



8EHQ-1194-13260 ①

DENDRITECH INC. A SUBSIDIARY OF MICHIGAN MOLECULAR INSTITUTE

3110 SCHUETTE DRIVE • MIDLAND, MICHIGAN 48642 • (517) 496-2016 • FAX (517) 496-2051

November 15, 1994

ORIGINAL

Ⓐ

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NOV 22 11:11 AM '94

Document Control Officer
Information Management Division
Office of Toxic Substance
U.S. Environmental Protection Agency
401 M St. S.W.
Washington, DC 20460

Dear Sir:

This letter is being submitted under Section 8(e) of the Toxic Substance Control Act. An acute oral screening study of polyamidoamine dendrimer, Generation 1.0 (copolymer of ethylene diamine and methyl acrylate), CAS# 26937-01-9 was conducted by NAMSA, Northwood OH 43619. At a 5 gm/kg of body weight dose (administered as approximately 50% dendrimer in water), results indicated possible signs of neurotoxicity (tremors) in two test animals. This appeared to be a somewhat toxic dose, as 2 out of 5 animals died. In addition, diarrhea and loss in body weight were noted, suggesting system overload. In a study conducted at the same time of Generation 5.0 dendrimer (higher molecular weight), no indications of any toxicity were noted at 5 gm/kg. A copy of both reports are enclosed.

Based on this data, we do not believe that this information represents a significant risk to health or environment, as even low levels of oral exposure are unlikely in the use of this material. However, we have decided to forward this data for your review.

Sincerely yours,

Lynne M. Galligan
Lynne M. Galligan
General Manager



LMG:smh
epal

Enclosure(s): Acute Oral; Toxicity Screen in the rat
Lab No. 94T 15159 00

Acute Oral; Toxicity Screen in the rat
Lab No. 94T 15660 00



12/15/94

CONFIDENTIAL

TA004-909

Lab No. 94T 15159 00

P.O. No. 407

Contains No CBI

STUDY TITLE:

ACUTE ORAL TOXICITY SCREEN (MODIFIED FHSA)
IN THE RAT

TEST ARTICLE:

STARBURST DENDRIMER GENERATION E1.0

IDENTIFICATION NO.:

E1.0-32

SPONSOR:

MARK KAISER
DENDRITECH INC
3110 SCHUETTE DRIVE
MIDLAND, MI 48642

NAHSA

World Leader in Testing Services
for the Medical Device Industry

2261 Tracy Road
Northwood, OH 43619
Phone 419-666-9455
FAX 419-666-2954

SUMMARY

The test article, STARBURST DENDRIMER GENERATION E1.0, E1.0-32, was screened for oral toxicity. The test was conducted in accordance with the guidelines of the Federal Hazardous Substances Act (FHSA) Regulations, 16 CFR 1500, but was modified by NAMSA to reduce the number of animals from ten to five and the number of observation days from 14 to 7.

A single dose of 5 g/kg of body weight was gavaged to five rats. The animals were then observed for up to 7 days for any signs of toxicity.

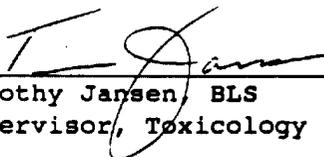
Under the conditions of this study, there was mortality observed in the rats. However, the test article would not be considered toxic at a dose of 5 g/kg by the oral route in the rat since more than 50% of the animals survived the seven day observation period; the LD₅₀ was greater than 5 g/kg of body weight.

Study and Supervisory

Personnel:

Patricia Mitchell
Karen D. Coburn, ALAT
John S. Bibart III, BS
Jeffrey J. Etue
Michael W. Osborne

Approved by:



Timothy Jansen, BLS
Supervisor, Toxicology

10-28-94
Date Completed

/pjf



World Leader in Testing Services
for the Medical Device Industry

2261 Tracy Road
Northwood OH 43619
Phone 419-666-9455
FAX 419-666-2954

INTRODUCTION

The test article identified below was screened for oral toxicity. The test was conducted in accordance with the guidelines of the Federal Hazardous Substances Act (FHSA) Regulations, 16 CFR 1500, but was modified by NAMSA to reduce the number of animals from ten to five and the number of observation days from 14 to 7. The purpose of the study was to determine the potential for systemic toxicity of the material following a single gavage in the rat. Animals were dosed on October 10, 1994, and the observations were concluded on October 17, 1994.

