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ATLANTIC RICHFIELD CO

Contractor

UBTL INC

Document Title

SUPPORT: CARBON BLACK OIL: NINETY DAY DERMAL TOXICITY STUDY IN RATS (DRAFT REPORT) WITH COVER LETTER DATED 111292

Chemical Category

CARBON BLACK OIL

SUPP

8EHQ-1192-0576

ARCO

515 South Flower Street
Los Angeles, California 90071
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William D. Leake
Vice President
Environment, Health & Safety

473-PP

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November 12, 1992

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EPA-OTS

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Document Control Officer (TS-790)
Attention: 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Subject: TSCA Section 8(e) Notice on Carbon Black Oil (CAS 64741-62-4; 8EHQ-1185-0576)

Dear Sir/Madam:

In accordance with the provisions of Section 8(e) of the Toxic Substances Control Act, the Atlantic Richfield Company (ARCO) is submitting information on the preliminary results of a 90 - day dermal toxicity study on carbon black oil (CBO; synonym, clarified slurry oil).

This is one of several follow-up studies initiated by ARCO in response to previous reports by Mobil and ARCO (8EHQ-1185-0576) of adverse effects on rats after dermal exposure to CBO. The objective of the ARCO study being reported in this letter was to further determine the subchronic dermal toxicity of CBO.

In this study, adult albino rats received dermal applications of CBO for 13 weeks (5 days/week) at dose levels of 0, 0.001, 0.05, 0.1 and 0.5 ml/kg/day. After application of CBO, the dosed site was occluded for six hours.

Nine animals either died or were sacrificed moribund in the top dose (0.5 ml/kg). The deaths were attributed to the dermal application of CBO. Other primary effects produced by the dermal application of CBO were changes in the hematology (including decreased RBC parameters, decreased platelet count, and cellular depletion of the bone marrow),

liver toxicity (including hepatic congestion, necrosis, vacuolar change, and alteration in liver blood chemistries), thymic effects (including thymic atrophy and chronic inflammation), and increased lung weight parameters.

The systemic effects Lowest Observable Effects Level (LOEL) for this study was determined to be 0.05 ml/kg/day (approximately 53 mg/kg/day).

The data from this study have received only a preliminary review. Additional statistical analysis and historic controls comparisons will be performed for the final report. This additional analysis may change the preliminary summary of adverse effects listed above.

Our current MSD Sheet on CBO is being reviewed with these results in mind.

We are attaching the preliminary information on this study which was contained in a draft report written by the testing laboratory. EPA will be sent a copy of the final reports once they are received by ARCO.

Sincerely yours,

Frank Koch for William D. Leake

William D. Leake

WDL/FJK/fjk

Attachment

UBTL, Inc.
520 Wakara Way
Salt Lake City, Utah 84108
(801) 583-3600

DRAFT REPORT

NINETY (90) DAY DERMAL TOXICITY STUDY IN RATS ADMINISTERED TEST ARTICLE F-179

UBTL STUDY NO. 66152
PROTOCOL NO. ATX-91-0012

Prepared For:

Francis J. Koschier, Ph.D.
ARCO
515 South Flower Street
Los Angeles, CA 90071

UBTL STUDY NO. 66152

PROTOCOL NO. ATX-91-0012

NINETY (90) DAY DERMAL TOXICITY
STUDY IN RATS ADMINISTERED
TEST ARTICLE F-179

APPROVALS

_____ _____
R. Wayne Ball, Ph.D. DATE
STUDY DIRECTOR

_____ _____
William H. Ford, M.S., D.A.B.T. DATE
MANAGER OF TOXICOLOGY

0 0 0 5

UBTL, INC.
520 WAKARA WAY
SALT LAKE CITY, UT 84108

UBTL Study No. 66152

NINETY (90) DAY DERMAL TOXICITY STUDY IN RATS ADMINISTERED TEST ARTICLE F-179

This study was conducted in accordance with the EPA Standards for Good Laboratory Practice, 40 CFR Part 792, with the exceptions as listed in the Data Integrity Statement found in Appendix D of this report. Evaluations relating to the chemical composition, purity, strength and stability of the test article were the responsibility of the sponsor and therefore were not performed by UBTL, Inc.

