

8EHQ-92-10519

CONFIDENTIAL

333206

Document Control Number:
OTS0546314 (88-920008764S) (8EHQ-0292-10470S)

February 25, 1992

Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 M. St. S.W.
Washington, DC 20460

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

Re: Submission of a study pursuant to TSCA Section 8(e) Compliance Audit Program and the CAP Agreement.

Regulatee:



Submitted by:



8 9 1 1 0 0 0 0 1 1 3 / S

RECEIVED
OFFICE OF TOXIC SUBSTANCES
11 FEB 16 AM 11:38

Company Sanitized

Composition of 85-26B

<u>Chemical</u>	<u>CAS #</u>
Water	7723-18-5
Cargill XP-32 CMLO	Experimental
Cargill XP-30	Experimental
Cargill XP-216 W/R Alkyd	Experimental
Minex 7	37244-96-5
Propasol B	5131-66-8
Michemlube 723 Wax Emulsion	N/A
Butylcarbitol	112-34-5
Ammonia 26"	7664-41-7
Nopocide N-40-D	1897-45-6
Isopar M	N/A
Syloid 221	632-31-67-4
Red Oxides RO 4097, RO 8097	1309-37-1
Polyphase	55406-53-6?
Cobalt Napthenate	61789-51-3 (45%)
Mineral Spirits	8032-32-4 (30%)
Cobalt Hydrocure 2	
Ben-A-Gel EW	N/A
Phenylmercuric Acetate 100	62-38-4
Nalco 2305	N/A
Black 877-9940	Mixture
Disponil WR400	Mixture
Anti-Skin (ASKA/EXKIN 2)	96-29-7
Phthalo Blue 895-7202	Mixture

Study Summary

The test material was applied to the skin of rabbits at 20.0 gm/Kg. Four animals died during the study. In the survivors, sedation was observed for as long as 7 days post-administration. A sensory response to pain and stimuli was also reported up to day 3 post-administration. The prolonged nature of the sedation, combined with the heightened sensory response are suggestive of a neurotoxic effect consistent with the guidance offered in the TSCA Section 8(e) Reporting guide (pp 31-34).

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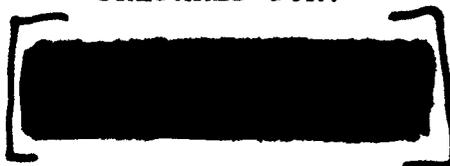
Fulfillment of
Purchase Order No. RD 15660
Acute Dermal Toxicity Screen



Identification: Sample No. 85-26B
Red Liquid with pH 8.03 and Specific Gravity 1.0381

Document Control Number:
OTS0546314 (88-920008764S) (8EHQ-0292-10470S)

PREPARED FOR:



SUBMITTED BY:

MIDECO, INC.
520 WAKARA WAY
UNIVERSITY OF UTAH RESEARCH PARK
SALT LAKE CITY, UTAH 84108


Taylor K. Davis, Study Director

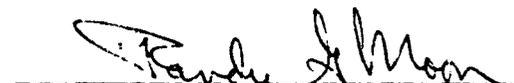

Randy Moon, Ph.D.

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APPENDICES

Appendix A:

Photocopies of the following raw data for Sample 85-26B:

Acute Dermal Toxicity Data Sheet
Acute Dermal Toxicity Detail Sheet
Acute Dermal Toxicity Result Sheet
Necropsy Sheets

Appendix B:

Copy of MIDECO Acute Dermal Toxicity Procedure SOP/RAB/024.

MIDECO, INC.
520 Wakara Way
Salt Lake City, Utah 84108

Statement of Compliance

Acute Dermal Toxicity Screen

by

Randy G. Moon, Ph.D.

Final Report Dated

19 Jun 85

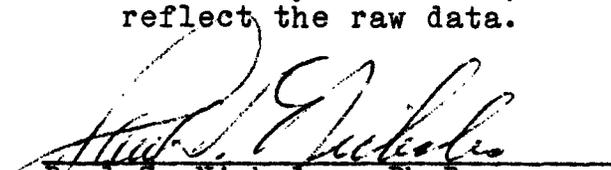
1. These tests were conducted in accordance with the Federal Good Laboratory Practices (21 CFR, Part 58). All laboratory data which pertain to this study are recorded in MIDECO Data File #57966.
2. Services covered by this report produced in conformity with the Fair Labor Standards Act as amended.
3. In accordance with the Federal Good Laboratory Practices, this study was inspected by the MIDECO Quality Assurance Unit on:

19 Apr; 19 Apr 85
Date(s)

and the findings of the inspection(s) were reported to MIDECO management and to the study director on:

22 Apr; 22 Apr 85
Date(s)

4. Quality Assurance has reviewed this report and has determined that the methods and standard operating procedures are accurately described, and that the reported results accurately reflect the raw data.


Paul S. Nicholes, Ph.D.
Quality Assurance

26 June 1985
Date

1.0 Study Dates and Test Substance Identification Number:

[REDACTED] requested that MIDEKO test ten animals, five males and 5 females dosed at 20 gm/kg, using one (1) liquid sample, 85-26B, using the Acute Dermal Toxicity Screen (Appendix A). Purchase order number RD 15660 was received as written authorization for the study.

Study Dates for Sample 85-26B:

Animals Received: 25 Mar 85 and 01 Apr 85
Animals Dosed: 19 Apr 85
Animals Observed: 19 Apr 85 -- 03 May 85
Animals Weighed: 26 Apr 85 and 03 May 85
Necropsy: 03 May 85
Final Report: 19 Jun 85

Test Substance Identification Number:

Upon receipt, the sample was coded with the following MIDEKO identification number for testing purposes:

<u>[REDACTED] Number</u>	<u>MIDEKO Number</u>
85-26B	57966

2.0 Objective:

The objective of this study is to evaluate the toxic potential of a test material as manifested by the production of visible symptoms and/or pharmacological reactions using an Acute Dermal Toxicity Screen Test.

3.0 Summary of Results:

MIDEKO test protocol SOP/RAB/024 (Appendix B) was followed in detail with the exception that the animals were dosed at 20 gm/kg instead of 2 gm/kg.

MIDEKO received a red liquid. The pH was measured at 8.03 and specific gravity was 1.0381.

Copies of the raw data, including necropsy results for this study, are contained in Appendix A. These data are summarized in Table 1.

4.0 Comments and Conclusions:

Sample 85-26B:

Four animals died during the study on days 3 (3 animals) and 4. Ten out of ten animals demonstrated erythema during this study. The erythema did not zero by day 14.

Ten out of ten animals demonstrated edema that cleared on days 12 (4 animals) and 13 (2 animals). The six living animals demonstrated sedation that cleared on days 1, 3 (2 animals), 4, 6, and 7. These six animals also demonstrated a sensory response which cleared on days 1 (2 animals), 2 (2 animals), and 3 (2 animals). Two animals also had diarrhea; one animal on day 4 and another animal on days 5-8.

Mean weight changes were recorded on days 7 and 14. The males demonstrated a mean weight loss of 0.10 kg at 7 days and a mean weight gain of 0.13 kg at 14 days. The females demonstrated a mean weight gain of 0.07 kg at 7 days and a mean weight gain of 0.20 kg at 14 days.

