Evaluation Report

BOSCALID

May 19, 2004

Food Safety Commission

Pesticides Expert Committee

(Progress of Evaluation)

August 1, 2002	Registration application submitted
November 17, 2003	The Ministry of Health, Labour and Welfare requests a health risk assessment in line with the establishment of a residue standard.
November 27, 2003	21st meeting of the Food Safety Commission (explanation of MHLW's request outline)
December 24, 2003	4th meeting of the Pesticides Expert Committee
March 22, 2004	Additional references accepted
April 7, 2004	9th meeting of the Pesticides Expert Committee
April 15, 2004	41st meeting of the Food Safety Commission (reporting of the discussion results from the Pesticides Expert Committee meeting)
April 15 to May 12, 2004	Public comments
May 19, 2004	Finalized

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Summary

Boscalid (IUPAC: 2-chloro-*N*-(4’-chlorobiphenyl-2-yl)nicotinamide), belonging to the anilide class of fungicides, was evaluated based on various tests. The acceptable daily intake (ADI) value for the compound has been determined as 0.044 mg/kg bw/day.

The test results used for the evaluation were animal metabolism (rats), plant metabolism (lettuces, grapes, kidney beans), soil degradation, photolysis in water, residues in crops, residues in soils, acute toxicity (rats, mice), subchronic toxicity (mice, rats, dogs), chronic toxicity (rats, dogs), carcinogenicity (mice, rats), two-generation reproductive toxicity (rats), developmental toxicity (rats, rabbits), genotoxicity, etc.

The compound did not show any developmental toxicity or genotoxicity. In the rat carcinogenicity test, thyroid neoplasm was observed in the treated group, but the incidence was not significantly different from that of the control group. The neoplasm was developed through a non-genotoxic mechanism, so the threshold dose might be determined for the implausible carcinogenicity of the compound.

Based on the lowest value among the no observed adverse effect levels (NOAELs), which was 4.4 mg/kg bw/day in the rat chronic toxicity test, the ADI for the compound has been determined as 0.044 mg/kg bw/day with a safety factor of 100.

I. Outline of the Pesticide to be Evaluated

1. Usage

Fungicide

2. Common Name (ISO name)

Boscalid

3. Chemical name

IUPAC name:

2-chloro-*N*-(4'-chlorobiphenyl-2-yl)nicotinamide

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

2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide

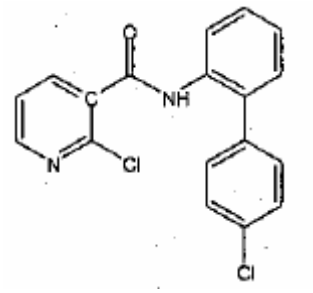
4. Chemical formula

$C_{18}H_{12}Cl_2N_2O$

5. Relative molecular mass

343.21

6. Chemical structure



7. Background of development

Boscalid is a fungicide belonging to the anilide class. The compound is effective against botrytis rot and crown rot by inhibiting the electron transfer of the succinate dehydrogenase complex in the mitochondrial inner membrane. Boscalid has been registered as a fungicide in the United States, Canada, the Republic of Korea, the Federal Republic of Germany, and the United Kingdom.

The compound was applied for registration according to the Agricultural Chemicals Regulation Law by BASF Japan Ltd. (hereinafter "The Applicant") in August 2002. (Ref. 1)

II. Summary of the Tests Results

1. Absorption, distribution, metabolism, and excretion

The study was conducted using Boscalid homogeneously labeled with ^{14}C at the diphenyl ring (hereinafter "Dip-^{14}C-Boscalid") and Boscalid labeled with ^{14}C at position 3 on the pyridine ring (hereinafter "Pyr-^{14}C -Boscalid"). (The procedure was also applied to all other metabolism tests.)

(1) Metabolism in rats (single dose)

The distribution was examined in Wistar rats with a single oral dose of 50 mg/kg bw (hereinafter "Dip Low") or 500 mg/kg bw (hereinafter "Dip High") of Dip-^{14}C Boscalid, and 500 mg/kg bw (hereinafter "Pyr High") of Pyr-^{14}C-Boscalid.

In the treatment with Dip Low, rats eliminated from 15.7 to 16.4% of the dosage in the urine and from 79.3 to 84.9% in the feces by 168 hours. Rats in Dip High and Pyr High excreted from 2.73 to 5.21% of the dosage in the urine and from 89.6 to 97.4% in the feces by 168 hours, respectively. In Dip Low and Dip High, from 39.3 to 39.9% and from 10.7 to 11.9% of the dosage were detected in the bile by 48 hours, respectively. Elimination through the breath was not detected.

The plasma radioactivity concentration reached the maximum at 8 hours after administration with Dip Low and Dip High, with the concentration ranging from 1.54 to 1.58 μg eq/g and from 3.77 to 4.46 μg eq/g, respectively; the half-lives were from 30.1 to 41.7 hours and from 20.2 to 27.4 hours, respectively.

In Dip Low, high tissue concentrations were found in the thyroid (from 0.20 to 0.23 μg eq/g) and in the liver (from 0.10 to 0.13 μg eq/g) at 168 hours after administration. In Dip High and Pyr High, tissue concentrations were high in the thyroid, bone marrow, liver, kidney, and adrenal gland, which were from 1.21 to 3.03 μg eq/g, from 0.66 to 2.09 μg eq/g, from 0.30 to 0.90 μg eq/g, from 0.27 to 0.50 μg eq/g, and from 0.20 to 0.37 μg eq/g, respectively.

The amounts of Boscalid detected in the urine by 48 hours after administration were 0.16% or less. The main metabolites were F01[1] (a metabolite hydroxylated at position 4 on the phenyl ring), F02 (a glucuronic acid conjugate), and F48 (an S-glucuronic acid conjugate), which accounted for from 9.58 to 15.8%, from 2.95 to 4.33%, and from 1.10 to 2.28% of the dosage, respectively, in rats treated with Dip Low, and from 0.51 to 2.93%, from 0.08 to 2.74%, and from 0.03 to 0.44%, respectively, with Dip High and Pyr High. The amounts of Boscalid detected in the feces were from 30.5 to 41.0% of the dosage with Dip Low and from 68.3 to 80.4% of the dosage with Dip High and Pyr High. The main metabolites detected in the feces were F01, F06 (an SH compound), F20 (an S-methyl compound), and F48, which were from 19.0 to 21.8%, from 4.88 to 7.57%, from 3.79 to 6.21%, and 2.84% or less of the dosage, respectively, with Dip Low, and from 4.10 to 5.50%, from 3.00 to 7.59%, undetectable, and 0.63% or less of the dosage, respectively, with Dip High and Pyr

High. Boscalid was not detected in the bile, and the main metabolites detected were F02 and F05 (a cysteine conjugate), at amounts of 19.3 and 14.2%, respectively, with Dip Low, and 4.78 and 3.59%, respectively, with Dip High.

