EASTMAN

Eastman Chemical Company
P. O. Box 511
Kingsport, Tennessee 37662

RECEIVED
OPPT CBIC

06 OCT 11 AM 10: 52

October 4, 2006

Document Control Office (DCO 7407M)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001
ATTN: 8(d) Health and Safety Reporting Rule (Notification/Reporting)

CONTAIN NO CBI

Dear Administrator,

The Eastman Chemical Company has reviewed their files in response to requests by the Environmental Protection Agency to report unpublished health and safety data pursuant to Section 8(d) of the Toxic Substances Control Act (71 Fed. Reg. 47,130, August 16, 2006; 71 Fed. Reg. 57,439, September 29, 2006).

The table below lists those chemicals for which Eastman possessed health and safety data. Copies of this data are organized by the chemical's CAS number on the enclosed compact disc. Please contact Dr. James A. Deyo at 423-229-5208 should you have any problems extracting the information from the disc.

CAS No.	Chemical Name
110-18-9	1,2-Ethanediamine, N,N,N',N'-tetramethyl-
110-33-8	Hexanedioic acid, dihexyl ester
111-85-3	Octane, 1-chloro-
124-63-0	Methanesulfonyl chloride
131-57-7	Methanone, (2-hydroxy-4-methoxyphenyl)phenyl-
25646-71-3	Methanesulfonamide, N-[2-[(4-amino-3-methylphenyl)ethylamino]ethyl]-, sulfate (2:3)
4170-30-3	2-Butenal
645-62-5	2-Hexenal, 2-ethyl-
68987-66-6	Ethene, hydrated, by-products from
7795-95-1	1-Octanesulfonyl chloride
81-07-2	1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide
94-96-2	1,3-Hexanediol, 2-ethyl-
97-00-7	Benzene, 1-chloro-2,4-dinitro-

Regards,

Marc G. Schurger
Director, Product Safety & Health

8 6 0 7 0 0 0 0 0 1

Enclosure: Compact Disc labeled "Eastman TSCA 8(d) Submission; October 4, 2006

299312

8607000001

Eastman Attachments (MR-29312)

81-07-2

94-96-2

97-00-7

110-18-9

110-33-8

111-85-3

124-63-0

131-57-7

4170-30-3

7795-95-1

25646-71-3

68987-66-6

Toxicity Data

906659

from L+F

Confidential
Special Report 33-57
7 Pages

R: 6-11-70

Chemical Hygiene Fellowship
MELLON INSTITUTE
Carnegie-Mellon University

"6-12" Insect Repellent Formulations, Containing as Active Ingredients

2-Ethyl-1,3-Hexanediol and N,N-Diethyl-meta-Toluamide

Modified Range Finding Toxicity Studies

Editor: C. S. Weil
Contributors: N. I. Condra, E. R. Kinkead
For: UNION CARBIDE CORPORATION, Chemicals and Plastics Operations Division

Summary

	No. Died/No. Dosed			Skin Irritation, rabbit, covered patch	Eye Injury, rabbit, 0.1 ml.
	Stomach Intubation, rat 0.5 gm./kg.	Skin Penetration, rabbit 2.0 gm./kg.	Inhalation, rat, 4 hour, mist		
Foam concentrate	0/12	0/4	0/12	none	irritant
Cream	0/12	0/4	0/12	none	irritant
Liquid	0/12	0/4	0/12	none	irritant
Liquid/spray	0/12	0/4	0/12	none	irritant
Spray concentrate	0/12	0/4	0/12	none	irritant
Towelette concentrate	0/12	0/4[1]	0/12	none	irritant
Spray	-	-	0/12	none	irritant
Foam	-	-	0/12	none	irritant
Stick	-	-	-	none	-
Towelette	-	-	-	none	irritant

1. At 4.0 gm./kg.

Interpretation

The 2-ethyl-1,3-hexanediol and N,N-diethyl-meta-toluamide formulations tested had a relatively low order of toxicity by the peroral, skin penetration or inhalation routes. No irritation resulted on the abraded or unabraded skin of rabbits with the materials retained under a covered patch. Rabbit eyes were irritated with 0.1 ml. quantities and human eye contact should be avoided.

Samples

Quantity: 6 to 18 ounces Date Received: 3-26-70 M. I. Sample No.: 33-59 to -6

Submitted by: R. B. Mitchell Division: Consumer Products Division Tarrytown, New York

Identification: as appended to 3-20-70 letter from Mitchell to Carpenter Charge No.: 01012

Procedures

Stomach Intubation - Rats

Five male and 5 female rats, weighing 120 to 180 grams, were dosed perorally with 0.5 grams of a formulation or concentrate per kilogram of body weight. The rats were fasted 24 hours before dose and observed 14 days thereafter. If death occurred at this maximum dosage level, an LD50 would have been determined.

Skin Penetration - Rabbits

Male albino rabbits, 3 to 5 months of age were immobilized during a 24-hour contact period with the formulation or concentrate retained under impervious sheeting on the clipped intact skin of the trunk. Thereafter, excess fluid was removed to prevent ingestion and the rabbits were observed for 14 days. The maximum dosage level used was 2.0 ml./kg. If mortality occurred at this level, an LD50 would have been determined.

Inhalation - Rats

The formulations or concentrates were atomized in a glass VAPONEFRIN nebulizer using dried compressed air at 9 liters/minute and 22 p.s.i. The plan was to expose 6 males and 6 females per material for one hour to a maximum concentration of 5 mg./L. and to determine the LC50 if mortality resulted within 14 days. Four-hour exposures were used and the concentrations attained are noted in the "Results" section.

Skin Irritation - Rabbits

The formulation or concentrate (0.5 ml. or 0.5 gram quantity) was applied to the clipped skin of each of 6 rabbits. One spot on each rabbit was previously abraded and one unabraded for each formulation. The area was covered with surgical gauze, two layers thick, held in place by a cross of adhesive tape. The entire trunk of the rabbit was wrapped with an impervious cover open at both ends and the rabbits were immobilized for 24 hours of exposure, when the patches were removed. The reactions were read one hour and 48 hours after patch removal; at 24 and 72 hours after application of the dose.

Eye Injury - Rabbits

Six eyes, not staining with 5% fluorescein in 20 seconds contact, were used for each formulation or concentrate. A single instillation of 0.1 ml. was made into the conjunctival sac, the eyes examined and the corneal injury graded 24, 48 and 72 hours after dose. An eye was judged "positive" or "negative" as defined in the Federal Register, September 17, 1964; 29 F.R. 13009 §191.12 (b) (1).

Results

Stomach Intubation - Rats

The results of single peroral doses of the 6 liquid formulations or concentrates are summarized in Table 33-60. None of the rats died during the 14-day postdose observation period. No abnormal symptoms or gross autopsy findings were observed. The body weight changes of some of the groups of rats were lower than those of others. The two groups which gained the least were those that received the foam concentrate or the spray concentrate. Contrariwise, the group that received the towelette concentrate had the highest weight gain. The body weight changes did not appear to be related to the concentration of either the 2-ethyl-1,3-hexanediol or the N,N-diethyl-meta-toluamide in the formulations.

Skin Penetration - Rabbits

The results of the rabbit skin penetration dosing of the 6 liquid formulations is presented in Table 33-61. As with the single peroral dose, none of the animals died at the screening dosage level or higher.

Inhalation - Rats

The results of the single inhalation exposure of rats to the 6 liquid and the foam and spray formulations are presented in Table 33-62. As with peroral and skin penetration doses, none of the rats exposed to these sprays died within 14 days of the dose. All rats appeared normal and gained equivalent amounts of body weight.

Skin Irritation - Rabbits

No summary table is presented for this criterion of effect as none of the groups of 6 rabbits for any of the 10 materials had any signs of skin irritation. No capillary injection, erythema, eschar, edema or necrosis was seen on any individual rabbit.

Eye Injury - Rabbits

The relative degree of eye injury for the 9 formulations or concentrates is summarized in Table 33-63. The quantity of each applied was 0.1 ml. or 0.1 gram. This amount of 2-ethyl-1,3-hexanediol or N,N-diethyl-meta-toluamide will produce severe eye injury. Therefore, it was not unexpected that all of the materials tested, except the foam, 33-61, were irritating to each of the eyes tested. Iritis, dullness of the cornea and eyelid irritation was noted. Even with the foam formulation, 4 of the 6 eyes had "positive" reactions. The mean corneal injury score for the foam and the foam concentrate were indicative of less injury than the other formulations and slightly better healing resulted in the 72-hour postdose observation period. In any case, eye contact with any of these formulations should be avoided.

Carrol S. Weil, M.A.
Senior Fellow

Approved:

Charles P. Carpenter, Ph.D.
Administrative Fellow

Acknowledgments:
Skin Penetration, Irritation Tests — Naomi I. Condra, B.S., Junior Fellow
Inhalation Studies — Edwin R. Kinkead, B.S., Junior Fellow

Typed: June 12, 1970 - wd

Table 33-60

Results of Single Peroral Dose[1] of Diol/Deet Formulations

Name	CHF No.	Mortality		Range of Body Weight Gains		Mean Body Weight Change		Rank of Mean Change	
		Males	Females	Males	Females	Males	Females	Males	Females
Foam concentrate	33-59	0/5	0/5	24 to 71	60 to 86	55.0	73.0	1	2
Cream	33-62	0/5	0/5	105 to 155	73 to 96	129.2	88.4	3	5
Liquid	33-63	0/5	0/5	132 to 191	70 to 121	150.0	84.8	5	4
Liquid/spray	33-64	0/5	0/5	126 to 170	66 to 83	147.6	77.6	4	3
Spray concentrate	33-65	0/5	0/5	82 to 138	65 to 87	112.6	72.8	2	1
Towelette concentrate	33-66	0/5	0/5	150 to 163	82 to 118	156.8	97.0	6	6
					Coefficient of Rank Correlation			+0.771	

Males

Mean Weight Change	55.0	112.6	129.2	147.6	150.0	156.8
CHF Sample No. 33-	59	65	62	64	63	66

Females

Mean Weight Change	72.8	73.0	77.6	84.8	88.4	97.0
CHF Sample No. 33-	65	59	64	63	62	66

Note: Any two means not underscored by the same line are significantly different ($P < 0.05$).
Any two means underscored by the same line are not significantly different ($P > 0.05$).
1. Dosage level = 0.5 ml./kg. of formulation to 120 to 160 gram rats fasted 24 hours before dose.

Table 33-61

Results of Single Skin Penetration Dose[1.] of Diol/Deet Formulations

Name	CHF No.	Mortality; Dead/Dosed	Body Wt. Changes	Mean Body Weight Change
Foam concentrate	33-59	0/4	-75,105,256,351	159
Cream	33-62	0/4	328,334,385,390	359
Liquid	33-63	0/4	-72, 85,149,256	104
Liquid/spray	33-64	0/4	-23,170,292,372	203
Spray concentrate	33-65	0/4	152,375,397,423	337
Towelette concentrate	33-66	1/4[2.]	103,231,235,388	239[2.]

1. Dosage level = 2.0 ml./kg. of formulation to 2295 to 2878 gram rabbits.
2. As 1 of 4 died at 2.0 ml./kg., 4 additional rabbits were dosed at 4.0 ml./kg. All survived; the weights listed are for the survivors at 4.0 ml./kg.

Table 33-62

Results of Single 4-Hour Inhalation Exposure to Diol/Deet Formulations

Name	CHF No.	Concentration; mg./L.	Mortality		Range of Body Weight Gains		Median Body Weight Gain	
			Males	Females	Males	Females	Males	Females
Foam concentrate	33-59	26.2	0/6	0/6	88 to 116	33 to 61	102	46
Cream	33-62[1]	11.1	0/6	0/6	77 to 100	38 to 66	95	52
Liquid	33-63	2.7	0/6	0/6	49 to 95	37 to 67	78	52
Liquid/spray	33-64	15.8	0/6	0/6	77 to 106	39 to 66	92	50
Spray concentrate	33-65	26.1	0/6	0/6	57 to 128	37 to 86	82	46
Towelette concentrate	33-66	7.7	0/6	0/6	89 to 103	36 to 71	94	43
Foam	33-61	34.4	0/6	0/6	83 to 114	39 to 72	89	48
Spray	33-60	19.8	0/6	0/6	73 to 137	41 to 62	101	48

No signs or symptoms were noted during or after exposure; nothing remarkable was noted on gross autopsy of survivors.

1. Nebulizer was placed in a water bath maintained at 60°C.

Table 33-63

Degree of Eye Injury - Rabbits

Name	CHF No.	Mean Corneal Injury Score at 24 Hrs.	48 Hrs.	72 Hrs.	Number of Eyes with Iritis 24 Hrs.	48 Hrs.	72 Hrs.	Dullness 24 Hrs.	48 Hrs.	72 Hrs.	Lids with Pus, Edema and Injection 24 Hrs.	48 Hrs.	72 Hrs.	"Positive" Test Results
Foam concentrate	33-59	5.2	3.5	2.0	4/4	2/4	1/4	2/4	1/4	1/4	4/4	4/4	1/4	4/4
Cream	33-62	7.0	6.5	6.5	4/4	1/4	2/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
Liquid	33-63	6.2	5.8	5.2	1/4	1/4	1/4	4/4	4/4	3/4	4/4	4/4	3/4	4/4
Liquid/spray	33-64	7.2	6.0	6.0	4/4	3/4	3/4	4/4	3/4	3/4	4/4	3/4	3/4	4/4
Spray concentrate	33-65	7.0	5.8	5.5	4/4	3/4	3/4	4/4	3/4	3/4	4/4	4/4	4/4	4/4
Towelette concentrate	33-66	6.2	5.2	5.0	2/4	1/4	3/4	4/4	4/4	3/4	4/4	4/4	4/4	4/4
Spray	33-60	6.8	5.8	4.8	3/4	1/4	0/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
Foam	33-61	4.3	3.8	3.2	2/6	2/6	2/6	3/6	3/6	3/6	5/6	4/6	4/6	4/6
Stick[1]	33-67	6.5	5.8	5.8	2/4	0/4	1/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4

1. 100 mg. placed onto rabbit eye. For all other samples, 0.1 ml. was used.

REPORT MAILING LIST B

Medical Directors

4 - C. U. Dernehl
1 - E. Q. Hull
1 - R. E. Joyner
1 - R. J. Sexton
1 - J. B. Block

Other Distributions

1 - M. B. VerNooy
2 - N. M. Ketcham
1 - P. W. McDaniel
1 - H. R. Guest

Libraries

2 - Chemicals Division (1 set each Library)
Building 701 and 770 Libraries
South Charleston, West Virginia

Project Initiator--to distribute as you see fit. No copies have been sent to others in your business or operations team, except summaries to the R/D Directors, V.P.'s and Libraries. More copies will be furnished upon your request.

Project Initiator

1 - R. B. Mitchell
1 - H. L. Haynes
1 - P. H. Lahr

* *

C O L L E C T E D S U M M A R I E S of all reports are sent to List A at monthly intervals. List A recipients are:

1 - R. I. Hoaglin
1 - J. J. Smith
1 - T. T. Szabo
1 - T. H. Welch
1 - N. L. Zutty

1 - J. V. Murray, Jr.
1 - L. Shechter
1 - Plastics Division Library
Bound Brook, N. J.
1 - Mining and Metals Library
Tuxedo, N. Y.
2 - Chemicals and Plastics Division
Bldg. 701 & 770 Libraries
South Charleston, W. Va.
1 - R & D Library
Tarrytown, N. Y.

1 - W. B. Ackart
1 - E. A. Barr

244970X
TX-88-168

ACUTE TOXICITY OF 2-ETHYL-1,3-HEXANEDIOL

HAEL NO. 88-0087 ACC. NO. 906659

BY KENNETH P. SHEPARD, B.S.

TOXICOLOGICAL SCIENCES LABORATORY
HEALTH AND ENVIRONMENT LABORATORIES
EASTMAN KODAK COMPANY
ROCHESTER, NY 14652-3615

DATE OF STUDY COMPLETION OCTOBER 21, 1988

244970X
TX-88-168

SUMMARY OF ACUTE TOXICITY STUDIES

Chemical: 2-Ethyl-1,3-hexanediol

Accession No.: 906659

HAEL No.: 88-0087

Source Reference I.D. No.: TX-1694-65

Source: Tennessee Eastman Company

Date of First Study Initiation: July 25, 1988

Comments: All animals were identified by metal ear tags/cage number. All specimens, raw data, and the final report of this work are stored in the archives of the Health and Environment Laboratories. Only limited analyses have been completed on the strength, purity, composition, stability, uniformity, and concentration of the test material. Professionals involved in this study other than the study director included: Gordon J. Hankinson, D.V.M., M.S., Laboratory Animal Medicine and Milan S. Vlaovic, D.V.M., Ph.D., Pathologist. Deviations from approved protocols or standard operating procedures included: None.

Director, Mammalian Toxicology Section
Study Director

October 21, 1988
Date

Director, Toxicological Sciences Laboratory

October 20, 1988
Date

ACUTE ORAL TOXICITY IN THE RAT

Dose levels tested: 5000 mg/kg

No. Rats/dose: 5 of each sex/dose

Vehicle: None

Solution/suspension: Administered as received

Initial Body weight range (g): Males: 135 - 153 Females: 138 - 153

Strain: Crl:CD®(SD)BR

Method of calculation: Weil method

Test SOP No.: TA 110, TA 120

DOSE mg/kg	NO. RATS DOSED(M,F)	NO. DEATHS (M,F)	TIME OF DEATH	WEIGHT GAIN* 1 WEEK(M,F)	WEIGHT GAIN* 2 WEEK(M,F)
5000	5,5	0,2	~2 Hrs - Day 1	5+,3+	5+,3+

* + = Number of animals gaining weight
– = Number of animals losing weight

SUMMARY OF CLINICAL SIGNS

DOSE (mg/kg)	CLINICAL SIGN	NO. OF RATS AFFECTED
5000	Slight Weakness	5M,3F
	Severe Weakness	5M,5F
	Prostration	2M,4F
	Vasodilation	5M,5F
	Clinically Recovered	5M,3F
	Death	2F

ESTIMATED ORAL LD_{50} IN RATS

MALES: > 5000 mg/kg - 95% C.I. No range calculable
FEMALES: > 5000 mg/kg - 95% C.I. No range calculable

ACUTE ORAL TOXICITY IN THE RAT CONT.

REMARKS: The test article was slightly toxic orally. Treatment-related signs observed after administration of a limit dose of 5000 mg/kg consisted of severe weakness (5/5 males, 5/5 females), vasodilation (5/5 males, 5/5 females), and prostration (2/5 males, 4/5 females) on the day of dosing. Other abnormal clinical signs noted during the remainder of the study were limited to slight weakness on Day 1 of the study. One female (Rat 239) died approximately two hours after dosing and a second female (Rat 238) died on Day 1. All other animals survived the scheduled 14-day observation period and gained weight normally.

The cause of death for the two females which died after exposure to the test material was not determined. No treatment-related changes were observed at autopsy. Only the stomach from Rat 239 was processed for microscopic evaluation. The grossly observed red discoloration in the glandular gastric mucosa of Rat 239 could not be confirmed microscopically. It could have been due to congestion, which is a common agonal change, and was not considered treatment-related.

ACUTE DERMAL TOXICITY IN RATS

Dose levels tested: 20 mL/kg

No. Rats/dose: 5 of each sex/dose

Vehicle: None

Preparation: Administered as received

Initial Body weight range (g): (M) 262 - 283 (F) 193 - 208

Strain: Crl:CD®(SD)BR

Method of calculation: Weil method

Test SOP No.: TA 310

DOSE mL/kg	NO. RATS DOSED(M,F)	NO. DEATHS (M,F)	TIME OF DEATH	WEIGHT GAIN* 1 WEEK(M,F)	WEIGHT GAIN* 2 WEEK(M,F)
20	5,5	0,0	----------	5+,5+	5+,5+

* + = Number of animals gaining weight
- = Number of animals losing weight

SUMMARY OF CLINICAL SIGNS		
DOSE (mL/kg)	CLINICAL SIGN	NO. OF RATS AFFECTED
20	Appeared Clinically Normal	5M,5F

ESTIMATED DERMAL LD_{50} IN RATS
MALES: > 20 mL/kg - 95% C.I. No range calculable
FEMALES: > 20 mL/kg - 95% C.I. No range calculable

Skin Absorption Not Evident
(Based on Dermal Toxicity and Repeated Skin studies)

REMARKS: The test article was, at most, slightly toxic by the dermal route. A limit dose of 20 mL/kg was applied to the skin after the hair was removed from the skin with an electric clipper. An occlusive wrap was used to hold the test material against the skin for 24 hours, and at the end of exposure, residual test material was washed off with running water. No abnormal clinical signs were observed, all animals gained weight normally, and no signs of percutaneous absorption were evident.

ACUTE TOXICITY - DERMAL IRRITATION IN GUINEA PIGS

24 hr. Occluded Single Dose

Slight Moderate Strong Severe

Dose levels tested: 0.5 mL

No. guinea pigs/dose: 5

Vehicle: None

Preparation: Administered as received

Initial Body weight range (g): 402 - 421

Strain: Crl:(HA)BR Hartley

Test SOP No.: TA 160

Sex: Female

Acute Skin Irritation

Slight

Moderate

Strong

Estimated Corrosivity

No

Questionable

Yes

RESULTS				
ANIMAL NO.	MAXIMUM EFFECT		WEIGHT CHANGE (g)	
	SKIN - 24/48 HOURS	SKIN - 2 WEEKS	1 WEEK	2 WEEKS
706	Normal	Normal	+29	+100
707	Normal	Normal	+17	+81
708	Normal	Normal	+20	+96
709	Normal	Normal	+16	+88
710	Normal	Normal	+24	+90

KEY: Slt. = Slight, Mod. = Moderate, Str. = Strong, Ery. = Erythema, Ed. = Edema, N. = Necrosis, Esc. = Eschar, Scr. = Scarring, V. Slt = Very Slight, St. = Staining, Ero. = Erosion

REMARKS: The test article was, at most, a slight skin irritant. A dose of 0.5 mL was applied to each depilated guinea pig abdomen, and an occlusive wrap was used to hold the test material against the skin for 24 hours. No signs of irritation were observed, all animals gained weight normally, and no signs of percutaneous absorption were evident.

ACUTE TOXICITY - REPEATED SKIN

Dose levels tested: 0.5 mL drop-on

No. of doses: 9 No. of days: 11

No. guinea pigs/dose: 5

Vehicle: None

Preparation: Administered as received

Initial Body weight range (g): 352 - 417

Strain: Crl:(HA)BR Hartley

Test SOP No.: TA 170

Sex: Not Determined

RESULTS	GREATEST EFFECT				
	ERYTHEMA	EDEMA	NECROSIS	ESCHAR	OTHER
1ST DOSE	0	0	0	0	0
LAST DOSE	2	0	0	0	0

REMARKS: The test material produced slight exacerbation of the irritant response with repeated application. No initial signs of irritation were observed when the material was applied topically to the backs of guinea pigs after the hair was removed with an electric clipper. Slight erythema was noted after the third dose. After nine daily applications over a period of eleven days, signs of irritation consisted of moderate erythema in three of five animals and slight erythema in two of five animals. There was no evidence of percutaneous absorption, and all animals gained weight over the course of the study.

ACUTE TOXICITY - SKIN SENSITIZATION
KODAK FOOTPAD METHOD

No. guinea pigs per dose: 10

Irritation drop-on body weight range (g): 418 - 561

Induction body weight range (g): 399 - 496

Strain: Crl:(HA)BR Hartley

Test SOP No.: TA 180

Sex: Female

Estimated Human Risk
Low
Moderate
High

Irritation Drop-on	
Concentrations tested:	0.05 mL of compound in 5.0 mL of Acetone + Dioxane + Guinea Pig Fat.
Highest average score:	0

Induction and Challenge Study	
Induction preparation:	0.05 mL of a 1.0% solution of compound in Freund's Complete Adjuvant.
No. of challenge doses:	1
Challenge preparation:	1.0 mL of compound in 10.0 mL of Acetone + Dioxane + Guinea Pig Fat.

SENSITIZATION	NUMBER POSITIVE				TOTAL SCORE
	NORMAL	SLIGHT	MODERATE	STRONG	
FREUND'S ONLY	10				0
1% CPD. IN FREUND'S	10				0

REMARKS: The test article has a low potential to cause human sensitization. No reaction was observed at challenge in any of the animals previously induced with Freund's adjuvant or the test article in Freund's adjuvant.

ACUTE TOXICITY - RABBIT EYE IRRITATION

Dose level tested: 0.1 mL

No. of doses: 1

No. rabbits/dose: 3 washed / 3 unwashed

Vehicle: None

Washing agent: Distilled water

Body weight range: Not determined

Strain: New Zealand white

Test SOP No.: TA 150

Sex: Not Determined

Acute Eye
Irritation
Slight
Moderate
Strong

RESULTS	3 UNWASHED EYES						
	IMMED.	1 HR.	24 HR.	48 HR.	72 HR.	DAY 7	DAY 14
Initial	Mod.						
Conjunctiva		Str.	Mod.	Mod.	Mod.	Mod.	
Lids		Slt.	Slt.	Slt.	Slt.	Slt.	
Nict. Membrane		Str.	Mod.	Mod.	Mod.	Mod.	
Corneal Opacity			Str.	Str.			
Iris				Slt.	Slt.		
Adnexal Stain			3/3				
Corneal Stain			3/3				
Discharge		Mod.	Slt.				
Number Normal	0	0	0	0	0	0	3

RESULTS	3 WASHED EYES						
	IMMED.	1 HR.	24 HR.	48 HR.	72 HR.	DAY 7	DAY 14
Initial	Slt.						
Conjunctiva		Mod.	Mod.	Slt.	Slt.		
Lids							
Nict. Membrane		Mod.	Mod.	Slt.	Slt.		
Corneal Opacity							
Iris							
Adnexal Stain			2/3				
Corneal Stain			0/3				
Discharge		Slt.					
Number Normal	0	0	0	0	2	3	3

KEY: Slt. = Slight Mod. = Moderate Str. = Strong

ACUTE TOXICITY - RABBIT EYE IRRITATION CONT.

NO. RESPONDING	Slight	Moderate	Strong	Severe	Fluorescein Stain	
					Adnexa	Cornea
UNWASHED EYES		3/3			3/3	3/3
WASHED EYES	3/3				2/3	0/3

REMARKS: The test article was a moderate eye irritant. It caused moderate (2/3) to strong (1/3) erythema and strong edema of the conjunctivae and nictitating membranes in unwashed eyes within 24 hours after administration of the test material. Slight erythema and edema of the lids, slight corneal opacity, and moderate discharges from the three eyes were also noted. When tested with fluorescein dye 24 hours after dosing, there was adnexal and corneal staining in the unwashed eyes. Slight erythema of the irides was noted in 1/3 eyes at 48 hours and 2/3 eyes at 72 hours. By Day 7, signs of irritation consisted of slight edema (2/3) and slight (1/3) to moderate (2/3) erythema of the adnexa. By Day 14, all unwashed eyes appeared clinically normal.

Immediate washing was palliative. In washed eyes, signs of irritation were restricted to slight (1/3) to moderate (2/3) erythema and moderate edema of the conjunctivae and nictitating membranes. Slight discharges from the eyes were observed only at the one-hour observation period. While adnexal staining was evident, no corneal staining was observed when the eyes were tested with fluorescein dye 24 hours after administration of the test article. By 72 hours, two of three washed eyes appeared clinically normal and the third eye was normal on Day 7 of the study.

Q.A. INSPECTION STATEMENT
(CFR 58.35(B)(7) 792.35(B)(7) 160.35(B)(7))

38-0087-1 STUDY DIRECTOR: TOPPING,D.C.
ION NUMBER: 906659

STUDY TYPE: ACUTE TOXICITY REPORT

(AUDITOR, QUALITY ASSURANCE UNIT) 10/12/88 DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF THE HAEL, EASTMAN KODAK COMPANY, ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES:

INSPECTION DATES	STUDY/PHASE INSPECTED	STATUS REPORT DATES
07/27/88	ACUTE DERMAL IRRITATION TEST PROTOCOL APPENDIX SUBMISSION	
07/27/88	REPEATED SKIN IRRITATION PROTOCOL APPENDIX SUBMISSION	
08/12/88	ACUTE DERMAL TOXICITY (LD50) PROTOCOL APPENDIX SUBMISSION	
08/16/88	SENSITIZATION PROTOCOL APPENDIX SUBMISSION IRRITATION DROP-ON	
08/17/88	SENSITIZATION PROTOCOL APPENDIX SUBMISSION FOOT PAD INJECTION	
08/17/88	ACUTE ORAL LD50 PROTOCOL APPENDIX SUBMISSION	
08/23/88	RABBIT EYE IRRITATION PROTOCOL APPENDIX SUBMISSION	
08/30/88	RABBIT EYE IRRITATION CLINICAL SIGNS AT 1 WEEK	
10/11/88	ACUTE TOXICITY REPORT FINAL REPORT REVIEW	10/11/88

244981B
TX-88-179

DEVELOPMENTAL TOXICITY PROBE STUDY OF 2-ETHYL-1,3-HEXANEDIOL IN THE RAT

HAEL NO. 88-0087 ACC. NO. 906659

BY LISA G. BERNARD, A.A.S.
WALTER J. KRASAVAGE, M.S.

SPONSOR: Eastman Chemicals Division
Eastman Kodak Company

TESTING FACILITY: Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Kodak Park (Bldg. 320)
1100 Ridgeway Avenue
Rochester, NY 14652-3615

JANUARY 11, 1989

244981B
TX-88-179

DEVELOPMENTAL TOXICITY PROBE STUDY OF 2-ETHYL-1,3-HEXANEDIOL IN THE RAT

HAEL NO. 88-0087 ACC. NO. 906659

Abstract

The potential toxicity of 2-ethyl-1,3-hexanediol (EHD) was determined in pregnant rats administered doses of 0, 500, 1000, 2000, or 4000 mg/kg EHD by gavage in corn oil on the 6th through the 15th days of gestation. Mortality was observed at 2000 (1/8) and 4000 (7/8) mg/kg. Clinical signs observed in dams at lethal levels consisted of weakness, respiratory difficulty, dehydration, sialorrhea, gait disturbances, nasal discharges, porphyrin tears, diarrhea, decreased volume of feces, haircoat wet and/or stained with urine, unkempt haircoats, hypothermia, partially closed eyes, and/or excessive tearing. No clinical abnormalities were seen in dams at the 0, 500, or 1000 mg/kg dose levels. Mean body weight gains and feed consumption were reduced at all dose levels during the first three days of treatment, but the differences were not statistically significant. Mean body weight gains were also reduced at all dose levels when calculated for the entire treatment period (Days 6-16 of gestation), but the differences were not statistically significant. Mean relative liver weight was significantly increased for the 2000 mg/kg dams. Gross pathologic changes were seen only in the dams that died or were euthanatized and included: necrosis of the glandular gastric mucosa, excessive mucus in the cecum, and atrophy of the thymus and adipose tissue. No necropsy lesions were noted in the 500 or 1000 mg/kg dams. Mean corpora lutea, implantation sites, viable fetuses per litter, and pre-implantation losses did not differ among the EHD-treated groups and the controls. Post-implantation losses (early resorptions) were statistically increased for the 2000 mg/kg group. A statistically significant increase was seen in the the incidence of malformation in fetuses from dams treated with 2000 mg/kg EHD. These malformations included rudimentary (filamentous) tails, missing tails, and abnormal curvature of the hindlimbs. In addition, incidences of arthrogryposis, shortened trunk (lumbar region), and umbilical hernia were seen at the 2000 mg/kg dose level. Malformations noted at 500 or 1000 mg/kg were restricted to rudimentary tails in one fetus at 500 mg/kg and two fetuses from different litters in the 1000 mg/kg dose group. Hematomas (a developmental variation) were seen on nine fetuses from four 2000 mg/kg litters. The incidence of this variation was statistically significant. Thus, preliminary data indicate that EHD produces maternal toxicity and lethality at oral doses of 2000 or 4000 mg/kg. Significant fetal toxicity and teratogenicity were evident at a maternally toxic dose (2000 mg/kg), while only one fetus in the 500 mg/kg group and two fetuses in the 1000 mg/kg group had malformations. A definitive developmental toxicity study is necessary to better delineate the toxicity of EHD in pregnant rats.

DEVELOPMENTAL TOXICITY PROBE STUDY OF 2-ETHYL-1,3-HEXANEDIOL IN THE RAT

PURPOSE

The purpose of this study was to evaluate the toxicity of 2-ethyl-1,3-hexanediol when administered to pregnant rats on the 6th through 15th days of gestation.

TESTING FACILITY

Toxicological Sciences Laboratory
Health and Environment Laboratories (HAEL)
Eastman Kodak Company
Kodak Park (Bldg. 320)
1100 Ridgeway Avenue
Rochester, NY 14652-3615

SPONSOR

Eastman Chemicals Division
Eastman Kodak Company

TEST ARTICLE CHARACTERIZATION

General Description

Test Article Name:	2-Ethyl-1,3-hexanediol
Synonyms:	EHD
CAS Number:	94-96-2
EK Accession Number:	906659
HAEL Number:	88-0087
SRID Number:	TX-1694-65
Study Number:	880087T2
Source Of Test Material:	Texas Eastman Company

Physicochemical Properties

Molecular formula:	$C_8H_{18}O_2$
Molecular weight:	146.23
Boiling point:	244°C
Melting point:	- 40°C
Specific gravity:	0.935
Vapor pressure:	10 mm Hg/29°C
Flash point:	265°C (closed cup)
Appearance:	clear, viscous liquid

PURITY, STABILITY, AND CONCENTRATION ANALYSES

The test material was analyzed for structure confirmation using gas chromatography/mass spectroscopy. The mass spectrum of the test sample was consistent with the structure of 2-ethyl-1,3-hexanediol.

The purity of EHD was determined to be 99.9±0.0% when analyzed by gas chromatography with flame ionization detection.

Stability of EHD in corn oil, at concentrations of approximately 2 and 40%, was determined by repeated analysis using gas chromatography with flame ionization detection on 0, 3, 7, and 9 days after test solution preparation. Mean concentrations of the test article were 2.3% and 44% prior to storage and 2.4% and 43% after 9 days of storage indicating the material was stable at these concentrations for at least 9 days. A 24-hour stability determination was performed on a 60% solution of EHD in corn oil. The concentration, when initially analyzed, was 64.5%. After a 24 hour period, the concentration was 59.0%, indicating that the test material was stable for at least 24 hours at this concentration. All solutions were stored at approximately 4°C during the stability studies.

For the first two days of dosing (Days 6 and 7 of gestation), the dosing factor was 10 mL/kg of concentrations of 5, 10, 20, or 40% EHD in corn oil, for the 500, 1000, 2000, and 4000 mg/kg groups, respectively. The mean concentrations of EHD in the solutions were 5.1, 10, 21, or 44% when determined using gas chromatography with flame ionization detection. For the balance of the treatments (Days 8 through 15 of gestation) the dosing factor was change to 6.67 mL/kg. This change was necessary because of difficulty encountered in administering the larger volume required with a dose factor of 10 mg/kg. The mean concentrations of EHD were 7.8, 16, 32, and 62% compared to target concentrations of 7.5, 15, 30, and 60%, respectively. Following the change of the dose factor, the 60% test solution was prepared daily.

All analysis were performed by the Chemical Quality Services Division, KP.

TREATMENT GROUPS AND TEST ARTICLE ADMINISTRATION

The treatment groups consisted of eight inseminated females each given 500, 1000, 2000, or 4000 mg/kg EHD in corn oil by gavage on the 6th through the 15th days of gestation. The dose levels were chosen on the basis of data from the first two weeks of a four-week toxicity study and an acute oal toxicity study. A control group of eight inseminated females was treated similarly to the test animals except that the animals were given only corn oil in a volume equivalent to the largest volume given a treated animal. The body weights on Day 6 of gestation were used to calculate the dose volume. Gavage was chosen as the route of administration because it is a route commonly used in toxicity testing.

ANIMALS

Timed-pregnant females rats (CD®(SD)BR) from Charles River Laboratories, Wilmington, MA, were randomly assigned to four treatment groups and a control group of eight animals each. The animals were received on Day 1 of gestation and immediately assigned to the study. Upon receipt, the rats weighed (mean ± SD) 184 ± 11 g.

ANIMALS (CON'T)

The rat was chosen as the test species because it is the primary rodent species recommended by the U.S. Environmental Protection Agency for use in developmental toxicity studies. There is much historical control data on the rat in the literature and this species has been shown to be sensitive to the effects of known developmental toxicants.

HOUSING

The rats were housed singly in stainless steel cages with wire mesh floors. The study was conducted in the vivarium area of Building 320. The study room was maintained at 72-74 °F and 44-55% relative humidity. A photo period of 12 hours from 6 a.m. to 6 p.m. was maintained. No other study was housed in the same room as this study. Cages and racks were washed once a week. Absorbent paper under the cages was changed daily.

FEED AND WATER

Agway® Prolab™ Animal Diet (RMH 3200), certified ground chow was fed ad libitum. Feed containers were cleaned weekly. Feed containers were refilled at least once a week. Water was supplied ad libitum through an automatic watering system. The source of the water was the Monroe County Water Authority. No known contaminants in feed or water were expected which would interfere with the outcome of this study.

IDENTIFICATION

Each rat was identified by a uniquely numbered metal ear tag. In addition, each female was assigned a study number which was cross-referenced to its ear tag number. Individual female cages were color coded according to group and had a card attached which contained the animal's ear tag and study numbers, the experiment number, and the dose group.

RANDOMIZATION

All culling and randomization were done by computer-generated lists using the Automated Animal Toxicology System.

CLINICAL SIGNS

Each rat was removed from its cage and examined by a trained technician on the mornings of body weight measurement and on treatment days (Days 6 to 15 of gestation). Cageside observations were conducted on mornings when animals were not treated or weighed, post-dose on treatment days, and in the afternoon. Cageside observations included, but were not limited to, examination of the hair, skin, eyes, motor activity, feces, and urine.

BODY WEIGHTS

Individual body weights were recorded for each female on gestation Days 1, 6, 9, 12, 16, and 19. Body weight gain was calculated for Days 1-6, 6-9, 9-12, 12-16, 16-19, and 6-16 of gestation.

FEED CONSUMPTION

Feed containers were weighed on Days 1, 6, 8, 9, 10, 12, 16, and 19 of gestation and individual feed intake was calculated for Days 1-6, 6-9, 9-12, 12-16, 16-19, and 6-16 of gestation.

POSTMORTEM EVALUATIONS

Maternal

Females that died spontaneously or were euthanatized because they were moribund, were necropsied with particular attention given to the uterine contents. Fetal implantation sites, if present, were evaluated to distinguish between normally developing fetuses and resorptions.

All dams that survived were fasted overnight and anesthetized on the 20th day of gestation by inhalation of carbon dioxide. The abdominal viscera were exposed by a mid-line incision through the abdominal wall and the animal was exsanguinated by severing the inferior vena cava (SOP No. TC 360). The terminal body weight was recorded. The uterus with ovaries attached was removed and weighed. The ovaries were dissected free, trimmed of extraneous tissue and the corpora lutea of pregnancy were counted and recorded (SOP No. TC 370). The thoracic cavity was also opened and a necropsy examination of the thoracic and abdominal viscera were conducted in situ on each female. The liver and kidneys were removed, trimmed of extraneous tissue, and weighed for organ/body weight comparisons. Samples of these organs were preserved in 10% neutral buffered formalin, but were not processed and examined for histopathology.

Fetal

After the gravid uterus was weighed, the uterine horns were opened and the implantation sites were counted and categorized as: live fetus, dead fetus (no visible degeneration), late resorption (partially or fully formed fetus undergoing degeneration), or early resorption (implantation but no conceptus or placenta present). The uteri of apparently nonpregnant females were stained with a 10% solution of sodium sulfide and examined for the presence of implantation sites (Kopf et al., 1964).

Viable fetuses were removed from each uterine horn, beginning at the ovary and proceeding to the vagina. Each fetus was blotted dry on absorbent material, examined for external abnormalities (SOP No. TC 490), sexed, and weighed. Viable fetuses with abnormalities were preserved in 95% alcohol in preparation for processing for skeletal examinations. Late resorptions were examined for external malformations and were save in 95% alcohol. Fetuses which were saved, were not processed for skeletal or histologic examination.

STATISTICAL ANALYSES

Statistical analyses compared the EHD treated groups to the control group. Incidence data were analyzed using Chi Square tables ($p \leq 0.05$). Continuous data were analyzed using a one-way analysis of variance ($p \leq 0.05$). Freeman Tukey transformations of the data were used where appropriate, but the data are reported untransformed. Bartlett's Tests were performed to test for equality of variances ($p \leq 0.01$). All analyses were two-tailed tests.

DATA STORAGE

The final report, raw data sheets, tissues, paraffin blocks, slides, and other non-perishable specimens will be stored in the HAEL Archives for a period of ten years.

GLP STATEMENT

This study was conducted in accordance with the Environmental Protection Agency Good Laboratory Standards 40 CFR Part 792, November 29, 1983 and Good Laboratory Practice for Nonclinical Laboratory Studies as promulgated by the Food and Drug Administration, 21 CFR Part 58, December 22, 1978 and revised September 4, 1987. The study was also conducted in accordance with OECD Principles of Good Laboratory Practice.

QUALITY ASSURANCE

The study was subjected to the quality assurance auditing procedures as set forth by the Quality Assurance Units of Eastman Kodak Company. A quality assurance statement is included in the final report.

PROJECT PARTICIPANTS

Study Director, Developmental Toxicologist	W. J. Krasavage, M.S.
Study Technician	L. G. Bernard, A.A.S.
Pathologist	M. S. Vlaovic, D.V.M., Ph.D.
Laboratory Animal Medicine	G. J. Hankinson, D.V.M., M.S.
Analytical Chemist	K. A. Robillard, Ph.D.
Quality Assurance	M. S. James, A.A.S.
Report Author(s)	L. G. Bernard, A.A.S. W. J. Krasavage, M.S.

The names of other personnel that participated in the study are documented in the raw data.

DATE OF STUDY INITIATION

September 7, 1988

EXPERIMENT START DATE

September 7, 1988

PROTOCOL AND SOP DEVIATIONS

In some litters with malformations, the normal fetuses were saved along with the malformed fetuses. All fetuses were preserved in 95% ethanol rather than formalin because the malformations noted appeared to be of skeletal origin.

RESULTS

Maternal Observations

DISTRIBUTION AND FATE OF ANIMALS

The distribution and fate of the animals in this study are shown in the table on page one of the appendix.

No females aborted or delivered early. Mortality was observed at the 2000 and 4000 mg/kg dose levels. Seven of the eight 4000 mg/kg females died following 2 to 6 doses of EHD and the one remaining female was moribund and therefore euthanatized after two doses. One 2000 mg/kg female died after four doses. No mortality was observed at the 500 or 1000 mg/kg dose levels. The pregnancy rates were low in the control and 1000 mg/kg dose groups, but were normal in all other groups compared to historical controls for this parameter. All litters examined at cesarian section had at least one viable fetus. The number of litters examined were 3, 6, 4, 6, and 0 for the control, 500, 1000, 2000, and 4000 mg/kg dose levels, respectively. Data for the nonpregnant animals are presented with the individual data in the appendices, but are not included in the calculations of the means.

CLINICAL SIGNS

Clinical abnormalities, seen in all 4000 mg/kg dams and the one 2000 mg/kg dam (R-629) that died, consisted of minimal to severe weakness, respiratory difficulty, dehydration, post-dose sialorrhea, gait disturbances, nasal discharges, porphyrin tears, diarrhea, decreased volume of feces, unkempt haircoats, and haircoats wet and/or stained with urine. Additional abnormalities observed in the 4000 mg/kg dams only, were hypothermia, partially closed eyes, and excessive tearing. Four of the six surviving 2000 mg/kg dams showed minimal to minor weakness, and one had urine staining of the haircoat. No clinical abnormalities were observed in the dams given 0, 500, and 1000 mg/kg EHD.

Treatment-related abnormalities observed in the nonpregnant animals given 2000 or 4000 mg/kg EHD were similar to those seen in the pregnant animals. No abnormalities were observed in the nonpregnant females in the 0, 500, or 1000 mg/kg groups, except for a single incidence of depressed activity and sialorrhea at the 1000 mg/kg dose level (R-624).

BODY WEIGHT

Mean body weight gain was less in all treated groups during the first three days of treatment (gestation Days 6-9) compared to the control, group, though these differences were not statistically significant (ANOVA). During this period, the control dams gained a mean of 16.7 grams, while the 500 and 1000 mg/kg dams gained 13.6 or 9.4 grams, respectively and the 2000 and 4000 mg/kg dams lost 1.3 or 13.7 grams, respectively. For the remainder of the study, the body weight gains were comparable among the control and treated groups at each time period except that the 2000 mg/kg dams gained less weight from Days 16-19 of gestation than the other groups.

Mean body weight gains during the treatment period (gestation Days 6-16) were less for all EHD-treated groups than the control group, but the differences did not reach statistical significance (ANOVA).

At study termination, the mean body weight of the control dams had increased 92±7% and the mean body weights of the 500, 1000, and 2000 mg/kg dams had increased 84±14%, 86±16%, and 73±13%, respectively.

The mean corrected body weights (terminal weight minus gravid uterine weight) were comparable among the control and EHD-treated groups.

FEED CONSUMPTION

Feed consumption was comparable between the EHD-treated groups and the control group from gestation Days 0 to 6 (pre-treatment). The 4000 mg/kg dams, that died or were euthanatized prior to Day 12, consumed only 10±7 grams/rat/day during this period of time.

From Day 6-9 of gestation (the first three days of treatment), mean feed consumption was reduced in a dose-related manner, but these differences were not statistically significant (ANOVA). During this time period the 500, 1000, 2000, and 4000 mg/kg animals consumed an average of 10, 19, 22, or 40% less feed than the control dams. Feed consumption for the one 4000 mg/kg dam that survived to Day 12 of gestation was significantly less than the control group, while the mean feed consumptions of the 500, 1000, and 2000 mg/kg dams were comparable to the control group for the remainder of the study.

TERMINAL BODY AND ORGAN WEIGHTS

Terminal body weights corrected for gravid uterine weight, the absolute kidney and liver weights, and kidney weights relative to body weight were comparable among the EHD-treated and control groups.

Mean relative liver weight was statistically significantly (ANOVA $p \leq 0.05$) heavier at the 2000 mg/kg dose level when compared to the control. The relative liver weights for the 500 and 1000 mg/kg animals were comparable to the control.

PATHOLOGY

Treatment-related changes observed in the 4000 mg/kg females that died or were euthanatized consisted of test compound in the stomach (5/8) and duodenum (1/8), necrosis of the glandular gastric mucosa (8/8), excessive mucus in the cecum (2/8), and atrophy of the thymus (2/8) and adipose tissue (2/8).

At the 2000 mg/kg dose level, treatment-related changes were seen only in the one dam that died. These lesions included hemorrhage in the glandular gastric mucosa and atrophy of the thymus and adipose tissue.

No treatment-related changes were observed in the dams treated with 500 or 1000 mg/kg EHD.

OBSERVATION OF THE DAMS AND FETUSES AT THE TIME OF CESARIAN SECTION

The pregnancy rates were low for the control and 1000 mg/kg groups, but the rates for the other groups (500, 2000,and 4000 mg/kg) were within the range for historical controls for this parameter in our laboratory.

The mean number of corpora lutea, implantation sites, viable fetuses per litter, and pre-implantation loss did not differ between the control and EHD-treated groups. Statistically significant increases (Duncan's Test $p \leq 0.05$) in the number of resorptions and post-implantation losses were observed at the 2000 mg/kg dose level. The mean fetal body weight for each sex analyzed separately and when combined were statistically significantly decreased (Duncan's Test $p \leq 0.05$) at the 2000 mg/kg level. There was a corresponding reduction of the mean gravid uterine weight of the 2000 mg/kg dams, but the difference did not quite reach statistical significance (ANOVA).

No differences were seen in these parameters at the 500 or 1000 mg/kg dose levels when they were compared to the control group.

EXTERNAL FETAL EXAMINATIONS

Statistically significant incidences of external malformations were seen in fetuses in the 2000 mg/kg group. These malformations consisted of rudimentary (filamentous) tails in 15 fetuses from 4 litters (Fisher's Exact Test $p = 0.003$) and missing tails in 11 fetuses from 3 litters (Fisher's Exact Test $p = 0.015$). Other malformations associated with the tail (fetus/litter) consisted of small tail (1/1), curly tail (1/1), edematous and/or hemorrhagic tails (2/2), and one fetus with a cyst on the tail (1/1). A statistically significant increase in the incidence of fetuses with abnormal curvature of the hindlimbs (13/4, Fisher's Exact Test $p = 0.009$) was also seen at this dose level. In addition, incidences of arthrogryposis (abnormal flexure of the wrist joint) (3/3), shortened trunk (lumbar region) (5/3), and umbilical hernia (4/2) were seen in fetuses from dams given 2000 mg/kg EHD. Hematomas were seen at the 2000 mg/kg dose level in 9 fetuses from 4 litters. The incidence of this variation was statistically significant (Fisher's Exact Test $p = 0.028$).

Malformations seen at the lower treatment levels (500 or 1000 mg/kg) were restricted to the tail. Two fetuses, each from different litters, from the 1000 mg/kg dose group and one fetus from the 500 mg/kg dose group had rudimentary (filamentous) tails. One fetus in the 1000 mg/kg dose group had a hematoma (a variation) on the face. No malformations or variations were observed in the control fetuses.

DISCUSSION AND INTERPRETATION

The potential toxicity of 2-ethyl-3-hexanediol (EHD) was determined in pregnant Sprague-Dawley rats when EHD was administered during the most sensitive period of pregnancy (gestation days 6-16). Maternal toxicity was evident as abnormal clinical signs and mortality at dose levels of 2000 and 4000 mg/kg. One 2000 mg/kg dam died after four daily doses and seven of eight 4000 mg/kg dams died after 2-6 daily doses of EHD. Slight to moderate reductions in body weight gain and feed consumption seen in all treated groups during the first three days of dosing and a statistically significant increase in the relative liver weight seen at necropsy were also indicative of maternal toxicity at this dose level. Compound-related gross pathology was seen only in those animals that died or were euthanatized. Necropsy lesions included hemorrhage and necrosis of the glandular gastric mucosa, excessive mucus in the cecum, and atrophy of the thymus and adipose tissue.

The pregnancy rates were much lower than historical controls for the concurrent control and 1000 mg/kg EHD groups. This finding was not treatment-related since the pregnancy rates for the 500, 2000, and 4000 mg/kg dams were within the historical control range (75-100%) for our laboratory. Thus, even doses high enough to produce maternal lethality did not interfere with the implantation process. However, the small number of control litters compromised statistical analyses of the data by reducing the number of litters and fetuses available for comparison with EHD-treated groups. The number of implantation sites resorbed was significantly increased for the 2000 mg/kg dams, thus increasing the post-implantation loss at this dose level. The mean body weight of the fetuses from dams treated with 2000 mg/kg of EHD was significantly lower than the controls. Statistically significant increases in the incidence of external malformations were seen in the 2000 mg/kg fetuses compared to the controls and consisted of tail defects (primarily rudimentary and missing tails) and abnormal curvature of the hindlimbs. Other malformations seen at this dose level, but not in the lower dose groups and the controls were arthrogryposis, shortened lumbar trunk, and umbilical hernias. The only malformations seen at the lower dose levels were rudimentary tails in two fetuses at 1000 mg/kg and one fetus at 500 mg/kg. A statistically significant incidence of hematomas (a developmental variation) was seen at the 2000 mg/kg dose level. No developmental variations were observed at the lower dose levels.

Thus, preliminary data indicate that EHD produces maternal toxicity and lethality at oral doses of 4000 or 2000 mg/kg. Significant fetal toxicity and teratogenicity were seen at a maternally toxic dose (2000 mg/kg), while only three fetuses at the lower doses had malformations; one in one litter at 500 mg/kg and one from two different litters at 1000 mg/kg. The significance of the effects seen at the lower doses is obscured by the small number of control fetuses available for examination. A definitive developmental toxicity study is necessary to better delineate these effects.

TABLES

Tables, including means and individual data points for body weight, feed consumption, hematology, clinical chemistries, and organ weights, and reports of individual contributors are appended.

REFERENCES

Kopf, R., Lorenz, D., and Salewski, E. (1964) Procedure for staining implantation sites of fresh rat uteri. Naunyn-Schmiedebergs Arch. Exp. Path. u. Pharmak. 247, 121-135.

Signature Page

Lisa Gayle Bonnard — 1-4-89
Report Author — Date

Walter J Krasavage — 1-11-89
Report Author — Date

Walter J Krasavage — 1-11-89
Manager, Reproductive/Developmental Toxicology Study Director — Date

Doyle C Tobey — Jan 10, 1989
Unit Director, Mammalian Toxicology Section — Date

[illegible] — 1-4-89.
Director, Toxicological Sciences Laboratory, HAEL — Date

[illegible] — 12/16/88
Quality Assurance Unit — Date

Q.A. INSPECTION STATEMENT
(CFR 58.35(B)(7) 792.35(B)(7) 160.35(B)(7))

STUDY: 88-0087-2 STUDY DIRECTOR: KRASAVAGE,W.J.
ACCESSION NUMBER: 906659

UDY TYPE: DEVELOPMENTAL TOXICITY SCREEN

M. Sue James 12/16/88
(AUDITOR, QUALITY ASSURANCE UNIT) DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF THE HAEL, EASTMAN KODAK COMPANY, ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES:

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
09/07/88	TEST SYSTEM WEIGH, CULL, AND RANDOMIZE TO HOUSING	09/07/88
09/08/88	SCALE/BALANCE CALIBRATION	
	TEST ARTICLE DISTRIBUTION RECORDS	
	CONTROL ARTICLE DISTRIBUTION RECORDS	
	TEST ARTICLE WEIGH AND MIX WITH CARRIER	
	SAMPLE COLLECTION	
	SAMPLE LABELLING	
	SAMPLE/SPECIMEN SENT FOR ANALYSIS	
	CONCENTRATION ANALYSIS DONE BY CQSD	
09/08/88	PROTOCOL SUBMISSION	
	PROBE STUDY	
09/26/88	NECROPSY	
	SPECIMEN/SAMPLE WEIGHT	
	SPECIMEN COLLECTION	
	COUNT CORPORA LUTEA	
	COUNT IMPLANTATION SITES	
	SEX DETERMINATION OF FETUSES	
	EXTERNAL EXAMINATION OF FETUSES	
10/05/88	PROTOCOL AMENDMENT	
	BODY WEIGHT RANGE CHANGED	
12/08/88	FINAL REPORT REVIEW	
12/09/88	FINAL REPORT REVIEW	
12/12/88	FINAL REPORT REVIEW	12/12/88

Supersedes reports from 10-04-88 to 10-05-88

ANALYTICAL QUALITY ASSURANCE INSPECTION STATEMENT

HAEL #: 88-0087 Accession #: 906659 CQS Job #: EE8H021

HAEL Study: Developmental Tox. Probe
Study Director: W. Krasavage
Auditee Group & Location: EAS/CQS, B-320
In-Process Inspection Date: ---
Date This Report Sent To Study Director: 12-02-88

Request for Analysis #	Analysis	Sample(s) Received Date	Test Report Date	Test Report Inspection Date
126691	Dose Verif.	09-15-88	09-28-88	10-04-88
126687	Dose Confirm.	09-08-88	09-29-88	10-05-88
126690	Dose Verif.	09-14-88	09-28-88	10-05-88

We have inspected the analytical work described above. Our findings have been sent to the study director and to management. This is done in accordance with Good Laboratory Practice Standards 40 CFR 792.35 and 160.35, and 21 CFR 58.35.

