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RHÔNE-POULENC INC.

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(A)

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October 16, 1992

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Document Processing Center (TS-790)
Attn: Section 8(e) Coordinator (CAP Agreement)
Office of Toxic Substances
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance
Audit Program

CAP ID NO.: 8ECAP - 0004

RP CAP REPORT NO.: RPS - 0308

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN5266, Princeton, NJ 08543-5266) and its subsidiaries, the attached report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA (8ECAP - 0004).

The enclosed report provides information on the following chemical substance:

Chemical Identity: Prenyl acetate

CAS Registry No.: 1191-16-8

CAS Registry Name: 2-Buten-1-ol, 3-methyl-, acetate

mm
1/30/95

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The title of the enclosed report is:

Acute Oral LD50 in Rats with Prenyl Acetate; Primary Eye Irritation in Rabbits with Prenyl Acetate; Primary Dermal Irritation with Prenyl Acetate in Rabbits

The following is a summary of the adverse effects observed in this report.

A single oral dose of test material was administered to rats at 1.5, 2.0, 3.0, 4.0, or 5.0 gm/kg. The acute oral LD50 in males (with 95% confidence limits) was 3.0 (2.5-3.6) gm/kg and in females (with 95% confidence limits) was 2.9 (2.2-3.8) gm/kg. Clinical signs of toxicity observed were trembling, convulsions, salivation, lacrimation, diarrhea, depression, ataxia, prostration, and dyspnea. In general, these signs were seen in animals surviving to study termination as well as those dying during the study.

RPI does not claim any portion of the information in this submission to be TSCA confidential business information (TSCA CBI).

RPI has not previously submitted any TSCA Section 8(e) notices or premanufacture notification on the subject chemical substance.

In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to Dr. Glenn S. Simon, Director of Toxicology at (919)549-2222 (Rhône-Poulenc, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709).

Sincerely,



Charles E. Moyer, Jr., Ph.D.
Director, Product Safety
(609)860-3589

CEMjr/mm
Enclosure



Contains No CBI

OFFICE MEMORANDUM

Post file

DIVISION CORPORATE - Process Development

To: B. BUCHNER
P. O'HEA
C. R. TEVEBAUGH

w/attachment

PD # 1422

Date: AUGUST 9, 1978

From: P. BOISDE

Subject: PRENOL & PRENYL ACETATE TOXICITY STUDY

CC: E. Clark
F. Darmory
B. Louvet
J. P. Sibeud
D. Liu
P. Bouis

Please find enclosed one copy each of the six reports on the Prenol and Prenyl Acetate toxicity study made by the Rhodia Toxicology - Pathology Laboratory at Ashland.

The results of this study can be summarized as follows:

TOXICITY TEST	PRENOL	PRENYL ACETATE
Acute oral LD ₅₀ in rats	1.25 gm/kg	3.0 gm/kg
Primary eye irritation in rabbits	Minimal	Minimal
Primary dermal irritation in rabbits	Extremely irritating	Non-Irritating

The finding of the strong skin irritating property of Prenol must be taken into consideration by those who can be in contact with the chemical.

P. Boilde

j



OFFICE MEMORANDUM

HESS AND CLARK

DIVISION _____

To: Mr. Paul Boisdé
Chemicals Division

Date: August 3, 1978

From: E. M. Kiggins

Subject: Prenyl Alcohol
Prenyl Acetate

cc: JGPage

I am enclosing one copy each of the following reports:

<u>Study No.</u>	<u>Report No.</u>	<u>Title</u>
RCP0678	SEH 78:36	Acute Oral LD ₅₀ in Rats with Prenyl Acetate
BCE1278	SEH 78:25	Primary Eye Irritation in Rabbits with Prenyl Acetate
BCD1078	JCW 78:24	Primary Dermal Irritation with Prenyl Acetate in Rabbits
RCP0578	JCW 78:39	Acute Oral LD ₅₀ with Prenyl Alcohol in Rats
BCE1178	SEH 78:26	The Effects of Prenol on the Eye Mucosa of New Zealand Albino Rabbits
BCD0978	JCW 78:30	Primary Dermal Irritation Study with Prenol in Rabbits

E. M. Kiggins
as

E. M. Kiggins

PRENYL ACETATE

- STUDY NO. RCP0678 - ACUTE ORAL LD₅₀ IN RATS WITH PRENYL
ACETATE
- STUDY NO. BCE1278 - PRIMARY EYE IRRITATION IN RABBITS WITH
PRENYL ACETATE
- STUDY NO. BCD1078 - PRIMARY DERMAL IRRITATION WITH PRENYL
ACETATE IN RABBITS.

TOXICOLOGY-PATHOLOGY LABORATORY
RHODIA INC.
Ashland, Ohio 44805

ACUTE ORAL LD₅₀ WITH PRENYL ACETATE IN RATS

Study No. RCP0678

Report No. SEH 78:36

Corrections: Individual and Average Body Weights

3 gm/kg Female - #360 day 1, should be 164
4 gm/kg Male - day 1, average should be 190
1.5 gm/kg Female - day 4, average should be 195
1.5 gm/kg Male - day 4, average should be 255
2.0 gm/kg Female - day 7, average should be 195

Table 4

#260 add WB day 2
#359 add Dp+ days 0-1
#360 add Dp+ day 1
#451 HSES days 8-14

Table 5

4.0 gm/kg Female - Dp day 8 is 1/1
WB day 6 is 1/2

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

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Protocol



RHODIA INC.
HESS & CLARK DIVISION
ASHLAND, OHIO 44805
Research Department



Author: S. E. Hastings, B.S.
Report No.: SEH 78:36
Date: July 21, 1978
Page: 1

Subject: Acute Oral LD₅₀, Prenyl Acetate
Book No. 13 Pages 1-67, 90-94
Study No. RCP0678 Dates: 7-6-78 to 7-21-78

TITLE

Acute Oral LD₅₀ in Rats with Prenyl Acetate

PURPOSE

To determine the acute toxicity and lethality of Prenyl Acetate in rats according to the EPA proposed guidelines of April, 1978; 162.81-1.

LOCATION

This study was conducted at the Rhodia Inc., Toxicology-Pathology facility on the Hess & Clark Research Farm, Ashland, Ohio 44805.

SPONSOR

This study was sponsored by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey.

SUMMARY

Young adult male and unbred female rats were given single oral doses of Prenyl Acetate at dose levels of 1.5, 2.0, 3.0, 4.0 or 5.0 gm/kg body weight (b.w.) in an acute oral LD₅₀ study. The rats were observed for 14 days and an LD₅₀ calculated from the mortality data. The LD₅₀ for the males was 3.0 gm/kg b.w. with 95% confidence limits of 2.5 to 3.6 gm/kg b.w. The calculated LD₅₀ for the females was 2.9 gm/kg b.w. with 95% confidence limits of 2.2 to 3.8 gm/kg b.w.

Surviving males and females in the 2.0, 3.0 and 4.0 gm/kg dose groups gained less weight during the study period than males and females in the 1.5 gm/kg dose group. There were no survivors at 5.0 gm/kg. The survival rate and average days to death were comparable between the males and females.

Clinical signs of toxicity included a mild to severe depression, diarrhea, salivation, lacrimation, wet belly, trembling, dyspnea, convulsions, occasional ataxia, prostration and death. A few of the rats in the higher dose groups 3.0, 4.0 or 5.0 gm/kg were observed to have very reddened appearing paws, ears and tails. The one surviving female at 4.0 gm/kg developed a hypersensitivity to external stimuli. As the dose levels increased the toxic signs were more severe with a shorter onset time.

Necropsy observations on the rats which died during the study included: hemorrhagic lungs, dark livers and sloughing and/or inflammation and erosion of the stomach mucosa. There were no significant necropsy findings on any of the survivors sacrificed at the termination of the study.



EXPERIMENTAL

MATERIALS AND METHODS

ANIMALS

One hundred (100) Sprague Dawley derived outbred albino rats, 50 males and 50 females, from Flow Laboratories, Dublin, Virginia, weighing between 150 and 200 grams at the start of the study period, were divided into 5 dose groups of 10 males and 10 females each.

HOUSING

QUARANTINE - the rats were held in a quarantine room for a 2 week acclimation period depending on the age and weight of the rats. The rats were randomly distributed from the shipping crates into the gang cages. The rats were housed 3 to 4 per sex per cage in suspended 1.3 cm wire mesh cages, 43 x 18 x 25 cm. The rats received feed and water ad libitum. The feeders, water bottles, cages and racks were changed once per week.

The quarantine and test rooms were temperature ($72^{\circ} \text{F} \pm 1^{\circ}$), humidity (50%) and light (12 hours on, 12 hours off) controlled.

During the quarantine-acclimation period the rats were examined by a veterinarian with respect to their state of health and suitability as test animals. Conventional disease control was practiced during the quarantine-acclimation and study period.

STUDY ROOM - at the end of the quarantine period, the cage racks containing the test animals were moved to the test room. The rats were randomly distributed from the quarantine racks to the test racks. The rats were housed in individual 1.3 cm wire mesh stainless steel suspended cages, 18 x 18 x 23 cm. The rats were weighed. If the mean body weights of any dose group varied significantly from any other group, the rats were redistributed so that the mean body weights of all dose groups did not vary significantly. The rats received food and water ad libitum. The feeders, water bottles, cages and racks were changed once per week.



RHODIA INC.
HESS & CLARK DIVISION
ASHLAND, OHIO 44805
Research Department



Author: S. E. Hastings, B.S.
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DIET

The rats were maintained on a diet of Wayne Lab-Blox, manufactured by Allied Mills, Fort Wayne, Indiana and containing 24% crude protein, 4% crude fat and 4.5% crude fiber. Tap water was provided by 8 oz. water bottles with sipper tubes.

IDENTIFICATION

The rats were identified by ear notches. An identifying tag was placed on each rat cage indicating the study number, rat number and treatment level. The rats were ear notched as follows:

<u>Rat No.</u>	<u>Treatment Level</u>
101-110 M 151-160 F	1.5 gm/kg
201-210 M 251-260 F	2.0 gm/kg
301-310 M 351-360 F	3.0 gm/kg
401-410 M 451-460 F	4.0 gm/kg
501-510 M 551-560 F	5.0 gm/kg

TEST SUBSTANCE

The test substance was Prenyl Acetate, a clear liquid supplied by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey and received June 16, 1978. Identifying numbers on the label were AV 307-25 (cut 25). Purity was 99.8%, density was 0.84, pH was 4

TEST PROCEDURE

The test substance was diluted in corn oil to give the dose levels of 1.5, 2.0, 3.0, 4.0 or 5.0 gm/kg b.w. Each concentration was mixed continuously on a magnetic stirrer during the dosing. Each rat received a dose volume of 10 ml/kg body weight. The rats were orally gavaged one time with a curved 18 x 2 w/2½ mm ball dosing needle. The rats were fasted from food 18 hours prior to dosing.



OBSERVATIONS

The animals were weighed prior to dosing to determine the volume of test substance to be administered. Survivors were weighed on days 1, 4, 7, 10 and 14 of the 14 day observation period. The weighing was performed on a Mettler electronic balance interfaced to a programmable calculator, HP 9815A. The day of dosing was designated as day 0. The rats were observed frequently during the first 8 hours post-treatment and twice daily (a.m. and p.m.) for the remaining 14 days. All relevant clinical signs including the nature, onset, severity and duration of each toxic or pharmacological sign, and time of death were recorded. The survivors were sacrificed on day 15.

GROSS NECROPSY

A gross necropsy was performed on all rats in the LD50 study. The examination included: heart, lung, spleen, liver, kidney, stomach, small and large intestine and urinary bladder. All lesions were recorded.

RECORDS MAINTAINED

A study record book was maintained and included the following records:

1. Body weights - days 0, 1, 4, 7, 10 and 14.
2. Day 0 observations.
3. Daily observations.
4. Necropsy observations.
5. Data analysis.