The amounts of Boscalid detected in the liver and kidney by 8 hours after administration were from 0.01 to 0.03% of the dosage. The main metabolites detected in the liver were F02, F43 (a glutathione conjugate), and F46 (a glutathione conjugate), which were from 0.20 to 0.38%, from 0.14 to 0.26%, and from 0.03 to 0.24% of the dosage, respectively. The amount of each metabolite detected in the kidney was 0.06% or less of the dosage.

The main metabolic pathway of Boscalid in rats could be the hydroxylation of the diphenyl ring (F1) and glutathione conjugation (F46), or the substitution of the thiol moiety in glutathione for the chlorine atom on the pyridine ring (F43). (Refs. 2-3)

[1] See Appendix 1 for the abbreviations for the metabolites.

(2) Metabolism in rats (repeated dose)

The distribution of Boscalid was examined in Wistar rats with a once-daily gavage administration of 500 mg/kg bw/day of non-labeled compound for 14 or 28 days followed by a single oral dose of the same dosage of Dip-^{14}C-Boscalid.

Rats excreted from 8.61 to 14.8% of the dosage in the urine and from 67.7 to 75.7% of the dosage in the feces by 48 hours. The main metabolites detected in the urine were F01 (from 0.77 to 2.89% of the dosage) and F02 (from 4.29 to 10.8% of the dosage). In the feces, the amounts of Boscalid detected were from 29.4 to 38.0%, and the main metabolite was F01, which accounted for from 12.9 to 24.5% of the dosage.

The metabolism in rats with repeated doses did not differ significantly from that with the single dose. (Ref. 4)

2. Plant metabolism

(1) Lettuces

Seven hundred g a.i./ha of Dip-^{14}C-Boscalid and Pyr-^{14}C-Boscalid were applied to pot-grown lettuce (cultivar: Nadine) three times (i.e., once on the 8th day after transplanting and subsequently twice at 14-day intervals). The lettuce leaves were sampled 18 days after the last application.

The total residual radioactivity (TRR) was in the range of 17.5 to 17.6 mg/kg, and almost all of the radioactive substances extracted (99.3% of TRR) was Boscalid.

The compound is considered to metabolize in lettuce only to a small degree. (Ref. 5)

(2) Grapes

Eight hundred g a.i./ha of Dip-^{14}C-Boscalid and Pyr-^{14}C-Boscalid were applied to grapes (cultivar: Mueller-Thurgau) three times. The grape bunches and leaves were sampled 45 days after the last application.

TRRs in the fruits, peduncles, and leaves were in the range of 1.18 to 2.07 mg/kg, 12.4 to 19.6 mg/kg, and 43.7 to 63.4 mg/kg, respectively. Boscalid was detected in the range of 92.2 to 92.7%, 96.4 to 97.6%, and 95.6 to 96.1% of TRR on the fruits, peduncles, and leaves, respectively.

Thus, the compound is considered to metabolize in grapes only to a small degree. (Ref. 6)

(3) Kidney beans

Five hundred g a.i./ha of Dip-^{14}C-Boscalid and Pyr-^{14}C-Boscalid were applied to kidney beans (cultivar: Hild's Maxi) three times (i.e., once in the early flowering period and subsequently twice at intervals of 8 to 10 days). On the days from 14 to 15 (prematurity stage) and from 51 to 53 (maturity stage) after the last application, the beans, pods, and foliage were sampled.

TRRs in the beans, pods, and foliage were in the range of 0.067 to 0.198 mg/kg, 0.108 to 0.903 mg/kg, and 17.0 to 66.2 mg/kg in the prematurity stage, respectively, and 0.126 to 0.205 mg/kg, 1.37 to 6.12 mg/kg, and 93.8 to 127 mg/kg in the maturity stage, respectively. Boscalid detected in the beans, pods, and foliage ranged from 64.9 to 87.5%, 87.0 to 96.7%, and 98.4 to 98.6% of TRR in the prematurity stage, respectively, and 36.9 to 72.0%, 79.7 to 94.5%, and 93.6 to 95.1% of TRR in the maturity stage, respectively. The metabolite F47 (chloronicotinic acid) was identified in plants treated with Pyr-^{14}C-Boscalid, accounting for 9.97 and 2.15% of TRR in premature beans and pods, respectively, and for 1.72 and 1.11% of TRR on mature beans and pods, respectively. The metabolite F62 (chlorophenylaminobenzene) was detected at 0.50% of TRR on the mature foliage in plants treated with Dip-^{14}C-Boscalid.

Boscalid would not be extensively metabolized in kidney beans, and the main metabolic pathway would be the cleavage of the amide linkage between the diphenyl and the pyridine rings. There would be pathways of hydroxylation of the diphenyl or the pyridine ring and the subsequent conjugation. (Ref. 7)

3. Fate in soil

(1) Degradation in aerobic soil

Dip-^{14}C-Boscalid and Pyr-14C-Boscalid were applied to sandy loam soil (Arrow) at 0.993 and 1.02 mg/kg, respectively. The test was carried out after 364 days of incubation at 20°C in the dark, under the aerobic soil condition.

In soils treated with Dip-^{14}C-Boscalid, non-extracted radioactivity was in 62.7% of the total administrative radioactivity (TAR) by 266 days and 60.0% by 364 days. The cumulative amount of carbon dioxide was 15.5% of TAR. In soils treated with Pyr-^{14}C-Boscalid, non-extracted radioactivity was 50.1% of TAR by 364 days, and the cumulative amount of carbon dioxide was 25.4%.

Extracted residual radioactivity (ERR) gradually decreased to the range of 17.8 to 18.4% by 364 days. Boscalid was detected in the range of 16.7 to 17.3% of TAR, and degraded products, F49 and F50, were detected in the range of 0.1 to 0.2% and 0.1% or less, respectively. The 50% and 90% degradation periods of Boscalid were 108 days and 360 days, respectively.

Boscalid would be slowly degraded in the aerobic soil, and the main degradation pathway would be hydroxylation of the pyridine ring (F50) and hydrolysis at the chloride atom on the pyridine ring (F49). (Ref. 8)

(2) Degradation in anaerobic soil

Dip-^{14}C-Boscalid was applied to flooded, anaerobic sandy loam soil at 1 and 30 mg/kg, and Pyr-^{14}C-Boscalid was applied at 1 mg/kg. The test was carried out after 120 days of incubation at 20°C in the dark.