M. J. Boccacino, Quality Assurance Engineer
GLP Compliance, QSO Quality Assurance
12-02-88

The analyses for initial purity, structure confirmation, and test solution stability were done in conjunction with the 28-day study. The QSO QA statement for these data are presented on the next page.

Walter J. Krasavage, M.S. Date
Study Director

Supersedes reports from 08/26/88 to 10/04/88

ANALYTICAL QUALITY ASSURANCE INSPECTION STATEMENT

HAEL #: 88-0087 Accession #: 906659 CQS Job #: EE8H021

HAEL Study: 28 Day Gavage
Study Director: W. Krasavage
Auditee Group & Location: EAS/CQS, B-320
In-Process Inspection Date: 09-01-88
Date This Report Sent To Study Director: 12-02-88

Request for Analysis #	Analysis	Sample(s) Received Date	Test Report Date	Test Report Inspection Date
084797	Init. Purity	06-28-88	08-22-88	08-26-88
126678	Dose Verif.	08-25-88	08-30-88	09-06-88
126684	Dose Conf.	09-01-88	09-09-88	09-13-88
126670	9 Day Stabil.	08-16-88	08-31-88	09-16-88
084797	Struct. Conf.	07-15-88	08-01-88	09-21-88
126688	Conc. Deter.	09-08-88	09-27-88	10-04-88
126692	Dose Verif.	09-15-88	09-28-88	10-04-88
126773	Dose verif.	09-22-88	09-28-88	10-04-88

We have inspected the analytical work described above. Our findings have been sent to the study director and to management. This is done in accordance with Good Laboratory Practice Standards 40 CFR 792.35 and 160.35, and 21 CFR 58.35.

Michael J. Boccacino

M. J. Boccacino, Quality Assurance Engineer
GLP Compliance, QSO Quality Assurance
12-02-88

Table of Contents for Appendix

	Appendix Page
Table of Distribution and Fate of Animals	1
Grouped Summary of Clinical Signs	2
Plot of Body Weights	8
Mean Body Weight	9
Individual Body Weights	10
Mean Body Weight Change	11
Individual Body Weight Changes	12
Plot of Feed Consumption	13
Mean Feed Consumption	14
Individual Feed Consumption	15
Mean Organ and Terminal Body Weight	16
Individual Organ and Terminal Body Weight	17
Pathologist's Report	18
Summary Gross Pathology Table	19
Individual Gross Pathology Table	20
Gross Pathology Comment	25
Summary of Observations Collected at the Time of Cesarian Section	26
Individual Female Data Collected at Cesarian Section	27
Individual Litter Data Collected at Cesarian Section	32
Summary of External Malformations and Variations	37
Individual Litter Data - External, Internal Soft Tissue, and Skeletal Alterations	38
Individual Litter Data - External Fetal Alterations - Key	43
Individual Litter Data - External Fetal Alterations	44
Purity Analysis Report	52
Structure Confirmation Report	53
Protocol and Amendments	54

DISTRIBUTION AND FATE OF FEMALES

HAEL NO. 88-0087
START DATE: 06-SEP-88

ACCESSION NO. 906659
ACCESSION NO. 906659
ROUTE: GAVAGE

EXPERIMENT NO. 880087T2

	DOSE GROUP (MG/KG) 0.000	500.000	1000.000	2000.000	4000.000
Females on Study	8	8	8	8	8
Total Females Dead/Euthanatized	0	0	0	1	8
Not Pregnant	0	0	0	0	1
Pregnant	0	0	0	1	7
Females Aborted/Delivered	0	0	0	0	0
Females Examined at C-Section	8	8	8	7	0
Not Pregnant	5	2	4	1	0
Pregnant	3	6	4	6	0
Females With Non-Viable Implants Only	0	0	0	0	0
Females With Viable Fetuses	3	6	4	6	0
Total Females Pregnant	3	6	4	7	7

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - FEMALE OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	3			601,606-607
TREATMENT ADMINISTERED	3	6.	0.	601,606-607
INDUCED DEATH, CARBON DIOXIDE	3	20.	0.	601,606-607
GROUP 2 - 500.000 MG/KG				
* NORMAL	6			611-616
TREATMENT ADMINISTERED	6	6.	0.	611-616
INDUCED DEATH, CARBON DIOXIDE	6	20.	0.	611-616
GROUP 3 - 1000.000 MG/KG				
* NORMAL	4			617-619,621
TREATMENT ADMINISTERED	4	6.	0.	617-619,621
INDUCED DEATH, CARBON DIOXIDE	4	20.	0.	617-619,621

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANITIZED : PREGNANT

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - FEMALE OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 4 - 2000.000 MG/KG				
• NORMAL	5			625-626,628,630-631
TREATMENT ADMINISTERED	7	6.	0.	625-631
WEAKNESS	1	7.	0.	629
DEHYDRATION	1	8.	0.	629
GENERAL BODY COND. POOR	1	9.	0.	629
EXCESSIVE WEIGHT LOSS	1	9.	0.	629
GAIT DISTURBANCE	1	9.	0.	629
SPONTANEOUS DEATH	1	10.	0.	629
INDUCED DEATH, CARBON DIOXIDE	6	20.	0.	625-628,630-631
RESPIRATORY TRACT				
RALES	1	7.	0.	629
EYES				
PORPHYRIN TEARS	1	8.	0.	629
NOSE				
PORPHYRIN NASAL DISCHARGE	1	8.	0.	629
HAIR OF INGUINAL REGION				
HAIRCOAT-WET BY URINE	1	8.	0.	629
HAIRCOAT-DRY URINE STAIN	1	9.	0.	627
HAIR OF ABDOMEN				
HAIRCOAT-WET BY URINE	1	8.	0.	629
HAIR				
UNKEMPT HAIRCOAT	1	8.	0.	629
FECES				
DIARRHEA	1	8.	0.	629
DECREASED VOLUME	1	9.	0.	629

KEY: •-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANITIZED : PREGNANT

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087T2

EXPERIMENT START DATE: 6-SEP-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - FEMALE

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 5 - 4000.000 MG/KG				
* NORMAL	1			634
TREATMENT ADMINISTERED	7	6.	0.	633-638,640
WEAKNESS	5	8.	1.	635-638,640
HYPOTHERMIA	1	8.	0.	636
DEHYDRATION	3	9.	1.	635-636,638
SPONTANEOUS DEATH	2	10.	3.	633,640
INDUCED DEATH, CARBON DIOXIDE	1	8.	0.	636
GAIT DISTURBANCE	2	9.	0.	635,638
EXCESSIVE WEIGHT LOSS	1	9.	0.	635
NOSE				
PORPHYRIN NASAL DISCHARGE	4	8.	1.	633,636-638
SKIN OF FOOT AND TOE				
DISCOLORATION,RED	1	7.	0.	637
RESPIRATORY TRACT				
DYSPNEA	1	8.	0.	636
WHEEZING	1	9.	0.	635
HAIR				
UNKEMPT HAIRCOAT	1	8.	0.	636
FECES				
DIARRHEA	2	9.	1.	635-636
DECREASED VOLUME	2	9.	0.	635,638
EYES				
PORPHYRIN TEARS	3	9.	1.	635,637-638
PARTIALLY OPEN	1	10.	0.	638
HAIR OF ABDOMEN				
HAIRCOAT-WET BY URINE	2	9.	1.	637-638
HAIR OF INGUINAL REGION				
HAIRCOAT-WET BY URINE	3	9.	1.	635,637-638
HAIRCOAT-DRY URINE STAIN	1	8.	0.	638

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANITIZED : PREGNANT

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087T2

EXPERIMENT START DATE: 6-SEP-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - FEMALE

OBSERVATION PERIOD - POST DOSE

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	3			601,606-607
GROUP 2 - 500.000 MG/KG				
* NORMAL	6			611-616
GROUP 3 - 1000.000 MG/KG				
* NORMAL	4			617-619,621
GROUP 4 - 2000.000 MG/KG				
* NORMAL	1			628
WEAKNESS	5	8.	2.	625-627,629,631
GENERAL BODY COND. POOR	1	9.	0.	629
MOUTH				
SIALORRHEA	2	9.	2.	629-630
RESPIRATORY TRACT				
RALES	1	7.	0.	629
DYSPNEA	1	8.	0.	629
EYES				
PORPHYRIN TEARS	1	8.	0.	629
NOSE				
PORPHYRIN NASAL DISCHARGE	1	8.	0.	629
HAIR				
UNKEMPT HAIRCOAT	1	8.	0.	629
FECES				
DECREASED VOLUME	1	9.	0.	629
DIARRHEA	1	9.	0.	629

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANITIZED : PREGNANT

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087T2

EXPERIMENT START DATE: 6-SEP-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - FEMALE

OBSERVATION PERIOD - POST DOSE

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 5 - 4000.000 MG/KG				
WEAKNESS	7	6.	0.	633-638,640
SPONTANEOUS DEATH	3	9.	1.	635,637-638
RESPIRATORY TRACT				
DYSPNEA	2	7.	1.	636,640
WHEEZING	1	9.	0.	635
MOUTH				
SIALORRHEA	6	8.	1.	633-634,636-638,640
NOSE				
PORPHYRIN NASAL DISCHARGE	4	8.	1.	633,635,637-638
SKIN OF FOOT AND TOE				
DISCOLORATION,RED	1	7.	0.	637
EYES				
PORPHYRIN TEARS	3	9.	1.	635,637-638
PARTIALLY OPEN	1	10.	0.	638
FECES				
DECREASED VOLUME	2	9.	0.	635,638
DIARRHEA	1	9.	0.	635

KEY: •-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANITIZED : PREGNANT

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087T2

EXPERIMENT START DATE: 6-SEP-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

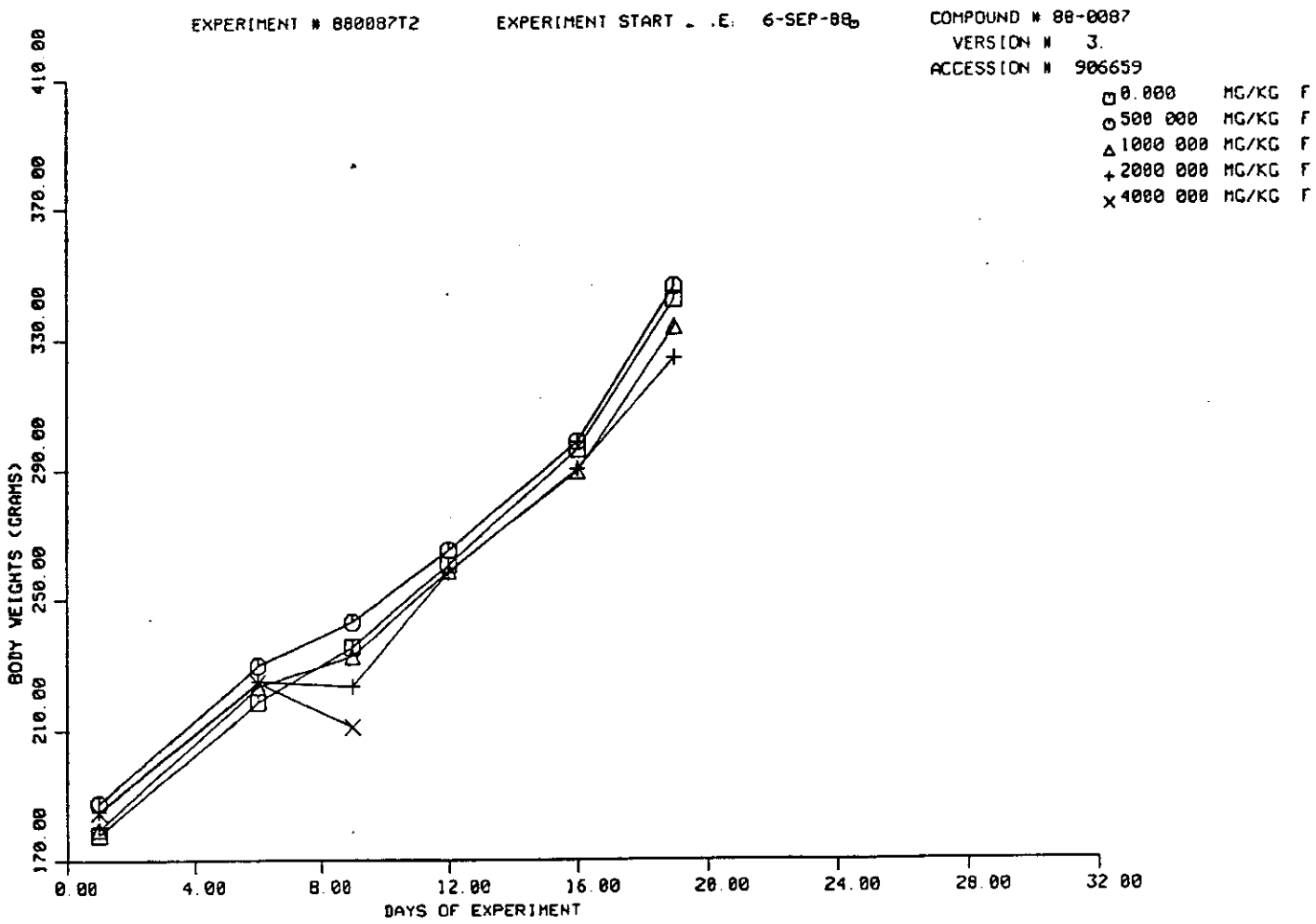
SEX - FEMALE

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	3			601,606-607
GROUP 2 - 500.000 MG/KG				
* NORMAL	6			611-616
GROUP 3 - 1000.000 MG/KG				
* NORMAL	4			617-619,621
GROUP 4 - 2000.000 MG/KG				
* NORMAL	4			625-626,628,630
WEAKNESS	3	8.	1.	627,629,631
GENERAL BODY COND. POOR	1	8.	0.	629
NOSE				
PORPHYRIN NASAL DISCHARGE	1	8.	0.	629
EYES				
PORPHYRIN TEARS	1	8.	0.	629
HAIR				
UNKEMPT HAIRCOAT	1	8.	0.	629
RESPIRATORY TRACT				
RALES	1	9.	0.	629
GROUP 5 - 4000.000 MG/KG				
WEAKNESS	7	6.	0.	633-638,640
SPONTANEOUS DEATH	1	7.	0.	634
RESPIRATORY TRACT				
DYSPNEA	2	7.	1.	636,640
BODY AS A WHOLE, NOS				
GAIT DISTURBANCE	1	7.	0.	633
MOUTH				
SIALORRHEA	2	7.	0.	637,640
EYES				
EXCESSIVE TEARING	1	7.	0.	640
NOSE				
PORPHYRIN NASAL DISCHARGE	1	9.	0.	638
FECES				
DECREASED VOLUME	1	9.	0.	638

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANITIZED : PREGNANT


EXPERIMENT # 880087T2
EXPERIMENT START . .E: 6-SEP-88
COMPOUND # 88-0087
VERSION # 3.
ACCESSION # 906659
0.000 MG/KG F
500 000 MG/KG F
1000 000 MG/KG F
2000 000 MG/KG F
4000 000 MG/KG F
BODY WEIGHTS (GRAMS)
170.00
210.00
250.00
290.00
330.00
370.00
410.00
0.00
4.00
8.00
12.00
16.00
20.00
24.00
28.00
32.00
DAYS OF EXPERIMENT

MEAN FOR BODY WEIGHT (GRAMS)

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP-F	500.000 MG/KG GROUP-F	1000.000 MG/KG GROUP-F	2000.000 MG/KG GROUP-F	4000.000 MG/KG GROUP-F
WEEK # 1					
DAY 1	177.9 A	187.5	179.3	185.1	184.6
	10.5 B	11.9	14.5	10.5	13.0
	3 C	6	4	7	7
DAY 6	218.4	229.2	222.9	224.4	224.1
	15.7	16.2	17.9	18.7	10.0
	3	6	4	7	7
WEEK # 2					
DAY 9	235.1	242.8	232.3	223.1	210.4
	14.2	20.4	15.7	35.1	18.3
	3	6	4	7	3
DAY 12	260.4	264.5	258.2	257.8	
	18.5	24.5	20.5	25.7	
	3	6	4	6	
WEEK # 3					
DAY 16	296.0	298.3	288.9	289.6	
	24.7	28.7	22.5	29.8	
	3	6	4	6	
DAY 19	341.9	345.7	333.2	324.0	
	25.6	32.0	25.1	30.6	
	3	6	4	6	

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP

INDIVIDUAL ANIMAL BODY WEIGHTS (GRAMS)

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP-F

ANIMAL #	601	602	603	604	605	606	607	608
		NN	NN	NN	NN			NN
DAY 1	174.9	197.6	185.0	192.4	178.9	169.2	189.5	177.0
DAY 6	213.7	224.5	220.6	227.7	220.1	205.5	235.9	214.9
DAY 9	234.3	230.5	229.3	237.9	227.2	221.3	249.7	222.4
DAY 12	252.0	236.9	239.8	243.5	247.3	247.5	281.6	238.8
DAY 16	278.2	241.1	243.2	254.8	245.1	285.5	324.2	244.8
DAY 19	322.5	241.5	247.8	259.8	251.5	332.3	371.0	248.0

500.000 MG/KG GROUP-F

ANIMAL #	609	610	611	612	613	614	615	616
	NN	NN						
DAY 1	165.2	185.6	184.6	172.1	206.0	188.5	194.7	179.0
DAY 6	194.4	227.8	219.6	213.8	259.9	227.8	230.9	223.3
DAY 9	199.6	232.3	235.9	224.1	282.5	236.6	242.7	234.8
DAY 12	209.5	227.1	253.1	247.1	313.8	259.3	257.9	255.7
DAY 16	221.2	234.4	283.4	287.9	356.6	288.5	289.7	283.7
DAY 19	223.3	249.2	326.0	349.5	407.2	318.9	340.0	332.5

1000.000 MG/KG GROUP-F

ANIMAL #	617	618	619	620	621	622	623	624
				NN		NN	NN	NN
DAY 1	166.8	196.2	186.4	186.9	167.7	185.4	198.6	181.1
DAY 6	204.5	244.9	212.9	229.1	229.2	214.3	227.1	220.6
DAY 9	216.8	251.2	222.3	240.1	238.8	204.4	234.7	229.2
DAY 12	234.6	281.9	249.7	248.6	266.7	217.3	218.3	226.4
DAY 16	263.2	312.6	277.8	254.8	302.0	231.3	240.0	234.4
DAY 19	307.9	359.5	316.0	260.7	349.4	233.7	239.7	243.8

2000.000 MG/KG GROUP-F

ANIMAL #	625	626	627	628	629	630	631	632
					DP			NN
DAY 1	187.4	204.3	171.4	187.2	175.6	186.1	184.0	176.7
DAY 6	213.2	260.0	209.0	226.5	208.2	236.5	217.7	218.1
DAY 9	222.5	268.7	200.7	236.8	159.8	248.0	225.4	225.8
DAY 12	231.3	294.4	239.7	263.2		280.2	238.0	232.7
DAY 16	256.9	327.9	267.6	304.8		314.6	266.0	225.1
DAY 19	291.7	355.7	300.4	344.8		354.2	297.0	233.8

4000.000 MG/KG GROUP-F

ANIMAL #	633	634	635	636	637	638	639	640
	DP	DP	DP	EP	DP	DP	DN	DP
DAY 1	167.0	198.6	181.1	184.5	200.4	190.9	175.2	170.0
DAY 6	211.4	237.8	221.5	220.7	233.5	230.0	219.5	213.6
DAY 9	204.9		195.5			230.9	197.3	

NOTE: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

MEAN BODY WEIGHT CHANGE (GRAMS)

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

DAYS OF GESTATION	0.000 MG/KG GROUP-F	500.000 MG/KG GROUP-F	1000.000 MG/KG GROUP-F	2000.000 MG/KG GROUP-F	4000.000 MG/KG GROUP-F
0 - 6	40.5 A	41.7	43.6	39.3	39.4
	5.3 B	6.9	15.0	10.4	4.0
	3 C	6	4	7	7
6 - 9	16.7	13.6	9.4	-1.3	-10.5
	3.5	5.1	2.5	21.8	13.9
	3	6	4	7	3
9 - 12	25.3	21.7	25.9	24.1	
	7.1	5.6	5.6	11.5	
	3	6	4	6	
12 - 16	35.6	33.8	30.7	31.8	
	8.5	6.3	3.3	5.9	
	3	6	4	6	
16 - 19	46.0	47.4	44.3	34.3	
	1.4	10.3	4.2	4.8	
	3	6	4	6	
6 - 16	77.6	69.1	66.0	62.5	
	12.1	14.6	5.9	14.8	
	3	6	4	6	

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP

INDIVIDUAL ANIMAL BODY WEIGHTS CHANGES (GRAMS)

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP-F

	ANIMAL #	601	602 NN	603 NN	604 NN	605 NN	606	607	608 NN
DAYS	0 - 6	38.8	26.9	35.6	35.3	41.2	36.3	46.4	37.9
	6 - 9	20.6	6.0	8.7	10.2	7.1	15.8	13.8	7.5
	9 - 12	17.7	6.4	10.5	5.6	20.1	26.2	31.9	16.4
	12 - 16	26.2	4.2	3.4	11.3	-2.2	38.0	42.6	6.0
	16 - 19	44.3	0.4	4.6	5.0	6.4	46.8	46.8	80.0
	6 - 16	64.5	16.6	22.6	27.1	25.0	80.0	88.3	29.9

500.000 MG/KG GROUP-F

	ANIMAL #	609 NN	610 NN	611	612	613	614	615	616
DAYS	0 - 6	29.2	42.2	35.0	41.7	53.9	39.3	36.2	44.3
	6 - 9	5.2	4.5	16.3	10.3	22.6	8.8	11.8	11.5
	9 - 12	9.9	-5.2	17.2	23.0	31.3	22.7	15.2	20.9
	12 - 16	11.7	7.3	30.3	40.8	42.8	29.2	31.8	28.0
	16 - 19	2.1	14.8	42.6	61.6	50.6	30.4	50.3	48.8
	6 - 16	26.8	6.6	63.8	74.1	96.7	60.7	58.8	60.4

1000.000 MG/KG GROUP-F

	ANIMAL #	617	618	619	620 NN	621	622 NN	623 NN	624 NN
DAYS	0 - 6	37.7	48.7	26.5	42.2	61.5	28.9	28.5	39.5
	6 - 9	12.3	6.3	9.4	11.0	9.6	-9.9	7.6	8.6
	9 - 12	17.8	30.7	27.4	8.5	27.9	12.9	-16.4	-2.8
	12 - 16	28.6	30.7	28.1	6.2	35.3	14.0	21.7	8.0
	16 - 19	44.7	46.9	38.2	5.9	47.4	2.4	-0.3	9.4
	6 - 16	58.7	67.7	64.9	25.7	72.8	17.0	12.9	13.8

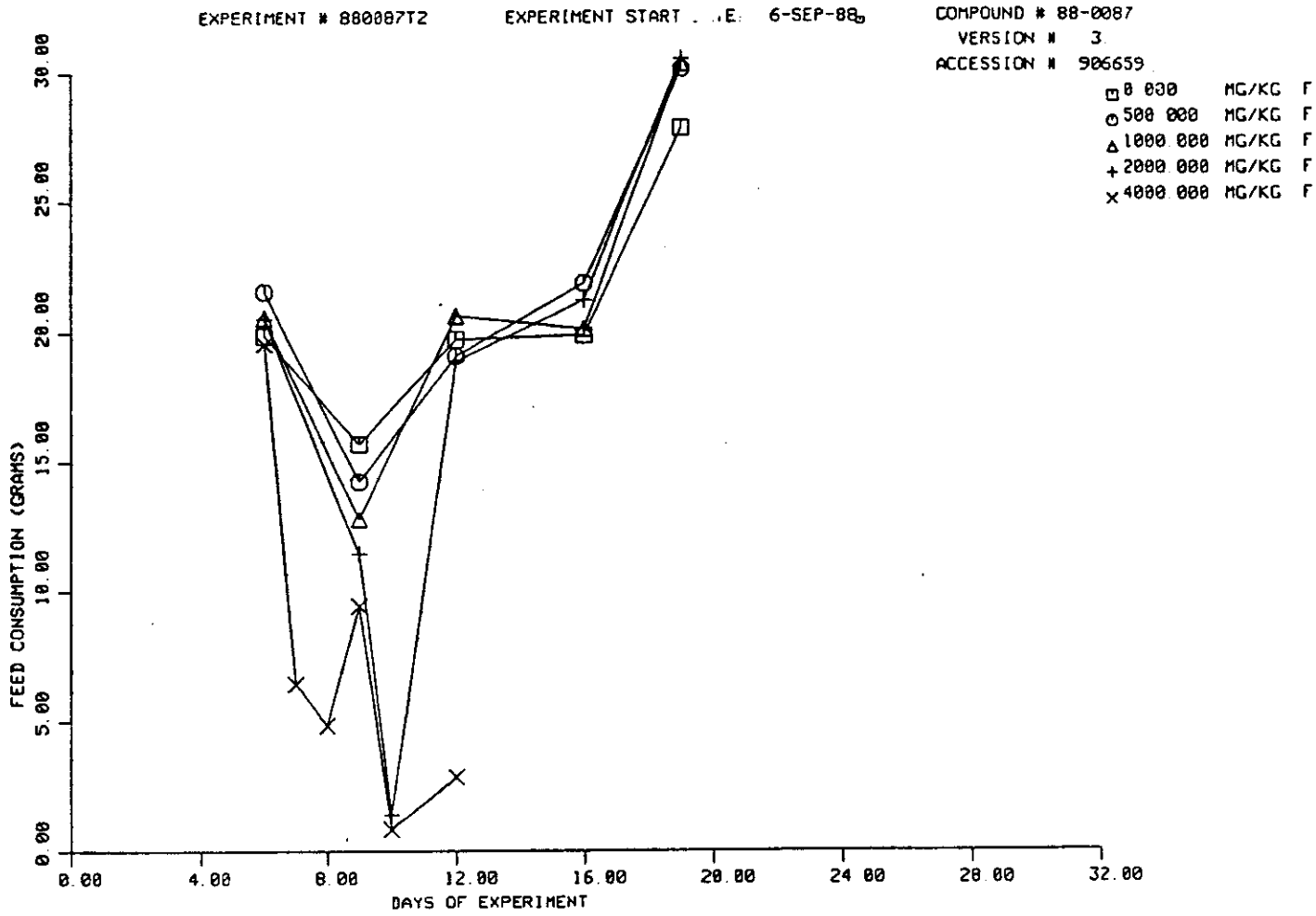
2000.000 MG/KG GROUP-F

	ANIMAL #	625	626	627	628	629 DP	630	631	632 NN
DAYS	0 - 6	25.8	55.7	37.6	39.3	32.6	50.4	33.7	41.4
	6 - 9	9.3	8.7	-8.3	10.3	-48.4	11.5	7.7	7.7
	9 - 12	8.8	25.7	39.0	26.4		32.2	12.6	6.9
	12 - 16	25.6	33.5	27.9	41.6		34.4	28.0	-7.6
	16 - 19	34.8	27.8	32.8	40.0		39.6	31.0	8.7
	6 - 16	43.7	67.9	58.6	78.3		78.1	48.3	7.0

4000.000 MG/KG GROUP-F

	ANIMAL #	633 DP	634 DP	635 DP	636 EP	637 DP	638 DP	639 DN	640 DP
DAYS	0 - 6	44.4	39.2	40.4	36.2	33.1	39.1	44.3	43.6
	6 - 9	-6.5		-26.0			0.9	-22.2	

NOTE: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT


EXPERIMENT # 880087T2
EXPERIMENT START . .E: 6-SEP-88
COMPOUND # 88-0087
VERSION # 3
ACCESSION # 906659
0 000 MG/KG F
500 000 MG/KG F
1000 000 MG/KG F
2000 000 MG/KG F
4000 000 MG/KG F
FEED CONSUMPTION (GRAMS)
0.00
5.00
10.00
15.00
20.00
25.00
30.00
0.00
4.00
8.00
12.00
16.00
20.00
24.00
28.00
32.00
DAYS OF EXPERIMENT

MEAN FOR FEED CONSUMPTION (GRAMS) λ

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP-F	500.000 MG/KG GROUP-F	1000.000 MG/KG GROUP-F	2000.000 MG/KG GROUP-F	4000.000 MG/KG GROUP-F
WEEK # 1					
DAY 6	19.9 A	21.6	20.6	20.5	19.6
	1.7 B	2.7	2.8	3.6	0.9
	3 C	6	4	7	7
WEEK # 2					
DAY 8					4.8
					1.7
					3
DAY 9	15.7	14.2	12.8	11.4	9.4
	1.8	1.9	1.7	5.2	3.1
	3	6	4	7	3
DAY 10				1.4	0.8
				0.0	0.0
				1	1
DAY 12	19.7	19.1	20.6	18.9	2.8
	1.9	2.8	3.8	4.3	0.0
	3	6	4	6	1
WEEK # 3					
DAY 16	19.9	21.9	20.1	21.2	
	2.5	3.8	0.9	4.4	
	3	6	4	6	
DAY 19	27.8	30.1	30.3	30.5	
	2.1	3.5	1.6	2.1	
	3	6	4	6	
DAYS 6 - 16	19.0	19.8	19.0	19.1	
	2.3	3.9	3.7	4.8	
	3	6	4	6	

NOTE: MEANS DO NOT INCLUDE NN OR DN VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP
λ = FEED CONSUMPTION REFERS TO GRAMS/ANIMAL/DAY.
DAYS 6 - 16 = AVERAGE CONSUMPTION BETWEEN DAYS 6 AND 16

INDIVIDUAL ANIMAL FEED CONSUMPTION (GRAMS) λ

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP-F

ANIMAL #	601	602	603	604	605	606	607	608
		NN	NN	NN	NN			NN
DAY 6	18.2	21.8	18.8	22.9	23.3	19.8	21.6	19.8
DAY 9	13.7	14.6	15.1	18.0	19.0	16.9	16.4	16.2
DAY 12	17.8	15.2	15.3	18.4	21.4	19.7	21.6	17.5
DAY 16	18.0	14.0	13.5	17.2	17.4	18.9	22.7	14.8
DAY 19	28.4	19.4	19.7	22.8	22.6	25.4	29.6	20.3
DAYS 6 - 16	16.6	14.5	14.5	17.8	19.0	18.5	20.4	16.0

500.000 MG/KG GROUP-F

ANIMAL #	609	610	611	612	613	614	615	616
	NN	NN						
DAY 6	15.9	20.4	20.7	18.9	26.9	20.9	20.5	21.6
DAY 9	12.7	13.8	14.3	11.4	17.3	14.0	13.7	14.8
DAY 12	13.4	11.8	18.8	17.7	24.3	18.1	16.0	19.7
DAY 16	13.8	13.5	21.0	27.4	25.8	19.1	19.0	19.0
DAY 19	18.6	23.7	28.4	29.8	37.0	27.5	29.3	28.9
DAYS 6 - 16	13.3	13.0	18.3	19.6	22.8	17.2	16.5	17.9

1000.000 MG/KG GROUP-F

ANIMAL #	617	618	619	620	621	622	623	624
				NN		NN	NN	NN
DAY 6	18.0	22.9	18.4	21.1	23.1	18.9	20.1	21.7
DAY 9	12.3	11.0	12.7	14.1	15.0	7.4	12.3	12.8
DAY 12	15.2	23.8	22.5	16.8	21.0	13.7	12.2	13.9
DAY 16	18.9	21.0	20.5	15.9	20.1	13.9	12.9	15.4
DAY 19	29.7	31.5	28.4	25.1	31.8	20.1	19.0	21.9
DAYS 6 - 16	15.8	18.8	18.7	15.6	18.8	11.8	12.5	14.1

2000.000 MG/KG GROUP-F

ANIMAL #	625	626	627	628	629	630	631	632
					DP			NN
DAY 6	17.7	26.3	18.0	22.4	17.0	23.5	18.7	23.4
DAY 9	12.2	17.8	7.0	13.3	2.2	14.8	12.5	12.5
DAY 10					1.4			
DAY 12	12.0	24.3	18.4	19.3		22.4	16.9	16.0
DAY 16	16.6	27.8	18.7	23.4		23.6	17.4	13.2
DAY 19	29.2	27.8	30.2	33.3		32.9	29.9	23.7
DAYS 6 - 16	13.9	23.7	15.1	19.1		20.6	15.7	13.8

4000.000 MG/KG GROUP-F

ANIMAL #	633	634	635	636	637	638	639	640
	DP	DP	DP	EP	DP	DP	DN	DP
DAY 6	19.5	19.1	19.1	19.4	18.6	21.4	20.7	20.0
DAY 7		6.4						
DAY 8				4.8	3.2			6.5
DAY 9	8.3		7.1			12.9	7.7	
DAY 10						0.8		
DAY 12	2.8							

NOTE: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: λ = FEED CONSUMPTION REFERS TO GRAMS/ANIMAL/DAY.
DAYS 6 - 16 = AVERAGE CONSUMPTION BETWEEN DAYS 6 AND 16

MEAN TERMINAL ORGAN WEIGHTS AND BODY WEIGHTS

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

KILL DAY - 20

GROUP		0.000 MG/KG F	500.000 MG/KG F	1000.000 MG/KG F	2000.000 MG/KG F	4000.000 MG/KG F
BODY WEIGHT	(G)	223.9 A	235.7	219.8	226.3	
		16.9 B	26.0	14.6	24.1	
		3 C	5	4	6	
KIDNEYS	(G)	1.7882	1.6914	1.6995	1.9540	
		0.1100	0.2295	0.1425	0.4231	
		3	6	4	6	
	%	0.7995	0.6872	0.7725	0.8594	
		0.0262	0.1148	0.0209	0.1325	
		3	6	4	6	
LIVER	(G)	9.7182	10.2024	10.4903	11.0300	
		0.9715	1.7540	1.2701	1.2314	
		3	6	4	6	
	%	4.3356	4.1240	4.7588	4.8768 *	
		0.1085	0.6666	0.2605	0.2513	
		3	6	4	6	

NOTE: BODY WEIGHT IS CORRECTED BODY WEIGHT
MEANS DO NOT INCLUDE NN, DP, DN, AND EP VALUES.
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP
* = STATISTICALLY DIFFERENT FROM CONTROLS ($p \leq 0.05$), ONE-WAY ANOVA

INDIVIDUAL ANIMAL ORGAN WEIGHTS AND TERMINAL BODY WEIGHT

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP - F

ANIMAL #		601	602	603	604	605	606	607	608
			NN	NN	NN	NN			NN
BODY WEIGHT	(G)	225.8					206.1	239.7	
KIDNEYS	(G)	1.8559					1.6612	1.8474	
	%	0.8217					0.8062	0.7706	
LIVER	(G)	9.7573					8.7278	10.6696	
	%	4.3203					4.2356	4.4509	

500.000 MG/KG GROUP - F

ANIMAL #		609	610	611	612	613	614	615	616
		NN	NN						
BODY WEIGHT	(G)			215.2	$	279.8	230.7	234.8	218.0
KIDNEYS	(G)			1.5264	1.5206	2.1079	1.5297	1.7774	1.6862
	%			0.7092	$	0.7533	0.6630	0.7569	0.7734
LIVER	(G)			8.6079	9.3788	13.5634	10.0057	10.3525	9.3058
	%			3.9992	$	4.8472	4.3364	4.4087	4.2681

1000.000 MG/KG GROUP - F

ANIMAL #		617	618	619	620	621	622	623	624
					NN		NN	NN	NN
BODY WEIGHT	(G)	202.9	237.1	214.2		225.2			
KIDNEYS	(G)	1.5625	1.8533	1.5952		1.7869			
	%	0.7700	0.7817	0.7447		0.7936			
LIVER	(G)	9.0302	12.0137	10.0200		10.8972			
	%	4.4503	5.0674	4.6774		4.8400			

2000.000 MG/KG GROUP - F

ANIMAL #		625	626	627	628	629	630	631	632
						DP			NN
BODY WEIGHT	(G)	198.9	266.6	209.5	231.9		236.0	214.8	
KIDNEYS	(G)	1.5741	2.2868	1.6377	1.8058		2.6497	1.7699	
	%	0.7912	0.8578	0.7818	0.7788		1.1228	0.8241	
LIVER	(G)	10.0453	12.4427	9.4364	11.8447		12.0273	10.3833	
	%	5.0494	4.6672	4.5049	5.1086		5.0965	4.8344	

4000.000 MG/KG GROUP - F

ANIMAL #		633	634	635	636	637	638	639	640
		DP	DP	DP	EP	DP	DP	DN	DP
BODY WEIGHT	(G)								
KIDNEYS	(G)								
	%								
LIVER	(G)								
	%								

NOTE: BODY WEIGHT IS CORRECTED BODY WEIGHT
NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: $ = GRAVID UTERUS WEIGHT WAS NOT COLLECTED; THE CORRECTED TERMINAL BODY WEIGHT AND RELATIVE ORGAN WEIGHTS COULD NOT BE DETERMINED.

Study No. 88-0087T2
Acc. No. 906659

PATHOLOGY REPORT

Compound: 2-Ethyl-1,3-hexanediol

Pregnant female rats given 0, 500, 1000, 2000, or 4000 mg/kg of the test material by gavage for 10 treatments over a 20-day period, as part of a developmental toxicity study, were necropsied. Necropsy lesions are listed in computer-generated tables.

The cause of death for rats which died after exposure to the test material was not identified.

GROSS PATHOLOGY

Female Rats - 4000 mg/kg dose group: Treatment-related changes included test compound in the stomach (5/8) and duodenum (1/8), necrosis (8/8) and hemorrhage (1/8) in the glandular gastric mucosa, excessive mucus (2/8) in the cecum, and thymic (2/8) and adipose tissue (2/8) atrophy. Single rats died on Days 7, 10, and 12, one rat was killed *in extremis* and two rats died on Day 8, and two rats died on Day 9.

2000 mg/kg dose group: Treatment-related changes in a rat which died on Day 10 included hemorrhage in the glandular gastric mucosa and thymic and adipose tissue atrophy. No treatment-related changes were observed in seven rats which survived the 20-day observation period.

1000 and 500 mg/kg dose groups: No treatment-related changes were observed in either group. All rats survived the 20-day observation period.

All other lesions listed in the attached tables were not considered treatment-related. From some rats the kidneys and livers were collected, but were not processed, for microscopic examination.

Milan S. Vlaovic, D.V.M., Ph.D.

MSV:cpp
10/26/88

4067T

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

GROUP	0.000 MG/KG F	500.000 MG/KG F	1000.000 MG/KG F	2000.000 MG/KG F	4000.000 MG/KG F
TRACHEA	8	8	8	8	8
LUNGS	8	8	8	8	8
HEART	8	8	8	8	8
ESOPHAGUS	8	8	8	8	8
STOMACH	8	8	8	8	8
DISTENTION	0	0	0	0	1
TEST COMPOUND IN LUMEN	0	0	0	0	5
STOMACH, GLANDULAR					
HEMORRHAGE	0	0	0	1	1
NECROSIS	0	0	0	0	8
DUODENUM	8	8	8	8	8
DISTENTION	0	0	0	0	1
TEST COMPOUND IN LUMEN	0	0	0	0	1
JEJUNUM	8	8	8	8	8
DISTENTION	0	0	0	0	1
ILEUM	8	8	8	8	8
DISTENTION	0	0	0	0	1
CECUM	8	8	8	8	8
HYPERSECRETION	0	0	0	0	2
COLON	8	8	8	8	8
URINARY BLADDER	8	8	8	8	8
DISTENTION	0	0	0	0	1
PANCREAS, NOS	8	8	8	8	8
MESENTERIC LYMPH NODES	8	8	8	8	8
THYMUS	8	8	8	8	8
ATROPHY	0	0	0	1	2
HEMORRHAGE	0	0	0	0	3
ADRENALS	8	8	8	8	8
SPLEEN	8	8	8	8	8
OVARIES	8	8	8	8	8
FALLOPIAN TUBES	8	8	8	8	8
UTERUS	8	8	8	8	8
VAGINA	8	8	8	8	8
KIDNEYS	8	8	8	8	8
HYDRONEPHROSIS, UNILATERAL	0	0	0	1	0
LIVER	8	8	8	8	8
ADIPOSE TISSUE	0	0	0	1	2
ATROPHY	0	0	0	1	2

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY.

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP - F

ANIMAL #	601	602 NN	603 NN	604 NN	605 NN	606	607	608 NN
DAYS ON TEST	20	20	20	20	20	20	20	20
TRACHEA	X	X	X	X	X	X	X	X
LUNGS	X	X	X	X	X	X	X	X
HEART	X	X	X	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X	X	X	X
STOMACH	X	X	X	X	X	X	X	X
DUODENUM	X	X	X	X	X	X	X	X
JEJUNUM	X	X	X	X	X	X	X	X
ILEUM	X	X	X	X	X	X	X	X
CECUM	X	X	X	X	X	X	X	X
COLON	X	X	X	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X	X	X	X
THYMUS	X	X	X	X	X	X	X	X
ADRENALS	X	X	X	X	X	X	X	X
SPLEEN	X	X	X	X	X	X	X	X
OVARIES	X	X	X	X	X	X	X	X
FALLOPIAN TUBES	X	X	X	X	X	X	X	X
UTERUS	X	X	X	X	X	X	X	X
VAGINA	X	X	X	X	X	X	X	X
KIDNEYS	N	N	N	N	N	N	N	N
LIVER	N	N	N	N	N	N	N	N

NOTE: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

500.000 MG/KG GROUP - F

ANIMAL #	609 NN	610 NN	611	612	613	614	615	616
DAYS ON TEST	20	20	20	20	20	20	20	20
TRACHEA	X	X	X	X	X	X	X	X
LUNGS	X	X	X	X	X	X	X	X
HEART	X	X	X	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X	X	X	X
STOMACH	X	X	X	X	X	X	X	X
DUODENUM	X	X	X	X	X	X	X	X
JEJUNUM	X	X	X	X	X	X	X	X
ILEUM	X	X	X	X	X	X	X	X
CECUM	X	X	X	X	X	X	X	X
COLON	X	X	X	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X	X	X	X
THYMUS	X	X	X	X	X	X	X	X
ADRENALS	X	X	X	X	X	X	X	X
SPLEEN	X	X	X	X	X	X	X	X
OVARIES	X	X	X	X	X	X	X	X
FALLOPIAN TUBES	X	X	X	X	X	X	X	X
UTERUS	X	X	X	X	X	X	X	X
VAGINA	X	X	X	X	X	X	X	X
KIDNEYS	N	N	N	N	N	N	N	N
LIVER	N	N	N	N	N	N	N	N

NOTE: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

1000.000 MG/KG GROUP - F

ANIMAL #	617	618	619	620 NN	621	622 NN	623 NN	624 NN
DAYS ON TEST	20	20	20	20	20	20	20	20
TRACHEA	X	X	X	X	X	X	X	X
LUNGS	X	X	X	X	X	X	X	X
HEART	X	X	X	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X	X	X	X
STOMACH	X	X	X	X	X	X	X	X
DUODENUM	X	X	X	X	X	X	X	X
JEJUNUM	X	X	X	X	X	X	X	X
ILEUM	X	X	X	X	X	X	X	X
CECUM	X	X	X	X	X	X	X	X
COLON	X	X	X	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X	X	X	X
THYMUS	X	X	X	X	X	X	X	X
ADRENALS	X	X	X	X	X	X	X	X
SPLEEN	X	X	X	X	X	X	X	X
OVARIES	X	X	X	X	X	X	X	X
FALLOPIAN TUBES	X	X	X	X	X	X	X	X
UTERUS	X	X	X	X	X	X	X	X
VAGINA	X	X	X	X	X	X	X	X
KIDNEYS	N	N	N	N	N	N	N	N
LIVER	N	N	N	N	N	N	N	N

NOTE: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

2000.000 MG/KG GROUP - F

ANIMAL #	625	626	627	628	629 DP	630	631	632 NN
DAYS ON TEST	20	20	20	20	10	20	20	20
TRACHEA	X	X	X	X	X	X	X	X
LUNGS	X	X	X	X	X	X	X	X
HEART	X	X	X	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X	X	X	X
STOMACH	X	X	X	X		X	X	X
STOMACH, GLANDULAR HEMORRHAGE					2			
DUODENUM	X	X	X	X	X	X	X	X
JEJUNUM	X	X	X	X	X	X	X	X
ILEUM	X	X	X	X	X	X	X	X
CECUM	X	X	X	X	X	X	X	X
COLON	X	X	X	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X	X	X	X
THYMUS	X	X	X	X		X	X	X
ATROPHY					3			
ADRENALS	X	X	X	X	X	X	X	X
SPLEEN	X	X	X	X	X	X	X	X
OVARIES	X	X	X	X	X	X	X	X
FALLOPIAN TUBES	X	X	X	X	X	X	X	X
UTERUS	X	X	X	X	X	X	X	X
VAGINA	X	X	X	X	X	X	X	X
KIDNEYS	N	N		N	X	N	N	N
HYDRONEPHROSIS, UNILATERAL			2					
LIVER	N	N	N	N	X	N	N	N
ADIPOSE TISSUE								
ATROPHY					3			

NOTE: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

4000.000 MG/KG GROUP - F

ANIMAL #	633 DP	634 DP	635 DP	636 EP	637 DP	638 DP	639 DN	640 DP
DAYS ON TEST	12	7	9	8	8	10	9	8
TRACHEA	X	X	X	X	X	X	X	X
LUNGS	X	X	X	X	X	X	X	X
HEART	X	X	X	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X	X	X	X
STOMACH								
DISTENTION				3				
TEST COMPOUND IN LUMEN	P		P		P	P	P	
STOMACH, GLANDULAR								
NECROSIS	1	1	1	2	1	1	2	1
HEMORRHAGE							2	
DUODENUM	X	X	X			X	X	X
DISTENTION				3				
TEST COMPOUND IN LUMEN					P			
JEJUNUM	X	X	X		X	X	X	X
DISTENTION				3				
*ILEUM	X	X	X		X	X	X	X
DISTENTION				3				
*CECUM	X	X	X			X	X	X
HYPERSECRETION				2	2			
COLON	X	X	X	X	X	X	X	X
*URINARY BLADDER		X	X	X	X	X	X	X
DISTENTION	2							
PANCREAS, NOS	X	X	X	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X	X	X	X
THYMUS		X		X	X		X	
HEMORRHAGE	1		2					1
ATROPHY	3					2		
ADRENALS	X	X	X	X	X	X	X	X
SPLEEN	X	X	X	X	X	X	X	X
OVARIES	X	X	X	X	X	X	X	X
FALLOPIAN TUBES	X	X	X	X	X	X	X	X
UTERUS	X	X	X	X	X	X	X	X
VAGINA	X	X	X	X	X	X	X	X
KIDNEYS	X	X	X	X	X	X	X	X
LIVER	X	X	X	X	X	X	X	X
ADIPOSE TISSUE								
ATROPHY	3						3	

NOTE: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT,
DN - SPONTANEOUS DEATH : NOT PREGNANT, EP - EUTHANATIZED : PREGNANT

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

GROSS PATHOLOGY COMMENT REPORT

EXPERIMENT # 880087T2 EXPERIMENT START DATE: 6-SEP-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

DAY	DOSE LEVEL	ANIMAL #	COMMENT
22	4000.000 MG/KG	636	STOMACH THROUGH ILEUM DISTENDED WITH GAS.
22	4000.000 MG/KG	636	CECUM CONTAINED YELLOW MUCOUS.
22	4000.000 MG/KG	637	CECUM CONTAINED MUCUS.
22	4000.000 MG/KG	633	URINARY BLADDER CONTAINED APPROX. 7.5 ML OF URINE.

SUMMARY OF OBSERVATIONS COLLECTED AT TIME OF CESARIAN SECTION

HAEL NO. 88-0087
START DATE: 06-SEP-88

ACCESSION NO. 906659
ROUTE: GAVAGE

EXPERIMENT NO. 880087T2
REPORT DATE: 17-OCT-88

	DOSE GROUP (MG/KG) 0.000	500.000	1000.000	2000.000	4000.000
Females on Study	8	8	8	8	8
# Females Pregnant (%)	3 (37)	6 (75)	4 (50)	7 (87)	7 (87)
# Litters with Viable Fetuses	3	6	4	6	(E)
# Litters Completely Resorbed	0	0	0	0	
# Corpora Lutea	40	98	50	92	
Mean ± SD	13.3± 2.5	16.3± 4.8	12.5± 1.3	15.3± 1.0	
# Implantations	38	83	45	83	
Mean ± SD	12.7± 2.1	13.8± 1.7	11.3± 1.5	13.8± 1.0	
% Pre-Implantation Loss (A)	4.6± 4.1	11.8± 22.7	10.0± 7.4	9.4± 9.5	
# Viable Fetuses	38	75	45	66	
Mean Litter Size ± SD	12.7± 2.1	12.5± 2.2	11.3± 1.5	11.0± 2.0	
# Resorptions	0	8	0	17 (F)	
Mean ± SD	0.0± 0.0	1.3± 1.0	0.0± 0.0	2.8± 2.4	
# Dead Fetuses	0	0	0	0	
Mean ± SD	0.0± 0.0	0.0± 0.0	0.0± 0.0	0.0± 0.0	
% Post-Implantation Loss (B)	0.0± 0.0	9.9± 7.9	0.0± 0.0	19.9± 17.0(F)	
Mean Fetal Body Weight (g) (C)	4.6± 1.1	4.3± 0.9	4.6± 0.3	2.8± 0.7(F)	
Male Body Weight (g) (C)	4.7± 1.1	4.4± 1.1	4.7± 0.3	2.9± 0.7(F)	
Female Body Weight (g) (C)	4.5± 1.1	4.2± 0.8	4.4± 0.3	2.7± 0.7(F)	
Mean Sex Ratio (M:F)	45: 55	43: 57	49: 51	55: 45	
Gravid Uterine Weight (g) (D)	82.3± 17.0	71.9± 12.0	76.1± 8.2	59.1± 10.7	
Corrected Body Weight (g) (D)	223± 16.9	236± 26.0	219± 14.6	226± 24.1	

(A) $\frac{\text{(No. of corpora lutea - No. implantations) x 100}}{\text{No. of corpora lutea}}$ calculated for each litter and averaged

(B) $\frac{\text{(No. of implantations - No. of viable fetuses) x 100}}{\text{No. of implantations}}$ calculated for each litter and averaged

(C) Mean of the Litter Means ± 1 standard deviation

(D) Mean ±1 standard deviation

(E) Dams died or were euthanatized before the end of the treatment period.

(F) Statistically different from control ($p \leq 0.05$), one-way ANOVA

INDIVIDUAL FEMALE DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: CONTROL REPORT DATE: 17-OCT-88

DAM'S NUMBER STUDY	EAR TAG	PREGNANT STATUS	GRAVID UTERINE WEIGHT (g)	CORPORA LUTEA LEFT	CORPORA LUTEA RIGHT	IMPLANTATIONS LEFT	IMPLANTATIONS RIGHT	COMMENT
601	H0278	PF	62.74	6	5	6	5	
602	H0305	NN	0.00	0	0	0	0	
603	H0292	NN	0.00	0	0	0	0	
604	H0284	NN	0.00	0	0	0	0	
605	H0280	NN	0.00	0	0	0	0	
606	H0297	PF	89.81	7	6	6	6	
607	H0295	PF	94.21	8	8	8	7	
608	H0307	NN	0.00	0	0	0	0	

KEY: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT, DN - SPONTANEOUS DEATH : NOT PREGNANT,
EP - EUTHANATIZED : PREGNANT, PF - PREGNANT : FULL TERM

INDIVIDUAL FEMALE DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 500.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S NUMBER STUDY	EAR TAG	PREGNANT STATUS	GRAVID UTERINE WEIGHT (g)	CORPORA LUTEA LEFT	RIGHT	IMPLANTATIONS LEFT	RIGHT	COMMENT
609	H0308	NN	0.00	0	0	0	0	
610	H0267	NN	0.00	0	0	0	0	
611	H0270	PF	72.68	6	7	6	7	
612	H0296	PF	*	7	8	6	8	
613	H0283	PF	86.19	7	7	7	9	
614	H0279	PF	52.77	13	13	5	6	
615	H0282	PF	73.46	9	7	8	7	
616	H0310	PF	74.27	7	7	7	7	

KEY: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT, DN - SPONTANEOUS DEATH : NOT PREGNANT,
EP - EUTHANATIZED : PREGNANT, PF - PREGNANT : FULL TERM
* = No gravid uterine weight was collected; No corrected body weight could be determined.

INDIVIDUAL FEMALE DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 1000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S NUMBER STUDY	EAR TAG	PREGNANT STATUS	GRAVID UTERINE WEIGHT (g)	CORPORA LUTEA LEFT	CORPORA LUTEA RIGHT	IMPLANTATIONS LEFT	IMPLANTATIONS RIGHT	COMMENT
617	H0294	PF	68.59	6	5	5	5	
618	H0272	PF	85.31	5	9	4	8	
619	H0302	PF	69.78	9	3	7	3	
620	H0291	NN	0.00	0	0	0	0	
621	H0269	PF	80.55	9	4	9	4	
622	H0299	NN	0.00	0	0	0	0	
623	H0309	NN	0.00	0	0	0	0	
624	H0281	NN	0.00	0	0	0	0	

KEY: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT, DN - SPONTANEOUS DEATH : NOT PREGNANT,
EP - EUTHANATIZED : PREGNANT, PF - PREGNANT : FULL TERM

INDIVIDUAL FEMALE DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 2000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S NUMBER STUDY	EAR TAG	PREGNANT STATUS	GRAVID UTERINE WEIGHT (g)	CORPORA LUTEA LEFT	CORPORA LUTEA RIGHT	IMPLANTATIONS LEFT	IMPLANTATIONS RIGHT	COMMENT
625	H0277	PF	56.77	7	9	5	7	
626	H0271	PF	50.71	8	8	6	8	
627	H0286	PF	54.41	5	11	4	10	
628	H0273	PF	70.16	8	6	8	6	
629	H0301	DP	0.00	0	0	0	0	IMPLANTATION SITES: 6 RIGHT, 5 LEFT. SITES APPEAR SMALL FOR STAGE OF GEST.
630	H0285	PF	74.25	8	8	8	7	
631	H0293	PF	48.25	8	6	8	6	
632	H0311	NN	0.00	0	0	0	0	

KEY: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT, DN - SPONTANEOUS DEATH : NOT PREGNANT,
EP - EUTHANATIZED : PREGNANT, PF - PREGNANT : FULL TERM

INDIVIDUAL FEMALE DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 4000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S STUDY COMMENT	NUMBER EAR TAG	PREGNANT STATUS	GRAVID UTERINE WEIGHT (g)	CORPORA LUTEA LEFT	CORPORA LUTEA RIGHT	IMPLANTATIONS LEFT	IMPLANTATIONS RIGHT	
633	H0274	DP	0.00	0	0	0	0	IMPLANTATION SITES: 4 LEFT, 8 RIGHT.
634	H0298	DP	0.00	0	0	0	0	IMPLANTATION SITES: 10 LEFT, 5 RIGHT.
635	H0268	DP	0.00	0	0	0	0	IMPLANTATION SITES: 10 LFET, 5 RIGHT.
636	H0303	EP	0.00	0	0	0	0	IMPLANTATION SITES: 7 LEFT, 4 RIGHT
637	H0287	DP	0.00	0	0	0	0	IMPLANTATION SITES: 6 LEFT, 7 RIGHT.
638	H0306	DP	0.00	0	0	0	0	IMPLANTATION SITES: 4 LEFT, 9 RIGHT.
639	H0290	DN	0.00	0	0	0	0	
640	H0288	DP	0.00	0	0	0	0	IMPLANTAION SITES: 10 LEFT, 3 RIGHT.