R. Wayne Ball, Ph.D.
STUDY DIRECTOR

DATE

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UBTL STUDY NO. 66152
PROTOCOL NO. ATX-91-0012

ABSTRACT

The purpose of this study was to determine the systemic no-observed-effect level and dermal irritation associated with repeated dermal exposure to F-179 in Sprague-Dawley rats for a period of 90 days.

Five groups of twenty male and twenty female young adult albino Sprague-Dawley rats were administered F-179 to clipped areas on the back, five days per week for 13 weeks, at a dose of 0.001, 0.010, 0.050, 0.100 and 0.500 ml/kg/day. The site of application was occluded for six hours after administration of the test article. A sixth group of animals served as a control and was treated in the same manner as were the test article-treated animals, with the exception of the application of test article.

Animals were observed twice daily for viability and daily for signs of toxicity. Dermal irritation was evaluated once each day just prior to dosing, twenty-four hours after the fifth dose each week and again just prior to necropsy. Body weights were recorded weekly during the study. At the time of necropsy, fasted body weights and organ weights were determined, blood samples were collected for clinical pathology evaluation and selected tissues were collected for histopathological evaluation.

Under the conditions of this study, F-179 induced slight dermal irritation in males at a dose of 0.50 ml/kg and in females at doses of 0.10 and 0.50 ml/kg as evidenced by by microscopic histopathological changes in the skin.

Nine deaths (died on test or sacrificed moribund) occurred during the study in the 0.50 ml/kg dose group that were attributed to the dermal application of F-179.

Treatment related decreases in mean body weights were noted in the high dose group females during study weeks 5, 6, 9 and 10, and in males in the high dose group during weeks 6-13.

Systemic effects were observed in males and females at doses greater than 0.01 ml/kg that included: decreased red blood cell parameters, decreased platelet count, cellular depletion in the bone marrow; increased liver weights, liver-to-body and liver-to-brain weight ratios, hepatic congestion, necrosis and vacuolar change in the liver; decreased thymus weights, and thymic atrophy; and chronic inflammation in the thyroid glands. Treatment related changes noted in the clinical chemistry parameters included increased blood urea nitrogen (BUN), cholesterol, creatinine, serum glutamic oxalic transaminase (SGOT) and alkaline phosphatase values.

In addition, one incidence of thymic atrophy was noted in males in the 0.01 ml/kg dose group, and the mean platelet value was significantly lower in males in the 0.01 ml/kg dose group compared to the sham control group value.

Lung weights, lung-to-body weight and lung-to-brain weight ratios were increased in males and females at doses greater than 0.01 ml/kg. However, there were no histologic lesions that were attributed to the dermal application of F-179.

No other effects were observed in any of the other parameters evaluated that could be attributed to the dermal administration of F-179.

Under the conditions of this study, the dermal irritation no-observed-effect level (NOEL) for F-179 was determined to be 0.05 ml/kg for females and 0.10 ml/kg for males. The systemic NOEL for dermal exposure to F-179 was determined to be 0.001 ml/kg for males and 0.01 ml/kg for females.

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PROTOCOL NO. ATX-91-0012

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UBTL STUDY NO. 66152
PROTOCOL NO. ATX-91-0012

UBTL, INC.
520 WAKARA WAY
SALT LAKE CITY, UT 84108

QUALITY ASSURANCE STATEMENT

STUDY NO: 66152
PROTOCOL NO: ATX-91-0012

STUDY TITLE: NINETY (90) DAY DERMAL TOXICITY STUDY IN RATS ADMINISTERED TEST ARTICLE F-179

1. This study was inspected by the Quality Assurance Unit and the findings of the inspections were reported to management and to the Study Director on the dates given below.

2. Quality Assurance has reviewed this report and has determined that the methods and standard operating procedures are accurately described, and that the reported results accurately reflect the raw data. Any protocol or SOP deviations that are known to have occurred are stated in the report or in the raw data.

