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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: 21-APR-2009

Subject: **Pyridalyl**: **Revised** Human-Health Risk Assessment for Uses on Cotton, Fruiting Vegetables, Leafy Vegetables, Head & Stem *Brassica* Vegetables, *Brassica* Leafy Greens, and Turnip Greens, Shrubs, Ornamentals and Non-bearing Trees.

PC Code: 295149
Decision No: 305466

Petition Nos.: 2F6459, 3E6592
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D363102
Registration Nos.: 59639-125, 59639-REU, 59639-REO
Regulatory Action: Section 3 Registration
Case No.: NA
CAS No.: 179101-81-6
40 CFR: §180.640

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed and registered uses of pyridalyl [2-[3-[2,6-dichloro-4-[(3,3-dichloro-2-propenyl)oxy]phenoxy]propoxy]-5-(trifluoromethyl)pyridine].

The current assessment is an update in response to data submitted by the registrant, which includes revisions to the proposed tolerance levels and tolerances for indirect/inadvertent residues. The most recent risk assessment for pyridalyl (Memo, M. Clock-Rust, *et al.*, DP#: 301446, 8/26/2004) can be applied to the current action in part. See below for those sections of the last risk assessment which are applicable to the current action.

The risk assessment was provided by Mary Clock-Rust (RAB1), the residue chemistry review and the dietary exposure analysis were provided by George Kramer (RAB1), the hazard

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assessment was provided by Anwar Dunbar and Robert Mitkus (RAB1), and the drinking water assessment was provided by Mark Corbin of the Environmental Fate and Effects Division (EFED). An occupational and residential assessment was not necessary as no new direct uses are proposed.

The most recent human-health risk assessment (2004) was conducted in conjunction with a request for use of pyridalyl on cotton, fruiting vegetables, *Brassica* head and stem vegetables, leafy vegetables, shrubs, ornamentals and non-bearing trees (Memo, M. Clock-Rust, *et al.*, 8/26/04; D301446). HED has reviewed the conclusions and regulatory recommendations made in the last risk assessment and ensured that they are consistent with current HED policy with a few exceptions that are addressed in this risk assessment. The following information from the 8/12/04 risk assessment can be applied directly to this action:

- Ingredient Profile (Sections 2.0);
- Metabolism Assessment (Section 3.0); additional information relevant to the current action is included in this document (Section 3.1);
- Environmental Degradation (Section 3.3);
- Tabular Summary of Metabolites and Degradates (Section 3.4);
- Toxicity Profile of Major Metabolites and Degradates (Section 3.5);
- Summary of Residues of Concern: Tolerance Expression and Risk (Section 3.6);
- Hazard Characterization/Assessment (Section 4.0); see Appendix for relevant toxicity tables;
- Cumulative Risk Assessment (Section 8.0); and
- Occupational Exposure/Risk Pathway (Section 9.0).

This document contains only those aspects of the risk assessment which are affected by the data submitted in support of tolerances on rotational crops associated with uses on cotton, fruiting vegetables, *Brassica* head and stem vegetables, leafy vegetables, shrubs, ornamentals and non-bearing trees.

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1.0 Executive Summary

Background
Pyridalyl is an insecticide for use on cotton, fruiting vegetables, *Brassica* head and stem vegetables, leafy vegetables, shrubs, ornamentals and non-bearing trees. These uses were assessed by HED in 2004 (Memo, M. Clock-Rust, *et al.*, DP#: 301446, 8/26/2004). The current assessment is an update which includes revisions to the proposed tolerance levels and tolerances for indirect/inadvertent residues. No new *direct* uses are proposed in this action.

Hazard Database
The hazard database is complete for the purposes of this risk assessment. However, due to the revision of the CFR Part 158 toxicity data requirements, neurotoxicity and immunotoxicity studies are required. See Section 4.0 of this document for more details.

Food Quality Protection Act (FQPA) Safety Factor (SF) *Considerations*
Based on the hazard data, the Hazard Identification and Review Committee (HIARC) recommended the FQPA SF be reduced to 1x because there are no concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. The pyridalyl risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the FQPA SF be reduced to 1x.

Endpoints for Risk Assessment
Endpoints for risk assessment have been identified for chronic dietary exposure and short- and intermediate-term inhalation exposure (occupational).

chronic dietary	NOAEL = 3.4 mg/kg/day	chronic RfD and cPAD = 0.034 mg/kg/day
short-term and intermediate-term inhalation	oral NOAEL = 2.8 mg/kg/day	Target MOE = 100 (occupational)

An acute dietary risk assessment was not performed since an endpoint of concern attributable to a single exposure was not identified by HIARC from oral toxicity studies including the developmental toxicity studies in rats and rabbits. Short- and intermediate-term dermal endpoints were not identified since the 28-day dermal toxicity study in rats did not produce any signs of dermal or systemic toxicity at 1000 mg/kg/day (limit dose).

Exposure Assessment
This document includes a revised dietary exposure assessment which includes revisions to the proposed tolerance levels, tolerances for indirect/inadvertent residues, and drinking water. No new *direct* uses are proposed in this action. There are no existing or proposed residential uses.

While the dietary exposure assessment has been revised in this document, a new occupational exposure assessment is not necessary (the conclusions for occupational risk from the 2004 risk assessment apply).

The residues of concern for pyridalyl are summarized below:
Primary Crops and Livestock: pyridalyl

Cotton, gin by-products: pyridalyl + S-1812-DP
Rotational Crops: pyridalyl + HTFP & HPDO
Drinking Water: pyridalyl + S-1812-DP & HTFP

Chronic Dietary Exposure Analysis
A chronic aggregate dietary (food and drinking water) exposure and risk assessment was conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03) which use food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The Tier 1 chronic analysis assumed 100% crop-treated (CT), DEEM™ 7.81 default concentration factors, and tolerance-level residues for all commodities. Drinking water was incorporated directly into the dietary assessment using the concentration for ground water generated by the Screening Concentration in Ground Water (SCI-GROW) model. The chronic dietary exposure and risk estimates (food + water) were 0.010980 mg/kg/day for the general U.S. population (32% of the chronic population-adjusted dose (cPAD)) and 0.014534 mg/kg/day (43% of the cPAD) for the most highly-exposed population subgroup (children 1-2 years old) and are thus below HED's level of concern (<100% cPAD).

Aggregate Risk Estimates
A chronic aggregate exposure risk assessment was assessed by incorporating the drinking water directly into the dietary-exposure assessment. As the chronic dietary exposure estimates are not of concern to HED for the general U.S. population or any population subgroup, the chronic aggregate risk is not of concern for these populations. Short-, intermediate-, and long-term aggregate-risk assessments were not performed because there are no registered or proposed uses of pyridalyl which may result in residential exposures. Acute and cancer aggregate-risk assessments were not performed because no appropriate endpoint was available to determine the acute reference dose (aRfD) for the general population or any population subgroup and pyridalyl is not carcinogenic, respectively.

Environmental Justice Considerations
Potential areas of environmental justice concerns, to the extent possible, were considered in the human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf). The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Review of Human Research
This risk assessment relies in part on data from Pesticide Handler's Exposure Database (PHED) studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies have been determined to require a review of their ethical conduct, and have received that review.

Regulatory Recommendations

Provided revised Sections B and F, analytical standards of HTFP and HPDO, and a successful independent laboratory validation (ILV) of Method RM-38M-2 are submitted, HED concludes there are no residue toxicology or chemistry data requirements that would preclude granting conditional registrations for application of pyridalyl to cotton, fruiting vegetables, leafy vegetables, head and stem *Brassica* vegetables, *Brassica* leafy greens, and turnip greens, and the establishment of the following permanent tolerances for residues of the insecticide pyridalyl *per se*:

Vegetable, leafy, except *Brassica*, group 4	20 ppm
Brassica, head and stem, subgroup 5A	3.5 ppm
Cotton, undelinted seed	1.0 ppm
Vegetable, fruiting, group 8	1.0 ppm
Milk, fat	0.10 ppm
Cattle, fat	0.40 ppm
Goat, fat	0.40 ppm
Horse, fat	0.40 ppm
Sheep, fat	0.40 ppm
Cattle, meat byproducts	0.02 ppm
Goat, meat byproducts	0.02 ppm
Horse, meat byproducts	0.02 ppm
Sheep, meat byproducts	0.02 ppm
Brassica, leafy greens, subgroup 5B	30 ppm
Turnip greens	30 ppm

A permanent tolerance for combined residues of pyridalyl and its metabolite 3,5-dichloro-4-[3-(5-trifluoromethyl-2-pyridyloxy)]propoxy phenol in/on:

Cotton, gin byproducts	35 ppm

And permanent tolerances for indirect/inadvertent combined residues of pyridalyl and its metabolites 2-hydroxy-5-trifluoromethylpyridine (free and conjugated), and 3-hydroxy-5-trifluoromethyl-2-pyridone (free and conjugated) in/on:

Vegetable, leaves of root and tuber, group 2	0.20 ppm
Vegetable, legume, group 6	0.10 ppm
Vegetable, foliage of legume, group 7	0.60 ppm
Grain, cereal, forage, fodder, & hay, group 16	0.90 ppm
Grass, forage, fodder, & hay, group 17	0.45 ppm
Animal feed, nongrass, group 18	0.80 ppm
Herbs and spices, group 19	0.90 ppm
Artichoke	0.90 ppm

Registration of pyridalyl formulations should be conditional until the petitioner has fulfilled the data requirements pertaining to the revised 158 toxicity guideline requirements, the method for plant commodities, MRM testing of metabolites HTFP and HPDO, and livestock metabolism studies with HTFP and HPDO.