KEY: NN - NOT PREGNANT : NEGATIVE STAIN, DP - SPONTANEOUS DEATH : PREGNANT, DN - SPONTANEOUS DEATH : NOT PREGNANT,
EP - EUTHANATIZED : PREGNANT, PF - PREGNANT : FULL TERM

INDIVIDUAL LITTER DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: CONTROL REPORT DATE: 17-OCT-88

DAM'S STUDY	NUMBER EAR TAG	NUMBER CORPORA LUTEA	IMPLAN-TATIONS NO.	VIABLE FETUSES NO.	RESORPTIONS EARLY NO.	RESORPTIONS LATE NO.	DEAD FETUSES NO.	POST IMPLAN-TATION LOSS NO.	SEX NO. MALES	SEX NO. FEMALES	SEX M:F RATIO	MEAN FETAL BODY WEIGHT MALE	MEAN FETAL BODY WEIGHT FEMALE	MEAN FETAL BODY WEIGHT M & F	GRAVID UTERINE WT. GRAMS	CORRECTED BODY WT. (g)
601	H0278	11	11	11	0	0	0	0	6	5	55: 45	3.56	3.46	3.52	62.74	225.85
602	H0305	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
603	H0292	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
604	H0284	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
605	H0280	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
606	H0297	13	12	12	0	0	0	0	6	6	50: 50	5.62	5.68	5.65	89.81	206.06
607	H0295	16	15	15	0	0	0	0	5	10	33: 67	4.94	4.51	4.65	94.21	239.72
608	H0307	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
	MEAN	13.3	12.7	12.7	0.0	0.0	0.0	0.0	5.7	7.0	45: 55	4.71	4.55	4.61	82.25	223.88
	SD	2.5	2.1	2.1	0.0	0.0	0.0	0.0	0.6	2.6	—	1.05	1.11	1.07	17.04	16.92

INDIVIDUAL LITTER DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 500.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S STUDY	NUMBER EAR TAG	NUMBER CORPORA LUTEA	IMPLAN-TATIONS NO.	VIABLE FETUSES NO.	RESORPTIONS EARLY NO.	RESORPTIONS LATE NO.	DEAD FETUSES NO.	POST IMPLAN-TATION LOSS NO.	SEX NO. MALES	SEX NO. FEMALES	SEX M:F RATIO	MEAN FETAL BODY WEIGHT MALE	MEAN FETAL BODY WEIGHT FEMALE	MEAN FETAL BODY WEIGHT M & F	GRAVID UTERINE WT. GRAMS	CORRECTED BODY WT. (g)
609	H0308	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
610	H0267	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
611	H0270	13	13	10	3	0	0	3	3	7	30: 70	5.73	5.09	5.28	72.68	215.24
612	H0296	15	14	14	0	0	0	0	6	8	43: 57	5.13	4.92	5.01	*	*
613	H0283	14	16	15	1	0	0	1	5	10	33: 67	3.91	3.73	3.79	86.19	279.82
614	H0279	26	11	10	1	0	0	1	4	6	40: 60	3.13	3.14	3.14	52.77	230.74
615	H0282	16	15	14	1	0	0	1	8	6	57: 43	3.38	3.43	3.40	73.46	234.82
616	H0310	14	14	12	2	0	0	2	6	6	50: 50	5.22	4.78	5.00	74.27	218.03
	MEAN	16.3	13.8	12.5	1.3	0.0	0.0	1.3	5.3	7.2	43: 57	4.42	4.18	4.27	71.87	235.73
	SD	4.8	1.7	2.2	1.0	0.0	0.0	1.0	1.8	1.6	—	1.08	0.85	0.94	12.03	25.99

KEY: * = No gravid uterine weight was collected; No corrected body weight could be determined.

INDIVIDUAL LITTER DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 1000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S STUDY	NUMBER EAR TAG	NUMBER CORPORA LUTEA	IMPLANTATIONS NO.	VIABLE FETUSES NO.	RESORPTIONS EARLY NO.	RESORPTIONS LATE NO.	DEAD FETUSES NO.	POST IMPLANTATION LOSS NO.	SEX NO. MALES	SEX NO. FEMALES	SEX M:F RATIO	MEAN FETAL BODY WEIGHT MALE	MEAN FETAL BODY WEIGHT FEMALE	MEAN FETAL BODY WEIGHT M & F	GRAVID UTERINE WT. GRAMS	CORRECTED BODY WT. (g)
617	H0294	11	10	10	0	0	0	0	4	6	40: 60	4.79	4.65	4.70	68.59	202.91
618	H0272	14	12	12	0	0	0	0	7	5	58: 42	4.75	4.50	4.64	85.31	237.08
619	H0302	12	10	10	0	0	0	0	6	4	60: 40	4.91	4.47	4.74	69.78	214.22
620	H0291	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
621	H0269	13	13	13	0	0	0	0	5	8	38: 62	4.29	4.01	4.12	80.55	225.15
622	H0299	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
623	H0309	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
624	H0281	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
	MEAN	12.5	11.3	11.3	0.0	0.0	0.0	0.0	5.5	5.8	49: 51	4.69	4.41	4.55	76.06	219.84
	SD	1.3	1.5	1.5	0.0	0.0	0.0	0.0	1.3	1.7	—	0.27	0.28	0.29	8.18	14.65

INDIVIDUAL LITTER DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 2000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S STUDY	NUMBER EAR TAG	NUMBER CORPORA LUTEA	IMPLANTATIONS NO.	VIABLE FETUSES NO.	RESORPTIONS EARLY NO.	RESORPTIONS LATE NO.	DEAD FETUSES NO.	POST IMPLANTATION LOSS NO.	SEX NO. MALES	SEX NO. FEMALES	SEX M:F RATIO	MEAN FETAL BODY WEIGHT MALE	MEAN FETAL BODY WEIGHT FEMALE	MEAN FETAL BODY WEIGHT M & F	GRAVID UTERINE WT. GRAMS	CORRECTED BODY WT. (g)
625	H0277	16	12	12	0	0	0	0	6	6	50: 50	2.78	2.35	2.57	56.77	198.94
626	H0271	16	14	11	3	0	0	3	5	6	45: 55	2.48	2.05	2.25	50.71	266.60
627	H0286	16	14	10	2	2	0	4	7	3	70: 30	2.35	2.13	2.28	54.41	209.47
628	H0273	14	14	14	0	0	0	0	7	7	50: 50	2.75	2.80	2.78	70.16	231.86
629	H0301	SPONTANEOUS DEATH : PREGNANT				—	—	—	—	—	—	—	—	—	—	—
630	H0285	16	15	11	4	0	0	4	7	4	64: 36	4.20	3.91	4.10	74.25	235.99
631	H0293	14	14	8	2	4	0	6	4	4	50: 50	3.06	2.79	2.93	48.25	214.78
632	H0311	NOT PREGNANT - NEGATIVE STAIN				—	—	—	—	—	—	—	—	—	—	—
	MEAN	15.3	13.8	11.0	1.8	1.0	0.0	2.8	6.0	5.0	55: 45	2.94	2.67	2.82	59.09	226.27
	SD	1.0	1.0	2.0	1.6	1.7	0.0	2.4	1.3	1.5	—	0.67	0.68	0.68	10.65	24.14

INDIVIDUAL LITTER DATA COLLECTED AT CESARIAN SECTION

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 4000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S STUDY	NUMBER EAR TAG	NUMBER CORPORA LUTEA	IMPLAN-TATIONS NO.	VIABLE FETUSES NO.	RESORPTIONS EARLY NO.	RESORPTIONS LATE NO.	DEAD FETUSES NO.	POST IMPLAN-TATION LOSS NO.	SEX NO. MALES	SEX NO. FEMALES	SEX M:F RATIO	MEAN FETAL BODY WEIGHT MALE	MEAN FETAL BODY WEIGHT FEMALE	MEAN FETAL BODY WEIGHT M & F	GRAVID UTERINE WT. GRAMS	CORRECTED BODY WT. (g)
633	H0274	SPONTANEOUS DEATH : PREGNANT				—	—	—	—	—	—	—	—	—	—	—
634	H0298	SPONTANEOUS DEATH : PREGNANT				—	—	—	—	—	—	—	—	—	—	—
635	H0268	SPONTANEOUS DEATH : PREGNANT				—	—	—	—	—	—	—	—	—	—	—
636	H0303	EUTHANITIZED : PREGNANT				—	—	—	—	—	—	—	—	—	—	—
637	H0287	SPONTANEOUS DEATH : PREGNANT				—	—	—	—	—	—	—	—	—	—	—
638	H0306	SPONTANEOUS DEATH : PREGNANT				—	—	—	—	—	—	—	—	—	—	—
639	H0290	SPONTANEOUS DEATH : NOT PREGNANT				—	—	—	—	—	—	—	—	—	—	—
640	H0288	SPONTANEOUS DEATH : PREGNANT				—	—	—	—	—	—	—	—	—	—	—
	MEAN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0: 0	0.00	0.00	0.00	0.00	0.00
	SD	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	—	0.00	0.00	0.00	0.00	0.00

EXTERNAL MALFORMATIONS AND VARIATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2
START DATE: 06-SEP-88 ROUTE: GAVAGE

	DOSE GROUP (MG/KG) 0.000		500.000		1000.000		2000.000		4000.000	
	F	L	F	L	F	L	F	L	F	L
NUMBER EXAMINED:	38	3	75	6	45	4	66	6	0	0
MALFORMATIONS:									†	
RUDIMENTARY, FILAMENTOUS TAIL	0	0	1	1	2	2	15κ	4		
EDEMATOUS, HEMORRHAGIC TAIL	0	0	0	0	0	0	2	2		
SMALL (MINIATURE) TAIL	0	0	0	0	0	0	1	1		
CURLY TAIL	0	0	0	0	0	0	1	1		
MISSING TAIL	0	0	0	0	0	0	11κ	3		
CYST ON TAIL	0	0	0	0	0	0	1	1		
TOTAL TAIL	0	0	1	1	2	2	29	6		
ABNORMAL CURVATURE HINDLIMB(S)	0	0	0	0	0	0	13κ	4		
ARTHROGRYPOSIS (CARPUS)	0	0	0	0	0	0	3	3		
SHORTENED TRUNK (LUMBAR REGION)	0	0	0	0	0	0	5	3		
UMBILICAL HERNIA	0	0	0	0	0	0	4	2		
VARIATIONS:										
HEMATOMA (BODY AS A WHOLE)	0	0	0	0	1	1	9κ	4		

KEY: F = FETUSES
L = LITTERS
κ = Statistically different from control ($p \leq 0.05$), Fisher's Exact Test
† = Dams died or were euthanatized before the end of the treatment period.

INDIVIDUAL LITTER DATA - EXTERNAL, INTERNAL SOFT TISSUE AND SKELETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: CONTROL REPORT DATE: 17-OCT-88

DAM'S EAR TAG NO.	H 2 7 8	H 3 0 5	H 2 9 2	H 2 8 4	H 2 8 0	H 2 9 7	H 2 9 5	H 3 0 7	TOTAL	
DAM'S STUDY NO.	601	602	603	604	605	606	607	608	FETUSES	LITTERS
NO. FETUSES EXAMINED:										
EXTERNAL	11	NN	NN	NN	NN	12	15	NN	38	3
EXTERNAL ALTERATIONS:										
RUDIMENTARY STRUCTURE										
TAIL										
HEMATOMA										
FACE										
HEAD										
LEFT HINDLIMB										
RIGHT HINDLIMB										
RIGHT FORELIMB										
NECK										
SCAPULAR REGION										
ARTHROGRYPOSIS										
CARPUS										
EDEMA										
TAIL										
HEMORRHAGE										
TAIL										
SMALL										
TAIL										
BODY AS A WHOLE, NOS										
CURLED										
TAIL										
ABSENT OR MISSING										
TAIL										
ABNORMAL CURVATURE										
HINDLIMB										
LEFT HINDLIMB										
HERNIA										
UMBILICUS										
SHORT TRUNK										
TRUNK, NOS										
ENLARGED,NOS										
HINDLIMB										
CYST										
TAIL										

INDIVIDUAL LITTER DATA - EXTERNAL, INTERNAL SOFT TISSUE AND SKELETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 500.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S EAR TAG NO.	H308	H267	H270	H229	H283	H279	H282	H310	TOTAL	
DAM'S STUDY NO.	609	610	611	612	613	614	615	616	FETUSES	LITTERS
NO. FETUSES EXAMINED:										
EXTERNAL	NN	NN	10	14	15	10	14	12	75	6
EXTERNAL ALTERATIONS:			1						1	1
RUDIMENTARY STRUCTURE										
TAIL			1						1	1
HEMATOMA										
FACE										
HEAD										
LEFT HINDLIMB										
RIGHT HINDLIMB										
RIGHT FORELIMB										
NECK										
SCAPULAR REGION										
ARTHROGRYPOSIS										
CARPUS										
EDEMA										
TAIL										
HEMORRHAGE										
TAIL										
SMALL										
TAIL										
BODY AS A WHOLE, NOS										
CURLED										
TAIL										
ABSENT OR MISSING										
TAIL										
ABNORMAL CURVATURE										
HINDLIMB										
LEFT HINDLIMB										
HERNIA										
UMBILICUS										
SHORT TRUNK										
TRUNK, NOS										
ENLARGED,NOS										
HINDLIMB										
CYST										
TAIL										

INDIVIDUAL LITTER DATA - EXTERNAL, INTERNAL SOFT TISSUE AND SKELETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 1000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S EAR TAG NO.	H292942	H272292	H302239	H292091	H262199	H292299	H302399	H282191	TOTAL FETUSES	TOTAL LITTERS
DAM'S STUDY NO.	617	618	619	620	621	622	623	624		
NO. FETUSES EXAMINED:										
EXTERNAL	10	12	10	NN	13	NN	NN	NN	45	4
EXTERNAL ALTERATIONS:	1	2							3	2
RUDIMENTARY STRUCTURE										
TAIL	1	1							2	2
HEMATOMA										
FACE		1							1	1
HEAD										
LEFT HINDLIMB										
RIGHT HINDLIMB										
RIGHT FORELIMB										
NECK										
SCAPULAR REGION										
ARTHROGRYPOSIS										
CARPUS										
EDEMA										
TAIL										
HEMORRHAGE										
TAIL										
SMALL										
TAIL										
BODY AS A WHOLE, NOS										
CURLED										
TAIL										
ABSENT OR MISSING										
TAIL										
ABNORMAL CURVATURE										
HINDLIMB										
LEFT HINDLIMB										
HERNIA										
UMBILICUS										
SHORT TRUNK										
TRUNK, NOS										
ENLARGED,NOS										
HINDLIMB										
CYST										
TAIL										

INDIVIDUAL LITTER DATA - EXTERNAL, INTERNAL SOFT TISSUE AND SKELETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 2000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S EAR TAG NO.	H 2 7 7	H 2 7 1	H 2 8 6	H 2 7 3	H 3 0 1	H 2 8 5	H 2 9 3	H 3 1 1	TOTAL	
DAM'S STUDY NO.	625	626	627	628	629	630	631	632	FETUSES	LITTERS
NO. FETUSES EXAMINED:										
EXTERNAL	12	11	10	14	DP	11	8	NN	66	6
EXTERNAL ALTERATIONS:	4	9	7	5		4	8		37	6
RUDIMENTARY STRUCTURE										
TAIL		4	5	3		3			15	4
HEMATOMA										
FACE										
HEAD	1	1							2	2
LEFT HINDLIMB		1	1						2	2
RIGHT HINDLIMB		1							1	1
RIGHT FORELIMB		3							3	1
NECK		1							1	1
SCAPULAR REGION							1		1	1
ARTHROGRYPOSIS										
CARPUS	1	1					1		3	3
EDEMA										
TAIL	1			1					2	2
HEMORRHAGE										
TAIL	1			1					2	2
SMALL										
TAIL	1								1	1
BODY AS A WHOLE, NOS	3	2		2					7	3
CURLED										
TAIL		1							1	1
ABSENT OR MISSING										
TAIL		2				1	8		11	3
ABNORMAL CURVATURE										
HINDLIMB		1	3			1	3		8	4
LEFT HINDLIMB							5		5	1
HERNIA										
UMBILICUS		1					3		4	2
SHORT TRUNK										
TRUNK, NOS			2	1			2		5	3
ENLARGED,NOS										
HINDLIMB			1						1	1
CYST										
TAIL			1						1	1

INDIVIDUAL LITTER DATA - EXTERNAL, INTERNAL SOFT TISSUE AND SKELETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2

START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 4000.000 MG/KG REPORT DATE: 17-OCT-88

DAM'S EAR TAG NO.	H274	H298	H268	H303	H287	H306	H290	H288	TOTAL	
DAM'S STUDY NO.	633	634	635	636	637	638	639	640	FETUSES	LITTERS
NO. FETUSES EXAMINED:										
EXTERNAL	DP	DP	DP	EP	DP	DP	DN	DP	0	0
EXTERNAL ALTERATIONS:										
RUDIMENTARY STRUCTURE										
TAIL										
HEMATOMA										
FACE										
HEAD										
LEFT HINDLIMB										
RIGHT HINDLIMB										
RIGHT FORELIMB										
NECK										
SCAPULAR REGION										
ARTHROGRYPOSIS										
CARPUS										
EDEMA										
TAIL										
HEMORRHAGE										
TAIL										
SMALL										
TAIL										
BODY AS A WHOLE, NOS										
CURLED										
TAIL										
ABSENT OR MISSING										
TAIL										
ABNORMAL CURVATURE										
HINDLIMB										
LEFT HINDLIMB										
HERNIA										
UMBILICUS										
SHORT TRUNK										
TRUNK, NOS										
ENLARGED,NOS										
HINDLIMB										
CYST										
TAIL										

INDIVIDUAL LITTER DATA - EXTERNAL FETAL ALTERATIONS

KEY

SEX:	M = Male	F = Female	U = Unknown
STATUS:	A = Alive L = Late Resorption	D = Dead	E = Early Resorption
EXTERNAL EXAM:	N = Normal	A = Abnormal	
FIXATIVE:	B = Bouin's	A = Alcohol	

INDIVIDUAL LITTER DATA - EXTERNAL FETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 880087T2
START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: CONTROL REPORT DATE: 17-OCT-88

DAM	FETUS	SEX (M/F/U)	WEIGHT (GRAMS)	STATUS (A/D/E/L)	CROWN-RUMP LENGTH (MM)	EXTERNAL EXAM (N/A)	FIXATIVE (B/A/)
	LOCATION			ABNORMALITY		SEVERITY	
			COMMENT				
601	L 1	M	3.34	A		N	
	L 2	M	3.65	A		N	
	L 3	F	3.34	A		N	
	L 4	F	3.40	A		N	
	L 5	F	3.54	A		N	
	L 6	M	3.86	A		N	
	R 1	F	3.49	A		N	
	R 2	M	3.63	A		N	
	R 3	F	3.53	A		N	
	R 4	M	3.44	A		N	
	R 5	M	3.46	A		N	
606	L 1	F	5.52	A		N	
	L 2	F	5.42	A		N	
	L 3	M	5.57	A		N	
	L 4	F	5.79	A		N	
	L 5	M	5.99	A		N	
	L 6	M	5.68	A		N	
	R 1	M	5.72	A		N	
	R 2	F	5.70	A		N	
	R 3	M	5.52	A		N	
	R 4	F	5.84	A		N	
	R 5	M	5.27	A		N	
	R 6	F	5.79	A		N	
607	L 1	M	4.80	A		N	
	L 2	F	4.55	A		N	
	L 3	F	4.62	A		N	
	L 4	M	4.67	A		N	
	L 5	F	4.35	A		N	
	L 6	M	5.05	A		N	
	L 7	F	4.56	A		N	
	L 8	F	5.06	A		N	
	R 1	F	4.57	A		N	
	R 2	F	4.95	A		N	
	R 3	M	5.00	A		N	
	R 4	F	2.87	A		N	
	R 5	M	5.20	A		N	
	R 6	F	4.59	A		N	
	R 7	F	4.96	A		N	

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE, P - PRESENT, A - ABSENT

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 88008712
START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 500.000MG/KG REPORT DATE: 14-DEC-88

DAM	FETUS	SEX (M/F/U)	WEIGHT (GRAMS)	STATUS (A/D/E/L)	CROWN-RUMP LENGTH (MM)	EXTERNAL EXAM (N/A)	FIXATIVE (B/A/)
		LOCATION	COMMENT	ABNORMALITY		SEVERITY	
611	L 1	U	0.00	E		A	
	L 2	U	0.00	E		A	
	L 3	F	5.32	A		N	A
	L 4	U	0.00	E		A	
	L 5	M	5.88	A		N	A
	L 6	F	5.37	A		N	A
	R 1	F	5.06	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	R 2	F	5.12	A		N	A
	R 3	F	5.01	A		N	A
	R 4	M	5.77	A		N	A
	R 5	F	4.32	A		N	A
	R 6	M	5.54	A		N	A
	R 7	F	5.44	A		N	A
612	L 1	F	4.93	A		N	
	L 2	F	4.84	A		N	
	L 3	M	5.15	A		N	
	L 4	M	5.24	A		N	
	L 5	M	5.00	A		N	
	L 6	F	5.19	A		N	
	R 1	F	4.98	A		N	
	R 2	M	4.82	A		N	
	R 3	F	4.77	A		N	
	R 4	M	5.22	A		N	
	R 5	F	4.71	A		N	
	R 6	F	5.02	A		N	
	R 7	M	5.33	A		N	
	R 8	F	4.92	A		N	
613	L 1	M	3.78	A		N	
	L 2	F	3.54	A		N	
	L 3	F	3.75	A		N	
	L 4	M	3.87	A		N	
	L 5	M	4.17	A		N	
	L 6	F	3.94	A		N	
	L 7	F	3.82	A		N	
	R 1	M	3.99	A		N	
	R 2	F	3.60	A		N	
	R 3	M	3.73	A		N	
	R 4	F	3.74	A		N	
	R 5	F	3.64	A		N	
	R 6	F	3.90	A		N	
	R 7	F	3.61	A		N	
	R 8	F	3.74	A		N	
	R 9	U	0.00	E		A	
614	L 1	F	3.02	A		N	
	L 2	F	3.16	A		N	
	L 3	U	0.00	E		A	
	L 4	M	3.23	A		N	
	L 5	F	3.29	A		N	

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE, P - PRESENT, A - ABSENT

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 88008712
START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 500.000MG/KG REPORT DATE: 17-OCT-88

DAM	FETUS	SEX (M/F/U)	WEIGHT (GRAMS)	STATUS (A/D/E/L)	CROWN-RUMP LENGTH (MM)	EXTERNAL EXAM (N/A)	FIXATIVE (B/A/)
		LOCATION	COMMENT	ABNORMALITY		SEVERITY	
614	R 1	F	2.94	A		N	
	R 2	M	2.93	A		N	
	R 3	M	3.26	A		N	
	R 4	M	3.11	A		N	
	R 5	F	3.11	A		N	
	R 6	F	3.32	A		N	
615	L 1	M	3.31	A		N	
	L 2	F	3.43	A		N	
	L 3	M	3.66	A		N	
	L 4	F	3.41	A		N	
	L 5	F	3.49	A		N	
	L 6	M	3.49	A		N	
	L 7	M	3.28	A		N	
	L 8	F	3.43	A		N	
	R 1	F	3.35	A		N	
	R 2	F	3.47	A		N	
	R 3	M	3.34	A		N	
	R 4	M	3.16	A		N	
	R 5	M	3.39	A		N	
	R 6	M	3.38	A		N	
	R 7	U	0.00	E		A	
616	L 1	M	5.42	A		N	
	L 2	F	4.45	A		N	
	L 3	M	4.92	A		N	
	L 4	F	4.65	A		N	
	L 5	F	4.78	A		N	
	L 6	U	0.00	E		A	
	L 7	F	5.24	A		N	
	R 1	M	5.41	A		N	
	R 2	F	4.59	A		N	
	R 3	M	5.12	A		N	
	R 4	U	0.00	E		A	
	R 5	M	5.13	A		N	
	R 6	F	4.98	A		N	
	R 7	M	5.31	A		N	

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE, P - PRESENT, A - ABSENT

INDIVIDUAL LITTER DATA - EXTERNAL FETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 905659 EXPERIMENT NO. 88008712
START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 1000.000MG/KG REPORT DATE: 17-OCT-88

DAM	FETUS	SEX (M/F/U)	WEIGHT (GRAMS)	STATUS (A/D/E/L)	CROWN-RUMP LENGTH (MM)	EXTERNAL EXAM (N/A)	FIXATIVE (B/A/)
		LOCATION	COMMENT	ABNORMALITY		SEVERITY	
617	L 1	M	4.93	A		N	A
	L 2	M	4.56	A		N	A
	L 3	F	4.94	A		N	A
	L 4	F	4.91	A		N	A
	L 5	F	4.60	A		N	A
	R 1	F	4.23	A		N	A
	R 2	M	4.87	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	R 3	F	4.57	A		N	A
	R 4	M	4.80	A		N	A
	R 5	F	4.64	A		N	A
618	L 1	M	4.50	A		N	A
	L 2	F	4.72	A		N	A
	L 3	F	4.49	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	L 4	M	4.91	A		N	A
	R 1	F	4.44	A		N	A
	R 2	M	4.73	A		N	A
	R 3	M	4.61	A		A	A
		FACE		HEMATOMA		P	
			BRUISE PRESENT ON LOWER JAW.				
	R 4	M	4.86	A		N	A
	R 5	F	4.32	A		N	A
	R 6	F	4.53	A		N	A
	R 7	M	4.52	A		N	A
	R 8	M	5.11	A		N	A
619	L 1	M	4.86	A		N	
	L 2	F	4.23	A		N	
	L 3	F	4.57	A		N	
	L 4	M	4.63	A		N	
	L 5	M	4.82	A		N	
	L 6	M	5.03	A		N	
	L 7	M	5.25	A		N	
	R 1	M	4.87	A		N	
	R 2	F	4.68	A		N	
	R 3	F	4.41	A		N	
621	L 1	F	3.85	A		N	
	L 2	F	3.97	A		N	
	L 3	M	4.53	A		N	
	L 4	M	4.69	A		N	
	L 5	F	4.18	A		N	
	L 6	F	3.95	A		N	
	L 7	M	4.37	A		N	
	L 8	M	4.52	A		N	
	L 9	F	4.26	A		N	
	R 1	F	3.47	A		N	
	R 2	M	3.36	A		N	
	R 3	F	4.11	A		N	
	R 4	F	4.26	A		N	

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE, P - PRESENT, A - ABSENT

INDIVIDUAL LITTER DATA - EXTERNAL FETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 88008712
START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 2000.000MG/KG REPORT DATE: 17-OCT-88

DAM	FETUS	SEX (M/F/U)	WEIGHT (GRAMS)	STATUS (A/D/E/L)	CROWN-RUMP LENGTH (MM)	EXTERNAL EXAM (N/A)	FIXATIVE (B/A/)
		LOCATION		ABNORMALITY		SEVERITY	
			COMMENT				
625	L 1	F	2.59	A		N	A
	L 2	M	2.85	A		N	A
	L 3	M	2.59	A		N	A
	L 4	F	2.60	A		N	A
	L 5	M	2.97	A		A	A
		CARPUS		ARTHROGRYPOSIS		P	
			ABNORMAL FLEXURE OF RIGHT WRIST.				
	R 1	F	2.12	A		A	A
		TAIL		EDEMA		P	
		TAIL		HEMORRHAGE		P	
		TAIL		SMALL		P	
		BODY AS A WHOLE, NOS		SMALL		P	
	R 2	F	2.48	A		A	A
		HEAD		HEMATOMA		P	
		BODY AS A WHOLE, NOS		SMALL		P	
			FETUS HAD BRUISE ON LEFT SIDE OF HEAD.				
	R 3	F	2.78	A		N	A
	R 4	M	2.71	A		N	A
	R 5	F	1.54	A		A	A
		BODY AS A WHOLE, NOS		SMALL		P	
	R 6	M	2.79	A		N	A
	R 7	M	2.77	A		N	A
626	L 1	M	1.94	A		A	A
		LEFT HINDLIMB		HEMATOMA		P	
		TAIL		CURLED		P	
			BRUISE OF LEFT HINDQUARTERS.				
	L 2	U	0.00	E		A	
	L 3	M	2.88	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	L 4	F	2.60	A		A	A
		TAIL		ABSENT OR MISSING		A	
		RIGHT HINDLIMB		HEMATOMA		P	
		RIGHT FORELIMB		HEMATOMA		P	
	L 5	F	2.85	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
		RIGHT FORELIMB		HEMATOMA		P	
	L 6	F	1.73	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
		CARPUS		ARTHROGRYPOSIS		P	
			ABNORMAL FLEXURE OF BOTH WRISTS.				
	R 1	F	1.45	A		A	A
		BODY AS A WHOLE, NOS		SMALL		P	
		HEAD		HEMATOMA		P	
			BRUISE ON TOP OF HEAD.				
	R 2	M	1.98	A		A	A
		RIGHT FORELIMB		HEMATOMA		P	
			BRUISE ON RIGHT FORELIMB AT ELBOW.				
	R 3	F	2.04	A		N	A
	R 4	M	3.06	A		N	A

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE, P - PRESENT, A - ABSENT

INDIVIDUAL LITTER DATA - EXTERNAL FETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 88008712
START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 2000.000MG/KG REPORT DATE: 17-OCT-88

DAM	FETUS	SEX (M/F/U)	WEIGHT (GRAMS)	STATUS (A/D/E/L)	CROWN-RUMP LENGTH (MM)	EXTERNAL EXAM (N/A)	FIXATIVE (B/A/)
		LOCATION		ABNORMALITY		SEVERITY	
			COMMENT				
626	R 5	F	1.63	A		A	A
		TAIL		ABSENT OR MISSING		A	
		HINDLIMB		ABNORMAL CURVATURE		P	
		UMBILICUS		HERNIA		P	
		BODY AS A WHOLE, NOS		SMALL		P	
		NECK		HEMATOMA		P	
			ABNORMAL FLEXURE OF BOTH HINDLIMBS.				
	R 6	M	2.54	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	R 7	U	0.00	E		A	
	R 8	U	0.00	E		A	
627	L 1	M	2.74	A		N	
	L 2	M	2.04	A		N	
	L 3	U	0.00	E		A	
	L 4	M	1.37	A		A	A
		HINDLIMB		ABNORMAL CURVATURE		P	
		TRUNK, NOS		SHORT TRUNK		P	
			LUMBAR AREA APPEARS REDUCED IN SIZE, ABNORMAL FLEXURE OF BOTH HINDLIMBS.				
	R 1	F	1.97	A		A	A
		LEFT HINDLIMB		HEMATOMA		P	
			HEMATOMA PRESENT ON ANKLE OF LEFT HINDLIMB.				
	R 2	M	2.68	A		A	A
		HINDLIMB		ENLARGED,NOS		P	
		HINDLIMB		ABNORMAL CURVATURE		P	
		TAIL		RUDIMENTARY STRUCTURE		P	
			HINDLIMBS WERE SWOLLEN WITH ABNORMAL FLEXURE.				
	R 3	U	0.00	L		A	
	R 4	M	2.67	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	R 5	M	1.93	A		A	A
		HINDLIMB		ABNORMAL CURVATURE		P	
		TAIL		RUDIMENTARY STRUCTURE		P	
		TRUNK, NOS		SHORT TRUNK		P	
			ABNORMAL FLEXURE OF HINDLIMBS; LUMBAR REGION APPEARS REDUCED IN SIZE.				
	R 6	U	0.00	L		A	A
	R 7	M	3.01	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
		TAIL		CYST		P	
			CYST-LIKE STRUCTURE WAS PRESENT AT THE TIP OF THE TAIL.				
	R 8	U	0.00	E		A	
	R 9	F	1.73	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	R 10	F	2.68	A		N	
628	L 1	F	2.95	A		N	A
	L 2	M	2.13	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
		BODY AS A WHOLE, NOS		SMALL		P	
	L 3	F	2.78	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
		TRUNK, NOS		SHORT TRUNK		P	
			LUMBAR AREA APPEARS REDUCED IN SIZE.				

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE, P - PRESENT, A - ABSENT

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 88008772
START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 2000.000MG/KG REPORT DATE: 17-OCT-88

DAM	FETUS	SEX (M/F/U)	WEIGHT (GRAMS)	STATUS (A/D/E/L)	CROWN-RUMP LENGTH (MM)	EXTERNAL EXAM (N/A)	FIXATIVE (B/A/)
628	L 4	F	2.36	A		A	A
		LOCATION		ABNORMALITY		SEVERITY	
		TAIL		EDEMA		P	
		TAIL		HEMORRHAGE		P	
	L 5	M	3.15	A		N	A
	L 6	F	2.75	A		N	A
	L 7	M	3.16	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	L 8	M	3.01	A		N	A
	R 1	M	1.65	A		A	A
		BODY AS A WHOLE, NOS		SMALL		P	
	R 2	M	3.09	A		N	A
	R 3	F	2.97	A		N	A
	R 4	F	2.87	A		N	A
	R 5	F	2.92	A		N	A
	R 6	M	3.07	A		N	A
630	L 1	U	0.00	E		A	
	L 2	M	4.20	A		N	A
	L 3	U	0.00	E		A	
	L 4	U	0.00	E		A	
	L 5	F	4.43	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
		HINDLIMB		ABNORMAL CURVATURE		P	
			ABNORMAL FLEXURE OF HINDLIMBS.				
	L 6	F	2.85	A		N	A
	L 7	F	4.49	A		N	A
	L 8	M	5.22	A		N	A
	R 1	U	0.00	E		A	
	R 2	M	3.12	A		N	A
	R 3	M	4.42	A		N	A
	R 4	M	3.89	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	R 5	M	4.53	A		A	A
		TAIL		RUDIMENTARY STRUCTURE		P	
	R 6	F	3.86	A		N	A
	R 7	M	4.05	A		A	A
		TAIL		ABSENT OR MISSING		A	
631	L 1	U	0.00	L		A	
	L 2	U	0.00	E		A	
	L 3	M	3.43	A		A	A
		TAIL		ABSENT OR MISSING		A	
		LEFT HINDLIMB		ABNORMAL CURVATURE		P	
		SCAPULAR REGION		HEMATOMA		P	
			ABNORMAL FLEXURE OF THE HINDLIMBS.				
	L 4	M	2.78	A		A	A
		TAIL		ABSENT OR MISSING		A	
		HINDLIMB		ABNORMAL CURVATURE		P	
			ABNORMAL FLEXURE OF THE HINDLIMBS.				
	L 5	U	0.00	L		A	
	L 6	U	0.00	L		A	

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE, P - PRESENT, A - ABSENT

INDIVIDUAL LITTER DATA - EXTERNAL FETAL ALTERATIONS

HAEL NO. 88-0087 ACCESSION NO. 906659 EXPERIMENT NO. 88008712
START DATE: 06-SEP-88 ROUTE: GAVAGE DOSE: 2000.000MG/KG REPORT DATE: 17-OCT-88

DAM	FETUS	SEX (M/F/U)	WEIGHT (GRAMS)	STATUS (A/D/E/L)	CROWN-RUMP LENGTH (MM)	EXTERNAL EXAM (N/A)	FIXATIVE (B/A/)
631	L 7	F	2.99	A		A	A
		LOCATION		ABNORMALITY		SEVERITY	
		TAIL		ABSENT OR MISSING		A	
		HINDLIMB		ABNORMAL CURVATURE		P	
		UMBILICUS		HERNIA		P	
		COMMENT: ABNORMAL FLEXURE OF HINDLIMBS.					
	L 8	M	2.92	A		A	A
		TAIL		ABSENT OR MISSING		A	
		LEFT HINDLIMB		ABNORMAL CURVATURE		P	
		UMBILICUS		HERNIA		P	
		COMMENT: ABNORMAL FLEXURE OF THE LEFT HINDLIMB.					
	R 1	F	2.77	A		A	A
		TAIL		ABSENT OR MISSING		A	
		LEFT HINDLIMB		ABNORMAL CURVATURE		P	
		COMMENT: ABNORMAL FLEXURE OF LEFT HINDLIMB.					
	R 2	F	2.67	A		A	A
		TAIL		ABSENT OR MISSING		A	
		LEFT HINDLIMB		ABNORMAL CURVATURE		P	
		UMBILICUS		HERNIA		P	
		TRUNK, NOS		SHORT TRUNK		P	
		COMMENT: ABNORMAL FLEXURE OF LEFT HINDLIMB; LUMBAR AREA APPEARS REDUCED IN SIZE.					
	R 3	U	0.00	E		A	
	R 4	U	0.00	L		A	
	R 5	M	3.11	A		A	A
		TAIL		ABSENT OR MISSING		A	
		LEFT HINDLIMB		ABNORMAL CURVATURE		P	
		COMMENT: ABNORMAL FLEXURE OF LEFT HINDLIMB.					
	R 6	F	2.73	A		A	A
		TAIL		ABSENT OR MISSING		A	
		HINDLIMB		ABNORMAL CURVATURE		P	
		CARPUS		ARTHROGRYPOSIS		P	
		TRUNK, NOS		SHORT TRUNK		P	
		COMMENT: ABNORMAL FLEXURE OF THE HINDLIMBS AND WRISTS; LUMBAR REGION APPEARS REDUCED.					

KEY: N - EXAMINED AND NORMAL, 1 - MINIMAL, 2 - MINOR, 3 - MODERATE, 4 - SEVERE, P - PRESENT, A - ABSENT

CHEMICALS QUALITY SERVICES DIVISION REPORT

ANALYSIS REQUESTED BY: Toxicology DATE REQUESTED: 6/28/88

DATE ANALYZED: 8/18/88

CQSD JOB FILE NUMBER: EE8H021

REQUEST FOR ANALYSIS: 084797

TITLE: Initial Purity of 88-0087

AUTHOR: N. Porter DATE REPORTED: 8/22/88

FOR ADDITIONAL INFORMATION OR WORK CONTACT: K. Robillard, N. Porter

SAMPLE IDENTIFICATION: Received one sample labelled HAEL # 88-0087, Acc. # 906659

REPORT:

The sample was submitted for initial purity, and was analyzed using the following chromatographic conditions:

30m, DB-5 wide bore 0.25um J+W column
carrier: Helium at 8 psi
50°C (2 min.) - 200°C at 10°/min. (hold at 200°C for 1min)
split injection, sample load approx. 2.0 uL
electron ionization
inj. temp. @ 250°C
det. temp. @ 250°C

The sample was diluted in ethyl acetate and analyzed. The results were as follows:

Area % 88-0087
99.9

n = 3
SD = 0

Signed N. Porter
BLR

CHEMICALS QUALITY SERVICES DIVISION REPORT

ANALYSIS REQUESTED BY: Toxicology **DATE REQUESTED:** 7/15/88

STUDY TYPE: 28 Day Gavage

DATE ANALYZED: 7/29/88

CQSD JOB FILE NUMBER: EE8H021 Req # 064797

STUDY DIRECTOR: Walt Krasavage

TITLE: Structure Confirmation of 88-0087

AUTHOR: N. Porter **DATE REPORTED:** 8/1/88

FOR ADDITIONAL INFORMATION OR WORK CONTACT: K. Burgess, N. Porter

SAMPLE IDENTIFICATION: Received one sample labelled HAEL # 88-0087, Acc. # 906859

REPORT:

The sample was submitted for GC/MS characterization, and was analyzed using the following chromatographic conditions:

30m, DB-5 wide bore 1.0um J+W column
carrier: Helium at 10 psi
50°C (2 min.) - 220°C at 10°/min. (hold at 220°C for 2min)
split injection, sample load approx. 1.0 uL
electron ionization

The sample was diluted in acetone (1080 mg/l conc.) and analyzed. The spectra of the two peaks which elute at 12.9 min. and 13.0 min. are both consistent with the structure of HAEL # 88-0087.

Signed N. Porter
S Spinardy

PROTOCOL

Developmental Toxicity Probe Study with 2-Ethyl-1,3-Hexanediol in the Rat

TESTING FACILITY: Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Kodak Park (Bldg. 320)
1100 Ridgeway Avenue
Rochester, NY 14652-3615

SPONSOR: Eastman Chemicals Division
Eastman Kodak Company

DATE: September 6, 1988

A Developmental Toxicity Probe Study with 2-Ethyl-1,3-Hexanediol in the Rat

PURPOSE:

The purpose of this study is to determine the toxicity of the test material in pregnant rats when administered on the 6th through 15th days of gestation. The data from this study may be used to establish appropriate dose levels for a developmental toxicity study of this material in the rat.

TESTING FACILITY:

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Kodak Park (Bldg. 320)
1100 Ridgeway Avenue
Rochester, NY 14652-3615

SPONSOR:

Eastman Kodak Company

PROPOSED STUDY DATES:

Receipt of test animals -	September 7, 1988
Acclimation period -	None
Treatment period -	September 12 - 21, 1988
Cesarian Sections -	September 26, 1988
Final Report -	April 1,1989

REGULATORY COMPLIANCE:

The study will be conducted in accordance with the Environmental Protection Agency Good Laboratory Standards 40 CFR Part 792, November 29, 1983 and Good Laboratory Practices for Nonclinical Laboratory Studies (GLP's) as promulgated by the Food and Drug Administration, 21 CFR Part 58, December 22, 1978 and revised September 4, 1987. The study will also be conducted in accordance with OECD Principles of Good Laboratory Practice. The study will be subjected to the quality assurance auditing procedures as set forth by the Quality Assurance Units of the Health and Environment Laboratories and the Chemical Quality Services Division, Eastman Kodak Company. A quality assurance statement will be included in the final report. A copy of the final report, raw data sheets, tissues, paraffin blocks, slides, and other non-perishable specimens will be stored in the HAEL Archives for a period of ten years.

TEST ARTICLE CHARACTERIZATION:

General Description

Test Article Name:	2-Ethyl-1,3-hexanediol
Synonyms:	EHD
CAS Number:	94-96-2
EK Accession Number:	906659
HAEL Number:	88-0087
SRID Number:	TX-1694-65
Study Number:	880087T2
Source Of Test Material:	Texas Eastman Company

Physicochemical Properties

Molecular formula -	$C_8H_{18}O_2$
Molecular weight -	146.23
Boiling point -	244 °C
Melting point -	- 40 °C
Specific gravity -	0.935
Vapor pressure -	10 mm Hg/29 °C
Flash point -	265 °C (closed cup)
Appearance -	clear, viscous liquid

Test Article Purity and Stability

Gas chromatographic analysis will be performed by the Kodak Park Chemical Quality Services Division (CQSD) to determine the purity, structural confirmation, and stability of the test article. Solutions of the test material in corn oil will be made prior to the start of the study to determine the stability of the test compound in the carrier.

Safety Precautions

No special safety precautions are necessary when handling the test material. Standard industrial hygiene practices will be followed. A Material Safety Data Sheet is attached.

Storage Conditions

The test article will be stored at room temperature in a chemical room.

TEST SYSTEM:

Animals

Species	Rat
Strain	CRL:(CD®(SD)BR)

TEST SYSTEM (CON'T):

Supplier	Charles River Laboratories Wilmington, MA
Number	40
Sex and Age	Timed-Pregnant Females, sexually mature
Acclimation Period	None. The animals will be received on Day 1 of gestation and immediately assigned to the study. Treatment will begin on Day 6 of gestation.

The animals will be examined by a veterinarian on arrival and only normal appearing animals will be accepted into the study.

The rat was chosen as the test species because it is the primary rodent species recommended by the U.S. Food and Drug Administration for use in developmental toxicity studies. There is much historical control data on the rat in the literature and this species has been shown to be sensitive to the effects of known developmental toxicants.

Husbandry	Housing -individually, in stainless steel suspended cages with wire mesh bottoms. Feed - Agway® Prolab™ Animal Diet (RHM 3200) certified rodent diet. Water - Municipal Tap Water (Monroe County Water Authority) will be available *ad libitum*.

No known contaminants are expected to be present in the feed or the water that would interfere with the conduct of the study.

Environmental Conditions	Temperature and relative humidity will be controlled at target levels of 72 $\pm 3^{o}$ F and 30-70%, respectively and will be recorded at least once a day. A photocycle of 12 hours light/dark (6 am - 6 pm) will be maintained.

Identification

Each rat will be identified by a metal ear tag containing a unique number. In addition, each female will be assigned a study number which will be cross referenced to its ear tag number. Individual female cages will be color coded according to group and have a card attached which will contain the animal's ear tag number, the animal's study number, the experiment number, and the dose group.

TEST SYSTEM (CON'T):

Mating

Timed-pregnant females will be ordered from the supplier to arrive on Day 1 of gestation.

Group Assignment

The study will consist of four treated groups and a control group of eight animals each. Inseminated females will be assigned to the groups using a computer-generated randomization scheme so as to most nearly equalize the group mean body weights.

STUDY DESIGN:

Treatment Groups and Test Article Administration

The treated groups of 8 inseminated females each will be given 500, 1000, 2000, or 4000 mg/kg EHD in corn oil by gavage on the 6th through the 15th days of gestation. The dose levels were chosen on the basis of data from the first two weeks of a four-week toxicity study and LD_{50} studies. A control group of eight inseminated females will be treated similarily to the test animals except they will be given only corn oil in a volume equivalent to the largest volume given a treated animal. The body weights on Day 6 of gestation will be used to calculate the dose volume. Gavage was chosen as the route of administration because it is a route commonly used in toxicity testing.

Solutions will be prepared as frequently as indicated by the stability data and samples of these preparations will be analyzed for concentration by CQSD, Kodak Park.

IN-LIFE EVALUATIONS:

Maternal Observations:

Clinical Signs

The females will be observed in their cages for clinical signs of toxicity twice daily (except week-ends). On treatment days (Days 6-15 of gestation), they will be observed in the morning, post-dose, and in the afternoon. A detailed examination will be performed on each female when handled for dosing or to measure body weight, which will include, but not be limited to, examination of the hair, skin, eyes, motor activity, feces, and urine.

IN-LIFE EVALUATIONS (CON'T):

Maternal Observations (Con't):

Body Weights

Individual body weights will be recorded for each female on gestation Days 1, 6, 9, 12, 16, and 19. Body weight gain will be calculated for Days 1-6, 6-9, 9-12, 12-16, 16-19, and 6-16 of gestation.

Feed Consumption

Feed containers will be weighed on Days 1, 6, 9, 12, 16, and 19 of gestation and individual feed intake will be calculated for Days 1-6, 6-9, 9-12, 12-16, 16-19, and 6-16 of gestation.

POSTMORTEM EVALUATIONS:

Maternal

Females that die spontaneously or are killed because they are moribund, and dams showing signs of abortion will be necropsied with particular attention given to the uterine contents. Tissues may be collected at the discretion of the pathologist if further analyses would help to determine the cause of death, illness, or abortion. Fetal implantion sites, if present, will be evaluated to distinguish between normally developing fetuses and resorptions.

All dams that survive will be fasted overnight and anesthetized on Day 20 of gestation by CO_2 inhalation. The abdominal viscera will be exposed by a mid-line incision through the abdominal wall and the animal will be exsanguinated by severing the inferior vena cava (SOP No. TC 360). The terminal body weight will be recorded. The uterus with ovaries attached will be removed and gravid uteri with ovaries will be weighed. The ovaries will be dissected free, trimmed of extraneous tissue and the corpora lutea of pregnancy will be counted and recorded (SOP No. TC 370). The thoracic cavity will also be opened and a necropsy examination of the thoracic and abdominal viscera will be conducted in situ on each female. The liver and kidneys will be removed, trimmed of extraneous tissue, and weighed for organ/body weight comparisons. Samples of these organs will be preserved in 10% neutral buffered formalin. Histologic examination of these tissues may be performed at the discretion of the study director or the pathologist.

POST MORTEM EVALUATIONS (CON'T):

Fetal

After the gravid uterus has been weighed, the uterine horns will be opened and the implantation sites will be counted and categorized as: live fetus, dead fetus (no visible degeneration), late resorption (partially or fully formed fetus undergoing degeneration) or early resorption (implantation but no conceptus or placenta present). The uteri of apparently nonpregnant females will be stained with a 10% solution of sodium sulfide and examined for the presence of implantation sites (Kopf et al., 1964). When stained foci are found the female will be considered pregnant for the purpose of calculating the pregnancy index, but these data will not be used in the calculation of other implantation data.

Viable fetuses will be removed from the uterus beginning at each ovary and proceeding to the vagina. Each fetus will be blotted dry on absorbent material, examined for external abnormalities (SOP No. TC 490), sexed, and weighed. Only fetuses with abnormalities will be saved in 10% neutral buffered formalin.

Late resorptions will be examined for external malformations and only those with malformations will be save in 10% neutral buffered formalin for histologic examination, if deemed necessary by the study director or pathologist.

STATISTICAL ANALYSES:

If group sizes warrant, statistical analyses will be used to compare the treated groups to the control group.

Incidence data will be analyzed using Chi Square tables ($p \leq 0.05$). Continuous data will be analyzed using a one-way analysis of variance ($p \leq 0.05$). Bartlett's Test will be performed to test for equal variances ($p \leq 0.01$) and Freeman Tukey transformations will be performed where appropriate; though the data will be presented untransformed. All analyses will be two-tailed tests.

FINAL REPORT:

The final report will include the following:

Abstract
Introduction
Materials and Methods

Results to include:

Maternal Mortality
Mean Maternal Body Weight and Body Weight Change
Mean Maternal Feed Consumption For Each Period Measured
Mean Organ Weight (Absolute and Relative to Bdy. Wt.)
Number of Females Pregnant and Pregnancy Rate
Mean Number of Corpora Lutea per Dam
Mean Number of Implantations, Live Fetuses, Dead Fetuses, and Resorptions per Litter
Fetal Sex Ratio
Mean Fetal Body Weight (by sex and as sexes combined)
Percent Pre- and Post-Implantation Losses
Incidences of External Malformations/Variations per Group
Incidences of Litters With At Least One Fetus With A Malformation or Variation
Summary Statement of Maternal Clinical Signs
Summary Statement of Gross Pathologic Examinations
Discussion and Conclusion

Appendices to the final report will include:

Individual Body Weight and Body Weight Gain Data
Individual Feed Consumption
Individual Female Organ and Uterine Weight Data
Individual Female Reproductive Data, i.e., Number of Corpora Lutea, Implantations, Resorptions, Live and Dead Fetuses,and Fetal Sex and Body Weight Data
Individual Female Clinical Sign Data
Individual Litter External Examination Results
Analytical Results of Compound and Dose Solutions (diet) Analyses
List of Participating Personnel
Quality Assurance Statement
Copy of the Study Protocol and Amendments

STUDY PERSONNEL:

Walter J. Krasavage, M.S.	Study Director
Lisa G. Bernard, A.A.S.	Study Technican
Gordon J. Hankinson, D.V.M., M.S.	Laboratory Animal Veterinarian
Milan S. Vlaovic, D.V.M., Ph.D.	Pathologist
Kenneth A. Robillard, Ph.D.	Analytical Chemist
M. Susan James, A.A.S.	Quality Assurance

Additional personnel may participate in this study as needed. Their names will be documented in the raw data.

PROTOCOL AMENDMENTS:

Changes to the protocol may be necessary as the study progresses. When a change is made it will be documented by issuing a written, signed protocol amendment. The original amendment will be attached to the protocol and copies sent to the Quality Assurance Unit and the sponsor.

REFERENCES:

Kopf, R., Lorenz, D., and Salewski, E. "Procedure for staining implantation sites of fresh rat uteri." Naunyn-Schmiedebergs Arch. Exp. Path. u. Pharmak. 247:121-135, 1964.

PROTOCOL PREPARED BY:

Walter J. Krasavage, M.S. Manager,
Reproductive/Developmental Toxicology
Toxicological Sciences Laboratory, HAEL

Date: 9/7/88

PROTOCOL REVIEWED AND ACCEPTED BY:

Douglas C. Topping, Ph.D.,
Unit Director, Mammalian Toxicology
Toxicological Sciences Laboratory, HAEL

Date: 9/6/88

M.S. James, A.A.S
Coordinator
Quality Assurance Unit, HAEL

Date: 9/6/88

John L. O'Donoghue, V.M.D., Ph.D.
Director, Toxicological Sciences
Laboratory, HAEL

Date: 9/6/88

MATERIAL SAFETY DATA SHEET

EASTMAN KODAK COMPANY
343 State Street
Rochester, New York 14650

For Emergency Health, Safety, and Environmental Information, call 716-722-5151
For all other purposes, call 800-225-5352, in New York State call 716-458-4014

Date of Preparation: 07/20/87 Kodak Accession Number: 906659

SECTION I. IDENTIFICATION

- Product Name: 2-Ethyl-1,3-hexanediol
- Synonym(s): Octylene Glycol
- Formula: C8 H18 O2
- CAT No(s): 118 7723; 118 7749; 118 7764
- Chem. No(s): 06659
- Kodak's Internal Hazard Rating Codes: R: 1 S: 2 F: 1 C: 0

SECTION II. PRODUCT AND COMPONENT HAZARD DATA

COMPONENT(S):	Percent	ACGIH TLV(R)	CAS Reg. No.
2-Ethyl-1,3-hexanediol	ca. 100	---	94-96-2

SECTION III. PHYSICAL DATA

- Appearance: Colorless liquid
- Boiling Point: 244 C (471 F)
- Vapor Pressure: Negligible
- Evaporation Rate (n-butyl acetate = 1): Negligible
- Volatile Fraction by Weight: Negligible
- Specific Gravity (Water = 1): 0.94
- Solubility in Water (by Weight): Moderate

SECTION IV. FIRE AND EXPLOSION HAZARD DATA

- Flash Point: 127 C (261 F) Open cup
- Extinguishing Media: Water spray; Dry chemical; Carbon dioxide; "Alcoho" foam
- Special Fire Fighting Procedures: Wear self-contained breathing apparatus and protective clothing.
- Unusual Fire and Explosion Hazards: None

SECTION V. REACTIVITY DATA

- Stability: Stable
- Incompatibility: Strong oxidizers
- Hazardous Decomposition Products: Combustion will produce carbon dioxide and probably carbon monoxide.
- Hazardous Polymerization: Will not occur.

