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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Data Evaluation for Sumilarv Technical (Pyriproxyfen, S-3113, 2-[1-methyl-2-(4-phenoxyphenoxy) ethoxy] pyridine)

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TO: Joseph M. Tavano, PM 10
Registration Division (7505C)

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Health Effects Division (7509C)

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Health Effects Division (7509C) KB 11/29/93

Registrant: Sumitomo Chemical Company, Ltd.
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Osaka, Japan

Action Requested:

Review the toxicology data submitted to support the registration of Sumilarv as an insect growth regulator (IGR). Insect growth regulators are naturally occurring or synthetic chemicals which mimic the activity of endogenous insect hormones. These compounds disrupt the insects' normal development, preventing them from reaching maturity and/or causing sterility.

The application is for the use of Sumilarv to control cockroaches, fleas, and crawling insects in households and commercial establishments. The product to be registered is NYLAR 10 EC, an emulsifiable concentrate containing 10% Sumilarv. It is to be mixed at the rate of 0.5 ml to 1 gallon of water for spraying 1,000 square feet of infested area on baseboards and other infested areas, as a spot treatment, or as crack and crevice spray. The applications are to be repeated as necessary every 3-4 months.

Conclusions:

The data in the current submission have been reviewed to assess the toxicological potential of Sumilarv. The acute studies are acceptable for labeling purposes. The subchronic studies (MRID Nos. 413217-16 and 421783-07) satisfy the Subdivision F Guideline requirements for registration purposes. In the rat, the NOEL was 400 ppm (equivalent to 23.5 mg/kg/day, males, and 27.7 mg/kg/day, females), and the LOEL was 2,000 ppm (117.8 mg/kg/day males, and 141.3 mg/kg/day, females), based on higher mean total cholesterol and phospholipids, decreased mean red blood cell, hematocrit, and hemoglobin counts, and significantly higher liver-to-body weight ratios in males. In the dog, the NOEL was 100 mg/kg/day (both sexes) and the LOEL was 300 mg/kg/day, based on significantly higher absolute liver weights and liver-to-body weight ratios in the males, and enlargement of hepatocytes in females. The subacute inhalation toxicity study (MRID No. 421783-08) was classified as Supplementary and not upgradeable, because the test material stability and exposure atmospheres were inadequately characterized, and the inhalation equipment did not provide adequate dynamic air flow rate. However, the study does not need to be repeated, because it is not required for registration purposes.

Metabolism data (MRID Nos. 421783-18 and 422014-02) demonstrate that 92-97% of orally administered 14C-labeled Sumilarv was excreted rapidly within a 7 day period into the urine (5-12%) and feces (81-92%); most (63-83%) of the dose was excreted within 24 hours. Eleven metabolites were detected in urine, and 17 metabolites were detected in feces. This study was acceptable for satisfying Subdivision F Guideline requirements for a metabolism study.

A chronic toxicity study in dogs (MRID No. 421783-09) demonstrated a NOEL of 100 mg/kg/day, and a LOEL of 300 mg/kg/day, based on significantly decreased body weight gain and increased relative liver weights in both sexes. This study satisfies the Guideline requirements. A carcinogenicity study in mice (MRID 421783-10) did not satisfy the Guideline requirements, because it appeared that an MTD had not been reached. Although there were no neoplastic findings related to the compound observed in the study, there were also no signs of systemic toxicity. Therefore, a NOEL could not be established. The study was classified Supplementary, and it is recommended that the study be repeated at higher dietary dose levels. A NOEL could not be established in the rat chronic/carcinogenicity study (MRID 421783-14), because additional information is required. It was core-graded Supplementary but upgradeable, pending receipt of information concerning the dosing rationale, organ weights for all high dose and control animals, and any other animals that exhibited significant effects. In addition, the satellite and

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main study data should be combined and reported for all appropriate end points, gross and histopathological data provided, and the biological significance or potential effects of Sumilarv on the hematopoietic system should be assessed and reported.