Six animals were terminated at 14 days and necropsied. The other four animals were necropsied after being found dead on days 3 (3 animals) and 4. Necropsy results are contained in Appendix A. Necropsy results for the ten animals did not reveal any abnormalities greater than those normally seen in untreated animals other than irritation at the site of sample application with the exception of dark spots (1-5mm) on the inner surface of the stomach of the four animals that died during the study.

5.0 Problems or Deviations from Protocol: A dose level of 2 gm/kg is stated in the protocol for the Acute Dermal Toxicity Screen. The sponsor requested the dose level of 20 gm/kg for this study be used.

6.0 Location of all Raw Data:

A copy of the final report and the raw data are stored in the archives at MIDEKO, INC., 520 Wakara Way, University of Utah Research Park, Salt Lake City, Utah.

TABLE 1

SPONSOR:
 TEST REQUESTED: Dermal Toxicity Test
 IDENTIFICATION: 85-26B
 LAB NUMBER: 57966
 SPECIES: New Zealand White Rabbits
 DOSE: 20 gm/kg

DOSE: 20 GM/KG

<u>SYMPTOM</u>	<u>Male</u>	<u>Female</u>
Autonomic: Nasal discharge or salivation	0/5	0/5
Behavior: Sedation or abnormal activity	5/5	5/5
Cardiovascular: Cyanosis or hemorrhage	0/5	0/5
Cutaneous: Erythema or edema	5/5	5/5
Gastrointestinal: Salivation, diarrhea	2/5	0/5
Neuromuscular: Ataxia or protiation	1/5	1/5
Ocular: Mydriasis, myosis or lacrimation	0/5	0/5
Respiratory: Hypopnea or dyspnea	1/5	0/5
Sensory: Sound and touch	5/5	5/5
Other:	0/5	0/5
 Death:	 2/5	 2/5
Normal throughout test:	0/5	0/5
Return to normal:	0/5	0/5
 Mean Weight Change:		
a. 0 - 7 days*	-0.10 kg	0.07 kg
b. 7 - 14 days*	0.13 kg	0.20 kg

*Calculated for three animals

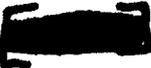
APPENDIX A

CONFIDENTIAL

ACUTE DERMAL TOXICITY DATA, SOP DETAIL
& PREPARATION SHEET

GLP

LAB NUMBER: 57966

SPONSOR: 

IDENTIFICATION: SAMPLE 85-26B

DATE STARTED: 19 APR 85 DATE COMPLETED: 3 May 85

CALCULATIONS: SHEET ATTACHED BY SPONSOR

PREPARATION BY: sponsor DATE: _____ VEHICLE: _____ LOT # _____

SAMPLE DESCRIPTION: SOLID LIQUID

ANIMALS SHAVED BY: PM am DATE: 19 APR 85

ROOM: 135 TIME: 1230

CONTROLS: UNTREATED NONE

AMOUNT DOSED AREA PER ANIMAL: _____

OCCLUSIVE (LATEX) NONOCCLUSIVE

RANDOMIZATION: YES NO

NUMBER OF DOSE LEVELS: one

NUMBER ANIMALS PER GROUP: ten

J Davis

STUDY DIRECTOR REVIEW

3 May 85

DATE

SPONSOR

DATE

DELMAR ^{20 APR 85} ~~23 APR 85~~
ACUTE ORAL TOXICITY RESULT SHEET

CONFIDENTIAL

LAB NUMBER: 57966

SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL [X] MALE [X] FEMALE []

RABBIT # R616

ROOM # 135

Amount dosed 48.5 ml
 Dose level 20 gm/kg

0 DAY WEIGHT 2.5 kg

7 DAY WEIGHT 2.0 kg

14 DAY WEIGHT 2.1 kg

SYSTEM	P R E N	S C R E E N	P I N H R S	O H R S	J 4	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
																					DAY
AUTONOMIC	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SENSORY	0			+1	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NEUROMUSCULAR	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RESPIRATORY	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCULAR	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GASTROINTEST.	0			0	0	0	0	0	+1	-1	+2	+1	0	0	0	0	0	0	0	0	0
CUTANEOUS	0			0	3/2	3/3	3/4	2/4	2/4	2/4	2/4	2/4	2/4	2/3	2/2	2/2	4/0	4/0	4/0	7/0	7/0
BEHAVIORAL	0			+1	+2	+1	+1	0	0	0	0	+1	0	0	0	0	0	0	0	0	0
CARDIOVAS.	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

DATE	19 APR	19 APR	19 APR	20 APR	21 APR	22 APR	23 APR	24 APR	25 APR	26 APR	27 APR	28 APR	29 APR	30 APR	1 MAY	2 MAY	3 MAY
TIME	1230	1300	1650	1330	1315	1345	0935	0940	0940	0905	1130	1400	1100	1100	0745	1030	1100
TECHNICIAN	om	om	ms	SPM	SPM	SPM	om	om	om	om	SPM	SPM	om	om	om	om	om

COMMENTS:

+2 Behavioral - sedation 20 APR 85 SPM
 +1 no response to stimuli
 +1 Beh - sedation 21 APR 85 SPM
 +1 Beh - sedation 23 APR 85 SPM
 24 APR 85
 +1 diarrhea
 26 APR 85
 +2 diarrhea
 +1 sedation

J. Davis
 STUDY DIRECTOR REVIEW

3 May 85
 DATE

DEC MAR 22 APR 25
ACUTE ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966 SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL MALE FEMALE []

RABBIT # R591 ROOM # 135

Amount dosed 46.5 ml
 Dose level 20 gm/kg

0 DAY WEIGHT 2.4 kg 7 DAY WEIGHT 2.6 kg 14 DAY WEIGHT 2.7 kg

SYSTEM	P R E T N	S C R E T N	P I N J O H R S	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
				HRS	DAY													
AUTONOMIC	(0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SENSORY	(+1	+1	+1	0	0	0	0	0	0	0	0	0	0	0	0
NEUROMUSCULAR	(0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RESPIRATORY	(0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCULAR	(0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GASTROINTEST.	(0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CUTANEOUS	0			0	3/2	3/2	2/4	3/4	3/4	3/4	4/3	4/2	4/2	4/2	4/1	4/0	4/0	4/0
BEHAVIORAL	0			+1	+1	+1	0	+1	0	0	0	0	0	0	0	0	0	0
CARDIOVAS.	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

DATE	16 APR	19 APR	19 APR	20 APR	21 APR	22 APR	23 APR	24 APR	25 APR	26 APR	27 APR	28 APR	29 APR	30 APR	1 MAY	2 MAY	3 MAY
TIME	1230	1300	1030	1330	1315	1315	0930	0945	0940	0905	1130	1100	1100	0945	0945	0945	1100
TECHNICIAN	am	am	MB	SDM	SDM	SDM	am	am	am	am	SDM	SDM	am	am	am	am	am

COMMENTS: +1 Sedate
 +1 - inability to respond to pain

+1 Behavioral sedation
 +1 Sensory - no response to stimuli
 20 APR 85
 23 APR 85

