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EASTMAN KODAK CO		
		
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Document Title		
FOUR-WEEK ORAL TOXICITY STUDY ON 2-((4-AMINO-3-METHYLPHENYL))ETHYLAMINO)ETHANOL SULFATE WITH COVER LETTER DATED 032687		
		
Chemical Category		
2-((4-AMINO-3-METHYLPHENYL)ETHYLAMINO)ETHANOL SULFATE		

10/PP

[CONTAINS NO CBI]



8EHQ-0487-0575 (flwp)
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March 26, 1937

Document Control Officer (WII-557)
Management Support Division
Office of Toxic Substances
U. S. Environmental Protection Agency
401 M Street, SW
Washington, D.C. 20460

EPA-OTS



Dear Sir or Madam:

000290777W

Enclosed please find a copy of the Four-Week Oral Toxicity Study conducted on 2-((4-amino-3-methylphenyl)ethylamino)ethanol sulfate (EPA Document Control Number 8EHQ-1185-0575). This report is being submitted as a follow up to our submission of November 11, 1985 on this compound. We have updated our Material Safety Data Sheet (MSDS) to reflect our findings. A copy of the MSDS is enclosed for your information. If you have questions concerning this report, please contact me at the address below.

Sincerely,

R. Hays Bell

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

RHB:JAF
Enc.

cc: W. Hart
B. Klanderman
E. Stern
R. Reynolds
J. O'Donoghue

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 other purposes, call the Marketing and Distribution Center in your area.

Revised Date of Preparation: 3/23/87 Kodak Accession Number: 904984

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SECTION I. IDENTIFICATION

- Product Name: KODAK Color Developing Agent, CD-4
- Synonym(s): 2-((4-Amino-3-methylphenyl)ethylamino)ethanol sulfate;
4-(N-Ethyl-N-2-hydroxyethyl)-2-methylphenylenediamine sulfate
- Formula: C₁₁H₁₈N₂O-H₂SO₄
- Kodak Photographic Chemicals Catalog Number(s): CAT 197 8337 - 50
Pounds;
CAT 160 0279 - 200 Pounds
- Component Number: 12417, 12413
- Kodak's Internal Hazard Rating Codes: R: 2 S: 3 F: 1 C: 1

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SECTION II. PRODUCT AND COMPONENT HAZARD DATA

A.	COMPONENT(S):	Percent	Weight TLV(R)	Kodak Accession No.	CAS Reg. No.
	4-(N-Ethyl-N-2-hydroxyethyl)-2-methylphenylenediamine sulfate	approx 100	---	904984	25646-77-9

- B. PRECAUTIONARY LABEL STATEMENT(S):
- CONTAINS: 4-(N-Ethyl-N-2-hydroxyethyl)-2-methylphenylenediamine sulfate
- DANGER!
POISON
CAN BE FATAL IF SWALLOWED
HARMFUL IF INHALED
MAY CAUSE KIDNEY INJURY
CAUSES SKIN AND EYE IRRITATION
CAN CAUSE ALLERGIC SKIN REACTION
THIS MATERIAL, LIKE MOST ORGANIC MATERIALS IN POWDER FORM, IS CAPABLE OF CREATING A DUST EXPLOSION. REFER TO NFPA PAMPHLET NO. 654
- Avoid breathing dust.
Avoid contact with eyes, skin, and clothing.
Use with adequate ventilation.
Wash thoroughly after handling.
First Aid: In case of eye contact, immediately flush with plenty of water for at least 15 minutes. In case of skin contact, immediately wash with soap and plenty of water. If inhaled, remove to fresh air. If swallowed, if conscious, immediately rinse mouth and induce vomiting by giving 2 glasses of water and touching back of throat with finger or blunt object. Call a physician immediately.

