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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 25 1996

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Subject: I.D. Nos.: 010308-00010. Cyphenothrin (Gokilaht). Evaluation of Product Labeling Data Submitted and Identification of Outstanding Toxicology Data Requirements

Tox. Chem. No.	725A
PC Code No.	010308
DP Barcode Nos.	D190032, D192756
Submission Nos.	S438500, S443850

From: Myron S. Ottley, Ph.D.
Section IV, Toxicology Branch I
Health Effects Division (7509C)

Myron S. Ottley 4/18/96

To: Adam Heyward/George Larocca (PM13)
Registration Division (7505C)

To: Deborah McCall (Cover memo only)
RCAB/Health Effects Division (7509C)

Through: Marion P. Copley, D.V.M., D.A.B.T.
Section Head
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)

Marion Copley 4/18/96 MPC 4/24/96

I. CONCLUSIONS

The existing database supports the following proposed uses for Cyphenothrin in the table below.

Product I.D.	Submission	Formulation	Application
010308-00010 (Sumitomo Chemical Corp.)	Registration	Gokilaht 10 MC	Household fumigant (pest control operators only).

II. ACTION REQUESTED

TB-1 received for evaluation applications for registration of Gokilaht 10 MC (cyphenothrin) as a household fumigant for use by pest control operators only. The data submitted are summarized below. TB-1 was asked to evaluate these against the data submitted previously on the on cyphenothrin to determine if they are adequate to fulfill relevant data requirements.

Executive Summaries

Reference was made (D190032) to a battery of acute studies submitted to EPA (MRIDs 42681103, 42681104, 42681105, 42681106), but for which data were not provided to TB1. These data were not reviewed by HED, but by RSB/RD. Therefore they are not summarized here. Reference was also made (D192756) to a rabbit developmental toxicity study (42826006). This is an addendum to a Core Minimum study which corrected inconsistencies in data reporting and had no bearing on the core grading of the study, or its usefulness in assessing developmental toxicity in the rabbit.

Subchronic Oral Toxicity in Rat (82-1)
MRID 42681112

Cyphenothrin was administered daily in the feed to Charles River CD rats for three to six months. dietary levels were 0 ppm, 100 ppm (5.6/6.6 mg/kg/d for M/F), 300 ppm (16.8/19.6 mg/kg/d for M/F) or 1,000 ppm (56.4/65.2 mg/kg/d for M/F).

Systemic toxicity was not observed at any level. Minor increases in absolute and relative kidney weights at 100, 300 and 1,000 ppm (106 - 113% of control) and absolute and relative liver weights at 1,000 ppm (114 - 116% of control), and decreases in body weight (96 - 97% of control), body weight gain (95% of control), water intake (93% of control), and food intake (98% of control) at 1,000 ppm were considered significant. **The systemic LOEL was greater than 1,000 ppm. The NOEL was equal to or greater than 1,000 ppm.**

This study is core minimum and satisfies the Guideline requirements for a subchronic oral toxicity (82-1) study in rats.

Oncogenicity Study in the Mouse (83-2)
MRIDs 42706905, 42826001, 42826002, 42681117, 42681116, 42717505

In a two-year carcinogenicity study, cyphenothrin (94.6 - 94.9% pure) was administered via the diet to 50/sex/dose $B6C3F_1$ mice (main study) at dose levels of 1,

100, 300, or 1,000 ppm. The equivalent average daily test material intakes were 0, 14.6, 42.9 or 145.7 mg/kg/day in males and 0, 15.8, 47.4, or 154.5 mg/kg/day in females. An additional 30 mice/sex/dose received the same diets (satellite group). Ten mice/sex/dose in the satellite group were sacrificed after 52 weeks of exposure, and the remaining surviving mice in the satellite group were sacrificed after 78 weeks of exposure.

Treatment-related systemic toxicity was not observed at any dose level. However, at 300 ppm increases were observed in the incidence of lymphoid hyperplasia in the mesenteric lymph nodes in males (51% vs 29% in controls) and females (62% vs 37% in controls) and decreases were observed in absolute kidney weight (84 - 91% of control) and kidney-to-body weight ratios of vacuolation of the epithelium of the proximal convoluted tubules (20% vs 90% in controls) in males. No additional effects were seen at 1,000 ppm that were not also observed at 300 ppm (the magnitude of the changes observed at 1,000 ppm were similar to that seen at 300 ppm). The toxicological significance of these effects is unclear. **The LOEL for systemic toxicity was greater than 1,000 ppm. The NOEL wa equal to or greater than 1,000 ppm.**

There was no evidence of carcinogenic potential. Dosing was adequate based on data from a 13-week rangefinding study (MRID 42717505) indicating that raising the dose level above 1,000 ppm resulted in excessive toxicity (40% mortality was observed at 2,000 ppm).

This study is classified as core guideline and satisfies the guideline requirements for an oncogenicity study (83-2) in the mouse.

Combined chronic toxicity/oncogenicity study in the rat (83-5)
MRIDs 42796904,42826004,42826005,42826003,42717504,42681115

Cyphenothrin was fed to male and female Fischer (F-344) rats (80/sex/dose) for two years at dietary levels of 0, 100, 300, or 1000 ppm. average dosages for males and females, respectively, were 4.84 and 5.89 mg/kg/d for the 100 ppm groups; 14.49 and 17.77 mg/kg/day for the 300 ppm groups; and 48.16 and 58.52 mg/kg/day for the 1000 ppm groups.

No toxicologically significant treatment-related systemic effects were observed at dose levels of $\leq$ 1000 ppm. Although only minimal toxicity was observed at the high-dose level of 1000 ppm, this dose level is sufficiently high for a two-year chronic/oncogenicity study since it is greater than one-half the maximally tolerated dose (MTD) established in the 13-week range-finding study (MRID 42717504) in which mortality was observed at 2000 ppm in males (100% by week six) and females (40% by week seven), indicating that 2000 ppm exceeded the MTD. Therefore, 1000 ppm, one-half the 2000 ppm level, is acceptable for the chronic/onco study despite the minimal toxicity observed at 1000 ppm. **The NOEL for systemic toxicity in male an**

female rats is 1000 ppm (48.16 mg/kg/day for males and 58.52 mg/kg/day for females).

There was no treatment-related in the incidence of neoplasms at any site.

This study is core guideline and satisfies the guideline requirements (83-5) for a combined chronic toxicity/oncogenicity study in rats.

III. Data Requirements and Data Gaps (CFR §158.35):

PC CODE: 129013

REGISTRANT: Sumitomo Chemical Company, Ltd.

REGISTERED USE PATTERNS: Indoor insecticide (kitchens, living areas, garages, attics, basements, and pet living areas).

NOTE: The data base has not received FIFRA 88 review because this is a new chemical (Category A).

Technical:	Gokilaht (cyphenothrin, S-2703F; 93.6% a.i. consisting of 18.4% cis isomer and 81.6% trans isomer) Registration No. 10308-IO

	Required	Satisfied	
81-1	Y	Y	Acute Oral Toxicity
81-2	Y	Y	Acute Dermal Toxicity
81-3	Y	Y	Acute Inhalation Toxicity
81-4	Y	Y	Primary Eye Irritation
81-5	Y	Y	Primary Dermal Irritation
81-6	Y	Y	Dermal sensitization
81-7	N	-	Acute Delayed Neurotoxicity (hen)
82-2	W[1]	-	21-Day Dermal
82-3	N	-	90-Day Dermal
82-4	N	-	21-Day Inhalation (tobacco use)
82-4	Y[2]	Y	90-Day Inhalation
82-5a	N	-	90-Day Neurotoxicity (hen)
82-5b	N	-	90-Day Neurotoxicity (mammal)
83-1a	Y	Y	Chronic Toxicity (rodent)
83-1b	N	-	Chronic Toxicity (nonrodent)
83-2	Y	Y	Carcinogenicity (two species)
83-3a	Y	Y	Developmental Toxicity (first species)

	Required	Satisfied	
83-3b	Y	Y	Developmental Toxicity (second species)
83-4	N	-	Reproduction
84-2a	Y	Y	Mutagenicity - Gene Mutation
84-2b	Y	Y	Mutagenicity - Structural Chrom. Aberr.
84-2c	Y	Y	Mutagenicity - Other Genotoxic Effects
85-1	N	-	General Metabolism
85-2	N	-	Dermal Penetration
86-1	N	-	Domestic Animal Safety

Y -Yes
N - No
W - Waived
P - Partially

[1] The requirement for a 21-day dermal is waived because of the minimal risk of dermal exposure and the dermal Toxicity Category of III.

[2] This requirement is satisfied by a 28-Day Inhalation study because of the minimal risk of inhalation exposure, even if the product is misused.

IV. Toxicology Profile: (Last updated March, 1996)

Technical: Gokilaht (cyphenothrin, S-2703F; 93.6% a.i. consisting of 18.4% cis isomer and 81.6% trans isomer)
Registration No. 10308-IO

	STUDY	RESULTS
81-1	**Acute Oral, Rat** Guideline / Toxicity Category II HED Document No. 5237 MRID No. 00155346	LD_{50} = 318 (219-463) mg/kg, ♂ 419 (281-624) mg/kg, ♀ Clinical signs: Muscular fibrillation, tremors, hyperexcitability, lethargy, ataxia, limb paralysis, hyperpnea, dyspnea, soft feces, loss of righting reflex, salivation, and urinary incontinence. Gross pathology: Attachment of saliva to mouth, discoloration of the stomach mucosa, and remnant of an unspecified colored material in the stomach and small intestine.
81-2	**Acute Dermal, Rat** Guideline / Toxicity Category III HED Document No. 5237 MRID No. 00155347	LD_{50} > 5000 mg/kg, ♂+♀ Clinical signs: Negative Gross pathology: Negative
81-3	**Acute Inhalation, Rat** Minimum / Toxicity Category II HED Document No. 5237 MRID No. 00155348	LC_{50} > 1.850 mg/l (MMAD = 1.0 μm) Clinical signs: Hyperpnea, deep respiration, salivation, urinary incontinence (♂), muscular fibrillation, and tremors. Gross pathology: Negative
81-4	**Primary Eye Irritation, Rabbit** Minimum / Toxicity Category IV HED Document No. 5237 MRID No. 00155350	One hour after instilling the doses, two rabbits with unrinsed eyes had injected conjunctival vessels and discharge with moistening of the lids and hairs just adjacent to the lids.
81-5	**Primary Dermal Irritation, Rabbit** Minimum / Toxicity Category IV HED Document No. 5237 MRID No. 00155350	Nonirritating to intact and abraded skin.
81-6	**Dermal Sensitization, Guinea Pig** Minimum HED Document No. 5237 MRID No. 00155351	Not a sensitizer.

	STUDY	RESULTS
82-1a	**6-Month Feeding, Rat** Minimum HED Document No. 5237, 6866 MRID No. 00155352	NOEL >1000 ppm (56.4/65.2 mg/kg/day, HDT)
82-1a	**Subchronic Oral Toxicity, Rat** Minimum HED Document No. MRID No. 43681112	NOEL $\geq$ 1000 ppm (56.4/65.2 mg/kg/day, M/F resp.)
82-4	**28-Day Inhalation, Rat** Minimum (when considered in conjunction with Study No. EET-30-0020) HED Document Nos. 5237, 6866 MRID Nos. 00155353, 407785-01	NOEL = 0.006 mg/l LEL = 0.019 mg/l - Decreased activity, irregular respiration, urinary incontinence (♀), and increased water consumption (♀). The kerosene vehicle caused decreased activity in all dosed groups and vehicle controls. Clinical pathology: Negative Gross pathology: Negative Histopathology: Not done
83-3a	**Developmental Toxicity, Rat** Minimum HED Document No. 5237 MRID No. 00155356	Maternal (F_0): NOEL = 150 mg/kg/day LEL = 500 mg/kg/day - lethality Developmental (F_1): NOEL (functional) = 500 mg/kg/day NOEL (learning) = 500 mg/kg/day NOEL (conditioned avoidance) = 500 mg/kg/day NOEL (behavioral) = 150 mg/kg/day LEL (behavioral) = 500 mg/kg/day - increased incidences of grooming, urination, and defecation in males in an open field test.
83-3b	**Developmental Toxicity, Rabbit** Guideline HED Document No. 5237 MRID No. 00155355	Maternal NOEL >250 mg/kg/day (HDT) Developmental NOEL >250 mg/kg/day Gross pathology: Viscosity [sic] and retention of yellowish oily liquid (probably unabsorbed compound at injection sites).
83-2	**Oncogenicity Study, Mouse** Guideline HED Document No. MRIDs 42706905, 42826001, 42826002, 42681117, 42681116, 42717505	NOEL $\geq$ 1000 ppm (145.7/154.5 mg/kg/d in M/F, resp.(HDT) LOEL > 1000 ppm Gross pathology: no treatment related effects observed Oncoginicity: no evidence of carcinogenic potential

	STUDY	RESULTS
83-5	**Combined Chronic Toxicity/ Oncogenicity, Rat** Guideline HED Document No. MRIDs 42796904, 42826004, 42826005, 42826003, 42717504,42681115	NOEL = 1000 ppm (48.16/58.52 mg/kg/d in M/F, respectively (HDT) LOEL > 1000 ppm Gross pathology: no treatment related effects observed Oncoginicity: no evidence of carcinogenic potential
84-2a	**Gene Mutation:**	
	Ames Assay Acceptable HED Document No. 5237 MRID No. 00155359	Negative for *S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538; and *E. coli* WP2 (trp$^-$), uvrA with or without metabolic activation. There was no evidence of cytotoxicity.
84-2b	**Structural Chromosome** Aberration:	
	Sister Chromosome Exchange in CHO-K1 Cells Acceptable HED Document No. 5237 MRID No. 00155360	Negative for induction of sister chromatid exchange with or without metabolic activation.
84-2c	**Other Genotoxic Effects:**	
	Micronucleus Assay Acceptable HED Document Nos. 5237, 6881 MRID Nos. 00155357, 406602-01	Negative for induction of micronuclei in male ICR mice.