+1 Response to stimuli
 +1 Beh - sedation
 21 APR 85
 23 APR 85

23 APR 85
 abdomen distended
 behavioral sedation

24 APR 85
 abdomen distended

J. Davis
 STUDY DIRECTOR REVIEW

3 May 85
 DATE

DELMAI POWERS TEST 23 APR 85
ACUTE ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966

SPONSOR: 

CONTROL ANIMAL [] TEST ANIMAL

MALE FEMALE []

RABBIT # R572

ROOM # 135

Amount dosed 44.5ml
 Dose level 20 gm/kg

0 DAY WEIGHT 2.31kg

7 DAY WEIGHT 2.31kg

14 DAY WEIGHT 2.5kg

SYSTEM	P R E N	S C R E E N	P I N J	0 HRS	4 HRS	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY	
AUTONOMIC				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SENSORY				+1	+2	+1	+1	0	0	0	0	0	0	0	0	0	0	0	0	0
NEUROMUSCULAR				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RESPIRATORY				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCULAR				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GASTROINTEST.				0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0
CUTANEOUS				0	3/2	3/2	3/2	4/3	4/2	4/3	4/2	4/2	4/2	4/2	4/2	4/2	4/1	4/2	4/2	4/2
BEHAVIORAL				+1	+2	+1	+1	0	0	0	0	0	0	0	0	0	0	0	0	0
CARDIOVAS.				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

DATE	19 APR	19 APR	19 APR	20 APR	21 APR	22 APR	23 APR	24 APR	25 APR	26 APR	27 APR	28 APR	29 APR	30 APR	1 MAY	2 MAY	3 MAY
TIME	1230	1300	1400	1330	1315	1315	0930	0945	0945	0905	1130	1400	1100		0945	1050	
TECHNICIAN	SM	SM	SM	SDM	SDM	SDM	SM	SM	SM	SM	SDM	SDM	SM		SM	SM	SM

COMMENTS: +1 - sedate
 +1 - inabilif towards stimuli.
 +2 - sedation
 +2 ^{NE} response to stimuli 20 APR 85 SM

+1 Response to stimuli
 +1 Beh - sedation 21 APR 85 SM
 +1 Response to stimuli
 +1 Beh - sedation 22 APR 85 SM

23 APR 85
 g.i. - constipation

J Davis
 STUDY DIRECTOR REVIEW

3 May 85
 DATE

*DERMAL WEIGH TEST
25 APR 85*
ACUTE ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966

SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL MALE FEMALE []

RABBIT # R573

ROOM # 135

Amount dosed 48.5 ml
Dose level 20 gm/kg

0 DAY WEIGHT 2.5 kg

7 DAY WEIGHT _____

14 DAY WEIGHT _____

SYSTEM	P R E N	S E N	P I O N	J	0 HRS	4 HRS	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY	
AUTONOMIC	0				0	0	0	0	0	*											
SENSORY	0				+1	+2	+2	+2													
NEUROMUSCULAR	0				0	0	0	0	+2												
RESPIRATORY	0				0	0	0	0	+1												
OCULAR	0				0	0	0	0													
GASTROINTEST.	0				0	0	0	0													
CUTANEOUS	0				0	3/2	3/2	2/4													
BEHAVIORAL	0				+1	+2	+2	+2													
CARDIOVAS.	0				0	0	0	0													

DATE	19 APR	19 APR	19 APR	20 APR	21 APR	22 APR															
TIME	1230	1300	1650	1330	1315	1315															
TECHNICIAN	am	am	MB	SDM	SDM	SDM															

COMMENTS:

** Weighing error
SDM 22 APR 85*

+2 Response to stimuli 20 APR 85
+2 Behavior - sedation SDM

+2 Response to stimuli 21 APR 85
+2 Beh - sedation SDM

+2 Response to stimuli 22 APR 85
+2 Beh - sedation SDM

+2 Neuromusc - Ataxia
+1 Resp - hypopnea

* Found dead 0830 23 APR 85 pm

J. Davis
STUDY DIRECTOR REVIEW

3 May 85
DATE

CONFIDENTIAL

DERMAL ^{WRAP-POST TO 23 APR 85}
ACUTE ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966

SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL MALE FEMALE []

RABBIT # RS69

ROOM # 135

Amount dosed 48.5 ml
 Dose level 20 gm/kg

0 DAY WEIGHT 2.5 kg

7 DAY WEIGHT _____

14 DAY WEIGHT _____

SYSTEM	P R E T E N	S E R E T	P O HRS	I N HRS	4 DAY	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY	
AUTONOMIC	0		0	0	0	*														
SENSORY	0		0	+2	+2															
NEUROMUSCULAR	0		0	0	0															
RESPIRATORY	0		0	0	0															
OCULAR	0		0	0	0															
GASTROINTEST.	0		0	0	0															
CUTANEOUS	0		0	3/3	3/3															
BEHAVIORAL	0		1	+2	+2															
CARDIOVAS.	0		0	0	0															

DATE	19 APR	19 APR	19 APR	20 APR	21 APR	21 APR														
TIME	1230	1300	1650	1330	1315	500														
TECHNICIAN	sm	sm	MB	SOM	SOM	sm														

COMMENTS: +1 sedat
 +2 Sedation 20 APR EST SOM
 +2 No response to stimuli
 +2 Sedation 21 APR EST SOM
 +2 Response to stimuli SOM
 * Full dead in cage
 0900 22 APR 85 sm

J. Davis
 STUDY DIRECTOR REVIEW

3 May 85
 DATE

DERMAL TO WOUND TEST APR 85
ACUTE ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966

SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL [] MALE [] FEMALE []

RABBIT # R5744 wtag # 14 APR 85

ROOM # 135

Amount dosed 46.5 ml
 Dose level 20 gm/kg

0 DAY WEIGHT 2.4 kg

7 DAY WEIGHT 2.4 kg

14 DAY WEIGHT 2.6 kg

SYSTEM	P R E N	S E T	P I N O	C O N J E T	4 HRS	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY
AUTONOMIC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SENSORY	0	0	0	0	+2	+2	+1	+1	0	0	0	0	0	0	0	0	0	0	0
NEUROMUSCULAR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RESPIRATORY	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCULAR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GASTROINTEST.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CUTANEOUS	0	0	0	0	0	3/3	3/3	2/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2
BEHAVIORAL	0	0	0	0	+	+1	+1	+1	+1	0	+	0	0	0	0	0	0	0	0
CARDIOVAS.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

DATE	19 APR	19 APR	19 APR	22 APR	21 APR	22 APR	23 APR	24 APR	25 APR	26 APR	27 APR	28 APR	29 APR	30 APR	1 MAY	2 MAY	3 MAY
TIME	1230	1300	1050	1330	1315	1345	0930	0745	0740	0905	1130	1400	1100	0900	0945	1030	1100
TECHNICIAN	SM	SM	MCJ	SBM	SBM	SBM	SM	SM	SM	SM	SBM	SBM	SM	SM	SM	SM	SM

COMMENTS: *1 - sedate 19 APR 84 MCJ
 +2. Sensory ^{Touch} 20 APR 85 SBM
 +1 Behavioral - sedation
 +1 Response to stimuli 21 APR 85 SBM
 +1 Beh - sedation 22 APR 85 SBM

