CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA

Pyriproxyfen

Chemical Code # 4019**, Document Processing Number (DPN)** 52080
SB 950 # NA
2/16/16
Revised: 9/9/16, 9/26/16

DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect
Developmental toxicity, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 290343 (Document No. 52080-0327) were examined. This includes all relevant studies indexed by DPR as of 9/26/16.

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T160926
Revised by T. Moore, 9/26/16

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

027; 141691-2; "Sumilarv -- Metabolism of S-31183 in Rats" (A. Yoshitake, Sumitomo Chemical Co.,Ltd., Takarazuka Research Center, Hyogo, Japan, Study #s 807, and 809-811, 4/14/88). 5 Spraque-Dawley rats/sex were given a single oral dose of [phenoxyphenyl-14C]S-31183 (Lot # C-86-92, 58.2 mCi/mmol) at 2 mg/kg or at 1000 mg/kg (diluted with unlabeled S-31183 (99% purity) to adjust the S.A. to 0.116 mCi/mmol). Also 5 rats/sex were pretreated with unlabeled S-31183 daily at 2 mg/kg for 14 days prior to pulsing with a single dose of 14C labeled S-31183. No significant difference in excretion was noted between sexes, dosage level and dosing regimen. 80-90% and 5-12% of the total dose was excreted in the feces and urine, respectively, within 7 days. By 48 hours, 87.9-95.8% of the dose was eliminated. Fecal excretion of the unmetabolized S-31183 ranged from 6.5-11.4% of the dose for the multiple dose group and 25.1-37.2% for the low and high dose groups. The major metabolite in feces (4-OH-31183; 24.5-54.4% of the dose) was formed by oxidation at the 4'-position of the terminal phenyl group. Each of the other metabolites resulting from oxidation at the 5'-position of pyridine, cleavage of the ether linkage and conjugation of the resultant phenols with sulfuric acid, accounted for less than 9% of the administered dose. **acceptable**. (Leung, 5/20/96)

52080-0072; 147751; “Metabolism of [Pyridyl-2,6-^{14}C] Pyriproxyfen in Rats”; (H. Yoshino; Environmental Health Science Laboratory, Sumitomo, Chemical Co., Ltd., Konohana-Ku, Osaka, Japan; Study No. 2590; 9/2/93); Five Sprague-Dawley rats/sex were dosed orally by gavage with 2 or 1000 mg/kg of [Pyridyl-2,6-^{14}C]Pyriproxyfen (lot no. C-92-001A, specific activity: 115 mCi/mmol, radiochemical purity: >99%, chemical purity: >99%) and urine and fecal samples were collected for 7 days. Expired air was recovered up to 2 days post-dose. The feces were the predominant route of excretion with 85 to 93% of the administered dose being recovered via that route. Only 6 to 12% of the radiolabel was recovered in the urine. Only a fraction of one percent of the administered dose was captured in the expired air over the 1st 48 hours post-dose. Fifty four to 70% of the administered dose was excreted within the 1st 24 hours. There were no apparent dose-related or sex-related differences in the profile. The residual radiolabel in the animals at 7 days after treatment was largely isolated in the liver, kidneys, fat and blood. The identifiable metabolites revealed the following metabolic reactions: 1) hydroxylation of the phenolic and/or pyridyl rings and 2) further conjugation with sulfate or glucuronide. Hydroylsis of either of the ether linkages in the structure of the test material did not constitute a major pathway of metabolism. No biliary excretion study was performed in an effort to characterize the absorption of the test material. In addition, no pharmacokinetic parameters

were assessed with a time course collection of blood samples. **Study supplemental**. (Moore, 2/26/16)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

012; 141604; "Acute Oral Toxicity Study of S-31183 in Rats Amendment to the Final Report" (Misaki, Y. et. al., Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Company, Hyogo, Japan, Laboratory Project ID No. NNT-70-0005, 3/5/93); 811; Sumilarv Technical Grade (Lot No. PTG-86011, 97.2% purity) was administered in corn oil by gavage to 5 rats/sex/dose with doses of 1000, 2500, and 5000 mg/kg. No test animals died. No toxic signs were observed at the 1000 mg/kg level. At the 2500 mg/kg level, a decrease in spontaneous activity was observed in 1 male that cleared by day 1. At the 5000 mg/kg level, decrease in spontaneous activity (in 4 males and in 2 females) and soft stool and diarrhea (in 5 males and 4 females) were observed with signs clearing in all by day 2. Necropsy revealed no treatment-related gross abnormalities. $LD_{\leftarrow\leftarrow}$ (M/F)> 5000 mg/kg. NOEL (M)=1000 mg/kg (based on absence of clinical signs), NOEL (F)=2500 mg/kg (based on absence of clinical signs). Toxicity Category IV. **Acceptable.** (Corlett, 2/26/96)