In the soils treated with 1 mg/kg of Dip-^{14}C-Boscalid and Pyr-^{14}C-Boscalid, ERR gradually decreased to the range of 73.9 to 84.2% by 120 days. Boscalid was detected in the range of 73.6 to 77.0% of TAR. Degraded product F47 was detected at 6.7% in the soils treated with Pyr-^{14}C-Boscalid. In the soils treated with 30 mg/kg of Dip-^{14}C-Boscalid, F08 (dechlorinated compound of pyridine ring), F49, F50, etc., were detected. The amount of carbon dioxide generated reached from 0.1 to 0.4% by 120 days. The half-life of Boscalid was in the range of 261 to 345 days.

Boscalid would not be extensively degraded in the anaerobic soil, and the main degradation pathway would be the cleavage of the amide linkage between the diphenyl and the pyridine rings. The minor pathway through hydroxylation of the pyridine ring (F50) or dechlorination (F08) and hydroxylation (F49) of the chloro moiety on the pyridine ring was suggested. (Refs. 9-10)

(3) Photolysis at soil surface

The moisture of sandy loam soil was adjusted to 40% of its maximum water capacity, and Pyr-^{14}C-Boscalid was applied to the soil at 4.6 μg/g dry soil. Then, the soil was exposed to Xenon light (3 mW/cm^2 at 290 nm wavelength) at 22±1°C for 15 days to study photolytic degradation.

After 15 days of exposure, 90.6% of the treated Boscalid remained, and the amount of carbon dioxide generated was 0.2% of TAR. The half-life of Boscalid was 135 days. Degradation of the

compound was not observed under the dark conditions.

The photolysis of Boscalid would progress slowly at the soil surface and accelerate by light. (Ref. 11)

(4) Adsorption to soils

An adsorption test in Japanese soil was made using Light-colored Andosol (upland field soil), Gray lowland soil (upland field soil), Gray lowland soil (paddy soil), and Sand-dune Regosol (upland field soil).

The adsorption coefficient K^{ads} was in the range of 15.5 to 37.2, and the adsorption coefficient K^{ads}_{oc} based on organic carbon content was in the range of 6.72×10^2 to 1.76×10^3. (Ref. 12)

4. Test of the fate in water

(1) Hydrolysis in water

Dip-^{14}C-Boscalid was dissolved in buffer solutions of pH 4.0, 7.0, and 9.0 to prepare Boscalid solutions of 3 mg/L. The solutions were incubated at 50°C for 5 days or at 25°C for 30 days.

Amounts of radioactivity detected in the buffer solutions incubated at 50°C for 5 days or at 25°C for 30 days were in the range of 100.3 to 101.1% and 99.4 to 99.5% of TAR. Boscalid was hardly hydrolyzed, so its half-life could not be calculated. (Ref. 13)

(2) Photolysis in water (buffer solution and lake water)

Pyr-^{14}C-Boscalid was dissolved in sterilized acetate buffer solution of pH 5.0 and in non-sterilized lake water to prepare Boscalid solutions of about 3 and 2.33 μg/mL, respectively. The buffer solution and the lake water were exposed to Xenon light (3 mW/cm^2 measured in the range of 315-400 nm wavelength) at 22±1°C for 15 and 8 days, respectively, to study photolytic degradation.

The amounts of radioactivity detected in the buffer solution on day 15 and in the lake water on day 8 were both 94.4% of TAR. The half-life of the compound could not be calculated. (Refs. 14-15)

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

Boscalid was dissolved in sterilized distilled water and river water at about 1 mg/L. The distilled water and the river water were exposed to Xenon light (609 and 612 W/m^2, respectively, in the range of 290-800 nm wavelength) from 24.6 to 24.8°C and from 24.9 to 26.6°C, respectively, for 120 hours to study photolytic degradation.

The amounts of radioactivity remaining in the distilled water and the river water after 120

hours were 0.996 and 0.944 mg/L, respectively. The half-life of the compound could not be calculated. (Ref. 16)

(4) Photolytic fate in water (under the natural condition)

In the bottom sediment phase, Dip-^{14}C-Boscalid was dissolved in non-sterilized natural water to prepare a Boscalid solution of 700 g a.i./ha (i.e., 460 μg a.i./2L test system). The solution was incubated under exposure to sunlight for 120 days.

The amount of radioactivity in the aqueous phase gradually decreased to 22.0% of TAR after 120 days. Meanwhile, the amount of radioactivity in the bottom sediment phase reached its maximum at 80.3% of TAR by day 103 and then decreased to 51.2% of TAR by day 120. The material balance loss was 26.8% by day 120, which was probably due to CO_2 generation.

Among the extracted radioactive substances, 19.2 and 26.5% of Boscalid were detected in the aqueous phase and the bottom sediment phase by day 120, respectively. Degraded product F64 (*p*-chlorobenzoic acid) was identified in the aqueous phase and the amount detected was 9.42% of TAR at the maximum.

The major pathway for the photolysis of Boscalid in water would involve its degradation into *p*-chlorobenzoic acid and unknown degradates, conversion into inorganic forms, etc. (Ref. 17)

5. Residuals in crops

Grapes, strawberries, tomatoes, eggplants, cucumbers, onions, red beans, kidney beans, apples, pears, and cherries were used for Boscalid (parent compound) residual tests in crops. As indicated by the results shown in Table 1, the highest residual value detected was 7.39 mg/kg on strawberries, which were collected 1 day after the last application. The values decreased to 7.00 and 4.46 mg/kg on day 3 and 7, respectively. (Refs. 18-19)

Table 1. Results of Residual Tests in Crops

Crops Year	Number of fields	Formulations	Amount used (g a.i./ha)	Applications (times)	PHI (days)	Residues (mg/kg)	
						Highest	Average
Grape (large-fruit cultivar) 2000	2	DF	1410—1880	3	7 14 21	5.20 4.19 3.85	3.83 3.31 2.96
Strawberry 2000	2	DF	735.6—1175	3	1 3 7	7.39 7.00 4.46	4.22 3.76 2.21