J. Davis

STUDY DIRECTOR REVIEW

3 May 85

DATE

DERMAL TO ^{25 APR 85} ~~ACUTE~~ ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966

SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL [✓]

MALE [] FEMALE [✓]

RABBIT # R581

ROOM # 135

Amount dosed 46.5 ml
Dose level 20 gm/kg

0 DAY WEIGHT 2.4 kg

7 DAY WEIGHT 2.5 kg

14 DAY WEIGHT 2.7 kg

SYSTEM	P R E N	S E T	P E T	I N J E C T	0 HRS	4 HRS	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY	
AUTONOMIC	0				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SENSORY	0				+2	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NEUROMUSCULAR	0				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RESPIRATORY	0				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCULAR	0				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GASTROINTEST.	0				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CUTANEOUS	0				0	2/2	3/3	2/4	3/4	3/4	3/4	3/4	4/4	4/4	4/4	4/2	4/1	4/2	4/0	4/0	4/0
BEHAVIORAL	0				+1	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CARDIOVAS.	0				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

DATE	19 APR	19 APR	19 APR	20 APR	21 APR	22 APR	23 APR	24 APR	25 APR	26 APR	27 APR	28 APR	29 APR	30 APR	1 MAY	2 MAY	3 MAY
TIME	1230	1300	1650	1330	1315	1345	0930	0945	0940	0905	1130	1400	1100		0945	1030	1100
TECHNICIAN	om	om	MS	SPM	SPM	SPM	om	fm	fm	om	SPM	SPM	om	P	om	om	fm

COMMENTS:

+1 Behavioral - sedation 20 APR EST
50M
+1 Response to stimuli

J Davis
STUDY DIRECTOR REVIEW

3 May 85
DATE

DERMAL AND TEST TO 23 APR 85
ACUTE ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966

SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL

MALE [] FEMALE

RABBIT # R584

ROOM # 135

Amount dosed 46.5 ml
 Dose level 20 gm/kg

0 DAY WEIGHT 2.4 kg

7 DAY WEIGHT 2.5 kg

14 DAY WEIGHT 2.7 kg

SYSTEM	P R E T N	S C R E T	P I N O HRS	0 HRS	4 DAY	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY
AUTONOMIC	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SENSORY	0			+2	+2	+1	0	0	0	0	0	0	0	0	0	0	0	0	0
NEUROMUSCULAR	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RESPIRATORY	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OCULAR	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GASTROINTEST.	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CUTANEOUS	0			0	3/3	3/2	3/3	3/3	3/3	3/3	3/3	4/3	4/3	4/3	4/2	4/1	4/0	4/1	4/0
BEHAVIORAL	0			+1	+1	+1	+1	0	0	0	0	0	0	0	0	0	0	0	0
CARDIOVAS.	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

DATE	19 APR	19 APR	19 APR	20 APR	21 APR	22 APR	23 APR	24 APR	25 APR	26 APR	27 APR	28 APR	29 APR	30 APR	1 MAY	2 MAY	3 MAY
TIME	1230	1300	1650	1330	1315	1345	0930	0945	0940	0905	1130	1400	1100	1200	0900	1130	0900
TECHNICIAN	AM	AM	UB	SDM	SDM	SDM	AM	AM	AM	AM	SDM	SDM	AM	AM	AM	AM	AM

COMMENTS: +2 - inability to respond to stimuli
 +1 - sedation

+2 - response to pain 20 APR 85
 +1 - Behavioral sedation SDM

+1 Response to stimuli 21 APR 85
 +1 Beh sedation SDM

+1 Beh sedation 22 APR 85
 SDM

J Davis
 STUDY DIRECTOR REVIEW

3 May 85
 DATE

CONFIDENTIAL

DEFMRL W. L. SNL TEST TO 22 APR 85
ACUTE ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966

SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL [/] MALE [] FEMALE [/]

RABBIT # R613

ROOM # 135

Amount dosed 50.5 ml
Dose level 20 gm/kg

0 DAY WEIGHT 2.6 kg

7 DAY WEIGHT _____

14 DAY WEIGHT _____

SYSTEM	P R E N	S E T	P I N J 0	4 HRS	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY
AUTONOMIC	0		0	0	0	0	*											
SENSORY	0		+2	+2	+2													
NEUROMUSCULAR	0		0	0	0	+2												
RESPIRATORY	0		0	0	0													
OCULAR	0		0	0	0													
GASTROINTEST.	0		0	0	0													
CUTANEOUS	0		0	3/3	3/3													
BEHAVIORAL	0		+1	+2	+2*													
CARDIOVAS.	0		0	0	0													

DATE	19 APR	19 APR	19 APR	20 APR	21 APR	21 APR												
TIME	1230	1300	1650	1330	1315	0700												
TECHNICIAN	SM	SM	MB	SM	SM	SM												

COMMENTS: +1 sedate
+2 Behavioral - sedation 21 APR 85 SM
+2 No response to stimuli
+2 Prestrate
+2 No response to stimuli
+2 Beh - sedation *MERIBOND 21 APR 85 SM
* Faint feces in cage 0900 22 APR 85

J Davis
STUDY DIRECTOR REVIEW

3 May 85
DATE

CONFIDENTIAL

DERMAL TO WEAN TEST 25 APR 65
ACUTE-ORAL TOXICITY RESULT SHEET

LAB NUMBER: 57966

SPONSOR: [REDACTED]

CONTROL ANIMAL [] TEST ANIMAL []

MALE [] FEMALE []

RABBIT # R607

ROOM # 135

Amount dosed 54.0 ml

Dose level 20 gm/kg

0 DAY WEIGHT 2.8 kg

7 DAY WEIGHT _____

14 DAY WEIGHT _____

SYSTEM	P R E N	S R E T	P I N O	J S T	4 HRS	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY
AUTONOMIC					0	0	0	+											
SENSORY	0				0	0	+2												
NEUROMUSCULAR	0				0	0	0												
RESPIRATORY	0				0	0	0												
OCULAR	0				0	0	0												
GASTROINTEST.	0				0	0	0												
CUTANEOUS	0				0	4/3	4/3												
BEHAVIORAL	0				+1	+1	+2												
CARDIOVAS.	0				0	0	0												

DATE	19 APR	19 APR	19 APR	20 APR	21 APR	22 APR													
TIME	1230	1300	1650	1300	1315	1300													
TECHNICIAN	SM	SM	HB	SM	SM	SM													

COMMENTS:
+1 Behavioral - sedation 20 APR 65 SM
+2 Response to stimuli 20 APR 65 SM
+2 Beh-sedation 20 APR 65 SM

J Davis
STUDY DIRECTOR REVIEW

3 May 65
DATE

NECROPSY FORM

LAB # 57966

ANIMAL # R613

TIME 0900

DATE OF DEATH 22 APR 85

SEX F

SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS Normal
edema eschar.

