Evaluation Report

Flufenoxuron

April 2007

Food Safety Commission

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<Progress of Evaluation>

1993	November 8	First registration in Japan
2004	July 20	The Ministry of Agriculture, Forestry and Fisheries notifies the Ministry of Health, Labour and Welfare of the application for expansion of use and requests the establishment of standards (expansion to: soybean, vegetable soybean, etc.)
2004	August 3	The Ministry of Health, Labour and Welfare requests a health risk assessment in line with the establishment of maximum residues limits (Shokuan-No. 0803002 notified by the Ministry of Health, Labour and Welfare), the request accepted (Refs. 2-38, 42-83)
2004	August 5	57th meeting of the Food Safety Commission (explanation of MHLW's request outline) (Ref. 84)
2004	September 1	16th meeting of the Pesticides Expert Committee (Ref. 85)
2005	November 29	Announcement of maximum residues limits (Ref. 86)
2006	March 17	The Ministry of Agriculture, Forestry and Fisheries notifies the Ministry of Health, Labour and Welfare of the application for expansion of use and requests the establishment of standards (expansion of use: cherry tomato, broccoli, squash, etc.)
2006	July 18	The Ministry of Health, Labour and Welfare additionally requests a health risk assessment in line with the establishment of maximum residues limits (provisional standards) (Shokuan-No. 0718003 notified by the Ministry of Health, Labour and Welfare) , the request accepted (Ref. 87)
2006	July 20	153rd meeting of the Food Safety Commission (explanation of MHLW's request outline) (Ref. 88)
2006	July 24	Additional references accepted (Refs. 89-97)
2006	November 20	6th meeting of the Pesticides Expert Committee Second Council for Comprehensive Evaluation (Ref. 98)
2006	December 6	8th Executive Board Meetingof the Pesticides Expert Committee (Ref. 99)
2007	January 15	7th meeting of the Pesticides Expert Committee Second Council for Comprehensive Evaluation (Ref. 100)
2007	February 7	10th Executive Board Meeting of the Pesticides Expert Committee (Ref. 101)
2007	February 22	179th meeting of the Food Safety Commission (reporting)
2007	February 22 to March 23	Public Comments
2007	April 18	Reporting from the Chairman of the Pesticides Expert Committee to the Chairman of the Food Safety Commission
2007	April 19	187th meeting of the Food Safety Commission (reporting) (Notification to the Ministry of Health, Labour and Welfare on the same date)

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Summary

Flufenoxuron (IUPAC: 1-[4-(2-chloro-α,α,α-trifluoro-*p*-tolyloxy)-2-fluorophenyl]-3-(2,6-difluorobenzoyl)urea), belonging to the benzophenyl urea family of insecticides, was evaluated based on various toxicity tests.

The test results used for the evaluation were animal metabolism (rats, mice, dogs), plant metabolism (Chinese cabbages, tomatoes, apples), fate in soil, fate in water, residues in soils, residues in crops, acute toxicity (rats, mice, dogs), subchronic toxicity (rats, mice, dogs), chronic toxicity (rats, dogs), carcinogenicity (rats, mice), two-generation reproductive toxicity (rats), developmental toxicity (rats, rabbits), genotoxicity, etc.

The compound did not show any neurotoxicity, reproductive toxicity, teratogenicity or genotoxicity.

Based on the lowest value among NOAELs, which was 3.7 mg/kg bw/day in the 1-year study of chronic toxicity in dogs, and after dividing this lowest value by a safety factor of 100, the ADI was settled as 0.037 mg/kg bw/day.

I. Outline of the Pesticide to be Evaluated

1. Usage

Insecticide

2. Common name (ISO name)

Flufenoxuron

3. Chemical name

IUPAC name:

1-[4-(2-chloro-α,α,α-trifluoro-*p*-tolyloxy)-2-fluorophenyl]-3-(2,6-difluorobenzoyl)urea

CAS chemical name (No. 101463-69-8):

N -[[[4-[2-chloro-4-(trifluoromethyl)phenoxy]-2-fluorophenyl]amino]carbonyl]-2,6-difluorobenzamide

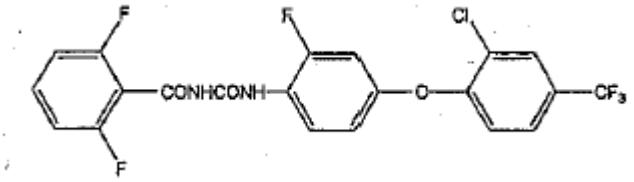
4. Chemical formula

$C_{21}H_{11}ClF_6N_2O_3$

5. Molecular weight

488.5

6. Chemical structure



7. Background of the development

Flufenoxuron is a benzophenyl urea insecticide and was developed by Shell Research Ltd. (U.K.). The compound acts through the inhibition of chitin synthesis.

Flufenoxuron has been registered in more than 20 countries, including European countries such as France, Italy and Spain, China, Australia, Latin American countries and African countries for its application to fruit trees, vegetables, beans, etc. In Japan, the compound has been first registered for its application to fruits, vegetables, beans, etc. on November 8, 1993. In pesticide fiscal year 2002, 7.7 tons of technical grade compound were produced (Ref. 1). In March 2004, BASF Agro, Ltd. applied for the registration of the compound's expanded application according to the Agricultural Chemicals Regulation Law, and submitted Refs. 2-38, 42-83, 89-97.

II. Summary of the Test Results

The radiolabeled forms of Flufenoxuron used in various metabolism studies (II. 1-4) were abbreviated as below. Unless otherwise noted, radioactivity concentrations and metabolite concentrations were calculated in terms of Flufenoxuron. Abbreviations for the metabolites/degradates and abbreviations for test values, etc. are shown in Appendices 1 and 2, respectively.

Abbreviation	Labeling position
Ani-^{14}C-Flufenoxuron	Flufenoxuron labeled with ^{14}C at the aniline ring
Ben-^{14}C-Flufenoxuron	Flufenoxuron labeled with ^{14}C at the benzoyl ring
Ani-^{14}C -^{15}N-Flufenoxuron	A mixture of approximately equal amounts of Flufenoxuron labeled with ^{14}C at the aniline ring and Flufenoxuron labeled with ^{15}N at the aniline-N
Acy-^{14}C-Flufenoxuron	Flufenoxuron labeled with ^{14}C at the acylcarbonyl group

1. Absorption, distribution, metabolism, and excretion

(1) Single high-dose administration to rats

The distribution was examined in Fischer rats with a single administration of a high dose (350 mg/kg bw) of Ani-^{14}C-Flufenoxuron by gavage.

About 85% of the total applied radioactivity (TAR) was eliminated within 72 hours after the administration. By 72 hours after the administration, rats eliminated from 84.2 to 85.4% and from 0.38 to 0.60% of the TAR in the feces and urine, respectively. By 24 hours after the administration, rats eliminated less than 0.01% of the TAR in the breath.

Residual radioactivity levels in major tissues are shown in Table 1.

Table 1. Residual Radioactivity Levels in Major Tissues after Single High-dose Administration (μg/g organ)

Dose		72 hours after administration
Ani-^{14}C-Flufenoxuron (High Dose)	Male	Perinephric fat (192), gastrointestinal tract wall (76.5), liver (24.3), gastrointestinal tract contents (21.9), bone marrow (21.6), skin (18.1), kidney (14.1), carcass (12.6), lung (12.3)
	Female	Perinephric fat (203), gastrointestinal tract wall (88.8), bone marrow (52.6), ovary (52.0), gastrointestinal tract contents (43.8), skin (24.6), liver (24.8), kidney (13.8), carcass (13.7)

The amount of Flufenoxuron eliminated in the feces by 72 hours after the administration was from 77.2 to 78.7% of the TAR. Metabolites could be detected only at extremely small amounts and thus could not be identified. (Ref. 3)

(2) Single low-dose administration to rats

The distribution was examined in Fischer rats with a single administration of a low dose (3.5 mg/kg bw) of Ani-^{14}C-Flufenoxuron by gavage.

From 26.3 to 28.8% of the TAR was eliminated within 168 hours after the administration. Rats

eliminated from 21.1 to 23.9% and from 4.75 to 5.13% of the TAR in the feces and urine, respectively, by 168 hours after the administration, and less than 0.001% of the TAR in the breath by 24 hours after the administration.

Residual radioactivity levels in major tissues are shown in Table 2.

Table 2. Residual Radioactivity Levels in Major Tissues after Single Low-dose Administration (μg/g organ)

Dose		168 hours after administration
Ani-^{14}C-Flufenoxuron (Low Dose)	Male	Perinephric fat (11.4), gastrointestinal tract (including the contents) (2.69), bone marrow (2.20), liver (1.38), skin (1.65), kidney (1.16), carcass (1.03)
	Female	Perinephric fat (11.0), bone marrow (3.29), skin (2.53), gastrointestinal tract (including the contents) (2.32), liver (1.39), ovary (1.21), kidney (0.87), carcass (0.85)

A major portion of the radioactivity detected in the liver, fat, gastrointestinal tract, skin and carcass was attributed to Flufenoxuron. As metabolites, many minor radioactive components each accounting for 1% or less of the TAR were found, but none of them could be identified. The proportions of Flufenoxuron in the liver, perinephric fat (total fat), gastrointestinal tract, skin and carcass to the TAR were from 1.0 to 1.1%, from 6.0 to 7.2% (from 24.0 to 24.4%), from 5.8 to 6.4%, from 12.1 to 13.6% and from 24.7 to 31.0%, respectively.

The amount of Flufenoxuron eliminated in the urine by 168 hours was from N.D. to 0.01% of the TAR. As metabolites, WL129183 (hereinafter "urea form"), WL115096 (hereinafter "aniline form") and eight unidentified minor components were detected from the urine at from 0.02 to 0.06%, from 0.02 to 0.07% and from 0.72 to 1.30% of the TAR, respectively. The amount of Flufenoxuron eliminated in the feces by 168 hours was 9.6% of the TAR. As metabolites, 20 or more unidentified minor components were detected from the feces at from 5.14 to 6.22% of the TAR in total but individually accounted for 1% or less of the TAR. (Ref. 4)

(3) Repeated low-dose administration to rats

The distribution was examined in Fischer rats (groups of 3 females) with once-daily administration of a low dose (3.5 mg/kg bw) of Ani-^{14}C-Flufenoxuron by gavage for up to 28 days.

Residual radioactivity levels in major tissues are shown in Table 3. The half-lives of the radioactivity in various organs and tissues ranged from 28.0 to 47.6 days. In any of the tissues, the residual concentration increased with the number of doses during the administration period (28 days). The residual concentration reached near equilibrium in the skin but not in other tissues. The in vivo distribution pattern was similar to that achieved by single administration. When the radioactive component in the fat was extracted with dichloromethane and partitioned between hexane and acetonitrile, a major portion of the radioactivity was recovered from the acetonitrile layer, of which 97 to 98% could be attributed to Flufenoxuron. (Ref. 5)

Table 3. Residual Radioactivity Levels in Major Tissues after Repeated Low-dose Administration (μg/g organ)

Dose		Day 29[1)]	Day 205[1)]
Ani-^{14}C-Flufenoxuron (Low Dose)	Female	Perinephric fat (144), bone marrow (32.6), ovary (20.2), skin (17.5), digestive tract (18.1), liver (15.7), kidney (11.2), carcass (15.5), blood (2.68)	Perinephric fat (1.82), bone marrow (0.74), ovary (0.59)

[1)] The day on which the first administration was given was counted as Day 1.

(4) Single low-dose administration to dogs

The distribution was examined in Beagle dogs (groups of 2 males and 2 females) with a single administration of a low dose (3.5 mg/kg bw) of Ani-^{14}C-Flufenoxuron by gavage.

The change in plasma radioactivity concentration is shown in Table 4.

Table 4. Change in Plasma Radioactivity Concentration

Dose	Low Dose (3.5mg/kg bw)	
Sex	Male	Female
T_{max} (hr)	3.0	4.0
C_{max} (μg/mL)	0.39	0.42
$T_{1/2}$ (hr)	702 (29.2 days)	639 (26.6 days)

T_{max}: Time to achieve maximum concentration, C_{max}: Maximum concentration, $T_{1/2}$: Half-life

In both sexes, 67.6% of the TAR was eliminated within 168 hours after the administration. By 168 hours after the administration, the amounts of radioactivity eliminated in the feces (including diarrhea stool) and urine were from 57.9 to 64.0% and from 2.85 to 8.52%, respectively.

Residual radioactivity levels in major tissues are shown in Table 5.

Table 5. Residual Radioactivity Levels in Major Tissues after Single Low-dose Administration (μg/g organ)

Dose		168 hours after administration
Ani-^{14}C-Flufenoxuron (Low Dose)	Male	Subcutaneous fat (3.20), perinephric fat (3.03), bone marrow (1.43)
	Female	Subcutaneous fat (3.16), perinephric fat (2.80), bone marrow (1.08)

Flufenoxuron accounted for 97% or more of the radioactivity detected in the urine collected at from 0 to 6 hours after the administration and from the diarrhea stool extract obtained at from 0.5 to 1 hour after the administration. Flufenoxuron accounted for from 93 to 97% of the radioactivity detected in the feces extract obtained within 24 hours after the administration, and the aniline form accounted for from 3.6 to 5.2% of the radioactivity detected in the feces extract obtained at from 24 to 48 hours after the administration. (Ref. 6)

(5) Single low-dose and high-dose administration to rats

The distribution was examined in Fischer rats with a single administration of a low dose (3.5 mg/kg bw) or a high dose (350 mg/kg bw) of Ben-^{14}C-Flufenoxuron by gavage.

The change in plasma radioactivity concentration is shown in Table 6.

Table 6. Change in Plasma Radioactivity Concentration

Dose		Low Dose (3.5 mg/kg bw)		High Dose (350 mg/kg bw)	
Sex		Male	Female	Male	Female
T_{max} (hr)		6	6	4	6
C_{max} (μg/mL)		0.27	0.39	0.77	1.10
$T_{1/2}$ (hr)	Phase 1	6.5	6.1	-	-
	Phase 2	155	428	22[1)]	13[1)]

[1)] For the High-Dose group, values were calculated from the curve corresponding to from 6 to 48 hours after the administration

Rats eliminated from 24.0 to 29.7% (Low Dose) and from 0.50 to 0.67% (High Dose) of the TAR in the urine, from 11.9 to 18.5% (Low Dose) and from 92.8 to 102% (High Dose) of the TAR in the feces by 168 hours after the administration. Amounts of radioactivity eliminated in the breath were below the detection limit in both Low- and High-Dose groups. From 1.49 to 1.88 (Low Dose) and 0.01% (High Dose) of the TAR were detected in the gastrointestinal tract (including the contents), and from 45.5 to 58.7% (Low Dose) and from 0.54 to 0.87% (High Dose) of the TAR were detected in the carcass. In rats administered Low Dose, from 4.51 to 4.65 of the TAR was eliminated in the bile by 48 hours after the administration, while from 9.64 to 14.4% and from 4.03 to 11.0% of the TAR were eliminated in the urine and feces, respectively.

Residual radioactivity levels in major tissues are shown in Table 7.

Table 7. Residual Radioactivity Levels in Major Tissues (μg/g organ)

Dose	Sex	4 hours[1)]	168 hours
Single Low Dose	Male	Adrenal gland (19.0), gastrointestinal tract (including the contents) (16.9), thyroid gland (9.14), liver (8.60), bone marrow (7.75), pancreas (5.75), perinephric fat (5.23)	Perinephric fat (10.5), subcutaneous fat (9.87), adrenal gland (2.93), pancreas (2.18), thyroid gland (2.03), bone marrow (1.66), carcass (1.55)
	Female	Adrenal gland (28.3), bone marrow (17.3), gastrointestinal tract (including the contents) (14.7), thyroid gland (12.5), ovary (8.91), liver (8.74), pancreas (6.81)	Perinephric fat (11.3), subcutaneous fat (9.47), bone marrow (2.94), adrenal gland (2.67), carcass (1.97), pancreas (1.76), thyroid gland (1.75)

Single High Dose	Male	Gastrointestinal tract (including the contents) (4140), thyroid gland (20.0), adrenal gland (13.9), liver (7.54), bone marrow (7.46)	Thyroid gland (11.1), perinephric fat (9.30), subcutaneous fat (8.89), adrenal gland (4.50), gastrointestinal tract (including the contents) (3.25), bone marrow (2.03)
	Female	Gastrointestinal tract (including the contents) (4690), thyroid gland (13.6), adrenal gland (13.3), bone marrow (12.5), liver (6.17)	Thyroid gland (15.5), perinephric fat (9.35), subcutaneous fat (8.67), bone marrow (5.47), adrenal gland (3.10), pancreas (2.42), ovary (2.12), gastrointestinal tract (including the contents) (2.05)

[1)] Around T_{max} in the Low-Dose group

By 48 hours after the administration, Flufenoxuron was not detected in the urine of the Low-Dose group, and 2,6-difluorobenzoic acid and 2,6-difluorobenzamide were detected as major metabolites, accounting for from 10.1 to 12.1% and from 0.2 to 0.3% of the TAR, respectively. As other metabolites, three unidentified substances with high polarity were detected, each accounting for from 0.3 to 1.2% of TAR.

By 48 hours after the administration, Flufenoxuron was detected in the feces of Low- and High-Dose groups and accounted for from 9 to 14% and from 90 to 91% of the TAR, respectively.

The only radioactive component detected in the extract of the subcutaneous fat collected at 20 hours after the administration of Low Dose turned out to be Flufenoxuron.

Based on the results of the studies using Ani- and Ben-^{14}C-Flufenoxuron, the main metabolic pathways of Flufenoxuron could be the hydrolysis of the benzoyl-urea bond resulting in the production of 2,6-difluorobenzoic acid and the urea form and further metabolism of the urea form resulting in the production of the aniline form, or the hydrolysis of the urea bond in Flufenoxuron resulting in the production of 2,6-difluorobenzamide and unstable *N*-phenylcarbamic acid and further metabolism of *N*-phenylcarbamic acid resulting in the production of the aniline form. (Refs. 3-4, 7-8)

(6) Test of biliary elimination in rats

Biliary elimination of Flufenoxuron was studied in Fischer rats (groups of 3 males and 3 females) with a single administration of a low dose (3.5 mg/kg bw) of Ani-^{14}C-Flufenoxuron by gavage.

By 48 hours after the administration, rats eliminated from 6.65 to 19.7%, from 1.58 to 2.59% and from 3.95 to 30.2% of the TAR in the bile, urine and feces, respectively. From 4.44 to 4.98% and from 47.3 to 59.1% of the TAR were detected in the gastrointestinal tract (including the contents) and carcass, respectively.

From 73.7 to 79.1% of radioactivity in the bile specimen before acid hydrolysis could be attributed to polar substances. Flufenoxuron accounted for from 16.3 to 20.9% of the radioactivity in the bile specimen, while the aniline form accounted for from 0.6 to 0.9% of the radioactivity as a metabolite.

After acid hydrolysis, the amount of polar substances decreased to from 61.7 to 65.7% of the radioactivity in the bile specimen. Flufenoxuron accounted for from 13.4 to 18.2% of the radioactivity in the bile specimen. As metabolites, the aniline form was detected at from 5.9 to 6.5%, and substances that were not detected before acid hydrolysis were also detected at from 7.8 to 18.2%. The total amount of unidentified metabolites was increased by acid hydrolysis. In the bile, the aniline form could mainly exist in a conjugated form with a high polarity. (Refs. 8-9)

(7) *In vitro* metabolism test in hepatocyte fractions of mice, rats and dogs

In vitro metabolism was examined in male and female ICR mice, male Fischer rats and male beagle dogs by adding Ani-^{14}C-Flufenoxuron to liver S9 fractions and microsome fractions.

Radioactivity was hardly incorporated into the crude protein fractions in any of the animal species or sexes. The major radioactive component in the extracts was Flufenoxuron, and the aniline form and the urea form accounted for from 1.13 to 3.73% and from 3.17 to 7.56%, respectively. (Ref. 10)

2. Plant metabolism

(1) Chinese cabbages

A treatment solution containing 0.5mg/mL Ani-^{14}C-^{15}N-Flufenoxuron (100 g ai/ha) was applied to the entire foliage of Chinese cabbages (variety: Jade Pagoda) at 19 days after transplanting. Samples were collected immediately and 28 days after the treatment.

The extraction efficiencies of the radioactivity from samples collected immediately and 28 days after the treatment were 97.2% and 94.8% of the total residual radioactivity (TRR), respectively. The radioactivity distribution in the plant changed over time; 84% of the TRR remained at the surface immediately after the treatment, while 19% of the TRR remained at the surface and 76% was detected from the tissue extract at 28 days after the treatment. In samples collected 28 days after the treatment, Flufenoxuron accounted for 99% or more and 96% or more of the radioactivity in the surface washing and the tissue extract, respectively, and no metabolites were detected. The residual radioactivity concentration was 6.3 mg/kg on the treatment day but reduced to 0.35 mg/kg after 28 days. The total recovered radioactivity in Chinese cabbage plants collected 28 days after the treatment accounted for 72% of the TAR. (Ref. 11)

(2) Tomatoes

A treatment solution containing 0.5mg/mL Ani-^{14}C-^{15}N-Flufenoxuron (125 g ai/ha) was applied to the entire foliage of tomatoes (variety: Moneymaker) at 70 days after transplanting. Samples were collected immediately and 28 days after the treatment.

The extraction efficiencies of the radioactivity from samples collected immediately and 28 days after the treatment were 98.0% and from 93.8 to 95.4%, respectively. The radioactivity distribution in tomato fruits remained constant regardless of the harvest time; from 93.8 to 98.0% of the TRR remained at the fruit surface, while only 1% or less of the TRR was detected from the fruit extract collected at any timing. Flufenoxuron hardly penetrated into the fruits. In samples collected 28 days after the treatment, the compound accounted for 98% or more of the radioactivity in the surface washing was flufenoxuron.

The residual radioactivity concentration was 0.38 mg/kg on the treatment day but reduced to 0.19 mg/kg after 28 days. (Ref. 11)

(3) Apples

A treatment solution containing 100 mg ai/L Ani-^{14}C-Flufenoxuron was applied to apple trees (variety: Cox's OrAniige Pippin) bearing immature fruits. The solution was applied until it ran down the trees. Fruit samples were harvested 4 hours (immature stage), 46 days and 99 days (mature stage) after the treatment.

The residual radioactivity level in the whole fruit reduced over time, being 2.55 mg/kg, 0.163 mg/kg and 0.055 mg/kg at 4 hours, 46 days and 99 days after the treatment, respectively. A major portion of the residual radioactivity in the whole fruit was localized at the pericarp surface; the radioactivity at the pericarp surface accounted for 96% of the TRR at 4 hours after the treatment but decreased to 89% and 77% of the TRR by 46 days and 99 days after the treatment, respectively. Meanwhile, the radioactivity in washed fruit accounted for 4% of the TRR at 4 hours after the treatment but increased to 11% and 23% of the TRR by 46 days and 99 days after the treatment, respectively. Within the whole fruit at the mature stage, radioactivity was detected in the pericarp surface, pericarp, flesh and seed at from 85.7 to 97.5%, from 2.0 to 9.4%, from 0.5 to 5.0% and from 0 to 0.1% of the TRR, respectively. In the whole fruit at the immature and mature stages, 96.5% (2.46 mg/kg) and 90.9% (0.050 mg/kg) of the TRR were attributed to Flufenoxuron, respectively, and no metabolite was detected.

Autoradiography results revealed that the residual radioactivity was localized in the pericarp, suggesting that the compound hardly penetrates into apple flesh. (Ref. 12)

3. Fate in soil

(1) Degradation in aerobic soil

Ani-^{14}C-Flufenoxuron was applied to a non-airtight container filled with clay loam (Woodstock soil: U.K.) or sandy loam soil (Keycol soil: U.K.) at 0.5 mg/kg, based on the dry weight of the soil. The test was carried out through incubation under aerobic conditions at 25±2°C in the dark.

The half-life of Flufenoxuron in Woodstock soil was approximately 42 days. In Keycol soil, 69% of the applied compound remained in the soil by 181 days after the treatment. In Woodstock soil, Flufenoxuron, the urea form (major degradate) and the aniline form (degradate) accounted for 9.8%, 3.2% and 0.2% of the TAR, respectively, at 360 days after the treatment. The urea form and the aniline form reached their maximum levels of 14.2% and 1.2% of the TAR, respectively, at 30 days and 120 days after the treatment, respectively. In Keycol soil, Flufenoxuron and the urea form accounted for 68.7% and 9.5% of the TAR, respectively, at 181 days after the treatment, while the aniline form was detected as another degradate, accounting for 0.1% of the TAR at 15 and 30 days after the treatment. The residual radioactivity level in the extraction residue increased over time, reaching 65.0% and 13.6% of the TAR in Woodstock soil and Keycol soil, respectively, at 360 days and 181 days after the treatment, respectively. The radioactivity recovery rate in Woodstock soil was 97% at the beginning but reduced to 85% after 360 days, which could be attributed to the mineralization of the aniline ring.

The major degradation pathways of Flufenoxuron in soil could be the cleavage of the C-N bond

adjacent to the difluorophenyl moiety by hydrolysis to yield the urea form. (Ref. 13).

(2) Comparative study of degradation in anaerobic and aerobic soils

Ani-^{14}C-Flufenoxuron was applied to silt soil (U.K.) at 0.5 mg/kg, based on the dry weight of the soil. The test was carried out through incubation under a flooded, nitrogen-purged condition (anaerobic) or an upland field condition (aerobic) at 21±2°C in the dark.

The half-life of Flufenoxuron under the aerobic condition was 120 days. Under the anaerobic condition, approximately 88% of the applied compound remained in the soil by 152 days after the treatment; the degradation of the compound was so slow that the half-life could not be calculated. Under the aerobic condition, Flufenoxuron and the urea form accounted for 35.8% and 14.5% of the TAR, respectively, at 152 days after the treatment. The urea form reached its maximum level (15.6% of the TAR) at 90 days after the treatment. As other degradates, the aniline form and CO^2 were detected at 0.4% and 3.7% of the TAR, respectively, at 152 days after the treatment. Under the anaerobic condition, Flufenoxuron, the urea form and the aniline form (degradate) accounted for 80.5%, 2.4% and 0.5% of the TAR, respectively, in the dichloromethane phase at 152 days after the treatment. The major portion of the radioactivity (7.1% of the TAR) detected in the aqueous phase was attributed to Flufenoxuron. No CO_2 was detected. The residual radioactivity level in the extraction residue increased over time, reaching 34.0% and 5.6% of the TAR under aerobic and anaerobic conditions, respectively, at 152 days after the treatment. (Ref. 14)

(3) Soil adsorption screening study - Solubility test as a preliminary test

As a preliminary test for a soil adsorption screening study, a solubility test of Flufenoxuron (pure form) was conducted. Since the compound showed an extremely low solubility in water, soil adsorption screening study could not be conducted. (Ref. 15)

(4) Adsorption to and desorption from soil and silt

Adsorption tests in two kinds of soils (Hoath soil and Headcorn silt) were conducted using Acy-^{14}C-Flufenoxuron.

The adsorption coefficient (K_F^{ads}) was in the range of 55 to 78, and the organic carbon adsorption coefficient ($K_F^{ads}oc$) was in the range of 2050 to 4300 (3200 in average) (Ref. 16).

(5) Migration in soils

Migration tests of Ani-^{14}C-Flufenoxuron in soils were conducted using two kinds of sandy loam soils (U.S. and U.K.).

Flufenoxuron did not migrate in soils. (Ref. 17)

(6) CO_2 release from non-extractable residual component and migration to plants

CO_2 release from the non-extractable residual component and its migration to plants were studied. Ani-^{14}C-Flufenoxuron was applied to silt soil (U.K.) at 0.5 mg/kg, based on the dry weight of the soil to prepare the compound-containing soil. The obtained compound-containing soil was further incubated

for 127 days at 22±2°C in the dark, and 600 g (dry weight) of the soil (containing non-extractable radioactivity accounting for 38.9% of the TAR) was mixed with 1800 g (dry weight) of newly collected soil to prepare the mixed soil. (Ref. 18)

(i) CO_2 release from soil

The mixed soil and the compound-containing soil were incubated for 98 days at 22±2°C in the dark. CO_2 release from soil was studied by scavenging $^{14}CO_2$ by KOH.

In the mixed soil, 6.9% of the radioactivity detected at the beginning of incubation remained in the soil by 98 days after the treatment, and the CO_2 release rate was constant. In the compound-containing soil, 2.8% of the radioactivity detected at the beginning of incubation remained in the soil by 98 days after the treatment; the CO_2 release rate was slow immediately after the beginning of the study but increased thereafter.

(ii) Migration of non-extractable component to plants

Seeds of wheat and Brown mustard were sown in pots filled with the mixed soil and the compound-containing soil, and after an incubation for 27 days, the terrestrial portion of the plants (wheat plant height: from 25 to 40 cm, mustard plant height: from 7 to 10 cm) were harvested and used to study the migration of the non-extractable component to plants. For the analysis, wheat plants were divided into the upper 2/3 and the lower 1/3 portions.

When grown in the mixed soil, radioactivity was detected from neither of the plant species. When grown in the compound-containing soil, trace radioactivity was detected in the mustard plant (0.002 mg/kg), wheat upper 2/3 portion (0.002 mg/kg) and wheat lower 1/3 portion (from 0.004 to 0.006 mg/kg), but the amounts greatly varied among the samples. Thus, the radioactivity detected in the plants could have migrated from the soil through the contact between the plants and the soil and not through root uptake.

(7) Migration to plants using unlabeled Flufenoxuron

Flufenoxuron emulsion (10%) was applied to light clay (Kakegawa City, Shizuoka Prefecture) at 0.8 mg ai/kg. The soil was filled in pots and incubated for 30 days in a greenhouse. Then, radish seeds were sown in the pots, and plants were harvested 28 days after sowing. Soil samples were collected immediately, 30 days (sowing date) and 58 days (harvest time) after the treatment to study the migration of unlabeled Flufenoxuron to plants.

In soil, the Flufenoxuron level was 0.70 mg/kg immediately after the treatment but reduced to 0.26 mg/kg by 58 days after the treatment. The major degradate was the urea form, which was detected at 0.045mg/kg, calculated in terms of Flufenoxuron.

Flufenoxuron was not detected in radish foliage, and neither Flufenoxuron nor the urea form was detected in radish root. Under normal conditions, Flufenoxuron and its major degradate, the urea form, would not be taken up by succeeding crops. (Ref. 19)

(8) Ready biodegradability

A closed bottle test, a modified Sturm test and a microbial growth inhibition test were conducted to evaluate the ready biodegradability of Flufenoxuron.

In the closed bottle test, Flufenoxuron did not consume oxygen and was thus considered undegradable. The result of the modified Sturm test suggested that the compound did not undergo mineralization (degradation into CO_2). Meanwhile, Flufenoxuron did not inhibit microbial growth. These results demonstrated that Flufenoxuron is not readily biodegradable. (Ref. 20)

4. Fate in water

(1) Hydrolysis

Unlabeled Flufenoxuron was added to buffer solutions of pH5, 7, 9, 12 and 14 to prepare Flufenoxuron solutions of 2 μg/L. The solutions were incubated at a given temperature for a given time to study hydrolysis of Flufenoxuron.

The half-lives of Flufenoxuron at 25°C were 20.6 days, 267 days, 36.7 days, 2.7 days and 0.1 days in buffer solution of pH5, 7, 9, 12 and 14, respectively. The compound was stable under neutral conditions but relatively unstable under acidic or alkaline conditions. The major degradate was the aniline form. (Ref. 21)

(2) Photolysis in water (purified water, natural water)

Ben-^{14}C-Flufenoxuron was added to purified water and natural water to prepare Flufenoxuron solutions of 2 μg/L. The solutions were exposed to Xenon light (19.4 W/m^2 (measured in the range of 300-800 nm wavelength)) at 25±1°C for 15 days to study photolysis of Flufenoxuron in water.

In both purified water and natural water after 15 days, Flufenoxuron and 2,6-difluorobenzamide (major degradate) were detected at from 11.8 to 20.0% and from 74.0 to 88.9% of the TAR, respectively. Several other trace degradates were detected, but since neither of them accounted for more than 6.0% of the TAR, they were not characterized.

Flufenoxuron was degraded by light, and the half-lives were 7.1 and 6.8 days in purified water and natural water, respectively, which were calculated as 17.7 and 17.0 days, respectively, under the spring sunlight at 35 degrees north latitude and as 21.4 and 20.5 days, respectively, under the spring sunlight at 50 degrees north latitude. The 90% decay times were 23.6 and 22.5 days in purified water and natural water, respectively. (Ref. 22).

(3) Photolysis in water under natural sunlight (buffer solution)

Acy-^{14}C-Flufenoxuron was dissolved in a buffer solution (pH7) to prepare a Flufenoxuron solution of 2 μg/L. The solution was incubated in a quartz vessel or a Pyrex glass® vessel at 5-25°C under natural sunlight to study photolysis of Flufenoxuron in water.

In the quartz vessel, Flufenoxuron and 2,6-difluorobenzamide (major degradate) were detected at 23.7% and 42.1% of the total recovered radioactivity, respectively, after 31 days. Other degradates detected were the hydroxyphenyl form and polar substances, which accounted for 3.2% and 29.2% of the total recovered radioactivity, respectively. Flufenoxuron was degraded by light, and the half-life was

approximately 11 days. In the Pyrex glass® vessel, the residual ratios of Flufenoxuron and 2,6-difluorobenzamide were 38.9% and 49.2%, respectively, after 26 day. The degradates detected were the same as those detected from the quartz vessel. The half-life of Flufenoxuron in the Pyrex glass® vessel was 24 days, which was longer than that in the quartz vessel, because Pyrex glass® showed a restricted transmission of light having the wavelength shorter than 350 nm.

Regarding the degradates, an acetonitrile-water (1:9 v/v) solution of the aniline form and an aqueous solution of 2,6-difluorobenzamide were exposed to natural sunlight. Two-thirds of the aniline form was degraded after 72 hours, while 2,6-difluorobenzamide was not degraded, even after 38 days. (Ref. 23)

5. Residues in soils

Residual values of Flufenoxuron and a degradate (the urea form) in soils were studied (both in the vessel and the field) using volcanic ash loam (Kanagawa Horticultural Experiment Station) and alluvial mineral clay loam (Japan Plant Protection Association Kochi Experiment Station).

As shown in Table 8, the assumed half-lives for the sum of Flufenoxuron and the urea form were from 60 to 111 days and from 8 to 182 days in the vessel and the field, respectively. (Ref. 42)

Table 8. Results of Residual Tests in Soils (assumed half-lives)

Type of test	Concentration[1)]	Kind of soil	Flufenoxuron + degradate (urea form)
Vessel	0.4mg/kg	Volcanic ash loam	60 days
		Alluvial mineral clay loam	111 days
Field	200g ai/ha × 4 times	Volcanic ash loam	182 days
		Alluvial mineral clay loam	8 days

1) Pure material and emulsion were used in the vessel and field tests, respectively

6. Residues in crops

Vegetables, fruits, beans and tea plants were used for residual tests in crops for Flufenoxuron. For the analysis, samples were extracted, purified and quantified by HPLC-UV.

As indicated in the results shown in Appendix 3, the highest residual value of Flufenoxuron was 11.1 mg/kg, which was observed in Garland Chrysanthemum when the compound was applied at from 80 to 100g ai/ha for three times and the samples were collected 3 days after the final application. The residual value decreased to 7.37 mg/kg, 5.04 mg/kg and 0.61 mg/kg on 7, 14 and 21 days after the application, respectively. (Refs. 24-38, 90-97)

Based on the results of the residual tests in crops shown in Appendix 3, the estimated Flufenoxuron (parent compound only) intakes through agricultural products cultivated in Japan are shown in Table 9 (see Appendix 4).

The estimated intakes were calculated based on the assumption that Flufenoxuron was applied to all of the applicable crops under conditions that would give the highest total residual value of Flufenoxuron

among the possible methods, and that processing or cooking of the crops would not affect the amounts of residual pesticides.

Table 9. Estimated Amounts of Flufenoxuron Exposure through Food

	National average (body weight: 53.3 kg)	Infants (ages 1 to 6) (body weight: 15.8 kg)	Pregnant women (body weight: 55.6 kg)	Elderly (ages 65 or above) (body weight: 54.2 kg)
Intake (μg/person/day)	171	86.2	150	201

7. General pharmacology

General pharmacology tests were performed using mice, rats, rabbits and guinea pigs. The results are summarized in Table 10. (Ref. 82)

Table 10. Summary of General Pharmacology Test

Types of test		Animals	Number of animals per group	Dose (mg/kg bw) (route)	NOELs (mg/kg bw)	LOELs (mg/kg bw)	Summary
Central Nervous System	General condition (modified Irwin test)	Mice	3 males	0,300,1000, 3000 (oral)	3000	-	No specific effect.
	General condition	Rabbits	3 males	0,300,1000, 3000 (oral)	3000	-	No effect attributed to dosing.
	Hexobarbital sleeping time	Mice	6 males	0,3000 (oral)	3000	-	No effect.
	Coordination	Mice	5 males	0,3000 (oral)	3000	-	No effect.
	Locomotor activity	Mice	4 males	0,3000 (oral)	3000	-	No effect.
	Body temperature	Rats	6 males	0,3000 (oral)	3000	-	No effect.
	Spontaneous brain wave	Rats	4 males	0→100 (single dose) 0→250→1000 (ascending dose) (oral)	100	250	Shorter duration of arousal accompanying electromyographic activity, longer duration of arousal without

							electromyographic activity, somnolence and extension of REM sleep were observed, but no abnormal electroencephalogram indicative of toxicity was observed.
Peripheral nervous system/ Skeletal muscle	Local anesthesia	Guinea pigs	5 males	0.03mL (10% suspension) (ocular instillation into conjunctival sac)	0.03mL (10% suspension)	-	No corneal anesthetic effect.
	Skeletal muscle	Rats	4 males	0→30 (femoral intravenous)	30	-	No effect.
Respiratory/ Circulatory organs	Blood pressure	Rabbits	4 males	0→30 (intravenous)	-	30	No effect except for one case of arrhythmia (ventricular bigeminy).
	Heart rate						
	Electrocardiogram						
	Respiratory rate						
	Blood flow volume						
Digestive organs	Intestinal transport	Mice	6 males	0,3000 (oral)	3000	-	No effect.
	Gastric secretion	Rats	6 males	0,300,1000, 3000 (intraduodenal)	3000	-	No effect.
	Salivation	Rats	5 males	0,3000 (intraperitoneal)	3000	-	No effect.
Autonomic nerves/ Smooth muscle	Nictitating membrane	Rats	3 males	0,30 (intravenous)	30	-	No effect.
	Uterine motility	Rats	3 pregnant females 3 nonpregnant females	0,30 (intravenous)	30	-	No effect.

Renal function	Urine, pathological tests	Rats	6 males	0,3000 (oral)	3000	-	No effect.
Blood	Blood clotting, General blood test	Rabbits	6 males	0,3000 (oral)	3000	-	No effect.

-: NOEL or LOEL could not be determined.

8. Acute toxicity

The acute oral toxicity of Flufenoxuron was studied using Fischer rats, ICR mice, STCF1 mice and beagle dogs, the acute dermal toxicity was studied using Fischer rats and STCF1 mice, and the acute inhalation toxicity was studied using SD rats.

The individual test results are summarized in Table 11. The acute oral LD_{50}s were >5000 mg/kg bw in male and female rats, ICR mice and dogs and >3000 mg/kg bw in male and female STCF1 mice. The acute dermal LD_{50} was >2000 mg/kg bw in male and female rats and mice, and the acute inhalation LC_{50} was >5.1 mg/L in male and female rats.

(Ref. 43-48)

Table 11. Summary of Acute Toxicity Tests (Flufenoxuron)

Administration route	Animals	LD_{50} (mg/kg bw)		Observed symptoms
		Male	Female	
Oral	Fischer rats	>5000	>5000	No toxic symptoms
	Fischer rats	>3000	>3000	Lethargy, lacrimation, chromodacryorrhea, etc.
	ICR mice	>5000	>5000	Piloerection
	STCF1 mice	>3000	>3000	No toxic symptoms
	Beagle dogs	>5000	>5000	No toxic symptoms
Dermal	Fischer rats	>2000	>2000	No toxic symptoms
	STCF1 mice	>2000	>2000	No toxic symptoms
Inhalation	SD rats	LC_{50} (mg/L)		No toxic symptoms
		>5.1	>5.1	

The acute oral toxicities of metabolites, i.e. the urea form and the aniline form, and a contaminant in the technical grade, i.e. WL131767 (hereinafter "bis form"), were studied using ICR mice. The LD_{50}s of the urea form were 433 mg/kg bw and 302 mg/kg bw in male and female mice, respectively. The LD_{50}s of the aniline form were 1940 mg/kg bw and 2900 mg/kg bw in male and female mice, respectively. The LD_{50} of the bis form was >5000 mg/kg bw in male and female mice. (Ref. 49)

9. Skin and eye irritation and skin sensitization

Primary eye and skin irritation tests in NZW rabbits demonstrated that Flufenoxuron would not irritate

the eye or the skin. (Refs. 50-51)

Skin sensitization potential was assessed in Hartley/Dunkin guinea pigs by the Maximization method. No skin sensitization was observed. (Ref. 52)

10. Subchronic toxicity

(1) Subchronic toxicity test for 90 days in rats

Fischer rats (groups of 10 males and 10 females, the control group consisted of 20 males and 20 females) were fed diets containing Flufenoxuron, technical grade at 0, 50, 500, 5000, 10000 or 50000 ppm (see Table 12 for average test substance intake) for 90 days. The result from a preliminary test suggested that the diet used in this study lacked vitamin K, so all diets were supplemented with 3mg/kg vitamin K throughout the test period.

Table 12. Average Test Substance Intake in Subchronic Toxicity Test for 90 days in Rats

Dose		50 ppm	500 ppm	5000 ppm	10000 ppm	50000 ppm
Test substance intake (mg/kg bw/day)	Male	3.3	32.9	336	657	3500
	Female	4.0	39.3	386	800	4070

Major toxicological findings observed at individual doses are shown in Table 13. An increase in relative liver weight[1)] was observed in females at 10000 ppm and higher. However, it was only a mild increase and was not accompanied by any relevant histopathological or blood biochemical change, so it could not be attributed to the treatment.

An increase in methemoglobin level was observed in males and females at 50 ppm and higher. However, there was no increase in the methemoglobin level when measured by a more specific method (Evelyn & Malloy method), which examined the cyanide-binding capacity of methemoglobin, using a blood sample collected in the third month of the 2-year chronic toxicity study in **11.(2)**. Thus, this finding was not considered to be of toxicological significance.

The NOAELs in this study would be 500 ppm (32.9 mg/kg bw/day) for males and 50 ppm (4.0 mg/kg bw/day) for females. (Ref. 53)

Table 13. Toxicological Findings from Subchronic Toxicity Test for 90 days in Rats

Dose	Male	Female
50000 ppm	• Increase in white blood cell count, decrease in M/E ratio* • Increases in MCHC, plasma AST, ALT and potassium levels	• Increase in white blood cell count, decrease in M/E ratio
10000 ppm and higher	• Decrease in plasma calcium level	• Decrease in plasma calcium level • Decrease in plasma albumin level

[1)] Relative weight against body weight will be described as relative weight hereafter.

5000 ppm and higher	• Decrease in plasma TG level • Decrease in MCV	• Decrease in plasma TG level • Increases in reticulocyte count and platelet count, decreases in red blood cell count and Ht, increase in relative spleen weight
500 ppm and higher	No toxicological findings at 500 ppm and lower	• Increase in mean corpuscular diameter, decrease in Hb concentration, increase in plasma cholesterol level
50 ppm		No toxicological findings

* Myeloid/erythroid ratio.

(2) Subchronic toxicity test for 90 days in mice

C57/C3H F_1 hybrid mice (groups of 10 males and 10 females, the control group consisted of 20 males and 20 females) were fed diets containing Flufenoxuron, technical grade at 0, 50, 500, 5000, 10000 or 50000 ppm (see Table 14 for average test substance intake) for 90 days.

Table 14. Average Test Substance Intake in Subchronic Toxicity Test for 90 days in Mice

Dose		50 ppm	500 ppm	5000 ppm	10000 ppm	50000 ppm
Test substance intake (mg/kg bw/day)	Male	10.2	102	1060	2100	10900
	Female	11.4	127	1260	2460	13000

Major toxicological findings observed at individual doses are shown in Table 15.

The lowest observed adverse effect level (LOAEL) and the NOAEL in this study would be 500 ppm and 50 ppm (10.2 mg/kg bw/day for males, 11.4 mg/kg bw/day for females), respectively, for both males and females. (Ref. 54)

Table 15. Toxicological Findings from Subchronic Toxicity Test for 90 days in Mice

Dose	Male	Female
50000 ppm	• Decreases in red blood cell count, Hb concentration and Ht, increases in platelet count and red blood cell volume distribution width	• Increases in monocyte and eosinophil ratios, shortened APTT, decrease in lymphocyte ratio, increase in relative kidney weight
10000 ppm and higher	• Increase in plasma inorganic phosphorus level, decreases in plasma TG and calcium levels	• Decrease in red blood cell volume distribution width, increases in plasma albumin and total protein levels, decrease in plasma urea nitrogen level
5000 ppm and higher	• Suppression in body weight gain,	• Decrease in plasma glucose level

	decrease in plasma urea nitrogen level	
500 ppm and higher	• Increases in plasma bilirubin level and relative liver weight	• Increases in plasma bilirubin level and relative liver weight
50 ppm	No toxicological findings	No toxicological findings

(3) Subchronic toxicity test for 90 days in dogs

Beagle dogs (groups of 4 males and 4 females) were fed diets containing Flufenoxuron, technical grade at 0, 500, 5000 or 50000 ppm (see Table 16 for average test substance intake) for 90 days.

Table 16. Average Test Substance Intake in Subchronic Toxicity Test for 90 days in Dogs

Dose		500 ppm	5000 ppm	50000 ppm
Test substance intake (mg/kg bw/day)	Male	18.9	164	1930
	Female	21.1	180	2040

Major toxicological findings observed at individual doses are shown in Table 17.

The LOAEL in this study would be 500 ppm (18.9 mg/kg bw/day for males, 21.1 mg/kg bw/day for females) for both males and females. The NOAEL could not be determined in this study. (Ref. 55)

Table 17. Toxicological Findings from Subchronic Toxicity Test for 90 days in Dogs

Dose	Male	Female
50000 ppm	• Paleness of gingiva and sclera • Suppression in body weight gain • Increase in neutrophils • Increase in yellow pigmentation in sternal bone marrow, increasing tendency of yellow pigmentation in renal proximal tubule	• Paleness of gingiva and sclera • Increases in platelet count and plasma cholesterol level
5000 ppm and higher	• Increase in MCV • Increases in reticulocyte count, platelet count and plasma cholesterol level • Increase in relative liver weight • Increased pigmentation in liver Kupffer cells	• Increase in MCV • Increasing tendency of yellow pigmentation in sternal bone marrow
500 ppm and higher	• Decreases in Hb concentration, red blood cell count, Ht and MCHC • Increases in sulfhemoglobin and methemoglobin	• Decrease in lymphocytes • Increases in sulfhemoglobin and methemoglobin • Increasing tendency of hyperplasia in

	• Increasing tendency of hyperplasia in femoral bone marrow	femoral bone marrow • Increasing tendency of pigmentation in liver Kupffer cells

(4) Subchronic neurotoxicity test for 28 days in rats

Wistar rats (groups of 10 males and 10 females) were fed diets containing Flufenoxuron, technical grade at 0, 1000, 5000 or 20000 ppm (see Table 18 for average test substance intake) for 28 days.

Table 18. Average Test Substance Intake in Subchronic Neurotoxicity Test for 28 days in Rats

Dose		1000 ppm	5000 ppm	20000 ppm
Test substance intake (mg/kg bw/day)	Male	88.3	435	1770
	Female	94.9	475	1930

At 5000 ppm and higher, low body weight and suppression in body weight gain were observed in males. The compound showed no neurotoxicity.

The NOAELs regarding general toxicity in this study would be 1000 ppm (88.3mg/kg bw/day) and 20000 ppm (1930 mg/kg bw/day) for males and females, respectively. (Ref. 56)

11. Chronic toxicity/carcinogenicity study

(1) Chronic toxicity study for 1 year in dogs

Beagle dogs (groups of 4 males and 4 females) were fed diets containing Flufenoxuron, technical grade at 0, 10, 100, 500 or 50000 ppm (see Table 19 for average test substance intake) for 1 year.

Table 19. Average Test Substance Intake in Chronic Toxicity Test for 1 year in Dogs

Dose		10 ppm	100 ppm	500 ppm	50000ppm
Test substance intake (mg/kg bw/day)	Male	0.4	3.9	19	2100
	Female	0.4	3.7	19	1880

Major toxicological findings observed at individual doses are shown in Table 20.

Increases in methemoglobin and sulfhemoglobin levels observed in females at 100 ppm were sporadic and thus considered not to be of toxicological significance.

The LOAEL and NOAEL in this study would be 500 ppm and 100 ppm (3.9 mg/kg bw/day for males, 3.7 mg/kg bw/day for females), respectively, for both males and females. (Ref. 57)

Table 20. Toxicological Findings from Chronic Toxicity Test for 1 year in Dogs

Dose	Male	Female
50000 ppm	• Decrease in Hb concentration • Increases in reticulocyte count and neutrophils • Increases in cell density and pigmentation in bone marrow, liver fatty vacuolation, increased pigmentation in renal proximal tubule	• Decrease in Hb concentration • Increases in MCV, reticulocyte count and platelet count, decreases in red blood cell count and MCHC • Increases in cell density and pigmentation in bone marrow, liver fatty vacuolation
500 ppm and higher	• Increases in MCV, methemoglobin, sulfhemoglobin and platelet count, decreases in red blood cell count, MCHC and plasma creatinine level • Increase in relative liver weight	• Increase in white blood cell count • Increasing tendency of liver fat staining (+)
100 ppm and lower	No toxicological findings	No toxicological findings

(2) Chronic toxicity study for 2 years in rats

Fischer rats (main group (2-year group): 20 males and 20 females, control group consisting of 40 males and 40 females, satellite group (1-year group): 10 males and 10 females, control group consisting of 20 males and 20 females) were fed diets containing Flufenoxuron, technical grade at 0, 1, 5, 50, 500, 5000 or 50000 ppm (see Table 21 for average test substance intake) for 2 years.

Table 21. Average Test Substance Intake in Chronic Toxicity Test for 2 years in Rats

Dose		1 ppm	5 ppm	50 ppm	500 ppm	5000 ppm	50000ppm
Test substance intake (mg/kg bw/day)	Male	0.044	0.226	2.21	22.0	233	2470
	Female	0.055	0.279	2.82	28.3	301	3200

Major findings observed at individual doses are shown in Table 22.

A decrease in relative spleen weight observed in males at 50 ppm and higher was not accompanied by any pathological change and thus was considered not to be of toxicological significance.

The LOAEL and NOAEL in this study would be 5000 ppm and 500 ppm (22.0 mg/kg bw/day for males, 28.3 mg/kg bw/day for females), respectively, for both males and females. (Ref. 58)

Table 22. Toxicological Findings from Chronic Toxicity Test for 2 years in Rats

Dose	Male	Female
50000 ppm	• Increases in Ht and mean platelet volume, decrease in normoblast count, decreases in plasma urea	• Increases in platelet count and platelet volume, decrease in plasma chloride level

	nitrogen, calcium and creatinine levels	• Perivascular lymphocytic infiltration in the liver
5000 ppm and higher	• Suppression in body weight gain • Decreases in Hb concentration, red blood cell count, MCV and MCH, increase in mean corpuscular diameter, decrease in plasma TG level	• Suppression in body weight gain • Decreases in Hb concentration, red blood cell count, MCV and MCH, increase in mean corpuscular diameter, decrease in plasma TG level, increase in plasma bilirubin level • Increase in relative adrenal weight
500 ppm and lower	No toxicological findings	No toxicological findings

(3) Carcinogenicity study for 2 years in rats

Fischer rats (groups of 50 males and 50 females) were fed diets containing Flufenoxuron, technical grade at 0, 500, 5000 or 50000 ppm (see Table 23 for average test substance intake) for 2 years. The compound was dissolved in acetone and added to the diets.

Table 23. Average Test Substance Intake in Carcinogenicity Study for 2 years in Rats

Dose		500 ppm	5000 ppm	50000ppm
Test substance intake (mg/kg bw/day)	Male	21.6	218	2290
	Female	25.9	276	2900

Major findings observed at individual doses are shown in Table 24. The compound showed no carcinogenicity.

The LOAEL and NOAEL in this study would be 5000 ppm and 500 ppm (21.6 mg/kg bw/day for males, 25.9 mg/kg bw/day for females), respectively, for both males and females. (Ref. 59)

Table 24. Toxicological Findings from Carcinogenicity Study for 2 years in Rats

Dose	Male	Female
50000 ppm	• Increase in food consumption • Decrease in relative liver weight • Basophilic altered foci in the liver	
5000 ppm and higher	• Suppression in body weight gain • Decrease in relative kidney weight	• Suppression in body weight gain • Increase in relative adrenal weight
500 ppm	No toxicological findings	No toxicological findings

(4) Carcinogenicity study for 2 years in mice (i)

B6C3F_1 mice (main group (2-year group): 50 males and 50 females, satellite group (1-year group): 10 males and 10 females) were fed diets containing Flufenoxuron, technical grade at 0, 500, 5000 or 50000 ppm (see Table 25 for average test substance intake) for 2 years. The compound was dissolved in

acetone and added to the diets.

Table 25. Average Test Substance Intake in Carcinogenicity Study for 2 years in Mice (i)

Dose		500 ppm	5000 ppm	50000ppm
Test substance intake (mg/kg bw/day)	Male	56.0	559	7360
	Female	73.2	739	7780

Major toxicological findings other than neoplastic lesions are shown in Table 26. As neoplastic lesions, results of a trend test revealed significant differences in the total incidence of angiosarcoma and hemangioma of the liver in males and the total incidence of hemangiosarcoma and hemangioma of the spleen and the total incidence of hemangiosarcoma and hemangioma of all organs in females at 50000 ppm. Moreover, the incidence of hepatocellular carcinoma significantly increased in males at 500 ppm and higher and in females at 500 ppm, but this finding did not show any dose-relationship and was not accompanied by any significant difference in the total incidence of hepatocellular carcinoma and adenoma at any dose tested. (Table 27-28)

Relative heart and kidney weights increased in females at 500 ppm and higher, but since these findings did not show any clear dose-relationship, they were considered not to be of toxicological significance.

Table 26. Toxicological Findings from Carcinogenicity Study for 2 years in Mice (i)
(other than neoplastic lesions)

Dose	Male	Female
50000 ppm	• Pawing out of feed • Increase in relative liver weight • Necrosis and hypertrophy of hepatocytes • Syncytial macrophage in the spleen • Liver Kupffer cell aggregates, inflammation of the liver and the stomach gland	• Necrosis and hypertrophy of hepatocytes • Syncytial macrophage in the spleen
5000 ppm and higher	• Suppression in body weight gain • Increase in lymphocytes (week 78) • Forestomach ulcer	• Pawing out of feed • Suppression in body weight gain • Lordosis, local hair loss • Liver Kupffer cell aggregates
500 ppm	No toxicological findings	No toxicological findings

Table 27. Occurrence Rates of Hepatic Tumors Observed in Carcinogenicity Study for 2 years in Mice (i)

Sex	Male				Female			
Number of animals tested	50	50	50	50	50	50	50	50
Dose (ppm)	0	500	5000	50000	0	500	5000	50000

Liver	Hepatocellular adenoma	15	3	11	10	10	6	2	13
	Hepatocellular carcinoma	3	19***	15**	15**	3	9*	7	5
	Adenoma + carcinoma	18	22	26	25	13	15	9	18

*:P<0.05, **:P<0.01, ***:P<0.001(Fisher's exact test)

Table 28. Occurrence Rates of Hemangioma and Angiosarcoma Observed in Carcinogenicity Study for 2 years in Mice (i)

Sex		Male				Female			
Number of animals tested		50	50	50	50	50	50	50	50
Dose (ppm)		0	500	5000	50000	0	500	5000	50000
Liver	Hemangiosarcoma	2	1	0	5	0	0	0	1
	Hemangioma	0	0	0	2 $	0	0	0	0
	Hemangiosarcoma + hemangioma	2	1	0	7 $	0	0	0	1
Spleen	Hemangiosarcoma	4	3	0	3	0	1	1	7**
	Hemangioma	0	0	0	0	0	0	1	0
	Hemangiosarcoma + hemangioma	4	3	0	3	0	1	2	7 $$
Others	Hemangiosarcoma	2	0	1	1	1	0	1	2
	Hemangioma	0	1	0	1	0	1	0	1
	Hemangiosarcoma + hemangioma	2	1	0	2	1	1	1	3
All organs	Hemangiosarcoma	8	4	1	9	1	1	2	10
	Hemangioma	0	1	0	3	0	1	1	1
	Hemangiosarcoma + hemangioma	8	5	1	12	1	2	3	11 $$

**:P<0.01, (Fisher's exact test) $: P<0.05, $$: P<0.01 (trend test by Peto et al.)

The LOAEL and NOAEL in this study would be 5000 ppm and 500 ppm (56.0 mg/kg bw/day for males, 73.2 mg/kg bw/day for females), respectively, for both males and females. (Refs. 60-61)

(5) Carcinogenicity study for 2 years in mice (ii)

B6C3F$_1$ mice (groups of 50 males and 50 females) were fed diets containing Flufenoxuron, technical grade at 0, 100, 1000 or 10000 ppm (see Table 29 for average test substance intake) for 2 years.

Table 29. Average Test Substance Intake in Carcinogenicity Study for 2 years in Mice (ii)

Dose		100 ppm	1000 ppm	10000 ppm
Test substance intake	Male	15.3	152	1590

(mg/kg bw/day)	Female	17.4	187	1890

Suppression in body weight gain and an increase in extramedullary hematopoiesis were observed in females at 10000 ppm. The compound showed no carcinogenicity. The LOAELs in this study would be 10000 ppm for females but could not be determined for males. The NOAELs in this study would be 10000 ppm (1590 mg/kg bw/day) and 1000 ppm (187 mg/kg bw/day) for males and females, respectively. (Ref. 62)

12. Reproductive/developmental toxicity

(1) Two-generation reproductive toxicity study in rats

SD rats (P generation: groups of 28 males and 28 females, F_1 generation: groups of 24 males and 24 females) were fed diets containing Flufenoxuron, technical grade at 0, 50, 190, 710 or 10000 ppm) (see Table 30 for average test substance intake) for two generations.

Table 30. Average Test Substance Intake in Two-generation Reproductive Toxicity Study in Rats

Dose			50 ppm	190 ppm	710 ppm	10000 ppm
Test substance intake (mg/kg bw/day)	P	Male	3.8	14.3	53.6	772
		Female	4.3	16.0	61.0	907
	F_1	Male	4.2	16.1	62.5	865
		Female	4.8	18.6	69.2	956

In the parent animals, hair loss was observed in female P and F_1 parent animals at 10000 ppm, relative brain weight decreased in male F_1 parent animals at 710 ppm and higher, relative kidney weight increased in male P parent animals at 190 ppm and higher and a suppression in body weight gain and a decrease in relative liver weight were observed in male F_1 parent animals.

In the offspring, at 10000 ppm, post-weaning survival rates decreased in F_1 and F_2 offspring, a delay in auditory startle reaction was observed in F_1 offspring, relative heart weight increased in males and females, weaning weight decreased in F_2 offspring and relative liver weight increased and relative brain and kidney weights decreased in females. At 710 ppm and higher, relative brain weight decreased in female F_1 offspring and relative heart and liver weights increased and relative kidney weight decreased in male F_2 offspring. At 190 ppm, weaning weight decreased in F_1 offspring and relative liver weight increased in males and females.

The LOAEL in this study for parent animals and offspring would be 190 ppm, and the NOAELs would be 50 ppm (P male: 3.8 mg/kg bw/day, P female: 4.3 mg/kg bw/day, F_1 male: 4.2 mg/kg bw/day, F_1 female: 4.8 mg/kg bw/day) for both males and females. The compound showed no reproductive toxicity (Ref. 63)

(2) Developmental toxicity study in rats

SD rats (groups of 26 females) were given Flufenoxuron, technical grade at 0, 10, 100, or 1000 mg/kg bw/day on days 6-16 of pregnancy by gavage.

The compound showed no effect on dams or fetuses.

The NOAELs in this study would be 1000 mg/kg bw/day for dams and fetuses. No teratogenicity of Flufenoxuron was evident. (Ref. 64)

(3) Developmental toxicity study in rabbits

NZW rabbits (groups of 15 females) were given Flufenoxuron, technical grade at 0, 10, 100 or 1000 mg/kg bw/day on days 6-18 of pregnancy by gavage.

The compound showed no effect on dams or fetuses. The NOAEL in this study would be 1000 mg/kg bw/day for dams and fetuses. No teratogenicity of Flufenoxuron was evident. (Ref. 65)

13. Genotoxicity

Flufenoxuron has been tested in a range of *in vivo* and *in vitro* standard protocols (Table 31). It was not mutagenic in reverse mutation tests in bacteria and genetic mutation tests in Chinese hamster cultured cells (V79). It did not affect *in vivo*/*in vitro* unscheduled DNA synthesis (UDS) or replicative DNA synthesis (RDS) in rat hepatocytes. Flufenoxuron induced *in vitro* chromosomal aberrations in Chinese hamster cultured cells (CHO-K1) but not in cultured rat hepatocytes (RL-4) or cultured human lymphocytes. It did not induce *in vivo* chromosomal aberrations in rat bone marrow cells, gene conversion in yeasts or micronucleus in mice.

Flufenoxuron induced chromosomal aberrations in the presence of S9 mix in Chinese hamster cultured cells (CHO-K1), but it did not induce *in vitro* chromosomal aberrations in cultured rat hepatocytes or cultured human lymphocytes or *in vivo*/*in vitro* unscheduled DNA synthesis (UDS) in rat hepatocytes. Moreover, since it gave negative results in the *in vivo* chromosomal aberration test or the *in vivo* micronucleus test, which were performed using sufficiently high doses, the committee concluded that Flufenoxuron was not genotoxic at least *in vivo*. (Refs. 66-76, 81)

Table 31. Summary of Genotoxicity Test Results (Flufenoxuron)

Test systems		Cells/animals	Dose	Results
in vitro	Reverse mutation	*S.typhimurium* TA98,TA100,TA1535, TA1537, TA1538 strains *E.coli* WP2*uvr*A strain	31.3-4000 μg/plate (±S9)	Negative
	Reverse mutation (standard plate test)	*S.typhimurium* TA1535, TA100, TA1537, TA98 strains *E.coli* WP2*uvr*A strain	20-5000 μg/plate (±S9)	Negative
	Reverse mutation (preincubation test)	*S.typhimurium* TA1535, TA100, TA1537, TA98 strains *E.coli* WP2*uvr*A strain	4-2500 μg/plate (±S9)	Negative
	Gene conversion	*S.cerevisiae* JD1 strain	0.01-1.0 mg/mL (±S9)	Negative
	Genetic mutation	Cultured Chinese hamster lung cells (V79)	50-1350 μg /mL (±S9)	Negative

	Chromosomal aberration	Cultured Chinese hamster ovary cells (CHO-K1)	15-150 μg / mL (±S9)	Positive (+S9)
	Chromosomal aberration	Cultured rat hepatocytes (RL-4)	45-450 μg / mL (-S9) 16-160 μg / mL (+S9)	Negative
	Chromosomal aberration	Cultured human lymphocytes	78.4-160 μg/ mL (±S9)	Negative
in vivo/ in vitro	Unscheduled DNA synthesis (UDS)	Fischer rats (groups of 3 males)	188-1500mg/kg bw (single administration by gavage)	Negative
in vivo	Replicative DNA synthesis (RDS)	Fischer rats (groups of 4 males)	2000, 4000 mg/kg bw (single administration by gavage)	Negative
	Chromosomal aberration	SD rats (bone marrow cells) (groups of 5 males and 5 females)	4000 mg/kg bw (single administration by gavage)	Negative
	Micronucleus	ICR mice (groups of 6 males)	500-2000 mg/kg bw (intraperitoneal administration for 2 consecutive days)	Negative

±S9: with/without exogenous metabolic activation

The urea form (a metabolite) and the bis form (a contaminant in the technical grade) were not mutagenic in the bacterial reverse mutation test. The aniline form (a metabolite) induced an increasing tendency in the number of reversely mutated colonies (up to twice the number in the solvent control) in the presence of S9 mix in the bacterial reverse mutation test but did not induce *in vitro* chromosomal aberration in cultured Chinese hamster cells (CHO-K1) (Table 32). (Refs. 77-78)

Table 32. Summary of Genotoxicity Test Results (metabolites and contaminants)

Test systems	Test substance (metabolites)	Cells	Dose	Results
Reverse mutation	Urea form	*S.typhimurium* TA98,TA100,TA1535, TA1537,TA153 strains *E.coli* WP2*uvr*A strain	31.3-5000 μg/plate	Negative
	Bis form			Negative
	Aniline form			False positive (+S9)
Chromosomal aberration	Aniline form	Chinese hamster cultured cell line (CHO-K1)	6.25-50 μg/mL	Negative

±S9: with/without exogenous metabolic activation

14. Other toxicity tests (short-term studies on liver function and carcinogenicity)

(1) Effects on activities of hepatic drug-metabolizing enzymes in mice

B6C3 mice (groups of 8 males) were fed diets containing Flufenoxuron, technical grade at 0 or 5000 ppm for 7, 21, 63 or 105 days to study the effects on activities of hepatic drug-metabolizing enzymes. (Positive control: 500 ppm PB administered for 21 days)

Flufenoxuron did not increase the P-450 level or the activities of five mixed-function oxidases.

Animals administered PB showed an increase in relative liver weight, hypertrophy of centrilobular

hepatocytes, an increase in the P-450 level and increased activities of five mixed-function oxidases.

It was considered that Flufenoxuron would not induce hepatic drug-metabolizing enzymes. (Ref.79)

(2) Test of applicability of PCNA and BrdU methods using preneoplastic and neoplastic changes as markers in mice

B6C3F1 mice (groups of 5 males and 5 females) were fed diets containing Flufenoxuron, technical grade at 0, 500 or 50000 ppm for 4 weeks. The animals were intraperitoneally administered BrdU (50mg/kg bw) 60 minutes before they were systematically killed. After the animals were killed, immunostaining of PCNA and BrdU were performed to test the applicability of PCNA and BrdU methods using preneoplastic and neoplastic changes as markers.

Relative liver weight increased in males at 50000 ppm. When compared with the control group, there was no increase in the number of PCNA- or BrdU-positive cells in either sex at any dose tested. (Ref. 80)

III. Evaluation

The pesticide Flufenoxuron was evaluated using the documents listed in References.

Absorption, distribution, metabolism and excretion of Flufenoxuron were studied in rats. The plasma concentration of the compound reached the maximum at 6 hours and from 4 to 6 hours after single administration of Low dose and High dose, respectively. In individual tissues, the compound was detected at relatively high concentrations in the gastrointestinal tract (including the contents), thyroid gland, adrenal gland, liver and bone marrow around T_{max}. By 168 hours after the treatment, the compound was distributed mainly in the fat and also in other tissues including the gastrointestinal tract (including the contents), bone marrow, liver and kidney. The compound was mainly eliminated through fecal and urinary excretions, mostly as Flufenoxuron. Metabolites detected in the urine were the urea form, the aniline form, 2,6-difluorobenzoic acid and 2,6-difluorobenzamide. Twenty or more metabolites were detected in the feces but only in trace amounts. Besides Flufenoxuron, the aniline form was detected in the bile as a metabolite.

The main metabolic pathways of Flufenoxuron could be the hydrolysis of the benzoyl-urea bond resulting in the production of 2,6-difluorobenzoic acid and the urea form and further metabolism of the urea form resulting in the production of the aniline form, or the hydrolysis of the urea bond in Flufenoxuron resulting in the production of 2,6-difluorobenzamide and unstable *N*-phenylcarbamic acid and further metabolism of *N*-phenylcarbamic acid resulting in the production of the aniline form.

In the study of absorption, distribution, metabolism and excretion of Flufenoxuron in dogs, the plasma concentration of the compound reached the maximum at from 3 to 4 hours after single administration of Low dose. By 168 hours after the administration, the compound was detected at high levels in the fat and bone marrow. The compound was mostly eliminated as Flufenoxuron in the urine, diarrhea stool and feces. The aniline form was detected in the feces as a metabolite.

In vitro metabolism was examined in mice, rats and dogs using liver S9 and microsome fractions. Besides Flufenoxuron, the aniline form and the urea form were detected as metabolites. No sexual or interspecific difference was observed in the metabolite profile.

Plant metabolism of Flufenoxuron was studied in Chinese cabbages, tomatoes and apples. The major portion of the residual radioactivity was attributed to Flufenoxuron, and no metabolite was detected.

The fate of Flufenoxuron in soils was studied, and its half-lives under aerobic conditions were 42 days in clay loam and 181 days or longer in sandy loam soil. Under anaerobic conditions, the degradation of the compound was so slow that the half-life could not be calculated. Under either condition, the major degradate was the urea form, and the aniline form was also detected as a degradate. Flufenoxuron did not migrate in soils. Flufenoxuron, the urea form and its non-extractable radioactive component were not taken up by plants.

In the test of hydrolysis in water, Flufenoxuron was stable against hydrolysis under neutral conditions. In the test of photolysis in water, the compound was degraded by light, and the half-life was from 6.8 to 7.1 days, which was calculated as from 17.0 to 17.7 day under the spring sunlight at 35 degrees north latitude.

The residual value for the sum of Flufenoxuron and the urea form (a degradate) in soils was studied (both in the vessel and the field) using volcanic ash loam and alluvial mineral clay loam. The half-lives were from 60 to 111 days and from 8 to 182 days in the vessel and the field, respectively.

The residual levels of Flufenoxuron in crops were examined in vegetables, fruits, beans and tea plants. The

highest residual value of Flufenoxuron was 11.1 mg/kg, which was observed in Garland Chrysanthemum when the compound was applied at from 80 to 100g ai/ha for three times and the samples were collected 3 days after the final application. The residual value decreased to 7.37 mg/kg, 5.04 mg/kg and 0.61 mg/kg at 7, 14 and 21 days after the application, respectively.

The LD_{50}s of Flufenoxuron were >5000 mg/kg bw in male and female rats, ICR mice and dogs and >3000 mg/kg bw in male and female STCF1 mice by oral dose, >2000 mg/kg bw in male and female rats and mice by dermal treatment, and>5.1 mg/L in male and female rats by inhalation.

The NOAELs of Flufenoxuron were 4.0 mg/kg bw/day in rats and 10.2mg/kg bw/day in mice in subchronic toxicity tests. The compound showed no neurotoxicity.

The NOAELs of Flufenoxuron were 22.0 mg/kg bw/day in rats and 3.7 mg/kg bw/day in dogs in chronic toxicity tests.

In the carcinogenicity test in mice, the compound increased the incidences of hepatocellular carcinoma and vascular tumors. Regarding the increased incidence of hepatocellular carcinoma, there was no significant difference between the treated groups and the control group in the total incidence of hepatocellular carcinoma and adenoma. The occurrence rates in treated groups were within the range of the background data, while the occurrence rate in the control group was below the range of the background data. Moreover, the compound gave negative results in replicative DNA synthesis test in hepatocytes. Based on these findings, the increased incidence of hepatocellular carcinoma was not attributed to the administration of Flufenoxuron. The increased incidence of vascular tumors was a background lesion in mice and was not attributed to the administration of Flufenoxuron.

The NOAELs were 21.6 mg/kg bw/day in rats and 56.0 mg/kg bw/day in mice in carcinogenicity tests.

The NOAELs were 3.8 mg/kg bw/day in the two-generation reproductive toxicity study in rats. The compound showed no reproductive toxicity.

Developmental toxicity tests were performed in rats and rabbits, and the NOAELs were 1000 mg/kg bw/day for dams and fetuses in rats and 1000 mg/kg bw/day for dams and fetuses in rabbits. The compound showed no teratogenicity.

Flufenoxuron was not mutagenic in reverse mutation tests in bacteria and genetic mutation tests in cultured Chinese hamster lung cells (V79). It did not affect *in vivo*/*in vitro* unscheduled DNA synthesis (UDS) or replicative DNA synthesis (RDS) in rat hepatocytes. Flufenoxuron induced *in vitro* chromosomal aberrations in cultured Chinese hamster ovary cells (CHO-K1) but not in cultured rat hepatocytes (RL-4) or cultured human lymphocytes. It did not induce *in vivo* chromosomal aberrations in rat bone marrow cells, gene conversion in yeasts or micronucleus in mice. Flufenoxuron induced chromosomal aberrations in cultured Chinese hamster ovary cells (CHO-K1), but it did not induce *in vitro* chromosomal aberrations in cultured rat hepatocytes or cultured human lymphocytes or *in vivo*/*in vitro* unscheduled DNA synthesis in rat hepatocytes. Moreover, since it gave negative results in the *in vivo* chromosomal aberration test or the *in vivo* micronucleus test, which were performed using sufficiently high doses, the committee concluded that Flufenoxuron was not genotoxic at least *in vivo*.

Based on the results from the various tests, the residues for exposure assessment in crops were defined as

Flufenoxuron (parent compound only).

The NOAELs and LOAELs determined by the individual tests are shown in Table 33.

Table 33. NOAELs and LOAELs Determined in Toxicity Evaluation Tests

Species	Evaluation test	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Note[1)]
Rats	90-days subchronic toxicity	Male: 32.9 Female: 4.0	Male: 336 Female: 39.3	Male: decrease in MCV, etc. Female: increase in mean corpuscular diameter, etc.
	28-days subchronic neurotoxicity	Male: 88.3 Female: 1930	Male: 435 Female: -	Male: low body weight, suppression in body weight gain (No neurotoxicity)
	2-years chronic toxicity	Male: 22.0 Female: 28.3	Male: 233 Female: 301	Male and female: suppression in body weight gain, etc.
	2-years carcinogenicity	Male: 21.6 Female: 25.9	Male: 218 Female: 276	Male and female: suppression in body weight gain, etc. (No carcinogenicity)
	Two-generation reproductive toxicity	Parent animals and offspring: P male: 3.8 P female: 4.3 F1 male: 4.2 F1 female: 4.8	Parent animals and offspring: P male: 14.3 P female: 16.0 F1 male: 16.1 F1 female: 18.6	Parent animals: suppression in body weight gain, increase in relative kidney weight, etc. Offspring: decrease in weaning weight, increase in relative liver weight (No reproductive toxicity)
	Developmental toxicity	Dam: 1000 Fetus: 1000	-	(No teratogenicity)
Mice	90-days subchronic toxicity	Male: 10.2 Female: 11.4	Male: 102 Female: 127	Male and female: increases in plasma bilirubin and relative liver weight
	2-years carcinogenicity (i)	Male: 56.0 Female: 73.2	Male: 559 Female: 739	Male: suppression in body weight gain, Stomach, keratinized ulcer Female: suppression in body weight gain, liver Kupffer cell aggregates, etc. (increased incidence of vascular tumors)
	2-years carcinogenicity (ii)	Male: 1590 Female: 187	Male: - Female: 1890	Female suppression in body weight gain, increase in extramedullary

				hematopoiesis (No carcinogenicity)
Rabbits	Developmental toxicity	Dam: 1000 Fetus: 1000	-	(No teratogenicity)
Dogs	90-days subchronic toxicity	Male: - Female: -	Male: 18.9 Female: 21.1	Male and female: increasing tendency of hyperplasia in femoral bone marrow, etc.
	1-year chronic toxicity	Male: 3.9 Female: 3.7	Male: 19 Female: 19	Male: increases in MCV, methemoglobin and sulfhemoglobin, etc. Female: increase in white blood cell count, etc.

- : NOAEL or LOAEL could not be determined.

[1)]: Note summarizes the findings observed at LOAELs.

Based on the lowest value among NOAELs, which was 3.7 mg/kg bw/day in the one-year study of chronic toxicity in dogs, and after dividing this lowest value by a safety factor of 100, the Food Safety Commission established the ADI value of Flufenoxuron as 0.037 mg/kg bw/day.

ADI	0.037 mg/kg bw/day
(Referred data for ADI)	Chronic toxicity study
(Laboratory animal tested)	Dogs
(Duration)	1 year
(Administration route)	Dietary administration
(NOAEL)	3.7 mg/kg bw/day
(Safety factor)	100

<Appendix 1: Abbreviations for metabolites/degradates>

Abbreviation	Chemical name
WL129183 (urea form)	4-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-2-fluorophenyl urea
WL115096 (aniline form)	4-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-2-fluoroAniiiline
WL131767 (bis form)	1,3-bis-[4-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-2- fluorophenyl] urea

<Appendix 2: Abbreviations for test values. etc.>

Abbreviation	Name
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BrdU	5-bromo-2'-deoxyuridine
C_{max}	Maximum concentration
Hb	Hemoglobin
Ht	Hematocrit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
PB	Phenobarbital sodium
PCNA	Proliferating cell nuclear antigen
$T_{1/2}$	Half-life
TAR	Total applied radioactivity
TG	Triglyceride
T_{max}	Time to achieve maximum concentration
TRR	Total residual radioactivity

<Appendix 3: Results from residual tests in crops>

Crop (Cultivation type) (Parts analyzed) Year tested	Number of fields	Amount used (g ai/ha)	Applications (times)	PHI elapsed days (days)	Residues (mg/kg) Flufenoxuron	
					Highest	Average
Soybean (Field) (Dried grain) FY 1989	2	200	2 2	14 21	0.065 0.043	0.050 0.033
Soybean (Dried grain) FY 2002	2	37.5-50	2 2 2	7 14 21	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01
Immature cowpea (Bean) FY 2003	2	50	2 2 2	1 3 7	0.3 <0.1 <0.1	0.2 <0.1 <0.1
Immature broad bean (Field/greenhouse) (Grain) FY 1999	2	75-100	3 3 3	1 3 7	0.02 <0.01 <0.01	0.01* 0.01* 0.01*
Broad bean (Field) (Dried grain) FY 1999	2	100	3 3 3	1 3 7	0.03 0.02 0.02	0.02* 0.01* 0.01*
Immature hyacinth bean (Greenhouse) (Fruit) FY 2004	2	50	2 2 2 2	1 3 7 14	0.3 0.3 0.1 <0.1	0.2 0.3 0.1* <0.1
Sugar beet (Root) FY 1989	2	100	4	7 14	0.070 0.062	0.040 0.030
Japanese radish (Root) FY 1995	2	100	2 2 2 3 3 3	13-14 20-21 29-30 13-14 20-21 29-30	0.02 0.01 0.01 0.02 0.02 0.02	0.01* 0.01* 0.01* 0.01* 0.02* 0.01*
Japanese radish (Leaf) FY 1995	2	100	2 2 2 3 3 3	13-14 20-21 29-30 13-14 20-21 29-30	2.06 0.92 0.57 2.47 0.93 0.56	1.12 0.49 0.25 1.30 0.48 0.25
Horseradish (Greenhouse) (Flower bud) FY 2005	2	30	3 3 3	21 28 45	0.07 0.03 0.01	0.05 0.02 0.01*
Chinese cabbage (Foliage) FY 1989 FY 1990	2 2 2 8 8 2 6 6	50-100	1 1 1 2 2 2 4 4	7 14 21 7 14 21 7 14	0.059 0.076 0.003 0.193 0.152 0.012 0.240 0.209	0.041 0.029 0.004* 0.068 0.033 0.006* 0.161 0.179
Cabbage (Foliage) FY 1989	2	50-100	2 2 4 4	7 13-14 7 13-14	0.061 0.040 0.054 0.052	0.045 0.024 0.040 0.034

Crop (Cultivation type) (Parts analyzed) Year tested	Number of fields	Amount used (g ai/ha)	Applications (times)	PHI elapsed days (days)	Residues (mg/kg) Flufenoxuron	
					Highest	Average
Komatsuna (Greenhouse) (Foliage) FY 1999	2	50	1 1 2 2	3 7 3 7	2.32 2.30 3.90 3.11	1.51 1.33 2.43 1.70
Mizuna (Field/greenhouse) FY 1997	2	100	1 1 1 2 2 2	7 10 14 7 10 14	3.32 1.66 1.12 3.24 2.33 1.61	1.89 1.23 0.78 2.29 1.72 0.94
Brassica rapa var. chinensis (Greenhouse) (Foliage) FY 1999	2	100-200	2 2 2	1 3 7	4.42 3.50 2.51	2.90 2.08 1.40
Broccoli (Flower bud)(Fruit) FY 2004	2	100-150	2 2 2	7 14 21	1.59 0.99 0.49	0.72 0.52 0.24*
Shirona (Field) (Foliage) FY 1997 FY 1998	1 2 2 2	75	2 2 2 2	1 7 14 21	2.45 2.24 1.60 0.26	2.05 1.52 0.71 0.11
Garland Chrysanthemum (Greenhouse) (Foliage) FY 1993	1 2 2 1 1 2 2 1	80-100	2 2 2 2 3 3 3 3	3 7 14 21 3 7 14 21	8.61 5.85 3.28 0.72 11.1 7.37 5.04 0.61	8.13 4.27 2.12 0.59 9.92 4.69 2.69 0.51
Lettuce (Greenhouse) (Foliage) FY 1998	2	62.5-71.3	3 3 3	3 7 14	0.48 0.16 0.08	0.20 0.11 0.04
Leaf lettuce (Foliage) FY 2003	1	50	4[a] 4[a] 4[a]	3 7 14	2.36 0.87 <0.05	2.26 0.81 <0.05
	1	50	3 3 3	3 7 14	1.24 0.07 0.06	1.14 0.06* 0.06*
Butterhead lettuce (Foliage) FY 2004	2	37.5-50	3 3 3	3 7 14	3.7 1.7 0.6	2.22 1.32 0.38
Welsh onion (Hanegi) (Foliage) FY 1995	2	37.5	2 2 3 3	14 21 14 21	0.91 0.71 1.54 0.98	0.49 0.30* 0.74 0.43
Welsh onion (Fukanegi) (Foliage) FY 1989	2	100	4 4	7 14	1.53 1.06	0.99 0.60
Asparagus (Greenhouse) (Stem) FY 1996	2	70-75	2 2 2 2	1 3 7 14	0.15 0.01 0.01 <0.01	0.13 0.01* 0.01* 0.01*

Crop (Cultivation type) (Parts analyzed) Year tested	Number of fields	Amount used (g ai/ha)	Applications (times)	PHI elapsed days (days)	Residues (mg/kg) Flufenoxuron Highest	Residues (mg/kg) Flufenoxuron Average
Parsley (Greenhouse) (Foliage) FY 2001	2	50-62.5	1 1 1	7 14 21	4.84 4.63 4.53	3.85 2.90 2.94
Celery (stem) FY 1994	2	75-90	2 2 3 3	14 21-22 14 21-22	0.76 0.34 1.00 0.22	0.42 0.21 0.53 0.12
Celery (Leaf) FY 1994	2	75-90	2 2 3 3	14 21-22 14 21-22	5.88 5.58 8.17 2.79	3.56 2.31 4.70 1.32
Celery (Foliage) FY 1994	2	75-90	2 2 3 3	14 21-22 14 21-22	2.24 1.65 3.22 1.15	1.33 0.76 1.78 0.51
Japanese honewort (Greenhouse/hydroponics) (Foliage) FY 2000	2	75	2 2 2	7 14 21	5.94 5.67 4.12	4.23 3.76 2.58
Tomato (Greenhouse) (Fruit) FY 1994	2	100-150	2 3 3 3 4	1 1 3 7 1	0.08 0.14 0.11 0.15 0.15	0.08 0.10 0.09 0.10 0.12
Cherry tomato (Greenhouse) (Fruit) FY 2004	2	100-150	2 2 2	1 3 7	0.18 0.19 0.19	0.12 0.13 0.13
Green pepper (Capsicum annuum var. grossum) (Greenhouse) (Fruit) FY 1999	2	100-125	3 3 3	1 3 7	0.51 0.43 0.45	0.41 0.33 0.30
Eggplant (Greenhouse) (Fruit) FY 1996	2	200-250	4 4 4	1 3 7	0.74 0.57 0.20	0.42 0.33 0.13
Green pepper (Capsicum annuum var. angulosum) (Greenhouse) (Fruit) FY 2004	2	153.5-175	3 3 3	1 3 7	0.92 1.15 0.59	0.60 0.66 0.32
Cucumber (Greenhouse) (Fruit) FY 1997	2	92.5-150	4 4 4	1 3 7	0.14 0.11 0.04	0.13 0.09 0.03
Squash (Greenhouse) (Fruit) FY 2004	1	85	3 3 3	1 8 15	<0.2 <0.2 <0.2	0.12* 0.12* 0.11*
	1	75	4 4 4	1 3 7	<0.2 <0.2 <0.2	0.11* 0.11* 0.11*

Crop (Cultivation type) (Parts analyzed) Year tested	Number of fields	Amount used (g ai/ha)	Applications (times)	PHI elapsed days (days)	Residues (mg/kg) Flufenoxuron	
					Highest	Average
Oriental pickling melon (Fruit) FY 2003	2	100	1 1 1	1 3 7	<0.05 <0.05 <0.05	<0.05 <0.05 <0.05
Watermelon (Greenhouse) (Fruit) FY 1996	2	125-150	4 4 4	7 14 21	0.02 0.03 0.03	0.01* 0.02* 0.02*
Melon (Greenhouse) (Fruit) FY 1990	2	150	3	7 14	0.002 0.002	0.004* 0.004*
Spinach (Greenhouse/field) (Foliage) FY 2000	2	37.5-75	3 3 3	3 7 14	4.60 3.21 1.50	3.63 2.80 1.02
Immature green pea (Greenhouse) (Pod) FY 2001	2	73.5-75	2 2 2	1 3 7	0.37 0.21 0.18	0.32 0.19 0.16
Immature common bean (Greenhouse) (Pod) FY 2000	2	75-150	2 2 2	1 7 14	0.48 0.29 0.19	0.42 0.17 0.09*
Vegetable soybean (Immature soybean) (Pod) FY 2002	2	50-62.5	2 2 2	1 7 14	1.93 1.54 0.85	1.27 1.10 0.66
Japanese ginger (Greenhouse) (Flower bud) FY 2004	2	150	3 3 3	1 3 7	<0.04 <0.04 <0.04	<0.04 <0.04 <0.04
Satsuma orange (Greenhouse) (Fruit flesh) FY 1989	2	500	2	7 14	0.026 0.020	0.008* 0.009*
Satsuma orange (Greenhouse) (Peel) FY 1989	2	500	2	7 14	3.21 4.18	2.08 2.27
Satsuma orange (Greenhouse) (Whole fruit) FY 1989	2	500	2	7 14	0.499 0.630	0.341 0.352
Chinese citron (Fruit flesh) FY 1989	2	500-900	2	7 14	0.039 0.058	0.019* 0.022*
Chinese citron (Peel) FY 1989	2	500-900	2	7 14	1.29 1.35	1.15 1.09
Sudachi (Field) (Fruit) FY 2004	1	500	2 2 2	6 14 21	0.69 0.60 0.41	0.68 0.60 0.41
Citrus sphaerocarpa (Field) (Fruit) FY 2004	1	640	2 2 2	7 14 20	0.38 0.26 0.27	0.38 0.26 0.26

Crop (Cultivation type) (Parts analyzed) Year tested	Number of fields	Amount used (g ai/ha)	Applications (times)	PHI elapsed days (days)	Residues (mg/kg) Flufenoxuron	
					Highest	Average
Apple (Fruit) FY 1989 FY 1990	5	200-300	1	13-14	0.190	0.133
	5		1	20-21	0.187	0.108
	5		1	28-30	0.198	0.099
	3		1	45	0121	0.084
	3		1	60	0.117	0.068
	3		1	90	0.073	0.040*
	5		2	13-14	0.267	0.211
	5		2	20-21	0.224	0.177
	5		2	28-30	0.349	0.230
	3		2	45	0.192	0.127
	3		2	60	0.209	0.136
	3		2	90	0.112	0.095
Pear (Fruit) FY 1990	2	120-250	1	14	0.079	0.048
			1	21	0.070	0.050
			1	30	0.053	0.041
			2	14	0.145	0.099
			2	21	0.092	0.075
			2	30	0.110	0.079
Peach (Field) (Fruit flesh) FY 1990	2	150-200	1	14	<0.01	<0.008
			1	21	<0.01	<0.008
			2	14	0.006	0.008*
			2	21	<0.01	<0.008
Nectarine (Field) (Fruit) FY 2003	2	135-150	2	14	0.59	0.37
			2	21	0.23	0.18
			2	28	0.19	0.16
Cherry (Greenhouse) (Fruit) FY 1995	2	75-100	1	7	0.56	0.27
			1	14	0.46	0.25
			2	7	0.67	0.35
			2	14	0.60	0.34
			2	21	0.57	0.29
Strawberry (Greenhouse) (Fruit) FY 1995	2	37.5	2	1	0.09	0.06
			3	1	0.14	0.07
			3	3	0.10	0.06
			3	7	0.07	0.04
Tea plant (Field) (Unrefined leaf) FY 1990	2	100	1	7	7.78	7.02
			1	14	5.66	4.78
			2	7	7.98	7.36
			2	14	6.86	4.95
Tea plant (Field) (Leachate) FY 1990	2	100	1	7	0.10	0.06
			1	14	0.05	0.04
			2	7	0.07	0.06
			2	14	0.05	0.03

note) ai: active ingredient, PHI: pre-harvest interval

a: There was a rainfall 20 minutes after application was completed, so the compound was re-applied the following day.

· The compound was applied in the form of an emulsion.

· For data including values below the detection limit, the average was calculated using the detection limit values and marked *.

· In cases where all data were blow the detection limit, the average of the detection limit values was taken and marked <.

<Appendix 4: Estimated intakes>

Crop	Residues (mg/kg)	National average (body weight: 53.3 kg)		Infants (ages 1 to 6) (body weight: 15.8 kg)		Pregnant women (body weight: 55.6 kg)		Elderly (ages 65 or above) (body weight: 54.2 kg)	
		ff (g/person/day)	Intake (μg/person/day)	ff (g/person/day)	Intake (μg/person/day)	ff (g/person/day)	Intake (μg/person/day)	ff (g/person/day)	Intake (μg/person/day)
Red beans	0.2	1.4	0.28	0.5	0.1	0.1	0.02	2.7	0.54
Broad bean	0.02	0.2	0.004	0.1	0.002	0.1	0.002	0.4	0.008
Sugar beet	0.04	4.5	0.18	3.7	0.15	3.4	0.14	4	0.16
Japanese radishes (root)	0.02	45	0.9	18.7	0.37	28.7	0.57	58.5	1.17
Japanese radishes (leaf)	1.3	2.2	2.86	0.5	0.65	0.9	1.17	3.4	4.42
Horseradish	0.01	0.1	0.00	0.1	0.00	0.1	0.00	0.1	0.00
Chinese cabbage	0.033	29.4	0.97	10.3	0.34	21.9	0.72	29.9	0.99
Cabbage	0.024	22.8	0.55	9.8	0.24	22.9	0.55	23.1	0.55
Komatsuna	1.7	4.3	7.31	2.0	3.40	1.60	2.72	4.3	7.31
Mizuna	2.29	0.3	0.69	0.1	0.23	0.1	0.23	0.3	0.69
Brassica rapa var. chinensis	1.4	1.40	1.96	0.3	0.42	1	1.40	1.9	2.66
Broccoli	0.72	4.5	3.24	2.8	2.02	4.7	3.38	4.1	2.95
Shirona	1.52	2.1	3.19	0.3	0.46	0.2	0.30	3.1	4.71
Garland Chrysanthemum	4.27	2.5	10.7	0.6	2.56	1.9	8.11	3.7	15.8
Lettuce	2.22	6.1	13.54	2.5	5.55	6.4	14.21	4.2	9.32
Welsh onion	0.74	11.3	8.36	4.5	3.33	8.2	6.07	11.5	8.51
Asparagus	0.13	0.9	0.12	0.3	0.04	0.4	0.05	0.9	0.12
Parsley	3.85	0.1	0.39	0.1	0.39	0.1	0.39	0.1	0.39
Celery	1.78	0.4	0.71	0.1	0.18	0.3	0.53	0.4	0.71
Japanese honewort	4.23	0.2	0.85	0.1	0.42	0.1	0.42	0.2	0.85
Tomato	0.13	24.3	3.16	16.9	2.20	24.5	3.19	18.9	2.46
Green pepper (Capsicum annuum var. grossum)	0.41	4.4	1.80	2	0.82	1.9	0.78	3.7	1.51
Eggplant	0.42	4	1.68	0.9	0.38	3.3	1.39	5.7	2.39
Green pepper (Capsicum annuum var. angulosum)	0.66	0.2	0.13	0.1	0.07	0.1	0.07	0.3	0.20
Cucumber	0.13	16.3	2.12	8.2	1.07	10.1	1.31	16.6	2.16
Squash	0.12	9.4	1.13	5.8	0.70	6.9	0.83	11.5	1.38
Watermelon	0.02	0.1	0.002	0.1	0.002	0.1	0.002	0.1	0.002
Melon	0.004	0.4	0.002	0.3	0.001	0.1	0.0004	0.3	0.001
Spinach	3.63	18.7	67.9	10.1	36.7	17.4	63.2	21.7	78.8
Immature green pea	0.32	0.6	0.19	0.2	0.06	0.7	0.22	0.6	0.19
Immature common bean	0.42	1.9	0.80	1.2	0.50	1.8	0.76	1.8	0.76

Crop	Residues (mg/kg)	National average (body weight: 53.3 kg)		Infants (ages 1 to 6) (body weight: 15.8 kg)		Pregnant women (body weight: 55.6 kg)		Elderly (ages 65 or above) (body weight: 54.2 kg)	
		ff (g/person/day)	Intake (μg/person/day)	ff (g/person/day)	Intake (μg/person/day)	ff (g/person/day)	Intake (μg/person/day)	ff (g/person/day)	Intake (μg/person/day)
Vegetable soybean	1.1	0.1	0.11	0.1	0.11	0.1	0.11	0.1	0.11
Immature hyacinth bean	0.3	12.6	3.78	9.7	2.91	9.6	2.88	12.2	3.66
Mandarin orange	0.009	41.6	0.37	35.4	0.32	45.8	0.41	42.6	0.38
Chinese citron (Fruit flesh)	0.022	0.1	0.00	0.1	0.00	0.1	0.00	0.1	0.00
Chinese citron peel	1.15	0.1	0.12	0.1	0.12	0.1	0.12	0.1	0.12
Other citrus	0.6	0.4	0.24	0.1	0.06	0.1	0.06	0.6	0.36
Apple	0.230	35.3	8.12	36.2	8.33	30	6.90	35.6	8.19
Japanese pear	0.099	5.1	0.50	4.4	0.44	5.3	0.52	5.1	0.50
Peach	0.008	0.5	0.004	0.7	0.006	4	0.032	0.1	0.0008
Nectarine	0.18	0.1	0.018	0.1	0.018	0.1	0.018	0.1	0.018
Cherry	0.35	0.1	0.035	0.1	0.035	0.1	0.035	0.1	0.035
Strawberry	0.07	0.3	0.021	0.4	0.028	0.1	0.007	0.3	0.021
Tea plant	7.36	3	22.1	1.4	10.3	3.5	25.8	4.3	31.6
Mandarin orange peel	2.27	0.1	0.23	0.1	0.23	0.1	0.23	0.1	0.23
Total			171.3		86.2		149.8		201.1

note) · The residual values used here are the highest values for Flufenoxuron among the average residual values obtained in test groups treated for various periods and frequencies filed (see Appendix 3).

· "ff": Agricultural product consumption (g/person/day) based on the results from the National Nutrition Surveys in 1998-2000 (Refs. 39-41)

· "Intake": Estimated intakes (μg/person/day) of Flufenoxuron calculated from residual values and agricultural product consumptions

· Intakes were not calculated for soybean, Oriental pickling melon and Japanese ginger, because all data were below the detection limit.

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99 8th Executive Board Meeting of the Food Safety Commission Pesticides Expert Committee (URL; http://www.fsc.go.jp/senmon/nouyaku/kanjikai_dai8/index.html)
100 7th meeting of the Food Safety Commission Pesticides Expert Committee Second Council for Comprehensive Evaluation (URL; http://www.fsc.go.jp/senmon/nouyaku/sougou2_dai7/index.html)
101 10th Executive Board Meeting of the Food Safety Commission Pesticides Expert Committee (URL; http://www.fsc.go.jp/senmon/nouyaku/kanjikai_dai10/index.html)