

Microfiche No. []
[] OTS0509762-3

New Doc I.D. [] Old Doc I.D. []
[] 89-880000178 [] BEHQ-0588-0575

Date Produced [] 5/05/88 Date Recieved [] 5/24/88 TSCA section [] BE

Submitting Organization [] EASTMAN KODAK COMPANY

Contractor []

Document Title []

ACUTE DERMAL TOXICITY STUDY OF
4-(N-ETHYL-N-2-HYDROXYETHYL)-2-METHYLPHENYLENEDIAMINE
SULFATE (CD-4) WITH ATTACHED APPENDIX FOR ACUTE INHALATION
STUDY & COVER LETTER DATED 051988

Chemical Category []

CD-4

Fed. Ek. 6380884860

16388EHQ-0588-0575 Supp
PDCN: 88-860000032
89-880000178



EPA-OTS



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CONTAINS NO CBI

May 19, 1988

88 MAY 24 AM 9:03
OTS REGISTRY CONTROL
OFFICE

Document Processing Center (TS-790) Room L-100
Office of Toxic Substances
Environmental Protection Agency
401 M Street S.W.
Washington, D.C. 20460
Attention: 8 (e) Coordinator

Dear Sir or Madam:

This letter with enclosures provides supplemental information on a previous TSCA section 8(e) notification on 4-(N-ethyl-N-2-hydroxyethyl)-2-methylphenylenediamine sulfate, otherwise known as CD-4. The notification has been identified by EPA control number 8EHQ-1185-0575.

Enclosed please find copies of an acute oral LD50 study in mice and an acute dermal dosing study in rats.

The original submission was based on an oral LD50 study in rats that showed kidney toxicity at low dose levels. The oral LD50 study in mice was conducted in order to investigate whether the kidney toxicity observed in rats would also be seen in other species. The results indicate that kidney lesions were observed in mice only at the lethal dose of 200 mg/kg. Comparison of the mouse data with the previously submitted acute rat data indicate that the rat is more than an order of magnitude more sensitive to the kidney effects.

The in vivo acute dermal dosing study in rats was conducted because a calculation based on a previously submitted in vitro dermal penetration study suggested that toxic amounts of CD-4 may be absorbed from solutions through rat skin. The results from the in vivo study showed that dermal application of a highly concentrated solution resulted in no kidney or other target organ toxicity in a sensitive species. These data suggest that the in vivo rate of absorption through the skin may be an important factor in limiting the toxicity of CD-4 after dermal exposures (i.e., the rate of skin absorption after dermal exposure may not be sufficient to result in an acutely toxic blood concentration of CD-4).

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May 19, 1988

We have also conducted an acute inhalation LC50 study and a 90-day repeated oral dose study in rats. The LC50 study is undergoing quality assurance review and will be submitted to EPA upon completion of the review. The 90-day study is in the histopathological evaluation stage and will be submitted upon completion and quality assurance review. The data reviewed to date indicate that CD-4 is no more toxic after subchronic exposure than after acute exposure. We estimate that the 90-day study will be completed and submitted in mid- to late-summer of 1988.

We feel that the data in the enclosed reports further define the toxicology of CD-4 and places the in vitro dermal penetration data into perspective. If you have any technical questions or would like to discuss the reports, please call William L. Hart, a toxicologist in the Health and Environment Laboratories, at (716) 722-5991.

Sincerely,

R. Hays Bell

R. Hays Bell, Ph.D., Director
Health and Environment Laboratories

WLH
Enc

cc: Dr. Judy Loranger, OTS, EPA

244879B
TX-88-77

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ACUTE DERMAL TOXICITY OF CD-4
HAEL NO. 87-0098 ACC. NO. 904984

BY DOUGLAS C. TOPPING, PH.D., DABT

TOXICOLOGICAL SCIENCES LABORATORY
HEALTH AND ENVIRONMENT LABORATORIES
EASTMAN KODAK COMPANY
ROCHESTER, NY 14650

DATE OF STUDY COMPLETION MAY 5, 1988

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TX-88-77

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**FINAL REPORT
ACUTE DERMAL TOXICITY**

TESTING FACILITY

Toxicological Sciences Laboratory
Health and Environment Laboratories (HAEL)
Eastman Kodak Company
Rochester, NY 14650
U.S.A.

DATE OF TEST INITIATION

February 16, 1988

STUDY DIRECTOR

Douglas C. Topping, Ph.D., DABT

OTHER SCIENTISTS/TECHNICAL PERSONNEL

John W. Mosher, B.S., and
Chris M. Ashley, Study Technicians
Milan S. Vlaovic, D.V.M., Ph.D., Pathologist

PURPOSE/OBJECTIVE

The purpose of the study was to estimate the single dose dermal LD₅₀ of the test compound in male and female rats and the clinical signs of toxicity associated with a single dermal dose.

TEST SUBSTANCE

Chemical Name: 2-((4-Amino-3-methylphenyl)ethylamino)ethanol sulfate
Alternate Name : CD-4
EK Accession No.: 904984
HAEL Laboratory No.: 87-0098
SRID or Lot I.D. No.: 75013

TEST SYSTEM

Species: Rat
Strain: CD®(SD)BR
Source: Charles River Laboratories, Wilmington, MA, U.S.A.
No. of Animals: 5 of each sex per dose group
Sex: Male and Female
Body Weight Range at Dosing (g): (M) 270 - 294 (F) 199 - 226
Age: Approximately 7-10 weeks old

HUSBANDRY AND ENVIRONMENTAL CONDITIONS

Housing

All animals were individually housed in suspended stainless steel mesh cages.

