

Evaluation Report

PYRIDALYL

January 14, 2004
Food Safety Commission
Pesticides Expert Committee

(Progress of Evaluation)

September 26, 2002	Registration application submitted
October 29, 2003	The Minister of Health, Labour and Welfare requests a health risk assessment in line with the establishment of a maximum residue limit.
November 6, 2003	18 th meeting of the Food Safety Commission (explanation of request outline)
December 3, 2003	3 rd meeting of the Pesticides Expert Committee
December 11, 2003	23 rd meeting of the Food Safety Commission (reporting of the discussion results from the Pesticides Expert Committee meeting)
From December 11, 2003 to January 7, 2004	Public comments
January 14, 2004	Finalized

(Food Safety Commission Members)

Dr. Masaaki Terada (Chairman), Dr. Tadao Terao (Deputy Chairman), Dr. Naoko Koizumi, Dr. Motoko Sakamoto, Yasuhiko Nakamura, Dr. Seiichi Honma, Dr. Takeshi Mikami

(Food Safety Commission Pesticides Expert Committee Members)

Dr. Katsushi Suzuki (Chairman), Dr. Masao Hirose (Deputy Chairman), Dr. Yasuo Ishii, Dr. Makoto Ema, Dr. Toshihiro Ohta, Dr. Shogo Ozawa, Dr. Atsuya Takagi, Dr. Mitsuharu Takeda, Dr. Hiroyuki Tsuda, Dr. Masakuni Degawa, Dr. Makoto Hayashi, Dr. Akira Hiratsuka, Dr. Midori Yoshida

Abstract

The acceptable daily intake (ADI) of the insecticide "pyridalyl," having a phenoxy-pyridaloxo derivative structure, was determined to be 0.028 mg/kg bw/day in view of the results of various tests including that of animal (rats, goats) and plant (Chinese cabbage, tomato, strawberry) metabolisms, and the fate of pyridalyl in soil, hydrolytic and photolytic fates in water, residual tests in crops and soils, acute toxicity tests (rats), subchronic toxicity tests (rats, dogs), chronic toxicity tests (dogs), chronic toxicity tests/carcinogenicity tests (rats), carcinogenicity tests (mice), two-generation reproductive toxicity tests (rats), development toxicity tests (rats, rabbits), and genotoxicity tests.

No such adverse effect as carcinogenicity, genotoxicity, reproductive toxicity, or teratogenicity could be attributed to the compound.

The lowest no-observable-adverse-effect level (NOAEL) was 2.80 mg/kg bw/day, based on two-generation reproductive toxicity tests in rats. Therefore, a safety factor of 100 was applied to calculate ADI, thus yielding 0.028 mg/kg bw/day.

I. Outline of the Pesticide to be Evaluated

1. Usage

Insecticide

2. Common name (ISO name)

Pyridalyl

3. Chemical name

IUPAC name:

2,6-dichloro-4-(3,3-dichloro-2-allyloxy)phenyl-3-[5-(trifluoromethyl)-2-pyridyloxy]propyl ether

CAS chemical name (No. 179101-81-6):

2-[3-[2,6-dichloro-4-[(3,3-dichloro-2-propenyl)oxy]phenoxy]propoxy]-5-(trifluoromethyl)pyridine

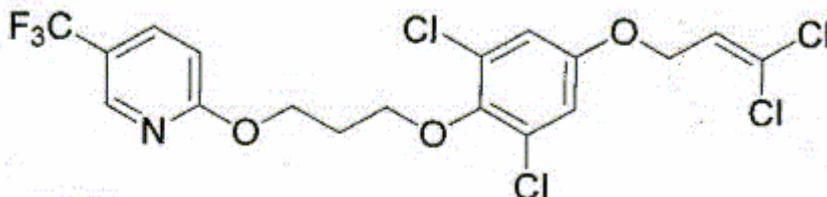
4. Chemical formula

$C_{18}H_{14}Cl_4F_3NO_3$

5. Molecular weight

491.12

6. Structural formula



7. Background of the development

Pyridalyl is an insecticide that has a phenoxy-pyridaloxo derivative structure. The compound displays a killing effect on the pests of order *Lepidoptera* and *Thysanoptera*.

In September 2002, Sumitomo Chemical Co., Ltd. (hereinafter "The Applicant") applied for the registration of the compound according to the Agricultural Chemicals Regulation Law. (Ref. 1)

II Summary of the Test Results

1. Animal metabolism

The study was conducted using [¹⁴C-phenylring] labeled pyridalyl (hereinafter “Phe-¹⁴C-pyridalyl”), [¹⁴C-propenyl] labeled pyridalyl (hereinafter “Pro-¹⁴C-pyridalyl”) and [¹⁴C-pyridyl] labeled pyridalyl (hereinafter “Pyr-¹⁴C-pyridalyl”).

The concentrations of radioactivity or metabolite were expressed in the concentration of pyridalyl, unless otherwise noted.

(1) Absorption, distribution, metabolism, and excretion (ADME) in rats (a single dose)

The ADME was examined in SD rats with a single oral dose of 5 mg/kg bw (hereinafter “Low Dose”) of Phe-¹⁴C-pyridalyl, Pro-¹⁴C-pyridalyl and Pyr-¹⁴C-pyridalyl, or 50 mg/kg bw (hereinafter “High Dose”) of these compounds except for Pyr-¹⁴C-pyridalyl.

At 168 hours after the treatment, the amount of Phe-¹⁴C-pyridalyl, Pro-¹⁴C-pyridalyl and Pyr-¹⁴C-pyridalyl eliminated in feces reached 83.8-96.1%, 54.9-58.8% and 92.7-96.7% of the dosage, and those in urine 0.1-2.0%, 9.7-17.7% and 2.0-2.1%, respectively. The amount of Pro-¹⁴C-pyridalyl eliminated in expiration was 10.8-11.6%.

The plasma concentrations of Phe-¹⁴C-pyridalyl in Low Dose reached a maximum level of 0.586 µg /g at 6 hours after treatment in males, and 0.308 µg /g at 8 hours in females. In High Dose, the plasma concentration reached a maximum level of 21.7 µg /g in males and 25.9 µg /g in females, both at 12 hours after the treatment. The plasma concentration of Pro-¹⁴C-pyridalyl at Low Dose reached a maximum level of 0.961 µg /g at 6 hours after the treatment in males, and 0.423 µg /g at 12 hours in females. The plasma concentration at High Dose reached a maximum level of 45.7 µg /g at 12 hours in males, and 44.3 µg /g at 24 hours in females.

The plasma half-lives of Phe-¹⁴C-pyridalyl and Pro-¹⁴C-pyridalyl were 16-20 hours and 47-92 hours, respectively. The elimination of Pro-¹⁴C-pyridalyl from the blood was slower than that of Phe-¹⁴C-pyridalyl, which could be due to the formation of vital elements such as amino acids from the propenyl group.

Among the tissue distributions at 168 hours after the treatment in male and female rats, the highest level was consistently found in the fat, regardless as to the treated chemicals labeled differently as Phe-¹⁴C-pyridalyl and Pro-¹⁴C-pyridalyl. The highest levels found in the fat of Low Dose and High Dose were 0.809-1.68 µg /g and 173-293 µg /g, respectively. Higher tissue distributions were also found in the adrenal gland, hair/skin, ovary, thyroid, pancreas, salivary gland, kidney, and liver.

