	07/16/98	30	5
I05235	3	MALE	T	SCHEDULED	TERMINAL SACRIFICE	07/16/98	30	5
I05351	3	MALE	T	SCHEDULED	TERMINAL SACRIFICE	07/16/98	30	5
I05416	3	MALE	T	SCHEDULED	TERMINAL SACRIFICE	07/16/98	30	5

Appendix 2

Individual Clinical Observations

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

PAGE: 1

ANIMAL NUMBER	DEATH CODE	WK OF DEATH	CATEGORY KEYWORD QUALIFIER	GROUP: M1 DAYS 1-30	DOSE: 0 MG/KG/DAY	'C' - OBS	COMMENTS	LISTED AT 30 MIN	END OF 60 MIN	OBSERVATIONS 90 MIN	FOR SEX/GROUP DISPATCH
I05353	T	5	SKIN & PELAGE BROKEN SKIN DIGIT(S)-HIND-RIGHT			18	-	P	P	P	-
			NORMAL NO REMARKABLE OBSERVATIONS			1	P	-	-	-	-
						8	P	-	-	-	-
						15	P	-	-	-	-
						22	P	-	-	-	-
						29	P	-	-	-	-
						30	P	-	-	-	P
I05417	T	5	NORMAL NO REMARKABLE OBSERVATIONS			1	P	-	-	-	-
						8	P	-	-	-	-
						15	P	-	-	-	-
						22	P	-	-	-	-
						29	P	-	-	-	-
						30	P	-	-	-	P
			QUALITATIVE FOOD CONSUMPTION LOW			21	P	-	-	-	-

Appendix 2

Individual Clinical Observations

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

PAGE: 2

ANIMAL NUMBER	DEATH CODE	WK OF DEATH	CATEGORY KEYWORD QUALIFIER	GROUP: M2 DAYS 1-30	DOSE: 2 MG/KG/DAY DAY	'C' - OBS	LISTED AT 30 MIN	END OF 60 MIN	OBSERVATIONS 90 MIN	FOR SEX/GROUP DISPATCH
I05231	T	5	NORMAL NO REMARKABLE OBSERVATIONS		1 8 15 22 29 30	P P P P P P	- - - - - -	- - - - - -	- - - - - -	- - - - - P
I05352	T	5	NORMAL NO REMARKABLE OBSERVATIONS		1 8 15 22 29 30	P P P P P P	- - - - - -	- - - - - -	- - - - - -	- - - - - P
I05419	T	5	APPEARANCE UNDER EFFECTS OF ANESTHESIA		23	-	-	-	P	-
			SKIN & PELAGE BROKEN SKIN THIGH-LEFT		24 25	P -	P P	P P	P P	- -
			SCAB(S) LIMB-HIND-LEFT		26 27 28 29 30	P P P P P	P P P - -	P P P - -	P P P - -	- - - - P
			NORMAL NO REMARKABLE OBSERVATIONS		1	P	-	-	-	-

Appendix 2

Individual Clinical Observations

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

PAGE: 3

ANIMAL	DEATH	WK OF	CATEGORY	GROUP: M2	DOSE: 2 MG/KG/DAY	'C' -	COMMENTS	LISTED AT	END OF	OBSERVATIONS	FOR SEX/GROUP
NUMBER	CODE	DEATH	KEYWORD				OBS	30 MIN	60 MIN	90 MIN	DISPATCH
			QUALIFIER	DAYS 1-30		DAY					
=====											
(CONTINUED FROM PREVIOUS PAGE)											
I05419	T	5	NORMAL								
			NO REMARKABLE OBSERVATIONS			8	P	-	-	-	-
						15	P	-	-	-	-
						22	P	-	-	-	-
			QUALITATIVE FOOD CONSUMPTION								
			LOW			24	P	-	-	-	-

Appendix 2

Individual Clinical Observations

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

PAGE: 4

ANIMAL NUMBER	DEATH CODE	WK OF DEATH	CATEGORY KEYWORD QUALIFIER	GROUP: M3 DOSE: 20 MG/KG/DAY DAYS 1-30	'C' - OBS DAY	COMMENTS	LISTED AT 30 MIN	END OF 60 MIN	OBSERVATIONS 90 MIN	FOR SEX/GROUP DISPATCH
I05235	T	5	EXCRETION NO FECES		17	P	-	-	-	-
			NORMAL NO REMARKABLE OBSERVATIONS		1	P	-	-	-	-
					8	P	-	-	-	-
					15	P	-	-	-	-
					22	P	-	-	-	-
					29	P	-	-	-	-
					30	P	-	-	-	P
			QUALITATIVE FOOD CONSUMPTION LOW		5	P	-	-	-	-
					7	P	-	-	-	-
					11	P	-	-	-	-
					14	P	-	-	-	-
					16	P	-	-	-	-
					17	P	-	-	-	-
					24	P	-	-	-	-
			NONE		12	P	-	-	-	-
I05351	T	5	NORMAL NO REMARKABLE OBSERVATIONS		1	P	-	-	-	-
					8	P	-	-	-	-
					15	P	-	-	-	-
					22	P	-	-	-	-
					29	P	-	-	-	-
					30	P	-	-	-	P

Appendix 2

Individual Clinical Observations

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

PAGE: 5

ANIMAL NUMBER	DEATH CODE	WK OF DEATH	CATEGORY KEYWORD QUALIFIER	GROUP: M3 DAYS 1-30	DOSE: 20 MG/KG/DAY DAY	'C' - OBS	COMMENTS	LISTED AT 30 MIN	END OF 60 MIN	OBSERVATIONS 90 MIN	FOR SEX/GROUP DISPATCH
I05416	T	5	NORMAL NO REMARKABLE OBSERVATIONS			1 8 15 22 29 30	P P P P P P	- - - - - -	- - - - - -	- - - - - -	- - - - - P

APPENDIX 3

Individual Body Weight Data (kg)

Appendix 3

Individual Body Weight Data (kg)

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

PAGE: 1

ANIMAL NUMBER	WEEK -2	WEEK ^a -1	WEEK ^b -1	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
GROUP: MALE 1 - 0 MG/KG/DAY								
I05353	2.5	2.5	2.5	2.6	2.7	2.7	2.6	2.7
I05417	3.5	3.5	3.6	3.6	3.5	3.6	3.5	3.6
GROUP: MALE 2 - 2 MG/KG/DAY								
I05231	2.7	2.9	2.8	2.9	2.9	3.0	2.9	3.0
I05352	2.1	2.1	2.1	2.1	2.2	2.2	2.2	2.2
I05419	3.5	3.6	3.6	3.6	3.6	3.6	3.6	3.7
GROUP: MALE 3 - 20 MG/KG/DAY								
I05235	2.7	2.8	2.7	2.8	2.7	2.7	2.8	2.8
I05351	2.2	2.3	2.3	2.2	2.3	2.3	2.3	2.4
I05416	3.2	3.3	3.3	3.3	3.4	3.4	3.3	3.5

a Day -7.

b Day -1.

APPENDIX 4

Individual Clinical Hematology Data
Individual Clinical Chemistry Data

Appendix 4

Individual Clinical Hematology Data

Males Day -8

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

ANIMAL NUMBER	RBC X10 ⁶ /μL	HGB G/DL	HCT %	MCV FL	MCH PG	MCHC %	PLT X10 ³ /μL	RETIC %	RETIC X10 ³ /μL
Group: 1	Dose Level: 0	Dosage Unit: mg/kg/day							
I05353	4.44	11.9	35.8	80.5	26.8	33.3	376	.7	31
I05417	7.49	13.2	45.2	60.3	17.7	29.3	483	.1	7
MEAN	5.96	12.6	40.5	70.4	22.2	31.3	430	.4	19
S.D.	2.157	.92	6.65	14.28	6.43	2.83	75.7	.42	17.0
N	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2	Dosage Unit: mg/kg/day							
I05231	7.08	13.1	43.5	61.5	18.5	30.0	455	.4	28
I05352	5.56	14.2	43.5	78.3	25.6	32.7	376	1.2	67
I05419	7.92	13.4	45.6	57.5	16.9	29.3	435	.1	8
MEAN	6.85	13.6	44.2	65.8	20.3	30.7	422	.6	34
S.D.	1.196	.57	1.21	11.04	4.63	1.80	41.1	.57	30.0
N	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20	Dosage Unit: mg/kg/day							
I05235	7.18	12.4	42.7	59.4	17.2	29.0	530	.2	14
I05351	5.37	14.3	42.8	79.6	26.5	33.4	649	.6	32
I05416	6.61	13.1	41.5	62.7	19.9	31.7	386	.2	13
MEAN	6.39	13.3	42.3	67.2	21.2	31.4	522	.3	20
S.D.	.925	.96	.72	10.84	4.78	2.22	131.7	.23	10.7
N	3	3	3	3	3	3	3	3	3

