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DATA EVALUATION RECORD

Study Type: 21-Day Dermal Toxicity - Rabbits Guideline: 82-2

MRID No.: 417994-06 DP Barcode:D164205 SUBMISSION#: 5395637

Caswell No.: 454E HED Project No.: 1-1237

Test Material: Sulfluramid (96.6% linear and 3.4% branched isomeric mixture) MRD-89-472

Synonym: N-Ethyl perfluoro-octanesulfonamide

Dosages: 0, 100, 300, and 1000 mg/kg/day

Test Animals: New Zealand White Rabbits

Sponsor: Griffin Corporation, Valdosta, Georgia 31603

Study Number: 147209

Testing Facility: EXXON Biomedical Sciences, Inc., East Millstone, New Jersey

Title of Report: Repeated Dose Dermal Study in Rabbits with Sulfluramid MRD-89-472 (Sulfluramid 100%)

Author: Gary W. Trimmer Report Issued: October 8, 1990

Conclusions:

Repeated topical application of sulfluramid (96.6% linear and 3.4% branched isomeric mixture; MRD-89-472) at 100, 300, 1000 mg/kg dose levels on the shaved skin of five rabbits/sex/group for a period of 21 days produced the following major treatment-related effects:

- o Increased mortality and emaciation in the 1500 mg/kg dose group.
- o Reduction of the mean body weight and mean food consumption values in the 300 and 1500 mg/kg dose groups.
- o Elevation of blood urea nitrogen, bilirubin, and chloride values and a decrease of calcium and sodium values in the 300 and 1500 mg/kg dose groups.

- o Increased incidence of tan striations on the liver in the 300 and 1500 mg/kg dose groups.

- o Increased incidence of hepatocellular effects (vacuolation in the centrilobular and midzonal locations, centrolobular necrosis, and multiple and variable-sized foci necrosis) in the 300 and 1500 mg/kg dose groups.

- o Increased incidence of testicular and epididymal atrophy, aspermia in the epididymides, and seminal vesicle distension in the 300 and 1500 mg/kg males.

No treatment-related dermal effects were noted. The systemic NOEL is 100 mg/kg/day and the systemic LOEL is determined to be 300 mg/kg/day for both sexes based on the treatment-related effects including hematological, clinical chemistry, and gross and microscopic findings listed above.

Since no stability data of the test material was provided, this study is currently classified as core-supplementary. This study may be upgraded if the registrant provide the stability data of the test material.

Core Classification:

Core-supplementary. This study dose not satisfy the guideline requirements (82-2) for a 21-day Dermal Toxicity Study in rabbits. This study is upgradable after satisfactory review of the requested information.

Compliance Statements:

Signed statements of Confidentiality Claim, compliance with GLP, and Quality Assurance were provided.

Study Title: Repeated Dose Dermal Study in Rabbis with Sulfluramid MRD-89-472 (Sulfluramid 100%)

Authors: Gary W. Trimmer

Study Number: 147209

Testing Facility: EXXON Biomedical Sciences, Inc., East Millstone, New Jersey

A. OBJECTIVE

This 21-day dermal toxicity study was conducted to assess the dermal irritation potential and systemic toxicity of sulfluramid (MRD-89-472; 96.6% linear and 3.4% branched isomeric mixture) following repeated topical application at 100, 300, 1000 mg/kg/day dose levels.

B. MATERIALS AND METHODS

The in-life and necropsy phases and the histopathologic evaluations of this study were conducted at the Toxicology Laboratory of the EXXON Biomedical Sciences, East Millstone in New Jersey.

Test Material

Physical Description: White powder (96.6% linear and 3.4% isomeric mixture); Batch No.: AN90247 Exxon ID # MRD-89-472
Vehicle: Reverse osmosis water
Storage Conditions: Room temperature
Source: Griffin Corporation, Valdosta, Georgia

Test Animals

Species: New Zealand White Rabbits
Source: Hare Marland, Hewitt, New Jersey
Number of Animals: 54 animals received and 20 males and 20 females were selected for study
Age: 13 to 14 weeks old at study initiation
Mean Starting Weights: ♂ = 2580 - 3000 g; ♀ = 2430 - 2860 g
Caging: Individual suspended stainless steel wire cage
Acclimation Period: Twenty-six days
Feed: Agway Certified Diet RCA Rabbit pellets) and water ad libitum.