Acute dermal toxicity

012; 141605; "Acute Dermal Toxicity Study of S-31183 in Rats Amendment to the Final Report" (Misaki, Y. et. al., Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Company, Hyogo, Japan, Laboratory Project ID No. NNT-70-0006, 3/5/93); 812; Sumilarv Technical Grade (Lot No. PTG-86011, 97.2% purity), suspended in corn oil, was applied to the sheared skin of 5 rats/sex/dose with 1 dose of 2000 mg/kg for 24 hours, covered. No test animals died. No clinical signs were observed. Necropsy revealed no treatment-related gross abnormalities. $LD_{\leftarrow\leftarrow}$ (M/F)> 2000 mg/kg. Toxicity Category III. **Acceptable.** (Corlett, 2/26/96)

Acute inhalation toxicity, rat

012, 102; 141606, 141607, 141608, 147862; "Acute Inhalation Toxicity Study of S-31183 in Rats Amendment to the Final Report" (Kawaguchi, S. et. al., Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Company, Hyogo, Japan, Laboratory Project ID No. NNT-70-0022, 1/29/93); 813; Sumilarv Technical Grade (Lot No. PTG-86011, 97.2% purity) was administered in corn oil by the inhalation route to 5 rats/sex/ dose with doses (reported analytical concentrations) of 0.600 (25% w/v solution) and 1.300 (50% w/v solution) mg/l with median aerodynamic diameters of 0.86 and 0.75 mm, respectively. All animals were exposed for 4 hours. No test animals died. No toxic signs were observed in the 0.600 mg/l dose group. In the 1.300 mg/l dose group, salivation (in 2/5 males and in 1/5 females) and urinary incontinence (in 2/5 females) were observed with signs clearing in all within 1 day. Necropsy revealed no treatment-related abnormalities. Study originally reviewed as unacceptable/supplemental, but upgraded to **acceptable** after subsequent reviewed with submission of data and calculations used to determine the analytical concentrations. $LC_{\leftarrow\leftarrow}$(M/F) = 1.300 mg/l, Toxicity Category III; (Corlett, 2/27/96, upgraded, Moore, 6/21/96).

Primary eye irritation, rabbit

012; 141610; "Primary **Eye** and Skin Irritation Tests with S-31183 in Rabbits" (Suzuki, T., Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Company, Hyogo, Japan, Laboratory Project ID No. NNT-70-0004 (MRID 413217-14), 1/27/87); 814; 100 mg of Sumilarv Technical Grade (Lot No. PTG-86011, 97.2% purity) was administered to one eye of each of 6 New Zealand White rabbits. No corneal opacity or iritis was observed in any treated eye. Grade 1 conjunctival irritation (redness and/or chemosis) was observed in 2

animals 24 hours after treatment clearing in both 48 hours after treatment. Toxicity Category IV. **Acceptable.** (Corlett, 2/27/96)

Primary dermal irritation

012; 141610; "Primary Eye and **Skin** Irritation Tests with S-31183 in Rabbits" (Suzuki, T., Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Company, Hyogo, Japan, Laboratory Project ID No. NNT-70-0004 (MRID 413217-14), 1/27/87); 815; 500 mg of Sumilarv Technical Grade (Lot No. PTG-86011, 97.2% purity), moistened with a small amount of physiological saline, was applied for 4 hours to the clipped skin of each of 6 New Zealand White rabbits. No erythema or edema was observed in any test animal at any time during a 72 hour observation period following application. Toxicity Category IV. **Acceptable.** (Corlett, 2/27/96)

Dermal sensitization

52080-0012; 141612; The Worker Health and Safety Branch has reviewed the dermal sensitization and determined that S-31183 (Sumilarv Technical) is not a dermal sensitizer as assessed by the Guinea Pig Maximization Assay.

