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Environmental Protection Agency
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8EHC-92-10171
INIT 08/31/92

Attn: Section 8(e) Coordinator (CAP Agreement)



Dear Sir:

88920008473

92 AUG 31 PM 1:28

The following study is being submitted in accordance with the provisions of the TSCA section 8(e) Compliance Audit Program and CAP Agreement # 8ECAP-028.

Category of Study: Unit II.B.2.b - Other Studies
Name of Study: Acute Oral Toxicity of Acculith Solvents
P-Exp., P-2025, P-129C
Chemical: Mixture of 5-6 organic glycol ethers and alcohols
CAS#: ?

Summary: Three Acculith products, P-Exp, P-2025 and P-129C were administered orally once to male and female Fischer 344 rats via gavage at dose levels ranging from 1 ml/kg to 10 ml/kg. The animals were observed for signs of toxicity for fourteen days following dosing. Significant mortality was seen in rats of both sexes at dose levels of 7.5 ml/kg and higher. The majority of deaths occurred within 72 hours of exposure. Within minutes of dosing, animals at the higher dose levels became deeply sedated, unresponsive and prostrate. Severe lacrimation and salivation along with hypothermia and respiratory difficulties were evident. In surviving animals, the above neurobehavioral effects (with varying degrees of intensity) lasted in some cases as long as seven days post-dosing, followed by gradual recovery. Weight loss was evident at higher dose levels as long as seven days post-dosing. A dose-related decrease in testicular and splenic weight was found fourteen days after exposure in males. Liver weights were elevated in the males at dose levels of 5.0 ml/kg and higher. Similar trends in the spleen and liver weights were observed in females although the effects were not statistically significant. Histopathological examination revealed low level hepatotoxicity. Spleen and testes were not examined histopathologically (see appendix A).

Sincerely,
Joel B. Charm
Joel B. Charm, Director
Product Safety and Integrity
(201) 455-4057

- 84-791

Department of Toxicology
Allied Corporation
Morristown, New Jersey 07960

ACUTE ORAL TOXICITY STUDY OF ACCULITH SOLVENTS:

P-Exp., P-2025, P-129C

Report No. MA-182-81-17

Michael J. Derelanko, Ph.D.

To: _____

July 2, 1984



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MA-182-81-17

ACUTE ORAL TOXICITY OF ACCULITH SOLVENTS: P-EXP, P-2025, P-129C

Project No.: MA-182-A

Files: In Department of Toxicology Archives, Project File
MA-182-81.

Data Source: Mammalian Toxicology data forms are in a ring binder
labelled "Acute Oral Toxicity Study of 3 Acculith Solvents:
P-Exp, P-2025, P-129C. MA-182-81-17."

Pathology data are in Pathology Notebook 8147,
and Pathology ring binder labelled "1982 Necropsy Data
Sheets".

Test Dates: Started: 3/22/82
Completed: 4/7/82

Test Location: Department of Toxicology
Allied Corporation
Morristown, NJ 07960

Test Compound Information:

<u>Sample No.</u>	<u>Commercial Name</u>	<u>Synonym</u>	<u>Physical State</u>
8185-30	Acculith™ P-Exp Photoresist	P-Exp	Liquid
8185-7	Acculith™ P-2025 Positive Working Photoresist	P-2025	Liquid
8185-97	Acculith™ P-129C	P-129C	Liquid

All test substances were supplied by the Chemical Company of Allied
Corporation on the following dates: P-Exp (2/16/82); P-2025 (1/13/82); P-129C
(12/9/81). Additional information is available in Department of Toxicology
Archives.

MA-182-81-17

COMPLIANCE STATEMENT

This study was conducted in accordance with the TSCA GLP Regulations (FR48, No. 230), with the exception of Sections 792.105 b,e and 792.113a.

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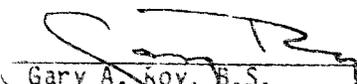
Cleared for Internal Distribution: William E. Rinehart 9/6/84
William E. Rinehart, Sc.D. Date
Director, Department of Toxicology

MA-182-81-17

This final report was reviewed according to Department of Toxicology Standard Operating Procedures. Study inspections and reports to the Study Director and management were accomplished on the dates listed below.

Protocol No. 82053

3-15-82; 3-16-82; 11-22-82; 12-30-82; 6-7-84; 6-(11-14)-84; 7-31-84;
8-(2-3)-84; 9-6-84



Gary A. Koy, B.S. 9-6-84
Manager, Quality Assurance Date

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SUMMARY

Three Acculith products, P-Exp, P-2025 and P-129C were administered orally once to male and female Fischer 344 rats via gavage at dose levels ranging from 1 mL/kg to 10 mL/kg. The animals were observed for signs of toxicity for fourteen days following dosing. Significant mortality was seen in rats of both sexes at dose levels of 7.5 mL/kg and higher. The majority of deaths occurred within 72 hours of exposure. Within minutes of dosing, animals at the higher dose levels became deeply sedated, unresponsive and prostrate. Severe lacrimation and salivation along with hypothermia and respiratory difficulties were evident. In surviving animals, the above neurobehaviorial effects (with varying degrees of intensity) lasted in some cases as long as seven days post-dosing, followed by gradual recovery. Weight loss was evident at higher dose levels as long as seven days post-dosing. A dose-related decrease in testicular and splenic weight was found fourteen days after exposure in males. Liver weights were elevated in the males at dose levels of 5.0 mL/kg and higher. Similar trends in the spleen and liver weights were observed in females although the effects were not statistically significant. Histopathological examination revealed low level hepatotoxicity. Spleen and testes were not examined histopathologically (see appendix A).

INTRODUCTION

The Chemical Company of Allied Corporation produces a line of specialty chemicals for use as solvents and cleaning solutions in the electronics industry. Because of the relatively small volumes produced and the use of hoods during the preparation of these solvents, the potential for exposure is limited and would occur predominantly by accident. The various Acculith products consist of several components appearing in more than one formulation. While toxicity information is available on a number of the individual components, the toxicity of complex mixtures of these chemicals is unknown.

The Mammalian Toxicology Section of the Department of Toxicology evaluated the acute oral toxicity of three of the Acculith Solvents, namely, P-Exp, P-2025, P-1290. This study was part of a larger program to evaluate the toxic properties of this product line to provide toxicity data which can be utilized for the development of safety data sheets, proper product labelling and for establishing general biological risk levels.

METHODS

Animal Species, Source, Selection, and Identification

Sixty-five male and sixty-five female Fischer 344 rats received from Charles River, Kingston, NY, on March 2, 1982 were used in this study. All animals were identified by numbered ear tags upon arrival. The animals were quarantined for at least two weeks prior to the initiation of the study to insure that only healthy animals were utilized. All animals were weighed at seven days and again one day prior to the initiation of the study. General health of the animals was assessed by outward appearance and by weight gain during this period. The animals were randomly assigned by sex to groups of five animals each in accordance with SOP GTX-025 on the day preceding initiation of the study. This procedure ensures that on initiation of the study, the mean body weights of each group within a sex do not statistically differ ($p \geq 0.05$). On the day of the initiation of the study, males weighed 194.0 to 237.4 and females weighed from 138.9 to 162.2 g.

Animal Husbandry

Rats were housed individually in suspended stainless steel cages with wire mesh on the front and bottom. Deotized Animal Cage Board¹ was placed under each shelf of cages. The environment of the room housing the animals was maintained at a temperature of $72^\circ \pm 2^\circ\text{F}$, a humidity of $50 \pm 5\%$ and a light/dark photoperiod of twelve hours. Animals were allowed water from an automatic system and Purina Rodent Chow #5001 ad libitum except during dosing and observation procedures. The cage board was changed at least three times per week and clean cages were provided weekly.

¹ Upjohn Co., Kalamazoo, MI

Test Substances

Samples of the three Acculiths tested were submitted by the Chemical Company and sent to the Department of Toxicology for testing. The samples were received on 12/9/81 (P-129C), 1/13/82 (P-2025), and 2/16/82 (P-Exp) and were assigned sample numbers 8168-97, 8185-7, and 8185-30, respectively. All pertinent analysis data are on file in Department of Toxicology Archives. House distilled water was used as a control.

Experimental Design

All animals assigned to each group were weighed immediately prior to dosing. The test article was administered by gavage in accordance with SOP GTX-008. The dose volume was based on the body weight of each animal at the time of dosing. The experimental design was as follows:

<u>Group Title (5 rats/group)</u>	<u>Male Group designation</u>	<u>Female group designation</u>	<u>Treatment-Received one dose of</u>
Distilled water control	A	N	10 mL/kg distilled water
<u>P-Exp Groups</u>			
High dose	B	O	10 mL/kg P-Exp.
Intermediate dose	E	R	7.5 mL/kg P-Exp.
Intermediate dose	C	P	5.0 mL/kg P-Exp.
Low dose	D	Q	1.0 mL/kg P-Exp.
<u>P-2025 Groups</u>			
High dose	F	S	10 mL/kg P-2025
Intermediate dose	I	V	7.5 mL/kg P-2025
Intermediate dose	G	T	5.0 mL/kg P-2025
Low dose	H	U	1.0 mL/kg P-2025
<u>P-129C Groups</u>			
High dose	J	W	10 mL/kg P-129C
Intermediate dose	M	Z	7.5 mL/kg P-129C
Intermediate dose	K	X	5.0 mL/kg P-129C
Low dose	L	Y	1.0 mL/kg P-129C

Daily Observations

All animals were closely observed immediately following dosing and at least twice each day until the completion of the study. All clinical signs were recorded daily in accordance with GTX-005. Signs of morbidity and mortality were recorded in accordance with SOP GTX-011 at least twice daily.

Body Weights

Rat body weights were measured and recorded in accordance with SOP GTX-003 seven days prior to the initiation of the study and on days -1, 0, 1, 4, 7, 11, and 14 or until death, with day 0 being the day of dosing. Changes in body weight during the study were calculated from these measurements using the day 0 weights as the baseline.

Neurobehavioral Screen Observations

Neurobehavioral assessment was performed by a modified Irwin screen according to SOP GTX-031. This method, which evaluates the neuromuscular status of each test animal was performed on the day of dosing approximately one hour after the administration of the test material.

Pathology

The pathologist reviewed a complete record of the clinical observations prior to animal termination and necropsy. All surviving animals were terminated by CO₂ asphyxiation and necropsied immediately thereafter. Gross examination upon necropsy followed Pathology SOP #4, which included examination of the lining and contents of all body cavities; exterior and cut surface of major viscera and brain; interior lining of esophagus, stomach, and urinary bladder; and serosal and interior surfaces of the bowel.

The brain with nerve cord, lungs with trachea, liver, spleen, each kidney, each testis with epididymis, and each ovary were weighed at sacrifice. Organ weight/body weight ratios (mg/g) were calculated from these organ weight measurements and the terminal body weight measurements.

Portions of the following tissues and organs were saved in 10% buffered formalin: brain and cervical cord; lungs with trachea; heart; thymus and mediastinal contents; thyroid with parathyroids and larynx; lymph nodes from several sites; portions of the stomach and bowel including duodenum, ileum, and colon; liver; pancreas; adrenals; kidneys; urinary bladder; testes with epididymides and a portion of sternbrae with marrow and attached muscle.

Wet tissue will be saved for one year from the final report of the apparent final toxicological study of the agent; blocks for two years; and tissue sections for one year. These times will be modified to fit future EPA standards.

Histopathological examination included the following organs and tissues: brain and spinal cord from all Acculith-exposed rats and controls; liver and kidneys from high dose and control animals. All tissues were prepared routinely and stained with hematoxylin-phloxine eosin.

Statistical Analysis

The results of quantitative continuous variables were intercompared for the test groups versus the control group by use of the following tests: Bartlett's homogeneity of variance, analysis of variance (ref. 2) and Duncan's multiple range procedure (ref. 1). The latter was used to delineate which groups differed from controls when the F for analysis of variance was significantly large.

Data Collection, Storage, and Retention

Data for body weight, morbidity and mortality, clinical signs, and gavage volumes, dosage calculations, sample preparation, and all other observations were recorded on MAM Data Sheets. Data sheets were prepared in advance of the study with animal numbers entered as appropriate. All data sheets were stored in the study binders.

RESULTS

In general, of the data analyzed statistically, only those criteria that differed significantly from vehicle controls are discussed. Omission of comment is indicative that no statistically significant ($p \geq 0.05$) differences were found. Some of the data presented in this report have been rounded to reflect the limits of significant figures. Unless specified, no sex difference was noted.

Mortality

A summary of mortality data for both males and females for all three Acculith products tested is presented in Tables 1 and 2, respectively. In the males, the LD₅₀s for P-Exp, P-2025 and P-129C were approximately 8-9 mL/kg. The onset of death was more rapid following dosing with P-2025 (all animals dying within 48 hours of exposure) as compared to P-Exp and P-129C. Death of two of the five P-129C-exposed animals which died at the high dose level did not occur until five and six days post-dosing, respectively.

All three of the Acculith products were slightly more toxic in the females than males. LD₅₀ values ranged from 6.8 to 7.7 mL/kg. In the females, the relative toxicity of the three Acculiths was similar with all animals dying within 72 hours of dosing at a dose level of 7.5 mL/kg and within 48 hours at a dose level of 10 mL/kg.

Clinical Observations:

In-life clinical observations for both male and female animals are summarized in Tables 3 and 4, respectively. Within minutes of receiving the test materials at dose levels of 7.5 and 10.0 mL/kg, both males and females became deeply sedated, prostrate and were unresponsive to all stimuli except pain.

Many of the rats were observed to have small (miotic) fixed pupils along with pronounced lacrimation and salivation. Muscle tone was greatly reduced. Over the next few hours, the rats appeared dehydrated and to have distended bladders. The animals were hypothermic with decreased, labored and irregular respiration. Those rats which survived longer than 24 hours developed a disheveled appearance with piloerection (hair erect) and apparent weight loss. Other clinical signs of toxicity which occurred at a moderate incidence at the higher dose levels included chromodacryorrhea, red staining around the mouth and nares, yellow staining of the anal-genital area, hypersensitivity, vocalization, an apparent distension and firmness of the cecum, small tarry feces, and paleness. In general, these signs were apparently not sex or compound specific as they were evidenced in both sexes with all three of the Acculiths tested.

Animals from both sexes which did not die showed a gradual recovery with persistent lacrimation, chromodacryorrhea, urinary staining and apparent weight loss evident as long as 11 days post-dosing. Signs such as piloerection, paleness, and hypoactivity persisted, on the average, from four to seven days after administration of the Acculiths. Corneal opacities were noted in three of the five males which were exposed to P-Exp and P-2025 while none were observed in rats dosed with P-129C or controls. The opacities were not evident until day 5 of the study and persisted until day 14. A corneal opacity was only observed in one of the female rats which was exposed to P-2025. This abnormality was not noted in females dosed with the other two Acculiths.

Animals dosed at the lower dose levels (5 mL and 1 mL/kg) displayed some of the clinical signs seen with higher doses but the incidence and degree of severity were lower. These animals did not become unresponsive after dosing but various degrees of hypoactivity were noted. The rats which received Acculiths at the lowest dose level (1 mL/kg) displayed few clinical signs and these, when noted, were only of a minimal degree of severity. The most common clinical observations made at dose levels of 5 and 1 mL/kg were lacrimation, red nasal discharge, hypoactivity, yellow staining of the anal genital area and apparent weight loss.

Clinical signs which occurred in low incidence in both sexes receiving Acculith products included pelvic elevation, red staining of the anal-genital area, diarrhea, decreased feces size, audible respiration and tremors.

