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~~8324~~

Great Lakes Chemical Corporation

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Research and Development

July 21, 1998

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ATTN: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460-0001

PDIN: 88970000268

RE: TSCA 8(e) Follow-up Submission of 2,4,6-Tribromophenol
(8EHQ-97-14018)
(When responding, please refer to DWA-98-24)

Gentlemen:

Great Lakes Chemical Corporation submitted a Section 8(e) substantial risk notification concerning an acute oral toxicity study of PH-73 (2,4,6-tribromophenol) in albino rats. The CAS Registry Number for this halogenated phenol is 118-79-6. The original submission was dated August 25, 1997. Enclosed with the follow-up submission, is a copy of the final study report for your files.

If you have any questions, please feel free to contact me at (765) 497-6637.

Sincerely,

Contains No CBI

Dennis W. Arnold

Dennis W. Arnold
Regulatory Toxicologist
Regulatory Affairs

DWA/da
enclosure

8EHQ-97-14018

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FINAL REPORT

Laboratory Project ID:

WIL Project No.: WIL-12389

Study Title

Acute Oral Toxicity Study of PH-73 in Albino Rats

Contracting Laboratory

WIL Research Laboratories, Inc.
1407 George Road
Ashland, OH 44805-9281

Study Director

Tom G. Kern, B.S.

Study Completed On:

December 8, 1997

Sponsor

Great Lakes Chemical Corporation
One Great Lakes Boulevard
West Lafayette, IN 47906

Acute Oral Toxicity Study of PH-73 in Albino Rats

COMPLIANCE STATEMENT

This study, designated WIL-12389, was conducted in compliance with the Environmental Protection Agency (EPA) Good Laboratory Practice Regulations (40 CFR Parts 160 and 792), the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice [C(81)30 (Final) Annex 2], the Ministry of International Trade and Industry (MITI), the European Economic Communities (EEC) guidelines and the Standard Operating Procedures of WIL Research Laboratories, Inc.

Study Director: _____ 12/8/97

Tom G. Kern, B.S. Date

Acute Oral Toxicity Study of PH-73 in Albino Rats

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Acute Oral Toxicity Study of PH-73 in Albino Rats

SUMMARY:

The acute oral toxicity potential of PH-73 was evaluated in this single-dose study in rats. The test material was administered once orally via gastric intubation to groups of five male and five female albino rats at dose levels of 2924, 3824 and 5000 mg/kg.

Mortality, pharmacotoxic signs, body weights and gross necropsy findings were evaluated.

All deaths were noted at one or three hours post-dosing on day 0. There were 2/10, 5/10 and 9/10 deaths for rats dosed at 2924, 3824 and 5000 mg/kg, respectively.

Clinical findings included various external material, hypoactivity, convulsions, clear ocular discharge, tremors and rales. There were no other clinical findings. All animals appeared normal by day 6 or earlier and throughout the remainder of the study.

There were no remarkable changes or differences observed in body weights during the study.

Gastrointestinal abnormalities were noted for all 16 rats that died during the study. Findings noted for one or two animals found dead included dark red lungs, dilated renal pelves, a reddened and prolapsed penis and distended ureters. Various external matting was observed on eight rats. There were no other gross necropsy findings for animals that died during the study.

There were no findings for any examined tissues at the terminal necropsy.

Based on the data obtained, the LD_{50} of PH-73 was calculated to be 3704 mg/kg with 95% confidence limits of 3163-4339 mg/kg when administered once orally via gastric intubation to fasted male and female rats.

Acute Oral Toxicity Study of PH-73 in Albino Rats

OBJECTIVE AND INTRODUCTION:

The objectives of this study were to determine the acute oral median lethal dose and evaluate potential systemic toxicity of the test material when administered as a single dose to albino rats.

The protocol was designed and the study was conducted in compliance with the principles of Good Laboratory Practice as described by the Environmental Protection Agency (40 CFR Parts 160 and 792) and the Organization for Economic Cooperation and Development (OECD), the Toxic Substances Control Act (TSCA) Health Effects Test Guidelines (40 CFR 798.1175), the OECD Guidelines for Testing of Chemicals (section 401) and the European Economic Communities (EEC) guidelines (Directive 92/69/EEC adaptation of 67/548/EEC, Annex V).

MATERIALS AND METHODS:

Study Title:	Acute Oral Toxicity Study of PH-73 in Albino Rats
WIL Study No.:	WIL-12389
Experimental Start Date:	July 31, 1997
Experimental Termination Date:	August 28, 1997
Test Facility:	WIL Research Laboratories, Inc. Ashland, OH 44805-9281
Study Sponsor:	Great Lakes Chemical Corporation One Great Lakes Boulevard West Lafayette, IN 47906
Study Director:	Tom G. Kern, B.S. Senior Group Supervisor - Acute Toxicology
Sponsor Representative:	John A. Biesemeier, B.S. Regulatory Toxicologist Regulatory Affairs

Test System:

Species:	Albino rat
Strain:	Crl:CD®(SD)BR
Justification for Species Selection:	The albino rat is generally recognized as appropriate for acute oral toxicity studies and considerable historical data are available.
Source:	Charles River Laboratories, Inc. Portage, MI
Number on Study:	Fifteen males and 15 females
Body Weight Range:	206 to 264 grams at initiation of dosing
Age at Start of Study:	Young adults approximately nine weeks old for males and 12 weeks old for females

Test System (continued):

Method of Identification: Monel metal eartag. Individual cage cards were affixed to each cage and displayed the animal number, group and study number.

Housing: Individual suspended wire-mesh cages elevated above cage-board which were changed at least three times per week. The animals were maintained by the animal husbandry staff of WIL Research Laboratories, Inc., in accordance with Standard Operating Procedures.

Quarantine: Upon receipt, each animal was inspected by a qualified technician and the rats judged to be in good health and suitable as test animals were acclimated to laboratory conditions for a minimum of seven days. All rats were initially weighed and permanently identified with an eartag. During the acclimation period each rat was observed twice daily for changes in general appearance and behavior.

Food and Water: PMI Feeds, Inc.© Certified Rodent LabDiet© 5002 and reverse osmosis-treated municipal water were provided *ad libitum*. Analysis of feed for the presence of heavy metals and pesticides was performed and provided by the manufacturer. Filters servicing the automatic watering system were changed regularly according to Standard Operating Procedures. Water supplying the laboratory was analyzed in accordance with Standard Operating Procedures. Contaminants were not present in animal feed or water at levels expected to interfere with the objectives of this study. Results of analyses are available upon Sponsor request.

Environmental Conditions: Controls were set to maintain temperature at 72° ± 4°F and a relative humidity of approximately 30-70%. Room temperature and relative humidity were recorded once daily. Temperatures ranged from 72.1°F to 72.7°F and relative humidity ranged from 40.2% to 47.5%. Light timers were calibrated to provide a 12-hour light/12-hour dark photoperiod.

Test Material Data:

Identification:	PH-73
Lot Number:	637149C2
Source:	Great Lakes Chemical Corporation South Plant 324 Southfield Cutoff El Dorado, AR 71730
Date Received:	July 3, 1997
Purity:	100% PH-73. A Certificate of Analysis is presented in Appendix A. Test material purity data are the responsibility of the Sponsor.
Stability:	Test material stability data are the responsibility of the Sponsor.
Physical Description:	White crystals
Storage Conditions:	Original container at room temperature

Test Material Preparation:

The ground test material was prepared for dosing as a weight-to-volume (w/v) suspension in 0.5% carboxymethylcellulose by weighing the appropriate amount of test material from the original container and diluting with sufficient vehicle to obtain the desired concentration. The formulation was mixed using an OMNI TH (tissue homogenizer) for approximately three minutes. A stir bar was added, and the preparation was maintained on a magnetic stir plate. Immediately prior to dosing, the preparation was mixed with an OMNI TH for 4-5 seconds and then an appropriate amount of test material for each animal was drawn into a syringe.

Route and Rationale of Test Material Administration:

The route of test material administration was oral by gastric intubation. This is a possible route of exposure in humans and is the standard for assessment of acute oral toxicity.

Method of Test Material Administration:

The rats were fasted approximately 18-20 hours prior to dosing. Feed was returned to the rats 3-4 hours after dosing.

Method of Test Material Administration: (continued)

Individual doses were calculated based on body weights taken just prior to dosing and a dose volume of 20 ml/kg.

