FOOD SAFETY

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Fluazifop

Summary

Food Safety Commission of Japan

The Food Safety of Commission (FSCJ) conducted a risk assessment of fluazifop (fluazifop-butyl (racemate): CAS No. 69806–50–4 and fluazifop-P-butyl (R-selective): CAS No. 79241–46–6), aryloxy phenoxypropionic acid herbicides, based on results from various studies. Fluazifop-butyl and fluazifop-P-butyl show bioequivalence in pharmacokinetics in the following animal experiments, and thus data on both the chemicals were used for the assessment irrespective of the chemical forms. The lowest no-observed-adverse-effect level (NOAEL) obtained in all the studies was 0.44 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity study of fluazifop-butyl in rats. FSCJ specified the acceptable daily intake (ADI) of 0.0044 mg/kg bw/day, applying a safety factor of 100 to the NOAEL. The lowest NOAEL for adverse effects that would be likely to be elicited by a single oral administration of fluazifop-butyl or fluazifop-P-butyl was 2 mg/kg bw/day obtained in developmental toxicity studies of fluazifop-P-butyl in rats and rabbits. Applying a safety factor of 100 to the NOAEL, FSCJ specified the acute reference dose (ARfD) of 0.02 mg/kg bw for women of child-bearing ages. For general population, the lowest NOAEL of a single oral administration of fluazifop was 948 mg/kg bw obtained in an acute toxicity study of fluazifop-P-butyl in rats. FSCJ, thus, considered it unnecessary to specify ARfD due to the NOAEL above the cut-off level (500 mg/kg bw).

Conclusion in Brief

The Food Safety of Commission (FSCJ) conducted a risk assessment of fluazifop (fluazifop-butyl (racemate): CAS No. 69806–50–4 and fluazifop-P-butyl (R-selective): CAS No. 79241–46–6), aryloxy phenoxypropionic acid herbicides, based on results from various studies. Fluazifop-butyl and fluazifop-P-butyl show bioequivalence in pharmacokinetics in the following animal experiments, and thus data on both the chemicals were used for the assessment irrespective of the chemical forms.

The data used in the assessment include the fate in animals (rats, mice, dogs, cattle, chickens and goats), fate in plants (soybeans, sugar beets, etc.), residues in crops, subacute toxicity (rats, dogs and hamsters), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats and mice), carcinogenicity (hamsters), two-generation and three-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of fluazifop-butyl include increased liver weights, increased kidney weights, chronic nephrosis, decreased testis weights with seminiferous epithelial-tubular atrophy, as well as cataracts in dogs. No neurotoxicity, carcinogenicity or genotoxicity was observed. In studies of two-generation and three-generation reproductive toxicity in

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rats, prolonged gestational period, decreased number of postimplantation and decreased conception rate were observed. In studies of developmental toxicity, diaphragmatic hernia and hydronephrosis were observed in rat fetuses. No teratogenicity was observed in rabbits at dose levels in which maternal toxicity was not observed.

Major adverse effects of fluazifop-P-butyl include increased organ weights in the liver and kidney, and seminiferous tubular degeneration and cataracts in hamsters. No carcinogenicity or genotoxicity was observed. In developmental toxicity studies, no teratogenicity was observed in rats at doses up to 300 mg/kg bw/day, in which maternal toxicity was not observed.

Based on the above results, fluazifop-butyl, fluazifop-P-butyl and the de-butylated metabolite were identified as chemicals for the residue definition for dietary risk assessment in agricultural and livestock products.

FSCJ considered it appropriate to specify an acceptable daily intake (ADI) and an acute reference dose (ARfD) based on the lowest no-observed-adverse-effect level (NOAEL) obtained in various toxicity studies of fluazifop-butyl and fluazifop-P-butyl based on the bioequivalence *in vivo* of both herbicides.

The lowest NOAEL obtained in all the studies was 0.44 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity study of fluazifop-butyl in rats. FSCJ specified the ADI of 0.0044 mg/kg bw/day, applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for adverse effects that would be likely to be elicited by a single oral administration of fluazifop-butyl or fluazifop-P-butyl was 2 mg/kg bw/day obtained in developmental toxicity studies of fluazifop-P-butyl in rats and rabbits. Delayed fetal skeletal ossification was observed without accompanying the decreased fetal body weight. Consequently, applying a safety factor of 100 to the NOAEL, FSCJ specified the ARfD of 0.02 mg/kg bw for women of child-bearing ages.

For general population, the lowest NOAEL of a single oral administration of fluazifop was 948 mg/kg bw obtained in an acute toxicity study of fluazifop-P-butyl in rats. FSCJ, thus, considered it unnecessary to specify ARfD due to the NOAEL above the cut-off level (500 mg/kg bw).