Flometoquin (Pesticides)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of flometoquin (CAS No. 875775-74-9), a quinoline insecticide, based on results from various studies. Major adverse effects of flometoquin observed were suppressed body weight and hepatocellular steatosis in rats, and ovarian atrophy with decreased numbers of small follicle in rats and mice. Neither teratogenicity nor genotoxicity relevant to human health was detected. Increased incidences of gonadal stromal tumor in female rats and of small intestine adenocarcinomas in male mice were identified in carcinogenicity studies. Genotoxic mechanisms were, however, unlikely involved in their tumor developments, and these enabled FSCJ to establish a threshold in the assessment. Mechanism and toxicity studies suggested that ovarian atrophy triggered the development of gonadal stromal tumor, through continuous stimulation of gonadotropin to the gonadal stroma, via negative feedback. A reproductive study showed the decreases in numbers of small follicle, implantation and also in litter size. Based on the results from various studies, flometoquin (parent compound only) was the residue definition for dietary risk assessment in agricultural products. The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 0.8 mg/kg bw/day in a developmental toxicity study in rabbits. FSCJ specified an acceptable daily intake (ADI) of 0.008 mg/kg bw/day by applying a safety factor of 100 to the NOAEL. FSCJ recognized that in considering the ambiguity of the underlying mechanism, the adverse effect on small follicle possibly occurred after single oral administration of flometoquin. Thus FSCJ specified an acute reference dose (ARfD) to be 0.044 mg/kg bw by applying a safety factor of 100 to the NOAEL of 4.45 mg/kg bw per day in a two-generation reproductive toxicity study in rats, based on a comprehensive evaluation of NOAEL for ovarian toxicity.

Conclusion in Brief

FSCJ conducted a risk assessment of flometoquin (CAS No. 875775-74-9), a quinoline insecticide, based on results from various studies. The data used in the assessment include fate in animals (rats), fate in plants (tomatoes, cabbages and others), 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), and genotoxicity, and also on mechanism studies related to ovarian toxicity in rodents and tumors of small intestine in mice.

Major adverse effects of flometoquin observed were suppressed body weight and hepatocellular steatosis in rats, and ovarian atrophy with decreased numbers of small follicle in rats and mice. Neither teratogenicity nor genotoxicity relevant to human health was detected.

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<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Dose (mg/kg bw/day)</th>
<th>NOAEL (mg/kg bw/day)</th>
<th>LOAEL (mg/kg bw/day)</th>
<th>Critical endpoints</th>
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<tbody>
<tr>
<td>Rat</td>
<td>90-day subacute toxicity study</td>
<td>0, 30, 60, 120, 240 ppm M: 0, 1.80, 3.61, 7.05, 13.9 F: 0, 2.12, 4.27, 8.48, 14.8</td>
<td>M: 7.05 F: 4.27</td>
<td>M: 13.9 F: 8.48</td>
<td>M: Suppressed body weight, etc. F: Decreased number of small follicle</td>
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<td>One-year chronic toxicity study</td>
<td>0, 15, 30, 90, 180 ppm M: 0, 0.649, 1.28, 3.84, 7.42 F: 0, 0.815, 1.60, 4.82, 9.17</td>
<td>M: 3.84 F: 1.60</td>
<td>M: 7.42 F: 4.82</td>
<td>FM: Suppressed body weight, etc.</td>
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<td>Two-year carcinogenicity study</td>
<td>0, 30, 90, 180 ppm M: 0, 1.10, 3.24, 6.46 F: 0, 1.39, 4.22, 8.25</td>
<td>M: 3.24 F: 1.39</td>
<td>M: 6.46 F: 4.22</td>
<td>FM: Suppressed body weight, etc. (Carcinogenicity, F: Increased incidence of ovarian tumors at 180 ppm)</td>
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<td>Two-generation developmental toxicity study</td>
<td>0, 25, 50, 100 ppm Parent PM: 1.69, 3.38, 6.67 PF: 0, 2.00, 3.97, 7.67 F, M: 0.194, 3.93, 8.14 F, F: 0.282, 4.45, 8.84</td>
<td>Parent PM: 3.38 PF: 2.00 F1M: 3.93 F1F: 2.20 Offspring PM: 1.69 PF: 2.00 F1M: 1.94 F1F: 2.20 Fertility PM: 3.38 PF: 3.97 F1M: 3.93 F1F: 4.45 Offspring Fertility PM: 3.38 PF: 3.97 F1M: 3.93 F1F: 4.45 Fertility PM: 3.38 PF: 3.97 F1M: 3.93 F1F: 4.45</td>
<td>Parent FM: Suppressed body weight Offspring: Reduced absolute/relative thymus weight Fertility: Decreased numbers of implantation and infant, etc.</td>
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<td>Developmental toxicity study</td>
<td>0, 2, 5, 5.0, 7.5 Maternal: 5.0 Embryo/fetus: 7.5</td>
<td>Maternal: 7.5 Embryo/fetus: 7.5</td>
<td>Maternal: Death, etc. Embryo/fetus: Lower body weight, etc. (Not carcinoenic)</td>
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<td>Mouse</td>
<td>90-day subacute toxicity study</td>
<td>0, 50, 125, 250 ppm M: 0, 7.10, 16.7, 29.9 F: 0, 7.66, 18.5, 30.5</td>
<td>M: 16.7 F: 7.66</td>
<td>M: 29.9 F: 18.5</td>
<td>M: Suppressed body weight, etc. F: Decreased number of small follicle</td>
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<td>18-month carcinogenicity study</td>
<td>0, 30/152, 90, 180 ppm M: 0, 2.66, 9.86, 19.6 F: 0, 2.57, 9.95, 19.5</td>
<td>M: 2.66 F: 2.57</td>
<td>M: 9.86 F: 9.95</td>
<td>FM: Suppressed body weight (Carcinogenicity, M: Increased incidence of carcinoma in small intestine at 180 ppm)</td>
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<tr>
<td>Rabbit</td>
<td>Developmental toxicity study</td>
<td>0, 0.8, 1.2, 2 Maternal: 0.8 Embryo/fetus: 2</td>
<td>Maternal: 1.2 Embryo/fetus: -</td>
<td>Maternal: Death Embryo/fetus: No toxicity (Not teratogenic)</td>
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<tr>
<td>Dog</td>
<td>90-day subacute toxicity study</td>
<td>0, 1.25, 2.5, 5 FM: 1.25</td>
<td>FM: 2.5</td>
<td>FM: Vomit</td>
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<tr>
<td></td>
<td>One-year chronic toxicity study</td>
<td>0, 1.25, 2.5, 5 FM: 1.25</td>
<td>FM: 2.5</td>
<td>FM: Vomit</td>
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<td>ADI</td>
<td>NOAEL: 0.8 SF: 100 ADI: 0.008</td>
<td>Developmental toxicity study in rabbits</td>
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</tbody>
</table>

