

8EHQ-0396-13603

(A)

March 6, 1996

Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205-9741
Phone: 412 777-2000

Document Processing Center (TS-790)
ATTN: Section 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

ORIGINAL

Contains No CBI

Dear Sir:

Bayer Corporation is submitting the results of a Dermal Sensitization study on V159808 known as DBT, CAS# 168612-06-4: 1H-tetrazole-1-acetamide, N,N-dibutyl-2,5-dihydro-5-thioxo-, (LVE 96-33) that were concluded to be reportable under TSCA 8(e) as it was judged to be a strong sensitizer in this assay. This material will be arriving in the U.S. within the next week, thus triggering the reporting data.

This information will be provided in our hazard communication literature and training programs. The information submitted in this report is not considered "Confidential Business Information". Please contact me if you have any questions.

Sincerely,

D. W. Lamb

Donald W. Lamb, Ph.D
Vice President
Product Safety & Regulatory Affairs
412-777-7431



8EHQ-96-13603
INIT 03/11/96

96-2-3.doc.vmk
Attachment
Certified Mail: P 921 654 945



889600000083

mm
4/8/96

50 APR 21 AM 9:11

RECEIVED
APR 11 1996

SCHEM 11 1111:13

REPORT

ASSESSMENT OF ACUTE DERMAL TOXICITY WITH

V159808

IN THE RAT

NOTOX Project 142785
NOTOX Substance 50373

STATEMENT OF GLP COMPLIANCE

NOTOX B.V., 's-Hertogenbosch, The Netherlands

The study described in this report was conducted in compliance with the most recent edition of:

The OECD Principles of Good Laboratory Practice

which are essentially in conformity with:

The United States Food and Drug Administration. Title 21 Code of Federal Register Part 58.

The United States Environmental Protection Agency, (FIFRA). Title 40 Code of Federal Regulations Part 160.

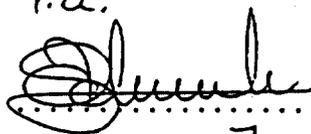
The United States Environmental Protection Agency, (TSCA). Title 40 Code of Federal Regulations Part 792.

with the following exception:

Concentration, stability and homogeneity of test substance in vehicle were not determined by analytical procedures.

Study Director:

Dr.Ir. W.R. Pels Rijcken

i.a.


Date: 29 June 1995

QUALITY ASSURANCE STATEMENT

NOTOX B.V., 's-Hertogenbosch, The Netherlands

Study procedures were subject to periodic inspections and general non study specific processes were also inspected at periodic intervals.

This report was audited by the Quality Assurance Unit and the methods and results accurately reflect the raw data.

Dates of Q.A.U. Inspections/Audits	Reporting Date
22 March 1995	22 March 1995
14 April 1995	14 April 1995
28 June 1995	28 June 1995

Manager, Quality Assurance Unit

C.J. Mitchell B.Sc.



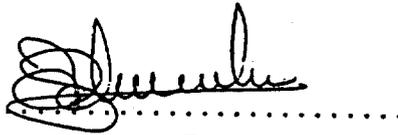
Date: 3-7-95

REPORT APPROVAL

STUDY DIRECTOR :

Dr.Ir. W.R. Pels Rijcken

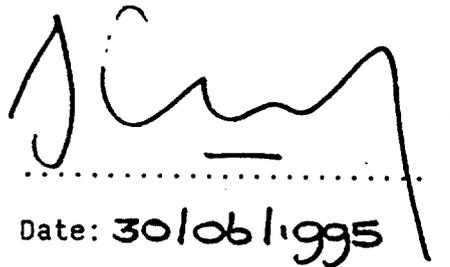
i.a.



Date: 29 June 1995

MANAGEMENT :

Dr. I.C. Enninga
Technical Director



Date: 30/06/1995

SUMMARY

Assessment of acute dermal toxicity with V159808 in the rat.

The study was carried out in accordance with OECD Guideline No. 402, "Acute Dermal Toxicity" and EEC Directive 92/69/EEC, Part B.3, "Acute Toxicity - Dermal".

