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

C10848

MAR 17 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: **Flumiclorac pentyl (S-23031, V-23031):** Registration, permanent tolerance, and food/feed use in/on corn and soybeans

EPA IDENTIFICATION NUMBERS

P.C. Code: 128723 Caswell No.: 958

| DP Barcode: | Submission No.: |
|---|---|
| D195817 | S449777 |
| D195823 | S449778 |
| D195862 | S449824 |
| D195865 | S449825 |

FROM: Robert F. Fricke, Ph.D. Robert F. Fricke 14 Mar 1994
Toxicology Branch II, Section IV
Health Effects Division

TO: Daniel Kenny
Product Manager (74)
Registration Division (H7508C)

THRU: Jess Rowland, M.S. Jess Rowland 3/14/94.
Toxicology Branch II, Head Section IV
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 3/16/94
Chief, Toxicology Branch II

Registrant: Valent U.S.A. Corporation
1333 N. California Blvd
Walnut Creek, CA 94596

Chemical: V-23031 0.83 EC
S-23031, Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

Action Requested: Review of toxicity data to support registration, permanent tolerance, and food/feed use in/on corn and soybeans.

Conclusions: The Registrant has submitted a toxicology data package to support a permanent tolerance [3F04234], food/feed use tolerance [3H05682], and registration of the technical product [059639-IR] and formulated product Resource [059639-IE].

**As shown in the following tables, based on studies submitted under this submission and the previous one [8447043], the Registrant has completed all toxicology data requirements. Therefore, Toxicology Branch II recommends approval of these petitions.**

1. Summary of toxicology data requirements for technical compound (Table 1) and formulated product (Table 2).

TABLE 1: SUMMARY OF TOXICOLOGY DATA REQUIREMENTS FOR TECHNICAL COMPOUND

| Guideline | | Required | Met | MRID |
|---|---|---|---|---|
| Acute Toxicity Studies | | | | |
| §81-1 | Acute Oral Toxicity | Yes<br>Yes | Yes<br>Yes | 421698-11†<br>421698-12† |
| §81-2 | Acute Dermal Toxicity | Yes | Yes | 421698-14† |
| §81-3 | Acute Inhalation Toxicity | Yes | Yes | 421698-16† |
| §81-4 | Primary Eye Irritation | Yes | Yes | 421698-18† |
| §81-5 | Primary Dermal Irritation | Yes | Yes | 428839-01 |
| §81-6 | Primary Dermal Sensitization<br>Buehler<br>Maximization | <br>Yes<br>Yes | <br>Yes<br>Yes | <br>428839-02<br>421698-22† |
| Subchronic Toxicity | | | | |
| §82-1(a) | Subchronic Toxicity<br>Rat | Yes | Yes | 421698-26†<br>423108-01† |
| | Rat | Yes | Yes | 428839-03 |
| §82-1(b) | Subchronic Toxicity (dog) | Yes | Yes | 421698-27†<br>423108-02† |
| §82-2 | 21-Day Dermal | Yes | Yes | 428258-15 |
| Chronic Toxicity | | | | |
| §83-1(b) | Chronic Oral (dog) | Yes | Yes | 428258-17 |
| §83-2(b) | Oncogenicity (mouse) | Yes | Yes | 428839-05 |
| §83-5 | Combined Chronic/Carcinogenicity (rat) | Yes | Yes | 428839-06 |
| Reproductive Toxicity | | | | |
| §83-3(a) | Teratology (rat) | Yes | Yes | 421698-32† |
| §83-3(b) | Teratology (rabbit) | Yes | Yes | 421698-30† |
| §83-4 | Reproduction, 2 Generation | Yes | Yes | 421698-35† |

*Table 1, Continued*

C10848

| | | | | |
|---|---|---|---|---|
| **Mutagenicity** | | | | |
| §84-2(a) | Gene Mutation - Ames Assay | Yes | Yes | 421698-36†<br>428258-18 |
| | - Micronucleus | Yes | Yes | 421698-37† |
| §84-2(b) | Structural chromosome aberration | Yes | Yes | 421698-38†<br>428258-19 |
| §84-4(a) | Other genotoxic effects - UDS | Yes | Yes | 421698-39† |
| **Metabolism** | | | | |
| §85-1 | Metabolism, general | Yes | Yes | 421698-40†<br>428258-22<br>428258-23<br>428258-21 |

† Denotes studies reviewed under the previous submission

TABLE 2: SUMMARY OF TOXICOLOGY DATA REQUIREMENTS FOR FORMULATED PRODUCT

| Guideline | | Required | Met | MRID |
|---|---|---|---|---|
| **Acute Toxicity Studies** | | | | |
| §81-1 | Acute Oral Toxicity | Yes | Yes | 421698-13† |
| §81-2 | Acute Dermal Toxicity | Yes | Yes | 421698-15† |
| §81-3 | Acute Inhalation Toxicity | Yes | Yes | 421698- ?† |
| §81-3 | Acute Inhalation Toxicity | Yes | Yes | 428258-14 |
| §81-4 | Primary Eye Irritation | Yes | Yes | 421698-19† |
| §81-5 | Primary Dermal Irritation | Yes | Yes | 421698-20† |
| | Buehler | Yes | Yes | 421698-23† |
| | Maximization | Yes | Yes | 421698-24† |
| **Subchronic Toxicity** | | | | |
| §82-2 | 21-Day Dermal | Yes | Yes | 428258-16 |

† Denotes studies reviewed under the previous submission

2. Summary of Toxicity Data

C10848

a. **Acute inhalation - Rats (§81-3)**

STUDY TITLE: V-23031 0.83 EC, Acute Inhalation Toxicity in Rats, Four-hour exposure, Determination of the no-effect level, Supplement to V-23031 0.83 EC, Acute Inhalation Toxicity in Rats, Four-hour exposure MRID No. 42169817

MRID NO.: 428258-14

RESULTS: The objective of this study was to ascertain a NOEL for respiratory effects, since an acute $LC_{50}$ had been established in a previous study. In this study, rats, 5/sex/group, were randomly assigned to control (air only), vehicle control (formulation blank at 3.47 or 6.14 mg/l) and V-23031 0.83EC treatment (0.6, 1.13, or 3.24 mg/l) groups. Following a four-hour exposure, animals were observed for 14 days. No deaths occurred during the study. The only treatment-related effects consisted of exaggerated breathing in the mid- (1.13 mg/l) and high-dose (3.24 mg/l) treatment groups during the entire 14-day post-exposure observation period. The corresponding vehicle control animals (3.47 mg/l) did not show any adverse clinical signs past Day 4. No treatment-related changes were noted in body weight, body weight gain, lung weights, gross pathology or histopathology. A NOEL for respiratory effects is 0.6 mg/l for male and female rats.

CLASSIFICATION: Core - Supplementary

b. **Primary Skin Irritation in Rabbits (§81-5)**

STUDY TITLE: Skin Irritation Test with S-23031 in Rabbits

MRID NO.: 428839-02

RESULTS: The dermal sensitivity of S-23031 (0.5 g/animal) was evaluated in male Hartley Guinea Pigs (10/group) using Buehler's method. S-23031 did not cause any dermal sensitization; positive controls (DNCB) responded appropriately. Based on the results of the study, the test compound did not exhibit any sensitization potential.

CLASSIFICATION: Core - Minimum

c. **Skin Sensitization - Guinea-Pig (§81-6)**

STUDY TITLE: Skin Sensitization Test of S-23031 in Guinea-Pigs

MRID NO.: 428839-02

RESULTS: The dermal sensitivity of S-23031 (0.5 g/animal)

was evaluated in male Hartley Guinea Pigs (10/group) using Buehler's method. S-23031 did not cause any dermal sensitization; positive controls (DCNB) responded appropriately. Based on the results of the study, the test compound did not exhibit any sensitization potential.

CLASSIFICATION: Core - Minimum

d. **90-Day Feeding - Mice (§82-1)**

STUDY TITLE: Three-Month Subacute Toxicity Study of S-23031 by Dietary Administration in Mice

MRID NO.: 428839-04

RESULTS: In a 13-week study, male and female CD-1 mice (6/group/sex) were fed test diets containing 0, 1000, 3000 or 10000 ppm (equivalent to 0, 125, 379, or 1274 mg/kg/day, males; 0, 150, 366 or 1224 mg/kg/day, females). Males at 3000 ppm showed increased absolute and relative liver weights, altered hematology (decreased erythrocyte count, hemoglobin concentration and hematocrit) and increased incidence of gross (mottled, enlarged livers) and histopathological findings (hepatocellular hypertrophy, hepatocellular vacuolation, and single cell necrosis). Based on these findings the LOEL is 3000 ppm (379 mg/kg/day) for systemic toxicity in males; LOEL was not established in females. NOELs were established at 1000 ppm (125 mg/kg/day) in males and 10000 ppm (1224 mg/kg/day) in females.

CLASSIFICATION: core - Supplementary

e. **90-Day Feeding - Rats (§82-1)**

STUDY TITLE: 13-Week Subchronic Toxicity Study of S-23031 Pure in Rats

MRID NO.: 428839-03

RESULTS: Male and female rats were fed S-23031 daily, for 13 weeks, at dosages 0, 100, 1000, 10000, or 30000 ppm (equivalent to 0, 6.46, 64.9, 659 or 2087 mg/kg/day for males and 0, 6.93, 70.6, 724 or 2249 mg/kg/day for females, respectively). The relative liver weights of high-dose males were significantly increased. The only treatment-related effect was the significant increase in the number of epithelial cells appearing in the urinary sediment of 10000 and 30000 ppm males and females. Based on these findings, a LOEL of 10000 ppm (659 mg/kg/day, males; 724 mg/kg/day, females) and a NOEL of 1000 ppm (64.9 mg/kg/day, males; 70.6 mg/kg/day, females) are established for systemic toxicity in male and female rats

CLASSIFICATION: Core - Guideline

f. **21-Day Dermal - Rats (§82-2)**

i. STUDY TITLE: 21-Day Dermal Toxicity Study in Rats with S-23031

MRID No.: 428258-15

RESULTS: Male and female Sprague-Dawley rats received repeated dermal dosing of test compound at 0, 100, 300, or 1000 mg/kg/day for 6 hours/day, 7 days/week for 21 days. No treatment-related effects were noted in mortality, body weight gain, food consumption, clinical pathology, or absolute and relative organ weights. Although gross pathological examination of the livers revealed an increased incidence of pale areas, no relevant histopathological findings were found. The gross changes in the liver were attributed to the occlusive dressing. Based on the results of this study, the LOEL for systemic and dermal toxicity of S-23031 in male and female rats is greater than 1000 mg/kg/day (high dose tested).

CLASSIFICATION: Core - Guideline

ii. STUDY TITLE: 21-Day Dermal Toxicity Study in Rats with V-23031 (0.83EC)

MRID No.: 428258-16

RESULTS: Male and female Sprague-Dawley rats (5/dose/sex) received repeated dermal dosing of test compound at 0, 100, 300, or 1000 mg/kg/day for 6 hours/day, 7 days/week for 21 days. No treatment-related effects were noted in mortality, body weight gain, food consumption, clinical pathology, or absolute and relative organ weights. Significant, treatment-related effects, present in mid- and high-dose males and females, were limited to treated skin only; no systemic toxicity was noted. Slight erythema was present in mid- and high-dose females; slight to moderate desquamation was observed in mid- and high-dose animals. Gross pathological observations (desquamation; encrustations) were confirmed histologically (athancosis, hyperkeratosis, inflammation, incrustations, ulcerations).

CLASSIFICATION: Core - Minimum

g. **1-Year Oral - Dog §83-1(b)**

STUDY TITLE: Chronic oral toxicity study in dogs with S-23031

MRID No.: 428258-17

RESULTS: In a 1-year oral chronic toxicity study, male and female beagle dogs (5/group) were dosed at 0, 10, 100, or

1000 mg/kg body weight/day with S-23031. All animals survived to terminal sacrifice without any treatment-related clinical signs. High-dose males showed consistently lower mean body weights and lower body weight gains throughout the study. Activated partial thromboplastin times, alkaline phosphatase activities and relative liver weights were elevated in high-dose males and females. Based on these findings, a LOEL of 1000 mg/kg/day and a NOEL of 100 mg/kg/day were established for systemic toxicity in male and female dogs.

CLASSIFICATION: Core - Guideline

h. **Oncogenicity - Mouse §83-2(b)**

STUDY TITLE: Oncogenicity Study of S-23031 by Dietary Administration in Mice

MRID No.: 428839-05

RESULTS: In a 79 week oncogenicity study, mice were fed diets containing 0, 300, 3000, or 7000 ppm. Treatment-related findings were limited to males. At both the interim and terminal sacrifices mid- and high-dose males had significant decreases in hematocrit, hemoglobin concentration and RBC count. High-dose males also had significantly increased absolute and relative liver weights at the interim sacrifice; at terminal sacrifice the absolute and relative liver weights were increased, but the differences were not statistically significant. Histopathological findings showed an significantly increased incidence of hypertrophy of the hepatocytes of mid- and high-dose males at both the interim and terminal sacrifices. The occurrence of neoplastic appeared to be spontaneous and not dose-related. Based on these findings, a LOEL of 3000 ppm (307.9 mg/kg/day) and a NOEL of 300 ppm (31.5 mg/kg/day) were established for systemic toxicity in male rats. In female mice, the NOEL was the highest dose tested (7000 ppm, 850.2 mg/kg/day). There was no evidence that S-23031 was carcinogenic in this study.

CLASSIFICATION: Core - Guideline

i. **Combined Chronic Toxicity/Carcinogenicity - Rats §83-5**

STUDY TITLE: Combined Chronic Toxicity and Oncogenicity Study of S-23031 by Dietary Administration in Rats

MRID No.: 428839-06

RESULTS: In a chronic toxicity/carcinogenicity study, CD (SD) rats (50/dose/sex, main study; 14/dose/sex, satellite study) were administered S-23031 at dietary concentrations of 0, 100, 1000, 10000 or 20000 ppm (respective mg/kg/day equivalents: 0, 3.5, 35.4, 360.4 or 744.9, males; 0, 4.3, 43.6, 443.8, or 919.4, females). Male rats showed clear and

consistent treatment-related changes at both 10000 and 20000 ppm. The liver appears to be the target organ as evidenced by increased activity of γ-glutamyl transpeptidase, increased absolute and relative organ weights, and increased incidence on hyperplastic nodules was within the historical control range. Other incidental effects included significant urinalysis findings (increased urine volume and appearance of squamous epithelial cells in the sediment) in the high-dose males. No treatment-related effects were noted in females at the highest dose tested (20000 ppm, 919 mg/kg/day). There was no evidence of carcinogenicity. Based on these findings, a LOEL of 10000 ppm (360 mg/kg/day) and a NOEL of 1000 ppm (35 mg/kg/day) were established for systemic toxicity in male rats. In female rats, the NOEL was the highest dose tested (20000 ppm, 919.4 mg/kg/day). There is no evidence that S-23031 was carcinogenic in this study.

CLASSIFICATION: core - Guideline

j. **Structural chromosomal aberration test, §84-2**

STUDY TITLE: *In vitro* Chromosomal Aberration Test of S-23031 in Chinese Hamster Ovary Cells (CHO-K1)

MRID No.: 421698-38 (Original Study), 428258-19 (Amended Study)

The original study submitted by the Registrant was reviewed and found to be unacceptable (HED Doc No.: 009587). The Registrant submitted an amended study which corrected the deficiencies. The guideline (§84-2) requirement for a "Structural chromosomal aberration test" have been satisfied.

CLASSIFICATION: Core: Acceptable

k. **Gene Mutation, §84-2**

STUDY TITLE: Reverse Mutation Test of S-23031 in Salmonella typhimurium and Escherichia coli

MRID No.: 421698-36 (Original Study), 428258-18 (Amended Study)

The original study submitted by the Registrant was reviewed and found to be unacceptable (HED Doc No.: 009587). The Registrant submitted additional information which corrects the deficiencies of the original study and satisfies the guideline (§84-2) requirements for a "Gene Mutation" study.

CLASSIFICATION: Core: Acceptable

1. **Metabolism - Rats §85-1** 010848

i. STUDY TITLE: Metabolism of S-23031 in Rats Revised

MRID No.: 421698-40 (HED Doc No.: 009587)

This was previously submitted and after review it was classified as Core Supplementary. The Registrant has submitted three additional studies: (1) an additional metabolism study in rats (MRID No.: 428258-22) using [tetrahydrophthalonyl-1,2$^{14}$C] S-23031, (2) a special metabolism study which evaluated biliary excretion (MRID No.: 428258-21), and (3) a study detailing the analytical methodology (MRID No.: 428258-23). These additional studies have been reviewed and corrected the deficiencies of the original study. The guideline requirements for a metabolism study (§85-1) in rats has been satisfied.

CLASSIFICATION: Core - Supplementary However, when taken with other metabolism studies (MRID No.: 421698-40, 428258-23 and 428258-21) the guideline requirements (§85-1) are satisfied.

ii. STUDY TITLE: Metabolism of S-23031 in Rats; [tetrahydrophthalonyl-1,2$^{14}$C] S-23031

MRID No.: 428258-22

RESULTS: The metabolism of [THP-C$^{14}$]S-23031 was studied in male and female rats treated by oral gavage with single low dose (1 mg/kg/day), single high dose (500 mg/kg/day) or repeated low dose (1 mg/kg/day of unlabeled test compound, followed on the 15th day with a dose of 1 mg/kg of labeled compound). Animals were sacrificed seven days after administration of labeled compound. Essentially all (> 93.1%) of the administered dose was eliminated within two days of dosing. The tissue accumulation of $^{14}$C-labeled residues was very low, with highest levels found in blood, plasma and kidneys of all three dose groups. Metabolic conversions include deesterification and/or imide bond cleavage, followed by a series of hydroxylation and/or sulfonation reactions. Due to lack of absorption, high amounts of S-23031 were present in the feces of high dose animals. Urinary metabolite profiles for low dose males and females were similar. High dose males, however, showed higher amounts of urinary metabolites resulting from imide bond cleavage (THPA) and hydroxylated and sulfonated compounds. In high dose females, deesterified parent compound (IMCA) and 4-OH-IMCA predominated. Repeat low dose females showed higher amounts of urinary IMCA, THPA and 4-OH-IMCA.

CLASSIFICATION: Core - Supplementary However, when taken with other metabolism studies (MRID No.: 421698-40,

428258-23 and 428258-21) the guideline requirements (§85-1) are satisfied.

m. **Special Metabolism - Rats**

i. STUDY TITLE: Bile Excretion Study of [Phenyl-$^{14}$C]S-23031 in Male Rats

MRID No.: 428258-21

RESULTS: The metabolism of [phenyl-$C^{14}$]S-23031 was studied in male rats treated by oral gavage with a single low dose (1 mg/kg/day) or a single high dose (500 mg/kg/day) of labeled test compound). Biliary, urinary and fecal samples were collected over a 48-hour period and analyzed for radioactivity. At 48-hours post-dosing, animals were sacrificed and radioactivity in carcass determined. Major biliary metabolites were isolated and identified. Essentially all (> 98%) of the administered dose was eliminated within two days of dosing. Biliary excretion accounted for approximately 19% of the administered dose, while the cumulative urinary and fecal elimination were 55% and 33% for the low dose, respectively and 31% and 44% for the high dose, respectively. The profiles of biliary metabolites indicated that no detectable (< 0.05%) amounts of unmetabolized S-23031 were present. For both dose groups, AFCA ((2-chloro-4-fluoro-5-amino)phenoxyacetic acid) accounted for 11 to 12% of the administered dose; IMCA ([2-chloro-4-fluoro-5-(3,4,5,6-tetrahydro)phthalimido]-phenoxyacetic acid) was present at 0.5% or less. Based on the results of this study, the high amounts of unmetabolized S-23031 present in the feces is due to lack of absorption rather than biliary excretion.

CLASSIFICATION: Core - Supplementary However, when taken with other metabolism studies (MRID No.: 421698-40, 428258-22 and 428258-2)3 the guideline requirements (§85-1) are satisfied.

ii. STUDY TITLE: Purification and Identification of Fecal and Urinary Metabolism of S-23031 in Rats, MRID No.: 428258-23

RESULTS: Male rats were dosed for six days with 250 mg/kg/day of [phenyl-$C^{14}$]S-23031 (0.31 MBq/mmol). Excreta were collected separately using glass metabolism cages. The urinary and fecal metabolites, from pooled samples) were separated using several chromatographic techniques and. Using NMR, MS and FTIR spectoanalyses, the identity and structure of the urinary metabolite (4-OH-IMCA, [2-chloro-4-fluoro-5-(4-hydroxy-1,2-cyclohexenedicarboximido)] phenoxyacetic acid) and four fecal metabolites (IMCA-SA, [2-chloro-4-fluoro-5-(1-sulfo-1,2-cyclohexane-

dicarboximido)]phenoxyacetic acid; 4-OH-IMCS-SA1 and 2, [2-chloro-4-fluoro-5-(1-sulfo-4-hydroxy-1,2-cyclohexane-dicarboximido)]phenoxyacetic acid; and 5-OH-IMCS-SA, [2-chloro-4-fluoro-5-(1-sulfo-5-hydroxy-1,2-cyclohexane-dicarboximido)] phenoxyacetic acid) were determined. Three metabolites, 4-OH-IMCA-SA1, 4-OH-IMCA-SA2 and 5-OH-IMCA-SA, which could not be resolved using TLC, had sufficiently different HPLC retention times (40, 21, and 19 min, respectively) to allow separation and subsequent identification.

CLASSIFICATION: Core - Supplementary However, when taken with other metabolism studies (MRID No.: 421698-40, 428258-22 and 428258-23 the guideline requirements (§85-1) are satisfied.

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 11 Mar 94.
Section IV, Tox. Branch II (H7509C)
Secondary Reviewer: Jess Rowland, M.S. [signature] 3/14/94.
Section IV, Tox. Branch II (H7509C)

**DATA EVALUATION RECORD** 010848

**STUDY TYPE:** Acute Inhalation - Rat (§81-3)

**EPA ID NOs:**
MRID NO.: 428258-14
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** V-23031 (0.83EC)

**SYNONYMS:** S-23031, Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimidc]phenoxy acetate

**STUDY NUMBER:** VLT 14/920395

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Huntingdon Research Centre Ltd.
Huntingdon, Cambridgeshire, England

**TITLE OF REPORT:** V-23031 0.83 EC, Acute Inhalation Toxicity in Rats, Four-hour exposure, Determination of the no-effect level, Supplement to V-23031 0.83 EC, Acute Inhalation Toxicity in Rats, Four-hour exposure MRID No. 42169817

**AUTHORS:** G.C. Jackson, C.J. Hardy, J. Morrow, D.J. Lewis and C. Gopinath

**REPORT ISSUED:** 21 December 1992

**EXECUTIVE SUMMARY:** Rats, 5/sex/group, were randomly assigned to control (air only), vehicle control (formulation blank at 3.47 or 6.14 mg/l) and V-23031 0.83EC treatment (0.6, 1.13, or 3.24 mg/l) groups. Following a four-hour exposure, animals were observed for 14 days. The objective of this study was to ascertain a NOEL for respiratory effects, since an acute $LC_{50}$ had been established in a previous study.

No deaths occurred during the study. The only treatment-related effects consisted of exaggerated breathing in the mid- (1.13 mg/l) and high-dose (3.24 mg/l) treatment groups during the entire 14-day observation period. The corresponding vehicle control animals (3.47 mg/l) did not show any adverse clinical signs past Day 4. No treatment-related changes were noted in body weight, body weight gain, lung weights, gross pathology or histopathology.

**A NOEL for respiratory effects is 0.6 mg/l for male and female rats.**

This study is classified as Core Supplementary since it was designed to ascertain a NOEL for respiratory tract changes. This study does not satisfy guideline requirements (§81-3) for an acute inhalation toxicity study in the rat. A previous study (MRID No.: 421698-17, HED Doc No: 009587) using V-23031 0.83EC established an $LC_{50}$ of 5.51 mg/l with a Toxicity category of IV.

