8-1-92

009642

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

AUG 0 1 1992

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Review of Seven Toxicology Studies with Sulfluramid

TO: Phillip Hutton/Michael Mendelsohn PM-18
RD (H7505C)

FROM: David S. Liem, Ph.D. David Liem 7/27/92
Section II, Toxicology Branch II/HED (H7509C)

THROUGH: K. Clark Swentzel, Section Head K. Clark Swentzel 7/27/92
Section II, Toxicology Branch II/HED (7509C)
and
Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II/HED (H7509C) M van Gemert 7/30/92

MRID#: 418184-01,-04,-05,-06,-07,-08 and -09

DP Barcode#: D164205 Caswell No.:454E HED Project No.: 1-1237

ACTION REQUESTED

To review the following toxicology studies with sulfluramid submitted by Griffin Corporation:

1. A 90-Day Subchronic Dietary Toxicity Study in Dogs with Sulfluramid (MRID# 418184-01)

2. A 90-Day Subchronic Dietary Toxicity Study in Rats with Sulfluramid MRD-89-472 (MRID# 417994-05)

3. Repeated Dose Dermal Study in Rabbits with Sulfluramid MRD-89-472 (Sulfluramid 100%) (MRID# 417944-06)

4. Developmental Toxicity Study in Rabbits with Sulfluramid (MRID# 417994-08)

5. Developmental Toxicity Study in Rats with Sulfluramid (MRID#417994-09)

6. Acute Dermal Toxicity Study of Harness in New Zealand White Rabbits (MRID#417994-07)

7. Acute Inhalation Toxicity Study in Rats with sulfluramid (MRID#417994-04)

EVALUATION RESULTS:

1. A 90-Day Subchronic Dietary Toxicity Study in Dogs with Sulfluramid (MRID# 418184-01)

Test Material: Sulfluramid (96.5% linear and 3.5% branched isomers) - (Batch # AN90247)

Test Animal: Beagle Dogs

Dosages: 0 , 33, 100, 500 ppm, and 1500 ppm (20 mg/kg/day)

Conclusions: Oral administration of sulfluramid (96.6% linear and 3.4% branched isomeric mixture - MRD-89-472) in dogs via the diet at 33 ppm, 100 ppm, and 500 ppm) and in capsular form at 20 mg/kg/day (initially 1500 ppm in the diet) for varying times up to 103 days produced the following major effects:

- o Increased mortality in the 1500 ppm:20 mg/kg/day males.
- o Reduction of body weight in the 500 ppm and 1500 ppm: 20 gm/kg/day groups
- o Increased liver weight in the 500 ppm and 1500 ppm: 20 gm/kg/day males
- o Increased blood urea nitrogen in the 500 ppm and 1500 ppm: 20 gm/kg/day groups
- o Increased renal hyperemia and nephrosis in the 1500 ppm: 20 mg/kg/day males
- o Reduction of epididymides and testes weights in the 500 ppm and 1500 ppm:20 gm/kg/day groups
- o Increased epididymal and testicular lesions affecting the seminiferous tubules of the testes of the 100 ppm, 500 ppm, and 1500 ppm:20 mg/kg/day dose groups.
- o Reduced percent motile sperm, and the reduction of epididymal sperm and testicular spermatid concentration of the 500 ppm and 1500 ppm: 20 mg/kg/day dose groups.

The systemic NOEL is 33 ppm. The LOEL is 100 ppm based on the increased epididymal and testicular lesions. The doses employed in this study were sufficient to produce compound-related effects. Sulfluramid appears to be a direct acting testicular toxin in the dog with primary effect on the late spermatids and possibly Sertoli cells.

CLASSIFICATION: Core-Minimum. This study satisfies the guideline requirements (82-1) for a 90-day Subchronic Feeding Toxicity Study in dogs.

