



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

## **Risk Assessment Report**

### **Pyroxasulfone**

(Pesticides)

Food Safety Commission of Japan (FSCJ)  
August 2019

#### **ABSTRACT**

FSCJ established health based guidance values of pyroxasulfone (CAS No.447399-55-5), an isoxazoline herbicide, based on results from various studies in the risk assessment.

The data used in the assessment include fate in animals (rats, goats and others), fate in plants (corns, soybeans and others), residue in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental neurotoxicity (rats), genotoxicity, immunotoxicity (rats and mice), and

Major adverse effects of pyroxasulfone were neurotoxicities in central and peripheral nervous system such as axonal/myelin degeneration, myocardial degeneration/necrosis in rats and mice, inflammation, degeneration or necrosis of the skeletal muscle in rats and dogs, decreased kidney weight, retrograde (ascending) nephropathy in mice and urinary bladder mucosal hyperplasia in rats.

No reproductive toxicity, teratogenicity, developmental neurotoxicity, genotoxicity relevant to human health or immunotoxicity was observed.

Increased incidences of transitional cell papillomas in the urinary bladder in males and adrenal pheochromocytomas in females were observed in a two-year carcinogenicity study in rats, however, a genotoxic mechanism was unlikely to be involved in the tumor induction and it was considered possible to establish a threshold dose in the assessment.

Based on various studies, pyroxasulfone (parent compound only) was identified as a relevant substance for residue definition for dietary risk assessment in agricultural products.

The overall no-observed-adverse-effect level (NOAEL) of a 90-day toxicity study and its additional study in dogs were 2 mg/kg bw/day. The value was the same as one-year chronic toxicity study in dogs. Taken together, 2 mg/kg bw was the lowest NOAEL in all tests. FSCJ specified an acceptable daily intake (ADI) of 0.02 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), since no adverse effects would be likely to be elicited by a single oral administration of pyroxasulfone.