Environmental Parameters

Ambient Temperature: 65 - 70°F; Relative Humidity: 40-60%;
Dark/Light Cycle: 12 hours; Room Air Exchanges: not given

Group Arrangement

The test animals were housed individually. They were acclimated for 26 days and observed for clinical signs abnormalities. Forty-eight hours prior to topical application the dermal fur (± 10% of body surface of each rabbit) was clipped. Elizabethan collars were placed around the rabbits necks at this time to acclimate rabbits to wearing collars. The basis of dose levels used in this study was not provided. The rats were randomly allotted to one of the following groups:

Groups	Dose Level (mg/kg)	No. of Animals Males/Females
Control[a]	0	5/5
Low Dose	100	5/5
Mid Dose	300	5/5
High Dose	1000	5/5

a = osmosis water at 2 ml/kg

Test Material Preparations and Analysis

It was noted that the sponsor was responsible for the stability of the test material used in this study. This information was not provided in the study report.

Test Material Application

The test material was applied (fresh and undiluted on a mg/kg basis) daily to the shaved backs of the test animals, five days a week for three consecutive weeks. A moistened gauze patch (one ml of water per gram of test material administered) was placed on the shaved skin and this gauze was secured with a tape. The animal was then wrapped in an impervious plastic sleeve to prevent evaporation. The binders and patches were left in place for six hours daily. After the 6-hour exposure period, the wraps were removed and the application sites were wiped with water-moistened gauze pads. The back and the flanks of the animals were clipped once a week. The amount of test article was adjusted based on the most recent weekly body weight data. The controls were administered reverse osmosis water (2 ml/kg) under the same experimental conditions.

Clinical Observations

All rabbits were checked for mortality twice daily. Clinical signs were observed at least once daily. The application sites were examined for signs of erythema, edema, desquamation and other adverse dermal reactions immediately prior to dosing on days 1, 4, 7, 11, 18, and 21. Dermal scores were also recorded prior to dosing on days 2, 3 and 8. The Draize scale was used.

Individual Body Weights and Food Consumption

Individual body weights were recorded prior to start of study, on first day of dosing (day 0) and weekly thereafter. Food consumption was recorded weekly throughout the study.

Clinical Pathology Evaluations

At terminal sacrifice blood samples were drawn from the auricular artery of all animals after an overnight fast. The checked (√) hematology and clinical chemistry parameters were evaluated in this study as per required guideline:

a. Hematology:

√Erythrocyte count (RBC)
√Hemoglobin (HB)
√Hematocrit (HCT)
√Differential WBC count
√Total leukocyte count (WBC)
√Platelet count

b. Clinical Chemistry

√Total Bilirubin
√Creatinine
√Total Protein
√Aspartate aminotransferase (ASAT)
√Alanine aminotransferase (ALAT)
√Blood Urea Nitrogen
√Glucose
√Potassium
√Chloride
√Phosphorus
√Calcium
√Sodium
√Albumin

c. Urinalysis

No urinalysis was conducted in this study.

Pathology:

a. Gross Macroscopic Evaluations

All animals were sacrificed and necropsied at the end of the test period (day 21). The animals were anesthetized by sodium pentobarbital injection and killed by exsanguination. The gross macroscopic examinations included physical examination of all external surfaces, all orifices, and all internal body cavities with their associated organs. All guideline-required organs, the brain, liver, kidneys, testes, epididymides, seminal vesicles, ovaries, spinal cord (cervical and thoracic), sciatic nerve, treated and untreated skin, and any gross lesions, were harvested and fixed in 10% neutral buffered formalin for further histopathological evaluations. The above organs were also harvested from found-dead and moribund-sacrificed animals

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b. Organ Weights

All guideline-required organs weights, the liver, kidneys, ovaries and testes, were recorded at terminal necropsy.

c. Histopathological Evaluations

All fixed tissues and organs of the controls and high dose groups as well as from found-dead and moribund-sacrificed animals were processed, sectioned, and stained with hematoxylin and eosin. The liver, testes epididymis, nerve and gross lesions of the low-dose were also evaluated histopathologically.

C. Statistical Analysis of the Data

A number of statistical analyses were used and they are described in Appendix A.