The tissue concentrations of radioactivity were at the lowest in all tissues except for fat at the time of terminal kill regardless as to the treated labeled chemicals, as the level of the fat

increased with time. The radioactivity in most of the organs in each Phe-¹⁴C-pyridalyl dose group of both sexes decreased with the elimination half-lives of approximately 1-3 days. The elimination half-lives of Pro-¹⁴C-pyridalyl were longer than those of Phe-¹⁴C-pyridalyl.

Three metabolites (S-1812-Ph-CH₂COOH,¹ S-1812-DP, and HPHM) were detected in the extracts of the liver, kidney, lung, whole blood, and fat. There were polar metabolites and residual components of extracts in each organ.

The unchanged form of the compound was the main components in the feces, and a major metabolite was S-1812-DP. S-1812-Py-OH, HPHM, and DCHM were also detected in small amounts. In the case of Pyr-¹⁴C-pyridalyl, about 2% of the dosage was excreted in urine, where the sulfuric acid and glucuronide conjugates of HTFP and HPDO were found. ¹⁴CO₂ was detected in expiration only after administration with Pro-¹⁴C-pyridalyl. The polar metabolites including S-1812-DP and its glucuronide conjugates were found in the bile.

The main metabolic pathway of the compound was the cleavage of the dichloropropenyl group, through which S-1812-DP was produced from Phe-¹⁴C-pyridalyl and Pyr-¹⁴C-pyridalyl; and CO₂ and a small amount of polar metabolites were produced from Pro-¹⁴C-pyridalyl. Formation of DCHM and HPHM that would arise from the oxidative cleavage of the methylene group between the pyridine ring and the dichlorophenyl ring would be a minor metabolic pathway. A small amount of S-1812-Py-OH, a hydroxylated pyridalyl, would arise from all kinds of labeled substances; pyridalyl and HPDO, the sulfuric acid and glucuronide conjugates of HTFP, N-methyl-HTFP and N-methyl-HPDO from Pyr-¹⁴C-pyridalyl. (Refs. 2-5)

(2) ADME in rats (repeated doses)

The ADME was examined in SD rats with the repeated oral gavage administrations of 5 mg/kg bw/day of Phe-¹⁴C-pyridalyl for 14 days.

Most of the ¹⁴C was eliminated in the feces of males and females, and the total amount of excreted ¹⁴C for 27 days reached about 96-97% of the dosage. The total amount of ¹⁴C detected on day 27 in the blood and tissues was 2.6-3.2% of the total of the repeatedly administered dose. The level of ¹⁴C in the white adipose tissue did not reach a steady state by day 14, and showed a relatively high accumulation rate. The half-life was 10-15 days. The highest concentration in fat tissues (brown and white adipose tissues) was 38.4-57.5 µg /g. The concentrations in other organs were relatively low, in which half-lives of α and β phase were 1-5 and 4-24 days, respectively.

The major metabolic pathways could be: 1) the formation of S-1812-DP by the cleavage of

¹ See Appendix for abbreviations of metabolites (hereinafter the same)

the propenyl side chain; 2) the formation of S-1812-Ph-CH₂COOH by the oxidation of the propenyl side chain; 3) the formation of S-1812-Py-OH by the hydroxylation of the pyridine ring; and 4) the formation of HPHM by the cleavage of the ether bond between the pyridine and trimethylene chain. (Ref. 6)

(3) ADME in lactating goats

The ADME was examined in lactating goats with the repetitive doses of 17.84-20.00 mg/goat/day of Phe-¹⁴C-pyridalyl, Pro-¹⁴C-pyridalyl and Pyr-¹⁴C-pyridalyl for 4.5 days and a half.

Approximately 46-73% of the dosage was recovered from feces and urines, and 15-19% from alimentary tract contents. The levels of residue radioactivity in milk and organs were low in the goats treated with Phe-¹⁴C-pyridalyl and Pyr-¹⁴C-pyridalyl, and relatively high in those with Pro-¹⁴C-pyridalyl. The main metabolites in the milk and tissue of the goats with Phe-¹⁴C-pyridalyl and Pyr-¹⁴C-pyridalyl were S-1812-DP, and its sulfuric acid and glucuronide conjugates. The concentrations of S-1812-DP (free and conjugated) in the milk, liver and kidney were 0.004-0.011, 0.056-0.075 and 0.020-0.039 µg /g, respectively, and, in muscle and fat, there were less than 0.007 µg /g. Minor metabolites such as DCHM, S-1812-Ph-CH₂COOH, HTFP and unidentified compounds were detected in the milk, liver and kidney.

The major metabolic pathways in goats would be similar to those in rats and plants, including: 1) the formations of S-1812-DP by the cleavage of the propenyl group, following the conjugation with glucuronic acid and sulfuric acid; 2) the formation of S-1812-Ph-CH₂COOH by the oxidation of the propenyl group; 3) the formation of DCHM by the cleavage of the ether linkage; 4) the formation of low molecular weight compound by the metabolism of the propenyl group and the incorporation into biomacromolecules; and 5) the formations of S-1812-PyP, TPPA, and HTFP by the cleavage of the ether bond plus the formation of HPDO by the oxidation of the pyridalyl group. (Ref. 7)

2. Plant metabolism

(1) Chinese cabbage

Phe-¹⁴C-pyridalyl and Pro-¹⁴C-pyridalyl were applied to Chinese cabbage (cultivar: Jade Pagoda), 4 times at 224 g ai/ha (i.e., 45 days, 31 days, 17 days and 3 days before the harvesting, respectively). Three days after the final treatment, the heads and outer leaves of the mature Chinese cabbage were collected as samples for the metabolic test of the compound.

On the heads and outer leaves, 1.116-3.163 mg/kg and 4.711-5.007 mg/kg of the total residual radioactive (TRR) were found, respectively. A major part of an unchanged compound and metabolites, S-1812-DP, S-1812-Ph-CH₂COOH (trace amount) were found on the heads and outer leaves of the mature Chinese cabbage.

The major metabolic pathway of the compound in Chinese cabbage would be the cleavage of the propenyl-ether moiety at the phenyl ring. (Ref. 8)

(2) Tomato

Phe-¹⁴C-pyridalyl and Pro-¹⁴C-pyridalyl were applied to tomato plants (cultivar: Bush Beefsteak), 4 times at 224 g ai/ha (i.e., 78 days, 43 days (5-7 leaves stage), 22 days and 1 day before harvesting, respectively). A metabolic test of the compound in tomato plants was conducted in mature tomatoes collected 1 and 7 days after the final treatment, with the leaves collected 7 days after the treatment.

The radioactivity remained mostly on the leaves to which the compound was applied and a very low amount was detected on the tomatoes, suggesting the radioactivity hardly migrated into the fruit. TRR on the mature tomato collected 7 days after the final treatment were 0.085-0.172 mg/kg, and that after washed off was 0.056-0.135 mg/kg.

Major ¹⁴C residue on the mature tomatoes was the unchanged form, and a major metabolite was S-1812-DP, which amounted to 5.5% of TRR. S-1812-Ph-CH₂COOH was found only on the tomato leaves, and not detected on the mature tomatoes.

The major metabolic pathway of the compound in tomato would be the cleavage of the propenyl-ether moiety at the phenyl ring. (Ref. 9)

(3) Strawberry

Phe-¹⁴C-pyridalyl and Pro-¹⁴C-pyridalyl were applied 4 times to strawberry (cultivar: Hohkoh-wase) leaves and berries at 200 g ai/ha before harvesting (i.e., once at the early stage of berry formation and, subsequently, 3 times on a once-a-week basis). For the treatment of mixing the chemical into the soil, 800 g ai/ha of the compound was applied to the soil once at the same time as the first application to the plant. The metabolic test of

the compound in strawberry plants was conducted in the leaves and berries, collected 1 day and 7 days after the final treatment, and, in the soil, collected 22 and 28 days after the treatment.