2.0 Proposed Use Pattern

The proposed products and uses for pyridalyl are listed below in Tables 2.0.1 and 2.0.2.

Table 2.0.1. Summary of End-Use Pyridalyl Products.

Trade Name	Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Label Version
S-1812 35 WP	59639-REU	35	WP	Fruiting vegetables (except cucurbits); *Brassica* Leafy Vegetables; Leafy vegetables	Larvae of various lepidopteran insect pests	Draft; not dated
S-1812 4 EC	59639-REO	45 (4 lb/gal)	EC	Fruiting vegetables (except cucurbits); *Brassica* Leafy Vegetables; Leafy vegetables	Larvae of various lepidopteran insect pests	Draft; not dated
S-1812 35 PPG	59639-125	35	WP (packaged in water-soluble packets)	Fruiting vegetables (except cucurbits); *Brassica* Leafy Vegetables; Leafy vegetables	Larvae of various lepidopteran insect pests	Draft; not dated
V-10132	59639-RGU	25	EC	Cotton; Fruiting vegetables (except cucurbits); *Brassica* Leafy Vegetables; Leafy vegetables	Larvae of various lepidopteran insect pests	Draft; not dated

Table 2.0.2. Summary of Directions for Use of Pyridalyl.

Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Cotton						
59639-RGU	Early, mid & late season; Foliar spray; Ground or aerial	0.1-0.15	Not specified (NS)	0.6	21	Applications may be made in a minimum of 3 gal/A using aerial equipment or 25 gal/A using ground equipment. Begin applications when insects reach an economic threshold and repeat as needed to maintain control, with a minimum RTI of 14 days. Grazing of animals on treated areas is prohibited.
Fruiting Vegetables (Except Cucurbits)						
S-1812 35 WP S-1812 4 EC S-1812 35 PPG	Foliar spray; Ground or aerial	0.1-0.2	NS	0.8	1	Applications may be made in a minimum of 5 gal/A using aerial equipment or 25 gal/A using ground equipment. Begin applications when insects reach an economic threshold and repeat as needed to maintain control, with a minimum RTI of 14 days.
***Brassica* Leafy Vegetables**						
S-1812 35 WP S-1812 4 EC S-1812 35 PPG	Foliar spray; Ground or aerial	0.1-0.2	NS	0.8	3	Applications may be made in a minimum of 5 gal/A using aerial equipment or 25 gal/A using ground equipment. Begin applications when insects reach an economic threshold and repeat as needed to maintain control, with a minimum RTI of 14 days.
Leafy Vegetables (Except *Brassica* Vegetables)						
S-1812 35 WP S-1812 4 EC S-1812 35 PPG	Foliar spray; Ground or aerial	0.1-0.2	NS	0.8	1	Applications may be made in a minimum of 5 gal/A using aerial equipment or 25 gal/A using ground equipment. Begin applications when insects reach an economic threshold and repeat as needed to maintain control, with a minimum RTI of 147 days.

Table 2.0.2. Summary of Directions for Use of Pyridalyl.						
Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Leafy *Brassica* Greens: Broccoli raab, Chinese cabbage (bok choy), Collards, Kale, Mizuna, Mustard greens, Mustard spinach, Rape greens, and Turnip greens						
S-1812 35 WP S-1812 4 EC S-1812 35 PPG	Foliar spray; Ground or aerial	0.1-0.2	NS	0.8	3	Applications may be made in a minimum of 5 gal/A using aerial equipment or 25 gal/A using ground equipment. Begin applications when insects reach an economic threshold and repeat as needed to maintain control, with a minimum RTI of 14 days.

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

The available data from metabolism studies with cabbage, tomato, and cotton indicate that metabolism of pyridalyl is similar in three dissimilar crops. Pyridalyl was the major component identified in all three crops, accounting for 43-87% of the total radioactive residues (TRR) in cabbage, tomato, and cotton gin byproducts. In cotton seed, where metabolism was much more extensive, pyridalyl was the major identified component at 5.7-13.2% TRR. Metabolite S-1812-DP was also identified in all crops at lower levels, accounting for 3-12% TRR. Although metabolism of pyridalyl was generally more extensive in cotton, the major metabolic pathways in all three crops were hydroxylation and cleavage of the ether linkage of pyridalyl followed by further oxidation, conjugation, and incorporation into natural products. The available data indicate that the metabolism of pyridalyl is similar in goats and hens. Pyridalyl was the major component identified in all goat matrices (1.9-90.0% TRR) and in hen egg yolk, liver, muscle, and fat (29.9-91.7% TRR); in egg white, pyridalyl was present at lower levels and metabolite HTFP was the major component (68.7% TRR). Metabolite HTFP was also identified in goat milk, liver, and kidney, as well as hen egg yolk, liver, muscle, and fat. Metabolite S-1812-DP and/or its glucuronide and sulfate conjugates were identified in significant amounts (>10% TRR) in goat liver and kidney and hen egg yolk, and at lower levels in other goat and hen matrices. The major metabolic pathways in livestock were cleavage of the propenyl group followed by conjugation, oxidation of the propenyl group, and cleavage of the ether linkage, followed by extensive metabolism of the molecules and incorporation into tissue biological products. HED determined that pyridalyl *per se* is the residue of concern in the subject crops (except cotton gin byproducts in which S-1812-DP is included) and ruminants (Memo, M. Clock-Rust, *et al.*; DP# 304470). S-1812-DP was excluded as a residue of concern in ruminants due to low levels in the cattle feeding study.

Rotational crops did not take up parent pyridalyl or its metabolite S-1812-DP from the soil, but did take up metabolite HTFP. HTFP was then metabolized in rotational crops via oxidation to HPDO. Metabolites HTFP and HPDO are assumed to be of equivalent toxicity to the parent compound and are included as residues of concern. Rotational crop tolerances are being set on all non-labeled crops which can be rotated, except for bulb and cucurbit vegetables. However, rotation to crops with livestock feed items should be prohibited until livestock metabolism

studies with HTFP and HPDO have been submitted. Thus, the labels should be revised by adding a statement prohibiting rotation to bulb and cucurbit vegetables, turnips, sugar beets, cowpeas, soybeans, cereal grains, grass, or nongrass animal feeds.

Pyridalyl is expected to be persistent in both soil and aquatic environments. However, as the major metabolites in the terrestrial field-dissipation studies, S-1812-DP and HTFP, are expected to be more soluble and mobile than the parent compound, they should be included in the drinking water assessment.

The residues of concern for tolerance expression and risk assessment are shown in Table 3.1 below.

Table 3.1. Summary of Pyridalyl Metabolites and Degradates for Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crops	pyridalyl	pyridalyl
	Cotton, gin byproducts	pyridalyl + S-1812-DP	pyridalyl + S-1812-DP
	Rotational Crop	pyridalyl + HTFP & HPDO	pyridalyl + HTFP & HPDO
Livestock	Ruminant	pyridalyl	pyridalyl
	Poultry	pyridalyl	pyridalyl
Drinking Water		pyridalyl + S-1812-DP & HTFP	Not Applicable

4.0 Hazard Characterization and FQPA Considerations

4.1 Hazard Characterization

With the exception of the newly required immunotoxicity and neurotoxicity testing (as required by Revised Part 158), the toxicology database for pyridalyl is complete. In addition to the core studies, special studies were carried out to evaluate the effect of pyridalyl on steroid synthesis and the endocrine system. The subchronic and chronic toxicity studies in the rat included satellite groups to evaluate neurotoxicity.

Technical pyridalyl shows low acute toxicity (Toxicity Category IV) via the oral, dermal, and inhalation routes of exposure. Technical pyridalyl was neither an eye nor dermal irritant (Toxicity Category IV), but showed dermal sensitization in both the Buehler and Maximization assays. Two pyridalyl formulations were evaluated for acute toxicity, a wettable-powder (WP) formulation and an emulsifiable-concentrate (EC) formulation. The WP showed low acute toxicity via the oral, dermal, and inhalation routes of exposure (Toxicity Category IV) and was a mild eye irritant (Toxicity Category III). The WP formulation produced slight dermal irritation, but did not produce dermal sensitization. The EC showed moderate acute toxicity (Toxicity Category III) via the oral route, Toxicity Category IV via the dermal and inhalation routes of exposure, and it was a mild eye irritant (Toxicity Category III). The WP formulation produced slight dermal irritation, but did not produce dermal sensitization.

Subchronic oral toxicity was evaluated in the rat, mouse, and dog and a 28-day dermal toxicity study in the rat. Decreased body weight and/or body-weight gain were observed in the rat, mouse, and dog. No treatment-related clinical pathological effects were observed in either the rat or dog. Mice, however, had hematological (decreased HCT, RBC, and HGB) and blood biochemical (increased cholesterol and decreased triglycerides) effects. Increased liver weights were observed in the rat, mouse, and dog studies, while kidney weights were either increased (dog and rat) or decreased (mouse). Female mice also had decreased ovary weight.