D. RESULTS

Mortality

Four high-dose males and four high-dose females died before terminal necropsy. One male died on day 14, one female on day 15, two males and one female on day 16, one male and one female on day 17, and one female on day 21 of the study period (Appendix B). Because of these mortalities, the terminal necropsy was conducted on day 21 instead of on day 22 of the study.

Clinical Signs

The summary of pertinent clinical signs observation data is presented in Appendix B. Emaciation associated with little sign of stool and decreased food consumed were evident in the treated rabbits. These observations increased with increasing dose and occurred earlier in higher doses. In the high-dose group, emaciation, little sign of stool and decreased food consumption were observed beginning on days 7, 6, and 3, respectively. These observations persisted through study termination. These findings are considered to be related to treatment.

Body Weights

The summary mean body weight data are presented in Appendix C. The mean body weights of the mid- and high-dose groups of both sexes were significantly decreased as compared to the controls. Statistically significant decrease started on day 7 of study for mid-dose females and high-dose males and females, and on day 14 of study for the mid-dose males. The body weight reduction of the mid- and high-dose groups are considered to be related to treatment.

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Food Consumption

The food consumption data are presented in Appendix D. Food consumption reductions were evident in all treated groups as compared to the controls. A linear trend was also evident. The food consumption reductions of the mid- and high-dose rabbits (except for weeks 1 and 3 of the mid-dose males) were statistically significant. These food consumption reductions were reflected in the mean body weights in the mid- and high-dose groups (see discussion above). The food consumption in the mid- and high-dose groups are considered to be related to treatment.

Application Site Gross Changes

Gross dermal changes were minimal for the treated groups. Only three animals were noted with very slight erythema, one control on day 18, two high-dose group (one on day 1 and another on days 3 and 4 (p. 45-49 of the study report). Pustules and the resulting eschar seen in the controls were probably the result of mechanical friction of a combination of occlusive wrapping with the moist gauze and were not the result of reversed osmosis water itself. None of the skin changes observed were related to treatment.

Hematology Data

The summary hematology data are presented in Appendix E. The white blood cell count were decreased in the treated groups in both sexes. Except for the mid-dose females, this decrease was not statistically significant. A slight increase in the red blood cell count (except the high-dose males) and a slight decrease in the platelet count (except low-dose females) was noted in the treated groups as compared to the control. There was no evidence that these hematological changes were related to treatment.

Clinical Chemistry Data

Appendix F showed a linear dose-related increase of blood urea nitrogen, bilirubin, and chloride values and a decrease of calcium and sodium values were noted in both sexes. The changes in blood urea nitrogen in the mid- and high-dose females, calcium in the mid- and high-dose males, and the chloride in the mid- and high-dose males and females were statistically significant compared to respective controls. Other changes did not appear to be related to treatment.

Organ Weights and Organ Weight Ratios

The mean organ weights and mean organ/body weight ratios are given in Appendices G and H. The absolute kidney weights in the treated females were decreased (only the mid-dose females were statistically significant). The relative kidney weights in the treated rabbits of both sexes were increased but only the mid- and high-dose females were statistically significant. The absolute liver weights were decreased and the relative liver weights were slightly increased in the treated rabbits. Only the absolute liver weight decrease in of the mid-dose female was statistically significant. The absolute and relative ovary weights of the treated females were decreased but only the relative ovary weight of the high-dose females was statistically significant. The absolute and relative testes weights were decreased in the treated males but they were not statistically significant. The testes weight reduction in the high-dose and probably in the mid-dose males appears to be related to treatment because increased small testes was noted in the high-dose males during necropsy and the increased incidence of testicular atrophy was noted in the mid- and high-dose males during histopathological evaluations (see discussion below). The other organ weights differences discussed above are not considered to be related to treatment, but rather the result of significant body weight reductions noted in the mid- and high-dose groups.