TRR of 308.0-326.7 mg/kg and 2.727-4.502 mg/kg were detected on the leaves and berries, which were collected 7 days after the final application to the leaves and berries, where 97-99% of TRR was the unchanged compound. When Phe-¹⁴C-pyridalyl was applied to the leaves and berries, the metabolite S-1812-DP was detected at 6.67 mg/kg on the leaves and 0.06 mg/kg on the berries, respectively. Migration of the radioactivity from treated leaves to untreated berries was hardly detected and vice versa. In the case of the soil treatment, a trace of radioactivity was detected from the roots, crown, foliage and berries, and most of the residual radioactivity (78.6-94.4%) was detected (2.1-6.5 mg/kg) from the surface (0-2 cm depth) of the soil.

The test results showed that migration of the unchanged form and metabolites from the soil to the plant body or from the treated part of the plant to the other parts would scarcely occur. Although a small amount of S-1812-DP and polar compounds were formed in the leaves, berries and soil, most of the compound would remain unmetabolized. (Ref. 10)

3. Fate in soil

Phe-¹⁴C-pyridalyl, Pro-¹⁴C-pyridalyl and Pyr-¹⁴C-pyridalyl were applied to field soil (Ushiku), at 200 g ai/ha, and the fate was examined over 180 days of incubation. Extractable radioactive residues (ERR) gradually decreased with time and reached 71.2-87.9% by 180 days, while ¹⁴CO₂ gradually increased to 13.6-25.7% by 180 days. Total residual radioactivity (TRR) also gradually increased with time and registered 25.1-30.3% at 180 days.

S-1812-DP, S-1812-DP-Me and HTFP as degradation substances were detected, although those amounting to more than 10% of the total applied radioactivity (TAR) were not found. S-1812-DP and S-1812-DP-Me were detected up to 8.1% and 8.0% of TAR, respectively. HTFP, a degradation product specific to Pyr-¹⁴C-pyridalyl, reached 6.5% of TAR 61 days after the treatment, and then decreased to 3.4% of TAR by 180 days. These substances either underwent further degradation to inorganic carbon dioxide or bound strongly with the soil. The elimination half-lives of Pyr-¹⁴C-pyridalyl, Phe-¹⁴C-pyridalyl and Pro-¹⁴C-pyridalyl were calculated as 93.3, 174.3 and 148.2 days, respectively.

The compound is considered to have degraded through the cleavage of the propenylether moiety at the phenyl ring, the methoxylation of the resulting hydroxyl group and the formation of HTFP in the soil. (Ref. 11)

4. Hydrolytic fate test in water

Pyr-¹⁴C-pyridalyl was added to each buffer solution of pH5.0, 7.0, and 9.0 to make solutions at about 4 µg/L. These solutions were then incubated at 25 °C for 30 days. Significant decomposition was not observed under the given conditions, and 96.8%, 96.3% and 95.8% of TAR remained unchanged as pyridalyl in the buffer solution of pH5.0, 7.0 and 9.0, respectively, suggesting the compound as being very stable to hydrolysis. The half-lives of Pyr-¹⁴C-pyridalyl due to hydrolysis in solutions with pH 5.0, 7.0 and 9.0 were calculated to be 4.0, 3.3, and 2.9 years, respectively. (Ref. 12)

5. Photolytic fate test in water

Pyr-¹⁴C-pyridalyl and Phe-¹⁴C-pyridalyl were dissolved in sterilized buffer solution (pH7.0) and sterilized humic acid solution (pH7.0) (SHW) to make solutions at 0.004 µg/ml. The photolytic fate test was conducted at 25 ± 1 °C using an Xenon lamp (300-800 nm) as a light source for 30 days under a period of 12 hours light and 12 hours dark. Pro-¹⁴C-pyridalyl was similarly tested for photolysis in the buffer solution for 14 days, and in the SHW for 7 days.

The half-lives under the spring sunlight at latitude 35°N were estimated to be 9.1 days (pH7.0) and 3.5 days (SHW) for Pyr-¹⁴C-pyridalyl, 8.6 days (pH7.0) and 3.8 days (SHW) for Phe-¹⁴C-pyridalyl, and 5.8 days (pH7.0) and 4.0 days (SHW) for Pro-¹⁴C-pyridalyl.

Major photolytic reactions of Pyr-¹⁴C-pyridalyl and Phe-¹⁴C-pyridalyl in the buffer solutions were degradation to S-1812-PYP and HTFP, and very few remained as S-1812-DP and S-1812-PH-CH₂COOH. Major photolytic reactions of Pro-¹⁴C-pyridalyl in the buffer solution were the formation of 3,3-dichloropropenol and 3,3-dichloropropenic acid, and the subsequent formation of malonic acid. (Refs. 13-14)

6. Residual in crops

Pyridalyl (as for the compound to be analyzed) was analyzed through residual tests in crops such as cabbage, Chinese cabbage, lettuce, Chinese radish, leek, eggplant, tomato, green pepper and strawberry. As shown in Table 1, the highest residue detected was 6.77 mg/kg from lettuces, which were collected on the 3rd day after the last application with a single spray at 150 g ai/ha. The value, however, then decreased to 1.64 mg/kg on the 7th day and 0.40 mg/kg on the 14th day, respectively. In foliage of Chinese radish, residues were detected in the range from 0.24 to 4.22 mg/kg under the given test conditions, but in the roots, the residues were almost below the detection limit. Therefore, no overt signs for the migration from foliage to roots and the absorption from the soil existed. (Refs. 15-16)

Table 1. The results of residual tests in crops

Crop (Cultivation Type) (Part analyzed) Year tested	No. of Fields	Formulations	Amount Used (g ai/ha)	Applications (Times)	PHI (Days)	Residues (mg/kg)	
						Highest	Average
Cabbage (Field) (Heads) 2000	2	SC	150	2	1	0.23	0.13
				2	3	0.24	0.13
				2	7	0.04	0.03
				4	1	0.55	0.22
				4	3	0.38	0.18
				4	7	0.38	0.16
Chinese cabbage (Field) (Foliage) 2000	2	SC	150	2	7	0.37	0.18
				2	14	0.20	0.10
				2	21	0.23	0.10
Lettuce (Greenhouse) (Foliage) 2000	2	SC	150	1	3	6.77	3.86
				1	7	1.64	1.36
				1	14	0.40	0.28
				2	3	1.72	1.45
				2	7	1.05	0.48
				2	14	0.26	0.17
Chinese radish (Field) (Leaves) 2000	2	SC	150	1	3	6.23	4.22
				1	7	4.73	2.83
				1	14	2.08	1.30
				2	14	2.34	1.42
				2	21	1.57	0.86
				2	28	0.75	0.24
Chinese radish (Field) (Roots) 2000	2	SC	150	1	3	<0.01	<0.01
				1	7	0.01	0.01
				1	14	<0.01	<0.01
				2	14	0.02	0.01
				2	21	<0.01	<0.01
				2	28	<0.01	<0.01