ADRENALS Normal

ORAL CAVITY Normal

STOMACH: *dark black spots, 3-5mm diameter all over insides*
FUNDUS Normal

ESOPHAGUS Normal

PHYLORUS Normal

TRACHEA Normal

INTESTINAL TRACT:
DUODENUM Normal

THYROID Normal

JEJUNUM Normal

THYMUS Normal

ILEUM Normal

LUNGS Normal

CAECUM Normal

HEART Normal

SPLEEN Normal

LIVER Normal

KIDNEYS Normal

BLADDER Normal

COMMENTS: *SUBCUTANEOUS EDEMA*

MB
NECROPSY TECHNICIAN

JK Davis
STUDY DIRECTOR

DESCRIBE ORGANS AND TISSUES WITH SIMPLE TERMS AND ADJECTIVES. DO NOT USE TERMS OR DESCRIBE CONDITIONS WHICH CAN ONLY BE PROPERLY CONFIRMED BY MICROSCOPIC EXAMINATION OR SPECIAL TECHNIQUES: FOR EXAMPLE, AN ABNORMAL MASS SHOULD BE DESCRIBED AS A MASS OF CERTAIN SIZE AND LOCATION, NOT AS A TUMOR OR CANCEROUS GROWTH. 0F = NORMAL; 1+ = SLIGHT BUT SCORABLE; 2+ = MODERATE; 3+ = MARKED OR SEVERE; C.F. = CANNOT FIND; N.E. = NOT EXAMINED.

NECROPSY FORM

LAB # 57966

ANIMAL # R569

TIME 0900

DATE OF DEATH 22 APR 85

SEX M

SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS [] Normal
EDEMA ESCHAR

ADRENALS [✓] Normal

ORAL CAVITY [✓] Normal

STOMACH: *dark black spots 3-5mm diameter all over inside?*
FUNDUS [] Normal *Black sem solid thrombotic coag.*

ESOPHAGUS [✓] Normal

PHYLORUS [] Normal

TRACHEA [✓] Normal

INTESTINAL TRACT:
DUODENUM [✓] Normal

THYROID [✓] Normal

JEJUNUM [✓] Normal

THYMUS [✓] Normal

ILEUM [✓] Normal

LUNGS [✓] Normal

CAECUM [✓] Normal

HEART [✓] Normal

SPLEEN [✓] Normal

LIVER [✓] Normal

KIDNEYS [✓] Normal

BLADDER [✓] Normal

COMMENTS:

SM
NECROPSY TECHNICIAN

JK Davis
STUDY DIRECTOR

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NECROPSY FORM

LAB # 57966 ANIMAL # R107
 TIME 0900 DATE OF DEATH 22 APR 85
 SEX F SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS	[] Normal	ADRENALS	[/] Normal
<i>ROSEN</i>	<i>ESCHER</i>		
ORAL CAVITY	[/] Normal	STOMACH: <i>dark black spots 3-5mm diameter all over inside</i>	
		FUNDUS	[] Normal <i>black spots solid</i>
			<i>fluorimetric</i>
ESOPHAGUS	[/] Normal	PHYLORUS	[] Normal
TRACHEA	[/] Normal	INTESTINAL TRACT:	
THYROID	[/] Normal	DUODENUM	[/] Normal
THYMUS	[/] Normal	JEJUNUM	[/] Normal
LUNGS	[/] Normal	ILEUM	[/] Normal
HEART	[/] Normal	CAECUM	[/] Normal
LIVER	[/] Normal	SPLEEN	[/] Normal
KIDNEYS	[/] Normal		
BLADDER	[/] Normal		

COMMENTS: *urine stain on coat*

SS JK Davis
 NECROPSY TECHNICIAN STUDY DIRECTOR

DESCRIBE ORGANS AND TISSUES WITH SIMPLE TERMS AND ADJECTIVES. DO NOT USE
 TERMS OR DESCRIBE CONDITIONS WHICH CAN ONLY BE PROPERLY CONFIRMED BY
 MICROSCOPIC EXAMINATION OR SPECIAL TECHNIQUES: FOR EXAMPLE, AN ABNORMAL
 MASS SHOULD BE DESCRIBED AS A MASS OF CERTAIN SIZE AND LOCATION, NOT AS
 A TUMOR OR CANCEROUS GROWTH. 0 = NORMAL; 1+ = SLIGHT BUT SCORABLE; 2+ =
 MODERATE; 3+ = MARKED OR SEVERE; C = CANNOT FIND; N = NOT EXAMINED.

NECROPSY FORM

LAB # 57966 ANIMAL # R 573
TIME 0830 DATE OF DEATH 23 APR 85
SEX m SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS	<input type="checkbox"/> Normal	ADRENALS	<input checked="" type="checkbox"/> Normal
ORAL CAVITY	<input checked="" type="checkbox"/> Normal	STOMACH:	
ESOPHAGUS	<input checked="" type="checkbox"/> Normal	FUNDUS	<input type="checkbox"/> Normal
TRACHEA	<input checked="" type="checkbox"/> Normal	PHYLORUS	<input type="checkbox"/> Normal
THYROID	<input checked="" type="checkbox"/> Normal	INTESTINAL TRACT:	
THYMUS	<input checked="" type="checkbox"/> Normal	DUODENUM	<input checked="" type="checkbox"/> Normal
LUNGS	<input checked="" type="checkbox"/> Normal	JEJUNUM	<input checked="" type="checkbox"/> Normal
HEART	<input checked="" type="checkbox"/> Normal	ILEUM	<input checked="" type="checkbox"/> Normal
LIVER	<input checked="" type="checkbox"/> Normal	CAECUM	<input checked="" type="checkbox"/> Normal
KIDNEYS	<input checked="" type="checkbox"/> Normal	SPLEEN	<input checked="" type="checkbox"/> Normal
BLADDER	<input checked="" type="checkbox"/> Normal		

COMMENTS: *severe subcutaneous edema at test side and severe erythema
small 1-2mm black spots on interior of stomach lining*

MB JK Davis
NECROPSY TECHNICIAN STUDY DIRECTOR

DESCRIBE ORGANS AND TISSUES WITH SIMPLE TERMS AND ADJECTIVES. DO NOT USE
TERMS OR DESCRIBE CONDITIONS WHICH CAN ONLY BE PROPERLY CONFIRMED BY
MICROSCOPIC EXAMINATION OR SPECIAL TECHNIQUES: FOR EXAMPLE, AN ABNORMAL
MASS SHOULD BE DESCRIBED AS A MASS OF CERTAIN SIZE AND LOCATION, NOT AS
A TUMOR OR CANCEROUS GROWTH. 0F = NORMAL; 1+ = SLIGHT BUT SCORABLE; 2+ =
MODERATE; 3+ = MARKED OR SEVERE; C/F = CANNOT FIND; NL = NOT EXAMINED

NECROPSY FORM

LAB # 57966 ANIMAL # R591
TIME 1100 DATE OF DEATH 3MAY85
SEX M SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS	<input type="checkbox"/> Normal	ADRENALS	<input checked="" type="checkbox"/> Normal
ORAL CAVITY	<input checked="" type="checkbox"/> Normal	STOMACH:	
ESOPHAGUS	<input checked="" type="checkbox"/> Normal	FUNDUS	<input checked="" type="checkbox"/> Normal
TRACHEA	<input checked="" type="checkbox"/> Normal	PHYLORUS	<input checked="" type="checkbox"/> Normal
THYROID	<input checked="" type="checkbox"/> Normal	INTESTINAL TRACT:	
THYMUS	<input checked="" type="checkbox"/> Normal	DUODENUM	<input checked="" type="checkbox"/> Normal
LUNGS	<input checked="" type="checkbox"/> Normal	JEJUNUM	<input checked="" type="checkbox"/> Normal
HEART	<input checked="" type="checkbox"/> Normal	ILEUM	<input checked="" type="checkbox"/> Normal
LIVER	<input checked="" type="checkbox"/> Normal	CAECUM	<input checked="" type="checkbox"/> Normal
KIDNEYS	<input checked="" type="checkbox"/> Normal	SPLEEN	<input checked="" type="checkbox"/> Normal
BLADDER	<input checked="" type="checkbox"/> Normal		