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SECTION III. PHYSICAL DATA

- Appearance and Odor: Pink to lavender crystals; slight sweet odor
- Melting Point: 157 C (315 F)
- Boiling Point: Decomposes
- Vapor Pressure: Negligible
- Evaporation Rate (n-butyl acetate = 1): Negligible
- Vapor Density (Air = 1): Not Applicable
- Volatile Fraction by Weight: Negligible
- Specific Gravity (H2O = 1): Not Available
- Solubility in Water (by Weight): Appreciable

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SECTION IV. FIRE AND EXPLOSION HAZARD DATA

- Combustible dust
- Extinguishing Media: Water spray; Dry chemical; CO2
- Special Fire Fighting Procedures:
 - Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.
- Unusual Fire and Explosion Hazards:
 - Fire or excessive heat may cause production of hazardous decomposition products.
 - This material, like most organic materials in powder form, is capable of creating a dust explosion.

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SECTION V. REACTIVITY DATA

- Stability: Stable, however, material can decompose above 230 C. Avoid temperatures above 130 C.
- Incompatibility: Strong oxidizers
- Hazardous Decomposition Products:
 - As with any other organic material, combustion will produce carbon dioxide and probably carbon monoxide.
 - Oxides of nitrogen and sulfur may also be present.
- Hazardous Polymerization: Will not occur.

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SECTION VI. TOXICITY AND HEALTH HAZARD DATA

A. THRESHOLD LIMIT VALUE: Not established

B. EXPOSURE EFFECTS:

General: Systemic exposure may cause kidney injury.

Inhalation: Harmful if inhaled.

Dust may cause upper respiratory tract irritation.

Eyes: Contact with the powder can cause eye irritation.

Skin: Causes skin irritation. Can cause an allergic skin reaction.

Ingestion: Harmful or fatal if swallowed.

C. FIRST AID:

Inhalation: Remove from exposure, treat symptomatically, and get medical attention if symptoms persist.

Eyes: Immediately flush eyes with plenty of water for at least 15 minutes and get medical attention.

Skin: Flush skin with plenty of water and wash with a non-alkaline (acid) type of skin cleanser. If skin irritation or an allergic skin reaction develops, get medical attention. Remove contaminated clothing.

Ingestion: If swallowed, if conscious, rinse mouth and induce vomiting immediately by giving 1 or 2 glasses of water and touching back of throat with finger or blunt object and/or induce vomiting with syrup of ipecac. Never give anything by mouth to an unconscious person. CALL A PHYSICIAN AT ONCE.

D. TOXICITY DATA:

<u>Test</u>	<u>Species</u>	<u>Result(1)</u>	<u>Classification(2)</u>
Acute Oral LD50	Rat (male)	81 mg/kg	Moderately toxic
Acute Oral LD50	Rat (female)	35 mg/kg	Highly toxic
Acute Oral LD50	Mouse	100-200 mg/kg	
Skin Absorption	Guinea Pig	No evidence of absorption at 1.0 g/kg based on lack of mortality, body weight changes, and clinical signs.	
Skin Irritation	Guinea Pig	Moderate irritation	
Skin Sensitization	Guinea Pig	None sensitized	
Intraperitoneal LD50	Rat, Mouse	10-25 mg/kg	

Other: Skin sensitization has been reported in humans handling this chemical.

The NOEL for rats fed CD-4 in a 4-week subacute oral study was 1.0 mg/kg/day in females and more than 10.0 mg/kg/day in males. The target organ for toxicity was the kidney, confirming the findings seen in the acute oral studies.

===== SECTION VII. VENTILATION AND PERSONAL PROTECTION =====

A. VENTILATION:

Good general ventilation* should be used. Local exhaust ventilation or an enclosed handling system may be needed to control air contamination.

*Typically 10 room volumes per hour is considered good general ventilation: Ventilation rates should be matched to conditions of use.

B. RESPIRATORY PROTECTION:

A NIOSH-approved dust respirator should be worn if needed. If respirators are used, a program should be instituted to assure compliance with OSHA standard 29CFR 1910.134.

C. SKIN AND EYE PROTECTION:

Natural rubber, neoprene or nitrile gloves should be worn. Safety glasses should be worn. The routine use of a non-alkaline (acid) type of hand cleanser will help minimize the possibility of allergic skin reaction.