Reproductive toxicity data (MRID 421783-13) demonstrated a systemic NOEL of 1,000 ppm (87 mg/kg/day, males, 96 mg/kg/day, females) and LOEL of 5,000 ppm (453 mg/kg/day, males, 498 mg/kg/day, females), based on decreased body weight, body weight gain, and food consumption in both sexes of rats, increased liver weights in the F1 males and females, and histopathological changes in the liver and kidney of F1 males. The reproductive NOEL was 5,000 ppm (highest dose tested). This study was classified core-Minimum, and meets Guideline requirements for reproductive toxicity.

Developmental toxicity in the rabbit (MRID No. 421783-11) indicated that the developmental NOEL was > 1,000 mg/kg/day; however, only 4 litters were available for evaluation at that dose level. The maternal NOEL/LOEL was 100/300 mg/kg/day, based on premature delivery or abortions, soft stools, emaciation, lusterless fur, decreased activity, and bradypnea. At 1,000 mg/kg/day, there were increased premature births or abortions. This study was coregraded Supplementary/upgradeable, pending receipt of summary data for gravid uterine weights, total resorptions, separation of early and late resorptions from stillbirths, and litter incidence of malformations/variations. A developmental toxicity study in rats (MRID No. 421783-12) demonstrated a developmental NOEL/LOEL of 100/300 mg/kg/day, based on increased incidence of skeletal variations (opening of foramen transversarium of the 7th cervical vertebrae); a maternal NOEL/LOEL of 100/300 mg/kg/day, based on decreased body weight, body weight gain, and food consumption; and a postnatal developmental toxicity NOEL/LOEL of 300/1,000 mg/kg/day, based on increased incidence of visceral and skeletal variations.

Mutagenicity was tested in a Salmonella typhimurium/ Escherichia coli/mammalian microsome preincubation reverse mutation assay (MRID No. 421783-15); a gene mutation study in cultured Chinese Hamster V79 cells (MRID No. 421783-16); and unscheduled DNA synthesis assay in mammalian (HeLa) cells (MRID No. 421783-17); and an in vitro chromosome aberration in chinese hamster ovary cells (MRID No. 413217-22). Sumilarv was not mutagenic in any of these studies, with or without metabolic (S-9) activation. These studies are acceptable for fulfilling Subdivision F Guideline requirements for mutagenicity testing.

Data Evaluation Reports (DERs) of the individual studies, and a Toxicology Profile (conclusions of the DERs) of the chemical are attached for your reference.

Toxicology Data Base:

a. Acute Toxicity: **MRID Nos. 421783-02 through 421783-06, 423432-05**

The following table summarizes the acute toxicity studies for technical Sumilarv. The studies are acceptable for labeling purposes, under Subdivision F Guidelines series 81-1 through 81-6.

ACUTE TOXICITY VALUES

TEST	RESULT (mg/kg)	CATEGORY
Oral LD_{50}	> 5,000	IV
Inhalation LC_{50}	> 1.3	III
Dermal LD_{50}	> 2,000	III
Eye Effects	Mild Irritant	IV
Skin Effects (81-5, 81-6)	Nonirritant, Not a dermal sensitizer	IV

b. Subchronic Toxicity

1. Subacute Inhalation Toxicity in Rats: **MRID No. 421783-08.**

A 28-day inhalation study was conducted in rats in which the test material was administered at 269, 482 and 1,000 mg/m^3. The NOEL was 482 mg/m^3, and the LOEL was 1,000 mg/m^3, based on salivation in 3 males and 4 females during the first few days of exposure, body weight decrease in males throughout the study, and elevated serum lactate dehydrogenase (44%) in males. The study was classified as supplementary under Subdivision F Guidelines series 82-4, but not upgradeable, due to lack of characterization of stability of the test material, inadequate characterization of the exposure atmospheres, and the inhalation equipment did not provide an adequate dynamic air flow rate.

2. Subchronic Oral Toxicity in Rats: **MRID No. 413217-16.**

A 90-day feeding study was conducted in Crl:CDBR rats at doses of 0, 400 ppm (equivalent to a mean of 23.49 mg/kg/day for males (♂), and 27.68 mg/kg/day, females (♀)), 2,000 ppm (117.79 mg/kg/d ♂, and 141.28 mg/kg/d ♀), 5,000 ppm (309.05 mg/kg/d ♂, 356.30 mg/kg/d ♀), and 10,000 ppm (641.81 mg/kg/d ♂, 783.96 mg/kg/d ♀). The NOEL for systemic toxicity in rats of either sex was 400 ppm, and the LOEL was 2,000 ppm, based on higher mean

body weight gain, and food consumption. At 1,000 mg/kg/day, increased mortality and clinical signs were also observed.