COMMENTS: *Skin: Eschar*

Pi. Morza
NECROPSY TECHNICIAN

J. Davis
STUDY DIRECTOR

DESCRIBE ORGANS AND TISSUES WITH SIMPLE TERMS AND ADJECTIVES. DO NOT USE TERMS OR DESCRIBE CONDITIONS WHICH CAN ONLY BE PROPERLY CONFIRMED BY MICROSCOPIC EXAMINATION OR SPECIAL TECHNIQUES: FOR EXAMPLE, AN ABNORMAL MASS SHOULD BE DESCRIBED AS A MASS OF CERTAIN SIZE AND LOCATION, NOT AS A TUMOR OR CANCEROUS GROWTH. OF = NORMAL; 1+ = SLIGHT BUT SCORABLE; 2+ = MODERATE; 3+ = MARKED OR SEVERE; C.F. = CANNOT FIND; N.E. = NOT EXAMINED.

NECROPSY FORM

LAB # 57966

ANIMAL # R616

TIME 1100

DATE OF DEATH 3 MAY 85

SEX M

SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS Normal

ADRENALS Normal

ORAL CAVITY Normal

STOMACH:
FUNDUS Normal

ESOPHAGUS Normal

PHYLORUS Normal

TRACHEA Normal

INTESTINAL TRACT:
DUODENUM Normal

THYROID Normal

JEJUNUM Normal

THYMUS Normal

ILEUM Normal

LUNGS Normal

CAECUM Normal

HEART Normal

SPLEEN Normal

LIVER Normal

KIDNEYS Normal

BLADDER Normal

COMMENTS: Skin: Fchar

P. Morgan
NECROPSY TECHNICIAN

J. Davis
STUDY DIRECTOR

DESCRIBE ORGANS AND TISSUES WITH SIMPLE TERMS AND ADJECTIVES. DO NOT USE
TERMS OR DESCRIBE CONDITIONS WHICH CAN ONLY BE PROPERLY CONFIRMED BY
MICROSCOPIC EXAMINATION OR SPECIAL TECHNIQUES: FOR EXAMPLE, AN ABNORMAL
MASS SHOULD BE DESCRIBED AS A MASS OF CERTAIN SIZE AND LOCATION, NOT AS
A TUMOR OR CANCEROUS GROWTH. 0K = NORMAL; 1+ = SLIGHT BUT SCORABLE; 2+ =
MODERATE; 3+ = MARKED OR SEVERE; C.F. = CANNOT FIND; N.E. = NOT EXAMINED.

NECROPSY FORM

LAB # 57966

ANIMAL # R581

TIME 1100

DATE OF DEATH 3 MAY 85

SEX F

SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS [] Normal

ADRENALS [✓] Normal

ORAL CAVITY [✓] Normal

STOMACH:
FUNDUS [✓] Normal

ESOPHAGUS [✓] Normal

PHYLORUS [✓] Normal

TRACHEA [✓] Normal

INTESTINAL TRACT:
DUODENUM [✓] Normal

THYROID [✓] Normal

JEJUNUM [✓] Normal

THYMUS [✓] Normal

LUNGS [✓] Normal

ILEUM [✓] Normal

HEART [✓] Normal

CAECUM [✓] Normal

LIVER [✓] Normal

SPLEEN [✓] Normal

KIDNEYS [✓] Normal

BLADDER [✓] Normal

COMMENTS: epidermis - large eschar formation @ exposure site

gn
NECROPSY TECHNICIAN

J. Davis
STUDY DIRECTOR

DESCRIBE ORGANS AND TISSUES WITH SIMPLE TERMS AND ADJECTIVES. DO NOT USE
TERMS OR DESCRIBE CONDITIONS WHICH CAN ONLY BE PROPERLY CONFIRMED BY
MICROSCOPIC EXAMINATION OR SPECIAL TECHNIQUES: FOR EXAMPLE, AN ABNORMAL
MASS SHOULD BE DESCRIBED AS A MASS OF CERTAIN SIZE AND LOCATION, NOT AS
A TUMOR OR CANCEROUS GROWTH. 0F = NORMAL; 1+ = SLIGHT BUT SCORABLE; 2+ =
MODERATE; 3+ = MARKED OR SEVERE; C.F. = CAN'T FIND; N.E. = NOT EXAMINED.

NECROPSY FORM

LAB # 57966

ANIMAL # R584

TIME 1100

DATE OF DEATH 3 MAY 85

SEX F

SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS [] Normal

ADRENALS [✓] Normal

ORAL CAVITY [✓] Normal

STOMACH:
FUNDUS [] Normal

ESOPHAGUS [] Normal

PHYLORUS [] Normal

TRACHEA [✓] Normal

INTESTINAL TRACT:
DUODENUM [] Normal

THYROID [✓] Normal

JEJUNUM [] Normal

THYMUS [✓] Normal

ILEUM [✓] Normal

LUNGS [] Normal

CAECUM [✓] Normal

HEART [✓] Normal

SPLEEN [] Normal

LIVER [✓] Normal

KIDNEYS [✓] Normal

BLADDER [✓] Normal

COMMENTS: Skin; Eschar

SDM 3 MAY 85
NECROPSY TECHNICIAN

J. Davis
STUDY DIRECTOR

DESCRIBE ORGANS AND TISSUES WITH SIMPLE TERMS AND ADJECTIVES. DO NOT USE
TERMS OR DESCRIBE CONDITIONS WHICH CAN ONLY BE PROPERLY CONFIRMED BY
MICROSCOPIC EXAMINATION OR SPECIAL TECHNIQUES: FOR EXAMPLE, AN ABNORMAL
MASS SHOULD BE DESCRIBED AS A MASS OF CERTAIN SIZE AND LOCATION, NOT AS
A TUMOR OR CANCEROUS GROWTH. 0 = NORMAL; 1+ = SLIGHT BUT SCORABLE; 2+ =
MODERATE; 3+ = MARKED OR SEVERE; CND = CANNOT FIND; NL = NOT EXAMINED.