SECTION VI. TOXICITY AND HEALTH HAZARD DATA

A. EXPOSURE LIMITS: Not established.

B. EXPOSURE EFFECTS: Overexposure to high concentrations may result in central nervous system depression.
Inhalation: Low hazard for usual industrial handling.
Skin: Causes irritation. May be absorbed through the skin.
Eye: Causes irritation.

C. FIRST AID:
Inhalation: Remove to fresh air. Treat symptomatically. If symptoms are present get medical attention.
Skin: Immediately flush skin with plenty of water for at least 15 minutes. Get medical attention if symptoms are present after washing.
Eye: Immediately flush eyes with plenty of water for at least 15 minutes and get medical attention.

SECTION VII. VENTILATION AND PERSONAL PROTECTION

A. VENTILATION AND RESPIRATORY PROTECTION:
Good ventilation should be sufficient. Supplementary ventilation or respiratory protection may be needed in special circumstances.

B. SKIN AND EYE PROTECTION:
Protective gloves and clothing should be worn. Safety glasses, goggles, or a face shield should be worn.

SECTION VIII. SPECIAL STORAGE AND HANDLING PRECAUTIONS

Keep from contact with oxidizing materials.

SECTION IX. SPILL, LEAK, AND DISPOSAL PROCEDURES

Absorb material in vermiculite or other suitable absorbent and place in impervious container. Dispose by incineration or contract with licensed chemical waste disposal agency. Discharge, treatment, or disposal may be subject to federal, state or local laws.

For transportation information regarding this product, please phone the Eastman Kodak Distribution Center nearest you: Rochester, NY (716) 254-1300; Oak Brook, IL (312) 654-5300; Chamblee, GA (404) 455-0123; Dallas, TX (214) 241-1611; Whittier, CA (213) 945-1255; Honolulu, HI (808) 833-1661.

The information contained herein is furnished without warranty of any kind. Users should consider these data only as a supplement to other information gathered by them and must make independent determinations of the suitability and completeness of information from all sources to assure proper use and disposal of these materials and the safety and health of employees and customers.

Accession Number 606659
Study Number 880087T2

Septmber 13, 1988

To: File
From: Walter Krasavage
Subject: Protocol Amendment

Protocol Amendment:

The female body weight range was changed from 225.0 ± 50.0g to 200.0 ± 50.0g.

Reason:

The body weight range of animals received was lower than anticipated.

Walter J. Krasavage, M.S.
Study Director

9-13-88
Date

252956U
TX-89-46

FOUR WEEK ORAL TOXICITY STUDY OF 2-ETHYL-1,3-HEXANEDIOL IN THE RAT

HAEL NO. 88-0087 ACC. NO. 906659

BY LISA G. BERNARD, A.A.S.

TOXICOLOGICAL SCIENCES LABORATORY
HEALTH AND ENVIRONMENT LABORATORIES
EASTMAN KODAK COMPANY
ROCHESTER, NY 14652-3615

DATE OF STUDY COMPLETION MAY 19, 1989

252956U
TX-89-46

FOUR WEEK ORAL TOXICITY STUDY OF 2-ETHYL-1,3-HEXANEDIOL IN THE RAT

HAEL NO. 88-0087 ACC. NO. 906659

Abstract

Twenty-one daily doses of 2-ethyl-1,3-hexanediol (EHD) was administered by gavage in corn oil to groups of five male and five female rats at dose levels of 0, 100, 300, or 1000 mg/kg/day, five days per week, over a 29 day period. No mortality or abnormal clinical signs were observed during the study. Though not statistically significant, mean body weights were slightly reduced for the 300 and 1000 mg/kg males and slightly higher for the 100 mg/kg males at the end of the treatment period when compared to controls. The 100 and 1000 mg/kg males and the 1000 mg/kg females consumed slightly more feed compared to the controls. Hematologic changes consisted of higher white blood cell counts for both sexes at all dose levels, but the differences were statistically different from the controls only for females at the 300 and 1000 mg/kg dose level. Platelet counts were reduced only for the 1000 mg/kg females. No other differences from controls were observed for other hematologic parameters. No treatment-related changes in clinical chemistry parameters were observed for either sex at any dose level. Organ weight changes were restricted to increased absolute and relative liver weights for the 1000 mg/kg females and increased relative liver and spleen weights for the 1000 mg/kg males. Since liver enzyme tests were normal and no histopathology was seen in either the liver or splenic tissue, the changes in organ weights are probably adaptive in nature rather than due to a direct toxic effect. No treatment-related organ weight changes were observed for the 100 and 300 mg/kg males and females. No treatment-related gross or histopathologic lesions were seen in any of the tissues examined. The no-effect-level was 100 mg/kg/day, based upon a lack of treatment-related changes at this level.

FOUR WEEK ORAL TOXICITY STUDY OF 2-ETHYL-1,3-HEXANEDIOL IN THE RAT

PURPOSE: The purpose of this study was to evaluate the subacute effects of 2-ethyl-1,3-hexanediol when given to rats orally for four weeks.

TESTING FACILITY:
Toxicological Sciences Laboratory
Health and Environment Laboratories (HAEL)
B-320 Kodak Park
Eastman Kodak Company
Rochester, NY 14652-3615

TEST ARTICLE CHARACTERIZATION:
Chemical Name: 2-Ethyl-1,3-hexanediol (EHD)
HAEL No.: 88-0087
EK ACC. No.: 906659
CAS No.: 94-96-2
SRID OR Lot No.: TX-1694-65
EXPERIMENT No.: 880087G1

PURITY, STABILITY, and CONCENTRATION ANALYSES: The test material was analyzed for structure confirmation using gas chromatography/mass spectrosopy. The mass spectrum of the test sample was consistent with the structure of 2-ethyl-1,3-hexanediol.

The purity of EHD was determined to be 99.9±0.0% (mean±SD) at the start of the study when analyzed by gas chromatography with flame ionization detection (GC/FID).

Stability of EHD in corn oil, at concentrations of approximately 2 and 40%, was determined by GC/FID on 0, 3, 7, and 9 days after preparation of mixtures. Mean concentrations of the test article were 2.3 and 44% prior to storage and 2.4 and 43% after 9 days of storage, indicating the material was stable at these concentrations for at least 9 days.

The concentration of EHD in each batch of test solution was determined prior to use by GC/FID analysis. The mean concentrations of the test article were (mean ± SD) 4.3±0.3%, 12.9±0.7%, and 42.0±1.9% compared to target concentrations of 4.0, 12.0, and 40.0%.

All analysis were performed by the Chemical Quality Services Division, KP.

TEST PROCEDURE: This study was conducted by methods comparable to OECD GUIDELINES for TESTING of CHEMICALS TG-407, Repeated Dose Oral Toxicity - Rodent: 28-day or 14-day study, and Annex V B.7.

TEST SUBSTANCE EXPOSURE: Rats were given 100, 300, or 1000 mg/kg of the test material in corn oil for 21 doses over 29 days. Doses were given five days per week including holidays. Controls received daily doses of corn oil equal in volume to that of the highest test group.

ANIMALS: Five male and five female rats (CD®(SD)BR) from Charles River Laboratories, Kingston, NY, were randomly assigned to each test group. Animals were isolated for five days prior to testing. At the start of the study, rats were approximately 6 weeks old (males and females) and weighed (mean±SD) 155±9 g (males) and 156±5 g (females). Rats were chosen for this study because they are a common representative species for toxicity studies.

HOUSING: Rats were housed in groups of five segregated by sex. The study was conducted in the vivarium area of Building 320. The study room was maintained at 70-73 °F and 48-58% relative humidity. A photoperiod of 12 hours from 6 a.m. to 6 p.m. was maintained. No other study was housed in the same room as this study. Cages and racks were washed once a week. Absorbent paper under the cages was changed daily.

FEED AND WATER: Agway® Prolab™ Animal Diet (RMH 3200), certified ground chow was fed *ad libitum*. Feed containers were cleaned weekly. Feed containers were refilled at least once a week. Water was supplied *ad libitum* through an automatic watering system. The source of the water was the Monroe County Water Authority. No known contaminants in feed or water were expected which would interfere with the outcome of this study.

IDENTIFICATION: All rats were identified by a uniquely numbered metal ear tag and by ear punch.

RANDOMIZATION: All culling and randomization were done by computer-generated lists using the Automated Animal Toxicology System.

BODY AND FEED WEIGHT DETERMINATIONS: Body weights were collected on Days 0, 4, 8, 14, 21, and 28. Feed consumption was determined on Days 4, 8, 11, 14, 18, 21, 25, and 28.

CLINICAL OBSERVATIONS: Every workday morning each rat was removed from its cage and examined by a trained technician. Immediately after dosing and again in the afternoon cageside observations were conducted. Cageside observations included, but were not limited to, examination of the hair, skin, eyes, motor activity, feces, and urine.

HEMATOLOGY AND CLINICAL CHEMISTRY EXAMINATIONS: At the time of necropsy, blood was collected from the posterior vena cava while the rats were under CO_2 anesthesia. All assays were conducted by the Animal Clinical Analysis Group, HAEL. Hematology tests included: hemoglobin concentration, hematocrit, red blood cell count, white blood cell count, differential white blood cell count, platelet count, red blood cell indices, prothrombin time, and examination of the blood smears for cellular morphology. Clinical chemistry tests included: aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase, alkaline phosphatase, total bilirubin, total protein, albumin, albumin/globulin ratio, creatinine, urea nitrogen, and glucose.

NECROPSY: Rats were fasted overnight, anesthetized with CO_2, and exsanguinated by severing the posterior vena cava after collecting blood for analysis. Necropsies were conducted according to pathology SOP No. TP 180. The liver, kidneys, adrenal glands, testes, spleen, and thymus were weighed. Paired organs were weighed together. Organ/body weight ratios were calculated. The following organs were fixed in 10% buffered formalin: trachea, lungs, heart, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, liver, salivary glands, kidneys, urinary bladder, pituitary gland, adrenal glands, thyroid glands, parathyroid glands, thymus, spleen, mesenteric lymph nodes, bone marrow (femoral), brain, testes, epididymides, male accessory sex glands, ovaries, vagina, uterus, Fallopian tubes, and gross lesions. All tissues were examined microscopically from the control and high-dose groups and gross lesions were examined from other groups.

STATISTICAL PROCEDURES: Mean values were calculated for body weight, feed consumption, organ weights, hematology, and clinical chemistries. All mean data, except feed consumption, were evaluated using the following computer-generated statistical tests: Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Duncan's multiple range test ($p \leq 0.05$) to indicate statistical significance. Feed consumption was not analyzed statistically because the animals were group housed.

DATA STORAGE: The final report, tissues, paraffin blocks, slides, data sheets, and all non-perishable raw data were stored in the HAEL archives.

GLP STATEMENT: This study was conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies as promulgated by the Food and Drug Administration, 21 CFR Part 58, December 22, 1978 amended September 4, 1987; Environmental Protection Agency Good Laboratory Practice Standard 40 CFR Part 792, November 29, 1983; and Annex 2 of the OECD guidelines for Testing of Chemicals (C(81)30 (Final)) as required by Council Directive 87/18/EEC of December 18, 1986.

PROJECT PARTICIPANTS:

Study Director	W. J. Krasavage, M.S.
Study Technician	L. G. Bernard, A.A.S.
Necropsy Pathologist	M. S. Vlaovic, D.V.M., Ph.D.
Histopathologist	M. S. Vlaovic, D.V.M., Ph.D.
Laboratory Animal Medicine	G. J. Hankinson, D.V.M., M.S.
Hematologist/Clinical Chemist	R. E. Emmons, B.S.
Analytical Chemist	K. A. Robillard, Ph.D.
Report Author	L. G. Bernard, A.A.S.

DATE OF STUDY INITIATION: August 18, 1988

EXPERIMENT START DATE: August 29, 1988

PROTOCOL AND SOP DEVIATIONS: Animals were weighed on Day 8 instead of Day 7 because of a holiday. Dosing volumes calculated on Day 4 were used for dosing on both Day 4 and 7. Dosing volumes were recalculated on Day 8. These protocol deviations had no effect on the outcome of the study.

RESULTS

MORTALITY: No mortality occurred during the study.

CLINICAL SIGNS: No abnormal clinical signs were observed at any dose level during this study.

BODY WEIGHT AND FEED CONSUMPTION: Mean body weights were comparable to controls for all female EHD-treatment levels. No statistically significant body weight changes were observed in males at any dose level. However, the mean body weights for the 300 and 1000 mg/kg males, were slightly lower than controls on Days 21 and 28 of the study; the mean body weight gain for these animals over the course of the study was 9 and 6% less than controls, respectively. Mean body weight of the 100 mg/kg males was slightly higher than controls, and their body weight gain was 8% more than controls over the course of the study.

Mean feed consumption was slightly higher than the feed consumption of the controls for the 100 and 1000 mg/kg males and for the 1000 mg/kg females. Feed consumption by the 100 and 300 mg/kg females and the 300 mg/kg males was comparable to that of the controls.

HEMATOLOGY: The mean white blood cell (WBC) counts were higher than the control mean for the EHD-treated males and females at all levels. For females, this change was dose-dependent, reaching statistical significance at the 300 and 1000 mg/kg dose levels. For males, a few animals from each dose level had high WBC counts, but the mean values were not statistically different from the control mean. Except for a statistically significantly lower platelet count for the 1000 mg/kg female dose group, all other hematologic determinations for both sexes were comparable to the controls.

CLINICAL CHEMISTRY: All mean serum clinical chemistry values for all dose levels of EHD-treated males and females were comparable to their respective controls.

ORGAN WEIGHTS: Mean terminal body weights of EHD-treated males and females were comparable with controls.

Mean absolute and relative (to body weight) liver weights for the 1000 mg/kg female group and the relative liver weights for the 1000 mg/kg male group were statistically significantly higher than for the control group. Mean absolute liver weights for the 1000 mg/kg males were 15% higher than controls, but this difference was not statistically significant, while the mean absolute liver weight for the 1000 mg/kg females ($P \leq 0.05$) was 16% greater than the control group. The mean relative spleen weight was statistically significantly higher than control group for the 1000 mg/kg males; mean absolute spleen weights were also somewhat higher than the control group but the difference was not statistically significant. No other significant alterations in organ weight were observed at this dose level.

At the 100 and 300 mg/kg dose levels, no compound-related organ weight changes were observed for either sex. A slight statistically significant lower mean relative kidney weight for the 100 mg/kg males was not dose-related and was not considered biologically significant.

PATHOLOGY: No compound-related lesions were identified at necropsy or on histological examination of tissues.

DISCUSSION AND INTERPRETATION

Twenty-one doses as high as 1000 mg/kg of EHD over a 29 day period did not produce mortality, adverse clinical signs, statistically significant differences in mean body weight or clinical chemistry determinations, or adverse morphological changes in organs or tissues in male or female rats.

The mean body weights and the mean body weight changes for the 300 and 1000 mg/kg males was slightly less than the control group, though not statistically different, from the controls at the end of the treatment period.

The 100 and 1000 mg/kg male rats and the 1000 mg/kg female rats ate slightly more feed than the control group and the 300 mg/kg animals.

White blood cell counts for the EHD-treated groups were higher than the control groups for both sexes. Among all EHD-dose levels, the greatest differences were seen for the 300 and 1000 mg/kg females. While the WBC counts were higher than the control group the differential WBC counts were comparable to the controls and cellular morphology was normal. Reduced platelet counts at the 1000 mg/kg dose level in females were the only other hematologic difference seen in the blood profile. The biological significance of the hematologic changes is uncertain, since platelet counts and WBC counts are commonly variable and can be confounded by group housing conditions.

Liver and spleen weight changes at the 1000 mg/kg dose level may have been adaptive changes rather than direct toxic effects. Serum enzymes related to the liver were normal and histopathologic examination of the tissue revealed no morphological lesions. The significance of the higher spleen weights is uncertain since there were no major effects on hematologic parameters and histologic examination of splenic tissue revealed no pathology. A significantly lower relative kidney weight seen in the low dose level male group. This was due both to the slightly higher mean terminal body weight, and slightly lower mean absolute kidney weights seen in this dose group. Since no effect on absolute or relative kidney weight was seen with the 300 or 1000 mg/kg dose groups, this finding was considered spurious and not related to treatment with the test article.

EHD did not produce significant organ toxicity in male or females rats. A site of toxic action was not identified. Based upon a lack of treatment-related changes at the 100 mg/kg dose level, the no-effect-level was considered to be 100 mg/kg/day.

TABLES: Tables, including means and individual data points for body weight, feed consumption, hematology, clinical chemistries, and organ weights, and reports of individual contributors are included in the appendix.

SIGNATURE PAGE

REPORT AUTHOR	DATE 5-19-89
STUDY DIRECTOR	DATE 5-19-89
UNIT DIRECTOR, MAMMALIAN TOXICOLOGY SECTION	DATE May 19, 1989
DIRECTOR, TOXICOLOGICAL SCIENCES LABORATORY	DATE MAY 19, 1989
QUALITY ASSURANCE UNIT	DATE 5/19/89

Q.A. INSPECTION STATEMENT
(CFR 58.35(B)(7) 792.35(B)(7) 160.35(B)(7))

STUDY: 88-0087-1 STUDY DIRECTOR: KRASAVAGE,W.J.
ACCESSION NUMBER: 906659

05/18/89

JDY TYPE: BASIC REPEATED GAVAGE (28-DAY)

(AUDITOR, QUALITY ASSURANCE UNIT) DATE 5/19/89

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF THE HAEL, EASTMAN KODAK COMPANY, ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES:

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
08/29/88	PROTOCOL SUBMISSION	
09/08/88	SCALE/BALANCE CALIBRATION TEST ARTICLE DISTRIBUTION RECORDS CONTROL ARTICLE DISTRIBUTION RECORDS TEST ARTICLE WEIGH AND MIX WITH CARRIER SAMPLE COLLECTION SAMPLE LABELLING SAMPLE/SPECIMEN SENT FOR ANALYSIS CONCENTRATION ANALYSIS DONE BY CQSD	
09/27/88	BLEEDING-NECROPSY-HEMATOLOGY-CLINICAL CHEMISTRY	
05/18/89	FINAL REPORT REVIEW	05/18/89

Supersedes reports from 08/26/88 to 10/04/88

ANALYTICAL QUALITY ASSURANCE INSPECTION STATEMENT

HAEL #: 88-0087 Accession #: 906659 CQS Job #: EE8H021

HAEL Study: 28 Day Gavage
Study Director: W. Krasavage
Auditee Group & Location: EAS/CQS, B-320
In-Process Inspection Date: 09-01-88
Date This Report Sent To Study Director: 12-02-88

Request for Analysis #	Analysis	Sample(s) Received Date	Test Report Date	Test Report Inspection Date
084797	Init. Purity	06-28-88	08-22-88	08-26-88
126678	Dose Verif.	08-25-88	08-30-88	09-06-88
126684	Dose Conf.	09-01-88	09-09-88	09-13-88
126670	9 Day Stabil.	08-16-88	08-31-88	09-16-88
084797	Struct. Conf.	07-15-88	08-01-88	09-21-88
126688	Conc. Deter.	09-08-88	09-27-88	10-04-88
126692	Dose Verif.	09-15-88	09-28-88	10-04-88
126773	Dose verif.	09-22-88	09-28-88	10-04-88

We have inspected the analytical work described above. Our findings have been sent to the study director and to management. This is done in accordance with Good Laboratory Practice Standards 40 CFR 792.35 and 160.35, and 21 CFR 58.35.

Michael J. Boccacino

M. J. Boccacino, Quality Assurance Engineer
GLP Compliance, QSO Quality Assurance
12-02-88

TABLE OF CONTENTS FOR APPENDIX

	PAGE
GROUPED SUMMARY OF CLINICAL SIGNS - MALES	1
GROUPED SUMMARY OF CLINICAL SIGNS - FEMALES	4
PLOT OF BODY WEIGHTS - MALES	7
MEAN BODY WEIGHT - MALES	8
INDIVIDUAL BODY WEIGHT - MALES	9
PLOT OF BODY WEIGHTS - FEMALES	10
MEAN BODY WEIGHT - FEMALES	11
INDIVIDUAL BODY WEIGHT - FEMALES	12
PLOT OF FEED CONSUMPTION - MALES	13
MEAN FEED CONSUMPTION - MALES	14
INDIVIDUAL FEED CONSUMPTION - MALES	15
PLOT OF FEED CONSUMPTION - FEMALES	16
MEAN FEED CONSUMPTION - FEMALES	17
INDIVIDUAL FEED CONSUMPTION - FEMALES	18
MEAN HEMATOLOGY - MALES	19
INDIVIDUAL HEMATOLOGY - MALES	20
MEAN HEMATOLOGY - FEMALES	22
INDIVIDUAL HEMATOLOGY - FEMALES	23
MEAN CELL MORPHOLOGY - MALES	25
INDIVIDUAL CELL MORPHOLOGY - MALES	26
MEAN CELL MORPHOLOGY - FEMALES	27
INDIVIDUAL CELL MORPHOLOGY - FEMALES	28
MEAN CLINICAL CHEMISTRIES - MALES	29
INDIVIDUAL CLINICAL CHEMISTRIES - MALES	30
MEAN CLINICAL CHEMISTRIES - FEMALES	31
INDIVIDUAL CLINICAL CHEMISTRIES - FEMALES	32
MEAN ORGAN AND TERMINAL BODY WEIGHT - MALES	33
INDIVIDUAL ORGAN AND TERMINAL BODY WEIGHT - MALES	34
MEAN ORGAN AND TERMINAL BODY WEIGHT - FEMALES	35
INDIVIDUAL ORGAN AND TERMINAL BODY WEIGHT - FEMALES	36
PATHOLOGIST'S REPORT	37
SUMMARY GROSS PATHOLOGY TABLE - MALES	39
INDIVIDUAL GROSS PATHOLOGY TABLE - MALES	40
SUMMARY GROSS PATHOLOGY TABLE - FEMALES	44
INDIVIDUAL GROSS PATHOLOGY TABLE - FEMALES	45
SUMMARY HISTOPATHOLOGY TABLE - MALES	49
INDIVIDUAL HISTOPATHOLOGY TABLE - MALES	51
SUMMARY HISTOPATHOLOGY TABLE - FEMALES	56
INDIVIDUAL HISTOPATHOLOGY TABLE - FEMALES	57
INITIAL PURITY ANALYSIS REPORT	61
STRUCTURE CONFIRMATION REPORT	62

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - MALE OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	5			551-555
TREATMENT ADMINISTERED	5	0.	0.	551-555
INDUCED DEATH, CARBON DIOXIDE	5	29.	0.	551-555
GROUP 2 - 100.000 MG/KG				
* NORMAL	5			556-560
TREATMENT ADMINISTERED	5	0.	0.	556-560
INDUCED DEATH, CARBON DIOXIDE	5	29.	0.	556-560
GROUP 3 - 300.000 MG/KG				
* NORMAL	5			561-565
TREATMENT ADMINISTERED	5	0.	0.	561-565
EAR TAG LOST	1	21.	0.	563
EAR TAG REPLACED	1	21.	0.	563
INDUCED DEATH, CARBON DIOXIDE	5	29.	0.	561-565
GROUP 4 - 1000.000 MG/KG				
* NORMAL	5			566-570
TREATMENT ADMINISTERED	5	0.	0.	566-570
EAR TAG LOST	1	21.	0.	567
EAR TAG REPLACED	1	21.	0.	567
INDUCED DEATH, CARBON DIOXIDE	5	29.	0.	566-570

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - MALE OBSERVATION PERIOD - POST DOSE

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	5			551-555
GROUP 2 - 100.000 MG/KG				
* NORMAL	5			556-560
GROUP 3 - 300.000 MG/KG				
* NORMAL	5			561-565
GROUP 4 - 1000.000 MG/KG				
* NORMAL	4			566,568-570
WEAKNESS	1	22.	0.	567

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - MALE OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	5			551-555
GROUP 2 - 100.000 MG/KG				
* NORMAL	5			556-560
GROUP 3 - 300.000 MG/KG				
* NORMAL	5			561-565
GROUP 4 - 1000.000 MG/KG				
* NORMAL	5			566-570

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - FEMALE OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	5			571-575
TREATMENT ADMINISTERED	5	0.	0.	571-575
INDUCED DEATH, CARBON DIOXIDE	5	29.	0.	571-575
GROUP 2 - 100.000 MG/KG				
* NORMAL	5			576-580
TREATMENT ADMINISTERED	5	0.	0.	576-580
INDUCED DEATH, CARBON DIOXIDE	5	29.	0.	576-580
GROUP 3 - 300.000 MG/KG				
* NORMAL	5			581-585
TREATMENT ADMINISTERED	5	0.	0.	581-585
EAR TAG LOST	1	15.	0.	582
EAR TAG REPLACED	1	15.	0.	582
INDUCED DEATH, CARBON DIOXIDE	5	29.	0.	581-585
GROUP 4 - 1000.000 MG/KG				
* NORMAL	5			586-590
TREATMENT ADMINISTERED	5	0.	0.	586-590
INDUCED DEATH, CARBON DIOXIDE	5	29.	0.	586-590

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

SEX - FEMALE OBSERVATION PERIOD - POST DOSE

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	5			571-575
GROUP 2 - 100.000 MG/KG				
* NORMAL	5			576-580
GROUP 3 - 300.000 MG/KG				
* NORMAL	5			581-585
GROUP 4 - 1000.000 MG/KG				
* NORMAL	5			586-590

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

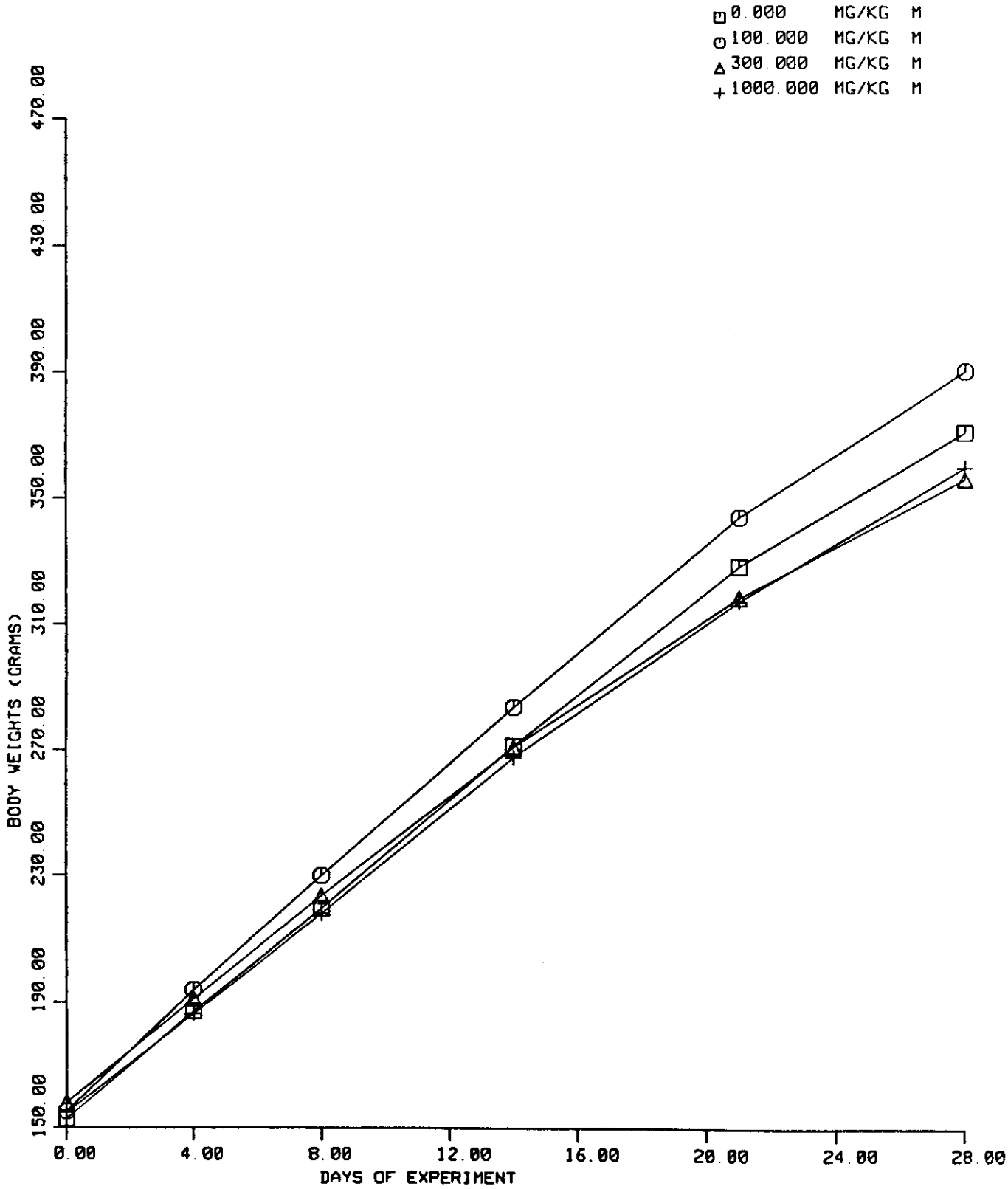
SEX - FEMALE OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 1 - 0.000 MG/KG				
* NORMAL	5			571-575
GROUP 2 - 100.000 MG/KG				
* NORMAL	5			576-580
GROUP 3 - 300.000 MG/KG				
* NORMAL	5			581-585
GROUP 4 - 1000.000 MG/KG				
* NORMAL	5			586-590

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL OR CAGESIDE OBSERVATION NORMAL

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
VERSION # 3
ACCESSION # 906659



MEAN FOR BODY WEIGHT (GRAMS)

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

		0.000 MG/KG GROUP-M	100.000 MG/KG GROUP-M	300.000 MG/KG GROUP-M	1000.000 MG/KG GROUP-M
WEEK #	1				
DAY	0	152.7 A	154.9	157.9	154.4
		12.4 B	7.7	7.4	10.5
		5 C	5	5	5
DAY	4	187.1	193.7	190.9	186.2
		14.2	11.0	7.3	13.0
		5	5	5	5
WEEK #	2				
DAY	8	219.4	229.9	223.6	217.7
		15.1	14.9	11.4	14.4
		5	5	5	5
DAY	14	271.5	284.0	270.9	267.8
		17.4	24.6	19.0	17.8
		5	5	5	5
WEEK #	3				
DAY	21	328.6	344.2	318.6	317.5
		19.9	34.9	28.5	22.7
		5	5	5	5
WEEK #	4				
DAY	28	371.5	390.7	356.8	360.4
		20.3	36.4	37.2	25.0
		5	5	5	5

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP

INDIVIDUAL ANIMAL BODY WEIGHTS (GRAMS)

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP-M

ANIMAL #	551	552	553	554	555
DAY 0	172.4	146.5	156.9	142.1	145.5
DAY 4	209.2	179.5	193.4	175.3	178.1
DAY 8	242.7	213.6	225.9	205.7	209.3
DAY 14	295.5	264.9	282.2	251.1	263.8
DAY 21	356.2	315.8	343.2	310.7	317.1
DAY 28	394.9	358.8	392.3	352.6	359.1

100.000 MG/KG GROUP-M

ANIMAL #	556	557	558	559	560
DAY 0	151.5	166.3	159.0	147.4	150.4
DAY 4	188.1	206.0	204.8	181.8	187.8
DAY 8	223.6	244.1	247.4	214.6	219.8
DAY 14	271.9	294.2	322.3	261.2	270.2
DAY 21	324.0	359.5	398.6	314.2	324.6
DAY 28	369.7	399.8	450.2	359.7	374.0

300.000 MG/KG GROUP-M

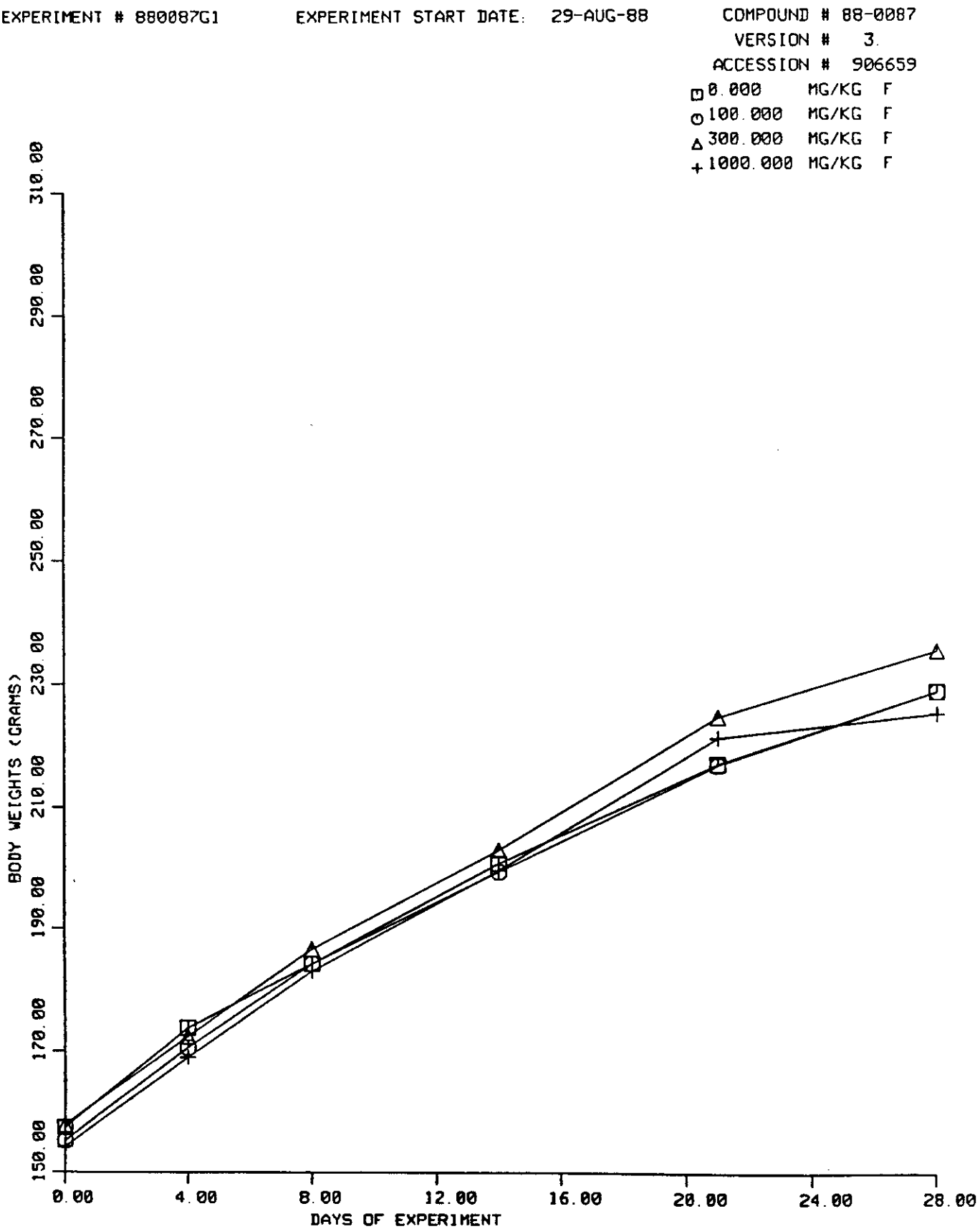
ANIMAL #	561	562	563	564	565
DAY 0	162.8	151.4	165.3	161.6	148.7
DAY 4	195.0	195.5	195.3	190.4	178.5
DAY 8	224.7	238.0	225.8	223.5	206.0
DAY 14	274.9	298.3	271.8	263.5	246.1
DAY 21	324.1	361.3	315.7	309.4	282.6
DAY 28	364.7	414.7	346.2	344.3	313.9

1000.000 MG/KG GROUP-M

ANIMAL #	566	567	568	569	570
DAY 0	152.0	171.9	144.1	149.8	154.4
DAY 4	191.7	204.6	174.5	173.2	187.2
DAY 8	228.9	236.3	204.2	205.1	213.9
DAY 14	290.1	283.3	251.8	252.4	261.5
DAY 21	350.8	331.0	303.6	296.9	305.2
DAY 28	402.0	364.6	345.5	339.7	350.0

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
VERSION # 3.
ACCESSION # 906659



MEAN FOR BODY WEIGHT (GRAMS)

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP-F	100.000 MG/KG GROUP-F	300.000 MG/KG GROUP-F	1000.000 MG/KG GROUP-F
WEEK # 1				
DAY 0	157.2 A	155.0	157.6	154.2
	3.2 B	5.3	4.1	6.7
	5 C	5	5	5
DAY 4	173.7	170.5	172.3	168.8
	1.6	8.5	8.6	7.1
	5	5	5	5
WEEK # 2				
DAY 8	184.1	184.2	186.5	182.9
	5.2	7.7	9.6	10.6
	5	5	5	5
DAY 14	200.7	199.2	203.0	199.4
	6.2	8.2	10.2	16.2
	5	5	5	5
WEEK # 3				
DAY 21	217.2	216.9	224.6	221.4
	4.6	10.7	13.2	18.7
	5	5	5	5
WEEK # 4				
DAY 28	229.0	228.9	235.6	225.3
	11.6	12.3	11.2	20.7
	5	5	5	5

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP

INDIVIDUAL ANIMAL BODY WEIGHTS (GRAMS)

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP-F

ANIMAL #	571	572	573	574	575
DAY 0	152.4	158.4	159.7	155.8	159.8
DAY 4	172.9	171.4	174.6	173.9	175.7
DAY 8	182.4	177.3	191.6	184.0	185.1
DAY 14	200.7	191.8	208.1	204.2	198.5
DAY 21	213.8	222.4	220.3	211.2	218.2
DAY 28	212.6	227.7	245.2	230.8	228.6

100.000 MG/KG GROUP-F

ANIMAL #	576	577	578	579	580
DAY 0	162.7	153.7	149.9	157.8	151.0
DAY 4	180.7	166.6	160.2	177.7	167.3
DAY 8	195.1	181.7	175.8	188.7	179.6
DAY 14	211.3	190.6	192.5	200.6	201.1
DAY 21	230.2	212.3	204.4	225.8	211.6
DAY 28	243.6	224.4	214.7	240.0	222.1

300.000 MG/KG GROUP-F

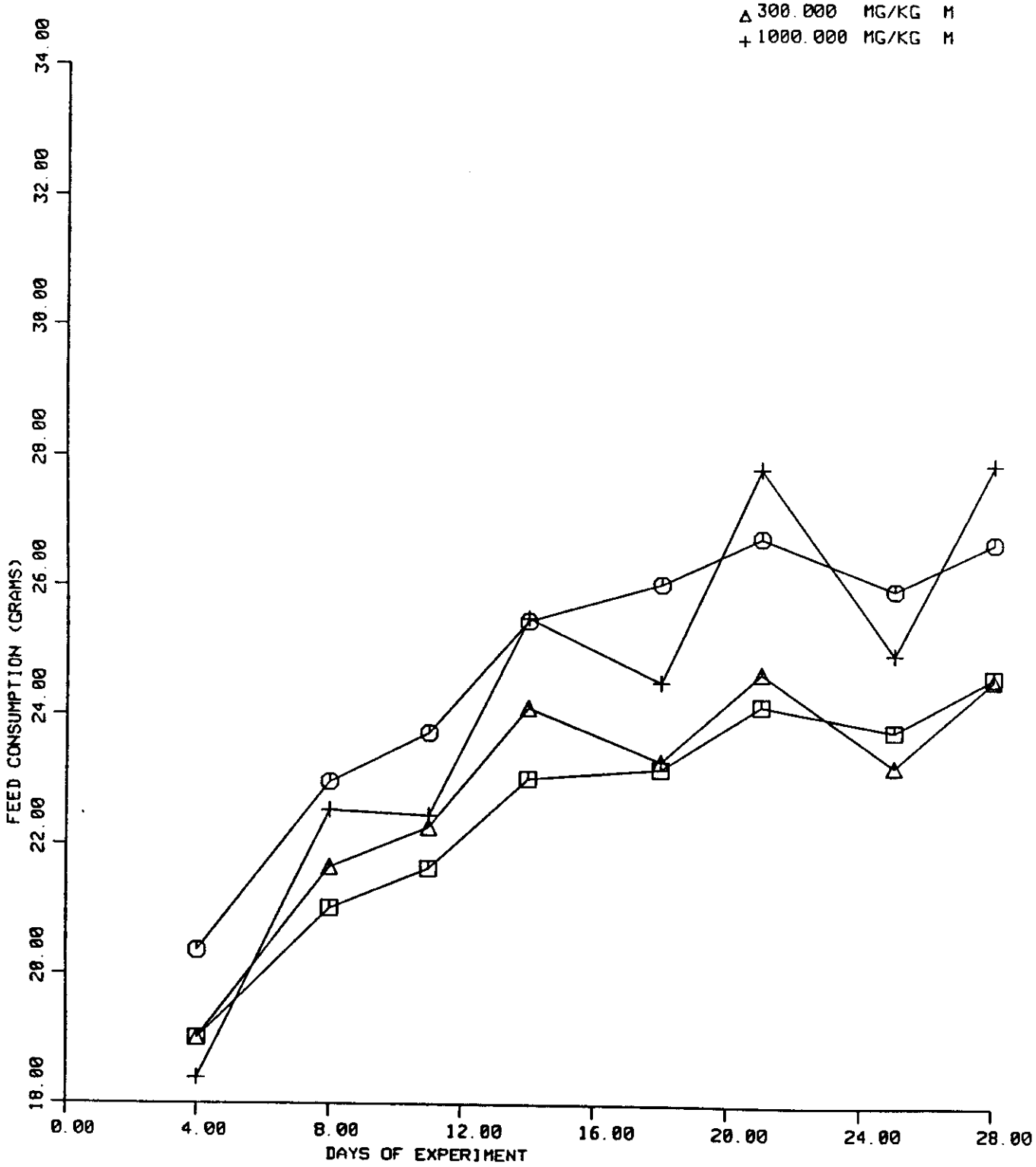
ANIMAL #	581	582	583	584	585
DAY 0	157.2	157.7	162.8	151.5	159.0
DAY 4	174.5	165.6	182.9	161.6	176.7
DAY 8	188.1	174.8	194.9	178.4	196.2
DAY 14	214.1	195.5	210.4	189.7	205.2
DAY 21	237.9	209.3	234.3	211.9	229.6
DAY 28	241.9	227.3	247.3	220.4	241.0

1000.000 MG/KG GROUP-F

ANIMAL #	586	587	588	589	590
DAY 0	152.4	156.5	156.8	143.6	161.6
DAY 4	168.1	173.4	171.6	156.8	174.3
DAY 8	180.5	186.5	184.1	167.0	196.3
DAY 14	189.5	207.4	203.9	177.3	219.0
DAY 21	216.6	215.6	225.7	198.9	250.0
DAY 28	217.7	228.9	229.0	196.9	254.0

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
VERSION # 3
ACCESSION # 906659



MEAN FOR FEED CONSUMPTION (GRAMS) λ

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP-M	100.000 MG/KG GROUP-M	300.000 MG/KG GROUP-M	1000.000 MG/KG GROUP-M
WEEK # 1				
DAY 4	19.0	20.4	19.0	18.4
	0.0	0.0	0.0	0.0
	5	5	5	5
WEEK # 2				
DAY 8	21.0	23.0	21.6	22.5
	0.0	0.0	0.0	0.0
	5	5	5	5
DAY 11	21.6	23.7	22.3	22.4
	0.0	0.0	0.0	0.0
	5	5	5	5
DAY 14	23.0	25.5	24.1	25.5
	0.0	0.0	0.0	0.0
	5	5	5	5
WEEK # 3				
DAY 18	23.2	26.1	23.3	24.5
	0.0	0.0	0.0	0.0
	5	5	5	5
DAY 21	24.2	26.8	24.7	27.8
	0.0	0.0	0.0	0.0
	5	5	5	5
WEEK # 4				
DAY 25	23.8	26.0	23.2	25.0
	0.0	0.0	0.0	0.0
	5	5	5	5
DAY 28	24.6	26.7	24.6	27.9
	0.0	0.0	0.0	0.0
	5	5	5	5

NOTE: FOR GROUP HOUSED ANIMALS, FEED CONSUMPTION IS DERIVED FROM A COMMON CONTAINER

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP
λ = FEED CONSUMPTION REFERS TO GRAMS/ANIMAL/DAY.

INDIVIDUAL ANIMAL FEED CONSUMPTION (GRAMS)

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP-M

ANIMAL #	551	552	553	554	555
DAY 4	19.0	19.0	19.0	19.0	19.0
DAY 8	21.0	21.0	21.0	21.0	21.0
DAY 11	21.6	21.6	21.6	21.6	21.6
DAY 14	23.0	23.0	23.0	23.0	23.0
DAY 18	23.2	23.2	23.2	23.2	23.2
DAY 21	24.2	24.2	24.2	24.2	24.2
DAY 25	23.8	23.8	23.8	23.8	23.8
DAY 28	24.6	24.6	24.6	24.6	24.6

100.000 MG/KG GROUP-M

ANIMAL #	556	557	558	559	560
DAY 4	20.4	20.4	20.4	20.4	20.4
DAY 8	23.0	23.0	23.0	23.0	23.0
DAY 11	23.7	23.7	23.7	23.7	23.7
DAY 14	25.5	25.5	25.5	25.5	25.5
DAY 18	26.1	26.1	26.1	26.1	26.1
DAY 21	26.8	26.8	26.8	26.8	26.8
DAY 25	26.0	26.0	26.0	26.0	26.0
DAY 28	26.7	26.7	26.7	26.7	26.7

300.000 MG/KG GROUP-M

ANIMAL #	561	562	563	564	565
DAY 4	19.0	19.0	19.0	19.0	19.0
DAY 8	21.6	21.6	21.6	21.6	21.6
DAY 11	22.3	22.3	22.3	22.3	22.3
DAY 14	24.1	24.1	24.1	24.1	24.1
DAY 18	23.3	23.3	23.3	23.3	23.3
DAY 21	24.7	24.7	24.7	24.7	24.7
DAY 25	23.2	23.2	23.2	23.2	23.2
DAY 28	24.6	24.6	24.6	24.6	24.6

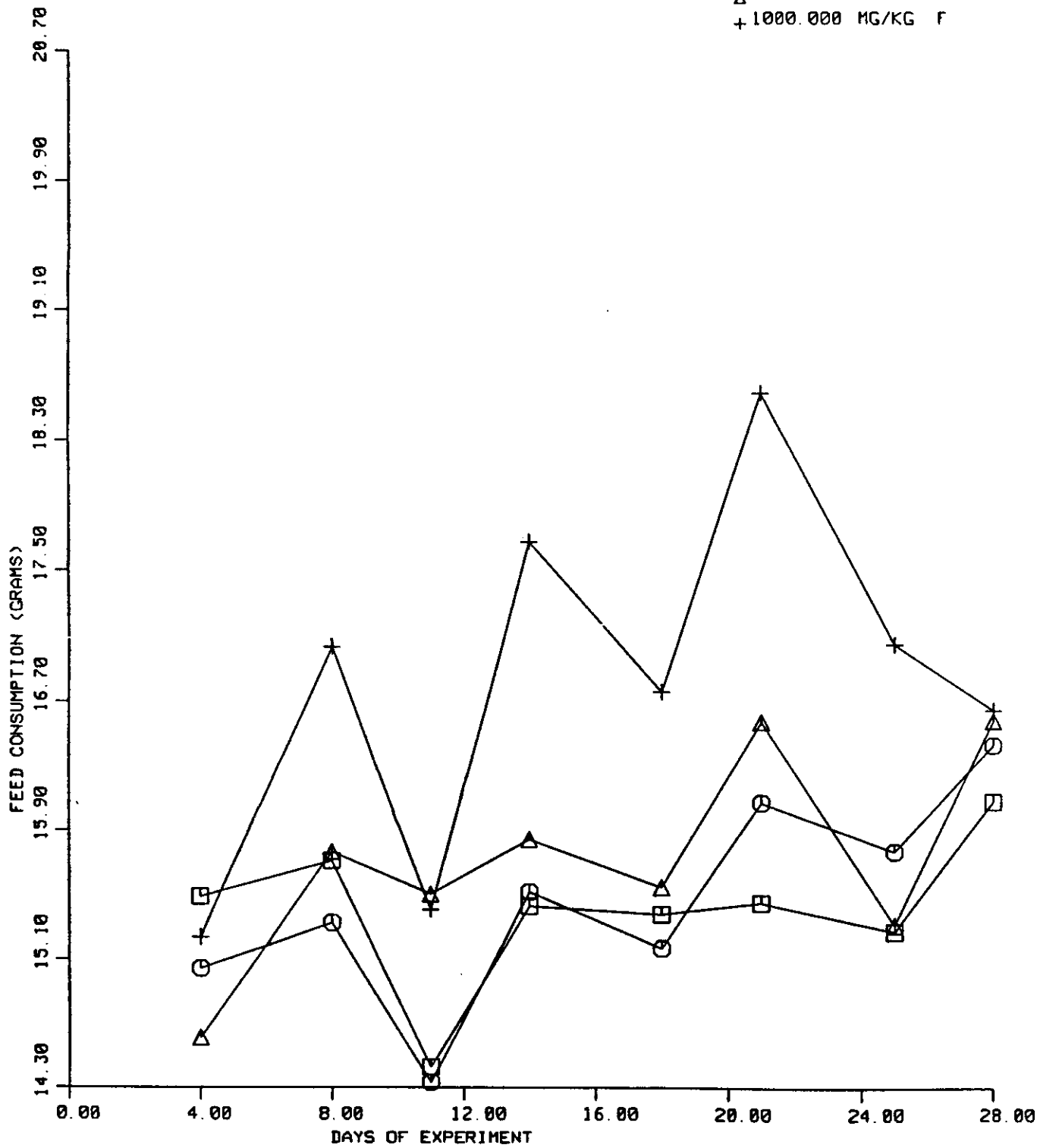
1000.000 MG/KG GROUP-M

ANIMAL #	566	567	568	569	570
DAY 4	18.4	18.4	18.4	18.4	18.4
DAY 8	22.5	22.5	22.5	22.5	22.5
DAY 11	22.4	22.4	22.4	22.4	22.4
DAY 14	25.5	25.5	25.5	25.5	25.5
DAY 18	24.5	24.5	24.5	24.5	24.5
DAY 21	27.8	27.8	27.8	27.8	27.8
DAY 25	25.0	25.0	25.0	25.0	25.0
DAY 28	27.9	27.9	27.9	27.9	27.9

NOTE: FOR GROUP HOUSED ANIMALS, FEED CONSUMPTION IS DERIVED FROM A COMMON CONTAINER

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
VERSION # 3.
ACCESSION # 906659



MEAN FOR FEED CONSUMPTION (GRAMS)λ

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP-F	100.000 MG/KG GROUP-F	300.000 MG/KG GROUP-F	1000.000 MG/KG GROUP-F
WEEK # 1				
DAY 4	15.5	15.0	14.6	15.2
	0.0	0.0	0.0	0.0
	5	5	5	5
WEEK # 2				
DAY 8	15.7	15.3	15.8	17.0
	0.0	0.0	0.0	0.0
	5	5	5	5
DAY 11	14.4	14.3	15.5	15.4
	0.0	0.0	0.0	0.0
	5	5	5	5
DAY 14	15.4	15.5	15.8	17.7
	0.0	0.0	0.0	0.0
	5	5	5	5
WEEK # 3				
DAY 18	15.4	15.2	15.5	16.8
	0.0	0.0	0.0	0.0
	5	5	5	5
DAY 21	15.4	16.1	16.6	18.6
	0.0	0.0	0.0	0.0
	5	5	5	5
WEEK # 4				
DAY 25	15.3	15.8	15.3	17.0
	0.0	0.0	0.0	0.0
	5	5	5	5
DAY 28	16.1	16.4	16.6	16.6
	0.0	0.0	0.0	0.0
	5	5	5	5

NOTE: FOR GROUP HOUSED ANIMALS, FEED CONSUMPTION IS DERIVED FROM A COMMON CONTAINER

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP
λ = FEED CONSUMPTION REFERS TO GRAMS/ANIMAL/DAY.

