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

MAY 7 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: EPA ID # 524-UGN: Dithiopyr (a.i. in Dimension®) - Review of 21-Day Dermal Toxicity Study Submitted for New Chemical Registration and Evaluation of Complete Data Base

Tox. Chem. Number: 717C
Project Number: 0-0342
Record Number: 240294

From: Paul Chin, PhD Paul Chin 4/26/90
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Hazard Evaluation Division (H7509C)

To: Joanne Miller, PM 23
Registration Division (H7505C)

Thru: Marion P Copley, DVM, DABT Marion P. Copley 4/30/90
Head, Section 2, Toxicology Branch I (IRS) KB 4/31/90
Hazard Evaluation Division (H7509C)

NOTE 1: This memorandum includes review of the toxicology data base required for new registration of dithiopyr and the formulation Dimension Turf Herbicide (MON-15104) for non-food crop use. We recommend the Registration Division submit the entire memorandum to the registrant for their reference.
NOTE 2: The registrant will be submitting a summary of additional toxicology data on dithiopyr and thiazopyr (in corn oil vs. carboxymethylcellulose vehicle) in response to the EPA's request for additional information on the developmental toxicity study in either rats or rabbits (telephone conversation with Dennis Ward, Monsanto, 4/24/90).

CONCLUSION 1:

The Toxicology Branch I has reviewed a 21-day dermal toxicity study in rats with dithiopyr. This study received core-guideline classification. Here are the conclusions of the evaluations. [The Data Evaluation Reports of the 21-day dermal toxicity study is appended to this memorandum.]

NOEL= 500 mg/kg/day
LEL= 1000 mg/kg/day based on increased liver weights in male and female rats

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Dermal effects: Limited to transient mild irritation in some animals in all dose groups. Incidence was generally dose-related and higher in females than in males.
Dose levels tested: 0, 50, 500, or 1000 mg/kg/day.
Test species [strain]: rat [CD (Sprague-Dawley derived)]
Route of administration: dermal

CONCLUSION 2:

The toxicology data base for MON-15100/MON-7200 technical grade dithiopyr does not support the registration of dithiopyr for non-food crop use. The following data gaps have been identified.

1. Developmental toxicity study in either rats or rabbits.
2. Mutagenicity --Chromosome damage in vitro.
3. 90-day feeding study.[1]

ACTION REQUESTED:

Review and evaluate the 21-day dermal toxicity study in rats with dithiopyr (MRID Number 413056-01). Also included is an evaluation of the data base required for registration of dithiopyr technical.

DATA BASE SUMMARY:

The toxicology data requirements for the registration of dithiopyr (Technical MON-7200)

The toxicology data required for registration of dithiopyr technical for non-food crop use include 6 acute toxicity studies, a 21-day subchronic dermal toxicity study, mutagenicity studies (in all 3 categories), a developmental toxicity study (1 species), and a 90-day feeding study (all on the technical). Also required for registration of the formulation are 6 acute toxicity studies on the formulation.

The following required toxicology studies have been submitted and reviewed:

ACUTE STUDIES (previous actions)

For each study, the study type/test substance/species/study number, accession number, conclusion, toxicity category, and core classification are listed below.

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[1] This is required to be consistent with what is currently being required for reregistration under the 1988 amendments to FIFRA. However, this gap would not delay registration of this pesticide.

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TECHNICAL

1. Acute Oral Toxicity/Rat/MON-7200/87-0045/ET-87-121

   MRID number 406386-07
   LD50 > 5000 mg/kg.
   Toxicity category IV
   Core classification is minimum

2. Acute Oral Toxicity/Mouse/MON-7200/87-0046/ET-87-122

   MRID number 406386-08
   LD50 > 5000 mg/kg
   Toxicity category IV
   Core classification is minimum.

3. Acute Dermal Toxicity/Rat/MON-7200/87-0047/ET-87-123

   MRID number 406386-09
   LD50 > 5000 mg/kg
   Toxicity category III
   Core classification is minimum

4. Acute Inhalation Toxicity/Rat/MON-7200/87-0048/ET-87-124

   MRID number 406386-10
   LD50 > 5.98 mg/l
   Toxicity category III
   Core classification is minimum

5. Primary Eye Irritation/Rabbit/MON-7200/4313-87/BD-87-131.
   MRID number 406386-11
   No corneal opacity; irritation reversible within 7 days.
   Toxicity category III
   Core classification is minimum

