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

# Risk Assessment Report

## Lancotrione-sodium

(Pesticides)

Food Safety Commission of Japan (FSCJ)
April 2018

## ABSTRACT

FSCJ conducted a risk assessment of Lancotrione-sodium (CAS No. 1486617-22-4), a triketone herbicide, based on results from various studies.

The data used in the assessment include fate in animals (rats), 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), genotoxicity, and a comparison of sequential change in plasma tyrosine levels in rats, mice and rabbits .

Major adverse effects of lancotrione-sodium observed are keratitis, vacuolation in molecular layer of cerebellum in rats, dermatitis, hepatocellular hypertrophy, hypertrophy of follicular epithelial cells of the thyroid, and calculus in gallbladder in mice. Lancotrione-sodium showed no adverse effects on reproductivity, no teratogenicity and genotoxicity relevant to human health.
Incidences of corneal squamous papillomas and squamous cell carcinomas were increased by lancotrione-sodium treatment in a two-year carcinogenicity stdy in rats. This carcinogenicity was attributable to the persistent inflammation, and it is unlikely that lancotrione-sodium exerts the carcinogenicity through a genotoxic mechanism. Therefore, FSCJ recognized it as feasible to set the threshold value.

Based on the results from various studies, lancotrione-sodium (parent compound only) was identified as the relevant substance for a residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained in all tests was 0.1 mg/kg bw/day in a developmental toxicity study in rabbits. FSCJ specified an acceptable daily intake (ADI) of 0.001 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for adverse effects likely to be elicited after a single oral dose of lancotrione-sodium was 10 mg/kg bw/day obtained in a developmental toxicity 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 lancotrion-sodium*

| Species | Study | Dose (mg/kg bw/day) | NOAEL (mg/kg bw/day) | LOAEL (mg/kg bw/day) | Critical endpoints[1)] |
|---|---|---|---|---|---|
| Rats | 90-day subacute toxicity study | 0, 1, 10, 1 000, 5 000 ppm<br>M: 0, 0.07, 0.68, 67.9, 348<br>F: 0, 0.08, 0.79, 84.9, 424 | M: 0.68<br>F: 0.79 | M: 67.9<br>F: 84.9 | M/F: Keratitis |
| | One-year chronic toxicity study | 0, 1, 3, 300, 3 000 ppm<br>M: 0, 0.047, 0.139, 14.4, 150<br>F: 0, 0.060, 0.178, 19.3, 198 | M: 0.139<br>F: 0.178 | M: 14.4<br>F: 19.3 | M/F: Keratitis |
| | Two-year carcinogenicity study | 0, 1, 3, 300, 3 000 ppm<br>M: 0, 0.040, 0.119, 12.7, 130<br>F: 0, 0.053, 0.160, 16.7, 173 | M: 0.119<br>F: 0.160 | M: 12.7<br>F: 16.7 | M/F: Keratitis<br><br>(M: Corneal squamous papilloma and squamous cell carcinoma) |
| | Two-generation reproductive toxicity study | 0, 1, 3, 100, 1 000 ppm<br>PM: 0, 0.066, 0.198, 6.76, 68.3<br>PF: 0, 0.086, 0.255, 8.67, 86.8<br>$F_1$M: 0, 0.077, 0.233, 8.05、82.3<br>$F_1$F: 0, 0.093, 0.276, 9.37, 94.0 | PM: 0.198<br>PF: 0.225<br>$F_1$M: 0.233<br>$F_1$F: 0.276 | PM: 6.76<br>PF: 8.67<br>$F_1$M: 8.05<br>$F_1$F: 9.37 | Parent and offspring.<br>M/F : Keratitis<br><br>(No reproductive toxicity) |
| | Developmental toxicity study | 0, 0.1, 10, 1 000 | Dams and Fetuses: 10 | Dams and Fetuses: 1 000 | Dams: Decreased body weight/suppressed body weight gain.<br>Fetuses: Low body weight<br><br>(No teratogenicity) |