Tomato 2000	2	DF	940	3	1 3 7	1.09 0.561 0.656	0.84 0.50 0.52
Eggplant 2000	2	DF	860.1－ 940	3	1 3 7	0.940 0.647 0.363	0.67 0.46 0.22
Cucumber 2000	2	DF	940－1175	3	1 3 7	2.13 1.06 0.53	1.23 0.72 0.35
Onion 2000	2	DF	705	3	1 7 14	0.070 0.036 0.007	0.022 0.011 0.0053
Red bean (dried bean) 2000	2	DF	705	3	7 14 20	0.138 0.078 0.064	0.122 0.071 0.055
Kidney bean (dried bean) 2000	2	DF	705	3	7 14 21	0.402 0.551 0.685	0.19 0.31 0.41
Kidney bean (dried bean) 2002	2	DF	705	2	21 28 35 45	0.446 0.455 0.288 0.138	0.36 0.36 0.23 0.10
Apple 2000	2	SE	408－425	3	1 7 14	0.579 0.530 0.409	0.39 0.40 0.30
Pear 2000	2	SE	204－272	3	1 7 14	0.569 0.403 0.459	0.44 0.32 0.33
Cherry 2000	2	SE	340	3	1 3 7	1.32 1.31 0.83	0.82 0.78 0.59

a.i.: Active ingredient

PHI: Pre-harvest interval

DF: Dry Flowable

SE: Suspension emulsion (mixture of suspension and emulsion)

*For data including values below the detection limit (<0.01), the average was calculated as 0.01.

Based on the results of the residual tests in crops, the estimated amounts of Boscalid

consumed through domestically cultivated agricultural products are shown in Table 2. The estimated amounts were calculated based on the assumption that Boscalid was applied to all of the applicable crops under conditions that would give the highest residual value of Boscalid among the applied methods, and that processing or cooking of the crops would not affect the amounts of residual pesticides.

Table 2. Estimated Amounts of Boscalid Exposure through Food (unit: μg/person/day)

Crops	Residues (mg/kg)	National average		Infants (ages 1 to 6)		Pregnant women		Elderly (age 65 or above)	
		ff	Consumption	ff	Consumption	ff	Consumption	ff	Consumption
Grapes	3.83	5.8	22.2	4.4	16.9	1.6	6.1	3.8	14.6
Strawberry	4.22	0.3	1.3	0.4	1.7	0.1	0.4	0.3	1.3
Tomato	0.84	24.3	20.4	16.9	14.2	24.5	20.6	18.9	15.9
Eggplant	0.67	4.0	2.7	0.9	0.6	3.3	2.2	5.7	3.8
Cucumber	1.23	16.3	20.0	8.2	10.1	10.1	12.4	16.6	20.4
Onion	0.022	30.3	0.7	18.5	0.4	33.1	0.7	22.6	0.5
Red bean	0.122	1.4	0.6	0.5	0.2	0.1	0.0	2.7	1.1
Kidney bean	0.41								
Apple	0.40	35.3	14.1	36.2	14.5	30.0	12.0	35.6	14.2
Pear	0.44	5.1	2.2	4.4	1.9	5.3	2.3	5.1	2.2
Cherry	0.82	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Totals			85.8		61.5		57.9		75.4

- The residual values listed here are the maximum values among the averages for individual test groups treated with the compound over various periods and frequencies registered (see Table 1).
- "ff": Agricultural product consumptions (g/person/day) based on the results of the National Nutrition Surveys in 1998-2000. (Refs. 20-22)
- "Consumptions": Estimated consumptions (μg/person/day) of Boscalid calculated from residual values and agricultural product consumptions.
- The agricultural product consumptions for red bean and kidney bean were calculated collectively, so the value obtained for kidney bean, which had a higher residual value, was adapted.

6. Residual in soil

Residual values of Boscalid in soils were studied (both in the vessel and in the field) using volcanic ash light clay, sand-dune Regosol, and alluvium clay loam. As shown in Table 3, the assumed half-life of the compound was about 160-285 days in the vessel and about 30-110 days in

the field, respectively. (Ref. 23)

Table 3. Results of Residual Tests in Soils (Assumed half-life)

Type of tests	Kinds of soil	Concentration	Assumed half-life (days)
Vessel	Volcanic ash light clay	Pure form	ca. 270
	Sand-dune Regosol	1.40 mg/kg	ca. 170
	Volcanic ash light clay	Pure form	ca. 285
	Alluvium clay loam	2.80 mg/kg	ca. 160
Field	Volcanic ash light clay	DF	ca. 30
	Sand-dune Regosol	1410 g a.i./ha	ca.110

DF: Dry Flowable

7. Acute toxicity

(1) Acute toxicity test through oral, dermal, and inhalation administrations in rats and mice

The acute toxicity tests of Boscalid, technical grade, were carried out in Wistar rats and ICR mice (oral toxicity only). The Oral LD_{50} was >5000 mg/kg bw in male and female rats and mice, the dermal LD_{50} was >2000 mg/kg bw in male and female rats, and the inhalation LC_{50} was >6.7 mg/L in male and female rats. (Refs. 24-27)

The acute oral LD_{50} of the metabolite F49 was >2000 mg/kg bw in male and female Wistar rats. (Ref. 28)

(2) Acute neurotoxicity test in rats

Acute neurotoxicity was studied in Wistar rats (groups of 10 males and 10 females) with the single gavage administration of Boscalid, technical grade at 0, 500, 1000, or 2000 mg/kg bw.

The compound showed no neurotoxicity in any of the treated groups, although piloerection was observed in a few females at the dose of 2000 mg/kg bw.

The NOAELs for general toxicity would be 2000 mg/kg bw for males and 1000 mg/kg bw for females, and the NOAEL for neurotoxicity would be 2000 mg/kg bw for males and females. (Ref. 29)

8. Skin and eye irritation, and skin sensitization

The test on New Zealand White rabbits revealed no sign of irritation. (Refs. 30-31)

Skin sensitization potential was assessed in guinea pigs by the Maximization method. No skin

sensitization was observed. (Ref. 32)

9. Subchronic toxicity

(1) Subchronic toxicity test for 90 days in rats

Wistar rats (groups of 10 males and 10 females) were fed diets containing Boscalid, technical grade at 0, 100, 500, 2000, 5000, or 15000 ppm, for 90 days.

At 15000 ppm, there were decreases in the blood triglyceride concentration and the relative spleen weight (relative weight against body weight will be described as relative weight hereafter) in males, increases in the relative thyroid weight in males and females, decreases in the prothrombin time and increases in the total protein, globulin and total cholesterol levels in the blood in females. There were increases in relative liver weight and centrilobular hypertrophy of hepatocytes in males and females at 5000 ppm and higher. Also there were increases in the blood calcium, total protein, and albumin levels and decreases in the relative adrenal weight in males, and increases in the blood γ-GTP[2] level and the relative thyroid weight in females. There were increases in the blood γ-GTP level, hypertrophy of the thyroid follicular epithelial cells, and diffuse hyperplasia of the thyroid in males at 2000 ppm and higher.