Phase Inspected	Date Inspected	Date Reported
Protocol	18 Feb 91	18 Feb 91
Dosing	18 Feb 91	18 Feb 91
	15 Mar 91	15 Mar 91
	22 Mar 91	22 Mar 91
	03 May 91	03 May 91
Test Article Records	18 Feb 91	18 Feb 91
Weighing	28 Feb 91	28 Feb 91
	25 Apr 91	25 Apr 91
Scoring	28 Feb 91	28 Feb 91
	15 Mar 91	15 Mar 91
	22 Apr 91	22 Apr 91
	03 May 91	03 May 91
Feed Weights	25 Apr 91	25 Apr 91
General Health Check	25 Apr 91	25 Apr 91
Observations (P.M.)	03 May 91	03 May 91
Necropsy	20 May 91	20 May 91
Draft Report/ Raw Data	27-29 May 92	
	1-3 Jun 92	04 Jun 92

Quality Assurance _____ Date _____

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UBTL STUDY NO. 66152
PROTOCOL NO. ATX-91-0012

NINETY (90) DAY DERMAL TOXICITY STUDY IN RATS ADMINISTERED TEST ARTICLE F-179

INTRODUCTION

OBJECTIVE

The objective of this study was to determine the systemic no-observed-effect level and dermal irritation associated with repeated dermal exposure to the test article for a period of 90 days.

TEST SYSTEM DESCRIPTION

A description of the test system is presented in the Protocol, Appendix A. Any known deviations from the protocol are described in Appendix D.

EXPERIMENTAL DESIGN

Five groups of twenty male and twenty female young adult albino Sprague-Dawley rats were administered F-179 dermally once daily, five days per week for 13 weeks, at a dose of 0.001, 0.010, 0.050, 0.100 and 0.500 ml/kg/day. The test article was applied to previously clipped sites on the backs of the animals. The site of application was occluded for a period of at least six hours following application of the test article. A sixth group of twenty male and twenty female rats served as a control. The backs of the control group animals were clipped and the occlusive wrap was applied daily, five days per week, for 13 weeks.

Study Design

Treatment	Dose (ml/kg)	Male	Female
Sham control	0.000	20	20
F-179	0.001	20	20
F-179	0.010	20	20
F-179	0.050	20	20
F-179	0.100	20	20
F-179	0.500	20	20

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The animals were observed twice daily for viability and once daily (p.m.) for signs of toxicity. Dermal irritation at the site of application was evaluated daily just prior to the application of the test article, twenty-four hours after the fifth application of F-179 and just prior to necropsy. Body weights were determined weekly during the study and just prior to necropsy. Feed consumption was determined weekly beginning study week 6.

At the time of necropsy, blood was collected for hematology and clinical chemistry evaluations, selected organs were weighed and tissues were collected and preserved in 10% neutral buffered formalin for later histopathological examination. Hematological and clinical chemistry analyses were performed at UBTL. The results of these analyses are found in Appendix B.

Details concerning the materials and methods used in this study are found in the Protocol and Amendments in Appendix A, and in Appendix F.

The tissues and organs collected for histopathological evaluation were sent to Colorado Histo-Prep Inc., Fort Collins, Colorado, where they were trimmed, processed, embedded, sectioned and stained with hematoxylin and eosin. The prepared slides were evaluated by Donald N. Kitchen, D.V.M., Ph.D., Colorado Pathology Services, Inc., Fort Collins, Colorado. The detailed results of the histopathological evaluation are found in Appendix G.

STUDY DATES

Animals received:	Jan 30, 1991
Test article use/Dosing initiated.	Feb 18, 1991
Test article use/Dosing ended:	May 23, 1991
Animal termination:	May 20-24, 1991

TEST ARTICLE IDENTIFICATION

A description of the test article is presented in the Protocol-Appendix A.