MATERIALS

The sample provided by the sponsor was identified and handled as follows:

Test Article: STARBURST DENDRIMER GENERATION E1.0
Identification No: E1.0-32
Storage Conditions: Controlled room temperature
Preparation: The liquid test article was dosed as received. For this study, the density of the test article was determined to be 1.1 g/ml.
Sample Disposition: Any remaining sample was discarded.

METHODSAnimal Management:

Five healthy albino rats of the Sprague-Dawley® strain (three male, two female) were obtained from an approved supplier traceable in NAMSA records. The animals were acclimated to the laboratory for at least 5 days. Rat body weights were between 200 g and 300 g, as prescribed in the FHSA Regulations, before a predose food deprivation of 16 to 20 hours.

Rats, identified individually by ear punch at dosing, were group housed by sex (wire mesh suspended cages) and received a commercial rodent feed on a daily basis; tap water was freely available. No diet or water analysis was performed since there were no contaminants suspected that could interfere with this study. Animal husbandry and environmental conditions conformed to current NAMSA SOP's which are based on the "Guide for the Care and Use of Laboratory Animals," NIH Publication No. 85-23.



World Leader in Testing Services
for the Medical Device Industry

2261 Tracy Road
Northwood, OH 43619
Phone 419-666-9455
FAX 419-666-2954

Experimental Procedure:

Each rat was weighed and gavaged with the test article (via stainless steel blunt-tipped cannula) at a dose of 5 g/kg of body weight. The animals were then returned to their cages and food was returned after treatment.

Animals were observed immediately after dosing, at 4 hours, and daily for up to 7 days for signs of illness or mortality. Body weights were recorded at dosing and at 7 days for survivors. Animals found dead during the study or those euthanatized (carbon dioxide inhalation) at termination of the study were subjected to a macroscopic examination of the viscera. The substance was considered "toxic" if it produced death within 7 days in $\geq 50\%$ of the rats gavaged with a single 50 mg/kg to 5 g/kg dose.

RESULTS

Individual observations appear in Table I.

Body Weight: The range of body weights at dosing was 211 to 231 g. Animals maintained or lost body weight during the study; the mean body weight at termination was not considered typical for rats on a 7 day study.

Mortality: Two animals died during the 7 day study.

Clinical Observations: On day 1, all five animals appeared to have diarrhea. On days 2 and 3, only animal #2 appeared to have diarrhea. On day 6, animal #1 appeared ungroomed with tremors. On day 7, animal #4 appeared to be lethargic with tremors and cold to the touch.

Necropsy: There were macroscopic changes in the viscera at necropsy that could be attributed to the single oral dose.

CONCLUSION

Under the conditions of this study, the test article would not be considered toxic at a dose of 5 g/kg by the oral route in the rat; the LD₅₀ was greater than 5 g/kg of body weight.

RECORD STORAGE

All raw data pertaining to this study and a copy of the final report are to be stored in the designated archive files at North American Science Associates, Inc. (NAmSA®), 2261 Tracy Road, Northwood, Ohio 43619-1397.

TABLE I
SUMMARY OF OBSERVATIONS

ANIMAL NUMBER	SEX	BODY WEIGHT (g)		CLINICAL OBSERVATIONS (DAYS 0-7)	NECROPSY (DAY 7)
		DAY 0	DAY 7		
1	M	218	---	Days 1-2 - reduced feces Days 3-5 - appeared normal Day 6 - tremors Day 7 - found dead	a, c
2	M	231	---	Day 1 - reduced feces Days 2-3 - diarrhea Day 4 - found dead	a, b
3	M	218	218	Days 1-2 - reduced feces Days 3-7 - appeared normal	a, b
4	F	211	169	Days 1-2 - reduced feces Days 3-6 - appeared normal Day 7 - appeared lethargic with tremors	b, c
5	F	212	206	Days 1-2 - reduced feces Days 3-7 - appeared normal	MN
MEAN:		218	198		

M = Male
F = Female

AN = Appeared normal
MN = Macroscopically normal

a = apparent pulmonary congestion
b = kidneys appeared pale
c = stomach contained black fluid

Confidential

TA004-909

Lab No. 94T 15660 00

P.O. No. 417

Contains No CBI

STUDY TITLE:

ACUTE ORAL TOXICITY SCREEN (MODIFIED FHSA)
IN THE RAT

TEST ARTICLE:

STARBURST DENDRIMER GENERATION E 5.0

IDENTIFICATION NO.:

E 5.0-38

SPONSOR:

MARK KAISER
DENDRITECH INC
3110 SCHUETTE DRIVE
MIDLAND, MI 48642

NAHSA

World Leader in Testing Services
for the Medical Device Industry

2261 Tracy Road
Northwood, OH 43619
Phone 419-666-9455
FAX 419-666-2954

SUMMARY

The test article, STARBURST DENDRIMER GENERATION E 5.0, E 5.0-38, was screened for oral toxicity. The test was conducted in accordance with the guidelines of the Federal Hazardous Substances Act (FHSA) Regulations, 16 CFR 1500, but was modified by NAMSA to reduce the number of animals from ten to five and the number of observation days from 14 to 7.

A single dose of 5 g/kg of body weight was gavaged to five rats. The animals were then observed for up to 7 days for any signs of toxicity.

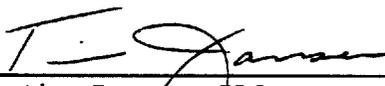
Under the conditions of this study, there was no mortality or significant evidence of toxicity observed in the rats. The test article would not be considered toxic at a dose of 5 g/kg by the oral route in the rat; the LD₅₀ was greater than 5 g/kg of body weight.

Study and Supervisory

Personnel:

Patricia Mitchell
John S. Bibart III, BS
Karen D. Coburn, ALAT
Michael W. Osborne
Jeffrey J. Etue

Approved by:



Timothy Jansen, BLS
Supervisor, Toxicology

10-31-94
Date Completed

/pjf



INTRODUCTION

The test article identified below was screened for oral toxicity. The test was conducted in accordance with the guidelines of the Federal Hazardous Substances Act (FHSA) Regulations, 16 CFR 1500, but was modified by NAMSA to reduce the number of animals from ten to five and the number of observation days from 14 to 7. The purpose of the study was to determine the potential for systemic toxicity of the material following a single gavage in the rat. Animals were dosed on October 18, 1994, and the observations were concluded on October 25, 1994.

MATERIALS

The sample provided by the sponsor was identified and handled as follows:

Test Article: STARBURST DENDRIMER GENERATION E 5.0

Identification No: E 5.0-38

Storage Conditions: Controlled room temperature

Preparation: The test article was dosed as received. For this study, the density of the test article was determined to be 1.1 g/ml.

Sample Disposition: Any remaining sample was discarded.

METHODS

Animal Management:

Five healthy albino rats of the Sprague-Dawley® strain (three male, two female) were obtained from an approved supplier traceable in NAMSA records. The animals were acclimated to the laboratory for at least 5 days. Rat body weights were between 200 g and 300 g, as prescribed in the FHSA Regulations, before a predose food deprivation of 16 to 20 hours.

Rats, identified individually by ear punch at dosing, were group housed by sex (wire mesh suspended cages) and received a commercial rodent feed on a daily basis; tap water was freely available. No diet or water analysis was performed since there were no contaminants suspected that could interfere with this study. Animal husbandry and environmental conditions conformed to current NAMSA SOP's which are based on the "Guide for the Care and Use of Laboratory Animals," NIH Publication No. 85-23.

Experimental Procedure:

Each rat was weighed and gavaged with the test article (via stainless steel blunt-tipped cannula) at a dose of 5 g/kg of body weight. The animals were then returned to their cages and food was returned after treatment.

Animals were observed immediately after dosing, at 4 hours, and daily for up to 7 days for signs of illness or mortality. Body weights were recorded at dosing and at 7 days for survivors. Animals found dead during the study or those euthanatized (carbon dioxide inhalation) at termination of the study were subjected to a macroscopic examination of the viscera. The substance was considered "toxic" if it produced death within 7 days in $\geq 50\%$ of the rats gavaged with a single 50 mg/kg to 5 g/kg dose.

RESULTS

Individual observations appear in Table I.

Body Weight: The range of body weights at dosing was 207 to 273 g. Animals gained body weight during the study; the mean body weight at termination was considered typical for rats on a 7 day study.

Mortality: No animals died during the 7 day study.

Clinical Observations: Animal #1 had diarrhea at the 4 hour observation interval and on day 1. Otherwise, all other animals appeared clinically normal throughout the study.

Necropsy: There were no macroscopic changes in the viscera at necropsy that could be attributed to the single oral dose.

CONCLUSION

Under the conditions of this study, the test article would not be considered toxic at a dose of 5 g/kg by the oral route in the rat; the LD₅₀ was greater than 5 g/kg of body weight.