The NOAEL has been determined to be 500 ppm (34 mg/kg bw/day for males, 40 mg/kg bw/day for females). (Ref. 33)

(2) Subchronic toxicity test for 90 days in mice

C57BL/6 mice (groups of 10 males and 10 females) were fed diets containing Boscalid, technical grade at 0, 150, 1000, 4000, or 8000 ppm, for 90 days.

There were decreases in the blood triglyceride concentration in females at 8000 ppm. There were decreases in the blood levels of total protein, albumin, and globulin and increases in severe fatty change of the hepatocytes in males, and increases in the blood ALT in females at 4000 ppm and higher. There were increases in the absolute liver weight (except for females at the dose of 1000 ppm) and the relative liver weight in male and females at 1000 ppm and higher.

The NOAEL has been determined to be 150 ppm (29 mg/kg bw/day for males, 42 mg/kg bw/day for females). (Ref. 34)

(3) Subchronic toxicity test for 90 days in dogs

Beagle dogs (groups of 5 males and 5 females) were fed diets containing Boscalid, technical grade at 0, 250, 2500, or 25000 ppm, for 90 days.

At 25000 ppm, there were decreases in the body weight, body weight gain, and food consumption in males and females. There were increases in the blood ALP, calcium levels, and the

relative liver weight, and decreases in the blood chlorine level and relative kidney weight in males. There were decreases in RBC and hemoglobin, prolongation of the activated partial thromboplastin time, and increases in the relative thyroid weight in females. At 2500 ppm and higher, there were light brown stool, loose stool, and increases in the blood triglyceride level in males and females, increases in thrombocytes in males, and increases in blood ALP and the relative liver weight in females.

The NOAEL has been determined to be 250 ppm (7.6 mg/kg bw/day for males, 8.1 mg/kg bw/day for females). (Refs. 35-36)

[2] See Appendix 2 for the abbreviations for the test values, etc.

(4) Subchronic neurotoxicity test for 90 days in rats

Wistar rats (groups of 10 males and 10 females) were fed diets containing Boscalid, technical grade at 0, 150, 1500, or 15000 ppm, for 90 days.

The compound showed no neurotoxicity in any of the treated groups.

The NOAEL has been determined to be 15000 ppm (1050.0 mg/kg bw/day for males, 1272.5 mg/kg bw/day for females). (Ref. 37)

10. Chronic toxicity/carcinogenicity study

(1) Chronic toxicity study for 12 months in dogs

Beagle dogs (groups of 5 males and 5 females) were fed diets containing Boscalid, technical grade at 0, 200, 800, 2000, or 20000 ppm, for 12 months.

At 20000 ppm, there were light-brown loose stool and decreases in the blood chlorine level in males and females. There were increases in the blood levels of ALP, total protein, globulin, total cholesterol and relative thyroid weight and decreases in blood ALT in females. At 2000 ppm and higher, there were increases in blood triglyceride in males and females, increases in blood ALP and relative thyroid weight in males, and a suppression of body weight gain and increases in relative liver weight in females. There was no histopathological change due to the administration of the compound.

The NOAEL has been determined to be 800 ppm (21.8 mg/kg bw/day for males, 22.1 mg/kg bw/day for females). (Ref. 38)

(2) Chronic toxicity study for 24 months in rats

Wistar rats (groups of 20 males and 20 females) were fed diets containing Boscalid, technical grade at 0, 100, 500, 2500, or 15000 ppm, for 24 months. At 15000 ppm, the administration was

discontinued and the animals were terminated at 17 months.

At 2500 ppm, there were increases in total protein and globulin, centrilobular hypertrophy of hepatocytes, diffuse hypertrophy of the thyroid follicular cell, and focal hyperplasia of the thyroid follicular cell (not significant) both in males and females. There were increases in blood albumin, total cholesterol in the blood and the absolute thyroid weight, acidophilic altered foci in the liver and cystic change of the testis in males, and decreases in Ht, MCV and MCH and increases in the γ-GTP and relative liver weight in females. There were increases in the γ-GTP in males and total cholesterol level, and a shortening of prothrombin time in females at 500 ppm and higher.

The cystic change in the testis observed in males at 2500 ppm could not be attributed to the administration of Boscalid, because the incidences of seminiferous tubule atrophy, interstitial cell hyperplasia in the testis and Leydig cell tumor were not significantly different among the doses.

The NOAEL in this study has been determined to be 100 ppm (4.4 mg/kg bw/day for males, 5.9 mg/kg bw/day for females). (Refs. 36 and 39)

(3) Carcinogenicity test for 24 months in rats

Wistar rats (groups of 50 males and 50 females) were fed diets containing Boscalid, technical grade at 0, 100, 500, 2500, or 15000 ppm, for 24 months. For the group treated with 15000 ppm, the administration was discontinued and animals were terminated after 17 months.

At 2500 ppm, there were centrilobular hypertrophy of hepatocytes and diffuse hypertrophy of the thyroid follicular cell in males and females, focal hyperplasia of the thyroid follicular cell and increases in relative thyroid weight in males, and suppression in body weight gain in females. There were focal hyperplasia of the thyroid follicular cell and thyroid follicular cell adenoma in females at 2500ppm, and acidophilic altered foci in the liver and thyroid follicular cell adenoma in males at 500 ppm or higher, although they were not significantly different from those of the controls.

The total incidence of focal hyperplasia of the thyroid follicular cell, follicular cell adenoma, and follicular cell adenocarcinoma (10 out of 50 animals) significantly increased compared to that in the controls (2 out of 50 animals), although the incidence of focal hyperplasia of the thyroid follicular cell did not significantly increase in females at 2500 ppm.

The above described effects of Boscalid on the thyroid including thyroid follicular cell adenoma, diffuse hypertrophy, and focal hyperplasia of the thyroid follicular cell could be attributed to the administration of the compound. As shown in 13(2), Boscalid induced hepatic drug-metabolizing enzymes, which enhanced the excretion of T4 -glucuronide, resulting in a decrease in T4 levels in the blood. Then, through negative feedback mechanisms of the pituitary-thyroid axis, TSH levels would continuously increase to cause neoplastic alteration in the thyroid. In addition, the compound was negative in all genotoxicity tests. Therefore, tumors might

develop in rat thyroids through a non-genotoxic mechanism, so we could determine the threshold doses for the compound.