Neurobehavioral screen observations are shown in Tables 5 and 6 for males and females, respectively. This test was performed one hour after dosing. A high incidence of lacrimation and miosis was apparent in both sexes exposed to Acculith products at the higher dose levels and to a lesser degree at the lower dose levels. Visual placing was reduced at the high dose level in both males and females exposed to P-2025 and P-129C but was not evident in those animals which received P-Exp. Respiration was reduced in both sexes for all three Acculiths at the high dose level but was variable, ranging from increased to decreased at lower dose levels. Touch escape was generally reduced but, with the exception of those animals dosed with P-129C, the response was not dose-related. Grasp irritation and muscle tone were reduced and limb rotation generally decreased at the higher dose level for all three Acculith products. Locomotor activity was decreased with all three Acculiths at dose levels of 5.0 mL/kg and greater. Spatial locomotion was only affected in those animals exposed to P-129C. The righting reflex was completely absent for all three

Acculiths at the higher dose levels. The wire maneuver and grip strength were greatly reduced at higher dose levels in rats which received P-Exp, P-2025 and P-129C. Hypothermia was evident with all three Acculiths in females at a dose level of 10 mL/kg. Urination was increased in both males and females dosed with the Acculith products at higher dose levels although the incidence of this observation was variable.

In general, with a few exceptions, all three Acculith products produced equivalent neurobehavioral screen responses in both males and females. P-Exp did appear, however, to have less of an effect on muscle tone at the lower dose levels.

Body Weight Parameters

Mean absolute body weights for male and female rats are presented in Tables 7-12. A significant decrease in body weight was observed in surviving males and females four days following exposure to P-Exp at dose levels of 7.5 mL/kg for males ($p < 0.01$) and 7.5 and 5.0 mL/kg for females ($p < 0.01$ and $p < 0.05$ respectively) (Tables 7 and 8). In the females, the absolute body weights were slightly less but not statistically different from controls during the remainder of the study. The absolute body weight of the males in the 7.5 mL/kg dose level group were still significantly depressed at day 7 ($p < 0.01$) but was not statistically different from control values on day 11 or 14 of the study.

Absolute body weights of males exposed to P-2025 (Table 9) were significantly depressed ($p < 0.01$) four and seven days after dosing at a dose level of 7.5 mL/kg and four days after dosing at 5.0 mL/kg ($p < 0.05$). One female rat treated with P-2025 at a dose level of 7.5 mL/kg (the only survivor at this dose level) had a markedly lower body weight than the control animals four days after dosing which gradually returned to near control values by Day 14 (Table 10).

No other statistically significant body weight effects were noted in females or males dosed with P-2025 during the two-weeks of the study.

Absolute body weights for male and female rats exposed to P-129C are presented in Tables 11 and 12, respectively. A significant depression in body weight occurred in surviving male rats at P-129C dose levels of 7.5 and 5.0 mL/kg four days after dosing ($p < 0.01$ and $p < 0.05$, respectively). Similarly, the mean body weight of the two surviving males from the 10 mL/kg group was greatly reduced relative to the controls at this time. No other statistically significant body weight effects were noticed in the males at any of the dose levels tested during the remainder of the study. With the exception of a significant depression in body weight on days 4 and 7 of the one surviving female dosed with P-129C at a 7.5 mL/kg, no other effects on absolute body weight occurred in the females at any of the remaining dose levels tested.

Mean body weight changes for both male and female rats dosed with the three Acculith products are shown in Tables 13 and 18. Male and females which received P-Exp (Tables 13 and 14) showed a significant dose-related loss in body weight during the first 24 hours following administration of the test compound. Animals dosed with P-Exp at 5 and 7.5 mL/kg continued to lose weight during the next 72 hours. At the 7.5 mL/kg dose, surviving females regained weight nearly equivalent to pre-dosing levels by seven days after exposure while this did not occur in the 7.5 mL/kg male dose group until day 11. In the males, body weight gain was still significantly ($p < 0.01$) reduced relative to controls on day 14 while no statistically significant difference was seen between the surviving females and the corresponding control group at this time.

Mean body weight changes for male and female rats dosed with P-2025 are presented in Tables 15 and 16, respectively. As with P-Exp, a significant loss in body weight was seen 24 hours after dosing in rats of both sexes. At the higher dose levels, the body weight continued to decrease during the next 72 hours. Despite a subsequent weight gain, body weights of the 7.5 mL/kg groups were still below pre-dose levels in surviving females at day +7 and males at day + 11. A dose-related depression in body weight was still evident in both sexes at day 14 but only statistically differed from controls for the males.

Mean body weight changes for rats dosed with P-129C are shown in Tables 17 for males and 18 for females. The results were similar to that seen with P-Exp and P-2025. A significant weight loss occurred one day after dosing. At the higher dose levels, the body weights continued to decrease during the next 72 hours followed by a weight gain. Body weights at the higher dose level did not exceed pre-dose values until day 4 for the females and day 7 for the males. Body weight gains were still depressed relative to corresponding controls in both males and females on day 14 of the study but the difference was only statistically significant in the males.

Gross Necropsy Observations

Necropsy observations for all three Acculith products tested are summarized in Tables 19, 20 and 21. All surviving animals were necropsied 14 days after administration of the test articles except those animals which received P-Exp, P-2025 or P-129C at a dose level of 5 mL/kg. These animals were necropsied 15 days post-dosing (4/7/82) since sufficient necropsy personnel were not available on day 14 (4/6/82) due to a severe snowstorm.

The most prominent finding in the males was a decreased testicular size which was evident both in animals dying spontaneously and in those surviving until

the end of the study. This finding was associated with the higher dose levels of all three Acculiths. In the majority of the surviving animals, the testes appeared abnormally dark in color. The seminal vesicles also appeared to be abnormally small although the incidence of occurrence was less.

Significant observations noted mainly in those males which died spontaneously included: the presence of dark gelatinous material in the gastrointestinal tract (possibly due to gastrointestinal hemorrhage); gastric mucosal erosions; dry cecal contents; and decreased spleen size. In addition, many of the males which died had red granular material in the stomach. Most likely this indicates that the test materials were not entirely absorbed prior to death of the animals.

Various organs in the males which died spontaneously were noted to be abnormally dark in color. This was most likely the result of autolytic changes and was not directly compound related. In many of the surviving males exposed to the test materials as well as the controls, the lungs appeared abnormally red in color and had a mottled appearance. This is a common finding when death is induced by CO₂ asphyxiation. This finding in animals dying spontaneously may have resulted from autolytic changes.

Observations which had a low incidence in the males exposed to the Acculiths included: distention of the urinary bladder, enlargement of the liver; the presence of red or brown granules in the cecum; a soft appearance to the brain; an enlargement of the adrenals and a depressed thymus size.

In the females, for the most part, abnormal gross necropsy observations were associated mainly with those rats which died spontaneously. These findings were similar for all three Acculiths and resembled those noted in the males. These included the presence of black, gelatinous material in gastrointestinal tract; dry cecal contents; decreased spleen size; red granular material in the gastrointestinal tract and gastric mucosal erosions. As with the males, various organs in the females were abnormally dark in color most likely the result of congestion associated with autolytic changes. An abnormally soft appearance to the brain and spinal cord was more prevalent in the females than males occurring in a moderate incidence in animals dying spontaneously. A green discoloration of the ovaries was noted in two of five females and a green discoloration of the peritoneum was noted in four of five of the females dosed with P-2025 at 7.5 mL/kg. Other abnormal observations in the females included enlargement of the adrenals, decrease in size of the thymus and distension of the urinary bladder. The latter two observations were solely associated with exposure to P-2025. Additional findings included a pale discoloration of the spleen (P-Exp) and a yellow-green discoloration of the liver (P-2025, P-129C). Other than the exceptions noted above, the abnormal gross necropsy findings were similar for all three Acculith products in the females although the degree of incidence varied.

Organ Weights:

Mean organ weights (absolute and as organ weight/body weight ratios) for animals surviving the length of the study are shown in Tables 22 through 27 for all three of the Acculith products tested. The only organ weight effects which occurred with statistical significance ($p < 0.05$) were found in the males. Testicular weights and ratios were reduced in a dose related manner (Tables 22,

24, 26), being statistically different from control at dose levels of 5.0 and 7.5 mL/kg in those rats dosed with P-129C and P-2025 ($p < 0.01$) and at 1.0, 5.0 and 7.5 mL/kg for exposure to P-Exp ($P < 0.05 - 0.01$). A "no-effect" level on the testis was not found.

A statistically significant depression in spleen weight parameters occurred in a dose-related manner in males treated with P-Exp and P-2025 at dose levels of 5.0 and 7.5 mL/kg. While a similar pattern of diminished spleen weights was seen in males exposed to P-129C, the effect was not statistically different from control values.

Relative liver weights were significantly greater than control in both P-Exp and P-2025 treated males at a dose level of 7.5 mL/kg. Although the mean relative liver weight was apparently elevated in those rats exposed to P-129C at a dose level of 7.5 mL/kg, the values were not statistically different from control.

In the female animals (Tables 23, 25, 27), although no statistically significant differences in organ weight parameters were noted between animals exposed to the Acculith products and controls, mean absolute and relative liver spleen weights of Acculith treated rats tended to be higher and lower than control values, respectively.

Histopathological Examination:

A copy of the pathology report is included as Appendix A. Liver and kidneys were studied from high dose and control animals only. No morphological abnormalities associated with Acculith exposure were observed in the kidneys. Changes were found in the livers which were judged to be treatment-related.

These included hepatic hypertrophy, hepatocytic cytoplasmic vacuolation and hepatocyte necrosis of scattered cells along the central portion of hepatic lobules or adjacent to the larger veins. The necrosis was considered to be associated with a low level hepatotoxicity of the Acculiths tested. All the hepatocellular alterations were felt to be minimal and reversible in nature.

The brains and spinal cords of all rats, Acculith exposed and controls, had vacuolative changes in the myelinated tracts. Although the abnormalities were more prominent in high dose level rats than controls, the effect was judged to be an artifact of fixation and processing and accentuated due to post-mortem change. This effect was not considered treatment-related.

TABLE 1: Mortality Summary - Males

TEST SUBSTANCE	Dose Level				Estimated LD50
	1.0 mL/kg	5 mL/kg	7.5 mL/kg	10.0 mL/kg	
Distilled Water	-	-	-	0/5	-
P-149	0/5	0/5	0/5	5/5 (Day 2,3)	7.5 mL/kg <LD50 <10 mL/kg
P-2025	0/5	0/5	0/5	5/5 (Day 1,2)	7.5 mL/kg <LD50 <10 mL/kg
P-129C	0/5	0/5	1/5(Day 2)	5/5 (Day 1,2,3,5,6)	8.0 ¹

¹ Determined by Probit Analysis

TABLE 2: Mortality Summary - Females

TEST SUBSTANCE	Dose Level				Estimated LD50
	1.0 mL/kg	5 mL/kg	7.5 mL/kg	10.0 mL/kg	
Distilled Water	-	-	-	0/5	-
P-Exp	0/5	0/5	2/5(Day 2)	5/5 (Day 1,2)	7.71
P-2025	0/5	0/5	4/5(Day 3)	5/5 (Day 2)	6.81
P-1290	0/5	0/5	4/5(Day 2)	5/5 (Day 1)	6.81

1 determined by Probit Analysis

TABLE 3: Summary Incidence of In-life Observations¹ - Mice

GROUP	P-2025												P-129C											
	A		B		C		D		E		F		G		H		I		J		K		L	
	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN	TEST LEVEL	NO. AN
Lactation	DAY 0																							
	DAY 1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
	2-4	1	1	3	12	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	5-7				8	5	1	1																
	8-11																							
	12-14																							
	TOTAL	1	1	8	5	25	5	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	DAY 0																							
	DAY 1																							
	Chromom- dactylography	2-4																						
5-7																								
8-11																								
12-14																								
TOTAL																								
Pitted Cornea	DAY 1																							
	DAY 1																							
	2-4																							
	5-7																							
	8-11																							

1. See Irwin Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary Incidence of In-Life Observations¹ - Males (cont'd)

GROUP	TEST MATERIAL	A		B		C		D		E		F		G		H		I		J		K		L			
		DIST. N2O		10 ml/kg		10 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		10 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		5.0 ml/kg		1.0 ml/kg			
		POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM		
Eye partially closed	DAY 0																										
	DAY 1																										
	2-4																										
	5-7																										
	8-11																										
	12-16																										
	TOTAL																										
	DAY 0																										
	DAY 1																										
	2-4																										
5-7																											
8-11																											
12-16																											
TOTAL																											
Hydrocete	DAY 0																										
	DAY 1																										
	2-4																										
	5-7																										
	8-11																										
	12-16																										
	TOTAL																										
	DAY 0																										
	DAY 1																										
	2-4																										
5-7																											
8-11																											
12-16																											
TOTAL																											

1. Yes/No Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary Incidence of In-Life Observations¹ - Males (cont'd)

GROUP	TEST MATERIAL	A		B		E		C		D		F		I		G		H		J		M		K		L							
		10 ml/kg	#OBS	10 ml/kg	#OBS	7.5 ml/kg	#OBS	5.0 ml/kg	#OBS	1.0 ml/kg	#OBS	1.0 ml/kg	#OBS	10 ml/kg	#OBS	7.5 ml/kg	#OBS	5.0 ml/kg	#OBS	1.0 ml/kg	#OBS	10 ml/kg	#OBS	7.5 ml/kg	#OBS	5.0 ml/kg	#OBS	1.0 ml/kg	#OBS				
Cornell Genetics	DAY 0																																
	DAY 1																																
	2-4																																
	5-7					3	3																										
	8-11					2	2																										
Eyes appear sunken	12-14					2	2																										
	TOTAL					7	7																										
	DAY 0																																
	DAY 1																																
	2-4																																
	5-7																																
	8-11																																
	12-14																																
	TOTAL																																

1. See Irwin Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary Incidence of In-Life Observational - Males (cont'd)

GROUP	TEST MATERIAL	A		B		E		C		D		F		I		G		H		J		M		K		L			
		10 ml/kg POBS / AM	10 ml/kg POBS / AM	7.5 ml/kg POBS / AM	5.0 ml/kg POBS / AM	5.0 ml/kg POBS / AM	1.0 ml/kg POBS / AM	1.0 ml/kg POBS / AM	10 ml/kg POBS / AM	10 ml/kg POBS / AM	7.5 ml/kg POBS / AM	7.5 ml/kg POBS / AM	5.0 ml/kg POBS / AM	5.0 ml/kg POBS / AM	1.0 ml/kg POBS / AM	1.0 ml/kg POBS / AM	10 ml/kg POBS / AM	10 ml/kg POBS / AM	7.5 ml/kg POBS / AM	7.5 ml/kg POBS / AM	5.0 ml/kg POBS / AM	5.0 ml/kg POBS / AM	1.0 ml/kg POBS / AM						
Fissoid abdominal and skeletal musculature	DAY 0																												
	DAY 1		5	5	5																								
	2-4																												
	5-7																												
	8-11																												
	12-14																												
TOTAL		5	5	5	5																								
Hypertensive	DAY 0																												
	DAY 1			5	5																								
	2-4		3	3	15	5																							
	5-7																												
	8-11																												
	12-14																												
TOTAL		3	3	20	5																								
Feed room discharge	DAY 0																												
	DAY 1																												
	2-4																												
	5-7																												
	8-11																												
	12-14																												
TOTAL		1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	

1. See Train Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary Incidence of In-Life Observational - Malee (cont'd)

GROUP	TEST MATERIAL	A		B		E		C		D		F		I		G		H		J		M		K		L			
		DIST. #20		P-EXP		P-2025		P-129C																					
		10 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	7.5 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	1.0 ml/kg #OBS	#AN	5.0 ml/kg #OBS	#AN	7.5 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	1.0 ml/kg #OBS	#AN	5.0 ml/kg #OBS	#AN	7.5 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	5.0 ml/kg #OBS	#AN	7.5 ml/kg #OBS	#AN
	Red stains around nose and mouth																												
	Decreased respiration																												
	Labored breathing																												
	DAY 0																												
	DAY 1																												
	2-4																												
	5-7																												
	8-11																												
	12-14																												
	TOTAL																												
	DAY 0																												
	DAY 1																												
	2-4																												
	5-7																												
	8-11																												
	12-14																												
	TOTAL																												
	DAY 0																												
	DAY 1																												
	2-4																												
	5-7																												
	8-11																												
	12-14																												
	TOTAL																												

