Evaluation Report

Cyazofamid

November 2, 2004

Food Safety Commission

Pesticides Experts Committee

(Progress of Evaluation)

April 26, 2001	First registration in Japan
May 22, 2003	Registration application submitted (expansion of application)
July 12, 2004	The Ministry of Health, Labour and Welfare requests a health risk assessment in line with the establishment of a maximum residue limit
July 15, 2004	54th meeting of the Food Safety Commission (explanation of MHLW's request outline)
July 21, 2004	14th meeting of the Pesticides Expert Committee
September 16, 2004	62nd meeting of the Food Safety Commission
September 16 to October 13, 2004	Public comments
November 2, 2004	Finalized

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Summary

Cyazofamid (IUPAC:4-chloro-2-cyano-*N*,*N*-dimethyl-5-p-tolylimidazole-1-sulfonamide), belonging to the cyanoimidazole class of fungicides was evaluated for its health effects, based on various tests.

The test results used for the evaluation were animal metabolism (rats), plant metabolism (tomatoes, Irish potatoes, and grapes), soil degradation, hydrolysis in water, photolysis in water, residues in crops, residues in soil, acute toxicity (rats, mice), subchronic toxicity (rats, dogs), chronic toxicity (dogs), combined study of chronic toxicity and carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats, rabbits), and genotoxicity, etc.

The compound did not show any carcinogenicity, teratogenicity, genotoxicity or effects on reproductive ability were recognized from the test results.

Based on the lowest value among the no observed adverse effect levels (NOAELs), which was 17.07 mg/kg bw/day for the Combined test of combined study of chronic toxicity and carcinogenicity using rats, and after dividing this lowest value by a safety factor of 100, the acceptable daily intake (ADI) was settled as 0.17 mg/kg bw/day.

I. Outline of pesticide to be evaluated

1. Usages

Fungicide

2. Common name of active element

English: Cyazofamid (ISO name)

3. Chemical name

IUPAC name:

English: 4-chloro-2-cyano-*N*,*N* -dimethyl-5-p -tolylimidazole-1-sulfonamide

CAS chemical name (No. 188425-85-6):

4-chloro-2-cyano-*N*,*N* -dimethyl-5-(4-methylphenyl)-1*H* -imidazole-1-sulfonamide

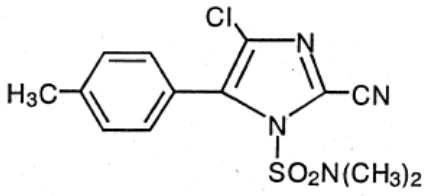
4. Chemical formula

$C_{13}H_{13}ClN_4O_2S$

5. Relative molecular mass

324.8

6. Chemical structure



7. Background of development

Cyazofamid is a cyanoimidazole-type fungicide which was discovered by Ishihara Sangyo Co., Ltd. in 1987 and first registered in Japan in April 2001. Approximately 100 tons of technical grade compound were produced in pesticide fiscal year 2002 (reference 1).

The mechanism of action is the inhibition of Qi sites of internal electron transfer-type complex III of mitochondria, and it is said to have a species-specific effect against algal fungi. It has already been registered for use on Irish potatoes and other crops in France, Germany and England.

In May 2003, Ishihara Sangyo Co., Ltd. (hereinafter "The Applicant") applied for the registration of the compound's expanded application according to the Agricultural Chemicals Regulation Law. Ref. 2 through 28 and 32 through 59 were submitted (Ref. 2).

II. Summary of the Test Results

1. Absorption, distribution, metabolism, and excretion

Various studies were conducted using Cyazofamid homogeneously labeled with at ^{14}C at the benzene ring (hereinafter "Bz-^{14}C-Cyazofamid"), or Cyazofamid labeled with ^{14}C at position 4 of the imidazole ring (hereinafted "Im-^{14}C-Cyazofamid"). Unless otherwise noted, radioactivity concentrations and metabolite concentrations were calculated in terms of Cyazofamid (The procedure was also applied to all other metabolism tests).

(1) Absorption, distribution, metabolism, and excretion (Single dose)

The ADME of cyazofamid was examined in SD rats, after a single oral administration of 0.5 mg/kg bw (hereinafter "Low Dose") or 1000 mg/kg bw (hereinafter "High Dose") of Bz-^{14}C-cyazofamid or Im-^{14}C-cyazofamid.

The whole-blood concentration of the compound after the administration of Bz-^{14}C-cyazofamid or Im-^{14}C-cyazofamid reached its maximum at 0.5 hours for the Low Dose group and at 0.25 hours for the High Dose group, respectively. The Cmax for each group were 243 to 354 μg/g and 48.1 to 75.6 μg/g respectively. The half-lives of the Low Dose and High Dose group were 4.4 to 5.8 hours, and 7.6 to 11.6 hours respectively. No significant difference was observed among the position of labeled with ^{14}C .

At Tmax, in the Low Dose group, the compound had been distributed to the kidneys, liver and whole-blood, and in other areas were 0.2 μg/g or less. In the High Dose group, the compound had been distributed to the kidneys, liver, blood, adrenal glands, adipose tissue, lungs, ovaries, thyroid, uterus, and heart, and in other tissues were 10 μg/g or less. 168 hours later, excluding the kidneys with distribution of 0.5 μg/g of Bz-^{14}C-cyazofamidof the High Dose group, the compound was either undetected or under 0.2 μg/g in each of the tissues.

Twenty-four hours after administration, 90% or more of the dose (TAR) was excreted in the urine and feces, and 168 hours after administration less than 0.5% TAR remained in the tissues. The major route of excretion for the Low Dose group was urine, and 49.0% to 68.2% TAR was excreted 168 hours after administration. The major route of excretion for the High Dose group was feces, and 94.2% to 97.6% TAR was excreted by 168 hours after administration.

In the Low Dose group, the amount of metabolites CCBA[1], CH_3SO-CCIM, and CH_3SO_2-CCIM ranged from 23.1 to 59.3%, from 0.4 to 8.3%,and 0.2% to 5.8% of TAR in the urine and from 13.5 to 20.8% TAR of Cyazofamid was detected in the feces. In the High Dose group, the amount of metabolites CCBA, CH_3SO-CCIM, and CH_3SO_2-CCIM ranged form 1.14 to 1.93%, from 0.01 to 0.14%, from 0.01 to 0.08% of TAR in the urine and from 78.4 to 92.9% TAR of Cyazofamid was detected in the feces. The main metabolite in the liver and kidneys was CCBA. The main metabolic pathways of Cyazofamid in rats could be the hydrolysis of the sulfonamide group (CCIM) and the oxidation of the methyl on the tolyl group (CCBA) and conjugation (Ref. 3-5).