STORAGE OF DATA

All raw data generated during this study and the final report are stored in the archives at Rhodia Inc., Toxicology-Pathology facility in Ashland, Ohio.



RESULTS AND DISCUSSION

Preliminary results from a pilot study indicated that the oral LD₅₀ of Prenyl Acetate in rats was between 2.5 and 5.0 gm/kg b.w.

Mortalities per test day are presented in Table 1. The individual day 0 body weights, dose volumes and days to death are recorded in Table 2. The individual and average body weights for days 0, 1, 4, 7, 10 and 14 are recorded in Table 3. Table 4 is the record of the individual clinical and necropsy observations. Table 5 shows the number of survivors with toxic signs per observation period. Figures 1 and 2 are the graphical illustration of the calculation of the acute oral LD₅₀ for males and females, respectively.

Surviving males in the lower dose groups of 1.5 and 2.0 gm/kg began gaining weight by day 1 post administration. Survivors in the mid dose groups of 3.0 and 4.0 gm/kg began gaining weight by day 4 post administration. There were no surviving males in the high dose group of 5.0 gm/kg. Surviving males in the 2.0, 3.0 and 4.0 gm/kg dose groups gained less weight during the study period than males in the 1.5 gm/kg dose group. Surviving females in the 1.5, 2.0 and 3.0 gm/kg dose groups began gaining weight by day 1 post administration. The one survivor in the 4.0 gm/kg group did not show any weight gain until day 14 post administration. There were no surviving females at 5.0 gm/kg. Surviving females in the 2.0, 3.0 and 4.0 gm/kg dose groups gained less weight during the study period than females in the 1.5 gm/kg dose group.

The survival rate was comparable between the males and females. There were no male or female survivors at the high dose level of 5.0 gm/kg. One of 10 males and 1 of 10 females survived at 4.0 gm/kg, 6 of 10 males and 6 of 10 females survived at 3.0 gm/kg, 10 of 10 males and 9 of 10 females survived at 2.0 gm/kg and all 10 males and 10 females survived at the low dose level of 1.5 gm/kg.

The average days to death were comparable between males and females. Males at dose levels of 1.5, 2.0, 3.0, 4.0 or 5.0 gm/kg lived an average of 14, 14, 9.3, 2.1 and 0.7 days, respectively. Females at the same dose levels lived an average of 14, 13.6, 9.4, 2.9 and 0.7 days, respectively.

Clinical signs of toxicity were observed in all dose groups. A mild depression and diarrhea were the most common toxic signs observed in the 1.5 and 2.0 gm/kg dose groups. A few females in the 2.0 gm/kg group were observed with salivation, lacrimation or wet belly. All survivors at 1.5 or 2.0 gm/kg were asymptomatic by day 1 or 2 post administration. The toxic signs became more severe with a shorter onset time as the dose



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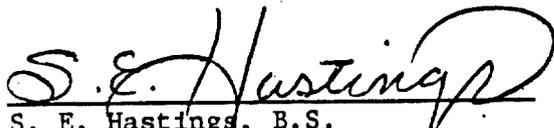


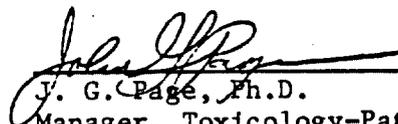
Author: S. E. Hastings, B.S.
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levels increased. The most common toxic signs observed in the 3.0, 4.0 or 5.0 gm/kg dose groups included: a mild to severe depression, diarrhea, salivation, lacrimation, wet belly, trembling, dyspnea, convulsions, occasional ataxia, prostration and death. In a few of these rats, the paws, ears and tail appeared reddened. The one surviving female in the 4.0 gm/kg dose group developed a hypersensitivity to external stimuli, which continued until the termination sacrifice. Survivors in the 3.0 gm/kg dose group and the one male survivor at 4.0 gm/kg were asymptomatic by day 2 or 3 post administration.

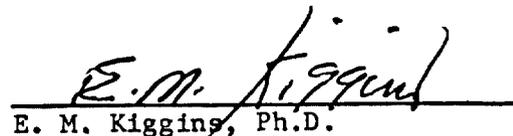
Necropsy observations on rats which died during the study period included: hemorrhagic lungs, dark liver, and sloughing and/or inflammation and erosion of the stomach mucosa. No significant gross alterations or lesions were noted in any of the survivors sacrificed at the termination of the study.

When doses of 1.5, 2.0, 3.0, 4.0 or 5.0 gm/kg b.w. were plotted against the percent mortality, an LD₅₀ was apparent for the males at 3.0 gm/kg b.w. with 95% confidence limits of 2.5 to 3.6 gm/kg b.w. The calculated LD₅₀ for the females of 2.9 gm/kg b.w. with 95% confidence of 2.2 to 3.8 gm/kg b.w. was comparable to the males.


S. E. Hastings, B.S.
Toxicologist


J. G. Page, Ph.D.
Manager, Toxicology-Pathology
Rhodia Inc.


J. C. Winbigler, B.S., M.T.
Toxicologist


E. M. Kiggins, Ph.D.
Director of Research
& Product Development

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 2

Individual Day 0 Body Weights, Dose Volumes and Days to Death

MALES				FEMALES			
Rat No.	Body Wt (gm)	Dose Volume (ml)	Days to Death	Rat No.	Body Wt (gms)	Dose Volume (ml)	Days to Death
<u>DOSE GROUP: 1.5 GM/KG</u>							
101	196	2.0	14	151	186	1.9	14
102	194	1.9	14	152	171	1.7	14
103	221	2.2	14	153	164	1.6	14
104	214	2.1	14	154	172	1.7	14
105	212	2.1	14	155	168	1.7	14
106	224	2.2	14	156	165	1.7	14
107	230	2.3	14	157	181	1.8	14
108	217	2.2	14	158	155	1.6	14
109	207	2.1	14	159	149	1.5	14
110	211	2.1	14	160	163	1.6	14
Average	213	2.1	14	Average	167	1.7	14
<u>DOSE GROUP: 2.0 GM/KG</u>							
201	233	2.3	14	251	157	1.6	14
202	219	2.2	14	252	178	1.8	14
203	201	2.0	14	253	167	1.7	14
204	194	1.9	14	254	166	1.7	FD, 1
205	198	2.0	14	255	148	1.5	14
206	213	2.1	14	256	173	1.7	14
207	214	2.1	14	257	177	1.8	14
208	206	2.1	14	258	170	1.7	14
209	237	2.4	14	259	167	1.7	14
210	194	1.9	14	260	156	1.6	14
Average	211	2.1	14	Average	166	1.7	13.6

KEY: FD = found dead

TABLE 2 (Cont'd)

Individual Day 0 Body Weights, Dose Volumes and Days to Death

MALES				FEMALES			
Rat No.	Body Wt (gm)	Dose Volume (ml)	Days to Death	Rat No.	Body Wt (gms)	Dose Volume (ml)	Days to Death
<u>DOSE GROUP: 3.0 GM/KG</u>							
301	239	2.4	14	351	157	1.6	14
302	189	1.9	14	352	173	1.7	14
303	206	2.1	FD, 1	353	173	1.7	FD, 1
304	211	2.1	D, 0	354	181	1.8	FD, 1
305	213	2.1	14	355	156	1.6	FD, 1
306	194	1.9	14	356	175	1.8	14
307	200	2.0	14	357	166	1.7	FD, 1
308	224	2.2	FD, 1	358	174	1.7	14
309	226	2.3	14	359	191	1.9	14
310	212	2.1	FD, 1	360	164	1.6	14
Average	211	2.1	9.3	Average	171	1.7	9.4
<u>DOSE GROUP: 4.0 GM/KG</u>							
401	225	2.3	FD, 1	451	152	1.5	14
402	229	2.3	FD, 1	452	173	1.7	FD, 7
403	218	2.2	14	453	166	1.7	D, 0
404	218	2.2	FD, 1	454	162	1.6	FD, 1
405	206	2.1	FD, 1	455	163	1.6	D, 0
406	182	1.8	D, 0	456	158	1.6	FD, 1
407	227	2.3	D, 0	457	176	1.8	FD, 1
408	210	2.1	FD, 2	458	174	1.7	FD, 1
409	228	2.3	D, 0	459	185	1.9	FD, 2
410	189	1.9	D, 0	460	180	1.8	FD, 1
Average	213	2.2	2.1	Average	169	1.7	2.9
<u>DOSE GROUP: 5.0 GM/KG</u>							
501	209	2.1	D, 0	551	166	1.7	FD, 1
502	204	2.0	D, 0	552	158	1.6	FD, 1
503	242	2.4	FD, 2	553	162	1.6	FD, 1
504	211	2.1	FD, 1	554	189	1.9	FD, 1
505	203	2.0	D, 0	555	171	1.7	D, 0
506	216	2.2	FD, 1	556	163	1.6	FD, 1
507	178	1.8	FD, 1	557	161	1.6	D, 0
508	210	2.1	FD, 1	558	166	1.7	FD, 1
509	226	2.3	FD, 1	559	160	1.6	D, 1
510	214	2.1	D, 0	560	170	1.7	D, 0
Average	211	2.1	0.7	Average	167	1.7	0.7

KEY: FD = found dead
D = died

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 3

Individual and Average Body Weights (gm)

Rat No.	MALES					FEMALES						
	Test Day					Rat No.	Test Day					
	0	1	4	7	10		14	0	1	4	7	10
	<u>DOSE GROUP: 1.5 GM/KG</u>											
101	196	214	228	251	265	287	151	200	215	226	233	241
102	194	218	238	264	275	301	152	186	197	204	211	219
103	221	239	265	283	309	334	153	164	188	193	203	208
104	214	227	247	259	277	287	154	172	206	205	213	223
105	212	229	250	264	281	305	155	168	185	191	196	202
106	224	248	268	291	312	327	156	165	191	198	201	214
107	230	251	285	306	325	354	157	181	215	223	236	242
108	217	235	264	284	304	325	158	155	191	198	204	214
109	207	224	243	258	272	296	159	149	172	179	186	194
110	211	233	258	280	305	336	160	163	193	202	206	210
Average	213	232	255	274	293	315	Average	167	183	195	209	217
	<u>DOSE GROUP: 2.0 GM/KG</u>											
201	233	238	256	271	301	320	251	157	166	173	180	196
202	219	224	252	263	282	304	252	178	188	205	215	229
203	201	221	246	269	289	317	253	167	173	188	192	206
204	194	199	227	249	269	287	254	166	D ^a	-	-	-
205	198	210	222	231	250	266	255	148	161	172	184	187
206	213	234	247	275	297	316	256	173	189	192	203	211
207	214	226	248	268	283	314	257	177	198	200	216	231
208	206	227	245	264	281	306	258	170	185	200	208	227
209	237	253	271	297	330	354	259	167	162	170	177	188
210	194	212	229	252	266	288	260	156	137	148	184	228
Average	211	224	244	264	285	307	Average	166	173	183	195	211

^a D = Dead

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 3 (Cont'd)

Individual and Average Body Weights (gm)

