This is provisional English translation of an excerpt from the original full report.

# Risk Assessment Report

# Benzovindiflupyr (2nd Edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)

September 2020

## ABSTRACT

FSCJ conducted the risk assessment of a pyrazole carboxamide fungicide, benzovindiflupyr (CAS No. 1072957-71-1), based on various documents. Data on acute toxicity (rats), an eye/skin irritation (rabbits), and residue in crops (blueberries and Coffee beans) were newly available in this assessment.

The data used in the assessment include fate in animals (rats), fate in plants (spring wheat and tomatoes), residues in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity study (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity study (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity, immunotoxicity (mice), and mechanism of thyroid tumor in rats.

Major adverse effects of benzovindiflupyr observed are suppressed body weight, centrilobular hypertrophy of hepatocytes in the liver (rats), and mucosal hyperplasia of the large intestine (rats). Benzovindiflupyr showed no effects on reproduction, teratogenicity, genotoxicity and immunotoxicity.

In a combined chronic toxicity/carcinogenicity study in male rats, an increased incidence of follicular adenomas in the thyroid was observed. However, a genotoxic mechanism was unlikely involved in tumor induction, and it was considered possible to establish a threshold dose in the assessment.

FSCJ identified benzovindiflupyr (parent compound only) as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest value of the no-observed-adverse-effect level (NOAEL) in all tests was 4.88 mg/kg bw/day in a combined two-year chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.048 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for potential adverse effects of a single oral administration of benzovindiflupyr was 10 mg/kg bw/day obtained in an acute neurotoxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 0.1 mg/kg bw by applying a safety factor of 100 to the NOAEL.

**Table 1.** *Levels relevant to toxicological evaluation of benzovindiflupyr*

| Species | Study | Dose (mg/kg bw/day) | NOAEL (mg/kg bw/day) | LOAEL (mg/kg bw/day) | Critical endpoints[1)] |
|---|---|---|---|---|---|
| Rat | 90-day subacute toxicity study | 0, 100, 750, 1 500 ppm<br>M: 0, 7.6, 53.8, 109<br>F: 0, 8.2, 58.8, 109 | M: 7.6<br>F: 8.2 | M: 53.8<br>F: 58.8 | M/F: Suppressed body weight |
| | 90-day subacute neurotoxicity study | M: 0, 100, 400, 800 ppm<br>F: 0, 100, 250, 500 ppm<br>M: 0, 6.31, 26.0, 50.7<br>F: 0, 7.48, 19.2, 38.0 | M: 6.31<br>F: 19.2 | M: 26<br>F: 38 | M/F: Suppressed body weight, decreased feed intake<br>(No subacute neurotoxicity) |
| | Two-year combined chronic toxicity/carcinogenicity study | M: 0, 25, 100, 600 ppm<br>F: 0, 25, 100, 400 ppm<br>M: 0, 1.21, 4.88, 30.2<br>F: 0, 1.65, 6.66, 27.4 | M: 4.88<br>F: 6.66 | M: 30.2<br>F: 27.4 | M/F: Suppressed body weight, centrilobular hypertrophy of hepatocytes<br>(M: Increased incidence of follicular cell adenomas in the thyroid) |
| | Two-generation reproductive toxicity study | M: 0, 25, 100, 600 ppm<br>F: 0, 25, 100, 250 ppm<br>PM：0, 1.7, 6.8, 40.5<br>PF：0, 2.0, 8.2, 19.4<br>$F_1$M：0, 1.9, 7.8, 48.0<br>$F_1$F：0, 2.1, 8.7, 22.0 | PM: 6.8<br>PF: 8.2<br>$F_1$M: 7.8<br>$F_1$F: 8.7 | PM: 40.5<br>PF: 19.4<br>$F_1$M: 48.0<br>$F_1$F: 22.0 | Parent:<br>M/F: Suppressed body weight<br>Offspring:<br>M/F: Suppressed body weight<br>(No effect on reproductive activity) |
| | Developmental toxicity study | 0, 7.5, 15, 30 | Dams: 15<br>Fetuses: 15 | Dams: 30<br>Fetuses: 30 | Dams: Ataxia, decreased activity, suppressed body weight<br>Fetuses: Low body weight<br>(No teratogenicity) |
| Mouse | 90-day subacute toxicity study | 0, 100, 300, 500 ppm<br>M: 0, 17.0, 55.6, 97.9<br>F: 0, 20.9, 59.6, 103 | M: 17.0<br>F: 20.9 | M: 55.6<br>F: 59.6 | M/F: Suppressed body weight, mucosal hyperplasia of the colon and rectum |
| | 80-week carcinogenicity study | 0, 20, 60, 200 ppm<br>M: 0, 2.62, 7.55, 26.2<br>F: 0, 2.89, 8.67, 29.3 | M: 7.55<br>F: 8.67 | M: 26.2<br>F: 29.3 | M/F: Simple mucosal hyperplasia of the colon and cecum<br>(No carcinogenicity) |

| Species | Study | Dose (mg/kg bw/day) | NOAEL (mg/kg bw/day) | LOAEL (mg/kg bw/day) | Critical endpoints[1)] |
|---|---|---|---|---|---|
| Rabbit | Developmental toxicity study | 0, 10, 20, 35 | Dams: 10<br>Fetuses: 35 | Dams: 20<br>Fetuses: -a | Dams: Suppressed body weight<br>Fetuses: No toxicity was observed.<br><br>(No teratogenicity) |
| Dog | 90-day subacute toxicity study | M/F: 0, 30, 375, 750 | M/F: 30 | M/F: 375 | M/F: Suppressed body weight |
| | One-year chronic toxicity study | M/F: 0, 25, 250, 500 | M/F: 250 | M/F: 500 | M: Suppressed body weight<br>F: Decreased/suppressed body weight |
| ADI | | | NOAEL: 4.88<br>SF: 100<br>ADI: 0.048 | | |
| The critical study for setting ADI | | | Two-year combined chronic toxicity/carcinogenicity study in rats | | |

ADI, Acceptable daily intake; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
-a, LOAEL could not be specified.
[1)]The adverse effect observed at LOAEL

**Table 2.** *Potential adverse effects of a single oral administration of benzovindiflupyr*

| Species | Study | Dose (mg/kg bw or mg/kg bw/day) | Endpoints relevant to setting NOAEL and ARfD[1] (mg/kg bw or mg/kg bw/day) |
|---|---|---|---|
| Rat | Acute toxicity study | F: 17.5, 55, 175 | F: 17.5<br><br>F: Cases of death (1/4 cases), decreased activity, prone position, ataxia, piloerection, dyspnea, decreased respiration, clonic convulsion, decreased body temperature and hunched position |
| | | F: 55, 175, 550 | F: -<br><br>F: Decreased activity, hunched position, ataxia, piloerection |
| | Acute neurotoxicity study | M/F: 0, 10, 30, 80 | M: 30<br>F: 10<br><br>M: Decreased activity, loose stool, decreased body temperature, decreased feed intake<br>F: Abnormal gait, decreased activity, piloerection, decreased body temperature, forelimb grip weakness, decreased total number of moving distance and rises in locomotor activity, and decreased feed intake |
| | Developmental toxicity study | F: 0, 7.5, 15, 30 | Dams: 15<br><br>Dams: Ataxia, hunched position, prone position, decreased activity, piloerection, suppressed body weight, and decreased feed intake |
| ARfD | | | NOAEL: 10<br>SF: 100<br>ARfD: 0.1 |
| The critical study for setting ARfD | | | Acute neurotoxicity study in rats |

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor;
-, NOAEL could not be specified.
1) The adverse effect observed at LOAEL