The NOAELs have been determined to be 100 ppm (4.6 mg/kg bw/day) for males, and 500 ppm (29.7 mg/kg bw/day) for females. (Refs. 36 and 40)

(4) Carcinogenicity test for 18 months in mice

C57BL/6 mice (groups of 50 males and 50 females) were fed diets containing Boscalid, technical grade at 0, 80, 400, 2000, or 8000 ppm, for 18 months.

There were perilobular hypertrophy of hepatocytes and decreases in focal atrophy of the adrenal cortex in males, and suppression in body weight gain, increases in relative adrenal weight and proliferation of hepatic oval cells in females at 8000 ppm. There were increases in the relative liver weight and perilobular hypertrophy of hepatocytes in females at 2000 ppm and higher. There were suppression in body weight gain and increases in relative liver weight in males, and increased incidence of centrilobular fatty vacuolation of hepatocytes and decreased incidence of diffuse fatty vacuolation of hepatocytes in females at 400 ppm and higher. There were increases in relative adrenal weight in males at 80 ppm and higher. No significant difference was found between the treated groups and the control group for the incidence of neoplastic lesions.

Increases in the relative adrenal weight in males at 80 ppm and higher, and in females at 8000 ppm, were within the range of the background control data for the past 10 tests performed in this strain of mice in the testing laboratory concerned. Therefore, the effect would not be attributed to the administration of the compound. Also, the increased incidence of centrilobular fatty vacuolation of hepatocytes and the decreased incidence of diffuse fatty vacuolation of hepatocytes observed in females at 400 ppm were not accompanied by increased liver weight or histological evidence of hepatocyte hypertrophy, suggesting that such effects were not toxicologically significant.

The NOAELs have been determined to be 80 ppm (13 mg/kg bw/day) for males, and 400 ppm (90 mg/kg bw/day) for females. (Refs. 36 and 41)

11. Reproductive/developmental toxicity

(1) Two-generation reproductive toxicity study in rats

Wistar rats (groups of 25 males and 25 females) were fed diets containing Boscalid, technical grade at 0, 100, 1000, or 10000 ppm, for two generations.

In the parent animals, there were increases in relative weight of the liver (except for F_0 males) in males and females, suppression in body weight gain (F_1) and decreases in sperm motility (F_1) in males, and decreases in the number of implantations (F_0) and increases in post-implantation

embryonic loss (F_1) in females at 10000 ppm. There were decreases in relative and absolute weights of the spleen (except for F_0 males) and centrilobular hypertrophy of hepatocytes in males and females, and centrilobular fatty degeneration of hepatocytes (F_1) in males at 1000 ppm and higher. In the offspring, there were decreases in body weight (F_1), number of pups delivered (F_1) and viability of pups (F_2) in males and females, and relative weight of the spleen (F_2) in males and absolute weights of the thymus (F_1) and spleen (F_2) in females at 10000 ppm. There were decreases in body weight (F_2) in males and females, and absolute weight of the spleen (F_2) in males at 1000 ppm and higher. There were decreases in absolute (F_2 males) and relative (F_2 (only at 100 ppm)) weight of the thymus in males and females at 100 ppm and higher.

As for the decrease in number of implantations in F_0 parents, there were decreases in sperm motility and increases in post-implantation loss in F_1 parents, and decreases in the number of pups delivered in F_1 offspring. These changes were small, and were within the range of the background control data. Therefore, the committee did not consider these changes to be attributable to the administration of the compound.

Also, the decreases in weights of the spleen and thymus were observed in parent animals at 1000 ppm and higher, and in offspring at 100 ppm and higher. They did not accompany the corresponding histopathological changes. In addition, the compound did not show any immunological effect in the immunotoxicity test in 13 (3). Therefore, the committee took these changes as being either incidental or secondary effects to the decreased body weight and did not consider them to be directly attributable to the administration of the compound.

The NOAELs in this study for parent animals and their offspring have been determined to be 100 ppm (F_0 male: 10.1 mg/kg bw/day, F_0 female: 10.7 mg/kg bw/day, F_1 male: 12.3 mg/kg bw/day, F_1 female: 12.5 mg/kg bw/day) in both sexes of rats. (Ref. 42)

(2) Developmental toxicity study in rats

A developmental toxicity study was conducted in Wistar rats (groups of 25 females). The animals were given Boscalid on days 6-19 of pregnancy at 0, 100, 300, or 1000 mg/kg bw/day by gavage.

No adverse effect was found in dams in any of the treated groups. In fetuses, there were increases in the incidence of fetuses with incomplete ossification of the thoracic centrum at 1000 mg/kg bw/day and increases in the incidence of fetus with skeletal variations at 300 mg/kg bw/day and higher. These increases were within the range of the background control data, and, therefore, could not be attributed to the administration of the compound.

The NOAEL in this study for dams and fetuses has been determined to be 1000 mg/kg bw/day. No teratogenicity of Boscalid was evident. (Ref. 43)

(3) Developmental toxicity study in rabbits

Himalayan rabbits (groups of 25 females) were given Boscalid on days 7-28 of pregnancy at 0, 100, 300, or 1000 mg/kg bw/day by gavage.

In dams, there were abortion/premature deliveries and decreases in body weight and food consumption at 1000 mg/kg bw/day, and there were abortions at 300 mg/kg bw/day and higher. In fetuses, there were increases in the incidence of fetuses with incomplete ossification of the thoracic centrum at 1000 mg/kg bw/day, but the incidence was within the range of the background control data and would not be attributed to the administration of the compound.

The NOAELs in this study have been determined to be 100 and 1000 mg/kg bw/day for dams and fetuses, respectively. No teratogenicity of Boscalid was evident. (Ref. 44)

12. Genotoxicity

Boscalid has been tested in a range of *in vitro* and *in vivo* standard protocols (Table 4). It was not mutagenic in bacteria with and without an exogenous metabolic activation system. Boscalid did not induce unscheduled DNA synthesis in rat primary cell cultures or micronucleus in mouse bone marrow cells. It also did not induce chromosomal aberrations or genetic mutations in cultured Chinese hamster cells.