I. MATERIALS

A. Test Compound: V-23031 0.83 EC Description: clear dark brown liquid Lot #: V803L11 Purity: 10.5% ai in formulation blank Contaminants: not given

B. Vehicle: Blank Formulation of SB-1297 10EC, Lot No. AC09L11

C. Test Animals: Species: Rat Strain: Sprague-Dawley Age (weeks): 6 (males) and 8 (females) Weight (g): 190 - 235 (males), 193 - 230 (females) Source: Charles River U.K., Ltd. Housing: five/cage Feed: SDS RM1, Special Diets Services, Witham, Essex, England, *ad libitum* Water: Tap water, *ad libitum* Environment: Temperature: 18 to 24°C; Humidity: ambient (22 to 65%); Air changes: 12.5/hr; Light cycle: 12hr light/12hr dark

II. METHODS

A. Study Design and Observations: Animals were randomly assigned to control, vehicle control and treatment groups (Table 1). Groups of four animals were placed in separate compartments in the exposure chamber. After an 11-minute equilibration period, animals were exposed continuously for four hours to either air only, vehicle or test compound.

Animals were observed continuously during the exposure period, clinical signs were recorded at the end of the equilibration period, 15 min, 30 min, 1 hr, 2 hr, 3 hr and 4 hr. During the 14-day observation period, clinical signs were recorded once daily. Rats were weighed daily, starting five days before the start of the study and through the end of the observation period.

All animals were necropsied for gross pathological and histopathological examinations of the nasal turbinates, lung, larynx, trachea, liver and kidneys. The absolute and relative lung weights were also determined.

Table 1: Animal assignment to study groups

| Group | Target Concentration | Animals | |
|---|---|---|---|
| | | Male | Female |
| 1: Control | 0 mg/l | 5 | 5 |
| 2: Low Vehicle Control | 3 mg/l | 5 | 5 |
| 3: High Vehicle Control | 5 mg/l | 5 | 5 |
| 4: Low Treatment | 0.5 mg/l | 5 | 5 |
| 5: Mid Treatment | 1.0 mg/l | 5 | 5 |
| 6: High Treatment | 3.0 mg/l | 5 | 5 |

B. Test Atmosphere Generation: The test compound was pumped into the aerosol generator from syringe fitted into a constant drive syringe pump. The flow rate of the syringe pump was adjusted to deliver an amount of vehicle or test compound necessary to yield the desired final aerosol concentration. The aerosol generator was supplied by 25 l/min of dried, filtered and oil-free compressed air. The test atmosphere entered into a whole body exposure chamber through a center port at the base. The whole body chamber had a total internal volume of 120 liters and was subdivided into 10 separate animal holding compartments. Samples of test atmosphere were taken at 30 min, 1 hr, 2 hr, 3 hr, and 3 hr:50 min of the exposure period. In addition to determining the concentration of test compound, the amount of active ingredient (V-23031) was determined from its concentration in the formulated product and the density of the formulation. Two additional samples, used for particle size distribution analysis, were taken at 1.5 hr and 3.5 hr. The relative humidity in aerosol chamber ranged from 35 to 65% except on two occasions where values of 66% and 72% were recorded. The temperature ranged from 25 to 26°C.

C. Statistics: Means and standard deviations of animal body weights, chamber temperatures and relative humidities were calculated for descriptive purposes.

## III. RESULTS

A. Test Atmosphere: Samples taken during the exposure indicated that the test atmospheres within the chamber were in equilibrium. The actual concentrations of the vehicle (Groups 2 and 3) and V-23031 (Groups 4, 5 and 6) were measured from samples of the test atmospheres. Based on the measured amount of vehicle or V-23031, an equivalent amount of the formulated product (V-23031 0.83EC) was calculated (Table 2). The concentration of vehicle in Group 2 (3.88 mg/l) was essentially equal to that of Group 6 (3.24 mg/l).

Table 2: Mean Concentration of Vehicle, V-23031 and the Calculated Equivalent Concentration of the Formulation (Summarized from Table 1 of study)

| | Concentration in Air (mg/l) | | |
|---|---|---|---|
| Group | Measured Vehicle | Measured V-23031 | Calculated Equivalent |
| 2 | 3.47 | -- | 3.88 |
| 3 | 6.14 | -- | 6.86 |
| 4 | -- | 0.065 | 0.60 |
| 5 | -- | 0.12 | 1.13 |
| 6 | -- | 0.35 | 3.24 |

The particle size distributions were determined for vehicle control and treatment groups. The MMAD could not be determined for the vehicle control groups. The ranges of particle sizes and the percent of respirable particles (< 5.5 μm) are summarized in Table 3. For treatment groups, the aerodynamic particle sizes were acceptable (MMAD = 1.5 to 2.0 μm) with 19 to 27% of the particles having an aerodynamic diameter of less than 1.0 μm.

Table 3: Mean Particle Size Range of Vehicle Control Groups[a]

| | Cumulative % Within Range | |
|---|---|---|
| Range (μm) | Group 2 | Group 3 |
| > 5.5 | 14.2 | 14.2 |
| 2.0 - 5.5 | 19.2 | 20.1 |
| < 2.0 | 66.7 | 65.1 |
| < 5.5 | 85.8 | 85.9 |

[a] Summarized from Table 2 of report

Table 4: Mean Particle Size Distribution[a]

| | Cumulative Percent Less That Cut-off Size | | |
|---|---|---|---|
| Cut-Off Size (μm) | Group 4 | Group 5 | Group 6 |
| 9.8 | 100 | 98.1 | 99.8 |
| 6.0 | 97.6 | 94.4 | 94.9 |
| 3.5 | 85.0 | 76.5 | 76.0 |
| 1.55 | 41.7 | 35.1 | 35.7 |
| 0.93 | 21.7 | 18.1 | 17.6 |
| 0.52 | 9.5 | 3.9 | 4.2 |
| < 1.0 | 27 | 19 | 19 |
| MMAD (μm) | 1.5 | 2.0 | 1.8 |
| σg | 1.95 | 2.13 | 1.97 |

[a] Summarized from Table 2 of report

B. Clinical Signs and Mortality: During the exposure period, vehicle control and treated animals showed clinical signs consisting of partial closing of the eyes, exaggerated breathing, and wetness around the eyes and mouth; during the last hour of the exposure, animals in the middle and high treatment groups also showed piloerection. Post-exposure clinical signs are presented in Appendix 1. Animals in the low treatment group showed essentially normal appearance and behavior throughout the 14 day observation period. Exaggerated breathing was observed through Day 5 in the low vehicle control group and through Day 14 for the high

vehicle control and the middle and high treatment groups. Bright yellow/orange urine, yellow urogenital staining and matted fur were generally observed from Day 1 through 4. No animals died during the study.

C. Body Weights: Two days post-exposure, vehicle control animals (Groups 2 and 3) showed the greatest change in mean body weights and body weight gains; treated animals were less severely affected. From Days 2 to 14, the animals appeared to be recovering as demonstrated by the weight gains.

Table 5: Mean Body Weights and Body Weight Gains[a]

| | | Study Group | | | | | |
|---|---|---|---|---|---|---|---|
| Sex | Day | 1 | 2 | 3 | 4 | 5 | 6 |
| Body Weights (g) | | | | | | | |
| Male | 0 | 219 | 221 | 203 | 205 | 213 | 216 |
| | 2 | 237 | 204 | 163 | 212 | 224 | 217 |
| | 14 | 334 | 284 | 282 | 312 | 311 | 318 |
| Female | 0 | 209 | 209 | 212 | 205 | 215 | 212 |
| | 2 | 221 | 207 | 186 | 211 | 219 | 218 |
| | 14 | 262 | 232 | 264 | 248 | 253 | 263 |
| Body Weight Gain (g) | | | | | | | |
| Male | 0-2 | 18 | -17 | -40 | 7 | 11 | 1 |
| | 2-14 | 97 | 80 | 119 | 100 | 87 | 101 |
| Female | 0-2 | 12 | -2 | -26 | 6 | 4 | 5 |
| | 2-14 | 41 | 25 | 76 | 37 | 34 | 45 |

[a] Body weight data summarized from Table 5 of the report, body weight gains were calculated by the reviewer.

D. Pathology

1. Lung weights: The lungs weights (relative to body weights) at terminal sacrifice had relative lung weights which were comparable to control values. Although means and standard deviations were determined, determination of statistical significance was not performed.

2. Gross pathology: At terminal sacrifice, no abnormalities were detected during gross pathological examination.

3. Histopathology: Histopathological findings are summarized in Appendix 2. Lesions were limited to the nasal turbinates and the larynx; all other tissues appeared normal. Lesions in the nasal turbinates consisted of disorganization of the olfactory epithelium with/without rosette formation in both vehicle control groups and the high-dose treatment group; the vehicle control groups also sowed epithelial atrophy of the nasal septum and hyperplasia of the pseudoglandular goblet cells. The ventral cartilage of the larynx in both vehicle control groups and all the treatment groups was necrotic and mineralized; signs of regeneration were also observed.

IV. CONCLUSIONS: Rats, 5/sex/group, were randomly assigned to control (air only), vehicle control (formulation blank at 3.47 or 6.14 mg/l) and V-23031 0.83EC treatment (0.6, 1.13, or 3.24 mg/l) groups. Following a four-hour exposure, animals were observed for 14 days.

No deaths occurred during the study. The only treatment-related effects consisted of exaggerated breathing in the mid- (1.13 mg/l) and high-dose (3.24 mg/l) treatment groups during the entire 14-day post-exposure observation period. The corresponding vehicle control animals (3.47 mg/l) did not show any adverse clinical signs past Day 4. No treatment-related changes were noted in body weight, body weight gain, lung weights, gross pathology or histopathology.

A NOEL for respiratory effects is 0.6 mg/l for male and female rats.

This study is classified as Core Supplementary since it was designed to ascertain a NOEL for respiratory tract changes. This study does not satisfy guideline requirements (§81-3) for an acute inhalation toxicity study in the rat. A previous study (MRID No.: 421698-17, HED Doc No: 009587) using V-23031 0.83EC established an $LC_{50}$ of 5.51 mg/l with a Toxicity category of IV.

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Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 8 Mar 94
Section IV, Tox. Branch II (H7509C)

Secondary Reviewer: Jess Rowland, M.S. Jess Rowland 3/14/94
Section IV, Tox. Branch II (H7509C)

010848

**DATA EVALUATION RECORD**

**STUDY TYPE:** Skin Sensitization - Guinea-Pig (Buehler's Method) (§81-6)

**EPA ID NOs:** MRID NO.: 428839-02
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031

**SYNONYMS:** V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**STUDY NO.:** 2649

**SPONSOR:** Valent U.S.A. Corporation
1333 N. California Blvd
Walnut Creek, CA 94596

**TESTING FACILITY:** Environmental Health Science Laboratory
Sumitomo Chemical Co., Ltd.
1-98, 3-Chome, Kasugade-naka, Konohana-ku
Osaka, Japan

**TITLE OF REPORT:** Skin Sensitization Test of S-23031 in Guinea-Pigs

**AUTHOR:** T. Nakanishi

**REPORT ISSUED:** 11 November 1992

**EXECUTIVE SUMMARY:** The dermal sensitivity of S-23031 (0.5 g/animal) was evaluated in male Hartley Guinea Pigs (10/group) using Buehler's method. S-23031 did not cause any dermal sensitization; positive controls (DNCB) responded appropriately.

**Based on the results of the study, the test compound did not exhibit any sensitization potential.**

This study is classified as core minimum and satisfies guideline requirements (§81-6) for a dermal sensitization study in guinea pigs.

I. MATERIALS

A. Test Compound: S-23031 Description: light tan powder Batch #: PYG-88092-M Purity: 94.7% Contaminants: CBI Index

B. Positive Control Material: 2,4-dinitrochlorobenzene (DNCB) Lot No.: ECQ 4278 Purity: >98.5% Source: Waco Pure Chemical Industries, Ltd, Osaka, Japan

C. Test Animals: Species: Guinea pig Strain: male, Hartley Age: 5 weeks Weight (g): 285 - 375 Source: Charles River Japan, Co., Ltd. Housing: Five animals/cage Feed: GC-4 diet *ad libitum* (Oriental Yeast Co, Ltd, Tokyo, Japan) Water: Tap water, *ad libitum* Environment: Temperature, 24 ± 2°C; Humidity, 55 ± 15%; Light cycle, 12 hr light/12 hr dark; Ventilation, 10 air changes/hr

II. METHODS

A. Preliminary Dermal Irritation Study: A preliminary dermal irritation test showed that topical application of 0.5 g of test compound, moistened with corn oil, did not result in the formation of either erythema or edema.

B. Main Study

a. Induction Phase: Animals were randomly assigned to two treatment groups (10/group) or two positive control groups (5 animals/group). Applications sites were trimmed free of fur.

For treated animals 0.5 g of test compound was spread onto a lint patch moistened with corn oil and applied to the skin. Treatment Control animals were treated similarly, but without any test compound. Positive Control animals (DNCB-sensitized animals) were treated topically with a lint patch saturated with 0.5 ml of 1.0% DNCB in acetone. The DNCB-control animals were treated in a similar manner using acetone only.

Patches were held in place with an occlusive dressing. After six hours, the dressing was removed and the application site cleaned to remove test material. Animals were exposed at weekly intervals for three weeks.

b. Challenge Phase: Following a two-week resting phase, the animals in both the treatment groups were again challenged with 0.5 g of S-23031, using the procedure described for the induction phase. Positive controls were challenged with 0.5% DCNB. The sites were scored 24 and 48 hours. Erythema and edema were evaluated using the following scoring system: Grade 0, no reaction; Grade 1, slight reaction (edges of area

not defined); Grade 2, moderate reaction (area well defined); Grade 3, severe reaction.

C. Statistical Evaluations: The Mann-Whitney U test was used to compare sensitized animals with their respective controls.

III. REGULATORY COMPLIANCE: Quality assurance was documented by signed and dated GLP and quality assurance statements.

IV. RESULTS AND CONCLUSIONS

A. Results: The results of the study are presented in the attached appendix. None of the animals in the treatment, control, or DNCB-control groups showed any sensitivity at either 24 or 48 hours after the appropriate challenge. Th DNCB-sensitized group responded appropriately with slight to moderate erythema and erythema present at 24 and 48 hours.

B. Conclusions: The dermal sensitivity of S-23031 (0.5 g/animal) was evaluated in male Hartley Guinea Pigs (10/group) using Buehler's method. S-23031 did not cause any dermal sensitization; positive controls (DCNB) responded appropriately.

Based on the results of the study, the test compound did not exhibit any sensitization potential.

CLASSIFICATION: CORE - Minimum

This study satisfies guideline requirements (81-6) for a dermal sensitization study in guinea pigs.

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**NEW ENTRY** 010848

**ONE-LINER**

**CITATION**

**STUDY TYPE:** Skin Sensitization - Guinea-Pig (§81-6)

**STUDY TITLE:** Skin Sensitization Test of S-23031 in Guinea-Pigs

**MRID NO.:** 428839-02

**STUDY NO (DATE):** 2649 (11 Nov 1992)

**TEST COMPOUND:** S-23031, V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

Purity: 94.7%

**P.C. CODE:** 128724

**CASWELL NO.:** 958

**RESULTS:** The dermal sensitivity of S-23031 (0.5 g/animal) was evaluated in male Hartley Guinea Pigs (10/group) using Buehler's method. S-23031 did not cause any dermal sensitization; positive controls (DCNB) responded appropriately. Based on the results of the study, the test compound did not exhibit any sensitization potential.

**CLASSIFICATION:** CORE - ~~Acceptable~~ minimum

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 11 Mar 94
Section IV, Tox. Branch II (H7509C)

Secondary Reviewer: Jess Rowland, M.S. Jess Rowland 3/14/94
Section IV, Tox. Branch II (H7509C)

010848

**DATA EVALUATION RECORD**

**STUDY TYPE:** Primary Skin Irritation in Rabbits (§81-5)

**EPA ID NOs:**
MRID NO.: 428839-01
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031

**SYNONYMS:**
V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**STUDY NUMBER:** 2648

**SPONSOR:**
Valent U.S.A. Corporation
1333 N. California Blvd
Walnut Creek, CA 94596

**LABORATORY:**
Environmental Health Science Laboratory
Sumitomo Chemical Co., Ltd.
1-98, 3-Chome, Kasugade-naka, Konohana-ku
Osaka, Japan

**REPORT TITLE:** Skin Irritation Test with S-23031 in Rabbits

**AUTHOR:** T. Nakanishi

**DATE ISSUED:** 7 October 1992

**EXECUTIVE SUMMARY:** The dermal irritation potential of S-23031, at a single dose 0f 0.5 g/kg, was evaluated in New Zealand white rabbits. Dermal responses were measured at 0.5, 24, 48 and 72 hours post-dosing. There was no evidence of erythema or edema formation at any of the time points.

**Based on the results of this study, S-23031 was nonirritating (Primary Irritation Score = 0).**

This study is classified as core minimum with a Toxicity Category IV and satisfies guideline requirements for primary dermal irritation (§81-5) in rabbits.

I. MATERIALS

A. Test Compound: S-23031 Description: light tan powder Batch #: PYG-88092-M Purity: 94.7% Contaminants: CBI Index

B. Test animals: Species: Rabbit Strain: New Zealand White Age: 15 weeks Weight (kg): 2.46 - 2.79 Source: Kitayama LABES Co., Ltd, Kyoto, Japan Housing: Individually housed in aluminum cages Feed: RC-4 diet 100 g/day (Oriental Yeast Co, Ltd, Tokyo, Japan) Water: Tap water, *ad libitum* Environment: Temperature, 22 ± 2°C; Humidity, 55 ± 15%; Light cycle, 12 hr light/12 hr dark; Ventilation, at least 10 air changes/hr

II. METHODS

A. Study design: The application sites were prepared by clipping the fur from the dorsal region of three male and three female rabbits. A dose of 0.5 g of test material was applied to a 2.5 $cm^2$ gauze pad (moistened with corn oil), applied to the exposed skin and held in place with an occlusive dressing. The test material remained in contact with the skin for 4 hours, at which time the gauze pad was removed and the application site cleaned and wiped with acetone to remove any remaining material. The skin was examined after 0.5, 24, 48 and 72 hours. Application sites were scored for edema and erythema using the Draize method.

III. REGULATORY COMPLIANCE

A. Quality assurance: Quality assurance was documented by signed and dated GLP and quality assurance statements.

IV. RESULTS and CONCLUSIONS: The dermal irritation potential of S-23031, at a single dose 0f 0.5 g/kg, was evaluated in New Zealand white rabbits. Dermal responses were measured at 0.5, 24, 48 and 72 hours post-dosing. There was no evidence of erythema or edema formation at any of the time points (Table 1). Under the conditions of the assay the test material was nonirritating (Primary Irritation Score = 0).

Toxicity category IV

Classification: core - minimum

This study satisfies guideline requirements (§81-5) for a primary skin irritation study in rabbits.

Table 1: Dermal Responses (Taken from Table 3 of the study)

C10848

| Rabbit | Erythema/Eschar Observation Time (hr) | | | | Edema Observation Time (hr) | | | | Score |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 24 | 48 | 72 | 0.5 | 24 | 48 | 72 | |
| 1, Male | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.00 |
| 2, Male | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.00 |
| 3, Male | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.00 |
| 4, Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.00 |
| 5, Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.00 |
| 6, Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.00 |
| | | | | | | | | Average Score | 0.00 |

Primary Review by: Robert F. Fricke, Ph.D. Robert Fricke 8 Mar 94
Review Section IV, Toxicology Branch II/HED (H7509C)

010848

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/14/94
Review Section IV, Toxicology Branch II/HED (H7509C)

**DATA EVALUATION REPORT**

**STUDY TYPE:** 21-Day Dermal - Rats (§82-2)

**EPA ID NOs:**
MRID NO.: 428258-16
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** V-23031 (0.83EC)

**SYNONYMS:**
S-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**STUDY NUMBER:** 2615-100

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Hazleton Washington, Inc., Rockville, MD

**TITLE OF REPORT:** 21-Day Dermal Toxicity Study in Rats with V-23031 (0.83EC)

**AUTHOR:** M. Moore

**REPORT ISSUED:** 16 October 1992

**EXECUTIVE SUMMARY:** Male and female SD rats (5/dose/sex) received repeated dermal dosing of test compound at 0, 100, 300, or 1000 (limit dose) mg/kg/day for 6 hours/day, 7 days/week for 21 days. No treatment-related effects were noted in lethality, body weight gain, food con-sumption, clinical pathology, or absolute and relative organ weights.

Significant, treatment-related effects, present in mid- and high-dose males and females, were limited to treated skin only; no systemic toxicity was noted. Slight erythema was present in mid- and high-dose females; slight to moderate desquamation was observed in mid- and high-dose animals. Gross pathological observations (desquamation; encrustations) were confirmed histologically (athancosis, hyperkeratosis, inflammation, incrustations, ulcerations). No systemic toxicity was present.

**Based on these findings, a LOEL of 300 mg/kg/day and a NOEL of 100 mg/kg/day was established for dermal toxicity for male and female rats. The NOEL for systemic toxicity was 1000 mg/kg/day (limit dose)**

This study is classified as **core minimum** and satisfies guideline requirements (§82-2) for a 21-day dermal toxicity study in rats.

## I. MATERIALS

A. Test Material: V-23031 (0.83EC) Description: medium brown liquid Batch #: V 803L01 Purity: 10.2% Contaminants: CBI Index

B. Test animals: Species: Rat Strain: Crl:CD BR Age: 55 days Weight at initiation (g): 220-265 (males), 200 - 233 (females) Source: Charles River Breeding Laboratories, Inc., Raleigh, NC Housing: Individually in suspended cages Feed: Purina Certified Rodent Chow #5002 Water: Tap water, *ad libitum* Environment: Temperature, 72 ± 6 °F; Humidity, 50 ± 20%; Light cycle, 12 hr light/12 hr dark

## II. METHODS

A. Prestudy Acclimation: Healthy animals were acclimated to the cages for two weeks prior to the start of the study. Seven days before the start date, hair on the entire trunk (approximately 6 cm x 10 cm) the animals was clipped; clipping was repeated one day before treatment. Plastic collars were placed on the animals five days prior to dosing to acclimate the animals to the collar.

B. Preparation of Skin and Dosing: Animals were reclipped before the initial dosing and as needed during the study. The test solutions were applied to a 5 cm x 5 cm of skin, covered with a gauze patch, and covered with an occlusive dressing. After a six hour exposure, the dressing was removed. After the test site was cleaned using a gauze patch moistened with distilled water, plastic collars were placed on each of the animals. Collars remained on the animals until approximately 1 to 2 hours prior to dosing. Dosing was repeated daily for 21 days.

C. Animal assignments: Animals were randomly assigned to study test groups as shown in Table 1.

Table 1: Animal Assignment to Study Groups

| Study Group | Dosage[a] (mg/kg/day) | Animals/Group Male | Female |
|---|---|---|---|
| Control | 0 | 5 | 5 |
| Low | 100 | 5 | 5 |
| Mid | 300 | 5 | 5 |
| High | 1000 | 5 | 5 |

[a] Not adjusted for percent purity of test compound

D. Dose preparation: Appropriate amounts of S-23031 were dissolved in vehicle (corn oil) to yield doses of 100, 300, or 1000 mg/kg when applied in a volume of 2 ml/kg. Control animals were dosed with vehicle only. The prepared solutions were analyzed for homogeneity and concentration.

E. Statistical Evaluations: Parametric data were initially analyzed for homogeneity of variances using Levene's test. Homogeneous data were further analyzed using analysis of variance (ANOVA). Data sets yielding a significant ANOVA result were further analyzed using pooled variance t-tests. Heterogeneous data sets were analyzed using ANOVA for unequal variances followed by separate variance t-tests. Nonparametric data were analyzed using Kruskal-Wallis' test or the Wilcoxon rank sum test as modified by Mann-Whitney. The Fisher's exact test was used to analyze frequency data.

III. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. A statement of "no confidentiality claims" was provided.

IV. RESULTS

A. Analysis of Test Solutions: Analysis of test solution samples, taken from the top, middle and bottom of the low and mid dosing solutions, indicated that the test compound was homogeneously distributed (mean coefficient of variation 0.75 to 4.27%); the mean nominal concentrations ranged from 93.9 to 101%.

B. Clinical Observations and Mortality: Animals were inspected twice daily for signs of toxicity, moribundity and mortality. A detailed clinical exam was performed once each week. Dermal responses were graded immediately before dosing using a modification of the Draize scoring method.