Since the last risk assessment (2004), a 28-day inhalation toxicity study has been submitted by the registrant and reviewed by HED. In the study, effects included the death of one animal with both macroscopic and microscopic evidence of acute lung injury and pulmonary edema observed at the LOAEL of 0.173mg/L/day (45.13 mg/kg bw/day). A NOAEL of 0.024mg/L/day (6.26 mg/kg bw/day) was identified.

Histopathological changes in the liver included necrosis and/or hypertrophy in rats, mice, and dogs. Other histological findings were observed in the ovaries of rats (vacuolation of interstitial gland cells) and mice (atrophy), the adrenals of both rats and dogs (vacuolation) and mice (pigmentation), and lungs of rats (foamy cell accumulation) and dog (thickening of arterial and arteoriole walls). The 28-day dermal toxicity study in rats did not produce any signs of dermal or systemic toxicity at 1000 mg/kg/day (limit dose).

Pyridalyl has been tested in chronic studies with dogs, rats, and mice. Observations in the combined chronic toxicity/oncogenicity study in rats included decreased body-weight gain, hematological alterations, and histopathological alterations of the spleen. In the 78-week feeding study in mice, decreased body-weight gain and food consumption/efficiency, and increased liver and kidney weights were observed. In a 12-month oral (capsule) study with dogs, pyridalyl produced increased alkaline phosphatase and alanine aminotransaminase and increased liver weights.

The oncogenic potential of pyridalyl was evaluated in the rat and mouse. No treatment-related neoplastic lesions were observed in either rats or mice. Pyridalyl has a "not likely" cancer classification.

Acceptable developmental toxicity studies in the rat and rabbit are available, as well as a two-generation reproductive toxicity study in the rat. In the developmental toxicity studies, the maternal toxicity consisted of reduced body-weight gain in both the rat and rabbit and abortion and premature delivery in the rabbit. The only cesarean section finding in either the rat or rabbit was decreased fetal body weight in rabbits. Fetal examinations did not show any treatment-related effects in rabbits; visceral examination of rats revealed decreased incidence of thymic remnants in the neck. In the two-generation reproduction study, the parental systemic toxicity included decreased body weight, body-weight gain in males and females, decreased food consumption in males, and lesions in the thyroid in females. No treatment-related differences were observed in estrus cycle and estrus cycle length in females or sperm counts, motility, and morphology in males. Mating, fertility, and gestation indices, number of days to mating, and gestation length were not affected by treatment of either generation during litter production. Offspring toxicity consisted of reduced body weight and body-weight gain of pups in both generations.

In the two-generation reproduction study, delayed vaginal opening, increase in ovary weights, and vacuolation of interstial gland cells in the ovary were observed with statistical significance. In the subchronic study in the rat, cytoplasmic vacuolation in the adrenal gland was observed. In another subchronic toxicity study in the rat, decreases in serum testosterone and estradiol levels were observed at the highest dose level. These results suggested that pyridalyl affects steroid synthesis. In a series of *in vitro* cell culture studies with isolated Leydig or ovarian cells from Crj:CD (SD) male and female rats, no treatment-related effects were found on the production of progesterone, estradiol, 17α-OH-progesterone or testosterone and no cytotoxicity was observed. In addition, there was no effect on aromatase activity in cultured ovarian cells. These results suggest that 17β-hydroxysteroid dehydrogenase (HSD) inhibition is not the mechanism for the increased androstenedione production in Leydig cells.

The genotoxic potential of pyridalyl was studied *in vitro* in bacteria (Ames test), in mammalian cells (HGPRT and mouse lymphoma L5178Y TK+/-), in the chromosome aberration assay, and *in vivo* in the unscheduled DNA synthesis test and the mouse micronucleus test. The test systems assayed did not show any evidence of pyridalyl genotoxicity except the *in vitro* mammalian cytogenetics (chromosome aberration) assay. Two metabolites of pyridalyl, HTFP and HPDO, that occur in extremely low levels in plants and animals, were also tested for genetic toxicity. Each metabolite was tested in an *in vitro* bacterial (Ames test) and mammalian (HGPRT assay) mutagenesis assay, as well as in an *in vitro* chromosome aberration test. Both metabolites were positive in the bacterial assay, but were negative in the mammalian mutagenesis assay. One metabolite, HPDO, was positive in the chromosome aberration test. The biological significance of this finding is uncertain given that only low levels of these compounds are detectible in plants or animals and that pyridalyl does not appear to be carcinogenic at high and chronic doses. The weight of the evidence indicates that pyridalyl does not raise significant genotoxicity concerns.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Database

The toxicology database for pyridalyl is adequate for FQPA assessment. Acceptable developmental toxicity studies in the rat and rabbit are available, as well as a reproductive toxicity study in the rat. In general, the hazard database for pyridalyl remains unchanged since the last risk assessment (2004). The conclusions stated in Section 4.2, *FQPA Hazard Considerations* of the 2004 risk assessment remain consistent with HED's current policies. Based on the hazard data, the HIARC recommended the FQPA SF be reduced to 1x because there are no concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. However, due to the revision of the Part 158 toxicology data requirements, neurotoxicity and immunotoxicity studies are required for pyridalyl. A discussion of HED's conclusions regarding neurotoxicity and immunotoxicity is presented below.

Neurotoxicity

There was no evidence of neurotoxicity resulting from exposure to pyridalyl in either the subchronic and chronic toxicity studies or the developmental and reproductive toxicity studies. Limited neurotoxicity evaluations [clinical signs/functional observation battery (FOB) and motor activity] were included as part of the subchronic and chronic studies in rats. In the subchronic study, no treatment-related changes were seen in FOB or motor activity in either sex at any dose

level. In the chronic study, no treatment-related changes were seen in the FOB parameters. Increases in rearing and motor activity were seen in females only at the highest dose tested. These increases were attributed to the severe systemic toxicity seen at this dose and were not considered to be indication of frank neurotoxicity (Memo, R. Fricke, TXR# 0052759, 8/3/2004).

The acute and subchronic neurotoxicity studies are required as part of the revised Part 158 toxicology data requirements for pyridalyl. However, since there is no evidence of neurotoxicity for pyridalyl in the toxicology database, the Agency determined that an additional factor (UF_{DB}) for database uncertainties is not needed to account for lack of these data.

Immunotoxicity

The toxicology profile indicate a potential concern for immunotoxicity based on the following findings: 1) in the prenatal developmental toxicity study in rats with pyridalyl, a significant decrease in the number of litters containing fetuses with thymic remnant in the neck was observed at the highest dose tested; and 2) In the two-generation reproduction study in rats, significantly decreased mean thymus weights were observed in male and female F1 and F2 weanlings.

The concerns that pyridalyl directly targeted the immune system, however, is lessened by the following weight-of-the-evidence considerations: 1) no treatment-related changes were seen in any of the potential target organs (bone marrow, thymus, spleen, or lymph nodes) for immunotoxicity in the prenatal developmental toxicity study in rats; 2) no histopathological changes were seen in the bone marrow, thymus, spleen, or lymph nodes of either the parental or offspring in the two-generation reproduction study; 3) no treatment-related changes were seen in hematology parameters, organ weights, gross lesions, or histopathological changes in the bone marrow, thymus, spleen, or lymph nodes after subchronic or chronic exposures to mice, rats or dogs; and 4) the endpoint of concern (thymus effects) observed in the most sensitive population (offspring) at the lowest NOAEL (2.8 mg/kg/day) is used for the overall risk assessment. Consequently, an additional uncertainty factor is not needed to account for potential immunotoxicity.

4.2.2 FQPA Safety Factor Recommendation

Based on the hazard data, the HIARC recommended the FQPA SF be reduced to 1x because there are no concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. The recommendation is based on the following:

- In the pre-natal developmental toxicity study in rats, developmental effects were seen at a dose higher than the dose that caused maternal toxicity. In the pre-natal developmental toxicity study in rabbits, developmental effects (attributable to maternal toxicity) were seen at the same dose that caused severe toxicity in the dams.

- There was low concern for the quantitative susceptibility in the two-generation reproduction study, since 1) there was a clear NOAEL for the offspring toxicity; and 2) the effects of concern were well defined and used for risk assessment.

- The HIARC concluded that there is not a concern for developmental neurotoxicity resulting from exposure to pyridalyl. Therefore, a DNT study is not required.

- The lack of immunotoxicity and neurotoxicity studies due to the revision of the Part 158 toxicology data requirements does not indicate a concern; additional safety factors to account for these data are not necessary.

- The dietary food exposure assessment utilizes proposed tolerance-level residues and 100% CT information for all commodities. By using these screening-level assumptions, chronic exposures/risks will not be underestimated.

- The dietary drinking water assessment (Tier II for surface water and Tier I for ground water) utilizes values generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

- There are no existing or proposed residential uses.