V. Action Taken to Obtain Additional Information or Clarification:

There are no data gaps.

VI. Reference Dose (RfD):

None

VII. Pending Regulatory Actions:

There are no pending regulatory actions against the Registration of this pesticide.

VIII. Toxicologic Issues Pertinent to Granting this Request:

None

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDE PROGRAMS/HED/TB1

TOX ONELINERS

ToxChem No. 725A **Cyphenothrin, Gokilaht, S-2703F** **PC Code 129013** **April 18, 1996**

Study Identification	Material	MRID No.	Results	Classification
82-1 Subchronic Oral Toxicity in rats Sumitomo Chemical Co. Ltd. Study No. F-83-03 Jan. 28, 1985	S-2703 Forte 93.6% Lot # PK81051	42681112	S-2703 Forte was administered daily in the feed to Charles River CD rats for 3 to 6 months. Dietary levels were 0 ppm, 100 ppm (5.6 mg/kg/d for males and 6.6 mg/kg/d for females), 300 ppm (16.8 mg/kg/d for males and 19.6 mg/kg/d for females), and 1,000 ppm (56.4 mg/kg/d for males and 65.2 mg/kg/d for females). Systemic toxicity was not observed at any level. Minor increases in absolute and relative kidney weights at 100, 300, and 1,000 ppm (106-113% of control) and absolute and relative liver weights at 1,000 ppm (114-116% of control), and decreases in body weight (96 - 97% of control), body weight gain (95% of control), water intake (93% of control) and food intake (98% of control) at 1,000 ppm were considered to be possibly treatment related. The systemic LOEL was greater than 1,000 ppm. The NOEL was equal to or greater than 1,000 ppm. This study is minimum and satisfies the Guideline requirements for a subchronic oral toxicity study in rats.	Core Minimum
83-2 Oncogenicity Study in Mice Sumitomo Chemical Co. Ltd. Study No. F-83-03 August 17, 1989	S-2703 Forte 94.6% Lot # PKG84036	42706905 42826001 42826002 42681117 42681116 42717505	In a two-year carcinogenicity study, S-2703F was administered via the diet to 50/sex/dose B6C3F1 mice (main study) at dose levels of 0, 100, 300, and 1,000 ppm. The equivalent average daily test material intakes were 0, 14.6, 42.9, and 145.7 mg/kg/d in males and 0, 15.8,47.4 and 154.5 mg/kg/d in females. An additional 30/sex/dose received the same diets (satellite group). Ten mice/sex/dose in the satellite group were sacrificed after 52 weeks of exposure, and the remaining surviving mice in the satellite group were sacrificed after 78 weeks of exposure. Treatment related systemic toxicity was not observed at any dose level. However, at 300 ppm increases were observed in the incidence of lymphoid hyperplasia in the mesenteric lymph nodes in males (51% vs. 29% in controls) and females (62% vs 37% in controls) and decreases were observed in absolute kidney weight (84 - 91% of control) and kidney to body-weight ratios of vacuolation of the epithelium of the proximal convoluted tubules (20% vs 90% in controls) in males. No additional effects were seen at 1,000 ppm that were not also observed at 300 ppm (the magnitude of the changes observed at 1,000 ppm were similar to that seen at 300 ppm). The toxicological significance of these effects is unclear. The LOEL for systemic toxicity was greater than 1,000 ppm The NOEL was > = 1,000 ppm. There was no evidence of carcinogenic potential. Dosing was adequate based on data from a 13-week range-finding study that indicated that raising the dose level above 1,000 ppm resulted in excessive toxicity (40% mortality was observed at 2,000 ppm).	Core Guideline
83-5 Combined chronic toxicity/Oncogenicity Study in rats Sumitomo Chemical Co. Ltd. Study No. 87/Sumo-15/405 Sept. 28, 1988	S-2703 Forte 95.0% Lot # PY83024	42796904 42826004 42526005 42826003 42717504 42681115	S-2703F was fed to male and female Fischer (F-344) rats (80/sex/dose) for two years at dietary levels of 0, 100, 300 or 1,000 ppm. Average dosages for males and females, respectively, were 4.84 and 5.89 mg/kg/d for the 100 ppm groups; 14.49 and 17.77 mg/kg/d for the 300 ppm groups; and 48.16 and 58.52 mg/kg/d for the 1000 ppm groups. No toxicologically significant treatment-related systemic effects were observed at dose levels of $\leq$ 1000 ppm. There was no treatment-related increase in the incidence of neoplasms at any site. The NOEL for systemic toxicity in male and female rats is 1000 ppm (48.16 mg/kg/d for males and 58.52 mg/kg/d for females). There was no evidence of carcinogenic potential.	Core Guideline

FINAL

DATA EVALUATION REPORT

S-2703 Forte
(Cyphenothrin)

Study Type: Subchronic Toxicity Study in Rats

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer: Carin Kolb for — Date 4/6/94
Laura Kolb, M.P.H.

Independent Reviewer: Carin Kolb for — Date 4/6/94
John Liccione, Ph.D.

QA/QC Manager: William L McLellan — Date 4/6/94
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 3-04
Clement Number: 27
Project Officer: Caroline Gordon

EPA Reviewer: Edwin Budd, M.A.
Review Section III, Toxicology Branch I
Health Effects Division (7509C)

Signature: Edwin Budd
Date: 4/13/94

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I
Health Effects Division (7509C)

Signature: Marion Copley
Date: 4/13/94

DATA EVALUATION REPORT

STUDY TYPE: Subchronic oral toxicity, Guideline 82-1

TEST MATERIAL: S-2703 Forte

SYNONYMS: Cyphenothrin, Gokilaht, α-cyano-3-phenoxybenzyl-(+)-*cis/trans*-chrysanthemate

TOX CHEM NUMBER: 725A

PC NUMBER: 129013

MRID NUMBER: 426811-12

STUDY NUMBER: F-83-03

SPONSOR: Sumitomo Chemical Company, Ltd., Chuo-ku, Osaka 541, Japan

TESTING FACILITIES: Sumitomo Chemical Company, Laboratory of Biochemistry & Toxicology, Takarazuka Research Center, Hyogo, Japan

TITLE OF REPORT: A Six-Month Feeding Toxicity Study of S-2703 Forte in Rats (EET-40-0038)

STUDY DIRECTOR: Tomoyuki Watanabe

REPORT ISSUED: Study date - January 28, 1985

QUALITY ASSURANCE/COMPLIANCE: A signed Quality Assurance Statement (dated January 24, 1985) and a list of quality assurance inspection dates were included. A statement of No Data Confidentiality Claims and a GLP Compliance statement were present, signed, and dated. This study was not conducted in compliance with GLP regulations since it was performed before the regulations became effective.

EXECUTIVE SUMMARY: S-2703 Forte was administered daily in the feed to Charles River CD rats for 3 or 6 months. Dietary levels were 0 ppm, 100 ppm (5.6 mg/kg/day for males and 6.6 mg/kg/day for females), 300 ppm (16.8 mg/kg/day for males and 19.6 mg/kg/day for females), and 1,000 ppm (56.4 mg/kg/day for males and 65.2 mg/kg/day for females).

Systemic toxicity was not observed at any level. Minor increases in absolute and relative kidney weights at 100, 300, and 1,000 ppm (106-113% of control) and absolute and relative liver weights at 1,000 ppm (114-116% of control), and decreases in body weight (96-97% of control), body weight gain (95% of

control), water intake (93% of control), and food intake (98% of control) at 1,000 ppm were considered to be possibly treatment-related but not biologically significant. **The systemic LOEL was greater than 1,000 ppm. The NOEL was equal to or greater than 1,000 ppm.**

This study is core minimum and satisfies the Guideline requirements for a subchronic oral toxicity (82-1) study in rats. See below.

COMMENTS ON CORE CLASSIFICATION: No significant adverse effects were observed in the 6-month study in rats administered S-2703 Forte at dose levels up to 1,000 ppm (56.4 mg/kg/day in males and 65.2 mg/kg/day in females) although some minor effects were reported. Slight increases in kidney weights in high-dose males were not considered to be biologically significant since there were no corresponding gross or microscopic changes. Although a dose of 1,000 ppm was reported to be associated with slight tremors in the early phase of a 5-week range finding study, tremors were not observed in this study (presumably due to decreased food consumption in this study). At 2,000 ppm in the range finding study, however, toxic signs included tremors and hypersensitivity to touch and/or sound, and considerably decreased body weight gain throughout the 5-week study in both males and females. In addition, these results at 2,000 ppm in the 5-week range finding study are fully consistent with nearly identical results observed at 2,000 ppm in a 13-week subchronic feeding study in rats (LSR report number 84/SUM013/666, MRID 427175-04) conducted at about the same time (study report dated 10/16/85). Considerable mortality also occurred in the 13-week study at 2,000 ppm (100% in males ≤ 6 weeks and 40% in females ≤ 7 weeks).

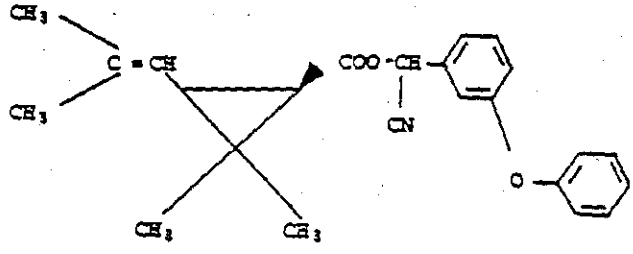
It is clear that although only minimal signs of toxicity were observed in this 6-month study at the highest dose level tested (1,000 ppm), excessive toxicity would have been observed at higher doses (e.g., 2,000 ppm).

A. MATERIALS, METHODS AND RESULTS

1. Test Article Description

Name: S-2703 Forte

Structural Formula:



Lot number: PK-81051

Purity: 93.6%

Isomer ratios: D-*cis*:l-*cis*:d-*trans*:l-*trans* = 17.6%:0.8%:78.2%:3.3%
X-*cis*:y-*cis*:x-*trans*:y-*trans* = 8.6%:9.5%:43.5%:38.4%

Physical property: Yellow-brown oily liquid

Storage: Not reported

Stability: The test compound was reported to be stable in the diet over a period of 4 weeks when kept under cold (4°C) and light-shielded conditions, and under study conditions (23±2°C, 55±10% relative humidity).[1] The data were not included in this study report.

2. Diet Preparation

Diets were prepared once every 4 weeks for a total of 7 preparations. To prepare the treated diets, weighed amounts of basal diet and test compound were mixed with a mortar and pestle to form a concentrated mix. This mix was then combined (using a mixer for 10 min.) with more basal diet and stored in a cold room until use. An analysis to determine the concentration of the test compound in the diet was performed once per month for seven months; the results are shown below:

Date of Diet Preparation	Target Level (ppm)			
	0	100	300	1,000
4/26/83	<5	97	288	962
5/20/83	<5	95	267	908
6/17/83	<5	96	288	929
7/15/83	<5	92	278	908
8/11/83	<5	93	278	940
9/9/83	<5	88	267	919
10/7/83	<5	91	267	876
Average	<5	93	276	920

Abstracted from Appendix A, study report. Analysis was performed by Sumika Chemical Analysis Service Ltd. Method of analysis was unspecified. Values were corrected for stated purity (93.6%). Averages calculated by the reviewers.

3. Animals

Charles River CD rats (145 males and 144 females) were purchased from Charles River Japan Inc. The animals were quarantined and acclimatized to laboratory conditions for 1 week. The study was begun when the rats reached 5 weeks of age. During quarantine, the animals behavior, appearance, and body weights were observed. Animals (132/sex) without abnormalities were randomly allocated into test groups. Body weights at the start of administration were

[1]Ohnishi, J., Stability on Storage, Measurement of Concentrations and Homogeneity of S-2703 Forte in Diet, Technical Report of Sumitomo Chemical Col, Ltd. (1983)

129-160 g for males and 104-144 g for females. The composition of the test groups is shown below:

	Dietary Level (ppm)	Satellite Group No. of Animals Male	Satellite Group No. of Animals Female	Main Group No. of Animals Male	Main Group No. of Animals Female
Control	0	12	12	21	21
Low	100	12	12	21	21
Mid	300	12	12	21	21
High	1,000	12	12	21	21

Animal room conditions included a temperature of 23±2°C, a relative humidity of 55±10%, ventilation at 16 times/hour with fresh air, and a 12-hour light/dark cycle. Food (pulverized diet, CE-2, Clea Japan, Inc.) and water were provided *ad libitum*. Animals were caged three per cage (same sex) in aluminum cages with wire-mesh floors; cages were rotated once a month within the cage rack. Animals were identified by staining their coats with picric acid and color coding the cages.

4. Dose Selection

Doses were selected on the basis of a 5-week rat feeding study[2] in which slight tremors were noted during the early part of the study in both sexes at 1,000 ppm and a decreased tendency for weight gain was apparent in females at 1,000 ppm. At 2,000 ppm, tremors, hyperexcitability to touch and/or sound, "remarkable" depression of bodyweight were reported; decreases in food and water consumption during the early part of the study were also reported in both sexes.

5. Statistical Analyses

Body weights, food consumption, organ weights, water intake, and hematologic and biochemical data were analyzed using the F-test and the t-test or Fisher-Behrens' test. The χ^2 test was performed for gross and histopathological findings if necessary. The U-test was used on urinalysis data (except urinary sediment).

6. General Observations

(a) Mortality/moribundity

All animals were examined "twice in the morning and evening everyday" for mortality or morbidity.

No unscheduled deaths occurred throughout the treatment period.

[2]Watanabe, T. et al. 1984. A 5-week Subacute Feeding Toxicity Study of S-2703 Forte in Rats. Technical Report of Sumitomo Chemical Co., Ltd.