Gross Pathology Evaluations

The summary of pertinent gross findings are as follows:

Findings	0 mg/kg	100 mg/kg	300 mg/kg	1500 mg/kg
	M/F	M/F	M/F	M/F
Pustules/Dose Site	4/2	0/0	0/0	0/0
Emaciation	0/0	0/1	2/5	5/5
Liver/tan stripes	0/0	1/0	3/1	2/2
Lung discoloration	0/0	0/0	0/0	3/3
Ingesta compact in Cecum	0/0	0/0	0/0	3/3
Uterus: distended and fluid-filled	na/2	na/0	na/0	na/0
Ovaries small	na/0	na/0	na/0	na/3
Small testes	0/na	0/na	1/na	3/na

M/F = Males/Females; na = not applicable

Increased incidence of emaciation and liver tan striations was noted in the mid- and high-dose groups. Increased incidence of small testes and compact ingesta in the cecum were noted in the high-dose group. These observations appear to be related to treatment. Increased incidence of lung discoloration in both sexes and small ovaries in the high-dose group appears to be secondary because no compound-related microscopic changes were evident. These changes are probably due to the poor physical condition and the significant body weight decrease.

Histopathology Evaluations

Histopathological findings are summarized in Appendix I. Treatment-related microscopic changes of the liver were noted in the mid- and high-dose females such as hepatocellular vacuolation in the centrilobular and midzonal areas. Treatment-related centrolobular necrosis of the liver occurred in one high-dose male and multiple and variable-sized foci necrosis in two mid- and three high-dose females. It is unclear whether these liver findings are related to the slight liver weight decrease noted above.

Testicular atrophy was observed in three mid- and in four high-dose males. Findings associated with the males sex organ included increased incidence of aspermia in the epididymis and epididymal atrophy both found in one mid-dose and in four high-dose males, and seminal vesicle distension in one mid-dose and in three high-dose males. Increased incidences of these findings found in the mid- and high-dose males are judged to be related to treatment.

All other histopathological findings are considered to be unrelated to treatment, because the incidence and severity observed in the treated groups were comparable with the controls.

E. Conclusions:

Repeated topical application of sulfluramid (96.6% linear and 3.4% branched isomeric mixture; MRD-89-472) at 100, 300, 1000 mg/kg dose levels on the shaved skin of five rabbits/sex/group for a period of 21 days produced the following treatment-related increase (↑) or decrease (↓) of the following parameters:

Parameters		0 mg/kg	100 mg/kg	500 mg/kg	1500 mg/kg
Mortality	↑				♂,♀
Emaciation	↑			♂,♀	♂,♀
Body Weight & Food Intake	↓			♂,♀	♂,♀
Total Bilirubin	↑			♂,♀	♂,♀
Blood Urea Nitrogen	↑			♂,♀	♂,♀
Serum Calcium and Sodium	↓			♂,♀	♂,♀
Serum Chloride	↑			♂,♀	♂,♀
Compact Ingesta in Cecum	↑				♂,♀
Liver: Tan Striations	↑			♂,♀	♂,♀
Liver Vacuolation	↑			♂,♀	♂,♀
Liver Necrosis	↑			♀	♂,♀
Small Testes	↑				♂
Testicular Atrophy	↑			♂	♂
Epididymal Atrophy	↑			♂	♂
Aspermia in Epididymides	↑			♂	♂
Seminal Vesicle Distention	↑			♂	♂

No treatment-related dermal effects were noted. The systemic NOEL is 100 mg/kg/day and the systemic LOEL is determined to be 300 mg/kg/day for both sexes based on the treatment-related effects including hematological, clinical chemistry, and gross and microscopic findings listed above. Since no stability data of the test material was provided, this study is currently classified as core-supplementary. This study may be upgraded if the registrant provides the stability data of the test material.

Core Classification: Core-supplementary. This study is upgradable after satisfactory review of the requested information.

LIST OF APPENDICES

APPENDIX A: Statistical Analysis (Copied from p. 21 of the study report)

APPENDIX B: Summary Clinical Sign Observations (Derived from p. 32 - 41 of the study report)

APPENDIX C: Mean Body weights in Grams (Copied from p. 42-44 of the study report)

APPENDIX D: Food consumption data-mg/animal/day (Copied from p. 30-31 of the study report)

APPENDIX E: Summary Hematology Data (Derived from p. 50-51 of the study report)

APPENDIX F: Clinical Chemistry Data (Copied from p. 52-54 of the study report)

APPENDIX G: Summary of Pertinent Mean Organ Weights Data (Copied from p. 56 of the study report)

APPENDIX H: Summary of Percent Mean Organ/Body Weights Data (Copied from p. 57 of the study report)

APPENDIX I: Summary Microscopic Findings (Derived from p. 139 of the study report)

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Sulfluramid

Page_____ is not included in this copy.

Pages 12 through 22 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

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