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

# Risk Assessment Report

## 1,4-Dimethylnaphthalene

(Pesticides)

Food Safety Commission of Japan (FSCJ)
May 2023

## ABSTRACT

The FSCJ conducted a risk assessment of 1,4-dimethylnaphthalene (CAS No. 571-58-4), an alkyl naphthalene plant growth regulator, based on submitted documents.

The data used in the assessment include fate in plants (potatoes), residues in crops, fate in livestock (goats and chickens), residues in livestock products (chicken), fate in animals (rats), subacute toxicity (rats), combined chronic toxicity/carcinogenicity (rats), extended one-generation reproductive toxicity (rats), developmental toxicity (rabbits) and genotoxicity.

Test results contained in the documents fell short of data used in conventional risk assessments, since rat was the only species evaluated for subacute toxicity and carcinogenicity, and likewise, rabbit was the only species tested for developmental toxicity. However, a risk assessment was considered feasible after a comprehensive evaluation of factors including the lack of species differences observed in metabolic pathways among rats, mice and dogs, the lack of carcinogenicity observed in rats, the results of the extended one-generation reproductive toxicity study on rats, the results of tests conducted on other alkyl naphthalenes (reference materials), and the fact that 1,4-dimethylnaphthalene is a component commonly found in food.

Major adverse effects of 1,4-dimethylnaphthalene were observed in body weight (suppressed weight gain), the kidneys (including increased organ weights and karyomegaly of renal tubular epithelial cells in rats) and the liver (including increases in organ weights and total cholesterol in rats). Neither carcinogenicity, effects on fertility, teratogenicity, biologically significant genotoxicity, immunotoxicity nor developmental immunotoxicity was observed.

Based on these results, 1,4-dimethylnaphthalene and metabolite C (including conjugates) were identified as the relevant substances for residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from these studies was 10 mg/kg bw per day from the two-year combined chronic toxicity/carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.10 mg/kg per day by applying a safety factor of 100 to this NOAEL.

NOAEL and lowest-observed-adverse-effect level (LOAEL) values were compared across studies for potential adverse effects of a single oral administration, of which the lowest value was a NOAEL of 500mg/kg bw in a micronucleus test using mice. While the LOAEL obtained from the acute toxicity study in rats was 750mg/kg bw and a NOAEL value could not be obtained, it was reasonable to assume a NOAEL value above the cut-off level of 500mg/kg bw for rats after a comprehensive evaluation of the extent of the adverse effects observed and other test results. Consequently, the FSCJ deemed it unnecessary to specify an acute reference dose (ARfD), since the NOAEL for potential adverse effects of a single oral administration was considered to be above the cut-off level.

**Table 1.** *Levels relevant to toxicological evaluation of 1.4-dimethylnaphthalene*

| Species | Study | Dose (mg/kg bw per day) | NOAEL (mg/kg bw per day) | LOAEL (mg/kg bw per day) | Critical endpoints[1)] |
|---|---|---|---|---|---|
| Rat | 90-day subacute toxicity study | 0, 500, 2 500, 10 000 ppm<br>M: 0, 32, 161, 677<br>F: 0, 38, 186, 747 | M: 32<br>F: 186 | M: 161<br>F: 747 | M/F: Suppressed body weight gain, increased T.Chol, etc. |
| | Two-year combined chronic toxicity/carcinogenicity study | 0, 150, 500, 3 750 ppm<br>(Carcinogenicity cohort)<br>M: 0, 8, 27, 208<br>F: 0, 10, 33, 247 | M: 27<br>F: 10 | M: 208<br>F: 33 | M/F: Increased T.Chol, karyomegaly of renal tubular epithelial cells, etc.<br><br>(No carcinogenicity is observed.) |
| | Extended one-generation reproductive toxicity study | 0, 500, 2 000, 7 500 ppm<br>Parental generation<br>M/F: 0, 40, 160, 510<br><br>$F_1$ generation<br>M/F: 0, 45, 170, 700 | Parents:<br>PM: 40<br>PF: 40<br>$F_1$M: 45<br>$F_1$F: 45<br><br>Offspring:<br>PM: 160<br>PF: 160<br>$F_1$M:170<br>$F_1$F:170 | Parents:<br>PM:160<br>PF: 160<br>$F_1$M:170<br>$F_1$F:170<br><br>Offspring:<br>PM: 510<br>PF: 510<br>$F_1$M: 700<br>$F_1$F: 700 | Parents:<br>M/F: Increased T. Chol, increased relative weights of the liver, etc.<br><br>Offspring:<br>M/F: Suppressed body weight gain, etc.<br><br>(No effect on fertility is observed.) |
| Rabbit | Developmental toxicity study | 0, 25, 80, 250 | Dams: 80<br>Fetuses: 250 | Dams: 250<br>Fetuses: - | Dams: Body weight loss, suppressed body weight gain and decreased food intake<br><br>Fetuses: No toxicity<br><br>(No teratogenicity is observed.) |
| ADI | | | NOAEL: 10<br>SF: 100<br>ADI: 0.10 | | |
| The critical study for setting ADI | | | Two-year combined chronic toxicity/carcinogenicity study (rat) | | |

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

**Table 2.** *Potential adverse effects of a single oral administration of 1,4-dimethylnaphthalene*

| Species | Study | Dose (mg/kg bw) | Endpoints relevant to setting NOAEL and ARfD (mg/kg bw)[1)] |
|---|---|---|---|
| Rat | Acute toxicity study | M/F: 750, 1 000, 1 300, 1 700, 2 000, 2 100, 2 300, 2 500 | M/F: -<br><br>Salivation, perioral discoloration and red discoloration of perinasal fur |
| | UDS test (*in vivo*) | M: 500, 1 000 | M: 1 000<br><br>No toxicity |
| Mouse | Micronucleus test (Dose range finding study) | M/F: 500, 900, 1 300, 1 625, 2 750, 3 875, 5 000 | M/F: 500<br><br>M/F: Death |
| | Micronucleus test (Main study) | M/F: 225, 450, 900 | M: 450<br><br>Prone position accompanying dyspnea or decreased activity, death |
| | Comprehensive assessment | | 500 |
| ARfD | | | Considered unnecessary to specify (Above the cut-off level of 500mg/kg bw) |

ARfD, Acute reference dose; UDS, Unscheduled DNA synthesis test
-: NOAEL could not be specified.
[1)] The adverse effect observed at LOAEL