UBTL STUDY NO. 66152
PROTOCOL NO. ATX-91-0012

RAW DATA and SPECIMENS

The raw data and specimens generated as a result of this study, the original protocol, protocol amendments and the original final report will be maintained in the archives at UBTL, Inc., 520 Wakara Way, Salt Lake City, Utah, 84108. Raw data generated at Colorado Histo-Prep, Inc. and Colorado Pathology Services, Inc. will be maintained in their archives.

RESULTS AND DISCUSSION

Mortality

Ten animals either died on test or were sacrificed moribund during the study beginning study day 59 which included; one male in the 0.05 ml/kg dose group, seven males and two females in the high dose group (0.50 ml/kg). The deaths and moribund condition of the animals in the high dose group were considered to be related to the dermal application of F-179. The death of the animal in the 0.05 ml/kg dose group was considered to be related to injuries sustained while wrapped.

General Observations

The individual animal general observations are presented in Table 1B, Appendix B.

Treatment related findings noted during the study included: cold to touch, pale in color, lethargic, pale eyes, ears, nose and feet, labored breathing, ataxia, gasping and tremors. These findings were observed primarily in the high dose group and in those animals that died on test or were sacrificed moribund.

Lethargy was also observed in one animal in the 0.001 ml/kg dose group. The lethargy in this animal was considered to be related to the dehydration noted the previous day caused by a faulty lixit.

Yellow anogenital staining was also noted in treated animals only during the study with the highest incidence noted during study days 2-4. Only five animals were observed with anogenital staining on days other than 2-4. The anogenital staining was considered spurious and incidental unrelated to the dermal application of F-179.

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Other abnormal findings noted during the study included: broken tail, tape irritation, swollen preputial gland, shaving nick, torn toenail, red discharge from penis, aggressive behavior, swelling around eye, red staining around nose, ocular and red nasal discharge. Since these findings were noted sporadically and in low incidence, they were not considered to be test article related.

Findings observed in the male in the 0.05 ml/kg dose group that died on test (day 59) included swelling of front paws, cephalic and cervical regions; red nasal discharge and labored breathing. These findings were not considered to be test article related.

In addition to the daily observations, the skin at the site of application was evaluated once daily, six days per week, using a modified Draize scoring system. The results of these evaluations are discussed in Dermal Irritation.

Dermal Irritation

Mean daily dermal irritation scores for male and female rats are found in Table 1 and are graphically represented in Graphs 3 and 4. The individual animal dermal irritation scores are found in Tables 2B and 3B, Appendix B.

No dermal irritation was observed in the Sham control group.

Very slight dermal irritation was noted sporadically among groups administered F-179 which included very slight erythema, slight eschar and slight dried skin.

Since the dermal irritation occurred sporadically among treatment groups, and neither the incidence nor severity of the irritation was dose dependent, the grossly observed dermal irritation was not considered to be test article related.

Since very slight erythema was difficult to see at the application site due to the the dark brown staining of the test article,and the majority of the erythema noted during the study was scored on study day 16 by the same technician, the erythema scores on day 16 were considered to be in error and were discounted.

Body Weights

Mean body weights of male and female rats are found in Table 2 and are graphically represented in Graphs 1 and 2. The individual animal body weight data are found in Table 4B, Appendix B.

Significantly ($p<0.05$) lower and dose dependent ($p<0.01$) decreases in mean body weights were noted in the high dose group (0.50 ml/kg) females during study weeks 5, 6, 9 and 10, and in males in the high dose group during weeks 6-13. The decreased body weights are considered to be test article related.

Feed Consumption

The mean absolute feed consumption (g/animal/day) data is presented in Table 3 and individually in Table 5B, Appendix B. The mean relative feed consumption (g/kg/day) data is presented in Table 4 and individually in Table 6B, Appendix B.

Since statistically significant decreases were noted in body weights in females for two consecutive weeks beginning study Week 5, feed consumption data was collected beginning Week 6.