The test material was administered orally via gastric intubation with ball-tipped oral dosing needles which were affixed to the appropriate size syringes. Feed was returned to the rats 3-4 hours after dosing.

Dose Level(s)/Group(s)/Treatment Regimen:

Three groups of five males and five females were administered single doses at levels of 2924, 3824 and 5000 mg/kg based on a dose volume of 20 ml/kg.

Initially, a 5000 mg/kg level was dosed using a 16-gauge oral dosing needle and a 15 ml/kg dose volume which resulted in 2/10 deaths. Due to the uneven distribution of clinical signs of toxicity which may have resulted from a non-uniform dosing suspension, the level was repeated based on a 20 ml/kg dose volume. In addition, the test material was stirred for an hour, mixed using an OMNI TH and administered via a 14-gauge cannula to ensure a uniform suspension was received. There were 9/10 deaths observed with the latest 5000 mg/kg level. Therefore, it was determined that the aforementioned actions and a 20 ml/kg dose volume were necessary to ensure accurate dose delivery. Data using the 15 ml/kg dose volume will be archived with the other data from this study but are not further discussed.

OBSERVATIONS:

Mortality:

The rats were observed at approximately 1, 3, and 4 hours post-dose on day 0 and twice daily (morning and afternoon) thereafter for 14 days.

Pharmacotoxic Signs:

The rats were observed at approximately 1, 3, and 4 hours post-dose on day 0 and once daily thereafter for 14 days.

Body Weights:

Body weights were obtained and recorded on study days -1, 0 (initiation), 7, and 14 (termination).

Necropsy:

Upon termination, surviving rats were euthanized by carbon dioxide asphyxiation. The major organ systems of the cranial, thoracic and abdominal cavities were examined for all animals.

RESULTS:

Mortality (Tables 1 and 5):

Dosage Level (mg/kg)	Study Day 0 M	Study Day 0 F	Study Day 1-14 M	Study Day 1-14 F	Total Mortality (no. dead/no. dosed) M	Total Mortality (no. dead/no. dosed) F	Total Mortality (no. dead/no. dosed) C
2924	1	1	-	-	1/5	1/5	2/10
3824	2	3	-	-	2/5	3/5	5/10
5000	5	4	-	-	5/5	4/5	9/10

M = Male F = Female C = Combined

Based on the data obtained, the following LD_{50} values and slopes (with 95% confidence limits) were calculated by the method of Litchfield and Wilcoxon:

	LD_{50} (95% confidence limits)	Slope (95% confidence limits)
Males:	3686 (2870-4734) mg/kg	1.22 (0.95-1.57)
Females:	3705 (2954-4647) mg/kg	1.37 (0.96-1.96)
Combined:	3704 (3163-4339) mg/kg	1.29 (1.06-1.58)

Pharmacotoxic Signs (Tables 1 and 5):

Clinical findings were noted in all dose groups. Various external material (described as wet and/or dried red, clear and/or yellow around the eye(s), nose, mouth, forelimb(s) and/or urogenital area) was noted on 18 rats. Seventeen and eleven animals were observed with hypoactivity and convulsions, respectively. Seven rats each had clear ocular discharge and tremors. A single female had rales. There were no other clinical findings. All animals appeared normal by day 6 or earlier and throughout the remainder of the study.

All deaths were noted on the day of dosing. There were 2/10, 5/10 and 9/10 deaths for rats dosed at 2924, 3824 and 5000 mg/kg, respectively.

Body Weights (Tables 2 and 6):

There were no remarkable changes or differences observed in body weights during the study.

RESULTS (continued):

Necropsy (Tables 3, 4, 7 and 8):

Sixteen rats that died had white fluid and/or thick white contents in the intestine and/or stomach. Dark red lungs were noted for two animals. Single rats each had dilated renal pelves, distended ureters or a reddened, prolapsed penis. Eight animals had various external matting (red, clear and/or yellow around the eye(s), nose, mouth and/or urogenital area). There were no other gross necropsy findings for animals that died.

There were no findings for animals that survived to the scheduled necropsy.

DISCUSSION AND CONCLUSIONS:

Clinical findings included various external material, hypoactivity, convulsions, clear ocular discharge, tremors and rales. There were no other clinical findings. All animals appeared normal by day 6 or earlier and throughout the remainder of the study.

There were no remarkable changes or differences observed in body weights during the study.

Gastrointestinal abnormalities were noted for all 16 rats that died during the study. Findings noted for one or two animals found dead included dark red lungs, dilated renal pelves, a reddened and prolapsed penis and distended ureters. Various external matting was observed on eight rats. There were no other gross necropsy findings for animals that were found dead during the study.

There were no findings for any examined tissues at the terminal necropsy.

Based on the data obtained, the LD_{50} of PH-73 was calculated to 3704 mg/kg with 95% confidence limits of 3163-4339 mg/kg when administered once orally via gastric intubation to fasted male and female rats.

Tom G. Kern, B.S.
Study Director

12/8/97
Date

PERSONNEL AND REPORT SUBMISSION:

Key Personnel:

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Director of Metabolism and Analytical Chemistry

Carney B. Jackson, D.V.M., D.A.C.V.P., D.A.C.V.P.M.
Assistant Director of Pathology and Veterinary Medicine

Tammye Fleeman, B.S.
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Anita F. Wilmot, B.S.
Biologist II/Report Writer II - Acute Toxicology

12/8/97
Date

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Gary R. Kiplinger, B.S.
Manager of General Toxicology

12/8/97
Date

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Acting Assistant Director of Toxicology

12/8/97
Date

Approved and Submitted By:

Tom G. Kern, B.S.
Study Director

12/8/97
Date

QUALITY ASSURANCE UNIT STATEMENT:

Date(s) of Inspection(s)	Phase Inspected	Date(s) Findings Reported to Study Director	Date(s) Findings Reported to Management
7/18/97	Clinical Observations	7/18/97	8/29/97
7/31/97	Animal Care/Equipment	7/31/97	8/29/97
9/11-12/97	Study Records (I-1)	9/12/97	10/27/97
9/12/97	Draft Report	9/12/97	10/27/97

This study was conducted and inspected in accordance with the Good Laboratory Practice Regulations, the Standard Operating Procedures of WIL Research Laboratories, Inc., and the protocol and protocol amendment(s), if any. Quality Assurance findings, derived from the inspection(s) during the conduct of the study and from the inspections of the raw data and draft report, are documented and have been reported to the Study Director. A status report is submitted to management monthly.

The raw data, the retention sample(s), if applicable, and the final report will be stored in the Archives at WIL Research Laboratories, Inc., or another location specified by the Sponsor.

Deborah L. Little
Manager of Quality Assurance

12/8/97
Date

Acute Oral Toxicity Study of PH-73 in Albino Rats

Tables 1-8

PROJECT NO.:WIL-12389R

TABLE 1
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
SUMMARY OF PHARMACOTOXIC SIGNS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- M A L E -----

TABLE RANGE: DAY 0 TO DAY 14			
GROUP:	1	2	3
DISPOSITION			
-FOUND DEAD AT OBSERVATION	1/ 1	2/ 2	5/ 5
-TERMINAL NECROPSY	4/ 4	3/ 3	0/ 0
ACUTES			
-APPEARED NORMAL	46/ 4	40/ 3	0/ 0
-FOUND DEAD	1/ 1	2/ 2	5/ 5
-CONVULSIONS	5/ 3	3/ 3	1/ 1
-HYPOACTIVE	7/ 5	8/ 5	1/ 1
-WET YELLOW MATERIAL UROGENITAL AREA	8/ 4	4/ 3	0/ 0
-WET CLEAR MATERIAL AROUND MOUTH	6/ 4	2/ 2	0/ 0
-CLEAR OCULAR DISCHARGE	2/ 1	1/ 1	0/ 0
-TREMORS	2/ 2	0/ 0	0/ 0
-DRIED YELLOW MATERIAL UROGENITAL AREA	8/ 3	4/ 2	0/ 0
-DRIED YELLOW MATERIAL AROUND MOUTH	2/ 1	0/ 0	0/ 0
-DRIED RED MATERIAL AROUND NOSE	13/ 4	4/ 2	0/ 0
-DRIED RED MATERIAL AROUND MOUTH	2/ 1	0/ 0	0/ 0
-DRIED RED MATERIAL ON FORELIMB(S)	2/ 1	0/ 0	0/ 0
-DRIED RED MATERIAL AROUND EYE(S)	2/ 1	0/ 0	0/ 0