4.3 Doses and Endpoints for Risk Assessment

Since the last risk assessment (2004), a 28-day inhalation toxicity study has been submitted by the registrant and reviewed by HED. In the study, effects included the death of one animal with both macroscopic and microscopic evidence of acute lung injury and pulmonary edema observed at the LOAEL of 0.173 mg/L/day (45.13 mg/kg/day). A NOAEL of 0.024 mg/L/day (6.26 mg/kg/day) was identified. The results of this study do not impact the selections of doses and endpoints for risk assessment, as the results of the inhalation study are less conservative than those chosen for inhalation risk assessment (based on the results of the 2-generation reproductive toxicity study in rats).

Table 4.3. Summary of Toxicological Doses and Endpoints for Pyridalyl.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population) Acute Dietary (Females 13-49 years old)	An effect of concern attributable to a single exposure (dose) was not identified from the oral toxicity studies, including the developmental toxicity studies in rats and rabbits.		
Chronic Dietary (All populations)	NOAEL= **3.4** mg/kg/day UF = **100x** **Chronic RfD** = **0.034** mg/kg/day	FQPA SF = **1x** **cPAD** = chronic RfD / FQPA SF = 0.034 mg/kg/day	Combined Chronic Toxicity/ Carcinogenicity Study- Rats LOAEL = 17.1 mg/kg/day (males) and 21.1 mg/kg/day (females) based on decreased body weights, weight gain, and food efficiency.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Incidental Oral (1-30 days)	Offspring NOAEL= **2.8** mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	2-Generation Reproduction Study - Rat Offspring LOAEL = 13.8 mg/kg/day, based on decreased thymus weights.
Intermediate-Term Incidental Oral (1- 6 months)	Offspring NOAEL= **2.8** mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	2-Generation Reproduction Study - Rat Offspring LOAEL = 13.8 mg/kg/day, based on decreased thymus weights.
Short-Term Dermal (1 to 30 days)	Not required. No dermal toxicity was observed at 1000 mg/kg/day (limit dose) in a 28-day dermal toxicity study in the rat and there are no neurotoxicity, developmental, or reproductive toxicity concerns.		
Intermediate-Term Dermal (1 to 6 months)	Not required. No dermal toxicity was observed at 1000 mg/kg/day (limit dose) in a 28-day dermal toxicity study in the rat and there are no neurotoxicity, developmental, or reproductive toxicity concerns.		
Long-Term Dermal (>6 months)	Oral NOAEL= **3.4** mg/kg/day Dermal absorption factor = 11.4%	**Residential** LOC for MOE = 100 **Occupational** = 100	Combined Chronic Toxicity/ Carcinogenicity Study - Rat LOAEL = 17.1 mg/kg/day (males) and 21.1 mg/kg/day (females) based on decreased body weights, weight gain, and food efficiency.
Short-Term Inhalation (1 to 30 days)	Offspring oral NOAEL= **2.8** mg/kg/day Inhalation absorption factor = 100%	**Residential** LOC for MOE = 100 **Occupational** = 100	2-Generation Reproduction Study - Rat Offspring LOAEL = 13.8 mg/kg/day, based on decreased thymus weights.
Intermediate-Term Inhalation (1 to 6 months)	Offspring oral NOAEL= **2.8** mg/kg/day Inhalation absorption factor = 100%	**Residential** LOC for MOE = 100 **Occupational** =100	2-Generation Reproduction Study - Rat Offspring LOAEL = 13.8 mg/kg/day, based on decreased thymus weights.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Long-Term Inhalation (>6 months)	NOAEL= **3.4** mg/kg/day Inhalation absorption factor = 100%	**Residential** LOC for MOE = 100 **Occupational** = 100	Combined Chronic Toxicity/ Carcinogenicity Study - Rat LOAEL = 17.1 mg/kg/day (males) and 21.1 mg/kg/day (females) based on decreased body weights, weight gain, and food efficiency.
Cancer (oral, dermal, inhalation)	"Not likely to be Carcinogenic to Humans."		

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no-observed adverse effect level, LOAEL = lowest-observed adverse effect level, PAD = population-adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level-of-concern, NA = Not Applicable.

4.4 Endocrine Disruption

EPA is required under the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) *"may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."* Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, pyridalyl may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Exposure Characterization/Assessment

5.1 Dietary Exposure/Risk Pathway

References:

Pyridalyl in/on Cotton, Fruiting Vegetables, Leafy Vegetables, Head and Stem *Brassica* Vegetables, *Brassica* Leafy Greens and Turnip Greens. Summary of Analytical Chemistry and Residue Data. D289704. G. Kramer. 08/31/04.

Pyridalyl in/on Fruiting Vegetables, Leafy Vegetables, Head & Stem *Brassica* Vegetables, *Brassica* Leafy Greens, and Turnip Greens. Response to Registration Action Branch 1 (RAB1) Review of 8/31/04. D318304. G. Kramer. 05/18/06.

Pyridalyl in/on Cotton, Fruiting Vegetables, Leafy Vegetables, Head & Stem *Brassica* Vegetables, *Brassica* Leafy Greens, Turnip Greens, and Livestock Commodities. Response to Health Effects Division (HED) Review of 18-MAY-2006. D342411. G. Kramer. 04/17/09.

5.1.1 Residue Profile

Adequate crop field trial data have been submitted reflecting the proposed use pattern for the 35% WP and 4 lb/gal EC formulations. Adequate processing data have been submitted which indicate that no tolerances are required on processed commodities. An adequate ruminant feeding study has been submitted which indicates that tolerances are needed for residues in fat, meat byproducts, and milk fat. The petitioner did not submit a poultry feeding study with this petition, but submitted a waiver request for magnitude of the residues in poultry and eggs. HED granted the waiver for currently proposed uses. The available gas chromatography/nitrogen-phosphorus detector (GC/NPD) analytical method for plants and livestock is considered to be adequate for tolerance enforcement. However, Method RM-38P-1-1 should be rewritten to include instructions for the analysis of all crops (and their associated processed commodities) for which the petitioner is requesting tolerances.

The petitioner submitted extensive field rotational crop studies, performed in accordance with a protocol approved by HED, in order to set tolerances for HTFP and HPDO in/on rotational crops. Samples of rotational crop commodities were analyzed by gas chromatography/mass spectroscopy (GC/MS) for residues of the free and conjugated forms of HTFP and HPDO using Valent Method RM-38M-2. Based on acceptable concurrent-recovery data, the method was deemed adequate for data gathering (Memo G. Kramer, 8/31/04, DP# 289704). Satisfactory radiovalidation data have been submitted for Method RM-38M-2. However, a successful ILV is necessary before Method RM-38M-2 can be determined to be adequate for tolerance enforcement. As tolerances are now proposed for residues HTFP and HPDO, MRM testing of these metabolites is now required. Livestock metabolism studies with HTFP and HPDO are required to support rotation to crops with livestock feed items.

The proposed tolerances are shown in Table 5.1.1. The petitioner is requested to submit a revised Section F as specified below. There are currently no U.S. or international Codex tolerances established for pyridalyl.

Table 5.1.1. Tolerance Summary for Pyridalyl.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Correct Commodity Definition/Comments
For residues of pyridalyl *per se*			
Vegetable, leafy, except *Brassica*, group 4	20	20	Vegetable, leafy, except *Brassica*, group 4
Brassica, head and stem, group 5	3.5	3.5	*Brassica*, head and stem, subgroup 5A
Cotton, undelinted seed	0.40	1.0	
Vegetable, fruiting, group 8	1.0	1.0	
Brassica, leafy greens, subgroup 5B	-	30	
Turnip greens	30	30	
Milk	0.10	-	
Milk, fat	2.0	0.10	
Cattle, meat	0.04	-	
Cattle, fat	1.0	0.40	
Cattle, meat byproducts	0.05	0.02	
Goat, meat	0.04	-	
Goat, fat	1.0	0.40	

Goat, meat byproducts	0.05	0.02	
Hog, fat	1.0	-	
Sheep, meat	0.04	-	
Sheep, fat	1.0	0.40	
Sheep, meat byproducts	0.05	0.02	
Horse, meat	0.04	-	
Horse, fat	1.0	0.40	
Horse, meat byproducts	0.05	0.02	
Poultry, meat	0.04	-	There is no reasonable expectation of residues in poultry commodities (180.6(a)(3)).
Poultry, fat	0.04	-	
Poultry, meat byproducts	0.04	-	
Eggs	0.04	-	
For combined residues of pyridalyl and its metabolite 3,5-dichloro-4-[3-(5-trifluoromethyl-2-pyridyloxy)]propoxy phenol			
Cotton, gin byproducts	23	35	
For the indirect/inadvertent combined residues of pyridalyl, 2-hydroxy-5-trifluoromethylpyridine (free and conjugated), and 3-hydroxy-5-trifluoromethyl-2-pyridone (free and conjugated)			
Vegetable, leaves of root and tuber, group 2	0.3	0.20	
Vegetable, bulb, group 3	0.3	-	No rotational crop data submitted, registrant plans on adding as primary crops.
Vegetable, cucurbit, group 9	0.3	-	
Vegetable, legume, group 6	0.3	0.10	
Vegetable, foliage of legume, group 7	0.3	0.60	
Grain, cereal, forage, fodder, & hay, group 16	0.3	0.90	
Grass, forage, fodder, & hay, group 17	0.3	0.45	
Animal feed, nongrass, group 18	0.3	0.80	
Herbs and spices, group 19	0.3	0.90	HED agreed to translate residue data from other rotational crops. (Artichoke).
Artichokes	0.3	0.90	

5.2 Water Exposure/Risk Pathway

The residues of concern for drinking water assessment are pyridalyl and the metabolites S-1812-DP & HTFP. EFED provided drinking water estimates for pyridalyl and its metabolites for use in HED's risk assessment (see below).