1. See Irvin Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary incidence of In-Life observations - Meiosis (cont'd)

GROUP	A		B		C		D		E		F		G		H		I		J		K		L	
	TEST MATERIAL	DIST. (M/D)	10 ml/kg	10 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg	1.0 ml/kg	10 ml/kg	10 ml/kg	7.5 ml/kg	7.5 ml/kg	5.0 ml/kg	5.0 ml/kg	1.0 ml/kg	1.0 ml/kg	10 ml/kg	10 ml/kg	7.5 ml/kg	7.5 ml/kg	5.0 ml/kg	5.0 ml/kg	1.0 ml/kg	1.0 ml/kg
EXPERIMENT			POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM	POBS	AM
Audible breathing	DAY 0																							
	DAY 1																							
	2-4																							
	5-7																							
	8-11																							
Irregular breathing	12-14																							
	TOTAL																							
	DAY 0																							
	DAY 1																							
	2-4																							
Pericardial Allogeneic	5-7																							
	8-11																							
	12-14																							
	TOTAL																							
	TOTAL																							

1. See table screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 1: Summary Incidence of In-Life Observations¹ - Males (cont'd)

GROUP	TEST MATERIAL	DISEASE LEVEL / (REATMENT)	OBSERVATION	A		B		E		C		D		F		I		G		H		J		M		K		L	
				DIST. H ₂ O		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg	
				#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM
Piloerection	DAY 0																												
	DAY 1																												
	2-4								2	2																			
	5-7							10	5																				
	8-11							5	5																				
Hypothermia	DAY 0																												
	DAY 1																												
	2-4																												
	5-7																												
	8-11																												
TOTAL								15	5	2	2																		
Yellow stain in anal-genital area	DAY 0																												
	DAY 1																												
	2-4																												
	5-7																												
	8-11																												
TOTAL								5	5																				

1. See In-life Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary Incidence of In-Life Observations - Males (cont'd)

GROUP	TEST MATERIAL	A		B		E		C		D		F		I		G		H		J		M		K		L				
		DIST. N2O		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		1.0 ml/kg		
		POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	POBS	0AM	
Red staining in anal genital area	DAY 0																													
	DAY 1																													
	2-4																													
	5-7																													
	8-11																													
	12-14																													
	TOTAL																													
	DAY 0																													
	DAY 1																													
	Diarrhea	2-4																												
5-7																														
8-11																														
12-14																														
TOTAL																														
DAY 0																														
DAY 1																														
2-4																														
5-7																														
8-11																														
12-14																														
TOTAL																														
Feces on, retained in rectum in white, gray black feces	DAY 0																													
	DAY 1																													
	2-4																													
	5-7																													
	8-11																													
	12-14																													
	TOTAL																													
	DAY 0																													
	DAY 1																													
	2-4																													
5-7																														
8-11																														
12-14																														
TOTAL																														

1. See Initial Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

Table 1: Summary Incidence of In-Life Observations - Meles (cont'd)

GROUP	TEST MATERIAL	A		B		C		D		E		F		G		H		I		J		K		L			
		DIST. #20		6 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg	
		#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM	#OBS	#AM
Cecum, dis- tended and firm	DAY 0																										
	DAY 1		5		5																						
	2 - 4																										
	5 - 7																										
	8 - 11																										
	TOTAL		5		5																						
Urinary blad- der markedly distended	DAY 0																										
	DAY 1		5		5																						
	2 - 4																										
	5 - 7																										
	8 - 11																										
	TOTAL		5		5																						
Blind in urine	DAY 0																										
	DAY 1																										
	2 - 4																										
	5 - 7																										
	8 - 11																										
	TOTAL																										

1. See Irwin Screener for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary Incidence of In-Life Observations - Maloe (cont'd)

TEST MATERIAL	A		B		C		D		E		F		G		H		I		J		K		L	
	1.0 ml/hm																							
SOBE LEVEL/TREATMENT	1.0 ml/hm																							
OBSERVATION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
note																								
Weight loss (mm)																								
0 - observed no. events																								

1. See "Data Screen for additional observations"
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary Incidence of In-Life Disease/Vitamins - Males (cont'd)

GROUP	DISEASE	A		B		E		C		D		F		I		G		H		J		M		Y		L		
		10 ml/kg	5.0 ml/kg	10 ml/kg	5.0 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg	7.5 ml/kg	5.0 ml/kg																		
		#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	
Salivation	DAY 0																											
	DAY 1			5	5																							
	2-4																											
	5-7																											
	8-11																											
	12-14																											
TOTAL				5	5																							
Hypersecretive	DAY 0																											
	DAY 1																											
	2-4																											
	5-7																											
	8-11																											
	12-14																											
TOTAL																												
Aggressive	DAY 0																											
	DAY 1																											
	2-4																											
	5-7																											
	8-11																											
	12-14																											
TOTAL																												

1. See main screen for significant observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 3: Summary Incidence of In-Life Observational - Males (cont'd)

GROUP	A		B		E		C		D		F		I		G		H		J		M		K		L			
	DIST. H2O		10 ml/kg		7.5 ml/kg		5.0 ml/kg		3.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		3.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		3.0 ml/kg		1.0 ml/kg	
	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM	NOBS	AM
Hypertension	DAY 0																											
	DAY 1																											
	2-4			10	5	1	1																					
	5-7					1	1																					
	8-11																											
	TOTAL				11	5	1	1																				
Leukopenia	DAY 0																											
	DAY 1					5	5																					
	2-4																											
	5-7																											
	8-11																											
	TOTAL																											
Pneumonia	DAY 0																											
	DAY 1																											
	2-4																											
	5-7																											
	8-11																											
	TOTAL																											

1. Sum Leish Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

FIG. 3. Summary Incidence of In-Life Observational - Pelou (cont'd)

TEST MATERIAL	A		B		E		C		D		F		I		G		H		J		M		K		L		
	DIST. HDZ.		1.0 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		
	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	#AN	#OBS	
Uzinary to Pelou	DAY 0																										
	DAY 1																										
	2 - 4																										
	5 - 7																										
	8 - 11																										
	12-14																										
	TOTAL																										
Tremore	DAY 0																										
	DAY 1																										
	2 - 4																										
	5 - 7																										
	8 - 11																										
	12-14																										
	TOTAL																										
	DAY 0																										
	DAY 1																										
	2 - 4																										
	5 - 7																										
	8 - 11																										
	12-14																										
	TOTAL																										

1. See Irwin Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 41 Summary Incidence of In-Life Observational - Female

GROUP	TEST SERIAL	M	O		P		R		S		V		U		W		Z		Y		
			10 mL/kg		5.0 mL/kg		7.5 mL/kg		10 mL/kg		7.5 mL/kg		5.0 mL/kg		10 mL/kg		7.5 mL/kg			5.0 mL/kg	
			OBS	PAN	OBS	PAN	OBS	PAN	OBS	PAN	OBS	PAN	OBS	PAN	OBS	PAN	OBS	PAN		OBS	PAN
Corneal opacity	DAY 0																				
	DAY 1																				
	2 - 4																				
	5 - 7																				
	8 - 11																				
Scab on right rear foot	12-14																				
	TOTAL																				
	DAY 0																				
	DAY 1																				
	2 - 4																				
Prostrate	5 - 7																				
	8 - 11																				
	12-14																				
	TOTAL																				
	DAY 0																				
Prostate	DAY 1																				
	2 - 4																				
	5 - 7																				
	8 - 11																				
	12-14																				
TOTAL																					

1. Saw I/Fain Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 4: Summary Incidence of In-Life Observational - Female (cont'd)

TEST MATERIAL	N	O	R	P	Q	P-2025						P-129C									
						10 ml/kg		7.5 ml/kg		5.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		1.0 ml/kg	
						OBS	AM	OBS	AM	OBS	AM	OBS	AM	OBS	AM	OBS	AM	OBS	AM	OBS	AM
Fluoridated water (control) and mineral supplement	DAY 0																				
	DAY 1		3	3	5	5															
	2-4																				
	5-7																				
	8-11																				
	TOTAL		3	3	5	5															
Hypocretive	DAY 0																				
	DAY 1																				
	2-4																				
	5-7																				
	8-11																				
	TOTAL																				
Lactogenic	DAY 0																				
	DAY 1																				
	2-4																				
	5-7																				
	8-11																				
	TOTAL																				

1. See In-life Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 4. Summary Incidence of In-Life Observations - Females (cont'd)

GROUP	TEST MATERIAL	H		O		R		P		Q		S		V		T		U		W		Z		X		Y			
		DIST. H2O		P-EXP		P-2025		P-129C																					
		10 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	7.5 ml/kg #OBS	#AN	5.0 ml/kg #OBS	#AN	1.0 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	5.0 ml/kg #OBS	#AN	3.0 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	10 ml/kg #OBS	#AN	7.5 ml/kg #OBS	#AN	5.0 ml/kg #OBS	#AN	3.0 ml/kg #OBS	#AN
Hyper-sensitive	DAY 0																												
	DAY 1																												
	2-4						5	3																					
	5-7					7	3																						
	8-11					11	3																						
	12-14					8	3																						
	TOTAL					26	3	5	3																				
Vocalization	DAY 0																												
	DAY 1																												
	2-4					9	3	8	5																				
	5-7																												
	8-11																												
	12-14																												
	TOTAL					9	3	8	5																				
Pelvic Flotation	DAY 0																												
	DAY 1																												
	2-4							1	1																				
	5-7																												
	8-11																												
	12-14																												
	TOTAL																												

1. Sex Irwin Screen for additional observations
 2. Number of feces observation made
 3. Number of animals with observation

TABLE 4: Summary Incidence of In-Life Observations¹ - Females (cont'd)

GROUP	H	O	R	P	Q	S	P-200 ²						P-129C							
							10 ml/kg		5.0 ml/kg		7.5 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		10 ml/kg	
							OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM
Weight loss apparent	DIST. H2O																			
	DOSE LEVEL/TREATMENT																			
	OBSERVATION																			
	DAY 0																			
	DAY 1		5	5																
	2-4		2	2	9	5														
5-7		4	3																	
8-11																				
12-14		1	1																	
TOTAL		12	5	9	5					16	5	10	5							
Pilo	DAY 0																			
	DAY 1																			
	2-4			4	3															
	5-7			4	2															
	8-11			4	2															
	12-14																			
TOTAL			8	3						9	2	1	1							
Discovered appearance	DAY 0																			
	DAY 1																			
	2-4																			
	5-7			2	2															
	8-11																			
	12-14																			
TOTAL																				

1. 1.5 m In-vitro Screen for additional observations
 2. Number of times observation made
 3. Number of animals with observation

TABLE 4. Summary Incidence of In-Life Observational - Female (cont'd)

GROUP	TEST MATERIAL	M	O		R		P		Q		S		V		T		U		W		Z		Y
			DOSE LEVEL/TREATMENT	10 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg	10 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg	5.0 ml/kg	7.5 ml/kg	10 ml/kg	1.0 ml/kg	5.0 ml/kg	7.5 ml/kg	10 ml/kg	1.0 ml/kg	5.0 ml/kg	7.5 ml/kg	10 ml/kg	
		DOBS	EM	DOBS	EM	DOBS	EM	DOBS	EM	DOBS	EM	DOBS	EM	DOBS	EM	DOBS	EM	DOBS	EM	DOBS	EM	DOBS	EM
Salivation	DAY 0																						
	DAY 1			3	3	2	2					5	5	2	2			1	1				
	2-4																						
	5-7																						
	8-11																						
Piloerection	TOTAL			3	3	2	2					5	5	2	2			1	1				
	DAY 0																						
	DAY 1					5	5																
	2-4							10	5														
	5-7					2	1							1	1								
Hypothermia	5-11																						
	TOTAL					7	5	10	5					1	1	9	5						
	DAY 0																						
	DAY 1			3	3	2	2							5	5			1	1				
	2-4																						
TOTAL			3	3	2	2							5	5			1	1					
TOTAL			5	5	2	2							5	5			1	1					

1. See I twin Screen for additional observations.
 2. Number of times observation made.
 3. Number of animals with observation.

TABLE 4: Summary Incidence of In-Life Observational Failure (cont'd)

GROUP	N	O		R		P		S		V		T		U		W		X		Y	
		10 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg	10 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg	10 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg	10 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg	10 ml/kg	7.5 ml/kg	5.0 ml/kg	1.0 ml/kg
Periosteal atrophy	DAY 0																				
	DAY 1																				
	2-6																				
	5-7																				
	8-11																				
Red nasal discharge	DAY 0																				
	DAY 1																				
	2-6																				
	5-7																				
	8-11																				
Mucoid nasal discharge	DAY 0																				
	DAY 1																				
	2-6																				
	5-7																				
	8-11																				
TOTAL																					

1. See Iwin for additional observations
 2. Number of time observation made
 3. Number of animals with observation

TABLE 6: Summary Incidence of In-Life Observational - Female (cont'd)

GROUP	TEST MATERIAL	DIS. H2O	N		D		R		P		Q		S		Y		T		U		V		W		X		Y					
			10 ml/kg		1.0 ml/kg		5.0 ml/kg		7.5 ml/kg		10 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg		10 ml/kg		7.5 ml/kg		5.0 ml/kg		1.0 ml/kg			
			OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM	OBS	PM		
Audible breathing	DAY 0	DAY 0																														
Irregular breathing	DAY 0	DAY 0																														
Yellow staining anal-genital area	DAY 0	DAY 0																														

1. See table below for additional observations
 2. Number of live observation made
 3. Number of animals with observation

TABLE 6: Summary Incidence of In-Life Observations - Female (cont'd)

GROUP	TEST MATERIAL	DIST. NO.	M		D		R		P		E		S		V		T		U		W		X		Y						
			10 ml/kg PDS	10 ml/kg PDS	7.5 ml/kg PDS	5.0 ml/kg PDS	3.0 ml/kg PDS	1.0 ml/kg PDS	10 ml/kg PDS	7.5 ml/kg PDS	5.0 ml/kg PDS	3.0 ml/kg PDS	1.0 ml/kg PDS	10 ml/kg PDS	7.5 ml/kg PDS	5.0 ml/kg PDS	3.0 ml/kg PDS	1.0 ml/kg PDS	10 ml/kg PDS	7.5 ml/kg PDS	5.0 ml/kg PDS	3.0 ml/kg PDS	1.0 ml/kg PDS	10 ml/kg PDS	7.5 ml/kg PDS	5.0 ml/kg PDS	3.0 ml/kg PDS	1.0 ml/kg PDS			
Carcin diagnosed and T1a	DUST TREATMENT	10 ml/kg PDS	DAY 0																												
			DAY 1																												
			2-6																												
			5-7																												
			8-11																												
			12-14																												
			17A																												
			DAY 0																												
			DAY 1																												
			2-6																												
Dehydrated	DUST TREATMENT	10 ml/kg PDS	DAY 0																												
			DAY 1																												
			2-6																												
			5-7																												
			8-11																												
			12-14																												
			17A																												
			DAY 0																												
			DAY 1																												
			2-6																												
Urinary bladder necrosis die T1a	DUST TREATMENT	10 ml/kg PDS	DAY 0																												
			DAY 1																												
			2-6																												
			5-7																												
			8-11																												
			12-14																												
			17A																												
			DAY 0																												
			DAY 1																												
			2-6																												