6. Primary Dermal Irritation/Rabbit/MON-7200/4312-87/BD-87-131.
   MRID number 406386-12
   Mild or slight irritation at 72 hours.
   Toxicity category III
   Core classification is minimum

7. Dermal Sensitization/Guinea Pig/MON-7200/4314-87/BD-87-130.
   MRID number 406386-13
   MON-7200 is not a dermal sensitizer in this study.
   Toxicity category NA
   Core classification is minimum

MON-15151 (Formulation)

8. Acute Oral Toxicity/Rat/MON-15151/4195-87/BD-87-132.
   MRID number 406386-14

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LD50 = 4100 mg/kg in males and 3000 mg/kg in females.
Toxicity category III
Core classification is minimum

9. Acute Dermal Toxicity/Rabbit/MON-15151/4196-87/BD-87-132.
MRID number 406386-15
LD50 > 5000 mg/kg
Toxicity category III
Core classification is minimum

10a. Acute Inhalation Toxicity/Rat/MON-15151/ML-87-145/EHL-87093
MRID number 406386-16
LC50 >3.5 and <5.0 mg/l for males and 3.3 mg/l for females.
Tentative Toxicity category III
Core classification is supplementary

10b. Acute Inhalation Toxicity/Rat/MON-15151/89-8189/BD-89-42
MRID number 411356-02
LC50 11 mg/l for males and 8.9 mg/l for females.
Toxicity category IV
Core classification is supplementary

11. Primary Eye Irritation/Rabbit/MON-15151/4198-87/BD-87-132.
MRID number 406386-17
Corneal corrosion reversible within 21 days, and possibly within 7 days; corneal opacity reversible within 7 days; irritation reversible within 7 days.
Toxicity category II
Core classification is minimum

12. Primary Dermal Irritation/Rabbit/MON-15151/4197-87/BD-87-132.
MRID number 406386-18
MON-15151 caused severe dermal irritation at 72 hours.
Toxicity category II
Core classification is minimum

13. Dermal Sensitization/Guinea Pig/MON-15151/4199-87/BD-87-133.
MRID number 406386-19
MON-15151 is a dermal sensitizer in this study.
Toxicity category NA
Core classification is minimum

<u>MON-15104 (Formulation)</u>

1. Acute Oral Toxicity/Rat/MON-15104/5352-88/BD-89-21

MRID number 411300-04
LD50 > 5000 mg/kg.
Toxicity category IV
Core classification is minimum

2. Acute Dermal Toxicity/Rabbit/MON-15104/5353-88/BD-89-21

MRID number 411300-05
LD50 > 5000 mg/kg
Toxicity category IV
Core classification is minimum

3. Acute Inhalation Toxicity/Rat/MON-15104/89098/MSL-9084

MRID number 411300-06
LD50 3.4 mg/l for males and 4.5 mg/l for females
Toxicity category III
Core classification is supplementary

4. Primary Eye Irritation/Rabbit/MON-15104/5355-88/BD-89-21.

MRID number 411300-07
No corneal opacity; irritation reversible within 24 hours
Toxicity category IV
Core classification is minimum

5. Primary Dermal Irritation/Rabbit/MON-15104/5354-88/BD-89-21.

MRID number 411300-08
Very slight to slight irritation at 72 hours.
Toxicity category IV
Core classification is minimum

6. Dermal Sensitization/Guinea Pig/MON-15104/5356-88/BD-89-21.
MRID number 411300-09
MON-15104 is not a dermal sensitizer in this study.
Toxicity category NA
Core classification is minimum

SUBCHRONIC DERMAL (21-DAY) TOXICITY STUDY IN RATS

MRID Number 413056-01
NOEL= 500 mg/kg/day
LEL= 1000 mg/kg/day based on increased liver weights in male and female rats
Dermal effects: Limited to transient mild irritation in some animals in all dose groups. Incidence was generally dose-related and higher in females than in males.
Dose levels tested: 0, 50, 500, or 1000 mg/kg/day.
Test species [strain]: rat [CD (Sprague-dawley derived)]
Route of administration: dermal
Core classification is guideline

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MUTAGENICITY STUDIES (previous action)

Five mutagenicity studies (MRID Nos.410015-09, -10, -11, -12, and -13) with dithiopyr were reviewed by Irving Mauer. Four studies (MRID No. 410015-09, -10, -11, and -13) were core-graded acceptable and one study (MRID No. 4110015-12) was core-graded unacceptable because the study cannot be evaluated until essential procedural information and other unexplained items are provided. Here are the conclusions of the evaluations.