[1] Refer to attachment for abbreviations of metabolites, etc. (Same below.)

(2) Absorption, distribution, metabolism, and excretion in rats (Repetitive doses)

The ADME of Cyazofamid SD rats, after repetitive oral administrations of 0.5 mg/kg bw/day of unlabeled Cyazofamid for 14 days and, following that, 0.5 mg/kg bw of single oral administration of Bz-^{14}C-Cyazofamid.

More radioactivity was recovered in the urine in the group administered repetitive doses compared with the group administered single dose. By 168 hours after administration, from 62.8 to 72.8% TAR was excreted in the urine and from 20.8 to 31.6% TAR was excreted in the feces(Reference 6).

(3) Excretion into bile in rats

The excretion into bile was examined in bile-duct cannulated SD rats, with single oral administrations of Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid at weights of 0.5 mg/kg (Low Dose) and 1,000 mg/kg (High Dose) respectively.

By 72 hours after administration, excretion in the bile was from 12.2 to 38.8% TAR in the Low Dose group, from 0.8 to 1.4% TAR in the High Dose group, and excretion in the urine was from 40.5 to 61.6% TAR in the Low Dose group and from 2.73 to 5.16% TAR in the High Dose group. Excretion into feces was from 9.8 to 42.3% TAR in the Low Dose group and from 94.7 to 96.0% TAR in the High Dose group. Major metabolites were CCBA and conjugates, and CCBA was recovered from 2.8 to 6.4% TAR in the bile and from 25.4 to 67.7% TAR in the urine, and conjugates (including conjugate of CCIM, CCBA and CHCN) were recovered from 7.4 to 25.2% TAR in the bile and from 1.1 to 2.9% TAR in the urine. Cyazofamid was recovered in the feces from 2.7 to 34.7%TAR (Reference 7).

(4) *In vitro* metabolism test in the blood and in gastric contents

Bz-^{14}C-Cyazofamid or Bz-^{14}C-CCIM was added to an *in vitro* metabolism system of blood or gastric contents of male CD rats. Bz-^{14}C-Cyazofamid or Bz-^{14}C-CCIM was added to the metabolism system of blood to the concentration of 0.4 μg/mL, and to the metabolism system of gastric contents to the concentration of 13.8 μg/g.

Cyazofamid was metabolized quickly in the blood, and 60 minutes after the treatment, approximately 30% of the added amount was metabolized. The main metabolite was CCIM, and CCIM was not metabolized further 60 minutes after the treatment. In the gastric contents, either Cyazofamid or CCIM was not metabolized 60 minutes after the treatment. It appears that they are stabilized in the gastric contents. CCBA, the main metabolite in rats, could be via CCIM (Ref. 8).

(5) Comparative metabolism of Cyazofamid and CCIM in rats

Bz-^{14}C-Cyazofamid or Bz-^{14}C-CCIM was administered to SD rats (groups of 5males) by oral gavage at a dose level of 0.5 mg/kg bw.

Concentrations in whole blood and liver were greater in the CCIM-dosed animals, suggesting that a dose of CCIM was much more rapidly absorbed than that of Cyazofamid. At 0.5 hour after a dose of Cyazofamid, analysis of the liver of this group showed 6.1, 24.2, and 41.9% TAR of Cyazofamid, CCIM, and CCBA respectively. In the plasma, there was no Cyazofamid, while 61.7, 34.4, and 4.0% TAR of CCIM, CCBA, and

CHCN were recovered respectively. Most of the radiolabel in the stomach was Cyazofamid, representing 97.2% TAR, and a small fraction was CCIM, representing 2.8%. In the CCIM-dosed animals, all of the radiolabel in the stomach was CCIM, while in the liver, 76.5, 18.2, and 3.8% TAR was CCIM, CCBA, and CHCN, respectively. In the plasma, 67.9, 26.6 and 5.6% TAR was CCIM, CCBA, and CHCN, respectively. In could be concluded that the main pathway of metabolism of Cyazofamid in rats involves conversion to CCIM at the early stage in the metabolism, and then CCIM could be metabolized to CCBA (Reference 9).

2. Plant metabolism

(1) Tomatoes (spray application)

Solution containing Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid was sprayed onto the entire surface of tomatoes (variety: Bush Beefsteak) under field growing conditions at the annual rate of 100 ai g/ha (normal rate) or 400 ai g/ha (exaggerated rate: for metabolite identification) for 4 times at one-week intervals. The fruit, stems and leaves from all plants were harvested one day after the final application.

The total radioactive residue (TRR) in the fruits of the normal rate was0.0801 to 0.290 mg/kg. Surface-washed fruits contained 17.4 to 45.8% TRR. Most of the radioactivity of surface-washed fruits was present in pulp, accounting for 71.0 to 87.0% TRR pulp, and the remaining 13 to 29% TRR were in the juice. Cyazofamid accounted for most of the radioactivity in the fruits (76.4 to 79.9% TRR), and the major metabolites were CCIM and CCTS. Major residue in foliage was Cyazofamid accounting for 77.6 to 79.1% TRR, while CCIM was 1.12 to 5.36% TRR. It could be concluded that the main pathway of metabolism of Cyazofamid in tomatoes involves migration of the -$SO_2N(CH_3)_2$ function (CCTS) , elimination of the -$SO_2N(CH_3)_2$ function (CCIH), and other metabolism and conjugations (Ref. 10).

(2) Plant metabolism in tomatoes (soil application)

Solution containing Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid was applied in the soil of potted tomatoes (variety: Ponteroza) under greenhouse conditions at with 100 g ai g/ha for 4 times at one week intervals. The fruits, stems and leaves from all plants were harvested and the soil of every 4 cm from the surface were collected one day after the final application (22 days after the first application)..