		MALES					FEMALES						
Rat No.	Test Day					Rat No.	Test Day						
	0	1	4	7	10		14	0	1	4	7	10	14
	<u>DOSE GROUP: 3.0 GM/KG</u>												
301	239	246	255	280	306	339	351	157	159	154	170	183	192
302	189	200	228	255	275	292	352	173	165	173	188	193	204
303	206	D ^a	-	-	-	-	353	173	D	-	-	-	-
304	211	D	-	-	-	-	354	181	D	-	-	-	-
305	213	211	221	240	264	282	355	156	D	-	-	-	-
306	194	181	183	200	232	258	356	175	174	180	189	197	202
307	200	199	214	235	252	271	357	166	D	-	-	-	-
308	224	D	-	-	-	-	358	174	190	197	207	212	218
309	226	220	247	266	289	307	359	191	196	206	206	202	201
310	212	D	-	-	-	-	360	164	164	175	182	186	194
Average	211	210	225	246	270	292	Average	171	175	181	190	196	202
	<u>DOSE GROUP: 4.0 GM/KG</u>												
401	225	D	-	-	-	-	451	152	150	131	165	165	174
402	229	D	-	-	-	-	452	173	163	126	D	-	-
403	218	201	213	230	259	286	453	166	D	-	-	-	-
404	218	D	-	-	-	-	454	162	D	-	-	-	-
405	206	D	-	-	-	-	455	163	D	-	-	-	-
406	182	D	-	-	-	-	456	158	D	-	-	-	-
407	227	D	-	-	-	-	457	176	D	-	-	-	-
408	210	178	D	-	-	-	458	174	D	-	-	-	-
409	228	D	-	-	-	-	459	185	184	D	-	-	-
410	189	D	-	-	-	-	460	180	D	-	-	-	-
Average	213	190	213	230	259	286	Average	169	166	129	165	165	174

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 3 (Cont'd)

Individual and Average Body Weights (gm)

Rat No.	MALES						FEMALES					
	Test Day						Test Day					
	0	1	4	7	10	14	0	1	4	7	10	14
	DOSE GROUP: 5.0 GM/KG											
501	209	D ^a	-	-	-	-	166	D	-	-	-	-
502	204	D	-	-	-	-	158	D	-	-	-	-
503	242	222	D	-	-	-	162	D	-	-	-	-
504	211	D	-	-	-	-	189	D	-	-	-	-
505	203	D	-	-	-	-	171	D	-	-	-	-
506	216	D	-	-	-	-	163	D	-	-	-	-
507	178	D	-	-	-	-	161	D	-	-	-	-
508	210	D	-	-	-	-	166	D	-	-	-	-
509	226	D	-	-	-	-	160	151	D	-	-	-
510	214	D	-	-	-	-	170	D	-	-	-	-
average	211	222	-	-	-	-	167	151	-	-	-	-

^a D = Dead

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4

Individual Clinical and Necropsy Observations

KEY TO SYMBOLS

Dp	-	Depressed
Lc	-	Lacrimation
Sl	-	Salivation
Dr	-	Diarrhea
Pr	-	Prostrate
Dy	-	Dyspnea
Cv	-	Convulsion
Tr	-	Trembling
At	-	Ataxia
WB	-	Wet Belly
Extrem.		
Red	-	Paws, ears, tail appeared very red
HSES	-	Hypersensitive to external stimuli
+	-	Mild
++	-	Moderate
+++	-	Severe
NS	-	Nothing significant
TS	-	Termination sacrifice
D	-	Died
FD	-	Found dead

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4 (Cont'd)

Individual Clinical and Necropsy Observations

Rat No.	Day of Death	Clinical	Necropsy
<u>DOSE GROUP: 1.5 GM/KG - MALES</u>			
101	TS, 15	NS days 0-14	NS
102	TS, 15	NS days 0-14	NS
103	TS, 15	NS days 0-14	NS
104	TS, 15	NS days 0-14	NS
105	TS, 15	NS days 0-14	NS
106	TS, 15	Dr day 0 NS days 1-14	NS
107	TS, 15	NS days 0-14	NS
108	TS, 15	NS days 0-14	NS
109	TS, 15	NS days 0-14	NS
110	TS, 15	NS days 0-14	NS
<u>DOSE GROUP: 1.5 GM/KG - FEMALES</u>			
151	TS, 15	NS days 0-14	NS
152	TS, 15	NS days 0-14	NS
153	TS, 15	NS days 0-14	NS
154	TS, 15	NS days 0-14	NS
155	TS, 15	Dp+ day 0 NS days 0-14	NS
156	TS, 15	NS days 0-14	NS
157	TS, 15	Dr day 0 NS days 1-14	NS
158	TS, 15	NS days 0-14	NS
159	TS, 15	NS days 0-14	NS
160	TS, 15	NS days 0-14	NS

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4 (Cont'd)

Individual Clinical and Necropsy Observations

Rat No.	Day of Death	Clinical	Necropsy
<u>DOSE GROUP: 2.0 GM/KG - MALES</u>			
201	TS, 15	Dp+ days 0-1 NS days 2-14	NS
202	TS, 15	Dp+ day 0 NS days 1-14	NS
203	TS, 15	NS days 0-14	NS
204	TS, 15	NS days 0-14	NS
205	TS, 15	NS days 0-14	NS
206	TS, 15	Dr day 0 NS days 1-14	NS
207	TS, 15	Dp+ day 0 NS days 1-14	NS
208	TS, 15	NS days 0-14	NS
209	TS, 15	Dp+ day 0 NS days 1-14	NS
210	TS, 15	NS days 0-14	NS
<u>DOSE GROUP: 2.0 GM/KG - FEMALES</u>			
251	TS, 15	NS days 0-14	NS
252	TS, 15	Dp+, Lc, S1 day 0 NS days 1-14	NS
253	TS, 15	Dp+, Dr day 0 Dp+ day 1 NS days 2-14	NS
254	FD, 1	Dr day 0	Gastric intestinal tract filled
255	TS, 15	Dr day 0 NS days 1-4	NS
256	TS, 15	Dp++, S1, Dr day 0 Dp+ day 1 NS days 2-14	NS
257	TS, 15	NS days 0-14	NS

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4 (Cont'd)

Individual Clinical and Necropsy Observations

<u>Rat No.</u>	<u>Day of Death</u>	<u>Clinical</u>	<u>Necropsy</u>
<u>DOSE GROUP: 2.0 GM/KG - FEMALES (Cont'd)</u>			
258	TS, 15	Dp+, S1, Lc day 0 NS days 1-14	NS
259	TS, 15	Dr day 0 WB, Dp+ day 1 NS days 2-14	NS
260	TS, 15	Dp+, Dr day 0 WB, Dp+ day 1 WB day 2 NS days 3-14	NS
<u>DOSE GROUP: 3.0 GM/KG - MALES</u>			
301	TS, 15	Dp+, S1 day 0 Dp+, WB day 1 NS days 2-14	NS
302	TS, 15	Dp+, Dr day 0 Dp+ day 1 NS days 2-14	NS
303	FD, 1	Dp++, Tr day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - slou and eroded
304	D, 0	Dp+, S1 day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - slou and inflamed.
305	TS, 15	Dp+, Dr, S1 day 0 Dp+, WB, Dr day 1 NS days 2-14	NS
306	TS, 15	Dp++, Dr, S1 day 0 Dp+ day 1 WB days 1-2 NS days 3-14	NS
307	TS, 15	Dp+, Dr day 0 Dp+, WB day 1 NS days 2-14	NS
308	FD 1	Dp+, S1, Lc day 0	Stomach, mucosa - slightly sloughed and inflamed

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4 (cont'd)

Individual Clinical and Necropsy Observations

<u>Rat No.</u>	<u>Day of Death</u>	<u>Clinical</u>	<u>Necropsy</u>
<u>DOSE GROUP: 3.0 GM/KG - MALES (Cont'd)</u>			
309	TS, 15	Dp+ day 0 NS days 1-14	NS
310	FD, 1	Dp+, Dr day 0	Liver - dark; stomach, mucos. sloughed and inflamed
<u>DOSE GROUP: 3.0 GM/KG - FEMALES</u>			
351	TS, 15	Dp+, Dr, WB, day 0 Dp+, WB day 1 NS days 2-14	NS
352	TS, 15	Dp+, Dr, Sl day 0 Dp+, Dr, WB day 1 NS days 2-14	NS
353	FD, 1	Dp++, Sl day 0	Lungs - hemorrhagic; stomach mucosa - slightly sloughed a few eroded areas
354	FD, 1	Dp+, Sl day 0	Stomach, mucosa - sloughed
355	FD, 1	Dp+ day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - slou and eroded
356	TS, 15	Dp+, WB day 0-1 NS days 2-14	NS
357	FD, 1	Dp+++ , Dr, Sl, Lc day 0 Extrem. Red day 0	Liver - dark; stomach, mucos sloughed and inflamed; gastr intestinal tract - gas fille
358	TS, 15	Dp+, Sl day 0 NS days 1-14	NS
359	TS, 15	Dp+ day 0-1 NS days 2-14	NS
360	TS, 15	Dp+, Dr day 0 Dp+ day 1 NS days 2-14	NS

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4 (Cont'd)

Individual Clinical and Necropsy Observations

Rat No.	Day of Death	Clinical	Necropsy
<u>DOSE GROUP: 4.0 GM/KG - MALES</u>			
401	FD, 1	Dp++, Sl, Dr. day 0	Liver - dark; gastrointestinal tract - gas filled; stomach mucosa - sloughed and eroded
402	FD, 1	Dp++, Sl, Lc day 0	Lungs - hemorrhagic; liver dark; stomach, mucosa - sloughed and inflamed
403	TS, 15	Dp+, Sl day 0 Dp++, WB days 1-2 Dp+ day 3 NS days 4-14	NS
404	FD, 1	Dp++, Sl, Dr day 0 Extrem Red, Pr day 0	Lungs - hemorrhagic; liver dark; stomach, mucosa - sloughed and eroded
405	FD, 1	Dp+++, Dr, day 0	Lungs - hemorrhagic; liver dark; stomach, mucosa - slightly sloughed and eroded
406	D, 0	Pr, Sl, Dy, Lc day 0	Lungs - hemorrhagic; liver dark; kidneys - renal pelvis enlarged; stomach, mucosa - inflamed
407	D, 0	Dp+++, WB, Sl, Dy day 0	Lungs - hemorrhagic; liver dark; stomach, mucosa - sloughed
408	FD, 2	Dp+, Sl, Dr day 0 Dp+++, Tr, Sl, WB day 1	Lungs - hemorrhagic; liver dark; stomach, mucosa - sloughed and eroded
409	D, 0	Dp+++, Sl, Pr day 0	Liver - dark; stomach, mucosa - sloughed
410	D, 0	Pr, Cv, Dy, Sl day 0	Lungs - hemorrhagic; liver dark; stomach, mucosa - sloughed and inflamed

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4 (Cont'd)

Individual Clinical and Necropsy Observations

Rat No.	Day of Death	Clinical	Necropsy
<u>DOSE GROUP: 4.0 GM/KG - FEMALES</u>			
451	TS, 15	Dp+, Sl, day 0 Dp+++ , Sl, Tr days 1-2 Dp+ days 3-8 HSES days 8-14	NS
452	FD, 7	Dp++, Sl, Lc day 0 Dp+++ , Tr, WB days 1-2 Dp++ , WB, At days 3-6	Stomach, mucosa - sloughed and eroded
453	D, 0	Pr, Sl day 0	Stomach, mucosa - inflamed appearing
454	FD, 1	Dr, Sl, Pr, Cv, WB day 0 Extrem red, Dy day 0	Lungs - hemorrhagic; stomach mucosa - sloughed and eroded
455	D, 0	Sl, Lc, Pr, Dy day 0 Extrem red day 0	Lungs - hemorrhagic; liver-dark; stomach, mucosa - sloughed and eroded
456	FD, 1	Dp++ , Lc, Dr, Sl day 0	Liver - dark; stomach, mucosa - sloughed and eroded
457	FD, 1	Dp+ day 0	Lungs - hemorrhagic; stomach mucosa - sloughed, eroded and inflamed
458	FD, 1	Dp++ , Dr day 0	Lungs - hemorrhagic; stomach mucosa - sloughed
459	FD, 2	Dp+ , Sl day 0 Dp++ , WB day 1	Stomach, mucosa - sloughed and eroded
460	FD, 1	Dr, Sl, Pr, Cv, WB, Dy day 0 Extrem red day 0	Lungs - hemorrhagic; stomach mucosa - inflamed, sloughed; Gastrointestinal tract - gas filled

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4 (Cont'd)