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

** 013; 141613; "Subchronic Toxicity Study with S-31183 in Rats", (R.H. Cox; Hazleton Laboratories America, Inc., Vienna, VA; Study No. HLA 343-208; 3/8/89); Sumilarv Technical Grade (S-31183) (purity: 95.3%) was administered in the diet to 10 rats/sex/group at doses of 0, 400, 2000, 5000, or 10000 ppm (males-0, 23.5, 118, 309, 642 mg/kg/day, females-0, 27.7, 141, 356, 784 mg/kg/day) for 13 weeks. No treatment-related mortalities occurred. Body weight gain was reduced in the two higher treatment groups. The target tissue was the liver. Total cholesterol and phosphoslipid levels were elevated for the males in the 2000 ppm and higher treatment groups. Mean liver weights were greater for both sexes in the two higher dosing groups. An increased incidence of cytoplasmic changes in the liver were noted in the 2000 ppm and higher treatment groups. **No adverse effects** indicated. **NOEL (M/F):** 400 ppm (based upon the increased incidence of cytoplasmic changes in the liver of the 2000 ppm and higher treatment groups); **Study acceptable.** (Moore, 4/25/96)

Dog Subchronic Oral Toxicity Study

** 015; 141617; "Sumilarv--Three Month Oral Toxicity Study of S-31183 in Dogs", (M. Nakano; Sumitomo Chemical Co., Ltd, Osaka, Japan; Study No. 220; 5/6/88); Sumilarv Technical Grade (S-31183) (purity: 97.2%) was administered in capsules to 4 dogs/sex/group at doses of 0, 100, 300, or 1000 mg/kg/day for 13 weeks. No treatment-related mortalities occurred. Body weight gain was not affected by treatment. The target tissue was the liver. Hepatocellular enlargement was noted in the higest dose for both males and females and for females in the 300 mg/kg/day treatment group. An increase in endoplasmic reticulum in the livers of the high dose group was indicated by electron microscopy. **No adverse effects** were indicated. **NOEL (M):** 300 mg/kg/day (based on increase in smooth endoplasmic reticulum and the presence of heptocellular enlargement in the liver of the 1000 mg/kg/day treament group); **NOEL (F):** 100 mg/kg/day (based on the presence of hepatocellular enlargement in the 300 and 1000 mg/kg/day treatment groups); **NOAEL (M/F):** 1000 mg/kg/day. **Study acceptable.** (Moore, 4/25/96)

Mouse Subchronic Dietary Toxicity Study

** 014; 141615; "Sumilarv - Subchronic Toxicity Study in Mice", (R.H. Cox; Hazleton Laboratories America, Inc., Vienna, VA; Study No. HLA 343-209; 1/23/90); Sumilarv Technical Grade (S-31183) (purity: 95.3%) was administered in the diet to 10 mice/sex/group at doses of 0, 200, 1000, 5000, or 10000 ppm (males-0, 28.2, 149, 838, 2,035 mg/kg/day, females-0, 37.9, 197, 964, 2,345 mg/kg/day) for 13 weeks. Six males and 9 females in the high dose group and 2 males died in the 5000 ppm treatment group. Body weight gain was reduced in these two groups. The target tissue was the kidney. Histopathology exam revealed tubular nephrosis, dilatation of the pelvis and microconcretion of tubules in mice treated at doses ≥ 5000 ppm. Blood urea nitrogen was elevated in the two highest treatment groups. Likewise, an increased incidence of renal lesions were noted in these two groups. **No adverse effect** indicated; **NOEL (M/F):** 1000 ppm (based upon death, reduced body weight gain and renal lesions in the 5000 and 10000 ppm treatment groups); **Study acceptable.** (Moore, 4/24/96)

Rat Repeated Dosing 21-Day Dermal Toxicity Study

** 016; 141619; "Sumilarv--21-Day Dermal Toxicity Study in Rats with S-31183", (M.R. Moore; Hazleton Laboratories America, Inc., Vienna, VA; Study No. HWA 343-244; 1/11/93; Sumilarv Technical Grade (S-31183) (purity: 97.2%) was administered dermally to 5 rats/sex/group at doses of 0, 100, 300, or 1000 mg/kg/day (6 hour exposures) for 21 days. No treatment-related effects were noted. **No adverse effects** evident. **NOEL (M/F):** 1000 mg/kg/day; **Study acceptable.** (Moore, 4/26/96)