1. Row 17A Screen for additional observations
 2. Row 17A Screen observations made
 3. Number of additional observations

Table 3: Summary Incidences of Endpoints Screen Observations - Males

GROUP	A		B		C		D		E		F		G		H		I		J		K		L	
	10 ml/kg	5.0 ml/kg	10 ml/kg																					
TEST MATERIAL																								
DOSE OF TREATMENT	AM	AM	AM	AM																				
OBSERVABLE EFFECT	5																							
ROUTE DEATH																								
ACRIMATION																								
SALIVATION																								
PUPIL SIZE																								
PUPIL RESPONSE																								
CORNEAL RESPONSE																								
PERINAL RESPONSE																								
VISUAL PLACING																								
FINGER ACTIVITY																								
RESPIRATION																								
TOUCH ESCAPE																								
TOE PINCH																								
TAIL PULL																								
GRASP IRRITATION																								
BODY TONE																								
ABNORMAL TONE																								
LIMB ROTATION																								
BODY POSITION																								
LOCOMOTOR ACTIVITY																								
SPATIAL LOCOMOTION																								

1. Number of animals with observations
 + : Increased response
 - : Decreased response

TABLE 3: Summary Incidences of Twin Screen Observations - Helms (cont'd)

GROUP	A		B		E		C		D		F		I		E		H		J		M		K		L			
	10 ml/kg	5.0 ml/kg	7.5 ml/kg	5.0 ml/kg	3.0 ml/kg	1.0 ml/kg	10 ml/kg	5.0 ml/kg	3.0 ml/kg	1.0 ml/kg	10 ml/kg	5.0 ml/kg	3.0 ml/kg	1.0 ml/kg	10 ml/kg	5.0 ml/kg	3.0 ml/kg	1.0 ml/kg	10 ml/kg	5.0 ml/kg	3.0 ml/kg	1.0 ml/kg	10 ml/kg	5.0 ml/kg	3.0 ml/kg	1.0 ml/kg		
TEST MATERIAL	DIST. 420																											
DOSE LEVEL/TREATMENT	10 ml/kg		7.5 ml/kg		5.0 ml/kg		3.0 ml/kg		1.0 ml/kg		10 ml/kg		5.0 ml/kg		3.0 ml/kg		1.0 ml/kg		10 ml/kg		5.0 ml/kg		3.0 ml/kg		1.0 ml/kg			
OBSERVATION	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM										
HYPOTENSIVE GAIT	+	5	+	5							+	5	+	5														
IMPAIRED GAIT																												
PERVIC ELEVATION																												
"ALL" ELEVATION																												
POSITION PASSIVITY																												
RIGHTING REFLEX?	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5		
WIDE SCISSOR	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5		
LAP STRETCH	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5		
5. WHOLE RESPONSE	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5		
LOCALIZATION																												
MEMORIES																												
SWIMMING																												
PLUMBERTS																												
MITO (HMM)																												
UP-MOTION/DECELERATION																												
DIAPHRAGM																												

7. Numbers under observation column represents mean righting scores per group. Maximum score possible = 10.

TABLE 6: Summary Incidence¹ of Train Screen Obstructions - Females (cont'd)

GROUP	H	O		R		P		Q		S		V		T		U		W		Z		Y		
		10 ml/Air	5.0 ml/Air	7.5 ml/Air	10 ml/Air	5.0 ml/Air	7.5 ml/Air	10 ml/Air	1.0 ml/Air	1.0 ml/Air	10 ml/Air	5.0 ml/Air	7.5 ml/Air	1.0 ml/Air	1.0 ml/Air	10 ml/Air	5.0 ml/Air	7.5 ml/Air	1.0 ml/Air	1.0 ml/Air	10 ml/Air	5.0 ml/Air	7.5 ml/Air	1.0 ml/Air
TEST MATERIAL	DISC, M20																							
GROUP LEVEL/TREATMENT	10 ml/Air	5.0 ml/Air	7.5 ml/Air	10 ml/Air	5.0 ml/Air	7.5 ml/Air	10 ml/Air	1.0 ml/Air	1.0 ml/Air	10 ml/Air	5.0 ml/Air	7.5 ml/Air	1.0 ml/Air	1.0 ml/Air	10 ml/Air	5.0 ml/Air	7.5 ml/Air	1.0 ml/Air	1.0 ml/Air	10 ml/Air	5.0 ml/Air	7.5 ml/Air	1.0 ml/Air	
INCUBATION	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM
APPROXIMATE GALT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
APPROXIMATE GALT																								
PLASTIC ELEVATION																								
TAIL ELEVATION																								
POSITION PASSIVITY																								
RIGHTING REFLEX	10	2	10	5	10	5	10	1	1	10	5	5	1	1	10	5	10	5	10	5	10	5	2	1
WING SPREAD	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5
WING SPREAD	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5	-	5
STABLE RESPONSE																								
PRECALCULATION																								
TEMPERS																								
FOLLOWERS																								
UNUSUALS/OPS																								
PALLIDIFICATION																								
WETTING/OPS																								
UNUSUALS/PRECALCULATION																								
DISMAY																								

¹ - No full set of, controls
² - Number under observation column represents mean righting score per group. Maximum score possible = 10.

TABLE 7: Mean¹ Body Weights (g) of Male Test and Control Groups, P-Exp

Treatment and Dose Level	Group	Days Relative to Administration of Test/Control Material							
		-1	0	+1	+4	+7	+11	+14	
Distilled Water 10 mL/kg	A	215.98 + 7.31 -- (5) 2	215.84 + 7.20 -- (5)	216.32 + 8.13 -- (5)	219.44 + 8.69 -- (5)	225.78 + 9.73 -- (5)	239.90 +11.10 -- (5)	243.68 +11.25 -- (5)	
		P-Exp 1 mL/kg	210.82 +24.00 -- (5)	212.74 +24.18 -- (5)	211.40 +25.33 -- (5)	219.38 +27.14 -- (5)	218.74 +28.52 -- (5)	228.60 +31.50 -- (5)	232.92 +30.54 -- (5)
			P-Exp 5 mL/kg	220.52 + 3.70 -- (5)	221.34 + 4.50 -- (5)	210.20 + 4.75 -- (5)	202.18 + 7.34 -- (5)	222.78 + 8.36 -- (5)	233.40 +10.00 -- (5)
P-Exp 7.5 mL/kg	212.12 +12.34 -- (5)	216.50 +13.39 -- (5)		197.10 +10.37 -- (5)	172.44 ^b +14.31 -- (5)	191.20 ^b +15.19 -- (5)	215.1 +16.0 -- (5)	224.52 +18.07 -- (5)	
	P-Exp 10 mL/kg	215.28 + 5.76 -- (5)	214.90 + 7.13 -- (5)	201.50 + 7.18 -- (5)	- -- (0)	-	-	-	

1 = + Standard deviation

2 = Number of surviving animals indicated in parentheses

b = Significantly different from control (p < 0.01)

TABLE 8: Mean¹ Body Weights (g) of Female Test and Control Groups, P-Exp

Treatment and Dose Level	Group	Days Relative to Administration of Test/Control Material						
		-1	0	+1	+4	+7	+11	+14
Distilled Water 10 mL/kg	N	150.82 + 7.89 - (5) 2	149.80 + 8.68 - (5)	149.94 + 9.08 - (5)	149.74 + 9.04 - (5)	151.90 + 9.92 - (5)	152.86 + 9.89 - (5)	158.66 +12.38 - (5)
		149.88 + 4.80 - (5)	151.50 + 5.62 - (5)	146.40 + 6.73 - (5)	155.84 + 5.25 - (5)	152.16 + 5.10 - (5)	156.76 + 5.52 - (5)	157.14 + 5.01 - (5)
P-Exp 1 mL/kg	Q	148.18 + 6.96 - (5)	148.94 + 7.66 - (5)	142.62 + 8.88 - (5)	138.52 ^a + 8.66 - (5)	152.62 + 7.99 - (5)	158.40 + 9.34 - (5)	156.68 + 9.10 - (5)
		146.48 + 4.11 - (5)	146.52 + 4.22 - (5)	138.30 + 3.22 - (5)	127.97 ^b + 3.92 - (3)	140.33 + 1.70 - (3)	147.67 + 1.93 - (3)	150.97 + 2.68 - (3)
P-Exp 7.5 mL/kg	R	150.24 + 7.25 - (5)	148.64 + 6.79 - (5)	144.47 + 5.90 - (3)	- (0)	-	-	-
		146.48 + 4.11 - (5)	146.52 + 4.22 - (5)	138.30 + 3.22 - (5)	127.97 ^b + 3.92 - (3)	140.33 + 1.70 - (3)	147.67 + 1.93 - (3)	150.97 + 2.68 - (3)

1 = + Standard deviation

2 = Number of surviving animals indicated in parentheses

^a = Significantly different from control (p < 0.05)^b = Significantly different from control (p < 0.01)

TABLE 9: Mean¹ Body Weights (g) of Male Test and Control Groups, P-2025

Treatment and Dose Level	Group	Days Relative to Administration of Test/Control Material						
		-1	0	+1	+4	+7	+11	+14
Distilled Water 10 mL/kg	A	215.98 + 7.31 — (5)2	215.84 + 7.20 — (5)	216.32 + 7.13 — (5)	219.44 + 8.69 — (5)	225.78 + 9.73 — (5)	239.90 +11.10 — (5)	243.68 +11.25 — (5)
		218.32 + 7.73 — (5)	221.04 + 8.63 — (5)	218.48 + 7.96 — (5)	229.34 + 9.96 — (5)	229.10 +11.46 — (5)	237.10 +13.10 — (5)	241.76 +13.43 — (5)
		216.94 +13.09 — (5)	219.72 +12.71 — (5)	207.96 +16.49 — (5)	202.10 ^a +17.11 — (5)	220.74 +15.86 — (5)	231.40 +15.50 — (5)	236.82 +17.18 — (5)
P-2025 7.5 mL/kg	I	225.66 +13.30 — (5)	228.02 +12.06 — (5)	204.88 +13.35 — (5)	181.68 ^b + 6.43 — (5)	199.02 ^b + 8.04 — (5)	222.00 +10.20 — (5)	234.24 + 9.75 — (5)
		217.64 +10.21 — (5)	218.06 +10.04 — (5)	200.55 + 6.47 — (4)	— (0)	—	—	—

1 = + Standard deviation

2 = Number of surviving animals indicated in parentheses

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

TABLE 10: Mean¹ Body Weights (g) of Female Test and Control Groups, P-2025

Treatment and Dose Level	Group	Days Relative to Administration of Test/Control Material						
		-1	0	+1	+4	+7	+11	+14
Distilled Water 10 mL/kg	N	150.82 + 7.89 - (5)2	149.80 + 8.68 - (5)	149.94 + 9.08 - (5)	149.74 + 9.04 - (5)	151.90 + 9.92 - (5)	152.86 + 9.89 - (5)	158.66 +12.38 - (5)
		148.84 + 6.51 - (5)	150.0 + 7.01 - (5)	145.86 + 7.68 - (5)	154.14 + 8.95 - (5)	151.92 + 7.34 - (5)	156.34 + 9.27 - (5)	157.32 + 7.68 - (5)
P-2025 5 mL/kg	T	150.62 + 7.59 - (5)	151.88 + 7.28 - (5)	142.26 + 8.10 - (5)	142.36 + 7.43 - (5)	153.84 + 9.19 - (5)	158.58 + 9.35 - (5)	157.46 + 8.75 - (5)
		147.08 + 5.49 - (5)	147.76 + 5.80 - (5)	135.02 + 6.29 - (5)	119.40 ^b - (1)	131.70 - (1)	143.60 - (1)	145.60 - (1)
P-2025 10 mL/kg	S	150.96 +10.45 - (5)	149.24 +11.20 - (5)	142.30 + 9.89 - (5)	- (0)	-	-	-

1 * + Standard deviation
 2 * Number of surviving animals indicated in parentheses
 3 * Significantly different from control (p < 0.05)
 b * Significantly different from control (p < 0.01)

TABLE 11. Mean¹ Body Weights (g) of Male Test and Control Groups², P-129C

Treatment and Dose Level	Group	Days Relative to Administration of Test/Control Material						
		-1	0	+1	+4	+7	+11	+14
Distilled Water 10 mL/kg	A	215.98 + 7.31 — (5)2	215.84 + 7.20 — (5)	216.32 + 8.13 — (5)	219.44 + 8.69 — (5)	225.78 + 9.73 — (5)	239.90 +11.10 — (5)	243.68 +11.25 — (5)
		211.70 +12.31 — (5)	214.02 +12.61 — (5)	206.76 +16.46 — (5)	213.48 +17.56 — (5)	216.28 +14.77 — (5)	227.84 +12.70 — (5)	232.84 +10.66 — (5)
		218.98 + 6.23 — (5)	220.94 + 6.31 — (5)	208.60 + 8.32 — (5)	203.94 ^a + 8.57 — (5)	222.08 + 9.10 — (5)	231.68 + 9.36 — (5)	238.14 + 8.07 — (5)
P-129C 7.5 mL/kg	H	227.58 +13.05 — (5)	229.96 +12.48 — (5)	210.14 +15.06 — (5)	195.05 ^b + 3.32 — (4)	209.82 + 1.80 — (4)	227.42 + 4.69 — (4)	236.28 + 5.99 — (4)
		215.62 + 3.50 — (5)	215.72 + 3.29 — (5)	200.27 + 3.00 — (4)	158.55 ^b + 2.19 — (2)	— (0)	—	—

1 = + Standard deviation

2 = Number of surviving animals indicated in parentheses

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

TABLE 12: Mean¹ Body Weights (g) of Female Test and Control Groups, P-129C

Treatment and Dose Level	Group	Days Relative to Administration of Test/Control Material						
		-1	0	+1	+4	+7	+11	+14
Distilled Water 10 mL/kg	N	150.82 + 7.89 - (5)2	149.80 + 8.68 - (5)	149.94 + 9.08 - (5)	149.74 + 9.04 - (5)	151.90 + 9.92 - (5)	152.86 + 9.89 - (5)	158.66 +12.38 - (5)
		147.66 + 3.40 - (5)	148.68 + 4.07 - (5)	143.26 + 8.32 - (5)	150.52 + 6.14 - (5)	149.88 + 3.31 - (5)	154.76 + 4.65 - (5)	154.96 + 4.13 - (5)
P-129C 5 mL/kg	X	150.73 + 5.14 - (5)	149.56 + 4.49 - (5)	141.50 + 6.28 - (5)	143.06 + 4.52 - (5)	153.88 + 4.98 - (5)	157.08 + 4.72 - (5)	159.40 + 5.85 - (5)
		150.40 + 8.40 - (5)	152.20 + 9.07 - (5)	140.78 +10.22 - (5)	132.70 - (1)	143.30 - (1)	150.20 - (1)	153.30 - (1)
P-129C 10 mL/kg	W	154.56 + 6.38 - (5)	154.20 + 5.20 - (5)	152.90 - (1)				