The major routes of degradation for pyridalyl in laboratory studies are photodegradation in water and soil, and to a lesser degree, aerobic microbial degradation. Based on registrant submitted environmental fate data, this compound is expected to be persistent in both soil and aquatic environments with a low solubility and a high potential to bioconcentrate. These properties are expected to influence potential exposure pathways.

Pyridalyl is highly immobile with K_d values between 2,473 and 3,848 and corresponding K_{oc} values between 402,000 and 2,060,000, respectively. Pyridalyl is expected to be persistent in soil, sediment, and water and may accumulate over time with repeated use. These properties

are expected to control runoff in that movement off-site is expected to be dominated by soil/sediment bound residues.

The estimated drinking water concentrations (EDWCs) used in the dietary exposure risk assessment were provided by EFED in a memorandum dated 2/25/09 (Memo, M. Corbin; DP# 360715). Water residues were incorporated directly into the DEEM-FCID™ into the food categories "water, direct, all sources" and "water, indirect, all sources."

EDWCs for pyridalyl in drinking water were estimated using the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) Tier II simulation for surface water and SCI-GROW for ground water. Table 5.2 summarizes the EDWCs for pyridalyl in surface and ground water.

For dietary risk assessment, HED chose to use the highest EDWCs provided by EFED in order to produce a more conservative estimate of dietary exposure. For surface water, the EDWC for combined parent pyridalyl plus its metabolites HTFP and S-1812-DP was used (annual mean, 1.95 ppb), and for ground water the EDWC for the combined residues of parent pyridalyl plus its metabolites HTFP and S-1812-DP was used (21.9 ppb).

Table 5.2. Tier II EDWCs for Combined Residues of Pyridalyl, S-1812-DP, and HTFP.

Assessment	Concentration (μgL^{-1})		
	Peak	Annual Mean	30-year Mean
Tier II Surface Water [a]	6.96	1.95	1.18
Ground Water	21.9		

[a] NY grape ornamental – non-bearing vines scenario.

5.3 Chronic Dietary Exposure and Risk

Reference:

Pyridalyl. Revised Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action in/on Cotton, Fruiting Vegetables, Leafy Vegetables, Head & Stem *Brassica* Vegetables, *Brassica* Leafy Greens, and Turnip Greens. D361804. G. Kramer. 04/17/09.

NOTE: The dietary exposure analysis document supersedes the previous assessment of dietary risk (Memo, S. Piper, 8/12/2004, DP# 361804). This assessment has been updated to include revisions to the recommended tolerance levels, tolerances for indirect/inadvertent residues, and drinking water.

A chronic aggregate dietary (food and drinking water) exposure and risk assessment was conducted using DEEM-FCID™ (Version 2.03) which uses food consumption data from the U.S. Department of Agriculture's CSFII from 1994-1996 and 1998. The analysis was performed to support a Section 3 request for the use of pyridalyl in/on cotton, fruiting vegetables, leafy vegetables, head & stem *Brassica* vegetables, *Brassica* leafy greens, and turnip greens.

The chronic analysis assumed 100% crop treated, DEEM™ 7.81 default concentration factors, and tolerance-level residues. Drinking water was incorporated directly in the dietary assessment using the concentration for ground water generated by the SCI-GROW model. The chronic

dietary exposure and risk estimates (food + dietary water) were 0.010980 mg/kg/day for the general U.S. population (32% of the cPAD) and 0.014534 mg/kg/day (43% of the cPAD) for the most highly exposed population subgroup (children 1-2 years old) and are thus below HED's level of concern (<100% cPAD).

Table 5.3. Summary of Chronic Dietary Exposure (Food + Drinking Water) and Risk for Pyridalyl.

Population Subgroup	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.010980	32
All Infants (<1 year old)	0.006766	20
Children 1-2 years old	**0.014534**	**43**
Children 3-5 years old	0.014494	43
Children 6-12 years old	0.011178	33
Youth 13-19 years old	0.009479	28
Adults 20-49 years old	0.010739	32
Adults 50+ years old	0.011062	33
Females 13-49 years old	0.010826	32

Characterization
These chronic dietary exposure and risk estimates are conservative since they assumed 100% CT, DEEM™ 7.81 default concentration factors, and tolerance-level residues and were based on screening level estimates of drinking water concentrations generated by the SCI-GROW model. They could be further refined through the use of anticipated residues, empirical processing factors, and % CT data, as well as refined drinking water estimates.

Conclusions
The chronic dietary exposure and risk analysis using DEEM-FCID™ indicates that dietary risk to pyridalyl from food and drinking water is well below HED's levels of concern for this pesticide. Estimated chronic dietary risks are less than 44% of the cPAD for the general U.S. population and all population subgroups.

6.0 Aggregate Risk Assessment

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. However, there are no existing or proposed residential uses for pyridalyl; therefore, aggregate exposure is made up of dietary exposure from food and drinking water sources only. Short-, intermediate-, and long-term aggregate-risk assessments were not performed due to the absence of residential uses.

Aggregate risks were assessed by incorporating the drinking water directly into the dietary-exposure assessment for the chronic exposure scenario. The chronic dietary exposure analysis described above in Section 5.3 represents aggregate risk for pyridalyl. The chronic dietary exposure estimates are not of concern to HED for the general U.S. population and all population subgroups (see Table 5.3). Therefore, the chronic aggregate risk for pyridalyl is not of concern for HED for the general U.S. population or any population subgroups.

Acute and cancer aggregate-risk assessments were not performed because no appropriate endpoint was available to determine the aRfD for the general population or any population subgroup and because pyridalyl is not carcinogenic.

7.0 Data Needs and Label Recommendations

7.1 Toxicology

- A neurotoxicity study is required as part of the revised Part 158 toxicology data requirements for pyridalyl.
- An immunotoxicity study is required as part of the revised Part 158 toxicology data requirements for pyridalyl.

7.2 Residue Chemistry

OPPTS 860.1200 Directions for Use

Based on the available confined and field rotational crop data, the labels should be revised by adding a statement prohibiting rotation to bulb and cucurbit vegetables, turnips, sugar beets, cowpeas, soybeans, cereal grains, grass, or nongrass animal feeds.

OPPTS 860.1300 Livestock Metabolism

Livestock metabolism studies with HTFP and HPDO are required to support rotation to crops with livestock feed items.

OPPTS 860.1340 Residue Analytical Methods

Method RM-38P-1-1 should be rewritten to include instructions for the analysis of all crops (and their associated processed commodities) for which the petitioner is requesting tolerances.

A successful ILV is necessary before Method RM-38M-2 for residues of HTFP and HPDO can be determined to be adequate for tolerance enforcement.

860.1360 MRMs

As tolerances are now proposed for residues HTFP and HPDO, MRM testing of these metabolites is now required.

860.1650 Submittal of Analytical Reference Standards

Analytical standards of HTFP and HPDO are not currently available in the National Pesticide Standards Repository [source: personal communication with T. Cole of ACL/BEAD, 3/13/09]. The reference standards should be sent to the ACL.

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F as specified above.

860.1900 Field Accumulation in Rotational Crops

Rotation to crops with livestock feed items should be prohibited until livestock metabolism studies with HTFP and HPDO have been submitted.

cc: M. Clock-Rust, G. Kramer
RDI: RAB1 Chemists (4/15/09); RAB1 Branch (4/15/09); D. Vogel (4/15/09)
M. Clock-Rust: S-10947: Potomac Yard 1 (PY1): (703) 308-2718: 7509P: RAB1

Appendix A: Toxicology Assessment

Appendix A.1. Acute Toxicity Profile for Pyridalyl Technical (93.7%)

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute Oral (Rat)	45685204	LD_{50} => 5000 mg/kg (males & females)	IV
870.1200	Acute Dermal (Rat)	45685205	LD_{50} => 5000 mg/kg (males and females)	IV
870.1300	Acute Inhalation (Rat)	45685206	LC_{50} => 2.01 mg/L (males and females)	IV
870.1300	Acute Inhalation (Rat)	45685207	Non-irritating	IV
870.2400	Primary Eye Irritation (Rabbit)	45685208	Non-irritating	IV
870.2600	Dermal Sensitization	45685209	Sensitizer	–
870.2600	Dermal Sensitization	45685210	Sensitizer	--