2. A 90-Day Subchronic Dietary Toxicity Study in Rats with Sulfluramid (MRD-89-472) (MRID# 417994-05)

Test Material: Sulfluramid (96.6% linear and 3.4% branched isomers) - MRD-89-472 (Batch #I)

Test Animal: CDBR Sprague-Dawley Rats

Dosages: 0, 10, 50, and 150 ppm

Conclusions:

Sulfluramid (96.6% linear and 3.4% branched isomeric mixture - MRD-89-472) was fed in the diet of Sprague-Dawley rats at dose levels of 0, 10, 50, and 150 ppm for a period of 90 days. Treatment-related effects are as follows:

- o Increased mortality in the 150 ppm rats (6♂ and 4♀ died prior).
- o Increased incidence of agitation, convulsions, hyperactivity, and emaciation in the 150 ppm dose groups.
- o Reduced body weight and food intake in the 150 ppm dose groups.
- o Increased absolute liver weight and liver/body weight ratio in the 50 ppm and 150 ppm dose groups.
- o Depression of red blood cell, hematocrit, and hemoglobin in the 150 ppm dose groups.
- o Elevation of alkaline phosphatase and bilirubin in the 150 ppm males and females and alanine aminotransferase in the 150 ppm females.
- o Increased incidence of gross abnormalities in the 150 ppm dose rats (emaciation, fur staining, liver discoloration, thickened liver, abnormal GI tract contents, dark areas on the stomach, and undescended testes in the males).
- o Increased incidence of centrilobular hepatocellular hypertrophy and hepatocellular vacuolation in the 50 ppm and 150 ppm rats.

The NOEL for Sulfluramid 96.6% linear and 3.4% branched isomeric mixture (MRD-89-472) was determined to be 10 ppm, when fed in the diet of rats for period of 90 days. The LOEL is 50 ppm based on body weight, food consumption, hematology, clinical chemistry, organ weight, and histo-pathological findings listed above.

CLASSIFICATION: Core-Minimum. This study satisfies the guideline requirements (82-1) for a 90-day Subchronic Feeding Toxicity Study in rats.

3. Repeated Dose Dermal Study in Rabbits with Sulfluramid MRD-89-472 (Sulfluramid 100%)

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

Test Animals: New Zealand White Rabbits

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

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 per 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 provides 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.

4. Developmental Toxicity Study in Rabbits with Sulfluramid (MRID#417994-08)

Test Material: Sulfluramid (96.6% linear and 3.4% branched isomeric mixture); Lot #AN-90247

Test Animal: New Zealand Rabbit

Dosages: 0, 0.1, 0.5 and 1.5 mg/kg/day

CONCLUSIONS: Based on the results of this study, administration of Sulfluramid (96.6% linear and 3.4% branched isomeric mixture; Lot no. #AN-90247) at dose levels of 0.1, 0.5 and 1.5 mg/kg/day from day 6 to day 19 of gestation did not produce any treatment-related maternal and developmental toxicity.

Since no treatment-related maternal toxicity was evident in any dose group, it appears that adequate dosages were not used. Based on the data submitted, the maternal LOEL is greater than 1.5 mg/kg/day. The developmental toxicity was not observed at any dosage. It was noted on p. 16 of the study report that the doses selected for this study were based on two Dose-Range-Finding studies (PH 329DR-GC-001-89 and PH 329DR-GC-001-90). These studies, however, were not submitted to this Agency. This study is not acceptable and it is classified as core-supplementary.

Classification: Core-supplementary

5. Developmental Toxicity Study in Rats with Sulfluramid (MRID#417994-09)

Test Material: Sulfluramid (96.6% linear and 3.4% branched isomeric mixture); Lot #AN-90247.

Test Animals: Sprague-Dawley rats

Dosages: 0, 1 (0.8 actual), 4 (3.3 actual) and 16 (13.3 actual) mg/kg/day

CONCLUSIONS: Since the average test article administered to the low-, mid, and high-dose groups dose were -18%, -17%, and -13% less than the nominal concentrations of 1, 4, 16 mg/kg/day, the actual dose levels administered to rats were 0.8, 3.3, and 13.3 mg/kg/day for the low-, mid-, and high-dose groups, respectively.