1 = + Standard deviation

2 = Number of surviving animals indicated in parentheses

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

Table 13: Mean Body Weight Changes (g) of Male Test and Control Groups, P-Exp

Treatment and Dose Level	Group	Day - 1	Day 0	Day 0	Day 0	Day 0	Day 0	Day 0
		to Day - 0	to Day + 1	to Day + 4	to Day + 7	to Day + 11	to Day + 14	
Distilled Water 10 mL/kg	A	- 0.14	0.48	3.60	9.94	17.04	27.84	
		+ 0.92 ¹	+ 1.19	+ 2.60	+ 3.05	+ 4.63	+ 4.79	
		- (5)3	- (5)	- (5)	- (5)	- (5)	- (5)	
P-Exp 1 mL/kg	D	1.92	- 1.34	6.64	6.00	15.88	20.18	
		+ 0.58	+ 1.66	+ 4.66	+ 5.73	+ 9.79	+ 8.71	
		- (5)	- (5)	- (5)	- (5)	- (5)	- (5)	
P-Exp 5 mL/kg	C	0.82	-11.14 ^b	-19.16 ^b	1.44 ²	12.10	19.68	
		+ 1.13	+ 2.23	+ 4.05	+ 4.76	+ 6.44	+ 5.21	
		- (5)	- (5)	- (5)	- (5)	- (5)	- (5)	
P-Exp 7.5 mL/kg	E	1.38	-19.40 ^b	-44.06 ^b	-25.30 ^b	-1.38 ^b	8.02 ^b	
		+ 1.34	+ 3.52	+ 8.04	+ 5.51	+ 5.57	+ 4.99	
		- (5)	- (5)	- (5)	- (5)	- (5)	- (5)	
P-Exp 10 mL/kg	B	- 0.38	13.40 ^b	-	-	-	-	
		+ 2.40	+ 1.33	-	-	-	-	
		- (5)	- (5)	- (0)	-	-	-	

1 = + Standard deviation
 2 = Body weight (g)
 3 = Number of surviving animals indicated in parentheses
 a = Significantly different from control (p < 0.05)
 b = Significantly different from control (p < 0.01)

TABLE 14: Mean¹ Body Weight Changes (g) of Female Test and Control Groups, P-Exp

Treatment and Dose Level	Group	Day - 1 to Day - 0		Day 0 to Day + 1		Day 0 to Day + 4		Day 0 to Day + 7		Day 0 to Day + 11		Day 0 to Day + 14	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Distilled Water 10 mL/kg	N	- 1.020		0.14		- 0.060		2.10		3.06		8.86	
		+ 1.787	(5)	+ 1.48	(5)	+ 0.826	(5)	+ 1.27	(5)	+ 1.72	(5)	+ 3.93	(5)
P-Exp 1 mL/kg	Q	1.62		- 5.10 ^b		4.34 ^a		0.66		5.26		5.64	
		+ 1.27	(5)	+ 2.12	(5)	+ 2.23	(5)	+ 2.08	(5)	+ 2.21	(5)	+ 1.49	(5)
P-Exp 5 mL/kg	P	0.760		- 6.32 ^b		- 10.42 ^b		3.68		9.46 ^b		7.74	
		+ 1.074	(5)	+ 1.78	(5)	+ 3.30	(5)	+ 2.66	(5)	+ 2.14	(5)	+ 2.83	(5)
P-Exp 7.5 mL/kg	R	0.040		- 8.22 ^b		- 16.30 ^b		- 3.93 ^b		3.40		6.70	
		+ 0.573	(5)	+ 2.12	(5)	+ 5.84	(3)	+ 1.46	(3)	+ 0.46	(3)	+ 2.17	(3)
P-Exp 10 mL/kg	O	- 1.60		- 7.87 ^b		-		-		-		-	
		+ 2.11	(5)	+ 1.84	(3)	-	(0)	-		-		-	

1 * + Standard deviation

2 * Body Weight (g)

3 * Number of surviving animals indicated in parentheses

a * Significantly different from control (p < 0.05)

b * Significantly different from control (p < 0.01)

TABLE 5: Mean Body Weight Changes (g) of Male Test and Control Groups, P-2025

Treatment and Dose Level	Group	Day - 1	Day 0	Day 0	Day 0	Day 0	Day 0	Day 0	Day 0
		to Day - 0	to Day + 1	to Day + 4	to Day + 7	to Day + 11	to Day + 14	to Day + 14	to Day + 14
Distilled water 10 mL/kg	A	- 0.14	0.48	3.60	9.94	17.04	27.84		
		+ 0.921	+ 1.19	+ 2.60	+ 3.05	+ 4.63	+ 4.79		
		(5)3	(5)	(5)	(5)	(5)	(5)		
P-2025 1 mL/kg	H	2.72	- 2.56	8.30	8.06	16.10	20.72 ^a		
		+ 2.39	+ 1.30	+ 1.86	+ 3.47	+ 5.12	+ 5.18		
		(5)	(5)	(5)	(5)	(5)	(5)		
P-2025 5 mL/kg	G	2.78	-11.76 ^b	-17.62 ^b	1.02 ^b	11.68	17.10 ^b		
		+ 1.86	+ 4.13	+ 6.81	+ 4.04	+ 3.66	+ 5.28		
		(5)	(5)	(5)	(5)	(5)	(5)		
P-2025 7.5 mL/kg	I	2.36	-23.14 ^b	-46.34 ^b	-29.00 ^b	-5.98 ^b	6.22 ^b		
		+ 1.60	+ 2.69	+ 6.78	+ 5.29	+ 4.90	+ 3.89		
		(5)	(5)	(5)	(5)	(5)	(5)		
P-2025 10 mL/kg	F	0.42	-15.70 ^b	-	-	-	-		
		+ 2.06	+ 2.55	-	-	-	-		
		(5)	(4)	(0)					

1 = Standard deviation

2 = Body Weight (g)

3 = Number of surviving animals indicated in parentheses

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

TABLE 16: Mean¹ Body Weight Changes (g) of Female Test and Control Groups, P-2025

Treatment and Dose Level	Group	Day - 1		Day 0 ²	Day 0 to Day + 1		Day 0 to Day + 4		Day 0 to Day + 7		Day 0 to Day + 11		Day 0 to Day + 14	
		Mean	SD		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Distilled Water 10 mL/kg	N	- 1.020		149.80	0.14	- 0.060	2.10	3.06	8.86					
		+ 1.787 (5)		+ 8.68 (5)	+ 1.48 (5)	+ 0.826 (5)	+ 1.27 (5)	+ 1.72 (5)	+ 3.93 (5)					
P-2025 1 mL/kg	U	1.160 ^b		150.00	- 4.14 ^a	4.140 ^a	1.92	6.34	7.32 ^a					
		+ 0.971 (5)		+ 7.01 (5)	+ 3.78 (5)	+ 3.26 (5)	+ 3.09 (5)	+ 3.34 (5)	+ 2.14 (5)					
P-2025 5 mL/kg	T	1.260 ^b		151.88	- 9.62 ^b	- 9.52 ^b	1.96	6.70	5.58					
		+ 1.405 (5)		+ 7.28 (5)	+ 4.29 (5)	+ 3.21 (5)	+ 2.06 (5)	+ 2.62 (5)	+ 2.52 (5)					
P-2025 7.5 mL/kg	V	0.680		147.76	- 12.74 ^b	- 23.60 ^b	- 11.30 ^b	0.60	2.60					
		+ 0.622 (5)		+ 5.80 (5)	+ 1.36 (5)	(1)	(1)	(1)	(1)	(1)				
P-2025 10 mL/kg	S	- 1.720		149.24	- 6.94 ^b	-	-	-	-					
		+ 1.824 (5)		+ 11.20 (5)	+ 2.09 (5)	(0)	(0)	(0)	(0)	(0)				

1 = Standard deviation
 2 = Body Weight (g)
 3 = Number of surviving animals indicated in parentheses
 a = Significantly different from control (p < 0.05)
 b = Significantly different from control (p < 0.01)

TABLE 17: Mean Body Weight Changes (g) of Male Test and Control Groups, P-129C

Treatment and Dose Level	Group	Day - 1 to Day - 0		Day 02		Day 0 to Day + 1		Day 0 to Day + 4		Day 0 to Day + 7		Day 0 to Day + 11		Day 0 to Day + 14	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Distilled Water 1/5 mL/kg	A	- 0.14	215.84	0.48	- 3.60	9.94	17.04	27.84	17.04	9.94	17.04	27.84	17.04	9.94	27.84
		+ 0.921	+ 7.20	+ 1.19	+ 2.60	+ 3.05	+ 4.63	+ 4.79	+ 4.63	+ 3.05	+ 4.63	+ 4.79	+ 4.63	+ 3.05	+ 4.79
		(5)3	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
P-129C 1 mL/kg	L	2.32 ^a	214.02	- 7.26	- 0.54	2.25	13.82	18.82 ^a	13.82	2.25	13.82	18.82 ^a	13.82	2.25	18.82 ^a
		+ 0.867	+12.61	+12.10	+13.29	+10.54	+ 9.90	+ 9.51	+ 9.90	+10.54	+ 9.90	+ 9.51	+ 9.90	+10.54	+ 9.51
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
P-129C 5 mL/kg	K	1.96 ^a	220.94	-12.34 ^b	-17.00 ^b	1.14	10.74	17.20 ^a	-17.00 ^b	1.14	10.74	17.20 ^a	10.74	1.14	17.20 ^a
		+ 1.780	+ 6.31	+ 6.14	+ 5.70	+ 4.29	+ 4.42	+ 3.77	+ 5.70	+ 4.29	+ 4.42	+ 3.77	+ 4.42	+ 3.77	
		(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)	(5)
P-129C 7.5 mL/kg	M	2.38 ^a	229.96	-19.82 ^b	-30.65 ^b	-15.87 ^b	1.73 ^b	10.58 ^b	-30.65 ^b	-15.87 ^b	1.73 ^b	10.58 ^b	1.73 ^b	-15.87 ^b	10.58 ^b
		+ 1.556	+12.48	+ 2.75	+ 6.71	+ 9.76	+ 5.17	+ 4.66	+ 6.71	+ 9.76	+ 5.17	+ 4.66	+ 5.17	+ 4.66	+ 4.66
		(5)	(5)	(5)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
P-129C 10 mL/kg	J	- 0.100	215.72	-15.38 ^b	-59.80 ^b	-	-	-	-59.80 ^b	-	-	-	-	-	-
		+ 1.510	+ 3.29	+ 1.08	+ 1.56	-	-	-	+ 1.56	-	-	-	-	-	-
		(5)	(5)	(4)	(2)	(0)	(0)	(0)	(2)	(0)	(0)	(0)	(0)	(0)	(0)

1 = + Standard deviation
 2 = Body weight (g)
 3 = Number of surviving animals indicated in parentheses
 a = Significantly different from control (p < 0.05)
 b = Significantly different from control (p < 0.01)

TABLE 18: Mean¹ Body Weight Changes (g) of Female Test and Control Groups, P-129C

Treatment and Dose Level	Group	Day - 1 to Day - 0		Day 0 to Day + 1		Day 0 to Day + 4		Day 0 to Day + 7		Day 0 to Day + 11		Day 0 to Day + 14	
Distilled Water 10 mL/kg	N	-	1.020	0.14	- 0.060	2.10	3.06	8.86					
		+ 1.78/		+ 1.48	+ 0.826	+ 1.27	+ 1.72	+ 3.93					
		- (5)3		- (5)	- (5)	- (5)	- (5)	- (5)					
P-129C 1 mL/kg	Y	-	1.020 ^a	- 5.42 ^a	1.840	1.20	6.08	6.28					
		+ 1.190		+ 5.00	+ 3.302	+ 1.82	+ 3.61	+ 3.71					
		- (5)		- (5)	- (5)	- (5)	- (5)	- (5)					
P-129C 5 mL/kg	X	-	1.220	- 8.06 ^b	- 6.500 ^b	4.32 ^a	7.52	9.84					
		+ 1.112		+ 2.08	+ 1.91	+ 1.58	+ 1.92	+ 2.39					
		- (5)		- (5)	- (5)	- (5)	- (5)	- (5)					
P-129C 7.5 mL/kg	Z	-	1.800 ^b	-11.42 ^b	-14.00 ^b	- 3.40 ^b	3.50	6.60					
		+ 0.943		+ 5.23	+ (1)	+ (1)	+ (1)	+ (1)					
		- (5)		- (5)	- (5)	- (5)	- (5)	- (5)					
P-129C 10 mL/kg	W	-	0.360	- 1.70	- (0)	-	-	-					
		+ 1.436		+ (1)	+ (0)	+ (0)	+ (0)	+ (0)					
		- (5)		- (5)	- (0)	- (0)	- (0)	- (0)					

1 = Standard deviation

2 = Body weight (g)

3 = Number of surviving animals indicated in parentheses

4 = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

TABLE 19: Summary Incidence of Gross Necropsy Observations, P-Exp

GROUP	A		N		B		O		E		R		C		P		D		Q	
	Distilled Water 10 mL/kg		MALE	FEMALE																
GROSS LEVEL/TREATMENT	TYPE OF DEATH																			
GROSS NECROPSY OBSERVATIONS	Terminal Necropsy Spontaneous		4		4				4		3		5		4		5		5	
Lung: red discoloration mottled appearance	Terminal Necropsy Spontaneous		1		3				1				3		1					
Lung: red or brown foci	Terminal Necropsy Spontaneous																			
Liver: enlarged	Terminal Necropsy Spontaneous								1											
Liver: dark discoloration, mottled appearance	Terminal Necropsy Spontaneous								1											
Liver: yellow-brown discoloration	Terminal Necropsy Spontaneous						3		2		2									
Kidney: medulla congested, cortex pale	Terminal Necropsy Spontaneous		1						1		1				2					
Spleen: decreased size dark discoloration	Terminal Necropsy Spontaneous						4				1									

TABLE 20: Summary Incidence of Gross Necropsy Observations, F-2025
(cont'd)

GROUP	GROSS NECROPSY OBSERVATIONS	A		N		F		S		I		V		G		T		H		U	
		Distilled Water 10 mL/kg	MALE	FEMALE	P-2025 10 mL/kg	MALE	FEMALE	P-2025 7.5 mL/kg	MALE	FEMALE	P-2025 5.0 mL/kg	MALE	FEMALE	P-2025 1.0 mL/kg	MALE	FEMALE					
		TYPE OF DEATH																			
		Terminal Necropsy																			
		Spontaneous			2	3				2											
		Terminal Necropsy																			
		Spontaneous			3	4				3											
		Terminal Necropsy																			
		Spontaneous			1	1				3											
		Terminal Necropsy																			
		Spontaneous			1	3				2											
		Terminal Necropsy																			
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TABLE 20: Summary Incidence of Gross Necropsy Observations, P-2025
(cont'd)

GROUP	A	N	F	S	I	V	G	T	H	U
DOSE LEVEL/TREATMENT	Distilled Water 10 mL/kg		P-2025 10 mL/kg		P-2025 7.5 mL/kg		P-2025 5.0 mL/kg		P-2025 1.0 mL/kg	
GROSS NECROPSY OBSERVATIONS	TYPE OF DEATH		MALE		FEMALE		MALE		FEMALE	
Lymph node: dark dis- coloration (cervical)	Terminal									
	Necropsy									
	Spontaneous		3		4		1			
Pancreas: dark dis- coloration	Terminal									
	Necropsy									
	Spontaneous						3			
Peritoneum: green dis- coloration	Terminal									
	Necropsy									
	Spontaneous						4			

TABLE 22: Mean Organ Weights (g) and Organ Weight/Body Weight Ratios (mg/g) of Male Test and Control Groups¹