Results: Other than the dermal effects, individual and summarized clinical observations were not provided. Dermal effects were limited to treated skin of 300 mg/kg/day and 1000 mg/kg/day males and females (Table 2). Slight erythema was present in mid- and high-dose females; slight to moderate desquamation was observed in mid- and high-dose animals.

C. Body Weight, Body Weight Gains and Food Consumption: Animals were weighed at the start of the study, weekly, thereafter, and at terminal sacrifice. Food consumption was measured at weekly intervals.

Results: No treatment-related effects were noted. The mean body weights, body weight gains and food consumption for treated animals were comparable to controls values throughout the study.

F. Clinical Pathology: At terminal sacrifice, serum chemistry and hematological analyses were performed on animals, fasted overnight, using blood collected from retroorbital sinus.

Table 2: Treated Skin: Incidence of Dermal Observations (Data summarized from Table 3 of study)

| Observation Severity | Sex | Dose Group 0 | 100 | 300 | 1000 |
|---|---|---|---|---|---|
| Erythema | | | | | |
| Slight | Female | 0/5 | 0/5 | 3/5 | 2/5 |
| Desquamation | | | | | |
| Slight | Male | 0/5 | 0/5 | 5/5 | 5/5 |
| | Female | 0/5 | 0/5 | 5/5 | 5/5 |
| Moderate | Male | 0/5 | 0/5 | 0/5 | 3/5 |
| | Female | 0/5 | 0/5 | 0/5 | 5/5 |

1. Hematology parameters: No treatment-related effects were noted in any of the parameters listed below.

Hematocrit
Hemoglobin
Leukocyte count
Erythrocyte count
Platelet count
Reticulocyte count
Leukocyte differential count
Mean corpuscular HGB
Mean corpuscular HGB conc.
Mean corpuscular volume

2. Serum chemistry parameters: No treatment-related effects were noted in any of the parameters listed below.

Electrolytes
- Calcium
- Chloride
- Sodium
- Phosphorous
- Potassium

Enzymes
- Alanine aminotransferase (SGPT/ALT)
- Aspartate aminotransferase (SGOT/AST)

Other
- Glucose
- Blood creatinine
- Blood urea nitrogen
- Total bilirubin
- Protein, total
- Albumin
- Globulins
- A/G Ratio

H. Sacrifice and Pathology: Pathological examination was performed on animals in the control and treatment groups. Liver, kidneys, testes with epididymides, spleen, treated and untreated skin, and gross lesions were collected at necropsy and saved in 10% neutral buffered formalin. Histological examinations were performed on treated and untreated skin of all animals; the remaining tissues were examined in the control and high-dose animals only. Liver, kidneys, testes with epididymides, spleen were weighed before being fixed.

1. Organ weights: Absolute organ weights and organ weights relative to terminal body weight were measured. No significant, treatment-related findings were noted.

2. Gross pathology: Gross pathological examinations were performed on animals found dead or sacrificed in moribund condition during the study and surviving animals at terminal sacrifice. The treated skin of mid- and high-dose males and females was desquamated; crusted material was also present on the skin of high-dose animals (Table 3). Untreated skin did not show any lesions.

Table 3: Treated Skin: Incidence of Gross Pathological Observations[a]

| Observation | Sex | Dose Group 0 | 100 | 300 | 1000 |
|---|---|---|---|---|---|
| Desquamated | Male | 0/5 | 0/5 | 1/5 | 5/5 |
| | Female | 0/5 | 0/5 | 4/5 | 5/5 |
| Crusty material | Male | 0/5 | 0/5 | 0/5 | 2/5 |
| | Female | 0/5 | 0/5 | 0/5 | 1/5 |

a Data summarized from Table 7 of report

3. Histopathology: Significant, treatment-related histopathological changes were noted only in treated skin (Table 4); no treatment-related systemic lesions were present in any of the animals. A high incidence of athancosis, hyperkeratosis, and inflammation were observed in mid- and high-dose males and females. Mid- and high-dose females had a high incidence of incrustations; males were less severely affected. To a lesser extent mid- and high-dose males showed increased ulceration; ulceration was present in females, but the incidence did not appear to be dose-related.

V. DISCUSSION: Male and female Sprague-Dawley rats received repeated dermal dosing of test compound at 0, 100, 300, or 1000 mg/kg/day for 6 hours/day, 7 days/week for 21 days. No treatment-related effects were noted in mortality, body weight gain, food consumption, clinical pathology, or absolute and relative organ weights.

Significant, treatment-related effects, present in mid- and high-dose males and females, were limited to treated skin only; no systemic toxicity was noted. Slight erythema was present in mid- and high-dose females; slight to moderate desquamation was observed in mid- and high-dose animals. Gross pathological observations (desquamation; encrustations) were confirmed histologically (athancosis, hyperkeratosis, inflammation, incrustations, ulcerations).

Based on the results of this study, the NOEL and LOEL for dermal toxicity of S-23031 in male and female rats was 100 and 300 mg/kg/day, respectively. The NOEL for systemic toxicity was 1000 mg/kg/day (limit dose)

This study is classified as core minimum and satisfies guideline requirements (§82-2) for a 21-day dermal toxicity study in rats.

Table 4: Treated Skin: Incidence of Histopathological Observations[a]

| Observation | Sex | Dose Group 0 | 100 | 300 | 1000 |
|---|---|---|---|---|---|
| Acanthosis | Male | 0/5 (0,0,0)[b] | 0/5 (0,0,0) | 5/5 (5,0,0) | 5/5 (1,4,0) |
| | Female | 2/5 (2,0,0) | 3/5 (3,0,0) | 5/5 (2,3,0) | 5/5 (0,5,0) |
| Hyperkeratosis | Male | 0/5 (0,0,0) | 0/5 (0,0,0) | 2/5 (2,0,0) | 5/5 (1,4,0) |
| | Female | 2/5 (2,0,0) | 3/5 (3,0,0) | 5/5 (5,0,0) | 5/5 (1,4,0) |
| Inflammation | Male | 0/5 (0,0,0) | 0/5 (0,0,0) | 4/5 (4,0,0) | 4/5 (4,0,0) |
| | Female | 1/5 (1,0,0) | 2/5 (2,0,0) | 5/5 (4,1,0) | 5/5 (5,0,0) |
| Incrustation | Male | 0/5 (0,0,0) | 0/5 (0,0,0) | 1/5 (0,1,0) | 1/5 (0,1,0) |
| | Female | 2/5 (1,1,0) | 3/5 (2,1,0) | 5/5 (1,4,0) | 5/5 (0,4,1) |
| Ulcer | Male | 0/5 (0,0,0) | 0/5 (0,0,0) | 1/5 (0,1,0) | 2/5 (2,0,0) |
| | Female | 2/5 (2,0,0) | 3/5 (0,2,1) | 5/5 (1,4,0) | 2/5 (1,1,0) |

[a] Data summarized from Table 3 of report

[b] Incidence for severity of lesions (minimal, slight, moderate)

Primary Review by: Robert F. Fricke, Ph.D. Robert F. Fricke 14 Mar 199
Review Section IV, Toxicology Branch II/HED (H7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/14/94
Review Section IV, Toxicology Branch II/HED (H7509C)

010848

**DATA EVALUATION RECORD**

**STUDY TYPE:** 21-Day Dermal - Rats (§82-2)

**EPA ID NOs:**
MRID NO.: 428258-15
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031

**SYNONYMS:**
V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**STUDY NUMBER:** 343-229

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Hazleton Laboratories America, Inc.
Rockville, MD

**TITLE OF REPORT:** 21-Day Dermal Toxicity Study in Rats with S-23031

**AUTHOR:** M. Osheroff

**REPORT ISSUED:** 8 August 1991

**EXECUTIVE SUMMARY:** Male and female Sprague-Dawley rats received repeated dermal dosing of test compound at 0, 100, 300, or 1000 (limit dose) mg/kg/day for 6 hours/day, 7 days/week for 21 days. No treatment-related effects were noted in mortality, body weight gain, food consumption, clinical pathology, or absolute and relative organ weights. Although gross pathological examination of the livers revealed an increased incidence of pale areas, no relevant histopathological changes were found. The gross changes in the liver were attributed to the occlusive dressing. No treatment-related dermal toxicity was noted at the highest dose tested (1000 mg/kg/day).

**Based on these findings, a NOEL of 1000 mg/kg/day (limit dose) for systemic and dermal toxicity was established for male and female rats.**

This study is classified as Core Guideline and satisfies guideline requirements (§82-2) for a 21-day dermal toxicity study in rats.

## I. MATERIALS

A. Test Material: S-23031, technical Description: brown powder Batch #: PYG-88092-M Purity: 94.7% Contaminants: CBI Index

B. Test animals: Species: Rat Strain: Sprague-Dawley Crl:CD BR Age: 8 weeks Weight at initiation (g): 227.4 - 258.9 (males), 181.1 - 206.5 (females) Source: Charles River Breeding Laboratories, Inc., Portage, MI. Housing: Individually in suspended cages Feed: Purina Certified Rodent Chow #5002 Water: Tap water, *ad libitum* Environment: Temperature, 72 ± 6 °F; Humidity, 50 ± 20%; Light cycle, 12 hr light/12 hr dark

## II. METHODS

A. Prestudy Acclimation: Healthy animals were acclimated to the cages for two weeks prior to the start of the study. Seven days before the start date, hair on the entire trunk (approximately 6 cm x 10 cm) the animals was clipped; clipping was repeated one day before treatment. Plastic collars were placed on the animals five days prior to dosing to acclimate the animals to the collar.

B. Preparation of Skin and Dosing: Animals were reclipped before the initial dosing and as needed during the study. The test solutions were applied to a 5 cm x 5 cm of skin, covered with a gauze patch, and covered with an occlusive dressing. Following a six-hour exposure, the dressing was removed, and the test site cleaned using a gauze patch moistened with distilled water. Plastic collars were placed on each of the animals after cleaning the test site until approximately 1 to 2 hours prior to the next dosing. Dosing was repeated daily for 21 days.

C. Animal assignments: Animals were randomly assigned to study test groups as shown in Table 1.

Table 1: Animal Assignment to Study Groups

| Study Group | Dosage[a] (mg/kg/day) | Animals/Group Male | Female |
|---|---|---|---|
| Control | 0 | 5 | 5 |
| Low | 100 | 5 | 5 |
| Mid | 300 | 5 | 5 |
| High | 1000 | 5 | 5 |

a. Not adjusted for percent purity of test compound

D. Dose preparation: Appropriate amounts of S-23031 were dissolved in corn oil to yield doses of 100, 300, or 1000 mg/kg when applied in a volume of 2 ml/kg. Control animals were dosed with an appropriate volume vehicle (corn oil). The prepared solutions were analyzed for homogeneity and concentration.

E. Statistical Evaluations: Parametric data were initially analyzed for homogeneity of variances using Levene's test. Homogeneous data were further analyzed using analysis of variance (ANOVA). Data sets yielding a significant ANOVA result were further analyzed using pooled variance t-tests. Heterogeneous data sets were analyzed using ANOVA for unequal variances followed by separate variance t-tests. Nonparametric data were analyzed using Kruskal-Wallis' test or the Wilcoxon rank sum test as modified by Mann-Whitney. The Fisher's exact test was used to analyze frequency data.

III. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. A statement of "no confidentiality claims" was provided.

IV. RESULTS

A. Analysis of Test Solutions: Analysis of test solution samples, taken from the top, middle and bottom of the low and mid dose solutions, indicated that the test compound was homogeneously distributed (mean coefficient of variation 0.649 to 0.602%); the mean nominal concentrations ranged from 93.5 to 102%.

B. Clinical Observations and Mortality: Animals were inspected twice daily for signs of toxicity, moribundity and mortality. A detailed clinical exam was performed once each week.

Results: Individual and summarized clinical observations were not provided. The results section of the study indicated that one control male was cold to touch, two mid-dose males and one high-dose male had red colored discharge in the urine, and one high-dose male had a red discharge from the penis.

C. Dermal Irritation Results: Dermal responses were graded immediately before dosing using a modification of the Draize scoring method.

Results: Dermal responses were limited to desquamation of one high dose female on Days 15 and 17 of the study.

D. Body Weight and Body Weight Gains: Animals were weighed at the start of the study, weekly, thereafter, and at terminal sacrifice.

Results: No treatment-related effects were noted. The mean body weights and body weight gains for treated animals were comparable to controls throughout the study.

E. Food Consumption: Food consumption was measured at weekly intervals.

Results: Compared to controls, no significant differences in food consumption were noted in any of the treated groups at any time during the study.

F. Clinical Pathology: At terminal sacrifice, serum chemistry and hematological analyses were performed on animals, fasted overnight, using blood collected from retroorbital sinus.

1. Hematology parameters: The following hematology parameters listed below were evaluated. No treatment-related effects were noted in any of the parameters.

| | |
|---|---|
| Hematocrit | Reticulocyte count |
| Hemoglobin | Leukocyte differential count |
| Leukocyte count | Mean corpuscular HGB |
| Erythrocyte count | Mean corpuscular HGB conc. |
| Platelet count | Mean corpuscular volume |

Results: Significant hematological findings were limited to a slight decrease in the platelet count of all treated females (Table 2). The effect does not appear to be biologically significant since the values were within the background control range.

2. Serum chemistry parameters: The following serum chemistry parameters listed below were evaluated.

Electrolytes
- Calcium
- Chloride
- Sodium
- Phosphorous
- Potassium

Enzymes
- Alanine aminotransferase (SGPT/ALT)
- Aspartate aminotransferase (SGOT/AST)

Other
- Glucose
- Blood creatinine
- Blood urea nitrogen
- Total bilirubin
- Protein, total
- Albumin
- Globulins

Results: Significant clinical chemistry findings were limited to a slight decrease in glucose concentration of high dose females (Table 2). The effect does not appear to be biologically significant since the value was within the background control range.

Table 2: Clinical Chemistry and Hematology Results in Females[a]

| Observation | Dose Group 0 | 100 | 300 | 1000 |
|---|---|---|---|---|
| Platelets[b] ($10^3/\mu l$) | 1519 | 1137• | 1024• | 1119• |
| Glucose[b] (mg/dl) | 106 | 95 | 90 | 88• |

a Summarized from Tables 4 and 5 of the report
b Background control ranges: Platlets, 780 to 1534 $10^3/\mu l$
Glucose, 82 to 154 mg/dl
• $p \leq 0.05$

H. Sacrifice and Pathology: Gross pathological examinations were performed on animals found dead or sacrificed in moribund condition during the study and all surviving animals at terminal sacrifice. Liver, kidneys, testes with epididymides, spleen, treated and untreated skin, and gross lesions were collected at necropsy and saved in 10% neutral buffered formalin. Histological examinations were performed on the above tissues from the control and high-dose animals. Liver, kidneys, testes with epididymides, spleen were weighed before being fixed.

1. Organ weights: Absolute and organ weights relative to terminal body weight were measured. No significant, treatment-related findings were noted.

2. Gross pathology: The incidence of pale areas on the livers of high-dose males was increased over controls (Table 3).

3. Microscopic pathology: No treatment-related systemic lesions were present in any of the animals. Treated skin of high-dose animals appeared normal.

Table 3: Gross Pathological Lesions[a]

| Observation | Sex | 0 | 100 | 300 | 1000 |
|---|---|---|---|---|---|
| Liver - Pale area | Male | 1/5 | 1/5 | 1/5 | 3/5 |
| | Female | 1/5 | 1/5 | 2/5 | 0/5 |

a Data summarized from Table 6 of the report

V. DISCUSSION: Male and female Sprague-Dawley rats received repeated dermal dosing of test compound at 0, 100, 300, or 1000 mg/kg/day for 6 hours/day, 7 days/week for 21 days. No treatment-related effects were noted in mortality, body weight gain, food consumption, clinical pathology, or absolute and relative organ weights. Significant clinical chemistry

(decreased glucose levels) and hematology (decreased platelet counts) findings were present in females; the values, however, were within background control ranges and not considered treatment-related. Although gross pathological examination of the livers revealed an increased incidence of pale areas, the results were not confirmed histopathologically. Gross pathological changes in the liver were attributed to the occlusive dressing. No treatment-related dermal toxicity was noted at the the highest dose tested (1000 mg/kg/day).

Based on the results of this study, the LOEL for systemic and dermal toxicity of S-23031 in male and female rats is greater than 1000 mg/kg/day (limit dose).

Core Classification: Guideline

This study satisfies guideline requirements (§82-2) for a 21-day dermal toxicity study in rats.

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 10 Mar 94
Section IV, Tox. Branch II (H7509C)

Secondary Reviewer: Jess Rowland, M.S. Jess Rowland 3/14/94
Section IV, Tox. Branch II (H7509C)

C10848

**DATA EVALUATION RECORD**

**STUDY TYPE:** 90-Day Feeding - Mice (§82-1)

**EPA ID NOs:** MRID NO.: 428839-04
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031

**SYNONYMS:** V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**STUDY NUMBER:** 1650

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Environmental Health Science Laboratory
Sumitomo Chemical Co., Ltd., Osaka, Japan

**TITLE OF REPORT:** Three Month Subacute Toxicity Study of S-23031 by Dietary Administration in Mice

**AUTHOR:** H. Yamada

**REPORT ISSUED:** 26 November 1990

**EXECUTIVE SUMMARY:** Male and female CD-1 mice (6/group/sex) were fed diets containing 0, 1000, 3000 or 10000 ppm (equivalent to 0, 125, 379, or 1274 mg/kg/day, males; 0, 150, 366 or 1224 mg/kg/day, females) S-23031 for 13 weeks. Males at 3000 ppm showed increased absolute and relative liver weights, altered hematology (decreased RBC, hemoglobin concentration and hematocrit) and increased incidence of gross (mottled, enlarged livers) and histopathological (hepatocellular hypertrophy, hepatocellular vacuolation, and single cell necrosis) findings. No treatment-related effects were noted in females at the highest dose tested.

**Based on these findings the LOEL is 3000 ppm (379 mg/kg/day) for systemic toxicity in males; LOEL was not established in females. NOELs were established at 1000 ppm (125 mg/kg/day) in males and 10000 ppm (1224 mg/kg/day) in females.**

This study is classified as Core Supplementary and does not satisfy guideline requirements (§82-1) for a 90-day feeding study in mice. This study can not be upgraded since it did not conform to guideline requirements in number of animals tested, lack of ophthalmology, and deficiencies in clinical chemistry parameters.

I. MATERIALS

C10848

A. Test Material: S-23031, technical Description: brown granule or miconized powder Batch #: PYG-88092 (granule) and PYG-88092-M (powder) Purity: 94.4% (granule) and 94.7% (powder) Contaminants: CBI Index

B. Test Animals: Species: Mouse Strain: CD-1(ICR) Age: 5 weeks Weight at initiation (g): 24.1 - 28.6 (males), 19.3 - 24.3 (females) Source: Charles River Japan, Inc., Kanagawa, Japan Housing: Three animals/cage during study Feed: CRF-1 diet *ad libitum* (Oriental Yeast Co, Ltd, Tokyo. Japan) Water: Tap water, *ad libitum* Environment: Temperature, 24 ± 2°C; Humidity, 55 ± 10%; Light cycle, 12 hr light/12 hr dark; Ventilation, at least 10 air changes/hr.

II. METHODS

A. Animal assignment: Animals were assigned randomly to interim and main study test groups as shown in Table 1. An interim sacrifice was carried out after 4 weeks.

NOTE: Guideline requirements specify that at least 10 animals/group/sex should be used.

Table 1: Animal Assignment to Study Groups

| Test Group | Dose in Diet (ppm) | Interim Study | | Main Study | |
|---|---|---|---|---|---|
| | | Male | Female | Male | Female |
| Control (CON) | 0 | 6 | 6 | 6 | 6 |
| Low (LDT) | 1000 | 6 | 6 | 6 | 6 |
| Mid (MDT) | 3000 | 6 | 6 | 6 | 6 |
| High (HDT) | 10000 | 6 | 6 | 6 | 6 |

B. Diet preparation: Granulated and powdered forms of S-23031 were used in the study; both forms were equal in quality (synthesized at the same time and almost the same purity and composition of impurities). Because of the two different forms, the test diets were prepared using two different methods. For granular S-23031, a weighed amount was ground with a mortar and pestle and added to the basal diet to form a premix. The premix was blended with basal diet to the final desired concentration of 10000 ppm. Lower dietary concentrations were prepared by serial dilution of the 10000 ppm test diet with basal diet. For diets containing powdered S-23031, premixes were prepared by thoroughly mixing weighed amounts S-23031. The premixes were diluted with sufficient basal diet to yield final concentrations of 1000 and 10000 ppm. The 3000 ppm diet was prepared by diluting the 10000 ppm diet with basal diet.

C. Statistical Analysis: A one-way analysis of variance (ANOVA) was performed for body weight, food consumption, myeloid/erythroid, hematology, blood chemistry and organ weight. If a significant ANOVA result was found, pair-wise comparisons were carried out using the Least Significant Difference test. No statistical procedure was presented for the analysis of incidence data for gross pathological or histopathological observations.

IV. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. The sponsor applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of this study. This study neither meets nor exceeds any of the applicable criteria.

C. A statement of "no confidentiality claims" was provided.

V. RESULTS

A. Analytical Chemistry: The test diets were analyzed for stability, homogeneity and concentration. Stability results from another study (MRID No.: 428839-06) showed that test diets containing 100 and 20000 ppm were stable for six weeks when refrigerated and four weeks at room temperature; the same lot number of S-23031 was used in both studies. Samples taken from the top, middle and bottom of the diets were homogeneous with coefficients of variation of 1.9, 0.33 and 0.57%, respectively. The 1000, 3000 and 10000 ppm diets were within 95.0 - 98.6%, 99.7 - 100%, and 100 - 101% of the desired final concentration, respectively.

B. Observations: Animals were inspected twice (weekdays) or once (weekends, holidays) daily for signs of toxicity, moribundity and mortality.

1. Toxicity: No significant, treatment-related signs of toxicity were noted.

2. Mortality (survival): All animals survived until the scheduled sacrifice.

C. Body Weight: Animals were weighed at the start of the study, on Day 7 and weekly, thereafter.

Results: During the course of the study no significant, treatment-related differences in body weights were noted in either the male or female animals.

D. Food Consumption and Achieved Compound Intake: Food consumption, determined at weekly intervals, was measured during a consecutive 48 hour period.

1. Food consumption results: During the course of the study no significant, treatment-related differences in food consumption were noted in either the male or female animals.

2. Achieved compound intake: The mean compound intake is summarized in Table 2.

Table 2: Average Achieved Compound Intake (Data summarized from Table 4 of study)

| Dose in Diet (ppm) | Intake (mg/kg/day) Male | Female |
|---|---|---|
| 0 | 0 | 0 |
| 1000 | 125 | 150 |
| 3000 | 379 | 366 |
| 10000 | 1274 | 1224 |

F. Hematology and Clinical Chemistry: Hematology and clinical chemistry analyses were performed at the interim, and terminal sacrifices.

1. Hematology: The hematology parameters listed below were determined. Reticulocyte counts were measured only at terminal sacrifice.

| | |
|---|---|
| Hematocrit | Reticulocyte count |
| Hemoglobin | Leukocyte count |
| Leukocyte differential | Erythrocyte count |
| Platelet count | Erythroblast count |
| Mean corpuscular volume | Myeloid/erythroid ratio |
| Mean corpuscular HGB | Mean corpuscular HGB conc. |

Results: Hematology results for the interim and terminal sacrifices are summarized in Table 4. Statistically significant decreases in hemoglobin and hematocrit were observed in the mid- and high-dose males at the interim and terminal sacrifices. Erythrocyte counts were significantly lower in mid- and high-dose males at 4 weeks; at 13 weeks, significant differences were noted only in the high-dose males.

2. Clinical Chemistry: The parameters listed below were measured. Total and direct bilirubins were measured only at terminal sacrifice.

Blood creatinine
Blood urea nitrogen
Total Bilirubin
Direct Bilirubin
Serum alanine aminotransferase (SGPT/ALT)
Serum aspartate aminotransferase (SGOT/AST)

Results: Decreases in blood urea nitrogen and total bilirubin were observed in treated males sacrificed at 13 weeks (Table 3). The decreases in blood urea nitrogen and total bilirubin were slight and not considered biologically significant.