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG

TABLE 1
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
SUMMARY OF PHARMACOTOXIC SIGNS: TOTAL OCCURRENCE/NO. OF ANIMALS

----- F E M A L E -----

TABLE RANGE: DAY 0 TO DAY 14			
GROUP:	1	2	3
DISPOSITION			
-FOUND DEAD AT OBSERVATION	1/ 1	3/ 3	4/ 4
-TERMINAL NECROPSY	4/ 4	2/ 2	1/ 1
ACUTES			
-APPEARED NORMAL	61/ 4	27/ 2	9/ 1
-FOUND DEAD	1/ 1	3/ 3	4/ 4
-CONVULSIONS	1/ 1	2/ 2	1/ 1
-HYPOACTIVE	1/ 1	5/ 4	1/ 1
-WET YELLOW MATERIAL UROGENITAL AREA	2/ 1	2/ 2	3/ 1
-WET CLEAR MATERIAL AROUND MOUTH	1/ 1	1/ 1	3/ 1
-RALES	0/ 0	0/ 0	3/ 1
-CLEAR OCULAR DISCHARGE	1/ 1	3/ 3	2/ 1
-TREMORS	4/ 4	0/ 0	2/ 1
-DRIED YELLOW MATERIAL UROGENITAL AREA	2/ 2	4/ 1	5/ 1
-DRIED YELLOW MATERIAL AROUND MOUTH	0/ 0	0/ 0	2/ 1
-DRIED RED MATERIAL AROUND NOSE	0/ 0	1/ 1	0/ 0

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG

PROJECT NO.:WIL-12389R

TABLE 2
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- M A L E -----		
	GROUP:	2924 MG/KG	3824 MG/KG	5000 MG/KG
DAY -1				
	MEAN	281.	284.	260.
	S.D.	4.1	0.7	8.2
	N	5	5	5
0				
	MEAN	256.	254.	238.
	S.D.	5.2	3.0	7.7
	N	5	5	5
7				
	MEAN	288.	291.	NA
	S.D.	7.0	9.8	
	N	4	3	
14				
	MEAN	323.	339.	NA
	S.D.	8.1	5.5	
	N	4	3	

NA = NOT APPLICABLE

TABLE 2
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
BODY WEIGHTS (GRAMS) - SUMMARY OF MEANS

		----- F E M A L E -----		
	GROUP:	2924 MG/KG	3824 MG/KG	5000 MG/KG
DAY -1				
	MEAN	236.	250.	226.
	S.D.	1.1	0.9	3.6
	N	5	5	5
0				
	MEAN	216.	232.	210.
	S.D.	1.9	1.1	3.2
	N	5	5	5
7				
	MEAN	236.	255.	240.
	S.D.	0.8	7.8	0.0
	N	4	2	1
14				
	MEAN	248.	271.	249.
	S.D.	6.6	12.7	0.0
	N	4	2	1

PROJECT NO.:WIL-12389R

TABLE 3
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
GROSS NECROPSY OBSERVATIONS INCIDENCE SUMMARY

FOUND DEAD OR EUTHANIZED MORIBUND OR IN EXTREMIS

	MALE			FEMALE		
GROUP:	1	2	3	1	2	3
NUMBER OF ANIMALS IN DOSE GROUP	5	5	5	5	5	5
NUMBER OF ANIMALS EXAMINED	1	2	5	1	3	4
INTESTINE						
-WHITE FLUID CONTENTS	0	0	0	0	0	4
KIDNEYS						
-DILATED PELVIS	0	0	0	0	0	1
LUNGS						
-DARK RED	1	0	0	1	0	0
STOMACH						
-WHITE FLUID CONTENTS	0	0	5	0	0	2
-THICK WHITE CONTENTS	1	2	0	1	3	2
EXTERNAL SURFACE						
-RED MATTING	1	0	5	0	0	1
-CLEAR MATTING	1	0	0	1	0	0
-YELLOW MATTING	1	0	0	1	0	0
PENIS						
-REDDENED	0	0	1	0	0	0
-PROLAPSED	0	0	1	0	0	0
URETER(S)						
-DISTENDED	0	0	0	0	0	1
NO SIGNIFICANT CHANGES OBSERVED - ALL EXAMINED TISSUES	0	0	0	0	0	0

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG

PROJECT NO.:WIL-12389R

TABLE 4
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
GROSS NECROPSY OBSERVATIONS INCIDENCE SUMMARY

SCHEDULED NECROPSY

GROUP:	MALE 1	MALE 2	MALE 3	FEMALE 1	FEMALE 2	FEMALE 3
NUMBER OF ANIMALS IN DOSE GROUP	5	5	5	5	5	5
NUMBER OF ANIMALS TERMINALLY EUTHANIZED	4	3	0	4	2	1
NO SIGNIFICANT CHANGES OBSERVED - ALL EXAMINED TISSUES	4	3	0	4	2	1

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG

PROJECT NO.:WIL-12389R

TABLE 5
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL PHARMACOTOXIC SIGNS

OBSERVATION	NO.	SEX	GRP	HOUR POST-DOSE 1	3	4	DAY POST-DOSE 1	2	3	4	5	6	7	8	9	10	11	12	13	14
APPEARED NORMAL	73189	M	1	-	-	-	-	-	-	P	P	P	P	P	P	P	P	P	P	P
	73190	M	1	-	-	-	-	-	-	P	P	P	P	P	P	P	P	P	P	P
	73196	M	1	-	-	-	-	-	-	-	P	P	P	P	P	P	P	P	P	P
	73200	M	1	-	-	-	P	P	P	P	P	P	P	P	P	P	P	P	P	P
	73521	M	2	-	-	-	-	-	-	P	P	P	P	P	P	P	P	P	P	P
	73548	M	2	P	-	-	P	P	P	P	P	P	P	P	P	P	P	P	P	P
	73551	M	2	P	-	-	-	P	P	P	P	P	P	P	P	P	P	P	P	P
	73208	F	1	-	-	-	P	P	P	P	P	P	P	P	P	P	P	P	P	P
	73220	F	1	-	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
	73222	F	1	-	P	P	-	P	P	P	P	P	P	P	P	P	P	P	P	P
	73225	F	1	P	P	P	P	-	P	P	P	P	P	P	P	P	P	P	P	P
	73559	F	2	P	-	-	-	-	-	-	P	P	P	P	P	P	P	P	P	P
	73571	F	2	P	P	-	P	P	P	P	P	P	P	P	P	P	P	P	P	P
	72970	F	3	-	-	-	-	-	-	-	-	P	P	P	P	P	P	P	P	P
FOUND DEAD	73193	M	1	-	P															
	73538	M	2	-	P															
	73552	M	2	-	P															
	72939	M	3	P																
	72944	M	3	-	P															
	72945	M	3	P																
	72947	M	3	P																
	72948	M	3	P																

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG
GRP = GROUP
GRADE CODE: P = PRESENT S = SLIGHT M = MODERATE V = SEVERE - = NOT SEEN AT THAT INTERVAL
SEX CODE: M = MALE F = FEMALE

TABLE 5
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL PHARMACOTOXIC SIGNS

OBSERVATION	NO.	SEX	GRP	HOUR POST-DOSE 1	3	4	DAY POST-DOSE 1	2	3	4	5	6	7	8	9	10	11	12	13	14
FOUND DEAD	73212	F	1	-	P															
	73555	F	2	-	P															
	73567	F	2	-	P															
	73590	F	2	P																
	72949	F	3	P																
	72956	F	3	P																
	72961	F	3	P																
	72969	F	3	P																
CONVULSIONS	73189	M	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73193	M	1	P	-															
	73196	M	1	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73521	M	2	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73538	M	2	P	-															
	73552	M	2	P	-															
	72944	M	3	P	-															
	73212	F	1	P	-															
	73555	F	2	P	-															
	73567	F	2	P	-															
	72970	F	3	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HYPOACTIVE	73189	M	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73190	M	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73193	M	1	P	-															

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG
GRP = GROUP
GRADE CODE: P = PRESENT S = SLIGHT M = MODERATE V = SEVERE - = NOT SEEN AT THAT INTERVAL
SEX CODE: M = MALE F = FEMALE