Rat 28-Day Inhalation Toxicity Study

017, 102; 141621, 141623, 147862; "Sumilarv--Subacute Inhalation Toxicity Study of S-31183 in Rats", (S. Kawaguchi; Sumitomo Chemical Co., Ltd., Osaka Japan; Study No. 728; 4/14/88); Ten rats/sex/group were exposed to Sumilarv Technical Grade (S-31183) at reported concentrations of 0 (vehicle control-corn oil), 0 (air control), 269, 482, or 1000 mg/m3 for 4 hours per day for 28 consecutive days. The mean MMAD (GSD) were 0.84 (1.41) mm for 269, 0.84 (1.38) mm for 482, and 0.71 (1.29) for 1000 mg/m3. No treatment-related mortality occurred. The only apparent treatment-related sign of toxicity was salivation which was noted in the high exposure group during the first week of exposure. No treatment-related effects were noted for body weight gain, ophthalmology, urinalysis, hematology or clinical chemistry. No treatment-related lesions were noted. **NOEL (M/F):** 482 mg/m3 (based on salivation); **no adverse effects**; **acceptable**; (Moore, 4/26/96)

CHRONIC STUDIES

Chronic, rat

** 024, 025; 141657-9; "Sumilarv: Combined Chronic Toxicity and Oncogenicity Study in Rats with S-31183" (M.R. Osheroff, Hazleton Washington, Inc., Vienna, VA, Lab. Project ID # HWA 343-214, 9/6/91). S-31183 (Lot # PYG 87074, 95.3% purity) administered to 80 Sprague-Dawley rats/sex/dose in the diet at 0, 120, 600 or 3000 ppm for 104 weeks (0, 5.42, 27.31 and 138.0 mg/kg/day for males, respectively, and 0, 7.04, 35.10, and 182.7 mg/kg/day for females, respectively). Of the 80 rats/sex/dose, 50 were assigned to the main study and the remaining 30 were assigned to the satellite study (interim sacrifices). No treatment-related effects on survival, clinical signs, gross necropsy findings, ophthalmological or histopathological changes were noted throughout the study. However, mean body weight was significantly reduced in high dose males at weeks 13, 26, and 50 (92.7 - 95.3% of control, $p < 0.05$) and females at weeks 13, 26, 50 and 78 (86.1 - 88.1% of control, $p < 0.05$) without any consistent changes in food consumption. Although mid- and high-dose males at week 26 and all treated males at weeks 52 and 78 showed significantly elevated serum alkaline phosphatase, its toxicological significance

is questionable based on the relatively small magnitude of change and is within historical control values (45-114 u/l). Increased incidences of liver necrosis were detected in high dose male unscheduled deaths as compared to control males (0/22 vs. 8/23, $p < 0.01$) and is generally secondary to some other cause of death and not treatment-related since no incidence of liver necrosis was noted among high dose males killed at study termination. **no adverse effects** [NOAEL (M/F) = 3000 ppm]. NOEL (M/F) = 600 ppm (M: 27.31 mg/kg/day, F: 35.10 mg/kg/day, based on reduced mean body weight). no evidence of oncogenic potential. **Acceptable**. (Leung, 5/9/96)

Chronic, dog

**** 018; 141628;** "S-31183 Toxicity Study by Oral (Capsule) Administration to Beagle Dogs for 52 Weeks" (E.A. Chapman, Life Science Research Limited, Suffolk, UK, LSR Report 91/0776, 8/1/91). S-31183 (Lot PYG-87074, 94.9% purity) administered to 4 Beagle dogs/sex/dose in gelatin capsules at 0, 30, 100, 300, or 1000 mg/kg/day for 52 weeks. **Possible adverse effects:** Two males at 1000 mg/kg/day with evidence for hepatotoxicity were killed in extremis , one during week 17 and the other during week 31. Increased incidences of salivation, emesis, diarrhea and thin appearance were noted in dogs from the two highest doses. Throughout the treatment period, elevated plasma levels of alkaline phosphatase were detected in dogs receiving 300 and 1000 mg/kg/day and occasionally in dogs receiving 100 mg/kg/day. Gross necropsy revealed enlarged liver (increased mean absolute and relative liver weights) in dogs treated with doses $\geq$ 100 mg/kg/day. Hepatic damage was seen in the two early decedent males and in all but one of the dogs at the highest dose level. Hepatotoxicity was more marked in males than in females and was characterized by centriacinar fibrosis and bile duct hyperplasia. NOEL (M/F) = 30 mg/kg/day (based on increased mean liver weight); NOAEL (M/F) = 100 mg/kg/day (based on evidence of hepatotoxicity); **acceptable**; (Leung, 5/14/96).

Oncogenicity, rat

See Chronic Rat above.