(b) Clinical observations

All animals were examined "twice in the morning and evening everyday" for clinical signs of toxicity. In addition, palpation of each animal was performed weekly.

No treatment-related clinical effects were observed in the main or satellite groups.

(c) Body weights/body weight gains/food consumption/test material intake/water intake

Individual body weights were recorded on the first and second days of compound administration, weekly thereafter, and on the last day of compound administration. Food consumption and water intake were determined weekly throughout the administration period; measurements were made for three consecutive days, including the day of body weight measurement. Test article intake was calculated weekly using the mean body weight data of the three animals in each cage. Mean bodyweight gain was calculated for the animals in the main group at 3 months and at 6 months.

Body weight

Table 1 presents mean body weights and body weight gains at selected study intervals for the satellite and main study groups.

Females treated at 1,000 ppm exhibited slightly decreased mean body weights, particularly toward study termination, although the decreases were not statistically significant. Mean body weight gain for females treated at 1,000 ppm for 6 months was 95% of control; these decreases in mean body weight and mean body weight gain were considered to be minor possibly treatment-related effects.

Body weights were slightly elevated in males at 100 and 300 ppm, although the elevations were statistically significant only at sporadic intervals at 100 ppm; no significant increases were reported at 1,000 ppm. Body weight gain was significantly elevated in males treated at 100 ppm for 3 months. These slight elevations were not considered to be biologically significant.

Food consumption

For the satellite and main study groups combined, food consumption was generally similar in all groups, although for the first week, males in the 1,000 ppm-group exhibited significantly decreased ($p<0.01$) mean food consumption; this decrease is considered to be a minor possibly treatment-related effect. Food consumption data are summarized below.

TABLE 1. Mean Body Weight and Body Weight Gain Data for Rats Ingesting S-2703 in the Diet for up to 6 Months[a,b,c]

	Mean Body Weight and Body Weight Gain by Dietary Level (ppm)			
Day	0	100	300	1,000
		Males		
Body Weight (g)				
0	145.5	145.7 (100)	146.3 (101)	146.0 (100)
2	166.1	167.0 (101)	167.1 (101)	162.3 (98)
21	309.2	316.5* (102)	316.9 (102)	314.3 (102)
42	403.2	414.1 (103)	417.2 (103)	412.3 (102)
63	456.0	468.2 (103)	471.7 (103)	462.6 (101)
84	496.0	505.6 (102)	509.3 (103)	503.0 (101)
105	528.6	549.0 (104)	541.4 (102)	527.8 (100)
126	551.3	575.9* (104)	564.7 (102)	547.6 (99)
147	566.8	591.2 (104)	584.4 (103)	565.9 (100)
161	576.0	601.3 (104)	591.8 (103)	575.4 (100)
180	584.9	612.2 (105)	599.0 (102)	581.2 (99)
Body Weight Gain (g)				
0-90	350.4	359.9 (103)	363.0 (104)	357.0 (102)
0-180	438.8	466.1* (106)	451.9 (103)	434.9 (99)
		Females		
Body Weight (g)				
0	117.0	116.5 (100)	116.7 (100)	116.2 (99)
2	131.3	131.3 (100)	131.7 (100)	128.9 (98)
21	206.7	204.6 (99)	208.5 (101)	206.6 (100)
42	251.6	251.5 (100)	253.5 (101)	249.8 (99)
63	271.8	271.9 (100)	275.0 (101)	271.9 (100)
84	288.0	287.2 (100)	293.8 (102)	285.3 (99)
105	301.0	306.4 (102)	307.0 (102)	291.6 (97)
126	310.9	312.9 (101)	313.5 (101)	299.3 (96)
147	316.3	316.9 (100)	321.6 (102)	306.1 (97)
161	320.5	321.9 (100)	328.2 (102)	309.1 (96)
181	320.8	324.4 (101)	331.3 (103)	309.1 (96)
Body Weight Gain (g)				
0-90	171.0	170.6 (100)	177.0 (104)	169.1 (99)
0-181	204.3	209.0 (102)	215.1 (105)	193.7 (95)

[a]Data extracted from Study Report, Table 2.
[b]Numbers in parentheses indicate percent control.
[c]N = 33 for days 0-90, and N = 21 for days 91-181.

* Significantly different from control values, $p<0.05$.

Average cumulative food intake (g/kg/day) in the satellite and main study groups combined

	0 ppm	100 ppm	300 ppm	1,000 ppm
Male	55.1	56.4	55.9	56.4
Female	65.6	66.0	65.2	65.2

Abstracted from Table 4, study report.

Test material intake: Administration of the test diet was begun on April 27 for all test groups. For the satellite group, termination of test diet administration was on July 25 for males and July 26 for females. For the main group, termination of test diet administration was on October 24 for males and October 25 for females.

Test material intake in the satellite and main study groups combined

	Target level (ppm)			
Male	0	100	300	1,000
Female	0	100	300	1,000
	Mean compound intake (mg/kg/day)			
Male	0	5.6	16.8	56.4
Female	0	6.6	19.6	65.2

Abstracted from Table 4, study report.

Water intake: Table 2 presents mean water consumption data at selected study intervals for the main study group. Water consumption was generally similar in all groups in the main study, although for the first week, males in the 1,000 ppm group exhibited significantly decreased ($p<0.01$) mean water consumption (93% of control); this decrease is considered to be a minor possibly treatment-related effect.

(d) Ophthalmoscopic examination

Both eyes of all animals were examined within one week before sacrifice. The cornea, conjunctiva, iris, crystalline lens, vitreous body, retina, and optic disk were examined. A Varifocal ophthalmoscope was used.

No treatment-related effects were observed for the main or satellite groups.

7. Clinical Pathology

Laboratory samples were collected for hematology and clinical chemistry determinations from all survivors in the satellite and main groups (at 3 or 6 months, respectively). Blood was drawn from the abdominal aorta of fasted rats anesthetized with ether.

TABLE 2. Mean Water Consumption Data for Rats Ingesting S-2703 in the Diet for up to 6 Months[a,b,c]

	Mean Water Consumption (g/kg bw/day) by Dietary Level (ppm)			
Week	0	100	300	1,000
		Males		
1	189.9	197.4 (104)	184.8 (97)	175.7** (93)
5	116.5	115.5 (99)	118.2 (101)	118.0 (101)
10	81.7	81.8 (100)	80.4 (98)	81.5 (100)
15	64.8	67.0 (103)	69.9 (108)	67.5 (104)
20	63.8	63.4 (99)	67.3 (105)	66.4 (104)
25	52.8	53.4 (101)	55.8 (106)	55.1 (104)
		Females		
1	206.5	202.8 (98)	207.5 (100)	207.1 (100)
5	151.6	145.6 (96)	142.3 (94)	141.2 (93)
10	116.5	117.7 (101)	113.6 (98)	113.3 (97)
15	108.4	112.7 (104)	103.3 (95)	113.3 (105)
20	116.8	115.2 (99)	121.1 (104)	120.6 (103)
25	109.9	107.9 (98)	102.5 (93)	108.8 (99)

[a]Data extracted from Study Report, Table 5.
[b]Numbers in parentheses indicate percent control.
[c]N = 33 for days 0-90, and N = 21 for days 91-181.

** Significantly different from control values, $p<0.01$.

The parameters marked ("X") below were examined.

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count (PLT)*
X Leukocyte differential count*
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)

*Recommended by Subdivision F (November 1984) Guidelines

There were no treatment-related changes in any of the hematology parameters in either the main or satellite groups.

(b) Blood (clinical) chemistry

Electrolytes

X Calcium*
X Chloride*
Magnesium
Phosphorus*
X Potassium*
X Sodium*

Enzymes

X Alkaline phosphatase
X Cholinesterase (ChE)
X Creatine kinase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
Gamma glutamyltransferase (GGT)
X Lactic dehydrogenase
X Lecine amino peptidase

Other

X Albumin*
X Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol (total)*
Globulin
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
X Triglycerides
X Phospholipid

*Recommended by Subdivision F (November 1984) Guidelines

There were no treatment-related changes in any of the clinical chemistry parameters in either the main or satellite groups.

(c) Urinalysis

Urine was collected from all animals during the last week before sacrifice. The parameters marked ("X") below were examined.

Appearance	X Sediment (microscopic)	X Bilirubin
Volume	X Protein	X Blood
Specific gravity	X Glucose	Nitrite
X pH	X Ketones	X Urobilinogen

There were no treatment-related changes in urinary parameters in either the main or satellite groups.

8. Sacrifice and Pathology

All animals (in both the satellite and main groups) were autopsied immediately after sacrifice, and macroscopic lesions were reported. The tissues marked ("X") below were preserved for histologic examination in all groups. The tissues marked ("X") were also examined histopathologically for the satellite control and high-dose groups, and for all animals in the main group (only the sections with macroscopic abnormalities and the brains, lungs, heart, spleen, liver, kidneys, testes/ovaries, pituitary, thyroid, and adrenals were examined histopathologically for the mid-dose group). The organs marked ("XX") were also weighed at scheduled sacrifice.

Digestive System	Cardiovascular/Hematologic	Neurologic
X Tongue	Aorta*	XX Brain*#
X Salivary glands*	XX Heart*	X Peripheral nerve*
X Esophagus*	X Bone marrow*	(sciatic nerve)
X Stomach*	X Lymph nodes*	X Spinal cord
X Duodenum*	XX Spleen*	
X Jejunum*	X Thymus*	XX Pituitary*
X Ileum*		X Eyes
X Cecum*	Urogenital	
X Colon*		
X Rectum*	XX Kidneys*	Glandular
XX Liver*	X Urinary bladder*	
Gallbladder*	XX Testes*	XX Adrenals*
X Pancreas*	Epididymides	Lacrimal gland
	X Prostate	Mammary gland
Respiratory	Seminal vesicle	XX Thyroids*
	XX Ovaries	X Parathyroids*
X Trachea*	X Uterus*	X Harderian glands
XX Lungs*	Vagina and cervix	Zymbal's glands
Nasopharynx		
Larynx		

Other

X Bone (femur with bone marrow)
X Skeletal muscle* (thigh muscle)
X Skin
X All gross lesions*

*Recommended by Subdivision F (November 1984) Guidelines
#Recommended at three levels

(a) Organ weights

Table 3 summarizes selected (liver and kidney) organ weight data and organ-to-body-weight ratios.

Liver: In the satellite group, the mean absolute liver weights in the 1,000 ppm-males (114% of control) and females (103% of control) were slightly elevated, although the difference was statistically

TABLE 3. Mean Organ Weight Data for Rats Ingesting S-2703 in the Diet for up to 6 Months[a,b,c]

Organ	Mean Organ Weight (g) by Dietary Level (ppm)			
	0	100	300	1,000
Males				
Liver				
satellite				
absolute wt.	11.09	11.34 (102)	11.70 (106)	12.65* (114)
% body wt.	2.26	2.36 (104)	2.32 (103)	2.49 (110)
main				
absolute wt.	13.27	13.91 (105)	13.55 (102)	13.63 (103)
% body wt.	2.27	2.27 (100)	2.27 (100)	2.34 (103)
Kidney				
satellite				
absolute wt.	3.13	3.21 (103)	3.33 (106)	3.35 (107)
% body wt.	0.64	0.67 (105)	0.66 (103)	0.66 (103)
main				
absolute wt.	3.39	3.66**(108)	3.61* (106)	3.66* (108)
% body wt.	0.58	0.60 (103)	0.60 (103)	0.63**(109)
Females				
Liver				
satellite				
absolute wt.	6.53	6.29 (96)	6.63 (102)	6.75 (103)
% body wt.	2.26	2.19 (97)	2.25 (100)	2.26 (100)
main				
absolute wt.	7.33	7.43 (101)	7.50 (102)	7.55 (103)
% body wt.	2.29	2.29 (100)	2.32 (101)	2.66**(116)
Kidney				
satellite				
absolute wt.	1.89	1.96 (104)	1.92 (102)	2.04* (108)
% body wt.	0.66	0.68 (103)	0.65 (98)	0.68 (103)
main				
absolute wt.	2.14	2.13 (100)	2.14 (100)	2.15 (100)
% body wt.	0.67	0.66 (99)	0.66 (99)	0.76**(113)

[a]Data extracted from Study Report, Tables 12-13.
[b]Numbers in parentheses indicate percent control.
[c]N = 33 for days 0-90, and N = 21 for days 91-181.

* Significantly different from control values, $p<0.05$.
** Significantly different from control values, $p<0.01$.

significant only in the males. In the main group, the mean absolute liver weights in the 1,000 ppm-males (103% of control) and females (103% of control) were slightly elevated, although the differences were not statistically significant.

The mean liver-to-body-weight ratio was elevated in 1,000 ppm-males (110% of control) in the satellite group and in males (103% of control) and females (116% of control) in the 1,000 ppm-main test group, however, the increase was statistically significant only in females at 1,000 ppm in the main study group.

Kidney: In the satellite group, the mean absolute kidney weights were elevated in all dosed groups, however, the increase was statistically significant only for females at 1,000 ppm (108% of control). In the main group, the mean absolute kidney weights were significantly elevated in all dosed males (108%, 106% and 108% of control for the 100, 300, 1,000 ppm groups, respectively); females were unaffected.

In the satellite group, the mean kidney-to-body-weight ratio was elevated for males at all doses (105%, 103%, 103% of control for the 100, 300, and 1,000 ppm groups, respectively) and for females at 100 (103% of control) and 1,000 ppm (103% of control), however, the increases were not statistically significant. In the main group, the mean kidney-to-body-weight ratio was elevated for males at all doses (103%, 103%, 109% of control for the 100, 300, and 1,000 ppm groups, respectively) and for females at 1,000 ppm (113% of control), however, the increase was statistically significant only for females at 1,000 ppm.

(b) Macroscopic pathology

No treatment-related gross changes were observed in the main or satellite groups.

(c) Microscopic pathology

No treatment-related microscopic changes were observed in the main or satellite groups.