Statistically significant ($p<0.01$) decreases in absolute feed consumption was noted in males in the 0.05 ml/kg dose group during study week 7, and in the 0.5 ml/kg dose group during study weeks 7, 9, 11 and 12. Significantly ($p<0.05$) lower absolute feed consumption values were observed in females in the 0.001 ml/kg dose group during study week 8, in the 0.05 ml/kg group ($p<0.01$) during week 7, in the 0.10 ml/kg group ($p<0.01$) during week 8 and in the high dose group ($p<0.05$ & $p<0.01$)) during weeks 7-9.

When feed consumption values relative to body weight were compared, significantly ($p<0.05$) higher values were noted in males in the low dose group (0.001 ml/kg) during week 8, in the 0.01 ml/kg dose group during weeks 8, 9, and 11, and in the 0.05 and 0.10 ml/kg groups ($p<0.01$) during week 8. During week 7 the value was significantly ($p<0.01$) lower for the 0.05 ml/kg dose group compared to the sham control group value.

Significantly ($p<0.05$ & $p<0.01$) higher values were noted in females during week 6 in the 0.1 and 0.5 ml/kg dose groups. Significantly ($p<0.05$ & $p<0.01$) lower values were observed in the low dose group females

during week 8, in the 0.05 ml/kg group week 7, and in the 0.1 and 0.5 ml/kg dose groups during week 8 compared to the sham control group.

The decreased feed consumption in the high dose group correlated with the lower body weights and generally poor health status of the animals, and was considered to be related to the dermal application of F-179. Since there was no clear trends in the differences seen in the other treatment groups, the differences noted at doses less than 0.50 ml/kg were not considered to be treatment related.

Clinical Pathology

The summaries of hematology and clinical chemistry data are found in Tables 5 and 6. The details of the individual animal hematology data and clinical chemistry data are found in Tables 7B and 8B, Appendix B. UBTL historical control data is presented in Appendix E.

Hematology

Significantly ($p<0.05$ & $p<0.01$) decreased red blood cell (RBC) values were observed in males at doses less than 0.01 ml/kg, and decreased RBC values ($p<0.01$) were noted in females at doses less than 0.05 ml/kg compared to the sham control group values. Significantly ($p<0.05$ & $p<0.01$) lower hematocrit and hemoglobin values were also noted in males and females at doses less than 0.01 ml/kg compared to the sham control group values. A statistically significant ($p<0.01$) dose response relationship was noted between treatment groups in both sexes in the red blood cell p rameters.

Mean platelet values in males at doses less than 0.001 ml/kg and in females at doses less than 0.05 ml/kg were significantly ($p<0.01$) lower than the sham control group value. A significant ($p<0.01$) dose response relationship was noted between treatment groups.

Significantly ($p<0.05$) increased mean white blood cell counts were noted in females in the 0.01 and 0.05 ml/kg dose groups. Since these values were within the range of normal values for female Sprague-Dawley rats of this age and there was no dose response relationship, the differences were not considered to be test article related.

UBTL STUDY NO. 66152
PROTOCOL NO. ATX [illegible]-001[illegible]

Clinical Chemistry

Treatment related changes were noted in males and females in several clinical chemistry parameters which included blood urea nitrogen (BUN), creatinine (CRT), serum glutamic oxalic transaminase (SGOT), alkaline phosphatase (ALK PHOS), and cholesterol.

Significantly ($p<0.01$) increased BUN values were noted in males at doses greater than 0.01 ml/kg and in females at doses greater than 0.05 ml/kg.

Mean cholesterol values were significantly increased ($p<0.01$) in males and females at doses of 0.05, 0.10 and 0.50 ml/kg compared to the sham control group values.

Mean creatinine values in males and females in the 0.50 ml/kg dose group and in females in the 0.05 and 0.10 ml/kg dose group were significantly ($p<0.05$) higher than the sham control group values.

Significantly increased SGOT values were noted in males and females in the 0.50 ml/kg dose group. Mean alkaline phosphatase value in females in the high dose group was significantly ($p<0.01$) higher than the sham control group value.