Welsh onion (Hanegi) (Field) (Foliage) 2000	2	SC	100	2	3	1.63	1.00
				2	7	0.91	0.56
				2	14	0.51	0.36
				4	3	1.81	1.06
				4	7	1.11	0.92
4	14	0.76	0.57				
Welsh onion (Nebukanegi) (Field) (Foliage) 2000	2	SC	100	2	3	0.75	0.58
				2	7	0.66	0.47
				2	14	0.19	0.17
				4	3	1.25	0.82
				4	7	0.53	0.41
4	14	0.44	0.32				
Eggplant (Greenhouse) (Fruit) 2000	2	SC	200 ~	2	1	0.39	0.34
			202	2	3	0.29	0.20
				2	7	0.17	0.10
				4	1	0.27	0.25
				4	3	0.22	0.21
	4	7	0.12	0.11			
Tomato (Greenhouse) (Fruit) 2000	2	SC	225 ~	2	1	0.29	0.21
			300	2	3	0.39	0.25
				2	7	0.33	0.20
				2	14	0.21	0.17
Green Pepper (Greenhouse) (Fruit) 2001	2	SC	200	2	1	0.51	0.44
				2	3	0.76	0.54
				2	7	0.58	0.36
Strawberry (Greenhouse) (Fruit) 2000	2	SC	150 ~	2	1	1.28	0.95
			250	2	3	1.40	0.66
				2	7	0.91	0.62
				4	1	1.68	1.33
				4	3	1.44	1.20
	4	7	1.24	0.98			

• ai: active ingredients PHI: pre-harvest interval SC: soluble concentrate (i.e., flowable)

• Datum less than the detection limit (<0.01) is regarded as 0.01 and the average is calculated.

- In the case all the data is less than the detection limit, the average is noted as <0.01.

7. Residue test in soil

Residues of pyridalyl and two degradates (S-1812-DP, S-1812-DP-Me), the substances to be analyzed, in soil were studied using volcanic ash clay loam, unconsolidated sedimentary rocks clay loam, and unconsolidated sediments clay loam in vessels and in the field.

The results are shown in Table 2. The assumed half-life of those regarded as pyridalyl would be 78-361 days, and those regarded as the sum of pyridalyl and degradation products to be more than 82-361 days. (Ref. 17)

Table 2. The results of residue in soils (Assumed DT₅₀)

Type of test	Kind of soil	Unchanged compound	Total amount of pyridalyl and two degradates
Vessel	Volcanic ash clay loam	118 days	270 days
	Unconsolidated sedimentary rocks clay loam	361 days	>361 days
Field	Unconsolidated sediments clay loam	78 days	82 days
	Unconsolidated sedimentary rocks clay loam	245 days	255 days

Degradates: S-1812-DP and S-1812-DO-Me

8. Acute Toxicity

Acute Oral (p.o.), dermal and inhalation toxicities were studied in both male and female rats, respectively. LD₅₀s were determined as >5000 mg/kg bw (p.o. and dermal) and > 2.01 mg/L (inhalation). (Refs. 18-20)

9. Skin and eye irritation, and skin sensitization

Primary eye/skin irritation tests in New Zealand white rabbits revealed pyridalyl would have a slight irritable effect on the eye but not on the skin. (Refs. 21-22)

Skin sensitization potential was assessed in guinea pigs by the Maximization method. Erythema and swelling were observed on the tested animals with the sensitizing ratio of 80%; thus, severe skin sensitization was confirmed. (Ref. 23)

10. Subchronic toxicity test

(1) Subchronic toxicity test for 90 days in dogs

Beagle dogs (groups of 4 males and 4 females) were administered pyridalyl; technical

grade at 0, 10, 100, or 300 mg/kg bw /day (1000 mg/kg bw/day) for 90 days by gavage. At 300 mg/kg bw/day, abnormal respiration (tachypnea, stridor, abdominal breathing, dyspnea, etc.), decrease in hemoglobin content and hematocrit value, thickening of arterial and arteriolar wall in the lung, and vacuolization in fasciculata cells of the adrenal cortex were observed in males, and decrease in urinary nitrogen levels in the blood, increases in the absolute weight of the liver and relative weight of the kidneys against body weight ("relative weights against body weights" will be described as "relative weights" hereinafter) and centrilobular hepatocyte hypertrophy were observed in females. In the 100 mg/kg and higher dosage groups, there were increases of relative lung weights in both males and females, an increase in serum glucose level in males, and reduced body weight gain, abnormal respiration, a decrease in calcium concentration, hypertrophy of the pulmonary arterial and arteriolar wall, vacuolization of the fasciculata cell, vacuolization in hepatic cells at the intermediate zone, and brown pigmentation in the proximal renal tubules in females.

A male and a female died 2 or 3 days after commencing the treatment at 1000 mg/kg bw/day, so the test at this dose was discontinued. A female died 38 days after dosing was started at 300 mg/kg bw/day. The cause of death was diagnosed as respiratory insufficiency. A female became moribund on day 10 after starting the treatment at 100 mg/kg bw/day but recovered later.

The NOAEL was 10 mg/kg bw/day for both males and females. (Ref. 24)

(2) Subchronic toxicity test for 90 days in rats

SD rats (10 males and 10 females per group) were administered a diet containing pyridalyl; technical grade at 0, 100, 1000, or 2000 ppm for 90 days.

In males and females at 2000 ppm, increases in total cholesterol and relative heart weight, darkened color in the liver, and centrilobular hypertrophy of the hepatocytes were noted. In males at the same dose, there were a decrease in creatinine phosphokinase and increases in the albumin/globulin ratio and relative weights of the liver and kidneys. In females at the same dose, there were an increase in γ -GTP, intracytoplasmic vacuolization of the ovarian interstitial gland cells, single cell necrosis of hepatocytes, and intracytoplasmic vacuolization in zona reticularis of the adrenal cortex (no significant difference); one animal died due to hepatocellular necrosis. At 1000 ppm and higher, depression in body weight gain, aggregation of foamy cells in the lung (no significant difference) in males and females, a decrease in food consumption, increases in relative weights of the brain and lungs in males, and increases in relative weights of the liver and kidney in females were observed. No neoplastic lesions could be found.

The histopathological alterations found in the ovary and adrenal gland were considered to

be minor changes that might not affect the blood hormone levels, because there were no significant changes in blood corticosterone levels when tested with higher purity compound (see next paragraph (3)) and there were no significant changes in blood hormone levels in the test for possible hormonal effect of pyridalyl in rats treated for 31 days (see results described at 15. Other toxicological study).

The NOAEL could be 100 ppm for males and females (male: 5.56 mg/kg bw/day, female: 6.45 mg/kg bw/day). (Ref. 25)

(3) Subchronic toxicity test for 90 days in rats (highly purified substance)

SD rats (main groups of 10 males and 10 females, groups of 6 males and 6 females for hormone analysis, control and highest dosage administration) were administered diets containing pyridalyl (highly refined, at 0, 70, 700, 2000, or 3500 ppm) for 90 days. At 3500 ppm, both in males and females, increases in the relative weights of the kidneys and the adrenal, vacuolization in zona reticular cells of the adrenal cortex, and an increase in the incidences of aggregation of foamy cells/eosinophilic cells in the lungs (males: tendency with no statistical significance) were observed. At the same dose, there were an increase in mean corpuscular hemoglobin ("mean corpuscular hemoglobin" will be described as "MCH" hereinafter) and a decrease in serum testosterone in males, and a decrease in serum estradiol, increase in relative lung weight, centrilobular hypertrophy of hepatocytes, vacuolization in zona fascicular cell and decrease in vacuoles in zona glomerulosa of the adrenal cortex, and lower activity of serum cholinesterase in females. At doses of 2000 ppm and higher, a decrease in food consumption, increase in the number of blood lymphocytes and phospholipids were found both in males and females. At the same dose, increases in mean corpuscular volume ("mean corpuscular volume" will be described as "MCV" hereinafter) and γ -GTP, relative weights of the liver, lung and thyroid gland and centrilobular hypertrophy of the hepatocytes in males, and increases in platelet counts in the blood, total cholesterol, relative weight of the liver and ovaries and vacuolization in the ovarian interstitial gland cells in females were observed. At doses of 700 ppm and higher, depression of body weight and body weight gain in males and females, increases in hemoglobin, hematocrit, ratio of albumin/globulin, serum total cholesterol and phospholipids levels, increased intensity of single cell necrosis of hepatocytes (no statistical significant), portal vacuolization of hepatocytes (only for 700 ppm dose) in males, increase of leukocytes and serum, γ -GTP, single cell necrosis of hepatocytes and mononuclear cell infiltration in the liver in females were observed.