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SECTION VIII. SPECIAL STORAGE AND HANDLING PRECAUTIONS
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Keep from contact with oxidizing materials.

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SECTION IX. SPILL, LEAK, AND DISPOSAL PROCEDURES
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Small Amount - flush material to sewer with large amounts of water.
Large Amounts - make up into small packages with paper or other flammable material for incineration.
Dispose in incinerator equipped with afterburner and scrubber or contract with licensed chemical waste disposal agency.
Discharge, treatment, or disposal may be subject to federal, state, or local laws.

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SECTION X. ENVIRONMENTAL EFFECTS DATA
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A. SUMMARY:

This chemical has been tested for environmental effects. Some laboratory test data and published data are available for this chemical, and these data have been used to provide the following estimate of environmental impact: (1,3,4)

This chemical has a low biological oxygen demand, and it is expected to cause little oxygen depletion in aquatic systems. It has a high potential to affect aquatic organisms and secondary waste treatment microorganisms. It has a moderate potential to affect the germination of some plants. It has a low potential to affect the growth of some plants. This chemical is biodegraded or biotransformed to materials which are not likely to bioconcentrate and which have a low potential to affect aquatic organisms or secondary waste treatment microorganisms. The direct instantaneous discharge to a receiving body of water of an amount of this chemical which will rapidly produce, by dilution, a final concentration of 0.01 mg/L or less is not expected to cause an adverse environmental effect. However, after dilution with a large amount of water, followed by secondary waste treatment, this chemical is not expected to have any adverse environmental impact.

B. OXYGEN DEMAND DATA:

COD: 1.48 g/g(3)
 BOD5: 0.15 g/g

C. ACUTE AQUATIC EFFECTS:

96-hour LC50; Fathead minnow: 0.5 - 1.0 mg/L (static test) (3).

96-hour LC50; Fathead minnow (Replicate A):
 0.10 mg/L (0.08-0.26 mg/L) (a); NOEC: LT 0.08 mg/L (b)(1).

96-hour LC50; Fathead minnow (Replicate B):
 LT 0.32 mg/L (Inestimable) (c); NOEC: LT 0.09 mg/L (b)(1).

96-hour LC50; Water flea: 0.75 mg/L (Static test) (3).

48-hour EC50(d); Water flea (Replicate A):
 0.63 mg/L (0.26-1.43 mg/L)(c); NOEC: 0.26 mg/L (b)(1).

48-hour EC50(d); Water flea (Replicate B):
 0.78 mg/L (0.30-1.69 mg/L)(c); NOEC: 0.30 mg/L (b)(1).

- (a) 95% Confidence interval calculated by nonlinear interpolation.
 (b) NOEC: No Observed Effect Concentration.
 (c) 95% Confidence interval calculated by binomial method.
 (d) EC50 = Effect concentration causing immobilization of 50% of the test population.

D. SECONDARY WASTE TREATMENT COMPATIBILITY:

5-hour IC50: 200 mg/L(1)

E. PLANT GERMINATION EFFECTS:

No Adverse Effects at:
 Ryegrass 10 mg/L(1)
 Radish 10 mg/L
 Lettuce 10 mg/L

F. PLANT SEEDLING EFFECTS

No Adverse Effects at:
 Marigold 100 mg/L(1)
 Radish 100 mg/L
 Corn 100 mg/L
 Lettuce 100 mg/L

SECTION XI. TRANSPORTATION

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.