**Table 1. Levels relevant of toxicological evaluation of pyrooxasulfone**

| Species | Study                                                                                                   | Dose<br>(mg/kgbw/day)                                                                                                            | NOAEL<br>(mg/kg<br>bw/day)                                                                                                                                                      | LOAEL<br>(mg/kg bw/day)                                                                                                                                                  | Critical endpoint <sup>1)</sup>                                                                                                                                               |
|---------|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rat     | 90-day subacute toxicity study<br>(the 1 <sup>st</sup> study)                                           | 0, 100, 500, 2 500, 5 000 ppm                                                                                                    | M: 43.9<br>F: 48.9                                                                                                                                                              | M: 221<br>F: 256                                                                                                                                                         | FM: Myocardial degeneration/necrosis and others                                                                                                                               |
|         |                                                                                                         | M: 0, 8.9, 43.9, 221, 451<br>F: 0, 10.2, 48.9, 256, 514                                                                          |                                                                                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                               |
|         | 90-day subacute toxicity study<br>(the 2 <sup>nd</sup> study)                                           | 0, 25, 250, 2 500 ppm                                                                                                            | M: 16.4<br>F: 20.6                                                                                                                                                              | M: 171<br>F: 205                                                                                                                                                         | FM: Myocardial degeneration/inflammation and others                                                                                                                           |
|         |                                                                                                         | M: 0, 1.7, 16.4, 171<br>F: 0, 2.0, 20.6, 205                                                                                     |                                                                                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                               |
|         | Overall evaluation of 90-day subacute toxicity study<br>(the 1 <sup>st</sup> and 2 <sup>nd</sup> study) |                                                                                                                                  | M: 43.9<br>F: 48.9                                                                                                                                                              |                                                                                                                                                                          |                                                                                                                                                                               |
|         | 90 day-subacute toxicity study                                                                          | 0, 25, 250, 2 500 ppm                                                                                                            | M: 161<br>F: 200                                                                                                                                                                | M: —<br>F: —                                                                                                                                                             | FM: No toxicological effect<br><br>(Not subacute neurotoxic)                                                                                                                  |
|         |                                                                                                         | M: 0, 1.56, 15.9, 161<br>F: 0, 1.92, 19.6, 200                                                                                   |                                                                                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                               |
|         | One-year chronic toxicity study                                                                         | 0, 5, 50, 1 000, 2 000 ppm                                                                                                       | M: 2.22<br>F: 3.12                                                                                                                                                              | M: 46.2<br>F: 60.8                                                                                                                                                       | M: Urinary bladder mucosal hyperplasia (local/multifocal/diffuse) and others<br>F: Cardiomyopathy (multifocal myocardial degeneration /inflammation/fibrosis)                 |
|         |                                                                                                         | M: 0, 0.22, 2.22, 46.2, 91.9<br>F: 0, 0.30, 3.12, 60.8, 121                                                                      |                                                                                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                               |
|         | Two-year carcinogenicity study                                                                          | 0, 5, 50, 1 000, 2 000 ppm                                                                                                       | M: 2.05<br>F: 2.69                                                                                                                                                              | M: 42.6<br>F: 54.3                                                                                                                                                       | FM: Cardiomyopathy (myocardial degeneration/inflammation/fibrosis) and others<br><br>(M: Transitional cell papillomas in the urinary bladder<br>F: Adrenal pheochromocytomas) |
|         |                                                                                                         | M: 0, 0.21, 2.05, 42.6, 84.6<br>F: 0, 0.28, 2.69, 54.3, 107                                                                      |                                                                                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                               |
|         | Two-generation reproductive toxicity study                                                              | 0, 5, 100, 2 000 ppm                                                                                                             | Parent<br>PM: 5.75<br>PF: 6.94<br>F <sub>1</sub> M: 8.72<br>F <sub>1</sub> F: 9.93<br><br>Offspring<br>PM: 5.75<br>PF: 6.94<br>F <sub>1</sub> M: 8.72<br>F <sub>1</sub> F: 9.93 | Parent:<br>PM: 114<br>PF: 135<br>F <sub>1</sub> M: 173<br>F <sub>1</sub> F: 195<br><br>Offspring<br>PM: 114<br>PF: 135<br>F <sub>1</sub> M: 173<br>F <sub>1</sub> F: 195 | Parent<br>FM: Diffuse mucosal epithelial hyperplasia in the urinary bladder and others<br>Offspring<br>FM: Suppressed body weight<br>(No effect on reproduction)              |
|         |                                                                                                         | PM: 0, 0.29, 5.75, 114<br>PF: 0, 0.36, 6.94, 135<br>F <sub>1</sub> M: 0, 0.43, 8.72, 173<br>F <sub>1</sub> F: 0, 0.48, 9.93, 195 |                                                                                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                               |