TABLE 5
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL PHARMACOTOXIC SIGNS

OBSERVATION	NO.	SEX	GRP	HOUR POST-DOSE 1	3	4	DAY POST-DOSE 1	2	3	4	5	6	7	8	9	10	11	12	13	14
HYPOACTIVE	73196	M	1	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73200	M	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73521	M	2	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73538	M	2	P	-															
	73548	M	2	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73551	M	2	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73552	M	2	P	-															
	72944	M	3	P	-															
	73212	F	1	P	-															
	73555	F	2	P	-															
	73559	F	2	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73567	F	2	P	-															
	73571	F	2	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	72970	F	3	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
WET YELLOW MATERIAL UROGENITAL AREA	73189	M	1	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73190	M	1	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73193	M	1	P	-															
	73196	M	1	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73521	M	2	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73548	M	2	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73552	M	2	P	-															
	73208	F	1	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG
GRP = GROUP
GRADE CODE: P = PRESENT S = SLIGHT M = MODERATE V = SEVERE - = NOT SEEN AT THAT INTERVAL
SEX CODE: M = MALE F = FEMALE

TABLE 5
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL PHARMACOTOXIC SIGNS

OBSERVATION	NO.	SEX	GRP	HOUR POST-DOSE 1	3	4	DAY POST-DOSE 1	2	3	4	5	6	7	8	9	10	11	12	13	14
WET YELLOW MATERIAL UROGENITAL AREA	73555	F	2	P	-															
	73559	F	2	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	72970	F	3	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
WET CLEAR MATERIAL AROUND MOUTH	73189	M	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73193	M	1	P	-															
	73196	M	1	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73200	M	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73538	M	2	P	-															
	73552	M	2	P	-															
	73212	F	1	P	-															
	73567	F	2	P	-															
	72970	F	3	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
RALES	72970	F	3	-	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-
CLEAR OCULAR DISCHARGE	73196	M	1	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73538	M	2	P	-															
	73212	F	1	P	-															
	73555	F	2	P	-															
	73559	F	2	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73567	F	2	P	-															
	72970	F	3	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TREMORS	73190	M	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73200	M	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG
GRP = GROUP
GRADE CODE: P = PRESENT S = SLIGHT M = MODERATE V = SEVERE - = NOT SEEN AT THAT INTERVAL
SEX CODE: M = MALE F = FEMALE

TABLE 5
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL PHARMACOTOXIC SIGNS

OBSERVATION	NO.	SEX	GRP	HOUR POST-DOSE 1	3	4	DAY POST-DOSE 1	2	3	4	5	6	7	8	9	10	11	12	13	14
TREMORS	73208	F	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73220	F	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73222	F	1	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73225	F	1	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-
	72970	F	3	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DRIED YELLOW MATERIAL UROGENITAL AREA	73189	M	1	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-
	73190	M	1	-	-	-	P	P	P	-	-	-	-	-	-	-	-	-	-	-
	73196	M	1	-	-	-	P	P	P	P	-	-	-	-	-	-	-	-	-	-
	73521	M	2	-	-	-	P	P	P	-	-	-	-	-	-	-	-	-	-	-
	73548	M	2	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73222	F	1	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-
	73225	F	1	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-
	73559	F	2	-	-	-	P	P	P	P	-	-	-	-	-	-	-	-	-	-
	72970	F	3	-	-	-	P	P	P	P	P	-	-	-	-	-	-	-	-	-
DRIED YELLOW MATERIAL AROUND MOUTH	73189	M	1	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	72970	F	3	-	-	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-
DRIED RED MATERIAL AROUND NOSE	73189	M	1	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-
	73190	M	1	P	P	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-
	73196	M	1	P	P	P	-	P	-	-	-	-	-	-	-	-	-	-	-	-
	73200	M	1	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	73521	M	2	-	P	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-
	73551	M	2	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG
GRP = GROUP
GRADE CODE: P = PRESENT S = SLIGHT M = MODERATE V = SEVERE - = NOT SEEN AT THAT INTERVAL
SEX CODE: M = MALE F = FEMALE

TABLE 5
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL PHARMACOTOXIC SIGNS

OBSERVATION	NO.	SEX	GRP	HOUR POST-DOSE 1	3	4	DAY POST-DOSE 1	2	3	4	5	6	7	8	9	10	11	12	13	14
DRIED RED MATERIAL AROUND NOSE	73559	F	2	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DRIED RED MATERIAL AROUND MOUTH	73200	M	1	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DRIED RED MATERIAL ON FORELIMB(S)	73200	M	1	-	P	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DRIED RED MATERIAL AROUND EYE(S)	73189	M	1	-	-	-	-	P	P	-	-	-	-	-	-	-	-	-	-	-

1- 2924 MG/KG 2- 3824 MG/KG 3- 5000 MG/KG
GRP = GROUP
GRADE CODE: P = PRESENT S = SLIGHT M = MODERATE V = SEVERE - = NOT SEEN AT THAT INTERVAL
SEX CODE: M = MALE F = FEMALE

PROJECT NO.:WIL-12389R

TABLE 6
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL BODY WEIGHTS (GRAMS)

MALE GROUP: 2924 MG/KG

DAY	-1	0	7	14
ANIMAL				
73189	278.	252.	279.	314.
73190	278.	256.	289.	319.
73193	278.	251.	NA	NA
73196	287.	264.	289.	331.
73200	283.	258.	296.	329.
MEAN	281.	256.	288.	323.
S.D.	4.1	5.2	7.0	8.1
N	5	5	4	4

NA = NOT APPLICABLE

TABLE 6
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL BODY WEIGHTS (GRAMS)

MALE GROUP: 3824 MG/KG

DAY	-1	0	7	14
ANIMAL				
73521	284.	257.	297.	345.
73538	284.	254.	NA	NA
73548	285.	251.	297.	339.
73551	284.	258.	280.	334.
73552	283.	252.	NA	NA
MEAN	284.	254.	291.	339.
S.D.	0.7	3.0	9.8	5.5
N	5	5	3	3

NA = NOT APPLICABLE

TABLE 6
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL BODY WEIGHTS (GRAMS)

MALE GROUP: 5000 MG/KG

DAY	-1	0
ANIMAL		
72939	247.	225.
72944	267.	242.
72945	265.	242.
72947	265.	244.
72948	258.	238.
MEAN	260.	238.
S.D.	8.2	7.7
N	5	5

TABLE 6
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL BODY WEIGHTS (GRAMS)

FEMALE GROUP: 2924 MG/KG

DAY	-1	0	7	14
ANIMAL				
73208	237.	215.	236.	255.
73212	236.	219.	NA	NA
73220	235.	217.	237.	249.
73222	236.	214.	236.	247.
73225	234.	217.	235.	239.
MEAN	236.	216.	236.	248.
S.D.	1.1	1.9	0.8	6.6
N	5	5	4	4

NA = NOT APPLICABLE

TABLE 6
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL BODY WEIGHTS (GRAMS)

FEMALE GROUP: 3824 MG/KG

DAY	-1	0	7	14
ANIMAL				
73555	251.	233.	NA	NA
73559	249.	230.	249.	262.
73567	250.	232.	NA	NA
73571	249.	232.	260.	280.
73590	249.	232.	NA	NA
MEAN	250.	232.	255.	271.
S.D.	0.9	1.1	7.8	12.7
N	5	5	2	2

NA = NOT APPLICABLE

TABLE 6
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL BODY WEIGHTS (GRAMS)

FEMALE GROUP: 5000 MG/KG

DAY	-1	0	7	14
ANIMAL				
72949	221.	206.	NA	NA
72956	229.	214.	NA	NA
72961	227.	208.	NA	NA
72969	230.	212.	NA	NA
72970	225.	209.	240.	249.
MEAN	226.	210.	240.	249.
S.D.	3.6	3.2	0.0	0.0
N	5	5	1	1

