Evaluation Report

Azoxystrobin

December 2006

Food Safety Commission

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<Progress of Evaluation>

April 24, 1998	First registration
July 1, 2003	The Ministry of Health, Labour and Welfare (MHLW) requests a health risk assessment in line with the establishment of specification standards of soft drinks (MHLW-FS No. 0701015) (Ref. 1)
July 3, 2003	MHLW's request received
July 18, 2003	3rd meeting of the Food Safety Commission (explanation of MHLW's request outline) (Ref. 2)
October 8, 2003	Additional reference received (Ref. 3) (determination of 93 pesticides including Azoxystrobin for health risk assessment)
October 27, 2003	1st meeting of the Pesticides Expert Committee (Ref. 4)
January 28, 2004	6th meeting of the Pesticides Expert Committee (Ref. 5)
November 16, 2004	The Ministry of Agriculture, Forestry and Fisheries informs about the application for the extended coverage and requests to establish the standards (Japanese radish and green pepper) to MHLW
November 30, 2004	MHLW requests health risk assessment in line with the establishment of residue standards (MHLW-FS No. 1130001) (Refs. 6-57)
December 1, 2004	MHLW's request received
December 9, 2004	73rd meeting of the Food Safety Commission (explanation of MHLW's request outline) (Ref. 58)
January 12, 2005	22nd of the Pesticides Expert Committee (Ref. 59)
February 9, 2005	24th of the Pesticides Expert Committee (Ref. 60)
November 29, 2005	Residual pesticide standards announced (Ref. 61)
February 22, 2006	MAFF informs about the application for the extended coverage and requests to establish the standards (carrot and Welsh onion, etc.) to MHLW
March 6, 2005	Additional reference received (Ref. 62)
July 18, 2006	MHLW additionally requests health risk assessments in line with the establishment of residual pesticide temporary standards (MHLW-FS No. 0718005) MHLW's request received (Ref. 63)
July 20, 2006	153rd meeting of the Food Safety Commission (explanation of MHLW's request outline) (Ref. 64)
October 16, 2006	5th comprehensive evaluation meeting of the second division of the Pesticides Expert Committee (Ref. 65)
November 1, 2006	6th executive meeting of the the Pesticides Expert Committee (Ref. 66)
November 9, 2006	167th meeting of the Food Safety Commission (reporting of the discussion results from the Pesticides Expert Committee)
November 9 to December 8, 2006	Public comments
December 19, 2006	The chairman of the Pesticides Expert Committee reports the comments to

	the chairman of the Food Safety Committee
December 21, 2006	172nd meeting of the Food Safety Committee (reporting of the discussion results from the Pesticides Expert Committee) (notice of the results to MHLW as of December 21)

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(Until June 30, 2006)

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(Until December 20, 2006)

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(From December 21, 2006)

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(Until March 31, 2006)

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*: From October, 2005

(Form April 1, 2006)

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Summary

The health risk of Azoxystrobin (IUPAC: methyl=(*E*)-2-{2-[6-(2-cyanophenoxy) pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate), a fungicide having methoxyacrylate skelton, was evaluated based on the results from various toxicity studies.

The study results used for evaluation were absorption, distribution, metabolism, and excretion in animals (rats), plant metabolisms (paddy rice, wheat, grape and peanut), soil degradation, hydrolysis and photolysis in water, residues in soils, residues in crops, acute toxicity (rats and mice), subchronic toxicity (rats and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity, etc.

Azoxystrobin showed no carcinogenicity, teratogenicity or genotoxicity and have no effect on reproduction.

Based on 18.2 mg/kg bw/day of the no observed adverse effect level (NOAEL) in the 2-year combined chronic toxicity/carcinogenicity study using rats, the acceptable daily intake (ADI) was established to be 0.18 mg/kg bw/day with a safety factor of 100.

I. Outline of the Pesticide to be Evaluated

1. Usage

Fungicide

2. Common Name

Azoxystrobin (ISO name)

3. Chemical name

IUPAC name:

Methyl (*E*)-2-{2-[6-(2-cyanophenoxy) pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

CAS chemical name (No.131860-33-8)

Methyl (*E*)-2-[[6-(2-cyanophenoxy)-4-pyrimidinyl]oxy]-α-(methoxymethylene) benzeneacetate

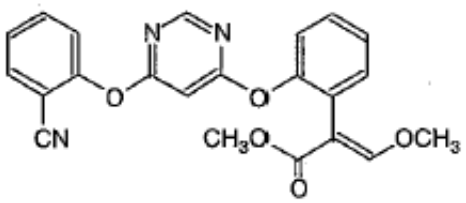
4. Chemical formula

$C_{22}H_{17}N_3O_5$

5. Relative molecular mass

403.4

6. Chemical structure



7. Background of development

Azoxystrobin is a strobilurin fungicide that was developed by Zeneca UK Ltd., in 1992. It would inhibit the electron transport system by binding the Qo site of mitochondrial cytochrome bcl complex to inhibit bacterial respiration. The compound may have a stereoisomer but its active ingredient is only E form.

Azoxystrobin has been registered mainly for rice, wheat, beans, and grape etc. in about 50 countries. In Japan, Azoxystrobin was registered first on April 24, 1998 and 308 tons per year of Azoxystrobin is produced on a drug basis (2002 Pesticide list). (Ref. 67)

Azoxystrobin was applied for registration for extended application (Japanese radish and green pepper etc.) according to the Agticultural Chemical Regulation Law. (Refs. 6 to 56, and 62).

II. Summary of the Test Results

Various studies (II-1 to 4) for examining the behavior or Azoxystrobin in animals, plants, soils and water were conducted using Azoxystrobin labeled with ^{14}C at C-5 of the pyrimidine ring (Py-^{14}C-Azoxystrobin), Azoxystrobin labeled evenly with ^{14}C at the phenyl ring of cyanophenyl (Cy-^{14}C-Azoxystrobin), and Azoxystrobin labeled evenly with ^{14}C at the phenyl ring of phenylacrylate (Ph-^{14}C-Azoxystrobin). The radioactivity and metabolite concentrations were reduced to the Azoxystrobin concentration unless otherwise noted. The abbreviations of metabolites, degradation products, and laboratory parameters are presented Appndixes 1 and 2.

1. Fate in rats

(1) Absorption, distribution, metabolism, and excretion (ADME) (1) (Py-^{14}C-Azoxystrobin)

The ADME of Azoxystrobin was examined in SD rats (3 males and 3 females in a group) receiving a single oral dose of 1 mg/kg bw (hereinafter "Low Dose") or 100 mg/kg bw (hereinafter "High Dose") of Py-^{14}C-Azoxystrobin.

For the change in blood radioactivity concentration, the time to maximum blood concentration (T_{max}) was 4 to 8 hours in males and 1 to 4 hours in females with with Low Dose, and 2 to 12 hours in males and females with High Dose; the maximum blood radioactivity concentration (C_{max}) was 0.101 to 0.218 μg/g in males and females with Low Dose and 5.10 to 12.4 μg/g in males and females with High Dose; and the elimination half-life ($T_{1/2}$) was 14 to 21 hours in males and females with Low Dose and 16 to 33 hours with High Dose.

The radioactivity in tissue distributed mainly in the small intestine, large intestine, liver and kidney with any dose. The rarioactivity was rapidly eliminated in any tissue and decreased to not more than 1/2000 to 1/10 of that at T_{max} by 192 hours after treatment. There were no sex differences in the blood concentration, tissue distribution, and elimination profile in various tissues.

Table 1 shows the residual radioactivities in the major tissues with a single dose of Azoxystrobin. (Ref. 7)

Table 1 Residual radioactivities in the major tissues (μg/g)

Dose		Around T_{max}*	192 hours post-dose
Low dose of Py-^{14}C-Azoxystrobin	Male	Small intestine (1.92), Large intestine (0.90), Liver (0.78), Kidney (0.44), Plasma (0.24), Whole blood (0.15)	Kidney (0.03), Liver, Lung, Heart, Femur, Whole blood (<0.01)
	Female	Small intestine (1.85), Large intestine (1.06), Liver (0.42), Kidney (0.27), Plasma (0.11), Whole blood (0.07)	Kidney (0.03), Whole blood (0.01)
High dose of Py-^{14}C-	Male	Large intestine (138), Small intestine (57.3), Liver (30.2), Kidney (18.6), Plasma (13.3), Whole blood (9.19)	Kidney (1.73), Large intestine (1.18), Small intestine (1.17), Muscle (0.90), Liver (0.84), Lung (0.69),Abdominal fat (0.60), Whole blood (0.52)

Dose		Around T_{max}*	192 hours post-dose
Azoxystrobin	Female	Large intestine (128), Small intestine (60.4), Liver (25.4), Kidney (13.8), Plasma (7.09), Heart (5.71), Whole blood (4.96)	Kidney (1.44), Large intestine (1.20), Small intestine (1.16), Muscle (0.92), Liver, Lung (0.63), Whole blood (0.49)

* Low dose: 4 hours post-dose, High dose: 12 hours post-dose

(2) ADME (2) (Py-^{14}C-Azoxystrobin)

The tissue concentrations of Azoxystrobin (kidney, liver, blood and plasma etc.) were determined in SD rats (5 males and 5 females in a group) receiving a single oral dose of 1 mg/kg bw (hereinafter "Low Dose") or 100 mg/kg bw (hereinafter "High Dose") of Py-^{14}C-Azoxystrobin.

Azoxystrobin was rapidly eliminated and the urinary and fecal excretions by 168 hours after treatment were 72.6 to 83.2% and 10.2 to 17.9% of the total administered radioactivity (TAR) with Low Dose and 84.5 to 89.4% and 8.54~11.5% of TAR with High Dose, respectively. Azoxystrobin was excreted mainly via feces in males and females.

The total radioactivity remained in tissue 7 days after treatment was below 0.7% of TAR with Low and High Doses. The highet rarioactivity was detected in the kidney (Hihg Dose: 1.12 to 1.37 μg/g, Low Dose: 0.023 to 0.027 μg/g) and the liver (Hihg Dose: 0.714 to 0.812 μg/g, Low Dose: 0.009 μg/g) in males and females. (Refs. 8 and 9).

(3) ADME (3) (Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin)

The urinary, fecal and biliary excretions of Azoxystrobin were determined in SD rats (2 males and 2 females in a group) fitted with a biliary cannular that received a single oral dose of 100 mg/kg bw of Py-^{14}C-Azoxystrobin, Ph-^{14}C-Azoxystrobin, and Cy-^{14}C- Azoxystrobin.

The biliary excretion 48 hours after treatment was 56.6 to 74.2% of TAR. The absorption of Azoxystrobin was dose-related; almost all of the dose was absorbed with Low Dose and about 70% of the dose was absorbed with High Dose.

There were no obvious differences in urinary, fecal or biliary excretion pattern among ^{14}C-labeled positions. The major excretion route would be bile in males and females.

Two major metabolic pathways of Azoxystrobin could be hydrolysis of methylester followed by glucuronic acid conjugation (metabolite Y); and glutathione conjugation of cyanophenyl ring (metabolite Z) followed by generation of mercapturic acid (metabolite AA, AB or AC).

There was a sex difference in the type of metabolite.

There were no large differences in the excretion patterns or metabolite profiles among ^{14}C-labeled positions. Table 2 shows the metabolites detected in the urine, feces and bile in the treatment with Py-^{14}C-Azoxystrobin. (Refs. 10 and 11)

Table 2 Metaboliets (%TAR) in urine, feces and bile in rats fitted with a biliary cannular that was treated with Py-^{14}C-Azoxystrobin

Metabolite	Male			Female		
	Urine	Feces	Bile	Urine	Feces	Bile
Azoxystrobin	-	15.1	-	-	13.6	-
K	-	-	6.5	0.3	0.1	6.8
V	0.1	-	-	-	-	1.7
W+Z*	-	-	6.8	0.3	-	9.0
X+Z*	-	-	-	0.2	0.1	1.4
Y	0.1	-	29.3	1.7	-	27.4
AA**	-	-	7.0	0.3	-	1.6
AB+AE*	0.1	-	3.2	0.3	-	6.1
AC	-	-	4.5	0.4	0.1	2.4
C	-	-	-	0.4	-	4.8
I	trace	-	2.8	trace	-	0.9
M	0.3	0.2	4.1	0.4	0.2	1.5
Total of 6 unidentified metabolites	1.4	0.1	8.0	2.6	0.1	10.2

-: There was no metabolite. *: Incomplete separation of peaks in HPLC. **: The metabolite includes unidentified metabolite.

2. Plant metabolism

(1) Rice (Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin)

Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin were applied to seedling of rice (cultivar: Ishikari) at third leaf stage that was transplanted in a simulated paddy field in a greenhouse to study the metabolism of Azoxystrobin in rice. In a foliage application test, they were applied to rice at 0.355 to 0.553 kg ai/ha equivalent once 69 days after transplantation and all ears were collected 75 to 95 days after application. In a water application test, they were applied to rice twice [i.e., once at 0.841 to 0.971 kg ai/ha equivalent 11 to 13 days after transplantation and once at 0.892 to 0.946 kg ai/ha equivalent 36 days after first application (immediately before head spout)] and all ears were collected 95 to 98 days after second application. The stubbles after ear collection were cut about 2 cm above the soil surface and used as rice straw samples.

The total residual radioactivity (TRR) in hulled rice was 0.527 to 0.743 mg/kg in the water application and 0.321 to 0.401 mg/kg in the foliage application. There was no difference among three labeled Azoxystrobins.

The translocation into plant body after absorption was 5.2 to 7.0% of the total applied radioactivity (TAR) in the water application and 19.0 to 28.9% of TAR in the foliage application. A little ^{14}C translocated into hulled rice with 0.1% of TAR in the water application and 0.2 to 0.3% of TAR in the foliage application.

The major radioactive residues in hulled rice samples in the water application were sugar (43.2 to 57.9% of TRR) and Azoxystrobin (3.4 to 5.3% of TRR). The radioactive residues in hulled rice samples in the foliage application were also Azoxystrobin (36.3 to 71.5% of TRR) and sugar (4.9 to 16.5% of TRR). Regardless of application methods, the radioactive residues in hulled rice were sugar and Azoxystrobin. Although a lot of sugar was detected particularly in hulled rice as a radioactive residue, this would be caused by taking ^{14}C derived from Azoxystrobin, which was degraded in soil, into rice.

In rice straw, TRR was 8.16 to 10.5 mg/kg in the water application and 5.71 to 7.81 mg/kg in the foliage application. The major residues detected in rice straw in the water application were Azoxystrobin with 3.3 to 5.6% of TRR, metabolite B with 3.6 to 6.7% of TRR, a mixture of metabolites J and K with 5.1 to 8.1% of TRR. In the foliage application area, Azoxystrobin and metabolite M were detected in rice straw with 37.6 to 45.9% of TRR and 5.2 to 8.5% of TRR, respectively (metabolite M was not detected in the application with Ph-^{14}C- Azoxystrobin). (Ref. 12)

(2) Wheat (Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin)

Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin were applied to wheat (cultivar: Mercia and Apollo) at 500 g ai/ha twice (i.e., once at internode elongation stage (about 130 days before harvest) and once at heading stage (about 60 days before harvest). The green wheat was collected 13 days after second application and the residual wheat was collected 61 to 62 days after second application as grains and straws to study the metabolism of Azoxystrobin in wheat.

The TRR in the plant body was 0.075 to 0.077 mg/kg in grains, 3.06 to 9.41 mg/kg in straws and 1.02 to 2.79 mg/kg in green wheat. The applied radioactivity was 5.1 to 11.5% in total. A little ^{14}C translocated into grains after absorption (0.08 to 0.10% of TAR).

The metabolism patterns in grain, straw and green wheat were similar and the major radioactive residue was Azoxystrobin.

The major residues in grain were Azoxystrobin with 17.1 to 22.0% of TRR (0.013 to 0.017 mg/kg) and glucose with 9.7 to 20.9% of TRR. These residues would be detected because ^{14}C derived from Azoxystrobin, which was degraded in soil, was taken into glucose.

In straws, Azoxystrobin was detected with 22.1 to 43.3% of TRR (0.676 to 4.07 mg/kg). The major metabolite was metabolite M (7.4 to 7.6% of TRR), which was also detected as a simple sugar conjugate (0.8 to 2.8% of TRR). Other major metabolites were metabolite D with 2.1 to 3.5% of TRR and metabolite B with 3.0 to 3.4% of TRR.

In green wheat, the major residue was Azoxystrobin with 54.9 to 64.7% of TRR (0.560 to 1.81 mg/kg), the major metabolite was metabolite D (1.9 to 2.9% of TRR), and metabolite M was detected as sugar conjugate (2.1% of TRR) and other free metabolite (1.1% of TRR).

The metabolite pathway of Azoxystrobin in winter wheat could be: (1) generation of metabolite M by cleavage between phenylacrylate ring and pyrimidyl ring and generation of metabolite F by cleavage of ether bond; (2) generation of metabolite U by photochemical reaction; (3) generation of Z isomer of Azoxystrobin by photochemical reaction; (4) generation of metabolites L and G by oxidative cleavage of acrylate bond followed by generation of metabolite N by oxidation; (5) generation of metabolite B by hydrolysis or oxidative *O*-dealkylation of ester group, generation of metabolite T by

hydroxylation of acrylate bond and generation of metabolite O by hydrolysis of ether group; (6) generation of metabolite S by reduction of acrylate bond of metabolite B; and (7) assimilation and conversion into sugar by CO_2 intake associated with mineralization in soil. (Ref. 13)

(3) Grape (Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin)

Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin were applied to grape (cultivar: Merlot) four times (i.e., 99, 70, 41 and 21 days before harvest) at 250 g ai/ha in the first and fourth application and at 1,000 g ai/ha in the second and third application, and ripe fruits were collected 21 days after the last application to study the metabolism of Azoxystrobin in grape.

The TRR in the fruits was 0.382 to 1.43 mg/kg.

The major radioactive component was Azoxystrobin with 34.6 to 64.6% of TRR (0.132 to 0.924 mg/kg). There were at least 15 metabolites and the major metabolites were metabolite D with 1.9 to 4.0% of TRR, metabolite F with 5.7% of TRR, metabolite L with 2.5 to 3.9% of TRR and metabolite M with 2.6 to 5.2% of TRR. In the water-soluble fraction, the majority of radioactivity was also detected as sugar (3.8 to 5.5% of TRR). The radioactive residues included sugar, which would result from intake of ^{14}C derived from Azoxystrobin that was degraded in soil. In the leave samples, metabolites D, M, N, O and S were detected. (Ref. 14)

(4) Peanut (Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin)

Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin were applied to peanuts (cultivar: Florunner) that were cultivated in a field with the customary method three times (i.e., 53, 95 and 144 days after planting) at 85 mg ai/m^2 of test area in the first and second applications and at 30 mg ai/m^2 of test area (the total application of active ingredient: 2kg ai/ha/m^2 of test area). The stems and leaves were cut little above the soil surface 10 days after the last application and the pods of peanuts were collected to study the metabolism of Azoxystrobin in peanut.

The plant body absorbed 22.6 to 23.3% of TAR. A little ^{14}C translocated into nuts (edible part) (0.10 to 0.27% of TAR).

The TRR in peanut was 0.241 to 0.650 mg/kg. The major residues in nut were fatty acids including oleic acid with 27.5 to 32.3% of TRR and linolenic acid with 11.2 to 16.3% of TRR. The radioactivity was also detected in sugars such as sucrose with 1 to 6% of TRR, which would result from intake of ^{14}C derived from Azoxystrobin that was degraded in soil.

In the stems and leaves (dry), the residual radioactivity was detected with 39.2 to 46.6 mg/kg. The major residue was Azoxystrobin with 33.0 to 43.8% of TRR. A total of 10 metabolites were identified and the major metabolites were metabolite M and its conjugate, metabolite R, (7.0 to 9.0% of TRR). In the hulls, the total residual radioactivity was 0.68 to 0.87 mg/kg and Azoxystrobin was detected as a major residue with 12.9 to 13.5% of TRR. Additionally, a total of 11 metabolites were identified; metabolite M and its conjugate, metabolite R, (4.5 to 5.5% of TRR) were mainly detected.

In the stems and leaves (raw), the residual radioactivity was detected with 16.4 to 19.6 mg/kg and the composition of residual radioactivity was similar to that in the stems and leaves (dry). (Ref. 15)

3. Fate in soil

(1) Aerobic submerged soil

Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin were added below the water surface of the system consisting of water and bottom sediment (10% soil of the total volume of 200 ml) at 84 to 91 μg/l (equivalent to 252 to 273 g ai/ha applied to a paddy with a water depth of 30 cm) and the air without CO_2 was taken into the system to study degradation of Azoxystrobin in the bottom sediment under the dark condition at 20°C±2°C in a fate test in aerobic submerged soil.

The half-life of Azoxystrobin was about 150 days in the river water/bottom sediment soil system using two bottom sediments (silt loam soil and sandy loam soil: U.K.). The parent compound was detected with 92.6 to 95.4% of TAR immediately after treatment and decreased to 49.3 to 69.8% of TAR 120 days after treatment. In two sterilized test soils, the parent compound was detected with 92.7% of TAR and 84.8% of TAR, respectively, suggesting that microorganism may affect the degradation of parent compound.

The major degradation product was degradation product B, whose radioactivity 152 days after treatment reached 20.3% at maximum. A small amount of degradation product C was generated with 2.7% at maximum. The cumulative amount CO_2 of was 1.5 to 6.2% even at the completion of test. (Ref. 16)

(2) Aerobic and anaerobic submerged soils

(English and American soils: Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin)

Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin were added in aerobic and anaerobic soils (sandy loam soil, sandy clay soil: U.K., sandy loam soil: U.S.) under aerobic and anaerobic submerged conditions so that the treatment amount would be 17μg per pot (0.56 μg/g soil, 0.56 g/ha). After mixing, the soils were incubated at 20°C under dark condition to study degradation of Azoxystrobin in aerobic and anaerobic soils.

The half-life of Azoxystrobin was 54 to 164 days under the aerobic condition and the slow degradation rate would be attributable to biomass quantity, which was 1/6 of those in other soils (note: the test in the soil with the slowest degradation rate under the field condition reported the half-life was 2 weeks, which would result from photolysis). Under the anaerobic condition, the half-life was about 2 days in the surface water and 50 to 56 days in the soil containing surface water (English soil). Under the aerobic condition, the major degradation product was degradation product B in all soils. Its generation rate varied depending on soils and reached 7 to 21% of TAR after 62 days and decreased to 9 to 16% of TAR after 120 days. The degradation product B increased to 12% of TAR only in the American soil with the slowest degradation rate. The degradation products C, M and P were also detected with not more than 3.2% of TAR. The cumulative amount of CO_2 for 120 days attained to 15.1 to 27% of TAR. Under the anaerobic condition, the degradation product B gradually increased and reached 14 to 69% of TAR during the test period of 120 days. The degradation product M was also detected with about 4% of TAR. Little CO_2 was generated (0 to 4.7% of TAR after 120 days). (Ref. 17)

(3) Aerobic soil

(American soil: Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin)

Py-^{14}C-Azoxystrobin, Ph-^{14}C- Azoxystrobin and Cy-^{14}C-Azoxystrobin were applied to the filed having the soil used in the test (2) (sandy loam soil: U.S.) to prepare the soils with 589, 575 and 536 g/ha per area, respectively, to study degradation of Azoxystrobin in the soil of bare ground. Soils were collected to 46 cm deep and separated according to the depth. Most of the radioactivity was recovered from the soils collected from 0 to 5cm. The half-life of Azoxystrobin was about 14 days and decreased to not more than 12% of the treated amount after 4 months. The degradation product M reached 8% of TAR at maximum as a major degradation product after 28 days and decreased to not more than 4% of TAR after 4 months. The degradation product N also attained to 6% of TAR at maximum after 28 days and decreased to not more than 2% of TAR after 4 months. These degradation products were found in the photolysis test. Little degradation product B that was found in the in-vessel test was generated. (Ref. 18)

(4) Photolysis on the surface of soil

Cy-^{14}C-Azoxystrobin, Py-^{14}C- Azoxystrobin and Ph-^{14}C-Azoxystrobin were applied to a soil (sandy loam soil: U.K.) to prepare the soil with 463 to 498 g/ha. The soil was exposed to Xenon light with a filter (38.2 W/m^2 at 300 to 400 nm) at 23.8 to 28°C for 19 days to study photolytic degradation of Azoxystrobin on the surface of soil.

The observed half-life was 6.6 days, which was equivalent to 32.4 days exposure of the spring sunlight in Tokyo. Nine photolytic degradation products (degradation products C, D, F, G, L, M, N, U, and CO_2) were found and the degradation products other than CO_2 did not exceed 10% of TAR. The major degradation product was $^{14}CO_2$ in all labeled Azoxystrobins and accounted for 28.6% of TAR. (Ref. 19)

(5) Absorption to soils (1) (Japanese soils)

An absorption test was made with Cy-^{14}C-Azoxystrobin using silt clay loam, sandy loam soil, silt loam soil and sandy soil (Japan).

The absorption coefficient K was 4.3 to 150 and the absorption coefficient corrected for organic carbon Koc was 270 to 4500.

Azoxystrobin moderately to strongly absorbed to 4 test soils, indicating the low mobility of Azoxystrobin in soils. The absorption coefficient corrected for organic carbon increased by 24 to 96%, showing that the absorption of Azoxystrobin to soils was not completely reversible. (Ref. 20)

(6) Absorption to soils (2) (English soils)

An absorption test was made with Cy-^{14}C-Azoxystrobin using sandy clay loam, two loamy sandy soils, sandy soil, silt clay loam, and clay loam (U.K.).

The absorption coefficient K was 1.5 to 15 and the absorption coefficient corrected for organic carbon Koc was 210 to 580.

Azoxystrobin moderately to strongly absorbed to 6 test soils, indicating the low mobility of Azoxystrobin in soils. The absorption coefficient corrected for organic carbon increased by 0 to 47%, showing that the absorption of Azoxystrobin to soils was not completely reversible. (Ref. 21)

(7) Soil column leaching (German soils)

A soil column leaching test was conducted using sandy soil, clay sandy soil and sandy loam soil (Germany).

After Azoxystrobin was applied to a soil column with 5 cm (internal diameter) × 35 cm (height) at a rate of 750g ai/ha, the column was eluted with 200 mm/day (rainfall equivalent) under the condition of 22±2°C for 48 hours.

There were no differences in smell and color of the eluates between the treated and non-treated areas. No Azoxystrobin was detected in the column eluates in any soils. There results would suggest the low mobility of Azoxystrobin in soils. (Ref. 22)

4. Fate in water

(1) Hydrolysis in water

Cy-^{14}C-Azoxystrobin was dissolved in sterilized buffer solutions of pHs 5, 7 (acetic buffer solution) and 9 (boric buffer solution) to prepare the solutions with about 2.5μg/cm^3. The solutions were incubated at 25 and 50°C for 31 days to study hydrolysis of Azoxystrobin.

The half-life of Azoxystrobin was in the solutions of pHs 5 and 7 and there was no hydrolysis at 25 and 50°C. In the solution of pH 9, only a little hydrolysis was observed at 25°C and significant hydrolysis was found at 50°C. The major degradation products identified were degradation products B and H with 12.0% of TAR at maximum after 288 hours and 7.6% of TAR after 288 hours, respectively. The half-life was 290 hours. (Ref. 23)

(2) Photolysis in water (sterilized buffer solution of pH 7)

Cy-^{14}C-Azoxystrobin, Py-^{14}C- Azoxystrobin and Ph-^{14}C- Azoxystrobin were dissolved in sterilized buffer solution of pH 7 (3,3-dimethylglutaric acid buffer solution) to prepare the solutions with 3.29, 3.27 and 3.04 μg/cm^3, respectively. The solutions were incubated under Xenon light exposure with an optical filter (29 to 33W/m^2 at 300 to 400 nm wavelength) at 25°C for 21 days to study photolytic degradation of Azoxystrobin in water.

The observed half-life of Azoxystrobin was 8.4 to 12.5 days, which were equivalent to the exposure levels under the spring sunlight in Tokyo (at latitude 35°N) of 49.7 days with Cy-^{14}C-Azoxystrobin, 32.2 days with Py-^{14}C- Azoxystrobin and 48.4 days with Ph-^{14}C- Azoxystrobin. The major degradation product was only degradation product D, a Z isomer of Azoxystrobin (maximum value: 14.5% of TAR after 24 hours with Cy-^{14}C-Azoxystrobin; 15.7% of TAR after 96 hours with Py-^{14}C- Azoxystrobin; and 12.9% of TAR after 24 hours with Ph-^{14}C- Azoxystrobin; these values decreased thereafter). The degradation product D was observed with 12.9 to 14.5% of TAR at maximum after 1 day and decreased to 2.7 to 6.6% of TAR after 21 days. The degradation products M and I were found with 4.9 to 8.6% of TAR and 1.7 to 5.4% of TAR, respectively. Additionally, the degradation products N, L

and F were detected with not more than 2.2% of TAR. There was little degradation in the dark control area.

Under the study conditions, the photolytic reaction occurred in a biphasic manner; photoisomerization would occur rapidly in the initial degradation, the Z isomer would be generated to achieve the equivalent, and then the degradation would be continued associated with the primary reaction. (Ref. 24)

(3) Photolysis in water (natural water and distilled water)

Azoxystrobin was dissolved in natural water (river water in the U.K.) and distilled water to preparer the waters with 0.5 μg/mL. The natural water and distilled water were exposed to Xenon light with a filter (24 to 25W/m^2 at 300 to 400 nm wavelength) at 24±0.9°C and 27.5±2.5°C, respectively, for 25 days to study photolytic degradation of Azoxystrobin in water.

Azoxystrobin was photolyzed in a biphasic manner. Photoisomerization occurred rapidly in the early phase and the degradation product D, a Z isomer of Azoxystrobin, was be generated followed by slightly slow photolysis. The degradation product D was included in the natural water with 17.8% of TAR and in the distilled water with 18.2% of TAR after 24 hours. The degradation product M was found below 2% of TAR. When the half-life was reduced to the exposure level under the spring sunlight in Tokyo (at latitude 35°N), the half-life in the natural water (8.3 days) was shorter than that in the distilled water (35.3 days). There was little degradation in the dark control area. (Ref. 25)

5. Residuals in soil

Volcanic ash clay loam and diluvial clay loam in filed soil and paddy soil were used for residual tests in soil for Azoxystrobin, the degradation products B, M and N (in a vessel and field).

The half-life was estimated to be within 1 to 180 days for Azoxystrobin and within 1 to 240 days for the sum of Azoxystrobin, the degradation products B, M and N (Table 3). (Ref. 26)

Table 3 Results of residual tests in soil (estimated half-life)

Test	Azoxystrobin concentration/amount/ no. of applications*		Soil		Azoxystrobin	Sum of Azoxystrobin and degradation products [1)]
In-vessel test	0.6 mg/kg	Pure	Field soil	Volcanic ash clay loam	180 days	240 days
				Diluvial clay loam	67 days	80 days
	0.6 mg/kg	Pure	Paddy soil	Volcanic ash clay loam	68 days	115 days
				Diluvial clay loam	110 days	170 days

Field test	20 g ai/10a, once 60 g ai /10a, 4 times	F F	Field soil	Volcanic ash clay loam	93 days	105 days
				Diluvial clay loam	31 days	38 days
	0.025 gai/box, once 60g ai /10a, once 60g ai /10a, twice	F G G	Paddy soil	Volcanic ash clay loam	4 days	10 days
				Diluvial clay loam	Within 1 day	Within 1 day

*F: Flowable, G: Granular formulation 1) Degradation products: B, M and N

6. Transfer to milk

Lactating Friesian cows (3 animals in a group) were continuously fed concentrate diet containing Azoxystrobin at 0, 5, 25, 75, or 250 ppm (equivalent to 0, 100, 500, 1500 or 5000 mg/animal/day) for 27 to 30 days to study transfer of Azoxystrobin to milk.

The Azoxystrobin concentration in all collected milk samples was below 0.01 mg/kg. When the milk was separated into cream and skim milk, the residue was found mainly in cream (the maximum value was 0.04 mg/kg at 250 ppm). At 250 ppm, the residue was found in the fatty tissue with 0.01 to 0.03 mg/kg and in the liver and kidney with 0.01 to 0.07 mg/kg. At 75 ppm, the residue was seen in the liver and kidney with 0.01 to 0.05 mg/kg. At 25 ppm, the residue was found in the liver with 0.01 mg/kg. The residue was not found in any other tissues at 5 or 25 ppm. No residue was observed in muscle samples at any doses. (Ref. 27)

7. Residuals in crops

Paddy rice, fruits, vegetables and tea etc. were used for residual tests for Azoxystrobin and the metabolites B, D, F, L and M in crops. The analysis method was as follow: Azoxystrobin, metabolites B, D, F, L and M were extracted by grinding the crops and purified; and the Azoxystrobin, metabolites D and L were determined by HPLC equipped with a UV detector, the metabolite B was determined by LC/MS, and the metabolites F and M were determined by gas chromatography. No monitoring data of soft drinks were submitted.

The highest value of Azoxystrobin detected was 11.9 mg/kg from Japanese horseradish (hatake wasabi) (stems and leaves) collected 7 days after the last application. The highest values of metabolites D, F, L and M were 0.12 mg/kg from hanegi (Welsh onion) (stems and leaves) collected 7 days after the last application, 0.07 mg/kg from wheat (grains) 21 days after the last application, 0.01 mg/kg from wheat (grains) 21 days after the last application, and 0.11 mg/kg from hanegi (stems and leaves) 7 days after the last application, respectively. The metabolite B was found in green pepper and cucumber etc. below the detection limit (<0.01 mg/kg) (see Appendix 3).

Based on the results of the residual tests in crops, the estimated amounts of Azoxystrobin (parent compound only) consumed through agricultural products are shown in Table 4 (see Appendix 4).

The estimated amount was calculated on the assumption that Azoxystrobin was applied to all of the

applicable crops including crops filed in this application (Japanese radish and green pepper etc.) under the conditions where the highest residual value of Azoxystrobin would be obtained among the filed methods, and that processing or cooking of the crops would not affect the amount of residual pesticide. (Refs. 28 and 29)

Table 4 Estimated amounts of Azoxystrobin exposure through food

	National average (Body weight: 53.3 kg)	Infant (age: 1 - 6 years) (Body weight: 15.8 kg)	Pregnant woman (Body weight: 55.6 kg)	Elderly (age: ≥ 65 years) (Body weight: 54.2 kg)
Consumption (μg/person/day)	131.8	79.2	95.3	133.7

8. General pharmacology

General pharmacological studies were conducted in mice, guinea pigs, dogs and rats. Table 5 shows the results of studies. (Refs. 11 and 30)

Table 5 General pharmacological studies

Study category		Animal	No. of animals/ group	Dose (mg/kg bw)	No effect level (mg/kg bw)	Effect level (mg/kg bw)	Results
Central nervous system	Performance status	Mouse	9 males	500, 1500, 5000 (Oral)	500	1500	500 mg/kg bw: No effect. 1500 and 5000mg/kg bw: A slight decrease in reactivity
	Hexobarbital sleep		10 males	500, 1500, 5000 (Oral)	5000	—	No effect.
	Pentetrazol-induced seizure						
	Electroconvulsive seizure						
	Motor coordination						
	Muscular relaxation						
Automatic nervous system		Guinea pig Ileum strip	5 males	1×10^{-6} ~ 1×10^{-4} g/mL	1×10^{-6} g/mL	1×10^{-5} g/mL	No direct effect. Anti-Ach and anti-His: Inhibitory action at levels of $\geq1\times10^{-5}$g/mL

Cardiovascular system/ breath/ blood pressure/ heart rate/ ECG/ blood volume		Dog	4 females	30,100, 300(*) (Interperiton eal)	30	100	30 mg/kg bw: No direct effect. 100 mg/kg bw: Increasing tendency in heart rate 300 mg/kg bw: An increase in heart rate and increasing tendency in respiratory rate
Digestive system Intragastrointestinal transport		Mouse	10 males	0, 800, 2000, 5000 (Oral)	5000	—	No effect.
Skeletal muscle Grip strength		Rat	9 males	300,1000, 3000(*) (Interperiton eal)	3000	—	No effect.
Blood	Hemolysis		9 males	500,1500, 5000 (Oral)	5000		
	Clotting						

*: Repeated administration at 30-minute intervals

9. Acute toxicity

(1) Acute toxicity study

Acute oral and dermal toxicity studies in Wistar rats, acute oral toxicity study in ICR mice, and acute inhalation toxicity study in SD rats were conducted for Azoxystrobin (technical grade).

Table 6 shows the summary of studies. The acute oral LD_{50} was above 5,000 mg/kg bw in male and female rats and in male and female mice; the acute dermal LD_{50} was above 2,000 mg/kg bw in male and female rats; and the acute inhalation LC_{50} was 962 μg/L in male rats and 698 μg/L in female rats. (Refs. 31 to 34)

Table 6 Summary of acute toxicity studies (technical grade)

Administration route	Animal	LD_{50} (mg/kg bw)		Observed symptoms
		Male	Female	
Oral	Wistar rat	> 5000	> 5000	Diarrhea, staining around nose and mouth, urinary incontinence, piloerection etc.
	ICR mouse	> 5000	> 5000	Piloerection, incontinence of urine etc.
Demral	Wistar rat	> 2000	> 2000	Staining around nose and mouth, urinary incontinence, avulsion/ scab/ erythema/ edema at the administration site
Inhalation	SD rat	LC_{50} (μg/L)		Hunchback position, piloerection, tremor, decreased activity, staining around nose,
		962	698	

				abnormal breathing, pale, death etc.

An acute oral toxicity study was conducted for the metabolite D in ICR mice and the acute oral LC_{50} was above 5,000 mg/kg bw in males and females. (Ref. 35)

(2) Acute neurotoxicity study

An acute neurotoxicity study was conducted in SD rats receiving Azoxystrobin at an oral dose of 0, 200, 600 or 2,000 mg/kg bw.

At 2,000 mg/kg bw, suppression of body weight gain was observed in males. In animals at 2,000, 600 and 200 mg/kg bw, tiptoe gait and/or hunched posture, and diarrhea (symptom) occurred more frequently as compared with control animals. In females at 2,000 and 600 mg/kg bw, the landing foot splay was increased. However, since there was no dose correlation, these findings could not result from the treatment with Azoxystrobin. In males at 2,000 mg/kg bw, the hindlimb grip strength decreased 15 days after treatment. Since it was an independent change, it could not result from the treatment with Azoxystrobin. There were significant differences in motor activity among some treatment groups. Since these changes in motor activity were transient without dose correlation, they could not result from the treatment with Azoxystrobin.

There were no neurobehavioral toxicological or neuro-histopathological findings.

The no observed adverse effect level (NOAEL) in this study was considered to be 600 mg/kg bw for general toxicity and 2,000 mg/kg bw for neurotoxicity. (Ref. 36).

10. Skin and eyes irritation, and skin sensitization

Primary eye irritation and skin sensitization tests were conducted in NZW rabbits.

In the primary eye irritation test, no change due to irritation of Azoxystrobin was observed in the cornea or iris. The irritation changes in the conjunctiva included mild to moderate redness and edema, and slight secretion. These changes, however, disappeared 1 day after treatment. Irritation signs including a small amount of secretion from the mucosa and harderian gland, and bleeding in a part of nictating membrane were observed, but disappeared after 2 days. No or mild irritation responses were observed in rabbits.

In the primary skin sensitization test, very mild redness and edema were found in 2 of 6 rabbits 30 to 60 minutes after applying Azoxystrobin, but disappeared with time. No other signs showing skin sensitization were seen.

There findings indicated that Azoxystrobin (technical grade) would have slight irritation potential to eye and skin.

A skin sensitization test was conducted in Hartley guinea pigs by Maximization method and the skin sensitization response to Azoxystrobin was negative in guinea pigs. (Refs. 37 to 39)

11. Subchronic toxicity

(1) 90-day subchronic toxicity study (rats)

A subchronic toxicity study was conducted in SD rats (12 males and 12 females in a group) fed diet

containing Azoxystrobin at 0, 200, 2000 or 4000[1] ppm (see Table 7 for average Azoxystrobin consumption) for 90 days.

Table 7 Average Azoxystrobin consumption in 90-day subchronic toxicity study

Dose		200 ppm	2000 ppm	4000 ppm
Azoxystrobin consumption (mg/kg bw/day)	Male	20.4	211	444
	Female	22.4	223	449

Table 8 shows the major findings in treatment groups.

In males at 4,000 ppm, findings showing general toxicity, intrahepatic bile duct /small bile duct and outgrowth of oval cells in 2 animals, extrahepatic cholangitis in 1 animal where extrahepatic bile duct dilation was observed with the naked eye, inflammatory cell infiltration in the pancreas, hepatocellular hyperplasia, and a reactive change in the hepatic lymph node were found.

Considering findings including suppression of body weight gain in males and females at 2,000 ppm, the NOAEL in this study was considered to be 200 ppm in males and females (male: 20.4mg/kg bw/day, female: 22.4mg/kg bw/day). (Ref. 40)

Table 8 Toxicological findings in 90-day subchronic toxicity study in rats

Dose	Male	Female
4000 ppm	· Increases in white blood cell count and GGT · An increase in relative weight of the liver[2]	· Increases in white blood cell count and GGT · Decreasing tendency in Ht, reduced MCV and MCH · An increase in relative weight of the liver
≥ 2000 ppm	· A decrease in food consumption, suppression of body weight gain, decreased food efficiency · A decrease in TG · Reduced ALT and AST · A decrease in cholesterol · Decreased ALP and CK	· A decrease in food consumption, suppression of body weight gain, decreased food efficiency · A decrease in TG · Reduced ALT and AST · A decrease in glucose
200 ppm	No toxicological finding	No toxicological finding

[1]: In the highst dose group, Azoxystrobin was given to animals at 6,000 ppm at first, but since the food consumption and body weight gain were reduced 2 weeks after the treatment initiation to adversely affect the development of animals, the dose was changed to 4,000 ppm from week 3.

[2] "Relative weight against body weight" is described as "relative weight" (hereinafter the same).

(2) 90-day subchronic toxicity study (dogs)

A subchronic toxicity study was conducted in Beagle dogs (4 males and 4 females in a group) receiving Azoxystrobin at an oral dose of 0, 10, 50 or 250 mg/kg bw/day for 90 days.

Table 9 shows the major findings in treatment groups.

The frequency and severity of peribronchial inflammation in the lung and interstitial pneumonia, and the frequency of granuloma were higher in females in the 250 and 50 mg/kg bw/day groups than those in the control and 10 mg/kg bw/day groups. However, these changes occurred naturally in a colony of Beagle dogs and would not result from the treatment with Azoxystrobin.

Considering salivation regurgitation and vomiting in males and suppression of body weight gain in females at 50 mg/kg bw/day, the NOAEL in this study was considered to be 10 mg/kg bw/day in males and females. (Refs. 11 and 41)

Table 9 Toxicological findings in 90-day subchronic toxicity study in dogs

Dose	Male	Female
250 mg/kg bw/day	・An increase in liquid stool ・Suppression of body weight gain and a decrease in food consumption ・An increase in platelet count and decreased MCV, MCH and MCHC ・Reduced albumin and increased ALP	・Salivation, spitting up and vomiting ・An increase in the frequency of liquid stool ・A decrease in food consumption ・An increase in platelet count ・Reduced albumin and increased TG and ALP
≥ 50 mg/kg bw/day	・Salivation, regurgitation and vomiting	・Suppression of body weight gain
10 mg/kg bw/day	No toxicological finding	No toxicological finding

(3) 90-day subchronic neurotoxicity study (rats)

A subchronic neurotoxicity study was conducted in SD rats (12 males and 12 females in a group) fed diets containing Azoxystrobin at 0, 100, 500, or 2,000 ppm (see Table 10 for average Azoxystrobin consumption) for 90 days.

Table 10 Average Azoxystrobin consumption in 90-day subchronic neurotoxicity study in rats

Dose		100 ppm	500 ppm	2000 ppm
Azoxystrobin consumption (mg/kg bw/day)	Male	8.0	38.5	161
	Female	9.1	47.9	202

The effect due to the treatment with Azoxystrobin in the neurotoxicity study included suppression of body weight gain in males and females and reduced food efficiency in males at 2,000 ppm.

In the comprehensive functional observation, a decrease in the landing foot splay was found in males at all doses on week 5 and in males at 2,000 ppm on week 9; decreases in the forelimb and hindlimb grip strengths were observed in males at all doses on week 5; and a decrease in the forelimb grip strength was found in females at 2,000 ppm on week 14. Since these changes were transient and fell within the range of background data, they would not result from the treatment with Azoxystrobin. A decrease in motor activity found in females at 2,000 ppm on week 9 was a transient, slight change without histopathological changes. This change would not result from the treatment with Azoxystrobin.

Although the brain width and relative weight of the brain increased in males at 500 ppm, Azoxystrobin had no effect on other measurement items on the brain and there was no dose correlation. These changes, therefore, would not result from the treatment with Azoxystrobin. There was no finding indicating neurotoxicity in animals at 2,000 ppm, the highest dose.

The NOAELs in this study were considered to be 500 ppm for general toxicity (male: 38.5 mg/kg bw/day, female: 47.9 mg/kg bw/day) because changes including suppression of body weight gain were observed in males and females at 2,000 ppm, and 2,000 ppm for neurotoxicity (male: 161 mg/kg bw/day, female: 202 mg/kg bw/day). (Refs. 11 and 42)

12. Chronic toxicity/carcinogenicity

(1) 1-year chronic toxicity study (dogs)

A chronic toxicity study was conducted in Beagle dogs (4 males and 4 females in a group) receiving Azoxystrobin (gelatin capsule) at an oral gavage dose of 0, 3, 25 or 200 mg/kg bw/day for 1 year.

At 200 mg/kg bw/day, an increase in the frequency of liquid stool (4 of 4 males and 4 of 4 females), increases in cholesterol and TG, increased ALP activity and an increase in the relative weight of the liver were observed in males and females; increases in blood potassium and phosphorous, a decrease in MCH and increases in the frequencies of vomiting and regrgitation were found in males; and an increase in the frequency of salivation was observed in females.

At 25 mg/kg bw/day, an increase in the relative weight of the liver was found in females. However, since the treatment with Azoxystrobin did not affect any blood biochemical change or histopathological finding, there would be no toxicological significance.

Since changes including increases in cholesterol and TG were observed in males and females at 200 mg/kg bw/day, the NOAEL in this study was considered to be 25 mg/kg bw/day. (Refs. 11 and 43)

(2) 2-year combined chronic toxicity/carcinogenicity study (rats)

A 104-week combined chronic toxicity/carcinogenicity study was conducted in SD rats (64 males and 64 females in a group) fed diets containing Azoxystrobin at 0, 60, 300 or 750[3] (for males)/ 1,500

[3]: In males in the highst dose group, Azoxystrobin was given to animals at 1,500 ppm (108.6 mg/kg bw/day) at first, but since the number of died animals increased 39 weeks after the treatment initiation, the dose was changed to 750 ppm from week 53.

ppm (for females) (see Table 11 for average Azoxystrobin consumption).

Table 11 Average Azoxystrobin consumption in 2-year combined chronic toxicity/carcinogenicity study in rats

Dose		60 ppm	300 ppm	750 ppm	1500 ppm
Azoxystrobin consumption (mg/kg bw/day)	Male	3.6	18.2	82.4	
	Female	4.5	22.3		117

At the highest doses (female: 1,500 ppm, male: 750 ppm), suppression of body weight gain, a decrease in food consumption, reduced food efficiency, decreased ALP, ALT and AST activities were observed; and decreases in TG and cholesterol were found in females.

In 13 males at 1,500 ppm that died before the completion of study, changes related to the treatment with Azoxystrobin including gross changes: choledoch dilation, ascites and duodenal distension; and histological changes: choledoch dilation, cholangitis, thickening of the duodenal wall and hyperplasia of the biliary epithelium were found. The frequencies of hyperplasia of the biliary epithelium in the liver and cholangiohepatitis were increased associated with those changes. The major target organ of Azoxystrobin could be the bile duct and the effect on the bile duct was found in only males and was not seen in females.

Since changes including suppression of body weight gain were observed in males and females at the highest doses, the NOAEL in this study was considered to be 300 ppm for males and females (male: 18.2 mg/kg bw/day, female: 22.3 mg/kg bw/day). Azoxystrobin showed no carcinogenicity. (Refs. 11 and 44)

(3) 2-year carcinogenicity study (mice)

A carcinogenicity study was conducted in C57BL/10 mice (55 males and 55 females in a group) fed diets containing Azoxystrobin at 0, 50, 300, or 2,000 ppm (see Table 12 for average Azoxystrobin consumption) for 104 weeks.

Table 12 Average Azoxystrobin consumption in 2-year carcinogenicity study in mice

Dose		50 ppm	300 ppm	2000 ppm
Azoxystrobin consumption (mg/kg bw/day)	Male	6.2	37.5	272
	Female	8.5	51.3	363

At 2,000 ppm, suppression of body weight gain, reduced food efficiency and an increase in relative weight of the liver were found in males and females. At 300 ppm, suppression of body weight gain was

observed in males, but its fluctuation was no large and the suppression did not tend to deteriorate. The change, therefore, would not be toxicologically significant. The treatment with Azoxystrobin did not affect histopathological findings in any treatment groups.

Since changes including suppression of body weight gain were observed in males and females at 2,000 ppm, the NOAEL in this study was considered to be 300 ppm for males and females (male: 37.5 mg/kg bw/day, female: 51.3 mg/kg bw/day). Azoxystrobin showed no carcinogenicity. (Ref. 45)

13. Reproductive/developmental toxicity

(1) Two-generation reproductive toxicity study (rats)

A two-generation reproductive toxicity study was performed in Alpk:ApfSD rats (26 males and 26 females in a group) fed diets containing Azoxystrobin at 0, 60, 300 or 1,500 ppm (see Table 13 for average Azoxystrobin consumption).

Table 13 Average Azoxystrobin consumption in two-generation reproductive toxicity study in mice (mg/kg bw/day)

		60 ppm	300 ppm	1500 ppm
P	Male	6.5	33.0	162
	Female	6.9	34.4	171
F_1	Male	6.3	31.7	168
	Female	6.7	33.2	179

In parental animals at 1,500 ppm, death was observed in 1 P male and 1 F_1 male, and choledoch dilation was seen in 2 P males and 10 F_1 males that were died before the completion of study or terminally sacrificed. Suppression of body weight gain, a decrease in food consumption and an increase in relatively weight of the liver were found in P and F_1 males and females. Suppression of body weight gain and a decrease in food consumption were observed in P and F_1 females during gestation; suppression of body weight gain was seen in P females during suckling; and a decrease in food efficiency was found in P males and females, F_1 females, and F_1 males from weeks 1 to 10. In P and F_1 males at 1,500 ppm, histopathological findings including choledoch dilation, epithelial hyperplasia, cholangitis, and basophilic deposits and ulceration in the bile duct lumen were observed. Proliferative cholangiohepatitis in the liver was found in many animals with choledoch dilation.

In offspring, low body weight was found in F_1 and F_2 animals at 1,500 ppm.

Since changes including suppression of body weight gain were observed in male and female parental animals at 1,500 ppm and low body weight was found in male and female offspring at 1,500 ppm, the NOAEL in this study was considered to be 300 ppm (31.7 mg/kg bw/day) for parental animals and offspring. Azoxystrobin had no effect on reproductive ability. (Refs. 11 and 46)

(2) Developmental toxicity study (rats)

A developmental toxicity study was performed in Alpk:ApfSD rats (24 females in a group) receiving

Azoxystrobin at an oral gavage dose of 0, 25, 100 or 300 mg/kg bw/day on days 6 to 15[4] of gestation.

In dams, 3 of 12 animals at 300 mg/kg bw/day died after second administration and 1 animal was imminently sacrificed. After that, the dose of 300 mg/kg bw/day was considered to exceed the maximum tolerance dose and the treatment was discontinued in the remaining 8 animals at 300 mg/kg bw/day. At 300 mg/kg bw/day, a decrease in body weight, diarrhea and urinary incontinence were found. At 100 mg/kg bw/day, diarrhea, incontinence of urine and decreases in body weight and food consumption were found, and salivation after treatment was seen frequently on days 8 to 15 of gestation. At autopsy, bleeding in the stomach was observed in two animals at 100 mg/kg bw/day.

In fetuses, an increase in the incidence of delayed ossification was found at 100 mg/kg bw/day.

Since changes including diarrhea and urinary incontinence of urine were seen in dams at 100 mg/kg bw/day and the increase in the incidence of delayed ossification was found in fetuses at 100 mg/kg bw/day, the NOAEL in this study was considered to be 25 mg/kg bw/day for dams and fetuses. No teratogenicity of Azoxystrobin was found. (Refs. 11 and 47)

(3) Developmental toxicity study (1) (rabbits)

A developmental toxicity study was conducted in NZW rabbits (21 females in a group) receiving Azoxystrobin at an oral gavage dose of 0, 50, 150 or 500 mg/kg bw/day (solvent: 1 mL/kg bw/day of corn oil) on days 7 to 19[5] of gestation.

In dams, diarrhea, ano-genital staingings, decreases in body weight and food consumption were seen at 500 mg/kg bw/day. At 150 and 50 mg/kg bw/day, a decrease in body weight and diarrhea were observed.

The treatment with Azoxystrobin did not affect fetuses.

Since changes including the decrease in body weight gain in dams at 50 mg/kg bw/day were found, the NOAEL in this study could not be determined for dams. The NOAEL was considered to be 500 mg/kg bw/day for fetuses. (Refs. 11 and 48)

(4) Developmental toxicity study (2) (rabbits, dams)

Since the NOAEL for dams was not determined in the developmental toxicity study in rabbits, an additional developmental toxicity study was performed in NZW rabbits (15 females in a group) receiving Azoxystrobin at an oral gavage dose of 0, 25, 40 or 150 mg/kg bw/day (solvent: 1 mL/kg bw of corn oil) on days 7 to 19[5] of gestation.

At 150 mg/kg bw/day, suppression of body weight gain, a decrease in food consumption, diarrhea and ano-genital staining etc. were found. At 40 mg/kg bw/day, low body weight, a decrease in food consumption, diarrhea and ano-genitalaetc. were observed on days 8 to 9 of gestation.

Since changes including low body weight and the decrease in food consumption were found at 40 mg/kg bw/day, the NOAEL in this study was considered to be 25 mg/kg bw/day for dams. (Refs. 11 and 49).

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[4]: Days 7 to 16 of gestation as day 1 at discovery of sperm
[5]: Days 8 to 20 as day 1 at confirming mating

14. Genotoxicity

Azoxystrobin (technical grade) was examined in the following *in vitro* and *in vivo* test: bacterial DNA repair test, bacterial reverse mutation assay, genetic mutation test using mouse lymphoma-derived culture cells (L5178Y), chromosomal aberration test using cultured human lymphocytes, *in vivo/in vitro* hepatic unscheduled DNA synthesis (UDS) tests using rats, and micronucleus test using mouse bone marrow cells.

Positive results were obtained in the genetic mutation test using mouse L5178Y cell and chromosomal aberration test using cultured human lymphocytes. In other tests, negative results were obtained.

Positive responses seen in the genetic mutation test and chromosomal aberration test may be weak considering their dose dependence, reproducibility and frequency etc. Additionally, since negative results were obtained in *in vivo/in vitro* hepatic UDS tests and the micronucleus test using mouse bone marrow cells at sufficiently high doses, it was unlikely that Azoxystrobin presented genotoxicity that was found in some *in vitro* tests. Azoxystrobin, therefore, would not have genotoxicity that presents a problem *in vivo* (Table 14). (Refs. 50 to 55)

Table 14 Summary of genotoxicity tests (technical grade)

Test system		Cells/animals	Dose or concentration	Results
In vitro	DNA repair (±S9)	*B. subtilis* H17, M45	78~2500 μg/disc	Negative
	Reverse mutation (±S9)	*S. typhimurium* TA98, TA100, TA1535, TA1537 *E. coli* WP2/pKM101, WP2*uvrA*/pKM101	100~5000 μg/plate	Negative
	Genetic mutation (±S9)	Mouse lymphoma-derived culture cell (L5178Y)	8~80 μg/ml	Positive ±S9
	Chromosome aberration (±S9)	Human peripheral blood lymphocyte	1.0~50 μg/ml(-S9) 25~200 μg/ml(+S9)	Positive ±S9
in vivo/ in vitro	Hepatic UDS	SD rat (Azoxystrobin group: 5 males)	1250, 2000 mg/kg bw (Single oral administration)	Negative
In vivo	Rodent micronucleus	C57BL/6 mouse (5 males and 5 females in a group)	5000 mg/kg bw (Single oral administration)	Negative

Note) ±S9: with/without exogenous metabolic activation

A bacterial reverse mutation test for metabolite D, a Z isomer of Azoxystrobin, was performed and

as a result, metabolite D was not mutagenic in bacteria with and without an exogenous metabolic activation system (Table 15). (Ref.56)

Table 15 Summary of genotoxicity test (metabolite D)

Test system	Cells	Concentration	Result
Reverse mutation (±S9)	*S. typhimurium* TA98, TA100, TA1535, TA1537 *E. coli* WP2/ pKM101, WP2*uvrA*/pKM101	100～5000 μg/plate	Negative

Note) ±S9: with/without exogenous metabolic activation

III. Evaluation

"Azoxystrobin" was evaluated using the data listed in References.

In rats, the blood concentration after a single oral dose of Azoxystrobin reached a maximum level with Low Dose at 1 to 8 hours after administration and with High Dose at 2 to 12 hours after administration. The tissue concentrations were relatively high in the small intestine, large intestine, liver, kidney, plasma and blood around Tmax. The major excretion route was fecal excretion. The urine included no Azoxystrobin but the metabolites Y and M etc. The feces included Azoxystrobin and the metabolite M etc. The bile included no Azoxystrobin but the metabolites Y etc. Azoxystrobin could be metabolized through two major pathways: hydrolysis of methylester followed by glucuronic acid conjugation; and glutathione conjugation of cyanophenyl ring followed by generation of mercapturic acid.

Plant metabolism of Azoxystrobin was examined in rice, wheat, grape trees, and peanuts. The residues included Azoxystrobin, metabolites B, D and M.

The half-life in soil of Azoxystrobin was 54 to 85 days in the English soil and 164 days in the American soil under the aerobic conditions; and 50 to 56 days under the anaerobic conditions. The major degradation product was the degradation product B in all soils.

When hydrolysis of Azoxystrobin was examined, the half-life of Azoxystrobin was 290 hours with pH 9 at 50°C and the major degradation products were the degradation products B and H. When photolysis of Azoxystrobin in water was studied, the half-lives of Azoxystrobin in sterilized distilled water and natural water were 35.8 and 8.3 days equivalent to the exposure levels under the spring sunlight in Tokyo (at latitude 35°N), respectively. The major degradation products were the degradation products D and M.

Volcanic ash clay loam and diluvial clay loam were used for residual tests in soil for Azoxystrobin, the degradation products B, M and N (in a vessel and field). The half-life was estimated to be within 1 to 180 days for Azoxystrobin and within 1 to 240 days for the sum of Azoxystrobin, the degradation products B, M and N.

Paddy rice, fruits, vegetables and tea etc. were used for residual tests for Azoxystrobin and its metabolites B, D, F, L and M in crops. The highest value of Azoxystrobin detected was 11.9 mg/kg from Japanese horseradish (hatake wasabi) (stems and leaves) collected 7 days after the last application. The highest values of metabolites D, F, L and M were 0.12 mg/kg from hanegi (stems and leaves) collected 7 days after the last application, 0.07 mg/kg from wheat (grains) 21 days after the last application, 0.01 mg/kg from wheat (grains) 21 days after the last application, and 0.11 mg/kg from hanegi (stems and leaves) 7 days after the last application, respectively. The metabolite B was below the detection limit (<0.01 mg/kg).

The acute oral LD_{50} of Azoxystrobin was above 5,000 mg/kg bw in male and female rats and male and female mice; the acute dermal LD_{50} of Azoxystrobin was above 2,000 mg/kg bw in male and female rats; and the acute inhalation LC_{50} of Azoxystrobin was 962 μg/L in male rats and 698 μg/L in female rats. The acute oral LD_{50} of metabolite D was above 5,000 mg/kg in male and female mice.

The NOAELs in the subchronic toxicity studies were 20.4 mg/kg bw/day in rats and 10 mg/kg bw/day in dogs.

The NOAELs in the chronic toxicity studies and carcinogenicity studies were 25 mg/kg bw/day in dogs, 18.2 mg/kg bw/day in rats and 37.5 mg/kg bw/day in mice. No carcinogenicity of Azoxystrobin was found.

The NOAEL in the two-generation reproductive toxicity study was 31.7 mg/kg bw/day for rats. Azoxystrobin had no effect on reproductive ability.

The NOAELs in the developmental toxicity studies were 25 mg/kg bw/day for dams and fetuses in rats; and 25 mg/kg bw/day for dams and 500 mg/kg bw/day for fetuses in rabbits. No teratogenicity of Azoxystrobin was found.

Azoxystrobin was examined in the following *in vitro* and *in vivo* test: bacterial DNA repair test, bacterial reverse mutation assay, genetic mutation test using mouse lymphoma-derived culture cells (L5178Y), chromosomal aberration test using cultured human lymphocytes, *in vivo/in vitro* hepatic unscheduled DNA synthesis (UDS) tests using rats, and micronucleus test using mouse bone marrow cells. Positive results were obtained in the genetic mutation test using mouse L5178Y and chromosomal aberration test using cultured human lymphocytes. In other tests, negative results were obtained.

Positive responses seen in the genetic mutation test and chromosomal aberration test may be weak considering their dose dependence, reproducibility and frequency etc. Additionally, since negative results were obtained in *in vivo/in vitro* hepatic UDS tests and the micronucleus test using mouse bone marrow cells at sufficiently high doses, it was unlikely that Azoxystrobin presented genotoxicity that was found in some *in vitro* tests. The metabolite D was not also mutagenic in bacteria with and without an exogenous metabolic activation system. Azoxystrobin, therefore, would not have genotoxicity that presents a problem *in vivo*.

Considering various study results, Azoxystrobin (parent compound only) was determined as an exposure assessment substance in food.

The NOAELs and lowest observed adverse effect levels (LOAELs) determined in the evaluation tests are shown in Table 16. The NOAEL, 10 mg/kg bw/day, in the 90-day subchronic toxicity study in dogs was the minimum level. However, considering that the LOAEL in this study was 50 mg/kg bw/day and the NOAEL in the chronic toxicity study in dogs with a longer study period was 25 mg/kg bw/day, the NOAEL in dogs was determined to be 25 mg/kg bw/day and the NOAEL in the 2-year combined chronic toxicity/carcinogenicity study in rats, 18.2 mg/kg bw/day, was used as a basis of establishment for the acceptable daily intake (ADI).

Table 16 NOAELs and LOAELs in various studies

Animal	Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Remarks[6]
Rat	90-day subchronic toxicity study	Male: 20.4 Female: 22.4	Male: 211 Female: 223	Male and female: Suppression of body weight gain etc.
	90-day subchronic neurotoxicity study	Male: 38.5 Female: 47.9	Male: 161 Female: 202	Male and female: Suppression of body weight gain etc. (No neurotoxicity was found.)
	2-year combined chronic toxicity/carcinogenicity study	Male: 18.2 Female: 22.3	Male: 82.4 Female: 117	Male and female: Suppression of body weight gain etc. (No carcinogenicity was observed.)
	Two-generation reproductive toxicity study	Parental animals and offspring: P male: 33.0 P female: 34.4 F_1 male: 31.7 F_1 female: 33.2	Parental animals and offspring: P male:162 P female: 171 F_1 male: 168 F_1 female: 179	Dam: Suppression of body weight gain etc. Offspring: Low body weight (No effect on reproduction was found.)
	Developmental toxicity study	Dam: 25 Fetus: 25	Dam: 100 Fetus: 100	Dam: Diarrhea and incontinence of urine etc. Fetus: An increase in the incidence in delayed ossification (No teratogenicity was observed.)
Mouse	2-year carcinogenicity study	Male: 37.5 Female: 51.3	Male: 272 Female: 363	Male and female: Suppression of body weight gain etc. (No carcinogenicity was observed.)
Rabbit	Developmental toxicity study	Dam:- Fetus: 500	Dam: 50 Fetus: -	Dam: A decrease in body weight etc. Fetus: No effect (No teratogenicity was observed.)
	Developmental toxicity study (dams)	Dam: 25	Dam: 40	Dam: Low body weight
Dog	90-day subchronic toxicity study	Male: 10 Female: 10	Male: 50 Female: 50	Male: Salivation, regurgitation and vomiting

[6] The summary of findings observed at LOAEL is shown in Remarks.

				Female: Suppression of bodyweight gain
	1-year chronic toxicity study	Male: 25 Female: 25	Male: 200 Female: 200	Male and female: Increases in cholesterol and TG etc.

-: There were no NOAEL and LOAEL.

The Food Safety Commission determined 0.18 mg/kg bw/day as the acceptable daily intake (ADI) of Azoxystrobin with a safety factor of 100 based on the NOAEL in the 2-year combined chronic toxicity/carcinogenicity study in rats, 18.2 mg/kg bw/day.

ADI:	0.18 mg/kg bw/day
(referred data for ADI)	2-year combined chronic toxicity/carcinogenicity study
Laboratory animal tested:	Rat
Duration:	2 years
Administration route:	mixed feeds
NOAEL:	18.2mg/kg bw/day
Safety factor:	100

<Appendix 1: Abbreviations of metabolites/degradation products>

Abbreviation	Chemical name
B	(*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
C	Methyl =(*E*)-2-{2-[(6-hydroxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
D	Methyl =(*Z*)-2-{2-[6-(2-cyanophenoxy)pyrimidin4-yloxy]phenyl}-3-methoxyacrylate
F	2-hydroxybenzonitrile
H	2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenylacetic acid
G	Methyl =2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl} oxyacetate
I	Methyl ={2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}acetate
J	Methyl =(*E*)- 2-{2-[6-(2-cyano-5-hydroxyphenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
K	Methyl =(*E*)- 2-{2-[6-(2-cyano-4-hydroxyphenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
L	Methyl =2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}glycolate
M	4-(2-cyanophenoxy)-6-hydroxypyrimidin
N	2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy] benzoate
O	2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl} glycolate
P	(*E*)-2-{2-[6-(2-carbamoylphenoxy)pyrimidin-4-yloxy]phenyl}-3- methoxyacrylate
S	2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxypropionate
T	2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxylactate
U	Methyl =3-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]-2-methoxy-2H-3-benzofloate
V	Methyl =(*E*)-2-{2-[6-(2-cyano-6-hydroxyoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
W	Methyl =(*E*)-2-{2-[6-(2-cyano-4-glucuronidyloxyphenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
X	Methyl =(*E*)-2-{2-[6-(2-cyano-6-glucuronidyloxyphenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
Y	Glucuronidyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]pheny-3-methoxyacrylate
Z	Methyl =(*E*)-2-{2-[6-(2-cyano-3-glutathionylphenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
AA	Methyl =(*E*)-2-{2-[6-(2-cyano-3-(cystein-glycinylphenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
AB	Methyl =(*E*)-2-{2-[6-(2-cyano-3-cysteinylphenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
AC	Methyl=(*E*)-2-{2-[6-(2-cyano-3-(N-acetylcysteinyl)phenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
AD	Methyl=(*E*)-2-(2-hydroxypheny) -3-methoxyacrylate
AE	Methyl=2-[x-hydroxy{2[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}acetate

<Appendix 2: Abbreviations of laboratory parameters>

Abbreviation	Name
Ach	Acetylcholine
ai	Active ingredient
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
AST	Aspartate aminotransferase (GOT)
CK	Creatinine kinase
C_{max}	Maximum drug concentration
GGT	γ- glutamyl transferase
Hb	Hemoglobin
His	Histamine
HPLC	High-performance liquid chromatography
Ht	Hematocrit
LC_{50}	50% lethal concentration
LC/MS	Liquid chromatography mass spectrometry
LD_{50}	50% lethal dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
$T_{1/2}$	Half-life
TAR	Total applied radioactivity
TG	Triglyceride
T_{max}	Time to maximum drug concentration
TRR	Total residual radioactivity

<Appendix 3: Results of residual tests in crops>

Crop (Part analyzed) Year tested	No. of fields	Amount used	Applications (Times)	PHI (Days)	Residues (mg/kg)										
					Azoxystrobin		Metabolite D		Metabolite F		Metabolite L		Metabolite M		Total
					Highest	Average	Highest	Average	Highest	Average	Highest	Average	Highest	Average	Average
Paddy rice (hulled rice) 1995	2	Seed: 3 g ai/box[G] Application: 600 g ai/ha[G]	4	35-39 39-41 46-50	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.05 <0.05 <0.05
Paddy rice (hulled rice) 1995	2	Seed: 3g ai/box[G] Application: 60 g ai/ha[P]	4	14 21 28	0.02 0.02 0.01	0.02 0.02 0.01*	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	0.020.02 0.01* <0.01	0.01* 0.01* <0.01	<0.01 0.01 0.01	<0.01 0.01* 0.01*	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	0.06* 0.06* 0.05*
Paddy rice (hulled rice) 1998	2	Seed: 3 g ai/box[G] Application: 120 g ai/ha	4	13-14 20-21 27-28	0.04 0.02 0.03	0.02* 0.02* 0.02									
Paddy rice (hulled rice) 2000	2	Seed: 3 g ai/box[G] Application: 400 g ai/ha	4	3 7 14	0.08 0.07 0.05	0.07 0.05 0.03									
Paddy rice (hulled rice) 2000	2	Seed: 3 g ai/box[G] Aerial application: 80 g ai/ha	4	3 7 14	0.04 0.04 0.03	0.02 0.02* 0.02*									
Paddy rice (rice straw) 1995	2	Seed: 3 g ai/box[G] Application: 600 g ai/ha[G]	4	35-39 39-41 46-50	1.00 0.84 0.54	0.81 0.61 0.41	<0.04 <0.04 <0.04	<0.03 0.03* 0.03	0.09 0.09 0.08	0.08 0.07 0.06	<0.04 0.03 <0.04	<0.03 0.03* 0.03*	0.17 0.14 0.17	0.14 0.10 0.10	1.11* 0.85* 0.64*
Paddy rice (rice straw) 1995	2	Seed: 3 g ai/box[G] Application: 60 g ai/ha[P]	4	14 21 28	1.15 0.64 0.29	0.81 0.51 0.24	0.11 0.06 <0.04	0.07* 0.04* 0.03	0.17 0.11 0.09	0.12 0.10 0.07	0.16 0.08 <0.04	0.09* 0.05* <0.03	0.30 0.20 0.13	0.19 0.15 0.09	1.31 0.86 0.48
Paddy rice (rice straw) 1998	2	Seed: 3 g ai/box[G] Application: 120 g ai/ha	4	13-14 20-21 27-28	0.96 0.56 0.45	0.65 0.43 0.30									
Paddy rice (rice straw) 2000	2	Seed: : 3 g ai/box[G] Application: 400 g ai/ha	4	3 7 14	4.91 2.41 0.94	4.11 1.85 0.69									
Paddy rice (rice straw) 2000	2	Seed: 3 g ai/box[G] Aerial application: 80 g ai/ha	4	3 7 14	4.37 2.72 1.75	2.56 1.80 0.97									
Paddy rice (early harvested rice) 1999	2	Aerial application: 120 g ai/ha	1	7	0.64	0.49									
	2	Application: 120 g ai/ha	1	7	0.72	0.62									
Wheat (seed) 1994年	2	Seed: : 1.6gai/kg Application: 250 g ai/ha 100 g ai/ha	2 5[a] 5[a] 5[a]	237 7 14 21	0.01 0.10 0.05 0.02	0.01* 0.06 0.03* 0.02*	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	<0.01 0.04 0.03 0.07	<0.01 0.02* 0.02* 0.03*	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	<0.01 0.01 0.01 <0.01	<0.01 0.01* 0.01* <0.01	<0.05 0.10* 0.08* 0.07*
Soybean (field) (dried bean) 2000	2	Application: 200-250 g ai/ha	3	7 14 21	0.02 <0.01 <0.01	0.02* <0.01 <0.01									
Soybean (field) (dried bean) 2001	2	Aerial application: 200 g ai/ha	2	21	0.01	0.01*									

Crop (Part analyzed) Year tested	No. of fields	Amount used	Applications (Times)	PHI (Days)	Residues (mg/kg)										
					Azoxystrobin		Metabolite D		Metabolite F		Metabolite L		Metabolite M		Total
					Highest	Average	Highest	Average	Highest	Average	Highest	Average	Highest	Average	Average
Red bean (field) (dried bean) 2004	2	Application: 120 g ai/ha	3	7 14 21	0.01 0.01 0.01	0.01* 0.01* 0.01									
Kidney bean (field) (dried bean) 2004	2	Application: 150-300 g ai/ha	3	7 14 21	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01									
Sugar beet (field) (root) 1996/2003	4	Application: 255-267 g ai/ha	3	14 21 30	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01									
Japanese radish (field) (root) 2002	2	Application: 107-250 g ai/ha	3	14 21 28	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01									
Japanese radish (field) (leaf) 2002	2	Application: 107-250 g ai/ha	3	14 21 28	0.46 0.26 0.24	0.26 0.14 0.10									
Turnip (field) (root) 2004	2	Application: 200 g ai/ha	2	7 14 21	0.03 0.04 0.03	0.02 0.02 0.02									
Turnip (field) (stem and leaf) 2004	2	Application: 200 g ai/ha	2	7 14 21	9.09 7.94 4.56	5.16 4.57 2.40									
Japanese horseradish (hatake wasabi) (green house) (stem and leaf) 2003	2	Application: 300 g ai/ha	2	7 14 21	11.9 9.95 8.19	8.83 6.50 4.90									
Japanese horseradish (hatake wasabi) (green house) (root and stem) 2003	2	Application: 300 g ai/ha	2	7 14 21	0.75 0.85 0.45	0.64 0.61 0.43									
Chinese cabbage (field) (stem and leaf) 1999	1	Application: 200 g ai/ha	4	7 14 21	0.06 0.03 0.02	0.04 0.03 0.02									
Shirona (green house) (stem and leaf) 2000	2	Application: 200 g ai/ha	1	14	2.39	1.16									

Crop (Part analyzed) Year tested	No. of fields	Amount used	Applications (Times)	PHI (Days)	Residues (mg/kg)											
					Azoxystrobin		Metabolite D		Metabolite F		Metabolite L		Metabolite M		Total	
					Highest	Average	Highest	Average	Highest	Average	Highest	Average	Highest	Average	Average	
Cabbage (field) (head) 2001	2	Application: 200 g ai/ha	4	7 14 21	0.08 <0.01 <0.01	0.03* <0.01 <0.01										
Komatsuna (green house) (stem and leaf) 2004/2005	2	Application: 214-400 g ai/ha	2	21	2.5	1.0*										
Leaf mustard (Ohyama sodachi) (green house) (stem and leaf) 2004	2	Application: 200 g ai/ha	2	21	2.23	1.48										
Sagami green (green house) (stem and leaf) 2003	2	Application: 200 g ai/ha	2	21	0.94	0.89										
Endive (green house) (stem and leaf) 2004	2	Application: 200 g ai/ha	1	21 28 35	1.20 0.27 <0.05	0.62* 0.16 <0.05										
Lettuce (green house) (foliage) 2000	2	Application: 200-300 g ai/ha	4	7 14 21	2.80 2.95 0.33	2.01 1.43 0.19										
Onion (field) (bulb) 2000	2	Application: 267 g ai/ha	4	1 7 14	0.02 <0.01 <0.01	0.02* <0.01 <0.01										
Welsh onion (Nebukanegi) (field) (stem and leaf) 1995	2	Application: 180-300 g ai/ha	4	3 7 14	0.96 0.32 0.19	0.58 0.22 0.11	0.02 0.01 0.01	0.02* 0.01* 0.01*	0.03 0.02 0.01	0.03 0.02 0.01*	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	0.03 0.03 0.01	0.03 0.03 0.01*	0.66* 0.29* 0.16*	
Welsh onion (hanegi) (field) (stem and leaf) 1995	2	Application: 300 g ai/ha	4	3 7 14	1.23 1.43 0.62	1.13 0.73 0.28	0.08 0.12 0.07	0.06 0.06 0.03*	0.04 0.04 0.03	0.03 0.04 0.03	0.01 0.01 0.01	0.01* 0.01 0.01*	0.09 0.11 0.05	0.06 0.07 0.04	1.31* 0.93* 0.39*	
Garlic (field) (head) 1998	2	Application: Aomori, 300 g ai/ha Miyagi, 150 g ai/ha	3	7 14 21	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01										

Crop (Part analyzed) Year tested	No. of fields	Amount used	Applications (Times)	PHI (Days)	Residues (mg/kg)										
					Azoxystrobin		Metabolite D		Metabolite F		Metabolite L		Metabolite M		Total
					Highest	Average	Highest	Average	Highest	Average	Highest	Average	Highest	Average	Average
Green chive (green house) (stem and leaf) 1999	2	Application: 150-200 g ai/ha	2	14	2.42	1.54									
Asparagus (green house) (stem) 2001	2	Application: 250-300 g ai/ha	4	1 3 6-7	0.84 0.23 0.02	0.44 0.09 0.01*									
Shallot (field) (bulb) 2003/2004	2	Application: 150 g ai/ha	3	3 7 14	0.02 0.02 <0.01	0.02* 0.02 <0.01									
Carrot (field) (root) 2003	2	Application: 96-192 g ai/ha	2	21 28	0.02 0.02	0.02* 0.02*									
Parsley (green house) (stem and leaf) 2003	2	Application: 250 g ai/ha	1	45 60	0.33 0.13	0.19* 0.09*									
Honewort (green house) (stem and leaf) 2004	2	Application: 100 g ai/ha	1	14 21	1.7 <0.5	1.6 <0.5									
Tomato (green house) (fruit) 1998	2	Application: 400 g ai/ha	4	1 3 7	0.40 0.37 0.26	0.20 0.20 0.17									
Green pepper (green house) (fruit) 2000	2	Application: 200 g ai/ha	4	1 3 7	1.30 1.28 0.90	1.23 1.05 0.74									
Eggplant (green house) (fruit) 1995	2	Application: 300 g ai/ha	4	1 3 7	0.59 0.34 0.06	0.41 0.21 0.05	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	0.02 0.02 0.01	0.02 0.02 0.01*	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	0.01 <0.01 <0.01	0.01* <0.01 <0.01	0.47* 0.29* 0.10*
Cucumber (green house) (fruit) 1994	2	Basal irrigation: 20 mg ai/plant Application: 200-400 g ai/ha	1 4 4 4	46-85 1 3 7	0.01 0.50 0.27 0.04	0.01* 0.32 0.14 0.03	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	0.01 <0.01 <0.01 <0.01	0.01* <0.01 <0.01 <0.01	0.05* 0.36* 0.18* 0.07*
Squash (green house) (fruit) 2003	2	Application: 293-300 g ai/ha	4[a]	7 14	0.10 <0.10	0.10* <0.10									
Watermelon (green house) (fruit) 1995	2	Application: 168-300 g ai/ha	4	1 3 7	<0.01 <0.01 0.01	<0.01 <0.01 0.01*	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.05 <0.05 0.05*

Crop (Part analyzed) Year tested	No. of fields	Amount used	Applications (Times)	PHI (Days)	Residues (mg/kg)										
					Azoxystrobin		Metabolite D		Metabolite F		Metabolite L		Metabolite M		Total
					Highest	Average	Highest	Average	Highest	Average	Highest	Average	Highest	Average	Average
Melon (green house) (fruit) 1995	2	Application: 30g ai/ha	4	1 3 7	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.05 <0.05 <0.05
Gumbo (green house) (fruit) 2004	2	Application: 180-250 g ai/ha	2	1 3 7	1.24 0.58 0.24	1.14 0.56 0.16									
Pea (green house) (legume) 2004/2005	2	Application: 200g ai/ha	3	1 3 7	1.32 0.92 0.54	0.77 0.59 0.30									
Japanese ginger (green house) (spicate inflorescence) 2004	2	Irrigation: 3000g ai/ha	4	3 7 14	0.51 0.16 0.08	0.42 0.15 0.07									
Apple (no cover) (fruit) 1994	2	Application: 500g ai/ha	5[a]	42	0.98	0.48	0.03	0.03*	0.02	0.02*	<0.01	<0.01	0.02*	0.02*	0.55*
Japanese pare (no cover) (fruit) 1995/1998	4	Application: 500g ai/ha	5	1 3 7	0.68 0.49 0.57	0.47 0.28 0.30									
				14 28 42	0.60 0.46 0.24	0.46 0.30 0.13	0.03 0.03 0.02	0.03 0.03 0.02*	0.01 0.01 0.01	0.01* 0.01* 0.01*	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	0.02 0.02 0.01	0.02* 0.02 0.01*	0.54* 0.27* 0.18*
Peach (no cover) (flesh) 1997	2	Application: 500g ai/ha	3	1 3 7	0.01 0.01 0.01	0.01* 0.01* 0.01*									
Peach (no cover) (pericarp) 1997	2	Application: 500g ai/ha	3	1 3 7	6.10 6.48 3.46	3.65 3.60 2.51									
Nectarine (field) (fruit) 2005	2	Application: 400g ai/ha	3	1 3 7 14	1.4 1.2 1.0 0.2	0.9 0.8 0.6 0.2									
Prune (field, no cover) (fruit) 2001	2	Application: 300-400 g ai/ha	3	1 3 7	0.13 0.11 0.06	0.09 0.08 0.05									
Cherry (green house) (fruit) 1996	2	Application: 500g ai/ha	3	1 3 7	0.89 1.30 0.74	0.65 0.76 0.43									
Strawberry (green house) (fruit) 1994	2	Application: 300-400 g ai/ha Soil irrigation: 20mg ai/plant	5[a] 8[a] 8[a] 8[a]	89-217 1 3-4 7-8	0.11 1.21 0.86 0.60	0.06 1.05 0.63 046	<0.01 0.01 <0.01 <0.01	<0.01 0.01* <0.01 <0.01	<0.01 0.03 0.03 0.02	<0.01 0.02* 0.02* 0.02*	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.01	0.11* 1.11* 0.68* 0.51*

Crop (Part analyzed) Year tested	No. of fields	Amount used	Applications (Times)	PHI (Days)	Residues (mg/kg)										
					Azoxystrobin		Metabolite D		Metabolite F		Metabolite L		Metabolite M		Total
					Highest	Average	Highest	Average	Highest	Average	Highest	Average	Highest	Average	Average
Grape (green house, no cover) (fruit) 1994	2	Dormant application: 3000-5000 g ai/ha Application: 500g ai/ha	5 [a]	45 60 75	4.35 1.42 1.36	2.61 1.19 0.69	0.02 0.02 0.03	0.02 0.02 0.03*	0.05 0.04 0.02	0.05 0.04 0.02*	<0.01 0.01 0.01	<0.01 0.01* 0.01*	0.03 0.01 0.01	0.03 0.01* 0.01*	2.76* 1.29* 0.79*
Persimmon (field) (fruit) 1998	2	Application: 300-400 g ai/ha	3	7 14 21	0.37 0.33 0.23	0.19 0.16 0.12									
Passion fruit (field) (fruit) 2000	2	Application: 300g ai/ha	3	1 3 7	0.36 0.30 0.17	0.30 0.24 0.11									
Fig (field, no cover) (fruit) 2001	2	Application: 230-300 g ai/ha	3	1 7 14	0.58 0.28 0.25	0.38 0.23 0.21									
Tea (coarsely cut leaves) 1998	4	Application: 200g ai/ha	3	14 21	4.77 1.52	1.74 0.63									
Tea (tea infusion) 1998	4	Application: 200g ai/ha	3	14 21	2.52 0.65	1.39 0.42									

Note) ai: Active ingredient, PHI: Pre-harvest interval

・In the column of amount used, the G mark means granular formulation, the P marks means powder formulation, and no mark means flowable formulation.

・"[a]" was marked on the number of applications when the application frequency of Azoxystrobin was larger than that in the registered application method.

・For data including values below the detection limit, the average was calculated as the detection limit and marked with *.

・When all data were below the detection limit, the average of the detection limits was marked with <.

・The metabolite B was observed in cabbage, Welsh onion, cucumber and nectarine below the detection limit (<0.01 mg/kg).

<Appendix 4: Estimated consumption>

Crop	Residue (mg/kg)	National average		Infant (age: 1 - 6 years)		Pregnant woman		Elderly (age: ≥ 65 years)	
		ff (g/person/day)	Consumption (μg/person/day)	ff (g/person/day)	Consumption (μg/person/day)	ff (g/person/day)	Consumption (μg/person/day)	ff (g/person/day)	Consumption (μg/person/day)
Rice	0.07	185.1	12.96	97.7	6.84	139.7	9.78	188.8	13.22
Wheat	0.06	116.8	7.01	82.3	4.94	123.4	7.40	83.4	5.00
Soybean	0.02	56.1	1.12	33.7	0.67	45.5	0.91	58.8	1.18
Red beans (including kidney bean, cherry bean and lentil)	0.01	1.4	0.01	0.5	0.01	0.1	0.00	2.7	0.03
Japanese radish (leaf)	0.26	2.2	0.57	0.5	0.13	0.9	0.23	3.4	0.88
Turnips (root)	0.02	2.6	0.05	0.7	0.01	0.7	0.01	4.2	0.08
Turnips (leaf)	5.16	0.5	2.58	0.1	0.52	0.3	1.55	1.1	5.68
Horseradish	8.83	0.1	0.88	0.1	0.88	0.1	0.88	0.1	0.88
Chinese cabbage	0.04	29.4	1.18	10.3	0.41	21.9	0.88	29.9	1.20
Cabbage	0.03	22.8	0.68	9.8	0.29	22.9	0.69	23.1	0.69
Komatsuna	1.0	4.3	4.3	2	2	1.6	1.6	5.9	5.9
Other cruciferous vegetable	1.16	3.5	4.06	0.6	0.70	1.2	1.39	3.6	4.18
Lettuce	2.01	6.1	12.26	2.5	5.03	6.4	12.86	4.2	8.44
Onion	0.02	30.3	0.61	18.5	0.37	33.1	0.66	22.6	0.45
Welsh onion	0.73	11.3	8.25	4.5	3.29	8.2	5.99	11.5	9.86
Green chive	1.54	1.6	2.46	0.7	1.08	0.7	1.08	1.6	2.46
Asparagus	0.44	0.9	0.40	0.3	0.13	0.4	0.18	0.9	0.40
Other liliaceae vegetable	1.54	2.5	3.85	0.8	1.23	0.8	1.23	2.5	3.85
Carrot	0.02	24.6	0.49	16.3	0.33	25.1	0.50	22.3	0.45
Parsley	0.19	0.1	0.02	0.1	0.02	0.1	0.02	0.1	0.02
Honewort	1.6	0.2	0.32	0.1	0.16	0.1	0.16	0.2	0.32

Tomato	0.20	24.3	4.86	16.3	3.26	25.1	5.02	25.0	5.00
Green pepper	1.23	4.4	5.41	2.0	2.46	1.9	2.34	3.7	4.55
Eggplant	0.41	4.0	1.64	0.9	0.37	3.3	1.35	5.7	2.34
Cucumber	0.32	16.3	5.22	8.2	2.62	10.1	3.23	16.6	5.31
Squash	0.10	9.4	0.94	5.8	0.58	6.9	0.69	11.5	1.15
Watermelon	0.01	0.1	0.00	0.1	0.00	0.1	0.00	0.1	0.00
Gumbo	1.14	0.3	0.34	0.2	0.23	0.2	0.23	0.3	0.34
Immature pea	0.77	0.6	0.46	0.2	0.15	0.7	0.54	0.6	0.46
Other vegetable	0.42	12.6	5.23	9.7	4.07	9.6	4.03	12.2	5.12
Apple	0.48	35.3	16.94	36.2	17.38	30.0	14.4	35.6	17.09
Japanese pare	0.47	5.1	2.40	4.4	2.07	5.3	2.49	5.1	2.40
Peach	0.01	0.5	0.01	0.7	0.01	4.0	0.04	0.1	0.00
Nectarine	0.9	0.1	0.09	0.1	0.09	0.1	0.09	0.1	0.09
Prune	0.09	0.2	0.02	0.1	0.01	1.4	0.13	0.2	0.02
Cherry	0.76	0.1	0.08	0.1	0.08	0.1	0.08	0.1	0.08
Strawberry	1.05	0.3	0.32	0.4	0.42	0.1	0.11	0.3	0.32
Grape	2.61	5.8	15.14	4.4	11.48	1.6	4.18	3.8	9.92
Persimmon	0.19	31.4	5.97	8.0	1.52	21.5	4.09	49.6	9.42
Passion fruit	0.30	0.1	0.03	0.1	0.03	0.1	0.03	0.1	0.03
Other fruit	0.38	3.9	1.48	5.9	2.24	1.4	0.53	1.7	0.65
Tea	1.74	3.0	5.22	1.4	2.44	3.5	6.09	4.3	7.48
Total			131.8		79.2		95.3		133.7

Note)

- The residual value is the average value in the test group showing the maximum value of Azoxystrobin among individual test groups treated with Azoxystrobin over periods and frequencies registered (see Appendix 3).
- "ff": Agricultural product consumption (g/person/day) based on the results of the National Nutrition Surveysin 1998-2000 (Refs. 68-70).
- "Consumption": Estimated consumption (μg/person/day) of Azoxystrobin calculated from the residual value and agricultural product consumption.
- "Other liliaceae vegetable" is "shallot"; "other cruciferous vegetable" is "Japanese ginger"; and "other fruit" is "fig".
- The consumptions of melon, sugar beet and garlic were not calculated since their residues were below the detection limit in all data.

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