Oncogenicity, mouse

** 019, 020; 141635, 141636, 141640, 141642; "Sumilarv - Oncogenicity Study in Mice with S-31183" (M.R. Osheroff, Hazleton Laboratories America, Inc., Vienna, VA, HLA Study # 343-215, 7/23/91). S-31183 (Lot # PYG-87074, 95.3% purity) administered to 60 CD-1 mice/sex/dose in the diet at 0, 120, 600, or 3000 pm for 78 weeks (0, 16.83, 87.97, and 419.83 mg/kg/day for males, respectively, and 0, 19.56, 101.41, and 476.51 mg/kg/day for females, respectively. Survival rate was reduced in mid (28% vs. 57%, $p < 0.01$) and high (18% vs. 57%, $p < 0.01$) dose males and high dose (36% vs. 61%, $p < 0.01$) females. Hunched appearance and reduced motor activity were noted in high dose mice. Their mean body weights were reduced at weeks 13, 24, and 52 for males and week 76 for females with comparable food consumption between control and treated mice. Histopathological examination of tissue sections revealed increased incidences/severity of chronic progressive nephropathy in high dose mice. **possible adverse effect**: Increased deposition of amyloid, especially in the kidney, appears to be responsible for the decreased survival rate. Increased incidences of amyloidosis were also evident in the adrenal cortex, thyroid (with parathyroid), heart, liver, glandular stomach, duodenum, jejunum, and ileum. NOAEL = NOEL (M) = 120 ppm (16.83 mg/kg/day) and (F) = 600 ppm (101.41 mg/kg/day): based on reduced survival rate, abnormal renal histopathology associated with systemic amyloidosis). no evidence of oncogenic potential). **Acceptable**. (Leung, 5/10/96).

GENOTOXICITY

Gene mutation

** 026; 141686; "Sumilarv--Reverse Mutation Test of S-31183 in Bacterial Systems", (S. Kogiso; Sumitomo Chemical Co., Ltd., Osaka Japan; Study No. 153; 4/23/88); ~7S. typhimurium~1 and ~7E. coli~1 strains were exposed to Sumilarv Technical Grade (S-31183) (purity: 97.2%) at concentrations ranging from 0 to 5000 mg/plate for 65 hours at 37°C under conditions of non-activation and activation (rat liver S-9 fraction induced with Kanechlor-400). Two trials were performed with duplicate plates for each concentration. No treatment-related increase in revertant colonies was noted. **No adverse effect** indicated. **Study acceptable.** (Moore, 4/29/96)

** 026; 141687; "Sumilarv--~7In Vitro~1 Gene Mutation Test of S-31183 in V79 Chinese Hamster Cells"; (S. Kogiso; Sumitomo Chemical Co., Ltd., Osaka Japan; Study No. 2087; 4/26/90); Chinese hamster cells, strain V79, were exposed to Sumilarv Technical Grade (S-31183) (purity: 95.3%) at concentrations ranging from 0 to 300 mg/ml, non-activated, or 0 to 100 mg/ml, activated with rat liver S-9 fraction induced with Kanechlor-400, for 5 hours at 37°C. Two trials were performed with ten plates for each concentration. No treatment-related increase in the mutation frequency was noted. **No adverse effect** indicated. **Study acceptable.** (Moore, 4/29/96)

Chromosome damage

** 026; 141688; "Sumilarv--~7In Vitro~1 Chromosomal Aberration Test of Pyriproxyfen in Chinese Hamster Ovary Cells (CHO-K1)"; (S. Kogiso; Sumitomo Chemical Co., Ltd., Osaka Japan; Study No. 1796; 6/27/89); Chinese hamster ovary cells were exposed to Sumilarv Technical Grade (S-31183) (purity: 97.2%) at 37 C at concentrations ranging from 0 to 100 mg/ml, non-activated, or 0 to 300 mg/ml, activated with rat liver S9 fraction induced with Kanechlor-400. Duplicate plates were cultured for each treatment level and two time points were assayed, 18 and 24 hours of treatment for non-activated samples and 2 hours of treatment followed by 16 or 22 hours of incubation in fresh medium for the activated samples. One hundred cells were examined for chromosomal aberrations/plate at each treatment level (200 cells total) for both time points. No treatment-related increase in chromosomal aberrations was evident. **No adverse effects** indicated. **Study acceptable.** (Moore, 5/2/96)