Environmental Conditions

A photoperiod of 12 hours from 6 a.m. to 6 p.m. was maintained. Room temperature was maintained at 70-74° F. Relative humidity was maintained at 46-50%, except for one day when the room was washed. On this day, relative humidity reached 97% transiently, and room temperature reached 78° F.

Diet and Water

Agway® Prolab™ Animal Diet (RMH 3000) certified pellets, and water, obtained from the Monroe County (NY) Water Authority, were provided ad libitum. No known contaminants which would interfere with the outcome of the study were expected to be present in feed or water from these sources. Analyses of feed and results of quarterly analyses of water are maintained on file within the testing laboratory.

Isolation

Animals were isolated and monitored for at least five days after arrival before release to the testing facility.

Animal Identification

All animals were identified by cage number and uniquely numbered metal ear tag.

TEST PROCEDURES AND CONDITIONS

Test Procedure Guideline

OECD Guideline for Testing of Chemicals: Guideline 402, Dated 12 May, 1981. (Annex V, Test B.3).

Dose Levels (in mg compound/kg body weight):

2000, 0 (Control)

Identification Numbers of Animals Used

2000 mg/kg males: 371 - 375

2000 mg/kg females: 401 - 405

0 mg/kg males: 376 - 380

0 mg/kg females: 406 - 410

Dosing Regimen

A single dose of the material was placed on a fiber pad having dimensions of approximately 4 x 5 cm. Distilled water was applied to the pad in sufficient quantity to dissolve the test material. The pad was then applied to the skin of the back of each animal after the hair had been removed with an electric clipper. An occlusive wrap was used to hold the pad against the skin for 24 hours. At the end of the exposure period, residual test material was removed with running water. Control animals were treated in an identical manner, except that only distilled water was applied to the fiber pad.

Control Substance

Distilled water

Vehicle

Distilled water

CLINICAL OBSERVATIONS

Animals were observed the day the wrap was removed and once each workday thereafter for the duration of the test for a total of 14 calendar days. Observation included, but was not limited to, examination of the hair, skin, eyes, motor activity, feces, and urine. Animals were checked for mortality on weekend days.

BODY WEIGHT DETERMINATIONS

Body weights were collected on the day of dosing and one and two weeks after dosing.

NECROPSY

All animals were necropsied at the completion of the study. Kidneys and hearts were collected and fixed in 10% buffered formalin for microscopic examination. Collection of these tissues, though not originally listed in the study protocol, was included because of possible target organ toxicity.

RESULTS

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)
2000	5,5	0,0	---	5+,5+	5+,5+
0	5,5	0,0	---	5+,5+	5+,5+

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

SUMMARY OF CLINICAL SIGNS		
DOSE (mg/kg)	CLINICAL SIGN	NO. OF RATS AFFECTED
2000	Purple Staining of the Skin Clinically Recovered from Staining	5M,5F 4M,4F
0	Clinically Normal	5M,5F

NECROPSY AND HISTOPATHOLOGY FINDINGS

See the attached pathology report for necropsy and histopathology findings.

DATA ANALYSIS

The data were analyzed using the method of Weil (1952). The results were as follows:

LD₅₀ IN MALE RATS: > 2000 mg/kg - 95% C.I. No range calculable
LD₅₀ IN FEMALE RATS: > 2000 mg/kg - 95% C.I. No range calculable

No dose/mortality curve was constructed, as one value is insufficient to construct a graph. Such graphs become statistically useful only with the use of large numbers of animals and dose groups.

DISCUSSION AND INTERPRETATION

A highly concentrated solution of GD-4 did not cause mortality at a limit dose of 2000 mg/kg. Treatment-related abnormalities observed in animals administered a limit dose of 2000 mg/kg consisted of purple discoloration of the skin of the back at the site of application. The staining gradually diminished, and by the day of scheduled necropsy, only one male and one female had residual discoloration of the skin. Abnormal findings noted at necropsy consisted only of the aforementioned purple staining in two animals. No signs of organ toxicity were observed. The kidneys and hearts were processed for microscopic evaluation. No treatment-related changes were noted in these organs. No abnormal clinical signs or microscopic abnormalities were noted in animals receiving only distilled water. The 2000 mg/kg dose was a no-toxic-effect dose for rats of both sexes.

CONCLUSION

Based upon the criteria set forth by Hodge and Sterner (1949), the test material was classified as at most, slightly toxic.

DATA STORAGE

The final report, tissues, paraffin blocks, slides, data sheets, and all non-perishable raw data have been 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, and Environmental Protection Agency Good Laboratory Practice Standard 40 CFR Part 792, November 29, 1983. This study was conducted in compliance with OECD Guidelines for Testing of Chemicals.

QUALITY ASSURANCE STATEMENT

The Quality Assurance Statement pertinent to this study is appended.

REFERENCES

Hodge, H.C. and J.H. Sterner, (1949). Tabulation of Toxicity Classes. Am. Indust. Hyg. Quart., 10: 93-96.

Weil, C.S. (1952). Tables of convenient calculations of medium-effective dose (LD₅₀ or ED₅₀) and instructions in their use. Biometrics, 8: 249-263.