ORGAN	TREATMENT AND DOSE LEVEL			
	Group Distilled Water 10 mL/kg (n=5)	Group P-Exp 1 mL/kg (n=5)	Group P-Exp 5 mL/kg (n=5)	Group P-Exp 7.5 mL/kg (n=5)
Body Weight at Necropsy	243.68 ± 11.25	233.04 ± 30.59	244.14 ± 8.54	223.92 ± 19.34
Lung Weight	1.11 ± 0.54	1.03 ± 0.13	1.11 ± 0.70	1.01 ± 0.08
Lung Ratio	4.57 ± 0.21	4.42 ± 0.38	4.53 ± 0.30	4.51 ± 0.29
Liver Weight	11.79 ± 0.93	10.25 ± 1.74	11.77 ± 0.59	12.35 ± 0.97
Liver Ratio	48.35 ± 2.83	43.87 ± 3.08 ^a	48.22 ± 1.67	55.22 ± 1.75 ^b
Spleen Weight	0.56 ± 0.03	0.53 ± 0.04	0.50 ± 0.03 ^a	0.41 ± 0.04 ^b
Spleen Ratio	2.30 ± 0.18	2.30 ± 0.24	2.03 ± 0.08 ^a	1.82 ± 0.09 ^b
Rt. Kidney Wt.	1.08 ± 0.08	0.90 ± 0.25	1.04 ± 0.03	1.06 ± 0.05
Rt. Kidney Ratio	4.44 ± 0.21	3.86 ± 0.86	4.27 ± 0.13	4.75 ± 0.22
L. Kidney Wt.	1.05 ± 0.07	2.60 ± 3.55	1.04 ± 0.06	1.06 ± 0.09
L. Kidney Ratio	4.33 ± 0.21	11.32 ± 15.66	4.28 ± 0.23	4.74 ± 0.19
Testes Weight ²	3.55 ± 0.13	2.40 ± 1.14 ^a	2.30 ± 0.67 ^a	1.25 ± 0.29 ^u
Testes Ratio ²	14.59 ± 0.35	10.22 ± 4.33 ^a	9.36 ± 2.54 ^b	5.63 ± 1.39 ^b
Brain Weight	1.77 ± 0.03	1.62 ± 0.36	1.73 ± 0.03	1.71 ± 0.06
Brain Ratio	7.29 ± 0.31	7.03 ± 1.67	7.09 ± 0.14	7.67 ± 0.53

¹ = Animals surviving until completion of study

² = Combined weight

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

TABLE 23: Mean Organ Weights (g) and Organ Weight/Body Weight Ratios (mg/g) of Female Test and Control Groups¹

ORGAN	TREATMENT AND DOSE LEVEL			
	Group Distilled Water 10 mL/kg (n=5)	Group P-Exp 1 mL/kg (n=5)	Group P-Exp 5 mL/kg (n=5)	Group P-Exp 7.5 mL/kg (n=5)
Body Weight at Necropsy	158.66 \pm 12.38	157.14 \pm 5.01	158.36 \pm 9.96	150.97 \pm 2.68
Lung Weight	0.84 \pm 0.06	0.90 \pm 0.08	0.97 \pm 0.12	0.84 \pm 0.02
Lung Ratio	5.32 \pm 0.36	5.73 \pm 0.53	6.09 \pm 0.37	5.59 \pm 0.20
Liver Weight	5.51 \pm 2.30	6.13 \pm 0.31	6.55 \pm 0.56	7.18 \pm 0.26
Liver Ratio	34.11 \pm 17.66	39.07 \pm 2.44	41.35 \pm 1.38	47.55 \pm 1.89
Spleen Weight	0.42 \pm 0.03	0.40 \pm 0.02	0.40 \pm 0.06	0.35 \pm 0.02
Spleen Ratio	2.64 \pm 0.20	2.56 \pm 0.17	2.54 \pm 0.24	2.32 \pm 0.15
Rt. Kidney Wt.	0.73 \pm 0.06	0.70 \pm 0.04	0.68 \pm 0.07	0.70 \pm 0.01
Rt. Kidney Ratio	4.61 \pm 0.31	4.43 \pm 0.15	4.30 \pm 0.20	4.64 \pm 0.15
L. Kidney Wt.	0.69 \pm 0.06	0.69 \pm 0.02	0.68 \pm 0.06	0.70 \pm 0.01
L. Kidney Ratio	4.35 \pm 0.27	4.38 \pm 0.16	4.30 \pm 0.17	4.66 \pm 0.06
Ovary Weight ²	0.050 \pm 0.016	0.052 \pm 0.011	0.055 \pm 0.006	0.044 \pm 0.0210
Ovary Ratio ²	0.311 \pm 0.092	0.262 \pm 0.047	0.349 \pm 0.033	0.312 \pm 0.046
Brain Weight	2.51 \pm 1.94	1.70 \pm 0.04	1.65 \pm 0.06	1.70 \pm 0.08
Brain Ratio	16.26 \pm 13.53	10.82 \pm 0.45	10.45 \pm 0.69	11.28 \pm 0.34

1 = Animals surviving until completion of study

2 = Combined weight

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

TABLE 24: Mean Organ Weights (g) and Organ Weight/Body Weight Ratios (mg/g) of Male Test and Control Groups¹

ORGAN	TREATMENT AND DOSE LEVEL			
	Group Distilled Water 10 mL/kg (n=5)	Group P-2025 1 mL/kg (n=5)	Group P-2025 5 mL/kg (n=5)	Group P-2025 7.5 mL/kg (n=5)
Body Weight at Necropsy	243.68 ± 11.25	241.76 ± 13.43	241.14 ± 17.06	234.24 ± 9.75
Lung Weight	1.11 ± 0.54	1.10 ± 0.04	1.12 ± 0.10	1.09 ± 0.05
Lung Ratio	4.57 ± 0.21	4.55 ± 0.40	4.66 ± 0.21	4.66 ± 0.27
Liver Weight	11.79 ± 0.93	10.67 ± 1.08	11.37 ± 1.44	12.46 ± 0.88
Liver Ratio	48.35 ± 2.83	44.08 ± 2.55	46.99 ± 3.02	53.26 ± 4.24 ^a
Spleen Weight	0.56 ± 0.03	0.53 ± 0.04	0.50 ± 0.05	0.44 ± 0.04 ^b
Spleen Ratio	2.30 ± 0.18	2.19 ± 0.13	2.09 ± 0.11 ^a	1.89 ± 0.12 ^b
Rt. Kidney Wt.	1.08 ± 0.08	1.03 ± 0.09	1.05 ± 0.07	1.05 ± 0.06
Rt. Kidney Ratio	4.44 ± 0.21	4.26 ± 0.22	4.34 ± 0.18	4.48 ± 0.18
L. Kidney Wt.	1.05 ± 0.07	1.02 ± 0.07	1.06 ± 0.07	1.27 ± 0.41
L. Kidney Ratio	4.33 ± 0.21	4.23 ± 0.12	4.39 ± 0.22	5.48 ± 2.02
Testes Weight ²	3.55 ± 0.13	3.33 ± 0.89	2.31 ± 0.48 ^b	1.43 ± 0.07 ^b
Testes Ratio ²	14.59 ± 0.35	14.59 ± 0.35	13.78 ± 3.79 ^b	9.53 ± 1.46 ^b
Brain Weight	1.77 ± 0.03	1.76 ± 0.03	1.75 ± 0.07	1.74 ± 0.03
Brain Ratio	7.29 ± 0.31	7.29 ± 0.32	7.26 ± 0.33	7.44 ± 0.32

¹ Animals surviving until completion of study

² Combined weight

^a = Significantly different from control (p < 0.05)

^b = Significantly different from control (p < 0.01)

TABLE 25: Mean Organ Weights (g) and Organ Weight/Body Weight Ratios (mg/g) of Female Test and Control Groups¹

ORGAN	TREATMENT AND DOSE LEVEL			
	Group Distilled Water 10 mL/kg (n=5)	Group P-2025 1 mL/kg (n=5)	Group P-2025 5 mL/kg (n=5)	Group P-2025 7.5 mL/kg (n=5)
Body Weight at Necropsy	158.66 + 12.38	157.32 + 7.68	159.50 + 9.56	145.60 + -
Lung Weight	0.84 + 0.06	0.87 + 0.02	0.92 + 0.13	0.81 + - ²
Lung Ratio	5.32 + 0.36	5.55 + 0.40	5.75 + 0.49	5.56 + -
Liver Weight	5.51 + 2.30	6.12 + 0.67	6.45 + 0.53	6.18 + -
Liver Ratio	34.11 + 17.66	38.87 + 3.14	40.42 + 1.10	42.45 + -
Spleen Weight	0.42 + 0.03	0.44 + 0.02	0.40 + 0.03	0.29 + -
Spleen Ratio	2.64 + 0.20	2.83 + 0.14	2.52 + 0.08	1.99 + -
Rt. Kidney Wt.	0.73 + 0.06	0.66 + 0.06	0.71 + 0.03	0.63 + -
Rt. Kidney Ratio	4.61 + 0.31	4.19 + 0.25	4.46 + 0.15	4.33 + -
L. Kidney Wt.	0.69 + 0.06	0.65 + 0.05	0.68 + 0.04	0.67 + -
L. Kidney Ratio	4.35 + 0.27	4.13 + 0.26	4.28 + 0.10	4.60 + -
Ovary Weight ²	0.050+ 0.016	0.049+ 0.008	0.053+ 0.008	0.035+ -
Ovary Ratio ²	0.311+ 0.092	0.013+ 0.061	0.329+ 0.039	0.240+ -
Brain Weight	2.51 + 1.94	1.65 + 0.04	1.62 + 0.06	1.60 + -
Brain Ratio	16.26 + 13.53	16.48 + 0.55	10.20 + 0.48	10.99 + -

1 = Animals surviving until completion of study

2 = Combined weight

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

TABLE 26: Mean Organ Weights (g) and Organ Weight/Body Weight Ratios (mg/g) of Male Test and Control Groups¹

ORGAN	TREATMENT AND DOSE LEVEL			
	Group Distilled Water 10 mL/kg (n=5)	Group P-129C 1 mL/kg (n=5)	Group P-129C 5 mL/kg (n=5)	Group P-129C 7.5 mL/kg (n=5)
Body Weight at Necropsy	243.68 ± 11.25	232.84 ± 10.66	241.28 ± 9.07	236.27 ± 5.99
Lung Weight	1.11 ± 0.54	1.11 ± 0.05	1.29 ± 0.54	1.15 ± 0.08
Lung Ratio	4.57 ± 0.21	4.77 ± 0.24	5.29 ± 1.99	4.89 ± 0.44
Liver Weight	11.79 ± 0.93	11.11 ± 0.66	9.37 ± 5.05	12.41 ± 1.44
Liver Ratio	48.35 ± 2.83	47.74 ± 2.05	38.43 ± 20.27	52.44 ± 4.97
Spleen Weight	0.56 ± 0.03	0.52 ± 0.02	0.53 ± 0.09	0.46 ± 0.03
Spleen Ratio	2.30 ± 0.18	2.22 ± 0.09	2.21 ± 0.35	1.96 ± 0.14
Rt. Kidney Wt.	1.08 ± 0.08	1.02 ± 0.06	1.06 ± 0.04	1.04 ± 0.04
Rt. Kidney Ratio	4.44 ± 0.21	4.37 ± 0.22	4.38 ± 0.18	4.41 ± 0.14
L. Kidney Wt.	1.05 ± 0.07	1.02 ± 0.06	1.00 ± 0.06	1.05 ± 0.04
L. Kidney Ratio	4.33 ± 0.21	4.39 ± 0.23	4.16 ± 0.28	4.45 ± 0.07
Testes Weight ²	3.55 ± 0.13	3.27 ± 0.27	2.26 ± 0.12 ^b	1.17 ± 0.52 ^b
Testes Ratio ²	14.59 ± 0.35	14.02 ± 0.69	9.36 ± 0.47 ^b	4.97 ± 2.27 ^b
Brain Weight	1.77 ± 0.03	1.78 ± 0.03	1.75 ± 0.06	1.73 ± 0.03
Brain Ratio	7.29 ± 0.31	7.64 ± 0.27	7.29 ± 0.25	7.33 ± 0.32

¹ = Animals surviving until completion of study

² = Combined weight

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

TABLE 27: Mean Organ Weights (g) and Organ Weight/Body Weight Ratios (mg/g) of Female Test and Control Groups¹

ORGAN	TREATMENT AND DOSE LEVEL			
	Group Distilled Water 10 mL/kg (n=5)	Group P-129C 1 mL/kg (n=5)	Group P-129C 5 mL/kg (n=5)	Group P-129C 7.5 mL/kg (n=5)
Body Weight at Necropsy	158.66 ± 12.38	154.96 ± 4.13	159.38 ± 5.81	153.30 ± -
Lung Weight	0.84 ± 0.06	0.86 ± 0.04	0.93 ± 0.08	0.91 ± -
Lung Ratio	5.32 ± 0.36	5.54 ± 0.35	5.83 ± 0.48	5.94 ± -
Liver Weight	5.51 ± 2.30	5.92 ± 0.82	6.48 ± 0.35	6.77 ± -
Liver Ratio	34.11 ± 17.66	38.17 ± 4.81	40.65 ± 1.20	44.16 ± -
Spleen Weight	0.42 ± 0.03	0.39 ± 0.04	0.37 ± 0.05	0.34 ± -
Spleen Ratio	2.64 ± 0.20	2.53 ± 0.27	2.36 ± 0.41	2.22 ± -
Rt. Kidney Wt.	0.73 ± 0.06	0.65 ± 0.05	0.69 ± 0.02	0.70 ± -
Rt. Kidney Ratio	4.61 ± 0.31	4.21 ± 0.25	4.32 ± 0.03	4.57 ± -
L. Kidney Wt.	0.69 ± 0.06	0.64 ± 0.05	0.68 ± 0.07	0.65 ± -
L. Kidney Ratio	4.35 ± 0.27	4.12 ± 0.29	4.27 ± 0.33	4.24 ± -
Ovary Weight ²	0.050± 0.016	0.048± 0.006	0.052± 0.003	0.153± -
Ovary Ratio ²	0.311± 0.092	0.306± 0.035	0.330± 0.032	0.287± -
Brain Weight	2.51 ± 1.94	1.66 ± 0.05	1.69 ± 0.04	1.69 ± -
Brain Ratio	16.26 ± 13.53	10.72 ± 0.54	10.63 ± 0.22	11.02 ± -

1 = Animals surviving until completion of study

2 = Combined weight

a = Significantly different from control (p < 0.05)

b = Significantly different from control (p < 0.01)

DISCUSSION

Similar toxic effects were noted for all three Acculith products tested. In males, a dose related reduction in testicular and splenic weight as well as a slight increase in liver weights was observed. While no statistically significant differences were noted in liver and spleen weights between controls and Acculith-treated females, slight, dose-related effects on the weights of these organs relative to controls were apparent. It should be kept in mind that the greatest effect on these organs was at a dose level of 7.5 mL/kg in the males, and since very few females survived at this dose level, a statistically significant effect on these organs may have been masked by the premature death.

Significant neurological effects were seen, especially at the higher doses, both in males and females exposed to all three Acculith products. At the higher dose levels this consisted of prolonged (24 to 72 hours) sedation, unresponsiveness (to all but painful stimuli) and depressed muscle tone. Other notable effects included severe lacrimation, salivation, miosis, general weakness and labored respiration. These effects suggest that the compounds either directly or indirectly affected the parasympathetic nervous system.

Gastrointestinal irritation was a common finding at the higher dose levels with all three Acculith products tested. This consisted mainly of gastric mucosal erosions and hemorrhage.

As stated above, the principal toxic effects associated with Acculith exposure were similar for P-Exp, P-2025 and P-129. Slight variations were noted, however, in the incidence of these effects among the various Acculiths tested. The lethal effect of all three of the Acculiths tested was greater in females than in males.

Each of the three Acculith products tested consists of a mixture of three or more chemically similar compounds. The only component common to all three Acculiths is Varcum 5328B resin. It is unlikely that the toxicity of the mixtures are directly due to Varcum 5328B as a previous acute oral study on this material (ref. 3) failed to detect any significant signs of toxicity associated with Varcum 5328B. On the other hand, photosensitizer B, a component of both P-2025 and P-129C and chemically similar to a component of P-Exp., was shown in this same study to cause some neurobehavioral effects such as lacrimation, reduced motor activity and reduced respiration. This compound also had an effect on both spleen and testis, causing a reduction in the absolute weight of these organs relative to control values. Histopathological examination of the testes in the surviving animals dosed with photosensitizer B revealed epithelial degeneration and oligospermia in three of the four males in the 5 g/kg and one of five males in the 1 g/kg dose level groups. No such effect was noted in the control animals in that study. It should be pointed out however, that both the lethal, as well as the other toxic effects of photosensitizer B, were delayed; not occurring until at least five days post-exposure.