Developmental NOEL/LOEL was 100/300 mg/kg/day, based on increased incidence of skeletal variations (opening of foramen transversarium of the 7th cervical vertebrae).

The postnatal developmental toxicity NOEL/LOEL 300/1,000 mg/kg/day, based on increased incidence of visceral and skeletal variations at 1,000 mg/kg/day.

This study meets the "Minimum" requirements for Subdivision F Guidelines for developmental toxicity (series 83-3a).

h. Mutagenicity

1. Reverse Mutation Assay - Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100, and E. coli WP2 uvrA/Mammalian Microsome Preincubation Mutagenicity Assay; **MRID No. 421783-15.**

Five doses of sumilarv (10, 50, 100, 500, and 1,000 µg/plate) were tested in reverse mutation assays (Ames test) in the above strains. A higher dose (5,000 µg/plate) was insoluble. The assays were performed with and without metabolic activation (S9). There was no evidence of mutagenicity at any dose, with or without S9 activation. This study is acceptable for meeting Guideline gene mutation (series 84-2a) requirements.

2. Gene Mutation in Cultured Chinese Hamster V79 Cells; **MRID No. 421783-16.**

Sumilarv was tested without metabolic activation at 10, 30, 100 and 300 µg/ml, and with S9-activation at 3, 10, 30, and 100 µg/ml for the potential to induce forward gene mutation at the HGPRT locus in Chines Hamster V79 cells. In the nonactivated trials, the 300 µg/ml dose was insoluble, and in the S9-activated trials, the 100 µg/ml dose was cytotoxic. There was no evidence that the test material induced a mutagenic response at any of the doses tested. This study is acceptable for meeting Guideline gene mutation (series 84-2a) requirements.

3. Unscheduled DNA Synthesis Assay in HeLa Cells; **MRID No. 421783-17.**

Sumilarv was tested at 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8, 25.6, 51.2, 102.4, and 204.8 µg/ml with and without metabolic activation (S-9) to evaluate its potential to induce unscheduled DNA synthesis in HeLa cells. The highest dose tested was insoluble, and doses $\geq$ 6.4 µg/ml in the nonactivated trials and $\geq$ 51.2 µg/ml in the S-9-activated trials were

total cholesterol and phospholipids, decreased mean red blood cell, hematocrit and hemoglobin counts, and significantly higher liver-to-body weight ratios at that concentration, in male rats compared with males on the control diet. Female rats did not demonstrate these effects until the 5,000 ppm level of the test substance, however, a negative trend in mean red blood cell volume at the 2,000 ppm concentration of the test substance was observed in the female rat. In addition, both sexes also demonstrated slightly increased hepatocyte cytoplasm and cytoplasm:nucleus ratios, and decreased sinusoidal spaces at the 2,000 ppm concentration of the test substance, but the significance of these observations is unclear. This study was classified "Guideline", indicating it meets the requirements for a subchronic oral toxicity study (rodent) under Subdivision F Guidelines, series 82-1a.

3. Subchronic Oral Toxicity Study in Dogs: **MRID No. 421783-07.**

When S-31183 was administered to male and female beagle dogs at doses of 0, 100, 300 and 1,000 mg/kg for 90 days, the NOEL for systemic toxicity in dogs of either sex was 100 mg/kg/d, and the LOEL was 300 mg/kg/d, based on significantly higher absolute liver weights and liver-to-body weight ratios in the males, and enlargement of hepatocytes observed in females at that concentration, compared with dogs on the control diet. The changes in liver weights, organ-to-body weight ratios, and increase in size observed in the hepatocytes at 300 mg/kg/d are probably not due to hepatotoxicity, however; rather, these changes appear to be adaptations of the liver to detoxifying the test substance, since these changes are observed in both groups at the highest dose tested. This study was classified "Guideline", indicating it meets the requirements for a subchronic oral toxicity study (non-rodent) under Subdivision F Guidelines, series 82-1b.