The total applied radioactivity (TAR) was 0.2% (0.004 to 0.005 mg/kg) in the fruits and 0.2 to 0.3% (0.010 to 0.014 mg/kg) in the leaves and stems. In the soil 66.0 to 74.9% TAR was recovered in the first layer (0 to 4 cm), and at lower layers less than 3% TAR was detected.

It could be concluded that Cyazofamid tends not to be absorbed by tomatoes, and remains at the surface of soil (reference 11).

(3) Absorption and translocation in tomato seedlings

Solution containing Bz-^{14}C-Cyazofamid and Im-^{14}C-Cyazofamid (125-127μ g/ml)was applied 40 μL on the fourth leaves of tomatoes (variety: Ponteroza) of 6 to 7 leaf stage. The whole plants were harvested 3 days and 7 days after application.

87.1 to 114.8% TAR was recovered in the surface wash of the tomato seedlings, and 0.3 to 0.5% TAR was recovered in the surface-washed tomato seedlings. Radioactivity was hardly recovered from the leaves not applied. It could be concluded that Cyazofamid is hardly absorbed from the leaf surface, and remains the site

of application even if absorbed (Ref. 12).

(4) Plant metabolism in potatoes

Solution containing Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid was applied to the potatoes under field growing conditions (variety: Kennebec), or under greenhouse condition (variety: Superior) at the annual rate of 100g ai/hg (normal rate) or 400g ai/hg (exaggerate rate: for metabolite identification). The number of application was 2 to 3 times for the plants under field growing conditions at the normal rate, 3 times for the plants under field growing conditions at the exaggerate rate, and 5 times for the plants under greenhouse condition. The plants were harvested after a week of the final application.

TRR in the tubers, was 0.0008 to 0.0019 mg/kg and 0.0165 to 0.0217 mg/kg for the samples of normal rate and exaggerate rate, respectively. Cyazofamid was <2 μ g/kg, and the polar fraction from extractable residues accounted for 19.7 to 55.6%. Bound residue, accounting for 16.5 to 60.9% TRR, consisted primarily of potato starch.

Since the residue levels in tubers were very low, foliage samples were also analyzed. Cyazofamid accounted for 95.04 to 95.19% TRR, and CCIM which accounted for 1.76 to 2.26% TTR was the largest single metabolite in foliage (Ref. 13).

(5) Plant internal reaction test in grapes

Solution containing Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid was applied the grapevines (variety: Pinot Noir) under field grown conditions at the annual rate of 100 g ai/ha for five times at 21 to 25 days intervals. The grapevines were harvested 44 days after the final application. Grapes were separated into pulp and juice, and further processed to free wine (vin de goutte: prepared by filtering the fermentation samples through nylon bags).

TRR in the fruits were 0.44 to 0.50 mg/kg. In the juice, the pulp, and the rinse the TRR levels were 0.073 to 0.077 mg/kg (15.4 to 16.4% TRR), 0.36 to 0.41 mg/kg (81.6 to 81.7% TRR), 0.009 to 0.0015 mg/kg (2.0 to 2.9% TRR), respectively. Cyazofamid accounted for 56.8 to 57.9%TRR in the pulp, the juice, and the rinse. The main metabolites were the polar natural products (e.g. sugars and plant acid, the same applies hereinafter) and CCIM, each were recovered approximately 10% TRR, and 4.5 to 6.6% TRR, respectively. Other metabolites recovered were 5-CGTC, conjugate of CCIM, CCTS, CCIM-AM, CCBA and HTID. Since recrystallized products were radioactive, it is concluded that Cyazofamid is broken down to compounds that are sufficiently simple to enter the carbon pool of the plant and be incorporated into natural products. In the free wine, Cyazofamid, polar natural products, 5-CGTC, and CCIM were recovered 5.4 to 7.2% TRR, 17.9 to 23.6% TRR, 4.9 to 7.5% TRR, and 28.4% TRR respectively. In the wine, Cyazofamid, polar natural products, CCIM, 5-CGTC, and conjugate of CCIM were recovered 10.2 to 10.9% TRR, 14.3 to 18.9% TRR, 30.4 to 31.1% TRR, 2.5 to 5.6% TRR, 1.5 to 3.7% TRR, respectively. On the basis of simple distillation, it was determined that ethanol accounted for 1.1 to 1.3% TRR in wines. In the foliage, Cyazofamid, polar natural products, and CCIM were recovered 34.2 to 31.1% TRR, 5.5 to 8.9% TRR, and 2.6 to 3.1% TRR, respectively (Ref. 14).

3. Fate in soil

(1) Aerobic soil metabolism

The aerobic soil metabolism of Cyazofamid was studied on a loamy sand soil. Bz-^{14}C-Cyazofamid or

Im-^{14}C-Cyazofamid was applied to loamy sand soil at a fortification level of 0.01 ppm, the rate corresponding 100 g ai/ha. The prepared soil samples from each label were placed in the dark incubation chamber kept under aerobic conditions at 20 ℃ for 59 days.

$^{14}CO_2$ was detected 11.9 to 14.1% TAR by the completion of the study.

The amount of applied dose found in the PES increased in the beginning of the study peaking at Day 15 to 20. This increase was followed by a decreased and subsequent final increase, accounting for 47.6 to 50.4% of TAR. The main degradates were isolated and identified as CCIM, CCIM-AM and CTCA. CCIM reached a maximum of 14.9 to 16.3% TAR at 5 days. CCIM-AM reached a maximum of 11.0% TAR at Day 26 (Bz-^{14}C-Cyazofamid), and 13.2% TAR at Day 15 (Im-^{14}C-Cyazofamid). CTCA peaked on Day 44 at 9.2 to 9.8% TAR. At Day 59,CCIM, CCIM-AM, and CTCA declined to 3.9 to 4.7%, 4.9 to 8.9% TAR, and 7.3 to 8.4% TAR, respectively. The DT_{50} was ≦5 days, and the DT_{90} ranged from 33 to 44 days.

Cyazofamid degraded rapidly in aerobic soil. Cyazofamid was covalently bound to organic matter after degraded to the major degradates such as CCIM and CTCA. Cyazofamid could be degraded to CO_2 (Ref. 15).

(2) Anaerobic aquatic soil metabolism

The anaerobic aquatic soil metabolism of Cyazofamid was studied on a sandy loam soil. Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid was applied to sandy loam soil, flooded with water, at fortification level of 100 ppm, corresponding 100 g ai/ha each. The soils were maintained under anaerobic conditions at 20 ℃ in the dark, and incubated for 360 days.