Decreases in serum estradiol (measured only for females) and testosterone (measured only for males) level were observed at 3500 ppm, which were restricted to the highest dose

and were slight in degree of alteration. Therefore, the possible influence of pyridalyl treatment on the endocrine system would not be so severe. It would not be of toxicological significance that lower serum cholinesterase activities were found at the doses of both 70 ppm and 700 ppm groups, since there was no obvious dose relationship.

The NOAEL could be 70 ppm for males and females (male: 4.68 mg/kg bw/day, female: 5.37 mg/kg bw/day). (Ref. 26)

11. Chronic toxicity/carcinogenicity study

(1) Chronic toxicity study for 12 months in dogs

Beagle dogs (groups of 4 males and 4 females) were administered pyridalyl; technical grade at 0, 1.5, 5, 20, or 80 mg/kg bw/day for 12 months by gavage. At 80 mg/kg bw/day, decreases in MCH were noted in males and females, and increases in blood glucose levels in males and increases in platelet counts and relative liver weight in females were observed. No histopathological changes could be attributed to the treatment.

The NOAEL could be 20 mg/kg bw/day in both males and females. (Ref. 27)

(2) Combined study of chronic toxicity for 24 months and carcinogenicity for 24 months in rats

SD rats (50 males and 50 females) were administered diets containing pyridalyl; technical grade at 0, 30, 100, 500, or 1000 ppm for 24 months. Increased motor activity was observed in males and females at the dose of 1000 ppm. At the same dose, increases of hematocrit, decreases in both hemoglobin contents and erythrocyte counts, and an increase in relative testis weight were observed in males, and an increase in rearing frequency was found in females. At doses of 500 ppm and higher, body weight gains were depressed in males and females. At the same dose, a decrease of absolute liver weight in males and increased brown pigmentation in the spleen in females were observed. There were no statistically significant differences in the occurrence of neoplastic lesions among the treated groups and the control group.

The NOAEL could be 100 ppm (male: 3.40 mg/kg bw/day, female: 4.10 mg/kg bw/day). Pyridalyl did not show any carcinogenicity in rats. (Ref. 28)

(3) 78-week carcinogenic study in mice

ICR mice (52 males and 52 females) were administered a diet containing pyridalyl; technical grade at 0, 15, 50, 1000, or 2500 ppm for 78 weeks. At the dose of 2500 ppm, an increase in relative testis weight was observed in males, and increases in relative weight of the liver and kidneys were found in females. At doses of 1000 ppm and higher, depressed

body weight gain was observed in males and females. There was no statistically significant difference in the occurrence of neoplastic lesion in the treated groups as compared to those in the control group. The increase in relative testis weight observed in males given 2500 ppm is considered accidental due to the relatively low values in the control group.

The NOAEL could be 50 ppm in males and females (male: 5.04 mg/kg bw/day, female: 4.78 mg/kg bw/day). Pyridalyl did not show any carcinogenicity in mice. (Ref. 29)

12. Reproductive/developmental toxicity

(1) Two generation reproductive toxicity study in rats

SD rats (groups of 24 males and 24 females) were fed a diet containing pyridalyl; technical grade at 0, 40, 200, or 1000 ppm for two generations. In the parent animals, a decrease in body weight (P: females, F₁: males), body weight gain (P: females, F₁: males and females), and food consumption (F₁: males), an increase in relative brain weight (P: males) and weight in the thyroid gland (P: females, F₁: males), ovary (P), lung (P: females), kidney (P: males, F₁: males), testis (P), epididymis (P) and seminal vesicle (F₁), a decrease in weight of the brain (F₁: females), liver (P: males), and spleen (P: males, F₁: males), an increase in small follicles in the thyroid gland (P: females, F₁: females), and vacuole alteration of the ovarian interstitial gland cell (F₁) were found at 1000 ppm. A decrease in body weight gain and food consumption in P males, and an increase in relative testis weight in F₁ males and relative ovary weight in F₁ females were observed at 200 ppm and higher. The vaginal opening was delayed in F₁ at 200 ppm and higher, and in F₂ at 1000 ppm.

A decrease in body weight gain of both F₁ and F₂ offspring were found at 200ppm and higher.

The NOAEL for parents and offspring could be 40 ppm (P: male: 2.80 mg/kg bw/day, P: female 3.11 mg/kg bw/day, F₁: male 3.40 mg/kg bw/day, F₁: female 3.62 mg/kg bw/day), respectively. (Ref. 30)

(2) Developmental toxicity study in rats

SD rats (groups of 24 females) were given pyridalyl; technical grade at 0, 10, 50, or 250 mg/kg bw/day by gavage on days 6–15 of gestation. In dams, decreases in body weight gain and food consumption at 250 mg/kg bw/day and a decrease in body weight gain at 50 mg/kg bw/day were observed. No effect was found in the number of live fetuses, incidence of post implantation loss, fetal weight, placental weight or sex ratio of live fetuses. Observation detected no increase in the incidence of fetuses with malformations or variation after administration of pyridalyl.

The NOAEL could be 10 mg/kg bw/day for dams and 250 mg/kg bw/day for fetuses in rats, respectively. No embryoletality or teratogenicity of pyridalyl was observed. (Ref. 31)

(3) Developmental toxicity study in rabbits

Japanese white rabbits (groups of 25 females) were given pyridalyl; technical grade at 0, 10, 50, or 150 mg/kg bw/day by gavage on days 6–19 of gestation. Decreases in maternal body weight gain and food consumption after day 15 of pregnancy were observed at 150 mg/kg bw/day. Although one dam died and 4 cases of abortion or premature birth were observed, these were considered to be due to the marked decrease in food consumption and body weight. Low fetal weight was found at 150 mg/kg bw/day.