Table 3: Clinical Chemistry Results for Male Mice Sacrificed at 13 Weeks[a]

| Parameter | Week of Study | Dose Level (ppm) 0 | 1000 | 3000 | 10000 |
|---|---|---|---|---|---|
| Blood Urea Nitrogen (mg/dl) | 13 | 34.9 | 27.9* | 27.5** | 27.3** |
| Total Bilirubin (mg/dl) | 13 | 0.1 | 0.0** | 0.0 | 0.0* |

a Data summarized from Table 7 of the report
* $p \leq 0.05$, ** $p \leq 0.01$

G. Sacrifice and Pathology: Detailed pathological examinations were performed on male and female animals in the control and all treatment groups. The tissues listed below were collected and preserved for histological examination; tissues in CAPITALIZED letters were weighed.

Digestive system
- Tongue
- Pancreas
- Esophagus
- Stomach
- Duodenum
- Jejunum
- Ileum
- Cecum
- Colon
- Rectum
- LIVER
- Gall bladder

Respiratory
- Trachea
- Lungs

Cardiovas./Hematol
- Aorta
- HEART
- Bone marrow
- Lymph nodes
- SPLEEN
- THYMUS

Urogenital
- KIDNEYS
- Urinary bladder
- TESTES
- Epididymides
- Prostate
- Seminal vesicle
- OVARIES
- Uterus
- Vagina

Neurologic
- BRAIN
- Periph. nerve
- Spinal cord
- Pituitary
- Eyes

Glandular
- ADRENALS
- Thyroids
- Mammary gland
- Parathyroids

Other
- Skin
- Harderian glands
- Skeletal muscle
- Submandibular glands
- Gross lesions

1. Organ Weights: Mid- and high-dose males showed increases in both absolute and relative liver weights at 4 and 13 weeks; the absolute heart weights were also slightly elevated (Table 5). Females showed no treatment-related changes in either the absolute or relative organ weights.

Table 4: Hematology Results for Male Mice Sacrificed at 4 and 13 Weeks[a]

| Parameter | Week of Study | Dose Level (ppm) 0 | 1000 | 3000 | 10000 |
|---|---|---|---|---|---|
| Erythrocyte Count ($10^6/\mu l$) | 4 | 9.27 | 8.75 | 8.41** | 8.05** |
| | 13 | 9.27 | 8.82 | 8.40 | 8.51 |
| Hemoglobin (g/dl) | 4 | 14.8 | 14.2 | 13.7* | 12.8** |
| | 13 | 14.5 | 13.9 | 13.1** | 13.0** |
| Hematocrit (%) | 4 | 43.4 | 41.6 | 41.1* | 38.1** |
| | 13 | 43.5 | 41.0 | 37.8** | 38.4** |

[a] Data summarized from Table 5 of the report
* $p \leq 0.05$, ** $p \leq 0.01$

Table 5: Mean Absolute (g) and Relative (g/kg body wt) Organ Weights of Male Mice Sacrificed at 4 and 13 Weeks[a]

| Parameter | Week of Study | Dose Level (ppm) 0 | 1000 | 3000 | 10000 |
|---|---|---|---|---|---|
| Absolute Liver Wt | 4 | 2.14 | 2.31 | 2.39* | 2.70** |
| | 13 | 2.10 | 2.39 | 2.65** | 3.03** |
| Absolute Heart Wt | 13 | 0.18 | 0.17 | 0.20* | 0.20* |
| Relative Liver Wt | 4 | 6.13 | 6.62 | 6.89** | 7.91** |
| | 13 | 5.60 | 5.93 | 6.30** | 7.51** |

[a] Data summarized from Tables 9 and 10 of the report
* $p < 0.05$, ** $p < 0.01$

2. Gross Pathology: Gross pathological finding are summarized in Table 6. At both the interim and terminal sacrifices, the incidence of enlargement and mottling of the livers was increased in high-dose males. Mid-dose males had a lower incidence of mottling of the livers at both 4 and 13 weeks; enlargement was evident only at 13 weeks. Females showed no treatment-related effects.

3. Histopathology: Treatment-related histopathological finding present males at both the interim and terminal sacrifices (Table 7). Findings included an increased incidence of hepatocellular hypertrophy and vacuolation in mid- and high-dose males and single cell necrosis in high-dose males. Finding in females were limited to increased incidence of hepatocellular vacuolation at the interim sacrifice; at terminal sacrifice histopathological findings in the treated females were comparable to controls.

Table 6: Gross Pathological Findings of Male Mice Sacrificed at 4 and 13 Weeks[a]

| Liver Finding | Week of Study | Dose Level (ppm) 0 | 1000 | 3000 | 10000 |
|---|---|---|---|---|---|
| Enlargement | 4 | 0/6 | 0/6 | 0/6 | 4/6 |
| | 13 | 0/6 | 0/6 | 2/6 | 6/6 |
| Mottling | 4 | 0/6 | 0/6 | 2/6 | 6/6 |
| | 13 | 0/6 | 1/6 | 3/6 | 5/6 |

a. Data summarized from Table 8 of the report

Table 7: Histopathological Findings[a]

| Liver Finding | Sex | Week of Study | Dose Group 0 | 1000 | 3000 | 10000 |
|---|---|---|---|---|---|---|
| Hepatocellular hypertrophy | Male | 4 | 0/6 | 0/6 | 3/6 | 6/6 |
| | | 13 | 0/6 | 0/6 | 3/6 | 6/6 |
| Hepatocellular vacuolation | Male | 4 | 1/6 | 0/6 | 2/6 | 6/6 |
| | | 13 | 3/6 | 3/6 | 6/6 | 6/6 |
| | Female | 4 | 1/6 | 0/6 | 2/6 | 6/6 |
| Single cell necrosis | Male | 4 | 1/6 | 2/6 | 0/6 | 5/6 |
| | | 13 | 4/6 | 2/6 | 1/6 | 5/6 |

a. Data summarized from Table 11 of the report

D. DISCUSSION: In a 13-week study, male and female CD-1 mice (6/group/sex) were fed test diets containing 0, 1000, 3000 or 10000 ppm (respective mg/kg/day equivalent: 0, 125, 379, or 1274 for males and 0, 150, 366 or 1224 for females).

No treatment-related effects on body weight, body weight gain or food consumption were noted during the study.

Treatment-related decreases in erythrocyte counts, hemoglobin and hematocrit in mid- and high-dose males were also observed in a 79-week oncogenicity study (MRID No.: 428839-05).

Both the absolute and relative liver weights of were significantly higher than controls at both the interim and terminal sacrifices for mid- and high-dose males. The changes in the absolute and relative liver weights were considered treatment-related since both gross (enlargement, mottling) and histological (hepatocellular hypertrophy, hepatocellular vacuolation, and single cell necrosis) findings were also present. The increases in absolute heart weights of mid- and high-dose males were slight and, in the absence of any gross or histopathological findings, the changes were not considered to be treatment-related. Effects observed in the females were limited

to increased incidence of single cell necrosis in the liver at the interim sacrifice. This effect was transient, no treatment-related effects were noted in any of the females at terminal sacrifice.

Based on these findings the LOEL is 3000 ppm (379 mg/kg/day) for systemic toxicity in males; LOEL was not established in females. NOELs were established at 1000 ppm (125 mg/kg/day) in males and 10000 ppm (1224 mg/kg/day) in females.

This study is classified as Core Supplementary and does not satisfy guideline requirements (§82-1) for a 90-day feeding study in mice. This study can not be upgraded since it did not conform to guideline requirements in number of animals tested, lack of ophthalmology, and deficiencies in clinical chemistry parameters.

Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 9 Mar 94
Section IV, Tox. Branch II (H7509C)

Secondary Reviewer: Jess Rowland, M.S. Jess Rowland 3/14/94
Section IV, Tox. Branch II (H7509C)

010848

**DATA EVALUATION RECORD**

**STUDY TYPE:** 90-Day Feeding - Rats (§82-1)

**EPA ID NOs:** MRID NO.: 428839-03
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031

**SYNONYMS:** V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**STUDY NUMBER:** 8803

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Sumitomo Chemical Co., Ltd, Osaka, Japan

**TITLE OF REPORT:** 13-Week Subchronic Toxicity Study of S-23031 Pure in Rats

**AUTHOR:** S. Tamano

**REPORT ISSUED:** 6 November 1990

**EXECUTIVE SUMMARY:** Male and female Sprague-Dawley rats (12/dose/sex) were fed diets containing 0, 100, 1000, 10000, or 30000 ppm (equivalent to 0, 6.46, 64.9, 659 or 2087 mg/kg/day for males and 0, 6.93, 70.6, 724 or 2249 mg/kg/day for females, respectively) S-23031 for 13 weeks. No treatment-related effects were noted in either body weight, body weight gain, food consumption, food efficiency, water consumption, hematology, or clinical chemistry. Significant increases in the relative liver weight was noted in high-dose males. Other treatment-related effect were the significant increase in the number of epithelial cells appearing in the urinary sediment of 10000 and 30000 ppm males and females.

**Based on these findings, a LOEL of 10000 ppm (659 mg/kg/day, males; 724 mg/kg/day, females) and a NOEL of 1000 ppm (65 mg/kg/day, males; 71 mg/kg/day, females) are established for systemic toxicity in male and female rats**

This study is classified as Core Guideline and satisfies guideline requirements (§82-1) for a 90-day feeding study in rats.

I. MATERIALS:

A. Test Compound: S-23031, technical Description: pale brown crystal Batch #: LN-80206 Purity: 99.2% Contaminants: CBI Index

B. Test Animals: Species: Rat Strain: Crj:CD(SD) Age: 5 weeks Weight (g): 118 - 141 (males), 103 - 122 (females) Source: Charles River Japan, Inc. Housing: three/cage Feed: CL-0921, Clea Japan, Inc, *ad libitum* Water: Tap water, *ad libitum* Environment: Temperature: 22 ± 2; Humidity: 55 ± 10%; Air changes: > 15/hr; Light cycle: 12 hr light/12 hr dark

II. METHODS

A. Animal Assignment: Animals were assigned to test groups using a randomized, weight-stratified technique (Table 1). No interim sacrifice was performed.

Table 1: Animal Assignment to Study Groups

| Test Group | Dose in Diet (ppm) | No. of Animals | |
|---|---|---|---|
| | | Male | Female |
| Control | 0 | 12 | 12 |
| Low | 100 | 12 | 12 |
| Middle 1 | 1000 | 12 | 12 |
| Middle 2 | 10000 | 12 | 12 |
| High | 30000 | 12 | 12 |

B. Dose Selection: Dose selection was based on a two-week feeding study with S-23031 at dietary levels of 0, 100, 1000, 10000 or 30000 ppm. At 30000 ppm rats showed increased liver weights, decreased serum glutamic pyruvic transaminase, total cholesterol, phospholipid and triglyceride and increased serum γ-glutamyl transpeptidase and sodium.

C. Diet Preparation: A weighed amount of S-23031 was added to powdered basal diet to yield the desired final concentration and mixed for 30 min. To prevent the formation of dust during mixing, corn oil was added at a final concentration of 2%. Test diets were prepared at four week intervals and stored at room temperature.

D. Statistical Analyses: Parametric data were analyzed for significance using two-sided Student's t-test. Incidence data were evaluated using the two-sided Fisher's exact test. Nonparametric data were analyzed using the Mann-Whitney U test.

NOTE: Multiple, pair-wise comparisons using the Student's t-test are not valid. Appropriate tests would include an initial evaluation for significance using ANOVA followed by one of the appropriate post hoc analyses for multiple comparisons (i.e., least significant difference test, Duncan's multiple range test). Where significant and possible treatment-related effects were indicated in the study, the reviewer reevaluated the data using ANOVA and least significant difference tests. In all cases, except for the increase noted in the relative liver weights of high-dose males, the differences were found to be insignificant.

IV. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. The sponsor applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of this study. This study neither meets nor exceeds any of the applicable criteria.

C. A statement of "no confidentiality claims" was provided.

V. RESULTS

A. Analytical Chemistry: The prepared diets were analyzed for stability, homogeneity and concentration. Test diets were stable up to six weeks when refrigerated and four weeks when stored at room temperature. Samples taken from the top, middle and bottom of the 100, 1000, 10000 and 30000 ppm diets were homogeneous with coefficients of variation of 4.87, 1.27, 0.97 and 0.73%, respectively. The concentrations of S-23031 in the 100, 1000, 10000 and 30000 ppm diets were within 89.0 to 105%, 94.0 to 98%, 96.9 to 99.9%, and 93.7 to 99.7% of nominal, respectively.

B. Observations: Animals were inspected at least once daily for signs of toxicity, moribundity and mortality.

1. Toxicity: No clinical signs attributable to the administration of S-23031 were observed during the study.

2. Mortality (survival): All animals survived until the scheduled sacrifice.

C. Body weight: Animals were weighed at the start of the study, weekly, thereafter, and at terminal sacrifice following a 16-hour fast.

Results: During the course of the study no significant, treatment-related differences in body weights were noted in either the male or female animals.

D. Food Consumption, Food Efficiency, Achieved Compound Intake and Water Consumption: Food and water consumption were measured weekly during a consecutive 48 hour period.

1. Food consumption results: No statistically or biologically significant differences were noted in the food consumption of either males or females during the study.

2. Food efficiency: No statistically or biologically significant differences were noted in the food efficiency of either males or females during the study.

3. Achieved compound intake: The mean compound intake is summarized in Table 2.

Table 2: Achieved Compound Intake (mg/kg/day)[a]

| | Dose Level (ppm) | | | |
|---|---|---|---|---|
| Sex | 100 | 1000 | 10000 | 30000 |
| Male | 6.46 | 64.9 | 659 | 2087 |
| Female | 6.93 | 70.6 | 724 | 2249 |

[a] Data summarized from Table 5 of report

4. Water consumption: No statistically or biologically significant differences were noted in the water consumption of either males or females during the study.

E. Ophthalmological Examinations: Examinations were performed on all animals during the prestudy quarantine period and during Week 13 of the study. No treatment-related eye lesions were observed either before or at the conclusion of the study.

F. Hematology, Clinical Chemistry and Urinalysis: Hematology, clinical chemistry and urinalysis were performed at the scheduled sacrifice on all animals following an overnight fast. Blood was collected under ether anesthesia from the abdominal aorta; urine was collected during a four-hour.

1. Hematology: The following hematology parameters were measured:

| | |
|---|---|
| Hematocrit | Reticulocyte count |
| Hemoglobin | Leukocyte differential count |
| Leukocyte count | Mean corpuscular HGB |
| Erythrocyte count | Mean corpuscular HGB conc. |
| Platelet count | Mean corpuscular volume |

Results: Hematological analyses performed at terminal sacrifice did not reveal any treatment-related effects. Although significant findings were noted in the study, statistical reevaluation of data by the reviewer did not reveal any statistically significant differences.

2. Clinical Chemistry: The following clinical chemistry parameters were measured:

Electrolytes
- Calcium
- Chloride
- Sodium
- Phosphorous
- Potassium

Enzymes
- γ-Glutamyl transpeptidase
- Alkaline phosphatase
- Cholinesterase
- Creatinine phosphokinase
- Lactic acid dehydrogenase
- Leucine aminopeptidase
- Serum alanine aminotransferase
- Serum aspartate aminotransferase

Other
- Albumin
- Blood creatinine
- Blood urea nitrogen
- Total cholesterol
- A/G Ratio
- Glucose
- Total Bilirubin
- Triglycerides
- Total Protein
- Phospholipid
- Direct Bilirubin

Results: No treatment-related changes in clinical chemistry parameters were present at terminal sacrifice. Although significant findings were noted in the study, statistsical reevaluation of the data by the reviewer did not reveal any statistically significant differences.

G. Urinalysis: Urinalysis was performed during weeks 4 and 12. The following parameters were examined:

- Volume
- Specific gravity
- Protein
- Appearance
- Sediment
- pH
- Glucose
- Ketone Bodies
- Occult Blood
- Urobilirubin
- Total Bilirubin

Results: Urinalysis results showed significant increases in epithelial cells in the urinary sediment of 10000 and 30000 ppm males and females (Table 3).

H. Sacrifice and Pathology: Detailed pathological examination was performed on all animals in the control and high-dose groups; selected tissues (lungs, kidneys, spleen, bone marrow, and gross lesions) were examined in the other treatment groups. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin and examined microscopically. Selected organs (CAPITAL LETTERS) were weighed before being preserved.

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Table 3: Urinalysis Results: Incidence of Epithelial Cells in Urinary Sediment[a]

| | Dose Level (ppm) | | | | |
|---|---|---|---|---|---|
| | 0 | 100 | 1000 | 10000 | 30000 |
| Males | 2/12 (2,0,0)[b] | 3/12 (3,0,0) | 3/12 (3,0,0) | 8/12• (6,2,0) | 7/12• (6,1,0) |
| Females | 1/12 (1,0,0) | 0/12 (0,0,0) | 1/12 (1,0,0) | 4/12• (3,1,0) | 5/12• (2,2,1) |

a Data summarized from Table 8 of the report
b Values in parentheses give the incidence by grade (+1,+2,+3)
• $p \leq 0.05$

Digestive system
- Tongue
- Salivary glands
- Esophagus
- Stomach
- Duodenum
- Jejunum
- Ileum
- Cecum
- Colon
- Rectum
- LIVER
- Pancreas

Respiratory
- Trachea
- Lungs

Cardiovas./Hematol
- Aorta
- HEART
- Bone marrow
- Lymph nodes
- SPLEEN
- THYMUS

Urogenital
- KIDNEYS
- Urinary bladder
- TESTES
- Epididymides
- Prostate
- Seminal vesicles
- OVARIES
- Uterus
- Vagina

Neurologic
- BRAIN
- Periph. nerve
- Spinal cord
- PITUITARY
- Eyes

Glandular
- ADRENALS
- Mammary gland
- PARATHYROIDS/ THYROIDS

Other
- Skin
- Bone
- Skeletal muscle
- Harderian glands
- Gross lesions

1. Organ Weights: Although the study indicated statistically significant differences in absolute and relative organ weights, statistical reevaluation of the data did not reveal any significant differences except for the relative liver weights of high-dose males (Table 4).

Table 4: Relative Organ Weights[a]

| Parameter | Sex | Dose Level (ppm) 0 | 100 | 1000 | 10000 | 30000 |
|---|---|---|---|---|---|---|
| Relative Liver Wt (g/100 g BW) | Males | 2.43 | 2.44 | 2.51 | 2.52 | 2.72• |
| | Females | 2.41 | 2.32 | 2.38 | 2.40 | 2.47 |

a Data summarized from Table 14 of the report
• $p \leq 0.05$

2. Gross Pathology: The gross examinations at terminal sacrifice did not reveal any treatment-related effects in either males or females.

3. Histopathology: The histopathological examinations at terminal sacrifice did not reveal any treatment-related effects in either males or females.

VI. DISCUSSION: Male and female rats were given S-23031 daily, for 13 weeks, at dosages 0, 100, 1000, 10000, or 30000 ppm (equivalent to 0, 6.46, 64.9, 659 or 2087 mg/kg/day for males and 0, 6.93, 70.6, 724 or 2249 mg/kg/day for females, respectively). No treatment-related effects were noted in either body weight, body weight gain, food consumption, food efficiency, water consumption, hematology, or clinical chemistry. Significant increases in the relative liver weight of high-dose males was also noted. The only potentially treatment-related effect was the significant increase in the number of epithelial cells appearing in the urinary sediment of 10000 and 30000 ppm males and females.

Based on these findings, a LOEL of 10000 ppm (659 mg/kg/day, males; 724 mg/kg/day, females) and a NOEL of 1000 ppm (64.9 mg/kg/day, males; 70.6 mg/kg/day, females) are established for systemic toxicity in male and female rats

Classification: core - Guideline

This study satisfies guideline requirements (§82-1) for a 90-day feeding study in rats.

Primary Review by: Robert F. Fricke, Ph.D. Robert F. Fricke 10 Mar 94
Review Section IV, Toxicology Branch II/HED (H7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/14/94
Review Section IV, Toxicology Branch II/HED (H7509C)

010848

**DATA EVALUATION RECORD**

**STUDY TYPE:** Chronic Oral - Dogs [§83-1(b)]

**EPA ID NOs:**
MRID NO.: 428258-17
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031

**SYNONYMS:**
V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**STUDY NUMBER:** 343-233

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Hazleton Washington, Inc., Vienna, VA

**TITLE OF REPORT:** Chronic oral toxicity study in dogs with S-23031

**AUTHOR:** D.W. Dalgard

**REPORT ISSUED:** 26 August 1992

**EXECUTIVE SUMMARY:** In a 1-year oral chronic toxicity study, male and female beagle dogs (5/group) were dosed at 0, 10, 100, or 1000 mg/kg body weight/day with S-23031. All animals survived to terminal sacrifice without any treatment-related clinical signs. High-dose males showed consistently lower mean body weights and lower body weight gains throughout the study. Activated partial thromboplastin times, alkaline phosphatase activities and relative liver weights were elevated in high-dose males and females.

**Based on these findings, a LOEL of 1000 mg/kg/day and a NOEL of 100 mg/kg/day were established for systemic toxicity in male and female dogs.**

This study is classified as Core Guideline and satisfies guideline requirements [§83-1(b)] for a chronic oral study in dogs.

## I. MATERIALS

A. Test Material: S-23031, technical Description: brown powder Batch #: PYG-89081-M Purity: 94.6% Contaminants: CBI Index

B. Test animals: Species: Dog Strain: Beagle Age: 7 months Weight (kg): 7.3 - 9.3 (males), 6.0 - 8.0 (females) Source: Hazleton Research Products, Inc., Cumberland, VA Housing: Individually in elevated cages Feed: Purina Certified Canine Diet #5007, *ad libitum* Water: Tap water, *ad libitum* Environment: Temperature: 64 - 79°F; Humidity: 22 - 90%; Air changes: > 10/hr; Light cycle: 12 hr light/12 hr dark

## II. METHODS

A. Animal Assignments: Animals were randomly assigned to main study test groups as shown in Table 1.

Table 1: Animal Assignment to Study Groups

| Test Group | Dosage[a] (mg/kg/day) | Animals/Group | |
|---|---|---|---|
| | | Male | Female |
| Control | 0 | 5 | 5 |
| Low | 10 | 5 | 5 |
| Mid | 100 | 5 | 5 |
| High | 1000 | 5 | 5 |

[a] Dosage not adjusted for percent purity of active ingredient

B. Dose Preparation: On a daily basis, animals were dosed orally with ½-oz gelatin capsules containing sufficient amount of S-23031 to yield the desired doses of 0 (empty capsule), 10, 100, or 1000 mg/kg. Capsules were prepared at least once weekly and stored at room temperature.

C. Statistical Evaluations: Levene's test was used to evaluate homogeneity of variances. Homogeneous data were initially analyzed using a one-way analysis of variance (ANOVA). If the ANOVA result was significant (F-test), pair-wise comparisons were carried out using Dunnett's test. Heterogeneous data were transformed ($\log_{10}X$, $X^2$, $\sqrt{X}$, 1/X, arcsine X, rank) and reevaluated for homogeneity. If transformed data was found to homogeneous, ANOVA and pair-wise comparisons were carried out. Activated partial thromboplastin times were evaluated using a repeated measures analysis of variance technique. Effects were evaluated using the Greenhouse-Geisser F-probabilities.

III. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. The sponsor applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of this study. This study neither meets nor exceeds any of the applicable criteria.

C. A statement of "no confidentiality claims" was provided.

IV. RESULTS

A. Analytical Chemistry: Stability data not given, however, the storage stability studies (MRID No.: 421698-01 and 421874-05) indicate that the technical material to stable for one year at ambient temperature.

B. Observations: Animals were observed twice daily for signs of mortality and moribundity. Animals were also observed for signs of toxicity approximately 1 to 3 hours after dosing. Detailed physical examinations were performed once weekly.

1. Clinical observations: No treatment-related effects were noted. The incidence of clinical signs was comparable among all treatment groups and controls.