Statistically significant ($p<0.05$) differences were noted in several other parameters that were not considered to be test article related. These differences included: increased glucose in females in 0.10 and 0.50 ml/kg dose group; increased total protein value in females in 0.10 ml/kg group; decreased albumin value in males in 0.10 ml/kg group; increased sodium values in males in 0.10 ml/kg dose group and in females at doses $\geq$ 0.01 ml/kg; increased phosphorus value in males in the 0.1 ml/kg dose group; and increased triglyceride values in males in 0.05 and 0.10 ml/kg groups and in females in the 0.01 ml/kg dose group. Since there was no clear dose dependent relationship in these parameters among treatment groups, and the mean glucose, total protein, albumin and phosphorus values were within the range of historical control values, the differences were not considered to be test article related. Although the sodium and triglyceride values were outside the range of historical control values, the changes were not dose dependent, therefore the differences were considered spurious.

Gross Pathology

The summary of the gross pathology findings is presented in Table 9B, Appendix B.

At the time of necropsy, treatment-related findings were noted in the skin which included brown staining at the test site. This finding represented a continuation of the in-life dermal findings.

Non-dermal findings noted that were not considered to be treatment related included: dark red cervical lymph nodes, dried red material around eyes, herniated diaphragm with protruding liver, mottled lungs, enlarged heart, small mass on ear, clear fluid in abdominal and thoracic cavity, pale ovaries, red foci on lungs, red fluid filled mass on ovary, and right kidney with small hole (pit) surrounded with yellow material.

Since these non-dermal findings occurred sporadically and in low incidence among the treated groups including the sham control group, they are not considered to be treatment-related.

Findings noted in animals that died on test or were sacrificed moribund included: small thymus, pale brain, white pituitary, discolored thymus with multiple small dark red masses, pale lungs, pale liver, multiple foci on testes, enlarged heart and right atrium, small testes, fluid filled peritoneum and thoracic cavity, small mass on right apical lobe of lung, enlarged dark red mesenteric lymph nodes, liquid and gas filled intestinal track, pale kidneys, blackened areas on liver, purple testes with purple foci, red brown testes, clear to yellow fluid filled seminal vesicles, and red mottled and enlarged cervical lymph nodes. The deaths and moribund condition of these animals were considered to be treatment related. With the exception of the findings in the thymus, these findings were likely secondary effects related to the moribund condition of these animals.

Small thymus and discolored thymus with multiple small dark red masses were noted in treated animals at doses greater than 0.001 ml/kg. The thymic findings were considered to be related to the dermal application of F-179.

Findings observed in the animal that died on test in the 0.05 ml/kg dose group included: sunken eyes, dried material around nose, swollen head, red fluid around brain and pituitary, mottled lungs, distended stomach, slightly autolized tissues, fluid filled thoracic cavity, and severe edema in dermis in thoracic, abdominal and cervical regions. These findings were not considered to be test article related.

Terminal Body Weight and Organ Weights

The summary of mean terminal body weights and mean absolute organ weights is found in Table 7. Mean organ weights relative to body weight and to brain weight are found in Table 8. The individual animal terminal body weights, absolute organ weights and individual organ weights relative to body weight and brain weight are found in Tables 10B and 11B, Appendix B. UBTL historical control data is presented in Appendix E.

Significantly ($p<0.05$) lower mean terminal body weights were observed in males and females in the 0.50 ml/kg dose group compared to the sham control group value. Mean absolute brain weight in males in the high dose group was significantly ($p<0.05$) lower than the control group value. The mean brain weight in females in the high dose group was also notably lower, although not statistically different from the control group value. However, when brain weights are compared relative to term body weights, no significant differences were noted. The decreased brain weights corresponded to the lower body weights. The decreased terminal body weights were considered to be treatment related.