The amount of CO_2 released by the Day 360 accounted for 2.9 to 3.4% TAR.

By Day 360, the majority (80 to 83%TAR) was bind. The major degrades were CCIM, CCIM-AM, and CTCA. After the application, CCIM, CCIM-AM, and CTCA reached its maximum of 21 to 27% TAR at Day 7, 10.3 to 14.1% TAR at Day 7, and 18.9 to 21.3% TAR at Day 56, respectively. But they dropped to 0.5 to 1.0% TAR, 1.6 to 2.1% TAR, and 10.8 to 12.1% TAR by Day 360. The DT_{50} and DT_{90} for Cyazofamid were 4.75 to 6.8 days, and 28.0 to 37.6 days.

Cyazofamid could be degraded rapidly in aquatic soil under anaerobic conditions, and Cyazofamid was covalently bound to organic matter after degraded to the major degradates such as CCIM and CTCA. Cyazofamid could be degraded to CO_2(Ref. 16).

(3) Soil adsorption (1)

The adsorption properties of Cyazofamid were investigated on four different domestic soils (sandy loam, clay loam, clay, and sandy clay).

The adsorption coefficient, Kd, ranged form 4.92 to 15.4, and the adsorption coefficient related to organic carbon, K'oc, ranged form 375-615 (Ref. 17).

(4) Soil adsorption (2)

The adsorption properties of Cyazofamid were examined on four different overseas soils (loamy sand (US), sandy loam (UK, pH 7.6), sandy loam (UK, pH 6.9), sand (Germany)).

The adsorption coefficient, Kd, ranged from 4.14 to 87.0, and the adsorption coefficient related to organic carbon, K'oc, ranged from $6.57x10^2$ to $2.90x10^3$ (Ref. 18).

(5) Photochemical degradation on soil

The photolysis of Bz-^{14}C-Cyazofamid and Im-^{14}C-Cyazofamid was studied at a concentration of approximately 0.1 ppm on a loamy sand soil (UK).. The soil sample of a uniform depth of approximately 3 mm was exposed to xenon arc lump with filters to cut the radiation below 290 nm for an equivalent of a twelve hour light/twelve hour dark cycle for 30 days at a temperature of 20±3 ℃.

The major degrades were CCIM and CCBA. The formation of CCIM was rapid in both the dark control and light-exposed samples. However, the conversion to CCBA was rapid under darkness. The DT_{50} for Cyazofamid ranged form 93 to 104 hours for light-exposed samples, from 95 to 113 hours for dark control samples, and the DT_{90} for Cyazofamid ranged from 310 to 345 hours for light-exposed samples, and from 315 to 376 hours for dark control samples. It could be concluded that photolysis did not accelerate the soil degradation of Cyazofamid as observed in the aqueous photolysis study (Ref. 19).

4. Fate in water

(1) Hydrolysis

Bz-^{14}C-Cyazofamid or IM-^{14}C-Cyazofamid was added to sterile buffered solutions at pH 4, 5, 7 and 9. The concentration of each Cyazofamid was approximately 70 μ g/L. These solutions were maintained in the dark at at 25 ℃ for 30 days.

At pH 4, 5, and 7 at 25℃, the main product was CCIM. At pH 9, other than CCIM, some further reaction occurred CCIM-AM. After 30 days, Cyazofamid, CCIM and CCIM-AM (pH9 only) were recovered 14 to 21% TAR, 74 to 83% TAR, and 9 to 10% TAR, respectively. The DT_{90} for Cyazofamid was from 10.6 to 13.3 days (Ref. 20).

(2) Aqueous photolysis (distilled water, natural water)

Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid was added to distilled water or unsterilized natural water (Lake Biwa, Hino River). The concentration of each Cyazofamid was approximately 70 μ g/L. These solutions were placed within the area illuminated by the xenon arc lamp with filter (wave length: 290 to 800 nm, 646 W/m² (measured wavelength of 300-800 nm)) at 21±3 ℃ for an equivalent of a 12 hours/ 12 hour dark cycle for .

Cyazofamid broke down slowly, and after one day had reduced by 90%. Cyazofamid broke down rapidly for light-exposed samples And degraded completely. The half-lives ranged form 3.7 to 5.0 minutes. Major metabolites were CCIM, CCTS, CDTS and HTID. CCTS accounted for approximately 40% TAR after 10 to minutes, and declined to 2 to 3% TAR after 24 hours. CCIM accounted for 40 to 45% TAR after 20 to 60 minutes, and it declined to 2 to 25% TAR after 24 hours. CDTS and HTID increased gradually, and reached 3.9 to 14.9% TAR and 11.5 to 18.3% TAR after 24 hours, respectively. After 24 hours, further degradation occurred to yield polar metabolites were accounting for 55 to 61% TAR for the Bz-^{14}C-Cyazofamid samples, and accounting for 28 to 42% TAR for the Im-^{14}C-Cyazofamid treatment samples. The Loss of radioactivity in the Im-^{14}C-Cyazofamid samples could be attributed to the production of CO_2 (Ref. 21).

(3) Aqueous photolysis (buffered solution at pH 5)

Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid was added to sterile buffered solution at pH 5. The concentration of each test substances was approximately 70 μ g/L. These solutions were placed within the area illuminated by the xenon arc lamp (wavelength: excluding wavelengths under 290 nm, 12.0 W/m² (measured wavelength 290-398 nm)) at 25±2℃ for 30 days for Bz-^{14}C-Cyazofamid or for 36 days for Im-^{14}C-Cyazofamid.

Cyazofamid degraded rapidly, and the half-lives of Cyazofamid ranged from 28 to 34 minutes. The major degrades were CCIM, CCTS and HTID. The half-lives of CCIM, CCTS, and HTID ranged from 20.7 to 25.6 days, from 2.1 to 2.3 days, and from 41.6 to 46.1 days, respectively (Ref. 22).

5. Mobility in soil

(1) Aged residue leaching study

Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid was dosed on a loamy sand soil at a rate of 100 g ai/ha and aged aerobically for 90 hours. The dosed soil was added to a top of soil column of 30 cm, and was irrigated with 0.01 M $CaCl_2$ over a 48 hours period, an equivalent of 200 mm of rainfall over 2 days(181 ml/2 times per day).