2. Mortality: All animals survived until the scheduled sacrifice.

C. Body Weight and Body Weight Gain: Body weights were measured at the start of the study and at weekly intervals, thereafter. The mean body weight and body weight gains of high-dose males were lower than controls throughout the study (Table 2). The mean body weights and body weight gains of treated females were comparable to controls.

D. Food Consumption and Food Efficiency: Food consumption was measured at weekly intervals throughout the study. Although the high-dose males consumed slightly less food than controls, this appears to be a reflection of lower body weights of these animals, rather than a treatment-related effect. Food efficiency results varied widely among the treated animals with no clear, treatment-related effect.

E. Ophthalmological examinations: Examinations were performed during the prestudy acclimation period and during Weeks 26 and 52. No treatment-related effects were noted.

F. Clinical Pathology: Clinical chemistry, hematology and urinalysis were performed during the pre-study period (-2 weeks) and after 13, 26, 39 and 52 weeks of treatment. Blood was collected from animals deprived of food and water overnight.

Table 2: Mean Body Weight (% of Control) and Body Weight Gain of Male Animals at Selected Intervals During the Study[a]

| Week | Dose Level (ppm) 0 | 10 | 100 | 1000 |
|---|---|---|---|---|
| Mean Body Weight (kg) | | | | |
| 0 | 8.5 | 8.3 | 8.5 | 8.4 (-1) |
| 4 | 9.5 | 8.8 | 9.2 | 8.6 (-9) |
| 13 | 10.3 | 9.8 | 10.4 | 9.1 (-12) |
| 26 | 10.0 | 10.1 | 10.4 | 9.2 (-8) |
| 39 | 10.6 | 10.6 | 11.0 | 9.2 (-13) |
| 52 | 10.9 | 11.0 | 11.5 | 9.4 (-14) |
| Mean Body Weight Gain (kg) | | | | |
| 0-4 | 1.0 | 0.6 | 0.7 | 0.3 (-70) |
| 0-13 | 1.8 | 1.5 | 1.9 | 0.8*(-56) |
| 0-26 | 1.5 | 1.9 | 2.0 | 0.7*(-53) |
| 0-39 | 2.1 | 2.4 | 2.5 | 0.9 (-57) |
| 0-52 | 2.4 | 2.7 | 3.0 | 1.0 (-58) |

a Data summarized from Tables 2A and 2B of the report
* $p \leq 0.05$

1. Hematology: The following hematology parameters were examined:

Cell morphology
Leukocyte count
Erythrocyte count
Leukocyte differential
Prothrombin time
Reticulocyte count
Platelet count
Hematocrit
Corrected leukocyte count
Hemoglobin
Activated partial thromboplastin time
Absolute reticulocyte count

Results: Significant changes in some clinical hematology parameters were noted in both males and females at different times during the study. No clear trends or dose-response relationships were evident, suggesting that the differences were not treatment-related. Treatment-related effects were noted, however, in the activated partial thromboplastin times (APTT) of both males and females (Table 3). Significant increases in APTT were found in high-dose males at 13 and 26 weeks and females at 13, 26 and 52 weeks; a single significant finding in the mid-dose males was noted at Week 26.

To further evaluate the APTT data, a repeated measures analysis of variance was performed. In this evaluation the effect of time and treatment were evaluated independently and in combination. Analysis for all groups indicated a significant treatment and time effect in both sexes. The reanalysis concluded

that there was a significant effect on high-dose males and females, while the mid- and low-dose groups were comparable to controls.

Table 3: Mean Activated Partial Thromboplastin Times (sec)[a]

| | Dose Level (ppm) | | | |
|---|---|---|---|---|
| Week | 0 | 10 | 100 | 1000 |
| Males | | | | |
| -2 | 10.4 | 11.1 | 11.7 | 11.0 |
| 13 | 11.1 | 10.8 | 17.0 | 17.3* |
| 26 | 10.1 | 10.8 | 14.2* | 15.9* |
| 39 | 10.0 | 10.5 | 11.1 | 12.0 |
| 52 | 10.5 | 10.3 | 11.4 | 12.8 |
| Females | | | | |
| -2 | 10.7 | 11.4 | 12.1 | 11.5 |
| 13 | 11.7 | 15.3 | 12.2 | 23.3* |
| 26 | 12.1 | 14.4 | 14.9 | 23.0* |
| 39 | 10.7 | 11.1 | 11.5 | 15.3 |
| 52 | 11.2 | 11.7 | 11.8 | 17.1* |

[a] Data summarized from Table 5 of the report.
* $p \leq 0.05$

2. Clinical Chemistry: The following clinical chemistry parameters were examined:

Electrolytes
- Calcium
- Chloride
- Sodium
- Phosphorous
- Potassium

Enzymes
- γ-Glutamyl transpeptidase
- Creatine kinase
- Alanine aminotransferase (SGPT/ALT)
- Aspartate aminotransferase (SGOT/AST)
- Alkaline phosphatase
- Leucine aminopeptidase
- Lactate dehydrogenase

Other
- Glucose
- Blood creatinine
- Blood urea nitrogen
- Total bilirubin
- Protein, total
- Albumin
- Total cholesterol
- Globulin
- Phospholipid
- Triglycerides
- Protein electrophoresis

Results: Treatment-related changes consisted of elevated alkaline phosphatase activities of high-dose males and females. Activities were elevated throughout the study, achieving statistical significance on Weeks 26, 39 and 52 for males and Week 26 for females (Table 4). Other significant findings were observed, however, they were not attributed to treatment since either the magnitude of the response was low or the occurrence was sporadic.

Table 4: Mean Alkaline Phosphatase Activities (U/l)[a]

| | | Dose Level (ppm) | | | |
|---|---|---|---|---|---|
| | Week | 0 | 10 | 100 | 1000 |
| Males | -2 | 85 | 79 | 82 | 87 |
| | 13 | 60 | 58 | 66 | 83 |
| | 26 | 48 | 49 | 53 | 80* |
| | 39 | 41 | 35 | 45 | 75* |
| | 52 | 35 | 29 | 39 | 87* |
| Females | -2 | 72 | 75 | 84 | 89 |
| | 13 | 50 | 54 | 61 | 78 |
| | 26 | 45 | 41 | 51 | 124* |
| | 39 | 46 | 42 | 45 | 74 |
| | 52 | 40 | 37 | 39 | 67 |

[a] Data summarized from Table 6 of the report
* $p \leq 0.05$

3. Urinalysis: The following urinalysis parameters were examined:

| | | |
|---|---|---|
| Appearance | Glucose | Specific gravity |
| Ketone Bodies | Protein | Volume |
| Urobilirubin | Sediment | Total Bilirubin |
| pH | Occult Blood | Reducing substances |

Results: No treatment-related effects were noted in any of the animals.

G. Sacrifice and Pathology: Detailed pathological examination was performed on male and female animals in the control and treatment groups. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin and examined microscopically. Selected organs (CAPITAL LETTERS) were weighed before being preserved.

Digestive system
- PANCREAS
- SALIVARY GLANDS
- Esophagus
- Stomach
- Duodenum
- Jejunum
- Ileum
- Cecum
- Colon
- Rectum
- LIVER
- Gallbladder

Respiratory
- LUNGS
- Trachea

Cardiovas./Hematol
- Aorta
- HEART
- Bone marrow
- Lymph nodes
- SPLEEN
- THYMUS

Urogenital
- KIDNEYS
- Urinary bladder
- TESTES/EPIDIDYMIDES
- OVARIES
- PROSTATE
- UTERUS

Neurologic
- BRAIN with STEM
- Periph. nerve
- Spinal cord
- PITUITARY
- Eyes + optic nerve

Glandular
- ADRENALS
- THYROIDS/PARATHYROIDS
- Mammary gland

Other
- Gross lesions
- Skin
- Bone
- Skeletal muscle
- Tongue

1. Organ Weights: High-dose males and females showed increases in absolute liver weights at terminal sacrifice; none of the weights, however, were significantly different from controls. Relative liver weights were significantly higher in high-dose males and females. No other significant findings were observed.

2. Gross Pathology: Gross examination of tissues taken at the terminal sacrifice did not reveal any treatment-related abnormalities.

3. Histopathology: Histopathological examination at terminal sacrifice did not reveal any changes which could be attributable to treatment.

Table 4: Mean Terminal Body Weights (kg), Absolute (g) and Relative (g/kg terminal body wt) Liver Weights[a]

| Parameter | Sex | Dose Level (ppm) 0 | 10 | 100 | 1000 |
|---|---|---|---|---|---|
| Terminal Body Wt | Male | 10.66 | 10.74 | 11.04 | 9.08 |
| | Female | 8.22 | 8.68 | 8.68 | 8.02 |
| Absolute Liver Wt | Male | 236 | 236 | 231 | 246 |
| | Female | 188 | 197 | 228 | 240 |
| Relative Liver Wt | Male | 2.2 | 2.2 | 2.1 | 2.7* |
| | Female | 2.3 | 2.3 | 2.6 | 3.0* |

[a] Data summarized from Tables 8 and 9 of the report
* $p < 0.05$

V. DISCUSSION: In a 1-year oral chronic toxicity study, male and female beagle dogs (5/group) were dosed at 0, 10, 100, or 1000 mg/kg body weight/day with S-23031. All animals survived to terminal sacrifice without any adverse clinical signs.

The body weights and body weight gains of high-dose males were lower than controls throughout the study, at terminal sacrifice the mean body weights were 14% lower than controls. The body weights and body weight gains of treated females were comparable to controls. Although the high-dose males consumed slightly less food than controls, this observation appears to be due to lower body weights, rather than a treatment-related effect. Food efficiency results varied widely among the treated animals with no clear treatment-related effect.

Treatment-related clinical pathological effects were generally limited to high-dose animals. APTT was significantly greater in high-dose males at 13 and 26 weeks and females at 13, 26 and 52 weeks; a single significant finding in the mid-dose males was noted at Week 26. Similar findings were observed in a 90-day

oral toxicity study with S-23031 in beagle dogs (MRID 421698-27 and 423108-02, addendum; HED Doc. No. 009587), APTT for females were elevated significantly after 4, 8, and 12 weeks treatment at 1000 mg/kg/day and after 4 and 8 weeks at 100 mg/kg/day. For treated males, APTT values were comparable to control values.

Alkaline phosphatase activities were elevated in high-dose animals throughout the study, achieving statistical significance on Weeks 26, 39 and 52 for males and Week 26 for females. Urinalysis did not reveal any treatment-related changes.

High-dose males and females showed increases in absolute liver weights at terminal sacrifice; none of the weights, however, were significantly different from controls. Relative liver weights were significantly increased in high-dose males and females. Both gross and histopathological examinations of the livers did not reveal any lesions or abnormalities. No treatment-related changes were noted in any of the other tissues.

In summary, treatment-related changes were limited to high-dose males and females. High-dose males showed consistently lower mean body weights and lower body weight gains throughout the study. APTT and alkaline phosphatase activities were elevated in high-dose males and females.

Based on these findings, a LOEL of 1000 mg/kg/day and a NOEL of 100 mg/kg/day were established for systemic toxicity in male and female dogs.

This study is classified as Core Guideline and satisfies the guideline requirements [§83-1(b)] for a chronic oral toxicity study in dogs.

Primary Review by: Robert F. Fricke, Ph.D. Robert F. Fricke 10 Mar 94
Review Section IV, Toxicology Branch II/HED (H7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/14/94
Review Section IV, Toxicology Branch II/HED (H7509C)

C10848

**DATA EVALUATION RECORD**

**STUDY TYPE:** Oncogenicity study - mouse [§83-2(b)]

**EPA ID NO's:** MRID No.: 428839-05
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031

**SYNONYMS:** V-23031, Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Sumitomo Chemical Co., Ltd, Osaka, Japan

**TITLE OF REPORT:** Oncogenicity Study of S-23031 by Dietary Administration in Mice

**STUDY NUMBER:** 1842

**AUTHOR:** H. Adachi

**REPORT ISSUED:** 8 May 1992

**EXECUTIVE SUMMARY:** In a 79 week oncogenicity study, CD-1 (ICR) mice (Charles River, Japan) were randomly assigned to the main study (51/dose/sex) or satellite study (15/dose/sex) groups and administered S-23031 at dietary concentrations of 0, 300, 3000, or 7000 (limit dose) ppm (respective mg/kg/day equivalents: 0, 31.5, 307.9 or 731.4 for males and 0, 37.8, 368.1, 850.2 for females).

Treatment-related findings were limited to males. At both the interim and terminal sacrifices mid- and high-dose males had significant decreases in hematocrit, hemoglobin concentration and RBC count. High-dose males also had significantly increased absolute and relative liver weights at the interim sacrifice; at terminal sacrifice the absolute and relative liver weights were increased, but the differences were not statistically significant. Histopathological findings showed an significantly increased incidence of hypertrophy of the hepatocytes of mid- and high-dose males at both the interim and terminal sacrifices. The occurrence of neoplastic appeared to be spontaneous and not dose-related. No treatment-related effects were noted in females at

the highest dose tested (7000 ppm, 850.2 mg/kg/day). The highest dose tested was judged to be adequate to assess carcinogenicity since it was the limit dose.

**Based on these findings, a LOEL of 3000 ppm (307.9 mg/kg/day) and a NOEL of 300 ppm (31.5 mg/kg/day) were established for systemic toxicity in male mice. In female mice, the NOEL was the highest dose tested (7000 ppm, 850.2 mg/kg/day). There is no evidence that S-23031 was carcinogenic in this study.**

This study is classified as Core - Guideline and satisfies guideline requirements [§83-2(b)] for an oncogenicity study in mice.

I. MATERIALS

A. Test compound: S-23031, technical Description: brown powder Batch #: PYG-88092-M Purity: 94.7% Contaminants: CBI Index

B. Test animals: Species: Mouse Strain: Crj:CD-1(ICR) Age: 5 weeks Weight (g): 24.8 - 33.1 (males), 19.6 - 25.8 (females) Source: Charles River Japan, Inc. Housing: Three/cage Feed: CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan, *ad libitum* Water: Tap water, *ad libitum* Environment: Temperature: 24 ± 2°C; Humidity: 55 ± 10%; Air changes: > 10/hr; Light cycle: 12 hr light/12 hr dark

II. METHODS

A. Study Design: Animals were assigned randomly to main and satellite study groups as shown in Table 1. An interim sacrifice was carried out at Week 52 on all surviving satellite group animals. All surviving main study animals were sacrificed after 78 weeks of treatment.

Table 1: Animal Assignment to Study Groups

| Test Group | Dose in Diet (ppm) | Main Group | | Satellite Group | |
|---|---|---|---|---|---|
| | | Male | Female | Male | Female |
| Control | 0 | 51 | 51 | 15 | 15 |
| Low | 300 | 51 | 51 | 15 | 15 |
| Mid | 3000 | 51 | 51 | 15 | 15 |
| High | 7000 | 51 | 51 | 15 | 15 |

B. Dose Selection: Dose selection was based on a 13-week feeding toxicity study. In this study (MRIL No.: 428839-04) rats were fed diets containing S-23031 at 0, 1000, 3000 or 10000 ppm (equivalent to 0, 125, 379, or 1274 mg/kg/day, males; 0, 150, 366 or 1224 mg/kg/day, females). Males at 3000 ppm showed increased absolute and relative liver weights, altered hematology (decreased erythrocyte counts, hemoglobin concentration and hematocrit) and increased incidence of gross (mottled, enlarged livers) and histopathological (hepatocellular hypertrophy, hepatocellular vacuolation, and single cell necrosis) findings. Based on these findings, a high dose of 7000 ppm (limit dose) was selected for this study.

C. Diet preparation: Test diets (one for each dose group) were prepared by thoroughly mixing a weighed amount of S-23031 with the basal diet. Test diets were stored in the dark at 0 to 10 °C. Diets were prepared approximately every four weeks.

D. Statistics: A one-way analysis of variance (ANOVA) was performed on body weight, food consumption, hematology, and organ weight. If a significant ANOVA result was found, pair-wise comparisons were carried out using the Least Significant Difference test. Fisher's exact test was used to evaluate histopathological data and cumulative mortality. The Mann-Whitney test was used to assess the severity of non-neoplastic lesions.

III. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. The sponsor applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of this study. This study neither meets nor exceeds any of the applicable criteria.

C. A statement of "no confidentiality claims" was provided.

IV. RESULTS

A. Analysis of Diet: Analysis of samples, taken from the top, middle and bottom of the prepared diets, showed that S-23031 was homogeneously distributed (coefficient of variation 0.15 to 0.20%) and within 5% of nominal concentration. The concentration of test compound was measured approximately every two months and were within 10% of the target values (285 to 300 ppm for 300 ppm dose, 2950 to 2990 ppm for 3000 ppm dose and 6750 to 7030 ppm for the 7000 ppm dose). Test diets were stable for six weeks in the refrigerator and four weeks at room temperature.

B. Observations: All animals were inspected twice (weekdays) or once (weekends, holidays) daily for signs of toxicity, moribundity and mortality. Detailed examinations were performed weekly on main study animals and every four weeks on satellite study group animals.

1. Toxicity: No treatment-related clinical signs were observed in either the satellite or main study groups.

2. Mortality (survival): Excluding accidental deaths, no significant treatment-related differences in the percent mortality were noted (Table 2).

Table 2: Cumulative Mortality of Main Study Animals[a]

| | Dose Level (ppm) | | | |
|---|---|---|---|---|
| | 0 | 300 | 3000 | 7000 |
| Males | 14/50 (26%) | 16/50 (30%) | 12/51 (23%) | 16/50 (30%) |
| Females | 16/51 (31%) | 13/51 (31%) | 10/51 (20%) | 15/50 (28%) |

a Summarized from Table 1 of the report
b Excludes accidental deaths

C. Body Weight and Body Weight Gain: All animals were weighed at the start of the study. Main study animals were weighed once weekly for the first 14 weeks and every four weeks, thereafter. Satellite study animals were weighed on Day 1 and 8 of treatment and every 4 weeks, thereafter. All animals were weighed at time of sacrifice.

Results: For satellite and main study animals, no significant treatment-related changes were noted in either mean body weight or body weight gain.

D. Food Consumption and Compound Intake: Food consumption for each cage was determined once a week for the first 14 weeks and once every four weeks for the remainder of the study. For animals in the satellite study, food consumption was measured every four weeks.

1. Food consumption: For satellite and main study animals, no significant treatment-related changes were noted in either the mean absolute or relative food consumption.

2. Compound intake: The mean compound intake is summarized in Table 3.

Table 3: Compound Intake (mg/kg body weight/day) for Main Study Animals for Weeks 1 to 78[a]

| | Dose Level (ppm) | | |
|---|---|---|---|
| | 300 | 3000 | 7000 |
| Males | 31.5 | 307.9 | 731.4 |
| Females | 37.8 | 368.1 | 850.2 |

[a] Data summarized from Table 5 of the report

E. Hematology: Hematology was performed at terminal sacrifice on all main study animals and 10 satellite animals/dose/sex. Unfasted animals were anesthetized with ether and blood was collected from the abdominal vein. The following parameters were examined:

| | |
|---|---|
| Hematocrit | Platelet count |
| Hemoglobin | Leukocyte differential count |
| Leukocyte count | Mean corpuscular HGB |
| Erythrocyte count | Mean corpuscular HGB conc. |
| Mean corpuscular volume | Reticulocyte count |

Results: Hematology results are summarized in Table 4. Mid- and high-dose males at both the interim and terminal sacrifices showed decreased hematocrits, hemoglobin levels and erythrocyte counts. No treatment-related effects were noted in females.

Table 4: Hematology Results for Male Mice[a]

| Parameter | Week | Dose Level (ppm) 0 | 300 | 3000 | 7000 |
|---|---|---|---|---|---|
| Hematocrit (%) | 53 | 41.6 | 40.2 | 36.4** | 38.3** |
| | 79 | 41.4 | 39.3 | 34.5** | 36.7** |
| Hemoglobin (g/dl) | 53 | 12.7 | 12.3 | 11.0** | 11.8* |
| | 79 | 13.0 | 12.5 | 10.8** | 11.7** |
| Erythrocyte Count ($10^6/\mu l$) | 53 | 8.72 | 8.53 | 7.78** | 8.24 |
| | 79 | 8.88 | 8.44 | 7.25** | 8.02** |

[a] Summarized from Table 6 of the report
* $p < 0.05$, ** $p < 0.01$

F. Sacrifice and Pathology: Gross pathological examinations were performed on animals from the satellite group (10/sex/dose group) during Week 53, surviving main study animals during Week 79, and all moribund sacrifices and animals which died during the study. The tissues listed (X) below were collected and preserved in 10% neutral formalin; eyes were preserved in Davidson's fixative. All tissues from the control and high-dose groups, moribund sacrifices and animals which died during the study were examined histologically. Selected tissues (liver, kidneys, lungs and gross lesions) of intermediate dose groups animals were examined histologically. Tissues (listed in CAPITAL letters) from 10 satellite study animals/sex/group and 12 main study animals/sex/group were also weighed.

Digestive system
- Tongue
- Salivary glands
- Esophagus
- Stomach
- Duodenum
- Jejunum
- Ileum
- Cecum
- Colon
- Rectum
- LIVER
- Gallbladder
- Pancreas

Respiratory
- Trachea
- Lungs

Cardiovas./Hematol
- Aorta
- Heart
- Bone marrow
- Lymph nodes
- Spleen
- Thymus

Urogenital
- KIDNEYS
- Urinary bladder
- TESTES
- Epididymides
- Prostate
- Seminal vesicle
- Ovaries
- Uterus
- Vagina

Neurologic
- BRAIN
- Periph. nerve
- Spinal cord
- Pituitary
- Eyes

Glandular
- ADRENALS
- Mammary gland (females only)
- Parathyroids
- Thyroids

Other
- Bone
- Skeletal muscle
- Skin
- Gross lesions
- Harderian glands

1. Gross Pathology: No treatment-related gross pathological changes were noted at either the interim or terminal sacrifices.

2. Organ Weights: At the interim sacrifice, high-dose males had significantly increased absolute and relative liver weights, at terminal sacrifice the organ weights were increased, but the differences were not statistically significant (Table 5). Organ weights of the treated females were not significantly different from control values. Terminal body weights of treated animals were comparable to control values.

Table 5: Terminal Body Weights, Absolute and Relative Organ Weights at Interim (Week 53) and Terminal (Week 79) Sacrifices[a]

| Observation | Sex | Week | Dose (ppm) 0 | 300 | 3000 | 7000 |
|---|---|---|---|---|---|---|
| Body Weights (g) | ♂ | 53 | 46.5 | 47.4 | 50.1 | 48.5 |
| | | 79 | 44.6 | 44.7 | 44.4 | 46.3 |
| | ♀ | 53 | 39.5 | 37.3 | 40.1 | 42.7 |
| | | 79 | 40.7 | 39.5 | 43.2 | 38.7 |
| Liver Weights | | | | | | |
| Absolute (g) | ♂ | 53 | 2.49 | 2.69 | 2.93 | 3.22** |
| | | 79 | 2.79 | 2.69 | 2.85 | 3.33 |
| Relative (g/kg BW) | ♂ | 53 | 5.33 | 5.71 | 5.91 | 6.62** |
| | | 79 | 6.22 | 6.07 | 6.41 | 7.20 |

[a] Data summarized from Tables 8-1 and 8-2 of the report
** $p < 0.01$

3. Histopathology

a. Non-neoplastic lesions: At both the interim and terminal sacrifices, mid- and high-dose males had statistically significant increases in the incidence of hypertrophy of the hepatocytes (Table 6); the severity of the lesion was graded as slight. Similar effects were not noted in females. Although other non-neoplastic lesions were noted, the occurrences appeared to be spontaneous in nature and lacked a clear dose-response relationship.

b. Neoplastic lesions: Although neoplastic lesions were noted, the incidences were low and/or did not show a dose-response relationship. A tabulation of neoplastic lesions is summarized in Appendix 1.

Table 6: Incidence of Non-neoplastic Liver Lesions in Male Mice at Interim (53 weeks) and Terminal (79 weeks) Sacrifices[a]

| Observation | Week | Dose (ppm) 0 | 300 | 3000 | 7000 |
|---|---|---|---|---|---|
| Hypertrophy of hepatocytes | 53 | 0/10 | 0/10 | 9/10** | 10/10** |
| | 79 | 4/51 | 7/51 | 34/51** | 37/51** |

[a] Data taken from Appendix 7, Table 3 of report
** $p < 0.01$

V. DISCUSSION: In a 79 week oncogenicity study, CD-1 (ICR) mice (Charles River, Japan) were randomly assigned to the main study (51/dose/sex) or satellite study (15/dose/sex) groups and administered S-23031 at dietary concentrations of 0, 300, 3000, or 7000 ppm (respective mg/kg/day equivalents: 0, 31.5, 307.9 or 731.4 for males and 0, 37.8, 368.1, 850.2 for females).