DNA damage or miscellaneous effects

** 026; 141689; "Sumilarv--Assessment of Unscheduled DNA Repair Synthesis in Mammalian Cells after Exposure to S-31183"; (L.M. Henderson and R.J. Proudlock; Huntingdon Research Center Ltd., Huntingdon, Cambridgeshire, England; Study No. SMO 298/88453; 6/29/88); Hela S3 cells were exposed to Sumilarv Technical Grade (S-31183) (purity: 95.3%) at concentrations ranging from 0 to 204.8 mg/ml for 3 hours at 37 C under conditions of non-activation and activation. Activation was mediated by S9 fraction isolated from Arochlor 1254 induced rat liver. Duplicate cultures were prepared for each treatment level in two trials. Unscheduled DNA synthesis was quantified by counting the number of grains in the nuclei and a corresponding area of cytoplasm of 100 cells/culture. No apparent increase in unscheduled DNA synthesis due to treatment was noted. **No adverse effect** indicated. **Study acceptable.** (Moore, 5/3/96)

REPRODUCTIVE TOXICITY, RAT

** 023; 141656; "A Dietary 2-Generation (1 Litter) Reproduction Study of S-31183 in the Rat", (K. Robinson, ~7et. al.~1; Bio-Research Laboratories Ltd., Senneville, Quebec, Canada; Project No. 83963; 9/23/91); Sumilarv Technical Grade (S-31183) (purity: 95.3%) was administered in the diet of 26 rats/sex/group for 10 weeks prior to mating and during mating, gestation and

lactation periods of the F0 generation, and for 12 weeks prior to mating and during mating, gestation and lactation periods of the F1 generation at treatment levels of 0, 200, 1000 or 5000 ppm. No treament-related mortality resulted. In the parental animals, the relative liver weights were increased in the 1000 and 5000 ppm treated males and in the 5000 ppm treated females of the F1 generation. Increased relative kidney weight in the 5000 ppm males of the F1 generation was accompanied by an increased incidence and severity of chronic interstitial nephritis. Body weight gain was reduced in the 5000 ppm treated animals. There were no treatment-related effects upon any of the reproductive parameters. However, pups in the 5000 ppm treatment groups of both generations exhibited reduced body weight gain during the lactation period. **No adverse effects** were indicated. **Parental NOEL:** 200 ppm (based upon increased relative liver weights for animals in the 1000 and 5000 ppm treatment groups); **Reproductive NOEL:** 5000 ppm; **Developmental NOEL:** 1000 ppm (reduced body weight gain for pups in 5000 ppm treatment group). **Study acceptable.** (Moore, 5/13/96)

DEVELOPMENTAL TOXICITY

Rat

** 021; 141648; "Sumilarv-Study of S31183 by Oral Administration during the Period of Fetal Organogenesis in Rats", (Saegusa, T; Sumitomo Chemical Co., Ltd., Osaka, Japan; Study No. 302-2358; 3/28/88); Sumilarv Technical Grade (S-31183) (purity: 97.2%) was administered by gavage to 36 to 47 females/group at doses of 0, 100, 300 or 1000 mg/kg/day from day 7 to day 17 of gestation. (Note: only 23 females at the three lower doses and 32 females at the highest dose were included in the teratogenicity portion of the study). Twelve of the 32 females in the high dose group died prior to completion of the study. An additional two dams had no live births. The dams in the 300 and 1000 mg/kg/day treatment groups demonstrated reduced food consumption and body weight gain. An increase in the percent of postimplantation loss in the high dose group was noted. The only fetal effect that appeared to be treatment-related was a skeletal variation, opening of the foramen transversarium of the 7th cervical vertebra. An increased incidence of this variation was noted in the two higher treatment groups. **No adverse effects** were identified. **Maternal NOEL:** 100 mg/kg/day (based upon reduced body weight gain and food consumption in the 300 and 1000 mg/kg/day treatment groups); **Developmental NOEL:** 100 mg/kg/day (based upon the increased incidence of skeletal variations in the 300 and 1000 mg/kg/day treatment groups); **Developmental NOAEL:** 1000 mg/kg/day; **Study acceptable.** (Moore, 4/23/96)