c. <u>Metabolism</u>: **MRID Nos. 421783-18 and 422014-02**

Sprague-Dawley rats (♂/♀) were given single doses of ^{14}C-labeled sumilarv at 2 or 1,000 mg/kg, or with 14 daily oral doses of unlabeled compound at 2 mg/kg followed by administration of a single oral dose of labeled sumilarv at 2 mg/kg on day 15. There were no significant sex-or dose-related differences in the absorption, distribution, or metabolism of sumilarv in any of the dosing regimens. Most (63-83%) of the dose was eliminated in the urine and feces within 24 hours after dosing, and over the 7-day period following the last dose, most (92-97%) of the test compound administered was excreted in the urine (5-12%) and feces (81-92%). No radioactivity was detected in expired air, and all tissue residues of radioactivity was very low except for fat. Recoveries of the administered doses in the tissues including carcass were not more than 0.3%, indicating that the potential

for bioaccumulation of sumilarv is minimal even after a high dose or repeated, low-dose exposures.

A total of 11 metabolites were detected in the urine; two of these (4'-OH-31183 sulfate and 4'-OH-POP sulfate) were identified. In the feces, unmetabolized Sumilarv (7-37% of the dose) and up to 17 metabolites were detected; 10 of these metabolites (6 unconjugated and 4 sulfate conjugates) were identified. The 4 major fecal metabolites were 4'-OH-31183, 4'-OH-31183 sulfate, 5,4'-OH-31183, and 4'-OH-POPA. The metabolites in the liver, kidney, blood, bile and fat were also examined. Based on the metabolites identified by TLC, the major biotransformation reactions of sumilarv included oxidation at the 4'-position of the terminal phenyl group, oxidation at the 5'-position of pyridine, cleavage of the ether linkage, and conjugation of the resultant phenols with sulfuric acid.

This study was classified as "Core-acceptable", for registration purposes under series 85-1.

d. Chronic Toxicity: **MRID No. 421783-09.**

When sumilarv was administered to beagle dogs of both sexes for approximately one year, the NOEL was 100 mg/kg/day, and the LOEL was 300 mg/kg/day, based on statistically and biologically significant decreased body weight gain and increased relative liver weights in both sexes.

Males receiving 300 mg/kg/day exhibited significantly increased cholesterol levels throughout the study and increased triglycerides at week 50. Mild anemia was also present in males at this dose, characterized by significant decreases in hemoglobin and red cell counts when compared with controls.

At 1,000 mg/kg/day, death (attributed to hepatic failure) was reported in two out of four males. In the remaining males, there was a significant increase in prothrombin time. Decreased body weight gain, increased relative and absolute liver weights, increased hepatic enzyme levels, and gross and microscopic hepatic lesions were reported for both sexes at the high dose level. This study was classified "Guideline" for registration purposes under series 83-1b.

e. Carcinogenicity

1. Mouse Study: **MRID No. 421783-10.**

Technical Sumilarv was incorporated in the diets of mice at levels of 0, 120, 600 and 3,000 ppm, corresponding to dietary consumptions of approximately 0, 22, 90, and 410 mg/kg/day. Fifty animals per sex per group were maintained on this diet for 78 weeks. An interim sacrifice (10/sex/group) was carried out

after week 52.

The systemic NOEL could not be determined, because it appeared that an MTD was not reached, since there were no signs of systemic toxicity, including body weight and body weight gain increments. No neoplastic findings relatable to Sumilarv were reported. This study was classified "Supplementary, but not upgradeable" for registration purposes under series 83-1a and 83-2, and it is recommended that the study be repeated at higher dietary dose levels.