Appendix 4

Individual Clinical Hematology Data

Males Day -8

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

ANIMAL NUMBER	WBC X10 ³ /μL	N-SEG X10 ³ /μL	LYMPH X10 ³ /μL	MONO X10 ³ /μL	EOSIN X10 ³ /μL	BASO X10 ³ /μL	N-SEG%	LYMPH%	MONO%	EOSIN%	BASO%
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day								
I05353	9.2	1.0	7.8	.4	.1	.0	11	84	4	1	0
I05417	11.5	2.6	6.9	.8	1.1	.0	23	60	7	10	0
MEAN	10.4	1.8	7.4	.6	.6	.0	17	72	6	6	0
S.D.	1.63	1.13	.64	.28	.71	.00	8.5	17.0	2.1	6.4	.0
N	2	2	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day								
I05231	9.3	4.0	4.3	1.0	.1	.0	43	46	10	1	0
I05352	8.5	1.0	7.0	.4	.1	.0	12	82	5	1	0
I05419	10.5	2.8	6.3	1.2	.2	.0	27	60	11	2	0
MEAN	9.4	2.6	5.9	.9	.1	.0	27	63	9	1	0
S.D.	1.01	1.51	1.40	.42	.06	.00	15.5	18.1	3.2	.6	.0
N	3	3	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day								
I05235	9.0	3.2	5.0	.4	.4	.0	35	56	5	4	0
I05351	9.0	.8	7.6	.5	.1	.1	9	84	5	1	1
I05416	10.9	4.4	5.5	.7	.3	.0	40	50	7	2	0
MEAN	9.6	2.8	6.0	.5	.3	.0	28	63	6	2	0
S.D.	1.10	1.83	1.38	.15	.15	.06	16.6	18.1	1.2	1.5	.6
N	3	3	3	3	3	3	3	3	3	3	3

Appendix 4					
Individual Clinical Hematology Data					
Males Day -8					
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO) IN CYNOMOLGUS MONKEYS					
ANIMAL NUMBER	ANISO	POLY	POIK	HYP0	TOXNEUT
-----	-----	-----	-----	-----	-----
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day		
I05353	-	-	-	-	-
I05417	-	-	-	-	-
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day		
I05231	-	-	-	-	-
I05352	-	-	-	-	-
I05419	-	-	-	-	-
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day		
I05235	-	-	-	-	-
I05351	-	-	-	-	-
I05416	-	-	-	-	-

Appendix 4
Individual Clinical Hematology Data

Males Day -5

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

ANIMAL NUMBER	RBC X10 ⁶ /μL	HGB G/DL	HCT %	MCV FL	MCH PG	MCHC %	PLT X10 ³ /μL	RETIC %	RETIC X10 ³ /μL

Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day						
I05353	4.26	11.3	34.2	80.5	26.5	33.0	360	1.2	51
I05417	6.68	11.8	40.5	60.7	17.6	29.0	447	.0	0
MEAN	5.47	11.5	37.3	70.6	22.0	31.0	404	.6	26
S.D.	1.711	.35	4.45	14.00	6.29	2.83	61.5	.85	36.1
N	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day						
I05231	6.27	11.5	38.9	62.0	18.3	29.5	418	.8	50
I05352	4.72	12.4	37.1	78.6	26.3	33.4	393	1.6	76
I05419	6.75	11.6	39.3	58.3	17.3	29.6	374	.4	27
MEAN	5.91	11.8	38.4	66.3	20.6	30.8	395	.9	51
S.D.	1.061	.49	1.17	10.81	4.93	2.22	22.1	.61	24.5
N	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day						
I05235	6.61	11.4	39.2	59.3	17.3	29.2	516	.1	7
I05351	4.57	12.2	36.3	79.4	26.6	33.6	593	.3	14
I05416	6.07	12.0	38.3	63.1	19.7	31.3	392	.1	6
MEAN	5.75	11.9	37.9	67.3	21.2	31.4	500	.2	9
S.D.	1.057	.42	1.48	10.68	4.83	2.20	101.4	.12	4.4
N	3	3	3	3	3	3	3	3	3

Appendix 4

Individual Clinical Hematology Data

Males Day -5

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

ANIMAL NUMBER	WBC X10 ³ /μL	N-SEG X10 ³ /μL	LYMPH X10 ³ /μL	MONO X10 ³ /μL	EOSIN X10 ³ /μL	BASO X10 ³ /μL	N-SEG%	LYMPH%	MONO%	EOSIN%	BASO%
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day								
I05353	10.0	1.2	8.2	.6	.1	.1	12	82	6	1	1
I05417	12.2	2.8	7.5	.8	1.0	.0	23	62	7	8	0
MEAN	11.1	2.0	7.8	.7	.6	.0	18	72	6	4	0
S.D.	1.56	1.13	.49	.14	.64	.07	7.8	14.1	.7	4.9	.7
N	2	2	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day								
I05231	9.0	4.6	3.7	.6	.2	.0	51	40	7	2	0
I05352	8.8	2.4	5.8	.6	.1	.0	27	65	6	1	0
I05419	14.4	6.0	7.2	.8	.3	.0	42	50	6	2	0
MEAN	10.7	4.3	5.6	.7	.2	.0	40	52	6	2	0
S.D.	3.18	1.81	1.76	.12	.10	.00	12.1	12.6	.6	.6	.0
N	3	3	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day								
I05235	11.1	4.8	5.1	.7	.3	.0	44	46	7	3	0
I05351	7.1	2.0	4.9	.2	.0	.0	28	69	3	0	0
I05416	13.2	5.6	6.3	.8	.4	.0	43	48	6	3	0
MEAN	10.5	4.1	5.4	.6	.2	.0	38	54	5	2	0
S.D.	3.10	1.89	.76	.32	.21	.00	9.0	12.7	2.1	1.7	.0
N	3	3	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Hematology Data
Males Day -5
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)
IN CYNOMOLGUS MONKEYS

ANIMAL NUMBER	ANISO	POLY	POIK	HYP0	TOXNEUT
-----	-----	-----	-----	-----	-----
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day		
I05353	-	-	-	-	-
I05417	-	-	-	-	-
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day		
I05231	-	-	-	-	-
I05352	-	-	-	-	-
I05419	-	-	-	-	-
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day		
I05235	-	-	-	-	-
I05351	-	-	-	-	-
I05416	-	-	-	-	-

Appendix 4
Individual Clinical Hematology Data

Males Day 30

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

ANIMAL NUMBER	RBC X10 ⁶ /μL	HGB G/DL	HCT %	MCV FL	MCH PG	MCHC %	PLT X10 ³ /μL	RETIC %	RETIC X10 ³ /μL
Group: 1	Dose Level: 0	Dosage Unit: mg/kg/day							
I05353	4.93	12.5	39.2	79.6	25.5	32.0	414	.4	20
I05417	6.99	12.3	42.4	60.6	17.7	29.1	508	.1	7
MEAN	5.96	12.4	40.8	70.1	21.6	30.5	461	.2	14
S.D.	1.457	.14	2.26	13.44	5.52	2.05	66.5	.21	9.2
N	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2	Dosage Unit: mg/kg/day							
I05231	7.03	13.2	43.6	62.0	18.7	30.3	412	.1	7
I05352	5.81	14.9	46.0	79.1	25.6	32.4	404	.4	23
I05419	7.38	12.6	43.2	58.5	17.1	29.2	406	.0	0
MEAN	6.74	13.6	44.3	66.5	20.5	30.6	407	.2	10
S.D.	.824	1.19	1.51	11.02	4.52	1.63	4.2	.21	11.8
N	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20	Dosage Unit: mg/kg/day							
I05235	6.95	12.0	42.0	60.5	17.3	28.6	489	.3	21
I05351	5.35	14.2	43.1	80.6	26.6	33.0	605	.4	21
I05416	6.41	12.8	40.5	63.2	20.0	31.6	373	.0	0
MEAN	6.24	13.0	41.9	68.1	21.3	31.1	489	.2	14
S.D.	.814	1.11	1.31	10.91	4.78	2.25	116.0	.21	12.1
N	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Hematology Data

Males Day 30

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

ANIMAL NUMBER	WBC X10 ³ /μL	N-SEG X10 ³ /μL	LYMPH X10 ³ /μL	MONO X10 ³ /μL	EOSIN X10 ³ /μL	BASO X10 ³ /μL	N-SEG%	LYMPH%	MONO%	EOSIN%	BASO%
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day								
I05353	9.9	1.1	7.8	.7	.2	.1	11	79	7	2	1
I05417	9.8	2.0	6.7	.4	.7	.0	21	68	4	7	0
MEAN	9.8	1.6	7.2	.6	.4	.0	16	74	6	4	0
S.D.	.07	.64	.78	.21	.35	.07	7.1	7.8	2.1	3.5	.7
N	2	2	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day								
I05231	6.2	1.9	3.8	.5	.0	.0	30	61	8	1	0
I05352	7.3	1.6	5.4	.2	.0	.0	22	74	3	1	0
I05419	10.6	3.1	7.0	.3	.1	.0	30	66	3	1	0
MEAN	8.0	2.2	5.4	.3	.0	.0	27	67	5	1	0
S.D.	2.29	.79	1.60	.15	.06	.00	4.6	6.6	2.9	.0	.0
N	3	3	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day								
I05235	9.2	4.1	4.3	.6	.2	.0	45	47	7	2	0
I05351	8.2	1.9	5.8	.5	.0	.0	23	70	6	1	1
I05416	7.5	3.3	3.2	.7	.2	.0	45	43	9	2	1
MEAN	8.3	3.1	4.4	.6	.1	.0	38	53	7	2	1
S.D.	.85	1.11	1.31	.10	.12	.00	12.7	14.6	1.5	.6	.6
N	3	3	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Hematology Data

Males Day 30

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

ANIMAL NUMBER	ANISO	POLY	POIK	HYP0	TOXNEUT
-----	-----	-----	-----	-----	-----
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day		
I05353	-	-	-	-	-
I05417	-	-	-	-	-
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day		
I05231	-	-	-	-	-
I05352	-	-	-	-	-
I05419	-	-	-	-	-
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day		
I05235	-	-	-	-	-
I05351	-	-	-	-	-
I05416 a	-	-	-	-	-

a Plasmodium was observed.