No biologically meaningful changes were noted in clinical signs, mean body weight, body weight gain, food consumption, food efficiency or gross pathological findings.

Treatment-related effects were limited to males. At both the interim and terminal sacrifices, mid- and high-dose males had statistically significant decreases hematocrit, hemoglobin concentration and erythrocyte count. Although the differences were slight, the effects appear to biologically meaningful since similar hematological changes were also noted in a 90-day feeding study (MRID No.: 428839-04). High-dose males had significantly increased absolute and relative liver weights at the interim sacrifice; at terminal sacrifice the liver weights were increased, but the differences were not statistically significant. Organ weights of the treated females were not significantly different from control values.

Histopathological findings showed a significantly increased incidence of hypertrophy of the hepatocytes in mid- and high-dose males at the interim and terminal sacrifices. The occurrence of the neoplastic lesions appeared to be spontaneous in nature and lacked clear dose-response relationship.

VI. CONCLUSIONS: Male mice showed clear and consistent treatment-related changes at both 3000 and 7000 ppm. The liver appears to be the target organ as evidenced by increased absolute and relative tissue weights and increased incidence of hypertrophy of the hepatocytes. In this study increases were noted in γ-glutamyl transpeptidase activity, absolute and relative liver weights, and increased incidence of hyperplastic (neoplastic) nodules in the liver.

Other effects included significant decreases in hematocrit, hemoglobin concentration and erythrocyte counts of mid- and high-

dose males at the interim and terminal sacrifices. No biologically significant findings were noted in any of the treated females.

The highest dose tested was judged to be adequate to assess carcinogenicity since it was the limit dose.

Based on these findings, a LOEL of 3000 ppm (307.9 mg/kg/day) and a NOEL of 300 ppm (31.5 mg/kg/day) were established for systemic toxicity in male mice. In female mice, the NOEL was the highest dose tested (7000 ppm, 850.2 mg/kg/day). There is no evidence that S-23031 was carcinogenic in this study.

CLASSIFICATION: Core - Guideline

This study satisfies guideline requirements [§83-2(b)] for an oncogenicity study in mice.

**APPENDIX 1: SUMMARY OF NEOPLASTIC LESIONS (Taken from Appendix 7, Table 3 of study)**

Page_____ is not included in this copy.

Pages 110 through 90 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.

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____ Sales or other commercial/financial information.

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Primary Review by: Robert F. Fricke, Ph.D. Robert F. Fricke 11 Mar 94
Review Section IV, Toxicology Branch II/HED (H7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/14/94
Review Section IV, Toxicology Branch II/HED (H7509C)

010848

**DATA EVALUATION RECORD**

**STUDY TYPE:** Combined chronic toxicity/carcinogenicity studies - rats (§83-5)

**EPA ID NO's:** MRID No.: 428839-06
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031

**SYNONYMS:** V-23031, Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Sumitomo Chemical Co., Ltd, Osaka, Japan

**TITLE OF REPORT:** Combined Chronic Toxicity and Carcinogenicity Study of S-23031 by Dietary Administration in Rats

**STUDY NUMBER:** 1716

**AUTHOR:** H. Adachi

**REPORT ISSUED:** 10 April 1992

**EXECUTIVE SUMMARY:** In a chronic toxicity/carcinogenicity study, CD (SD) rats (50/dose/sex, main study; 14/dose/sex, satellite study) were administered S-23031 at dietary concentrations of 0, 100, 1000, 10000 or 20000 (limit dose) ppm (respective mg/kg/day equivalents: 0, 3.5, 35.4, 360.4 or 744.9, males; 0, 4.3, 43.6, 443.8, or 919.4, females).

Male rats showed clear and consistent treatment-related changes at both 10000 and 20000 ppm. The liver appears to be the target organ as evidenced by increased activity of γ-glutamyl transpeptidase, increased absolute and relative organ weights, and increased incidence on hyperplastic nodules. Other incidental effects included significant urinalysis findings (increased urine volume and appearance of squamous epithelial cells in the sediment) in the high-dose males. At Week 25 and 52, 10000 and 20000 ppm females had increased absolute and relative water consumption, which was accompanied by increased urine volume. The effects were transient; no significant effects were noted at Weeks 77 or 103. No treatment-related effects were noted in females at the highest dose tested (20000 ppm, 919 mg/kg/day)

**Based on these findings, a LOEL of 10000 ppm (360 mg/kg/day) and a NOEL of 1000 ppm (35 mg/kg/day) were established for systemic toxicity in male rats. For females the NOEL was the highest dose tested(20000 ppm, 919.4 mg/kg/day).**

This study is classified as Core - Guideline and satisfies guideline requirements (§83-5) for a combined chronic toxicity/carcinogenicity study in rats.

I. MATERIALS

A. Test compound: S-23031, technical Description: brown powder Batch #: PYG-88092-M Purity: 94.7% Contaminants: CBI Index

B. Test animals: Species: Rat Strain: Crj:CD(SD) Age: 5 weeks Weight (g): 164 - 213 (males), 135 - 191 (females) Source: Charles River Japan, Inc. Housing: Three/cage Feed: CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan, *ad libitum* Water: Tap water, *ad libitum* Environment: Temperature: 24 ± 2°C; Humidity: 55 ± 10%; Air changes: > 10/hr; Light cycle: 12 hr light/12 hr dark

II. METHODS

A. Study Design: Animals were randomly assigned to main and satellite study groups as shown in Table 1. The animals in the satellite group were sacrificed after 52 weeks.

Table 1: Animal Assignment to Study Groups

| Test Group | Dose in Diet (ppm) | Main Group | | Satellite Group | |
|---|---|---|---|---|---|
| | | Male | Female | Male | Female |
| Control | 0 | 50 | 50 | 14 | 14 |
| Low | 100 | 50 | 50 | 14 | 14 |
| Middle 1 | 1000 | 50 | 50 | 14 | 14 |
| Middle 2 | 10000 | 50 | 50 | 14 | 14 |
| High | 20000 | 50 | 50 | 12* | 14 |

* Two animals were removed because of a technical error.

B. Dose Selection: Dose selection was based on two 13-week oral toxicity studies. In one study (MRID No.: 421698-26) rats were fed diets containing S-23031 at dosages of 0, 100, 1000, 10000 or 20000 (limit dose) ppm (equivalent to 0, 6.6, 67.0, 664 or 1359 mg/kg/day for males and 0, 7.4, 73.8, 726 or 1574 mg/kg/day for females, respectively). The LOEL of 20000 ppm for males was based on increased relative liver weights; the LOEL of 1000 ppm for females was based on increased plasma cholinesterase activity. In a second 13-week study (MRID No.: 428839-03) rats were fed diets containing S-23031 at dosages of 0, 100, 1000, 10000, or 30000 ppm (equivalent to 0, 6.46, 64.9, 659 or 2087 mg/kg/day for males and 0, 6.93, 70.6, 724 or 2249 mg/kg/day for females, respectively). The only potentially treatment-related effect was the significant increase in the number of epithelial cells appearing in the urine of 10000 and 30000 ppm males and females. Based on these findings, an upper dose of 20000 ppm was selected for the present study.

C. Diet preparation: Premixes (one for each dose group) was made using an appropriate amounts of S-23031 and

thoroughly mixing it with the basal diet. Additional basal diet was added to the different premixes to form the desired final concentration of S-23031.

D. Statistics: A one-way analysis of variance (ANOVA) was performed on body weight, food consumption, water consumption, hematology, blood chemistry and organ weight. If a significant ANOVA result was found, pair-wise comparisons were carried out using the Least Significant Difference test. Scheffe's mean rank test was used to test for significant differences in the urinalysis data; significant data were further analyzed using the Kruskal-Wallis analysis of ranks. Fisher's exact test was used to evaluate incidence data for clinical observations, gross pathological or histopathological observations.

III. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. The sponsor applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of this study. This study neither meets nor exceeds any of the applicable criteria.

C. A statement of "no confidentiality claims" was provided.

IV. RESULTS

A. Analysis of Diet: Analysis of samples, taken from the top, middle and bottom of the prepared diets, showed that the S-23031 was homogeneously distributed (coefficient of variation 0.29 to 0.68%) and within 96.9 and 100% of nominal concentration. The concentration of S-23031 in the test diets was measured approximately monthly; all values were within 10% of the target concentration. Test diets were stable for six weeks in the refrigerator and four weeks at room temperature.

B. Observations: Animals in the main study group were inspected twice (weekdays) or once (weekends, holidays) daily for signs of toxicity, moribundity and mortality. Animals in the satellite study group were inspected once daily.

1. Toxicity: The incidence urinary staining was significantly higher in 20000 ppm, main study males for Weeks 7 to 30 (excluding Week 15); staining was present from Week 31 through 44, but not statistically different from control values. Satellite study males did not show any treatment-related staining. Significant incidence of staining was observed in 20000 ppm, main study females from Weeks 7 through 105 (excluding Weeks 15, 82, 87, 94, 100, 102, 103, 104,

and 106); sporadic, but significant, findings were observed in the 10000 ppm main study females at Weeks 7 to 9, 21, 22, 34, 35, 38 to 42, 47 to 49, 52, and 53. Satellite study females showed significant incidences of staining from Weeks 26 through 35; staining was present from Weeks 37 through 52, but the incidence was not significantly different from control values. A low incidence of urinary incontinence was observed in 20000 ppm, main study females throughout the study; statistically significant differences were noted for Weeks 23, 30, 31, 34, 35, 40, 41 and 56.

2. Mortality (survival): Cumulative mortality for main study animals through terminal sacrifice is summarized in Table 2. For males, no statistically significant differences were noted in the mortality of treated animals compared to the control group. Females, however, showed statistically significant increases in mortality in the 100, 10000 and 20000 ppm dose groups. The values, however, are not significantly different from either of the two long-term (2-year) feeding studies conducted by the Registrant [68/150, (45%) and 25/50 (50%)]. The reason for the higher mortality in the females is not known, since there were no adverse clinical signs or treatment-related changes body weight or incidence of gross- and histopathological lesions in females.

Table 2: Mortality of Main Study Animals[a]

| Dose (ppm) | Cumulative (%) Mortality | |
|---|---|---|
| | Male | Female |
| 0 | 17/50 (34%) | 16/50 (32%) |
| 100 | 21/50 (42%) | 28/50•(56%) |
| 1000 | 19/50 (38%) | 19/50 (38%) |
| 10000 | 18/50 (36%) | 27/50•(54%) |
| 20000 | 16/50 (32%) | 29/50•(58%) |

[a] Data summarized from study Table 1 of the report
• $p \leq 0.05$

C. Body Weight and Body Weight Gain: Animals in the main study were weighed at the start of the study, once weekly for 14 weeks and every four weeks, thereafter. Animals in the satellite study were weighed every 4 weeks. All animals were weighed at terminal sacrifice.

1. Body weight: For male animals in both the main and satellite study groups, no significant differences in body weight were observed during the study. The only significant effects were increases in mean body weight for females in the 100 ppm group for Days 8 through 505 and Day 561 in the main study and Days 176 through 365 for the satellite study. Since similar

increases were not observed at higher doses, the effects were not attributed to treatment.

2. Body weight gain: No significant differences in body weight gains of male animals in either the main or satellite study groups. Main study females in the low-dose group showed significantly higher body weight gains from Day 1 through Days 176, 281, 365 and 449. Since animals in the higher dose groups did not show similar effects, the observed differences in the low-dose females was not attributed to treatment.

D. Food Consumption, Compound Intake and Water Consumption: Food consumption (measured over 6 or 7 consecutive days) was determined weekly through week 14 and once every four weeks for the remainder of the study. For animals in the satellite study, food consumption was measured every four weeks. During Weeks 25, 52, 77 and 105, water consumption was measured over a 48-hour period using 10 animals/sex/group.

1. Food consumption: Statistically significant increases in absolute food consumption were observed in the 20000 ppm, main study males throughout most of the study. The differences were judged to be slight (< 5%) and not considered toxicologically significant. No treatment-related changes were found in food consumption by females in the satellite or main studies.

Slight, but statistically significant, increases in relative food consumption were observed in 20000 ppm, satellite and main study males; occasional statistically significant findings were noted in the other treated males. Relative food consumption by 20000 ppm, main study females was generally higher than controls. Other treated females showed sporadic, but significant increases. For both males and females the increases in relative food consumption were considered to be slight (5.4%, males; 3.9%, females) and not of toxicological significance.

2. Compound intake: The mean compound intake is summarized in Table 3.

Table 3: Compound Intake (mg/kg body weight/day) for Main Study Animals for Weeks 1 to 104[a]

| | Dose Level (ppm) | | | |
|---|---|---|---|---|
| | 100 | 1000 | 10000 | 20000 |
| Males | 3.5 | 35.4 | 360.4 | 744.9 |
| Females | 4.3 | 43.6 | 443.8 | 919.4 |

a. Data summarized from Table 6 of the report

3. Water consumption: Males did not show any changes in either absolute or relative water consumption during the study. Absolute water consumption (Table 4) by females was increased at 10000 ppm (106% at Week 25 and 43% at Week 52) and 20000 ppm (44% at Week 25, 32% at Week 52 and 31% at Week 77) females. Relative water consumption (Table 4) by females was also increased at 10000 ppm (110% at Week 25 and 44% at Week 52) and 20000 ppm (54% at Week 25, 39% at Week 52 and 34% at Week 77) females.

Table 4: Absolute (ml/animal/day) and Relative (ml/kg body weight/day) Water Consumption by Female Rats[a]

| | | Dose Level (ppm) | | | | |
|---|---|---|---|---|---|---|
| | Week | 0 | 100 | 1000 | 10000 | 20000 |
| Absolute | 25 | 36 | 33 | 34 | 74** | 52 |
| | 52 | 44 | 38 | 40 | 63** | 58* |
| | 77 | 45 | 40 | 41 | 51 | 59 |
| Relative | 25 | 110 | 106 | 110 | 231** | 169* |
| | 52 | 113 | 106 | 108 | 163** | 157* |
| | 77 | 102 | 87 | 89 | 114 | 137 |

[a] Data summarized from Tables 7 and 8 of the report
* $p < 0.05$, ** $p < 0.01$

E. Ophthalmological Examinations: Examinations were performed on control and high dose animals in the main study group before the study was initiated and during Weeks 54 and 105. No treatment-related eye lesions were observed.

F. Hematology, Clinical Chemistry and Urinalysis: Hematological and biochemical analyses were performed using fasted animals (10/dose/sex) at Weeks 27, 53, 79 and 106 using animals. Urinalysis was performed during Weeks 25, 51, 77, and 103 using either 10 animals/dose/sex (satellite study) or 12 animals/dose/sex (main study).

1. Hematology: The following parameters were examined:

Hematocrit
Hemoglobin
Leukocyte count
Erythrocyte count
Mean corpuscular volume
Platelet count
Leukocyte differential count
Mean corpuscular HGB
Mean corpuscular HGB conc.

Results: Hematology results showed changes in the leukocyte differential counts of 10000 and 20000 ppm females at Week 53 of the study. The statistically significant increase in the percent neutrophils was

lymphocytes (Table 5). Hematology performed at Weeks 25, 79 and 103 did not reveal any significant findings.

Table 5: Hematology Results for Females at Week 53[a]

| | Dose Level (ppm) | | | | |
|---|---|---|---|---|---|
| Parameter | 0 | 100 | 1000 | 10000 | 20000 |
| Differential counts (%) | | | | | |
| Neutrophil | 16.3 | 17.7 | 19.5 | 27.0** | 22.1* |
| Lymphocyte | 79.3 | 78.4 | 75.7 | 68.9** | 74.0* |
| Absolute counts ($10^3/\mu l$) | | | | | |
| Leukocytes | 5.57 | 5.88 | 4.83 | 4.50 | 4.56 |
| Neutrophils | 0.79 | 1.04 | 0.94 | 1.22 | 1.00 |
| Lymphocytes | 4.51 | 4.61 | 3.66 | 3.09 | 3.38 |

[a] Data summarized from Table 10 of the report
* $p < 0.05$, ** $p < 0.01$

2. Clinical Chemistry: The following parameters were examined:

Electrolytes
- Calcium
- Chloride
- Sodium
- Phosphorous
- Potassium

Enzymes
- Leucine aminopeptidase
- Alkaline phosphatase
- Plasma cholinesterase
- Creatinine phosphokinase
- Lactic acid dehydrogenase
- γ-Glutamyl transpeptidase
- Glutamic-oxaloacetate transaminase
- Glutamic-pyruvate transaminase

Other
- Albumin
- Blood creatinine
- Blood urea nitrogen
- Total cholesterol
- Globulins
- Glucose
- Total bilirubin
- Triglycerides
- Total Protein
- Phospholipid
- Direct bilirubin
- Serum protein fractionation
- Albumin/Globulin ratio

Results: Clinical chemistry results, determined are summarized in Table 6. Significant, treatment-related effects were limited to high-dose males, which showed increased activities of γ-glutamyl transpeptidase (GGT) at Weeks 79 and 106. In high-dose females, the percent of $\alpha_1$-globulin was slightly, but significantly, increased at Weeks 27, 79 and 106. Although the effect was judged to be treatment-related, the toxicological significance is not known since there was no corroborative changes in the liver (organ or histopathology) at this dose/sex. Other significant findings were noted in the study, but the occurrence was random and/or not dose-related.

Table 6: Clinical Chemistry,

| Parameter | Sex | Week | Dose Level (ppm) 0 | 100 | 1000 | 10000 | 20000 |
|---|---|---|---|---|---|---|---|
| γ-Glutamyl transpeptidase | ♂ | 79 | 2 | 1 | 3 | 2 | 5•• |
| | | 106 | 1 | 0 | 1 | 2 | 5•• |
| $\alpha_1$-Globulin (%) | ♀ | 27 | 11.1 | 11.8 | 11.5 | 11.9 | 13.7•• |
| | | 79 | 11.2 | 12.8 | 11.2 | 12.7 | 13.5•• |
| | | 106 | 9.8 | 10.2 | 10.2 | 11.8 | 14.0•• |

a Summarized from Table 11 of the report
•• $p < 0.01$

3. Urinalysis: The following parameters were examined:

| | | |
|---|---|---|
| Volume | Glucose | Specific gravity |
| Ketone Bodies | Protein | Occult Blood |
| Appearance | Urobilirubin | Total Bilirubin |
| Sediment | pH | |

Results: Significant, treatment-related urinalysis results are summarized in Table 7. At Week 103, high-dose males showed increased urine volume and increased incidence of squamous epithelial cells in the urinary sediment. At Weeks 25 and 51, 10000 and 20000 ppm females showed increased urine volume.

Table 7: Urinalysis Results[a]

| Parameter | Sex | Week | Dose Level (ppm) 0 | 100 | 1000 | 10000 | 20000 |
|---|---|---|---|---|---|---|---|
| Volume (ml) | ♂ | 103 | 3.0 | 3.9 | 4.5 | 5.2 | 5.0• |
| | ♀ | 25 | 1.7 | 2.3 | 2.2 | 4.6•• | 4.2• |
| | | 51 | 2.0 | 1.9 | 2.3 | 4.2• | 4.1• |
| Squamous epithelium | | | | | | | |
| | ♂ | 103 | 2/12 | 2/12 | 3/12 | 7/12 | 9/11• |

a Data summarized from Table 9 of the report
• $p < 0.05$, •• $p < 0.01$

F. Sacrifice and Pathology: Gross pathological examinations were performed on animals from the satellite group (10/sex/dose group) during Week 53, surviving main study animals during Week 106, and all moribund sacrifices and animals which died during the study. The tissues listed below were collected and stored and preserved in 10% neutral formalin. All tissues from the control and high-dose groups, moribund sacrifices and animals which died during the study were examined histologically. Additionally, selected tissues (liver, spleen, kidneys,

lungs and gross lesions) of intermediate dose groups animals were examined histologically. Tissues (listed in CAPITAL LETTERS) from 10 satellite study animals/sex/group and 12 main study animals/sex/group were also weighed.

| Digestive system | Cardiovas./Hematol | Neurologic |
|---|---|---|
| Tongue | Aorta | BRAIN |
| Salivary glands | HEART | Periph. nerve |
| Esophagus | Bone marrow | Spinal cord |
| Stomach | Lymph nodes | PITUITARY |
| Duodenum | SPLEEN | Eyes |
| Jejunum | Thymus | Glandular |
| Ileum | Urogenital | ADRENALS |
| Cecum | KIDNEYS | Mammary gland |
| Colon | Urinary bladder | Parathyroids |
| Rectum | TESTES | THYROIDS |
| LIVER | Epididymides | Other |
| Pancreas | PROSTATE | Bone |
| Respiratory | Seminal vesicle | Harderian glands |
| Lungs | OVARIES | Skeletal muscle |
| Trachea | Uterus | Skin |
| | Vagina | Gross lesions |
| | | Tail |

1. Gross Pathology: Table 8 summarized pertinent gross pathological changes observed during the study. At the interim sacrifice, gross pathological findings were limited and consisted of enlarged livers ( 3/12, 25%, not significant) of the high-dose males; no changes attributable to treatment were noted in any of the females. At terminal sacrifice, the incidence of enlarged livers was only 3/34 (9%), however dark red spots were present in 47% of the animals. No treatment-related effects were noted in any of the treated females. Examination of animals which died during the study or were sacrifices *in extremis* did not reveal any treatment-related changes which would suggest an underlying cause of death.

Table 8: Incidence (%) of Gross Pathological Changes in the Livers of Male Rats (From study Table 12)

| Observation | Week | Dose Level (ppm) 0 | 100 | 1000 | 10000 | 20000 |
|---|---|---|---|---|---|---|
| Enlarged | 53 | 0/13 (0%) | 0/14 (0%) | 0/13 (0%) | 0/11 (0%) | 3/12 (25%) |
| | 106 | 1/33 (3%) | 0/29 (0%) | 0/31 (0%) | 0/32 (0%) | 3/34 (9%) |
| Dark Red Spots | 106 | 6/33 (18%) | 4/29 (14%) | 1/31 (3%) | 4/32 (13%) | 16/34 (47%) |

2. Organ Weights: The terminal body weights and organ weight data are presented in Table 9. Body weights of treated animals were not significantly different from controls at either the interim or terminal sacrifices. Males, dosed at 10000 ppm or 20000 ppm, showed significant increases in absolute liver weights at Week 106. At the interim sacrifice, 10000 and 20000 ppm males and females showed significantly increased relative liver weights; at terminal sacrifice, significant increases were noted in all of the treated males. Absolute kidney weights of 10000 ppm and 20000 ppm males and females were significantly increased in at the interim sacrifice and males at the terminal sacrifice. Relative kidney weights were increased at the interim sacrifice in 10000 ppm females and 20000 ppm males and females.