No genotoxicity of Boscalid was evident. (Refs. 45-49)

Table 4. Summary of Genotoxicity Test Results (Boscalid)

Test systems		Cells/animals	Dose (mg/kg bw)	Results
In vitro	Microbial reverse mutation (±S9 mix)	*S. typhimurium* TA100, TA98, TA1535, TA1537, *E. coli* WP2*uvrA*		Negative
	Unscheduled DNA synthesis	Rat primary hepatocyte culture		Negative
	Chromosome aberration (±S9 mix)	Chinese hamster-derived cell (V79)		Negative
	Genetic mutation (±S9 mix)	Chinese hamster ovary-derived cell		Negative
In vivo	Rodent micronucleus	NMRI mice, 5 males	500, 1000, 2000 (mg/kg bw peritoneal administration, twice at a 24-h interval)	Negative

±S9 mix: with/without exogenous metabolic activation.

The metabolite F49 has been tested in the microbial reverse mutation test (Table 5), and was not mutagenic. (Ref. 50)

Table 5. Summary of Genotoxicity Test Results (Metabolites)

Test substance	Test system	Cells	Result
Metabolite F49	Microbial reverse mutation (±S9 mix)	*S. typhimurium* TA100, TA98, TA1535, TA1537, *E. coli* WP2*uvrA*	Negative

±S9 mix: with/without exogenous metabolic activation.

13. Other toxicity tests

(1) Enzyme induction tests on hepatic drug-metabolizing enzymes in rats

Wistar rats (groups of 8 males and 8 females) were fed diets containing Boscalid, technical grade at 0 or 15000 ppm, for 14 days to study the induction of hepatic drug-metabolizing enzymes.

There were increases in liver weight, cytochrome P450 content and proliferation of smooth endoplasmic reticulum in centrilobular hepatocytes in males and females, and lipid peroxide in males at 15000 ppm. The administration of the compound had no effect on EROD or PROD, suggesting that Boscalid would not induce cytochrome P450 molecular species having affinities to ethoxyresorufin or penthoxyresorufin. These changes might belong to adaptive responses of the organism. (Ref. 51)

(2) Tests on induction of thyroid hormone and hepatic drug-metabolizing enzymes in rats

Wistar rats (groups of 5 males and 5 females) were fed diets containing Boscalid, technical grade at 0 or 15000 ppm, for 28 days to study the induction of thyroid hormone and hepatic drug-metabolizing enzymes.

There were decreases in T3 concentration and increases in TSH concentration, liver weight and phase II drug-metabolizing enzyme activities (pNP-GT, MUF-GT, HOBI-GT) in males and females, and decreases in T4 concentration in males at 15000 ppm. (Ref. 52)

In addition, Wistar rats (groups of 10 males and 10 females) were fed diets containing Boscalid, technical grade at 0, 500, 2000, or 5000 ppm, for 28 days to study the induction of thyroid hormone and hepatic drug-metabolizing enzymes.

There were increases in the relative weights of the liver and the thyroid in females at 5000 ppm, and increases in the phase I drug-metabolizing enzyme activities (EROD, PROD, BROD) in males and females, decreases in T4 concentration (not significant) and increases in TSH

concentration in males, and increases in absolute thyroid weight in females at 2000 ppm and higher. There were increases in the phase II drug-metabolizing enzyme activities (pNP-GT, MUF-GT, HOBI-GT) in males and females, and increases in relative liver weight in males at 500 ppm and higher. (Ref. 53)

(3) Immunotoxicity test in rats

Wistar rats (groups of 16 males and 16 females) were fed diets containing Boscalid, technical grade at 0, 100, 1000, or 10000 ppm, for 4 weeks to study immunotoxicity.

In all the treated groups, there were no adverse effects on parameters representing immunological effects, such as thymus and spleen weights, number of thymocytes and splenic cells, results of analyses on lymphocyte subsets in the thymus and the spleens and anti-sheep erythrocyte IgM antibody level.

No immunotoxicity of Boscalid was evident. (Ref. 54)

III. Evaluation

Absorption, distribution, metabolism, and excretion of Boscalid were studied using a chemical homogeneously labeled with ^{14}C at the diphenyl ring (Dip-^{14}C-Boscalid) and a chemical labeled with ^{14}C at position 3 on the pyridine ring (Pyr-^{14}C-Boscalid).

In rats, the plasma concentration of the compound reached the maximum concentration at 8 hours after administration with a single dose. The half-life was 20.2 to 41.7 hours, and the main elimination pathway was fecal excretion. The tissue concentrations by 168 hours were high in the thymus, liver, bone marrow, kidney, and adrenal gland. The amount of Boscalid detected in the urine by 48 hours after administration was 0.16% or less. The main metabolites were F01, F02, and F48. The amounts of Boscalid detected in the feces were from 30.5 to 41.0% of the dosage with a Dip Low and from 68.3 to 80.4% of the dosage with Dip High and Pyr High. The main metabolites detected in the feces were F01, F06, F20, and F48. Boscalid was not detected in the bile, and the main metabolites detected were F02 and F05. The main metabolic pathway of Boscalid in rats would be the hydroxylation of the diphenyl ring and glutathione conjugation, or the substitution of the thiol group in glutathione for the chloro atom on the pyridine ring.

Boscalid was stable in lettuces and grapes, and not much metabolized in kidney beans. The main metabolic pathway of the compound in kidney beans would be the cleavage of the amide linkage between the diphenyl ring and the pyridine ring, resulting in the metabolites F47 and F62.

Half-lives of Boscalid in soils were 108 days under aerobic conditions and 261-345 days under anaerobic conditions. Photolysis of Boscalid would progress slowly at the soil surface, with a half-life of 135 days, but be accelerated by light. The adsorption coefficient K^{ads}_{oc} was from 670 to 1760, suggesting that Boscalid would easily be adsorbed in soil and remain at the surface when dropped on the soil.

Boscalid was not hydrolyzed and was photolytically stable in the buffer solution of pH 5, distilled water and natural water. Meanwhile, in the water/bottom sediment phase test under natural light, Boscalid in the aqueous phase decreased to 22% of the dosage after 120 days. The main metabolite was F64.

The residual levels of Boscalid were examined in grapes, strawberries, tomatoes, eggplants, cucumbers, onions, red beans, kidney beans, apples, pears, and cherries. The highest residual value of the compound (7.39 ppm) was observed in strawberries cropped 1 day after the last application, but the value diminished to 7.00 ppm and 4.46 ppm after 3 and 7 days, respectively.

Residual values of Boscalid in soils were studied (both in the vessel and in the field) using volcanic ash light clay, sand-dune Regosol, and alluvium clay loam. Half-lives of Boscalid in soils were about 160-285 days in the vessel and about 30-110 days in the field.

The LD_{50} of Boscalid was >5000 mg/kg bw in male and female rats and mice by oral dose, >2000 mg/kg bw in male and female rats by dermal treatment, and the LC_{50} was >6.7 mg/L in male and female rats by inhalation. The LD_{50} of the metabolite F49 was >2000 mg/kg bw in male and female rats by oral dose.