RECORD STORAGE

All raw data pertaining to this study and a copy of the final report are to be stored in the designated archive files at North American Science Associates, Inc. (NAMSA®), 2261 Tracy Road, Northwood, Ohio 43619-1397.



World Leader in Testing Services
for the Medical Device Industry

2261 Tracy Road
Northwood, OH 43619
Phone 419-666-9455
FAX 419-666-2954

TABLE I
SUMMARY OF OBSERVATIONS

ANIMAL NUMBER	SEX	BODY WEIGHT (g)		CLINICAL OBSERVATIONS (DAYS 0-7)	NECROPSY (DAY 7)
		DAY 0	DAY 7		
1	M	262	297	Diarrhea at 4 hours and on day 1, otherwise AN	MN
2	M	259	315	AN	MN
3	M	273	328	AN	MN
4	F	207	247	AN	MN
5	F	217	234	AN	MN
MEAN:		244	284		

M = Male
F = Female

AN = Appeared normal
MN = Macroscopically normal



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

Lynne M. Galligan
General Manager
Dendritech, Inc.
3110 Schuette Drive
Midland, Michigan 48642

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

JAN 12 1995

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

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

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

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

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

Sincerely,

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

Enclosure

13260 A



Recycled/Recyclable
Printed with Soy/Canola Ink on paper that
contains at least 50% recycled fiber

Triage of 8(e) Submissions

Date sent to triage: APR 06 1995

NON-CAP

CAP

Submission number: 13260A

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - ~~Ernie Falke~~ (1 copy total)

~~ATOX~~ SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX
STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

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

Notes:

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

*Please evaluate record 2 - the generation
S.O Rindimer.*

Record 7 was already evaluated

For Contractor Use Only	
entire document: <u>0</u>	2 pages <u>—</u> pages <u>1, tabs</u>
Notes:	
Contractor reviewer: <u>UPS</u>	Date: <u>1/30/95</u>

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: BEHQ: 1194-13260 SEQ. A

Submission # BEHQ: 1194-13260 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Dendritech Inc.

DISPOSITION: (639) REFER TO CHEMICAL SCREENING

0678 CAP NOTICE

INFORMATION REQUESTED: FLWP DATE:
 0501 NO INFO REQUESTED
 0502 INFO REQUESTED (TEC1)
 0503 INFO REQUESTED (VOL ACTIONS)
 0504 INFO REQUESTED (REPORTING RATIONALE)

VOLUNTARY ACTIONS:
 0401 NO ACTION REQUIRED
 0402 STUDIES PLANNED/IN PROGRESS
 0403 NOTIFICATION OF WORK IN PROGRESS
 0404 LABEL/AMSDS CHANGES
 0405 PROCESS/AMSDS CHANGES
 0406 APP/USE DISCONTINUED
 0407 PRODUCTION DISCONTINUED
 0408 CONFIDENTIAL

SUB. DATE: 11/15/94 OTS DATE: 11/22/94 CSRAD DATE: 12/15/94

CHEMICAL NAME: 2-Propenoic acid, methyl ester, polymer

with 1,2-ethanediamine Starburst Dendrimer Generation E1.0

CASE# 26937-01-9 - per Cas on-line

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

TRIAGE DATA: NON-CBI INVENTORY
 YES
 CAS SR
 NO
 (IN PPM/MI)

ONGOING REVIEW
 YES (DROP/REFER)
 NO (CONTINUE)
 REFER

SPECIES: RAT
 TOXICOLOGICAL CONCERN:
 LOW
 MED
 HIGH

USE:
 PRODUCTION:

-CPSS-

> <ID NUMBER>
8(E)-13260A

> <TOX CONCERN>
L

> <COMMENT>
ACUTE ORAL TOXICITY IN SPRAGUE-DAWLEY RATS IS OF LOW CONCERN.
SINGLE GAVAGED DOSES OF 5 G/KG ADMINISTERED TO 3 MALE AND 2
FEMALE RATS WERE ASSOCIATED WITH DEATH OF 2/5 ANIMALS AND SIGNS
OF NEUROTOXICITY. CLINICAL SIGNS OF TOXICITY INCLUDED INCIDENCE
OF DIARRHEA, TREMORS, LETHARGY AND HYPOTHERMIA. VISCERAL
ABNORMALITIES NOTED UPON NECROPSY WERE RELATED TO TREATMENT.

\$\$\$\$