Appendix 4

Individual Clinical Chemistry Data

Males Day -8

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

ANIMAL NUMBER	GLU MG/DL	UN MG/DL	CREAT MG/DL	T PRO G/DL	ALB G/DL	GLOB G/DL	T BILI MG/DL	SBA UMOL/L	CHOL MG/DL	TRIG MG/DL
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day							
I05353	59	28	.9	7.0	4.4	2.6	.3	5	152	29
I05417	88	17	1.2	10.4	6.0	4.4	.5	13	139	40
MEAN	74	22	1.0	8.7	5.2	3.5	.4	9	146	34
S.D.	20.5	7.8	.21	2.40	1.13	1.27	.14	5.7	9.2	7.8
N	2	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day							
I05231	60	16	.9	8.3	5.1	3.2	.2	11	157	40
I05352	85	18	1.0	7.1	4.8	2.3	.4	6	170	28
I05419	84	20	1.4	9.7	5.4	4.3	.2	9	196	39
MEAN	76	18	1.1	8.4	5.1	3.3	.3	9	174	36
S.D.	14.2	2.0	.26	1.30	.30	1.00	.12	2.5	19.9	6.7
N	3	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day							
I05235	63	24	1.4	8.3	4.6	3.7	.2	12	126	39
I05351	70	20	.9	7.4	5.0	2.4	.1	11	149	27
I05416	60	24	1.2	8.4	4.7	3.7	.2	12	147	28
MEAN	64	23	1.2	8.0	4.8	3.3	.2	12	141	31
S.D.	5.1	2.3	.25	.55	.21	.75	.06	.6	12.7	6.7
N	3	3	3	3	3	3	3	3	3	3

Appendix 4

Individual Clinical Chemistry Data

Males Day -8

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

ANIMAL NUMBER	AST/SGOT IU/L	ALT/SGPT IU/L	ALK PHOS IU/L	GGT IU/L	SDH IU/L	CK IU/L	AMYLASE IU/L	LIPASE IU/L	P AMYL U/L
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day						
I05353	40	38	1144	130	2	520	442	42	228
I05417	42	52	550	114	2	175	541	44	275
MEAN	41	45	847	122	2	348	492	43	252
S.D.	1.4	9.9	420.0	11.3	2.0	244.0	70.0	1.4	33.2
N	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day						
I05231	43	33	1122	209	10	307	415	51	223
I05352	65	77	910	122	2	550	427	21	229
I05419	37	50	1007	145	3	250	723	67	298
MEAN	48	53	1013	159	5	369	522	46	250
S.D.	14.7	22.2	106.1	45.1	4.4	159.3	174.5	23.4	41.7
N	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day						
I05235	45	89	985	116	4	210	461	44	207
I05351	58	38	986	115	4	225	524	51	280
I05416	54	50	872	177	6	149	502	34	230
MEAN	52	59	948	136	5	195	496	43	239
S.D.	6.7	26.7	65.5	35.5	1.2	40.3	32.0	8.5	37.3
N	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data
Males Day -8
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)
IN CYNOMOLGUS MONKEYS

ANIMAL NUMBER	CA MG/DL	I PHOS MG/DL	NA MMOL/L	K MMOL/L	CL MMOL/L

Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day		
I05353	10.2	7.9	150	6.1	111
I05417	12.6	6.5	166	7.1	113
MEAN	11.4	7.2	158	6.6	112
S.D.	1.70	.99	11.3	.71	1.4
N	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day		
I05231	11.3	8.7	159	5.6	109
I05352	10.6	7.4	153	6.0	107
I05419	11.0	6.5	162	5.3	109
MEAN	11.0	7.5	158	5.6	108
S.D.	.35	1.11	4.6	.35	1.2
N	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day		
I05235	11.3	7.2	156	6.1	108
I05351	11.1	7.2	154	6.5	109
I05416	10.3	6.7	153	5.7	108
MEAN	10.9	7.0	154	6.1	108
S.D.	.53	.29	1.5	.40	.6
N	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data

Males Day -5

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

ANIMAL NUMBER	GLU MG/DL	UN MG/DL	CREAT MG/DL	T PRO G/DL	ALB G/DL	GLOB G/DL	T BILI MG/DL	SBA UMOL/L	CHOL MG/DL	TRIG MG/DL
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day							
I05353	55	24	1.1	7.2	4.4	2.8	.6	6	156	28
I05417	113	11	1.3	9.6	5.5	4.1	.7	3	119	29
MEAN	84	18	1.2	8.4	5.0	3.4	.6	4	138	28
S.D.	41.0	9.2	.14	1.70	.78	.92	.07	2.1	26.2	.7
N	2	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day							
I05231	66	14	1.0	8.1	4.9	3.2	.1	1	141	31
I05352	60	15	.9	7.1	4.8	2.3	.4	5	160	32
I05419	73	16	1.3	8.8	4.7	4.1	.4	9	164	38
MEAN	66	15	1.1	8.0	4.8	3.2	.3	5	155	34
S.D.	6.5	1.0	.21	.85	.10	.90	.17	4.0	12.3	3.8
N	3	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day							
I05235	78	14	1.1	8.2	4.4	3.8	.1	1	128	30
I05351	51	24	.9	7.4	4.9	2.5	.7	2	155	51
I05416	73	21	1.2	8.5	4.7	3.8	.3	0	140	35
MEAN	67	20	1.1	8.0	4.7	3.4	.4	1	141	39
S.D.	14.4	5.1	.15	.57	.25	.75	.31	1.0	13.5	11.0
N	3	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data

Males Day -5

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

ANIMAL NUMBER	AST/SGOT IU/L	ALT/SGPT IU/L	ALK PHOS IU/L	GGT IU/L	SDH IU/L	CK IU/L	AMYLASE IU/L	LIPASE IU/L	P AMYL U/L
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day						
I05353	42	34	1066	117	3	833	441	42	233
I05417	35	52	509	108	3	156	549	38	270
MEAN	38	43	788	112	3	494	495	40	252
S.D.	4.9	12.7	393.9	6.4	.0	478.7	76.4	2.8	26.2
N	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day						
I05231	31	35	1026	182	4	141	395	64	220
I05352	54	65	872	108	3	542	446	46	244
I05419	31	46	893	120	2	155	720	58	293
MEAN	39	49	930	137	3	279	520	56	252
S.D.	13.3	15.2	83.5	39.7	1.0	227.6	174.8	9.2	37.2
N	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day						
I05235	37	66	945	106	2	181	451	57	213
I05351	54	37	906	92	3	194	467	71	249
I05416	54	51	837	164	4	138	481	44	224
MEAN	48	51	896	121	3	171	466	57	229
S.D.	9.8	14.5	54.7	38.2	1.0	29.3	15.0	13.5	18.4
N	3	3	3	3	3	3	3	3	3

Appendix 4

Individual Clinical Chemistry Data

Males Day -5

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

ANIMAL NUMBER	CA MG/DL	I PHOS MG/DL	NA MMOL/L	K MMOL/L	CL MMOL/L

Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day		
I05353	10.0	7.7	149	4.8	107
I05417	11.8	5.9	162	6.1	110
MEAN	10.9	6.8	156	5.4	108
S.D.	1.27	1.27	9.2	.92	2.1
N	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day		
I05231	11.1	6.9	159	5.6	113
I05352	10.3	7.1	153	5.6	109
I05419	9.9	5.2	153	4.3	108
MEAN	10.4	6.4	155	5.2	110
S.D.	.61	1.04	3.5	.75	2.6
N	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day		
I05235	10.8	6.1	154	5.3	108
I05351	10.5	6.4	153	5.3	108
I05416	9.8	6.1	149	4.3	105
MEAN	10.4	6.2	152	5.0	107
S.D.	.51	.17	2.6	.58	1.7
N	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data

Males Day 2

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

ANIMAL NUMBER	GLU MG/DL	UN MG/DL	CREAT MG/DL	T PRO G/DL	ALB G/DL	GLOB G/DL	T BILI MG/DL	SBA UMOL/L	CHOL MG/DL	TRIG MG/DL
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day							
I05353	73	26	.8	7.5	4.5	3.0	.3	13	157	23
I05417	79	16	1.1	10.6	5.8	4.8	.6	6	146	34
MEAN	76	21	1.0	9.0	5.2	3.9	.4	10	152	28
S.D.	4.2	7.1	.21	2.19	.92	1.27	.21	4.9	7.8	7.8
N	2	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day							
I05231	64	17	.8	8.4	4.9	3.5	.4	6	143	49
I05352	70	26	.9	7.7	5.0	2.7	.3	9	183	45
I05419	62	18	1.2	9.0	4.8	4.2	.3	12	180	61
MEAN	65	20	1.0	8.4	4.9	3.5	.3	9	169	52
S.D.	4.2	4.9	.21	.65	.10	.75	.06	3.0	22.3	8.3
N	3	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day							
I05235	68	24	1.1	8.4	4.6	3.8	.1	11	121	35
I05351	70	22	.9	7.7	5.0	2.7	.2	12	136	57
I05416	66	23	.9	8.7	4.7	4.0	.1	19	140	43
MEAN	68	23	1.0	8.3	4.8	3.5	.1	14	132	45
S.D.	2.0	1.0	.12	.51	.21	.70	.06	4.4	10.0	11.1
N	3	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data