Appendix A.2. Toxicity Profile for Pyridalyl

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
870.3100 90-Day oral toxicity - Rat	45685221 (1999) 45685219 (2002) 45685220 (2002) 45685225 (1997) Acceptable/guideline 0, 100, 1000, or 2000 ppm M: 0, 5.56, 56.0, or 111.3 mg/kg bw/day F: 0, 6.45, 64.0, or 128.6 mg/kg bw/day	NOAEL = 5.56 (M), 6.45 (F)mg/kg/day LOAEL = 56.0 (M), 64.0 (F) mg/kg/day , based on decreased body-weight gain, decreased food consumption, and lung histopathology (alveolar foamy cells) in both sexes and microscopic changes in the ovary (vacuolation of interstitial gland cells) in females.
870.3100 90-Day oral toxicity-Mouse	45685223 (1999) Acceptable/guideline 0, 70, 700, 3500 and 7000 ppm M: 0, 8.169, 81.7, 378.5 and 720.8 mg/kg/day F: 0, 9.5, 86.78, 415.0 and 878.7 mg/kg/day	NOAEL 81.7 mg/kg/day (M), 86.78 (F) mg/kg/day LOAEL = 378.5 (M), 415.0 (F) mg/kg/day based on decreased body weight and body-weight gain in males and females, and pigmentation in the adrenal gland in males, and ovarian atrophy in females.
870.3100 90-Day oral (capsule) toxicity-Dog	45685218 (2000) Acceptable/guideline 0, 10, 100, or 300 mg/kg/day	NOAEL= 100 (M) and 10 (F) (mg/kg/day LOAEL = 300 (M) and 100 (F) mg/kg/day, based on histopathology findings in the adrenal glands (vacuolation of cortical cells).
870.3200 21/28-Day dermal toxicity-Rat	45685217 (2002) Acceptable/Guideline 0, 30, 100, or 1000 mg/kg bw/day, 6 hours/day for 28 consecutive days.	Systemic and dermal NOAEL = 1000 mg/kg/day Systemic and dermal LOAEL = not determined

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
870.3465 28 Day Subchronic Inhalation Study	46110601 (2003) Acceptable/ Guideline 0, 0.024, 0.173, or 0.958 mg/L/day	NOAEL= 0.024mg/L/day (6.26 mg/kg bw/day) LOAEL= 0.173mg/L/day (45.13 mg/kg bw/day) based on the death of one animal with both macroscopic and microscopic evidence of acute lung injury and pulmonary edema.
870.3700 Developmental Toxicity Study - Rat	45685305(2001) 45685304 (2001) Acceptable/Guideline 0, 10, 50, or 250 mg/kg /day on GD 6 through 19	Maternal toxicity (mg/kg/day.) NOAEL =10 LOAEL= 50 based on reduced body-weight gain Developmental toxicity (mg/kg/day) NOAEL = 50 LOAEL = 250 based on decreased incidence of thymic remnants in the neck.
870.3700 Developmental Toxicity - Rabbit	45685303 (2001) 45685302 (2001) RF Acceptable/guideline 0, 15, 50, or 150 mg/kg	Maternal toxicity NOAEL = 50 mg/kg/day. LOAEL = 150 mg/kg/day based on death, abortion/premature delivery, and decreased body-weight gain and food consumption. Developmental toxicity NOAEL = 50 mg/kg/day LOAEL = 150 mg/kg/day based on abortion/premature delivery and decreased fetal body weight.
870.3800 2-Gen Repro - Rat	45685307 (2002) 45685306 (2001) RF 45905202 (2002) Histo 0, 40, 200, or 1000 ppm. Acceptable/Guideline F0 Premating(mg/kg/day) 0, 2.80, 13.8, and 68.7 (M) 0, 3.11, 15.7, and 79.1 (F). F1 Premating (mg/kg/day) 0, 3.40, 17.0 and 83.7 (M) 0, 3.62, 18.3, and 91.4 (F)	Parental systemic toxicity (mg/kg/day) NOAEL = 13.8-17.0 (M) and 15.7-18.3 (F) LOAEL = 68.7-83.7 (M) and 79.1-91.4 (F), based on decreased body weight, body-weight gain and food consumption in males and decreased body weight, body-weight gain and lesions in the thyroid (an increase in small-sized follicles) in females. Reproductive toxicity (mg/kg/day) NOAEL ≥ 68.7-83.7 (M) and 15.7-18.3 (F). LOAEL = Not identified (M) and 79.1-91.4 (F) based on increased ovarian weight, microscopic lesions in the ovary of F0 and F1 adults and delayed vaginal opening in F1 and F2 offspring. Offspring toxicity (mg/kg/day) NOAEL = 2.8-3.4 (M) and 3.11-3.62 (F). LOAEL = 13.8-17.0 (M) and 15.7-18.3 (F) based on decreased thymus weights.
870.4100 12-Month Feeding Study - Dog	45685228 (2001) Acceptable/guideline 0, 1.5, 5, 20, or 80 mg/kg/day	NOAEL = 80 mg/kg/day (M,F) LOAEL was not identified
870.4200 Oncogenicity Study - Mouse	45685301 (2002) Acceptable/Guideline 0, 15, 50, 1000, or 2500 ppm 0, 1.57, 5.04, 103, or 267 mg/kg/day, 0, 1.46, 4.78, 99, or 264 mg/kg/day (F)	NOAEL = 5.04 (M) and 4.78 (F) mg/kg/day LOAEL = 103 (M) and 99 (F) mg/kg/day, based on decreased body weight (females only) and body-weight gain and decreased food efficiency. No evidence of carcinogenicity was observed.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
870.4300 24- Month Chronic Toxicity/ Carcinogenicity Study - Rat	45685227 (2002) Acceptable/Guideline 0, 30, 100, 500, or 1000 ppm 0, 1.01, 3.4, 17.1, 34.3 mg/kg/day (M) 0, 1.23, 4.1, 21.1, and 42.8 mg/kg/day (F)	NOAEL= 3.4 (M) and 4.1 (F) mg/kg/day LOAEL = 17.1 (M) and 21.1 (F) mg/kg/day based on decreased body weights, weight gain, and food efficiency. No evidence of carcinogenicity was observed
870.7600 In Vivo Dermal Penetration Study - Rat	45905211 (2002) Acceptable/Guideline 0.002, 0.02 or 0.2 mg/cm2 for 0.5, 1, 2, 4, 10, or 24 hours	In a dermal absorption study phenyl-14C]S-1812 (Pyridalyl) (lot no. RIS2001-006; 99.4% radiochemical purity) and non-labeled were applied to the dorsal skin of Sprague Dawley rats (four rats per group). An additional group of four rats was exposed for 10 hours at each dose after which the test material was washed off and the animals maintained to 168 hours. Excreta, cage washes, skin washes and swabs, and appliances were analyzed for radioactivity and absorption/excretion assessed. The slightly greater absorption of radioactivity in the low dose group (especially for those rats maintained to 168 hours) versus the mid- or high-dose groups suggests possible saturation of absorption/excretion processes. While the potential for increased absorption at high dose appeared to be limited (3.55±2.64% at 24 hours vs 3.30±1.13% at 168 hours), a dose-dependent decrease in relative absorption was not consistent among the exposure durations. Most absorbed radioactivity was excreted in the feces. Fecal excretion for the rats maintained to168 hours occurred primarily within 72 hours for the low dose group and within 96 hours for the mid- and high-dose groups. Most of the urinary excretion of radioactivity in these groups occurred within 48-72 hours.
870.7485 Metabolism Study- Rat	45685322, 45765701, 45685324, 45685325 and 45685326 (2002) Acceptable/Guideline 5 or 500 mg/kg	In a series of metabolic studies (MRIDs 45685322, 45765701, 45685324, 45685325 and 45685326) S-1812 (pyridalyl, labeled in the propenyl, phenyl, and pyridyl positions from Lot Nos. RIS98018, RIS98015, and RIS97020, respectively) was administered by gavage to male and female Sprague Dawley rats at concentrations of 5 or 500 mg/kg. Little absorption of the radiolabeled test material occurred following a single 5 mg/kg gavage dose. Absorption was ~15% for male rats and ~21% for female rats following a single 5 mg/kg oral dose of [phenyl-14C]S-1812. Greater than 72% of the radiolabel was recovered in the feces or gastrointestinal tract of male and female rats representing unabsorbed test material. In the 14-day repeat dose study, absorption of the radiolabeled test material was ~8% for male rats and 5% for female rats. Greater than 91% of the radiolabel was recovered in the feces of treated rats. No significant sex-related differences in tissue distribution were found. The majority of the test