Approximately 0.8% TAR was present in the leachate following elution of the soil column. A majority (86.6 – 90.7% TAR) of the uneluted radioactivity was on the top 0 - 5 cm section of the column, and very little radioactivity was found in lower column sections (< 4% TAR). The major residues in the top 0 - 5 cm section of the column were Cyazofamid, CCIM and CCIM-AM, accounting for 39.8 to 43.2% TAR, 22.3 to 28.4% TAR and 10.8 to 12.0% TAR, respectively (Ref. 23).

(2) Parent column leaching study

Bz-^{14}C-Cyazofamid or Im-^{14}C-Cyazofamid were applied on 4 soils (loamy sand (US), sandy loam, loamy sand, and sand (Germany)) at a rate of 100 g ai/ha. The dosed soil was added to a top of soil column of 30 cm, and was irrigated with 0.01 M $CaCl_2$ over a 48 hours period, an equivalent of 200 mm of rainfall over 2 days (181 ml/2 times per day).

The majority of the radioactive residues were found in the column soil, accounting for 84.7 to 95.0% TAR. Approximately 0.1 to 0.4% was present in the leachate following elution of the soil column. Approximately 81.9% to 93.5% TAR was present in the top 0 to 5 cm section of the column, and very little radioactivity was found in lower column sections (< 6 %TAR). The major residues in the top 0 to 5 cm section of the column were Cyazofamid, CCIM and CCIM-AM, accounting for the ratio of radioactivity of all the extractive from this soil, 45.9 to 72.3%, 11.0 to 41.3% and nd to 8.5%, respectively (Ref. 24).

6. Crop residue test

Field trials were performed on Cyazofamid and CCIM on cucumbers, melons, tomatoes, potatoes, grapes, nappa cabbage, onions, wheat, green peppers, watermelon, cabbage, komatsuna (Japanese mustard spinach) and spinach. The results are summarized in table 1. The highest mean Cyazofamid residue was 21.8 mg/kg at 1-day PHI on spinach. At the 3-day and 7-day PHI, the residue dissipated to 16.3 mg/kg and 12.7 mg/kg, respectively. CCIM residues was 1 – 2% of Cyazofamid on spinach, and on other commodities, the residues was non-detected or low level (Ref. 25 to 28).

Table 1 Crop residue test results

Crop name (Parts analyzed) Year	No. of fields	Amount used (g ai/ha)	Applications (times)	PHI (days)	Residues (mg/kg)			
					Cyazofamid		CCIM	
					Highest	Average	Highest	Average
Cucumbers (greenhouse) (fruit) 1998	2	188	4	1 3 7	0.23 0.20 0.07	0.15 0.10 0.04*	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01
Melons (greenhouse) (fruit) 1998	2	188	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
Tomatoes (greenhouse) (fruit) 1998	2	188	4	1 3 7	0.53 0.48 0.43	0.34 0.31 0.26	0.01 0.01 0.01	0.01* 0.01* 0.01*
Potatoes (open field) (tubers) 1998	2	188	4	7 14 21	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01
Large grapes (greenhouse) (fruit) 1998	2	282	3	14 21 28	1.27 1.13 1.19	0.82 0.78 0.65	0.01 0.01 0.01	0.01* 0.01* 0.01*
Small grapes (greenhouse) (fruit) 1998	2	282	3	14 21 28	6.28 6.49 5.97	3.46 3.66 3.03	0.07 0.08 0.07	0.04 0.03 0.03
Nappa cabbage (open field) (tubers) 2000	2	0.00293 g ai/ha ＋141 g ai/ha	5	14 21 28	0.25 0.09 0.08	0.12* 0.05* 0.04*	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01
Onions (open field) (bulbs) 2000	2	188	4	7 14 21	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01
Wheat (open field)	4	94～106	3	117 187 239	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01	<0.01 <0.01 <0.01

(crude wheat) 2001 2002				244	<0.01	<0.01	<0.01	<0.01
Green pepper (open filed) (fruit) 2001	2	94	4	1 3 7	0.34 0.23 0.14	0.26 0.19 0.11	0.01 0.01 <0.01	0.01* 0.01* <0.01
Watermelon (fruit) 2001	2	188～ 205	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
Cabbage (greenhouse) (tubers) 2001	2	0.0293 g ai/ha	1	75 97	<0.01 <0.01	<0.01 <0.01	<0.01 <0.01	<0.01 <0.01
Komatsuna (greenhouse) (tubers) 2002	2	47~71	3	1 3 7	12.3 9.26 7.64	7.73 6.04 4.33*	0.14 0.15 0.18	0.07 0.06* 0.06*
Spinach (open field) (tubers) 2002	2	64~71	3	1 3 7	21.8 16.3 12.7	12.9 9.74 9.18	0.50 0.46 0.40	0.21 0.17 0.15

ai: Active ingredient, PHI: Pre-harvest interval

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

·Formulation was flowable doses only.

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

· The analysis values for metabolite CCIM were expressed in terms of Cyazofamid. Cyazofamid / metabolite (CCIM) = 1.49 was used as conversion factor.

Based on the result of residual test in crops, the estimated Cyazofamid intakes through domestically cultivated agricultural products are shown in table 2. The estimated amounts were calculated based on the assumption that Cyazofamid was applied to all of the applicable croups under conditions giving the highest residual values of Cyazofamid among the applied method, and that processing or cooking of the crops would not affect the amount of residual pesticides.

Table 2 Estimated amount of Cyazofamid exposure through foods (unit: μg/person/day)

Crop name	residue (mg/kg)	National avg.	Children (ages 1 to 6)	Expectant mothers	Elderly (ages 65+)

		ff	intake	ff	intake	ff	intake	ff	intake
Cucumbers	0.15	16.3	2.4	8.2	1.2	10.1	1.5	16.6	2.5
Tomatoes	0.34	24.3	8.3	16.9	5.7	24.5	8.3	18.9	6.4
Grapes	3.46	5.8	20.1	4.4	15.2	1.6	5.5	3.8	13.1
Nappa cabbage	0.12	29.4	3.5	10.3	1.2	21.9	2.6	29.9	3.6
Green peppers	0.26	4.4	1.1	2.0	0.5	1.9	0.5	3.7	1.0
Mustards	6.04	4.3	26.0	2.0	12.1	1.6	9.7	4.3	26.0
Spinach	9.74	18.7	182.1	10.1	98.4	17.4	169.5	21.7	211.4
Total			243.5		134.3		197.6		264.0

· The residual values listed here are the maximum values among the averages for individual test groups treated with the compound over the various periods and frequencies registered (see Table 1).