Males Day 2

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

ANIMAL NUMBER	AST/SGOT IU/L	ALT/SGPT IU/L	ALK PHOS IU/L	GGT IU/L	SDH IU/L	CK IU/L	AMYLASE IU/L	LIPASE IU/L	P AMYL U/L
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day						
I05353	45	35	1123	129	1	181	435	28	228
I05417	49	71	620	121	1	269	519	30	270
MEAN	47	53	872	125	1	225	477	29	249
S.D.	2.8	25.5	355.7	5.7	.0	62.2	59.4	1.4	29.7
N	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day						
I05231	33	31	1151	200	1	113	366	45	204
I05352	91	82	927	119	4	2149	438	36	239
I05419	36	42	1009	126	2	121	644	51	289
MEAN	53	52	1029	148	2	794	483	44	244
S.D.	32.7	26.8	113.3	44.9	1.5	1173.2	144.3	7.5	42.7
N	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day						
I05235	49	80	1062	110	2	175	433	41	205
I05351	58	36	827	98	0	203	503	39	269
I05416	57	51	875	171	1	116	502	19	227
MEAN	55	56	921	126	1	165	479	33	234
S.D.	4.9	22.4	124.2	39.1	1.0	44.4	40.1	12.2	32.5
N	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data
Males Day 2
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)
IN CYNOMOLGUS MONKEYS

ANIMAL NUMBER	CA MG/DL	I PHOS MG/DL	NA MMOL/L	K MMOL/L	CL MMOL/L

Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day		
I05353	10.4	9.0	153	5.5	106
I05417	12.7	8.6	170	6.9	113
MEAN	11.6	8.8	162	6.2	110
S.D.	1.63	.28	12.0	.99	4.9
N	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day		
I05231	11.0	8.1	158	5.5	113
I05352	10.7	9.3	155	5.6	106
I05419	9.9	6.7	153	4.8	107
MEAN	10.5	8.0	155	5.3	109
S.D.	.57	1.30	2.5	.44	3.8
N	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day		
I05235	11.0	7.5	159	5.7	110
I05351	11.4	8.3	157	6.1	107
I05416	9.8	6.5	151	4.8	109
MEAN	10.7	7.4	156	5.5	109
S.D.	.83	.90	4.2	.67	1.5
N	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data

Males Day 30

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

ANIMAL NUMBER	GLU MG/DL	UN MG/DL	CREAT MG/DL	T PRO G/DL	ALB G/DL	GLOB G/DL	T BILI MG/DL	SBA UMOL/L	CHOL MG/DL	TRIG MG/DL
Group: 1	Dose Level: 0	Dosage Unit: mg/kg/day								
I05353	77	23	.9	7.3	4.6	2.7	.7	6	172	33
I05417	90	15	1.0	9.8	5.6	4.2	.3	1	127	32
MEAN	84	19	1.0	8.6	5.1	3.4	.5	4	150	32
S.D.	9.2	5.7	.07	1.77	.71	1.06	.28	3.5	31.8	.7
N	2	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2	Dosage Unit: mg/kg/day								
I05231	75	15	1.1	8.4	5.1	3.3	.2	2	137	45
I05352	80	16	1.2	7.7	5.1	2.6	.1	4	149	39
I05419	74	19	1.1	8.9	4.8	4.1	.1	5	155	44
MEAN	76	17	1.1	8.3	5.0	3.3	.1	4	147	43
S.D.	3.2	2.1	.06	.60	.17	.75	.06	1.5	9.2	3.2
N	3	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20	Dosage Unit: mg/kg/day								
I05235	64	16	1.5	8.0	4.4	3.6	.1	10	107	50
I05351	63	22	1.2	7.3	4.8	2.5	.0	1	138	63
I05416	67	22	.8	8.2	4.4	3.8	.3	6	170	42
MEAN	65	20	1.2	7.8	4.5	3.3	.1	6	138	52
S.D.	2.1	3.5	.35	.47	.23	.70	.15	4.5	31.5	10.6
N	3	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data

Males Day 30

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

ANIMAL NUMBER	AST/SGOT IU/L	ALT/SGPT IU/L	ALK PHOS IU/L	GGT IU/L	SDH IU/L	CK IU/L	AMYLASE IU/L	LIPASE IU/L	P AMYL U/L	PCOAO IU/G
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day							
I05353	52	42	1154	118	1	827	451	53	238	2
I05417	51	76	680	102	3	195	491	30	247	1
MEAN	52	59	917	110	2	511	471	42	242	2
S.D.	.7	24.0	335.2	11.3	1.4	446.9	28.3	16.3	6.4	.7
N	2	2	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day							
I05231	35	53	1155	177	1	145	344	36	186	0
I05352	72	113	1009	115	2	570	501	32	273	0
I05419	42	58	1170	115	3	256	654	47	272	3
MEAN	50	75	1111	136	2	324	500	38	244	1
S.D.	19.7	33.3	88.9	35.8	1.0	220.4	155.0	7.8	49.9	1.7
N	3	3	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day							
I05235	43	140	799	80	3	206	382	47	175	5
I05351	66	60	626	83	2	216	521	45	277	3
I05416	55	48	686	139	0	198	420	26	202	9
MEAN	55	83	704	101	2	207	441	39	218	6
S.D.	11.5	50.0	87.8	33.2	1.5	9.0	71.8	11.6	52.8	3.1
N	3	3	3	3	3	3	3	3	3	3

Appendix 4
Individual Clinical Chemistry Data
Males Day 30
4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTANOATE (APFO)
IN CYNOMOLGUS MONKEYS

ANIMAL NUMBER	CA MG/DL	I PHOS MG/DL	NA MMOL/L	K MMOL/L	CL MMOL/L
-----	-----	-----	-----	-----	-----
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day		
I05353	10.2	8.4	149	5.0	104
I05417	11.2	5.9	157	5.7	108
MEAN	10.7	7.2	153	5.4	106
S.D.	.71	1.77	5.7	.49	2.8
N	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day		
I05231	11.2	7.1	157	5.2	112
I05352	11.0	7.5	156	6.1	107
I05419	10.2	5.5	153	4.3	107
MEAN	10.8	6.7	155	5.2	109
S.D.	.53	1.06	2.1	.90	2.9
N	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day		
I05235	10.3	5.8	155	5.1	111
I05351	10.9	5.6	152	5.9	107
I05416	9.5	5.2	145	4.6	108
MEAN	10.2	5.5	151	5.2	109
S.D.	.70	.31	5.1	.66	2.1
N	3	3	3	3	3

APPENDIX 5

Individual Animal Pathology Data

APPENDIX 5

Individual Animal Pathology Data

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

PAGE: 1

ANIMAL NUMBER: I05353 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 07/16/98 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2500.0 GRAMS
DATE AND TIME OF NECROPSY: 07/16/98 11:10 PROSECTOR: KEVIN BILLINGS RECORDER: JILL PAUS
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: DR. JAMES L. CARTER WEIGHER: NOT AVAILABLE

NECROPSY

O B S E R V A T I O N S

HISTOPATHOLOGY

KIDNEY (KD) :
-LIGHT FOCUS(I)/AREA(S); RIGHT ON CORTICAL SURFACE, NEAR
HILUS: SINGLE TAN AREA, 0.2 CM IN DIAMETER; COLLECTED ON
ROUTINE SECTION
GENERAL COMMENT (GC) :
-EYES - DAVIDSONS

KIDNEY (KD) :
>NOT REQUIRED TO BE EXAMINED FOR ANIMAL

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:

LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), BONE, FEMUR (FE), MARROW, FEMUR (FM), MARROW, STERNUM (SE),
BONE, STERNUM (SB), EYE (EY), BRAIN (BR), LUNG (LU), HEART (HT), TRACHEA (TR), ESOPHAGUS (ES), THYROID (TY),
PARATHYROID (PT), THYMUS (TH), LN, MESENTERIC (MS), AORTA (AO), PITUITARY (PI), SALIV GL, MANDIB (SG),
MUSCLE, SKELETAL (SM), SPINAL CORD (SC), NERVE, SCIATIC (SN), STOMACH, GL (ST), DUODENUM (DU), GALLBLADDER (GB),
JEJUNUM (JE), ILEUM (IL), CECUM (CE), COLON (CO), RECTUM (RE), SKIN (SK), MAMMARY, MALE (MM), URINARY BLADDER (UB),
PROSTATE (PR), SEMINAL VESICLES (SV), EPIDIDYMIDES (EP), ADRENAL, CORTEX (AC), ADRENAL, MEDULLA (MA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:

LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), ADRENAL (AD)

APPENDIX 5

Individual Animal Pathology Data

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

PAGE: 2

ANIMAL NUMBER: I05417 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 07/16/98 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3325.0 GRAMS
DATE AND TIME OF NECROPSY: 07/16/98 11:15 PROSECTOR: JERALD W. JOHNSON RECORDER: JAMES T. CALLEN
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: DR. JAMES L. CARTER WEIGHER: NOT AVAILABLE

NECROPSY

O B S E R V A T I O N S

HISTOPATHOLOGY

STOMACH, GL (ST) :
-RED FOCUS(1)/AREA(S); MUCOSA: MULTIPLE RED AREAS, UP TO 0.8
X 0.5 CM; COLLECTED ON ROUTINE SECTION
GENERAL COMMENT (GC) :
-EYES - DAVIDSONS

STOMACH, GL (ST) :
>NOT REQUIRED TO BE EXAMINED FOR ANIMAL

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:

LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), BONE, FEMUR (FE), MARROW, FEMUR (FM), MARROW, STERNUM (SE),
BONE, STERNUM (SB), EYE (EY), BRAIN (BR), KIDNEY (KD), LUNG (LU), HEART (HT), TRACHEA (TR), ESOPHAGUS (ES),
THYROID (TY), PARATHYROID (PT), THYMUS (TH), LN, MESENTERIC (MS), AORTA (AO), PITUITARY (PI), SALIV GL, MANDIB (SG),
MUSCLE, SKELETAL (SM), SPINAL CORD (SC), NERVE, SCIATIC (SN), DUODENUM (DU), GALLBLADDER (GB), JEJUNUM (JE),
ILEUM (IL), CECUM (CE), COLON (CO), RECTUM (RE), SKIN (SK), MAMMARY, MALE (MM), URINARY BLADDER (UB),
PROSTATE (PR), SEMINAL VESICLES (SV), EPIDIDYMIDES (EP), ADRENAL, CORTEX (AC), ADRENAL, MEDULLA (MA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:

LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), ADRENAL (AD)

APPENDIX 5

Individual Animal Pathology Data

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

PAGE: 3

ANIMAL NUMBER: I05231 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 07/16/98 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2795.0 GRAMS
DATE AND TIME OF NECROPSY: 07/16/98 12:43 PROSECTOR: JERALD W. JOHNSON RECORDER: JAMES T. CALLEN
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: DR. JAMES L. CARTER WEIGHER: NOT AVAILABLE

NECROPSY

O B S E R V A T I O N S

HISTOPATHOLOGY

GENERAL COMMENT (GC) :
-EYES - DAVIDSONS
-NO MACROSCOPIC LESIONS

ADRENAL (AD) :
-MINERALIZATION, -MINIMAL, MULTI-FOCAL

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), BONE, FEMUR (FE), MARROW, FEMUR (FM), MARROW, STERNUM (SE),
BONE, STERNUM (SB), EYE (EY), BRAIN (BR), KIDNEY (KD), LUNG (LU), HEART (HT), TRACHEA (TR), ESOPHAGUS (ES),
THYROID (TY), PARATHYROID (PT), THYMUS (TH), LN, MESENTERIC (MS), AORTA (AO), PITUITARY (PI), SALIV GL, MANDIB (SG),
MUSCLE, SKELETAL (SM), SPINAL CORD (SC), NERVE, SCIATIC (SN), STOMACH, GL (ST), DUODENUM (DU), GALLBLADDER (GB),
JEJUNUM (JE), ILEUM (IL), CECUM (CE), COLON (CO), RECTUM (RE), SKIN (SK), MAMMARY, MALE (MM), URINARY BLADDER (UB),
PROSTATE (PR), SEMINAL VESICLES (SV), EPIDIDYMIDES (EP), ADRENAL, CORTEX (AC), ADRENAL, MEDULLA (MA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE)

APPENDIX 5

Individual Animal Pathology Data

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

PAGE: 4

ANIMAL NUMBER: I05352 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 07/16/98 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 1980.0 GRAMS
DATE AND TIME OF NECROPSY: 07/16/98 12:40 PROSECTOR: KEVIN BILLINGS RECORDER: JILL PAUS
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: DR. JAMES L. CARTER WEIGHER: NOT AVAILABLE

NECROPSY

O B S E R V A T I O N S

HISTOPATHOLOGY

GENERAL COMMENT (GC) :
-EYES - DAVIDSONS
-NO MACROSCOPIC LESIONS

TESTIS (TE) :
-IMMATURE, -MODERATE, DIFFUSE

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), BONE, FEMUR (FE), MARROW, FEMUR (FM), MARROW, STERNUM (SE),
BONE, STERNUM (SB), EYE (EY), BRAIN (BR), KIDNEY (KD), LUNG (LU), HEART (HT), TRACHEA (TR), ESOPHAGUS (ES),
THYROID (TY), PARATHYROID (PT), THYMUS (TH), LN, MESENTERIC (MS), AORTA (AO), PITUITARY (PI), SALIV GL, MANDIB (SG),
MUSCLE, SKELETAL (SM), SPINAL CORD (SC), NERVE, SCIATIC (SN), STOMACH, GL (ST), DUODENUM (DU), GALLBLADDER (GB),
JEJUNUM (JE), ILEUM (IL), CECUM (CE), COLON (CO), RECTUM (RE), SKIN (SK), MAMMARY, MALE (MM), URINARY BLADDER (UB),
PROSTATE (PR), SEMINAL VESICLES (SV), EPIDIDYMIDES (EP), ADRENAL, CORTEX (AC), ADRENAL, MEDULLA (MA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), ADRENAL (AD)

APPENDIX 5

Individual Animal Pathology Data

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

PAGE: 5

ANIMAL NUMBER: I05419 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 07/16/98 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3435.0 GRAMS
DATE AND TIME OF NECROPSY: 07/16/98 11:57 PROSECTOR: JERALD W. JOHNSON RECORDER: JAMES T. CALLEN
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: DR. JAMES L. CARTER WEIGHER: NOT AVAILABLE

NECROPSY

O B S E R V A T I O N S

HISTOPATHOLOGY

GENERAL COMMENT (GC) :

-EYES - DAVIDSONS

-NO MACROSCOPIC LESIONS

GENERAL INFORMATION (XX) :

>NOTE:>LEFT HIND LIMB, NEAR STIFLE JOINT: ANIMAL HAS SIX
SUTURES; POSSIBLY CONSISTENT WITH CLINICAL
OBSERVATIONS OF SCABS (HIND LEFT)

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:

LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), BONE, FEMUR (FE), MARROW, FEMUR (FM), MARROW, STERNUM (SE),
BONE, STERNUM (SB), EYE (EY), BRAIN (BR), KIDNEY (KD), LUNG (LU), HEART (HT), TRACHEA (TR), ESOPHAGUS (ES),
THYROID (TY), PARATHYROID (PT), THYMUS (TH), LN, MESENTERIC (MS), AORTA (AO), PITUITARY (PI), SALIV GL, MANDIB (SG),
MUSCLE, SKELETAL (SM), SPINAL CORD (SC), NERVE, SCIATIC (SN), STOMACH, GL (ST), DUODENUM (DU), GALLBLADDER (GB),
JEJUNUM (JE), ILEUM (IL), CECUM (CE), COLON (CO), RECTUM (RE), SKIN (SK), MAMMARY, MALE (MM), URINARY BLADDER (UB),
PROSTATE (PR), SEMINAL VESICLES (SV), EPIDIDYIMIDES (EP), ADRENAL, CORTEX (AC), ADRENAL, MEDULLA (MA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:

LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), ADRENAL (AD)

APPENDIX 5

Individual Animal Pathology Data

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

PAGE: 6

ANIMAL NUMBER: I05235 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 07/16/98 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2635.0 GRAMS
DATE AND TIME OF NECROPSY: 07/16/98 13:09 PROSECTOR: JERALD W. JOHNSON RECORDER: JAMES T. CALLEN
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: DR. JAMES L. CARTER WEIGHER: NOT AVAILABLE

NECROPSY

O B S E R V A T I O N S

HISTOPATHOLOGY

STOMACH, GL (ST) :
-RED FOCUS(I)/AREA(S); MUCOSA: MULTIPLE RED AREAS, UP TO 0.6
X 0.4 CM; COLLECTED ON ROUTINE SECTION
GENERAL COMMENT (GC) :
-EYES - DAVIDSONS

STOMACH, GL (ST) :
>NOT REQUIRED TO BE EXAMINED FOR ANIMAL

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), BONE, FEMUR (FE), MARROW, FEMUR (FM), MARROW, STERNUM (SE),
BONE, STERNUM (SB), EYE (EY), BRAIN (BR), KIDNEY (KD), LUNG (LU), HEART (HT), TRACHEA (TR), ESOPHAGUS (ES),
THYROID (TY), PARATHYROID (PT), THYMUS (TH), LN, MESENTERIC (MS), AORTA (AO), PITUITARY (PI), SALIV GL, MANDIB (SG),
MUSCLE, SKELETAL (SM), SPINAL CORD (SC), NERVE, SCIATIC (SN), DUODENUM (DU), GALLBLADDER (GB), JEJUNUM (JE),
ILEUM (IL), CECUM (CE), COLON (CO), RECTUM (RE), SKIN (SK), MAMMARY, MALE (MM), URINARY BLADDER (UB),
PROSTATE (PR), SEMINAL VESICLES (SV), EPIDIDYMIDES (EP), ADRENAL, CORTEX (AC), ADRENAL, MEDULLA (MA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), ADRENAL (AD)

APPENDIX 5

Individual Animal Pathology Data

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

PAGE: 7

ANIMAL NUMBER: I05351 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 07/16/98 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 2185.0 GRAMS
DATE AND TIME OF NECROPSY: 07/16/98 11:56 PROSECTOR: KEVIN BILLINGS RECORDER: JILL PAUS
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: DR. JAMES L. CARTER WEIGHER: NOT AVAILABLE

NECROPSY

O B S E R V A T I O N S

HISTOPATHOLOGY

GENERAL COMMENT (GC) :
-EYES - DAVIDSONS
-NO MACROSCOPIC LESIONS

TESTIS (TE) :
-IMMATURE, -MODERATE, DIFFUSE

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), BONE, FEMUR (FE), MARROW, FEMUR (FM), MARROW, STERNUM (SE),
BONE, STERNUM (SB), EYE (EY), BRAIN (BR), KIDNEY (KD), LUNG (LU), HEART (HT), TRACHEA (TR), ESOPHAGUS (ES),
THYROID (TY), PARATHYROID (PT), THYMUS (TH), LN, MESENTERIC (MS), AORTA (AO), PITUITARY (PI), SALIV GL, MANDIB (SG),
MUSCLE, SKELETAL (SM), SPINAL CORD (SC), NERVE, SCIATIC (SN), STOMACH, GL (ST), DUODENUM (DU), GALLBLADDER (GB),
JEJUNUM (JE), ILEUM (IL), CECUM (CE), COLON (CO), RECTUM (RE), SKIN (SK), MAMMARY, MALE (MM), URINARY BLADDER (UB),
PROSTATE (PR), SEMINAL VESICLES (SV), EPIDIDYMIDES (EP), ADRENAL, CORTEX (AC), ADRENAL, MEDULLA (MA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), ADRENAL (AD)