V159808 was administered to five rats of each sex by dermal application at 2000 mg/kg body weight for 24 hours. Animals were subjected to daily observations and weekly determination of body weight. Macroscopic examination was performed at the end of the experimental period (day 15).

No mortality occurred and no clinical signs were observed during the study period. Red staining was seen in the treated skin-area of three females during the first week of the observation period.

Body weight loss and low body weight gain were noted in the animals over the first week of the study period. Improved body weight gain was noted over the second week of the study.

No abnormalities were found in the animals at macroscopic post mortem examination.

The dermal LD₅₀ value of V159808 in rats was established as exceeding 2000 mg/kg body weight.

PREFACE

Sponsor Agfa-Gevaert N.V.
Septestraat 27
B-2640 MORTSEL
Belgium

Study Monitors Mr. G. Verbandt
Dr. A. Suys
Produktreglementeringen

Testing Facility NOTOX B.V.
Hambakenwetering 3
5231 DD 's-Hertogenbosch
The Netherlands

Study Director Dr.Ir. W.R. Pels Rijcken

Study Plan Start: 27 April 1995
End : 11 May 1995

TEST SUBSTANCE

The sponsor is responsible for the completeness and GLP Compliance of all test substance data.

Identification V159808
Description Light pink solid
Batch P 1 A
Purity >99% (HPLC)
Instructions for test substance storage At room temperature in the dark
Stability under storage conditions Stable
Expiry date January 01, 1997
Stability in vehicle Stable for at least 4 hours in polyethylene glycol

Vehicle Polyethylene glycol (300)
Specific gravity 1.127

Preparation The test substance was ground to a powder using a mortar and pestle before formulating. The formulation (w/w) was prepared immediately prior to dosing. Adjustment was made for specific gravity of vehicle. Homogeneity was accomplished to a visually acceptable level.

PURPOSE AND RATIONALE

The objective of this study was to assess the toxicity of V159808 when administered to rats as a single dermal application. Furthermore, the study was intended to derive the median lethal dose (LD₅₀). This study should provide part of a rational basis for risk assessment in man. The dermal route was selected as it is a possible route of human exposure during manufacture, handling or use of V159808.

GUIDELINES

The study procedures described in this report were in accordance with the following guidelines:

European Economic Community (EEC), Directive 92/69/EEC, Annex V of the EEC Directive 67/548/EEC; Part B, Methods for the determination of Toxicity, B.3: "Acute Toxicity-Dermal". Official Journal of the European Communities No. L383, December 1992.

OECD "Guidelines for Testing of Chemicals", Section 4, Health Effects, No. 402, "Acute Dermal Toxicity", Paris Cedex, February 24, 1987.

ARCHIVING

NOTOX B.V. will archive the following data for at least 10 years:
raw data, protocol, report and test substance reference sample.
All magnetic media produced on this study will be maintained indefinitely.

TEST SYSTEM

Species	Rat, Wistar strain CrI:(WI) BR (outbred, SPF-Quality). Recognised by international guidelines as the recommended test system (e.g. OECD, EEC). Source : Charles River, Germany.
Age at Start of Treatment	Approx. 10 weeks.
Body weight at start of treatment	Within \pm 20% of the sex mean
Number of animals	5 males and 5 females
Identification	Earmark

ANIMAL HUSBANDRY

Conditions

Air-conditioned room with approximately 15 air changes per hour and the environment controlled with optimal conditions considered as being a temperature of 21°C and a relative humidity of 50%. Fluctuations from these optimal conditions were noted, but were considered not to have affected study integrity. Lighting was 12 hours artificial fluorescent light and 12 hours dark per day.

Accommodation

Individually housed in labelled polycarbonate cages containing purified sawdust as bedding material (Woody SPF, supplied by B.M.I., Helmond, The Netherlands). Certificates of analysis were examined and then retained in the NOTOX archives. Acclimatisation period was at least 5 days before start of treatment under laboratory conditions.

Diet

Free access to standard pelleted laboratory animal diet (from Carfil-Quality BVBA, Oud-Turnhout, Belgium). Certificates of analysis were examined and then retained in the NOTOX archives.