1. Ames Assay/MON-7200/ML-87-11/EHL 87004

   MRID number: 41001509
   Conclusion: negative
   Core classification: Acceptable

2. Ames Assay/MON-7200/SR-86-375/LSC-2755-1

   MRID number: 41001510
   Conclusion: negative
   Core classification: Acceptable

3. CHO/HGPRT Mutation Assay/MON-7200/ML-87-10/EHL 87006

   MRID number: 41001511
   Conclusion: negative
   Core classification: Acceptable

4. In Vitro Cytogenetics Test/MON-7200/ET-86-79

   MRID number: 41001512
   Conclusion: negative
   Core classification: Unacceptable

5. Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures/MON-7200/SR-87-9/LSC 3116

   MRID number: 41001513
   Conclusion: negative
   Core classification: Acceptable

DEVELOPMENTAL TOXICITY STUDIES (previous action)

Developmental toxicity studies in rats and rabbits studies with dithiopyr were reviewed by the Toxicology Branch I. Both developmental studies were core-graded supplementary. However, these studies may be either upgraded to core-guideline or downgraded to invalid pending reevaluation of the additional information on bioavailability of MON-15100 (See section on ADDITIONAL INFORMATION NEEDED).

1. Developmental toxicity study in rats (MRID No. 41001507)

Maternal NOEL = 300 mg/kg/day
Maternal LEL = 1000 mg/kg/day (decreased food consumption)
Developmental Toxicity NOEL = 1000 mg/kg/day (the highest dose tested)
Developmental Toxicity LEL = not established
Dose levels tested: 0, 30, 300, or 1000 mg/kg/day.
Core classification: Core-supplementary.

2. Developmental toxicity study in rabbits (MRID No. 41001508)

Maternal NOEL = 500 mg/kg/day
Maternal LEL = 1000 mg/kg/day (reduced body weight gain)
Developmental Toxicity NOEL = 1000 mg/kg/day (the highest dose tested)
Developmental Toxicity LEL = not established
Dose levels tested: 0, 150, 500, or 1000 mg/kg/day
Core classification: Core-supplementary.

ADDITIONAL INFORMATION NEEDED:

Bioavailability data of MON-7200 in test animal

The Agency must be assured that the apparent low toxicity of MON-7200 demonstrated in the developmental toxicity study in test animal (marginal maternal toxicity at 1 g/kg/day, HDT) is not the result of the poor availability of the test material in carboxymethylcellulose (CMC). Therefore, the registrant must provide the following data and information.

a. The maternal liver weight from the developmental toxicity study in test animal.

b. Data on the bioavailability of MON-7200 in the 0.5 - 1 % CMC, such as information on the degree of binding of the vehicle for MON-7200.

a. Maternal Liver weight data

Liver weight data (liver weights and liver/body weight ratios) are needed because the liver was the common target organ in a 21-day dermal toxicity study in rats (see Background attached to this DER) with MON-7200 or the pilot dietary study in rats with MON-13200. The liver weight increase observed in these studies is apparently related to the absorbed dose of the test substance from 2 different routes of administration.

b. Bioavailability data

Carboxymethylcellulose (CMC), a widely used suspending

agent, binds some chemicals. The CMC used in the developmental toxicity study may sufficiently bind MON-7200 and cause a decrease in the availability of test material for absorption in test animals. Therefore, the registrant should demonstrate the availability of MON-7200 for absorption when test material is suspended in CMC.

DATA GAPS:

1. Developmental toxicity studies in rats and rabbits.
2. Mutagenicity --Chromosome damage in vitro.
3. 90-day feeding study.[2]

Label requirement:

The labels are adequate for dithiopyr technical (MON-15100 or MON-7200), MON-15151, and MON-15104 formulations (see memorandum from Paul Chin of TB to Robert Ikeda of Registration Division, dated February 26, 1990).

BACKGROUND:

Monsanto is requesting the registration of MON-15100 technical grade "dithiopyr" active ingredient for use in products to be applied to turf in both residential and nonresidential sites.

MON-15100 and MON-7200 are Monsanto designations for the same ingredient, ie., dithiopyr [3,5-pyridine-dicarbothioic acid, 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-S,S-dimethyl ester]. MON-15100 and MON-7200 are the designations for the active ingredient for registration in the United States and outside the United States, respectively.