APPENDIX 5

Individual Animal Pathology Data

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

PAGE: 8

ANIMAL NUMBER: I05416 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 07/16/98 STUDY DAY OF DEATH: 30 STUDY WEEK OF DEATH: 5 TERMINAL BODY WEIGHT: 3120.0 GRAMS
DATE AND TIME OF NECROPSY: 07/16/98 13:05 PROSECTOR: KEVIN BILLINGS RECORDER: JILL PAUS
POST-FIX WEIGHER: NOT AVAILABLE PATHOLOGIST: DR. JAMES L. CARTER WEIGHER: NOT AVAILABLE

NECROPSY

O B S E R V A T I O N S

HISTOPATHOLOGY

LUNG (LU) :
-ADHESION(S); ALL LOBES TO EACH OTHER, PLEURA AND CAUDAL
LOBES TO DIAPHRAGM: MULTIPLE TAN GRAY FIBROUS ADHESIONS;
COLLECTED INTACT
STOMACH, GL (ST) :
-RED FOCUS(I)/AREA(S); MUCOSA: SINGLE AREA, 0.5 X 0.2 CM
GENERAL COMMENT (GC) :
-EYES - DAVIDSONS

LUNG (LU) :
>NOT REQUIRED TO BE EXAMINED FOR ANIMAL

STOMACH, GL (ST) :
>NOT REQUIRED TO BE EXAMINED FOR ANIMAL

THE FOLLOWING ORGANS WERE UNREMARKABLE AT NECROPSY:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), BONE, FEMUR (FE), MARROW, FEMUR (FM), MARROW, STERNUM (SE),
BONE, STERNUM (SB), EYE (EY), BRAIN (BR), KIDNEY (KD), HEART (HT), TRACHEA (TR), ESOPHAGUS (ES), THYROID (TY),
PARATHYROID (PT), THYMUS (TH), LN, MESENTERIC (MS), AORTA (AO), PITUITARY (PI), SALIV GL, MANDIB (SG),
MUSCLE, SKELETAL (SM), SPINAL CORD (SC), NERVE, SCIATIC (SN), DUODENUM (DU), GALLBLADDER (GB), JEJUNUM (JE),
ILEUM (IL), CECUM (CE), COLON (CO), RECTUM (RE), SKIN (SK), MAMMARY, MALE (MM), URINARY BLADDER (UB),
PROSTATE (PR), SEMINAL VESICLES (SV), EPIDIDYMIDES (EP), ADRENAL, CORTEX (AC), ADRENAL, MEDULLA (MA)

THE FOLLOWING TISSUES WERE UNREMARKABLE AT MICROSCOPIC EXAMINATION:
LIVER (LI), SPLEEN (SP), PANCREAS (PA), TESTIS (TE), ADRENAL (AD)

APPENDIX 6

Quality Assurance Statement Summary and Individual Hormone Analyses Data

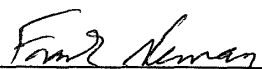
Note: The data included in this appendix were supplied by Ani Lytics Inc. and have been reviewed by the Quality Assurance Unit of Ani Lytics Inc.



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The reports listed below was reviewed for compliance with the FDA Good Laboratory Practices and with the EPA Good Laboratory Practices. The final report and all associated raw data were reviewed for accuracy and consistency and the findings were reported to management.

The methods used were the methods described and the report accurately reflects the data. Therefore, these studies were done in compliance with the FDA and EPA Good Laboratory Practices.


Franklin B. Newman
QA Auditor

SPONSOR: COVANCE LABS

STUDY: 6329-230

REPORT TYPE:	AUDIT DATE:	REPORT TO MGMT:	AUDIT #:
E1, E2, E3, T3, T4			
T3H, FT3, FT4	9-27-98	9-28-98	98-713


MANAGEMENT 9/28/98

Appendix 6

Summary and Individual Hormone Analyses Data

Day -8

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

ANIMAL NUMBER	ESTRONE pg/mL	ESTRADIOL pg/mL	ESTRIOL ng/mL	THYROID STIMULATING μIU/mL	TOTAL TRIIODOTHYRONINE ng/dL	TOTAL THYROXIN μg/dL	FREE TRIIODOTHYRONINE pg/mL	FREE THYROXIN ng/dL
Group: 1	Dose Level: 0			Dosage Unit: mg/kg/day				
I05353	163.53	12.39	0.00	1.40	205.95	5.11	5.08	1.08
I05417	236.08	39.04	0.00	1.61	159.89	4.28	4.77	1.14
MEAN	199.81	25.72	0.00	1.51	182.92	4.70	4.93	1.11
S.D.	51.301	18.844	0.000	0.148	32.569	0.587	0.219	0.042
N	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2			Dosage Unit: mg/kg/day				
I05231	195.55	23.04	0.00	1.17	187.06	3.41	7.61	1.21
I05352	187.55	30.44	0.00	1.18	174.59	5.71	2.96	1.17
I05419	191.95	30.63	0.00	1.64	166.70	3.12	5.58	0.97
MEAN	191.68	28.04	0.00	1.33	176.12	4.08	5.38	1.12
S.D.	4.007	4.328	0.000	0.269	10.265	1.419	2.331	0.129
N	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20			Dosage Unit: mg/kg/day				
I05235	183.99	9.10	0.00	1.50	145.43	3.73	5.92	1.41
I05351	186.13	14.61	0.00	0.74	176.53	5.99	3.75	2.06
I05416	213.49	12.69	0.00	1.10	172.10	3.69	3.44	0.67
MEAN	194.54	12.13	0.00	1.11	164.69	4.47	4.37	1.38
S.D.	16.449	2.797	0.000	0.380	16.823	1.317	1.351	0.695
N	3	3	3	3	3	3	3	3

Appendix 6

Summary and Individual Hormone Analyses Data

Day 30

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

ANIMAL NUMBER	ESTRONE pg/mL	ESTRADIOL pg/mL	ESTRIOL ng/mL	THYROID STIMULATING μIU/mL	TOTAL TRIIODOTHYRONINE ng/dL	TOTAL THYROXIN μg/dL	FREE TRIIODOTHYRONINE pg/mL	FREE THYROXIN ng/dL
Group: 1	Dose Level: 0		Dosage Unit: mg/kg/day					
I05353	182.68	13.13	0.00	1.68	188.20	5.50	4.93	1.66
I05417	48.21	34.20	0.00	1.55	137.22	4.31	4.72	1.43
MEAN	115.45	23.67	0.00	1.62	162.71	4.91	4.83	1.55
S.D.	95.085	14.899	0.000	0.092	36.048	0.841	0.148	0.163
N	2	2	2	2	2	2	2	2
Group: 2	Dose Level: 2		Dosage Unit: mg/kg/day					
I05231	29.31	25.88	0.00	1.28	173.12	3.84	5.91	0.99
I05352	30.04	16.03	0.00	1.17	150.56	3.60	4.98	1.14
I05419	21.10	17.89	0.00	0.98	193.34	5.44	6.82	1.69
MEAN	26.82	19.93	0.00	1.14	172.34	4.29	5.90	1.27
S.D.	4.964	5.233	0.000	0.152	21.401	1.000	0.920	0.369
N	3	3	3	3	3	3	3	3
Group: 3	Dose Level: 20		Dosage Unit: mg/kg/day					
I05235	14.55	10.34	0.00	1.71	138.52	4.71	4.55	1.12
I05351	28.80	11.50	0.00	1.06	143.31	5.00	4.67	1.19
I05416	26.67	11.45	0.00	1.06	129.89	2.62	3.78	0.68
MEAN	23.34	11.10	0.00	1.28	137.24	4.11	4.33	1.00
S.D.	7.687	0.656	0.000	0.375	6.801	1.298	0.483	0.276
N	3	3	3	3	3	3	3	3

APPENDIX 7

Cell Proliferation Report

Note: This appendix of the report contains information supplied by Pathology Associates, A Charles River Company and has been reviewed by the Quality Assurance Unit of Pathology Associates, A Charles River Company.



**FINAL
CELL PROLIFERATION REPORT**

**4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM
PERFLUOROOCTONOATE (APFO) IN CYNOMOLGUS MONKEYS**

COVANCE STUDY NUMBER 6329-230

PREPARED FOR:

**3M
TOXICOLOGY SERVICES
BUILDING 220-2E-02, 3M CENTER
ST. PAUL, MN 55144-1000**

PREPARED BY:

**PATHOLOGY ASSOCIATES – A CHARLES RIVER COMPANY
15 WORMAN’S MILL COURT, SUITE I
FREDERICK, MD 21701**

CELL PROLIFERATION REPORT

4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM PERFLUOROOCTONOATE (APFO) IN CYNOMOLGUS MONKEYS COVANCE STUDY NUMBER 6329-230

PURPOSE

The purpose of this study was to provide data for determining an estimated maximum-tolerated dose and lower dose levels to be used in a chronic toxicity study. In addition, the effect on critical enzyme levels, hormones, and other selected biochemical parameters, such as cell proliferation, were determined.

This report, submitted by Pathology Associates –A Charles River Company (PAI) formally Pathology Associates International to the study Sponsor, APME Ad-Hoc APFO Toxicology Working Group, represents the cell proliferation findings and interpretation for Covance Study Number 6329-230 entitled “4-Week Capsule Toxicity Study with Ammonium Perfluorooctonoate (APFO) in Cynomolgus Monkeys”. All aspects of the tasks associated with PAI’s portion of this study were conducted in compliance with the Environmental Protection Agency Good Laboratory Practice (GLP) Regulations as set forth in title 40 of the US Code of Federal Regulations, Part 792, issued November 29, 1983 (effective December 29, 1983), and any applicable amendments.

MATERIALS AND METHODS

Tissue Collection for Cell Proliferation

Two animals in group 1, and three animals each in groups 2 and 3 were sacrificed at the end of week 4. A section of the left lateral lobe of the liver, left and right testes, and pancreas from each animal was fixed in zinc formalin, processed and embedded to paraffin block by Covance per protocol specifications. Tissue blocks were shipped to PAI for sectioning and staining. From each block, a slide was prepared for H&E evaluation and immunohistochemical detection of proliferating cell nuclear antigen (PCNA), a marker of cell proliferation.

Immunohistochemistry for Cell Proliferation

Sections of paraffin-embedded tissues were cut at $\approx 5 \mu\text{m}$ and placed on positively charged slides (Sueprfrost Plus, fisher Scientific, Pittsburgh, PA) to ensure adhesion during processing for PCNA. Standard immunohistochemical methods were used to stain tissues for PCNA [PAI’s Standard Operating Procedure for Immunohistochemical Staining (SOP #707)]. Briefly, tissue sections were incubated with a monoclonal antibody to PCNA (DAKO, lot #016; PAI No. A1899) and reagents required for the avidin-biotin peroxidase (ABC Elite Kit; Vector, lot #PK-6100; PAI No. K 327) method for the detection of the antigen-antibody complex. PCNA expression in cells in all phases of the cell cycle (G_1 , S, G_2 and M) was localized by the

chromagen 3,3'-diaminobenzidine (DAB; Sigma Chemical Co., lot #18H8201). Tissue sections were counterstained with hematoxylin.

Cell Proliferation Measurements

The percentage of proliferating cells (proliferating index, PI) was determined by scoring at least 3000 hepatocytes in 10 fields of liver, at least 500 Leydig cells of the testis (except for animal #IO5417 in which 250 cells were scored), and at least 2000 acinar cells of the pancreas per animal. Although both testes presented on the slide were perused, only one testis was scored for proliferation; no attempt was made to distinguish left from right testis. A negative control slide was included in the staining run and consisted of study tissue from animal #IO516 that was not incubated with the primary antibody.

For cell proliferation evaluations, slides were first perused at low magnification (100X) to judge quality of staining, processing and sectioning, potential patterns of cellular proliferation, and histomorphologic changes. Cell proliferation was then quantified at higher magnification (200X for liver, and 400X for testes and pancreas) as described above. Histomorphology was further assessed by evaluating the H&E slide prepared from the same tissue block for each animal evaluated for cell proliferation.

Statistical Analysis

Due to the small sample size, statistical analysis was not performed.

RESULTS

Cell Proliferation

Individual animal and group mean cell proliferation data are presented in Section II (Table 1) and graphically in Section III (Figures 1-3).

Histopathology

Sections from the same tissue blocks used for preparation of PCNA-stained slides were stained with hematoxylin and eosin (H&E) for histopathologic evaluation to facilitate the interpretation of the immunostained slides. Individual animal findings are presented in Appendix I.

The results showed that no significant changes were observed in either the liver, pancreas, or testicular tissues from male monkeys, which would alter the interpretation of the PCNA staining in this study.

SUMMARY

Although a glance at the cell proliferation data suggest a "dose-response" in terms of cell proliferation in the liver and testes, the sample size is extremely small. Furthermore, in the liver, only one PCNA-labeled cell was detected in those animals with a proliferating index greater than

zero percent. In the testes, only one control animal was able to be evaluated due to immaturity of the only other animal in that group, and the proliferating indices in the two treatment groups overlapped. Therefore, the data are considered to be inconclusive and do not support a cell proliferative response to the test material.