M, Male; F, Female; M/F, both sexes; PM, Male in Parent (P) generation; PF, Female in P generation; F1M, Male in F1 generation; F1F, Female in F1 generation; -, LOAEL could not be specified; ADI, Acceptable daily intake; SF, Safety factor

1) The adverse effect observed at the lowest-observed-adverse-effect level (LOAEL)

2) Reduced to 15 ppm from 30 ppm for the low-dose group after the 45th (44th) week of dosing to M (F)
Table 2. Potential adverse effects of a single oral administration of flometoquin

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Dose (mg/kg bw/day)</th>
<th>NOAEL (mg/kg bw/day) and critical endpoints&lt;sup&gt;1)&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Rat     | General pharmacology study (Irwin) | 0, 5, 50, 100, 200 | FM: 50  
FM: Reduced motor activity (From 1 day after beginning of the treatment) |
| Rat     | General pharmacology study (FOB) | 0, 5, 50, 150 | FM: 5  
FM: Diarrhea or loose watery feces (From 1 hour after beginning of the treatment) |
| Rat     | General pharmacology study (Respiratory system) | 0, 5, 50, 150 | M: 50  
M: Bradypnea and reduced respiratory rate (From 1 day after beginning of the treatment) |
| Rat     | General pharmacology study (Circulatory system) | M: 0, 5, 50, 150 | M: 5  
M: Lower blood pressure (From 1 day after beginning of the treatment) |
| Rat     | General pharmacology study (Automatic nerve system) | M: 0, 5, 50, 150 | M: 5  
M: Effect on pupil diameter (From 1 hour after beginning of the treatment) |
| Rat     | Developmental toxicity study | F: 50, 300 | F: -  
F: Humid perianal fur and soft feces (From 3 hours after beginning of the treatment) |
| Rat     | 28-day subacute toxicity study | M: 0, 2.40, 7.99, 20.0, 29.0  
F: 0, 2.67, 8.66, 21.0, 29.0 | F: 8.66  
F: Decreased number of follicle (small, medium, large) |
| Rat     | 90-day subacute toxicity study | M: 0, 1.80, 3.61, 7.05, 13.9  
F: 0, 2.12, 4.27, 8.48, 14.8 | F: 4.27  
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| Rat     | Two-year carcinogenicity study | M: 0, 1.10, 3.24, 6.46  
F: 0, 1.39, 4.22, 8.25 | F: 4.22  
(Carcinogenicity,  
F: Decreased number of small follicle at 180 ppm) |
| Rat     | Two-generation developmental toxicity study | PM: 0, 1.69, 3.38, 6.67  
PF: 0, 2.00, 3.97, 7.67  
F,M: 0, 1.94, 3.93, 8.14  
F,F: 0, 2.20, 4.45, 8.84 | PF: 3.97  
F,F: 4.45  
PF: Decreased number of small follicle  
F,F: Decreased number of follicles (small, medium, large) |
| Rat     | Developmental toxicity study | 0, 2.5, 5.0, 7.5 | Maternal: 5.0  
Maternal: Suppressed body weight and decreased feed consumption (During and after GD6-9 (within 3 days after beginning of the treatment)) |
| Mouse   | General pharmacology study (Default) | 0, 50, 100, 200 | FM: 50  
FM: Reduced motor activity (From 1 day after beginning of the treatment) |
| Mouse   | 28-day subacute toxicity study | M: 0, 6.91, 16.9, 28.5, 27.8  
F: 0, 7.46, 17.8, 28.2, 38.9 | F: 17.8  
F: Decreased number of follicle (small, medium, large) |
| Mouse   | 90-day subacute toxicity study | M: 0, 7.10, 16.7, 29.9  
F: 0, 7.66, 18.5, 30.5 | F: 7.66  
F: Decreased number of small follicle |

ARfD, Acute reference dose; SF, Safety factor; -, LOAEL could not be specified; GD, gestation day
1) The adverse effect observed at LOAEL