· ”ff”: Agricultural product comsuptions (g/person/day) based on the results of the National Nutrition Surveys in 1998 to 2000 (Refs. 29 to 31)

· ”Intake”: Estimated intakes (μg/person/day) of Cyazofamid calculated from the residual values and agricultural product consumptions.

· The predicted intake for “grapes” was calculated using the higher residual value for “small grapes” of both residual values for “small grapes” and “large grapes”, since the consumptions of “grapes” are covering both of “large grapes and “small grapes”.

· The predicted intake for melons, potatoes, onions, wheat, watermelons and cabbage were not calculated, since all the data were below the detection limit

7. Residues in soils

Residual values of Cyazofamid and its degradates in soils were studied (both in the vessel and the field) using gray volcanic ash black soil clay loam and alluvial fine-grained gray low-lying gray-brown type loam. The calculated half-lives under the condition are shown in table 3. The estimated half-life of Cyazofamid alone was approximately 5 to 8 days for the vessel, and approximately 3 to 6 days in for the field. The estimated half-life of Cyazofamid and its degradates was approximately 8 to 26 days in the vessel, and approximately 7 to 14 days in the field (Ref. 32).

Table 3 Results of residual study in soil (estimated half-lives)

Test	Soil	Concentration	Estimated half-lives	
			Cyazofamid	Cyazofamid and degarades*
Vessel	Gray volcanic ash black soil clay loam	Pure quality 0.2 mg/kg dry dirt	5 days	8 days
	Alluvial fine-grained gray low-lying gray-brown type loam		8 days	26 days
Field	Gray volcanic ash black soil clay loam	Water dispersable powder 752 g ai/ha	6 days	14 days
	Alluvial fine-grained gray low-lying gray-brown type loam		3 days	7 days

*:CCIM, CCIM-AM, CTCA

8. Acute toxicity test

(1) Acute toxicity

Acute oral toxicity tests were studied using SD rats and CD-1 mice, acute dermal toxicity were studied using SD rats, and acute inhalation toxicity were studied using SD rats. The acute oral $LD_{50}$for rats and mice were > 5000 mg/kg bw in male and female. The acute dermal LD_{50} was > 2000 mg/kg bw in male and female rats. The acute inhalation $LC_{50}$for rats was > 5.5 mg/L in male and female.

Acute oral toxicities of metabolites CCIM, CCIM-AM, and CTCA were studied using SD rats. The acute oral LD_{50} s of metabolites CCIM, CCIM-AM, and CTCA for rats were 324 mg/kg bw in male, and 443 mg/kg bw in female, > 3000mg/kg bw in male and female, 2947 mg/kg bw in male, and 1863 mg/kg bw in female, respectively (Ref. 33-39).

(2) Acute neurotoxicity

SD rats (groups of 10 males and 10 females) were administered Cyazofamid, technical grade at 0, 80, 400, 2000 mg/kg bw by single oral gavage. The mean landing foot spread for females from the 400-mg/kg bw group was statistically greater than the controls. The difference was not considered treatment related because the mean foot spread for the 400-mg/kg bw group was higher than the control group before treatment. No treatment-related effect was observed in this study.

The NOAEL for the general toxicity, neurobehavioral effects, and neuropathological effects was the highest dose treated, 2000 mg/kg bw/day for male and female rats (Ref. 40).

9. Skin and eye irritation, and skin sensitization

Cyazofamid displayed a mild irritation of the eye and the skin in white New Zealand rabbits, a. Weak stimulus of the eyes and an extremely low level of stimulus of the skin were noted (Ref 41-42).

Skin sensitization potential was assessed in guinea pigs by the Maximization method. No skin sensitization was observed (Ref. 43).

10. Subchronic toxicity

(1) Subchronic toxicity study for 90 days in rats

Fischer rats (groups of 12 males and 12 females) were fed diet containing Cyazofamid, technical grade at 0, 10, 50, 500, 5000 ppm for male or 0, 50, 500, 5000, 20000 ppm for female.

An increase in the relative liver weight in the highest-dose female rats, increases in urine protein, urine volume, chlorine plasma, and cases of appearances of basophilic renal tubular, and decreases in total cholesterol, and triglyceride in the highest-dose male rats. An increase relative kidney weight was observed in female rats administered 5000 ppm.

The NOAEL would be 500 ppm (29.51 mg/kg bw/day for males, 33.32 mg/kg bw/day for females) (Ref. 44).

(2) Subchronic toxicity study for 90 days in dogs

Beagle dogs (group of 4 males and 4 females) were administered Cyazofamid by capsules, technical

grade at 0, 4, 200, or 1000 mg/kg bw/day for 90 days.

No treatment-related effects was observed for physical observations, body weight gain, food consumption, clinical pathology, ophthalmology, gross necropsy findings, organ weights, or histopathology findings in any treatment groups.

The highest dose administered 1000 mg/kg bw/day was the NOAEL for male and female dogs (Ref. 45).

11. Chronic toxicity/carcinogenicity study

(1) Chronic toxicity study for 1 year in dogs

Beagle dogs (groups of 6 males and 6 females) were administered Cyazofamid by capsules, technical grade at 0, 4, 200, 1000 mg/kg bw/day for one year.

Although a decrease in relative spleen weight was observed in the highest-dosed males, the histological evaluation of the spleen did not suggest that there were any test material–related effects on the spleen.

No treatment-related effect was observed.

The NOAEL would be 1000 mg/kg bw/day for both male and female (Ref. 46, 47).

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

Fischer rats (groups of 50 males and 10 females, interim sacrifice: 10 males and 10 females chose arbitrary 3 times from 35 males and 35 females of satellite groups) are fed diet containing Cyazofamid, technical grade at 0, 10, 50, 500, 5000 ppm for male, and 0, 50, 500, 5000, 20000 ppm for female.