NECROPSY FORM

LAB # 57966 ANIMAL # R572
TIME 1100 DATE OF DEATH 3 MAY 85
SEX M SPECIES RABBIT

GROSS PATHOLOGICAL OBSERVATIONS

EPIDERMIS	<input type="checkbox"/> Normal	ADRENALS	<input checked="" type="checkbox"/> Normal
ORAL CAVITY	<input checked="" type="checkbox"/> Normal	STOMACH:	
ESOPHAGUS	<input checked="" type="checkbox"/> Normal	FUNDUS	<input checked="" type="checkbox"/> Normal
TRACHEA	<input checked="" type="checkbox"/> Normal	PHYLORUS	<input checked="" type="checkbox"/> Normal
THYROID	<input checked="" type="checkbox"/> Normal	INTESTINAL TRACT:	
THYMUS	<input checked="" type="checkbox"/> Normal	DUODENUM	<input checked="" type="checkbox"/> Normal
LUNGS	<input checked="" type="checkbox"/> Normal	JEJUNUM	<input checked="" type="checkbox"/> Normal
HEART	<input checked="" type="checkbox"/> Normal	ILEUM	<input checked="" type="checkbox"/> Normal
LIVER	<input checked="" type="checkbox"/> Normal	CAECUM	<input checked="" type="checkbox"/> Normal
KIDNEYS	<input type="checkbox"/> Normal	SPLEEN	<input checked="" type="checkbox"/> Normal
BLADDER	<input checked="" type="checkbox"/> Normal		

COMMENTS: SKIN: ESCHAR

NJA
NECROPSY TECHNICIAN

J. Davis
STUDY DIRECTOR

DESCRIBE ORGANS AND TISSUES WITH SIMPLE TERMS AND ADJECTIVES. DO NOT USE TERMS OR DESCRIBE CONDITIONS WHICH CAN ONLY BE PROPERLY CONFIRMED BY MICROSCOPIC EXAMINATION OR SPECIAL TECHNIQUES: FOR EXAMPLE, AN ABNORMAL MASS SHOULD BE DESCRIBED AS A MASS OF CERTAIN SIZE AND LOCATION, NOT AS A TUMOR OR CANCEROUS GROWTH. 0F = NORMAL; 1+ = SLIGHT BUT SCORABLE; 2+ = MODERATE; 3+ = MARKED OR SEVERE; C.F. = CANNOT FIND; N.E. = NOT EXAMINED.

APPENDIX B

MIDECO

STANDARD OPERATING PROCEDURE (SOP)

APPROVAL SHEET

SOP DESIGNATION SOP/RAB/024

TITLE ACUTE DERMAL TOXICITY SCREEN (EPA - FIIRA)

EFFECTIVE DATE 01 NOV 82

SUPERSEDING NEW

APPROVALS:

DRAFTED BY *Steve Rubin* DATE 1 NOV 82

STUDY DIRECTOR *Steve Rubin* DATE 12 NOV 82

LAB DIRECTOR *J. Melan* DATE 12 NOV 82

QAU DIRECTOR *Rahit J. Lalit* DATE 12 NOV 82

RECORD OF REVISIONS							
1	2	3	4	5	6	7	8

SOP#	TITLE	PAGE	OF
SOP/RAB/024	ACUTE DERMAL TOXICITY SCREEN	1	13

ACUTE DERMAL TOXICITY SCREEN (EPA - FIFRA)

1.0 Introduction:

This procedure is employed to determine the dermal toxicity of test materials, solutions, drugs, etc. when applied to large areas of the skin of rabbits.

2.0 Justification:

The dermal route of administration was chosen as this represents a potential route of exposure to humans. The rabbit was chosen since this species has been used historically to determine dermal toxicity.

The objectives of this study are to test the toxicity of the test substance when administered dermally in a single dose to New Zealand white rabbits at 2.0 g/kg and to determine if the median lethal dose (LD₅₀) study is required for this test material.

3.0 References:

This study will be performed in accordance with the FDA Good Laboratory Practices Regulations (Federal Register, Vol. 43, December 22, 1978). This protocol is based on the proposed U.S. Federal Insecticide, Fungicide, and Rodenticide Act Guidelines (Federal Register, Vol. 43, August 22, 1978).

4.0 Equipment:

- 4.1 Balance, capable of \pm 10 g.
- 4.2 Stainless steel animal cages.
- 4.3 Clippers.
- 4.4 Vacuum Cleaner.

5.0 Supplies:

- 5.1 Syringes, 5 - 10 mL.
- 5.2 Latex dental dam.
- 5.3 Gauze swatches, 4" x 4".
- 5.4 Non-irritating tape.
- 5.5 18 g by 1-1/2" needle.

SOP#	TITLE	PAGE	OF
SOP/RAB/024	ACUTE DERMAL TOXICITY SCREEN	2	13

6.0 Reagents:

6.1 Sterile distilled or deionized water.

7.0 Records to be Maintained:

7.1 Completed data and results sheets (attached).

8.0 Animal Data: See attached sheets.

9.0 Within 24 hours before dosing, each animal is observed for general health. The back, sides, and belly are clipped free of fur. Examination of the skin is performed to eliminate any animal's which have dermal lesions, infections, or new fur growth which may obscure examination or affect absorption.

10.0 The animals to be abraded are subjected to dermal abrasions at the site of exposure with a clean hypodermic needle (see Detail Sheet). The skin must be abraded in such a way as to penetrate the corneum but not disturb the dermis; that is, not to obtain bleeding.

11.0 The test will be performed with 10 New Zealand young adult albino rabbits per sample (see Detail Sheet). The animals will weigh between 2.5 - 3.5 kg.

12.0 The animals are weighed just prior to dosing to establish the calculated dose (see Detail Sheet).

13.0 When testing solids, the test substance shall be moistened with physiological saline to make a paste that will ensure good contact with the skin.

14.0 The test substance is distributed evenly over a minimum 10% dorsal surface area. The test substance must remain in contact with the skin throughout the exposure period of 24 hours. Reapply any test material which leaks.

15.0 Liquid or solid substances shall be held in contact with the skin with a porous gauze dressing and non-irritating tape. The test site is then covered by a latex dental dam over the entire trunk of the rabbit.

16.0 At the end of the 24 hour exposure period, the wrapping is removed and the skin wiped (but not washed) to remove the test substance still remaining.

17.0 Skin reactions, and toxic signs are noted.

18.0 The observation period is 14 days. Examine each rabbit immediately after dosing at 4 hours and once each day thereafter.

19.0 Individual weight of rabbits are determined on the day the test substance is administered, weekly thereafter, and at the completion of the test.

20.0 Observations for toxic symptoms shall include the following organs or systems.

20.1 Autonomic: Nasal discharge and salivation.

20.2 Behavioral: Sedation and abnormal activity.

20.3 Sensory: Sound & Touch.

20.4 Neuromuscular: Ataxia and prostration.

20.5 Respiratory: Hypopnea and dyspnea.

20.6 Ocular: Mydriasis, myosis and lacrimation.

20.7 Gastrointestinal: Diarrhea and constipation.

20.8 Cutaneous: Erythema and edema.

21.0 Nine major organ or organ systems are evaluated for demonstrable toxic symptoms (20.1--20.7). All are scored as follows:

21.1 0 = Normal.

21.2 +1 = Observable, but modest.

21.3 +2 = Marked.

21.4 Cutaneous (20.8) will be scored as follows:

<u>Erythema</u>	<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 approx. 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond the area of exposure).	4

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- 22.0 All toxic responses are explained in detail on the result sheet.
- 23.0 All animals living at the termination of the observation period are sacrificed. All test animals, whether dying by sacrifice or during the test, are subjected to a complete gross necropsy following their death.
- 24.0 Animals are necropsied as soon as possible after death. If necropsy cannot be performed immediately after the animal is sacrificed or found dead, the animal is immediately refrigerated (but not frozen) at temperatures low enough to minimize tissue autolysis (4 - 8°C). Animals found dead upon routine clinical examination are necropsied as soon as possible to salvage usable tissues.
- 25.0 The gross necropsy includes an initial physical examination of the external surfaces and all orifices followed by an internal examination of tissues and organs in situ. The examination includes the following: epidermis, esophagus, trachea, thyroid, thymus, lungs, heart, liver, kidneys, bladder, adrenals, stomach, intestinal tract, spleen.