A third component of the three Acculith products tested in the present study is an ether of ethylene glycol; being the same compound in P-Exp and P-2025 and a structurally similar compound in P-129C. Significant neurobehavioral effects have been reported following oral exposure to ethylene glycol (ref. 4) including depression, drowsiness, coma, respiratory failure, convulsions and death. The ether components used in the Acculith mixtures could share similar effects with ethylene glycol. Moreover, oral LD₅₀ values for some ethers of ethylene glycol as well as ethylene glycol itself have been reported to range from roughly 2.5 to 5.8 g/kg (ref. 5). These values are in good agreement with the LD₅₀ values determined for P-Exp, P-2025 and P-129C in the present study when adjusted for the percent concentration of the ethers in the various mixtures.

Therefore, based on the observed toxicity of P-Exp, P-2025 and P-129 in the present study, predominantly lethality, neurological disturbances, and testicular and splenic weight effects, it would be difficult to associate these with any one component of the Acculith mixtures. It is quite possible that the observed toxicity of P-Exp, P-2025 and P-129C results from the combined effects of the various components of the mixtures and the combined toxicity represents an additive or possibly synergistic effect.

CONCLUSION

Acculith products P-Exp, P-2025 and P-129C caused death in Fischer 344 rats following oral exposures at dose levels of 7.5 mL/kg and higher. Oral LD₅₀ values ranged from roughly 8 to 9 mL/kg in males to 7-8 mL/kg in the females. The principal toxic effects of all three compounds occurred primarily in the central nervous system, digestive tract, testes, spleen and liver.

REFERENCES

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2. Snedecor, G.W. and Cochran, W.G. (1980), Statistical Methods. Iowa State University Press, Ames, Iowa, Seventh Edition.
3. Gad, S.C. (1983) Acculith Chemicals. Acute Oral Toxicity of 3 Acculiths. Allied Report MA-182-81-7.
4. The Merck Index Ed: P.G. Stacker, Merck and Co., Inc. Eight Edition, 1968.
5. Registry of Toxic Effects of Chemical Substances Ed: R.J. Lewis, Sr., U.S. Dept. of Health, Education and Welfare. 1978 edition.

APPENDIX A

ALLIED CORPORATION

MEMORANDUM

TO: S. C. GAD

4/26/83

FROM: M. J. DERELANKO

SUBJECT: TESTICULAR TOXICITY FOLLOWING ACUTE ORAL EXPOSURE TO ACCULITHS
MA-182A

Recent analysis of data generated in the acute oral toxicity study of Acculith products P-Exp, P-2025, and P-129C have revealed specific target organ effects on liver, spleen and testis based on both in-life clinical observations and post-mortem organ weights. To date, only the liver has been histologically examined revealing hepatic hypertrophy, vacuolation and central lobular necrosis fourteen days post-dosing. Spleen weights were significantly depressed in males receiving dose levels of 5 mL/kg and 7.5 mL/kg of all three Acculiths. Most disconcerting was a dose responsive reduction in testis weight parameters noted in surviving rats exposed to the three Acculith products. This data is presented in the accompanying table. Based on these results, I recommend that both testis and spleen be examined histologically to assess the extent of the damage to these organs.


MJD - 6090

/tab

attachment

cc: P.L. Foreman
G.M. Rusch
File



Memorandum

TO: M. J. Derelanko 4/29/83
FROM: G. M. Rusch
SUBJECT: ACCULITH CHEMICALS/BASELINE DATA
MA-182A

Testicular Toxicity Following Acute
Oral Exposure to Acculiths

I called Dan Levine today and discussed the results of the subject studies with him. The solvent used in P-129C is methyl cellosolve which is known to produce the testicular effect. The solvent in P-EXP and P-2025 is diglyme. It is unknown if these effects would also be associated with this solvent or other components in the mixture.

Since the Acculith product line is being reformulated, it was decided not to perform the recommended histological examination on tissues from the subject studies. Instead, this information will be communicated to the business area to underscore the need for prompt toxicological studies on new formulations as they become finalized. We should consider incorporating these recommendations (i.e. histopathology on the liver, spleen, and testes) in study protocols developed to evaluate the toxicity of these new formulations.


GMR - 3672

/amp

Attachment

cc: P. L. Foreman
S. C. Gad
D. Levine
File

ROBERT F. MCCONNELL, D.V.M., P.A.

CONSULTING PATHOLOGY SERVICES

PHONE 201-782-4674

December 7, 1982

DIPLOMATE
AMERICAN COLLEGE
OF
VETERINARY PATHOLOGISTS

807 WELLS ROAD
FLEMINGTON, NEW JERSEY 08824

TO: SHAYNE C. GAD, D.I.
MANAGER, MAMMALIAN TOXICOLOGY
ALLIED CORPORATION
MORRISTOWN, NEW JERSEY 07960

RE: DCF PROJECT MA-18-A ACUTE ORAL TOXICITY STUDY OF 3 AQUEOUS
SOLVENTS: P-EXP, P-2025, AND P-129C IN RATS 157/82

One hundred thirty male and female Fischer 344 rats were divided into groups of 5 ♂ and 5 ♀ each. Four groups of animals were allotted to each solvent group and dosed at 10, 7.5, 5.0, and 2.0 ml./kg. respectively. One group served as distilled water vehicle controls.

All rats received 1 oral dose of either the vehicle or test material at the prescribed levels and were then observed for any sign of toxicity. All rats at the 10 ml./kg. level became comatose shortly after the initial dose while only sporadic rats were affected similarly at the 7.5 ml./kg. dose level.

All rats at the 10 ml./kg. level died within the first 7 days of dosing. At the 7.5 ml./kg. level, deaths occurred as follows: P-EXP 2/5 ♀; P-2025 4/5 ♀; P-129C 1/5 ♂, 4/5 ♀. The remaining rats all survived until the 14-day study termination.

At the end of the test the survivors were sacrificed and necropsied. A limited selection of tissues were prepared for microscopic examination and included brain and spinal cord from all rats and liver and kidneys from control and high dose animals. The tissues were prepared routinely and stained with hematoxylin-phloxine eosin.

Kidneys from high dose and control rats were within normal histological limits. There was no histomorphological evidence of a treatment effect.

The livers from high dose rats, however, had changes judged to have been treatment related. They consisted of the following: hepatocyte enlargement (hypertrophy) either in a periportal or generalized

distribution pattern, hepatocyte cytoplasmic vacuolation, and hepatocyte necrosis of scattered cells usually near the central portion of the lobule or adjacent to larger veins.

The following chart shows the incidence of the liver alterations:

MICROSCOPIC ALTERATION - LIVER	GROUP			
	CONTROL	P-EXP	P-2025	P-129C
Hepatocyte hypertrophy	0/10	7/10	9/10	2/10
Hepatocyte necrosis of scattered individual cells	0/10	7/10	6/10	2/10
Hepatocyte cytoplasmic vacuolation	1/10	7/10	8/10	7/10

The hepatocyte hypertrophy was the most obvious liver alteration. It is a morphological change often associated with metabolic enzyme induction of the smooth endoplasmic reticulum. The hepatocyte vacuolation was not confirmed to have been lipid as special stains were not employed in the evaluation. The character of the deposits and their location, however, were often reminiscent of lipid.

Necrosis of scattered central lobular hepatocytes was considered to have been associated with a low level hepatotoxicity of each of the Acculith solvents.

All of the hepatocellular alterations were minimal in character and were considered to have been reversible in nature. It is doubtful that the alterations would have been present in any of the rats that survived for 14 days after the single oral administration of the compound.

The brains and spinal cords of all rats, including controls, had vacuolative changes in the myelinated tracts. The changes were more prominent in high dose rats which died than in any of the other animals. After reassessing the change, it was judged to have been an artifact of fixation and processing and accentuated due to post-mortem change. It was not considered to have been treatment related.

Shayne C. Gad, Ph.D.
Allied Corporation

- 3 -

December 7, 1982
Re: DOT Project MA-182A

In summation, the Acculith solvents P-EXP, P-2025, and P129C caused all rats at the 10 ml./kg. level and sporadic rats at the 7.5 ml./kg. level to become deeply anesthetized. The deep state of anesthesia resulted in the ultimate death of all high dose rats and several animals at the 7.5 ml./kg. level. Of the tissues evaluated, only the liver had changes associated with compound toxicity. It was of a low level and was not considered to have been of sufficient severity to have been the direct cause of the mortalities. The brain and kidney tissues were unaffected by the oral administration of the Acculith solvents.


ROBERT F. MCCONNELL, D.V.M.

DOT Allied Project
MA-182A
RFMc 157/82
12/7/82

LEGEND FOR TABLES

- N = tissue within normal histological limits
- 1, 2, 3 = degree of indicated change
- 1 = minimal
- 2 = mild
- 3 = moderate
- () = focal or localized change
- * = tissue not present for microscopic evaluation
- A = Autolysis, precludes complete evaluation
- = indicated change not present

RFMC 157/82
12/7/82

ALLIED CORPORATION
PROJECT MA-182A
ACUTE ORAL TOXICITY STUDY OF 3 ACCULITH SOLVENTS:
P-EXP, P-2025, AND P-129C IN RATS

INCIDENCE OF MICROSCOPIC FINDINGS

TABLE 2

GROUP SEX	SOLVENT P-EXP, 10 ml./kg.											
	B						0					
FATE: D = Died; T = Terminated	D	D	D	D	D	D	D	D	D	D	D	D
RAT NUMBER: AAJ, *AAK	961	936	934	915	912	979	023	986	039	027		
PATHOLOGY NUMBER: 82-0	636	637	650	651	653	623	624	636	639	647		
TISSUE/RESPONSE	N	N	N	N	N	N	N	N	N	N	N	N
BRAIN: Vacuolation, myelinated tracts of cerebellum and mid brain	3	3	1	1	1	1	2	1	3	2	2	2
SPINAL CORD: Vacuolation, myelinated tracts	2	1	-	1	1	1	2	1	2	2	2	2
LIVER: Central lobular hepatocyte vacuolation Generalized hepatocyte vacuolation Periportal hepatocyte vacuolation Hepatocyte hypertrophy, generalized Central lobular necrosis of scattered individual hepatocytes Hepatocyte hypertrophy, periportal Bacterial emboli/colony growth	1	2	-	-	-	-	1	2	2	2	3	2
KIDNEY: Dilated cortical tubules Cortical tubules with granular proteinaceous content Bacterial emboli	N	N	N	N	N	N	N	N	N	N	N	N

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PROJECT MA-182A
ACUTE ORAL TOXICITY STUDY OF 3 ACCULITH SOLVENTS:
P-EXP, P-2025, AND P-129C IN RATS

INCIDENCE OF MICROSCOPIC FINDINGS

TABLE 4

GROUP	SOLVENT P-129C													
	J ^σ							W ^s						
	D	D	D	D	D	D	D	D	D	D	D	D	D	D
SEX														
FATE: D = Died; T = Terminated														
RAT NUMBER: AAJ, -AAK	914	919	960	910	927	-028	987	975	976	-029				
PATHOLOGY NUMBER: 82-0	619	649	652	661	665	670	621	622	625	627				
TISSUE/RESPONSE														
BRAIN:														
Vacuolation, myelinated tracts of cerebellum and mid brain	N	N	N	N	3A	N	N	N	N	N	N	N	N	N
	1	1	2	1	-	1	1	1	2	-	1	1	2	-
SPINAL CORD:														
Vacuolation, myelinated tracts	N	N	N	N	3A	N	N	N	N	N	N	N	N	N
	1	1	1	-	2	1	2	1	2	-	1	1	2	-
LIVER:														
Central lobular hepatocyte vacuolation	1	3	-	2A	-	-	-	-	-	-	-	-	-	-
Generalized hepatocyte vacuolation	-	-	-	1	-	1	-	-	-	-	-	-	-	-
Periportal hepatocyte vacuolation	-	1	1	-	-	-	-	-	-	-	-	-	-	-
Hepatocyte hypertrophy, generalized	-	2	1	-	-	-	-	-	-	-	-	-	-	-
Central lobular necrosis of scattered individual hepatocytes	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatocyte hypertrophy, periportal	-	-	-	-	3	-	-	-	-	-	-	-	-	-
Bacterial emboli/colony growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
KIDNEY:														
Dilated cortical tubules	N	2	-	N	-	N	N	N	N	N	N	N	N	N
Cortical tubules with granular proteinaceous content	-	2	-	-	-	-	-	-	-	-	-	-	-	-
Bacterial emboli	-	-	-	-	3	-	-	-	-	-	-	-	-	-

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ALLIED CORPORATION
PROJECT MA-182A
ACUTE ORAL TOXICITY STUDY OF 3 ACCULITH SOLVENTS:
P-EXP, P-2025, AND P-129C IN RATS

INCIDENCE OF MICROSCOPIC FINDINGS

TABLE 6

GROUP	SOLVENT P-EXP 7.5 ml./kg.												
	E						R						
SEX	T	T	T	T	T	T	T	T	T	T	T	T	T
FATE: D = Died; T = Terminated	906	924	926	935	952	977	001	037	973	974			
RAT NUMBER: AAJ, *AAK	793	794	795	796	797	657	660	798	799	800			
PATHOLOGY NUMBER: 82-0													
TISSUE/RESPONSE	N	N	N	N	N	N	N	N	N	N	N	N	N
BRAIN: Vacuolation of myelinated tracts of cerebellum and mid brain	2	2	2	1	1	2	1	1	1	1	1	1	1
SPINAL CORD: Vacuolation, myelinated tracts	1	1	-	-	-	1	1	-	-	-	1	-	-

RFMC 157/82
12/7/82

ALLIED CORPORATION
PROJECT MA-182A
ACUTE ORAL TOXICITY STUDY OF 3 ACCULITH SOLVENTS:
P-EXP, P-2025, AND P-129C IN RATS

INCIDENCE OF MICROSCOPIC FINDINGS
TABLE 7

GROUP	SOLVENT P-2025 5.0 ml./kg.																							
	H [♂]						U [♀]						G [♂]						T [♀]					
SEX	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T
FATE: D = Died; T = Terminated																								
RAT NUMBER: AAJ, AAK	898	939	941	950	964	031-042	957	969	991	902	916	923	925	965	016	021	024	036	903					
PATHOLOGY NUMBER: 82-0	783	784	785	786	787	788	789	790	791	792	753	754	755	756	757	758	759	760	761	762				
TISSUE/RESPONSE																								
BRAIN: Vacuolation of myelinated tracts of cerebellum and mid brain	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
SPINAL CURD: Vacuolation, myelinated tracts	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	

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ALLIED CORPORATION
PROJECT MA-182A
ACUTE ORAL TOXICITY STUDY OF 3 ACCULITH SOLVENTS:
P-EXP, P-2025, AND P-129C IN RATS

INCIDENCE OF MICROSCOPIC FINDINGS

TABLE 8

GROUP	SOLVENT P-2025											
	7.5 ml./kg.											
SEX	M						F					
FATE:	D	T	T	T	T	T	D	D	D	D	D	D
RAT NUMBER: AAK, *AAK	891	911	947	949	956	011	019	038	002	994		
PATHOLOGY NUMBER: 82-0	801	802	803	804	805	662	663	664	666	806		
TISSUE/RESPONSE												
BRAIN:												
Vacuolation of myelinated tracts of cerebellum and mid brain	N	1	1	1	1	1	N	N	1	1	1	1
SPINAL CORD:												
Vacuolation, myelinated tracts	N	-	N	1	1	1	N	1	1	1	*	N 2