Weight gain suppression, a decrease in RBC count, an increase in urine volume, relative weights of brain, liver and kidney, and cataract incidence were observed in the highest-dosed female. An increase in chlorine plasma, urine volume, and relative weight of kidney and liver, a decrease in total cholesterol were observed in the highest-dosed male. An increase in relative kidney weight was observed in 5000 and 20000 ppm females. No treatment-related histopathological effect was observed. Although the testicular softening observed in all the groups (10/80 cases in the control group, 17/80 to 23/80 cases in the treated groups), there was no histopathological finding corresponding to testicular softening. Therefore, this increase would be contingent.

The NOAEL would be 500 ppm (17.07 mg/kg bw/day for males, 20.24 mg/kg bw/day for females). The compound showed no carcinogenicity (Ref. 48).

(3) Carcinogenicity study for 18 months in mice

ICR mice (groups of 60 males and 60 females) were administered Cyazofamid, technical grade at concentrations of 0, 70, 700, 7000 ppm in the diet.

Although a statistically significantly higher kidney relative weight was observed in the high dose females, there was no histopathological finding or clinical observations of functional change to the kidney. It was, therefore, considered that the higher kidney relative weight in the high dose female mice was not an adverse effect.

The NOAEL would be 7000 ppm (984.9 mg/kg bw/day for males, 1203.4 mg/kg bw/day for females). The compound showed no carcinogenicity (reference 49) .

12. Reproductive/developmental toxicity

(1) Two-generation reproductive toxicity study in rats

SD rats (groups of 30 males and 30 females) were administered Cyazofamid, technical grade at concentrations of 0, 200, 2000, 20000 ppm in the diet.

In parental high dose females, there were probable treatment-related effects on body weight. However, the biological significance of these differences is not clear. The mean body weight of offspring from the 20000 ppm dose group in all litters was lower compared to the control group.

The parental NOAELs would be 20000 ppm for males and (P male: 958.4 mg/kg bw/day, F_1 male: 936.0 mg/kg bw/day), and 2000 ppm for females(P female: 133.9 mg/kg bw/day, F_1 female: 138.0 mg/kg bw/day), The neonatal NOAELs would be 2000 ppm (F_1 male: 94.2 mg/kg bw/day, F_1 female: 133.9 mg/kg bw/day, F_2 male: 89.2 mg/kg bw/day, F_2 female: 138.0 mg/kg bw/day) (Ref. 50).

(2) Developmental toxicity study in rats

SD rats (groups of 25 females) on days 0-19 of gestation were administered Cyazofamid, technical grade at 0, 30, 100, or 1000 mg/kg bw/day via oral gavage.

There were no adverse effects for any groups examined.

The NOAELs for maternal and developmental toxicity would be 1000 mg/kg bw/day, the highest dose level evaluated. No teratogenecity of Cyazofamid was evident (Ref. 51).

(3) Developmental toxicity study in rabbits

White New Zealand rabbits (groups of 24 females) on days 4-28 of gestation were administered Cyazofamid, technical grade at 0, 30, 100, or 1000 mg/kg bw/day via oral gavage.

In dams, at a dose level of 1000 mg/kg bw/day, food consumption from day 4 to day 15 day of gestation was slightly lower than the control group. Consequently, mean daily food consumption over the entire day 4-29 gestation period was comparable to the control group in all treated groups. At this dose, body weight gain at various time points during the treatment period was slightly, not statistically reduced. .This slight decrease in body weight gain for this group is not considered an effect of treatment.

There were no adverse effects of treatment in the fetuses.

The NOAELs would be 1000 mg/kg bw/day for both dams and fetuses. No teratogenecity of Cyazofamid was evident (Ref. 49, 52).

13. Genetic toxicity test

Cyazofamid has been tested in vitro and in vivo following standard protocols (Table 4). It was not mutagenic in DNA repair test and reverse mutation tests in bacteria with and without an exogenous metabolic activation system. Cyazofamid did not induce chromosomal aberration in cultured human lymphoid cells. All genotoxicity tests were negative (Table 4).

Cyazofamid was not genotoxic (reference 53 to 56).

Table 4 Summary of genotoxicity test results (Cyazofamid)

Test systems	Cells/animals	Dose（mg/kg body weight）	Result

in vitro	DNA repair test （+/- S9）	*B. subtilis* H17, M45 strains		Negative
	Bacterial reverse mutation test （+/- S9）	*S. typhimurium* TA98, TA100, TA1535, TA1537 strains, *E.coli* WP2*uvrA*/pKM101 strain		Negative
	Chromosome aberration （+/- S9）	Cultured human lymphocyte cells		Negative
in vivo	Rodent Micronucleus	CD-1 mice (5males and 5females)	0, 500, 1000, 2000	Negative

Note: +/- S9: with/without exogenous metabolic activation.

The metabolites CCIM, CCIM-AM and CTCA, were tested in bacterial reverse tests (Table 5) and were not mutagenic (table 5) (Ref. 57-59).

Table 5 Summary of genotoxicity test results (degradates/metabolites)

tested substance	test	target	Results
CCIM	Bacterial reverse mutation test （+/-S9）	*S.typhimurium* TA98, TA100, TA1535, TA1537 strains, *E.coli* WP2*uvrA* strain	Negative
CCIM-AM	Bacterial reverse mutation test （+/-S9）	*S.typhimurium* TA98, TA100, TA1535, TA1537 strains, *E.coli* WP2*uvrA* strain	Negative
CTCA	Bacterial reverse mutation test （+/-S9）	*S.typhimurium* TA98, TA100, TA1535, TA1537 strains, *E.coli* WP2*uvrA* strain	Negative

Note: +/-S9: with/without exogenous metabolic activation

III. Overall evaluation

Absorption, distribution, metabolism and excretion of Cyazofamid were studied in rats. The whole blood concentration of the compound reached its maximum at 0.25 to 0.5 hours after a single oral administration, and the half-life was 4.4 to 11.6 hours. The major route of excretion for the Low Dose group was urine, and for the High Dose group was feces. 168 hours later, the compound had been distributed to the kidneys. 24 hours later, 90% or more of the dose was excreted in urine and feces. The major metabolites in urine were CCBA, CH_3SO-CCIM, CH_3SO_2-CCIM, and in bile were CCBA.