2. Rat Chronic Feeding and Oncogenicity Study: **MRID No. 421783-14.**

Sumilarv was administered to Sprague-Dawley rats (CRL:CD BR) at 0, 120, 600, and 3,000 ppm in the diet. Dose levels were determined to be 5.42, 27.31, and 138 mg/kg/day in males, and 7.04, 35.1, and 182.7 mg/kg/day for females, based on food-consumption data. This study was classified "Supplementary/ upgradeable" under series 83-1a and 83-2, because a NOEL for both chronic toxicity and carcinogenicity was not established, as the following additional information is required:

a) Dosing Rationale: The dose levels used in the study were inadequate for oncogenic assessment. No dosing rationale was presented, and the 90-day rat study (MRID No. 413217-16, discussed above under Subchronic Toxicity) suggests that higher dose levels could have been tolerated.

b) Organ weights for only 10 animals per sex were reported, and this plus body weight is required for all high dose and control animals, and any other animals that exhibited significant effects.

c) Data from the satellite and main study should be combined and reported for all appropriate end points where data are available.

d) Gross and histopathological data must be provided by the testing facility which combine appropriate data sets (e.g., moribund and terminal sacrifice data).

e) The biological significance potential effects of Sumilarv on the hematopoietic system (increased levels of acanthocytes and echinocytes) should be assessed and reported.

f. <u>Reproductive Toxicity</u>: **MRID No. 421783-13.**

Crl:CD (SD) BR rats were given dietary levels of sumilarv at 0, 200, 1,000, or 5,000 ppm (approximately 0, 18, 87, and 453 mg/kg/day for males, 0, 20, 96, and 498 mg/kg/day for females) during the premating period. The systemic NOEL was 1,000 ppm,

and systemic LOEL was 5,000 ppm, based on decreased body weight, body weight gain, and food consumption in both sexes and generations, increased liver weights in F_1 males and females, and histopathological changes in the liver and kidney or F_1 males.

The reproductive NOEL was 5,000 ppm (HDT). This study was classified "Core-Minimum" in satisfying the Subdivision F Guideline requirements under series 83-4.

g. Developmental Toxicity

1. Rabbit Study: **MRID No. 421783-11.**

SUMILARV was administered to pregnant JW-NIBS rabbits on days 6-18 of gestation, and the dams received doses of 0, 100, 300 and 1,000 mg/kg/day. The developmental NOEL was > 1,000 mg/kg/day; however, there were only 4 litters available for evaluation at this dose level.

The maternal NOEL was 100 mg/kg/d; the maternal LOEL was 300 mg/kg/day, based on the occurrence of premature delivery or abortions, soft stools, emaciation, lusterless fur, decreased activity and bradypnea or deep breathing. At 1,000 mg/kg/d, the number of premature births or abortions increased, as did the frequency and number of animals with the clinical symptoms that were reported at the 300 mg/kg dose. It appeared that the compound had dose-related effects on food consumption and weight gain during the dosing period; by the end of gestation, there was no difference in food consumption or body weight gain among the groups.

Upon gross examination, some hemorrhaging in the stomach, cecum, and colon, and retention of gas and a viscous material in the cecum were observed. There were several incidences of distended gallbladders and changes in bile and liver appearance in the high-dose group, which indicated the compound had an effect on the liver, perhaps due to its indigestibility.

This study was classified "Supplementary/upgradeable" under series 83-3b, pending receipt of summary data which provides gravid uterine weights, information on totally resorbed litters, data which separates early/later resorptions from stillbirths, and summary data for litter incidence of malformations/variations.

2. Rat Study: **MRID No. 421783-12.**

The effects of sumilarv on prenatal and postnatal development were assessed in Sprague-Dawley rats by administering the test substance via gavage at 0, 100, 300, or 1,000 mg/kg/day during gestation days 7-17. Maternal NOEL was 100 mg/kg/day; maternal LOEL was 300 mg/kg/day, based on decreased body weight,

cytotoxic; however, there was no evidence that sumilarv is genotoxic. This study is acceptable for meeting Guideline requirements under series 84-2c.

4. In vitro Chromosome Aberration in Chinese Hamster Ovary (CHO) Cells; **MRID No. 413217-22.**

Sumilarv was tested at nonactivated doses of 10, 30, and 100 μg/mL and S9-activated doses of 30, 100, and 300 μg/mL, for its potential to induce chromosome aberrations in Chinese Hamster Ovary cells. Owing to severe cell-cycle delay, cultures were harvested 18 or 24 hours after exposure to the test material, with and without S9 activation. Results indicated that Sumilarv was not clastogenic under the conditions of the study. This study is acceptable for meeting Guideline mutagenicity requirements under series 84-2b.