Rabbit

** 022; 141651, 141655; "Sumilarv-Study of S31183 by Oral Administration during the period of Fetal Organogenesis in Rabbits", (A. Hirohashi; Sumitomo Chemical Co., Ltd., Osaka, Japan; Study No. 376; 8/30/89); Sumilarv Technical Grade (S-31183) (purity: 97.2%) was administered by gavage to 15-18 female rabbits/group at doses of 0, 100, 300, or 1000 mg/kg/day from day 6 through day 18 of gestation. Three of the dams in the high dose group died or were sacrificed ~7in extremis~1. Reduced food consumption was evident in the two higher dose groups with lower body weight gain or body weight loss during the treatment period. Increased incidence of abortion occurred in the two higher dose groups. **No adverse effect indicated. Maternal NOEL:** 100 mg/kg/day (based upon increased number of dams which aborted and reduced food consumption and body weight gain in the 300 and 1000 mg/kg/day treatment groups); **Developmental NOEL:** 1000 mg/kg/day; **Study acceptable.** (Moore, 4/12/96)

NEUROTOXICITY

Acute neurotoxicity, rat

52080-0323; 290338; "A 28-Day Dietary Dose Range-Finding Subchronic Neurotoxicity Study of Pyriproxyfen T.G. in Rats"; (M.T. Herberth; WIL Research Laboratories, LLC, Ashland, OH; Project ID No. WIL-118047; 2/17/11); Five Crl:CD rats/sex/group received 0, 1000, 7500 or 15000 ppm of Pyriproxyfen T.G. (lot no. 080506TG; purity: 99.5%) in the diet for 28 days ((M) 0, 89, 691, 1359 mg/kg/day, (F) 0, 97, 762, 1468 mg/kg/day). No deaths resulted from the treatment. No treatment-related clinical signs were evident. The mean body weight gains of the males in the 7500 and 15000 ppm groups were less than that of the control group during the first week of the treatment ($p<0.01$). The food consumption of these males were likewise reduced over this same time period ($p<0.05$ or 0.01). The FOB did not reveal any treatment-related effect. There was no treatment-related effect noted in the motor activity assessment. The necropsy examination did not reveal any treatment-related lesions. The brain weights were not affected by the treatment. **No adverse effect was indicated. Rat 4-Week Dietary Toxicity NOEL:** (M) 1000 ppm (89 mg/kg/day) (based upon the reduced body weight gain of the males in the 7500 ppm group; (F) 15000 ppm (1468 mg/kg/day) (based upon the lack of treatment-related effect in the 15000 ppm females); **Study Supplemental.** (Moore, 7/22/16)

52080-0324; 290339; "An Oral (Gavage) Dose Range-Finding Acute Neurotoxicity Study of Pyriproxyfen"; (M.T. Herbeth; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-118045; 9/7/10); Three Crl:CD rats/sex/group were dosed orally by gavage with 0 (vehicle: corn oil), 300, 1000 or 2000 mg/kg of Pyriproxyfen T.G. (lot no. 080506G; purity: 99.5%). Detailed observations were performed at 1, 2, 3, 4, 5, 6, 7, and 8 hours post-dose. No treatment-related clinical signs were noted. Based on these results, a maximal treatment level of 2000 mg/kg was selected for the guideline acute neurotoxicity study. Eight hours post-dose was also selected as the time point for performing the initial FOB in the guideline study. **Supplemental Study.** (Moore, 7/22/16)

52080-0325; 290340; "An Oral (Gavage) Acute Neurotoxicity Study of Pyriproxyfen T.G. in Rats"; (M.T. Herberth; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-118046; 3/24/11); Twelve Crl:CD (SD) rats/sex/group were dosed orally by gavage with 0 (vehicle: corn oil), 300, 1000 or 2000 mg/kg of Pyriproxyfen T.G. (lot no. 080506TG; purity: 99.5%). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights over the course of the 14-day observation period. In the home cage observation of the Functional Observation Battery (FOB), the 1000 and 2000 mg/kg females demonstrated an apparent treatment-related effect in their posture and palpebral closure at 8 hours post-dose ($p<0.05$). In the motor activity assessment, the 2000 mg/kg males exhibited reduced total and ambulatory activity at 8 hours post-dosing ($p<0.05$). In the necropsy, there was no treatment-related effect on the brain weights or the dimensions of the brain. There were no treatment-related lesions in the histopathological examination. **No adverse effect** was evident. **Rat Acute Neurotoxicity NOEL:** (M/F) 2000 mg/kg (based upon the lack of neurotoxic effects noted for both sexes in the 2000 mg/kg treatment group). **Study acceptable.** (Moore, 7/25/16)