Table 9: Terminal Body Weights, Absolute and Relative Organ Weights at Interim (Week 53) and Terminal (Week 106) Sacrifices[a]

| Observation | Sex | Week | Dose Level (ppm) 0 | 100 | 1000 | 10000 | 20000 |
|---|---|---|---|---|---|---|---|
| Body Wt (g) | ♂ | 53 | 660 | 663 | 644 | 628 | 614 |
| | | 106 | 643 | 645 | 624 | 682 | 668 |
| | ♀ | 53 | 375 | 343 | 363 | 367 | 355 |
| | | 106 | 423 | 470 | 464 | 447 | 453 |
| Absolute Organ Weights (g) | | | | | | | |
| Liver | ♂ | 106 | 13.3 | 14.9 | 14.1 | 16.5•• | 17.1•• |
| Kidney | ♀ | 53 | 2.30 | 2.47 | 2.28 | 2.60• | 2.76•• |
| | ♂ | 106 | 4.33 | 4.45 | 4.35 | 4.89• | 4.99•• |
| Spleen | ♂ | 53 | 1.02 | 0.85• | 0.85• | 0.81•• | 0.83•• |
| Relative Organ Weights (g/kg body weight) | | | | | | | |
| Liver | ♂ | 53 | 2.25 | 2.37 | 2.19 | 2.45• | 2.66•• |
| | | 106 | 2.08 | 2.33• | 2.29• | 2.42•• | 2.51•• |
| | ♀ | 53 | 2.21 | 2.37 | 2.31 | 2.50•• | 2.63•• |
| Kidney | ♂ | 53 | 0.60 | 0.60 | 0.58 | 0.64 | 0.67• |
| | ♀ | 53 | 0.62 | 0.73•• | 0.64 | 0.71• | 0.78•• |

[a] Data summarized from Tables 13 and 14 of report
• $p < 0.05$, •• $p < 0.01$

3. Histopathology

i. Non-neoplastic Lesions: As shown in Table 10, there was an increase in hyperplastic nodules in the livers of high-dose males [5/50 (10%)] compared to controls [1/50 (2%)]. However, this increase was not attributed to treatment because the incidence was low in spite of being exposed to the Limit Dose; there was a lack of statistical significance or dose-response; a similar incidence [4/50 (8%)] was seen in one study conducted at the testing laboratory; and the incidence was within the historical control range [0 - 12%] of the Charles River Laboratories (Table 11). The incidence of other non-neoplastic lesions at the interim and terminal sacrifices did not reveal any treatment-related effects. The occurrence of lesions appeared to be spontaneous in nature and lacked clear dose-response relationships.

ii. Neoplastic Lesions: Neoplastic lesions observed in both control and treated animals were similar to the frequencies seen in aging/aged rats. The incidence of all neoplastic lesions is presented in Appendix 1.

Table 10: Incidence (%) of Non-neoplastic Liver Lesions in Main Study Males[a]

| Observation | Dose Level (ppm) | | | | |
|---|---|---|---|---|---|
| | 0 | 100 | 1000 | 10000 | 20000 |
| Nodular hyperplasia | 1/50 (2%) | 1/50 (2%) | 1/49 (2%) | 1/49 (2%) | 5/50 (10%) |

a Data taken from Appendix 14, Table 4 of the report

Table 11: Historical control values for nodular hyperplasia in male CD rats

| Observation | Incidence of Lesions[a] | | |
|---|---|---|---|
| | Lab[b] | CRJ[c] | CRL[d] |
| Nodular hyperplasia | 4.5%[e] (3.3 - 8.0%) | 1.7% (0 - 12.0%) | 0.7% (0 - 10.2%) |

a Overall % (Range)
b Sumitomo Chemical Co., Ltd.
c Charles River, Japan
d Charles River Laboratories, Spontaneous Neoplastic Lesions and Selected Non-neoplastic Lesions in the Crl:CD BR Rat, February, 1992, p 29.
e Mean of two studies: 5/150 (3.3%) and 4/50 (8.0%)

V. DISCUSSION: In a 2-year chronic toxicity/carcinogenicity study, CD (SD) rats were randomly assigned to the main study (50/dose/sex) or satellite study (14/dose/sex) and administered S-23031 at dietary concentrations of 0, 100, 1000, 10000 or 20000 ppm (respective mg/kg/day equivalents: 0, 3.5, 35.4, 360.4 or 744.9, males; 0, 4.3, 43.6, 443.8, or 919.4, females).

During the study significant clinical signs included an increase in urine incontinence of 10000 and 20000 ppm females and an increase in staining on the tails of 10000 and 20000 ppm males and females. Females in the 100, 10000 and 20000 ppm dose groups had statistically significant increases in mortality. The high death rate, however was not attributed to treatment, since there was no systemic toxicity or dose-response.

No biologically meaningful changes were noted in body weight, body weight change, food consumption or food efficiency. Although statistically significant increases in absolute food and relative food consumption were observed during the study, the differences were judged to be slight (< 5%). These increases were not great considering that 2% of the high-dose diet is composed of test compound. Treatment-related increases in water consumption were noted in 10000 and 20000 ppm females at Weeks 25 and 52.

Of the statistically significant clinical pathology findings, only the increase in γ-glutamyl transpeptidase activity in high-dose males appears to be treatment-related. The significant increases in the percent of $\alpha_1$-globulin in high-dose females not correlated with any toxicity. The slight increase may be a reflection of slightly elevated total protein levels in the high-dose group. The differences noted in the lymphocyte differential counts were slight and not suggestive of a treatment-related effect. The changes in differential counts were not accompanied by significant changes in the lymphocyte count or the absolute neutrophil and lymphocyte counts.

Significant, treatment-related urinalysis findings consisted of increased urine volume in 20000 ppm males at Week 103 and 10000 and 20000 ppm females at Weeks 25 and 51. Squamous epithelial cells in the urinary sediment was significantly increased in high-dose males at Week 103. In a 90-day feeding study (MRID No.: 428839-03) male and female rats treated with 100000 or 300000 ppm showed increased presence of epithelial cells in the urinary sediment.

Significant, treatment-related increases in absolute liver weights were observed in 10000 and 20000 ppm males at the terminal sacrifice; relative liver weights for animals in the 10000 and 20000 ppm animals were increased at the interim sacrifice in males and females and at terminal sacrifice in males only. Although increases in relative liver weights were noted in the 100 and 1000 ppm males at terminal sacrifice, the significant findings appear to be a statistical aberration rather than a true

biological effect. For animals in the 10000 and 20000 ppm dose groups, absolute kidney weights were significantly increased in females at the interim sacrifice and males at the terminal sacrifice. Relative kidney weights were increased at the interim sacrifice in 10000 ppm females and 20000 ppm males and females. The increase in the relative kidney weights of the 100 ppm females at the interim sacrifice was not judged to be treatment-related since no effect was noted in the next higher dose. Statistically, but not toxicologically, significant decreases in the absolute spleen weights were observed in all of the treated males at the interim sacrifice.

Gross pathological findings were limited males. At the interim sacrifice enlarged livers were noted in 25% of the high-dose animals (Control = 0%), at terminal sacrifice only 9% of the animals had enlarged livers, compared to 3% for controls. Dark red spotting of the livers was noted in 47% of high-dose males (Control = 18%) at terminal sacrifice. No treatment-related effects were noted in any of the females at either the interim or terminal sacrifices.

Histopathological findings did not reveal any treatment-related increased in the incidence on non-neoplastic lesions at the interim sacrifice or terminal sacrifice. The occurrence of the neoplastic lesions appeared to be spontaneous in nature and lacked clear dose-response relationships.

VI. CONCLUSIONS: Mid- and high-dose male rats showed clear and consistent treatment-related hepatic changes. The increased absolute and relative liver weights was also associated with increased activity of γ-glutamyl transpeptidase and increased incidence on hyperplastic nodules. Other effects included significant urinalysis findings (increased urine volume and appearance of squamous epithelial cells in the sediment) in the high-dose males.

Based on these findings, a LOEL of 10000 ppm (360 mg/kg/day) and a NOEL of 1000 ppm (35 mg/kg/day) were established for systemic toxicity in male rats. In female rats, the NOEL was the highest dose tested (20000 ppm, 919.4 mg/kg/day). There is no evidence that S-23031 was carcinogenic in this study.

CLASSIFICATION: core - Guideline

This study satisfies guideline requirements (§83-5) for a combined chronic toxicity/carcinogenicity study in rats.

Page_____ is not included in this copy.

Pages 95 through 99 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.

√ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Primary Review by: Robert F. Fricke, Ph.D. Robert F. Fricke 11 Mar 94
Review Section IV, Toxicology Branch II/HED (H7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/4/94
Review Section IV, Toxicology Branch II/HED (H7509C)

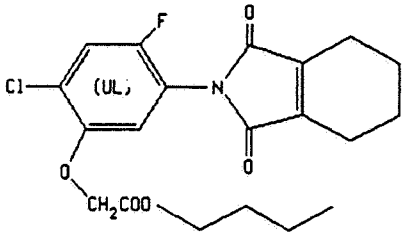
C10848

**DATA EVALUATION RECORD**

**STUDY TYPE:** Special metabolism study - rats

**EPA ID NO's:** MRID No.: 428258-23
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** [Phenyl-(UL)$C^{14}$]S-23031




**SYNONYMS:** V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Sumitomo Chemical Co., Ltd, Osaka, Japan

**TITLE OF REPORT:** Purification and Identification of Fecal and Urinary Metabolism of S-23031 in Rats

**STUDY NUMBER:** X0003

**AUTHOR:** H. Matsunaga

**REPORT ISSUED:** 8 April 1993

**EXECUTIVE SUMMARY:** Male rats were dosed for six days with 250 mg/kg/day of [phenyl-$C^{14}$]S-23031 (0.31 MBq/mmol). Excreta were collected separately using glass metabolism cages. The urinary and fecal metabolites, from pooled samples) were separated using several chromatographic techniques and. Using NMR, MS and FTIR spectoanalyses, the identity and structure of the urinary metabolite (4-OH-IMCA, [2-chloro-4-fluoro-5-(4-hydroxy-1,2-cyclohexenedicarboximido)] phenoxyacetic acid) and four fecal metabolites (IMCA-SA, [2-chloro-4-fluoro-5-(1-sulfo-1,2-cyclohexanedicarboximido)]phenoxyacetic acid; 4-OH-IMCS-SA1 and

2, [2-chloro-4-fluoro-5-(1-sulfo-4-hydroxy-1,2-cyclohexane-dicarboximido)]phenoxyacetic acid; and 5-OH-IMCS-SA, [2-chloro-4-fluoro-5-(1-sulfo-5-hydroxy-1,2-cyclohexanedicarboximido)] phenoxyacetic acid) were determined. Three metabolites, 4-OH-IMCA-SA1, 4-OH-IMCA-SA2 and 5-OH-IMCA-SA, which could not be resolved using TLC, had sufficiently different HPLC retention times (40, 21, and 19 min, respectively) to allow separation and subsequent identification.

This study is classified as Core - Supplementary, however, when taken with other metabolism studies (MRID No's: 421598-40, 428258-21 and 428258-22) the guideline requirement (§85-1) is satisfied.

101

C10848

## I. MATERIALS

### A. Test compound

1. Labeled Compound: [Phenyl-$^{14}$C]S-23031 Lot No.: C-88-12A (C-88-025) Radiochemical Purity: > 99% Chemical Purity: >99% Specific Activity: 7.22 GBq/mmol (195 mCi/mmole, 0.459 mCi/mg)

2. Unlabeled Compound: S-23031 Description: beige powder Lot No: LN-80206 Purity: 99.2% Contaminants: CBI Index

B. Test animals: Species: Rat Strain: Sprague-Dawley Age: 7 weeks Weight (g): Not given Source: Not given Housing: Individually in glass metabolism cages Feed: Not given Water): Not given Environment: Not given

## II. METHODS

A. Study Design: Fourteen male rats were orally dosed with 250 mg/kg of [phenyl-$^{14}$C]S-23031 for six consecutive days. Dosing solutions were prepared by isotopically diluting labeled test compound to achieve a specific activity of 0.31 MBq/mmol. The test compound was dissolved in corn oil. Fecal and urinary samples were collected separately over a 6-day period.

B. Purification and Identification of Metabolites

1. Thin Layer Chromatography (TLC): To track the purification process, fractions were subjected to silica gel TLC using 1-butanol:acetic acid:water (6:1:1, v/v/v).

2. Purification of Fecal Metabolites: Pooled fecal samples were weighed and homogenized in a 3-fold volume of methanol:water (9:1, v/v). The homogenate was centrifuge and the supernatant decanted off; the fecal residue was extracted two additional times. Most of the methanol:water was removed *in vacuo*. Half of the concentrated solution was applied to a silica gel (Silica Gel 60, Merck) column and eluted sequentially with n-hexane:acetone (1:1, v/v), acetone, acetone:methanol (3:1, v/v) and methanol to yield five fractions (A, B, C, D and E).

The other half of the concentrated fecal extract was extracted three times with a diethyl ether-water suspension. The aqueous phase was concentrated and applied to an ion exchange (Amberlite XAD-2 resin, Organo, Tokyo, Japan) and eluted sequentially with water, methanol:water (1:4 or 1:3, v/v) and methanol. Three fractions (F, G and H) were collected.

Fractions C, D, F, and G were applied to separate Sephadex LH-20 columns and eluted with methanol. Selected peaks were collected and subjected to high performance liquid chromatography (HPLC). The column effluent was monitored with a UV detector and a radioactivity monitor. Elution with methanol:water (2:3) yielded fraction FMP-0 with a retention time of 17 min. Further elution with methanol:water (3:97) yielded three more fractions (FMP-1, FMP-2, and FMP-3).

3. Purification of Urinary Metabolites: Pooled urine samples were lyophilized and the residue extracted with methanol. The methanol extract was concentrated and subjected to HPLC using methanol:water:acetic acid (40:60:1) as solvent. One fraction (U-LC-3) with a retention time of 34 min was collected.

4. Identification of Metabolites: Various spectroscopic procedures were used to identify the purified metabolites. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were obtained. Two-dimensional analysis of the NMR data was performed using H-H double Quantum Filter Correlation Spectroscopy (H-H DFQ-COSY), H-H phase sensitive H-H DFQ-COSY, and C-H Correlation Spectroscopy. Secondary ion - mass spectroscopy was performed with spectra recorded in positive or negative ion mode. Fourier transfer infrared (FTIR) spectra were also obtained.

III. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

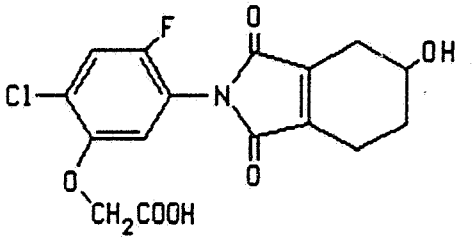
B. A statement of "no confidentiality claims" was provided.

IV. RESULTS and DISCUSSION: Male rats were dosed for six days with 250 mg/kg/day of [phenyl-$C^{14}$]S-23031 (0.31 MBq/mmol). Excreta were collected separately using glass metabolism cages. The urinary and fecal metabolites, from pooled samples, were separated using HPLC followed by NMR, MS and FTIR spectoanalyses. The identity and structure of the urinary metabolite (4-OH-IMCA) and four fecal metabolites (IMCA-SA, 4-OH-IMCS-SA1, 4-OH-IMCS-SA2, and 5-OH-IMCS-SA) were determined (Table 1). Three of the metabolites, 4-OH-IMCA-SA1, 4-OH-IMCA-SA2 and 5-OH-IMCA-SA, which could not be resolved using TLC, had sufficiently different HPLC retention times (40, 21, and 19 min, respectively) to allow separation and subsequent identification.

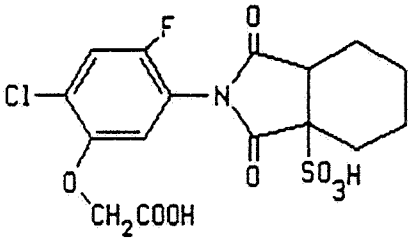
This study is classified as Core - Supplementary, however, when taken with other metabolism studies (MRID No's: 421598-40, 428258-21 and 428258-22) the guideline requirement (§85-1) is satisfied.

Table 1: Structures of Fecal and Urinary Metabolites

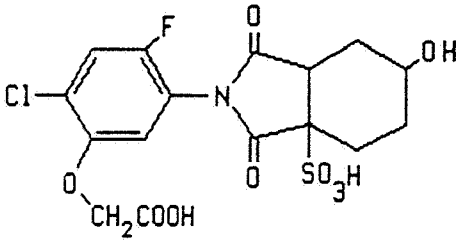
| | |
|---|---|
| 4-OH-IMCA | [2-chloro-4-fluoro-5-(4-hydroxy-1,2-cyclohexenedicarboximido)]phenoxyacetic acid |



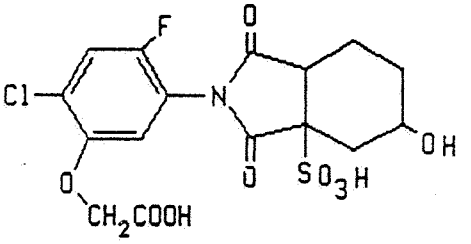

| | |
|---|---|
| IMCA-SA | [2-chloro-4-fluoro-5-(1-sulfo-1,2-cyclohexanedicarboximido)]phenoxyacetic acid |




| | |
|---|---|
| 4-OH-IMCA-SA1&2[a] | [2-chloro-4-fluoro-5-(1-sulfo-4-hydroxy-1,2-cyclohexanedicarbox-imido)]phenoxyacetic acid |




| | |
|---|---|
| 5-OH-IMCA-SA | [2-chloro-4-fluoro-5-(1-sulfo-5-hydroxy-1,2-cyclohexanedicarboximido)]phenoxyacetic acid |




[a] 4-OH-IMCA-SA1 and 4-OH-IMCA-SA2 are stereoisomers

Primary Review by: Robert F. Fricke, Ph.D. Robert F. Fricke 11 mar 94
Review Section IV, Toxicology Branch II/HED (H7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/14/94
Review Section IV, Toxicology Branch II/HED (H7509C)

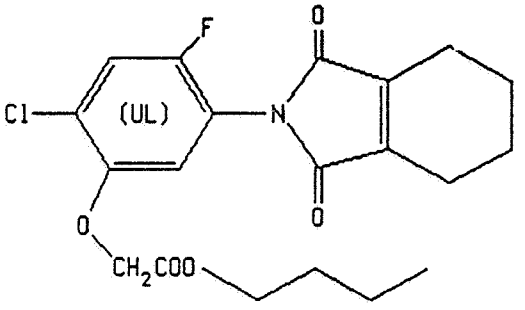
£10848

**DATA EVALUATION RECORD**

**STUDY TYPE:** Special metabolism study - rats

**EPA ID NO's:**
MRID No.: 428258-21
Pesticide Chemical Code: 12872
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031




**SYNONYMS:**
V-23031
Flumiclorac pentyl
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Sumitomo Chemical Co., Ltd, Osaka, Japan

**TITLE OF REPORT:** Bile Excretion Study of [Phenyl-$^{14}$C]S-23031 in Male Rats

**STUDY NUMBER:** 2661

**AUTHOR:** H. Matsunaga

**REPORT ISSUED:** 25 February 1993

**EXECUTIVE SUMMARY:** The metabolism of [phenyl-C$^{14}$]S-23031 was studied in male Crj:CD(SD) rats treated by oral gavage with a single low dose (1 mg/kg/day) or a single high dose (500 mg/kg/day) of labeled test compound). Biliary, urinary and fecal samples were collected over a 48-hour period and analyzed for radioactivity. At 48-hours post-dosing, animals were sacrificed and radioactivity in carcass determined. Major biliary metabolites were isolated and identified.

Essentially all (> 98%) of the administered dose was eliminated within two days of dosing. Biliary excretion accounted for approximately 19% of the administered dose, while the cumulative urinary and fecal elimination were 55% and 33% for the low dose, respectively and 31% and 44% for the high dose, respectively. The profiles of biliary metabolites indicated that no detectable (< 0.05%) amounts of unmetabolized S-23031 were present. For both dose groups, AFCA ((2-chloro-4-fluoro-5-amino)phenoxyacetic acid) accounted for 11 to 12% of the administered dose; IMCA ([2-chloro-4-fluoro-5-(3,4,5,6-tetrahydro)phthalimido]phenoxyacetic acid) was present at 0.5% or less.

**Based on the results of this study, the high amounts of unmetabolized S-23031 present in the feces is due to lack of absorption rather than biliary excretion.**

This study is classified as Core - Supplementary, however, when taken with other metabolism studies (MRID No's: 421598-40, 428258-22 and 428258-23) the guideline requirement (§85-1) is satisfied.

C10848

## I. MATERIALS

### A. Test compound

1. Labeled Compound: [Phenyl-$^{14}$C]S-23031 Lot No.: C-88-12A (C-88-025) Radiochemical Purity: > 99% Chemical Purity: >99% Specific Activity: 7.22 GBq/mmol (195 mCi/mmole, 0.459 mCi/mg)

2. Unlabeled Compound: S-23031 Description: beige powder Lot No: LN-80206 Purity: 99.2% Contaminants: CBI Index

B. Test animals: Species: Rat Strain: Crj:CD(SD) Age: 7 weeks Weight (g): 225- 258 (males) Source: Charles River Japan, Inc. Housing: Individually in metabolic cages Feed (Before Dosing): CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan, *ad libitum* Feed (After Dosing): Solita-T3, an electrolytic, nutritious fluid containing glucose, L-lactate, NaCl and KCl (Shimizu Pharmacy, Shizuoka, Japan) Water (Before Dosing): Filtered tap water, *ad libitum* Environment: Temperature: 23 ± 2°C; Humidity: 55 ± 10%; Air changes: > 10/hr in open cages; Light cycle: 12 hr light/12 hr dark

## II. METHODS

A. Dose Preparation: [Phenyl-$^{14}$C]S-23031 was purified before use by thin layer chromatography (TLC) developed with chloroform. The radioactive zone was scraped off and the silica gel extracted with diethyl ether. The ether extract was taken to dryness and the residue isotopically diluted with unlabeled S-23031 in acetone. Specific activities were adjusted to yield 9.23 MBq/mg and 18.5 kBq/mg for low- and high-dose groups, respectively. The acetone was evaporated and the residue dissolved in corn oil to yield a 0.2 mg/ml (low-dose group) or 100 mg/ml (high-dose group). After dosing, the concentration and radiochemical purity of the dosing solutions was confirmed by liquid scintillation counting (LSC) and TLC.

B. Study Design: Male rats, 3/dose group, were assigned to low- or high-dose study groups. While under ether anesthesia, the bile ducts of all study animals were cannulated. (NOTE: The bile ducts of additional rats were cannulated to assure sufficient number of animals for the study). Animals in the low- or high- dose groups were orally gavaged with a single dose of [phenyl-$^{14}$C]S-23031 to yield doses of 1 mg/kg or 500 mg/kg, respectively. Following the administration of labeled compound, the animals were placed individually in metabolic cages. After 48 hours, all animals were sacrificed.

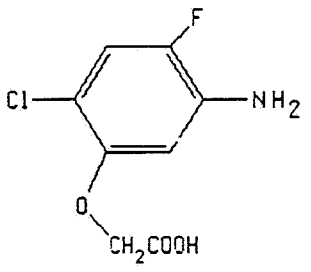
C. Analysis of Radioactivity in Bile, Feces and Urine: Pooled bile samples were collected for 0-6, 6-24 and 24-48 hours post-dosing, while fecal and urinary samples were pooled for 0-24 and 24-48 hours post-dosing. After each urine collection, the cage and pans underneath the cages were rinsed with water to collect any spilled urine; rinses were combined with the respective urine sample. Bile and feces were stored at -20°C until analyzed; urine was stored at room temperature. Duplicate aliquots of pooled, 0-6, 6-24 and 24-48 hour, bile and urine samples were assayed for radioactivity using LSC. Pooled fecal samples were homogenized in acetonitrile (3-5 ml/g feces) and filtered. The filter cake was rehomogenized and filtered. The filtrates were combined and assayed, in duplicate, for radioactivity using LSC. The amount of unextractable radioactivity was determined by combusting duplicate samples of the dried filter cakes in a sample oxidizer and measuring the amount of $^{14}CO_2$ released using LSC.

D. Tissue Radioactivity: All animals were sacrificed 48 hours after administration of labeled test compound. The carcasses were minced and dissolved in 2N NaOH (room temperature for approximately 3-4 days). Duplicate samples were assayed for radioactivity using LSC.

E. Identification of Major Metabolites in Bile

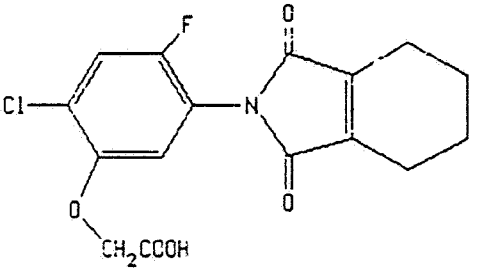
1. Metabolite standards: Unlabeled synthetic standards were prepared (Table 1). Structure of standards was confirmed by NMR and mass spectral analyses.