The NOAEL could be 50 mg/kg bw/day for dams and fetuses in rabbits, respectively. No teratogenicity of pyridalyl was noted. (Ref. 32)

13. Genotoxicity

Pyridalyl has been tested widely in *in vitro* and *in vivo* following standard protocols (Table 3). It was not mutagenic in bacteria and cultured Chinese hamster ovary (CHO) cells, with and without an exogenous metabolic activation system (9 mix). It was weakly clastogenic in the *in vitro* chromosomal aberration test using cultured Chinese hamster lung cells (CHL/IU). Negative results, however, were obtained in the micronucleus test in mouse bone marrow cells and *in vivo/in vitro* UDS in rats liver cells. Although increments of structural and numerical aberrations were observed by this chemical in the presence of S9 mix in (CHL/IU) cells, the expert committee considered that pyridalyl was not genotoxic in *in vivo* by the following reasons: 1) the positive cytogenetic effect *in vitro* was marginal; 2) the positive response was observed at only strongly cytotoxic concentration levels; 3) clear negative results were obtained both in the mouse micronucleus test of that endpoint was chromosome aberrations and *in vivo/in vitro* unscheduled DNA synthesis test. (Refs. 33-37)

Table 3. Summary of genotoxicity test results (technical grade)

Test system		Cells/animals	Dose (mg/kg bw)	Result
<i>In vitro</i>	Microbial reverse mutation (± S9)	<i>S.typhimurium</i> TA100, TA98, TA1535, TA1537, <i>E.coli</i> WP2 <i>uvrA</i>		Negative
	Mammalian cell chromosomal aberration (± S9)	Cultured Chinese hamster lung cell line (CHL/IU)		Weakly positive (+S9)

	Forward mutation test (± S9)	Cultured Chinese hamster ovary cell line (CHO)		Negative
<i>In vivo/in vitro</i>	Unscheduled DNA synthesis	4 male SD rats	500,1000,2000 (single oral dose)	Negative
<i>In vivo</i>	Rodent micronucleus	5 males ICR mice/group	500,1000,2000 (single oral dose)	Negative

± S9 mix with/without metabolic activation, +S9: with metabolic activation

Dehydrochloric acid of pyridalyl, an impurity of pyridalyl, showed double revertants frequency in *S. typhimurium* TA 1535 at the highest dose (1500 µg/plate) in the presence of an exogenous metabolic activation system compared to the corresponding solvent control. Negative results, however, were obtained in forward mutation tests with cultured Chinese hamster V79 cells and in the mouse bone marrow micronucleus test (Table 4). The expert committee considered that the response observed in the microbial reverse mutation test was not biologically relevant because the response was observed only in TA1535 at the highest dose; the increase was marginal; and neither a dose-response relationship nor reproducibility of the results was observed. Considering these findings, dehydrochloric acid of pyridalyl is not genotoxic. (Refs. 38-40)

Table 4. Summary of genotoxicity test results (Dehydrochloric acid of pyridalyl)

Test system		Cells/animals	Dose (mg/kg bw)	Result
<i>In vitro</i>	Microbial reverse mutation (± S9)	<i>S.typhimurium</i> TA100,TA98,TA1535,TA1537 <i>E.coli</i> WP2 <i>uvrA</i>		Weakly positive TA1535 (+S9)
	Forward mutation (± S9)	Chinese hamster lung cell (V79)		Negative
<i>In vivo</i>	Rodent micronucleus	5 males ICR mice	500,1000,2000 (single oral dose)	Negative

± S9 mix with/without metabolic activation, + S9: with metabolic activation

Metabolite of pyridalyl (S-1812-DP) was not mutagenic in the microbial reverse mutation test (Table 5). (Ref. 41)

Table 5. Summary of genotoxicity test results (metabolite)

Substance	Test system	Cells	Result
Metabolite S-1812-DP	Microbial reverse mutation (± S9)	<i>S.typhimurium</i> TA100,TA98, ,TA1535, TA1537, <i>E.coli</i> WPuvrA	Negative

± S9 mix with/without metabolic activation

14. General pharmacology

SD rats (groups of 3 males and 3 females) were administered pyridalyl; technical grade at 600, or 2000 mg/kg bw by gavage. No effects of pyridalyl on general conditions and behavior were observed. Beagle dogs (groups of 4 males) were also administered pyridalyl; technical grade 80, 400, or 2000 mg/kg bw into duodenum. Possible effects of pyridalyl on respiratory rates and blood pressure were suggested at doses of 400 mg/kg bw and higher. (Ref. 42)

15. Other toxicological study

A reporter gene assay with ER_a, AR and TR_a receptor was carried out to detect whether or not pyridalyl could exert effects via the various hormone receptors such as estrogen, androgen and thyroid hormonal receptors. The agonistic and antagonistic effects of pyridalyl on ER_a, AR and TR_a hormonal receptors were considered negative. (Ref. 43)

Possible effect of pyridalyl on the steroid synthesis pathway was surveyed in rats. It was revealed that pyridalyl affected the sex hormone synthetic pathway in the testis at the concentration of 3 μM and higher, and this effect was caused by an inhibition of testosterone synthesis, via weak but significant inhibition of 17_a-HSD activity. (Ref. 44)

SD rats (groups of 8 males and 16 females) were administered a diet containing pyridalyl; technical grade at 0, 100, 500, 1000, or 2000 ppm for 31 days. Increase in relative liver weight was observed in males and females at the dose of 2000 ppm. In this group, a decrease in relative prostate weight (dorsal lobe) was observed in males and vacuolation of interstitial gland cell in the ovary was noted in females, although there was neither any obvious effect on blood hormone levels (male: corticosterone, testosterone, female: estradiol, progesterone) nor any significant effect on the other relevant organs. Therefore,

pyridalyl would not affect the endocrine system so severely. A decrease in food consumption and suppression of body weight gain were observed in males at the dose of 500 ppm and higher, and in females at the dose of 1000 ppm.

The NOAEL could be 100 ppm (5.5 mg/kg bw/day) in males and 500ppm (29.5 mg/kg bw/day) in females. (Ref. 45)

. Evaluation

Absorption, distribution, metabolism, and excretion of pyridalyl were studied using ^{14}C labeled chemical at the phenyl ring, propenyl group, and pyridyl group. In rats, the concentration of pyridalyl in blood plasma reached the maximum level at 6-24 hours after a single oral administration. The main excretion pathway was that into the feces, but 11-12% of Pro- ^{14}C -pyridalyl was excreted into expiration. The distribution of pyridalyl was comparatively high in fat tissue and the adrenal gland. The elimination half-life ($T_{1/2}$) of Phe- ^{14}C -pyridalyl was 1-3 days in most tissues, although the $T_{1/2}$ of Pro- ^{14}C -pyridalyl was longer than that of Phe- ^{14}C -pyridalyl. No sex difference in $T_{1/2}$ was observed with the two differently ratio labeled compounds. A major metabolite detected in feces was S-1812-DP. The main metabolic pathways of pyridalyl were the oxidation and other pathways such as elimination of the dichloropropenyl function, and hydroxylation of the 3rd carbon in the pyridyl function, the cleavage of ether bond, and Nmethylation of the pyridyl function. Conjugations with glucuronic acid and with sulfuric acid were also observed. The residual concentrations of the Pro- ^{14}C -pyridalyl in a number of tissues were higher than those of Phe- ^{14}C -pyridalyl, which would be due to the fact that the oxidative cleavage products of the propenyl function were incorporated into amino acids to be finally distributed into vital tissues at relatively high concentrations.

Plant metabolism of pyridalyl was examined in Chinese cabbage, tomato, and strawberry. Pyridalyl would be scarcely metabolized in these vegetables, and there would be no migration from applied leaves or fruits to non-applied portions of the strawberry.

The degradation half-life (DT_{50}) of pyridalyl in soil was 93.3-174.3 days.

Pyridalyl was degraded by light in aqueous solution such that DT_{50} of pyridalyl in natural water would be 3.5-9.1 days under sunlight at latitude 35°N in springtime.