In the chronic toxicity test and the carcinogenicity test in rats, adverse effects of the compound were observed on the liver, as hepatocyte hypertrophy and acidophilic altered foci. The administration of the compound resulted in the induction of hepatic drug metabolizing enzymes involving the detoxification processes.

As a common adverse response to Boscalid, there were thyroid follicular cell adenoma (not significant), hypertrophy/hyperplasia of the thyroid follicular cell, and an increased relative thyroid weight in various (subchronic toxicity, chronic toxicity, carcinogenicity) tests in rats. In order to understand the possible mechanisms of the adverse effects on the thyroid, the hepatic drug-metabolizing enzyme induction test was performed. Boscalid was shown to induce hepatic drug-metabolizing enzymes, which would enhance the excretion of T4 conjugate with the glucuronic acid to decrease the blood T4 concentration. The negative feedback reaction to the decrease of T4 would continuously cause increased secretion of TSH from the pituitary gland thus causing neoplastic alterations in the thyroid gland. Together with the fact that the Boscalid was negative in all genotoxicity tests, the thyroid tumors would be developed through a non-genotoxic mechanism, so the threshold dose for the carcinogenicity could be determined.

The NOAELs of Boscalid were 29 mg/kg bw/day in mice, 34 mg/kg bw/day in rats, and 7.6 mg/kg bw/day in dogs in subchronic toxicity tests.

The NOAELs have also been determined as 13 mg/kg bw/day in mice, 4.4 mg/kg bw/day in rats, and 21.8 mg/kg bw/day in dogs in chronic toxicity tests and carcinogenicity tests.

In the two-generation reproductive toxicity test in rats, the NOAEL was 10.1 mg/kg bw/day.

The developmental toxicity studies were performed in rats and rabbits, and the NOAELs were 1000 mg/kg bw/day for both dams and fetuses in rats, 100 mg/kg bw/day for dams, and 1000 mg/kg bw/day for fetuses in rabbits. No teratogenicity was found in either rats or rabbits.

Boscalid was not mutagenic in bacteria with and without an exogenous metabolic activation system. Boscalid did not induce unscheduled DNA synthesis in rat primary cell cultures or micronuclei in mouse bone marrow cells. It also did not induce chromosomal aberrations or genetic mutations in cultured Chinese hamster cells. The Committee concluded that Boscalid would not be genotoxic. The metabolite F49 was not genotoxic in bacteria with and without an exogenous metabolic activation system.

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

Table 6. The NOAELs Determined in Several Toxicity Evaluating Tests

Species	Evaluating test	NOAEL (mg/kg bw/day)	Note
Mouse	90 days subchronic toxicity	Male: 29 Female: 42	
	18 months carcinogenicity	Male: 13 Female: 90	No carcinogenicity
Rat	90 days subchronic toxicity	Male: 34 Female: 40	
	90 days subchronic neurotoxicity	Male: 1050.0 Female: 1272.5	No neurotoxicity
	24 months chronic toxicity	Male: 4.4 Female: 5.9	
	24 months carcinogenicity	Male: 4.6 Female: 29.7	
	Two-generation reproductive toxicity study	Parent animals and offspring: F_0 male: 10.1 F_0 female: 10.7 F_1 male: 12.3 F_1 female: 12.5	
	Developmental toxicity study	Dam: 1000 Fetus: 1000	No teratogenicity
Rabbit	Developmental toxicity study	Dam: 100 Fetus: 1000	No teratogenicity
Dog	90 days subchronic toxicity	Male: 7.6 Female: 8.1	
	12 months chronic toxicity	Male: 21.8 Female: 22.1	

Based on the evaluation, the Pesticides Expert Committee of the Food Safety Commission determined the ADI value of Boscalid as:

ADI:	0.044 mg/kg bw/day
(referred data for ADI)	Chronic toxicity test
Laboratory animal tested:	Rat
Duration:	24 months
Administration route:	mixed feeds
NOAEL:	4.4 mg/kg bw/day
Safety factor:	100
Residue definition for exposure assessment:	
	Boscalid (parent chemical only)

(Appendix 1. Abbreviations for metabolites/degradation products)

Abbreviation	Chemical name
F01	2-chlroro-N-(4’-chloro-5-hydroxy-biphenyl-2-yl)nicotinamide
F02	4’-chloro-6-[[(2-chloro-3-pyridinyl)carbonyl]amino]biphenyl-3-yl glycopyranoside uronic acid
F05	[3-[[(4’-chlorobiphenyl-2-yl)amino]carbonyl]-2-pyridinyl]cysteine
F06	N-(4’-chlorobiphenyl-2-yl)-2-sulfanylnicotinamide
F08	N-(4’-chlorobiphenyl-2-yl)nicotinamide
F20	2-chloro-N-(4’-chloro-?-hydroxy-?-methylsulfanylbiphenyl-2-yl)nicotinamide
F43	N-(4’-chlorobiphenyl-2-yl)-2-glutathionylnicotinamide
F46	N^5-(2-[(carboxymethyl)amino]-1[[(5-(4-chlorophenyl)-4-[[(2-chloro-3-pyridinyl)carbonyl]amino]-6-hydroxy-2,4-cyclohexadien-1-yl)sulfanyl]methyl]-2-oxoethyl)glutamine
F47	2-chloronicotinic acid
F48	3-[[(4’-chlorobiphenyl-2-yl)-amino]carbonyl]-2-pyridinyl-1-thiohexopyranoside uronic acid
F49	N-(4’-chlorobiphenyl-2-yl)-2-hydroxynicotinamide
F50	2-chloro-N-(4’-chlorobiphenyl-2-yl)-?-hydroxynicotinamide
F62	4’-chlorophenyl-2-aminobenzene
F64	4’-chlorobenzoic acid

In some metabolites, the positions of the binding “groups” could not be specified and were expressed as “-?-” in the chemical name.

(Appendix 2. Abbreviations for test values, etc.)

Abbreviation	Name
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
BROD	Benzyloxyresorufin-O-debenzylase
EROD	Ethoxyresorufin-O-deethylase
γ -GTP	γ -Glutamyl transferase
HOBI-GT	4-Hydroxybiphenyl-glucuronic acid transferase
Ht	Hematocrit
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MUF-GT	4-Methylumbelliferone-glucuronic acid transferase
pNP-GT	p-Nitrophenol-glucuronic acid transferase
PROD	Pentoxyresorufin-O-depentylase
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid-stimulating hormone

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