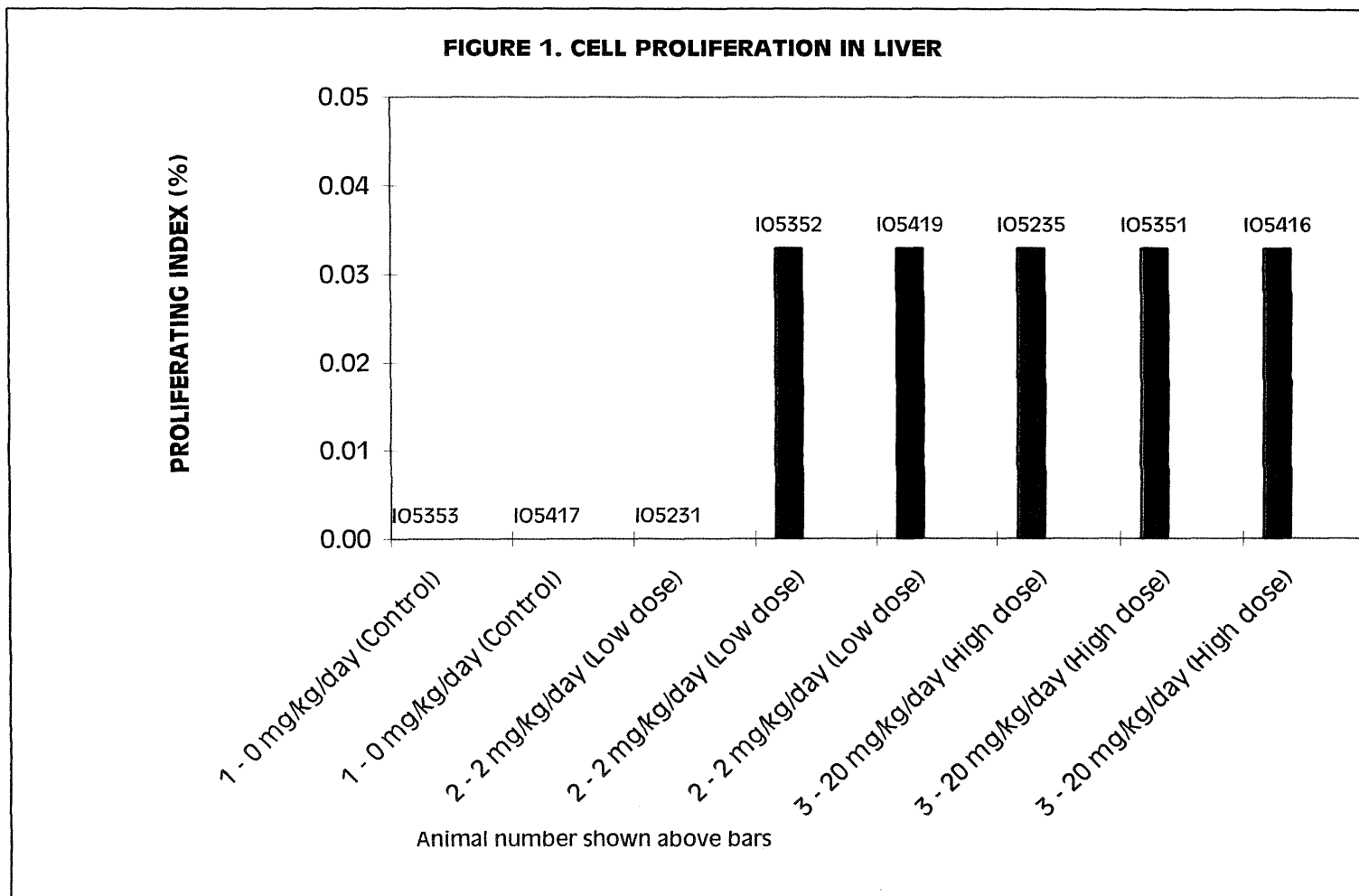
II. TABLE

COVANCE STUDY NO. 6329-230
TABLE 1. CELL PROLIFERATION IN MONKEYS

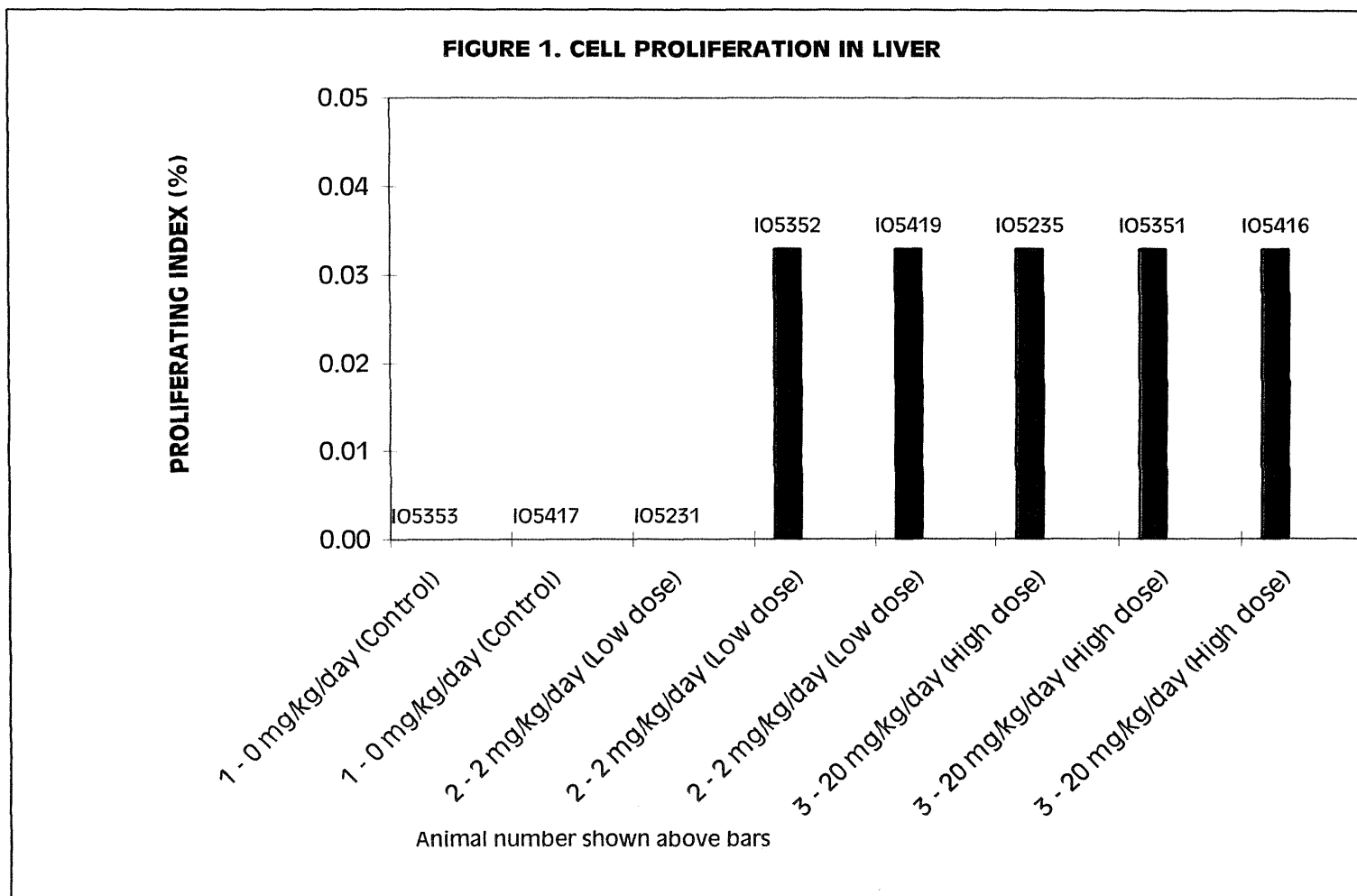
Dose Group	Animal Number	Proliferating Index Liver	Proliferating Index Testes	Proliferating Index Pancreas
1 - 0 mg/kg/day (Control)	IO5353	0.000%	ND	50.5%
1 - 0 mg/kg/day (Control)	IO5417	0.000%	9.6%	51.5%
	Mean	0.000%	9.6%	51.0%
	SEM	0.000%	Unable to calculate	0.5%
2 - 2 mg/kg/day (Low dose)	IO5231	0.000%	19.6%	49.7%
2 - 2 mg/kg/day (Low dose)	IO5352	0.033%	ND	49.6%
2 - 2 mg/kg/day (Low dose)	IO5419	0.033%	11.6%	42.5%
	Mean	0.022%	15.6%	47.3%
	SEM	0.011%	4.0%	2.4%
3 - 20 mg/kg/day (High dose)	IO5235	0.030%	20.4%	43.9%
3 - 20 mg/kg/day (High dose)	IO5351	0.033%	ND	35.6%
3 - 20 mg/kg/day (High dose)	IO5416	0.033%	15.6%	49.7%
	Mean	0.032%	18.0%	43.1%
	SEM	0.001%	2.4%	4.1%
ND, not determined due to immaturity				
SEM, standard error of the mean				

III. FIGURES

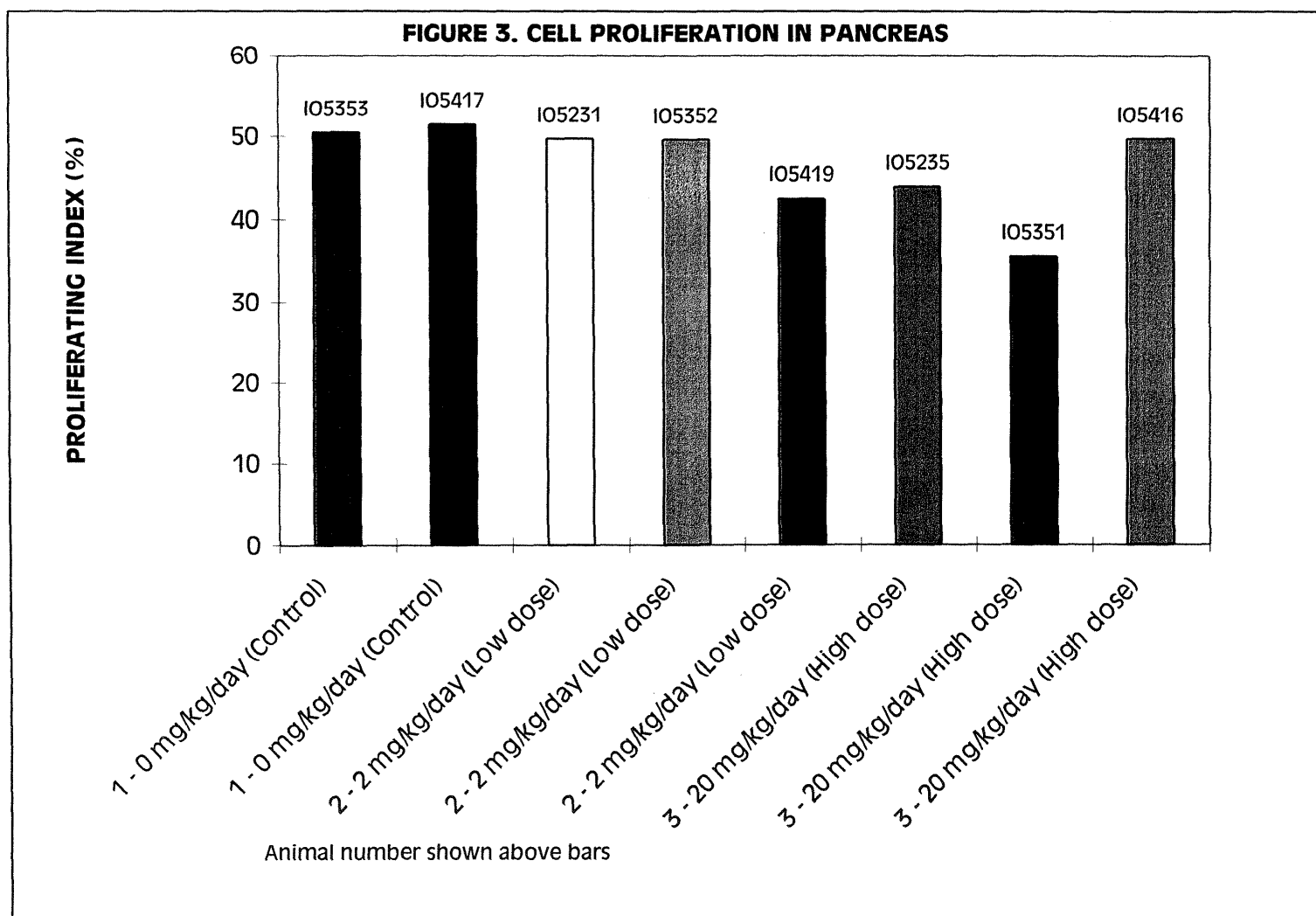
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COVANCE STUDY NO. 6329-230



COVANCE STUDY NO. 6329-230



IV. SIGNATURE PAGE

**4-WEEK CAPSULE TOXICITY STUDY WITH AMMONIUM
PERFLUOROOCTONOATE (APFO) IN CYNOMOLGUS MONKEYS
COVANCE STUDY NUMBER 6329-230**

Submitted by:

PAI Project Manager:


Sandra R. Eldridge, Ph.D.

8-2-01
Date

PAI Project Pathologist:


Carolyn Moyer, D.V.M., Diplomate, A.C.V.P.

7/27/01
Date

V. QUALITY ASSURANCE STATEMENT



Cell Proliferation Report

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

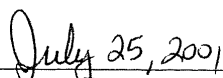
Covance Study Number 6329-230

QUALITY ASSURANCE STATEMENT

This cell proliferation project has been inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Environmental Protection Agency (EPA-TSCA). The cell proliferation report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU.

<u>Date of Inspection</u>	<u>Phase Inspected</u>	<u>Date Findings Reported to PAI Management/Project Manager</u>
08/12/98	Microtomy	08/12/98
10/05/98	Study Data and Supporting Documentation	10/06/98
10/05/98	Draft Cell Proliferation Report	10/06/98
07/25/01	Final Cell Proliferation Report	07/25/01


Sharon E. Abel
Quality Assurance Officer


Date

APPENDIX I

Covance Study Number 6329-230

Individual Animal Histopathologic Findings

4-Week Capsule Toxicity Study with Ammonium Perfluorooctonate (APFO) in Cynomolgus Monkeys

Tissues Examined: Liver, Testes, Pancreas

Animal Number	Sex	Dose Group	Histologic Findings (Liver, Testes, Pancreas)
I05353	M	1-0 mg/kg/day (Control)	No Significant Findings
I05417	M	1-0 mg/kg/day (Control)	Some tissue distortion in testis, changes do not preclude evaluations
I05231	M	2-2 mg/kg/day (Low Dose)	No Significant Findings
I05352	M	2-2 mg/kg/day (Low Dose)	No Significant Findings
I05419	M	2-2 mg/kg/day (Low Dose)	No Significant Findings
I05235	M	3-20 mg/kg/day (High Dose)	No Significant Findings
I05351	M	3-20 mg/kg/day (High Dose)	No Significant Findings
I05416	M	3-20 mg/kg/day (High Dose)	Some tissue distortion in testis, changes do not preclude evaluations