B. DISCUSSION

The study report assigned an EPA Guideline Series 82-4 to this study rather than a Series 82-1.

The reviewers agree with the study author's conclusion that survival, ophthalmology, hematology, clinical biochemistry, and urinalysis were not affected by dietary exposure to the test compound.

Females treated at 1,000 ppm exhibited slightly decreased mean body weights, particularly toward study termination, although the decreases were not statistically significant. Females treated at 1,000 ppm for 6 months also exhibited decreased mean body weight gain (95% of control). In addition, mean water consumption and mean food consumption in males treated at 1,000 ppm were significantly decreased for the first week of treatment; these slight decreases in mean body weight, mean body weight

gain, mean water consumption, and mean food consumption are considered to be minor possibly treatment-related effects. A previous 5-week study[3] (cited by the study authors) at 0-2,000 ppm reported decreased weight gain in both sexes at 1,000 ppm and 2,000 ppm, and decreased water and food intake at 2,000 ppm in both sexes during the early part of the study.

In males, mean kidney weights were significantly elevated in all groups treated for 6 months (although no dose response was apparent) and mean kidney-to-body weight ratios were significantly elevated in animals treated at 1,000 ppm for 6 months. In females, mean kidney weights were significantly elevated in animals treated at 1,000 ppm for 3 months and mean kidney-to-body weight ratios were significantly elevated in animals treated at 1,000 ppm for 6 months. Mean liver weights were elevated in males treated at 1,000 ppm for 3 months and mean liver to body weight ratios were significantly elevated in females treated at 1,000 ppm for 6 months. These changes in organ weight were also considered to be minor possibly treatment-related effects. The changes in organ weight were not considered to be biologically significant since there were no corresponding gross or microscopic changes.

The study author considered the NOEL for systemic effects to be 300 ppm based on slight effects on body weight, water intake and kidney weight at 1,000 ppm. Although a dose of 1,000 ppm was reported to be associated with slight tremors in the early phase of a 5-week range finding study, tremors were not observed in this study. Therefore, it is possible that the animals could have tolerated a higher dose. The reviewers conclude that the NOEL was 1,000 ppm for this study since the only reported effects were of minor significance.

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[3]Watanabe, T. et al. 1984. A 5-week Subacute Feeding Toxicity Study of S-2703 Forte in Rats. Technical Report of Sumitomo Chemical Co., Ltd.

FINAL

DATA EVALUATION REPORT

Cyphenothrin (Gokilaht)

Study Type: Oncogenicity in Mice

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

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April 8, 1994

Principal Reviewer: Carrie Rabe, Ph.D. Date 4/8/94

Independent Reviewer: William L. McLellan for John Liccione, Ph.D. Date 4/11/94

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Contract Number: 68D10075
Work Assignment Number: 3-04
Clement Numbers: 15-16, 23-25, 28
Project Officer: Caroline Gordon

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Review Section III, Toxicology Branch I
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Date: May 3, 1994

EPA Section Head: Marion Copley, D.V.M.
Review Section IV, Toxicology Branch I
Health Effects Division

Signature: Marion Copley
Date: 5/3/94

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity study in mice (Guideline Series 83-2)

TEST MATERIAL: S-2703F

TOX. CHEM. NUMBER: 725A P.C. CODE: 129013

CAS NUMBER: 39515-40-7

SYNONYMS: Cyphenothrin, Gokilaht

STUDY NUMBERS:		MRID NUMBERS:
	88/SUM023/262 (oncogenicity study)	427069-05
	(first addendum to final report)	428260-01
	(second addendum to final report)	428260-02
	(comments on study)	426811-17
	84/SUM014/452 (5-week range-finding)	426811-16
	84/SUM017/242 (13-week range-finding)	427175-05

SPONSOR: Sumitomo Chemical Company, Limited
Chuo-Ku, Osaka, Japan

TESTING FACILITY: Life Science Research
Eye, Suffolk IP23 7PX, England

TITLE OF REPORT: S-2703F: Oncogenicity Study by Dietary Administration to $B6C3F_1$ Mice for 104 Weeks

AUTHOR: P.A. Martin

STUDY COMPLETED: 88/SUM023/262 - August 17, 1989

QUALITY ASSURANCE: A signed Good Laboratory Practice Compliance Statement, signed Quality Assurance Statement, list of Quality Assurance Inspections, a No Data Confidentiality Statement, and a Flagging Statement were included.

EXECUTIVE SUMMARY: In a 2-year carcinogenicity study, S-2703F (94.6-94.9% pure) was administered via the diet to 50/sex/dose $B6C3F_1$ mice (main study) at dose levels of 0, 100, 300, and 1,000 ppm. The equivalent average daily test material intakes were 0, 14.6, 42.9, and 145.7 mg/kg/day in males and 0, 15.8,

47.4, and 154.5 mg/kg/day in females. An additional 30 mice/sex/dose received the same diets (satellite group). Ten mice/sex/dose in the satellite group were sacrificed after 52 weeks of exposure, and the remaining surviving mice in the satellite group were sacrificed after 78 weeks of exposure.

Treatment-related systemic toxicity was not observed at any dose level. However, at 300 ppm increases were observed in the incidence of lymphoid hyperplasia in the mesenteric lymph nodes in males (51% versus 29% in controls) and females (62% versus 37% in controls) and decreases were observed in absolute kidney weight (84-91% of control) and kidney-to-body weight ratios (87-93% of control) in males. Decreases were also observed in the incidence of vacuolation of the epithelium of the proximal convoluted tubules (20% versus 90% in controls) in males. No additional effects were seen at 1,000 ppm that were not also observed at 300 ppm (the magnitude of the changes observed at 1,000 ppm were similar to that seen at 300 ppm). The toxicological significance of these effects is unclear. The LOEL for systemic toxicity was greater than 1,000 ppm. The NOEL was equal to or greater than 1,000 ppm.

There was no evidence of carcinogenic potential. Dosing was adequate based on data from a 13-week range-finding study (84/SUM017/242) that indicated that raising the dose level above 1,000 ppm resulted in excessive toxicity (40% mortality was observed at 2,000 ppm).

This study is classified as core guideline and satisfies the guideline requirements for an oncogenicity study (83-2) in mice.

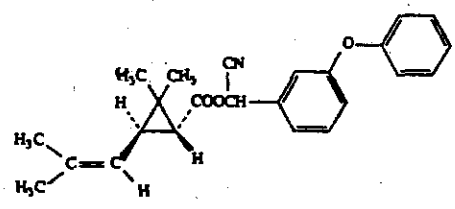
Special Review Criteria (40 CFR 154.7) None

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: S-2703F

Formula: 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid cyano(3-phenoxyphenyl)-methyl ester



Cis:trans ratio: Not reported

Lot number: PKG 84036

Purity: 94.6%-94.9%

Physical property: Amber viscous liquid

Stability: Not reported; however, when mixed with feed, negligible loss of test material was observed over 14 days

Storage: 4°C in light-proof containers

2. Rationale for Dose Selection

The doses selected for this study were based on the results of a 13-week range-finding study in $B6C3F_1$ mice (study no. 84/SUM017/242). The range-finding study (MRID no. 427175-05) was included for review and showed no effects at dietary levels of 250 or 500 ppm. During the first week of exposure both males and females showed increased irritability at 1,000 and 2,000 ppm and an increased incidence of spastic tail at 2,000 ppm. In addition, small increases in platelets (6%) in males and small decreases in hemoglobin (4%) in females were observed at 1,000 and 2,000 ppm. At the highest dose tested (2,000 ppm), both males and females showed increased mortality (4/10 males and 4/10 females), males showed a 15% decrease in body weight gain, and females showed small (2-4%) decreases in red blood cell count and packed cell volume. The cause of death was not identified. A more detailed review of this range-finding study is presented in Appendix 1. A 5-week range finding study (84/SUM014/452; MRID no. 426811-16) was also included for review and showed no effects in $B6C3F_1$ mice after administration of dietary levels of 50, 150, 500, or 750 ppm.

3. Test Article Analyses for Purity and Stability

The purity of the test material was not verified by the testing facility. However, the sponsor tested the purity at four intervals during the study (weeks 25, 51, 81, and at the end of the study) and showed purities ranging from 94.6% to 94.9%.

Test diets were prepared by mixing appropriate amounts of the test material with powdered diet to obtain a concentrated premix. The premix was then mixed with appropriate amounts of diet to obtain the desired concentrations. Fresh diets were prepared every other week and stored in sealed polyethylene bags until presentation to the animals.

Measurement of the homogeneity, stability, and actual concentration of the test material in the diets was conducted by the testing facility using solvent extraction (hexane:ethanol, 200:1) followed by high-performance liquid chromatography with spectrophotometric detection. Stability of the test material in the diet at room temperature was measured at week 5 to 6. Negligible loss of test material occurred over 14 days. After 28 days, loss of test material ranged between 6% and 13% at 100 ppm and between 0% and 7% at

1,000 ppm. The first-order rate constants for loss were determined to be 2.6×10^{-3}/day at 100 ppm and 6.9×10^{-4}/day at 1,000 ppm.

Homogeneity of sample batches of feed prepared prior to treatment showed unacceptable variability (coefficient of variation ≈ 10-11%). A different mixing procedure was instituted, and homogeneity of sample batches of feed measured at week 5 to 6 was found to be acceptable. Variation between dietary samples was less than 10% at both 100 and 1,000 ppm (coefficient of variation ≈ 3-4%). It was not reported whether animals received any diets before the mixing procedure was changed. The actual concentration of the test material in the diets offered to the mice was measured at weeks 1, 13, 25 to 26, 39, 52, 65 to 66, 78, 91, and 104. The average measured concentrations at each dose level were as follows:

Nominal Concentration (ppm)	Measured Concentration[a] (ppm)
100	97 ± 3
300	291 ± 14
1,000	990 ± 42

[a]Mean ± S.D., calculated by reviewers, data from Appendix 2D

4. Animals

B6C3F_1 mice were received from Charles River (UK) Ltd., Margate, England. The mice were approximately 21-28 days old upon arrival and were caged individually in polypropylene cages with stainless steel mesh lids. The animal room was operated on a 12-hour light/dark cycle with a minimum of 20 air changes/hour. Temperature and relative humidity were reported to have been targeted at 21°C and 55%, respectively, and recorded daily. However, actual ranges were not reported. Feed (Labsure Laboratory Animal Diet No. 2) and water were provided ad libitum.

Mice were randomly allocated to study groups (50/sex/dose, main study; 30/sex/dose, satellite study) upon arrival. Animals were weighed 2 days after arrival, and those with weights at extremes of the weight distribution were replaced with mice (from the same batch) with acceptable weights. After 52 weeks of exposure, 10/sex/dose from the satellite group were scheduled to be sacrificed. The remaining surviving mice in the satellite group were scheduled to be sacrificed after 78 weeks of exposure.

Dietary Level (ppm)	Number of Animals			
	Main Study		Satellite Study	
	Males	Females	Males	Females
0	50	50	30	30
100	50	50	30	30
300	50	50	30	30
1,000	50	50	30	30

The acclimatization period lasted 7 days. During this time, an additional 10 mice/sex (from the same batch) were randomly selected and used for hematological analysis and then discarded. At the time of the first exposure to test diets, group mean weights ranged between 18.1 and 19.0 g for males and between 16.3 and 16.9 for females, and standard deviations were less than 12% of the mean values. The mice were uniquely identified with ear marks and cage cards. Test diets or control diets were given to the mice from 6/19/85 until 6/17/87-7/7/87 (the terminal sacrifice took about 3 weeks).

5. Statistical Analyses

Data on survival, body weight gain, hematology, absolute and relative organ weights, and incidence of macroscopic and microscopic pathology findings were analyzed statistically. Survival data (homogeneity of survival curves and pairwise comparisons with controls) were analyzed using Cox's test. Tarone's test was used to evaluate dose-related trends and to assess deviations from linearity. Data omitted from the survival analyses included data from animals in the main study that were killed at terminal sacrifice, accidently, or because of incapacitating masses, data from animals that were inadvertently switched, and data from all animals in the satellite group. Body weight gain and applicable hematology data were analyzed using a series of Student's t-tests with a pooled within-treatment error variance. Differences in absolute or organ-to-body weight ratios were evaluated using the Dunnett's test. Incidence data for macroscopic and microscopic pathology were analyzed using Fischer's exact test with a Bonferroni correction.

6. General Observations

(a) Mortality/moribundity/survival

Animals were observed twice daily for mortality/moribundity.

No effect on mortality was observed. Survival to week 104 in the main study was as follows:

Dietary Level (ppm)	Percent Survival	
	Males	Females
0	82	76
100	78	70
300	82	86
1,000	82	72

Data from study 88/SUM023/262, Table 2

(b) Clinical observations

Animals were observed twice daily for overt adverse clinical signs. In addition, detailed physical examinations (including palpations) for adverse clinical signs were conducted weekly.

No increase in the incidence of clinical signs or palpable masses was observed. No irritability or spastic tail were observed (these signs were reported in the 13-week range-finding study at 1,000 and/or 2,000 ppm).

(c) Body weights/food consumption/feed efficiency/test article intake

Body weights--Individual body weights were determined weekly for the first 14 weeks of the study and every 2 weeks, thereafter.

No effect on body weight or body weight gain was observed.

Food consumption--Individual food consumption values were determined weekly throughout the duration of the study.

No effect on food consumption was observed.

Feed efficiency--Feed efficiency was calculated weekly for the first 14 weeks of the study.

No compound-related effects on feed efficiency were observed.

Test article intake--Test article intake (mg S-2703F/kg body weight/day) was calculated weekly for the first 14 weeks of the study and every 2 weeks thereafter. These values were calculated using the nominal dietary concentrations of S-2703F, mean daily food consumption, and mid-period body weights.