Treatment related changes in absolute organ weights and ratios were also noted in liver, thymus and lungs in both males and females compared to the sham control group. These changes included: significantly ($p<0.01$) increased mean liver and lung weights at doses of 0.05, 0.10 and 0.50 ml/kg (lungs in males in 0.50 ml/kg group not significantly different); and significantly ($p<0.01$) decreased thymus weights in males and females in the high dose group (0.50 ml/kg). When organ-to-body weight and organ-to-brain weight ratios are compared, the differences remain significantly different. Significantly ($p<0.01$) increased liver-to-body weight, liver-to-brain weight, lung-to-body and lung-to-brain weight ratios were observed in males and females at

doses of 0.05, 0.10 and 0.50 ml/kg. Significantly ($p<0.05$) decreased thymus-to-body weight and thymus-to-brain weight ratios were also noted in both sexes at the high dose of 0.50 ml/kg compared to the sham control group. Significant ($p<0.01$) dose response relationships were also noted among treatment groups in all these parameters. These changes were considered to be treatment related.

Other differences noted in organ weights and ratios that were statistically significant ($p<0.05$) included: increased spleen weights, spleen-to-body weight and spleen-to-brain weight ratios in males in the 0.05 and 0.10 ml/kg dose group; decreased kidney weight in males in 0.50 ml/kg group and increased kidney-to-brain weight ratio in males in the 0.10 ml/kg group; increased heart weight in males in 0.10 ml/kg group, increased heart-to-body and heart-to-brain weight ratio in males in 0.05 and 0.10 ml/kg groups and increased heart-to-body weight ratio in females in 0.50 ml/kg dose group. Since there were no treatment related histopathological findings in these tissues (with the exception of the secondary effects noted in the heart of 3 males in 0.5 ml/kg group), and the values were within the range of normal values for Sprague-Dawley rats of this age, the differences were not considered to be treatment related.

No significant differences were noted in any other mean organ weights, organ-to-body or organ-to-brain weight ratios between the sham control and the F-179 treated groups.

Histopathology

Details concerning the histopathological evaluation of tissues for this study are found in the HISTOPATHOLOGY REPORT, Appendix G.

Histopathological evaluation of selected tissues was conducted for the control and high dose group animals; and gross lesions, treated skin, lungs, liver, adrenal glands, thymus, bone (sternum), bone marrow and thyroids from all animals.

Lesions observed at the dermal application site included: acanthosis (trace), epidermal crusting (trace to mild), hyperkeratosis (trace), subacute inflammation (trace) and ulceration (moderate). Trace amounts of hyperkeratosis was observed at all dose levels in males which included 12 of 20 sham control, 17 of 19 low dose (0.001 ml/kg), 14 of 20 0.01 ml/kg dose, 16 of 20 in the 0.05 and 0.10 ml/kg dose groups, and 20 of 20 in the high dose group (0.50 ml/kg). No hyperkeratosis was noted in females in the sham control or low dose groups. Trace amounts were noted in females which included 1 of 20 in the 0.01 and 0.05 ml/kg dose groups, 8 of 20 in the 0.10 ml/kg group and 15 of 20 in the high dose group (0.50 ml/kg). Trace amounts of acanthosis were observed in 15 of 20 males in the 0.50 ml/kg dose group. Epidermal crusting was noted in 2 of 20 males in the 0.10 ml/kg group, 15 of 20 males in the high dose group, and 1 of 20 females in the high dose group. Subacute inflammation and ulceration were noted in one female in the 0.50 ml/kg dose group. The hyperkeratosis in females in 0.10 and 0.50 ml/kg dose groups; and acanthosis and epidermal crusting in high dose group males was considered to be related to the dermal application of F-179.

Treatment related histopathological changes observed in non-dermal tissues included: cellular depletion of the bone marrow; hepatic congestion, necrosis and vacuolar change; thymic atrophy and necrosis; and chronic inflammation in the thyroid glands (lymphocytic thyroiditis). These changes were observed primarily in the 0.10 and 0.50 ml/kg dose groups. Hepatic changes and thymic atrophy were also noted in a few animals from 0.05 ml/kg dose group. Thymic necrosis was observed in one rat in the high dose group. Thymic atrophy was also observed in a male in the 0.01 ml/kg dose group.

Findings noted less frequently in the 0.10 and 0.50 ml/kg dose groups included: Zenker's degeneration, cardiac thrombosis and vacuolar change in the heart; congestion of cervical lymph nodes; tubular degeneration and hemorrhage in the testis; and vacuolar change in the prostate and pituitary gland. These lesions were considered secondary responses to the moribund condition of the animals with these findings.