INDIVIDUAL ANIMAL FEED CONSUMPTION (GRAMS)

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP-F

ANIMAL #	571	572	573	574	575
DAY 4	15.5	15.5	15.5	15.5	15.5
DAY 8	15.7	15.7	15.7	15.7	15.7
DAY 11	14.4	14.4	14.4	14.4	14.4
DAY 14	15.4	15.4	15.4	15.4	15.4
DAY 18	15.4	15.4	15.4	15.4	15.4
DAY 21	15.4	15.4	15.4	15.4	15.4
DAY 25	15.3	15.3	15.3	15.3	15.3
DAY 28	16.1	16.1	16.1	16.1	16.1

100.000 MG/KG GROUP-F

ANIMAL #	576	577	578	579	580
DAY 4	15.0	15.0	15.0	15.0	15.0
DAY 8	15.3	15.3	15.3	15.3	15.3
DAY 11	14.3	14.3	14.3	14.3	14.3
DAY 14	15.5	15.5	15.5	15.5	15.5
DAY 18	15.2	15.2	15.2	15.2	15.2
DAY 21	16.1	16.1	16.1	16.1	16.1
DAY 25	15.8	15.8	15.8	15.8	15.8
DAY 28	16.4	16.4	16.4	16.4	16.4

300.000 MG/KG GROUP-F

ANIMAL #	581	582	583	584	585
DAY 4	14.6	14.6	14.6	14.6	14.6
DAY 8	15.8	15.8	15.8	15.8	15.8
DAY 11	15.5	15.5	15.5	15.5	15.5
DAY 14	15.8	15.8	15.8	15.8	15.8
DAY 18	15.5	15.5	15.5	15.5	15.5
DAY 21	16.6	16.6	16.6	16.6	16.6
DAY 25	15.3	15.3	15.3	15.3	15.3
DAY 28	16.6	16.6	16.6	16.6	16.6

1000.000 MG/KG GROUP-F

ANIMAL #	586	587	588	589	590
DAY 4	15.2	15.2	15.2	15.2	15.2
DAY 8	17.0	17.0	17.0	17.0	17.0
DAY 11	15.4	15.4	15.4	15.4	15.4
DAY 14	17.7	17.7	17.7	17.7	17.7
DAY 18	16.8	16.8	16.8	16.8	16.8
DAY 21	18.6	18.6	18.6	18.6	18.6
DAY 25	17.0	17.0	17.0	17.0	17.0
DAY 28	16.6	16.6	16.6	16.6	16.6

NOTE: FOR GROUP HOUSED ANIMALS, FEED CONSUMPTION IS DERIVED FROM A COMMON CONTAINER

SUMMARY HEMATOLOGY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: BLOOD SAMPLE DAY # 29

	0.000 MG/KG GROUP-M	100.000 MG/KG GROUP-M	300.000 MG/KG GROUP-M	1000.000 MG/KG GROUP-M
WBC/MM3 X3	10.7 A	13.4	12.9	14.5
	1.1 B	2.7	2.5	3.9
	5 C	5	5	5
RBC/MM3 X6	7.2	7.3	7.4	7.2
	0.2	0.4	0.2	0.3
	5	5	5	5
HB CONC , G/DL	14.3	14.6	14.4	14.1
	0.1	0.8	0.2	0.4
	5	5	5	5
HCT , %	43.8	43.9	43.6	42.9
	0.2	2.7	1.4	1.1
	5	5	5	5
MCV , U3	61.0	60.6	58.8	59.2
	1.2	0.9	1.8	1.5
	5	5	5	5
MCH , UUG	19.9	20.1	19.5	19.5
	0.3	0.4	0.2	0.5
	5	5	5	5
MCHC , %	32.7	33.2	33.1	32.9
	0.3	0.5	0.7	0.1
	5	5	5	5
PLATELETS/MM3 X3	1002.8	1086.6	1067.4	916.8
	80.6	134.1	80.9	224.5
	5	5	5	5
POLYS , %	22.6	16.0	19.6	20.0
	6.1	4.4	13.7	6.4
	5	5	5	5
BANDS , %	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
LYMPHOCYTES,%	75.2	82.6	79.4	76.8
	6.2	4.4	13.3	7.5
	5	5	5	5
MONOCYTES,%	1.2	1.2	0.6	2.6
	0.8	0.4	0.5	2.3
	5	5	5	5
EOSINOPHIL,%	1.0	0.2	0.2	0.6
	1.0	0.4	0.4	0.5
	5	5	5	5
BASOPHIL,%	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
LYMPHOCYTES ATYPICAL, %	0.0	0.0	0.2	0.0
	0.0	0.0	0.4	0.0
	5	5	5	5
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
PROTHROMBIN TIME,SEC	15.3	15.1	15.4	15.2
	0.4	0.4	0.3	0.4
	5	5	5	5

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP

INDIVIDUAL ANIMAL HEMATOLOGY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: BLOOD

SAMPLE DAY # 29

0.000 MG/KG GROUP-M

ANIMAL #	551	552	553	554	555
WBC/MM3 X3	9.8	9.9	12.1	9.9	11.8
RBC/MM3 X6	7.1	7.2	7.0	7.2	7.4
HB CONC , G/DL	14.3	14.3	14.3	14.3	14.5
HCT , %	44.1	43.8	43.7	43.8	43.7
MCV , U3	62.0	61.0	62.0	61.0	59.0
MCH , UUG	20.1	19.8	20.4	19.8	19.5
MCHC , %	32.4	32.6	32.7	32.6	33.2
PLATELETS/MM3 X3	1019.0	902.0	969.0	1123.0	1001.0
POLYS , %	13.0	25.0	25.0	21.0	29.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	85.0	72.0	73.0	77.0	69.0
MONOCYTES,%	0.0	1.0	2.0	2.0	1.0
EOSINOPHIL,%	2.0	2.0	0.0	0.0	1.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	0.0	0.0	0.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	14.9	15.1	15.4	15.6	15.6

100.000 MG/KG GROUP-M

ANIMAL #	556	557	558	559	560
WBC/MM3 X3	12.4	13.9	9.2	15.3	16.1
RBC/MM3 X6	7.6	6.9	6.9	7.8	7.1
HB CONC , G/DL	14.8	14.0	13.8	15.9	14.4
HCT , %	45.8	41.8	41.1	47.4	43.5
MCV , U3	61.0	61.0	59.0	61.0	61.0
MCH , UUG	19.6	20.3	19.9	20.5	20.3
MCHC , %	32.3	33.5	33.6	33.5	33.1
PLATELETS/MM3 X3	1153.0	991.0	945.0	1281.0	1063.0
POLYS , %	19.0	12.0	22.0	15.0	12.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	79.0	86.0	77.0	84.0	87.0
MONOCYTES,%	2.0	1.0	1.0	1.0	1.0
EOSINOPHIL,%	0.0	1.0	0.0	0.0	0.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	0.0	0.0	0.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	15.6	14.6	15.4	14.8	15.1

300.000 MG/KG GROUP-M

ANIMAL #	561	562	563	564	565
WBC/MM3 X3	9.6	14.4	12.0	16.1	12.5
RBC/MM3 X6	7.2	7.5	7.2	7.6	7.5
HB CONC , G/DL	14.2	14.7	14.2	14.5	14.4
HCT , %	42.9	45.7	42.7	44.4	42.3
MCV , U3	59.0	61.0	59.0	59.0	56.0
MCH , UUG	19.6	19.6	19.7	19.2	19.2
MCHC , %	33.1	32.2	33.3	32.7	34.0
PLATELETS/MM3 X3	1018.0	964.0	1148.0	1148.0	1059.0
POLYS , %	8.0	11.0	33.0	10.0	36.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	92.0	86.0	66.0	89.0	64.0
MONOCYTES,%	0.0	1.0	1.0	1.0	0.0
EOSINOPHIL,%	0.0	1.0	0.0	0.0	0.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	1.0	0.0	0.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	15.1	15.9	15.6	15.1	15.4

INDIVIDUAL ANIMAL HEMATOLOGY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: BLOOD

SAMPLE DAY # 29

1000.000 MG/KG GROUP-M

ANIMAL #	566	567	568	569	570
WBC/MM3 X3	17.5	19.0	10.6	10.5	15.1
RBC/MM3 X6	6.9	7.5	7.2	7.5	7.0
HB CONC , G/DL	13.8	14.1	14.2	14.7	13.7
HCT , %	41.9	42.9	43.4	44.5	41.7
MCV , U3	61.0	57.0	60.0	59.0	59.0
MCH , UUG	20.0	18.8	19.8	19.5	19.5
MCHC , %	32.9	32.9	32.7	33.0	32.9
PLATELETS/MM3 X3	869.0	833.0	1078.0	1190.0	614.0
POLYS , %	21.0	26.0	26.0	12.0	15.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	76.0	68.0	72.0	87.0	81.0
MONOCYTES,%	3.0	6.0	1.0	0.0	3.0
EOSINOPHIL,%	0.0	0.0	1.0	1.0	1.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	0.0	0.0	0.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	15.8	15.1	15.1	15.4	14.9

SUMMARY HEMATOLOGY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: BLOOD SAMPLE DAY # 29

	0.000 MG/KG GROUP-F	100.000 MG/KG GROUP-F	300.000 MG/KG GROUP-F	1000.000 MG/KG GROUP-F
WBC/MM3 X3	7.4 A	9.6	10.5 *	11.3 *
	1.1 B	1.4	2.2	2.6
	5 C	5	5	5
RBC/MM3 X6	7.7	8.0	7.8	7.7
	0.3	0.3	0.4	0.3
	5	5	5	5
HB CONC , G/DL	14.5	15.4	15.3	14.7
	0.5	0.8	0.6	0.5
	5	5	5	5
HCT , %	44.1	46.8	46.2	44.5
	1.8	2.1	1.6	1.4
	5	5	5	5
MCV , U3	57.0	58.6	59.4	58.0
	1.6	1.1	2.4	1.2
	5	5	5	5
MCH , UUG	18.9	19.2	19.7	19.1
	0.5	0.3	0.6	0.4
	5	5	5	5
MCHC , %	33.0	32.9	33.2	32.9
	0.3	0.4	0.4	0.4
	5	5	5	5
PLATELETS/MM3 X3	1069.2	1239.8	1003.8	850.0 *
	102.4	131.2	112.9	226.1
	5	5	5	5
POLYS , %	15.8	21.0	23.6	20.2
	8.0	7.1	14.5	5.4
	5	5	5	5
BANDS , %	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
LYMPHOCYTES,%	81.6	75.2	73.4	75.8
	7.1	7.3	15.7	5.4
	5	5	5	5
MONOCYTES,%	1.6	2.4	1.6	2.2
	1.3	0.9	0.9	2.2
	5	5	5	5
EOSINOPHIL,%	0.6	1.4	1.0	1.2
	0.9	0.5	1.2	0.8
	5	5	5	5
BASOPHIL,%	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
LYMPHOCYTES ATYPICAL, %	0.4	0.0	0.4	0.6
	0.5	0.0	0.9	0.5
	5	5	5	5
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0
	5	5	5	5
PROTHROMBIN TIME,SEC	13.0	13.6	14.0	13.9
	0.5	1.2	1.0	0.5
	5	4	5	4

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP
* = STATISTICALLY DIFFERENT FROM CONTROLS ($P \leq 0.05$), ONE-WAY ANOVA

INDIVIDUAL ANIMAL HEMATOLOGY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: BLOOD

SAMPLE DAY # 29

0.000 MG/KG GROUP-F

ANIMAL #	571	572	573	574	575
WBC/MM3 X3	7.5	6.4	9.0	7.7	6.4
RBC/MM3 X6	8.2	7.5	7.8	7.5	7.4
HB CONC , G/DL	15.0	14.3	15.0	14.5	13.9
HCT , %	45.6	43.3	46.1	43.5	41.8
MCV , U3	55.0	57.0	59.0	58.0	56.0
MCH , UUG	18.2	19.0	19.4	19.4	18.7
MCHC , %	32.9	33.0	32.5	33.3	33.3
PLATELETS/MM3 X3	1179.0	1132.0	1095.0	1023.0	917.0
POLYS , %	15.0	10.0	27.0	7.0	20.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	82.0	89.0	73.0	88.0	76.0
MONOCYTES,%	1.0	1.0	0.0	3.0	3.0
EOSINOPHIL,%	1.0	0.0	0.0	2.0	0.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	1.0	0.0	0.0	0.0	1.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	13.6	12.9	13.1	12.9	12.3

100.000 MG/KG GROUP-F

ANIMAL #	576	577	578	579	580
WBC/MM3 X3	8.1	11.2	11.0	8.6	9.3
RBC/MM3 X6	7.8	8.4	7.9	8.3	7.7
HB CONC , G/DL	14.6	16.4	15.3	15.9	14.7
HCT , %	44.1	49.6	46.4	48.0	45.7
MCV , U3	57.0	59.0	59.0	58.0	60.0
MCH , UUG	18.8	19.5	19.3	19.2	19.1
MCHC , %	33.1	33.1	33.0	33.1	32.2
PLATELETS/MM3 X3	1069.0	1426.0	1224.0	1191.0	1289.0
POLYS , %	18.0	12.0	30.0	26.0	19.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	78.0	84.0	65.0	71.0	78.0
MONOCYTES,%	3.0	3.0	3.0	2.0	1.0
EOSINOPHIL,%	1.0	1.0	2.0	1.0	2.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	0.0	0.0	0.0	0.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	13.1	12.8	15.4	13.1	¢

300.000 MG/KG GROUP-F

ANIMAL #	581	582	583	584	585
WBC/MM3 X3	8.7	13.2	10.5	8.1	12.0
RBC/MM3 X6	7.1	7.7	8.3	8.0	7.8
HB CONC , G/DL	14.7	14.9	16.0	15.3	15.8
HCT , %	44.1	45.7	48.0	45.4	47.6
MCV , U3	62.0	60.0	58.0	56.0	61.0
MCH , UUG	20.6	19.5	19.4	19.0	20.2
MCHC , %	33.3	32.6	33.3	33.7	33.2
PLATELETS/MM3 X3	936.0	968.0	1120.0	872.0	1123.0
POLYS , %	15.0	23.0	6.0	30.0	44.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	81.0	75.0	93.0	67.0	51.0
MONOCYTES,%	1.0	1.0	1.0	3.0	2.0
EOSINOPHIL,%	1.0	1.0	0.0	0.0	3.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	2.0	0.0	0.0	0.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	13.4	13.6	15.8	13.4	13.9

KEY: ¢ = SAMPLE LOST DUE TO CLOTTING OF SODIUM CITRATE TUBE.

INDIVIDUAL ANIMAL HEMATOLOGY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: BLOOD

SAMPLE DAY # 29

1000.000 MG/KG GROUP-F

ANIMAL #	586	587	588	589	590
WBC/MM3 X3	7.3	12.4	14.1	12.2	10.6
RBC/MM3 X6	8.1	7.6	7.7	7.8	7.3
HB CONC , G/DL	15.5	14.5	14.8	14.3	14.2
HCT , %	46.9	44.3	44.1	44.1	43.3
MCV , U3	58.0	58.0	57.0	57.0	60.0
MCH , UUG	19.1	19.1	19.3	18.5	19.6
MCHC , %	33.0	32.7	33.6	32.4	32.8
PLATELETS/MM3 X3	743.0	734.0	609.0	1165.0	999.0
POLYS , %	21.0	18.0	28.0	21.0	13.0
BANDS , %	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES,%	77.0	80.0	67.0	75.0	80.0
MONOCYTES,%	0.0	1.0	4.0	1.0	5.0
EOSINOPHIL,%	1.0	0.0	1.0	2.0	2.0
BASOPHIL,%	0.0	0.0	0.0	0.0	0.0
LYMPHOCYTES ATYPICAL, %	1.0	1.0	0.0	1.0	0.0
NUCLEATED RBC/100WBC	0.0	0.0	0.0	0.0	0.0
PROTHROMBIN TIME,SEC	13.6	¢	13.9	14.6	13.4

KEY: ¢ = SAMPLE LOST DUE TO CLOTTING OF SODIUM CITRATE TUBE.

STUDY SUMMARY OF CELL MORPHOLOGY

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL : BLOOD CELL MORPHOLOGY

DAY OF SAMPLE : 29

GROUP	0.000 MG/KG M	100.000 MG/KG M	300.000 MG/KG M	1000.000 MG/KG M
BLOOD ERYTHROCYTES	5	5	5	5
POIKILOCYTOSIS		2		
POLYCHROMASIA, INCREASED		1		
BLOOD LEUKOCYTES	5	5	5	5
BLOOD PLATELETS	5	5	5	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY.

INDIVIDUAL ANIMAL CELL MORPHOLOGY

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL : BLOOD CELL MORPHOLOGY

DAY OF SAMPLE : 29

0.000
MG/KG
M

ANIMAL #	551	552	553	554	555
BLOOD ERYTHROCYTES	N	N	N	N	N
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

100.000
MG/KG
M

ANIMAL #	556	557	558	559	560
BLOOD ERYTHROCYTES		N		N	N
POIKILOCYTOSIS	1		1		
POLYCHROMASIA, INCREASED	1				
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

300.000
MG/KG
M

ANIMAL #	561	562	563	564	565
BLOOD ERYTHROCYTES	N	N	N	N	N
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

1000.000
MG/KG
M

ANIMAL #	566	567	568	569	570
BLOOD ERYTHROCYTES	N	N	N	N	N
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

KEY:N-NORMAL,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE,P-PRESENT,A-ABSENT

STUDY SUMMARY OF CELL MORPHOLOGY

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL : BLOOD CELL MORPHOLOGY

DAY OF SAMPLE : 29

GROUP	0.000 MG/KG F	100.000 MG/KG F	300.000 MG/KG F	1000.000 MG/KG F
BLOOD ERYTHROCYTES	5	5	5	5
POIKILOCYTOSIS				1
BLOOD LEUKOCYTES	5	5	5	5
BLOOD PLATELETS	5	5	5	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY.

INDIVIDUAL ANIMAL CELL MORPHOLOGY

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL : BLOOD CELL MORPHOLOGY

DAY OF SAMPLE : 29

0.000
MG/KG
F

ANIMAL #	571	572	573	574	575
BLOOD ERYTHROCYTES	N	N	N	N	N
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

100.000
MG/KG
F

ANIMAL #	576	577	578	579	580
BLOOD ERYTHROCYTES	N	N	N	N	N
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

300.000
MG/KG
F

ANIMAL #	581	582	583	584	585
BLOOD ERYTHROCYTES	N	N	N	N	N
BLOOD LEUKOCYTES	N	N	N	N	N *
BLOOD PLATELETS	N	N	N	N	N

1000.000
MG/KG
F

ANIMAL #	586	587	588	589	590
BLOOD ERYTHROCYTES		N	N	N	N
POIKILOCYTOSIS	1				
BLOOD LEUKOCYTES	N	N	N	N	N
BLOOD PLATELETS	N	N	N	N	N

KEY:N-NORMAL,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE,P-PRESENT,A-ABSENT
1+ HYPERSEGMENTED NEUTROPHILS

SUMMARY CLINICAL CHEMISTRY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: SERUM SAMPLE DAY # 29

	0.000 MG/KG GROUP-M		100.000 MG/KG GROUP-M	300.000 MG/KG GROUP-M	1000.000 MG/KG GROUP-M
AST (GOT) , U/L	66.15	A	64.77	65.01	69.65
	5.25	B	5.46	6.97	8.00
	5	C	5	5	5
ALT (GPT) , U/L	23.97		26.96	23.66	27.83
	1.75		4.75	2.27	3.34
	5		5	5	5
AP , U/L	214.14		193.76	263.26	258.93
	20.99		31.43	79.33	78.64
	5		5	5	5
UREA NITROGEN,MG/DL	11.95		14.03	12.32	14.16
	2.24		1.89	1.81	2.90
	5		5	5	5
GLUCOSE,MG/DL	130.53		151.43	124.83	120.91
	10.62		58.60	23.63	12.29
	5		5	5	5
CREATININE,MG/DL	0.67		0.68	0.63	0.70
	0.04		0.03	0.04	0.05
	5		5	5	5
SDH , U/L	7.88		8.62	8.45	9.44
	2.37		2.77	2.46	3.41
	5		5	5	5
BILIRUBIN TOTAL,MG/DL	0.05		0.05	0.05	0.05
	0.02		0.02	0.02	0.02
	5		5	5	5
TOTAL PROTEIN,G/DL	5.61		5.96	5.77	5.72
	0.14		0.55	0.38	0.25
	5		5	5	5
A/G RATIO	1.25		1.23	1.16	1.25
	0.11		0.06	0.18	0.14
	5		5	5	5
ALBUMIN,G/DL	3.11		3.28	3.08	3.17
	0.09		0.30	0.14	0.05
	5		5	5	5

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: SERUM SAMPLE DAY # 29

0.000 MG/KG GROUP-M

ANIMAL #	551	552	553	554	555
AST (GOT) , U/L	69.13	57.87	65.18	66.82	71.77
ALT (GPT) , U/L	23.50	24.40	24.42	21.35	26.16
AP , U/L	200.43	185.68	223.06	238.86	222.69
UREA NITROGEN,MG/DL	14.90	13.82	10.26	10.06	10.73
GLUCOSE,MG/DL	138.18	133.61	131.06	137.55	112.27
CREATININE,MG/DL	0.72	0.72	0.65	0.62	0.66
SDH , U/L	8.08	7.28	11.58	5.03	7.44
BILIRUBIN TOTAL,MG/DL	0.06	0.02	0.03	0.07	0.05
TOTAL PROTEIN,G/DL	5.74	5.64	5.52	5.42	5.73
A/G RATIO	1.09	1.19	1.29	1.38	1.30
ALBUMIN,G/DL	2.99	3.06	3.10	3.14	3.24

100.000 MG/KG GROUP-M

ANIMAL #	556	557	558	559	560
AST (GOT) , U/L	67.16	62.14	64.72	72.21	57.61
ALT (GPT) , U/L	30.00	32.36	26.14	26.47	19.83
AP , U/L	229.37	209.15	190.74	195.12	144.40
UREA NITROGEN,MG/DL	11.55	14.87	13.62	16.65	13.45
GLUCOSE,MG/DL	254.20	124.88	140.41	129.31	108.33
CREATININE,MG/DL	0.64	0.67	0.71	0.72	0.68
SDH , U/L	6.59	8.11	9.20	13.06	6.13
BILIRUBIN TOTAL,MG/DL	0.06	0.05	0.02	0.07	0.05
TOTAL PROTEIN,G/DL	6.29	5.65	5.47	6.77	5.60
A/G RATIO	1.26	1.26	1.29	1.19	1.15
ALBUMIN,G/DL	3.51	3.15	3.08	3.68	3.00

300.000 MG/KG GROUP-M

ANIMAL #	561	562	563	564	565
AST (GOT) , U/L	71.87	71.28	55.61	60.64	65.66
ALT (GPT) , U/L	22.54	25.87	24.51	20.26	25.14
AP , U/L	283.90	362.78	191.68	173.63	304.33
UREA NITROGEN,MG/DL	11.01	10.41	14.71	11.84	13.65
GLUCOSE,MG/DL	104.71	164.14	127.75	117.75	109.81
CREATININE,MG/DL	0.67	0.67	0.59	0.63	0.59
SDH , U/L	7.75	9.44	6.74	6.11	12.23
BILIRUBIN TOTAL,MG/DL	0.04	0.09	0.03	0.04	0.05
TOTAL PROTEIN,G/DL	5.85	5.65	5.99	5.19	6.19
A/G RATIO	1.10	1.25	0.93	1.40	1.12
ALBUMIN,G/DL	3.06	3.14	2.88	3.03	3.27

1000.000 MG/KG GROUP-M

ANIMAL #	566	567	568	569	570
AST (GOT) , U/L	75.65	62.45	79.41	69.64	61.12
ALT (GPT) , U/L	28.36	32.63	27.22	27.70	23.26
AP , U/L	327.51	168.24	341.38	188.80	268.71
UREA NITROGEN,MG/DL	12.91	16.46	17.97	12.27	11.21
GLUCOSE,MG/DL	132.32	129.44	125.43	115.07	102.30
CREATININE,MG/DL	0.72	0.73	0.76	0.63	0.67
SDH , U/L	14.21	11.90	6.67	7.27	7.14
BILIRUBIN TOTAL,MG/DL	0.03	0.05	0.03	0.05	0.07
TOTAL PROTEIN,G/DL	5.93	6.04	5.50	5.64	5.49
A/G RATIO	1.17	1.05	1.33	1.32	1.40
ALBUMIN,G/DL	3.19	3.09	3.14	3.20	3.21

SUMMARY CLINICAL CHEMISTRY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: SERUM SAMPLE DAY # 29

	0.000 MG/KG GROUP-F	100.000 MG/KG GROUP-F	300.000 MG/KG GROUP-F	1000.000 MG/KG GROUP-F
AST (GOT) , U/L	68.30 A	72.28	72.28	67.05
	7.58 B	9.91	6.31	3.07
	5 C	5	5	5
ALT (GPT) , U/L	21.03	29.36	24.32	24.04
	2.17	7.06	4.35	2.48
	5	5	5	5
AP , U/L	139.54	144.77	161.97	154.52
	35.13	46.67	24.48	17.26
	5	5	5	5
UREA NITROGEN,MG/DL	15.82	18.47	16.04	16.86
	1.76	3.13	1.86	2.85
	5	5	5	5
GLUCOSE,MG/DL	120.54	101.32	114.55	113.40
	18.31	6.56	7.37	24.25
	5	5	5	5
CREATININE,MG/DL	0.66	0.65	0.64	0.66
	0.04	0.05	0.05	0.08
	5	5	5	5
SDH , U/L	6.67	8.82	6.61	7.49
	1.40	3.86	1.72	1.92
	5	5	5	5
BILIRUBIN TOTAL,MG/DL	0.06	0.08	0.07	0.05
	0.01	0.02	0.02	0.02
	5	5	5	5
TOTAL PROTEIN,G/DL	6.17	6.43	6.60	6.00
	0.19	0.19	0.55	0.39
	5	5	5	5
A/G RATIO	1.33	1.28	1.20	1.20
	0.15	0.07	0.23	0.11
	5	5	5	5
ALBUMIN,G/DL	3.51	3.61	3.58	3.27
	0.21	0.10	0.48	0.30
	5	5	5	5

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DETERMINATION

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

ANALYTICAL MATERIAL: SERUM SAMPLE DAY # 29

0.000 MG/KG GROUP-F

ANIMAL #	571	572	573	574	575
AST (GOT) , U/L	77.48	67.07	62.14	60.18	74.64
ALT (GPT) , U/L	22.00	22.00	17.17	22.31	21.65
AP , U/L	104.49	102.18	168.83	144.88	177.30
UREA NITROGEN,MG/DL	17.61	15.03	14.23	17.83	14.41
GLUCOSE,MG/DL	97.63	119.07	143.23	109.16	133.59
CREATININE,MG/DL	0.62	0.60	0.70	0.68	0.68
SDH , U/L	5.38	7.36	6.78	5.24	8.58
BILIRUBIN TOTAL,MG/DL	0.06	0.06	0.06	0.05	0.05
TOTAL PROTEIN,G/DL	6.23	5.83	6.21	6.24	6.33
A/G RATIO	1.22	1.24	1.54	1.43	1.21
ALBUMIN,G/DL	3.43	3.23	3.77	3.67	3.46

100.000 MG/KG GROUP-F

ANIMAL #	576	577	578	579	580
AST (GOT) , U/L	57.70	85.61	71.71	73.70	72.66
ALT (GPT) , U/L	18.21	30.44	28.41	37.36	32.37
AP , U/L	108.47	153.13	118.50	222.69	121.06
UREA NITROGEN,MG/DL	21.47	21.62	18.22	16.71	14.34
GLUCOSE,MG/DL	97.98	96.44	104.96	96.09	111.14
CREATININE,MG/DL	0.65	0.68	0.72	0.60	0.62
SDH , U/L	7.00	15.36	8.85	7.53	5.37
BILIRUBIN TOTAL,MG/DL	0.04	0.07	0.10	0.10	0.08
TOTAL PROTEIN,G/DL	6.19	6.62	6.29	6.58	6.47
A/G RATIO	1.29	1.18	1.30	1.27	1.38
ALBUMIN,G/DL	3.49	3.58	3.56	3.68	3.75

300.000 MG/KG GROUP-F

ANIMAL #	581	582	583	584	585
AST (GOT) , U/L	72.95	67.13	78.40	64.62	78.28
ALT (GPT) , U/L	17.68	24.92	29.24	23.07	26.67
AP , U/L	155.28	129.51	176.68	154.40	193.99
UREA NITROGEN,MG/DL	13.88	15.46	18.98	16.29	15.61
GLUCOSE,MG/DL	107.68	112.22	117.68	109.34	125.85
CREATININE,MG/DL	0.69	0.61	0.70	0.57	0.65
SDH , U/L	5.66	4.85	9.05	5.77	7.70
BILIRUBIN TOTAL,MG/DL	0.05	0.08	0.08	0.09	0.05
TOTAL PROTEIN,G/DL	5.75	6.71	7.06	6.41	7.07
A/G RATIO	1.08	1.21	0.93	1.21	1.56
ALBUMIN,G/DL	2.99	3.67	3.41	3.51	4.31

1000.000 MG/KG GROUP-F

ANIMAL #	586	587	588	589	590
AST (GOT) , U/L	71.24	68.04	62.84	65.84	67.30
ALT (GPT) , U/L	22.29	21.31	24.86	27.70	24.05
AP , U/L	171.13	166.08	150.58	127.03	157.76
UREA NITROGEN,MG/DL	14.45	21.54	15.78	17.47	15.08
GLUCOSE,MG/DL	92.14	151.17	105.03	95.71	122.95
CREATININE,MG/DL	0.59	0.78	0.68	0.61	0.62
SDH , U/L	10.62	6.52	6.52	5.81	7.98
BILIRUBIN TOTAL,MG/DL	0.05	0.04	0.08	0.06	0.04
TOTAL PROTEIN,G/DL	6.44	5.72	5.63	6.39	5.81
A/G RATIO	1.20	1.24	1.01	1.28	1.29
ALBUMIN,G/DL	3.50	3.16	2.83	3.58	3.28

MEAN TERMINAL ORGAN WEIGHTS AND BODY WEIGHTS

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
KILL DAY - 29 ACCESSION NUMBER 906659

GROUP		0.000 MG/KG M	100.000 MG/KG M	300.000 MG/KG M	1000.000 MG/KG M
BODY WEIGHT	(G)	324.7 A	341.6	312.4	310.9
		16.8 B	35.5	31.6	23.9
		5 C	5	5	5
KIDNEYS	(G)	2.8719	2.6231	2.8798	2.7451
		0.2181	0.2714	0.4689	0.3006
		5	5	5	5
	%	0.8843	0.7679 *	0.9201	0.8815
		0.0452	0.0094	0.0997	0.0392
		5	5	5	5
LIVER	(G)	10.9381	11.6358	10.7940	12.6205
		0.8122	1.1261	1.2538	1.5157
		5	5	5	5
	%	3.3679	3.4082	3.4542	4.0521 *
		0.1686	0.0518	0.1682	0.2564
		5	5	5	5
THYMUS	(G)	0.5621	0.6133	0.4947	0.5908
		0.0385	0.0805	0.0959	0.1426
		5	5	5	5
	%	0.1731	0.1802	0.1583	0.1904
		0.0087	0.0220	0.0259	0.0453
		5	5	5	5
SPLEEN	(G)	0.6782	0.7330	0.6934	0.8334
		0.0790	0.0873	0.1097	0.1444
		5	5	5	5
	%	0.2089	0.2145	0.2228	0.2669 *
		0.0223	0.0115	0.0351	0.0288
		5	5	5	5
ADRENALS	(G)	0.0555	0.0552	0.0505	0.0566
		0.0101	0.0096	0.0083	0.0066
		5	5	5	5
	%	0.0172	0.0163	0.0161	0.0182
		0.0039	0.0035	0.0012	0.0018
		5	5	5	5
TESTES	(G)	3.0499	2.8165	3.0457	2.5478
		0.2033	0.5342	0.1434	0.2408
		5	5	5	5
	%	0.9416	0.8315	0.9851	0.8259
		0.0843	0.1728	0.1353	0.1193
		5	5	5	5

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP
* = STATISTICALLY DIFFERENT FROM CONTROLS ($P \leq 0.05$), ONE-WAY ANOVA

INDIVIDUAL ANIMAL ORGAN WEIGHTS AND TERMINAL BODY WEIGHT

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP - M

ANIMAL #		551	552	553	554	555
BODY WEIGHT	(G)	342.2	314.0	342.9	306.4	318.2
KIDNEYS	(G)	3.2159	2.6233	2.9069	2.8198	2.7935
	%	0.9399	0.8354	0.8477	0.9205	0.8779
LIVER	(G)	11.6120	10.3544	11.8557	10.9311	9.9371
	%	3.3936	3.2975	3.4574	3.5682	3.1230
THYMUS	(G)	0.6031	0.5759	0.5855	0.5375	0.5083
	%	0.1763	0.1834	0.1707	0.1755	0.1597
SPLEEN	(G)	0.6262	0.5954	0.8010	0.6958	0.6724
	%	0.1830	0.1896	0.2336	0.2271	0.2113
ADRENALS	(G)	0.0499	0.0544	0.0467	0.0726	0.0541
	%	0.0146	0.0173	0.0136	0.0237	0.0170
TESTES	(G)	3.2428	2.8491	2.8112	3.1865	3.1600
	%	0.9477	0.9073	0.8198	1.0402	0.9931

100.000 MG/KG GROUP - M

ANIMAL #		556	557	558	559	560
BODY WEIGHT	(G)	324.4	361.0	394.9	311.1	316.8
KIDNEYS	(G)	2.5412	2.7402	3.0381	2.3785	2.4177
	%	0.7833	0.7591	0.7694	0.7645	0.7632
LIVER	(G)	11.1172	11.9834	13.4541	10.7133	10.9108
	%	3.4268	3.3196	3.4073	3.4434	3.4442
THYMUS	(G)	0.6237	0.5201	0.7278	0.5556	0.6395
	%	0.1923	0.1441	0.1843	0.1786	0.2019
SPLEEN	(G)	0.6397	0.8133	0.8346	0.6654	0.7119
	%	0.1972	0.2253	0.2114	0.2139	0.2247
ADRENALS	(G)	0.0492	0.0429	0.0608	0.0557	0.0674
	%	0.0152	0.0119	0.0154	0.0179	0.0213
TESTES	(G)	2.8632	1.9203	3.3505	2.9514	2.9970
	%	0.8826	0.5320	0.8485	0.9486	0.9461

300.000 MG/KG GROUP - M

ANIMAL #		561	562	563	564	565
BODY WEIGHT	(G)	323.2	358.7	305.9	301.2	272.9
KIDNEYS	(G)	3.2830	3.3627	2.3187	2.9579	2.4765
	%	1.0157	0.9375	0.7579	0.9821	0.9074
LIVER	(G)	10.4976	12.6692	10.4500	11.1262	9.2270
	%	3.2477	3.5323	3.4158	3.6943	3.3810
THYMUS	(G)	0.5525	0.6017	0.3469	0.4849	0.4874
	%	0.1709	0.1678	0.1134	0.1610	0.1786
SPLEEN	(G)	0.6104	0.7804	0.6121	0.8417	0.6223
	%	0.1888	0.2176	0.2001	0.2795	0.2280
ADRENALS	(G)	0.0501	0.0627	0.0482	0.0518	0.0396
	%	0.0155	0.0175	0.0158	0.0172	0.0145
TESTES	(G)	2.9872	3.0325	2.9480	2.9651	3.2959
	%	0.9242	0.8455	0.9636	0.9845	1.2077

1000.000 MG/KG GROUP - M

ANIMAL #		566	567	568	569	570
BODY WEIGHT	(G)	349.9	315.9	296.8	289.4	302.4
KIDNEYS	(G)	3.1648	2.8865	2.4795	2.4377	2.7571
	%	0.9045	0.9138	0.8353	0.8424	0.9116
LIVER	(G)	14.5134	13.9809	11.1492	11.6930	11.7659
	%	4.1479	4.4259	3.7560	4.0406	3.8903
THYMUS	(G)	0.5341	0.8125	0.4356	0.5365	0.6351
	%	0.1526	0.2572	0.1467	0.1854	0.2100
SPLEEN	(G)	1.0545	0.8791	0.6739	0.8043	0.7550
	%	0.3014	0.2783	0.2270	0.2779	0.2496
ADRENALS	(G)	0.0610	0.0602	0.0620	0.0466	0.0530
	%	0.0174	0.0191	0.0209	0.0161	0.0175
TESTES	(G)	2.2183	2.8187	2.5288	2.7393	2.4340
	%	0.6340	0.8923	0.8519	0.9466	0.8048

MEAN TERMINAL ORGAN WEIGHTS AND BODY WEIGHTS

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
KILL DAY - 29 ACCESSION NUMBER 906659

GROUP		0.000 MG/KG F	100.000 MG/KG F	300.000 MG/KG F	1000.000 MG/KG F
BODY WEIGHT	(G)	202.4 A	198.9	203.7	198.6
		9.1 B	10.6	9.5	17.9
		5 C	5	5	5
KIDNEYS	(G)	1.6933	1.5901	1.6126	1.7294
		0.0531	0.1319	0.1797	0.2059
		5	5	5	5
	%	0.8380	0.7987	0.7922	0.8731
		0.0512	0.0314	0.0837	0.0911
		5	5	5	5
LIVER	(G)	6.2591	6.0314	6.5876	7.2332 *
		0.6374	0.4661	0.5470	0.7636
		5	5	5	5
	%	3.0899	3.0301	3.2308	3.6458 *
		0.2510	0.1057	0.1391	0.2418
		5	5	5	5
THYMUS	(G)	0.4243	0.3764	0.3883	0.3894
		0.1009	0.0572	0.0787	0.0431
		5	5	5	5
	%	0.2089	0.1888	0.1898	0.1970
		0.0442	0.0241	0.0333	0.0235
		5	5	5	5
SPLEEN	(G)	0.4791	0.4426	0.4256	0.5010
		0.0331	0.0588	0.0741	0.0342
		5	5	5	5
	%	0.2374	0.2230	0.2081	0.2535
		0.0249	0.0308	0.0290	0.0228
		5	5	5	5
ADRENALS	(G)	0.0591	0.0569	0.0621	0.0712
		0.0054	0.0098	0.0102	0.0090
		5	5	5	5
	%	0.0292	0.0286	0.0303	0.0362
		0.0031	0.0041	0.0036	0.0065
		5	5	5	5

KEY: A = MEAN VALUE
B = ± STANDARD DEVIATION
C = NUMBER OF VALUES PER GROUP
* = STATISTICALLY DIFFERENT FROM CONTROLS ($P \leq 0.05$), ONE-WAY ANOVA

INDIVIDUAL ANIMAL ORGAN WEIGHTS AND TERMINAL BODY WEIGHT

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88

COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP - F

ANIMAL #		571	572	573	574	575
BODY WEIGHT	(G)	191.8	198.7	214.6	208.8	198.3
KIDNEYS	(G)	1.6578	1.7710	1.6316	1.7033	1.7026
	%	0.8644	0.8912	0.7602	0.8159	0.8586
LIVER	(G)	5.5624	6.4000	7.1695	5.7439	6.4196
	%	2.9004	3.2205	3.3402	2.7513	3.2373
THYMUS	(G)	0.4017	0.3180	0.4547	0.5812	0.3661
	%	0.2095	0.1600	0.2118	0.2784	0.1846
SPLEEN	(G)	0.4973	0.5274	0.4462	0.4569	0.4676
	%	0.2593	0.2654	0.2079	0.2189	0.2358
ADRENALS	(G)	0.0529	0.0643	0.0545	0.0591	0.0646
	%	0.0276	0.0324	0.0254	0.0283	0.0326

100.000 MG/KG GROUP - F

ANIMAL #		576	577	578	579	580
BODY WEIGHT	(G)	208.4	192.7	184.6	209.6	199.1
KIDNEYS	(G)	1.6622	1.5543	1.4330	1.7753	1.5256
	%	0.7974	0.8064	0.7763	0.8470	0.7662
LIVER	(G)	6.5170	5.4923	5.6197	6.4443	6.0839
	%	3.1266	2.8496	3.0444	3.0744	3.0554
THYMUS	(G)	0.3758	0.3747	0.2863	0.4040	0.4413
	%	0.1803	0.1944	0.1551	0.1927	0.2216
SPLEEN	(G)	0.5251	0.4574	0.4534	0.4090	0.3681
	%	0.2519	0.2373	0.2456	0.1951	0.1849
ADRENALS	(G)	0.0562	0.0461	0.0554	0.0729	0.0540
	%	0.0270	0.0239	0.0300	0.0348	0.0271

300.000 MG/KG GROUP - F

ANIMAL #		581	582	583	584	585
BODY WEIGHT	(G)	213.4	195.4	206.7	192.0	210.9
KIDNEYS	(G)	1.7136	1.6231	1.3384	1.5705	1.8173
	%	0.8031	0.8308	0.6475	0.8181	0.8616
LIVER	(G)	6.9548	6.0263	6.5994	6.0746	7.2829
	%	3.2597	3.0846	3.1926	3.1643	3.4528
THYMUS	(G)	0.4743	0.4102	0.3857	0.2603	0.4109
	%	0.2223	0.2100	0.1866	0.1356	0.1948
SPLEEN	(G)	0.4973	0.4129	0.4627	0.3045	0.4507
	%	0.2331	0.2113	0.2238	0.1586	0.2137
ADRENALS	(G)	0.0744	0.0521	0.0656	0.0509	0.0674
	%	0.0349	0.0267	0.0317	0.0265	0.0320

1000.000 MG/KG GROUP - F

ANIMAL #		586	587	588	589	590
BODY WEIGHT	(G)	193.6	200.4	202.9	173.0	222.8
KIDNEYS	(G)	1.7998	1.5150	1.6160	1.6676	2.0487
	%	0.9295	0.7560	0.7963	0.9638	0.9197
LIVER	(G)	7.4619	6.4883	7.3658	6.5211	8.3289
	%	3.8537	3.2377	3.6294	3.7690	3.7391
THYMUS	(G)	0.3976	0.4428	0.4147	0.3393	0.3525
	%	0.2053	0.2210	0.2043	0.1961	0.1582
SPLEEN	(G)	0.5125	0.4613	0.4824	0.4969	0.5521
	%	0.2647	0.2302	0.2377	0.2872	0.2479
ADRENALS	(G)	0.0648	0.0593	0.0785	0.0802	0.0732
	%	0.0335	0.0296	0.0387	0.0464	0.0329

PATHOLOGY REPORT

COMPOUND: 2-Ethyl-1,3 Hexanediol ACCESSION No. 906659
STUDY No. 88-0087G1

REPEATED EXPOSURE: Feeding____; Drinking Water____; Gavage X ; Inhalation____
No. Rats/Group: 5 ; No. Exposures: 21 ; No. Days: 29 ; Carrier: corn oil ; Sex M

Rat Numbers: Control: 0 mg/kg, 551 to 555 Dose: 1000 mg/kg, 566 to 570
Dose: 100 mg/kg, 556 to 560 Dose: ____, ____ to ____
Dose: 300 mg/kg, 561 to 565 Dose: ____, ____ to ____

ORGANS:
Nasal Cavity___ Trachea X Lungs X Thymus X Heart X Aorta___ Tongue___ Esophagus X Stomach X Small Intestine X Large Intestine X Liver X Kidneys X Urinary Bladder X Pituitary X Adrenal Glands X Pancreas X Thyroid Glands X Parathyroid X Testes X Epididymides X Male Accessory Sex Glands X Ovaries___ Fallopian Tubes___ Uterus___ Vagina___ Spleen X Mesenteric Lymph Node X Bone Marrow X Brain X Eyes___ Cervical Spinal Cord___ Sciatic Nerve___ Skin___ Quadriceps Femoris___ Femur___ Rib___ Salivary Glands X Mammary Gland___

FIXATIVE: 10% Formalin X EYE FIXATIVE: Modified Zenkers____

GROSS PATHOLOGY - TREATMENT-RELATED CHANGES: Observed: ____; Not Observed: X

Process: Control: X ; 100 mg/kg Dose: * ; 300 mg/kg Dose: * ;
1000 mg/kg Dose: X ; ____ Dose: ____

*Process gross lesions only.

Pathologist: Milan S. Vlaovic Date: 12/12/88
Milan S. Vlaovic, D.V.M., Ph.D.

HISTOPATHOLOGY - TREATMENT-RELATED CHANGES: Observed: ____; Not Observed: X

Pathologist: Milan S. Vlaovic Date: 12/12/88
Milan S. Vlaovic, D.V.M., Ph.D.

MSV:cpp
12/08/88

4198T

PATHOLOGY REPORT

COMPOUND: 2-Ethyl-1,3 Hexanediol

ACCESSION No. 906659
STUDY No. 88-0087G1

REPEATED EXPOSURE: Feeding____; Drinking Water____; Gavage X ; Inhalation____
No. Rats/Group: 5 ; No. Exposures: 21 ; No. Days: 29 ; Carrier: corn oil ; Sex F

Rat Numbers:					
Control:	0 mg/kg,	571 to 575	Dose:	1000 mg/kg,	586 to 590
Dose:	100 mg/kg,	576 to 580	Dose:	____,	____ to ____
Dose:	300 mg/kg,	581 to 585	Dose:	____,	____ to ____

ORGANS:
Nasal Cavity___ Trachea X Lungs X Thymus X Heart X Aorta___ Tongue___ Esophagus X Stomach X Small Intestine X Large Intestine X Liver X Kidneys X Urinary Bladder X Pituitary X Adrenal Glands X Pancreas X Thyroid Glands X Parathyroid X Testes___ Epididymides___ Male Accessory Sex Glands___ Ovaries X Fallopian Tubes X Uterus X Vagina X Spleen X Mesenteric Lymph Node X Bone Marrow X Brain X Eyes___ Cervical Spinal Cord___ Sciatic Nerve___ Skin___ Quadriceps Femoris___ Femur___ Rib___ Salivary Glands X Mammary Gland___

FIXATIVE: 10% Formalin X EYE FIXATIVE: Modified Zenkers____

GROSS PATHOLOGY - TREATMENT-RELATED CHANGES: Observed: ____; Not Observed: X

Process: Control: X ; 100 mg/kg Dose: * ; 300 mg/kg Dose: * ;
1000 mg/kg Dose: X ; ____ Dose: ____

*Process gross lesions only.

Pathologist: Milan S Vlaovic Date: 12/12/88
Milan S. Vlaovic, D.V.M., Ph.D.

HISTOPATHOLOGY - TREATMENT-RELATED CHANGES: Observed: ____; Not Observed: X

Pathologist: Milan S Vlaovic Date: 12/12/88
Milan S. Vlaovic, D.V.M., Ph.D.

MSV:cpp
12/08/88

4198T

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

GROUP	0.000 MG/KG M	100.000 MG/KG M	300.000 MG/KG M	1000.000 MG/KG M
TRACHEA	5	5	5	5
LUNGS	5	5	5	5
HEART	5	5	5	5
ESOPHAGUS	5	5	5	5
STOMACH	5	5	5	5
DUODENUM	5	5	5	5
JEJUNUM	5	5	5	5
ILEUM	5	5	5	5
CECUM	5	5	5	5
COLON	5	5	5	5
URINARY BLADDER	5	5	5	5
PITUITARY GLAND	5	5	5	5
PANCREAS, NOS	5	5	5	5
THYROID GLANDS	5	5	5	5
PARATHYROID GLANDS	5	5	5	5
MESENTERIC LYMPH NODES	5	5	5	5
BONE MARROW	5	5	5	5
BRAIN	5	5	5	5
SALIVARY GLANDS	5	5	5	5
EPIDIDYMIDES	5	5	5	5
ACCESSORY SEX ORGANS (MALE)	5	5	5	5
KIDNEYS	5	5	5	5
LIVER	5	5	5	5
THYMUS	5	5	5	5
HEMORRHAGE	0	1	1	1
SPLEEN	5	5	5	5
ADRENALS	5	5	5	5
TESTES	5	5	5	5
SMALL	0	1	0	0

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY.

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

0.000 MG/KG GROUP - M

ANIMAL #	551	552	553	554	555
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS	N	N	N	N	N
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N
ACCESSORY SEX ORGANS (MALE)	N	N	N	N	N
KIDNEYS	N	N	N	N	N
LIVER	N	N	N	N	N
THYMUS	N	N	N	N	N
SPLEEN	N	N	N	N	N
ADRENALS	N	N	N	N	N
TESTES	N	N	N	N	N

KEY:N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

100.000 MG/KG GROUP - M

ANIMAL #	556	557	558	559	560
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS	N	N	N	N	N
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N
ACCESSORY SEX ORGANS (MALE)	N	N	N	N	N
KIDNEYS	N	N	N	N	N
LIVER	N	N	N	N	N
THYMUS	N		N	N	N
HEMORRHAGE		2			
SPLEEN	N	N	N	N	N
ADRENALS	N	N	N	N	N
TESTES	N		N	N	N
SMALL		2			

KEY:N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

300.000 MG/KG GROUP - M

ANIMAL #	561	562	563	564	565
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS	N	N	N	N	N
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N
ACCESSORY SEX ORGANS (MALE)	N	N	N	N	N
KIDNEYS	N	N	N	N	N
LIVER	N	N	N	N	N
THYMUS	N		N	N	N
HEMORRHAGE		1			
SPLEEN	N	N	N	N	N
ADRENALS	N	N	N	N	N
TESTES	N	N	N	N	N

KEY:N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

1000.000 MG/KG GROUP - M

ANIMAL #	566	567	568	569	570
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS	N	N	N	N	N
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N
ACCESSORY SEX ORGANS (MALE)	N	N	N	N	N
KIDNEYS	N	N	N	N	N
LIVER	N	N	N	N	N
THYMUS		N	N	N	N
HEMORRHAGE	1				
SPLEEN	N	N	N	N	N
ADRENALS	N	N	N	N	N
TESTES	N	N	N	N	N

KEY:N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

GROUP	0.000 MG/KG F	100.000 MG/KG F	300.000 MG/KG F	1000.000 MG/KG F
TRACHEA	5	5	5	5
LUNGS	5	5	5	5
HEART	5	5	5	5
ESOPHAGUS	5	5	5	5
STOMACH	5	5	5	5
DUODENUM	5	5	5	5
JEJUNUM	5	5	5	5
ILEUM	5	5	5	5
CECUM	5	5	5	5
COLON	5	5	5	5
URINARY BLADDER	5	5	5	5
PITUITARY GLAND	5	5	5	5
PANCREAS, NOS	5	5	5	5
THYROID GLANDS	5	5	5	5
PARATHYROID GLANDS	5	5	5	5
MESENTERIC LYMPH NODES	5	5	5	5
BONE MARROW	5	5	5	5
BRAIN	5	5	5	5
SALIVARY GLANDS	5	5	5	5
OVARIES	5	5	5	5
FALLOPIAN TUBES	5	5	5	5
UTERUS	5	5	5	5
HYDROMETRA	2	1	2	0
VAGINA	5	5	5	5
KIDNEYS	5	5	5	5
LIVER	5	5	5	5
THYMUS	5	5	5	5
HEMORRHAGE	1	0	0	2
SPLEEN	5	5	5	5
ADRENALS	5	5	5	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY.

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP - F				
ANIMAL #	571	572	573	574	575
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS	N	N	N	N	N
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
OVARIES	N	N	N	N	N
FALLOPIAN TUBES	N	N	N	N	N
UTERUS	N			N	N
HYDROMETRA		1	2		
VAGINA	N	N	N	N	N
KIDNEYS	N	N	N	N	N
LIVER	N	N	N	N	N
THYMUS	N		N	N	N
HEMORRHAGE		1			
SPLEEN	N	N	N	N	N
ADRENALS	N	N	N	N	N

KEY:N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

100.000 MG/KG GROUP - F

ANIMAL #	576	577	578	579	580
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS	N	N	N	N	N
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
OVARIES	N	N	N	N	N
FALLOPIAN TUBES	N	N	N	N	N
UTERUS	N	N	N		N
HYDROMETRA				1	
VAGINA	N	N	N	N	N
KIDNEYS	N	N	N	N	N
LIVER	N	N	N	N	N
THYMUS	N	N	N	N	N
SPLEEN	N	N	N	N	N
ADRENALS	N	N	N	N	N

KEY:N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

300.000 MG/KG GROUP - F

ANIMAL #	581	582	583	584	585
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS	N	N	N	N	N
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
OVARIES	N	N	N	N	N
FALLOPIAN TUBES	N	N	N	N	N
UTERUS	N	N		N	
HYDROMETRA			1		2
VAGINA	N	N	N	N	N
KIDNEYS	N	N	N	N	N
LIVER	N	N	N	N	N
THYMUS	N	N	N	N	N
SPLEEN	N	N	N	N	N
ADRENALS	N	N	N	N	N

KEY:N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

1000.000 MG/KG GROUP - F

ANIMAL #	586	587	588	589	590
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS	N	N	N	N	N
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
OVARIES	N	N	N	N	N
FALLOPIAN TUBES	N	N	N	N	N
UTERUS	N	N	N	N	N
VAGINA	N	N	N	N	N
KIDNEYS	N	N	N	N	N
LIVER	N	N	N	N	N
THYMUS		N	N	N	
HEMORRHAGE	1				1
SPLEEN	N	N	N	N	N
ADRENALS	N	N	N	N	N

KEY:N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
P-PRESENT,A-ABSENT,*-SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

GROUP	0.000 MG/KG M	100.000 MG/KG M	300.000 MG/KG M	1000.000 MG/KG M
TRACHEA	5	0	0	5
LUNGS	5	0	0	5
CENTRIACINITIS (LUNG)	1	0	0	0
BRONCHUS				
LYMPHOCYTIC INFLAMMATORY INFILTRATE	5	0	0	5
THYMUS	5	1	1	5
HEMORRHAGE	3	1	1	3
HEART	5	0	0	5
ESOPHAGUS	5	0	0	5
STOMACH	5	0	0	5
DUODENUM	5	0	0	5
JEJUNUM	5	0	0	5
ILEUM	5	0	0	5
CECUM	5	0	0	5
COLON	5	0	0	5
LIVER	5	0	0	5
INFLAMMATION, CHRONIC FOCAL	5	0	0	4
HEPATOCYTE				
CYTOPLASMIC VACUOLIZATION	3	0	0	2
KIDNEYS	5	0	0	5
INFLAMMATION, CHRONIC FOCAL	1	0	0	0
PROXIMAL CONVOLUTED RENAL TUBULE				
DEGENERATION, HYALIN	4	0	0	5
URINARY BLADDER	5	0	0	5
PITUITARY GLAND	5	0	0	5
ADRENALS	5	0	0	5
PANCREAS, NOS	5	0	0	5
THYROID GLANDS	5	0	0	5
THYROID FOLLICLE				
METAPLASIA, SQUAMOUS	3	0	0	1
PARATHYROID GLANDS	4	0	0	5
SPLEEN	5	0	0	5
MESENTERIC LYMPH NODES	5	0	0	5
BONE MARROW	5	0	0	5
BRAIN	5	0	0	5
SALIVARY GLANDS	5	0	0	5
TESTES	5	1	0	5
SPERMATOZOA				
DECREASED	0	1	0	0
SPERMATID				
DECREASED	0	1	0	0
DEGENERATION, NOS	0	1	0	0
EPIDIDYMIDES	5	0	0	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY.

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

GROUP	0.000 MG/KG M	100.000 MG/KG M	300.000 MG/KG M	1000.000 MG/KG M
ACCESSORY SEX ORGANS (MALE)	5	0	0	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY.