According to the results of this study, administration of Sulfluramid (96.6% linear and 3.4% branched isomeric mixture; Lot no. #AN-90247) at dose levels of 0.8, 3.3 and 13.3 mg/kg/day from day 6 to day 15 of gestation reduced the mean maternal body weight and mean body weight gain in the 3.3 and 13.3 mg/kg/day dose groups, and reduced food consumption in the 13.3 mg/kg/day dose group. Treatment-related maternal toxicity effects, flaccid

body tone and piloerection, were noted in the 13.3 mg/kg/day group. A dose-related trend of increased incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle were noted in the high-dose group. The reduced fetal weights and increased incidence of cleft palate (3.5% of fetuses and 16.7% of litters in this study versus 0.02% fetuses in the fetal historical control) in the 13.3 mg/kg/day are other developmental toxicity effects.

The maternal toxicity NOEL is determined to be 0.8 mg/kg/day, and the maternal toxicity LOEL is 3.3 mg/kg/day based on reduced mean maternal body weight, mean body weight gain and reduced food consumption. The developmental toxicity NOEL is 3.3 mg/kg/day and the developmental toxicity LOEL is 13.3 mg/kg/day based on reduced fetal weights and increased incidence of cleft palate, incomplete ossification of the 3rd and 4th sternebrae and skull, and an enlarged fontanelle.

CLASSIFICATION: Core-minimum

6. Acute Dermal Toxicity Study of Harness in New Zealand White Rabbit (MRID#417994-07)

Test Material: Sulfluramid (batch# 13-2817; Lot# AN90247); the purity (isomeric mixtures?) was not specified.

Test Animals: Albino White New Zealand Rabbits

Dosage: 2000 mg/kg body weight

CONCLUSIONS: Dermal application of Sulfluramid at 2000 mg/kg body weight did not produce any mortalities in the 5♂ and 5♀ rabbits tested. Subdivision F Guideline requires a maximum dose of no more than 2000 mg/kg in an acute dermal toxicity study. It is not necessary to repeat this study. Thus the acute dermal LD50 of sulfluramid is considered to be greater than 2000 mg/kg body weight. Since the identity (isomeric mixtures?) and the purity of sulfluramid were not provided in the study report, this study is classified as core-supplementary and it is upgradable upon satisfactory review of the requested information. Toxicity category III.

CLASSIFICATION: Core-supplementary. Upgradable after satisfactory review of the requested information.

6

7. Acute Inhalation Toxicity Study - LC_{50} Rats (4 Hours Exposure) with Sulfluramid (MRID#417994-04)

STUDY TYPE: Acute Inhalation Toxicity Study Guideline: 81-3

TEST MATERIAL: Sulfluramid (98.2% linear and 1.8% branched isomers) Batch # RO92789EH-1

Test Animals: Crl:CD(SD)BR rats

CONCLUSIONS: Two groups of 5 male and 5 female rats/dose group, one group was exposed to aerosolized Sulfluramid (98.2% linear and 1.8% branched isomers) in acetone (at airborne concentration of 4.379±0.418 mg/L of sulfluramid and 5.162±0.177 mg/L of acetone). The other group was exposed to aerosolized acetone at airborne concentration at 4.470± 1.067 mg/L for four hours. The test animals were observed for a period of 14 days.

Signs of toxicity observed included clinical signs such as piloerection, lethargy, salivation, nasal secretion, and sore ear. A slight reduction of body weight gain occurred in the treated females, and kidney nephrosis was observed in four control males, eyesore in two treated females, and fur loss in one treated male.

Since no deaths occurred at the maximum practical concentration used in the study, the acute LC_{50} could not be accurately computed. The acute median LC50 is assumed to be greater than 4.379 mg/L and this is close to the limit concentration of 5 mg/L. Toxicity category III.

Classification: Core-minimum. This study satisfies data requirement (81-3) for an acute inhalation toxicity study in rats.

DERs of the above seven studies are attached.