Individual Clinical and Necropsy Observations

Rat No.	Day of Death	Clinical	Necropsy
<u>DOSE GROUP: 5.0 GM/KG - MALES</u>			
501	D, 0	Sl, Dy, Pr day 0 Extrem red day 0	Liver - dark; stomach, mucos slightly eroded
502	D, 0	NG day 0	Liver - dark; lungs - hemorr
503	FD, 2	Dp+++, Sl day 0 Dp+++, WB day 1	Lungs - hemorrhagic; liver - mottled; stomach, mucosa - sloughed and eroded
504	FD, 1	Sl, Dr, Pr, Cv day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - slou inflamed and eroded
505	D, 0	Sl, Dy, Pr day 0 Extrem Red day 0	Lungs - hemorrhagic, liver - dark; stomach, mucosa - slou and hemorrhagic
506	FD, 1	Dp++, Sl, Dr, Lc day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - slou gastrointestinal tract - gas filled
507	FD, 1	Dp++, Sl, Dr day 0 Extrem Red day 0	Lungs - hemorrhagic; stomach mucosa - sloughed, inflamed eroded
508	FD, 1	Dp+++, Dr, Cv day 0	Stomach, mucosa - sloughed, inflamed and eroded
509	FD, 1	Dp+, Sl day 0	Lungs - hemorrhagic; stomach mucosa - sloughed and erodec
510	D, 0	Sl, Pr day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - slou and eroded
<u>DOSE GROUP: 5.0 GM/KG - FEMALES</u>			
551	FD, 1	Dp+, Dr, Sl day 0	Liver - dark; stomach, mucos inflamed, eroded and sloughed
552	FD, 1	Dp++, Dr, Sl day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - slou and eroded; gastrointestinal tract - gas filled
553	FD, 1	Dp+, Sl day 0	Lungs - hemorrhagic; stomach mucosa - sloughed and erodec

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 4 (Cont'd)

Individual Clinical and Necropsy Observations

Rat No.	Day of Death	Clinical	Necropsy
<u>DOSE GROUP: 5.0 GM/KG - FEMALES (Cont'd)</u>			
554	FD, 1	Pr, Dr, Sl, Dy day 0	Stomach, mucosa - sloughed and eroded
555	D, 0	Dp+, Sl day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - sloughed
556	FD, 1	Pr, Sl, Lc, Dr day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - sloughed and inflamed
557	D, 0	Dp++, day 0	Lungs - congested; liver - dark; stomach, mucosa - a 3 dia dark area
558	FD, 1	Dp+++, Sl day 0	Lungs - hemorrhagic; liver - dark; stomach, mucosa - sloughed
559	D, 1	Dp++, Sl day 0 Dp++, WB day 1	Lungs - hemorrhagic; liver - dark; stomach, mucosa - sloughed
560	D, 0	Sl, Pr, Dy day 0 Extrem Red day 0	Liver - dark; stomach, mucosa - sloughed and inflamed

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 5

Survivors Showing Toxic Signs per Observation PeriodKEY TO SYMBOLS:

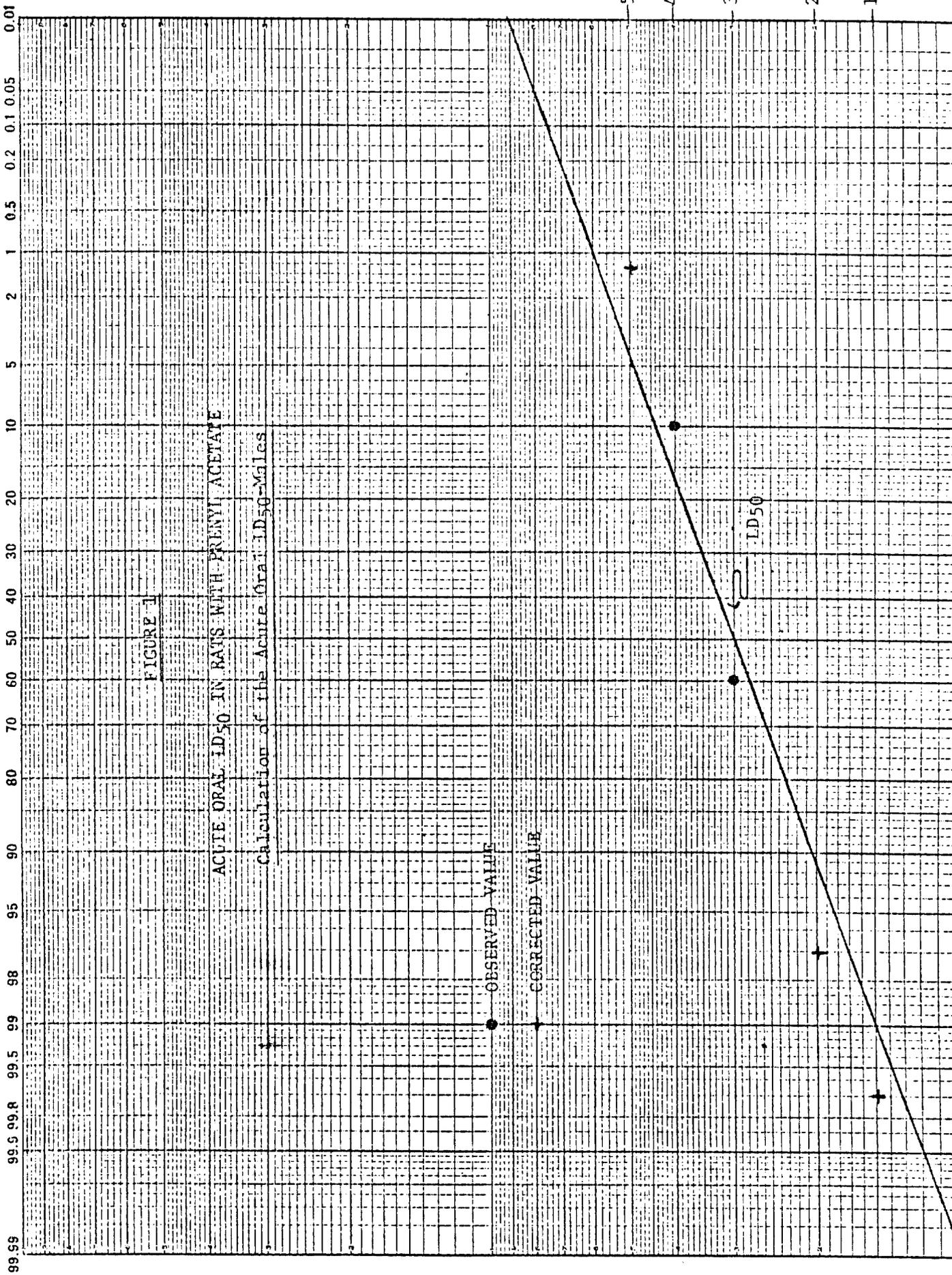
Dp	-	Depressed
Lc	-	Lacrimation
Sl	-	Salivation
Dr	-	Diarrhea
Pr	-	Prostrate
Dy	-	Dyspnea
Cv	-	Convulsion
Tr	-	Trembling
At	-	Ataxia
WB	-	Wet Belly
Extrem Red	-	Paws, ears, tail appeared very red
HSES	-	Hypersensitive to external stimuli

ACUTE ORAL LD₅₀ IN RATS WITH PRENYL ACETATE

TABLE 5 (Cont'd)

Survivors Showing Toxic Signs per Observation Period

Toxic Signs	HOURS POST ADMINISTRATION							DAYS POST ADMINISTRATION												
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	8	9	10	11	12	13
	DOSE GROUP: 4.0 GM/KG - MALES																			
Dp	8/10	8/10	8/9	9/9	6/7	6/6	4/6	2/2	1/1	1/1	-	-	-	-	-	-	-	-	-	-
Lc	-	1/10	-	1/9	1/7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sl	-	5/10	5/9	5/9	2/7	2/6	1/6	1/2	-	-	-	-	-	-	-	-	-	-	-	-
Dr	-	-	-	-	-	4/6	2/6	-	-	-	-	-	-	-	-	-	-	-	-	-
Pr	-	-	-	-	1/7	-	1/6	-	-	-	-	-	-	-	-	-	-	-	-	-
Dy	-	1/10	-	1/9	1/7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cv	-	-	-	-	1/7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tr	-	-	-	-	-	-	-	1/2	-	-	-	-	-	-	-	-	-	-	-	-
At	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
WB	-	-	-	1/9	-	-	-	2/2	1/1	-	-	-	-	-	-	-	-	-	-	-
Extrem Red	-	-	-	-	1/7	1/6	1/6	-	-	-	-	-	-	-	-	-	-	-	-	-
Death	-	-	1/10	-	2/9	1/7	-	4/6	1/2	-	-	-	-	-	-	-	-	-	-	-
HSES	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	DOSE GROUP: 4.0 GM/KG - FEMALES																			
Dp	7/10	7/10	8/9	9/9	8/9	7/8	6/8	3/3	2/2	2/2	2/2	2/2	2/2	1/1	1/1	-	-	-	-	-
Lc	-	-	-	2/9	1/9	1/8	1/8	-	-	-	-	-	-	-	-	-	-	-	-	-
Sl	-	4/10	4/9	6/9	5/9	3/8	3/8	1/3	1/2	-	-	-	-	-	-	-	-	-	-	-
Dr	-	2/10	3/9	3/9	3/9	2/8	2/8	-	-	-	-	-	-	-	-	-	-	-	-	-
Pr	-	1/10	-	-	1/9	1/8	2/8	-	-	-	-	-	-	-	-	-	-	-	-	-
Dy	-	-	-	-	1/9	1/8	2/8	-	-	-	-	-	-	-	-	-	-	-	-	-
Cv	-	-	-	-	-	1/8	2/8	2/3	2/2	-	-	-	-	-	-	-	-	-	-	-
Tr	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
At	-	-	-	-	-	-	-	-	-	1/2	1/2	1/2	1/2	1/2	1/2	-	-	-	-	-
WB	-	-	-	-	-	2/8	2/8	2/3	1/2	1/2	1/2	1/2	1/2	1/2	-	-	-	-	-	-
Extrem Red	-	-	-	-	1/9	1/8	2/8	-	-	-	-	-	-	-	-	-	-	-	-	-
Death	-	-	1/10	-	-	1/9	-	-	1/3	-	-	-	-	1/2	-	-	-	-	-	-
HSES	-	-	-	-	-	1/9	-	5/8	1/3	-	-	-	-	-	1/1	1/1	1/1	1/1	1/1	1





99.99 99.9 99.8 99.5 99 98 95 90 80 70 60 50 40 30 20 10 5 2 1 0.5 0.2 0.1 0.05 0.01