Other findings observed included: mineralization and adrenal cortical vacuolar change in the adrenal gland; congestion in various tissues; a renal infarct, a renal cyst, inflammation, hyaline casts or tubular degeneration; interstitial pneumonia, edema, the presence of alveolar macrophages, or ganulomatous inflammation in the lung; a cyst in the mesenteric lymph node; a ovarian cyst; chronic inflammation in the prostate gland; a pituitary cyst, chronic inflammation of the urinary bladder and dilatation of the uterus. These findings were considered spontaneous or naturally occurring lesions often seen in Sprague-Dawley rats and unrelated to the dermal application of F-179.

Based on the histopathological evaluation of tissues from rats dermally administered F-179 for 13 weeks, F-179 induced mild epidermal irritation at the dermal application site in males and females in the 0.50 ml/kg dose group and in females in the 0.10 ml/kg dose group. Systemic effects were observed at doses greater than 0.001 ml/kg in males and greater than 0.01 ml/kg in females that included cellular depletion in the bone marrow; hepatic congestion, necrosis and vacuolar change; thymic atrophy;and chronic inflammation in the thyroid glands. The only systemic lesion noted in males in the 0.01 ml/kg dose group was the one incidence of mild thymic atrophy.

SUMMARY AND CONCLUSIONS

Under the conditions of this study, F-179 induced slight dermal irritation in males at a dose of 0.50 ml/kg and in females at doses of 0.10 and 0.50 ml/kg as evidenced by by microscopic histopathological changes in the skin.

Nine animals either died on test or were sacrificed moribund during the study as a result of the dermal application of F-179 that included seven males and two females in the high dose group (0.50 ml/kg).

Treatment related findings were noted in animals in the high dose group during the study that included: cold to touch, pale in color, lethargic, pale eyes, ears, nose and feet, labored breathing, ataxia, gasping and tremors. These findings were observed primarily in those animals that died on test or were sacrificed moribund.

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Treatment related decreases in mean body weights were noted in the high dose group (0.50 ml/kg) females during study weeks 5, 6, 9 and 10, and in males in the high dose group during weeks 6-13.

Treatment related decreases were observed in red blood cell, hematocrit, hemoglobin and platelet values in males and females in the 0.05, 0.10 and 0.50 ml/kg dose groups. Decreased platelet values were also noted in males in the 0.01 ml/kg dose group. Cellular depletion of the bone marrow was observed microscopically in animals in the 0.10 and 0.50 ml/kg dose groups.

Changes noted in clinical chemistry parameters included: increased BUN values in males at doses greater than 0.01 and females at doses of 0.10 and 0.50 ml/kg; increased creatinine values in males and females in the 0.50 ml/kg dose group and in females in the 0.05 and 0.10 ml/kg dose groups; increased cholesterol values in males and females at doses greater than 0.01 ml/kg, increased SGOT values in males and females in the 0.50 ml/kg dose group; and increased mean alkaline phosphatase value in females in the high dose group. There were no findings noted in the kidneys that correlated with the increased BUN and creatinine values. The increased SGOT and alkaline phosphatase values in the high dose group are considered to be related to the generally poor health status of several of the high dose group animals at the time of necropsy.

Treatment related changes noted in the liver included increased mean liver weights, liver-to-body weight, and liver-to-brain weight ratios in males and females at doses greater than 0.01 ml/kg. Congestion, necrosis and vacuolar change were observed microscopically at doses of 0.10 and 0.50 ml/kg.

Treatment related effects were also noted in the thymus that included decreased thymus weights, thymus-to-body weight and thymus-to-brain weight ratios in males and females in the 0.50 ml/kg dose group. Thymic atrophy was also noted histopathologically in some animals in the 0.10 and 0.50 ml/kg dose groups.

Lung weights, lung-to-body weight and lung-to-brain weight ratios were increased in males and females at doses greater than 0.01 ml/kg. However, there were no histologic lesions that were attributed to the dermal application of F-179.