| Species | Study                                                                                                      | Dose<br>(mg/kgbw/day)                                            | NOAEL<br>(mg/kg<br>bw/day)              | LOAEL<br>(mg/kg bw/day)              | Critical endpoint <sup>1)</sup>                                                                                                                                        |
|---------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|-----------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | Developmental<br>toxicity study                                                                            | 0, 100, 500, 1 000                                               | Maternal: 500<br>Embryo/fetus:<br>1 000 | Maternal: 1 000<br>Embryo/fetus: —   | Maternal:<br>Suppressed body weight<br>Embryo/fetus:<br>No toxicological effect<br><br>(Not teratogenic)                                                               |
|         | Developmental<br>neurotoxicity study                                                                       | 0, 100, 300, 900                                                 | M: 900<br>F: 900                        | M: —<br>F: —                         | FM:<br>No toxicological effect<br>(Not developmental<br>neurotoxic)                                                                                                    |
| Mouse   | 90-day subacute<br>toxicity study<br>(the 1 <sup>st</sup> study)                                           | 0, 500, 1 000, 5 000, 10<br>000/7 500 ppm                        | M: —<br>F: 96                           | M: 103<br>F: 202                     | M: Decrease in TG<br>F: Glycogen vacuolation in<br>the liver and others                                                                                                |
|         |                                                                                                            | M: 0, 103, 206, 1 420,<br>2490<br>F: 0, 96, 202, 1 230, 1<br>940 |                                         |                                      |                                                                                                                                                                        |
|         | 90-day subacute<br>toxicity study<br>(the 2 <sup>nd</sup> study)                                           | 0, 25, 250, 2 500 ppm                                            | M: 394<br>F: 531                        | M: —<br>F: —                         | FM: No toxicological effect                                                                                                                                            |
|         |                                                                                                            | M: 0, 4.0, 39.8, 394<br>F: 0, 5.4, 51.2, 531                     |                                         |                                      |                                                                                                                                                                        |
|         | 78-week<br>carcinogenicity<br>study                                                                        | 0, 5, 150, 2 000/1 000<br>(M), 2 000/500 (F) ppm                 | M: 18.3<br>F: 22.4                      | M: 255<br>F: 76.5                    | FM: Sciatic nerve, dorsal<br>funiculus of spinal cord,<br>nasal trigeminal nerve,<br>axonal/myelin degeneration<br>and others<br><br>(Not carcinogenic)                |
|         |                                                                                                            | M: 0, 0.61, 18.3, 255<br>F: 0, 0.71, 22.4, 76.5                  |                                         |                                      |                                                                                                                                                                        |
| Rabbit  | Developmental<br>toxicity study                                                                            | 0, 250, 500, 1 000                                               | Maternal: 500<br>Embryo/fetus:<br>500   | Maternal: 1000<br>Embryo/fetus: 1000 | Maternal: Miscarriage and<br>decreased feed consumption<br>Embryo/fetus: Increase in<br>the early resorption rate and<br>lowered body weight<br><br>(Not teratogenic)  |
| Dog     | 90-day subacute<br>toxicity study<br>(the 1 <sup>st</sup> study)                                           | 0, 0.2, 2, 10                                                    | M: 2<br>F: 10                           | M: 10<br>F: —                        | M: Skeletal muscle satellite<br>cell proliferation, myofiber<br>degeneration in the<br>diaphragm and sciatic nerve<br>fiber degeneration<br>F: No toxicological effect |
|         | 90-day subacute<br>toxicity study<br>(the 2 <sup>nd</sup> study)                                           | 0, 15                                                            | FM: —                                   | FM: 15                               | FM: Sciatic nerve,<br>axonal/myelin degeneration<br>(vacuolation) and others                                                                                           |
|         | Overall evaluation of 90-day subacute toxicity<br>study<br>(the 1 <sup>st</sup> and 2 <sup>nd</sup> study) |                                                                  | M: 2<br>F: 10                           |                                      |                                                                                                                                                                        |

| Species                                | Study                           | Dose<br>(mg/kgbw/day) | NOAEL<br>(mg/kg<br>bw/day)                                                                                                                              | LOAEL<br>(mg/kg bw/day) | Critical endpoint <sup>1)</sup>                                                                  |
|----------------------------------------|---------------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|--------------------------------------------------------------------------------------------------|
|                                        | One-year chronic toxicity study | 0, 0.2, 2, 10         | FM: 2                                                                                                                                                   | FM: 10                  | FM: Sciatic nerve, (cervical/thoracic/lumbar) spinal cord, axonal/myelin degeneration and others |
| ADI                                    |                                 |                       | NOAEL: 2<br>SF: 100<br>ADI: 0.02                                                                                                                        |                         |                                                                                                  |
| The critical study for setting the ADI |                                 |                       | Overall evaluation of 90-day subacute toxicity study (the 1 <sup>st</sup> and 2 <sup>nd</sup> study) in dogs<br>One-year chronic toxicity study in dogs |                         |                                                                                                  |

ADI, Acceptable daily intake; NOAEL, No-observed-adverse effect level; SF, Safety factor

/: No test described

—: NOAEL or lowest-observed-adverse-effect level (LOAEL) was not derived

<sup>1)</sup>The adverse effect observed at LOAEL