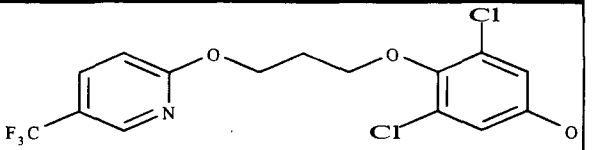
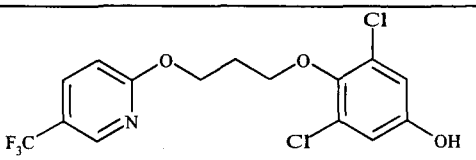
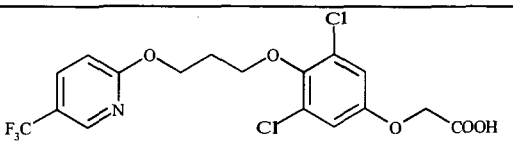
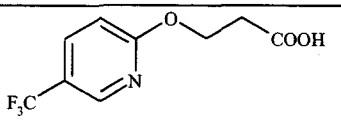
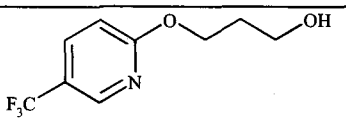
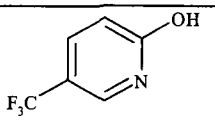
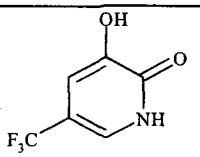
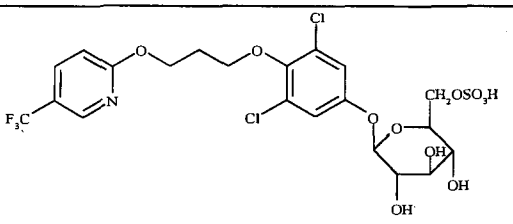
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
		material was eliminated in the feces, regardless of label position. Greater than 90% of the amount of radiolabel eliminated in the feces for all groups occurred within 72 hours of treatment. Of the approximately 8% of the radiolabel recovered in the bile during the 48-hour biliary study, the primary metabolite was S-1812-DP glucuronide (3,5-dichloro-4-(3-(5-trifluoromethyl-2-pyridyloxy)propoxy)phenol). This metabolite represented >80% of that recovered in the bile of male rats and all of the radiolabel recovered in the bile of female rats. Small traces of S-1812-DP were recovered in the bile of male rats. The study results were consistent with the oxidative cleavage of the dichloropropenyl group of S-1812 to yield S-1812-DP that was further conjugated with glucuronide in the liver. The predominant radiolabels recovered in the feces of rats treated with S-1812 labeled in the phenyl or pyridyl position were the parent compound or S-1812-DP. The primary metabolites S-1812-DP, S-1812-Py-OH, and HPHM are the result of cleavage of the propenyl side chain; hydroxylation of the pyridyl ring; and cleavage of the either bond between the pyridine and trimethylene chain, repsectively. This study is classified Acceptable/Guideline
Special Study in vitro cell culture studies	45905225. (2002) 0, 1, 3, 10, or 30 µM Acceptable/Non-guideline	In a series of *in vitro* cell culture studies with isolated Leydig or ovarian cells from Crj:CD(SD) male and female rats, no treatment-related effects were found on the production of progesterone, estradiol, 17α-OH-progesterone or testosterone and no cytotoxicity was observed. In addition, there was no effect on aromatase activity in cultured ovarian cells. These results suggest that 17β-HSD inhibition is not the mechanism for the increased androstenedione production in Leydig cells.
Special Study Subacute Steroid Hormone Study - Rat; Nonguideline	45905226 (2002) 45905223(2003) Acceptable/Nonguideline. 0, 100, 500, 1000, or 2000 ppm 0, 5.5, 25.5, 49.9, and 94.9 mg/kg/day for males 0, 6.1, 29.5, 54.9, and 102.2 mg/kg/day for females	No treatment-related effects were found on testasterone, estradiol or progesterone concentrations, uterine weight, or the estrus cycle. No histopathological effects were found in the adrenal gland and no effects on serum corticosterone concentration were found.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
870.5100 Bacterial reverse gene mutation assay	45685314 (1999), 45685315 (2001) Acceptable/Guideline	TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of E. coli were exposed to S-1812 (Lot No. PS-98041G, 93.7% a.i.) in DMSO at concentrations of 9.77, 19.5, 39.1, 78.1, 156 or 313 µg/plate without added metabolic activation (S9-mix) and at concentrations of 39.1, 78.1, 156, 313, 625 or 1250 µg/plate with S9-mix. The solvent and positive controls induced the appropriate responses in the corresponding strains. There was no evidence of induced mutant colonies over background.
870.5100 Bacterial reverse gene mutation assay	45685313 (2002) Unacceptable/Guideline	In a reverse gene mutation assay in bacteria (MRID 45685313), strains TA98, TA100, TA1535 and TA1537 of S. typhimurium and strain WP2(uvrA) of E. coli were exposed to dehydrochlorinated derivative of S-1812 (Lot No. Y-4298, 99.4% a.i.) in DMSO at concentrations of 0, 156, 313, 625, 1250, 2500 or 5000 µg/plate with and without added metabolic activation (S9-mix). The solvent and positive controls induced the appropriate responses in the corresponding strains. There was no evidence of a biologically significant induction of mutant colonies over background with or without metabolic activation.
870.5100 Bacterial reverse gene mutation assay	45685320 (2002) Unacceptable/Guideline	Bacteria strains TA98, TA100, TA1535 and TA1537 of *S. typhimurium* and strain WP2(uvrA) of E. coli were exposed to HPDO (Lot No. Y0001107B, 99.1% a.i.) in DMSO at concentrations of 0, 156, 313, 625, 1250, 2500 or 5000 µg/plate with and without added metabolic activation (S9-mix). The solvent and positive controls induced the appropriate responses in the corresponding strains. There was evidence of induced mutant colonies over background.
870.5100 Bacterial reverse gene mutation assay	45685321 (2002) Unacceptable/Guideline	In a reverse gene mutation assay in bacteria strains TA98, TA100 and TA1537 of *S. typhimurium* were exposed to HTFP in DMSO at concentrations of 0, 15, 50.0, 150, 500, 1500 or 5000 µg/plate with and without metabolic activation (S9-mix) and strains TA1535 of S. typhimurium and strain WP2(uvrA) of E. coli were exposed to HTFP at concentrations of 0, 156, 313, 625, 1250, 2500 or 5000 µg/plate with and without S9-mix. Results were negative in the second assay with TA100 in the presence of S9-mix. The solvent and positive controls induced the appropriate responses in the corresponding strains. There was evidence of induced mutant colonies over background.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
870.5300 CHO/HGPRT Forward Gene Mutation Assay	45685308 (2000) Acceptable/Guideline	In a mammalian cell gene mutation assay at the HGPRT locus Chinese hamster ovary CHO-K1-BH4 cells cultured in vitro were exposed to S-1812 in DMSO in two independent assays at concentrations of 0, 9.40, 18.8, 37.5, 75.0, 150.0 or 300 µg/mL for four hours in the absence of mammalian metabolic activation (S9-mix) and to concentrations of 0, 2.00, 4.00, 5.00, 6.00, 7.00, 8.00 or 10 µg/mL for four hours with S9-mix. No dose-dependency was seen and the actual mutant frequencies were well below the testing laboratory's criterion of 15 x 10-6 for a biologically significant response. The solvent and positive controls induced the appropriate responses. There was no evidence of induced mutant colonies over background.
870.5300 in vitro mutagenicity (mammalian forward gene mutation)	45685318 (2002) Acceptable/Guideline	Chinese hamster V79 cells cultured *in vitro* were exposed for four hours to HPDO (100% a.i., Lot No. YO001221) in DMSO at concentrations of 0, 110, 230, 450, 900 or 1800 µg/mL with and without metabolic activation (S9-mix). The solvent and positive controls (ethyl methanesulfonate) without S9-mix and N-nitrosodimethylamine with S9-mix) induced the appropriate responses. There was no evidence of induction of mutant colonies over background.
870.5300 in vitro mutagenicity (mammalian forward gene mutation)	45685319 (2002) Acceptable/Guideline	Chinese hamster lung V79 cells cultured *in vitro* were exposed to HTFP, (98.5% a.i., Lot No. 00209017) in DMSO in two independent assays at concentrations of 0, 100, 200, 400, 800 or 1600 µg/mL for four hours in the presence and absence of mammalian metabolic activation (S9-mix). In the confirmatory assay at the same five concentrations, the mutant frequency remained below a tripling of the respective solvent control value at all concentrations, with and without S9-mix. The solvent and positive controls induced the appropriate responses. There was no evidence of induced mutant colonies over background.