The mean intake values of S-2703F over the period of weeks 1-104 in the main study for mice receiving diets containing 100, 300, or 1,000 ppm were 14.6, 42.9, or 145.7 mg/kg/day, respectively, for males and 15.8, 47.4, or 154.5 mg/kg/day, respectively, for females. Intake values for mice in the satellite study receiving the same diets over the period of weeks 1-78 were 15.0, 47.0, or 156.8, respectively, for males and 18.7, 54.6, or 178.1, respectively, for females.

7. Clinical Pathology

Blood samples were obtained from 10 mice/sex/dose in the satellite study during weeks 52 and 78 and from 10 mice/sex/dose in the main study during week 104. Blood samples were obtained from the retroorbital sinus of ether-anesthetized animals.

The hematology parameters marked with an "X" below were examined.

X Hematocrit (HCT)
X Hemoglobin (HGB)
X Leukocyte count (WBC)
X Erythrocyte count (RBC)
X Platelet count
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)

No treatment-related changes in hematological parameters were observed. Several small, but statistically significant, changes were observed. These changes either were not dose related, were within historical control ranges (see addendum, MRID No. 428260-02), or were attributable to a single animal with extremely high or low values. Therefore, they were not considered to represent a toxic effect of the test material.

8. Sacrifice and Pathology

All rats that died, were sacrificed in extremis, or were sacrificed as scheduled, in both the main and satellite studies, received a complete gross examination. All mice in the main study, as well as mice from the 0- and 1,000-ppm groups in the satellite study that were sacrificed after 52 weeks, were also examined histologically. Tissues that are marked with an "X" below were examined. In addition, the kidneys were examined histologically from mice from the 100- and 300-ppm groups in the satellite study that were sacrificed after 52 weeks. All tissues were preserved in neutral buffered 4% formaldehyde solution except the eyes, optic nerves, and Harderian glands which were fixed in Davidson's fixative. Organs that are marked with a "XX" were also weighed at necropsy in both the main and addendum study.

Digestive System	Cardiovascular/Hematologic	Neurologic
X Pancreas*	X Aorta*	XX Brain*
X Salivary glands*	XX Heart*	X Peripheral nerve* (sciatic nerve)
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes*	X Pituitary*
X Duodenum*	XX Spleen*	X Eyes* (with optic nerve)
X Jejunum*	X Thymus*	
X Ileum*		
X Cecum*	Urogenital	Glandular
X Colon*		
X Rectum*	XX Kidneys*	X Adrenals*
XX Liver*	X Urinary bladder*	X Harderian gland
	XX Testes*	X Mammary gland*
Respiratory	XX Epididymides*	X Thyroids*
	X Prostate*	X Parathyroids*
X Trachea*	X Cervix	
XX Lungs* (with mainstem bronchi)	XX Ovaries*	
	XX Uterus*	
	X Seminal vesicles*	

Other

X Bone (femur and sternum)*
X Skeletal muscle*
X Skin*
X Gall bladder*
X All gross lesions and masses*

* Recommended by Subdivision F (November 1984) Guidelines

(a) Macroscopic examination

No treatment-related changes were observed in the incidence of macroscopic lesions in either the satellite or main studies.

(b) Organ weights

Statistically significant dose-related decreases in both absolute and relative kidney weights were observed in the 300- and 1,000-ppm satellite males sacrificed after either 52 or 78 weeks of exposure (Table 1). In addition, at terminal sacrifice in the main study, statistically significant decreases were observed in absolute kidney weight in males at 1,000 ppm and in kidney-to-body weight ratio in males at 300 and 1,000 ppm. No other treatment-related differences in organ weights or organ-to-body weight ratios were observed.

Table 1. Kidney Weight Data for Mice Ingesting S-2703F in the Diet for up to 2 Years[a,b]

	Kidney Weight (g) Data (Mean ± S.D.) by Dietary Level (ppm)			
Interval	0	100	300	1,000
		Males		
Kidneys				
52 weeks				
absolute weight	0.75 ± 0.06	0.73 ± 0.10 (97)	0.63 ± 0.06** (84)	0.65 ± 0.06* (87)
% body weight	1.75 ± 0.13	1.68 ± 0.13 (96)	1.52 ± 0.08** (87)	1.51 ± 0.06** (86)
78 weeks				
absolute weight	0.78 ± 0.09	0.78 ± 0.09 (100)	0.71 ± 0.07* (91)	0.72 ± 0.06* (92)
% body weight	1.78 ± 0.26	1.66 ± 0.14 (93)	1.57 ± 0.14** (88)	1.61 ± 0.13* (90)
104 weeks				
absolute weight	0.82 ± 0.12	0.82 ± 0.10 (100)	0.78 ± 0.09 (95)	0.75 ± 0.09** (91)
% body weight	1.88 ± 0.17	1.92 ± 0.24 (102)	1.74 ± 0.24* (93)	1.73 ± 0.22** (92)
		Females		
Kidneys				
52 weeks				
absolute weight	0.51 ± 0.04	0.49 ± 0.03 (98)	0.52 ± 0.04 (104)	0.50 ± 0.07 (100)
% body weight	1.20 ± 0.24	1.27 ± 0.20 (106)	1.23 ± 0.16 (103)	1.32 ± 0.19 (110)
78 weeks				
absolute weight	0.53 ± 0.05	0.55 ± 0.06 (104)	0.55 ± 0.04 (104)	0.56 ± 0.05 (106)
% body weight	1.18 ± 0.24	1.15 ± 0.11 (97)	1.21 ± 0.20 (103)	1.23 ± 0.18 (104)
104 weeks				
absolute weight	0.58 ± 0.06	0.60 ± 0.07 (103)	0.59 ± 0.06 (102)	0.61 ± 0.06 (105)
% body weight	1.29 ± 0.29	1.33 ± 0.28 (103)	1.28 ± 0.23 (99)	1.31 ± 0.21 (102)

[a]Data extracted from Study No. 88/SUM023/262, Tables 9-11.
[b]Numbers in parentheses indicate percent control.

* Significantly different from control values, $p \leq 0.05$.
** Significantly different from control values, $p \leq 0.01$.

(c) Microscopic examination

Satellite study

Neoplastic findings--No treatment-related increase in tumor incidence was observed in any of the tissues examined.

Nonneoplastic findings--A statistically significant decrease in the incidence of vacuolation of the proximal convoluted tubule epithelium of the kidney was observed in males at 300 and 1,000 ppm after 52 weeks of treatment (Table 2). It was not reported whether this finding was statistically significant after using the Bonferroni correction.

Main study

Neoplastic findings--No treatment-related increase in tumor incidence was observed in any of the tissues examined. Data regarding hepatic and pulmonary neoplasia is presented in Table 3.

Nonneoplastic findings--At 300 and 1,000 ppm, both males and females showed a statistically significant increase in the incidence of lymphoid hyperplasia of the mesenteric lymph node (Table 4). The percentage of animals affected at 300 ppm was similar to that at 1,000 ppm. No increase in the severity of this lesion occurred with increasing dose. After using the Bonferroni correction, significant increases in the incidence of this lesion were observed only in males at 300 ppm and females at 1,000 ppm at terminal sacrifice.

The study author also noted a statistically significant decrease in the incidence of lymphoid hyperplasia in the spleen of females at 1,000 ppm (9/50) when compared to controls (19/50) and suggested that this was also treatment-related. However, the incidence data among females at all doses failed to show a consistent trend (controls, 19/50; 100 ppm, 12/50; 300 ppm, 24/50; 1,000 ppm, 9/50). Similarly, average severity scores in females failed to show decreases with increasing dose (controls, 1.5; 100 ppm, 1.4; 300 ppm, 1.5; 1,000 ppm, 1.8). Therefore, this effect was likely to have been an incidental finding.

In addition, the number of males at 300 and 1,000 ppm that showed vacuolation of the epithelium of the proximal convoluted tubule of the kidney was significantly decreased relative to controls. This change was statistically significant both with and without using the Bonferroni correction. The toxicological significance of this finding is unclear. The study author considered this change to be treatment related and to possibly reflect a subtle metabolic change.

Table 2. Incidence and Severity of Histopathology in Mice Ingesting S-2703F in the Diet for 1 Year (52-Week Interim Sacrifice)[a,b,c]

	Histopathology Data by Dietary Level (ppm)							
	0		100		300		1,000	
	Incidence	Average severity	Incidence	Average severity	Incidence	Average severity	Incidence	Average severity
Males								
Kidney								
Vacuolation of proximal convoluted tubule epithelium								
total	9/10 (90)	1.2	9/10 (90)	1.4	2/10* (20)	2.0	0/10* (0)	NA
Females								
Kidney								
Vacuolation of proximal convoluted tubule epithelium								
total	0/10 (0)	NA	0/10 (0)	NA	0/10 (0)	NA	0/10 (0)	NA

[a]Data extracted from Study No. 88/SUM023/262, Tables 18-25 and Appendix 17, Table 20.
[b]Average severity values are defined as: 1 = slight, 2 = minimal, 3 = moderate, and 4 = severe.
[c]Numbers in parentheses indicate percent incidence.

NA = Not applicable
*Significantly different from control; $p \leq 0.05$ by Fisher's Exact test.
#Significantly different from control; $p \leq 0.05$ by Fisher's Exact test with Bonferroni correction.

Table 3. Incidence of Selected Neoplastic Lesions in Mice Ingesting S-2703F in the Diet for up to 2 Years[a]

	Incidence of Neoplastic Lesions by Dietary Level (ppm)			
	0	100	300	1,000
		Males		
Liver				
Hepatocytic adenoma	9/49	2/50	10/50	9/49
Hepatocytic carcinoma	19/49	20/50	15/50	14/49
Haemangioma	1/49	0/50	1/50	0/49
Lung				
Pulmonary adenoma	2/49	2/50	2/50	1/49
Pulmonary carcinoma	2/49	2/50	5/50	5/49
		Females		
Liver				
Hepatocytic adenoma	5/50	4/50	4/50	0/50
Hepatocytic carcinoma	2/50	6/50	1/50	2/50
Haemangioma	0/50	0/50	0/50	0/50
Lung				
Pulmonary adenoma	2/50	0/50	1/50	1/50
Pulmonary carcinoma	1/50	1/50	1/50	2/50

[a] Data extracted from Study No. 88/SUM023/262, Table 25.

Table 4. Incidence and Severity of Histopathology in Mice Ingesting S-2703F in the Diet for up to 2 Years[a,b,c,d]

	Histopathology Data by Dietary Level (ppm)							
	0		100		300		1,000	
	Incidence	Average severity	Incidence	Average severity	Incidence	Average severity	Incidence	Average severity
Males								
Mesenteric lymph node								
Lymphoid hyperplasia								
–pre-terminal	0/7 (0)	NA	0/8 (0)	NA	0/10 (0)	NA	0/6 (0)	NA
–terminal	13/38 (34)	1.7	15/37[d] (41)	1.3	24/37*# (65)	1.8	21/35* (60)	1.5
–combined	13/45 (29)	1.7	15/45 (33)	1.3	24/47* (51)	1.8	21/41* (51)	1.5
Kidney								
Vacuolation of proximal convoluted tubule epithelium								
–pre-terminal	5/9 (56)	1.8	5/12 (42)	1.8	1/10 (10)	2.0	0/9* (0)	NA
–terminal	35/40 (88)	1.1	33/38 (87)	1.3	6/40*# (15)	1.9	1/39*# (3)	2.0
–combined	40/49 (82)	1.1	38/50 (76)	1.3	7/50*# (14)	1.9	1/48*# (2)	2.0
Females								
Mesenteric lymph node								
Lymphoid hyperplasia								
–pre-terminal	1/8 (13)	4.0	0/12 (0)	NA	1/5 (20)	2.0	2/15 (13)	1.5
–terminal	15/35 (43)	1.6	20/30 (67)	1.5	27/40* (68)	1.5	27/34*# (79)	1.4
–combined	16/43 (37)	1.8	20/42 (48)	1.5	28/45* (62)	1.5	29/49* (59)	1.4
Kidney								
Vacuolation of proximal convoluted tubule epithelium								
–pre-terminal	0/12 (0)	NA	1/18 (6)	4.0	0/8 (0)	NA	0/15 (0)	NA
–terminal	0/38 (0)	NA	0/32 (0)	NA	0/42 (0)	NA	0/35 (0)	NA
–combined	0/50 (0)	NA	1/50 (2)	4.0	0/50 (0)	NA	0/50 (0)	NA

[a]Data extracted from Study No. 88/SUM023/262, Tables 18-25 and Appendix 17.
[b]Average severity values are defined as: 1 = slight, 2 = minimal, 3 = moderate, and 4 = severe.
[c]Numbers in parentheses indicate percent incidence.
[d]This value is listed as 17/37 in the summary table; however, the individual data only recognizes 15/37 with this histopathology.

NA = not applicable
*Significantly different from control; $p \leq 0.05$ by Fisher's Exact test.
#Significantly different from control; $p \leq 0.05$ by Fisher's Exact test with Bonferroni correction.

B. DISCUSSION

Review of the final report and supporting data indicates that the conduct and design of the study were adequate and the reporting of the results was accurate. No increase in tumor formation was observed under the conditions of this study. Only minimal toxicity was observed at the highest dose tested. For example, the only treatment-related effects observed in the current study were increases in the incidence of lymphoid hyperplasia in the mesenteric lymph nodes of males and females at 300 and 1,000 ppm, and decreases in kidney weights and vacuolation of the epithelium of the proximal convoluted tubules in males at 300 and 1,000 ppm. None of these effects challenged the health of the mice. The toxicological significance of the decrease in renal tubular vacuolation is unclear. The study author suggested that this was a result of subtle metabolic changes caused by the test material rather than a toxic effect; however, no data were presented to support this hypothesis.