90-day neurotoxicity, rat

** 52080-0326; 290341; "A 90-Day Oral Dietary Neurotoxicity Study of Pyriproxyfen T.G. in Rats"; (M.T. Herberth; WIL Research Laboratories, LLC, Ashland, OH; Study No. WIL-118048; 9/1/11); Twelve Crl:CD (SD) rats/sex/group received 0, 1500, 5000 or 15000 ppm of Pyriproxyfen T.G. (lot no. 080506TG; purity: 99.5%) in the diet for 13 weeks ((M) 0, 108, 359, 1111 mg/kg/day, (F) 0, 120, 407, 1212 mg/kg/day). No deaths resulted from the treatment. The mean body weights of both sexes in the 15000 ppm group were less than those of the control

group over the course of the study (p<0.01 or 0.05). Likewise the mean food consumption of these animals was less than that of the control group. Although individual parameters demonstrated statistically significant differences between the control and treated groups in the functional observational battery, motor activity assessments, and/or brain dimensions, there was no apparent treatment-related neurotoxic effect. No ocular lesions were noted in the ophthalmological examination. No treatment-related lesions were evident in the microscopic examination of the pertinent nervous tissue. **No adverse effect was evident. Rat Subchronic Neurotoxicity NOEL:** (M/F) 15000 ppm ((M) 1111 mg/kg/day, (F) 1212 mg/kg/day) (based upon the lack of neurotoxic effects noted for both sexes in the 15000 ppm treatment group); **Study acceptable.** (Moore, 7/28/16)

Developmental neurotoxicity, rat

Study is not required at this time.

Delayed neurotoxicity, hen

Study is not required.

IMMUNOTOXICITY

52080-0327; 290342; "Pyriproxyfen: Preliminary 4 Week Dietary Study in the Female CD-1 Mouse"; (M.D. Saunders; Huntingdon Life Sciences, LTD, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Study No. VRY0018; 6/29/11); Two cohorts of four female CD-1 mice/group received 0, 4000 or 7000 ppm of Pyriproxyfen Technical (batch no. 080506G, purity: 99.5%) in the diet for 4 weeks. One cohort was treated with sheep red blood cells on study day 25 and the other was not ((+ sRBC) 0, 848, 1507 mg/kg/day, (-sRBC) 0, 750, 1622 mg/kg/day). No deaths resulted from the treatment. Clinical signs included hunched posture, dull eyes and piloerection. The mean body weight gains of the 7000 ppm group animals in both cohorts were less than the control values over the course of the study (NS, p<0.01). In the clinical chemistry evaluation, the various parameters demonstrated variability which was not necessarily dose-related, particularly when comparing the two cohorts. However, the serum creatinine and blood urea nitrogen levels were elevated at 7000 ppm for both cohorts. In the necropsy, the mean relative liver and kidney weights of the 7000 ppm group in both cohorts were greater than the control values (p<0.05 and NS, respectively). In the macroscopic examination of the organs, the kidneys in the 7000 ppm of the +sRBC cohort were enlarged, pale and/or dilated. **No adverse effect noted. Supplemental Study.** (Moore, 7/29/16)

** 52080-0327; 290343; "Pyriproxyfen: 4 Week Dietary Study in the Female CD-1 Mouse"; (M.D. Saunders; Huntingdon Life Sciences, LTD, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, England; Study No. VRY0024; 11/9/11); Ten female CD1 mice/group received 0, 1000, 2000 or 5000 ppm of Pyriproxyfen technical (batch no. 080506G; purity: 99.5%) in the diet for 4 weeks (0, 228, 449, 1139 mg/kg/day). Another 8 females were dosed orally by gavage with 20 mg/kg/day of cyclophosphamide on study days 22 through 26 as the positive control group. On day 25, five days before necropsy on day 29, each animal received an iv injection of $4x10^8$ sheep red blood cells (SRBC). SRBC specific IgM plaques were determined for each animal by incubating a spleen cell suspension preparation with guinea pig complement and SRBC. No deaths occurred during the treatment period. The mean body weight gain of the 5000 ppm group was less than that of the control group over the course of the treatment (p<0.05). Food consumption was not affected by the treatment. There were no treatment-related lesions noted in the necropsy examination. There was no treatment-related effect on the spleen or thymus weights. The mean absolute and relative liver weights of the 2000 and 5000 ppm groups and the mean relative liver weight of the 1000 ppm group were greater than the

control values (p<0.005 or 0.01). No treatment-related effect was evident in the plaque-forming cell assay. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 8/1/16)

ENDOCRINE DISRUPTOR STUDIES

Studies are not required at this time.

SUPPLEMENTAL STUDIES

Studies are not required at this time.