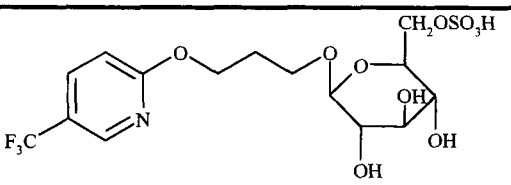
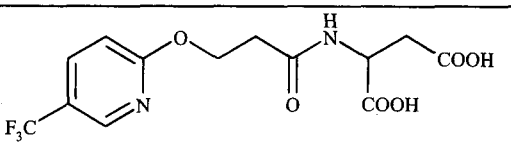
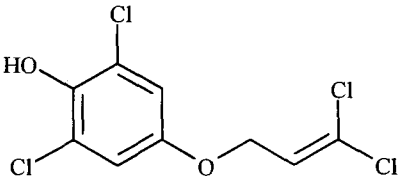
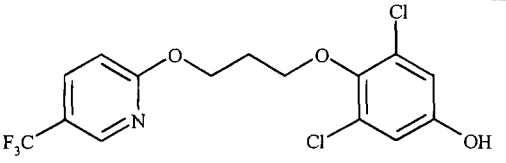
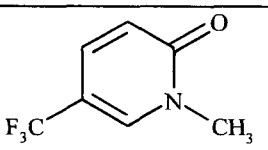
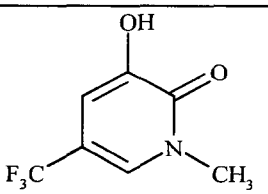
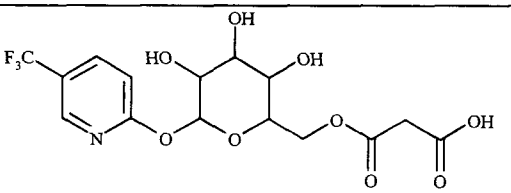
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
870.5300 Mouse lymphoma L5178Y TK± cells gene mutation assay at the TK locus	45685311 (2002) Acceptable/Guideline	In a mammalian cell gene mutation assay at the TK locus mouse lymphoma L5178Y TK± cells cultured *in vitro* were exposed for four hours to S-1812 at concentrations of 0, 3.13, 6.25, 12.5, 25.0, 50.0 or 100 µg/mL without metabolic activation (S9-mix) and at concentrations of 0, 2.50, 5.00, 7.50, 10.0, 12.5 or 15.0 µg/mL with S9-mix. The RTG at these three experimental points was below 10%, thus the increases in mutant frequency were not considered biologically significant. The solvent and positive controls (ethyl methanesulfonate without S9-mix and 20-methylcholanthrene with S9-mix) induced the appropriate responses. There was no evidence of biologically significant induction of mutant colonies over background.
870.5300 In Vitro Mammalian Cells in Culture Gene Mutation assay in V79 Chinese hamster lung fibroblasts	45685318 (2002) Acceptable/Guideline	Chinese hamster V79 cells cultured *in vitro* were exposed for four hours to HPDO in DMSO at concentrations of 0, 110, 230, 450, 900 or 1800 µg/mL with and without metabolic activation (S9-mix). The solvent and positive controls (ethyl methanesulfonate without S9-mix and N-nitrosodimethylamine with S9-mix) induced the appropriate responses. There was no evidence of induction of mutant colonies over background.
870.5375 In vitro mammalian cytogenetics (CHL cells)	45685316 (2002) Acceptable/Guideline	Chinese hamster CHL/IU cell cultures were exposed to HPDO in DMSO at concentrations of 0, 110, 230, 450, 900 or 1800 µg/mL for six hours with and without metabolic activation (S9-mix). The solvent and positive control values in both assays were appropriate and within the testing laboratory's historical control ranges. There was evidence of chromosome aberrations induced over background.
870.5375 In vitro mammalian cytogenetics (CHL cells)	45685317 (2002) Acceptable/Guideline	Chinese hamster CHL/IU cell cultures were exposed to HTFP in DMSO at concentrations of 0, 100, 200, 400, 800 or 1600 µg/mL for six hours with and without metabolic activation (S9-mix). The solvent and positive control values in both assays were appropriate and within the testing laboratory's historical control ranges. There was no evidence of biologically significant induction of chromosome aberrations over background.

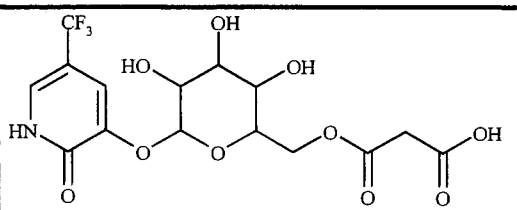
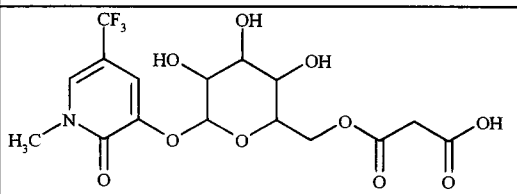
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
870.5375 In vitro mammalian cytogenetics (CHL cells)	45685317 (2002) Acceptable?/Guideline?	Chinese hamster CHL/IU cell cultures were exposed to HTFP (98.5% a.i., Lot # 00209017) in DMSO at concentrations of 0, 100, 200, 400, 800 or 1600 µg/mL for six hours with and without metabolic activation (S9-mix). The solvent and positive control values in both assays were appropriate and within the testing laboratory's historical control ranges. There was no evidence of biologically significant induction of chromosome aberrations over background.
870.5375 In vitro mammalian cytogenetics (CHL cells)	45685309 (2000) Acceptable?/Guideline?	Chinese hamster CHL/IU cell cultures were exposed to S-1812 in DMSO in three independent experiments. Cells were exposed at concentrations of 0, 20, 40 or 80 µg/mL (six-hour exposure, 18-hour recovery) without metabolic activation (S9-mix) in experiment 1 and at concentrations of 0, 15, 20 or 25 µg/mL The solvent and positive control values were appropriate. There was evidence of chromosome aberrations induced over background in the presence of S9-mix.
870.5395 Mouse Micronucleus assay	45905210 (2002) Acceptable/Guideline	In a CD-1 mouse bone marrow micronucleus assay, five male mice/dose were treated once orally with HPDO in 0.5% aqueous methylcellulose at doses of 0, 500, 1000 or 2000 mg/kg body weight. The solvent and positive control induced the appropriate responses. There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or harvest time.
870.5395 Mouse Micronucleus assay	45685312 (1999) Acceptable/Guideline	In a CD-1 mouse bone marrow micronucleus assay, five male mice/dose were treated once orally with S-1812 (93.7% a.i., lot # PS-98041G) in corn oil at doses of 0, 500, 1000 or 2000 mg/kg. There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or harvest time.
870.5395 Mouse Micronucleus assay	45905210 (2002) Acceptable/Guideline	In a CD-1 mouse bone marrow micronucleus assay five male mice/dose were treated once orally with HPDO (100% a.i., lot # YO001221) in 0.5% aqueous methylcellulose at doses of 0, 500, 1000 or 2000 mg/kg body weight. There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or harvest time.

Appendix 2. Chemical Name and Structure of Pyridalyl and its Transformation Products.		
Company Name	Chemical Name	Structure
Pyridalyl; S-1812	2-[3-[2,6-dichloro-4-[(3,3-dichloro-2-propenyl)oxy]phenoxy]propoxy] -5-(trifluoromethyl)pyridine	
S-1812-DP	3,5-dichloro-4-[3-(5-trifluoromethyl-2-pyridyloxy)propoxy phenol	
S-1812-Ph-CH_2COOH	2-{3,5-dichloro-4-[3-(5-trifluoromethyl-2-pyridyloxy)propoxy]phenoxy} acetic acid	
TPPA	3-(5-trifluoromethyl-2-pyridyloxy)propionic acid	
S-1812-PYP	3-(5-trifluoromethyl-2-pyridyloxy)propanol	
HTFP	2-hydroxy-5-trifluoromethylpyridine	
HPDO	3-hydroxy-5-trifluoromethyl-2-pyridone	
S-1812-DP glucose-6-sulfate conjugate	sulfuric acid mono-(6-{3,5-dichloro-4-[3-(5-trifluoromethyl-pyridin-2-yloxy)-propoxy]-phenoxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-ylmethyl) ester	

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Comments
870.5550 UDS	45685310 (2000) Acceptable/Guideline	In an in vivo/in vitro unscheduled DNA synthesis (UDS) assay in rat hepatocytes, S-1812 technical at doses of 0, 500, 1000 or 2000 mg/kg body weight, was administered once each to four Crl:CD (SD) IGS BR male rats per test group by gavage. The solvent and positive control (Dimethylnitrosamine) values were appropriate. There was no evidence that S-1812 technical increased the incidence of UDS over the solvent control values in this study.

Appendix 2. Chemical Name and Structure of Pyridalyl and its Transformation Products.

Company Name	Chemical Name	Structure
S-1812-PYP glucose-6-sulfate conjugate	sulfuric acid mono-{3,4,5-trihydroxy-6-[3-(5-trifluoromethyl-pyridin-2-yloxy)-propoxy]-tetrahydro-pyran-2-ylmethyl} ester	
TPPA aspartic acid conjugate	2-[3-(5-trifluoromethyl-pyridin-2-yloxy)-propionylamino]-succinic acid	
DCHM	3-[2,6-dichloro-4-(3,3-dichloro2-propenyl)oxy]phenol	
S-1812-DP-Py-OH	4-[3-[3-hydroxy-5-(trifluoromethyl)pyridin-2-yl]oxy]propoxy-3,5-dichlorophenol	
N-Methyl-HFTP	N-methyl-5-trifluoromethyl-2-pyridone	
N-Methyl-HPDO	N-methyl-3-hydroxy-5-trifluoromethyl-2-pyridone	
O-Malonyl glucoside of HTFP	Malonic acid mono-[3,4,5-trihydroxy-6-(5-trifluoromethyl-pyridin-2-yloxy)-tetrahydropyran-2-ylmethyl] ester	

Appendix 2. Chemical Name and Structure of Pyridalyl and its Transformation Products.		
Company Name	Chemical Name	Structure
O-Malonyl glucoside of HPDO	Malonic acid mono-[3,4,5-trihydroxy-6-(2-oxo-5-trifluoromethyl-1,2-dihydro-pyridin-3-yloxy)-tetrahydro-pyran-2-ylmethyl] ester	
O-Malonyl glucoside of N-methyl HPDO	Malonic acid mono-[3,4,5-trihydroxy-6-(1-methyl-2-oxo-5-trifluoromethyl-1,2-dihydro-pyridin-3-yloxy)-tetrahydro-pyran-2-ylmethyl] ester	

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R169200

Chemical Name: Pyridalyl

PC Code: 295149
HED File Code: 11000 Chemistry Reviews
Memo Date: 4/21/2009
File ID: DPD363102
DPD301446
Accession #: 000-00-0130

HED Records Reference Center
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