The doses used in the current study were selected based on the results of a 13-week range-finding study that showed minor hematological changes and transiently increased irritability at 1,000 ppm and above and 40% mortality, a 15% decrease in body weight gain, and transient occurrence of "spastic tail" at 2,000 ppm. The high mortality at 2,000 ppm indicated that this dose was too toxic for chronic exposure. Therefore, 1,000 ppm was selected as the highest dose to be tested for the chronic study. Although the current study failed to find substantial toxicity at 1,000 ppm; the choice of doses is considered to be adequate for a carcinogenicity study because the 13-week study indicated that 2,000 ppm exceeded the MTD and a steep dose-response for toxicity occurred between 1,000 and 2,000 ppm.

Potential reasons for the failure of the current study to show effects similar to those seen in the range-finding study at 1,000 ppm include biological or analytical variability (the effects seen at 1,000 ppm were minor, and detection was therefore likely to be variable), and the suggestion by the study author that the batches of test material differed between the two studies. Although the purity of the two batches was very similar (95.2% in the range-finding study and 94.6-94.9% in the current study), differences in the relative proportions of the cis and trans isomers of the test material may account for this difference. This information is to be provided by the registrant. *

In conclusion, the current study satisfied the guideline requirements for an oncogenicity study in mice and is classified as core guideline.

* Note by Ed Budd (5/3/94)
Examination of cis/trans and d/l ratios for the various isomers in the 2 batches (PY-83024 used in the 13-week study and PKG-84036 used in the 2-year study) did not indicate any meaningful differences between the 2 batches (based on information provided by the registrant on March 28, 1994).

Appendix 1

84/SUM017/242 (MRID 427175-05)
(a 13-week range-finding study in mice, completed 8/30/85)

EXECUTIVE SUMMARY: In a 13-week range-finding study, SF-2703F (batch PY-83024; 95.2% pure) was administered in the diet to 10/sex/dose B6C3F1 mice (Charles River Breeding Laboratories, Inc, USA) at dose levels of 0, 250, 500, 1,000, or 2,000 ppm (approximate doses of 0, 44, 86, 173, and 356 mg/kg/day in males and 0, 58, 114, 224, and 466 mg/kg/day in females [time-weighted averages]). At 1,000 ppm, 4/10 males and 7/9 females exhibited irritability and 1/9 females exhibited "spastic tail" (tail held rigidly horizontal) during the first week of the study. Hematological findings at 1,000 ppm at 13 weeks included a 4% decrease in hemoglobin in females and a 6% increase in platelets in males. At 2,000 ppm, 4/10 males and 4/10 females died within 24 hours of initiation of the study (daily intake of test material at 2,000 ppm was 494 mg/kg/day in males and 517 mg/kg/day during the first week of the study). In addition, among the surviving animals, 6/6 males and 6/6 females exhibited irritability, 4/6 males and 4/6 females exhibited spastic tail, and 1/6 males exhibited tremors during week 1-2 of the study. Body weight gain was decreased 15% and feed efficiency was decreased 14% in males at 2,000 ppm. Hematological findings at 2,000 ppm at 13 weeks included a 4% decrease in hemoglobin and a 4% decrease in red blood cell count in females and a 9% increase in platelets in males. The LOEL for systemic toxicity was 1,000 ppm based on the occurrence of irritability and spastic tail during week 1 of the study and minor hematological changes observed at week 13. The NOEL was 500 ppm.

Note: Additional information is available that indicates that the acute oral LD50 (by gavage) in mice (strain unknown) is probably between 100 and 200 mg/kg. Also, the acute oral LD50 (by gavage) in rats is about 300-400 mg/kg. Thus, the intake in mice at 2,000 ppm in the 13-week range-finding study exceeded the LD50 value.

FINAL

DATA EVALUATION REPORT

S-2703F (Cyphenothrin)

Study Type: Combined Chronic Toxicity/Oncogenicity in Rats

Prepared for:

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Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
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Prepared by:

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April 1994

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Contract Number: 68010075
Work Assignment Number: 3-04
Clement Number: 3-04/29
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EPA Section Head: Marion Copley, D.V.M.
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Signature: Marion Copley
Date: 5/9/94

DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 83-5, combined chronic toxicity/ oncogenicity in rats
CAS NUMBER:	39515-40-7
TOX CHEM. NUMBER:	725A
P.C. NUMBER:	129013
MRID NUMBERS:	427969-04 (combined study report) 87/SUM015/405 428260-04 (amendment to report) 93/SUM015/0043 428260-05 (first addendum to report) 93/SUM015/0044 428260-03 (second addendum to report) 93/SUM015/0135 427175-04 (13-week range-finding study) 84/SUM013/666 426811-15 (comments on study)
TEST MATERIAL:	S-2703F
SYNONYMS:	Cyphenothrin, Gokilaht, Forte
SPONSOR:	Sumitomo Chemical Company, Limited Environmental Health Science Laboratory Konohanu-ku Chuo-kuo, Osaka 541 Japan
STUDY NUMBER:	LSR Report No. 87/SUM015/405
TESTING FACILITY:	Pharmaco-LSR Ltd (formerly Life Science Research) Eye, Suffolk, IP23 7PX England
TITLE OF REPORT:	S-S703F: Combined oncogenicity and toxicity study in rats
AUTHOR:	P.A. Martin, B.Sc.
REPORT ISSUED:	September 28, 1988

EXECUTIVE SUMMARY: S-2703F was fed to male and female Fischer (F-344) rats (80/sex/dose) for two years at dietary levels of 0, 100, 300, or 1000 ppm. Average dosages for males and females, respectively, were 4.84 and

5.89 mg/kg/day for the 100-ppm groups; 14.49 and 17.77 mg/kg/day for the 300-ppm groups; and 48.16 and 58.52 mg/kg/day for the 1000-ppm groups.

No toxicologically significant treatment-related systemic effects were observed at dose levels of ≤1000 ppm. There was no treatment-related increase in the incidence of neoplasms at any site. **The NOEL for systemic toxicity in male and female rats is 1000 ppm (48.16 mg/kg/day for males and 58.52 mg/kg/day for females).**

The study is Core Guideline and satisfies the guideline requirements (83-5) for a combined chronic toxicity/oncogenicity study in rats.

CORE CLASSIFICATION: Core Guideline. This study satisfies the guideline requirements (83-5) for a combined chronic toxicity/oncogenicity study in rodents. Although only minimal toxicity was observed at the high-dose level of 1000 ppm, this dose level is sufficiently high for a 2-year chronic/oncogenicity study since it is ≥½ the maximally tolerated dose (MTD) established in the 13-week dose-range finding study. In the 13-week study, mortality observed at 2000 ppm in males (100% by week 6) and females (40% by week 7) indicates that the 2000 ppm level exceeds the MTD. Therefore, 1000 ppm, ½ the 2000 ppm level, is acceptable for the chronic toxicity/oncogenicity study despite the minimal toxicity observed at 1000 ppm.

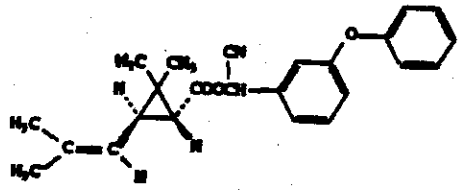
QUALITY ASSURANCE: A signed Good Laboratory Practice certification statement, a signed flagging statement, and a list of Quality Assurance Inspections were included.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: S-2703F

Chemical formula: 2,2-Dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylic acid cyano(3-phenoxyphenyl)-methyl ester



Lot number: PY 83024

Purity: 95.0%-95.5% during the study period

Cis:trans ratio: Not reported

Physical properties: Amber viscous liquid

Storage: 4°C in light-proof containers

Stability: Stable for up to 29 days at room temperature in rodent chow stored in light-proof plastic storage bins

2. Diet Preparation and Analysis

Test diets were prepared weekly at constant target concentrations of 100, 300, or 1000 ppm. A premix was prepared by mixing appropriate amounts of the test material with small amounts of the basal diet. The premix was then blended with additional basal diet (Laboratory Animal Diet No. 2, Labsure, Manea, Cambs) for 15 minutes using a horizontal, screw-type mixer (Gardner Type 50L 28GM). Diets were stored in light-proof plastic storage bins in the animal rooms.

Measurement of homogeneity, stability, purity, and actual concentration of the test material in the diets was conducted by the testing facility using hexane/ethanol extraction and quantification by HPLC with a UV detector. Homogeneity was determined using duplicate samples taken from low- and high-concentration test diets prepared before initiation of dosing. Homogeneity of mixing was acceptable at 89.8-105 ppm for the 100-ppm diets (mean 96.7 ± 5.0 ppm, coefficient of variation, 5.2%), and 942-1010 ppm for the 1000-ppm diets (mean 981 ± 29 ppm, coefficient of variation, 3.0%).

Purity was 95.0-95.5% throughout the study period, June 1985-January 1987. Stability after 29 days at room temperature in the rodent diets was acceptable at 83.3-91.2% in the 100-ppm diets and 89.6-99.8% in the 1000-ppm diets.

Actual concentration of S-2703 in the diet was determined for all diets prepared at weeks 1, 13, 26, 39, 52, 65, 78, 91, and 104. Concentrations averaged 98 ± 5.1%, 99 ± 3.5%, and 99 ± 2.9% of the intended low-, mid- and high-dose target concentrations, respectively. The ratios of achieved/intended concentrations were as follows: 92-108% for the low-dose diets; 95-106% for the mid-dose diets; and 93-103% for the high-dose diets.

3. Animals

Fischer (F-344) rats (379 males and 380 females) were received from Charles River (UK) Ltd., Margate, Kent, England, and were 3-5 weeks old upon arrival. Rats were randomly caged 5/sex in polypropylene cages with stainless steel mesh floors and lids during the 8-day acclimation period. Body weights 2-3 days after arrival were 51-95 g for males and 46-82 g for females.

Throughout acclimation and dosing, powdered basal diet and tap water (public supply) were available *ad libitum*. Target temperature and relative humidity were 21°C and 55%, respectively. A 12-hour dark/light cycle and at least 20 air changes per hour were maintained. Rats were uniquely identified with ear marks and cage cards.

After the acclimation period, rats were caged individually and randomly assigned to treatment groups for the oncogenicity and toxicity phases of the study. Rats at the extremes of the body weight distribution were discarded and replaced with surplus animals of suitable weight selected from the same batch. An additional 10 males and 10 females were designated veterinary controls to investigate any disease outbreak, and were housed and maintained under identical conditions as the study controls.

Fifty males and 50 females were used in the oncogenicity phase, and an additional 30 males and 30 females were used in the toxicity phase. Ten animals/sex/group from the toxicity phase were sacrificed for interim assessment after 54 weeks, and all surviving animals from the oncogenicity and toxicity phases were sacrificed after 104 weeks of treatment. Groups from the toxicity phase and the oncogenicity phase were divided into replicates A and B and were placed in two separate animal rooms. Allocation of test animals to the oncogenicity and toxicity phases was as follows:

Test Group	Dietary Level (ppm)	Number of Rats: Oncogenicity Phase 24 months M	Oncogenicity Phase 24 months F	Toxicity Phase[a] 24 months M	Toxicity Phase[a] 24 months F
1 (control)	0	50	50	30	30
2 (low dose)	100	50	50	30	30
3 (mid dose)	300	50	50	30	30
4 (high dose)	1000	50	50	30	30

[a] Ten males and 10 females in Groups 1-4 from the toxicity phase were sacrificed after 54 weeks of treatment. The remaining survivors from both phases were sacrificed after 104 weeks of treatment.

Rats received control or test diets from 12/20/84 to 12/19/86-1/9/87 (the terminal sacrifice took about 3 weeks). The 54-week interim sacrifice occurred on 1/6-7/86.

Rationale for dose selection: The 1000-ppm dietary level for the top dose in the current study was selected based on the results of a 13-week dose range-finding study (MRID 427175-04, LSR Report No. 84/SVM013/666, available for review). In the subchronic study, F-344 rats (10/sex/dose) received dietary levels of 0, 100, 300,

1000 or 2000 ppm S-2703F (lot no. PY-83024). Animals were obtained from Charles River (UK) Ltd., England.

At 300 ppm, sightly reduced cholesterol and increased albumin were noted in males. At 1000 ppm, both sexes exhibited transient mild irritability (weeks 1 and 2 only), increased urea concentration, reduced cholesterol levels, and increased albumin (males only). No histopathological effects were noted at 1000 ppm. Effects at 2000 ppm included marked irritability and body tremors in both sexes that persisted through week 9; mortality (100% in males within 6 weeks and 40% in females within 7 weeks); reduced body weight gain in both sexes; and coagulative necrosis in the livers of some males. Additional observations at 2000 ppm in both sexes were lateral displacement of hindlimbs; piloerection; and facial and urinogenital staining. Females at 2000 ppm exhibited slightly higher plasma alkaline phosphatase, alanine and aspartate amino-transferase activities and plasma phosphorus levels, and slightly lower glucose and calcium levels. In addition, congestion of several organs, particularly the liver, lungs, bone marrow, and adrenals, was consistently found in high-dose animals.

Additional toxicity data indicate that the acute oral (gavage) LD_{50} in rats is 318 mg/kg for males and 419 mg/kg for females. In the 13-week dose-range finding study, the 2000 ppm dose level during weeks 1-6 was 228-286 mg/kg/day for males (where 10/10 died) and 223-298 mg/kg/day for females (where 4/10 died). The animals dying during the first 6-7 weeks probably received doses of the test material that actually approached the acute oral LD_{50}. During the remainder of the study, 2000 ppm female survivors received 166-216 mg/kg/day.

4. Statistical Analyses

For body weight gain, hematology, and blood chemistry data, Student's t-tests were performed using a pooled within-treatment error variance. A least significant difference was calculated at 0.1%, 1%, and 5% levels of significance. Intergroup differences in mean absolute or relative organ weights were determined using Dunnett's test at the 1% and 5% levels of significance. Cox's test was used to determine homogeneity of survival curves and for pair-wise comparison against controls. Tarone's extension of Cox's test was used to examine linear trend on dose and to assess deviation from linearity. Fisher's Exact Probability test was applied as a two-tailed test to the distribution of ophthalmic and macroscopic pathological findings. Bonferroni's correction was applied to assist interpretation of findings. Fisher's Exact Probability test was also used to analyze non-neoplastic and neoplastic histopathological findings using the two- and one-tailed tests, respectively.