The Agency granted the extension of Experimental Use Permit 524-EUP-69 for both MON-15151 and MON-15104 formulations (dithiopyr end-use formulations under the Dimension Turf Herbicide trade name) to control annual grass and broad leaf weeds in turf grass.

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[2] This is required to be consistent with what is currently being required for reregistration under the 1988 amendments to FIFRA. However, this gap would not delay registration of this pesticide.

GUIDELINE: 82-2

Primary reviewer: Paul Chin, PhD. Paul Chin 4/25/90
Section 2, Tox. Branch 1 (IRS)(H7509C).
Secondary reviewer: Marion Copley, DVM, DABT, Section Head.
Section 2, Tox. Branch 1 (IRS)(H7509C). Marion Copley 4/25/90

DATA EVALUATION RECORD

Study Type: Subchronic 21-Day Dermal Toxicity Study in Rats

EPA Identification No.s: EPA MRID No. 413056-01
Caswell No. 717C

Test Material: MON-7200, technical

Synonyms: Dithiopyr; MON-15100; MON-7200; 92% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

Sponsor: Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, Missouri 63167

Study Number(s): BD-89-168/89-3440

Testing Facility: Bio/dynamics, Inc., Mettlers Road, East Millstone, NJ 08873

Title of Report: A 21-Day Dermal Toxicity Study in Rats with MON-7200

Author(s): C.S. Auletta

Report Issued: November 9, 1989

Conclusions on effect levels and no effect levels

NOEL= 500 mg/kg/day
LEL= 1000 mg/kg/day based on increased liver weights and liver/body weight ratios in both males and females
Dose levels tested: 0, 50, 500, or 1000 mg/kg/day.
Test species [strain]: rat [CD (Sprague-dawley derived)]
Route of administration: dermal
Dermal effects: Limited to transient mild irritation in some animals in all dose groups. Incidence was generally dose-related and higher in females than in males.

Core classification: Core-guideline. This study satisfies the requirements of Guideline 82-2 for subchronic dermal toxicity in rats.

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A. Materials

Test Compound: Purity: 92%
Description: yellow-amber powder
Lot No.: Day 8902-138T
Melting point: 48-51° C
Vapor pressure: 4 x 10^{-6} torr at 25° C
Solubility: 0.7 ppm in water. Soluble in toluene, ether, acetone, and chloroform

Compound preparation:

MON-7200 was ground into a powder over dry ice.

Test Animal(s):
Species: Rat
Strain: CD (Sprague-Dawley derived)
Source: Charles River Breeding Laboratories, Inc. Canada, 188 Lasalle, ST. Constant, Canada
Age: 8 weeks
Mean (range) Body Weight (g): male: 368 (348-384); female: 262 (245-281)
Acclimation Period: 14 days

Environmental Conditions: Temperature: 70-73° F
Humidity: 28-68%
Light:dark cycle: 12:12

B. Study Design

This study was designed to assess the potential toxicity of MON-7200 when administered dermally to rats.

Group Arrangement:
Animals were assigned randomly to the following test groups:

Test Group	Dose Level (mg/kg/day)	Number Assigned Male	Female
Control	0	5	5
Low Dose	50	5	5
Mid Dose	500	5	5
High Dose	1000	5	5

Preparation of animals:
On the day before initiation of dosing, the hair was removed from an area of up to 5 x 5 cm on the upper dorsal surface. Animals were reclipped as needed during the study.

Dosing:

The appropriate dose of test substance, calculated on the basis of the most recent body weight, was weighed and

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applied directly to the clipped skin of each animal, uniformly over the application site. The test site was then covered by gauze which was held in place by an adhesive bandage wrapped around the trunk. The bandage was tightened sufficiently to prevent the rat from wriggling free but not so tight as to cause undue stress. The bandage was constructed so that the test site was covered with gauze only, i.e., a semi-occlusive bandage. Control animals were sham-treated, i.e., the skin was covered with gauze held in place with a bandage in the same manner as the treated animals but did not receive test substance. Following approximately 6 hours of exposure, the wrappings were removed. Prior to each application the residual test substance was removed from the exposure site. Treatment continued daily (5 days per week) for 3 weeks for a total of 15 applications over 21 days.

Food and water:

Food and water were supplied ad libitum.

Observations:

The animals were checked twice daily for mortality or signs of toxicologic effects. Body weight determinations were made twice pretest, weekly during treatment and terminally. Food consumption was measured weekly beginning one week prior to treatment.

Dermal irritation was evaluated and noted as present or absent once daily, on each dose day, prior to test substance administration. Dermal irritation was evaluated and scored pretest and weekly, approximately 1/2 hour after removal of the wrappings, during the study.

Hematology and Clinical Chemistry:

Laboratory studies were performed on all animals at study termination. Blood was obtained via venipuncture of the orbital sinus of the fasted rats under light ether anesthesia. The CHECKED (X) parameters were examined.

Hematology:

X	Hemoglobin	X	Hematocrit
X	Erythrocyte count	X	Platelet count
X	Mean corpuscular volume	X	Mean corpuscular hemoglobin
X	Mean corpuscular Hemoglobin concentration		
X	Total and differential leukocyte counts		

Clinical chemistry:

X	Aspartate aminotransferase	X	Alanine aminotransferase
X	Alkaline phosphatase	X	Urea nitrogen
X	Glucose	X	Protein
X	Albumin	X	Creatinine
X	Total bilirubin	X	Sodium
X	Potassium	X	Chloride
X	Calcium	X	Inorganic phosphorus

Gross Pathology and Histopathology:

All of the animals were subject to gross pathological examination.

Organs weighed for all animals at study termination: Kidneys, testes with epididymides, and liver.

Tissues preserved and examined histopathologically: Kidneys, liver, skin (normal and treated), and gross lesions (including a section of normal-appearing portion of same tissue).

Statistical analysis:

See Appendix #1, taken from the study report.

Compliance:

A signed Statement of Confidentiality Claim was provided. A signed Statement of compliance with EPA GLP's was provided. A signed Quality Assurance Statement was provided by the Supervisor of Quality Assurance Unit, William Harrison, on 10/24/89.

C. Results

All animals survived throughout the study. Evaluations of body weights, food consumption, and hematology and clinical chemistry values revealed no evidence of an effect of test substance.

Dermal effects of MON-7200 administration were limited to transient mild irritation in some animals in all dose groups. Incidence was generally dose-related and higher in females than in males. Dermal abnormalities noted were as follows:

Daily observations

1. In males, erythema was present in one or two high-dose animals on two occasions (days 8 and 19)
2. In females, erythema was present in one or two animals in

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each of all treated groups on a few occasions (4 or 5 of the 15 days) and edema was present in one high-dose animal on two occasions (days 12 and 13).

Organ Weights
Liver weights and liver/body weight ratios for high-dose males and females were approximately 20% higher than control values. The differences were statistically significant ($p < 0.01$) (see I-2, APPENDIX I of the study report attached to this DER). Liver weights for low- and mid-dose animals and weights for kidneys and testes with epididymides for all treated groups were comparable for control weights.

Gross pathology findings were not considered to be related to test substance treatment. Gross pathology findings noted were as follows:

1. Discoloration in the following tissues:
   kidneys (1 low-dose male),
   liver (1 control female),
   lungs (1 control male, 2 low-and mid-dose males), and
   lymph nodes (2 control male, 1 low- and mid-dose male and 2 low-dose and 1 mid-dose female).
2. Dilated pelvis in the kidneys (1 mid-dose male, 1 control female),
   liver surface irregularities (1 high-dose female),
   enlarged lymph node (1 low-dose male),
   distended uterus (1 mid-dose female),
   hair loss (2 low-dose and 1 high-dose females), and
   nodule(s)/mass(s) in the skin (1 low-dose female).

Histopathological findings were not considered to be related to test substance treatment. Histopathological findings noted were as follows:

Liver--	tension lipidosis (2 control male, 1 high-dose female), hepatocellular vacuolation/vesiculation (1 control female)
Kidney--	hydronephrosis (1 control male, 2 control and 2 high-dose females), convoluted tubules with mineralization (1 control and 2 high-dose females), medullary cysts (1 control male),
Lymph node--	congestion/hemorrhage (1 control and 1 mid-dose male), lymphoid cell hyperplasia (1 low-dose male)
Lungs--	chronic interstitial pneumonia (2 low-dose and 1 mid-dose male)
Skin--	squamous cell papilloma (1 low-dose female)
Uterus--	hydrometra (1 mid-dose female)

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D. Discussion/Conclusions

Dithiopyr (MON-7200) was topically applied to the intact skin of 3 groups of 5 male and 5 female CD rats at dose levels of 0, 50, 500, and 1000 mg/kg/day, 5 days per week, for a total of 15 applications over 21 days. The test substance remained on the skin 6 hours/day under semi-occlusive dressing. Based on statistically significant increase in liver weights and liver/body weight ratios in both males and females, the lowest-effect-level (LEL) is 1000 mg/kg/day. The no-observed-effect level (NOEL) is 500 mg/kg/day. Dermal effects of dithiopyr administration were limited to transient mild irritation in some animals in all dose groups. Incidence was generally dose-related and higher in females than in males.