FIGURE 4

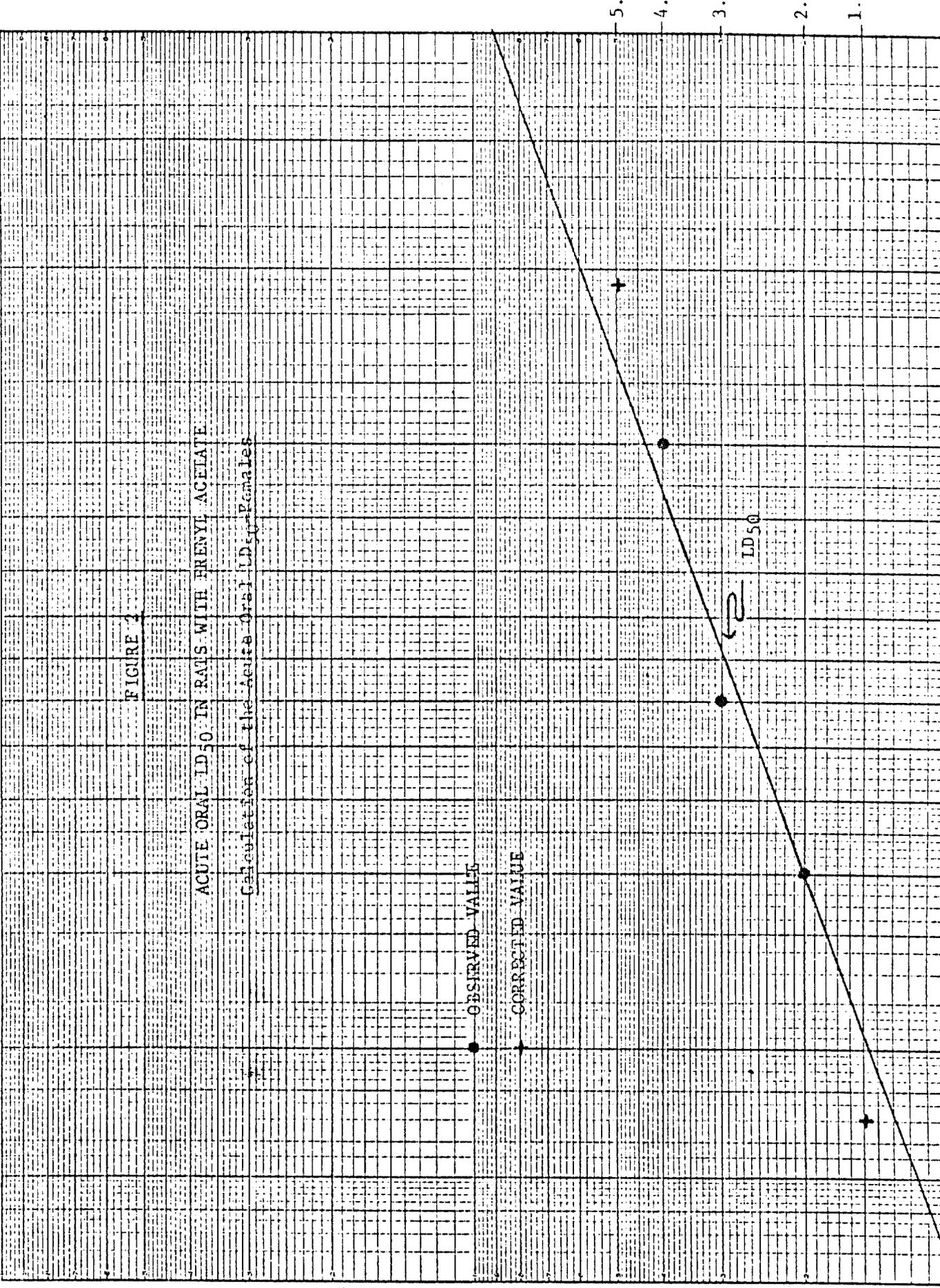
ACUTE ORAL LD₅₀ IN RATS WITH FRENYL ACETATE

Calculation of the Acute Oral LD₅₀ Females

OBSERVED VALUE

CORRECTED VALUE

LD₅₀



Front Sheet

Study No. RCP0678
Project No. Acute Oral LD₅₀ in Rats
Sponsor Chemical Division, Rhodia Inc.
Start Date 7-6-78
Duration 14 days
Finish Date 7-21-78
Study Director SEH
Study Personnel CM, JCW

Chemical Prenyl Acetate
Purity 99.8%
Animal Rat
No. M 50 F 50
Start Weight
M 150-200 gm
F 150-200 gm
Route Oral

<u>Animal No.</u>	<u>Tag Color</u>	<u>Treatment Level (gm/kg)</u>
101-110 M 151-160 F	White Tag	1.5
201-210 M 251-260 F	Blue Tag	2.0
301-310 M 351-360 F	Green Tag	3.0
401-410 M 451-460 F	Pink Tag	4.0
501-510 M 551-560 F	Yellow Tag	5.0

Assays or Special Procedures

OBSERVATIONS:

1. Body weights - days 0, 1, 4, 7, 10 and 14
2. Clinical observations - day 0 (frequently), days 1-14, twice daily (a.m. & p.m.)
3. Gross necropsy on all rats

Special Handling

Warning: Handle with care, avoid skin and eye contact. In case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.



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PROTOCOL

TITLE

Acute Oral LD₅₀ in Rats with Prenyl Acetate

PURPOSE

To determine the acute toxicity and lethality of Prenyl Acetate in rats according to the EPA proposed guidelines of April, 1978; 162.81-1.

LOCATION

This study will be conducted at the Rhodia Inc., Toxicology-Pathology facility on the Hess & Clark Research Farm, Ashland, Ohio 44805.

SPONSOR

This study is sponsored by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey.

ANIMALS

One hundred (100) Sprague Dawley derived outbred albino rats, 50 males and 50 females, from Flow Laboratories, Dublin, Virginia and weighing between 150 and 200 grams at the start of the study period, will be divided into 5 dose groups of 10 males and 10 females each.

HOUSING

Quarantine - the rats will be held in a quarantine room for a 1 to 2 week acclimation period depending on the age and weight of the rats. The rats will be randomly distributed from the shipping crates into the gang cages. The rats will be housed 3 to 4 per sex per cage in suspended 1.3 cm wire mesh cages, 43 x 18 x 25 cm. The rats will receive feed and water ad libitum. The feeders, water bottles, cages and racks will be changed once per week.

The quarantine and test room will be temperature (72°F ± 1°), humidity (50%) and light (12 hours on, 12 hours off) controlled.



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During the quarantine-acclimation period the rats will be examined by a veterinarian with respect to their state of health and suitability as test animals. Conventional disease control will be practiced during the quarantine-acclimation and study period.

Study room - at the end of the quarantine period, the cage racks containing the test animals will be moved to the test room. The rats will be randomly distributed from the quarantine racks to the test racks according to the Standard Operating Procedures, Manual #2. The rats will be housed in individual 1.3 cm wire mesh stainless steel suspended cages, 18 x 18 x 23 cm. The rats will be weighed. If the mean body weights of any dose group varies significantly from any other group, the rats will be redistributed so that the mean body weights of all dose groups do not vary significantly. The rats will receive food and water ad libitum. The feeders, water bottles, cages and racks will be changed once per week.

DIET

The rats will be maintained on a diet of Wayne Lab-Blox, manufactured by Allied Mills, Fort Wayne, Indiana and containing 24% crude protein, 4% crude fat and 4.5% crude fiber. Tap water will be provided by 8 oz. water bottles with sipper tubes.

IDENTIFICATION

The rats will be identified by ear notches. An identifying tag will be placed on each rat cage indicating the study number and rat number. The rats will be ear notched as follows:

101-110 M	1.5 gm/kg	white tag
151-160 F		
201-210 M	2.0 gm/kg	blue tag
251-260 F		
301-310 M	3.0 gm/kg	green tag
351-360 F		
401-410 M	4.0 gm/kg	pink tag
451-460 F		
501-510 M	5.0 gm/kg	yellow tag
551-560 F		



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TEST SUBSTANCE

The test substance will be Prenyl Acetate, a clear liquid supplied by Rhodia Inc., Chemical Division, Mormouth Junction, New Jersey and received June 16, 1978. Identifying numbers on the label are: AV-307-25 (cut 25). Purity is 99.8%, density is 0.84 and pH is 4.8.

Warning: Handle with care, avoid skin and eye contact. In case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.

TEST PROCEDURE

The test substance will be diluted in corn oil to give the dose levels recorded in Table 1. Each concentration will be mixed continuously on a magnetic stirrer during the dosing. Each rat will receive a dose volume of 10 ml/kg body weight according to the dose schedule recorded in Table 2. The rats will be orally gavaged one time with a curved 18 x 2 w/2½ mm ball dosing needle. The rats will be fasted from food 18 hours prior to dosing.

OBSERVATIONS

The animals will be weighed prior to dosing to determine the ml of test substance to be administered. Survivors will be weighed on days 1, 4, 7, 10 and 14 of the 14 day observation period. The weighing will be performed on a Mettler electronic balance interfaced to a programmable calculator, HP 9815A. The day of dosing will be designated as day 0. The rats will be observed frequently during the first 8 hours post-treatment and then twice daily (a.m. and p.m.) for the remaining 13 days. All relevant clinical signs including the nature, onset, severity and duration of each toxic or pharmacological sign, and time of death will be recorded. Survivors will be sacrificed on day 15.

GROSS NECROPSY

A gross necropsy will be performed on all rats in the LD₅₀ study. The examination will include: heart, lung, spleen, liver, kidney, stomach, small and large intestine and urinary bladder. Any lesions will be recorded.



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Research Department



RECORDS TO BE MAINTAINED

A study record book will be maintained according to Manual #19 in the Standard Operating Procedures and will include the following records:

1. Body weight - days 0, 1, 4, 7, 10 and 14
2. Day 0 observations
3. Daily observations
4. Necropsy observations
5. Data analysis

DATA ANALYSIS AND FINAL REPORT

A final report will be issued and the data will be tabulated by sex and dose level and will include:

1. animals showing clinical signs/animal dosed
2. animals dead/animal dosed
3. time to death after dosing

The LD₅₀ with 95% confidence limits will be calculated for each sex according to Litchfield and Wilcoxon and dose response curves drawn.

STORAGE OF DATA

All raw data generated during this study and the final report will be stored in the archives at Rhodia Inc., Toxicology-Pathology facility in Ashland, Ohio

Prepared by: S. E. Hastings
S. E. Hastings, B.S.
Study Director

Approved by: John G. Page
John G. Page, Ph.D.
Manager, Toxicology-Pathology
Rhodia, Inc.

Approved by: E. M. Kiggins
E. M. Kiggins, Ph.D.
Director of Research
& Product Development



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ASHLAND, OHIO 44805
Research Department



TABLE 1

LD₅₀ STUDY

Dose Level (g/kg)	No. Rats		Volume or Wt of Test Substance	Volume of Diluent or Susp. Agent	Mg of Test Substance per ml
	M	F			
1.5	10	10	8 ml	qs to 44.8 ml	150
2.0	10	10	10 ml	qs to 42 ml	200
3.0	10	10	15 ml	qs to 42 ml	300
4.0	10	10	20 ml	qs to 42 ml	400
5.0	10	10	24 ml	qs to 40.3 ml	500

Concentration of prenyl acetate/ml = 840 mg

Calculations

1500 mg/kg/10 ml/kg = 150 mg/ml dilute 1:5.60

2000 mg/kg/10 ml/kg = 200 mg/ml dilute 1:4.20

3000 mg/kg/10 ml/kg = 300 mg/ml dilute 1:2.80

4000 mg/kg/10 ml/kg = 400 mg/ml dilute 1:2.10

5000 mg/kg/10 ml/kg = 500 mg/ml dilute 1:1.68



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Research Department



TABLE 2

DOSE SCHEDULE

10 ml/kg body weight
or 1 ml/100 gm body weight

Gm Body Weight	Dose Volume ml
100	1.0
110	1.1
115	1.2
120	1.2
125	1.3
130	1.3
135	1.4
140	1.4
145	1.5
150	1.5
155	1.6
160	1.7
165	1.7
170	1.7
175	1.8
180	1.8
185	1.9
190	1.9
195	2.0
200	2.0

PRIMARY EYE IRRITATION IN RABBITS WITH PRENYL ACETATE

Study No. BCE1278

Report No. SEH 78:25

Toxicology-Pathology Laboratory
Rhodia Inc.
Ashland, Ohio 44805

June 14, 1978

PRIMARY EYE IRRITATION IN RABBITS WITH PRENYL ACETATE

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EXPERIMENTAL

MATERIALS AND METHODS

ANIMALS

Nine adult male New Zealand albino rabbits were purchased from Davidson's Mill Farm, Jamesburg, New Jersey and weighed between 2 and 3 kg at the start of the study.