Table 1: Metabolite Standards




AFCA

(2-chloro-4-fluoro-5-amino) phenoxyacetic acid




IMCA

[2-chloro-4-fluoro-5-(3,4,5,6-tetrahydro)phthalimido]phenoxy acetic acid

2. Thin layer chromatography: TLC plates (pre-coated silica gel 60 $F_{254}$ (Merck) and RP-18 $F_{254}$s (Merck)) were developed using the following solvent systems:

(A) toluene/ethyl formate/ formic acid (5/7/1)
(B) 1-butanol acetic acid/water (6/1/1), or
(C) acetonitrile/water (2/3)

The Rf values for authentic standards were determined for each of the solvent systems. Bile samples were cochromatographed with standards using solvent system (A). Radioactive metabolites were detected using autoradiography (SB-5 film, Kodak), while standards were visualized under UV light.

F. Statistics: Significant differences between sexes or dose groups was determined using Student's t-test.

III. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. A statement of "no confidentiality claims" was provided.

IV. RESULTS

A. Elimination Profiles: The cumulative amounts of excreted radioactivity is summarized in Table 2. For both the low and high dose groups, biliary excretion accounted for approximately 19% of the administered dose. For the low dose group elimination in the urine exceeded that of the feces (55% vs 33%). For high dose animals fecal elimination accounted for 44%, compared to 31% for urine. Total recovery exceeded 98%.

Table 2: Cumulative amounts of $^{14}C$-labeled residues in bile, feces, urine and carcass[a]

| | | % of Dosed $^{14}C$ | | |
|---|---|---|---|---|
| Dose Group | Sample | 0-6 hr | 0-24 hr | 0-48 hr |
| Low Dose | Bile | 7.7 | 18.0 | 18.8 |
| | Feces | --- | 20.3 | 33.1 |
| | Urine | --- | 41.3 | 55.0 |
| | Carcass | --- | --- | 3.9 |
| | Total | 7.7 | 79.5 | 110.8 |
| High | Bile | 8.0 | 16.5 | 18.5 |
| | Feces | --- | 17.4 | 44.0 |
| | Urine | --- | 24.0 | 30.9 |
| | Carcass | --- | --- | 5.0 |
| | Total | 8.0 | 57.9 | 98.5 |

a. Data compiled from study Table 3 of the report

B. Identification of Biliary Metabolites: The identification of biliary metabolites is presented in Table 3. Less than 0.05% (no detectable amounts) of unmetabolized S-23031 was present in the bile of either the low or high dose animals. AFCA was present in the highest amounts, representing 11.2% and 12.1% of the total administered radioactivity for the low and high dose groups, respectively. IMCA comprised < 0.5% of the administered dose in both study groups.

Table 3: Identification of Biliary Metabolites[a]

| | % of Dosed $^{14}C$ | |
|---|---|---|
| Metabolite | Low Dose | High Dose |
| S-23031 | < 0.05 | < 0.05 |
| AFCA | 11.2 | 12.1 |
| IMCA | 0.5 | 0.3 |
| Others | 7.2 | 6.1 |
| Total | 18.8 | 18.5 |

a. Data from Table 4 of the report

V. DISCUSSION: The metabolism of [phenyl-$C^{14}$]S-23031 was studied in bile duct cannulated male rats. Following a single oral gavage with 1 mg/kg or 500 mg/kg, biliary, urinary and fecal samples were collected and analyzed for radioactivity. Essentially all (> 98%) of the administered dose was eliminated within two days of dosing.

Biliary excretion accounted for approximately 19% of the administered dose, while the cumulative urinary and fecal elimination were 55% and 33% for the low dose, respectively and 31% and 44% for the high dose, respectively.

The profiles of biliary metabolites indicated that no detectable (< 0.05%) amounts of unmetabolized S-23031 were present. For both dose groups, AFCA accounted for 11 to 12% of the administered dose; IMCA was present at 0.5% or less.

This study confirms that the high amounts of unmetabolized S-23031 were present in the feces of high dose animals was due to lack of absorption rather than biliary excretion.

This study is classified as Core - Supplementary, however, when taken with other metabolism studies (MRID No's: 421598-40, 428258-22 and 428258-23) the guideline requirement (§85-1) is satisfied.

Primary Review by: Robert F. Fricke, Ph.D. Robert F. Fricke 11 Mar 94
Review Section IV, Toxicology Branch II/HED (H7509C)

Secondary Review by: Jess Rowland, M.S. Jess Rowland 3/14/94
Review Section IV, Toxicology Branch II/HED (H7509C)

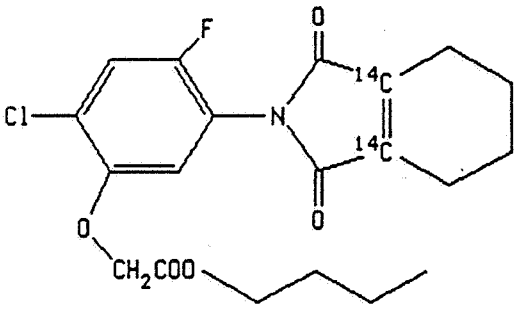
010848

**DATA EVALUATION RECORD**

**STUDY TYPE:** Metabolism - rats (85-1)

**EPA ID NO's:**
MRID No.: 428258-22
Pesticide Chemical Code: 128724
Toxicology Chemical Code: 958
DP Barcode: D195817
Submission No.: S449777

**TEST MATERIAL:** S-23031




**SYNONYMS:** V-23031, Flumiclorac pentyl ester
Pentyl 2-chloro-4-fluoro-5-[(3,4,5,6-tetrahydro)phthalimido]phenoxy acetate

**SPONSOR:** Valent U.S.A. Corporation, Walnut Creek, CA

**TESTING FACILITY:** Sumitomo Chemical Co., Ltd, Osaka, Japan

**TITLE OF REPORT:** Metabolism of S-23031 in Rats; [tetrahydrophthalonyl-1,2$^{14}$C] S-23031

**STUDY NUMBER:** 2474

**AUTHOR:** H. Matsunaga

**REPORT ISSUED:** 26 February 1993

**EXECUTIVE SUMMARY:** The metabolism of [Tetrahydrophthalony-1,2-C$^{14}$]S-23031 was studied in male and female Crj:CD(SD) rats (Charles River, Japan, Inc.) treated by oral gavage with single low dose (1 mg/kg/day), single high dose (500 mg/kg/day) or repeated low dose (1 mg/kg/day of unlabeled test compound, followed on the 15th day with a dose of 1 mg/kg of labeled compound). Urinary and fecal samples were collected over a seven day period and analyzed for radioactivity. At Day 7 post-dosing,

animals were sacrificed and radioactivity in tissues, blood and carcass determined. Major metabolites were isolated from pooled 0 to 2 day urinary and fecal samples and identified using a variety an analytical techniques.

By Day 2, essentially all (> 93.1%) of the administered dose was eliminated. Tissue accumulation of $^{14}C$-labeled residues was very low, with highest levels found in blood, plasma and kidneys of all three dose groups.

The metabolic profiles for each of the dose groups showed a total of up to 14 fecal and 13 urinary metabolites. Of these, seven fecal and six urinary metabolites were positively identified. Fecal elimination of unmetabolized S-23031 by low and repeat low dose animals was either low or not detectable. Due to lack of absorption (not biliary excretion) high amounts of S-23031 were present in the feces of high dose animals. Metabolic conversions include deesterification and/or imide bond cleavage, followed by a series of hydroxylation and/or sulfonation reactions. Low dose animals showed no remarkable sex differences in the metabolite distribution. Urine of high dose males, however, showed higher amounts of metabolites resulting from imide bond cleavage (THPA) and hydroxylated and sulfonated compounds. In females, deesterified parent compound (IMCA) and 4-OH-IMCA were higher. Repeat low dose females showed higher amounts of IMCA, THPA and 4-OH-IMCA in the urine.

This study is classified as Core - Supplementary, however, when taken with other metabolism studies (MRID No.: 421698-40, 428258-23 and 428258-21) the guideline requirements (§85-1) are satisfied.

## I. MATERIALS

### A. Test compound

1. Labeled Compound: [Tetrahydrophthalonyl-1,2$^{14}$C] S-23031 ([THP-C$^{14}$]S-23031) Lot No.: Main study: C-91-032A (C-91-045); Preliminary study: C-88-13A (C-88-017) Radiochemical Purity: > 99% Chemical Purity: >99% Specific Activity: 4.04 GBq/mmol (109 mCi/mmol, 257 μCi/mg)

2. Unlabeled Compound: S-23031 Description: beige powder Lot No: LN-80206 Purity: 99.2% Contaminants: Not given

B. Test animals: Species: Rat Strain: Crj:CD(SD) Age: 5-7 weeks Weight (g): 141 - 275 (males), 109 - 191 (females) Source: Charles River Japan, Inc. Housing: Individually in metabolic cages Feed: CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan, *ad libitum* Water: Filtered tap water, *ad libitum* Environment: Temperature: 23 ± 2°C; Humidity: 55 ± 10%; Air changes: > 10/hr in open cages, 200 - 300 ml/min in metabolism cages; Light cycle: 12 hr light/12 hr dark

## II. METHODS

A. Dose Preparation: [THP-$^{14}$C]S-23031 was purified before use by thin layer chromatography (TLC) developed with chloroform. The radioactive zone was scraped off and the silica gel extracted with diethyl ether. The ether extract was taken to dryness and the residue dissolved in corn oil (the test compound has limited solubility in water) to yield a 0.2 mg/ml solution with a specific activity of 257 μCi/mg. This solution was used for the single and repeat low-dose groups. The dosing solution for the high-dose group was prepared by adding unlabeled S-23031 to yield a concentration of 100 mg/ml and specific activity of 0.5 μCi/mg. The dosing solutions were analyzed to confirm concentration and specific activity. Stability of the dosing solutions was determined.

### B. Study Design

1. Preliminary Study: A preliminary experiment was carried out to (1) evaluate the amount of $^{14}CO_2$ appearing in expired air and (2) determine the excretion profiles. One male and one female rat were orally dosed with 1 mg (9.25 MBq)/5 ml/kg of labeled test compound and placed in glass metabolism cages fitted with $CO_2$ trap containing 200 ml of 10% NaOH. After 24 hours the amount of trapped $CO_2$ was determined by liquid scintillation counting (LSC) of a diluted aliquot of the trapping solution. Urine samples were

collected and pooled for days 0 to 1, 1 to 2, 2 to 3, 3 to 5, and 5 to 7. Cage washes were combined with the 3 to 5 and 5 to 7 day urine samples. Fecal samples were collected and pooled for days 0 to 1 and 1 to 2. Aliquots of the pooled urine samples were assayed for radioactivity using LSC. Fecal samples were homogenized in methanol, centrifuged and an aliquot of the supernatant assayed for radioactivity using LSC.

2. Main Study: Animals, 5/sex/group, were assigned to low, high and repeat low dose study groups. Animals in the low (1.0 mg/kg) and high dose (500 mg/kg) groups each received a single dose of [THP-$^{14}$C]S-23031 by oral gavage. Animals in the repeat dose group were dosed orally with S-23031 (1 mg/kg) for 14 consecutive days; on the 15th day, they received a single oral dose of [THP-$^{14}$C]S-23031 labeled test compound (1 mg/kg). Following the administration of labeled compound, the animals were placed individually in metabolic cages. Clinical signs for animals in the repeat-dose groups were evaluated at 10 min, 30 min, 1 hr, 2 hr, and 6 hr following the administration of unlabeled S-23031. Following the administration of [THP-$^{14}$C]S-23031, clinical signs were evaluated at 10 min, 30 min, 1 hr, 2 hr (repeat low dose group only), 6 hr and daily, thereafter, until terminal sacrifice.

D. Analysis Radioactivity in Fecal and Urinary Samples: Fecal and urinary samples were collected 6 hr (urine only), 1, 2, 3, 5, and 7 days after administration of labeled test compound. Following collection of the excreta, the cages were rinsed with water to remove any residual radioactivity. Excreta were stored at -20°C until analyzed. Duplicate aliquots of pooled urine samples (0 to 6 hr, 6 hr to 1 day, 1 to 2 days and 2 to 3 days) and cage washes were assayed for radioactivity using LSC. The 3 to 5 and 5 to 7 day urinary samples were combined with the respective cage washes and radioassayed. Fecal samples were collected and pooled for days 0 to 1 and 1 to 2, homogenized in acetonitrile (5 mg/g), centrifuged, and an aliquot of the supernatant assayed for radioactivity using LSC. The fecal samples were extracted three times with acetonitrile/ water (1/1, v/v). The 2 to 3, 3 to 5 and 5 to 7 day fecal samples were homogenized in water and combusted for determination of radioactivity by LSC.

E. Tissue Distribution of Radioactivity: All animals were sacrificed seven days after administration of labeled test compound. Blood, adrenals, bone, bone marrow, brain, fat sample, heart, kidney, liver, lung, muscle sample, spleen, pancreas, thyroid and testes or ovary and uterus were collected. Samples of each tissue, minced carcass and an aliquot of whole blood were combusted for determination of

radio-activity. Remaining whole blood was centrifuged to separate serum and red blood cells.

F. Identification of Major Metabolites

1. Metabolite standards: Metabolite standards were either synthesized or isolated from pooled urinary and fecal samples (Table 1). Four standards (IMCA, THPA, 4-OH-THPA, and 1-OH-HPA) were synthesized. Another five standards (one urinary: 4-OH-IMCA and four fecal: IMCA-SA, 4-OH-IMCA-SA1, 4-OH-IMCA-SA2, and 5-OH-IMCA-SA) were isolated and identified from pooled urinary and fecal extracts as detailed in a preliminary study[1]. Three metabolites (4-OH-IMCA-SA1, 4-OH-IMCA-SA2, and 5-OH-IMCA-SA) produced a single spot using TLC; they were, however, separated using HPLC and identified. The structures (Appendix 1) of the synthesized standards and purified metabolites were confirmed by NMR, infrared and mass spectral analyses.

Table 1: Metabolite Standards

| | |
|---|---|
| IMCA | [2-Chloro-4-fluoro-5-(3,4,5,6-tetrahydro) phthalimido]phenoxyacetic acid |
| THPA | 3,4,5,6-Tetrahydrophthalic acid |
| 4-OH-THPA | 4-Hydroxyl-1-cyclohexenedicarboxylic acid |
| 1-OH-HPA | 1-Hydroxyl-1,2-cyclohexanedicarboxylic acid |
| 4-OH-IMCA | [2-Chloro-4-fluoro-5-(4-hydroxy-1,2-cyclo hexenedicarboximido)]phenoxyacetic acid |
| IMCA-SA | [2-Chloro-4-fluoro-5-(1-sulfo-1,2-cyclohexane dicarboximido)]phthalimido)phenoxy acetic acid |
| 4-OH-IMCA-SA1 & 4-OH-IMCA-SA2[a] | [2-Chloro-4-fluoro-5-(1-sulfo-4-hydroxy-1,2-cyclohexanedicarboximido)]phenoxyacetic acid |
| 5-OH-IMCA-SA | [2-Chloro-4-fluoro-5-(1-sulfo-5-hydroxy-1,2-cyclohexanedicarboximido)]phenoxyacetic acid |

[a] Stereoisomers

[1] H. Matasunaga, Purification and Identification of Fecal and Urinary Metabolism of S-23031 in Rats, Project No. X0003, April 8, 1993, Sumitomo Chemical Co., Ltd., EPA MRID No.: 428258-23

2. Chromatography

a. Thin layer chromatography: TLC plates (pre-coated silica gel 60 $F_{254}$ (Merck) and RP-18 $F_{254}$s (Merck)) were developed using the following solvent systems: (A) toluene/ethyl formate/ formic acid (5/7/1), (B) 1-butanol acetic acid/water (6/1/1), or (C) acetonitrile/water (2/3). Non-radioactive standards were visualized under UV light or by coloring with bromocresol purple or 2,6-dichlorophenolindophenol, sodium salt. Radioactive standards were detected using autoradiography (SB-5 film, Kodak). The Rf values for authentic standards and identified metabolites were determined for each of the solvent systems.

b. High performance liquid chromatography (HPLC): HPLC analyses were performed using a SUMIPAX ODS A-212 column (Sumika Chemical Analysis Service). IMCA, THPA and 4-OH-THPA were separated on columns eluted with trifluoroacetic acid (0.1% in water) for 10 min, a linear gradient was then started to reach 100% acetonitrile after 50 min, elution was continued with 100% acetonitrile for 15 min. 1-OH-HPA was separated on columns eluted first with trifluoroacetic acid (0.1% in water) for 10 min, a linear gradient was then started to reach 40% acetonitrile at 30 min, elution was continued with 100% acetonitrile. The eluent was passed through a UV detector and a radioactivity monitor.

3. Urinary and fecal metabolites: Pooled, 0 to 2 day urinary samples and acetonitrile fecal extracts were concentrated in a rotary evaporator, *in vacuo*. Metabolites, co-chromatographed with authentic standards, were initially identified by TLC. Areas on the chromatographic plate corresponding to the metabolites were scraped, extracted and co-chromatographed with authentic standards using HPLC.

F. Statistics: Significant differences between sexes or dose groups was determined using Student's t-test.

III. REGULATORY COMPLIANCE

A. Quality assurance was documented by signed and dated GLP and quality assurance statements.

B. A statement of "no confidentiality claims" was provided.

## IV. RESULTS

A. Preliminary Study: Results of the preliminary study showed that essentially all (> 97%) of the administered radioactivity could be accounted for in the urine and feces after seven days; very little (< 0.01%) was present in the expired air. Therefore, for the main study only the urine and feces were collected for routine analysis of $^{14}C$-labeled residues.

B. Clinical Observations: No treatment-related clinical signs of toxicity were seen in any of the animals.

C. Distribution of Radioactivity in Excreta: The cumulative amounts of radioactivity in the feces and urine are summarized in Table 2. For all three study groups, essentially all (93.1 to 97.0%) of the administered radioactivity was excreted within the first two days post-dosing. At all collection time points, urinary elimination was higher in females, with pronounced differences in the repeat dose group females. Seven days post-dosing, urinary excretion by females accounted for approximately 48% of the dose, compared to approximately 34% for males.

D. Tissue Distribution of Radioactivity: At terminal sacrifice, the tissue levels of labeled residues was < 6 ppb for low and repeat dose groups and < 2500 ppb for high dose group (Table 3). All study groups showed high amounts of labeled residues in blood, plasma and kidneys. No detectable radioactivity was present in adrenals, brain, fat or thyroids.

E. Identification of Metabolites: The metabolic profiles for the three study groups are presented in Table 4. In addition to the parent compound, a total of seven metabolites were isolated and identified. Eighteen other metabolites, representing 1.0 to 6.3% of the total dose, were isolated, but not identified. Very minor metabolites (< 1%, each) were combined as "others" and accounted 3.8 to 6.5% of the total dose.

Differences were noted in the metabolic profiles among each of the study groups. Very low or undetectable amounts of S-23031 were present in the feces of low and repeat low dose animals; very high concentrations (32.2%, males; 27.4%, females) were present in high dose animals. Within each study group, no remarkable differences were noted between males and females of the low dose group. Both the high and repeat low dose groups showed some differences between the sexes. In the high dose group, males had higher amounts of 4-OH-THPA and OH-IMCA-SA in the urine, while in females, IMCA and 4-OH-IMCA were higher. Repeat low dose females showed higher amounts of IMCA, THPA and 4-OH-IMCA in the urine.

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Pages 118 through 119 are not included.

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_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

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The extent of each metabolic transformation for each of the study groups is summarized in Table 5. No marked intra-group differences were noted between the males and females. The extent of the metabolic transformations was lower in the high dose animals due to the high amount of unmetabolized parent compound present in the feces. The main metabolic transformations were (1) deesterification (2) cleavage of the imide bond, hydroxylation and (4) sulfonation.

Table 5: Metabolic transformations[a]

| | Low Dose | | High Dose | | Repeat Dose | |
|---|---|---|---|---|---|---|
| Transformation | Male | Female | Male | Female | Male | Female |
| Cleavage to ester | 44.4 | 40.5 | 27.1 | 28.4 | 45.4 | 44.8 |
| Cleavage of imide bond | 16.4 | 13.2 | 11.0 | 10.2 | 9.7 | 10.6 |
| Hydroxylation | 24.9 | 18.9 | 15.5 | 11.8 | 19.1 | 19.6 |
| Sulfonation | 24.7 | 21.4 | 16.6 | 12.7 | 35.6 | 27.9 |

a. Data compiled from Table 6 of the report

F. Proposed Metabolic Pathway: The proposed metabolic pathway is presented in Appendix 2. S-23031 is deesterified to form the phenoxyacetic acid derivative (IMCA), which is then hydroxylated to form 4-OH-IMCA or sulfonated to form IMCA-SA. 4-OH-IMCA also undergoes a sulfonation reaction to form either 4-OH-IMCA-SA or 5-OH-IMCA-SA. 4-OH-IMCA-SA exists at two isomers: 4-OH-IMCA-SA1 and 4-OH-IMCA-SA2. Breakage of the imide bond of either S-23031 or IMCA yielded THPA, which is hydroxylated to form 1-OH-HPA. The imide linkage of 4-OH-IMCA is also cleaved to form 4-OH-THPA.

V. DISCUSSION: The metabolism of [THP-$C^{14}$]S-23031 was studied in male and female rats treated by oral gavage with single low dose (1 mg/kg/day), single high dose (500 mg/kg/day) or repeated low dose (1 mg/kg/day of unlabeled test compound, followed on the 15th day with a dose of 1 mg/kg of labeled compound). Following the administration of labeled test compound, urinary and fecal samples were collected and analyzed for radioactivity. The urinary and fecal samples through Day 2 of the study were pooled and metabolic profiles determined for all three study groups. At the end of seven days, the animals were sacrificed and the amount of radioactivity in the tissues, blood and carcass was determined. Major metabolites were isolated from pooled 0 to 2 day urinary and fecal samples and identified using a variety an analytical techniques.

Essentially all (> 93.1%) of the administered dose were eliminated within two days of dosing; from Day 2 to 5 only 0.6 to 1.8% was eliminated. The tissue accumulation of $^{14}C$-labeled

residues was very low, with highest levels found in blood, plasma and kidneys of all three dose groups.

The metabolic profiles for each of the dose groups showed a total of up to 14 fecal and 13 urinary metabolites. Of these, seven fecal and six urinary metabolites were positively identified. Differences were noted in the metabolic profiles among each of the study groups. Very low or undetectable amounts of unmetabolized S-23031 were present in the feces of low and repeat low dose animals. The high amounts of S-23031 present in the feces of high dose animals was due to lack of absorption rather than biliary excretion. In a separate study[2], no S-23031 was found in the bile of male rats dosed at either 1 or 500 mg/kg with labeled [phenyl-$^{14}$C]S-23031. For low dose animals, no remarkable sex differences were noted in the metabolite distribution. High dose males had higher amounts of 4-OH-THPA and OH-IMCA-SA in the urine, while in females IMCA and 4-OH-IMCA were higher. Repeat low dose females showed higher amounts of IMCA, THPA and 4-OH-IMCA in the urine.

A previously submitted metabolism study using [phenyl-(UL)$^{14}$C]S-23031 (MRID No.: 421698-40, HED Doc No: 009587) was by itself incomplete and was classified as a Core - Supplementary. The deficiencies of this study included: (1) metabolites containing the tetrahydrophthalate ring were not adequately identified, (2) analytical techniques describing the separation and identification of the two 4-OH-IMCA-SA and 5-OH-IMCA-SA metabolites was inadequate, and (3) biliary excretion data was not presented. The present study along with two preliminary studies (MRID No's: 428258-23 and 428258-21) satisfactorily address the deficiencies noted. Summaries of the biliary excretion study (Appendix 3) and the identification of urinary and fecal metabolites (Appendix 4) are enclosed.

This study is classified as Core - Supplementary, however, when taken with other metabolism studies (MRID No.: 421698-40, 428258-23 and 428258-21) the guideline requirements (§85-1) are satisfied.

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[2] H. Matsunaga, Bile Excretion of [Phenyl-$^{14}$C]S-23031 in Male Rats, February 25, 1993, Laboratory Project Identification No. 2661, Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., EPA MRID No.: 428258-21.

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Pages 112 through 113 are not included.

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_____ A draft product label.

_____ The product confidential statement of formula.

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