SECTION XII. REFERENCES

1. Unpublished Data. Health, Safety, and Human Factors Laboratory. Eastman Kodak Company, Rochester, New York.
 2. Hodge, H.C., and Sterner, J.H., Am. Indust. Hyg. Assn. Quart. 10:93, 1949.
 3. National Association of Photographic Manufacturers, Inc. and Hydroscience, Inc., Environmental Effects of Photoprocessing Chemicals, National Association of Photographic Manufacturers, Harrison, New York, 1974, 2 vols.
 4. Kodak Publication J-41, BOD5 and COD of Photographic Chemicals, Eastman Kodak Co., 1981.
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F-0048.000D
@160-0279*
@197-8337*
82-0527

FOUR-WEEK ORAL TOXICITY STUDY OF 4-(N-ETHYL-N-2-HYDROXYETHYL)-2-METHYLPHENYLENE
DIAMINE SULFATE (CD-4)

PURPOSE: To evaluate the subacute effects of 4-(N-ethyl-N-2-hydroxyethyl)-2-methylphenylene diamine sulfate (CD-4) when given to rats orally for 29 days.

TESTING FACILITY: TOXICOLOGICAL SCIENCES SECTION
HEALTH AND ENVIRONMENT LABORATORIES (HAEL)
B-320 KODAK PARK
EASTMAN KODAK COMPANY
ROCHESTER, NY 14650

TEST ARTICLE CHARACTERIZATION:

CHEMICAL NAME: 4-(N-ethyl-N-2-hydroxyethyl)-2-methylphenylene diamine sulfate
ALTERNATE NAME: CD-4
HAEL NO.: 86-0039
EK ACC. NO.: 904984
CAS NO.: 25646-77-9
SRID OR LOT NO.: Lot A 15
EXPERIMENT NO.: 860039G1

PURITY, STABILITY, and CONCENTRATION ANALYSES: The purity of the test material was determined using high pressure liquid chromatography (HPLC). The purity was found to be 99.1% before initiation of the study and 98.0% after completion, demonstrating the stability of the test article.

The material was serially diluted and dosed as a solution in de-gassed, distilled water. A series of tests were conducted to verify concentrations and to determine the stability of solutions of the test material (0.5%, 0.05%, 0.005% test material). A freshly prepared 0.5% solution was periodically analyzed over approximately 3 hours. The mean concentration of 7 samples was 0.575%, and no degradation occurred. A 0.05% solution was analyzed over approximately 4 hours. The mean concentration of 10 samples was 0.0493%, and no degradation of the solution was noted. Several 0.005% solutions were analyzed. The first solution was contaminated with residual acetone from the glassware washing procedure, and was found to be approximately 23% below target concentration. Although contaminated and below target concentration, no degradation of the test material in this solution was seen over a three-hour period. The values from the contaminated sample were not used in the calculations. Subsequently, an additional 0.005% solution was submitted for concentration verification. It was found to be approximately 15% below target concentration. This solution and other 0.005% solutions used for dosing during the study were analyzed in duplicate over periods of up to two hours. No decrease in concentration of the test material was noted in any solution. Conversely, a slight increase in concentration of the test material was noted with time. No reason for this phenomenon was determined by Chemical Quality Services Division.

During the study, test solutions were prepared daily. Solutions were submitted for analysis on Days 0, 1, 3, 9, 16 and 23. The mean analyzed concentrations of these solutions were 0.521%, 0.0487%, and 0.00434% for the 0.5, 0.05 and 0.005% solutions, respectively. Mean recovery of standard addition samples was 105.8%. Mean analyzed concentrations of the dosing solutions, corrected for the standard addition samples, were 0.492%, 0.0460%, and 0.00410%.

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 0.1, 1.0 or 10.0 mg/kg of the test material in degassed distilled water for 21 doses over 29 days. Doses were given 5 days per week. Controls received a dose of degassed distilled water equal in volume to that of the highest test group.

ANIMALS: Five male and five female rats (CRL: CD®(SD)BR) from Charles River Breeding Laboratories, Wilmington, MA, were randomly assigned to each test group. Animals were isolated for approximately one week prior to testing. At the start of the study, rats were approximately 8 (males) and 11 (females) weeks old and weighed (mean ± SD) approximately 234 ± 5g (males) and 220 ± 5g (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 73-75 °F and 26-44% 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 was changed under the cages at least three times a week.