HOUSING

Quarantine - the rabbits were held in a quarantine room for a three week acclimation period depending on the age and weight of the rabbits. The rabbits were housed 3 per sex in large wire bottom animal cages, 71 x 86 x 71 cm. The rabbits received food and water ad libitum. The feeders, waterers and cage floor racks were cleaned once per week. The waste pans were flushed at least once per day and more often if required. The quarantine and test room were temperature ($69^{\circ}\text{F} \pm 1^{\circ}$), humidity (50%) and light (14 hours on, 10 hours off) controlled. During the quarantine-acclimation period, the rabbits were examined by a veterinarian with respect to their state of health and suitability as test animals. The eyes of the test rabbits were examined using the fluorescein dye procedure and only those rabbits without defects or irritation were used. The quarantine and test rooms were maintained so as to exclude materials that might produce eye irritation. Conventional disease control was practiced during the quarantine-acclimation and study period.

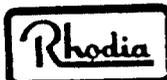
Study Room - at the end of the quarantine period, the rabbits were moved into the test room and transferred into individual suspended wire bottom rabbit cages, 46 x 51 x 33 cm. The rabbits received food and water ad libitum. The feeders, waterers and cage floor racks were cleaned once per week. A liquid litter from Pharmalac, Westport, Conn., was used in the litter pans and was changed twice weekly.

DIET

For the first 5 days of the acclimation period the rabbits were treated prophylactically with Pfizer's Neo-Terramycin soluble powder (5 g/gallon) in the drinking water.



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Report No. SEH 78:25
Page: 3

The rabbits were maintained on a diet of tap water and Wayne Rabbit Ration manufactured by Allied Mills, Fort Wayne, Indiana and containing 2% crude fat, 17% crude protein and 15% crude fiber and 0.025% of sulfaquinoxaline.

IDENTIFICATION

The rabbits were identified by a number tattooed in the right ear, 101-106, Group I; 201-203, Group II. An identifying tag was placed on each rabbit's cage indicating the rabbit's number, the study number and whether it was in Group I - no wash, or Group II - one minute wash.

TEST SUBSTANCE

The test substance was Prenyl Acetate, a clear liquid supplied by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey and received May 24, 1978. Identifying numbers on the label are: SD4 C/6 - 12 ref. JRT 291-175; greater than 99% purity and a density of 0.84.

TEST PROCEDURE

A 0.1 ml aliquot of the test substance was placed on the everted lower lid of the right eye of 9 rabbits. The upper and lower lids were gently held together for 20-30 seconds then released. The left eye remained untreated and served as a control. The treated eyes of 6 rabbits (Group I) remained unwashed. The remaining 3 rabbits had the treated eye flushed for 1 minute with lukewarm water starting no sooner than 20-30 seconds after instillation. These rabbits were designated as Group II.

OBSERVATIONS

The eyes were examined by the fluorescein dye technique and the grade of ocular reaction recorded at 24, 48, 72 hours and 4 and 7 days post instillation. The eyes were graded and the irritation scores determined by the Draize procedure in accordance with Table 1.



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Author: S. E. Hastings, B.S.
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RECORDS MAINTAINED

A study record book was maintained according to the Standard Operating Procedures. The following records were included:

Group I	observation sheets
Group II	observation sheets
Group I	irritation scores
Group II	irritation scores

STORAGE OF DATA

All raw data generated during this study and the final report are on file in the archives of Rhodia Inc., Toxicology-Pathology facility in Ashland, Ohio.



RESULTS AND DISCUSSION

The criteria for grading ocular reactions is presented in Table 1. Table 2 presents the individual eye irritation scores. Table 3 illustrates the corneal retention of 2% sodium fluorescein for the individual rabbits. Table 4 presents the averages and ranges for each test group. Table 5 is the classification of test substances based on eye irritation properties.

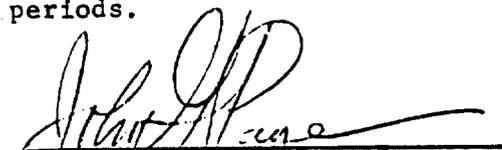
Group I No wash

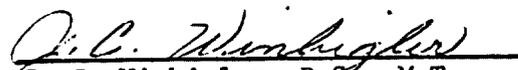
At 24 hours post instillation, 3 of the 6 test eyes had a corneal opacity grade of 1. One of these eyes also had a mild amount of discharge. These 3 test eyes had a positive fluorescein response at 24 hours. No conjunctivitis or chemosis was evident at 24 hours or at any other observation period. All the eyes were negative and exhibited a negative fluorescein response at the 48 hour observation period. No ocular irritation was observed at 72 hours, 4 or 7 days post instillation.

Group II One minute wash

No ocular irritation was observed at any of the observation periods during the study. All 3 test eyes had a negative response to the fluorescein test at all observation periods.


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Toxicologist


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TABLE 1
GRADES FOR OCULAR REACTIONS+

	<u>Cornea</u>	<u>Grade</u>
(A) Opacity		
No ulceration or opacity		0
Scattered or diffuse areas of opacity; details of iris clearly visible		1*
Easily discernible translucent areas of opacity; details of iris slightly obscured		2*
Nacreous areas of opacity; no details of iris visible; size of pupil barely discernible		3*
Complete corneal opacity; iris not discernible		4*
 (B) Area of Cornea involved		
Normal		0
One quarter (or less), but not zero		1
Greater than one quarter, but less than half		2
Greater than half, but less than three quarters		3
Greater than three quarters, up to whole area		4
A X B X 5	Total Maximum = 80	
	<u>Iris</u>	
(C) Values		
Normal		0
Markedly deepened folds; congestion; swelling; moderate circumcorneal injection; iris still reacting to light		1*
No reaction to light; hemorrhage; gross destruction		2*
C X 5	Total Maximum = 10	

TABLE 1 (Cont'd)

GRADES FOR OCULAR REACTIONS+

	<u>Conjunctivae</u>	<u>Grade</u>
(D) Redness		
Vessels normal		0
Some vessels definitely injected		1
Diffuse crimson red; individual vessels not easily discernible		2*
Diffuse beefy red		3*
(E) Chemosis		
No swelling		0
Any swelling above normal		1
Obvious swelling; partial eversion of lids		2*
Swelling with lids about half closed		3*
Swelling with lids more than half closed		4*
(F) Discharge		
No discharge		0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)		1
Discharge with moistening of the lids and hairs just adjacent to lids		2
Discharge with moistening of the lids and hairs and considerable area around the eye		3
(D + E + F) X 2		Total Maximum = 20

+ Grades constitute combination of FHSLA and Draize method.

* Grades considered positive for irritation.

"An animal should be considered as exhibiting a positive reaction if the test substance produced at any of the readings, ulceration of the cornea (other than a fine stippling); or opacity of the cornea (other than a slight dulling the normal luster); or inflammation of the iris (other than a slight deepening the folds; or rugae, or a slight circumcorneal injection of the blood vessels or if such substances produce in the conjunctivae (excluding the cornea and i an obvious swelling with partial eversion of the lids or a diffuse crimson re with individual vessels not easily discernible. 1"

1 Federal Register, Vol. 38, No. 187 - September 27, 1973, p 27019.

PRIMARY EYE IRRITATION IN RABBITS WITH PRENYL ACETATE

TABLE 2

Eye Irritation Scores

Animal Number	Cornea		Iris	Conjunctivae			Total Score per Animal
	A X	B X 5	C X 5	(D + E + F) X 2			
	<u>24 Hours</u>						
<u>No Wash</u>	A	B	C	D	E	F	
101	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0
103	1	1	0	0	0	1	7
104	0	0	0	0	0	0	0
105	1	1	0	0	0	0	5
106	1	1	0	0	0	0	5
<u>One Minute Wash</u>							
201	0	0	0	0	0	0	0
202	0	0	0	0	0	0	0
203	0	0	0	0	0	0	0
	<u>48 Hours</u>						
<u>No Wash</u>	A	B	C	D	E	F	
101	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0
<u>One Minute Wash</u>							
201	0	0	0	0	0	0	0
202	0	0	0	0	0	0	0
203	0	0	0	0	0	0	0

PRIMARY EYE IRRITATION IN RABBITS WITH PRENYL ACETATE

TABLE 2 (Cont'd)

Eye Irritation Scores

Animal Number	Cornea		Iris	Conjunctivae			Total Score per Animal
	A X	B X 5	C X 5	(D + E + F) X 2			
	<u>72 Hours</u>						
<u>No Wash</u>	A	B	C	D	E	F	
101	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0
<u>One Minute Wash</u>							
201	0	0	0	0	0	0	0
202	0	0	0	0	0	0	0
203	0	0	0	0	0	0	0
	<u>4 Days</u>						
<u>No Wash</u>	A	B	C	D	E	F	
101	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0
<u>One Minute Wash</u>							
201	0	0	0	0	0	0	0
202	0	0	0	0	0	0	0
203	0	0	0	0	0	0	0

PRIMARY EYE IRRITATION IN RABBITS WITH PRENYL ACETATE

TABLE 2 (Cont'd)

Eye Irritation Scores

Animal Number	Cornea		Iris	Conjunctivae			Total Score per Animal
	A X	B X 5	C X 5	(D + E + F) X 2			
	<u>7 Days</u>						
<u>No Wash</u>	A	B	C	D	E	F	
101	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0
<u>One Minute Wash</u>							
201	0	0	0	0	0	0	0
202	0	0	0	0	0	0	0
203	0	0	0	0	0	0	0

TABLE 3 : CORNEAL RETENTION OF 2% SODIUM FLUORESCEIN

3BIT IBER	PRE-DOSE *	24 HOURS POST-DOSE	48 HOURS POST-DOSE	72 HOURS POST-DOSE	4 DAYS POST-DOSE	7 DAYS POST-DOSE
01						
02						
03						
04						
05						
06						
01						
02						
03						

NO CORNEAL RETENTION

PRIMARY EYE IRRITATION IN RABBITS WITH PRENYL ACETATE

TABLE 4

Averages and Ranges for Each Test Group

Time	Group	Average	Range
24 hour	No wash	2.8	0-7
	One minute wash	0	0
48 hour	No wash	0	0
	One minute wash	0	0
72 hour	No wash	0	0
	One minute wash	0	0
4 day	No wash	0	0
	One minute wash	0	0
7 day	No wash	0	0
	One minute wash	0	0

Note: Using the average irritation scores, Prenyl Acetate would be classified as a minimal eye irritant.

TABLE 5

Classification of Test Substance
Based on Eye Irritation Properties

Rating	Range	Definition
Non-Irritating	0.0 - 0.5	To maintain this rating, all scores at the 24-hour reading must be zero; otherwise, increase rating one level
Practically Non-Irritating	> 0.5 - 2.5	To maintain this rating, all scores at the 24-hour reading must be zero; otherwise, increase rating one level.
Minimally Irritating	> 2.5 - 15.0	To maintain this rating, all scores at the 72-hour reading must be zero; otherwise, increase rating one level
Mildly Irritating	>15.0 - 25.0	To maintain this rating, all scores at the 7-day reading must be zero; otherwise, increase rating one level.
Moderately Irritating	>25.0 - 50.0	To maintain this rating, scores at 7 days must \leq 10 for 60% or more of the animals. Also, mean 7-day score must \leq 20. If 7-day mean score is \leq 20 but $<$ 60% of animals show scores $<$ 10, then no animals among those showing scores $>$ 10 can exceed a score of 30 if rating is to be maintained; otherwise, raise rating one level.