APPENDIX #1

METHODOLOGY AND REFERENCES--STATISTICAL ANALYSIS
(Study Report pp.25-26)

Methodology and References - Statistical Analysis (cont.)

Reference or Description

Statistical evaluation of equality of means was made by the appropriate one way analysis of variance technique, followed by a multiple comparison procedure if needed. First, Bartlett's test was performed to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not, nonparametric procedures were used. The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from the control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from control.

A statistical test for trend in the dose levels was also performed. In the parametric case (i.e., equal variance) standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1%, two-sided risk level. All other statistical tests were conducted at the 5% and 1%, two-sided risk level.

References for these techniques are Snedecor, G.W., and Cochran, W.G., Statistical Methods. 6th edition, Iowa State University Press (1967); Hollander, M. and Wolfe, D.A., Nonparametric Statistical Methods. John Wiley and Sons, New York (1973); Dunnett, C.W., J. Am. Sta. Assn. Vol. 50 (1955) and Biometrics. Vol. 20 (1964).

Bartlett's Test	pp. 296-298	S&C
ANOVA	pp. 277-279	S&C
Dunnett's	pp. 1096-1121	D
	pp. 482-491	Bio
Kruskal-Wallis	pp. 114-116	H&W
Summed Rank Test (Dunn)	p. 131	H&W
Regression Analysis		
Trend	pp. 149-152	S&C
Lack of Fit	pp. 456-459	S&C
Jonckheere's Statistic	pp. 120-123	H&W

Methodology and References - Statistical Analysis (cont.)

Reference or Description

TWO GROUP ANALYSIS SYMBOL			STATISTICAL STATEMENT
No Sig	$p \leq 0.05$	$p \leq 0.01$	
F-			Variances are equal.
		F+	Variances are unequal.
	*	**	Significantly different from control (t-tests).

The variances of the two groups were tested for equality using the F test. If the variances were equal, a standard independent two sample t-test was used to determine equality of means. If the variances differed at the 1% level of significance, Welch's t-test was used to determine equality of means. t-tests were conducted at the 5% and 1%, two-sided risk level.

References for these techniques are:

F-test: Gill, J.L., Design and Analysis of Experiments in the Animal and Medical Sciences. Iowa State University Press, Ames, Iowa (1978). Vol I, pp. 63-65.

t-test: Ibid., pp. 67-68.

Welch's t-test: Ibid., p. 71.

APPENDIX I (CONT.)
A 21-DAY DERMAL TOXICITY STUDY
IN RATS WITH MON 7200

TERMINAL ORGAN AND BODY WEIGHTS
AND ORGAN/BODY WEIGHT RATIOS
TERMINAL SACRIFICE - MALES

MEAN VALUES

	TERMINAL BODY WT. (G)	KIDNEYS WT. (G)	KIDNEYS ORG/TBW (X 1000)	LIVER WT. (G)	LIVER ORG/TBW (X 100)	TEST/EPID WT. (G)	TEST/EPID ORG/TBW (X 100)
STAT SYMBOL:	A-L-	A-L-	A-L-	A+L+	A+L+	A-L-	A-L-
GROUP I - 0 MG/KG/DAY							
MEAN	375.	2.807	7.47	9.839	2.63	4.3895	1.17
S.D.	13.	.425	.89	.654	.12	.4937	.11
N	5	5	5	5	5	5	5
GROUP II - 50 MG/KG/DAY							
MEAN	375.	2.834	7.57	10.299	2.74	4.3536	1.16
S.D.	16.	.315	.85	.951	.17	.2308	.05
N	5	5	5	5	5	5	5
GROUP III - 500 MG/KG/DAY							
MEAN	378.	3.012	8.01	10.702	2.84	4.5550	1.21
S.D.	16.	.292	1.04	.377	.15	.3179	.11
N	5	5	5	5	5	5	5
GROUP IV - 1000 MG/KG/DAY				**	**		
MEAN	382.	2.939	7.70	12.032	3.15	4.4092	1.15
S.D.	16.	.117	.40	.702	.17	.1637	.05
N	5	5	5	5	5	5	5