NA = NOT APLLICABLE

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73193 GROUP 1: 2924 MG/KG MALE FOUND DEAD 08/08/97 DATE OF DEATH: 08/08/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	250.	LUNGS	GROSS: DARK RED ALL LOBES	P
		STOMACH	GROSS: THICK WHITE CONTENTS	P
		EXTERNAL SURFACE	GROSS: RED MATTING NASAL	P
		EXTERNAL SURFACE	GROSS: CLEAR MATTING OCULAR, BILATERAL; NASAL; BUCCAL	P
		EXTERNAL SURFACE	GROSS: YELLOW MATTING UROGENITAL	P
		NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, EPIDIDYMIDES, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., MAMMARY GLAND, PANCREAS, PITUITARY, PROSTATE, SALIVARY GLANDS, SEMINAL VESICLES, SKIN, SPLEEN, TESTES, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73538 GROUP 2: 3824 MG/KG MALE FOUND DEAD 08/14/97 DATE OF DEATH: 08/14/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	248.	STOMACH NO SIGNIFICANT CHANGES OBSERVED	GROSS: THICK WHITE CONTENTS	P

GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, EPIDIDYMIDES, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, PANCREAS, PITUITARY, PROSTATE, SALIVARY GLANDS, SEMINAL VESICLES, SKIN, SPLEEN, TESTES, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

PROJECT NO.:WIL-12389R

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73552 GROUP 2: 3824 MG/KG MALE FOUND DEAD 08/14/97 DATE OF DEATH: 08/14/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	248.	STOMACH NO SIGNIFICANT CHANGES OBSERVED	GROSS: THICK WHITE CONTENTS	P

GROSS:

ADRENAL GLANDS	BRAIN	INTESTINE	EPIDIDYMIDES
ESOPHAGUS	EYES	HEART	KIDNEYS
LIVER	LYMPH NODE, ME.	LUNGS	MAMMARY GLAND
PANCREAS	PITUITARY	PROSTATE	SALIVARY GLANDS
SEMINAL VESICLES	SKIN	SPLEEN	TESTES
THYMUS GLAND	THYROID GLANDS	TRACHEA	URINARY BLADDER

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72939 GROUP 3: 5000 MG/KG MALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	227.	STOMACH	GROSS: WHITE FLUID CONTENTS	P
		EXTERNAL SURFACE	GROSS: RED MATTING NASAL; BUCCAL	P
		NO SIGNIFICANT CHANGES OBSERVED		

GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, EPIDIDYMIDES, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, PANCREAS, PITUITARY, PROSTATE, SALIVARY GLANDS, SEMINAL VESICLES, SKIN, SPLEEN, TESTES, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72944 GROUP 3: 5000 MG/KG MALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	242.	STOMACH	GROSS: WHITE FLUID CONTENTS	P
		EXTERNAL SURFACE	GROSS: RED MATTING NASAL; BUCCAL	P
		NO SIGNIFICANT CHANGES OBSERVED	GROSS:	

ADRENAL GLANDS	BRAIN	INTESTINE	EPIDIDYMIDES
ESOPHAGUS	EYES	HEART	KIDNEYS
LIVER	LYMPH NODE, ME.	LUNGS	MAMMARY GLAND
PANCREAS	PITUITARY	PROSTATE	SALIVARY GLANDS
SEMINAL VESICLES	SKIN	SPLEEN	TESTES
THYMUS GLAND	THYROID GLANDS	TRACHEA	URINARY BLADDER

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72945 GROUP 3: 5000 MG/KG MALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	243.	STOMACH	GROSS: WHITE FLUID CONTENTS	P
		EXTERNAL SURFACE	GROSS: RED MATTING NASAL; BUCCAL	P
		NO SIGNIFICANT CHANGES OBSERVED		

GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, EPIDIDYMIDES, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, PANCREAS, PITUITARY, PROSTATE, SALIVARY GLANDS, SEMINAL VESICLES, SKIN, SPLEEN, TESTES, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72947 GROUP 3: 5000 MG/KG MALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	246.	STOMACH	GROSS: WHITE FLUID CONTENTS	P
		EXTERNAL SURFACE	GROSS: RED MATTING NASAL; BUCCAL	P
		NO SIGNIFICANT CHANGES OBSERVED		

GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, EPIDIDYMIDES, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, PANCREAS, PITUITARY, PROSTATE, SALIVARY GLANDS, SEMINAL VESICLES, SKIN, SPLEEN, TESTES, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72948 GROUP 3: 5000 MG/KG MALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	240.	STOMACH	GROSS: WHITE FLUID CONTENTS	P
		EXTERNAL SURFACE	GROSS: RED MATTING OCULAR, RIGHT	P
		PENIS	GROSS: REDDENED	P
		PENIS	GROSS: PROLAPSED	P
		NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, EPIDIDYMIDES, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, PANCREAS, PITUITARY, PROSTATE, SALIVARY GLANDS, SEMINAL VESICLES, SKIN, SPLEEN, TESTES, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73212 GROUP 1: 2924 MG/KG FEMALE FOUND DEAD 08/08/97 DATE OF DEATH: 08/08/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	219.	LUNGS	GROSS: DARK RED ALL LOBES	P
		STOMACH	GROSS: THICK WHITE CONTENTS	P
		EXTERNAL SURFACE	GROSS: CLEAR MATTING OCULAR, BILATERAL; NASAL; BUCCAL	P
		EXTERNAL SURFACE	GROSS: YELLOW MATTING UROGENITAL	P
		NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., MAMMARY GLAND, OVARIES, PANCREAS, PITUITARY, SALIVARY GLANDS, SKIN, SPLEEN, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER, UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73555 GROUP 2: 3824 MG/KG FEMALE FOUND DEAD 08/14/97 DATE OF DEATH: 08/14/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	234.	STOMACH NO SIGNIFICANT CHANGES OBSERVED	GROSS: THICK WHITE CONTENTS	P
			GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, OVARIES, PANCREAS, PITUITARY, SALIVARY GLANDS, SKIN, SPLEEN, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER, UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73567 GROUP 2: 3824 MG/KG FEMALE FOUND DEAD 08/14/97 DATE OF DEATH: 08/14/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	231.	STOMACH NO SIGNIFICANT CHANGES OBSERVED	GROSS: THICK WHITE CONTENTS	P
			GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, OVARIES, PANCREAS, PITUITARY, SALIVARY GLANDS, SKIN, SPLEEN, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER, UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73590 GROUP 2: 3824 MG/KG FEMALE FOUND DEAD 08/14/97 DATE OF DEATH: 08/14/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	235.	STOMACH NO SIGNIFICANT CHANGES OBSERVED	GROSS: THICK WHITE CONTENTS	P
			GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, OVARIES, PANCREAS, PITUITARY, SALIVARY GLANDS, SKIN, SPLEEN, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER, UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72949 GROUP 3: 5000 MG/KG FEMALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

			GRADE
FINAL BODY WT(G) 207.	INTESTINE	GROSS: WHITE FLUID CONTENTS DUODENUM; JEJUNUM	P
	STOMACH	GROSS: WHITE FLUID CONTENTS	P
	NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS, BRAIN, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, OVARIES, PANCREAS, PITUITARY, SALIVARY GLANDS, SKIN, SPLEEN, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER, UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72956 GROUP 3: 5000 MG/KG FEMALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

			GRADE
FINAL BODY WT(G) 214.	INTESTINE	GROSS: WHITE FLUID CONTENTS ENTIRE LENGTH	P
	KIDNEYS	GROSS: DILATED PELVIS BILATERAL	1
	STOMACH	GROSS: THICK WHITE CONTENTS	P
	URETER(S)	GROSS: DISTENDED BILATERAL	2
	NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS, BRAIN, ESOPHAGUS, EYES, HEART, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, OVARIES, PANCREAS, PITUITARY, SALIVARY GLANDS, SKIN, SPLEEN, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER, UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72961 GROUP 3: 5000 MG/KG FEMALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

			GRADE
FINAL BODY WT(G) 210.	INTESTINE	GROSS: WHITE FLUID CONTENTS ENTIRE LENGTH	P
	STOMACH	GROSS: THICK WHITE CONTENTS	P
	EXTERNAL SURFACE	GROSS: RED MATTING OCULAR, RIGHT	P
	NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS, BRAIN, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, OVARIES, PANCREAS, PITUITARY, SALIVARY GLANDS, SKIN, SPLEEN, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER, UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 7
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72969 GROUP 3: 5000 MG/KG FEMALE FOUND DEAD 07/31/97 DATE OF DEATH: 07/31/97 STUDY DAY: 0