RFMc 157/82
12/7/82

ALLIED CORPORATION
PROJECT MA-182A
ACUTE ORAL TOXICITY STUDY OF 3 ACCULITH SOLVENTS:
P-EXP, P-2025, AND P-129C IN RATS

INCIDENCE OF MICROSCOPIC FINDINGS

TABLE 10

GROUP	SOLVENT P-129C											
	7.5 ml./kg.											
SEX	M						F					
FATE: D = Died; T = Terminated	D	T	T	T	D	D	D	T	T	T	D	D
RAT NUMBER: AAJ, *AAK	892	907	920	928	946	035	033	985	026	045		
PATHOLOGY NUMBER: 82-0	656	807	808	809	810	654	655	658	659	811		
TISSUE/RESPONSE	N	N	N	N	N	N	N	N	N	N	N	N
BRAIN: Vacuolation of myelinated tracts of cerebellum and mid brain	1	1	1	1	1	1	1	1	2	1	1	1
SPINAL CORD: Vacuolation, myelinated tracts	N	N	N	N	N	N	N	N	N	N	N	N

APPENDIX B

ALLIED CORPORATION
MORRISTOWN, NJ 07960

DEPARTMENT OF TOXICOLOGY
STUDY PROTOCOL

* Attach Test Material Submission Sheet

1. Study Title: Acute Oral Toxicity Study of 3 Acculith Solvents: P-EXP, P-2025 and P-129C.
2. Purpose and Objectives of the Study: To provide baseline data on the oral toxicity of 3 acculith solvents and, if possible, to determine an acute oral LD₅₀ in rats.
3. DOT Project Number: MA-182A
4. Test Location: MTC, CMA Building
5. Sponsoring Company: Chemical Company
6. Company Representative: B.F. Himmelsbach
7. DOT Liaison: G.M. Rusch
8. DOT Personnel Responsibilities:
 - Project Coordinator: S. C. Gad
 - Study Director: M.J. Derelanko
 - General Toxicology: B.J. Dunn; R.D. Walsh; S. Mulder; F.A. Gavigan;
M.J. Derelanko; W.J. Powers; S.C. Gad; K.M. Brand
 - Pathologist: H. Siegel
 - Necropsy Team: B.M. Hansen; C. Uber, and others to be arranged.
 - Histologist: F.B. Grossman
 - Animal Resources Section: G.H. Osman, Jr., C. Reilly, S.A. Dunn;
P.M. Wallace

9. Schedule:

Proposed Animal Arrival Date: 3/2/82
 Proposed Starting Date of Study: 3/22/82
 Proposed Dates of Terminal Sacrifice: 4/5/82 - 4/8/82
 Proposed Date of Final Report: 7/30/82

10. Test and Control Article Data:

	<u>P-EXP Test Substance</u>	<u>P-2025 Test Substance</u>	<u>P-129C Test Substance</u>	<u>Distilled Water Negative Control</u>
a. Identification (DOT Sample Number)	8185-30	8185-7	8168-97	N/A
b. Lot Number:	N/A	VXXA-131	C-237	N/A
c. Batch Number:	N/A	N/A	N/A	N/A
d. Date sample received:	2/16/82	1/13/82	12/9/81	N/A
e. Date of sample analysis report:	N/A	N/A	N/A	N/A
f. Purity:	99% +	99% +	99% +	99.7%
g. Shelf Life:	Greater than 1 yr.	Greater than 1 yr.	Greater than 1 yr.	Greater than 1 yr.
h. Storage Conditions:	At less than 100°C	At less than 100°C	At less than 100°C	At less than 100°C
i. Safety Precautions:	Normal toxicology laboratory practices to be not less than those described in Corporate Safety Manual and in SOP GTX-033.			
j. Stability:	Stable at room temperature.			
k. Material used to suspend test article:	None, materials are liquids			
1. Date of test/control article characterization report:	N/A			
m. Methods of synthesis, fabrication or derivation of test/control article:	See attached test material submission sheets.			

- n. Plan to determine uniformity of mixture and concentration of test/control article in mixture: N/A

11. Test Animals:

- a. Species: Rat
- b. Strain/Substrain: Fischer 344
- c. Source: Charles River, Kingston, N.Y.
- d. Weight at Study Initiation: female: 120-170 gm
male: 175-225 gm
- e. Method of Identification: Cage card and ear tag
- f. Housing (Number/Cage): One
- g. Quarantine: (Duration) Two Weeks
- h. Number to be used in Study: 50-65 Male 50-65 Female
- i. Reason for species selection: Historical and required by current regulations.
- j. Randomization: Via computerized method (GTX-025)

12. Study Duration: 14 days after dosing of animals

13. Method of Administration of Test Article: Gavage at start of test (in accordance with SOP GTX-008).

14. Justification for Method of Administration: Oral is a possible worker exposure route. Gavage is the most accurate method of delivery of a dose of a liquid to animals via this route.

15. Experimental Design (Identify groups, number of animals by sex, dosage levels, etc.)

Group	No. of animals		To receive one dose based on Body Weight
	Male	Female	
Dosing Control	5	5	10 mL/kg Distilled Water
<u>P-EXP</u> High Dose Group	5	5	Dose to be determined from probe study
Subsequent Test Groups	10-15	10-15	Lower dose levels as required
<u>P-2025</u> High Dose Group	5	5	Dose to be determined from probe study
Subsequent Test Groups	10-15	10-15	Lower dose levels as required
<u>P-129C</u> High Dose Group	5	5	Dose to be determined from probe study
Subsequent Test Groups	10-15	10-15	Lower dose levels as required
a. Interval sacrifice:	None		
b. Terminal sacrifice (animals/sex):	20 per sex on 4/5/82 15 per sex on 4/6/82 15 per sex on 4/7/82 15 per sex on 4/8/82 (if required)		
c. Starting of dosing (date):	3/22/82		
d. Animal Diet Data	Test Diet (Name/Brand): Purina Rodent Chow #5001 available <u>ad libitum</u> .*		
e. Drinking Water (Details, re: Supply, analysis, etc.):	Tap water <u>ad libitum</u> (analysis is done quarterly for Laboratory Animal Services) *		

* No known contaminants are expected to be present that would interfere with the conduct of this study.

- f. **Dosing Methods: (Give Details):** The test article will be administered by the gavage procedure outlined in SOP GTX-008. Animals will be weighed immediately prior to dosing according to SOP GTX-001 and doses will be based on that weight.
- g. **Methods for Determination of Dosing Levels.** The volume of test suspension administered to each animal will be recorded.
- h. **Observations: (Give details, i.e. clinical, body weights, water and food consumption, etc.).** All animals will be weighed 7 days prior to the dosing of the control group and on days -1, 0, 1, 4, 7, 11, and 14 (with day 0 being the day of dosing of each individual dose level group). The animals will be observed for morbidity and mortality at least twice a day (each morning and each afternoon) and clinical signs will be taken (in accordance with SOP GTX-005) at least once a day. Morbidity, mortality and clinical signs will be recorded immediately after observations are made. The neurobehavioral screen (SOP GTX-031) will be performed on all animals on the day of dosing.
- i. **Clinical Laboratory Studies (Details):** E/A
- j. **Anatomical Pathology: Acute Oral Toxicity Study in Rats**
Necropsy will be performed on each animal in the study. Each necropsy will be performed under the supervision of the pathologist.
 1. **Before the necropsy begins,** the pathologist will be supplied with a complete record of the clinical observations, and all clinical pathology data.
 2. **Sacrifice will be by CO₂ asphyxiation.** Rats will be examined within 16 hours of death during the standard work week. On weekends and holidays rats found dead will be refrigerated (not frozen) and examined on the next working day.
 3. **Gross examination**
 - (a) **External:** includes external inspection and palpation of the rat, and examination of all external orifices.
 - (b) **Internal:** examination of neck contents, all body cavities and their contents, and all major viscera. This includes the cranial cavity with exterior and cut surfaces of the brain; thoracic, abdominal, and pelvic cavities. The interior lining of the esophagus, stomach, and portions of the bowel will also be examined.

(c) Organ Weights

The following organs will be weighed: brain, lungs with trachea, liver, spleen, each kidney, each testis with epididymis, each ovary; and organs found abnormal on gross examination.

(d) Special Tissue Preparation

Lungs and bladder will be expanded with fixative before incision.

4. Histopathological Examination:

Discretion will be exercised by both the study director and the pathologist in the selection of tissues for histopathological examination. Factors which will influence the selection of tissues include mortality, survival time, clinical observations, gross necropsy findings and prior experience with the test materials.

Organs and tissues showing compound-related effects will be examined for all dosage and control groups. All tissues and organs showing gross pathological changes will be examined microscopically.

5. Trimming tissues will be as per SOP PAT-012.6. Histology will utilize hematoxylin and phloxin-eosin stains, and special stains as required (SOP PAT-013).7. Specimen preservation and retention: Portions of the following tissues and organs will be saved in fixative (10% neutral-buffered formalin): brain and cervical cord; lungs and trachea; heart; thymus and mediastinal contents; thyroid with parathyroids and larynx; lymph nodes from several sites; portions of stomach and bowel including duodenum, ileum, and colon; liver; spleen; pancreas; adrenals; kidneys; urinary bladder; testes with epididymides; ovaries, tubes, and uterus; and a portion of sternbrae with marrow and attached muscle. Testes with epididymides will be fixed in Bouin's solution, then stored in formalin.

Wet tissue will be saved one year from the final report of the apparent final toxicological study of the agent; blocks for two years; and tissue sections for ten years. These times will be modified to fit future EPA standards.

- k. Data Collection Storage and Retention:** Data will initially be recorded either on CIA record forms (for body weights, morbidity and mortality, or clinical signs) or in laboratory notebooks (for dosage calculations, doses, or other observations which may be made or required). Data sheets shall be prepared in advance of the study with animal numbers being entered as appropriate.

Specimens will be preserved and retained as specified in the appropriate Pathology SOPs.

m. Key Events:

Action Plan

<u>Action</u>	<u>Dates</u>
A. Weighing of animals	Dosing Date: March 15,21,22,23,26,29, 1982
1. One control and three test groups (high dose)	March 22 April 2,5, 1982
2. Subsequent test group(s)	Dosing Date: March 15,22,23,24,27,30, 1982
	March 23 April 3,6, 1982
	Dosing Date: March 15,23,24,25,28,31, 1982
	March 24 April 4,7, 1982
	Dosing Date: March 15,24,25,26,29, 1982
	March 25 April 1,5,8, 1982
B. Dosing via gavage	
1. One control and three test groups (high dose)	March 22, 1982
2. Subsequent test groups	March 23,24,25, 1982
C. Daily observation for mortality and morbidity (2X daily)	
1. One control and three test groups (high dose)	March 22 - April 5, 1982
2. Subsequent test groups	March 23 - April 5, 1982
D. Clinical Observations	
1. One control and three test groups (high dose)	March 22 - April 5, 1982
2. Subsequent test groups	March 23 - April 8, 1982
E. Neurobehavioral Screens	
1. One control and three test groups (high dose)	March 22, 1982
2. Subsequent test groups	March 23,24,25, 1982

F. Terminal Necropsies April 5,6,7,8, 1982

n. Quality Assurance/GLPs: This study will be conducted in compliance with existing GLP and QA regulations and guidelines. The results of this study are not intended for submission to a regulatory agency.

Prepared by: Michael J. Derelanko 3/4/82
Michael J. Derelanko, Ph.D. Date
Study Director

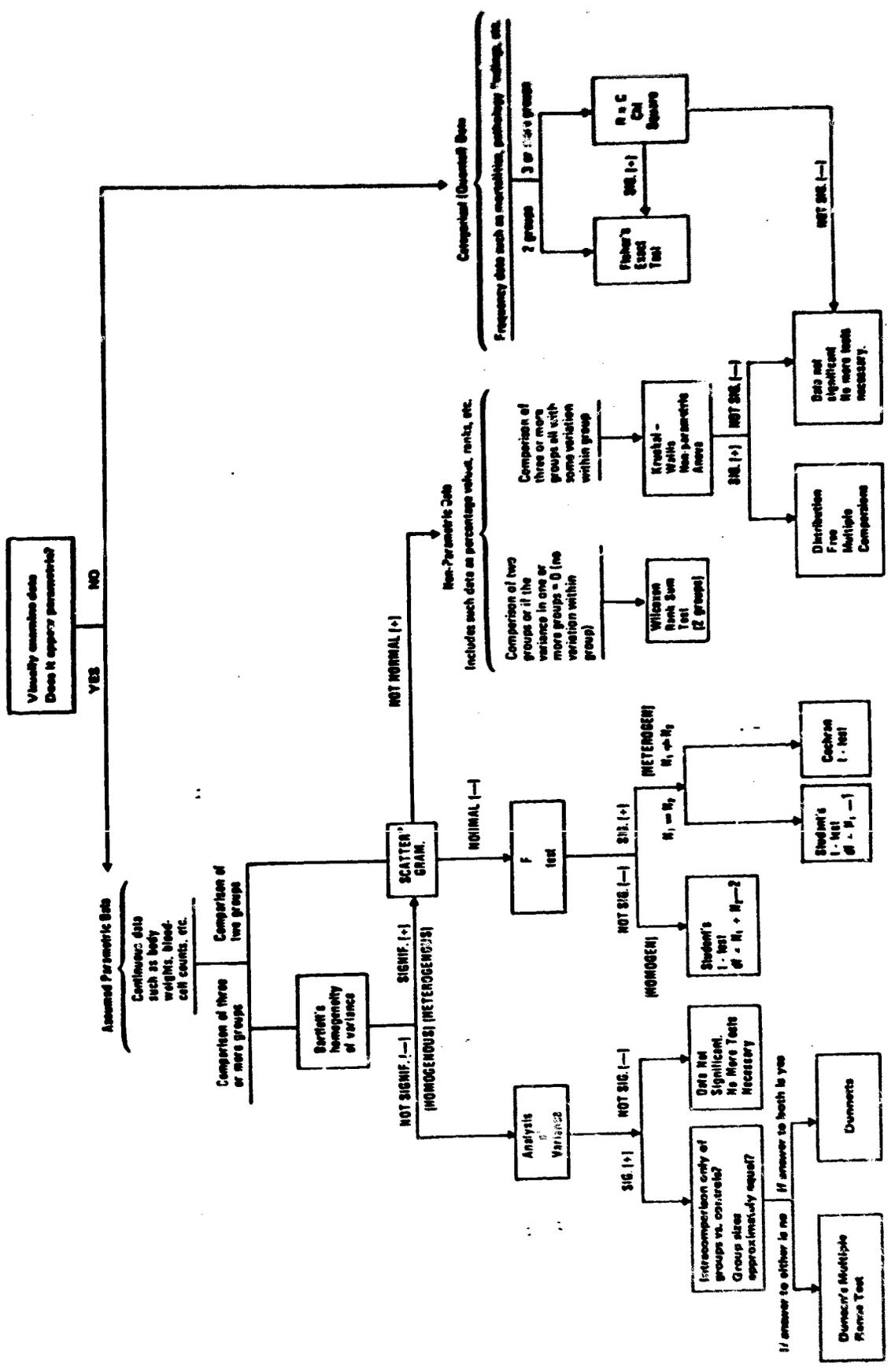
Reviewed by: Shayne C. Gad 3/4/82
Shayne C. Gad, Ph.D. Date
Project Coordinator & Manager, Mammalian Toxicology

Reviewed by: Robert F. McConnell 3/2/82
Robert F. McConnell, D.V.M. Date
Pathologist

Has this study been discussed at a staff meeting (YES/NO): NO
Study Director

Approved by: Ann C. Smith 3/16/82
Date
Quality Assurance Officer

FIGURE 1



* If p < .05: does not clearly demonstrate lack of normality exact tests may be employed.
 - If continuous data, Kolmogorov-Smirnov test.
 - If discontinuous data, Chi-Square G Goodness-of-Fit test may be used.

Contains No CBI