| | | | | | |
|---|---|---|---|---|---|
| Mice | 90-day subacute toxicity study | 0, 20, 140, 1 000, 7 000 ppm<br>M: 0, 2.95, 21.0, 148, 1 050<br>F: 0, 3.36, 23.3, 168, 1 130 | M: 148<br>F: 23.3 | M: 1 050<br>F: 168 | M: hypertrophy of thyroid follicular epithelial cells.<br>F: Decreased Glu. |
| | 18-month carcinogenicity study | M: 0, 70, 700, 7 000 ppm<br>F: 0, 70, 700, 7 000/5 000 ppm<br>---<br>M: 0, 8.04, 84.5, 907<br>F: 0, 7.61, 77.7, 739 | M: 8.04<br>F: – | M: 84.5<br>F: 7.61 | M: *Amyloid* deposition in the heart, duodenum, ileum, thyroid and exorbital lacrimal gland.<br>F: Colecystolithiasis<br><br>(No carcinogenicity) |
| Rabbits | Developmental toxicity study | 0, 0.1, 10, 1 000 | Dams: 10<br>Fetuses: 0.1 | Dams: 1 000<br>Fetuses: 10 | Dams: Decreased body weight /suppressed body weight gain<br>Fetuses: supernumerary ribs and 27-Supernumerary presacral vertebra(e)<br>(No teratogenicity) |
| Dogs | 90-day subacute toxicity study | 0, 3, 10, 1 000, 10 000 ppm<br>---<br>M: .086, 0.290, 29.4, 312<br>F: .092, 0.308, 32.3, 337 | M: 0.290<br>F: 0.308 | M: 29.4<br>F: 32.3 | M/F: Degeneration of Corneal Epithelial Cells. |
| | One-year chronic toxicity study | 0, 3, 5, 500, 5 000 ppm<br>---<br>M: 0, 0.092, 0.142, 15.4, 161<br>F: 0, 0.088, 0.145, 14.6, 163 | M: 0.142<br>F: 0.145 | M: 15.4<br>F: 14.6 | M/F: Degeneration of Corneal Epithelial Cells. |
| ADI | | | NOAEL: 0.1<br>SF: 100<br>ADI: 0.001 | | |
| The critical study for setting ADI | | | Developmental toxicity study in rabbits. | | |

NOAEL, No-observed-adverse-effect level; SF, Safety factor; ADI, Acceptable Daily Intake
[1)] the adverse effect observed at LOAEL
– : NOAEL could not be specified.

**Table 2** *Potential adverse effects of a single oral administration of lancotrion-sodium*

| Species | Study | Dose (mg/kg bw) | Endpoints relevant to setting NOAEL and ARfD (mg/kg bw) [1] |
|---|---|---|---|
| Rats | General pharmacology (General status) | 0, 200, 600, 2 000 | M/F: 600<br><br>M/F: Passivity、decreased locomotive activity |
| | General pharmacology (Respiration rate) | F: 0, 200, 600, 2 000 | 600<br><br>Decreased respiration rate |
| | General pharmacology (Blood pressure, heart rate) | F: 0, 200, 600, 2 000 | 600<br><br>Decreased heart rate |
| | Developmental toxicity study | 0, 0.1, 10, 1 000 | Dams: 10<br><br>Dams: Decreased body weight, decreased feed intake [b] |
| Mice | General pharmacology (General status) | 0, 200, 600, 2 000 | F: 600<br><br>F: Locomotive activity, decreased righting reflex |
| | General pharmacology (Locomotive activity) | F: 0, 200, 600, 2 000 | 600<br><br>Decreased locomotive activity |
| ARfD | | | NOAEL: 10<br>SF: 100<br>ARfD: 0.1 |
| The critical study for setting ARfD | | | Developmental toxicity study in rats |

ARfD, Acute reference dose; SF, Safety factor; NOAEL, No-observed-adverse-effect level

[a)] The adverse effect observed at LOAEL

[b)] Although the effect was possibly caused by the local irritation due to the gavage administration, a macroscopic pathological examination at the autopsy could not find effects on the stomach. Therefore, FSCJ attributed the observed effects to the systemic effect and considered it as endpoints relevant to ARfD.