				GRADE
FINAL BODY WT(G)	213.	INTESTINE	GROSS: WHITE FLUID CONTENTS ENTIRE LENGTH	P
		STOMACH	GROSS: WHITE FLUID CONTENTS	P
		NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS, BRAIN, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, OVARIES, PANCREAS, PITUITARY, SALIVARY GLANDS, SKIN, SPLEEN, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER, UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73189 GROUP 1: 2924 MG/KG MALE SCHEDULED EUTH 08/22/97 DATE OF DEATH: 08/22/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	ESOPHAGUS	
	LIVER	
	PANCREAS	
	SEMINAL VESICLES	
	TESTES	
	URINARY BLADDER	
	BRAIN	
	EYES	
	LYMPH NODE, ME.	
	PITUITARY	
	SKIN	
	THYMUS GLAND	
	INTESTINE	
	HEART	
	LUNGS	
	PROSTATE	
	SPLEEN	
	THYROID GLANDS	
	EPIDIDYMIDES	
	KIDNEYS	
	MAMMARY GLAND	
	SALIVARY GLANDS	
	STOMACH	
	TRACHEA	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73190 GROUP 1: 2924 MG/KG MALE SCHEDULED EUTH 08/22/97 DATE OF DEATH: 08/22/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	ESOPHAGUS	
	LIVER	
	PANCREAS	
	SEMINAL VESICLES	
	TESTES	
	URINARY BLADDER	
	BRAIN	
	EYES	
	LYMPH NODE, ME.	
	PITUITARY	
	SKIN	
	THYMUS GLAND	
	INTESTINE	
	HEART	
	LUNGS	
	PROSTATE	
	SPLEEN	
	THYROID GLANDS	
	EPIDIDYMIDES	
	KIDNEYS	
	MAMMARY GLAND	
	SALIVARY GLANDS	
	STOMACH	
	TRACHEA	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73196 GROUP 1: 2924 MG/KG MALE SCHEDULED EUTH 08/22/97 DATE OF DEATH: 08/22/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	ESOPHAGUS	
	LIVER	
	PANCREAS	
	SEMINAL VESICLES	
	TESTES	
	URINARY BLADDER	
	BRAIN	
	EYES	
	LYMPH NODE, ME.	
	PITUITARY	
	SKIN	
	THYMUS GLAND	
	INTESTINE	
	HEART	
	LUNGS	
	PROSTATE	
	SPLEEN	
	THYROID GLANDS	
	EPIDIDYMIDES	
	KIDNEYS	
	MAMMARY GLAND	
	SALIVARY GLANDS	
	STOMACH	
	TRACHEA	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73200 GROUP 1: 2924 MG/KG MALE SCHEDULED EUTH 08/22/97 DATE OF DEATH: 08/22/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	ESOPHAGUS	
	LIVER	
	PANCREAS	
	SEMINAL VESICLES	
	TESTES	
	URINARY BLADDER	
	BRAIN	
	EYES	
	LYMPH NODE, ME.	
	PITUITARY	
	SKIN	
	THYMUS GLAND	
	INTESTINE	
	HEART	
	LUNGS	
	PROSTATE	
	SPLEEN	
	THYROID GLANDS	
	EPIDIDYMIDES	
	KIDNEYS	
	MAMMARY GLAND	
	SALIVARY GLANDS	
	STOMACH	
	TRACHEA	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73521 GROUP 2: 3824 MG/KG MALE SCHEDULED EUTH 08/28/97 DATE OF DEATH: 08/28/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	ESOPHAGUS	
	LIVER	
	PANCREAS	
	SEMINAL VESICLES	
	TESTES	
	URINARY BLADDER	
	BRAIN	
	EYES	
	LYMPH NODE, ME.	
	PITUITARY	
	SKIN	
	THYMUS GLAND	
	INTESTINE	
	HEART	
	LUNGS	
	PROSTATE	
	SPLEEN	
	THYROID GLANDS	
	EPIDIDYMIDES	
	KIDNEYS	
	MAMMARY GLAND	
	SALIVARY GLANDS	
	STOMACH	
	TRACHEA	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73548 GROUP 2: 3824 MG/KG MALE SCHEDULED EUTH 08/28/97 DATE OF DEATH: 08/28/97 STUDY DAY: 14

	GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS, BRAIN, INTESTINE, EPIDIDYMIDES, ESOPHAGUS, EYES, HEART, KIDNEYS, LIVER, LYMPH NODE, ME., LUNGS, MAMMARY GLAND, PANCREAS, PITUITARY, PROSTATE, SALIVARY GLANDS, SEMINAL VESICLES, SKIN, SPLEEN, STOMACH, TESTES, THYMUS GLAND, THYROID GLANDS, TRACHEA, URINARY BLADDER

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73551 GROUP 2: 3824 MG/KG MALE SCHEDULED EUTH 08/28/97 DATE OF DEATH: 08/28/97 STUDY DAY: 14

	GRADE
NO SIGNIFICANT CHANGES OBSERVED	
GROSS: ADRENAL GLANDS	
BRAIN	
INTESTINE	
EPIDIDYMIDES	
ESOPHAGUS	
EYES	
HEART	
KIDNEYS	
LIVER	
LYMPH NODE, ME.	
LUNGS	
MAMMARY GLAND	
PANCREAS	
PITUITARY	
PROSTATE	
SALIVARY GLANDS	
SEMINAL VESICLES	
SKIN	
SPLEEN	
STOMACH	
TESTES	
THYMUS GLAND	
THYROID GLANDS	
TRACHEA	
URINARY BLADDER	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73208 GROUP 1: 2924 MG/KG FEMALE SCHEDULED EUTH 08/22/97 DATE OF DEATH: 08/22/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	BRAIN	
	INTESTINE	
	ESOPHAGUS	
	EYES	
	HEART	
	KIDNEYS	
	LIVER	
	LYMPH NODE, ME.	
	LUNGS	
	MAMMARY GLAND	
	OVARIES	
	PANCREAS	
	PITUITARY	
	SALIVARY GLANDS	
	SKIN	
	SPLEEN	
	STOMACH	
	THYMUS GLAND	
	THYROID GLANDS	
	TRACHEA	
	URINARY BLADDER	
	UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73220 GROUP 1: 2924 MG/KG FEMALE SCHEDULED EUTH 08/22/97 DATE OF DEATH: 08/22/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	BRAIN	
	INTESTINE	
	ESOPHAGUS	
	EYES	
	HEART	
	KIDNEYS	
	LIVER	
	LYMPH NODE, ME.	
	LUNGS	
	MAMMARY GLAND	
	OVARIES	
	PANCREAS	
	PITUITARY	
	SALIVARY GLANDS	
	SKIN	
	SPLEEN	
	STOMACH	
	THYMUS GLAND	
	THYROID GLANDS	
	TRACHEA	
	URINARY BLADDER	
	UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73222 GROUP 1: 2924 MG/KG FEMALE SCHEDULED EUTH 08/22/97 DATE OF DEATH: 08/22/97 STUDY DAY: 14

					GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS:	ADRENAL GLANDS	BRAIN	INTESTINE	ESOPHAGUS
		EYES	HEART	KIDNEYS	LIVER
		LYMPH NODE, ME.	LUNGS	MAMMARY GLAND	OVARIES
		PANCREAS	PITUITARY	SALIVARY GLANDS	SKIN
		SPLEEN	STOMACH	THYMUS GLAND	THYROID GLANDS
		TRACHEA	URINARY BLADDER	UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73225 GROUP 1: 2924 MG/KG FEMALE SCHEDULED EUTH 08/22/97 DATE OF DEATH: 08/22/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	EYES	
	LYMPH NODE, ME.	
	PANCREAS	
	SPLEEN	
	TRACHEA	
	BRAIN	
	HEART	
	LUNGS	
	PITUITARY	
	STOMACH	
	URINARY BLADDER	
	INTESTINE	
	KIDNEYS	
	MAMMARY GLAND	
	SALIVARY GLANDS	
	THYMUS GLAND	
	UTERUS	
	ESOPHAGUS	
	LIVER	
	OVARIES	
	SKIN	
	THYROID GLANDS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73559 GROUP 2: 3824 MG/KG FEMALE SCHEDULED EUTH 08/28/97 DATE OF DEATH: 08/28/97 STUDY DAY: 14

					GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS:	ADRENAL GLANDS	BRAIN	INTESTINE	ESOPHAGUS
		EYES	HEART	KIDNEYS	LIVER
		LYMPH NODE, ME.	LUNGS	MAMMARY GLAND	OVARIES
		PANCREAS	PITUITARY	SALIVARY GLANDS	SKIN
		SPLEEN	STOMACH	THYMUS GLAND	THYROID GLANDS
		TRACHEA	URINARY BLADDER	UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 73571 GROUP 2: 3824 MG/KG FEMALE SCHEDULED EUTH 08/28/97 DATE OF DEATH: 08/28/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	BRAIN	
	INTESTINE	
	ESOPHAGUS	
	EYES	
	HEART	
	KIDNEYS	
	LIVER	
	LYMPH NODE, ME.	
	LUNGS	
	MAMMARY GLAND	
	OVARIES	
	PANCREAS	
	PITUITARY	
	SALIVARY GLANDS	
	SKIN	
	SPLEEN	
	STOMACH	
	THYMUS GLAND	
	THYROID GLANDS	
	TRACHEA	
	URINARY BLADDER	
	UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

TABLE 8
ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS
INDIVIDUAL GROSS DESCRIPTION OF ORGANS

ANIMAL NO. 72970 GROUP 3: 5000 MG/KG FEMALE SCHEDULED EUTH 08/14/97 DATE OF DEATH: 08/14/97 STUDY DAY: 14

		GRADE
NO SIGNIFICANT CHANGES OBSERVED	GROSS: ADRENAL GLANDS	
	BRAIN	
	INTESTINE	
	ESOPHAGUS	
	EYES	
	HEART	
	KIDNEYS	
	LIVER	
	LYMPH NODE, ME.	
	LUNGS	
	MAMMARY GLAND	
	OVARIES	
	PANCREAS	
	PITUITARY	
	SALIVARY GLANDS	
	SKIN	
	SPLEEN	
	STOMACH	
	THYMUS GLAND	
	THYROID GLANDS	
	TRACHEA	
	URINARY BLADDER	
	UTERUS	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

Acute Oral Toxicity Study of PH-73 in Albino Rats

APPENDIX A

Certificate of Analysis

Great Lakes
Chemical Corporation

SOUTH PLANT: 324 SOUTHFIELD CUTOFF • EL DORADO, ARKANSAS 71730 • PHONE 501-862-1355 • FAX 501-864-2056

Certificate of Analysis

TRIBROMOPHENOL
TBP

CUSTOMER: WIL RESEARCH LABS, INC. June 26, 1997

PSO NUMBER: 020542

CUSTOMER ORDER NUMBER: SAMPLE

CAS NUMBER: 00118-79-6

LOT NUMBER: 637149C-2

ATTN: TOM KERNS
(1) 100 GR SAMPLE

PROPERTY	RESULTS	SPECIFICATIONS MINIMUM	SPECIFICATIONS MAXIMUM
APPEARANCE	WHITE	LIGHT CREAM TO TAN	
MELTING RANGE, °C	93	90	
BROMINE CONTENT, %	COMPLIES	71	
ASSAY, %	100	98	
APHA COLOR	10		200

REMARKS

Michael P. Greer
Manager, Quality Control

pm

058080000310

Another ISO 9002 Qualified Product
Great Lakes Chemical
El Dorado, AR

Acute Oral Toxicity Study of PH-73 in Albino Rats

APPENDIX B

Protocol and Protocol Amendment

Study Number: WIL-12389

PROTOCOL AMENDMENT I

Sponsor: Great Lakes Chemical Corporation

A. Title of Study:

Acute Oral Toxicity Study of PH-73 in Albino Rats

B. Protocol Modification:

1) III. STUDY SCHEDULE DATA

A. Experimental Start Date: July 18,1997

B. Experimental Termination Date: August 28, 1997

C. Proposed Audited Draft Report Date: October 10, 1997

2) IV. TEST MATERIAL DATA

B. Lot Number:	637149C2
C. Purity:	Test material purity data are the responsibility of the Sponsor.
D. Stability:	Test material stability data are the responsibility of the Sponsor.
E. Physical Description:	White crystals
F. Storage Conditions:	Original container at room temperature.

3) VIII. DOSAGE LEVELS AND TREATMENT REGIMEN

A. Treatment Levels

The following dosing scheme was used for LD_{50} determination.

Group Number	Dose Level	Volume	Dose Concentration
1	2924 mg/kg	20 ml/kg	146.2 mg/ml
2	3824 mg/kg	20 ml/kg	191.2 mg/ml
3	5000 mg/kg	20 ml/kg	250.0 mg/ml

C. Reason for Protocol Modification:

1) Scheduling information are added to the protocol.

2) Test material data are added to the protocol.

3) Dose levels are added to the protocol.

Approved By:

Great Lakes Chemical Corporation
One Great Lakes Boulevard
West Lafayette, IN 47906

John A. Biesemeier
Sponsor Representative

9/19/97
Date

Prepared By:

WIL Research Laboratories, Inc.
Ashland, OH 44805-9281

Tom G. Kern, B.S.
Study Director

9/16/97
Date

PROTOCOL

Acute Oral Toxicity Study of PH-73 in Albino Rats

(U.S. TSCA, OECD, MITI and EEC Guidelines)

Study No.: WIL-12389

For

Great Lakes Chemical Corporation
One Great Lakes Boulevard
West Lafayette, IN 47906

By

WIL Research Laboratories, Inc.
Ashland, OH 44805-9281

June 24, 1997

ACUTE ORAL TOXICITY STUDY OF PH-73 IN ALBINO RATS

WIL Study No.: WIL-12389

I. OBJECTIVE OF STUDY

To determine the acute oral median lethal dose and evaluate potential systemic toxicity of the test material when administered as a single dose to albino rats.

This study will be conducted in general compliance with the principles of Good Laboratory Practice as described by the Environmental Protection Agency (40 CFR Parts 160 and 792), the Ministry of International Trade and Industry (MITI) and the Organization for Economic Cooperation and Development (OECD), the Toxic Substances Control Act (TSCA) Health Effects Test Guidelines (40 CFR 798-1175), the OECD Guidelines for Testing of Chemicals (section 401) and the European Economic Communities (EEC) guidelines (Directive 92/69/EEC adaptation of 67/548/EEC, Annex V).

II. PERSONNEL INVOLVED IN THE STUDY

A. Sponsor Representative

John A. Biesemeier
Regulatory Toxicologist
Regulatory Affairs

B. WIL Study Director

Tom G. Kern, B.S.
Group Supervisor - Toxicology

C. WIL Deputy Director

Jonathan M. Hurley, B.S.
Senior Biologist - Acute Toxicology

D. WIL Department Responsibilities

1. James L. Schardein, M.S., A.T.S.
   Director of Research

2. Christopher P. Chengelis, Ph.D., D.A.B.T.
   Senior Toxicologist

3. Jozef J.W.M. Mertens, Ph.D., D.A.B.T.
   Staff Toxicologist

4. Gary R. Kiplinger, B.S.
   Manager of General Toxicology

II. PERSONNEL INVOLVED IN THE STUDY (continued)

5. Carney B. Jackson, D.V.M., D.A.C.V.P., D.A.C.V.P.M.
Assistant Director of Pathology and Veterinary Medicine

6. Daniel W. Sved, Ph.D.
Director of Metabolism and Analytical Chemistry

7. Sally A. Keets, A.S.
Manager of Vivarium

8. Tammye Fleeman, B.S.
Group Supervisor of Gross Pathology
and Developmental Toxicology Laboratory

9. Ronald E. Wilson, B.S.
Director of Informational Systems

10. Deborah L. Little
Manager of Quality Assurance

11. Charlene M. Lindsey, M.A.
Manager of Technical Report Writing

12. Jenny R. Randall
Biologist II - Acute Toxicology

III. STUDY SCHEDULE DATA

A. Proposed Experimental Start Date: To be added by Protocol Amendment.

B. Proposed Experimental Termination Date: To be added by Protocol Amendment.

C. Proposed Audited Draft Report Date: To be added by Protocol Amendment.

IV. TEST MATERIAL DATA

A. Identification: PH-73

B. Lot Number: To be added by Protocol Amendment.

C. Purity: To be added by Protocol Amendment.

D. Stability: To be added by Protocol Amendment.

IV. TEST MATERIAL DATA (continued)

E. Physical Description: To be documented by WIL Research Laboratories, Inc. and added by Protocol Amendment.

F. Storage Conditions: To be added by Protocol Amendment.

G. Personnel Safety Data: The toxicologic properties of the test material have not been determined. Latex or nitrile gloves, eye protection, long sleeves (lab coat) and cartridge respirator are to be worn when handling this material. Refer to Material Safety Data Sheet for complete available information.

V. TEST SYSTEM

A. Species: Albino rat

B. Strain: Crl:CD®(SD)BR

C. Source: Charles River Laboratories, Inc.
Portage, MI or Kingston, NY

D. Number on Study: Minimum required to establish LD_{50}; five males and five females for initial dosing at 5.0 g/kg and five males and/or five females per group for additional levels, if needed.

E. Sex: Male and female (Females will be nulliparous and non-pregnant).

F. Body Weight Range: 200 to 300 grams at initiation of dosing, ± 20% of the mean for each sex.

G. Approximate Age: Young adult (approximately 6 to 8 weeks old at receipt).

H. Identification System: Each animal will be uniquely identified by a metal eartag displaying the animal number. Individual cage cards will be affixed to each cage and will display the animal number, group and study number.

I. Justification for Selection: This species and strain is generally recognized as appropriate for acute oral toxicity studies. The experimental design uses the procedures and standards required by the current and proposed federal and international regulations.

VI. SPECIFIC MAINTENANCE SCHEDULE

A. Animal Housing

The animals will be individually housed in suspended wire-mesh cages in an environmentally controlled room. Animals will be housed in clean cages elevated above cage-board or other suitable material that will be changed at least three times each week. The facilities at WIL Research Laboratories, Inc. are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

B. Environmental Conditions

Controls will be set to maintain temperature at 72° ± 4°F and relative humidity at approximately 30-70%. Fluorescent lighting controlled by light timers will provide illumination for a 12-hour light/dark photoperiod. Temperature and relative humidity will be recorded once daily.

C. Drinking Water

Reverse osmosis-treated municipal water will be available *ad libitum*. Filters servicing the automatic watering system are changed regularly according to Standard Operating Procedures. Water supplying the laboratory is analyzed for contaminants according to Standard Operating Procedures.

D. Basal Diet

PMI Feeds, Inc.© Certified Rodent LabDiet© 5002 will be offered *ad libitum* during the study except during the 18- to 20-hour period immediately prior to dosing when food will be withheld. Periodic analyses of the certified feed for the presence of heavy metals and pesticides are performed and provided by the manufacturer.

VII. EXPERIMENTAL DESIGN

A. Animal Receipt and Acclimation

Each animal will be inspected by a qualified technician upon receipt. Rats judged to be in good health and suitable as test animals will be immediately acclimated to laboratory conditions for a minimum of seven days. All rats will be initially weighed and permanently identified with an eartag. During the acclimation period, each rat will be observed twice daily for changes in general appearance and behavior. Prior to initiation of dosing, those animals judged to be suitable test subjects will be identified.

VII. EXPERIMENTAL DESIGN (continued)

B. Route and Rationale of Test Material Administration

The route of administration will be oral by gastric intubation. This is an anticipated route of exposure for humans. Test animals are fasted approximately 18-20 hours prior to dosing.

C. Body Weights

The body weight of each animal will be determined on study days -1 (pre-fasted), 0, 7, and 14 (termination). In addition, animals that die on study will be weighed as soon as they are found in that condition.

VIII. DOSAGE LEVELS AND TREATMENT REGIMEN

A. Treatment Levels

Five males and five females will be tested at 5.0 g/kg. If no compound-related mortality is obtained at 5.0 g/kg, no further testing is required. If mortality is observed during the limit test, additional levels of 1000, 1710 and 2924 mg/kg may be dosed at the request of the Sponsor (additional cost).

B. Treatment Groups

Following the acclimation period, rats will be arbitrarily selected from available stock based upon health and a fasted body weight of 200 to 300 grams. Five males and/or five females per treatment group will be employed unless specified otherwise by the Sponsor.

C. Method of Administration

All animals on each level will receive the same concentration of test material. The test material will be suspended in 0.5% carboxymethylcellulose with suspension concentrations based on a dose volume of 10 ml/kg. Any dose volume greater than 10 ml/kg must be approved by the Study Director in a protocol amendment. Analysis of dosing preparations will be performed at the specific written request of the Sponsor (additional cost). Individual dosages will be calculated based upon the animal's fasted body weight taken just before administration of the test material. The animals will be returned to feed approximately 3-4 hours after dosing.

IX. OBSERVATIONS

Test animals will be observed for pharmacotoxic signs and mortality at approximately one, three and four hours after compound administration. The animals will be observed daily thereafter for 14 days for pharmacotoxic signs and twice daily (morning and afternoon) for mortality. If signs are present at the end of 14 days of observation that may be related to the test material, the observation period may be extended (after consultation with the Sponsor) until such signs are no longer present or are obviously irreversible (additional cost).

X. GROSS PATHOLOGY

At termination, surviving animals will be euthanized by carbon dioxide inhalation. A gross necropsy examination on major organ systems of the cranial, thoracic and abdominal cavities will be conducted on all animals found dead or euthanized at termination.

XI. DETERMINATION OF LD_{50}

At the termination of the project, all data will be collected and the acute oral median lethal dose (LD_{50}) of the test material will be determined by an appropriate method. If possible, an LD_{50} value with 95% confidence limits will be calculated by the method of Litchfield and Wilcoxon.

XII. REPORT

The final report will include the following: summary, objective, test material identification and receipt, methods, observations, mortality, body weights, gross necropsy findings, and an estimated or calculated LD_{50}. The report will also include a copy of the protocol, protocol amendment(s), and any study supporting information or data received from the Sponsor. One copy of the audited draft report will be provided approximately six weeks following completion of the study. One unbound copy of the report will be provided upon finalization.

XIII. RECORDS TO BE MAINTAINED

All original raw data records (as defined by the applicable GLPs and WIL SOPs) generated by WIL Research Laboratories, Inc. will be collected and maintained by WIL Research Laboratories, Inc.

XIV. WORK PRODUCT

Sponsor will have title to all documentation records, raw data, slides, specimens, or other work product generated during the performance of the study. All work product including raw paper data, magnetically encoded records and specimens will be retained at no charge for a period of six months following issuance of the final report in the Archives at WIL Research Laboratories, Inc. Thereafter, WIL Research Laboratories will charge a monthly archiving fee for retention of all work product. All work product will be stored in compliance with regulatory requirements.

XV. QUALITY ASSURANCE

The study will be audited by the WIL Quality Assurance Unit while in progress to assure compliance with Good Laboratory Practice regulations and adherence to the protocol and to WIL Standard Operating Procedures. The raw data and draft report will be audited by the WIL Quality Assurance Unit prior to submission to the Sponsor to assure that the final report accurately describes the conduct and the findings of the study.

XVI. PROTOCOL MODIFICATION

Modification of the protocol may be accomplished during the course of this investigation. However, no changes will be made in the study design without the verbal or written permission of the Sponsor. In the event that the Sponsor verbally requests or approves a change in the protocol, such changes will be made by appropriate documentation in the form of a protocol amendment. All alterations of the protocol and reasons for the modification(s) will be signed and dated by the Study Director and the Sponsor Representative.

XVII. ANIMAL WELFARE ACT COMPLIANCE

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR). The Sponsor should make particular note of the following:

1. The Sponsor signature on this protocol documents for the Study Director the Sponsor's assurance that the study described in this protocol does not unnecessarily duplicate previous experiments.

2. Whenever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress or pain to animals. All methods are described in this study protocol or in written laboratory Standard Operating Procedures.

3. Animals that experience severe or chronic pain or distress that cannot be relieved will be painlessly euthanized as deemed appropriate by the veterinary staff and Study Director. The Sponsor will be advised by the Study Director of all circumstances which could lead to this action in as timely a manner as possible.

XVII. ANIMAL WELFARE ACT COMPLIANCE (continued)

4. Methods of euthanasia used during this study are in conformance with the above-referenced regulation.

XVIII. PROTOCOL APPROVAL

Great Lakes Chemical Corporation
One Great Lakes Boulevard
West Lafayette, IN 47906

John A. Biesemeier
Sponsor Representative

6-26-97
Date

WIL Research Laboratories, Inc.
Ashland, OH 44805-9281

Tom G. Kern, B.S.
Study Director

6/24/97
Date