FEED AND WATER: Agway Prolab Animal diet (RMH 3200), certified ground chow was fed ad lib. Feed containers were cleaned weekly. Feed containers were refilled twice a week. Water was supplied ad lib 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 unique metal ear tag.

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

BODY AND FEED WEIGHT DETERMINATIONS: Body weights were collected on Days 0, 3, 7, 14, 21, and 28. Feed weights were collected on Days 3, 7, 10, 14, 17, 21, 24, and 28.

CLINICAL OBSERVATIONS: Every workday morning each rat was removed from its cage and examined by a trained technician. Every workday, post dose and afternoon cageside observations were conducted. Cageside observation included, but was not limited to, examination of the hair, skin, eyes, motor activity, feces, and urine. Animals were checked for mortality on weekends.

HEMATOLOGY AND CLINICAL CHEMISTRY EXAMINATIONS: At the time of necropsy, blood was collected from the posterior vena cava while the rats were under CO₂ 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, and examination of the blood smears for cellular morphology. Clinical chemistry tests included: aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase, alkaline phosphatase, creatinine, urea nitrogen, and glucose. Urine was collected on Day 29 for urinalysis and quantitation of urinary N-acetyl glucosaminidase (NAG).

NECROPSY: Rats were fasted overnight, anesthetized with CO₂, 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 target organs and gross lesions were examined from other groups.

STATISTICAL PROCEDURES: Mean values were calculated for body weight, feed consumption, organ weights, hematology, clinical chemistry and urinalysis. All mean continuous data, except feed consumption, were evaluated using the following computer-generated statistical tests: one-way analysis of variance (ANOVA), Bartlett's test, and Duncan's multiple range test using a P value of ≤ 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, and Environmental Protection Agency Good Laboratory Practice Standard 40 CFR Part 792, November 29, 1983. This study was also conducted in accordance with OECD Principles of Good Laboratory Practice.

PROJECT PARTICIPANTS:

Study Director	D. C. Topping, Ph.D.
Study Technician	R. S. Hosenfeld, A.A.S.
Necropsy Pathologist	J. L. O'Donoghue, V.M.D., 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	R. A. Schumacher, M.S.
Report Author	R. S. Hosenfeld, A.A.S.

DATE OF STUDY INITIATION: April 21, 1986

PROTOCOL AND SOP DEVIATIONS: Feed consumption was done on Day 3 instead of Day 4, in order to provide a demonstration for the Quality Assurance Section.

RESULTS

MORTALITY: No mortality was observed during the exposures.

CLINICAL SIGNS: On Day 7, a female rat from the 10.0 mg/kg group had alopecia on the back and on Day 21, a female rat from the 1.0 mg/kg group had a swollen eyelid. These abnormalities were not considered to be compound-related. Discolored brown urine was seen in the 10.0 mg/kg animals of both sexes, during the afternoon of the first dosing day and was present throughout the study.

BODY WEIGHT: Weight loss (16g) was observed in a 10.0 mg/kg female (Rat 40), on Day 3. This animal showed normal weight gain for the remainder of the study when compared to the controls. Other than this animal, body weight gains were comparable among treated and control animals of both sexes.

FEED CONSUMPTION: Feed consumption in the 10.0 mg/kg females was slightly decreased between Days 0 and 3. The feed consumption in this group and in all other groups for the remainder of the study was similar to the controls.

HEMATOLOGY: Statistically significant lower counts were found in the % of eosinophils for all treated female groups relative to controls. This difference was due to an abnormally high number of eosinophils in the control group and did not signify a biologically significant finding. No other differences were found in any hematological parameter.

CLINICAL CHEMISTRY: Serum clinical chemistry tests were comparable among treated and control animals.