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP - M				
ANIMAL #	551	552	553	554	555
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS					
CENTRIACINITIS (LUNG)				1	
BRONCHUS					
LYMPHOCYTIC INFLAMMATORY INFILTRATE	1	1	1	1	1
THYMUS				N	N
HEMORRHAGE	1	1	1		
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
LIVER					
INFLAMMATION, CHRONIC FOCAL	1	1	1	1	1
HEPATOCYTE					
CYTOPLASMIC VACUOLIZATION	1	1	1		
KIDNEYS		N			
INFLAMMATION, CHRONIC FOCAL					1
PROXIMAL CONVOLUTED RENAL TUBULE					
DEGENERATION, HYALIN	1		1	1	1
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
ADRENALS	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS		N			N
THYROID FOLLICLE					
METAPLASIA, SQUAMOUS	1		1	1	
PARATHYROID GLANDS	A	N	N	N	N
SPLEEN	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
TESTES	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP - M				
ANIMAL #	551	552	553	554	555
DAYS ON TEST	29	29	29	29	29
ACCESSORY SEX ORGANS (MALE)	N	N	N	N	N

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

100.000 MG/KG GROUP - M

ANIMAL #	556	557	558	559	560
DAYS ON TEST	29	29	29	29	29
TRACHEA					
LUNGS					
THYMUS					
HEMORRHAGE		2			
HEART					
ESOPHAGUS					
STOMACH					
DUODENUM					
JEJUNUM					
ILEUM					
CECUM					
COLON					
LIVER					
KIDNEYS					
URINARY BLADDER					
PITUITARY GLAND					
ADRENALS					
PANCREAS, NOS					
THYROID GLANDS					
PARATHYROID GLANDS					
SPLEEN					
MESENTERIC LYMPH NODES					
BONE MARROW					
BRAIN					
SALIVARY GLANDS					
TESTES					
SPERMATOZOA					
DECREASED		4			
SPERMATID					
DECREASED		3			
DEGENERATION, NOS		3			
EPIDIDYMIDES					
ACCESSORY SEX ORGANS (MALE)					

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

300.000 MG/KG GROUP - M

ANIMAL #	561	562	563	564	565
DAYS ON TEST	29	29	29	29	29
TRACHEA					
LUNGS					
THYMUS					
HEMORRHAGE		1			
HEART					
ESOPHAGUS					
STOMACH					
DUODENUM					
JEJUNUM					
ILEUM					
CECUM					
COLON					
LIVER					
KIDNEYS					
URINARY BLADDER					
PITUITARY GLAND					
ADRENALS					
PANCREAS, NOS					
THYROID GLANDS					
PARATHYROID GLANDS					
SPLEEN					
MESENTERIC LYMPH NODES					
BONE MARROW					
BRAIN					
SALIVARY GLANDS					
TESTES					
EPIDIDYMIDES					
ACCESSORY SEX ORGANS (MALE)					

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

1000.000 MG/KG GROUP - M

ANIMAL #	566	567	568	569	570
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS					
BRONCHUS					
LYMPHOCYTIC INFLAMMATORY INFILTRATE	1	1	1	1	1
THYMUS		N		N	
HEMORRHAGE	1		1		1
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
LIVER					N
INFLAMMATION, CHRONIC FOCAL	1	1	1	1	
HEPATOCYTE					
CYTOPLASMIC VACUOLIZATION		1		1	
KIDNEYS					
PROXIMAL CONVOLUTED RENAL TUBULE					
DEGENERATION, HYALIN	1	1	1	1	1
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
ADRENALS	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N		N	N
THYROID FOLLICLE					
METAPLASIA, SQUAMOUS			1		
PARATHYROID GLANDS	N	N	N	N	N
SPLEEN	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
TESTES	N	N	N	N	N
EPIDIDYMIDES	N	N	N	N	N
ACCESSORY SEX ORGANS (MALE)	N	N	N	N	N

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

SUMMARY HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

GROUP	0.000 MG/KG F	100.000 MG/KG F	300.000 MG/KG F	1000.000 MG/KG F
TRACHEA	5	0	0	5
LUNGS	5	0	0	5
BRONCHUS				
LYMPHOCYTIC INFLAMMATORY INFILTRATE	5	0	0	5
THYMUS	5	0	0	5
HEMORRHAGE	3	0	0	2
HEART	5	0	0	5
ESOPHAGUS	5	0	0	5
STOMACH	5	0	0	5
DUODENUM	5	0	0	5
JEJUNUM	5	0	0	5
ILEUM	5	0	0	5
CECUM	5	0	0	5
COLON	5	0	0	5
LIVER	5	0	0	5
INFLAMMATION, CHRONIC FOCAL	2	0	0	3
HEPATOCYTE				
CYTOPLASMIC VACUOLIZATION	2	0	0	2
KIDNEYS	5	0	0	5
HYDRONEPHROSIS, BILATERAL	0	0	0	1
URINARY BLADDER	5	0	0	4
PITUITARY GLAND	5	0	0	5
ADRENALS	5	0	0	5
PANCREAS, NOS	5	0	0	5
THYROID GLANDS	5	0	0	5
THYROID FOLLICLE				
METAPLASIA, SQUAMOUS	2	0	0	0
PARATHYROID GLANDS	2	0	0	4
SPLEEN	5	0	0	5
MESENTERIC LYMPH NODES	5	0	0	5
BONE MARROW	5	0	0	5
BRAIN	5	0	0	5
SALIVARY GLANDS	5	0	0	5
OVARIES	5	0	0	5
FALLOPIAN TUBES	5	0	0	5
UTERUS	5	1	2	5
HYDROMETRA	2	1	2	0
VAGINA	5	0	0	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY.

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

	0.000 MG/KG GROUP - F				
ANIMAL #	571	572	573	574	575
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS					
BRONCHUS					
LYMPHOCYTIC INFLAMMATORY INFILTRATE	1	1	1	1	1
THYMUS			N	N	
HEMORRHAGE	1	1			1
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
LIVER	N				N
INFLAMMATION, CHRONIC FOCAL		1		1	
HEPATOCYTE					
CYTOPLASMIC VACUOLIZATION		1	1		
KIDNEYS	N	N	N	N	N
URINARY BLADDER	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
ADRENALS	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N			N
THYROID FOLLICLE					
METAPLASIA, SQUAMOUS			1	1	
PARATHYROID GLANDS	A	A	A	N	N
SPLEEN	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
OVARIES	N	N	N	N	N
FALLOPIAN TUBES	N	N	N	N	N
UTERUS	N			N	N
HYDROMETRA		1	2		
VAGINA	N	N	N	N	N

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

100.000 MG/KG GROUP - F

ANIMAL #	576	577	578	579	580
DAYS ON TEST	29	29	29	29	29
TRACHEA					
LUNGS					
THYMUS					
HEART					
ESOPHAGUS					
STOMACH					
DUODENUM					
JEJUNUM					
ILEUM					
CECUM					
COLON					
LIVER					
KIDNEYS					
URINARY BLADDER					
PITUITARY GLAND					
ADRENALS					
PANCREAS, NOS					
THYROID GLANDS					
PARATHYROID GLANDS					
SPLEEN					
MESENTERIC LYMPH NODES					
BONE MARROW					
BRAIN					
SALIVARY GLANDS					
OVARIES					
FALLOPIAN TUBES					
UTERUS					
HYDROMETRA				1	
VAGINA					

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

300.000 MG/KG GROUP - F

ANIMAL #	581	582	583	584	585
DAYS ON TEST	29	29	29	29	29
TRACHEA					
LUNGS					
THYMUS					
HEART					
ESOPHAGUS					
STOMACH					
DUODENUM					
JEJUNUM					
ILEUM					
CECUM					
COLON					
LIVER					
KIDNEYS					
URINARY BLADDER					
PITUITARY GLAND					
ADRENALS					
PANCREAS, NOS					
THYROID GLANDS					
PARATHYROID GLANDS					
SPLEEN					
MESENTERIC LYMPH NODES					
BONE MARROW					
BRAIN					
SALIVARY GLANDS					
OVARIES					
FALLOPIAN TUBES					
UTERUS					
HYDROMETRA			1		2
VAGINA					

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

INDIVIDUAL ANIMAL HISTOPATHOLOGY INCIDENCE TABLE

EXPERIMENT # 880087G1 EXPERIMENT START DATE: 29-AUG-88 COMPOUND # 88-0087
SOFTWARE VERS # 3.0
ACCESSION NUMBER 906659

1000.000 MG/KG GROUP - F

ANIMAL #	586	587	588	589	590
DAYS ON TEST	29	29	29	29	29
TRACHEA	N	N	N	N	N
LUNGS					
BRONCHUS					
LYMPHOCYTIC INFLAMMATORY INFILTRATE	1	1	1	1	1
THYMUS		N		N	N
HEMORRHAGE	1		1		
HEART	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N
STOMACH	N	N	N	N	N
DUODENUM	N	N	N	N	N
JEJUNUM	N	N	N	N	N
ILEUM	N	N	N	N	N
CECUM	N	N	N	N	N
COLON	N	N	N	N	N
LIVER		N			
INFLAMMATION, CHRONIC FOCAL	1		1		1
HEPATOCYTE					
CYTOPLASMIC VACUOLIZATION	1			1	
KIDNEYS	N	N		N	N
HYDRONEPHROSIS, BILATERAL			1		
URINARY BLADDER	A	N	N	N	N
PITUITARY GLAND	N	N	N	N	N
ADRENALS	N	N	N	N	N
PANCREAS, NOS	N	N	N	N	N
THYROID GLANDS	N	N	N	N	N
PARATHYROID GLANDS	A	N	N	N	N
SPLEEN	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N
BONE MARROW	N	N	N	N	N
BRAIN	N	N	N	N	N
SALIVARY GLANDS	N	N	N	N	N
OVARIES	N	N	N	N	N
FALLOPIAN TUBES	N	N	N	N	N
UTERUS	N	N	N	N	N
VAGINA	N	N	N	N	N

KEY:P-PRESENT,A-ABSENT,N-NORMAL ,1-MINIMAL,2-MINOR,3-MODERATE,4-SEVERE
* - SEE COMMENT REPORT (FORM #3)

CHEMICALS QUALITY SERVICES DIVISION REPORT

ANALYSIS REQUESTED BY: Toxicology

DATE REQUESTED: 6/28/88

DATE ANALYZED: 8/18/88

CQSD JOB FILE NUMBER: EE8H021

REQUEST FOR ANALYSIS: 084797

TITLE: Initial Purity of 88-0087

AUTHOR: N. Porter

DATE REPORTED: 8/22/88

FOR ADDITIONAL INFORMATION OR WORK CONTACT: K. Robillard, N. Porter

SAMPLE IDENTIFICATION: Received one sample labelled HAEL # 88-0087, Acc. # 906659

REPORT:

The sample was submitted for initial purity, and was analyzed using the following chromatographic conditions:

30m, DB-5 wide bore 0.25um J+W column
carrier: Helium at 8 psi
50°C (2 min.) - 200°C at 10°/min. (hold at 200°C for 1min)
split injection, sample load approx. 2.0 uL
electron ionization
inj. temp. @ 250°C
det. temp. @ 250°C

The sample was diluted in ethyl acetate and analyzed. The results were as follows:

Area % 88-0087
99.9

n = 3
SD = 0

Signed N. Porter
BLR

CHEMICALS QUALITY SERVICES DIVISION REPORT

ANALYSIS REQUESTED BY: Toxicology

DATE REQUESTED: 7/15/88

STUDY TYPE: 28 Day Gavage

DATE ANALYZED: 7/29/88

CQSD JOB FILE NUMBER: EE8H021 Req # 084797

STUDY DIRECTOR: Walt Krasavage

TITLE: Structure Confirmation of 88-0087

AUTHOR: N. Porter

DATE REPORTED: 8/1/88

FOR ADDITIONAL INFORMATION OR WORK CONTACT: K. Burgess, N. Porter

SAMPLE IDENTIFICATION: Received one sample labelled HAEL # 88-0087, Acc. # 906659

REPORT:

The sample was submitted for GC/MS characterization, and was analyzed using the following chromatographic conditions:

30m, DB-5 wide bore 1.0um J+W column
carrier: Helium at 10 psi
50°C (2 min.) - 220°C at 10°/min. (hold at 220°C for 2min)
split injection, sample load approx. 1.0 uL
electron ionization

The sample was diluted in acetone (1080 mg/l conc.) and analyzed. The spectra of the two peaks which elute at 12.9 min. and 13.0 min. are both consistent with the structure of HAEL # 88-0087.

Signed N. Porter
S Spjewly

Toxicity Data

906659

from L+F

MAMMALIAN TOXICITY DATA
FOR A PERSONAL INSECT REPELLENT
CONTAINING 30% 2-Ethyl-1,3-HEXANEDIOL

RBM
7/2/70

MAMMALIAN TOXICITY DATA

FOR A PERSONAL INSECT REPELLENT

CONTAINING 30% 2-ETHYL-1,3-HEXANEDIOL

INTRODUCTION

This report summarizes toxicity test data associated with a personal insect repellent containing, as the active ingredient, 30% 2-ethyl-1,3-hexanediol. Data are provided for skin sensitization tests on animals and humans.

FORMULATIONS AND TEST PROCEDURES

The composition of the aerosol preparation tested is as follows:

Material	Formula Number 1450-112-7 Weight Per Cent
1. 2-Ethyl-1,3-Hexanediol (diol)	30.0
2. SD39B ethanol, 200 proof	40.0
3. Triethanolamine phosphate	1.0
4. Perfume W-1413-5	0.2
5. Deionized Water	18.8
6. Dichlorodifluoromethane	10.0
	100.0

This formula is also identified as 30EDH-water plus TEAP (2203-2448) in the South Mountain Laboratory report Appendix II, pages 12, 16. Other formulations noted in the report are not germane.

Laboratory Testing Procedure Used for Animals

Laboratory testing by Mellon Institute of the preparation on guinea pigs and rabbits was done by the procedures following:

The sample was prepared for testing by placing it in a freezer overnight. The contents were then removed and were allowed to reach room temperature slowly so that the propellant would evaporate slowly with no appreciable loss of the active ingredients.

A. Modified Landsteiner Test (See Appendix I , page 6 , for complete details)

Eighteen young adult male male albino guinea pigs were injected intradermally in the clipped upper right scapular area with 0.05 ml. of a 0.1% (W/V) solution of the formulation in physiological saline. A similar injection was made into the upper left scapular area with saline alone, which served as a control. A one ml. hypodermic syringe and a 26-gauge needle with beveled hub were used. The injected sites were examined at 24 and 48 hours and the reactions were graded according to a scale which considers the area, height, and intensity of color of the resulting bleb. Starting 48 hours after the initial injection, a series of seven intradermal sensitizing injections of 0.1 ml. of the formulation-saline solution were given into the clipped lumbo-sacral area at the rate of three injections per week. Each injection was made into an untreated site.

The animals were allowed a three-week "incubation period" and then were given challenge injections of 0.05 ml. of the formulation-saline solution into the clipped lower right scapular area, and 0.05 ml. of saline alone into the lower left scapular area. The injected sites were again examined at 24 and 48 hours. The reactions were compared to those observed after the initial injection and graded by a system wherein a final score of 25 or less indicates no sensitization potential and a final score of 100 indicates a moderate sensitization potential.

Three-Day Repeated Rabbit Skin Irritation Tests

The formulations were sprayed directly from the aerosol cans on to the same spot on the clipped skin of the rabbit belly at 9 a.m., 12 noon, and 3 p.m. each day for 3 days. Results were scored the morning after the 3rd, 6th, and 9th applications.

SUMMARY OF RESULTS

The data from the sensitizing tests on guinea pigs showed that the highest score was nine. Thus, under the conditions of the test, the formulation was found to have no sensitization potential.

Results of the rabbit skin irritation are given in Appendix I, page 11. The data show that the formulation is not a rabbbit skin irritant.

Testing Procedure Used on Humans

In vivo testing of the 30% diol preparation was conducted by South Mountain Laboratories Inc., 487 Valley Street, Maplewood, New Jersey 07040. The test procedure follows:

A. Skin Sensitization Test

Method of Test: The formulation was tested on groups of over 200 people. The groups were almost equally divided according to sex and was made up of children from age 7 through the teens and adults up to 68 years of age.

The spray was applied to the skin through a mask which prevented excessive spreading.

The treated areas were immediately covered with a Duke Patch #071 which is specially made for patch testing. The pad covered an area one inch square and had an occlusive backing. The treated areas were 3 on each forearm; this is the area recommended by the Food and Drug Administration in a

recent publication by Marzulli, Carson and Maibach. The forearm areas treated were (1) above the wrist (2) the mid arm and (3) just below the elbow.

Persons on Groups A and B were started on different days in order to facilitate application to and inspection of the areas. Each subject received a sheet designating the area to which the spray was applied over the 10 consecutive alternate day treatments. Recordings were noted to indicate if nothing was seen (0) at a particular area of (B) if redness was seen and (I) if itching was experienced, or an (R) and (I) if both occurred.

The test areas in each group were designated as follows:

(1) above left wrist area

(2) mid left arm area

(3) below left elbow area

(4) above right wrist area

The first 50 subjects in each group received their spray material in the 1 position.

The second 50 subjects in each group using the same spray, started on the number 2 area. The third 50 subjects started the spray in the number 3 area.

The fourth 50 or more subjects started the spray on the number 4 area. This permitted 4 different sets of areas of application for the spray within each group of 200 subjects.

Patches were kept on for 24 hours after which the area was scored. The test material was reapplied 48 hours after the proceeding application. A dot of merthiolate was used to mark beside the area for retreatment so that the material would be applied directly to the skin previously treated.

Two weeks after the last (10th) treatment, the same areas were again treated with the experimental material previously used on the sites. An occlusive patch was again applied for 24 hours after which the patch was removed and the area scored according to the reaction seen. The areas were scored for 96 hours after the challenge treatment.

B. Photosensitization Tests on Humans

Fifty subjects from each group were tested for possible skin photosensitization.

Twenty-four hours after the challenge dose was applied, the treated areas were exposed for 1 minute to a Westinghouse Sun Lamp held 6 inches from the skin. This exposure was found to be sufficient to cause a mild erythema lasting approximately 48 hours to certain test subjects known to be hypersensitive to sunlight.

Summary of Results: None of the reactions on the subjects showed any more than a very minimal positive response to the 30% diol formulation. There was no photosensitization.

A number of subjects could not be retained on the test because of a considerable response to the material. These hypersensitive individuals admitted to being sensitive to many things which they did not admit to when asked about hypersensitivities before starting the test.

A certain small percentage of the population would therefore find the preparation to be irritating under normal usage and thus could not use the preparation without considerable irritating effects.

RBMitchell/crc
5/12/70

Toxicity Data

906659

R: 3-1-54

~~9-3-54~~

Confidential

Report 17-37

from L+F

MELLON INSTITUTE OF INDUSTRIAL RESEARCH

UNIVERSITY OF PITTSBURGH

SPECIAL REPORT

on

Ninety-Day Repeated Oral Doses of 2-Ethylhexanediol-1,3 to Dogs

Carbide and Carbon Chem. Co., U.C.C. Industrial Fellowship No. 274-17

Summary

A group of 3 dogs was dosed by mouth 7 days a week for 90 days with 0.5 ml. per kg. of 2-ethylhexanediol per day. A similar group of litter-mates received 0.1 ml./kg./day while two litter-mates were observed as controls. No statistically significant differences or trends were found between the dosed and control group in the following criteria: body weight gain, mortality, pathology of the liver or kidney, hematocrit determination, bromsulfalein retention, prothrombin time and serum urea-nitrogen determinations. On the basis of this study it appears that dogs are no more sensitive than rats in response to ethylhexanediol. The previously reported dosage level that statistical evaluation of the criteria examined indicated produced no deviation from the controls for rats for 90 days was 0.48 gm./kg./day.

Previous Oral Work

The LD_{50} for male albino rats given a single oral dose of 2-ethylhexanediol-1,3 as a 10% dispersion in water (with 1% "Tergitol" 7 added) was 2.71 (2.52 to 2.93) gm./kg. In various other dispersants the LD_{50} varied from 2.16 to 4.29 gm./kg. For albino rabbits the single oral LD_{50} was 2.24 (1.60 to 3.16) ml./kg. and for adult guinea pigs the LD_{50} was 1.58 (1.35 to 1.86) gm./kg.

Ninety days of oral doses to rats resulted in no injury from 0.48 gm./kg./day (0.9% of the diet). Only growth was retarded at 0.70 gm./kg./day (1.35% of the diet).

Single oral doses of ethylhexanediol administered to rats produced cloudy swelling and congestion of the liver and kidney when the doses approached the LD_{50} but were not fatal. When fatal, toxic necrosis of the kidney resulted. Kidney pathology was not discovered, however, even after 90 oral doses of as high a dosage as 0.7 gm./kg./day.

Sample Used

The gallon sample of 2-ethylhexanediol-1,3 used in this study was received 9-14-53. It was labelled "active ingredient - 100%" and "Passed S 49854".

Study No. EN-102-906659-1

ES-89-028

248722C

READY BIODEGRADABILITY (USING THE MODIFIED OECD TEST)

(In accordance with US EPA 40 CFR Section 796.3240)

2-Ethyl-1,3-hexanediol

Accession No. 906659 HAEL No. 88-0087

CAS Reg. No. 94-96-2

By

Heather M. Watson

Environmental Sciences Section

Health and Environment Laboratories

Eastman Kodak Company

Rochester, New York 14652-3617

Completion Date: March 27, 1989

Abstract

A 35-day biodegradation test was performed to determine the ready biodegradability of 2-Ethyl-1,3-hexanediol using the Modified OECD Test (Annex V Test Guideline C.3 and US EPA/TSCA 40 CFR Section 796.3240). The test inoculum was a composite of microorganisms from the secondary effluent of a domestic waste treatment plant, from river water, and from soil. Biodegradability was determined by measuring the loss of dissolved organic carbon (DOC) from the test chemical solution. The test chemical was not readily biodegradable according to the definitions of this test but 93% mineralization occurred slowly over the course of the test in one Test Flask (by Day 27) and 53% occurred in the second Test Flask (by Day 35). An additional experiment in the second flask showed 74% biodegradation by Day 42, seven days after inoculation with acclimated organisms from the first flask. It is therefore likely that biodegradation in the environment will be very variable depending on the microbial species present.

Table of Contents

	Page
Testing Facility Operation	4
Date of Study Initiation	4
Date of Study Completion	4
Study Participants	4
Test Guideline	4
Purpose/Objective	4
Test Substance	4
Control Substance	5
Materials snd Methods	
A. Test System	5
B. Source and Preparation of the Inoculum	5
C. Preparation of Test Solutions	5
D. Test Procedure	6
E. Analytical Measurements	7
F. Data Evaluation and Interpretation	7
G. Calculations	8
Quality Assurance Monitoring	8
Good Laboratory Practice Statement	8
Data Storage and Records Retention	8
Results	8
Test Validity	9
Protocol Deviations	9
Discussion	9
Conclusion	10
References	10
Tables	
1. Composition of BSM and Stock Solutions	11
2. Preparation of Test Solutions	12
Figures	
1. Graph Showing Percent DOC Removal	13
Attachments	
1. Lotus Spreadsheet for Dissolved Organic Carbon	14
2. Data Sheets for DOC	15
3. CQS Division Reports on Chemical Purity	17
4. Quality Assurance Statements	21

HAEL No. 88-0087 Study No. EN-102-906659-1

Testing Facility
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-3617
USA

Sponsor
Eastman Kodak Company
Rochester, New York 14652-3617
USA

Date of Study Initiation
January 23, 1989
Date of Study Completion
March 27, 1989

Study Participants
Environmental Sciences Section:

T.J. Dagon, Supervisor, Environmental Sciences Section
J.W. Gorsuch, Group Leader, Eco-Chem Testing Group
M.M. McWilliams, Technician, Eco-Chem Testing Group
M.A. Shea, Technician, Eco-Chem Testing Group
H.M. Watson, Study Director and Principal Investigator, Eco-Chem Testing Group

Test Guideline
OECD Guideline 301E
EEC/Annex V Guideline C.3
US EPA/TSCA 40 CFR Section 796.3240

Purpose/Objective
The purpose of this test is to determine the ready biodegradability of the test substance by unacclimated microorganisms by measuring the loss of dissolved organic carbon (DOC) from the test solution over the 28-day test period.[1]

Test Substance
Identity: 2-Ethyl-1,3-hexanediol
Lot No.: TX-1694-65
Sample Laboratory No.: 88-0087

Composition (determined by the CQSD, Attachment 3):

Purity: Starting, 99.9%; final, 99.4% (area) by HPLC.

Stability (determined by CQSD, Attachment 3):

Shelf-life stability was confirmed by repeating the purity assay after testing.

Control Substance

Identity: Sodium benzoate; CAS Reg. No.: 532-32-1

Materials and Methods

A. Test System

Microorganisms were obtained from secondary effluent (Van Lare Wastetreatment Plant, Rochester, New York), from surface water (the Genesee River), and from garden soil (Monroe County). A composite inoculum was prepared from these samples. Viability of the microorganisms was confirmed after inoculation of the test solutions and activity was checked by means of a control substance. In studies of this sort no attempt is made to identify the large variety of organisms present in the sample or the degree of absorption of the test and control substance.

B. Source and Preparation of the Inoculum

A secondary effluent sample was collected, the sample was filtered through a coarse filter, and the first 200 mL were discarded. The filtrate was aerated until used (on the day of collection). A river water sample was prepared in a similar manner. A 100 g sample of fertile, non-sterile soil was suspended in 1.0 L of distilled water. After settling for approximately 90 minutes, the supernatant was filtered and prepared in the same manner as the first two samples. A composite inoculum solution was prepared by mixing equal volumes of the three filtrates.

C. Preparation of Test Solutions

Three solutions were prepared. Basal Salts Medium (Table 1) was prepared using high quality distilled water (which was monitored beforehand by DOC

analysis). The Basal Salts Medium (BSM) was aerated for 30 minutes using carbon dioxide-free air obtained by passing air through a sodium hydroxide (8.0 g/L) trap. The Test Chemical Solution and the Positive Control Solution were each made up by dissolving in the BSM to give 20 mg DOC/L. Adjustments to the pH were made using 6N HCl to bring solutions to a final pH of 7.2 ± 0.1 (Table 2).

D. Test Procedure

Test Chemical Solution (900 mL) was placed into each of two 2-L Erlenmeyer flasks and inoculated with 0.5 mL/L portions of the inoculum. Positive Control Solution (900 mL) was placed into another 2-L Erlenmeyer flask and inoculated with a 0.5 mL/L portion of the inoculum. A fourth 2-L Erlenmeyer was used as a Blank to determine background levels of DOC: BSM (900 mL) was placed into this vessel and inoculated with a 0.5 mL/L portion of the inoculum. The opening of each vessel was covered loosely with aluminium foil so that the exchange of air between the flask and the surrounding atmosphere was not unduly impeded. The vessels were then incubated in a Shel-Lab incubator in the dark at a temperature of 20 to 25^{0}C and oscillated at 100 rpm. Evaporation losses from the culture medium were made up by adding distilled water in the required amounts on each analysis day (culture medium levels were marked on the outside of each vessel).

All steps were performed with great care to ensure the cleanliness (but not sterility) of all vessels. The Erlenmeyer flasks, for example, were cleaned carefully before use, rinsed with hydrochloric acid followed by several tap water rinses and 5 final distilled water rinses.

The test was extended because biodegradation had not plateaued. On Day 35, Test B had still not degraded although mineralization had been achieved in Test A by Day 27. It was considered likely that Test Flask B lacked some needed species of microbes, and therefore on Day 35 a 5.0 mL aliquot of test solution containing microorganisms was transferred from Test A to Test B. This was thought to be enough to achieve mineralization in Test Flask B if the above hypothesis was correct.

E. Analytical Measurements

1. Dissolved Organic Carbon Analysis:

DOC concentrations were determined in duplicate for each vessel at the start of the test and on days 7, 14, 21, 27, 28, 34 and 35. Determinations were also made for the Blank and Test B on Day 42. Only the necessary volume of solution (30 mL) was withdrawn for each determination. The medium was mixed well before withdrawing a sample in order to dissolve or suspend material adhering to the wall of the vessel. The samples were centrifuged in a refrigerated centifuge at approximately 4000 x g for 15 minutes and the DOC concentration of the supernatant was determined after diluting 1 to 40 with distilled water. A SYBRON/Barnstead PHOTOchem® Total Organic Carbon Analyzer was used for the DOC analysis. This instrument was calibrated using 1 ppm and 0 ppm organic carbon standards; DOC values were printed out on the strip chart recorder.

2. Dissolved Oxygen (DO) and pH Measurements:

The DO of the purged BSM was recorded at the start of the test. DO levels in all test solutions were recorded at the end of the test. The pH of test solutions were measured at the beginning and end of the test.

F. Data Evaluation and Interpretation

Lotus 1-2-3® was used for data calculations and tabulations and also to generate the graph showing percentage DOC removal from the Test Chemical and the Positive Control Solutions. These values were corrected for background levels of DOC. The DOC concentrations were expressed to the nearest 0.1 mg/L and the mean DOC removal values were rounded to the nearest whole percent before plotting the graph. No statistical evaluation of the data was performed.

Owing to the stringency of this test, a low result does not necessarily mean that the test compound is not biodegradable under environmental conditions. Test chemicals showing a high DOC loss in this test should be regarded as easily biodegradable provided that this level is reached within the time window of 10 days, counting from the day that the observed level of biodegradation first exceeds 10%.

G. Calculations

The degradation is defined as the percentage DOC removal with respect to the test substance:

$$D_t = \left(1 - \frac{C_t - C_{bl(t)}}{C_0 - C_{bl(0)}}\right) \times 100$$

where:

D_t = degradation in percent DOC-removal at time t;

C_0 = starting Test Chemical Solution concentration (mg DOC/L);

C_t = Test Chemical Solution concentration at time t (mg DOC/L);

$C_{bl(0)}$ = starting background (blank) concentration (mg DOC/L);

$C_{bl(t)}$ = background (blank) concentration at time t (mg DOC/L).

Quality Assurance Monitoring

See the attached reports of Quality Assurance Monitoring (Attachment 4).

Good Laboratory Practice Statement

This study was conducted according to: Good Laboratory Practice for Nonclinical Laboratory Studies as promulgated by the Food and Drug Administration; 21 CFR Part 58, December 22, 1978 (revised September 4, 1987); Environmental Protection Agency Good Laboratory Practice Standard 40 CFR Part 792, November 29, 1983; and Organization of Economic Cooperation and Development Principles of Good Laboratory Practice specified in Annex 2 of the OECD Guidelines for Testing of Chemicals [C(81) 30(Final)] as required by Council Directive 87/18/EEC (December 18, 1986).

Data Storage and Records Retention

All raw data and summaries of data will be retained for at least ten years by the Health and Environment Laboratories, Eastman Kodak Company, Rochester, New York 14652-3617.

Results

Values for loss of DOC are shown graphically in Figure 1. The Lotus 1-2-3® spreadsheet for DOC is shown in Attachment 1.

Starting levels of DOC for Test A, Test B, and Positive Control were 23.1 mg/L, 22.5 mg/L, and 19.5 mg/L, respectively. Results from the two Test flasks were not averaged. On Day 35, DOC levels for these solutions were 2.1 mg/L, 10.6 mg/L, and 1.4 mg/L, respectively. These values represent a DOC loss of 91% for Test A, 53% for Test B, and 93% for the Positive Control. By the end of the test the pH values had dropped to 5.9 for the Blank, 6.6 for the Positive Control, and 6.1 for Test Flask A and 5.9 for Test Flask B.

Test Validity

At time 0 the test organisms were viable. During the test the Positive Control Solution yielded DOC removals of ≥ 70% within 7 days. These conditions fulfill the requirements for a valid test.

Protocol Deviations

None

Discussion

Different values for DOC losses were obtained from the two Test Flasks. DOC losses plateaued after about 7 days from both flasks, perhaps following primary degradation of the starting material. Next, after several more days, biodegradation resumed in Test Flask A until by Day 27, 93% mineralization was achieved. This was not achieved, however, within the time window of 10 days starting from the day when 10% biodegradation was first observed. This means that the test chemical is not readily biodegradable according to the strict definition of this test.

Although some further biodegradation also occurred in Test Flask B, it only reached 53-54% by the end of the test (which had been extended through Day 35). Following the inoculation of microorganisms from Test A to Test Flask B on Day 35, Test B also biodegraded showing 74% mineralization by Day 42. The most likely explanation for these results is that several species of micoorganisms may be needed for complete mineralization. Test Flask B may have lacked sufficient of the needed species, particularly for the breakdown of intermediate products; these needed species were provided on Day 35 by the transfer of acclimated microorganisms from Test A which had already degraded.

Conclusion

The test chemical was not readily biodegradable according to the definitions of this test but 93% mineralization occurred slowly over the course of the test in one Test Flask (by Day 27) and 53% occured in the second Test Flask (by Day 35). An additional experiment in the second flask showed 74% biodegradation by Day 42, seven days after inoculation with acclimated organisms from the first flask. It is therefore likely that biodegradation in the environment will be very variable depending on the microbial species present.

References

1. Degradation - Biotic Degradation: Modified OECD Screening Test, 1984. Part C. Methods for the Determination of Ecotoxicity. Test Guideline C.3. Official Journal of the European Communities, 27, 160-211.
2. OECD, Paris, 1981. Test Guideline 301E, Decision of the Council C(81) 30 final.
3. Gerike, P., Fischer, W.K., 1979. A Correlation Study of Biodegradability Determinations with Various Chemicals in Various Tests, Ecotoxicology and Environmental Safety, 3, (2), 159-173.
4. Gerike, P., Fischer, W.K., 1981. A Correlation Study of Biodegradability Determinations with Various Chemicals in Various Tests II. Additional Results and Conclusions, Ecotoxicology and Environmental Safety, 5, (1), 45-55.
5. US EPA/TSCA 40 CFR Section 796.3240

Table 1. Composition of BSM and Stock Solutions

		Stock Conc.
A.	KH_2PO_4 (potassium dihydrogen phosphate)	8.50 g
	K_2HPO_4 (dipotassium hydrogen phosphate)	21.75 g
	$Na_2HPO_4 \cdot 2H_2O$ (disodium hydrogen phosphate dihydrate) (= 26.64 g Na_2HPO_4)	33.40 g
	NH_4Cl (ammonium chloride)	20.00 g
	Dissolve in and make up to 1000 mL with water	
	The pH value should be 7.2	
B.	$MgSO_4 \cdot 7H_2O$ (magnesium sulphate heptahydrate)	22.50 g
	Dissolve in and make up to 1000 mL with water	
C.	$CaCl_2$ (calcium chloride)	27.50 g
	Dissolve in and make up to 1000 mL with water	
D.	$MnSO_4 \cdot 4H_2O$ (manganese (II) sulphate tetrahydrate) (= 30.23 mg $MnSO_4 \cdot H_2O$)	39.9 mg
	H_3BO_3 (boric acid)	57.2 mg
	$ZnSO_4 \cdot 7H_2O$ (zinc sulphate heptahydrate)	42.8 mg
	$(NH_4)_6Mo_7O_{24}$ (ammonium heptamolybdate(VI)) (= 36.85 mg $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$)	34.7 mg
	Fe-chelate ($FeCl_3 \cdot EDTA$) (= 35.69 mg $FeCl_3$ and 64.31 mg EDTA)	100.0 mg
	Dissolve in and make up to 1000 mL with water	
E.	$FeCl_3 \cdot 6H_2O$ (iron (III) chloride hexahydrate)	25.0 mg
	Dissolve in and make up to 100 mL with water	
F.	Yeast extract	15.0 mg
	Dissolve in and make up to 100 mL with water	

Solution Preparation

Stock solutions A-D were made up in advance, filter sterilized through 0.2 µm membranes, and refrigerated until needed (for a period of 6 months). Stock solutions E and F were made up immediately before use. BSM was prepared immediately before use and contained 1.0 mL of each stock solution A-F per liter.

Table 2. Preparation of Test Solutions and Test Measurements

Solutions	BSM[1]	BLANK[2]	POS[3]	TEST A[4]	TEST B[4]
BSM (mL)	4000	900	900	900	900
Inoculum (mL)	0	0.45	0.45	0.45	0.45
Test Chemical (mg/L)	0	0	0	31.2	31.2
Initial pH	7.236	as BSM	7.227	7.286	as TEST A
Final pH	7.236	as BSM	7.227	7.286	as TEST A
pH adjustment[5]	--------	as BSM	-----	-----	as TEST A
pH at end of test	-----	5.900	6.568	6.139	5.939
DO at end of test[6]	-----	8.7	8.8	8.7	8.8

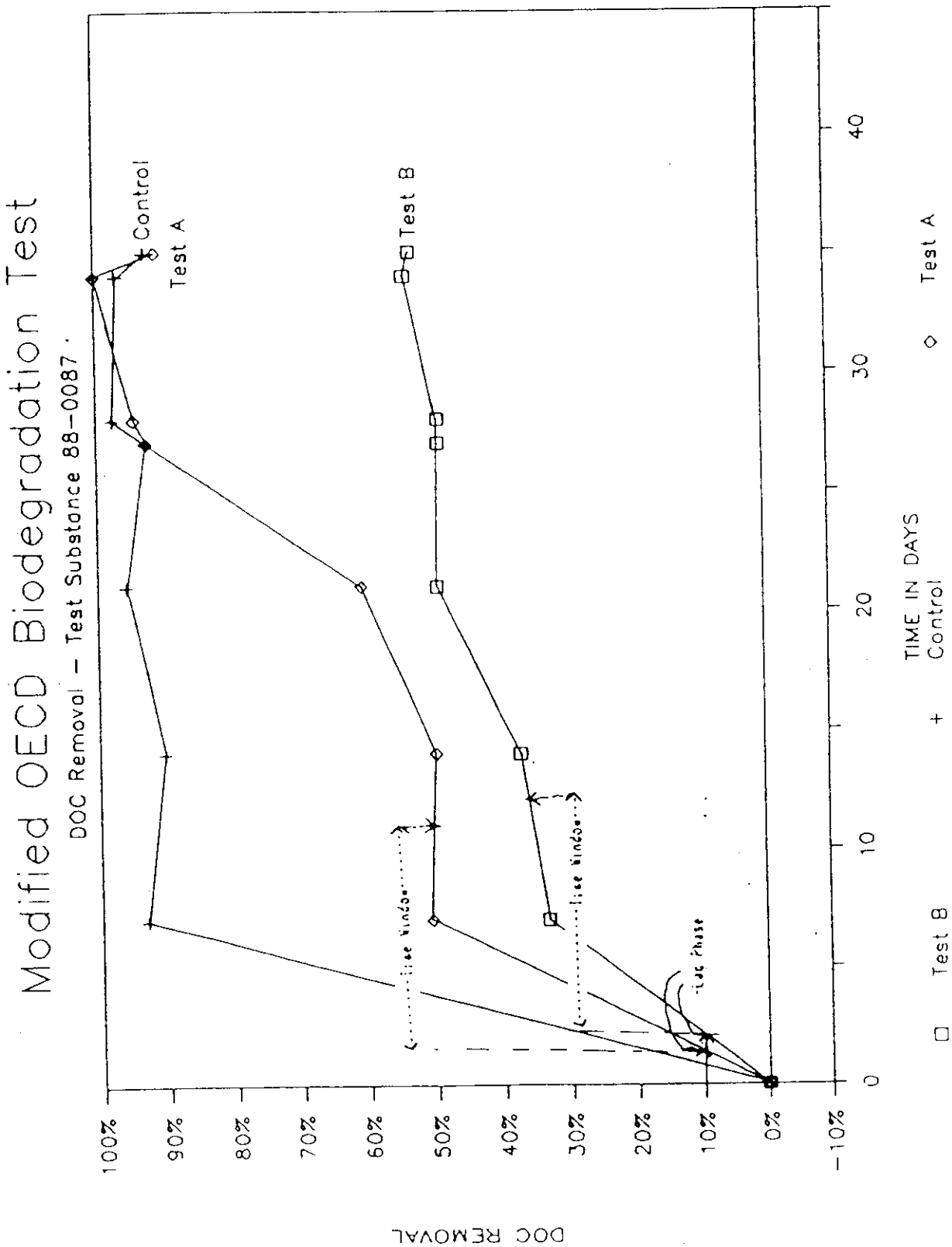
Positive Control Sodium benzoate CAS Reg. No. 532-32-1 Conc. 34.3 mg/L

Quality Control Check: Distilled Water DOC 0.159 mg/L; BSM DO 9.2 mg/L

TOC of Test Chemical = 30.24 mg/L; DOC of Test Chemical = 31.12 mg/L[7]

1. BSM = Basal Salts Medium from which all other solutions were prepared (after aerating for at least 30 min.).
2. BLANK = BSM + Inoculum (background).
3. POS = BSM + Inoculum + Positive Control.
4. TEST = BSM + Inoculum + Test Chemical (enough Test Chemical solution was prepared for both test vessels).
5. pH adjusted to 7.2 ± 0.1 with xx drops of H (HCl) or N (____ NaOH).
6. DO = dissolved oxygen.
7. All DOC values were obtained after centrifugation.

Figure 1. Graph Showing Percent DOC Removal



HAEL No. 88-0087 Study No. EN-102-906659-1

Attachment 1. Lotus Spreadsheet for Dissolved Organic Carbon

MEDIUM	DATE & DAY	VALUE1	VALUE2	MEAN(B)	DOC(C)	DOC(D)	DOC(E)
BLANK	DAY 0	0.228	0.212	0.220	8.800		
CONTROL	01-27-89	0.720	0.697	0.709	28.340	19.5	
TEST A		0.788	0.806	0.797	31.880	23.1	
TEST B		0.785	0.779	0.782	31.280	22.5	
BLANK	DAY 7	0.159	0.143	0.151	6.040		
CONTROL	02-03-89	0.185	0.182	0.184	7.340	1.3	93%
TEST A		0.435	0.436	0.436	17.420	11.4	51%
TEST B		0.529	0.524	0.527	21.060	15.0	33%
BLANK	DAY 14	0.121	0.086	0.104	4.140		
CONTROL	02-10-89	0.143	0.158	0.151	6.020	1.9	90%
TEST A		0.395	0.391	0.393	15.720	11.6	50%
TEST B		0.450	0.463	0.457	18.260	14.1	37%
BLANK	DAY 21	0.214	0.220	0.217	8.680		
CONTROL	02-17-89	0.244	0.231	0.238	9.500	0.8	96%
TEST A		0.440	0.449	0.445	17.780	9.1	61%
TEST B		0.501	0.505	0.503	20.120	11.4	49%
BLANK	DAY 27	0.202	0.194	0.198	7.920		
CONTROL	02-23-89	0.235	0.231	0.233	9.320	1.4	93%
TEST A		0.227	0.252	0.240	9.580	1.7	93%
TEST B		0.486	0.488	0.487	19.480	11.6	49%
BLANK	DAY 28	0.220	0.224	0.222	8.880		
CONTROL	02-24-89	0.229	0.239	0.234	9.360	0.5	98%
TEST A		0.245	0.265	0.255	10.200	1.3	94%
TEST B		0.500	0.522	0.511	20.440	11.6	49%
BLANK	DAY 34	0.255	0.234	0.245	9.780		
CONTROL	03-02-89	0.251	0.270	0.261	10.420	0.6	97%
TEST A		0.241	0.252	0.247	9.860	0.1	100%
TEST B		0.501	0.506	0.504	20.140	10.4	54%
BLANK	DAY 35	0.230	0.230	0.230	9.200		
CONTROL	03-03-89	0.266	0.266	0.266	10.640	1.4	93%
TEST A		0.277	0.287	0.282	11.280	2.1	91%
TEST B		0.498	0.493	0.496	19.820	10.6	53%

(A) values 1-2 derived from strip-chart recorder of DOC Analyzer
(B) MEAN(B) = Mean of data from DOC Analyzer
(C) DOC(C) = sample DOC (mg/L) = DOC(B) multiplied by dilution factor of 40
(D) DOC(D) = Final DOC values (mg/L) corrected for background (blank DOC(C)
(E) DOC(E) = % Loss of DOC since Time 0 = (1-DOC(D)/Day 0) x 100%

Prepared by Michele McWilliams Date 3-16-89

HAEL No. 88-0087 Study No. EN-102-906659-1

Attachment 2. Data Sheets for DOC

TEST DOC DATA FROM DOC ANALYZER

Modified OECD Solubility methods 88-0087
Acc #906659 1-6-89 MS

Test DOC	04	0.696 x40
BSM DOC	03	0.173 x40
Test TOC	02	0.698 x40
BSM TOC	01	0.172 x40

Time 0 TOC/DOC 1-27-89
Ready Biodeg / 88-0087 MS

DOC	03	0.778 x40
TOC	02	0.756 x40
DW	01	0.159 x1

Ready Biodeg / 88-0087
1-27-89, Day 0, MW

Test B	12	0.779 x40
	11	0.785
Test A	10	0.806
	09	0.788
POS	08	0.697
	07	0.720
Blank	06	0.212
	05	0.228 x40

Day 7 DOC 2-3-89 MS
Ready Biodeg / 88-0087

Test B	12	0.524 x40
	11	0.529
Test A	10	0.436
	09	0.435
POS	08	0.182
	07	0.185
Blank	06	0.143
	05	0.159 x40

Day 14 DOC 2-10-89 MS
Ready Biodeg/88-0087

Test B	12	0.463 x40
	11	0.459
Test A	10	0.391
	09	0.395
POS	08	0.158
	07	0.143
Blank	06	0.086
	05	0.121 x40

Day 21 DOC 2-17-89 MS
Ready Biodeg/88-0087

Test B	12	0.505
	11	0.501
Test A	10	0.449
	09	0.440
POS	08	0.231
	07	0.244
Blank	06	0.220
	05	0.214

Prepared by Heather Watson Date 2-17-89
Mary Shea 2-17-89
Michele McWilliams 2-17-89

HAEL No. 88-0087 Study No. EN-102-906659-1

TEST DOC DATA FROM DOC ANALYZER

Modified OECD Ready Biodeg
88-0087 2-23-89 MS
Day 27

Test B	12	0.188 × 40
	11	0.188
Test A	10	0.252
	09	0.227
Pos. Cont.	08	0.231
	07	0.235
Blank	06	0.194
	05	0.202 × 40

Pos. Cont.	08	0.239 × 40
	07	0.229
Blank	06	0.224
	05	0.220
Test B	04	0.522
	03	0.500
Test A	02	0.265
	01	0.245 × 40

Ready Biodeg 88-0087
2-24-89 Day 28 MS

Ready Biodeg 88-0087
3-2-89, Day 34 MS

Pos. Control	08	0.270 × 40
	07	0.251
Blank	06	0.234
	05	0.255
Test B	04	0.506
	03	0.501
Test A	02	0.252
	01	0.241 × 40

Ready Biodeg 88-0087
3-3-89 Day 35 MS

Pos. Control	08	0.266 × 40
	07	0.266
Blank	06	0.230
	05	0.230
Test B	04	0.493
	03	0.498
Test A	02	0.287
	01	0.277 × 40

Blank	02	0.049 × 40
	01	0.030
Test B	02	0.185
	01	0.184 × 40

OECD Ready Biodeg 88-0087
3-17-89 Day 42* MM

* Test B results on Day 42 following an inoculation of 5.0 mL of Test A solution on Day 35 to provide acclimated microorganisms. HMW

Prepared by Heather M Walton Date 3-17-89
Mary Ann 3-17-89
Michele McWilliams 3-17-89

Attachment 3. CQS Division Reports on Chemical Purity

CHEMICALS QUALITY SERVICES DIVISION REPORT

ANALYSIS REQUESTED BY: Toxicology DATE REQUESTED: 6/28/88

DATE ANALYZED: 8/18/88

CQSD JOB FILE NUMBER: EE8H021

REQUEST FOR ANALYSIS: 084797

TITLE: Initial Purity of 88-0087

AUTHOR: N. Porter DATE REPORTED: 8/22/88

FOR ADDITIONAL INFORMATION OR WORK CONTACT: K. Robillard, N. Porter

SAMPLE IDENTIFICATION: Received one sample labelled HAEL # 88-0087, Acc. # 906659

REPORT:

The sample was submitted for initial purity, and was analyzed using the following chromatographic conditions:

30m, DB-5 wide bore 0.25um J+W column
carrier: Helium at 8 psi
50°C (2 min.) - 200°C at 10°/min. (hold at 200°C for 1min)
split injection, sample load approx. 2.0 uL
electron ionization
inj. temp. @ 250°C
det. temp. @ 250°C

The sample was diluted in ethyl acetate and analyzed. The results were as follows:

Area % 88-0087
99.9

n = 3
SD = 0

Signed N. Porter
BuR

CHEMICALS QUALITY SERVICES REPORT FOR: ETS

PHASE: Purity for 88-0087

DATE RECEIVED: 01/28/89

STUDY TYPE: 28-Day Ready Biodegradability

DATE ANALYZED: 02/02/89

C.Q.S. FILE# EE9H417/142214

DATE REPORTED: 02/03/89

REQUESTED BY: H. M. Watson

STUDY DIRECTOR: H. M. Watson

AUTHOR: Lori J. Wieszczyk

SAMPLES:(LABELS AND DESCRIPTION) Acc # 906659, HAEL # 88-0087, Lot # TX-1694-65
One sample of 88-0087 was received for analysis.

FOR ADDITIONAL INFORMATION OR FURTHER WORK CONTACT: Lori J. Wieszczyk @ 85010
Karen Burgess @ 25925

REPORT:

A purity was performed on the test chemical using gas chromatography. The results are as follows.

mean = 99.4 % of 88-0087
n = 3
std. dev. = 0.0529

SIGNED: Lori J. Wieszczyk
K Burgess

METHODS OF DETECTION & DETERMINATION

GAS CHROMATOGRAPHY (GC)

Instrument:	Hewlett Packard 5890
Column:	J&W, 30 m, DB-5 wide bore 0.25 um
Carrier:	Helium at 8 psi
Gradient:	hold at 50 °C for 2 minutes 10 °C/minute to 200 °C hold at 200 °C for 5 minutes
Split injection:	60 cc/min. , sample load approx. 2.0 uL
Detector:	FID ~~54 mm~~ 8 mm 21/01/89
Injection temp.:	250 °C
Detection temp.:	250 °C

Attachment 4. Quality Assurance Statements

Q.A. INSPECTION STATEMENT
(CFR 58.35(B)(7) 792.35(B)(7) 160.35(B)(7))

STUDY: 88-0087-1 STUDY DIRECTOR: WATSON,H.M.
ACCESSION NUMBER: 906659

PAGE 1
03/23/89

STUDY TYPE: BIODEGRADATION (READY)

M. S. James
(AUDITOR, QUALITY ASSURANCE UNIT)

3/27/89
DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF THE HAEL, EASTMAN KODAK COMPANY, ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES:

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
01/24/89	PROTOCOL SUBMISSION	
02/10/89	SAMPLE COLLECTION	
	SAMPLE PREPARATION	
	SAMPLE ANALYSIS	
	DAY 14 DISSOLVED ORGANIC CARBON ANALYSIS	
03/01/89	PROTOCOL AMENDMENT	
	TEST EXTENDED FOR 7 MORE DAYS	
03/17/89	PROTOCOL AMENDMENT	
	AMENDMENT OF 3/3/89 RECEIVED	
03/23/89	FINAL REPORT REVIEW	03/23/89

ANALYTICAL QUALITY ASSURANCE INSPECTION STATEMENT

HAEL #: 88-0087 Accession #: 906659 CQS Job #: EE8H021

HAEL Study: *
Study Director: W. Krasavage
Auditee Group & Location: EAS/CQS, B-320
In-Process Inspection Date: ---
Date This Report Sent To Study Director: 08-26-88

Request for Analysis #	Analysis	Sample(s) Received Date	Test Report Date	Test Report Inspection Date
084797	Init. Purity	06-28-88	08-22-88	08-26-88

We have inspected the analytical work described above. Our findings have been sent to the study director and to management. This is done in accordance with Good Laboratory Practice Standards 40 CFR 792.35 and 160.35, and 21 CFR 58.35.

M. J. Boccacino, Quality Assurance Engineer
GLP Compliance, QSO Quality Assurance
08-26-88

Q.A. INSPECTION STATEMENT
(CFR 58.35(B)(7) 792.35(B)(7) 160.35(B)(7))

PAGE 1
02/07/89

STUDY: 88-0087-2 STUDY DIRECTOR: WATSON H.
ANALYTICAL DIRECTOR:
ACCESSION NUMBER: 906659
CQS JOB NUMBER: EE9H417

STUDY TYPE: 28 DAY READY BIODEGRADABILITY

Harriet L. Braugham 2/7/89
(AUDITOR, QUALITY ASSURANCE UNIT) DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF QSO, EASTMAN KODAK COMPANY, ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES:

INSPECT DATES	REQUEST NUMBER	PHASE(S) INSPECTED	STATUS REPORT DATES
02/07/89	142214	TEST REPORT INSPECTION	02/07/89

PURITY ANALYSIS

ENVIRONMENTAL FATE

Ready Biodegradability:

Test Endpoint: loss of DOC.

The Test Chemical was not readily biodegradable according to the strict definition of this test but loss of DOC was 93% by Day 27 in one test flask and 53% in the second flask by Day 35.

Duration of test: 28 days.

Concentration of Test Substance: 31.2 mg/L (20.5 mg DOC/L).

Method: Annex V Test Guideline C.3 (Modified OECD Test).

Test House: Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York, USA

Comments: The second flask showed 74% biodegradation by Day 42, seven days after inoculation with acclimated organisms from the first flask. It is therefore likely that biodegradation in the environment will be very variable depending on the microbial species present.

HAEL No. 88-0087 Study No. EN-102-906659-1

DIS No. 248722C

Prepared by Heather M. Watson Date 3-17-89
Heather M. Watson
Eco-Chem Testing Group

Approved by Joseph W. Gorsuch Date 3-21-89
Joseph W. Gorsuch
Group Leader
Eco-Chem Testing Group

Approved by T. J. Dagon Date 3/22/89
Thomas J. Dagon
Unit Director
Environmental Sciences Section

Reviewed by M. C. James Date 3/27/89
Quality Assurance Unit
Health and Environment Laboratories

Approved by Heather M. Watson Date 3-27-89
Heather M. Watson
Study Director
Eco-Chem Testing Group

0424W

DISTRIBUTION LIST

F.S. Amato

M.C. Beeler/O.J. McKamey

C.H. DiRenzo

W.L. Hart

B.H. Klanderman/T.J. Dagon

B.K. Rice

Environmental Sciences Section (Orig.)

Technical Report Office (3)

Study No. EN-603-906659-1

ES-89-029

248723D

SECONDARY WASTE TREATMENT COMPATIBILITY OF 2-Ethyl-1,3-hexanediol

Accession No. 906659

HAEL No. 88-0087

By

Heather M. Watson

Environmental Sciences Section

Health and Environment Laboratories

Eastman Kodak Company

Rochester, NY 14652-3617

Completion Date: March 23, 1989

Abstract

A radiorespirometric method was used to determine the compatibility of 2-Ethyl-1,3-hexanediol with secondary waste treatment microorganisms. The procedure used microorganisms from a domestic waste treatment plant. These microorganisms were exposed to [^{14}C]glucose and to the test chemical. The extent of conversion of the [^{14}C]glucose to [^{14}C]carbon dioxide was compared in the presence and absence of the test chemical. Nominal concentrations of 0.1, 1, 10, 100 and 1000 mg/L had no significant inhibitory effects on the microorganisms. The test chemical, 2-Ethyl-1,3-hexanediol, is not expected to affect secondary waste treatment microorganisms adversely at concentrations of less than or equal to 1000 mg/L.

Table of Contents

Page

Testing Facility and Sponsor 4
Date of Study Initiation 4
Date of Study Completion 4
Dates of Experiment 4
Study Participants 4
Test Guideline 4
Purpose/Objective 4
Test Substance 5
Reference Substance 5
Materials and Methods
A. Reagents and Solutions 5
B. Microorganisms 5
C. Test Vessel 6
Test Procedure
A. Selection of Microorganism for Testing 6
B. Preparation of Test Chemical Solutions and Flasks 6
C. Potassium Dichromate Positive Control Solutions 7
D. Test Procedure 7
Analytical Procedures
A. Test Chemical 8
B. $[^{14}C]CO_2$ Activity 8
Calculations 8
Quality Assurance Monitoring 10
Good Laboratory Practice Statement 10
Data Storage and Records Retention 10
Test Results 10
Test Validity 10
Conclusion 11
References 11
Tables
1. $[^{14}C]$Carbon Dioxide Recoveries 12
Figures
1. Respirometer Flask 13
2. IC_{50} Semi-log Plots for the Test and Reference Substance 14
Attachments
1. Lotus Spreadsheet for $[^{14}C]CO_2$ Activity 15
2. Preparation of Reagents and Solutions 16
3. Table of Flasks and Solutions 17
4. CQS Division Reports on Chemical Purity 18
5. Quality Assurance Statements 22

HAEL No. 88-0087 Study No. EN-603-906659-1

Testing Facility
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-3617
U.S.A.

Sponsor
Eastman Kodak Company
Rochester, New York 14652-3617
U.S.A.