5. General Observations

(a) Mortality/moribundity/survival

Rats were observed twice daily for mortality and moribundity.

Results - No treatment-related changes in mortality were observed. Survival of treated animals was comparable to that of controls; 67% of males and 77% of females in the oncogenicity phase survived through week 104.

(b) Clinical observations

Rats were observed twice daily for general appearance, behavior, and overt signs of toxicity. Animals were carefully examined for palpable masses once each week.

Results - No treatment-related effect on the number or multiplicity of palpable masses were observed in any animals from the oncogenicity phase of the study.

No overt clinical signs of toxicity were observed in animals from the oncogenicity or toxicity phases. No treatment-related signs of neurotoxicity, including tremors and ataxia, were observed.

Irritability was observed in several low-dose females from replicate B at weeks 26 and 27 only. However, this finding is not considered to be of toxicological significance because the irritability was transient and not related to dosage.

A mild, transitory infection was noted in 13 animals from replicate A and 106 animals from replicate B at weeks 51-54. The infection was characterized by swelling of the ventral cervical region, ocular and nasal staining and discharge, red-rimmed eyes, and respiratory rales. The animals recovered rapidly and the infection was not considered to be related to treatment.

(c) Body weight/body weight gain

Body weight/body weight gain--Individual body weights were measured 2-3 days after arrival, at initiation of dosing, weekly for the first 14 weeks, and every 2 weeks thereafter. Terminal body weights were also measured.

Results - Tables 1-4 present selected mean body weight and mean body weight gain data. No statistically significant changes in mean body weights between controls and treated groups were observed in either phase of the study; mean body weights for treated males and females were at least 95% of controls throughout the study. Mean body weight gain in

high-dose females was significantly ($p<0.01$) reduced by 5.2% compared with controls in the first 78 weeks of the oncogenicity phase. However, no significant reduction was observed in high-dose females in the toxicity phase at weeks 0-78. Reduced mean body weight gain in high-dose females is not considered toxicologically significant because it was slight, transient, not observed in the toxicity phase, and may have resulted from the mild infection observed in several animals at weeks 51-54.

(d) Food and water consumption

Food and water consumption--The weight of food consumed by each rat was measured weekly (g/rat/week) over consecutive 7-day periods. Water consumption was assessed daily by visual inspection of the water bottles. Accurate measurements were taken over 24-hour periods in weeks 1, 4, 8, 13, 26, 52, 78, and 104.

Results - Tables 5 and 6 show selected food consumption data. A slight dose-related reduction in food consumption (not statistically significant) was noted in treated animals from both the oncogenicity and toxicity phases. However, because the trend was slight (95-100% of controls for weeks 1-35, 36-70, 71-104, and 1-104), the reduction is considered to be of minor toxicological significance and may have been associated with the mild infection during weeks 51-54. Water consumption was not affected by treatment.

(e) Feed efficiency/test article intake

Feed efficiency--Group mean food conversion ratios were determined weekly for the first 14 weeks of treatment.

Results - No treatment-related effects were observed. Feed efficiency was 97-102% of controls for animals from both phases of the study.

Test article intake--Achieved dosages (mg/kg body weight/day) were calculated from the concentration of the test material in the diet and the animals' body weight and food consumption data.

Results - Mean daily doses and dose ranges for the oncogenicity and toxicity studies were as follows:

TABLE 1. Mean Body Weight (g ± S.D.) at Representative Intervals for Rats (Oncogenicity Phase) Fed S-2703 for 104 Weeks[a]

Dietary Level (ppm)	Mean Body Weight (g ± S.D.) at Week: 0	8	14	22	50	78	104
				Males			
0	104 ± 11	302 ± 13	349 ± 16	388 ± 16	449 ± 37	483 ± 27	432 ± 48
100	98 ± 9	295 ± 12	344 ± 15	386 ± 17	455 ± 24	482 ± 29	424 ± 41
300	100 ± 9	299 ± 14	344 ± 14	384 ± 16	451 ± 27	477 ± 28	408 ± 48
1000	101 ± 10	301 ± 14	345 ± 18	382 ± 21	449 ± 25	471 ± 27	417 ± 46
				Females			
0	85 ± 6	175 ± 9	197 ± 10	216 ± 13	262 ± 19	318 ± 25	327 ± 37
100	86 ± 7	177 ± 10	198 ± 9	215 ± 11	264 ± 20	317 ± 16	330 ± 26
300	86 ± 8	176 ± 8	196 ± 9	214 ± 10	261 ± 18	312 ± 23	323 ± 31
1000	86 ± 6	176 ± 8	193 ± 9	212 ± 11	257 ± 17	307 ± 23	318 ± 33

[a] Data extracted from Table 3A (oncogenicity phase), pages 63–68 of the study (87/SUM015/405).

TABLE 2. Mean Body Weight (g ± S.D.) at Representative Intervals for Rats (Toxicity Phase) Fed S-2703 for 104 Weeks[a]

Dietary Level (ppm)	Mean Body Weight (g ± S.D.) at Week: 0	8	14	22	50	78	104
				Males			
0	103 ± 9	303 ± 13	353 ± 13	394 ± 12	449 ± 37	490 ± 18	425 ± 26
100	100 ± 9	299 ± 13	350 ± 15	392 ± 17	455 ± 24	491 ± 26	433 ± 41
300	100 ± 9	299 ± 16	346 ± 18	386 ± 20	451 ± 27	474 ± 31	404 ± 48
1000	98 ± 9	297 ± 11	342 ± 13	381 ± 14	449 ± 25	464 ± 23	406 ± 47
				Females			
0	86 ± 7	176 ± 10	198 ± 11	217 ± 13	268 ± 21	318 ± 24	329 ± 29
100	86 ± 6	176 ± 9	196 ± 8	213 ± 8	258 ± 15	312 ± 18	331 ± 23
300	85 ± 5	178 ± 8	198 ± 8	215 ± 10	259 ± 15	311 ± 21	325 ± 24
1000	86 ± 5	175 ± 8	193 ± 9	209 ± 11	254 ± 15	312 ± 22	322 ± 31

[a] Data extracted from Table 3C (toxicity phase), pages 70–75 of the study (87/SUM015/405).

TABLE 3. Mean Body Weight Change (g ± S.D.) at Representative Intervals for Rats (Oncogenicity Phase) Fed S-2703 for 104 Weeks[a]

	Dietary Level (ppm) for Males			
Weeks:	0	100	300	1000
0-70	380	388	380	375
70-104	-49	-53	-70	-58
0-104	327	327	307	316
	Dietary Level (ppm) for Females			
Weeks:	0	100	300	1000
0-78	233	231	227	221[b] (94.8)[c]
78-104	8	12	14	12
0-104	241	244	238	232

[a] Data extracted from Table 3B (oncogenicity phase), page 69 of the study (87/SUM015/405).
[b] Significantly different from control value; $p<0.01$.
[c] Numbers in parentheses indicate percentage of control (0 ppm) value.

TABLE 4. Mean Body Weight Change (g ± S.D.) at Representative Intervals for Rats (Toxicity Phase) Fed S-2703 for 104 Weeks[a]

	Dietary Level (ppm) for Males			
Weeks:	0	100	300	1000
0-70	387	394	382	377
70-104	-66	-57	-72	-66
0-104	321	335	303	310
	Dietary Level (ppm) for Females			
Weeks:	0	100	300	1000
0-78	232	227	226	227
78-104	14	19	17	8
0-104	241	246	240	236

[a] Data extracted from Table 3D (toxicity phase), page 76 of the study (87/SUM015/405).

TABLE 5. Mean Food Consumption (g/rat/week) at Representative Intervals for Rats (Oncogencity Phase) Fed S-2703 for 104 Weeks[a]

Dietary Level (ppm)	Mean Food Consumption (g/rat/week) at Week: 1	8	14	22	50	78	104	total weeks 0-104
				Males				
0	108	127	128	126	111	134	124	13,116
100	106	122	128	127	119	134	120	13,214 (100)
300	107	124	127	127	118	135	121	13,018 (99)
1000	101	123	125	125	117	132	124	12,959 (99)
				Females				
0	91	90	94	91	93	112	104	10,178
100	94	89	94	91	94	109	101	10,052 (99)
300	93	89	93	91	94	108	101	9975 (98)
1000	87	87	90	89	91	103	100	9790 (96)

[a] Data extracted from Table 4A (oncogenicity phase), pages 77-79 of the study (87/SUM015/405).
[b] Numbers in parentheses indicate percentage of control (0 ppm) value.

TABLE 6. Mean Food Consumption (g/rat/week) at Representative Intervals for Rats (Toxicity Phase) Fed S-2703 for 104 Weeks[a]

Dietary Level (ppm)	Mean Food Consumption (g/rat/week) at Week: 1	8	14	22	50	78	104	total weeks 0-104
				Males				
0	107	129	131	129	121	137	131	13,278
100	107	126	129	130	115	140	123	13,212 (99.5)
300	108	126	128	129	119	138	114	13,153 (99.1)
1000	101	123	126	124	112	132	121	12,932 (97.4)
				Females				
0	89	90	94	91	95	106	106	10,010
100	90	90	95	91	95	107	101	9992 (99.8)
300	90	90	93	89	95	107	102	9884 (98.7)
1000	85	86	90	87	93	106	98	9773 (97.6)

[a] Data extracted from Table 4B (toxicity phase), pages 80–82 of the study (87/SUM015/405).
[b] Numbers in parentheses indicate percentage of control (0 ppm) value.

Dietary Level (ppm)	Achieved dose (mg/kg body weight/day)[a]			
	Oncogenicity Study		Toxicity Study	
	Mean[b]	Range[b]	Mean[c]	Range[b]
		Males		
100	4.84	12.99-3.61	N/A	12.94-3.4
300	14.49	38.54-10.61	N/A	39.1-11.2
1000	48.16	121.0-36.96	N/A	125.2-35.7
		Females		
100	5.89	13.8-4.36	N/A	13.25-4.27
300	17.77	41.0-13.13	N/A	39.74-12.9
1000	58.52	128.5-44.7	N/A	126.4-42.27

[a] Data extracted from Tables 6A and 6B, pages 85-88 of the study report.
[b] From weekly values in weeks 1-104.
[c] Not available. The mean for weeks 1-104 was not calculated for groups in the toxicity phase.

(d) Ophthalmoscopic examination

Eyes of all rats were examined prior to initiation of dosing. Eyes of rats from groups 1 and 4 of the oncogenicity phase were examined in weeks 26, 51, 78, and 103; eyes of rats from groups 2 and 3 of the oncogenicity phase were examined week 103 only.

Results - Table 7 presents the incidence of superficial corneal opacity in females. The incidence was significantly ($p<0.05$) higher in high-dose females (32/48) than in controls (21/48) after 77 weeks of treatment, and in mid-dose females after 102 weeks of treatment (17/38 versus control value of 9/42). The incidence was also significantly higher in high-dose females after 102 weeks (15/38), although the statistical significance disappeared after Bonferroni's correction was applied. The toxicological significance of the increased incidence of superficial corneal opacity is unclear because of the variation in statistical significance and the high incidence of superficial corneal opacity observed in treated controls compared to historical controls.

TABLE 7. Incidence of Superficial Corneal Opacity in Females at Representative Intervals in Rats Fed S-2703 for 104 Weeks

Dietary Level (ppm)	Incidence of Superficial Corneal Opacity in Treated Females at Week: 25	50	77	102
		Treated Females[a]		
0	1/50 (2)[b]	15/50 (30)	21/48 (44)	9/42 (21)
100	N/A	N/A	N/A	9/44 (20)
300	N/A	N/A	N/A	17/38* (45)
1000	3/48 (6)	18/48 (38)	32/48* (67)	15/38 (39)
		Historical Controls[c] (females)		
Study FSR027	4/78 (5)	5/78 (6)	3/48 (6)	3/42 (7)
Study FSR037	4/20 (20)	6/14 (43)	N/A	N/A

[a] Data extracted from Tables 8B, 8C, 8D, and 8E, pages 92–96 of the study report (87/SUM015/405).
[b] Numbers in parentheses indicate percent incidence.
[c] Historical control data extracted from Table I, page 11 of the second addendum (93/SUM015/0135) to the study report. Data are from two studies, FSR027 and FSR037.

* Significantly different from control value; $p<0.05$.
N/A Incidence data not reported.

6. Clinical Pathology

Blood was collected at weeks 26, 51, 79, and 103 from the retro-orbital sinus of 10 animals/sex from each group in the toxicity phase. Blood was collected from fasted animals under light ether anesthesia. The checked (X) parameters were examined:

(a) Hematology

X Packed cell volume (PCV)*
X Hemoglobin (HGB)*
X Leukocyte total count (WBC)*
X Leukocyte differential count*
X Erythrocyte count (RBC)*
Blood clotting measurements
(Thromboplastin time)
(Clotting time)
(Prothrombin time)

X Mean corpusc. HGB (MCH)
X Mean corpusc. volume (MCV)
X Mean corpusc. HGB conc. (MCHC)
X Reticulocyte count
X Platelet count*

* Recommended by Subdivision F (November 1984) Guidelines

Results - No treatment-related effects were observed. Although several hematology parameters were significantly different from controls (e.g., PCV, MCH, MCV, HGB, normoblasts), the differences generally were not related to dosage, time of onset, or sex. In addition, all parameters were well within the range of historical control values that were provided by the study author.