Residual levels of pyridalyl were examined in cabbage, Chinese cabbage, lettuce, Japanese radish, leek, eggplant, tomato, green pepper, and strawberry. The highest residual value of 6.77 mg/kg was observed in lettuce cropped at 3 days after the final spraying at 150 g ai/ha, which decreased to 1.64 mg/kg on day 7 and 0.40 mg/kg on day 14. Although 0.24-4.22 mg/kg of residual value of pyridalyl was found on the leaves of Japanese radish with the given conditions, the residual pyridalyl was below the detection limit in the root; thus, migration of the chemical within the radish would scarcely occur.

DT_{50} of pyridalyl in soil was 78-361 days, and that of the sum of pyridalyl and its two degradates was 82-361 days and longer in volcanic clay loam, unconsolidated sedimentary rocks clay loam and unconsolidated sediments clay loam (both in vessel and in the field).

Oral and subcutaneous LD_{50} of pyridalyl were more than 5000 mg/kg bw in rats. LC_{50} of pyridalyl was also more than 2.01 mg/L in rats in the inhalation toxicity tests. The NOAEL

of pyridalyl was 4.68 mg/kg bw/day in rats and 10 mg/kg bw/day in dogs in subchronic toxicity tests.

The lung toxicity (such as thickening of the pulmonary artery) of pyridalyl in rats and dogs could be due to damage of the arterial endothelium by pyridalyl, which subsequently led to the increased permeability of blood vessels, thus causing the edema.

As for one of the pathogenesis of the aggregation of foamy cells and/or eosinophilic cells in the lung, the applicant hypothesized in the discussion that pyridalyl or its metabolites might be exuded into the pulmonary alveoli by the increased permeability of blood vessels and pyridalyl-phagocytized macrophages, becoming visible as large foamy cells under histological examination. The Pesticides Expert Committee, however, did not agree with the applicant's view and concluded that the phenomenon could be due to other secondary reactions, because 1) this response was observed only in the highest dose group, and the threshold level of pyridalyl could be assumed in rats, 2) there was no obvious evidence that pyridalyl and its metabolites exuded into the lung, and 3) the aggregation of foamy cell in the lung would occur more frequently in rats than in other animal species.

Since vacuolization was observed in the endocrine organs such as the ovary and adrenal gland in rats, experiments for the direct effect of pyridalyl on hormone receptors and the effects on hormone synthesis and on sexual hormone levels were carried out. The results revealed that pyridalyl would not exert serious effects on the endocrine system.

The NOAEL was 3.40 mg/kg bw/day in rats, 4.78 mg/kg bw/day in mice, and 20 mg/kg bw/day in dogs in chronic toxicity tests and carcinogenicity tests. Pyridalyl was not carcinogenic in rats, mice, or dogs.

In the rat two-generation reproductive toxicity study, sexual maturation was delayed in females at 200 ppm and higher, but no adverse effect on the reproductive outcome was observed. An increase in the incidence of small follicles in the thyroid gland was observed in parous animals; although the incidence could be affected by such physiological alterations that hypothyroidism during pregnancy would quickly recover to normal states, which has been reported to occur. The NOAEL was 2.80 mg/kg bw/day in the rat two-generation reproductive toxicity study.

The NOAELs of pyridalyl were 10 mg/kg bw/day for dams and 250 mg/kg bw/day for fetuses in the rat developmental toxicity study. The NOAELs for both dams and fetuses were 50 mg/kg bw/day in the rabbit developmental toxicity study. Pyridalyl has no teratogenicity in either rats or rabbits.

Pyridalyl has been tested widely for its mutagenic or genotoxic potential in *in vitro* and *in vivo* standard protocols including the microbial reverse mutation test, chromosomal aberration in Chinese hamster lung-derived cell line, forward mutation test in Chinese

hamster ovary-derived cell line, unscheduled DNA synthesis and the micronucleus test. And pyridalyl was not mutagenic in bacteria and cultured Chinese hamster ovary (CHO) cells, with and without an exogenous metabolic activation system (S9mix). Although structural and numerical aberrations were induced by this chemical in the presence of S9mix in (CHL/IU) cells, the expert committee considered that pyridalyl was not genotoxic in the *in vivo/in vitro* unscheduled DNA synthesis test and in the mouse micronucleus test of that endpoint was chromosome aberration.

Dehydrochloric acid of pyridalyl, an impurity of pyridalyl, showed marginal increase of revertants in *S. typhimurium* TA1535 in the presence of S9mix. The dose-response relationship and reproducibility were unclear, and forward mutation tests with cultured mammalian cells and mouse bone marrow micronucleus tests gave negative results, suggesting dehydrochloric acid of pyridalyl would not be genotoxic.

Metabolites of pyridalyl, S-1812-DP, was not genotoxic in bacteria.

NOAELs determined by the test results are shown in Table 6.

Table 6. NOAELs determined in toxicity evaluation tests

Species	Evaluation Test	NOAEL	Note
Dog	90-days subchronic toxicity	Male: 10 mg/kg bw/day Female: 10 mg/kg bw/day	
	12-months chronic toxicity	Male: 20 mg/kg bw/day Female: 20 mg/kg bw/day	
Rat	90-days subchronic toxicity	Male: 5.56 mg/kg bw/day Female: 6.45 mg/kg bw/day	
	90-days subchronic toxicity (Highly refined chemicals)	Male: 4.68 mg/kg bw/day Female: 5.37 mg/kg bw/day	
	Combined study of chronic toxicity (24-months) /carcinogenicity	Male: 3.40 mg/kg bw/day Female: 4.10 mg/kg bw/day	No carcinogenicity
	Two-generation reproductive toxicity study	P Male: 2.80 mg/kg bw/day P Female: 3.11 mg/kg bw/day F ₁ Male: 3.40 mg/kg bw/day F ₁ Female: 3.62 mg/kg bw/day	Delayed sexual maturation in females
	Developmental toxicity study	Dam: 10 mg/kg bw/day Fetus: 250 mg/kg bw/day	No teratogenicity
Mouse	78-weeks carcinogenicity	Male: 5.04 mg/kg bw/day Female: 4.78 mg/kg bw/day	No carcinogenicity
Rabbit	Developmental toxicity study	Dam: 50 mg/kg bw/day Fetus: 50 mg/kg bw/day	No teratogenicity

Based on the evaluation, the Pesticides Expert Committee of The Food Safety Commission established the ADI value of pyridalyl as:

ADI: 0.028 mg/kg bw/day
 Referred study: Reproductive toxicity study
 Laboratory animal tested: Rat
 Duration: two-generation
 Administration route: mixed feeds
 NOAEL: 2.80 mg/kg bw/day
 Safety factor: 100
 Residue definition for exposure assessment:
 Pyridalyl (parent chemical only)

< APPENDIX: Abbreviations for metabolites >

Abbreviation	Chemical name
S-1812-Py-OH	2-[3-[2,6-dichloro-4-[(3,3,-dichloroallyloxy)]phenoxy]propoxy]-5-(trifluoromethyl)-3-pyridynol
S-1812-DP	3,5-dichloro-4- [3-(5-trifluoromethyl-2-pyridyloxy)]-propoxyphenol
S-1812-DP-Me	2-[3-(2,6-dichloro-4-methoxyphenoxy)propoxy]-5-(trifluoromethyl)pyridine
S-1812-Ph-CH ₂ COO H	2-[3,5-dichloro-4-[3-(5-trifluoromethyl-2-pyridinoxy)]-propoxy]phenoxy]acetic acid
HPHM	3-[2,6-dichloro-4-(3,3-dichloroprop-2-enyloxy)phenoxy]-propanol
DCHM	3-[2,6-dichloro-4-(3,3-dichloroprop-2-propanil)oxy]phenol
S-1812-PYP	3-(5-trifluoromethyl-2-pyridyloxy)propanol
TPPA	3-(5-trifluoromethyl-2-pyridyloxy)propionic acid
HTFP	5-trifluoromethyl-2-hydroxypyridine
HPDO	5-trifluoromethyl-3-hydroxy-2-pyridone
N-methyl-HTFP	5-trifluoromethyl- <i>N</i> -methyl-2-pyridone
N-methyl-HPDO	5-trifluoromethyl-3-hydroxy- <i>N</i> -methyl-2-pyridone