Date of Study Initiation
January 16, 1989

Date of Study Completion
March 23, 1989

Dates of Experiment
Collection and Preparation of Microorganisms: 1-16-89
Preparation of Chemical Stock Solutions and Dosing of Flasks: 1-17-89
Experimental Start Date (Chemical Exposure Start): 1-17-89
Experimental Termination Date (Last Day of Data Collection): 1-18-89

Study Participants
Environmental Sciences Section:
T.J. Dagon, Unit Director, Environmental Sciences Section
J.W. Gorsuch, Group Leader, Eco-Chem Testing Group
M.A. Shea, Technician, Eco-Chem Testing Group
H.M. Watson, Principal Investigator and Study Director, Eco-Chem Testing Group

Test Guideline
Eastman Kodak Company Protocol EN-603.

Purpose/Objective
Many publicly owned treatment works (POTW) and industrial treatment plants rely on biological secondary waste treatment to remove waste chemicals. Efficient plant operation may be impaired if chemicals present in the influent affect the sludge adversely by inhibiting microbial metabolism. The Secondary Waste Treatment Compatibility Test is a good indicator of potential adverse effects on treatment plant performance.(1) This test uses microorganisms from a domestic waste treatment plant. During the test, conversion of [^{14}C]glucose to [^{14}C]CO_2 by sludge microorganisms is measured with and without exposure to

the test article. Concentrations of test chemical usually do not exceed the maximum concentration likely to occur in a treatment plant influent; 1000 mg/L is considered a reasonable upper limit for many chemicals. The data are used to define a dose-response relationship and to calculate the concentration of test chemical that would inhibit glucose metabolism by 50% during the five-hour exposure, i.e., the five-hour IC_{50}. If lack of inhibition and/or solubility limitations do not permit an IC_{50} value to be calculated, the amount of inhibition at the highest actual exposure concentration is reported as the test result.

Test Substance

Identity: 2-Ethyl-1,3-hexanediol

Sample Reference No.: TX-1694-65

Sample Laboratory No.: 88-0087

Composition (determined by CQSD, Attachment 4):

Purity: Starting, 99.9%; final, 99.4% (area) by HPLC.

Stability (determined by CQSD, Attachment 4):

Shelf-life stability was confirmed by repeating the purity assay after testing.

Reference Substance

Potassium dichromate was used as the reference substance (positive control).

Materials and Methods

A. Reagents and Solutions

1. Potassium Phosphate Buffer (see Attachment 2).
2. Nutrient Broth Stock Solution (see Attachment 2).
3. D-[U-^{14}C]Glucose-Broth Solution (see Attachment 2).

B. Microorganisms

Microorganisms were collected as mixed liquor suspended solids (MLSS) from a domestic sewage waste treatment plant the day prior to performing the test. Approximately 1 L of MLSS was centrifuged at 7000 x g for 15 minutes. The supernatant liquid was decanted and the remaining sludge

solids resuspended in non-radiolabelled glucose-broth solution. The prepared sludge suspension was stirred and aerated overnight.

C. Test Vessels

Pyrex® 50 mL Erlenmeyer flasks, fitted with downward curving 1/2-inch diameter sidearms, were used for the radiorespirometric assay. Scintillation vials containing a CO_2-trapping solution composed of 0.2 mL distilled water and 1.0 mL diethanolamine were attached to the sidearms (see Figure 1). A 0.22 µm filter was placed between the sidearm and the scintillation vial to prevent microorganisms from contaminating the CO_2-trapping solution.

Test Procedure

A. Selection of Microorganisms for Testing

About 500 mL of the sludge suspension prepared earlier were centrifuged at 7000 x g for 15 minutes using two 250-mL centrifuge tubes. The supernatant liquid was decanted and the solids from each tube were resuspended and washed in about 250 mL of oxygenated 0.02M potassium phosphate buffer, pH 6.9. The washed solids and buffer were then placed in two tared centrifuge tubes and centrifuged as before. The supernatant liquid was decanted, and the tube and contents of one tube were weighed. The contents of this tube (4.0 g) were resuspended in 200 mL of oxygenated potassium phosphate buffer and homogenized in a Waring blender for 2 minutes. The final activated sludge concentration was therefore 20 mg/mL.

B. Preparation of Test Chemical Solutions and Flasks

Stock test solutions were prepared to give stock concentrations of 4000 mg/L, 400 mg/L, 40 mg/L, 4 mg/L, and 0.4 mg/L. Aliquots of stock solutions (2.5 mL) were dispensed into the appropriate test flasks (see Attachment 3). Three flasks were used per concentration for the test and positive control, and three flasks were used for the negative control. After the addition of the remaining test components, final nominal concentrations in the test vessels were 1000, 100, 10, 1.0, and 0.1 mg/L.

C. Potassium Dichromate Positive Control Solutions

A stock solution was prepared in a 100 mL volumetric flask by dissolving 0.1332 g of potassium dichromate (reagent grade) in sufficient phosphate buffer (0.02M, pH 6.9) to give a final volume of 100 mL. The pH was adjusted to 6.9 ± 0.1 using HCl or NaOH, as appropriate. Two aliquots of the stock solution were diluted as follows: one part stock solution with one part of phosphate buffer; and one part of stock solution with nine parts of phosphate buffer. A portion of the latter was further diluted 1:9 with phosphate buffer. In this manner, four stock solutions of potassium dichromate were prepared with concentrations of 1.332, 0.666, 0.1332, and 0.01332 g/L. Each of these four stock solutions were diluted by a factor of four in the test vessels to give final nominal concentrations of potassium dichromate of 333, 167, 33, and 3.3 mg/L.

D. Test Procedure (see Attachment 3)

To each of 36 respirometer flasks were added 5.0 mL of the prepared activated sludge solution. The positive control flasks received 2.5 mL of each stock potassium dichromate solution (three flasks per concentration). The test flasks containing test chemical, the negative control flasks, and the system control flasks each received 2.5 mL of 0.02M phosphate buffer. Each of the 36 flasks then received 2.5 mL of D-[U-^{14}C]glucose-broth solution (approx. 0.4 µCi). The flasks were sealed with clean serum stoppers and incubated in the dark at room temperature in a reciprocating incubator-shaker at 70 cycles per minute for 5 hours. At the end of the incubation period the flasks were removed from the shaker and 5 mL of 2N HCl was added through the serum stopper of each flask using a syringe. The addition of HCl stopped the metabolism of glucose within the respirometer flask and converted the [^{14}C]bicarbonate in solution to [^{14}C]CO_2, which was subsequently trapped in the scintillation vials. The flasks were stored overnight at room temperature prior to analysis.

Four scintillation vials were prepared containing CO_2-trapping solution. Three of these vials received 50 µL of the same D-[U-^{14}C]glucose-broth

solution that was added to the test vessels. The fourth vial received no radiolabelled compound and was used for determining the background counting rate of the scintillation spectrometer. Each of the four vials received 15 mL of scintillation cocktail (Attachment 2).

Analytical Procedures

A. Test Chemical

The concentrations of test chemical in the stock test article solutions were not measured; rather, nominal concentrations were used for reporting and calculation purposes.

B. $[^{14}C]CO_2$ Activity

The day following exposure, the $[^{14}C]CO_2$ absorbing vials were removed from the flasks and 15 mL of scintillation cocktail were added to each vial. The radioactivity in each vial was measured for ten minutes in a liquid scintillation spectrometer. The background counting rate was automatically subtracted from the dpm values for the test and control vials by the microprocessor in the spectrometer. Data from the three vials containing 50 µL of the D-[U-^{14}C]glucose broth solution were used to calculate the amount of radioactivity present initially in the [^{14}C]glucose-broth solution.

Calculations

A. Initial amounts of glucose in each respirometer flask, G, expressed in counts per minute (cpm).

$$G = (gs) \times \frac{2500}{50}$$

where, (gs) = average cpm of glucose standard vials
50 µL = volume of glucose broth solution added to vial
2500 µL = volume of glucose broth solution added to respirometer flask

B. Recovery, R, i.e., percent of glucose converted to CO_2.

$$R = \frac{Vi}{G} \times 100$$

where, Vi = amount of CO_2 in i^{th} scintillation vial, expressed in cpm
G = mean value of initial glucose concentration in respirometer flask, expressed in cpm

C. % of Control, C, i.e., the value of R for the ith flask compared to the mean value of R for the negative control flasks.

$$C = \frac{Ri}{Rnc} \times 100$$

where, Ri = % recovery for i^{th} respirometer flask
Rnc = mean value of R (%) for the three negative control flasks

D. Values of the means, standard deviations, and coefficients of variation were calculated by using the conventional statistical formula.[2]

mean, $\bar{X}$: $\bar{X} = (1/k) \times \sum_{i=1}^{k} Xi$

standard deviation, σ: $\sigma^2 = (1/k) \times \sum_{i=1}^{k} (X_i - \bar{X})^2$

coefficient of variation, V: $V = 100\sigma/\bar{X}$ %

E. The mean response for each set of triplicate flasks was plotted against the logarithm of the chemical concentration for the test chemical and the positive controls (Figure 2). The five-hour 50% inhibition concentration (five-hour IC_{50}), defined as the concentration of test chemical that reduced $[^{14}C]CO_2$ evolution to 50% of the controls in five hours, was determined from these semi-log plots according to the method of Finney[3] and also by regression analysis. Confidence intervals are not calculated due to the range-finding nature of the experimental design.

Quality Assurance Monitoring

See the attached report of Quality Assurance Monitoring (Attachment 5).

Good Laboratory Practice Statement

This study was conducted according to: Good Laboratory Practice for Nonclinical Laboratory Studies as promulgated by the Food and Drug Administration; 21 CFR Part 58, December 22, 1978 (revised September 4, 1987); Environmental Protection Agency Good Laboratory Practice Standard 40 CFR Part 792, November 29, 1983; and Organization of Economic Cooperation and Development Principles of Good Laboratory Practice specified in Annex 2 of the OECD Guidelines for Testing of Chemicals [C(81) 30(Final)] as required by Council Directive 87/18/EEC (December 18, 1986).

Data Storage and Records Retention

All raw data and summaries of data will be retained for at least ten years by the Health and Environment Laboratories, Eastman Kodak Company, Rochester, New York 14652-3617.

Test Results

Results are shown graphically in Figure 2. The [^{14}C]carbon dioxide recoveries are shown in Table 1 and the Lotus 1-2-3® spreadsheet in Attachment 1. Nominal concentrations of the test chemical were 0.1, 1, 10, 100 and 1000 mg/L; results of the amount of [^{14}C]glucose converted to ^{14}[C]CO_2 were expressed as a percentage of the negative control. These results ranged from 95.2% of the control at a concentration of 1.0 mg/L to 104.8% of the control at a concentration of 1000 mg/L. The calculated IC_{50} value for potassium dichromate was 47.9 mg/L.

Test Validity

In the negative control flasks, 39.5% of the [^{14}C]glucose initially present was converted to [^{14}C]CO_2. This meets the criteria for a valid test ($\leq$15%)

The positive control, potassium dichromate, gave an IC_{50} value of 47.9 mg/L. This meets the criteria for a valid test, that an IC_{50} value must be obtained for the positive control.

Conclusion

Concentrations of 2-Ethyl-1,3-hexanediol of 0.1, 1, 10, 100 and 1000 mg/L had no significant effect on glucose metabolism. The test chemical, 2-Ethyl-1,3-hexanediol, is not expected to affect secondary waste treatment microorganisms adversely at concentrations of less than or equal to 1000 mg/L.

References

1. The Compatibility of Process Chemicals and Effluents with Secondary Waste Treatment Microorganisms as Determined by Radiorespirometry, Lockhart, H.B., Blakeley, R.V., and Cunningham, S.L., Technical Report #125861L, Eastman Kodak Company, February, 1980.
2. Handbook of Probability and Statistics With Tables, Burington, R.S. and D.C. May, Jr., Handbook Publishers, Inc., Sandusky, Ohio, 1953, 332p.
3. Finney, D.J., in Probit Analysis, Cambridge University Press, Cambridge, England, p. 28 (1947).

Table 1. [^{14}C]Carbon Dioxide Recoveries

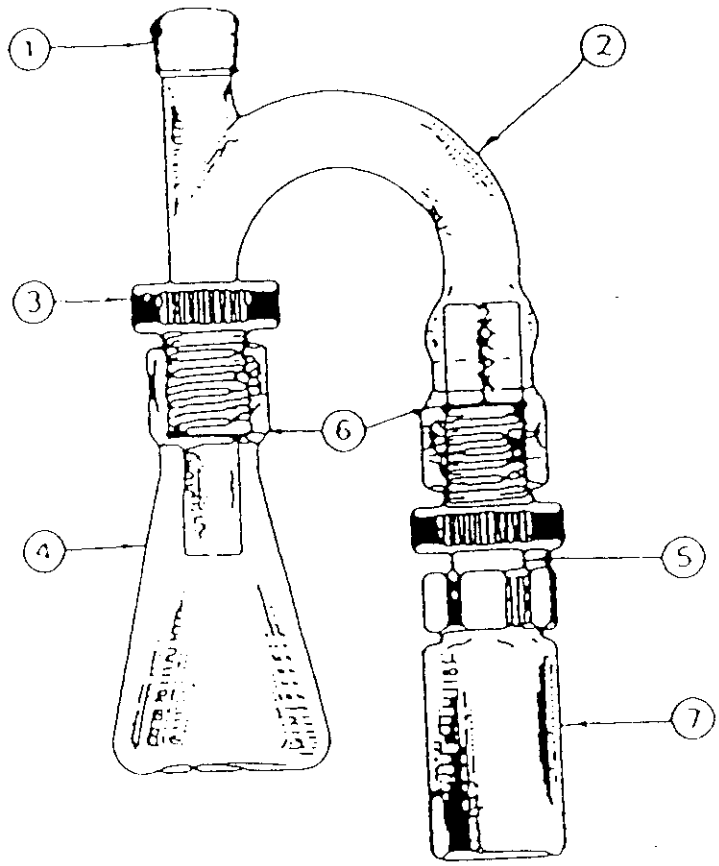
A. Test Substance

Exposure Concentration (mg/L)	% Control Mean	SD	CV
1000	104.79	5.46	5.2
100	103.82	4.44	4.3
10	101.34	2.34	2.3
1	95.17	4.73	5.0
0.1	98.92	2.61	2.6

B. Control Substance

Exposure Concentration (mg/L)	% Control Mean	SD	CV
333	28.49	1.07	3.8
167	33.72	2.39	7.1
33	44.85	3.19	7.1
3.3	93.80	2.94	3.1

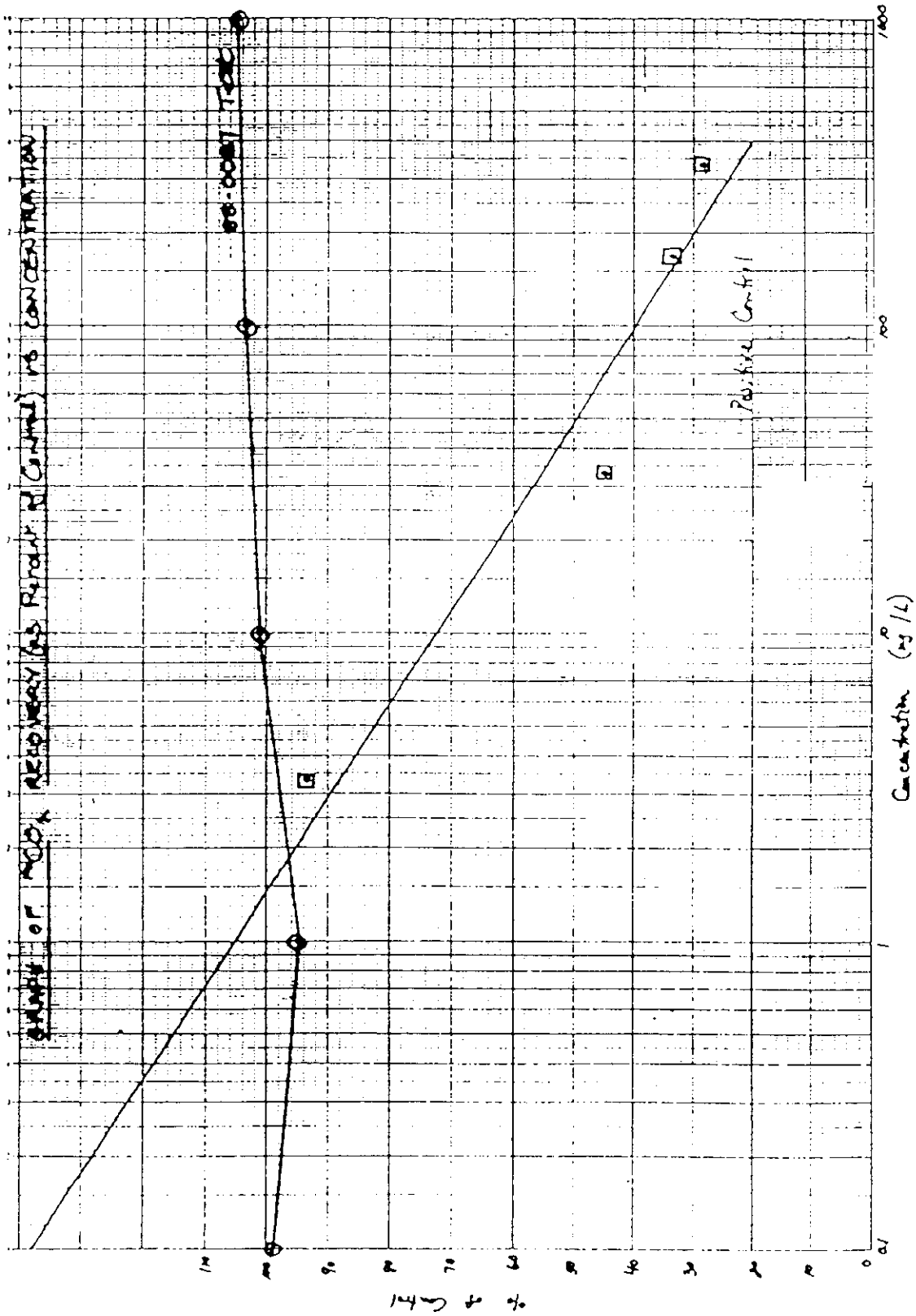
Figure 1. Radiorespirometry Flask



COMPONENTS

1. Rubber Serum stopper
2. Glass "U' Tube Adapter with Ace Thread and Tooled Fitting
3. Ace Bushing
4. Erlenmeyer Flask with Ace Thread
5. Teflon Tube Adapter with Drilled Scintillation Vial Cap and Silicon Rubber Gasket
6. Rubber 'O'-ring
7. Scintillation Vial

Figure 2. IC_{50} Semi-log Plots for the Test and Reference Substance



Attachment 1. Lotus Spreadsheet for [^{14}C]CO_2 Activity

FLASK	VALUE 1 (dpm)	VALUE 2 (dpm)	VALUE 3 (dpm)	MEAN	S.D.	C.V.	RECOVERY (B)
Glucose	13840.7	13843.6	13903.3	13862.5	28.9	0.2%	
Neg. Control	273239.0	287201.0	260619.0	273686.3	10856.7	4.0%	39.5%

TEST CONC. (mg/L)	VALUE 1 (dpm)	VALUE 2 (dpm)	VALUE 3 (dpm)	% OF CONTROL MEAN	S.D.	C.V.
1000.0	283981.0	306346.0	270100.0	104.79%	5.46	5.2%
100.0	288894.0	296063.0	267434.0	103.82%	4.44	4.3%
10.0	283177.0	280423.0	268451.0	101.34%	2.34	2.3%
1.0	261691.0	244014.0	275656.0	95.17%	4.73	5.0%
0.1	260719.0	276963.0	274471.0	98.92%	2.61	2.6%

POS. CONTROL CONC (mg/L)	VALUE 1 (dpm)	VALUE 2 (dpm)	VALUE 3 (dpm)	% OF CONTROL MEAN	S.D.	C.V.
333.0	82089.1	75374.2	76478.9	28.49%	1.07	3.8%
167.0	94372.2	83438.5	99058.1	33.72%	2.39	7.1%
33.0	114555.0	118822.0	134853.0	44.85%	3.19	7.1%
3.3	268081.0	251593.0	250498.0	93.80%	2.94	3.1%

(A) Values 1-3 from Scintillation Spectrometer Printout

(B) RECOVERY = % C-14 carbon dioxide recovered, corrected for volume:
50 uL of prepared C-14 glucose-broth solution in 'glucose' flasks
2.5 mL of prepared C-14 glucose-broth solution in all test and control flasks

Specific Activity Calculation:
Vol. glu-broth (uL) = 50.0
Activity of prepared glucose-broth solution = (Glu dpm)/([2.22 x E6 dpm] x 50 uL)
= 0.125 uCi/mL (where E6 = 1000000)
Total Vial Microcuries: 2.996

REMARKS: These are nominal concentrations.

Attachment 2. Preparation of Reagents and Solutions

Solutions	Amount
A. Potassium Phosphate Buffer Solution (0.02M)	
Potassium dihydrogen phosphate (KH_2PO_4)	1.36 g
Dipotassium hydrogen phosphate (K_2HPO_4)	1.74 g
Make up to 1.0 L with distilled water.	
Adjust pH to 6.9 ± 0.05 with 2N hydrochloric acid.	
Refrigerate and use within 1 month.	
B Nutrient Broth Stock Solution	
Bacto® nutrient broth	24.0 g
Urea	1.5 g
Make up to 3.0 L with distilled water.	
Autoclave under 15 psi at 121°C for 15 minutes.	
Refrigerate, keep sterile, and use within 1 month.	
C. Non-radiolabelled Glucose Solution	
Glucose	25 g
Make up to 50 mL with distilled water.	
Refrigerate and use within 1 month.	
D. D-[U-^{14}C]Glucose-Broth Solution	
Distilled water	95 mL
Nutrient broth stock solution	10.0 mL
Non-radiolabelled glucose solution	0.10 mL
D-[U-^{14}C]glucose solution contained in refrigerated ampoule (approx. 20 μ Ci)	1 mL (approx.)
This solution is prepared just before use and has an activity of approximately 0.19 μCi/mL.	
E. Non-radiolabelled Glucose-Broth Solution	
This is prepared as for D. above but without the D-[U-^{14}C]glucose solution. Solution E. is prepared just before use (usually 1.0 L).	
F. Scintillation Cocktail	
Toluene	2000 mL
PPO (2,5-diphenyloxazole)	16.0 g
POPOP [2,2'-p-phenylenebis(5-phenyloxazole)]	0.4 g
Mix until dissolved.	
Then add:	
2-Methoxyethanol	1000 mL
Mix, refrigerate, and use within 1 year.	

HAEL No. 88-0087 Study No. EN-603-906659-1

Attachment 3. Table of Flasks and Solutions

Test Flask #	Conc. (mg/L)	Test Chemical Stock	Pos. Control Stock	Buffer	Glucose (^{14}C)	Sludge
1-3	1000	2.5	---	---	2.5	5.0
4-6	100	2.5	---	---	2.5	5.0
7-9	10	2.5	---	---	2.5	5.0
10-12	1	2.5	---	---	2.5	5.0
13-15	0.1	2.5	---	---	2.5	5.0
Pos. Flask #						
16-18	333	---	2.5	---	2.5	5.0
19-21	167	---	2.5	---	2.5	5.0
22-24	33	---	2.5	---	2.5	5.0
25-27	3.3	---	2.5	---	2.5	5.0
Neg. Flask #						
28-30	---	---	---	2.5	2.5	5.0

Attachment 4. CQS Division Reports on Chemical Purity

CHEMICALS QUALITY SERVICES DIVISION REPORT

ANALYSIS REQUESTED BY: Toxicology DATE REQUESTED: 6/28/88

DATE ANALYZED: 8/18/88

CQSD JOB FILE NUMBER: EE8H021

REQUEST FOR ANALYSIS: 084797

TITLE: Initial Purity of 88-0087

AUTHOR: N. Porter DATE REPORTED: 8/22/88

FOR ADDITIONAL INFORMATION OR WORK CONTACT: K. Robillard, N. Porter

SAMPLE IDENTIFICATION: Received one sample labelled HAEL # 88-0087, Acc. # 906659

REPORT:

The sample was submitted for initial purity, and was analyzed using the following chromatographic conditions:

30m, DB-5 wide bore 0.25um J+W column
carrier: Helium at 8 psi
50°C (2 min.) - 200°C at 10°/min. (hold at 200°C for 1min)
split injection, sample load approx. 2.0 uL
electron ionization
inj. temp. @ 250°C
det. temp. @ 250°C

The sample was diluted in ethyl acetate and analyzed. The results were as follows:

Area % 88-0087
99.9

n = 3
SD = 0

Signed N. Porter
BLR

CHEMICALS QUALITY SERVICES REPORT FOR: ETS

PHASE: Purity for 88-0087 **DATE RECEIVED:** 01/28/89

STUDY TYPE: 28-Day Ready Biodegradability **DATE ANALYZED:** 02/02/89

C.Q.S. FILE# EE9H417/142214 **DATE REPORTED:** 02/03/89

REQUESTED BY: H. M. Watson **STUDY DIRECTOR:** H. M. Watson

AUTHOR: Lori J. Wieszczyk

SAMPLES:(LABELS AND DESCRIPTION) Acc # 906659, HAEL # 88-0087, Lot # TX-1694-65
One sample of 88-0087 was received for analysis.

FOR ADDITIONAL INFORMATION OR FURTHER WORK CONTACT: Lori J. Wieszczyk @ 85010
Karen Burgess @ 25925

REPORT:

A purity was performed on the test chemical using gas chromatography. The results are as follows.

mean = 99.4 % of 88-0087
n = 3
std. dev. = 0.0529

SIGNED: Lori J. Wieszczyk
K Burgess

METHODS OF DETECTION & DETERMINATION

GAS CHROMATOGRAPHY (GC)

Instrument:	Hewlett Packard 5890
Column:	J&W, 30 m, DB-5 wide bore 0.25 um
Carrier:	Helium at 8 psi
Gradient:	hold at 50 °C for 2 minutes 10 °C/minute to 200 °C hold at 200 °C for 5 minutes
Split injection:	60 cc/min. , sample load approx. 2.0 uL
Detector:	FID ~~54 mm~~ 8 21/7/89
Injection temp.:	250 °C
Detection temp.:	250 °C

Attachment 5. Quality Assurance Statements

Q.A. INSPECTION STATEMENT
(CFR 58.35(B)(7) 792.35(B)(7) 160.35(B)(7))

STUDY: 88-0087-1 STUDY DIRECTOR: WATSON,H.M.
ACCESSION NUMBER: 906659

PAGE 1
03/23/89

STUDY TYPE: SECONDARY WASTE TREATMENT COMPATIBILITY TEST - IC50

M. A. James
(AUDITOR, QUALITY ASSURANCE UNIT)

3/23/89
DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF THE HAEL, EASTMAN KODAK COMPANY, ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES:

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
01/16/89	PROTOCOL SUBMISSION	
01/17/89	SCALE/BALANCE CALIBRATION TEST ARTICLE WEIGH AND MIX WITH CARRIER SLUDGE WEIGHT SLUDGE PREPARATION	
03/23/89	FINAL REPORT REVIEW	03/23/89

ANALYTICAL QUALITY ASSURANCE INSPECTION STATEMENT

HAEL #: 88-0087 Accession #: 906659 CQS Job #: EE8H021

HAEL Study: *
Study Director: W. Krasavage
Auditee Group & Location: EAS/CQS, B-320
In-Process Inspection Date: ---
Date This Report Sent To Study Director: 08-26-88

Request for Analysis #	Analysis	Sample(s) Received Date	Test Report Date	Test Report Inspection Date
084797	Init. Purity	06-28-88	08-22-88	08-26-88

We have inspected the analytical work described above. Our findings have been sent to the study director and to management. This is done in accordance with Good Laboratory Practice Standards 40 CFR 792.35 and 160.35, and 21 CFR 58.35.

M. J. Boccacino, Quality Assurance Engineer
GLP Compliance, QSO Quality Assurance
08-26-88

Q.A. INSPECTION STATEMENT
(CFR 58.35(B)(7) 792.35(B)(7) 160.35(B)(7))

PAGE 1
02/07/89

STUDY: 88-0087-2 STUDY DIRECTOR: WATSON H.
ANALYTICAL DIRECTOR:
ACCESSION NUMBER: 906659
CQS JOB NUMBER: EE9H417

STUDY TYPE: 28 DAY READY BIODEGRADABILITY

Harriet L. Baughman 2/7/89
(AUDITOR, QUALITY ASSURANCE UNIT) DATE

THIS STUDY WAS INSPECTED BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF QSO, EASTMAN KODAK COMPANY, ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE SUBMITTED ON THE FOLLOWING DATES:

INSPECT DATES	REQUEST NUMBER	PHASE(S) INSPECTED	STATUS REPORT DATES
02/07/89	142214	TEST REPORT INSPECTION	02/07/89

PURITY ANALYSIS

HAEL No. 88-0087 Study No. EN-603-906659-1

DIS No. 248723D

Prepared by Heather M. Watson Date 3-21-89
Heather M. Watson
Eco-Chem Testing Group

Approved by Joseph W. Gorsuch Date 3/23/89
Joseph W. Gorsuch
Group Leader
Eco-Chem Testing Group

Approved by T. J. Dagon Date 3/22/89
Thomas J. Dagon
Unit Director
Environmental Sciences Section

Reviewed by M. Sue James Date 3/23/89
Quality Assurance Unit
Health and Environment Laboratories

Approved by Heather M. Watson Date 3-23-89
Heather M. Watson
Study Director
Eco-Chem Testing Group

0428W

DISTRIBUTION LIST

F.S. Amato

M.C. Beeler/O.J. McKamey

C.H. DiRenzo

W.L. Hart

B.H. Klanderman/T.J. Dagon

B.K. Rice

Environmental Sciences Section (Orig.)

Technical Report Office (3)

906659

THE ACUTE TOXICITY AND PRIMARY IRRITANCY OF 2-ETHYL-1,3-HEXANEDIOL*

Bryan Ballantyne MD, DSc, PhD, Applied Toxicology Department, Union Carbide Corporation, Danbury, Connecticut 06817
and
Dennis R Klonne PhD, Roy C Myers BS and Donald J Nachreiner BS, Bushy Run Research Center, Mellon Institute-Union Carbide Corporation, Export, Pennsylvania 15632

ABSTRACT. 2-Ethyl-1,3-hexanediol (EHD), an insect repellant, was found to have acute peroral LD_{50} values in the rat of 9.85 ml/kg (males) and 4.92 ml/kg (females). Acute percutaneous LD_{50} values in the rabbit were 10.8 ml/kg (males) and 9.51 ml/kg (females). There were neither deaths nor signs of toxicity during or following a 6 hr exposure to a statically or dynamically generated substantially saturated vapor atmosphere. A 4 hr exposure to a high concentration (3.8 mg/liter) of a respirable aerosol of EHD (mass median aerodynamic diameter of 2.0 um) produced only minor signs of irritation during exposure, but no signs of toxicity. Occluded dermal contact with EHD on rabbits (4 and 24 hr) produced mild local erythema and, in several animals, edema. Contamination of the eye with EHD (0.005 to 0.1 ml) produced marked to severe conjunctivitis, with moderate iritis and diffuse corneal injury; healing occured in most animals within 3 to 7 days. The major acute hazards with EHD are by swallowing and, to a greater extent, by contamination of the eye.

2-Ethyl-1,3-hexanediol (EHD), which has the identities and physicochemical properties shown in Table 1, has been used as a solvent for printing inks and a chelating agent for boric acid, but finds its principal use as an insect repellant (3,4). In view of its ready availability, and diliberate application to the skin, it was appropriate to investigate the acute toxicity of EHD perorally, percutaneously, and by inhalation exposure to the vapor and an aerosol. Its acute primary dermal and ocular irritant potential was also determined.

MATERIALS AND METHODS

Animals

Sprague-Dawley albino rats, weighing between 200 and 300 g were used for the acute peroral and for the aerosol inhalation studies. Hilltop-Wister albino rats of 200 to 300 g starting weight were used for the acute vapor inhalation studies. New Zealand White rabbits, of weight 2.0 to 3.0 kg, were used for the acute percutaneous, primary dermal irritation, and eye irritation studies.

All animals were acclimatized for at least 5 days prior to use. For the various studies, animals were randomly assigned to groups from pools whose body weights were within the range of mean ± 2 SD. Animals were kept at an environmental temperature of 68 to 80 °F and relative humidity 30 to 60%. A 12 hr light-dark cycle was used.

Acute Peroral Toxicity

Undiluted EHD was given intragastrically by means of a ball-ended stainless steel needle, with the sample being delivered from an attached syringe. Groups containing 5 male or 5 female Sprague-Dawley rats were used, and fasted overnight before dosing. Doses were 4, 8 and 16 ml/kg for males, and 2, 4 and 8 ml/kg for females. Animals were inspected twice daily for signs of toxicologic or pharmacologic effect during a 14-day postdosing period. Body weights were measured before dosing, and at 7 and 14 days postdosing. Survivors were sacrificed at the end of the observation period and they, as well as animals that died, were subjected to gross pathologic examination.

Acute Percutaneous Toxicity

Undiluted EHD was applied to the clipped skin of the trunk in groups containing 5 male or 5 female New Zealand White rabbits. The material was maintained in contact with skin for 24 hr using occlusive polyethylene sheeting, adhesive tape and plastic ties. Animals were immobilized for the contact period. Applied doses were 8.0, 11.3 and 16.0 ml/kg for males, and 4.0, 8.0 and 16.0 ml/kg for females. On removal of the polyethylene sheeting, any residual EHD was gently removed from the skin with moist tissue. Animals were examined twice daily for signs of local inflammation and systemic toxicity. Body weights were

Table 1. Identity and Physicochemical Properties of 2-Ethyl-1;3-Hexanediol (1-3)

Chemical Formula	$(C_3H_7)CH(OH)CH(C_2H_5)CH_2OH$
RETECS No.	MO2625000
CAS No.	94-96-2
Synonyms	Octylene Glycol, Compound 6-12, Ethyl Hexylene Glycol, 2-Ethly-3-Propyl-1:3-Propanediol
Physical State	Colorless, odorless, slightly viscous liquid
Molecular Weight	146.26
Specific Gravity	0.9422 (20/20 C)
Boiling Point	244 C (760 mm Hg)
Vapor Pressure	<0.01 mm Hg (20 C)
Vapor Density	5.03
Flash Point	260 F (Open Cup)
Viscosity	323 cp (20 C)
Solubility	Readily in alcohol and ether; partially in water

*This paper is based on a presentation at the 1985 AACT/AAPCC/ABMT/CAPCC Scientific Metting, 4-9 August 1985, held in Kansas City, Missouri.

measured before dosing, and at 7 and 14 days postdosing. Necropsies were performed on animals that died, and on survivors sacrificed at the end of the 14-day postdosing observation period.

Acute Inhalation Toxicity

The acute inhalation toxicity of EHD was investigated by exposing rats either to atmospheres essentially saturated with vapor from EHD or to high concentrations of a respirable aerosol of EHD. For the vapor exposures, statically generated and dynamically generated test atmospheres were used.

To produce the vapor saturated atmosphere by static means, a sample of EHD was introduced into sealed 120 L inhalation exposure chambers, and the vapor allowed to equilibrate for about 18 hr at a temperature of 25 °C. At the end of this period, 5 male or 5 female Wistar albino rats were introduced into separate chambers through gasketed draws designed to minimize loss of vapor from the chamber. The oxygen content of the chamber was monitored continuously with an oxygen meter, and oxygen added, as required, to maintain the oxygen concentration at 20%.

The dynamically generated vapor saturated atmosphere was produced by passing dry air at a rate of 2.5 L/min through a fritted glass disc immersed to a depth of about 1.5 inches below the surface of EHD in a gas washing bottle. The resultant vapor saturated air was passed through 9 L glass exposure chambers containing 5 male or 5 female Wistar albino rats. The mean chamber temperature during exposure was 23 C.

For both the statically and dynamically generated vapor atmospheres, the exposure period was 6 hr. Animals were observed for signs of toxicity during exposure and in a postexposure observation period of 14 days for the dynamic system and 15 days for the static system. Body weights were measured before exposure and at 7 and 14 days post-exposure. Survivors were sacrificed at the end of the observation period and subjected to necropsy.

The aerosol of EHD was generated using an atomizer (Spraying Systems Co., Wheaton, IL) attached to a compressed air source, and a piston pump (Fluid Metering Inc, Oster Bay, NY) for the recirculation of EHD. Five male and five female Sprague-Dawley rats were exposed to the aerosol for 4 hr. The atmospheric concentration of EHD was determined by drawing chamber air samples through glass fiber filters, which were weighed before and after the sampling period. Particle size was measured by a cascade impactor (Sierra Instruments Inc, Carmel Valley, CA). Animals were observed for daily toxicologic and pharmacologic signs during exposure and in a 14-day postexposure period. At the end of this time, they were sacrificed and subjected to gross pathologic examination.

Primary Dermal Irritation

The skin irritant potential of EHD by sustained single contact was investigated by applying 0.5 ml of undiluted material to the clipped dorsal skin of each of 6 New Zealand White rabbits (3 males and 3 females). The application site was covered with a gauze patch and impervious polyethylene sheeting. At the end of the contact period, any excess material was removed gently with moist tissue. The application site was inspected for signs of inflammation at 1 hr, and 1, 2, 3 and 7 days after removal of the occlusive dressing. Erythema and edema were scored according to the method of Draize (5), and the skin was closely examined for other dermal reactions.

Table 2. Scheme Used to Score Ocular Lesions Following the Instillation of EHD into Rabbit Eyes (after 7).

Tissue	Major Features	Score	Effect
Cornea	Opacity	0	None
		1	Just detectable: iris clearly visible
		2	Readily detectable: iris slightly obscured
		3	Opalescent: iris details not visible
		4	Opaque: iris not visible
	Area Involved	1	One-quarter or less
		2	One-quarter to one-half
		3	One-half to three-quarters
		4	Greater than three-quarters
Iris	Overall Injury	0	None
		1	Exaggerated folds: congested: swollen: reacts to light
		2	Gross destruction: hemorrhage: no reaction to light
Conjunctivae	Vessels	0	Normal
		1	Obviously injected
		2	Diffuse deep red: individual vessels not discernable
		3	Diffuse beefy red
	Chemosis	0	None
		1	Slight swelling
		2	Obvious swelling with partial eversion of lids
		3	Swelling with lids about half closed
		4	Swelling with lids more than half closed
	Discharge	0	None
		1	Slight
		2	Moderate with periocular moistening
		3	Marked with considerable periocular wetness

Primary Eye Irritation

Rabbits whose corneas did not stain with 2% fluorescein, applied for 20 sec, were used. EHD was instilled into the inferior conjunctival sac of one eye of each of 6 rabbits, and 0.01 or 0.005 ml of EHD was placed directly onto the cornea of further groups of 6 rabbits. The eyes were inspected for signs of local inflammation at 1 and 24 hr, and 2, 3 and 7 to 14 days after dosing. Particular attention was paid to the development of injection of the conjunctivae and nictitating membrane, chemosis, discharge, iritis and corneal injury. Effects were scored according to the scheme shown in Table 2.

Statistics

LD_{50} values were calculated by the moving average method (6).

Acute Peroral Toxicity

Dose-mortality data for rats given EHD intragastrically are shown in Table 3. These allowed the calculation of the following acute peroral LD_{50} values (with 95% confidence limits) for udiluted EHD:

Male rats =9.85 (7.15-13.60) ml/kg
Female rats=4.92 (3.58-6.78) ml/kg

Deaths occurred at 2 hr to 2 days postdosing,

Table 3. Mortalities and Body Weights for Rats and Rabbits Used to Determine the Acute Peroral and Acute Percutaneous Toxicity of Undiluted EHD.

Route	Species	Sex	Dose (ml/kg)	Mortality (No. Dead/No. Dosed)	Body Weight (g) as Mean ± S.D. Predosing	7 days	14 days
Peroral	Rat	Male	16	5/5	216± 7.1	-	-
			8	1/5	233± 7.2	306± 18.2	369± 14.2
			4	0/5	218± 11.8	305± 11.6	362± 9.4
		Female	8	5/5	238± 13.5	-	-
			4	1/5	238± 11.8	280± 10.5	294± 11.7
			2	0/5	223± 7.6	264± 11.5	287± 13.1
Percutaneous	Rabbit	Male	16	5/5	2754±106	-	-
			11.3	3/5	2667±101	2736	2890
			8	0/5	2521± 92	2437±194	2642±254
		Female	16	4/5	2746±100	2594	2952
			8	2/5	2704±208	2599±347	2812±391
			4	0/5	2603±246	2580±324	2795±377

with the majority dying within 1 day postdosing. Signs of toxicity before death included sluggishness and unsteady gait appearing at 5 to 10 min, prostration first seen at 15 to 50 min, followed by a comatose appearance. Signs of toxicity seen in the survivors included sluggishness, unsteady gait, prostration, and lachrymation, with recovery between 1 and 2 days postdosing. There were no significant effects on body weight, or body weight gain, in the survivors (Table 3).

Necropsy of rats that died showed mottling of the lungs in 3, but otherwise there was no significant gross pathology. Necropsy of survivors sacrificed at the end of the observation period, showed no gross pathological effects.

Acute Percutaneous Toxicity

Dose-mortality data for rabbits having a 24 hr occluded contact with EHD are shown in Table 3. These allowed the calculation of the following acute percutaneous LD_{50} values (with 95% confidence limits) for undiluted EHD:

Male rats =10.88 (8.95-13.10) ml/kg
Female rats=9.51 (5.36-16.90) ml/kg

Deaths occurred between 2 and 5 days after dosing, with preceeding sluggishness, prostration, and unsteady gait. Signs of toxicity seen in survivors of all except the 4.0 ml/kg dose level, were sluggishness and unsteady gait, with recovery by 2 days. There was decreased body weight at 7 days in the male and female rabbits at the intermediate and low doses, with recovery by 14 days.

Necropsy of animals that died revealed a few red mottled lungs, afew stomachs having black foci on their surface, and two instances of animals having brown colored liquid in the thoracic cavity. Survivors sacrificed at the end of the observation period did not show any gross pathologic features at necropsy.

Local signs of inflammation at the site of contact of EHD with skin were erythema and edema on the first day, persisting to death at the highest dose. Amongst the survivors, erythema and edema did not persist beyond 7 days. Desquamation was apparent at 7 days until sacrifice.

Acute Inhalation Toxicity

A 6-hr exposure to a statically or dynamiclly generated atmosphere saturated with vapor from EHD, did not result in deaths during exposure or in the postexposure observation period. There were no signs of toxicity from exposure to the statically generated atmosphere. With the dynamic conditions the only effect was hypoactivity within half-an-hour of the start of exposure, which rapidly disappeared on removal of the animals from the exposure chamber. Body weights were unaffected (Table 4). There was no gross pathology at necropsy of the sacrificed survivors.

For the aerosol study, the mean ± SD EHD concentration was 3.8 ± 0.21 mg/L. The particle size distribution had a mass median aerodynamic diameter of 2.0 um and geometric standard deviation of 4.3 um. There were no deaths during the 4-hr exposure or in the 14-day postexposure observation period. The only signs during exposure were perioral and perinasal wetness, with perioral and perinasal encrustation during the first postexposure day. Therafter the animals were free from signs of toxicity or irritation, and weight gain was normal (Table 4). There were no gross pathologic signs at necropsy following sacrifice of animals at the end of the 14-day postexposure observation period.

Primary Dermal Irritation

On removal of the occlusive dressing, 5 rabbits showed a slight local erythema and one had a well defined erythema. The erythema subsided within 24 to 48 hr. No other local signs of inflammation were present.

Primary Eye Irritation

The scores for the various ocular effects seen in eyes following the instillation of different volumes of undiluted EHD are shown in Table 5. Following 0.1 ml EHD there was a rapid development of mild to severe conjunctivitis, seen as moderate to marked injection, mild to severe chemosis, and mild to marked discharge, In one animal the conjuntivitis resolved rapidly, and the eye appeared normal by 24 hr postinstillation. However, in the remaining 5 animals the conjunctival

Table 4. Body Weights of Rats Acutely Exposed to Either a Vapor or an Aerosol of EHD.

Exposure	Sex	Body Weight (g) as Mean ± SD Pre-exposure	7 days	14 days
Vapor (Static)	M	236±4.9	299±8.7	348±15.9
	F	261±9.7	265±9.5	266±9.3
Vapor (Dynamic)	M	248±7.7	314±14.6	355±17.2
	F	242±8.4	257±14.2	257±13.6
Aerosol	M	300±9.0	361±12.0	425±17.0
	F	214±9.0	238±9.0	268±10.0

Table 5. Summary of Scores for Eye Lesions Observed After the Instillation of Various Volumes of EHD into the Eyes of Rabbits. Six Animals for each Volume Group. Scored According to the Scheme Shown in Table 2.

Volume	Observation	Effect as Average (and Range)					
		Cornea		Iris	Conjunctivae		
(ml)	Time	Opacity	Area		Redness	Chemosis	Discharge
0.1	1 hr	0.7(0-1)	2.7(0-4)	0.8(0-1)	2.8(2-3)	2.8(1-4)	2.7(1-3)
	4 hr	0.8(0-1)	2.8(0-4)	0.8(0-1)	2.5(1-3)	2.5(1-3)	2.7(1-3)
	1 day	1.0(0-2)	2.7(0-4)	0.8(0-1)	2.0(0-3)	1.2(0-2)	1.5(0-3)
	2 day	1.0(0-2)	2.3(0-4)	0.0	1.8(0-3)	0.8(0-1)	0.3(0-2)
	3 day	0.8(0-2)	2.3(0-4)	0.2(0-1)	1.3(0-2)	0.5(0-1)	0.3(0-2)
	7 day	0.2(0-1)	0.3(0-2)	0.0	0.0	0.2(0-1)	0
	14 day	0.0	0.0	0.0	0.0	0.0	0
0.01	1 hr	0.3(0-1)	0.8(0-3)	1.0(All 1)	2.8(2-3)	2.7(2-3)	2.7(2-3)
	4 hr	1.3(0-2)	2.0(0-4)	1.0(All 1)	2.8(2-3)	2.8(1-4)	2.7(1-3)
	1 day	1.5(0-2)	1.0(1-2)	0.8(0-1)	2.7(2-3)	1.3(0-2)	1.8(0-3)
	2 day	1.5(0-2)	0.8(0-1)	0.5(0-1)	1.8(0-3)	1.2(0-2)	1.0(0-2)
	3 day	0.7(0-2)	0.5(0-1)	0.5(0-1)	1.2(0-2)	1.2(0-2)	0.3(0-1)
	7 day	0.0	0.0	0.0	0.0	0.0	0.0
0.005	1 hr	0.7(0-1)	0.7(0-1)	0.5(0-1)	3.0(All 3)	2.3(2-3)	3.0(All 3)
	4 hr	0.3(0-1)	0.3(0-1)	1.0(0-1)	3.0(All 3)	3.2(2-4)	3.0(All 3)
	1 day	0.8(0-1)	0.8(0-1)	0.3(0-1)	2.5(2-3)	2.0(All 2)	1.3(2-3)
	2 day	0.8(0-1)	1.0(0-2)	0.0	1.5(1-2)	1.5(1-2)	0.7(1-2)
	3 day	0.5(0-2)	0.3(0-1)	0.2(0-1)	0.8(0-2)	0.8(0-2)	0.7(0-2)
	7 day	0.0	0.0	0.0	0.0	0.0	0.0

effects subsided slowly, being mild to moderate by 72 hr and taking up to 7 days for complete healing. A moderate iritis was seen in 5 of the 6 rabbits, which persisted for 24 to 48 hr. Just detectable to moderate corneal injury, in most instances affecting a large proportion of the surface of the cornea, was seen in 5 rabbits, and persisted for 3 days in 4 animals, and in one to about 7 days. The eye not affected by keratitis was also the one which did not demonstrate iritis and showed only mild transient conjunctivitis.

When the volume of EHD instilled was reduced to 0.01 or 0.005 ml, the effects on the conjunctivae were essentially similar to these observed with 0.1 ml. With both of the smaller volumes a moderate to severe conjunctivitis was present for the first 24 hr postinstillation. Additionally, the conjunctival injection, chemosis, and discharge required 2 to 7 days to resolve. The effects on the iris and cornea with 0.01 and 0.005 ml EHD were essentially similar to those seen after 0.1 ml. Thus, moderate iritis and just detectable to moderate corneal injury developed rapidly and were present for 3 to 7 days.

DISCUSSION

EHD was shown to be of slight to moderate acute peroral toxicity, with deaths occurring within 2 days. Signs of toxicity likely to develop in humans will be mild irritation of the mouth and throat, nausea, vomiting, diarrhea and, with large doses, dizziness, faintness, drowsiness and coma. Although it produced moderate to severe conjunctival irritation, EHD was only mildly irritating to the skin, and it is therefore appropriate to induce vomiting in cases of poisoning by swallowing EHD.

By 24 hr occluded dermal contact, EHD was of slight acute percutaneous toxicity, with LD_{50} values in rabbits of 10.8 ml/kg (males) and 9.5 ml/kg (females), and no mortalities at 4.0 ml/kg. Moderate dermal irritation accompanied these relatively large applied doses. The low potential for systemic adverse health effects from acute percutaneous absorption accords with in vitro studies on the penetration of EHD across human abdominal skin (4). For a 1 hr contact with 0.03 mg/cm^3, penetration was 12.0 ± 2.9 (SD) % of the applied dose. At 0.046 mg/cm^3, the minimum effective dose against mosquitoes, penetration was 1.0 ± 0.9%.

Exposure for several hours to atmospheres saturated with vapor from EHD, generated at ambient temperature, did not produce any toxic effects. Also, the only effects seen from exposure to a high concentration (average 3.8 mg/L) of a respirable aerosol of EHD (MMAD of 2.2 um) was minimal nasal irritation during exposure. These findings indicate a low potential for short-term adverse health effects by single sustained exposure to aerosols or vapor generated at ambient temperature.

The primary dermal irritation studies with undiluted EHD showed that after a 4 hr occluded contact there was mild local erythema and, in one of six animals, moderate erythema. The erythema persisted for about 24 hr, but there were no latent dermal effects. The mild to moderate skin irritant effects of EHD was confirmed with the more demanding conditions of the acute percutaneous toxicity study, involving a more prolonged contact (24 hr) with larger volumes of material (up to 16.0 ml/kg). With these conditions there was erythema and edema on the first postapplication day, and desquamation at 7 to 14 days.

The ocular irritation studies indicated that a major acute hazard from EHD is by splash contamination of the eye. Thus, EHD produced moderate to severe conjunctivitis with mild to moderate iritis and corneal injury. Eyes took up to one week to heal. The severity and duration of the ocular and periocular inflammatory effects were essentially the same within the volume range of 0.005 to 0.1 ml. Thus, when EHD is handled in circumstances that could lead to splashing of the material, eye protection should be worn. Also, aerosol spray devices containing EHD should not be pointed at the eye.

The above studies indicate that the major acute hazards with undiluted EHD are by swallowing and, to a greater extent, by contamination of the eye.

REFERENCES

1. Sax NL: Dangerous Properties of Industrial Materials. Van Nostrand Reinhold Company, New York, p 644, 1979.
2. Tatken RL and Lewis RJ Sr, Eds: Registry of Toxic Effects of Chemical Substances, Vol 2. US Department of Health and Human Services, National Institute for Occupational Safety and Health, Cincinnati, Ohio, p 426, 1983.

3. Hawley GG: The Condensed Chemical Dictionary. Van Nostrand Reinhold Company, New York, p 363, 1977.

4. Reifenrath WG and Robinson PB: In Vitro Skin Evaporation and Penetration Characteristics of Mosquito Repellants. J Pharm Sci 71:1014, 1982.

5. McCreesh AH and Steinberg M: Skin Irritation Testing in Animals. In, Dermatotoxicology and Pharmacology, Marzulli FN and Maibach HI, Eds. Hemisphere Publishing Corporation, Washington, p196, 1977.

6. Thompson WR: Use of Moving Averages and Interpolation to Estimate Median Effective Dose. Bact Rev 11:115, 1947.

7. Draize JH, Woodward G and Calvery HO: Method for the study of irritation and toxicity of substances applied topically to the skin and mucus membranes. J Pharmacol Expt Therap 82:377, 1944.

REGISTERED WITH COPYRIGHT CLEARANCE CENTER
REPRODUCED BY PERMISSION

SUICIDE PLAN BY NICOTINE POISONING: A REVIEW OF NICOTINE TOXICITY*

Kusum Saxena MD,
Department of Internal Medicine and Family Practice and Community Health,
University of Minnesota Medical Center; and

Andrew Scheman MD,
University of Minnesota Medical Center, Minneapolis, Minnesota.

From the Department of Emergency Medicine,
St Paul-Ramsey Medical Center, St Paul, Minnesota 55101

ABSTRACT. Nicotine is a toxic substance which is readily available from a wide variety of sources. Due to the universal availability of nicotine, the primary care physician may encounter accidental or deliberate poisoning in a variety of clinical settings and should be familiar with diagnosis and management of nicotine toxicity. We report a case in which a depressed patient attempted suicide using nicotine extracted from snuff as a lethal drug. Three other cases illustrating the effects and clinical management of nicotine poisoning are also reviewed. The etiology, diagnosis and management of nicotine overdose are discussed.

Nicotine is a water soluble alkaloid which is found in the tobacco plant (1). It is readily absorbed through the gastrointestinal tract, mucous membranes, skin and respiratory alveoli (2,3). The lethal adult dose is reported to be 40-60 mg (1,4) but dosages as small as 1-4 mg can be associated with toxic effects in some individuals (1,2,4).

The predominate use of nicotine is via tobacco consumed by millions in cigarettes, cigars, chewing tobacco leaves and snuff. Nicotine gum represents a newer source of nicotine usage. Although its use as an insecticide is not as prevalent, nicotine is freely available to the public in insecticides. It is also found in products used for dog control. Historically, it has been a vehicle for suicidal and accidental poisonings.

The various sources of nicotine and the resulting methods of overdose are remarkably diverse. The following are ingestion results: Nicotiana Glauca by adults and children, contains anabasine, which is similar in effect to nicotine (2); Tobacco by adults, 1-2 ounces fatal (5); Cigarettes by children (5), cigarettes can contain 20-30 mg of nicotine each (3), which represents a potentially lethal dose for a small child. However, the central emetic effect of nicotine usually induces emesis prior to absorption of a lethal dose (1); Insecticide, many cases of accidental, suicidal or homicidal ingestion of nicotine containing insecticides have been reported (5,7,8). Though largely replaced by organophosphates, insecticides containing as much as 40% nicotine are still widely available (9); Nicotine gum, gum containing 2 mg/piece is widely available without prescription (10) and use of as little as one piece has been reported to have induced overdose symptoms in one patient (4); and Nicotine extract, case #1 (our report). Absorption through mucous membranes can occur by: Use of nicotine-containing solution as an enema for constipation or pinworms (3,11-13); Overuse of snuff (5); and Tobacco chewing of dipping, symptomatic serum levels of nicotine can be reached within 5 min (14). Tobacco dipping refers to placement of tobacco between the cheek and gums. Percutaneous absorption results in: Fatal use of decoction of tobacco for skin ailments (5); Fatal use of tobacco powder on skin for favus (5); Insecticide accidently spilled on skin (13); and Ill effects sustained by tobacco harvesters (15). Inhalation is associated with: One case of fatal excessive pipe smoking, 17-18 successive pipefuls (5); and Cigarette smoking, the usual absorbed dose from smoking one cigarette is 1-2 mg (1).