TABLE 5 (Cont'd)

Classification of Test Substances
Based on Eye Irritation Properties*

Rating	Range	Definition
Severely Irritating	>50.0 - 80.0	To maintain this rating, scores at 7 days must be ≤ 30 for 60% or more of the animals. Also, mean 7-day score must be ≤ 40 . If 7-day mean score is ≤ 40 but $< 60\%$ of the animals show scores ≤ 30 , then no animal among those showing scores > 30 can exceed a score of 60 if rating is to be maintained; otherwise, raise rating one level.
Extremely Irritating	>80.0 - 110.0	

* From "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes", Draize

Front Sheet

Study No. BCE1278 Chemical Prenyl Acetate
Project No. Primary Eye Irritation Purity > 99%
Sponsor Chem. Division, Rhodia Inc. Animal Rabbit
Start Date 5-30-78 No. M 9 F
Duration 7 days Start Weight
Finish Date 6-6-78 M 2-3 kg
Study Director S. E. Hastings F
Study Personnel HEH, JCW Route Eye

<u>Animal No.</u>	<u>Treatment Level</u>
101	
102	
103	Group I - Eyes unwashed
104	
105	
106	
201	
202	Group II - Eyes washed
203	

Assays or Special Procedures

1. Eye exam prior to treatment
2. Eyes examined and scored at 24, 48 and 72 hours and 4 and 7 days post treatment

Special Handling

Prenyl Acetate should be handled with care. Avoid skin and eye contact, in case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.



PROTOCOL

TITLE

Primary Eye Irritation in Rabbits with Prenyl Acetate

PURPOSE

To determine if the instillation of Prenyl Acetate in the eyes of rabbits has any irritating effect according to the EPA proposed guidelines, April, 1978; 162-81-4.

LOCATION

The study will be conducted at the Rhodia Inc., Toxicology-Pathology facility on the Hess & Clark Research Farm in Ashland, Ohio.

SPONSOR

The study is sponsored by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey.

ANIMALS

Nine adult New Zealand albino rabbits will be purchased from Davidson's Mill Farm, Jamesburg, New Jersey and will weigh between 2 to 3 kg at the start of the study.

HOUSING

Quarantine - the rabbits will be held in a quarantine room for a 1 to 2 week acclimation period depending on the age and weight of the rabbits. The rabbits will be housed 3 per sex in large wire bottom animal cages, 71 x 86 x 71 cm. The rabbits will receive feed and water ad libitum. The feeders, waterers and cage floor racks will be cleaned once per week. The waste pans will be flushed at least once per day and more often if required. The quarantine and test room will be temperature ($69^{\circ} \text{F} \pm 1^{\circ}$), humidity (50%) and light (14 hours on, 10 hours off) controlled.

When the newly arrived rabbits are distributed into the gang cages, care will be taken to put as many box mates as possible in the same gang cage.

During the quarantine-acclimation period, the rabbits will be examined by a veterinarian with respect to their state of health and suitability as test animals.



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ASHLAND, OHIO 44805
Research Department



The eyes of the test rabbits will be examined using the fluorescein dye procedure and only those rabbits without defects or irritation will be used. The quarantine and test room will be maintained so as to exclude materials that might produce eye irritation. Conventional disease control will be practiced during the quarantine-acclimation and study period.

Study Room - At the end of the quarantine period, the rabbits will be moved into the test room and transferred into individual suspended wire bottom rabbit cages, 46 x 51 x 33 cm. The rabbits will receive food and water ad libitum. The feeders, waterers and cage floor racks will be cleaned once per week. A liquid litter from Pharmecal, Westport, Conn., will be used in the litter pans and will be changed twice weekly.

DIET

For the first 5 days of the acclimation period the rabbits will be treated prophylactically with Pfizer's Neo-Terramycin soluble powder (5 g/gallon) in the drinking water.

The rabbits will be maintained on a diet of tap water and Wayne Rabbit Ration manufactured by Allied Mills, Fort Wayne, Indiana and containing 2% crude fat, 17% crude protein and 15% crude fiber and 0.025% of sulfaquinoxaline.

IDENTIFICATION

The rabbits will be identified by a number tattooed in the right ear, 101-106, Group I; 201-203, Group II. An identifying tag will be placed on each rabbit's cage indicating the rabbit's number, the study number and whether it is in Group I or II.

TEST SUBSTANCE

The test substance will be Prenyl Acetate, a clear liquid supplied by Rhodia, Inc., Chemical Division, Monmouth Junction, New Jersey and received May 24, 1978. Identifying numbers on the label are: SD4 C/6 12 ref. JRT 291-175; purity greater than 99% and density of 0.84.

Warning: Handle with care, avoid skin and eye contact. In case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.



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TEST PROCEDURE

A 100 mg or 0.1 ml aliquot of the test substance will be placed on the everted lower lid of the right eye of 9 rabbits. The upper and lower lids will be gently held together for 20-30 seconds then released. The left eye will remain untreated and will serve as a control. The treated eyes of 6 rabbits (Group I) will remain unwashed. The remaining 3 rabbits will have the treated eye flushed for 1 minute with lukewarm water starting no sooner than 20-30 seconds after instillation. These rabbits will be designated as Group II.

OBSERVATIONS

The eyes will be examined by the fluorescein dye technique and the grade of ocular reaction recorded at 24, 48, 72 hours and 4 and 7 days post-instillation and daily thereafter, so long as injury persists (up to 14 days). The eyes will be graded and the irritation scores determined by the Draize procedure in accordance with Tables 1 and 2.

RECORDS TO BE MAINTAINED

A study record book will be maintained according to Manual #19 in the Standard Operating Procedures and the following records will be included:

Group I observation sheets
Group II observation sheets
Group I irritation scores
Group II irritation scores

DATA ANALYSIS AND FINAL REPORT

A final report will be issued. The data will be tabulated and will include the individual primary eye irritation score at 24, 48 and 72 hours and 4 and 7 days for each rabbit and the averages and range for each test group. Any serious lesions of the eye will be described.

STORAGE OF DATA

All raw data generated during this study and the final report will be stored in the archives of Rhodia, Inc., Toxicology-Pathology facility in Ashland, Ohio.

Prepared by: S. E. Hastings
S. E. Hastings, B.S.
Study Director

Approved by: John G. Page
John G. Page, Ph.D.
Manager, Toxicology-Path
Rhodia, Inc.

Approved by: E. M. Kiggins
E. M. Kiggins, Ph.D.
Director of Research
& Product Development

Table 1

Scale for Scoring Ocular Lesions

(1) Cornea

(A) Opacity-degree of density (area most dense taken for reading)	
No opacity	0
Scattered or diffuse area, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris invisible	4
(B) Area of cornea involved	
One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4
Score (AxB) x 5	Total Maximum = 80

(2) Iris

(C) Values	
Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, hemorrhage, gross destruction (any or all of these)	2
Score (C) x 5	Total Maximum = 10

(3) Conjunctivae

(D) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3
(E) Chemosis	
No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids about half closed to completely closed	4

Table 1 (Cont'd)

Scale for Scoring Ocular Lesions

(F) Discharge	
No discharge	0
Any amount different from normal (dose not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs, and considerable area around the eye	3
Score (D+E+F) x 2	Total Maximum = 20

NOTE: The maximum total score is the sum of all scores obtained for the cornea, iris and conjunctivae.

PRIMARY DERMAL IRRITATION WITH PRENYL ACETATE IN RABBITS

Study No. BCD1078

Report No. JCW 78:24

Toxicology-Pathology Laboratory
Rhodia Inc.
Ashland, Ohio 44805

June 13, 1978

PRIMARY DERMAL IRRITATION WITH PRENYL ACETATE IN RABBITS

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Protocol



RHODIA INC.
HESS & CLARK DIVISION
ASHLAND, OHIO 44805
Research Department



Author: J. C. Winbigler, B.S., M.T.
Report No. JCW 78:24
Date: June 13, 1978
Page: 1

Subject: Primary Dermal Irritation, Prenyl Acetate

Book No. 5407 Pages 33-36

Study No. BCD1078

Dates: 6-7-78 to 6-10-78

TITLE

Primary Dermal Irritation Study with Prenyl Acetate in Rabbits

PURPOSE

To determine if Prenyl Acetate has any irritating effect when applied to intact or abraded skin of rabbits.

LOCATION

The study was conducted at the Rhodia Inc., Toxicology-Pathology facility on the Hess & Clark Research Farm in Ashland, Ohio.

SPONSOR

The study was sponsored by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey.

SUMMARY

Prenyl Acetate was tested for possible skin irritation according to the EPA proposed guidelines of April, 1978; sec. 162.81-5.

Prenyl Acetate was found to be non-irritating to the skin of rabbits when evaluated under the conditions of this study.



EXPERIMENTAL

MATERIALS AND METHODS

ANIMALS

Six young adult male New Zealand albino rabbits were obtained from Davidson's Mill Farm, Jamesburg, New Jersey and weighed approximately 2 to 3 kg at the start of the study.

HOUSING

For a 1 to 2 week acclimation and quarantine period, the rabbits were gang housed in large wire bottom animal cages, 71 x 86 x 71 cm. Three rabbits from each shipping crate were placed in the same cage. Feeders, waterers and cage floors were cleaned weekly and waste pans were flushed once or twice daily as necessary. Temperature was maintained at $69^{\circ} \pm 1^{\circ}$ F, humidity at 50% and room lights were controlled automatically on a 14 hour light, 10 hour dark cycle for the quarantine and test periods.

A veterinarian examined the rabbits with respect to their state of health and suitability as test animals.

Following the quarantine period the rabbits were moved to the test rooms and placed in individual suspended wire bottom cages, 46 x 51 x 33 cm. Liquid litter from Pharmacal, Westport, Conn. was used in the litter pans and changed twice weekly.

DIET

The rabbits were maintained on Wayne Rabbit Ration, a nutritional balanced standard laboratory diet, manufactured by Allied Mills, Fort Wayne, Indiana, with an analysis of 2% crude fat, 17% crude protein, 15% crude fiber and containing 0.025% sulfaquinoxaline. For 5 days after arrival Pfizer's Neo-Terramycin soluble was added to the drinking water at 5 g/gallon to prevent illness from diet change. Food and water were available ad libitum throughout the quarantine and test periods.

IDENTIFICATION

After transfer from the quarantine room to the assigned test room the rabbits were numbered 101 through 106 by tattoo in the right ear. Each cage bore a label stating the study number, animal number and treatment.



RHODIA INC.
HESS & CLARK DIVISION
ASHLAND, OHIO 44805
Research Department



Author: J. C. Winbigler, B.S., M.T
Report No. JCW 78:24
Page: 3

TEST SUBSTANCE

The test substance was Prenyl Acetate, a clear liquid supplied by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey and received May 24, 1978. Identifying numbers on the label were: SD4 C/6 - 12 ref. JRT 291-175. Purity was more than 99% and the density was 0.84.

TEST PROCEDURE

Twenty-four hours before treatment, the backs of 6 adult rabbits were carefully clipped free of hair. The clipped area was large enough to accommodate 4, 2.5 x 2.5 cm application sites. The application sites were marked off on each rabbit and two of the sites, numbers 1 and 3 were abraded with a firm nylon toothbrush and the other two left intact. The abrasions were through the stratum corneum but not the dermis. Five tenths ml of the test material was applied directly to the application sites. A 2.5 cm square gauze pad was placed over the site. The pads were held securely in place with adhesive tape. The entire shaved area was covered with an impervious rubber cloth to prevent evaporation and maintain skin contact with the test material. The sheet was secured in place with adhesive tape. Protective collars were placed on the rabbits to prevent removal of the test material and they were returned to their appropriate cages.

After twenty-four hours the sheets were removed and the sites wiped (not washed) and the resulting reactions evaluated and scored at 24 and 72 hours post-treatment, according to Draize scoring system in Table 1. At termination of the study, all rabbits were euthanized by i.v. injection of pentobarbital sodium.



RESULTS AND DISCUSSION

The primary irritation scores for the 24 and 72 hour periods are shown in Table 2. Although good skin contact had been maintained, all sites were negative for irritation.

CONCLUSIONS

Prenyl Acetate is non-irritating to abraded or intact skin of rabbits.

RECORDS

A study record book was maintained according to Manual #19 of the Standard Operating Procedures and in addition, the following records were maintained:

1. Scores for erythema eschar and edema at 24 and 72 hours.
2. Primary skin irritation score for each animal according to Draize.