Water

Free access to tap-water. Certificates of analysis (performed quarterly) were examined and then retained in the NOTOX archives.

TREATMENT

Method	Dermal application.
Shaving	One day before exposure (day -1) an area of approximately 5x7 cm on the back of the animal was clipped.
Application	The formulation was applied to an area of approximately 25 cm ² (5x5 cm) for males and 18 cm ² (3.5x5 cm) for females by application on a gauze patch fixed successively to aluminium foil and flexible bandage (Coban, 3M, St. Paul, U.S.A.), with drops of petrolatum.
Frequency	Once, on day 1.
Dose level (volume)	2000 mg/kg (10 ml/kg) body weight.
Application period	24 hours, thereafter dressings were removed and residual test substance removed using a tissue moistened with tap water.

OBSERVATIONS

Mortality/Viability	Twice daily.
Body weights	Days 1 (pre-administration), 8 and 15.
Clinical signs	At periodic intervals on the day of treatment (day 1) and once daily thereafter, until day 15. The time of onset, degree and duration were recorded.
Necropsy	All animals surviving to the end of the observation period (day 15) were sacrificed by oxygen/carbon dioxide asphyxiation. All animals assigned to the study were subjected to necropsy and descriptions of all macroscopic abnormalities recorded.

STATISTICAL PROCEDURES

No statistical analysis was performed.

RESULTS

Mortality

No animals died during the study.

Clinical Signs

No clinical signs were observed during the study period. Red staining was seen in the treated skin-area of three females during the first week of the observation period.

Body Weight

Body weight loss and low body weight gain were noted in the animals over the first week of the study period. Improved body weight gain was noted in these animals over the second week of the study.

Macroscopic Findings

Macroscopic post mortem examination of the animals at termination did not reveal any abnormalities.

CONCLUSION

The dermal LD₅₀ value of V159808 in rats was established as exceeding 2000 mg/kg body weight.

**CLINICAL SIGNS
 MALES
 GROUP 1 (2000 MG/KG)**

Test day	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Time after treatment. Hours:	0	2	4														

ANIMAL NUMBER	SIGNS	MAX. GRADE
1	NO CLINICAL SIGNS NOTED	
2	NO CLINICAL SIGNS NOTED	
3	NO CLINICAL SIGNS NOTED	
4	NO CLINICAL SIGNS NOTED	
5	NO CLINICAL SIGNS NOTED	

**FEMALES
 GROUP 1 (2000 MG/KG)**

Test day	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Time after treatment. Hours:	0	2	4														

ANIMAL NUMBER	SIGNS	MAX. GRADE
6	NO CLINICAL SIGNS NOTED	
7	NO CLINICAL SIGNS NOTED	
8	SKIN / FUR / PLUMAGE RED STAINING (NECK)..... (3)	- - - 1 1 1 1 - - -
9	SKIN / FUR / PLUMAGE RED STAINING (NECK)..... (3)	- - - 1 1 1 1 - - -
10	SKIN / FUR / PLUMAGE RED STAINING (NECK)..... (3)	- - - 1 1 1 1 1 - - -

BODY WEIGHTS (GRAM)

GROUP / SEX	ANIMAL	DAY 1	DAY 8	DAY 15
GROUP 1 / MALES (2000 MG/KG)	1	378	373	406
	2	378	374	400
	3	418	417	451
	4	411	416	443
	5	368	366	390
	MEAN	391	389	418
	ST.DEV.	22	25	27
	N	5	5	5
GROUP 1 / FEMALES (2000 MG/KG)	6	237	235	248
	7	250	260	267
	8	219	226	243
	9	262	258	274
	10	277	281	292
	MEAN	249	252	265
	ST.DEV.	22	22	20
	N	5	5	5

MACROSCOPICAL FINDINGS
MALES
GROUP 1 (2000 MG/KG)

ANIMAL 1 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 2 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 3 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 4 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 5 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

FEMALES
GROUP 1 (2000 MG/KG)

ANIMAL 6 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 7 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 8 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 9 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 10 (SCHEDULED NECROPSY, 11-MAY-95, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED