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

# Risk Assessment Report
# Cyclopyrimorate
(Pesticides)

Food Safety Commission of Japan (FSCJ)
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## ABSTRACT

FSCJ conducted a risk assessment of cyclopyrimorate (CAS No.499231-24-2), an herbicide with a novel structural feature.

The data used in the assessment include fate in animals (rats and goats), fate in plants (paddy rice), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (rats and dogs), carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxcity, and the mechanism data of tumors induced by the treatment in rats and mice.

Major adverse effects of cyclopyrimorate are suppressed body weight, hepatocellular hypertrophy and follicular cell hypertrophy in rats, chronic progressive nephropathy in rats, and white matter vacuolation in cerebellum in dogs. No reproductive toxicity, teratogenicity and genotoxicity relevant to human health was observed.

Cyclopyrimorate increased incidences of hepatocellular adenomas, combined number of follicular cell adenomas and carcinomas in male rats in a two year-carcinogenicity study, and hepatocellular adenoma in male mice in an 18-month carcinogenicity study. However, a genotoxic mechanism was unlikely to be involved in the tumor induction. It was thus possible to establish a threshold dose in the assessment.

On the basis of various studies, cyclopyrimorate (parent compound only) was identified as a relevant substance for residue definition for dietary risk assessment in agricultural and fishery products, and cyclopyrimorate and its metabolite F were identified as relevant substances for residue definition in livestock products.

The lowest no-observed adverse effect level (NOAEL) obtained in all tests was 6.37 mg/kg bw/day in a two-year carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.063 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

FSCJ judged it unnecessary to specify an acute reference dose ARfD, in a view of since no adverse effects would be likely to be elicited by a single oral administration of cyclopyrimorate.

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

| Species | Studies | 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, 50, 500, 5 000 ppm<br>M: 0, 3.21, 33.1, 319<br>F: 0, 3.69, 37.9, 373 | M: 33.1<br>F: 37.9 | M: 319<br>F: 373 | FM: Increase in absolute and relative liver/kidney weights |
| | One-year chronic toxicity study | 0, 60, 500, 4 000 ppm<br>M: 0, 2.64, 22.6, 186<br>F: 0, 3.46, 30.3, 241 | M: 2.64<br>F: 30.3 | M: 22.6<br>F: 241 | M: Regenerative changes in renal tubular epithelial cells<br>F: Renal tubular epithelial cell hypertrophy and others |
| | Two-year carcinogenicity study | 0, 160, 800, 4 000 ppm<br>M: 0, 6.37, 32.0, 164<br>F: 0, 8.20, 41.6, 216 | M: 6.37<br>F: 41.6 | M: 32.0<br>F: 216 | FM: Altered hepatocellular foci (eosinophilic) and others<br><br>(M: Hepatocellular adenomas and thyroid tumors) |
| | Two-generation reproductive toxicity study | 0, 60, 300, 2 000 ppm<br>PM: 0, 3.56, 17.2, 118<br>PF: 0, 5.56, 28.4, 190<br>$F_1$M: 0, 3.96, 19.7, 136<br>$F_1$F: 0, 5.92, 29.2, 197 | Parent<br>PM: 17.2<br>PF: 28.4<br>$F_1$M: 19.7<br>$F_1$F: 29.2<br><br>Offspring<br>PM: 17.2<br>PF: 28.4<br>$F_1$M: 19.7<br>$F_1$F: 29.2 | Parent<br>PM: 118<br>PF: 190<br>$F_1$M: 136<br>$F_1$F: 197<br><br>Offspring<br>PM: 118<br>PF: 190<br>$F_1$M: 136<br>$F_1$F: 197 | Parent:<br>FM: Increase in absolute and relative liver/kidney/thyroid weights and others<br><br>Offspring: Decrease in absolute and relative spleen weights<br><br>(No effect on reproduction) |
| | Developmental toxicity study | 0, 40, 200, 1 000 | Maternal: 40<br>Embryo/fetus: 40 | Maternal: 200<br>Embryo/fetus: 200 | Maternal: Suppressed body weight and decreased feed consumption<br><br>Embryo/fetus: Lower body weight and delayed ossification and others<br><br>(Not teratogenic) |

| Species | Studies | Dose (mg/kg bw/day) | NOAEL (mg/kg bw/day) | LOAEL (mg/kg bw/day) | Critical endpoints[1)] |
|---|---|---|---|---|---|
| Mouse | 90-day acute toxicity study | 0, 100, 1 000, 3 000, 10 000 ppm<br>M: 0, 13.8, 139, 409, 1 350<br>F: 0, 15.8, 161, 469, 1 460 | M: 13.8<br>F: 15.8 | M: 139<br>F: 161 | M: Decrease in RBC, Hb and Ht<br>F: Increase in absolute and relative weight in kidney |
| | 18-month carcinogenicity study | 0, 300, 1 400, 7 000 ppm<br>M: 0, 32.4, 155, 760<br>F: 0, 31.9, 152, 752 | M: －<br>F: 152 | M: 32.4<br>F: 752 | M: Suppressed body weight<br>F: Diffuse fatty change in liver and others<br><br>(M: Hepatocellular adenomas) |
| Rabbit | Developmental toxicity study | 0, 30, 125, 500 | Maternal: 125<br>Embryo/fetus: 500 | Maternal: 500<br>Embryo/fetus: － | Maternal: Miscarriage and others<br>Embryo/fetus: No toxicity<br><br>(Not teratogenic) |
| Dog | 90-day subacute toxicity study | 0, 100, 1 000, 10 000 ppm<br>M: 0, 2.96, 30.2, 307<br>F: 0, 3.11, 31.5, 322 | M: 30.2<br>F: 31.5 | M: 307<br>F: 322 | FM: Diffuse hepatocellular hypertrophy and others |
| | One-year chronic toxicity study | 0, 100, 1,000, 10,000 ppm<br>M: 0, 2.59, 27.2, 297<br>F: 0, 2.89, 28.3, 285 | M: 27.2<br>F: 28.3 | M: 297<br>F: 285 | M: Diffuse hepatocellular hypertrophy and others<br><br>F: Eosinophilic cytoplasmic inclusion bodies in hepatocytes and others |
| ADI | | | NOAEL: 6.37<br>SF: 100<br>ADI: 0.063 | | |
| The critical dose for setting the ADI | | | Two-year carcinogenicity study in rats | | |

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