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SUPPLEMENTAL DATA SHEET (SDS-4)
ANIMAL INFORMATION

TEST: Acute Dermal Toxicity Screen (EPA-FIFRA)

SPECIES/STRAIN: New Zealand albino rabbits

SEX: Female and Male

AGE: N/A

WEIGHT RANGE: 2.5 - 3.5 kg

ANIMAL IDENTIFICATION SYSTEM: Permanent ear tag, alphanumeric

SOURCE: Local Vendors

DOSE: See Detail Sheet

ROUTE: Topical, dorsal area

FREQUENCY: Once

CONTROL ANIMALS: No exposure

PRETEST CONDITIONING: Quarantine/Observation, 7 days minimum

RANDOMIZATION: None

ROOM TEMPERATURE: 20 ± 3°C

HUMIDITY: 50 ± 20%

BEDDING: Untreated sawdust

CAGING: 18" x 30" x 16" wire bottom stainless steel cage

LIGHT/DARK CYCLE: 12 Hours Light/12 Hours Dark

FOOD: Rabbit Chow, ad libitum

WATER: Filtered city water, ad libitum

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DEFINITION OF TOXIC SIGNS

Autonomic:

Salivation:

- 0 Normal.
- +1 Secretions moistening area around mouth opening.
- +2 Secretion extending beyond mouth opening.

Nasal Discharge:

- 0 Normal, no secretions above normal.
- +1 Secretions moistening area around nasal opening.
- +2 Secretions extending beyond nasal opening.

Behavioral:

Sedation:

- 0 Normal, animal alert and active.
- +1 Animal showing slight effect of sedation, listless and not active. Stimuli response diminished.
- +2 Marked response--animal staying in one position for long periods of time. Inability to react to stimuli.

Abnormal Activity:

- 0 Normal behavior.
- +1 Increase in biting, fighting, rolling, righting response.
- +2 Persistence in biting, fighting, rolling, righting, response, or tail chasing.

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Sensory:

Sound & Touch:

- 0 Normal behavior to sound and touch. When cage is tapped, animal will look towards the location of the stimuli. When touched, animal will withdraw from the stimuli.
- +1 Slight deviation from normal.
- +2 Inability to respond to sound or touch. No response to a given stimulus.

Neuromuscular:

Ataxia:

- 0 Normal--no loss of muscle coordination.
- +1 Slight loss of muscle coordination, slight impairment to fulfill normal body motions.
- +2 Persistent loss of ability to perform normal body motions.

Prostration:

- 0 Normal, no marked loss of strength, exhaustion, able to keep body upright.
- +1 Slight loss of strength or exhaustion, legs spread apart.
- +2 Inability of animal to keep itself upright. Animal is prostrate.

Respiration:

Hypopnea:

- 0 Normal amount of air breathed per minute.
- +1 Slight difficulty in breathing; decreased amount of air breaths.
- +2 Extreme difficulty in breathing, excessive decrease amount of air breathed per minute to the point of fainting.

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Dyspnea:

- 0 No difficulty in breathing; normal amount of air breathed per minute.
- +1 Slight difficulty in breathing; an increase in amount of air breathed per minute.
- +2 Extreme difficulty in breathing; excessive increase in amount of air breathed per minute. Beyond control.

Ocular:

Lacrimation:

- 0 No secretion of tears.
- +1 Secretion of tears noted on orbit area only.
- +2 Secretion of tears is observed beyond orbit area.

Myosis:

- 0 Normal size of pupil.
- +1 Size of pupil is decreased by up to 1/2 normal size.
- +2 Size of pupil is decreased by greater than 1/2 normal size.

Mydriasis:

- 0 Normal size of pupil.
- +1 Size of pupil is increased by 1/2 the normal size.
- +2 Size of pupil is increased by more than 1/2 normal size.

Gastrointestinal:

Diarrhea:

- 0 No noted discharge.
- +1 Diarrhea observable in cage and around anus.
- +2 Diarrhea observable in cage around anus and found on animal coat.

Constipation:

- 0 Feces appears normal.
- +1 Slight observed change in size, shape and water content of feces.
- +2 Large decrease in amount of feces possibly due to intestinal blockage. Any noted feces appears greatly reduced in size, shape and water content.

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ACUTE DERMAL TOXICITY DATA SHEET

LAB NUMBER: _____ SPONSOR: _____

IDENTIFICATION: _____

DATE STARTED: _____ DATE COMPLETED: _____

CALCULATIONS: SHEET ATTACHED BY SPONSOR _____

PREPARATION BY: _____ DATE _____ VEHICLE _____ LOT # _____

SAMPLE DESCRIPTION: SOLID LIQUID _____

ANIMALS SHAVED BY: _____ #: _____ DATE: _____

ROOM: _____ TIME: _____

ABRADED BY: _____ DATE: _____ TIME: _____

CONTROLS: NO EXPOSURE SITES _____

EXPOSURE DATE: _____ TIME _____ ROOM _____ BY _____

AMOUNT DOSED AREA PER ANIMAL _____ # OF ANIMALS _____

OCCLUSIVE (latex) NONOCCLUSIVE

STUDY DIRECTOR REVIEW

DATE

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ACUTE DERMAL TOXICITY
DETAIL SHEET

DOCUMENT/LAB NUMBER: _____ SOP # _____

SPONSOR: _____

IDENTIFICATION: _____

NATURE: SOLID LIQUID EXTRACT _____

NUMBER OF DOSE LEVELS: _____

NUMBER ANIMALS PER GROUP: _____

DOSE: _____

METHOD OF EUTHANSIA: _____

STUDY DIRECTOR REVIEW

DATE

ACUTE DERMAL TOXICITY RESULT SHEET

LAB NUMBER: _____ SPONSOR: _____

CONTROL ANIMAL [] TEST ANIMAL [] MALE [] FEMALE []

RABBIT # _____ ROOM # _____

SAMPLE CONCENTRATION: _____ %

0 DAY WEIGHT _____ 7 DAY WEIGHT _____ 14 DAY WEIGHT _____

SYSTEM	P R E N	S E T	P E T	I N J E C T	0 HRS	4 HRS	1 DAY	2 DAY	3 DAY	4 DAY	5 DAY	6 DAY	7 DAY	8 DAY	9 DAY	10 DAY	11 DAY	12 DAY	13 DAY	14 DAY	
AUTONOMIC																					
SENSORY																					
NEUROMUSCULAR																					
RESPIRATORY																					
RENAL																					
GASTROINTEST.																					
CUTANEOUS																					
BEHAVIORAL																					
CARDIOVAS.																					
TOTALS																					

DATE																					
TIME																					
TECHNICIAN																					

COMMENTS:

STUDY DIRECTOR REVIEW _____

DATE _____