(b) Blood (clinical) chemistry

Electrolytes

X Calcium*
X Chloride*
X Phosphorus*
X Potassium*
X Sodium*
Magnesium

Other

X Albumin*
Albumin/globulin ratio
X Creatinine*
X Blood urea nitrogen*
X Electrophoretic protein
X Glucose (fasting)*
X Total protein*
X Total bilirubin*
X Cholesterol

Enzymes

X Alkaline phosphatase (ALP)
X Creatinine phosphokinase*
X Serum aspartate aminotransferase (SGOT)*
X Serum alanine aminotransferase (SGPT)*
X Lactic acid dehydrogenase (LDH)
Cholinesterase (ChE)
Gamma glutamyl transferase (GGT)
Glutamate dehydrogenase

* Recommended by Subdivision F (November 1984) Guidelines

Results - No treatment-related effects were observed. Several parameters were significantly different from controls; however, all parameters were within the range for historical controls (provided in the study report) and were not associated with dosage or time of onset.

(c) Urinalysis

Urine was collected over 16-hour periods from fasted animals at weeks 26, 51, 79, and 103. The checked (X) parameters were examined.

X Appearance*
X Volume*
X Specific gravity*
X pH
X Sediment (microscopic)*
X Protein*
X Total reducing substances
X Glucose*
X Ketones*
X Bilirubin*
X Blood*
X Nitrite
X Urobilinogen

* Recommended by Subdivision F (November 1984) Guidelines

Results - No treatment-related effects were observed. All parameters examined were well within the range for historical controls (provided in the study report) at the time of observation.

7. Sacrifice and Pathology

All animals that died during the study or were sacrificed on schedule were subject to gross pathological examination. Ten animals/sex/group from the toxicity phase were sacrificed after 54 weeks for interim study. Scheduled deaths were by carbon dioxide inhalation. The checked (X) tissues were collected from all rats. Tissues from all rats in the oncogenicity phase, and from rats in groups 1 and 4 in the toxicity phase sacrificed at 54 weeks, were examined microscopically. In addition, any tissues from rats in groups 2 and 3 in the toxicity phase that showed a potential treatment-related change were examined microscopically. Double checked (XX) organs were weighed.

Respiratory	Cardiovasc./Hemat.	Neurologic
X Trachea*	X Aorta*	XX Brain*+
X Lung*	XX Heart*	X Peripheral nerve*
Nose	X Bone marrow*	X Spinal cord* (3 levels)
Pharynx	X Lymph nodes*	XX Pituitary*
Larynx	XX Spleen	X Eyes (optic nerve)*
	X Thymus*	
Digestive system	**Urogenital**	**Glandular**
Tongue		XX Adrenal gland*
X Salivary glands*	XX Kidneys*+	Lacrimal gland
X Esophagus*	X Urinary bladder*	X Mammary gland*
X Stomach*	XX Testes*+	XX Parathyroids*
X Duodenum*	Epididymides	XX Thyroids*
X Jejunum*	X Prostate	
X Ileum*	X Seminal vesicle	**Other**
X Cecum*	XX Ovaries*+	
X Colon*	XX Uterus*	X Bone* (femoral)
X Rectum*		X Skeletal muscle*
Gall bladder*		X Skin*
X Pancreas*		X All gross lesions and masses*
XX Liver*+		

* Recommended by Subdivision F (November 1984) Guidelines
\+ Organ weight required

(a) Macroscopic

No toxicologically significant, dose-related macroscopic changes were observed at interim sacrifice, or in animals from the toxicity or oncogenicity phases at terminal sacrifice.

(b) Organ weight and body weight ratios

Tables 8 and 9 present selected organ weight and historical control data. No treatment-related effects on absolute or relative organ weights were observed during the toxicity or oncogenicity phases of the study. Statistically significant changes noted in several organs (particularly slight decreases in absolute and relative (to body weight) pituitary weights in treated females and reduced thyroid/parathyroid weights in mid-dose males) were not considered to be toxicologically significant because of the absence of a dose-response relationship and associated histopathological findings, as well as the fact that values were within the range for historical controls.

TABLE 8. Absolute and Relative Organ Weights (g ± S.D.) at Week 104 (Toxicity Phase) for Rats Fed S-2703 for 104 Weeks

Organ	Mean Organ Weight (g ± S.D.) at Dose Level: 0 ppm	100 ppm	300 ppm	1000 ppm
Toxicity Phase[a]		Males		
Kidney:				
Relative weight (historical control range[b]: 0.565 - 1.176 g)	1.080 ± 0.133	1.069 ± 0.181	1.074 ± 0.220	1.023 ± 0.149
Absolute weight (historical control range: 2.84 - 4.82 g)	4.37 ± 0.54	4.37 ± 0.53	4.21 ± 0.80	4.02 ± 0.38
Thyroid/parathyroid:				
Relative weight (historical control range: 0.0000 - 0.0629 g)	0.0071 ± 0.0015	0.0067 ± 0.0031	0.0061 ± 0.0019	0.0060 ± 0.0021
Absolute weight (historical control range: 0.000 - 0.248 g)	0.029 ± 0.007	0.027 ± 0.001	0.024 ± 0.007	0.023 ± 0.005
		Females		
Kidney:				
Relative weight (historical control range: 0.508 - 1.130 g)	0.978 ± 0.158	0.892 ± 0.064	0.882 ± 0.096*	0.878 ± 0.073*
Absolute weight (historical control range: 1.84 - 3.43 g)	3.07 ± 0.40	2.93 ± 0.22	2.82 ± 0.26	2.79 ± 0.21*
Thyroid/parathyroid:				
Relative weight (historical control range: 0.0000 - 0.0202 g)	0.0069 ± 0.0014	0.0054 ± 0.0016**	0.0049 ± 0.0008**	0.0059 ± 0.0010
Absolute weight (historical control range: 0.000 - 0.063 g)	0.022 ± 0.004	0.018 ± 0.006*	0.016 ± 0.003**	0.019 ± 0.003
Pituitary:				
Relative weight (historical control range: 0.0008 - 0.0058 g)	0.0039± 0.0026	0.0038 ± 0.0014	0.0028 ± 0.0007	0.0033 ± 0.0010
Absolute weight (historical control range: 0.002 - 0.019 g)	0.012 ± 0.006	0.012 ± 0.004	0.009 ± 0.002	0.011 ± 0.004

[a] Toxicity phase data extracted from Tables 14A and 14B, pages 137-140 of the study report (87/SUM015/405).

[b] Historical control data extracted from Tables 5A and 5B, second addendum (93/SUM015/0135) to the study report. Data are for males and females 109-115 weeks of age.

* Significantly different from control; $p<0.05$.

** Significantly different from control; $p<0.01$.

TABLE 9. Absolute and Relative Organ Weights (g ± S.D.) at Week 104 (Oncogenicity Phase) for Rats Fed S-2703 for 104 Weeks

Organ	Mean Organ Weight (g ± S.D.) at Dose Level: 0 ppm	100 ppm	300 ppm	1000 ppm
Oncogenicity Phase[a]		Males		
Kidney:				
Relative weight (historical control range: 0.565 - 1.176 g)	1.038 ± 0.197	1.014 ± 0.195	1.111 ± 0.374	1.069 ± 0.283
Absolute weight (historical control range: 2.84 - 4.82 g)	4.30 ± 0.44	4.21 ± 0.64	4.24 ± 1.07	4.19 ± 0.71
Thyroid/parathyroid:				
Relative weight (historical control range: 0.0000 - 0.0629 g)	0.0074 ± 0.0022	0.0069 ± 0.0020	0.0071 ± 0.0024	0.0069 ± 0.0024
Absolute weight (historical control range: 0.000 - 0.248 g)	0.031 ± 0.008	0.029 ± 0.007	0.027 ± 0.007	0.027 ± 0.007
		Females		
Kidney:				
Relative weight (historical control range[b]: 0.508 - 1.130 g)	0.925 ± 0.163	0.896 ± 0.120	0.880 ± 0.107	0.892 ± 0.121
Absolute weight (historical control range: 1.84 - 3.43 g)	2.93 ± 0.30	2.87 ± 0.20	2.80 ± 0.35	2.76 ± 0.24*
Thyroid/parathyroid:				
Relative weight (historical control range: 0.0000 - 0.0202 g)	0.0073 ± 0.002	0.0072 ± 0.113	0.0053 ± 0.0016**	0.0055 ± 0.0011**
Absolute weight (historical control range: 0.000 - 0.063 g)	0.023 ± 0.30	0.022 ± 0.031	0.017 ± 0.005**	0.017 ± 0.003**
Pituitary:				
Relative weight (historical control range: 0.0008 - 0.0058 g)	0.0043 ± 0.0010	0.0031 ± 0.0009**	0.0027 ± 0.0010**	0.0033 ± 0.0013*
Absolute weight (historical control range: 0.002 - 0.019 g)	0.014 ± 0.003	0.010 ± 0.003**	0.009 ± 0.004**	0.010 ± 0.004*

[a] Oncogenicity phase data extracted from Tables 13A and 13B, pages 133-136 of the study report (87/SUM015/405).
[b] Historical control data extracted from Tables 5A and 5B, second addendum (93/SUM015/0135) to the study report. Data are for males and females 109-115 weeks of age.

* Significantly different from control; $p<0.05$.
** Significantly different from control; $p<0.01$.

TABLE 10. Group Incidence Data of Neoplastic Findings for Rats Killed or Dying during the Oncogenicity Phase[a]

Neoplasm	Incidence at Dose Level: 0 ppm	100 ppm	300 ppm	1000 ppm
		Males		
Pituitary adenomas	5/17 (29)[c]	15/20* (75)	9/17 (53)	9/15 (60)
Historical control incidence[b]: 27% (range 6.0 - 48%)				
Pancreas islet cell adenomas	2/17 (12)	1/20 (5)	2/17 (12)	2/16 (12)
Historical control incidence: 2.4% (range 0.0 - 6.0%)				
Testes interstitial cell adenomas	13/17 (76)	14/20 (70)	16/17 (94)	15/16 (94)
Historical control incidence: 88.6% (range 76.0 - 98.0%)				
		Females		
Mammary area, caudal fibroepithelial tumors	0/13 (0)	0/9 (0)	0/15 (0)	3/14 (21)
Historical control incidence: 13.5% (range 0.0 - 26.0%)				

[a] Data extracted from Table 26, pages 266–272, of the study report (87/SUM015/405).
[b] Historical control data extracted from Table 6, pages 23-34 of the second addendum (93/SUM015/0135) to the study report.
[c] Numbers in parenthese indicate percent incidence.

* Significantly different from control; $p<0.01$.

TABLE 11. Group Incidence Data of Neoplastic Findings for all Rats in the Oncogenicity Phase[a]

Neoplasm	Incidence at Dose Level: 0 ppm	100 ppm	300 ppm	1000 ppm
		Males		
Pituitary adenomas	20/50 (40)[c]	30/50* (60)	19/50 (38)	22/49 (45)
Historical control incidence[b]: 27% (range 6.0 - 48%)				
Pancreas islet cell adenomas	5/50 (10)	3/50 (6)	9/50 (18)	8/50 (16)
Historical control incidence: 2.4% (range 0.0 - 6.0%)				
Testes interstitial cell adenomas	44/50 (88)	44/50 (88)	45/50 (90)	49/50 (98)
Historical control incidence: 88.6% (range 76.0 - 98.0%)				
		Females		
Mammary area, caudal fibroepithelial tumors	3/49 (6)	2/47 (4)	4/48 (8)	9/48 (19)
Historical control incidence: 13.5% (range 0.0 - 26.0%)				

[a] Data extracted from Table 28, pages 282-289, of the study report (87/SUM015/405).
[b] Historical control data extracted from Table 6, pages 23-34 of the second addendum (93/SUM015/0135) to the study report.
[c] Numbers in parenthese indicate percent incidence.

* Significantly different from control; $p<0.05$.

(c) Microscopic examination

Non-neoplastic lesions

A few statistically significant increases in non-neoplastic lesions compared to controls were not considered to be related to treatment because the changes lacked a clear dose-response relationship.

Neoplastic lesions

Tables 10 and 11 present incidence and historical control data for selected neoplasms. No treatment-related neoplasms were observed in animals from either the toxicity or oncogenicity phases of the study. Although a statistically significant increase in the incidence of pituitary adenoma was observed in low-dose males killed or dying during the oncogenicity phase (Table 10, $p<0.01$) and overall for low-dose males in the oncogenicity phase (Table 11, $p<0.05$), the trend test did not show any dose-related effect. The incidence of pituitary adenoma in low-, mid-, and high-dose males killed or dying during the oncogenicity phase (Table 10) exceed the range established for historical controls.

B. DISCUSSION

This study is rated Core Guideline. Review of the report and supporting data indicates that the conduct of the study was adequate and the reporting of the results was accurate. No toxicologically significant adverse systemic effects were observed at dose levels of ≤1000 ppm.

The high dose of 1000 ppm was selected based on the results of a 13-week dose range-finding study. In the 13-week study, mild toxicity was observed at 1000 ppm, including transient mild irritability in both sexes at weeks 1 and 2, increased urea concentration, reduced cholesterol levels, and increased albumin (males only). At 2000 ppm, effects included marked irritability and body tremors in both sexes that persisted through week 9; mortality (100% in males by week 6, 40% in females by week 7); transient reduced body weight gain in both sexes; histopathological changes in the livers of males; lateral displacement of hindlimbs; piloerection; facial and urinogenital staining; and changes in serum chemistry parameters in females. Although only minimal toxicity was observed at the high-dose level of 1000 ppm in either the combined chronic/oncogenicity study or the 13-week range-finding study, this dose level is sufficiently high for a 2-year chronic/oncogenicity study since it is ½ the maximally tolerated dose (MTD) established in the 13-week dose-range finding study. In the 13-week study, mortality observed at 2000 ppm in males (100% by week 6) and females (40% by week 7) indicates that the 2000 ppm level exceeds the MTD. Therefore, 1000 ppm, ½ the 2000 ppm level, is acceptable for the chronic toxicity/oncogenicity study despite the minimal toxicity observed. The reviewers assess that the NOEL for systemic toxicity in male and female rats is 1000 ppm.

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