(Appendix: List of References)

1. Extract of applicant dates for pyridalyl: Sumitomo Chemical Co., Ltd., 2003, unpublished.
2. Metabolism and distribution study in rats with high- and low- single doses of oral administration of pyridalyl (GLP study): PTRL West Inc. (U.S.A.), PTRL East Inc. (U.S.A.), 2002, unpublished.
3. Pyridalyl metabolism in rats (GLP study): PTRL East Inc. (U.S.A.), 2002, unpublished.
4. Pyridalyl distribution in the tissue of rats (GLP study): PTRL West Inc. (U.S.A.), PTRL East Inc. (U.S.A.), 2002, unpublished.
5. Bile discretion by pyridalyl in rats (GLP study): PTRL West Inc. (U.S.A.), PTRL East Inc. (U.S.A.), 2002, unpublished.
6. Metabolic test of pyridalyl in rats by dietary administration to rats for 14 days (GLP study): Sumitomo Chemical Co., Ltd., Institute of Biological Environmental Science, 2001, unpublished.
7. Metabolic test of pyridalyl in lactating goats (GLP study): Ricerca LLC (U.S.A.), 2002, unpublished.
8. Pyridalyl metabolism in Chinese cabbages (GLP study): Ricerca (U.S.A.), 2000, unpublished.
9. Pyridalyl metabolism in tomatoes (GLP study): Ricerca (U.S.A.), 2000, unpublished.
10. Pyridalyl metabolism in strawberries: Sumitomo Chemical Co., Ltd., 2000, unpublished.
11. Pyridalyl metabolism and degradation in soil: Sumitomo Chemical Co., Ltd., 2001, unpublished.
12. Pyridalyl hydrolysis distribution under laboratory conditions: Valent U.S.A. Corp., 2002, unpublished.
13. Pyridalyl (Pyr Labeled and P Labeled) photolytic degradation in water (GLP study): PTRL West Inc. (U.S.A.), 2002, unpublished.
14. Pyridalyl (Pro Labeled) photolytic degradation in water (GLP study): PTRL West Inc. (U.S.A.), 2002, unpublished.
15. Crops residual examination result of pyridalyl: Institute of Environment Toxicology, 2003, unpublished.
16. Crops residual examination result of pyridalyl: Sumitomo Chemical Co., Ltd., 2003, unpublished.
17. Soiling residual examination result of pyridalyl: Sumitomo Chemical Co., Ltd., 2003, unpublished.
18. Pyridalyl acute oral toxicity to rats (GLP study): Covance Laboratories Inc. (U.S.A.), 1999, unpublished.

19. Pyridalyl acute dermal toxicity to rats (GLP study): Covance Laboratories Inc. (U.S.A.), 1999, unpublished.
20. Pyridalyl acute inhalation toxicity study in rats (GLP study): Huntingdon Life Sciences Ltd. (U.K.), 2002, unpublished.
21. Irritant effects of pyridalyl on rabbit eyes (GLP study): Covance Laboratories Inc. (U.S.A.), 1999, unpublished.
22. Irritant effects of pyridalyl on rabbit skin (GLP study): Covance Laboratories Inc. (U.S.A.), 1999, unpublished.
23. Skin sensitization study of pyridalyl in guinea pigs (incorporating appositive control using hexyl cinnamic aldehyde) (GLP study): Sumitomo Chemical Co., Ltd., 2002, unpublished.
24. Pyridalyl subchronic toxicity study in dogs (GLP study): Panafarm Laboratories, 2000, unpublished.
25. Pyridalyl (technical material): subchronic toxicity study by dietary administration to rats for 13 weeks (GLP study): Institute of Environment Toxicology, 1999, unpublished.
26. Pyridalyl (highly refined): subchronic toxicity study by dietary administration to rats (GLP study): Sumitomo Chemical Co., Ltd., 1997, unpublished.
27. Pyridalyl chronic toxicity study by dietary administration to dogs (GLP study): Panafarm Laboratories, 2001, unpublished.
28. Pyridalyl combined carcinogenicity and chronic toxicity study by dietary administration to dogs (GLP study): Institute of Environment Toxicology, 2002, unpublished.
29. Pyridalyl carcinogenicity study by dietary administration to mice (GLP study): Institute of Environment Toxicology, 2002, unpublished.
30. Pyridalyl: Study of reproductive performance in rats treated continuously through two successive generations by dietary administration (GLP study): Institute of Environment Toxicology, 2002, unpublished.
31. Pyridalyl: Study of embryo-fetal toxicity with rats by oral gavages by dietary administration (GLP study): Institute of Environment Toxicology, 2001, unpublished.
32. Pyridalyl: Study of embryo-fetal toxicity with rabbits by oral gavages by dietary administration (GLP study): Institute of Environment Toxicology, 2001, unpublished.
33. Pyridalyl: Bacterial assay (GLP study): Sumitomo Chemical Co., Ltd., 1999, unpublished.
34. Chromosomal aberration test on PYRIDALYL by CHL/IU of Chinese hamsters (GLP study): Sumitomo Chemical Co., Ltd., 2000, unpublished.
35. Mouse micronucleus test on PYRIDALYL (GLP study): Sumitomo Chemical Co., Ltd., 1999, unpublished.
36. Genetic mutation test on PYRIDALYL by CHO-K1-BH4 of Chinese hamsters (GLP

- study): Covance Laboratories Inc. (U.S.A.), 2000, unpublished.
37. In vivo/in vitro UDS test on PYRIDALYL by primary cultured hepatocyte of rats, Covance Laboratories Inc. (U.S.A.), 2000, unpublished.
 38. Microbial reverse mutation test in dehydrochloric acid of pyridalyl, mixture of original pyridalyl, Sumitomo Chemical Co., Ltd., 2002, unpublished.
 39. Mouse micronucleus test in dehydrochloric acid of pyridalyl, mixture of original pyridalyl: Food, Agriculture Chemical Safety Assessment Center, 2002, unpublished.
 40. Genetic mutation test in dehydrochloric acid of pyridalyl, mixture of original PYRIDALY with cultured V79 cell from Chinese hamster's lungs: Institute of Environment Toxicology, 2002, unpublished.
 41. PYRIDALYL (S-1812-DP): Microbial reverse mutation test: Sumitomo Chemical Co., Ltd., 2002, unpublished.
 42. General pharmacological test on PYRIDALYL (GLP study): Panafarm Laboratories, 2002, unpublished.
 43. Reporter assay test on PYRIDALYL with ER , AR and TR : Sumitomo Chemical Co., Ltd., 2002, unpublished.
 44. Effect of pyridalyl on the sexual hormonal synthetic pathway in rats: Sumitomo Chemical Co., Ltd., 2002, unpublished.
 45. Effect of original pyridalyl on hormone by dietary administration to rats for 4 weeks: Sumitomo Chemical Co., Ltd., 2002, unpublished.

-