Plant metabolism of Cyazofamid was studied in tomatoes, potatoes and grapes. Cyazofamid and its metabolites CCIM and CCBA were detected.

Half-lives of Cyazofamid in soils were 5 days or less under aerobic conditions, and 4.75 to 6.8 days under anaerobic conditions. Half-life on soil ranged from 93 to 104 days, and photolysis did not accelerate the soil degradation of Cyazofamid. The adsorption coefficient related to organic carbon, K'oc, ranged from 375 to 6150, indicating that Cyazofamid would be easily adsorbed onto soils to remain on the soil. The major degradates were CCIM, CCIM-AM and CTCA.

Cyazofamid was broke down hydrolytically and accelerated by light exposure.

Field trials were performed on Cyazofamid and CCIM on cucumbers, melons, tomatoes, potatoes, grapes, nappa cabbage, onions, wheat, green peppers, watermelons, cabbage, komatsuna and spinach. The highest mean Cyazofamid residue was 21.8 mg/kg at 1-day PHI on spinach. At 3-day and 7-day PHI on the residue dissipated to 16.3 mg/kg and 12.7 mg/kg, respectively. CCIM residue was 1 to 2% of Cyazofamid in spinach, and on other commodities, the residues were non-detected or low level.

Residual values of Cyazofamid and its degradates in soils were studied using volcanic gray ash black soil clay loam and alluvial fine-grained gray low-lying gray-brown type loam. The calculated half-lives of Cyazofamid was approximately 5 to 8 days for the vessel, and approximately 3 to 6 days for the field.

The acute oral LD_{50} for rats and mice were> 5000 mg/kg bw in male and female. The acute dermal LD_{50} was > 2000 mg/kg bw for male and female rats. The acute inhalation LC_{50} for rats was >5.5 mg/L in male and female. The acute oral LD_{50}s of metabolites CCIM, CCIM-AM and CTCA for rats were 324 mg/kg bw in male, and 443 mg/kg bw in female, > 3000 mg/kg bw in male and female, and 2947 mg/kg bw in male and 1863 mg/kg bw in female.

The NOAELs were29.51 mg/kg bw/day for rats and 1000 mg/kg bw/day for dogs in subchronic toxicity studies.

The NOAELs were 984.9 mg/kg bw/day for mice, 17.07 mg/kg bw/day for rats, and 1000 mg/kg bw/day for dogs in chronic toxicity/carcinogenicity studies. The compound showed no carcinogenicity.

The NOAEL for parental toxicity was 133.9 mg/kg bw/day, and for offspring toxicity, 89.2 mg/kg bw/day. The compound showed no reproductive toxicity.

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 rabbit. Cyazofamid showed no teratogenicity in either rats or rabbits.

Cyazofamid was not mutagenic in DNA repair test and reverse mutation tests in bacteria with and without an exogenous metabolic activation system. Cyazofamid did not induce chromosomal aberration in cultured human lymphoid cells. Cyazofamid was not genotoxic. The metabolites CCIM, CCIM-AM, CTCA, were tested in bacterial reverse test and were not mutagenic.

The NOAELs in the evaluated toxicological studies are shown in Table 6.

Table 6 NOAELs obtained in each test

Species	Evaluating study	NOAELs	Remarks
Mouse	18-month carcinogenicity	male:984.9 mg/kg bw/day female:1203.4 mg/kg bw/day	No carcinogenicity
Rat	90-day subchronic toxicity	male:29.51 mg/kg bw/day female:33.32 mg/kg bw/day	

	24-month chronic toxicity/ carcinogenicity	male:17.07 mg/kg bw/day female:20.24 mg/kg bw/day	No carcinogenicity
	Two-generation reproductive toxicity	Parent P male:958.4 mg/kg bw/day P female:133.9 mg/kg bw/day F_1 male:936.0 mg/kg bw/day F_1 female:138.0 mg/kg bw./day Offspring F_1 male: 94.2 mg/kg bw/day F_1 female:133.9mg/kg bw/day F_2 male: 89.2 mg/kg bw/day F_2 female:138.0 mg/kgbw/day	No reproductive toxicity
	Developmental toxicity	Dams and fetuses: 1000 mg/kg bw/day	No teratogenicity
Rabbit	Developmental toxicity	Dams and fetuses: 1000 mg/kg bw/day	No teratogenicity
Dog	90-day subchronic toxicity test	male:1000 mg/kg bw/day female:1000 mg/kg bw/day	
	12-month chronic toxicity test	male:1000 mg/kg bw/day female:1000 mg/kg bw/day	

Based on the evaluation, the Pesticides Expert Commitee of the Food Safety Commission settled the ADI value of Cyazofamid as:

ADI:	0.17 mg/kg bw/day
（Referred data for ADI）	chronic toxicity/carcinogenicity
Laboratory animal tested:	rat
Duration:	24 months
administration route:	mixed feeds
NOAEL:	17.07 mg/kg bw/day
safety factor:	100
Residue definition for exposure assessment:	Cyazofamid (parent chemical only）

<Appendix 1: Abbreviations for metabolite/degrades>

Abbreviation	Chemical names
CCBA	4-(4-chloro-2-cyanoimidazole-5-yl)benzoic acid
CCIM	4-chloro-5-*p*-tolylimidazole-2-carbonitrile
CCIM-AM	4-chloro-5-*p*-tolylimidazole-2-carboxamide
CCTS	6-(4-chloro-2-cyanoimidazol-5-yl)-*N*,*N*-dimethyl-*m*-toluenesulfonamide
CDTS	2-cyano-*N*,*N*-dimethyl-5-*p*-tolylimidazole-4-sulfonamide

5-CGTC	5-chloro-1-β-D-glucopyranosyl-4-*p*-tolylimidazole-2-carbonitrile
CHCN	4-chloro-5-(4-hydroxymethylphenyl)imidazole-2-carbonitrile
CH_3SO-CCIM	4-chloro-5-[β-(methylsulfinyl)-*p*-tolyl]imidazole-2-carbonitrile
CH_3SO_2-CCIM	4-chloro-5-[β-(methylsulfonyl)-*p*-tolyl]imidazole-2-carbonitrile
CTCA	4-chloro-5-*p*-tolylimidazole-2-carboxylic acid
HTID	5-hydroxy-5-*p*-tolyl-2,4-imidazolidinedion

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