URINE TESTING: In the 10.0 mg/kg females, (Rat 36, 38 and 40) had increases in N-acetyl glucosaminidase (NAG) activity compared to controls. These same females had a great increase and one had a slight increase in the white blood cell count, when compared to the controls and the other dose groups. Rat 36 also had a greatly increased protein, specific gravity and creatinine level. In one of five males in both the 0.1 and the 1.0 mg/kg dose groups, and three of five males and two of five females in the 10.0 mg/kg dose group the nitrite levels of the urine were positive. Urine nitrite may be indicative of CD-4 metabolites in the urine.

ORGAN WEIGHTS: No statistical differences among control and treated animals in either absolute or relative (to body weight) organ weights were obtained. In a single high dose female (Rat 40), absolute and relative kidney weights were increased both over controls and values obtained from other high dose females. The percent increase relative to control animals was 31% and 40% for absolute and relative kidney weights, respectively. In the remaining organs no differences in organ weights were seen in either sex when compared to the controls.

PATHOLOGY: The only treatment-related changes observed at gross pathology examination were pale kidneys in three females from the 10.0 mg/kg dose group. No treatment-related changes were observed at the time of necropsy for any of the male test animals or the two lower female groups.

Treatment-related microscopic changes were localized to the kidneys and found only in the 10.0 mg/kg females. In this group, proximal convoluted tubular epithelium was necrotic (3/5), lightly vacuolated (1/5), and basophilic (3/5). Proximal tubules were dilated (2/5) and contained granular casts (3/5). The numbers in brackets indicate the number of affected over the total number examined. The affected areas formed columns within the inner cortex. In the interstitium, there was a minor inflammatory cell infiltrate consisting primarily of lymphocytes (2/5). No treatment related changes were observed in the 0.1, 1.0 and 10.0 mg/kg males, or the 0.1 and 1.0 mg/kg females.

DISCUSSION AND INTERPRETATION

In an Ld50 study on the test article, fasted rats were dosed once at 3.12, 6.25, 12.5, 25, 50, 100, 200 or 400 mg/kg. In that study, deaths occurred in both sexes at a dose of 25 mg/kg. No deaths occurred at 12.5 mg/kg but compound-related abnormalities were found histopathologically in the kidney. Kidney lesions were also found in a small percentage of the animals dosed with 6.25 mg/kg. For the present study, a high dose level of 10.0 mg/kg/day was chosen in order to induce compound-related organ specific toxicity. Middle and low doses of 1.0 mg/kg/day and 0.1 mg/kg/day were chosen in order to obtain a no-effect level.

In the present study, toxicity was observed only in the group of females administered the highest dose. Significant findings in that group indicated renal toxicity, i.e. necrosis of the proximal convoluted tubular epithelium, which was also lightly vacuolated and basophilic, increased N-acetyl glucosaminidase and the presence of highly elevated numbers of white blood cells in the urine. The effects were present primarily in 3/5 animals in that group. Inflammatory cell infiltrates consisting primarily of lymphocytes were noted in 2/5 animals and absolute and relative increases in kidney weights were present in 1/5. No abnormalities were observed in males at any dose level or in the other two groups of females in clinical signs, weight gain, feed consumption, hematology, serum clinical chemistry or urinary parameters. Similarly, no gross or histopathological abnormalities were seen in any of the other dose groups.

The results of this study demonstrated that the test material is less toxic in fed animals than in fasted animals and females are slightly more sensitive to the test article than males. In previous acute toxicity studies in fasted rats, mortality was observed in a proportion of animals administered single doses as low as 25 mg/kg. In the present study, abnormalities were observed in only 3/5 females administered a total cumulative dose of 210 mg/kg and no mortality was observed. No abnormalities were seen in males receiving the same dose. The lack of extensive abnormal findings in the present study may be due to a lack of bioaccumulation of the test article or toxic effects which were not cumulative under conditions of dosing where individual daily doses cause minimal or no immediate toxicity.

The target organ for toxicity in the present study was the kidney, confirming the findings seen in the acute oral studies. The no-effect level for rats administered CD-4 21 times in 29 days was 1.0 mg/kg/day in females and more than 10.0 mg/kg/day in males.

TABLES: Tables 1 and 2 summarize the results of this study. 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.