STORAGE OF DATA

All raw data generated by this study and the final report are on file in the archives of Rhodia Inc., Toxicology-Pathology facility in Ashland, Ohio.



J. C. Winbigler, B.S., M.T.
Toxicologist



John G. Page, Ph.D.
Manager, Toxicology-Pathology
Rhodia, Inc.



S. E. Hastings, B.S.
Toxicologist



E. M. Kiggins, Ph.D.
Director of Research
& Product Development



TABLE 1

Skin Reaction

Erythema and Eschar Formation:	<u>Value</u>
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema Formation:	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 millimeter)	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure)	4

Draize, J. H., 1959 - The Appraisal of Chemicals in Foods, Drugs, and Cosmetics, Association of Food and Drug Officials of the U.S.



TABLE 2

Primary Skin Irritation Scores of Rabbits

Study BCD1078

Findings	Exposure Time (hours)	Exposure Unit (Value)						Mean Score
		Rabbit Number						
		101	102	103	104	105	106	
Erythema and Eschar Formation								
Intact skin	24	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0
Abraded skin	24	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0
	Subtotal	0	0	0	0	0	0	0
Edema Formation								
Intact skin	24	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0
Abraded skin	24	0	0	0	0	0	0	0
	72	0	0	0	0	0	0	0
	Subtotal	0	0	0	0	0	0	0
	Total	0	0	0	0	0	0	0
								Average = 0

Draize Scoring Criteria

Primary Skin Irritation Indexes of 2 are mild irritants.
 Primary Skin Irritation Indexes of 2.0 to 5.0 are moderate irritants.
 Primary Skin Irritation Indexes of greater than 5.0 are severe irritants.

According to the Draize Scoring Criteria, the primary skin irritation index of Prenyl Acetate is zero.

Front Sheet

Study No. BCD1078
Project No. Primary Skin Irritation
Sponsor Chem. Division
Start Date 6-7-78
Duration 72 hours
Finish Date 6-10-78
Study Director J. Winbigler
Study Personnel H. Harrison

Chemical Prenyl Acetate
Purity >99%
Animal Rabbits
No. M 6 X
Start Weight
M 2-3 kg
F
Route Dermal

Animal No.

101
102
103
104
105
106

Treatment Level

0.5 mg/test site/animal

Assays or Special Procedures

1. Shave all backs
2. Prepare two intact and 2 abraded sites
3. Evaluate skins at 24 and 72 hours

Special Handling

Prenyl Acetate should be handled with care. Avoid skin and eye contact, in case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.



RHODIA INC.
HESS & CLARK DIVISION
ASHLAND, OHIO 44805
Research Department



PROTOCOL

TITLE

Primary Dermal Irritation with Prenyl Acetate in Rabbits

PURPOSE

To determine if the application of Prenyl Acetate on the skin of rabbits has any irritating effect according to the EPA proposed guidelines, April, 1978: 162.81-5.

LOCATION

This study will be conducted at the Rhodia Inc., Toxicology-Pathology facility on the Hess & Clark Research Farm, Ashland, Ohio 44805.

SPONSOR

This study is sponsored by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey.

ANIMALS

Six young adult male New Zealand albino rabbits will be obtained from Davidson's Mill Farm, Jamesburg, New Jersey and will weigh approximately 2 to 3 kg at the start of the study.

HOUSING

For a 1 to 2 week acclimation and quarantine period, the rabbits will be gang housed in large wire bottom animal cages, 71 x 86 x 71 cm. Three rabbits from each shipping crate will be placed in the same cage. Feeders, waterers and cage floors will be cleaned weekly and waste pans will be flushed once or twice daily as necessary. Temperature will be maintained at $69^{\circ} \pm 1^{\circ}$ F, humidity at 50% and room lights will be controlled automatically on a 14 hour light, 10 hour dark cycle for the quarantine and test periods.

A veterinarian will examine the rabbits with respect to their state of health and suitability as test animals.

Following the quarantine period the rabbits will be moved to the test rooms and placed in individual suspended wire bottom cages, 46 x 51 x 33 cm. Liquid litter from Pharmecal, Westport, Conn. will be used in the litter pans and changed twice weekly.



RHODIA INC.
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DIET

The rabbits will be maintained on Wayne Rabbit Ration, a nutritionally balanced standard laboratory diet, manufactured by Allied Mills, Fort Wayne, Indiana, with an analysis of 2% crude fat, 17% crude protein, 15% crude fiber and containing 0.025% sulfaquinoxaline. For 5 days after arrival Pfizer's Neo-Terramycin soluble will be added to the drinking water at 5 g/gallon to prevent illness from diet change. Food and water will be available ad libitum throughout the quarantine and test periods.

IDENTIFICATION

After transfer from the quarantine room to the assigned test room, the rabbits will be numbered 101 through 106 by tattoo in the right ear. Each cage will bear a label stating the study number, animal number and treatment.

TEST SUBSTANCE

The test substance will be Prenyl Acetate, a clear liquid supplied by Rhodia Inc., Chemical Division, Monmouth Junction, New Jersey and received May 24, 1978. Identifying numbers on the label are: SD4 C/6 - 12 ref. JRT 291-175. The purity is more than 99% and the density is 0.84.

Warning: Handle with care, avoid skin and eye contact. In case of accidental contact, immediately wash affected areas with large volumes of water and report the incident to the study director.

TEST PROCEDURE

Twenty-four hours before treatment, the backs of 6 male rabbits will be carefully clipped free of hair. The clipped area should be large enough to accommodate 4, 2.5 x 2.5 cm application sites. The application sites will be marked off on each rabbit and two of the sites, numbers 1 and 3 will be abraded with a firm nylon toothbrush and the other two left intact. The abrasions will be through the stratum corneum but not the dermis. Five-tenths gram or 0.5 ml of the test material will be applied directly to the application sites. A 2.5 cm square gauze pad will be placed over the site. The pads will be held securely in place with adhesive tape. The entire shaved area will be covered with an impervious rubberized cloth to prevent evaporation and maintain skin contact with the test material. The sheet will be secured in place with adhesive tape. Protective collars will be placed on the rabbits to prevent removal of the test material and they will be returned to their appropriate cages. After twenty-four hours the sheets will be removed and the sites wiped (not washed) and the



RHODIA INC.
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resulting reactions evaluated and scored at 24 and 72 hours post-treatment and any subsequent period according to Draize (Table 1). Following the study period all animals will be euthanized by i.v. injection of pentobarbital sodium.

RECORDS TO BE MAINTAINED

A study record book will be maintained according to Manual #19 of the Standard Operating Procedures and in addition, the following records will be maintained:

1. Scores for erythema eschar and edema at 24, 72 and any subsequent evaluation time.
2. Primary skin irritation score for each animal according to Draize.

DATA ANALYSIS AND FINAL REPORT

A final report will be issued and will contain the mean and range of erythema and edema scores for each time period, and the mean and range values for the primary irritation scores.

STORAGE OF DATA

All raw data generated by this study and the final report will be placed on file in the archives of Rhodia Inc., Toxicology-Pathology facility in Ashland, Ohio.

Prepared by:

J. C. Winbigler
J. C. Winbigler, B.S., M.T.
Study Director

Approved by:

John G. Page
John G. Page, Ph.D.
Manager, Toxicology-Pathology
Rhodia, Inc.

Approved by:

E. M. Kiggins
E. M. Kiggins, Ph.D.
Director of Research
& Product Development

TABLE 1

Skin Reaction

Erythema and Eschar Formation:	<u>Value</u>
No erythema	0
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Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema Formation:	
No edema	0
Very slight edema (bare perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 millimeter)	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure)	4

Draize, J. H., 1959 - The Appraisal of Chemicals in Foods, Drugs, and Cosmetics, Association of Food and Drug Officials of the U.S.

Triage of 8(e) Submissions

Date sent to triage: 12/14/95

NON-CAP

CAP

Submission number: 122291A

TSCA Inventory:

Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO

AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX

SBTOX

SEN

w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX

CTOX

EPI

RTOX

GTOX

STOX/ONCO

CTOX/ONCO

IMMUNO

CYTO

NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

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entire document: <u>0</u> 1 2 pages <u>42</u>	pages <u>1, 2, 10, 11, 12</u>
Notes:	
Contractor reviewer: <u>FOR</u>	Date: <u>2/13/95</u>



CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:

Submission # BEHQ-1092-12229 SEQ. A

TYPE: (NT) SUPP FLWP

SUBMITTER NAME: Rhone-Poulenc Inc.

INFORMATION REQUESTED: FLWP DATE: _____

- 0501 NO INFO REQUESTED
- 0502 INFO REQUESTED (TECH)
- 0503 INFO REQUESTED (VOL ACTIONS)
- 0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:

- 0639 REFER TO CHEMICAL SCREENING
- 0678 CAP NOTICE

VOLUNTARY ACTIONS:

- 0401 NO ACTION REPORTED
- 0402 STUDIES PLANNED/IN PROGRESS
- 0403 NOTIFICATION OF WORKERS
- 0404 LABEL/MSDS CHANGES
- 0405 PROCESS/HANDLING CHANGES
- 0406 APP/USE DISCONTINUED
- 0407 PRODUCTION DISCONTINUED
- 0408 CONFIDENTIAL

SUB. DATE: 10/16/92 OTS DATE: 10/21/92 CSRAD DATE: 01/30/95

CHEMICAL NAME:

Prenyl Acetate

CAS#

1191-16-8

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	0216 EPI/CLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	<u>0242</u> IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	<u>0243</u> CHEM/PHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 ECO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCC/REL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
<u>0209</u> NEURO (ANIMAL)	<u>01 02 04</u>	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0299 OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
<u>0212</u> ACUTE TOX. (ANIMAL)	<u>01 02 04</u>	0227 ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0239 METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAB/PHARMACO (HUMAN)	01 02 04		

<u>TRIAGE DATA:</u>	<u>NON-CBI INVENTORY</u>	<u>ONGOING REVIEW</u>	<u>SPECIES</u>	<u>TOXICOLOGICAL CONCERN:</u>	<u>USE:</u>	<u>PRODUCTION:</u>
CAS SR	<u>YES</u>	YES (DROP/REFER)	<u>RAT</u>	<u>LOW</u>		
	NO	NO (CONTINUE)	<u>RBT</u>	MED		
	<u>IN TERMINI</u>	<u>REFER</u>		HIGH		

12229A

L

Acute oral toxicity in rats is of low concern. Single oral gavage doses to Sprague Dawley rats (10/sex/dose) at levels of 1500, 2000, 300, 4000, or 5000 mg/kg resulted in death (0/10, 0/10, 4/10, 9/10, and 10/10, respectively, for males; 0/10, 1/10, 4/10, 9/10, and 10/10, respectively, for females). The LD₅₀ values were 3000 and 2900 mg/kg for males and females, respectively. Clinical signs included mild to severe depression, diarrhea, salivation, lacrimation, trembling, dyspnea, convulsions, occasional ataxia, and prostration. Necropsy findings in rats that died included hemorrhagic lungs, dark livers, and sloughing and/or inflammation and erosion of the gastric mucosa.

L

Eye irritation in rabbits is of low concern. Application of the substance to the everted lower eyelid of the right eye of nine New Zealand albino rabbits (6 unwashed/3 washed) resulted in minimal irritation. The following observations were made in unwashed eyes at 24 hours: diffuse corneal opacity (3/6), mild discharge (1/6), and positive fluorescein response (3/6). All symptoms in unwashed eyes cleared by 48 hours, and there was no ocular irritation in the washed eyes during the study.

L

Dermal irritation in rabbits is of low concern. Application of the substance to the intact and abraded skin of six New Zealand albino rabbits resulted in no irritation.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Charles E. Moyer, Jr., Ph.D.
Director, Product Safety
Rhône-Poulenc Inc.
CN 7500
Cranberry, New Jersey 08512-7500

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 06 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan
Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12229A



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Printed with Soy/Canola Ink on paper that
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