CASE PRESENTATIONS

Case #1

MI is a 18-year-old white male who had become upset after talking with his girlfriend and ingested a tincture of nicotine as a suicidal gesture. The patient claimed

*This paper is based on a presentation at the 1985 AACT/AAPCC/ABMT/CAPCC Scientific Meeting, 4-9 August 1985, held in Kansas City, Missouri.

Toxicity Data

906659

Copy to W. C. Barr
G. A. Neuman
FYI

from L+F

UNION CARBIDE

Blind copy to Dr. H. L. Haynes ✓
Main T of file

April 26, 1965

Donald E. Goldstone, M.D.
Latin American Regional Medical Officer
Medical Program Division
Peace Corps
Washington, D. C. 20525

Dear Dr. Goldstone:

Your letter to Union Carbide Corporation, Consumer Products Division, has been referred to my office for comment and reply.

You know that "6-12" insect repellent is an alcohol known as 2-ethylhexanediol-1,3 and listed in the most recent issue of the UNITED STATES PHARMACOPEIA as Ethohexadiol. It has been used as an insect repellent by humans for years. Millions of bottles of ethylhexanediol, straight and in mixtures, were used by our armed forces during recent wars, and no cases of harmful effects resulting therefrom were reported. Since the war, millions of bottles of the liquid "6-12" repellent, which is 100 percent ethylhexanediol, have been used by the general public, which includes not only adults but infants and children as well. Before it was accepted for use by the armed forces and before it was sold to the public, tests indicated its safety for use as a repellent. These included patch tests upon humans for allergic response.

While routine testing on humans indicated that "6-12" was not an irritant or sensitizer, as is frequently the case, a few persons of the millions who apply "6-12" will react with a rash. In all the years of experience we have not received more than ten complaints a year and some of these cases may well have been due to poison ivy. Usually complaints are only 4-5 per year which on a conservative estimate would be a prevalence rate of about one reactor to each million units sold. Aside from these occasional skin complaints we have no record of harm from "6-12" when used as an insect repellent.

Very truly yours,

Original Signed By
CARL U. DERNEHL, M.D.
Director of Toxicology

RECEIVED
APR 27 1965

Carl U. Dernehl, M.D.

Because of some peeling following this test and found to have no significance in regard to human use of the materials, we can use a given rabbit belly only once in about ten days. This peeling is caused by seventy per cent alcohol and sometimes by glycerin.

For acceptance a material must give no erythema or more severe reaction 24 hours after the test upon at least two of the five rabbit bellies and those bellies showing reaction must have only faint erythema; that is, its grade of irritation must be "13" or less.

Repellent "6-12" showed an irritation test of "1".
- Taken from Mellon Institute of Industrial Research Special Report 5-25 of February 7, 1942, and from monthly report dated July 31, 1942. Both reports signed by Dr. N. F. Smyth, Jr., Senior Industrial Fellow.

C. Human Patch Tests

See attached report from the independent Smyth Laboratories of Philadelphia signed by Dr. Herman Shelanski with a commentary by Dr. Joseph V. Klauder

The most important evidences of freedom from irritation and sensitization are the extensive tests and favorable findings of the following government agencies.

The Federal Food and Drug Administration
Insect Control Committee, Office of Scientific Research and Development
National Institute of Health
Orlando Laboratories, United States Department of AGriculture
Surgeon General's Office, United States Army

B. Skin Irritation

1. Primary Irritation Upon the Rabbit Belly

Before materials are applied to human skin, we apply them to the rabbit belly, for protection of our human subjects against possible unsuspected vesicants. This test is a very coarse screen to exclude frank irritants.

A group of about ten albino rabbits having normal appearing skin is selected and the bellies are closely clipped, carefully avoiding any abrasion. To select those having adequate sensitivity to irritants, a point low on the belly is swabbed with a glycol derivative irritating enough to produce definite erythema on most rabbits. Only those animals which show a detectable erythema at the point of application 24 hours later are used for the test.

Four samples of materials being considered are tested at one time, comparing them with two reference compounds. Five rabbits are immobilized upon their backs and with a wax pencil six areas about 3 cm. on a side are marked off upon the closely clipped belly. A test material or reference compound is applied to one area on each rabbit by running a cotton swab wet with the sample several times over a 2 cm. diameter circle of skin. Six samples are applied thus to the rabbits. The application is made eight times during four hours, each time recording degree of injection of blood vessels and erythema. At the end of the four hours the samples are removed by gently swabbing with acetone or 70% alcohol. A final reading of erythema is made 24 hours later, and we find this is the most consistent reaction. This reading is facilitated by wetting the new grown hair stubble.

We recognize four degrees of reaction less than edema or necrosis. For convenience each is given a numerical value and the grades of irritation of the material is the sum of these values for the five rabbits tested. These are:

0 - no reaction
1 - least visible injection of superficial blood vessels
2 - definite or marked injection of superficial blood vessels
3 - least visible general erythema
4 - definite or marked general erythema

The results on all five rabbits are discarded unless our reference material of known high irritation gives a grade of "17" or more, corresponding to erythema on all with definite or marked erythema on at least two.

not aware of the excretion of glucuronates caused by "6-12" may be alarmed by the high sugar content in the urine."

- Taken from Mellon Institute of Industrial Research Report No. 6-9, for the month ended December 31, 1942, dated January 5, 1943 and signed by Drs. Henry F. Smyth, Jr., Senior Industrial Fellow and Drs. Charles P. Carpenter and Charles B. Shaffer, Industrial Fellows.

V. Irritation

A. Corneal necrosis

"Various amounts of repellent "6-12", with n-Butanol for comparison, were instilled in rabbit eyes and the course of healing followed from day to day. The eye was considered to be healed when no corneal necrosis could be demonstrated with 5% aqueous fluorescein staining for 20-second intervals. All eyes were examined by the fluorescein method before dosing and were found to be free of corneal abrasions.

Rabbit No.	Eye	Material	Dose in ml.	% of Cornea Necrosed	Time for Healing
R20513	Left	"6-12"	0.05	70	4 days
"	Right	n-Butanol	0.05	98	7 "
H20519	Left	"6-12"	0.01	50	3 days
"	Right	n-Butanol	0.01	95	6 "
H20518	Left	"6-12"	0.005	5	3 days
"	Right	n-Butanol	0.005	10	5 "

Repellent "6-12" produces severe congestion, cloudiness of the cornea, necrosis of the lids and sclera and occasional swelling of the lids. The damage to the eye is less severe than that produced by equal amounts of n-Butanol. The eyes of H20518 which received "6-12" were examined by our ophthalmologist, Dr. Kutscher, after the corneal burn had healed. No internal damage to the eye could be seen with an ophthalmoscope. This indicates that eye burns caused by small amounts of "6-12" will not cause permanent damage to the eye unless complicated by infections."

- Taken from Mellon Institute of Industrial Research Report No. 5-102 for the month ended September 30, 1942, dated October 3, 1942 and signed by Drs. Charles P. Carpenter and Charles B. Shaffer, Industrial Fellows.

(A commentary on these data from A. G. Cranch, M.D. is attached.)

of manufacture is made."

- Taken from Mellon Institute of Industrial Research Report 5-115 for the month ended November 30, 1942 and dated November 30, 1942, and signed by Dr. Charles P. Carpenter, Industrial Fellow.

IV. Metabolism

A. Ascorbic Acid

"During five day trial repellent "6-12" did not increase the Vitamin C excretion of any of ten rats, and, therefore, it does not interfere with Vitamin C. metabolisms. (Ten male albino rats weighing 81 to 123 grams each received on 5 consecutive days 0.30 gms of the diol, making the average dose 3 gm./kg./day. This is of the order of magnitude of the single dose LD_{50}, but only two of the ten rats died.)

- Taken from Mellon Institute of Industrial Research Report No. 5-110 for the month ended October 31, 1942, dated November 4, 1942 and signed by Drs. Charles P. Carpenter and Charles B. Shaffer, Industrial Fellow.

B. Glucuronates

"An acetate of "6-12" was prepared and fed to two rabbits at a dosage of 2 gm./kg. This markedly increased the total glucuronic acid content of the urine for the next 24 hours but it was tolerated with less depression symptoms than a similar dose of the parent diol.

"Ten albino rats received 2 gm./kg. of "6-12" by mouth. Their urine was pooled in pairs and total glucuronic acid was determined on three successive days, once before and twice after the dose. The glucuronic acid level on the day following the dose was about five times that on the day before the dose. Thus rats excrete in the urine a glucuronate following a dose of "6-12". We can see no difference between rats and rabbits in this respect.

"Blood sugar and blood glucuronic acid analyses were made simultaneously on four rabbits before and after an oral dose (2 gm. per rabbit) of "6-12". The blood was drawn one-half hour after the dose. Glucuronic acid in rabbit blood was markedly elevated after the dose but blood sugar was not affected. Blood sugar of four rabbits which have received 100 daily inunctions of "6-12" at 1 ml./kg. was found to be normal.

"Three rabbits received an oral dose of "6-12" while dextrose was determined in their urine for the 24 hours before and after the dose, and this was repeated the following week adding glucuronate determinations. Glucuronates were increased 8 to 10 times by the dose of "6-12" and apparent dextrose was increased 2 to 3 times. We are uncertain that the dextrose increase was real because the adsorbent used to remove glucuronates from urine before dextrose determination is not known to remove them completely. (Glucuronates reduce the usual reagent employed to determine sugar in urine so many workers,

II. Micropathology from single doses

"A report on the micropathology of animals dosed with Repellent "6-12" has been received. Dosage of 10 to 20 ml./kg. by the rubber dam technique on rabbits indicate no residual damage of organs when the animals survived the 14-day observation period. General, marked, cloudy swelling of livers and kidneys resulted in all animals dying as a result of the applications.

"Oral doses of 2.52 and 3.16 ml./kg. to male albino rats produces cloudy swelling of tubules with many containing desquamated degenerated cells. Livers also showed varying degrees of cloudy swelling. Adrenal cortex and spleen was normal in all cases.

"Exposure of rats and pigs to mists produced by heating "6-12" to 170°C. affects livers and kidneys after an 8-hour exposure, producing the same type of pathology as noted above for oral doses. However, exposures for 1, 2, and 4 hours produces light cloudy swelling with occasional desquamated and degenerated cells in the tubules of the kidney but no liver pathology.

"Five different lots of "6-12" were used in the tests reported above with no indication that any one sample was more or less toxic than another."
- Taken from Mellon Institute of Industrial Research Special Report 6-40 dated May 3, 1943 and signed by Dr. H. P. Smyth, Jr., Senior Industrial Fellow.

III. Tests on Plant Production

"Our results on consecutive shipments of repellent "6-12" from the plant are tabulated below:

Lot	Works Lab. No.	Initial Boiling Point	Mortality among rats from 2.52 gm./kg. orally	No. of Rats Tested	Mortality among Rabbits from 12.6 gm/kg on the skin	No. of Rabbits Tested
-	D-388-25	240°	1	10	3	10
-	S-33409	*238	5	10	6	10
-	S-33798	*229.5	4	10	6	9
-	S-34130	240.2	0	10	4	9
-	S-34763	*217	1	10	6	10
7	S-35948	*229	2	10	-	9
8	S-36345	241.2	0	10	-	-

((*) Does not meet standard specifications for product.)

"Because of the steepness of the dosage-mortality curve, we believe these results show a substantially constant internal toxicity and skin penetration. There is no correlation between internal toxicity and specific gravity between 0.9396 and 0.9409 or initial boiling point between 217 and 241.2°C. We believe any specifications selected within these two ranges will yield a product of suitably low toxicity provided no material change in the process

(d) "Results to date on Single Skin Applications to Rabbits under a Rubber Dam.

Material	Dosage gm/kg.	No. dosed	No. died	Mortality %
Butyl "Carbitol" acetate	20	6	4	67
	15.8	6	4	67
	12.6	6	1	17
	7.95	6	1	17
Butyl "Carbitol" acetate + "Carbitol" (1 + 1)	20	6	6	100
	15.8	6	6	100
Butyl "Carbitol" acetate + propylene glycol (1 + 1)	20	6	6	100
"Sta-Way" Lotion	20	7	6	86
	15.8	6	5	83
2-Ethylhexanediol-1,3	10	2	0	0

- Taken from Report No. 5-73 for the month ended June 30, 1942 and dated July 2, 1942 and signed by Dr. N. F. Smyth, Jr., Senior Industrial Fellow and by Drs. Charles P. Carpenter and Charles B. Shaffer, Industrial Fellows.

2. Repeated skin absorption.
"Daily inunction of rabbit bellies with 1 ml./kg./day gave no liver or kidney injury, no effect on blood cells, or no blood urea nitrogen."
- Taken from Mellon Institute of Industrial Research special report 6-60 of July 29, 1943.

C. Inhalation
"To judge the safety of the use of ethylhexanediol as a plasticizer, six rats were exposed to mist produced by bubbling air through the material at 170°C. Four died in four and one-half hours, one out of six in one-half hour and one in seven and one-half hours. The mist was irritating to the eyes and caused comneal opacity. In the lungs it caused congestion. This material is thus irritating when mist or concentrated vapors are inhaled, but fatal results require a longer exposure than is the case with Dibutyl Phthalate, Triethylene Glycol, Di-2-ethylhexoate ("Flexol" Plasticizer 3GO) or Triethylene Glycol Di-2-ethyl Butyrate ("Flexol" Plasticizer 3GH)." -
(NOTE: This extreme test was designed to test the safety of "6-12" as a plasticizer - not as a repellent).
- Taken from Mellon Institute of Industrial Research report 5-115 for the month ended November 30, 1942 and dated November 30, 1942, and signed by Dr. Charles P. Carpenter, Industrial Fellow.

B. Skin Absorption

1. Single dose

(a) "The following results for single skin application of rabbits with rubber dam have been obtained:

Material	Dosage Gm/kg.	No. dosed	No. died	Mortality %
2-Ethylhexanediol-1,3 (Crude sample)	10	7	3	42
(fine sample)	6.3	6	0	0
(Note: The so-called "fine Sample" is equivalent to present commercial product)				
Oil of Citronella (62% total alcohols)	10	6	0	0
" " "	5	6	0	0
Oil of Pensyroyal, camphor and cedar mixed (60:30:10)	20	3	2	67
	10	3	2	67
	5	6	0	0

- Taken from the Mellon Institute of Industrial Research report 5-83 for the month ended July 31, 1942, dated August 4, 1942 and signed by Dr. Henry F. Smyth, Jr., Senior Industrial Fellow, and Charles P. Carpenter and Charles B. Shaffer, Industrial Fellows.

(b) "Six rabbits received a dosage of 15.8 ml/kg by single inunction for comparison with rubber dam results. At the end of three days only one of the six had died. This mortality from ununction appears to be somewhat less than that from the rubber dam applications."

- Taken from Mellon Institute of Industrial Research Report No. 5-115 for the month ended November 30, 1942 and dated November 30, 1942. This report is signed by Drs. Charles P. Carpenter and Charles B. Shaffer, Industrial Fellows.

(c) "By single inunction on the rabbit belly 15.8 ml./kg. produced a mortality of one in ten; a dosage of 20 ml/kg. resulted in a mortality of two out of six animals, and 25.2 ml./kg. produced a mortality of one out of six. These results were obtained using three different samples of "6-12" and indicate that rabbits usually survive doses which produce symptoms such as general weakness and poor coordination which almost approaches light anaesthesia."

- Taken from Mellon Institute of Industrial Research Report for the month ended January 30, 1943, dated February 6, 1943 and signed by Dr. Charles P. Carpenter, Industrial Fellow.

Mellon Institute Toxicological Tests on
2-Ethylhexanediol-1,3 (Insect Repellent "6-12")

The tests performed by the Carbide and Carbon Chemicals Corporation Industrial Toxicology Fellowship at the Mellon Institute of Industrial Research can be summarized as follows:

I. Toxicity

A. Oral

1. Single oral dose to rats.

"In spite of all the work we have done with ethylhexanediol, we have never administered single dose to enough rats to allow estimation of the LD_{50} by the method of probits. Before commercial production, a range finding test indicated the oral LD_{50} for rats to be close to 2.4 gms/kg. Recently, a composite of five early commercial batches was prepared and single doses were administered to 209 male albino rats as a 50% dispersion. The resulting LD_{50} was 2.71 gm/kg. (2.52-2.93).

"We used five times the usual number of rats so that the dosage mortality curve could be investigated more thoroughly than usual. Bliss gives theoretical reasons based on the Van't Hoff absorption formulae for expecting a break in the curve at about 30% mortality, with more animals killed at very low dosages than the rest of the curve indicates. This would be important for it would lower the safe human dose considerably if the curve broke to give a long tail on the low mortality side. No evidence for such a break was found with ethylhexanediol, although one-third of the animals used received dosages below that which killed 30% of the rats."

-Taken from Mellon Institute of Industrial Research Progress Report for the month ended May 31, 1944, and dated June 1, 1944. This report is signed by Dr. Henry F. Smyth, Jr., Senior Industrial Fellow, and Drs. Charles P. Carpenter, C. Boyd Shaffer and Walter L. Thompson.

2. Repeated oral dose to rats.

A special report summarizes the results of ninety-day repeated oral administration of 6-12 in the drinking water of rats. The rats received concentrations of 0.4 per cent, 0.2 per cent, 0.1 per cent, 0.05 per cent and 0.0 per cent of the material in their drinking water. "6-12" is soluble to the extent of 0.5% in water so no dispersing agent was necessary. Groups of eight rats or a total of forty in all were on this regimen. Fertility, weight gains and blood counts were followed. Over the ninety-day period a dosage of 0.70 g.kg. per day retarded growth, while a dosage averaging 0.48 g./kg. per day produced no injury.

- From Mellon Institute of Industrial Research special report No. 7-38 dated May 5, 1944 and signed by Dr. Henry F. Smyth, Jr., Senior Industrial Fellow, and Drs. Charles P. Carpenter and C. Boyd Shaffer.

Our tests have been developed in cooperation and consultation with opthalmologists with special experience with chemical injuries of the eye and are designed to establish as accurate a method as possible for comparison of industrial chemical materials with other commonly used materials with reference to the potential hazards to the eye.

In the case of ethylhexanediol, 0.005 ml. will produce some necrosis of corneal cells. This condition rapidly disappears, however, and unless infection should occur before healing has taken place, there would be no reason to expect any scarring following such an application. Other materials which will produce corneal necrosis in a range between 0.001 ml. and 0.005 ml. are tincture of green soap, Drene shampoo, Flit repellent, Packer's pine tar shampoo and such commonly used solvents as acetone and methanol. In our report on ethylhexanediol comparison was made with n-butanol, which has a reaction of the same degree, because this was of current interest to our workers at the plant and in the laboratory.

Obviously if full-strength ethylhexanediol entered the eye it would cause stinging and discomfort, just as would the shampoos mentioned or tincture of green soap. Not only our tests but actual experience in use indicate the effect is no more serious or far-reaching than is the use of the shampoos. We have not as yet ever heard of any serious injury to the eye in the use of such materials.

I would like again to emphasize definitely the fact that these tests of the products of Carbide and Carbon Chemicals Corporation on the cornea of the rabbit eye are made according to a carefully planned program in consultation with recognized ophthalmologists with experience in this field; that they are made primarily to establish comparative values from the point of view of irritation or injury to the eye and must be interpreted in comparison with tests of other materials to give a proper picture of their significance. So interpreted there is no reason to anticipate any serious harm from accidentally getting ethylhexanediol in the eye in the course of its use as an insect repellent.

Very truly yours,

A. G. CRANCH, M. D.

C
O
P
Y

A. G. CRANCH, M. D.
30 East 42nd Street
New York 17, N. Y.

July 24, 1945

Mr. W. F. Reich, Jr.
Carbide and Carbon Chemicals Corporation
30 East 42nd Street
New York 17, N. Y.

Dear Mr. Reich:

This will confirm our conversation of today on the effects of ethylhexanediol in the eye. Of course as you are aware, I am in charge of the toxicological investigation of the products of the Carbide and Carbon Chemicals Corporation and in connection with that work over a period of years, we have developed a definite program to cover all essential exposures in the manufacture and use of products tested and have also conducted comparative tests on many other materials in more common use. The effect on delicate membranes is of course important and such action is estimated on the basis of tests made on the cornea of the rabbit eye. The various materials tested have been graded according to their ability to produce necrosis in the corneal cells of the rabbit eye according to quantity introduced or according to concentration of material applied. The quantities introduced vary from 0.5 ml. which is the greatest quantity which can be introduced into the palpebral sac of the eye, down to 0.001 ml., an amount so small that it was necessary to make our own special pipettes for the introduction of this minute amount. These tests have been made on probably at least 200 materials and many of our results have been checked by Dr. Kutscher, one of the leading ophthalmologists of Pittsburgh, who has worked in close cooperation with the staff of our laboratory at Mellon Institute in this work. The material is introduced into the rabbit eye in appropriate quantity according to the nature of the material, and this amount varied until the minimum amount which will produce corneal necrosis is determined. After the material has been introduced into the eye, it is left for some hours. The eye is then flushed with normal saline solution and fluorescein stain introduced. The cornea is then examined under a strong light with magnification. In some doubtful cases, it may be examined under the slit lamp. Any staining is taken to indicate necrosis of some corneal cells. This necrosis may be so slight that in a few hours it disappears and in many cases eyes which may show stain shortly after the introduction of the material failed to show any necrotic cells after the few hours allowed to elapse in making this test. The presence of necrotic cells does not by any means necessarily indicate that a permanent scar will remain and unless the chemical has penetrated Bowman's membrane, healing will occur without any residual scar. Many common materials which one would not suppose would produce a chemical burn of the cornea will show some necrosis of corneal cells by this test.

A change in the reactibility of the skin; minor reactions are not read exactly the same, a plus minus reaction may be regarded as such and at another application may be read negative; the compound remains on the skin five days after the first application and two days after the second, this longer duration may give rise to positive reactions in contrast to negative ones after the shorter application.

Regarding the primary irritant action of compound No. 1, the percentage is scarcely appreciable. Moreover, all positive reactions were minor ones. Under the test conditions of five-day and two-day continuous application to the skin, the evidence of primary irritant action is not substantial. It can be regarded as from scarcely appreciable to mildly attenuated.

Very truly yours,

(Signed) Joseph V. Klauder, M.D.

JVK/kh

C
O
P
Y

6.1.2
man. of file

(Abstract from original, but containing all portions of report relating to ethylhexanediol and mixtures thereof.)

July 6, 1945

Dr. Herman Shelanski
Smyth Laboratories
34th & Chestnut Streets
Philadelphia, Pa.

Dear Dr. Shelanski:

I herewith report observations of patch test studies performed with the following compounds:

No. 1 - Ethylhexanediol
No. 2 - Ethylhexanediol - 20% isopropanol (99% technical)
No. 3 - Ethylhexanediol - 20% ethyl alcohol specially denatured No. 40 (3 oz. brucine sulfate, 0.125 gal. tertiary butyl alcohol per 100 gallons.)

The method employed and the interval between applications are detailed in your report. The method is the one suggested by Schwartz, ("An Outbreak of Dermatitis from New Resin Fabric Finishers", Jl, of the Amer. Med. Assoc., 115,906-911, 1940) to determine if a given substance has allergonic properties. In prior studies employing this method we observed allergic reactions with some compounds that were studied.

I observed the skin at the sites of applications of the aforementioned compounds on removal after the first application and on removal after the second application.

It is to be noted that with compound No. 1, there was a slight increase of positive reactions after second application compared with the first application. I do not regard this increase as evidence that the compound exerted an allergic reaction for the reason that there was no increase in the intensity of the reaction. Positive reactions after second applications were all minor ones, plus minus and one plus, the same as after first application.

Regarding the rather slight discrepancy of the percentage of positive reactions, after second application compared with the first, or conversely, the first compared with the second, I believe one or more of the following considerations serve in explanation.

Toxicity Data

906659

from L+F

2-Ethylhexane diol-1,3

310,020-7

1943		M	0.10 T7	2.71 (2.52 - 2.93)		
1952	15-131	M	"	3.40 (2.95 - 3.92)	F	3.56 (3.04 - 4.16)
1953		M	0.10 CO	5.37 (4.9 - 5.88)	F	4.34 (3.52 - 5.34)
1954	17-216	M	"	3.88 (3.12 - 4.83)		
1955	18-194	M	"	3.56 (3.13 - 4.05		undil. 6.67 (4.33 - 10.37)
1956	19-126	M	undil.	6.07 (4.49 - 8.21)		
1957	20-150	M	"	10.7 (7.7 - 14.9)		
1958	21-113	M	undil.	6.3 (5.42 - 7.31)		
1959	22-59	m	undil	5.61 (4.08 - 7.72)		
1960	23-268	m	undil.	8.92 (6.03 - 13.2)	Not. Rpt.	

RECEIVED

AUG 10 1961

H. L. H.

Ethylhexane Diol Card 1.

$CH_2OHCH(C_2H_5)CHOHCH_2CH_2CH_3$

Single Oral Doses

LD_{50} 6.7 (4.3 to 10.4) ml./kg. undiluted; 2.71 (2.52 to 2.93) gm./kg. as 10% in "Tergitol" 7 to rats (Report 19-132; 1956)

One sample in various dispersing agents gave LD_{50} from 2.16 to 4.29 gm./kg. (Spec. Report 7-74; 1944 and Montly Report 1-31-47)

Death is accompanied by severe kidney and liver injury (Spec. Rpt. 7-8; 1944)

90-Day Dose to Rats (Spec. Rpt. 7-83; 1944)

0.48 gm./kg./day no effect, 0.70 retarded growth, reduced appetite

Single Skin Absorption by Rabbits, 1-day dam (Spec. Rpt. 7-8; 1944)

LD_{50} 10.7 to 15.2 ml./kg. R.F.

Rabbit inunction 20 ml./kg. killed 2/6, LD_{50} 25 ml./kg. R.F. (Spec. Rpt. 7-8; 1944

Single Inhalation by Rats

Concentrated vapors 2 hours killed 0/6, 8 hours 6/6 (Monthly Rpt. 4-30-43)

Mist from 170°C. 2 hours killed 0/6, 8 hours 6/6 (Spec. Rpt. 7-8; 1944)

Fog from Nebulizer at 70°C. 4,800 ppm 8 hours killed 0/6 (Monthly Rpt. 1-31-47)

12-15-56 4785

Replaces 3285

Ethylhexane Diol Card 1.

Ethylhexand Diol Card 2

$CH_2OHCH(C_2H_5)CHOHCH_2CH_2CH_3$

Biochemistry (Spec. Rpt. 7-8; 1944; Monthly Rpts., 9-30-42, 12-31-42)
No effect on rat excretion of ascorbic acid. Rabbit urine may have mercaptan odor. Increases blood urea, blood and urine glucuronates.

Primary Irritation, Rabbit Belly Vesicant Test (Spec. Rpt. 7-8; 1944)
Grade 1. Undiluted sample gave no irritation

Primary Irritation, Rabbit Belly 4-Hour Test (Monthly Rpt. 2-29-47 summarizes all)
Various batches Grades A of B (Scores 1 to 10)

Primary Irritation, Human Skin
12 subjects on face 4 times a day for 5 days gave mild irritation on 9, papules on 3 (Monthly Rpt. 11-30-42)
20 subjects on arms at 0.01 ml./sq. cm. for 4 hours gave no reaction (Monthly Rpt. 11-30-46)

Eye Injury from Fluid to Rabbits (Spec. Rpt. 9-11; 1946)
Grade 5. 0.02 ml. severe, 0.005 ml. minor injury

Sensitization of G. Pig skin (Spec. Rpt. 8-83; 1945)
None of 12 pigs were sensitized

Sensitization of Human Skin, Patch Test
Undiluted on 23 subjects gave 4% definite sensitization as erythema (Monthly Rpt. 12-31-42)
Undiluted on 200 subjects gave 1% sensitization (Phila. consultant 1945)

9-1-53 3286
(Replaces B-1004)

Ethylhexane Diol Card 3

$CH_2OHCH(C_2H_5)CHOHCH_2CH_2CH_3$

150-Day Inunction on Rabbits (Spec. Rpt. 6-60; 1943)

1 gm./kg./day gave transient light desquamation but no liver or kidney injury

Repellent Stick formulations with sodium stearate were little more irritating than diol alone (Rpt. 16-102; 1953). Philadelphia consultant Jan. 7, 1954 reported no primary irritation, sensitization nor fatiguing in repeated insult patch test on 25 males and 25 females.

90-Day Oral Doses to Dogs (Rpt. 17-37; 1954)

No effect on 3 dogs from 0.1 or 0.5 gm./kg./day

3-15-54

4180
(Replaces 4139)

Ethylhexane Diol Card 3

Ethylhexane Diol Aerosol Bomb

10 or 20% 6-12 in Freon 11 and 12 gave severe but not extreme rabbit corneal injury at 6' or 12 inches. A Gulf insecticidal bomb caused no injury. The aerosol spray was choking to humans regardless of presence of ethanol or isopropanol but isopropyl myristate reduced the sensation. An allethrin aerosol was not choking. (Monthly Rpt. 9-30-53)

10-15-53 4021

Ethylhexane Diol Aerosol Bomb

6.12 Man T ox
936

August 7, 1961

Dr. H. F. Smyth, Jr.
Mellon Institute
4400 Fifth Avenue
Pittsburgh 13, Pennsylvania

Dear Henry:

Thanks for the information and Report 17-37 included in your letter of August 3, 1961.

We are having field tests run to find out how effective 6·12 is for repelling ticks on dogs.

When data come in, we can decide on future action or approach with the U. S. D. A.

Very truly yours,

Harry L. Haynes
Technical Manager
Biological Products

HLH:cmc

bcc: Mr. J. C. Kratzer

Toxicity Data

906659

from L+F

UNITED STATES DEPARTMENT OF AGRICULTURE

AGRICULTURAL RESEARCH SERVICE

PLANT PEST CONTROL BRANCH

WASHINGTON 25, D. C.

Vi

in Toxicology file on 6-12 Repellent

Dr. Thomas W. Nale, Medical Director
Ind. Med. & Toxicology Department
Union Carbide & Carbon Corporation
No. 30 East 42nd Street
New York 17, New York

Dear Doctor Nale:

Reference is made to your letter of April 15 concerning 2-ethylhexanediol and its possible toxicity.

Our statement "Severely toxic upon absorption * * * "was taken from the conclusions column Table 1 of the article by Draize, et al on Toxicological Investigations of Compounds Proposed for use as Insect Repellents," Journal of Pharmacology and Experimental Therapeutics 93, 26-29 (May 1948)

The conclusions were based on rather broad evaluation tests which were conducted under OSRD sponsorship as early as 1943.

The chemical was stated to be "safe for recommended uses," but as we brought out in our letter of review concerning Skeeter Chaser, that clearance was not for the material in a formulation which might favor absorption through the skin. We are not requesting extensive evidence that such is not the case, but we feel that a minimum amount of proof of safety is needed on each distinct repellent formula, as we are pleased to note you agree.

Should you have any detailed studies with formulations of 2-ethylhexanediol we would be glad to get it.

Very truly yours,

(Signed) R. O. White, in Charge

Registration Unit
Pesticide Regulation Section

TOXICOLOGICAL INVESTIGATIONS OF COMPOUNDS PROPOSED FOR USE AS INSECT REPELLENTS[1]

A. LOCAL AND SYSTEMIC EFFECTS FOLLOWING TOPICAL SKIN APPLICATION

JOHN H. DRAIZE, ELSIE ALVAREZ, AND MARIE F. WHITESELL

B. ACUTE ORAL TOXICITY

GEOFFREY WOODARD AND E. CONWAY HAGAN

C. PATHOLOGICAL EXAMINATION

ARTHUR A. NELSON

Division of Pharmacology, Food and Drug Administration, Federal Security Agency Washington 25, D. C.

Received for publication December 8, 1947

INTRODUCTION. Although insect pests and insect-borne diseases have plagued man through the ages, intensified research in the field of insect repellents is a relatively recent undertaking. Prior to World War II the most commonly used repellents were relatively ineffective substances such as citronella, oil of cloves, cinnamon, lemon, peppermint, camphor, pennyroyal and a few synthetic organic compounds such as terpinyl acetate, salicylic acid esters and ethylene glycol.

In 1940 Granett (1, 2) as a result of his entomological tests on more than one thousand chemical compounds or mixtures thereof listed nine conditions which an ideal insect repellent should satisfy. As a result of these researches, Granett found a mixture, which he called "Sta-Way," to meet most of the conditions listed. The only reference to irritation and toxicity stipulated in Granett's list of conditions for an ideal repellent is "It must be non-irritating to the skin and harmless when breathed or accidentally swallowed." The possibility of the percutaneous absorption of the repellent or of irritation following repeated daily use over a period of time was not considered. The effect of repeated application proved Sta-Way to be an undesirable repellent. Repellents which may be well tolerated following a few applications may, as reported by Hochn (3), become severely damaging following continued liberal use. Because of the inherent dangers from the use of repellents, the Surgeon General of the U. S. Army asked the U. S. Public Health Service and the Food and Drug Administration to conduct tests on proposed insect repellent candidates in order to establish their safety for use by the military personnel.

METHOD. A. *General Remarks.* Approximately 4000 compounds, prepared by various universities and chemical concerns, were submitted during the war program to the Food and Drug Administration for toxicological testing. Most of the compounds were organic chemicals; however, a few mixtures also were submitted. Ten thousand rabbits were used to determine the primary irritation and skin toxicity of these insect repellent candidates.

---

[1] A portion of the funds used in this investigation was supplied by a transfer recommended by the Office of Scientific Research and Development and the War Department to the Division of Pharmacology of the Food and Drug Administration.

Reprinted by the Federal Security Agency with permission of the Williams and Wilkins Company

The toxicological technics employed were described by Draize et al (4). During the course of these studies many compounds did not survive the initial screening procedures because of excessive skin irritation or because of systemic toxicity following initial exposure. Many of the compounds which passed the "screening for irritation" tests were eliminated in acute and 3-week subacute skin toxicity testing. In the final group surviving the initial tests there remained 42 compounds or mixtures which were studied intensively. Ninety-day subacute toxicity tests were employed whereby a series of rabbits were inunected daily with the insect repellent at varying dosage levels on a weight basis.

B. *Remarks on Acute Oral Toxicity.* As will be observed in the table, the acute oral LD 50's for 39 of the 42 compounds were determined on from one to five species of animals for each compound. Except where noted otherwise, the materials were given undiluted. The rats, guinea pigs, and chicks were routinely fasted for 18 hours prior to administering the chemical, while the mice and rabbits were not fasted. The animals were observed for six days following dosage, and deaths occurring in that period were recorded. The materials were given in graded doses to groups of ten animals each so that dosage-mortality curves could be constructed. The LD 50's were then estimated from these curves.

C. *Remarks on Pathological Examinations.* The portion of the table dealing with the pathological examination is based on material from 441 rabbits started on 90-day subacute inunction experiments only. Rabbits from other types of studies of these compounds are not included. About 7000 individual pieces of tissue were examined. It is obvious that the results must be given in a highly condensed form to allow inclusion in the table.

The lesions listed in the table are those which were present in a number or degree beyond the so-called spontaneous lesions seen in control animals. Where a gradation of a lesion is given (e.g., from moderate to slight) it means that the more marked lesions were seen at the higher dosage levels, and vice versa.

Changes resulting from inanition (atrophy of spleen, liver, fat, etc.) have usually not been listed, but "inanition" listed instead. It has often been difficult to allocate atrophy of the testis between inanition and the agent inunected, but where atrophy of the testis is mentioned, it is thought to be in major part a direct toxic effect of the agent used.

Rabbits dying during the first 72 hours of the experimental period were usually not sent to the pathological laboratory. The same was true for some rabbits dying on week ends and showing extensive autolysis when found. With few exceptions the remaining animals were examined grossly and microscopically.

Non-surviving rabbits, and survivors on the higher dosage levels, routinely had hematoxylin-eosin stained paraffin sections of formalin-fixed tissue made from heart, liver, gall bladder, spleen, pancreas, mesenteric lymph nodes, kidney, adrenal, thyroid, testis (or uterus and ovary), bone marrow, thigh muscle, skin, and four levels of brain. In addition, frozen sections of liver and kidney were stained for fat with an oil-soluble red dye, and a Giemsa-stained smear of bone marrow was made. Parathyroid was generally sectioned incidentally with the thyroid. Other structures were sectioned when indicated by gross examination; these were most frequently gastrointestinal tract and lung. Bouin and Zenker fixations

TABLE 1

CHEMICAL NAME	ACUTE ORAL TOXICITY		SKIN TOXICITY		LOCAL SKIN REACTION	PATHOLOGY	CONCLUSIONS
	Species and No. Used	Est'd. LD 50	Acute Est'd. LD 50	Subacute (90-day) LD 50			
		ml./kg.	ml./kg.	ml./kg.			
Alpha, alpha' di-methyl alpha carbobutoxy-dihydro-gamma pyrone (Indalone) (O-9)[1]	Rabbits (80) Mice (100) G. pigs (110) Chicks (50) Rats (70)	5.4 11.6 3.2 15.0 7.4	10+	2	Slight dermatitis in rabbits. Very mild erythema in the copiously perspiring human. (5.3)[1]	Focal necrosis of gall bladder and upper gastrointestinal tract, and of hepatic and renal tubular cells.[1] In survivors, possibly slight protein leakage in kidney, and slight hepatitis. Dermatitis ++++ to +++;[1] ++ to +	In single or acute dosage—little or no effects. Repetition of high doses causes moderately severe skin reactions. Skin which regenerated after initial injury was more resistant to the compound than original skin. Nonirritating to the conjunctiva of rabbits. Poorly absorbed by skin. Safe for restricted use.
2-ethyl hexano-diol 1,3 (Rutgers 612) (O-373)	G. pigs (40) Chicks (20) Mice (150) Rats (20)	1.9 1.4 4.2 2.5	10+	2	Moderate dermatitis in rabbits. No dermatitis in man. (4.3)	Moderate to slight hydropic degeneration of hepatic and renal cells; moderate tubular atrophy of testis. In survivors, no lesions. Dermatitis ++++ to +++; +.	Poorly absorbed by skin. Small amounts ad libitum produce anorexia. Skin lesions noted in doses as low as 0.5 ml./kg. in rabbits following multiple dose applications. Regenerated skin is more resistant to action of "612". Severely toxic upon absorption; considered safe for recommended use.
Dimethyl phthalate (NTM) (O-262)	G. pigs (80) Mice (110) Rats (40) Rabbits (80) Chicks (120)	2.4 7.2 5.9 4.4 8.5	10+	4+	No skin irritation. Irritating to mucous membrane. (0.7)	Pulmonary edema; slight kidney damage. In survivors, varying degrees of nephritis at two higher levels; lower two levels negative. Dermatitis absent.	Very poorly absorbed by the skin. Mild symptoms of systemic effects at highest dosage level employed (injections of 4.0 ml./kg./day). Safe for recommended use.
A mixture of following composition: Dimethyl phthalate—6 parts "R-612"-2-ethyl hexane-diol 1,3—2 parts Indalone—2 parts (O-1473)	G. pigs (50) Rabbits (40) Rats (56) Mice (80)	2.8 2.4 5.9 9.2	10+	2−	Slight dermatitis in rabbits. Mild erythema on repeated application in the human. (3.5)	Inanition; moderate hyperplasia of bone marrow; slight kidney damage. In survivors, mild changes of inanition. Dermatitis ++++ to +++; ±	Very poorly absorbed by the skin. Produces skin changes slightly less severe but of same nature as that produced by "Indalone" and "R-612". It is somewhat more toxic than either "R-612" or Indalone when used in comparable quantities. Animals survived only 7 to 8 daily injections of 4 ml./kg. Safe for recommended use.

906659

Chemical: 2-ethyl-1,3-hexanediol

SKIN ABSORPTION AND IRRITATION

Chemical	Formula	Animals* No. and Species	Route	Dose Range cc/kg	Approx. LD_{50} cc/kg	Symptoms	Time of Death	Wt. Change 2 wks
Undiluted		3 GP	cuff	5.0-20.0	>20.0	Slight edema and erythema.		-37
						Eschars, small necrotic areas, sparse hair and desquamation at 1 week.	-	+33
						Light scarring and sparse hair at 2 weeks.		+73
40% in 3A alcohol		3 GP	cuff	5.0-20.0	>20.0	Slight edema and #1 erythema, some spots of 2 erythema with necrosis along 1/2 of bottom of patch.		+34
						Eschars, some necrosis and desquamation at 1 week.	-	+92
						Scarring at periphery at 2 weeks.		+98
40% in 40% alcohol (3A) + 20% H_2O		3 GP	cuff	5.0-20.0	>20.0	Slight to moderate edema, up to 3 erythema or hemorrhagic with vesicles, some are necrotic, some necrosis at edges.		+42
						Eschars, desquamation and light scarring at top and bottom of patch at 1 week.	-	+33
						Scattered scarring at periphery at 2 weeks.		+100
						62-621 4-4-64		

* G.P. - Guinea Pig, M - Mouse, R - Rat, RB - Rabbit

A - Acetone, D - Dioxane, CO - Corn oil, O - Olive oil
P.G. - Propylene glycol

MAY 18 1964

KP 48893

Chemical: 2-ethyl-1,3-hexanediol

SKIN ABSORPTION AND IRRITATION

Chemical	Formula	Animals* No. and Species	Route	Dose Range cc/kg	Approx. LD_{50} cc/kg	Symptoms	Time of Death	Wt. Change 2 wks
Undiluted		3 GP	cuff-on abraded back	5.0-20.0	>20.0	Slight edema and erythema.		+55
						Desquamation at 1 week.	14 days	
						Animals Okay at 2 weeks.		+10
40% in 3A alcohol		3 GP	cuff-on abraded back	5.0-20.0	>20.0	Slight edema and up to 2 erythema.		+95
						Slight desquamation, sparse hair and spotty 1 erythema at 1 week.	-	-49
						Sparse hair and slight desquamation at 2 weeks.		+29
40% in 40% 3A alcohol +20% H_2O		3 GP	cuff-On abraded back	5.0-20.0	>20.0	Slight edema and up to 1 erythema.		+69
						Desquamation and slight erythema at 1 week.	9 days	
						Slight desquamation and slight erythema at 2 weeks.		-23

62-621 4-4-64

* G.P. - Guinea Pig, M - Mouse, R - Rat, RB - Rabbit

A - Acetone, D - Dioxane, CO - Corn oil, O - Olive oil
P.G. - Propylene glycol

Toxicity Data 906659

from L+F

SOUTH MOUNTAIN
LABORATORIES · INC.

487 VALLEY STREET • MAPLEWOOD, NEW JERSEY • (CODE 201) 762-8676

Also photosensitization

July 24, 1967

SUBMITTED TO:	Union Carbon and Carbide Corp. Consumer Products Division 270 Park Avenue New York, New York 10017
PROJECT NUMBER:	672264-1
MATERIAL:	6•12 Brand Insect Repellent Foam
TEST:	Human Skin Sensitization
OBJECT OF TEST:	To determine the possibility of the 6•12 Brand Insect Repellent Foam producing cutaneous sensitization upon repeated application to human skin.
METHOD OF TEST:	The Sensitization Technique in Man as described in "Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics," by J. H. Draize, published by the Editorial Committee of the Association of Food and Drug Officials of the United States.

PROCEDURE: The test involved the application of the 6•12 Brand Insect Repellent Foam to two hundred human subjects. A patch with an occlusive backing was completely saturated with the foam on each treatment day. The patch was applied to the arm of each subject, always at the same location, until a total of ten applications were made on alternate days. The patch was permitted to remain a full 24 hours, after which it was removed and a reading of the reaction was recorded.

A challenge dose was applied for a 24-hour period to the original treatment area fourteen days after the tenth exposure. The retest dose was similar to any one of the applications of the original ten exposures. The reaction after the 24-hour period was recorded. This area was inspected also at 48, 72, and 96 hours following the retest dose.

The two hundred individuals who participated in the test were divided equally between male and female. Their ages ranged from 7 to 64 years of age, with approximately 75 per cent between the ages of 18 to 45 years. The results of the tests are in the accompanying table.

RESULTS: None of the subjects tested developed any reaction to the ten consecutive alternate day treatments or the challenge dose. The conditions under which the 6•12 Brand Insect Repellant Foam was tested indicate that it is non-sensitizing in the human.

This test was carried out under the supervision of the Laboratory Director and the Medical Consultant to the laboratory, Dr. Irving Innerfield, M.D.

Very truly yours,

SOUTH MOUNTAIN LABORATORIES, INC.

C. N. Mangieri

C. N. Mangieri
Director

SOUTH MOUNTAIN LABORATORIES, INC.

HUMAN SKIN SENSITIZATION STUDY — RESPONSE

MATERIAL: 6•12 Brand Insect Repellent Foam
Union Carbon and Carbide Corp.

PROJECT NUMBER: 672264-1

Subject No.	Exposures										Challenge			
	1	2	3	4	5	6	7	8	9	10	24Hrs.	48Hrs.	72Hrs.	96Hrs.
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Key: O No Reaction + Mild Irritation + + Moderate Irritation + + + Severe Irritation

SOUTH MOUNTAIN LABORATORIES, INC.

HUMAN SKIN SENSITIZATION STUDY — RESPONSE

MATERIAL: 6•12 Brand Insect Repellent Foam
Union Carbon and Carbide Corp.

PROJECT NUMBER: 672264-1

Subject No.	Exposures								Challenge					
	1	2	3	4	5	6	7	8	9	10	24Hrs.	48Hrs.	72Hrs.	96Hrs.
51	0	0	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Key: O No Reaction +Mild Irritation ++Moderate Irritation +++Severe Irritation

SOUTH MOUNTAIN LABORATORIES, INC.

HUMAN SKIN SENSITIZATION STUDY — RESPONSE

MATERIAL: 6•12 Brand Insect Repellent Foam
Union Carbon and Carbide Corp.

PROJECT NUMBER: 672264-1

Subject No.	Exposures										Challenge			
	1	2	3	4	5	6	7	8	9	10	24Hrs.	48Hrs.	72Hrs.	96Hrs.
101	0	0	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	0	0	0	0	0
111	0	0	0	0	0	0	0	0	0	0	0	0	0	0
112	0	0	0	0	0	0	0	0	0	0	0	0	0	0
113	0	0	0	0	0	0	0	0	0	0	0	0	0	0
114	0	0	0	0	0	0	0	0	0	0	0	0	0	0
115	0	0	0	0	0	0	0	0	0	0	0	0	0	0
116	0	0	0	0	0	0	0	0	0	0	0	0	0	0
117	0	0	0	0	0	0	0	0	0	0	0	0	0	0
118	0	0	0	0	0	0	0	0	0	0	0	0	0	0
119	0	0	0	0	0	0	0	0	0	0	0	0	0	0
120	0	0	0	0	0	0	0	0	0	0	0	0	0	0
121	0	0	0	0	0	0	0	0	0	0	0	0	0	0
122	0	0	0	0	0	0	0	0	0	0	0	0	0	0
123	0	0	0	0	0	0	0	0	0	0	0	0	0	0
124	0	0	0	0	0	0	0	0	0	0	0	0	0	0
125	0	0	0	0	0	0	0	0	0	0	0	0	0	0
126	0	0	0	0	0	0	0	0	0	0	0	0	0	0
127	0	0	0	0	0	0	0	0	0	0	0	0	0	0
128	0	0	0	0	0	0	0	0	0	0	0	0	0	0
129	0	0	0	0	0	0	0	0	0	0	0	0	0	0
130	0	0	0	0	0	0	0	0	0	0	0	0	0	0
131	0	0	0	0	0	0	0	0	0	0	0	0	0	0
132	0	0	0	0	0	0	0	0	0	0	0	0	0	0
133	0	0	0	0	0	0	0	0	0	0	0	0	0	0
134	0	0	0	0	0	0	0	0	0	0	0	0	0	0
135	0	0	0	0	0	0	0	0	0	0	0	0	0	0
136	0	0	0	0	0	0	0	0	0	0	0	0	0	0
137	0	0	0	0	0	0	0	0	0	0	0	0	0	0
138	0	0	0	0	0	0	0	0	0	0	0	0	0	0
139	0	0	0	0	0	0	0	0	0	0	0	0	0	0
140	0	0	0	0	0	0	0	0	0	0	0	0	0	0
141	0	0	0	0	0	0	0	0	0	0	0	0	0	0
142	0	0	0	0	0	0	0	0	0	0	0	0	0	0
143	0	0	0	0	0	0	0	0	0	0	0	0	0	0
144	0	0	0	0	0	0	0	0	0	0	0	0	0	0
145	0	0	0	0	0	0	0	0	0	0	0	0	0	0
146	0	0	0	0	0	0	0	0	0	0	0	0	0	0
147	0	0	0	0	0	0	0	0	0	0	0	0	0	0
148	0	0	0	0	0	0	0	0	0	0	0	0	0	0
149	0	0	0	0	0	0	0	0	0	0	0	0	0	0
150	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Key: 0 No Reaction +Mild Irritation ++Moderate Irritation +++Severe Irritation

SOUTH MOUNTAIN LABORATORIES, INC.

HUMAN SKIN SENSITIZATION STUDY — RESPONSE

MATERIAL: 6•12 Brand Insect Repellent Foam
Union Carbon and Carbide Corp.

PROJECT NUMBER: 672264-1

Subject No.	Exposures										Challenge			
	1	2	3	4	5	6	7	8	9	10	24Hrs.	48Hrs.	72Hrs.	96Hrs.
151	0	0	0	0	0	0	0	0	0	0	0	0	0	0
152	0	0	0	0	0	0	0	0	0	0	0	0	0	0
153	0	0	0	0	0	0	0	0	0	0	0	0	0	0
154	0	0	0	0	0	0	0	0	0	0	0	0	0	0
155	0	0	0	0	0	0	0	0	0	0	0	0	0	0
156	0	0	0	0	0	0	0	0	0	0	0	0	0	0
157	0	0	0	0	0	0	0	0	0	0	0	0	0	0
158	0	0	0	0	0	0	0	0	0	0	0	0	0	0
159	0	0	0	0	0	0	0	0	0	0	0	0	0	0
160	0	0	0	0	0	0	0	0	0	0	0	0	0	0
161	0	0	0	0	0	0	0	0	0	0	0	0	0	0
162	0	0	0	0	0	0	0	0	0	0	0	0	0	0
163	0	0	0	0	0	0	0	0	0	0	0	0	0	0
164	0	0	0	0	0	0	0	0	0	0	0	0	0	0
165	0	0	0	0	0	0	0	0	0	0	0	0	0	0
166	0	0	0	0	0	0	0	0	0	0	0	0	0	0
167	0	0	0	0	0	0	0	0	0	0	0	0	0	0
168	0	0	0	0	0	0	0	0	0	0	0	0	0	0
169	0	0	0	0	0	0	0	0	0	0	0	0	0	0
170	0	0	0	0	0	0	0	0	0	0	0	0	0	0
171	0	0	0	0	0	0	0	0	0	0	0	0	0	0
172	0	0	0	0	0	0	0	0	0	0	0	0	0	0
173	0	0	0	0	0	0	0	0	0	0	0	0	0	0
174	0	0	0	0	0	0	0	0	0	0	0	0	0	0
175	0	0	0	0	0	0	0	0	0	0	0	0	0	0
176	0	0	0	0	0	0	0	0	0	0	0	0	0	0
177	0	0	0	0	0	0	0	0	0	0	0	0	0	0
178	0	0	0	0	0	0	0	0	0	0	0	0	0	0
179	0	0	0	0	0	0	0	0	0	0	0	0	0	0
180	0	0	0	0	0	0	0	0	0	0	0	0	0	0
181	0	0	0	0	0	0	0	0	0	0	0	0	0	0
182	0	0	0	0	0	0	0	0	0	0	0	0	0	0
183	0	0	0	0	0	0	0	0	0	0	0	0	0	0
184	0	0	0	0	0	0	0	0	0	0	0	0	0	0
185	0	0	0	0	0	0	0	0	0	0	0	0	0	0
186	0	0	0	0	0	0	0	0	0	0	0	0	0	0
187	0	0	0	0	0	0	0	0	0	0	0	0	0	0
188	0	0	0	0	0	0	0	0	0	0	0	0	0	0
189	0	0	0	0	0	0	0	0	0	0	0	0	0	0
190	0	0	0	0	0	0	0	0	0	0	0	0	0	0
191	0	0	0	0	0	0	0	0	0	0	0	0	0	0
192	0	0	0	0	0	0	0	0	0	0	0	0	0	0
193	0	0	0	0	0	0	0	0	0	0	0	0	0	0
194	0	0	0	0	0	0	0	0	0	0	0	0	0	0
195	0	0	0	0	0	0	0	0	0	0	0	0	0	0
196	0	0	0	0	0	0	0	0	0	0	0	0	0	0
197	0	0	0	0	0	0	0	0	0	0	0	0	0	0
198	0	0	0	0	0	0	0	0	0	0	0	0	0	0
199	0	0	0	0	0	0	0	0	0	0	0	0	0	0
200	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Key: 0 No Reaction +Mild Irritation ++Moderate Irritation +++Severe Irritation

SOUTH MOUNTAIN
LABORATORIES · INC.

487 VALLEY STREET • MAPLEWOOD, NEW JERSEY • (CODE 201) 762-8676

July 24, 1967

SUBMITTED TO:	Union Carbon and Carbide Corp. Consumer Products Division 270 Park Avenue New York, New York 10017
PROJECT NUMBER:	672264-2
MATERIAL:	6•12 Brand Insect Repellent Foam
TEST:	Photosensitization - Human
OBJECT OF TEST:	To determine the possibility of 6•12 Brand Insect Repellent Foam causing cutaneous photosensitization following the repeated topical application of the product.
METHOD OF TEST:	Fifty subjects used in the Human Skin Sensitization Study were exposed to ultraviolet light, twenty-four hours after the tenth sensitizing dose was read.

PROCEDURE: Twenty-four hours after the tenth sensitizing dose was given to 50 subjects, they were subjected to irradiation from an ultraviolet sunlamp. Conditions were predetermined to give the proper suberythemal dose to the subjects. Each subject was exposed for 3 minutes at a distance of 6 inches from the lamp.

RESULTS: The irradiated areas were observed at intervals up to forty-eight hours after exposure. No photosensitization was seen in any of the subjects.

CONCLUSION: On the basis of the results obtained, 6·12 Brand Insect Repellent Foam may be regarded as being non-photosensitizing to the human.

Very truly yours,

SOUTH MOUNTAIN LABORATORIES, INC.

C. N. Mangieri

C. N. Mangieri
Director