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

Risk Assessment Report

Quizalofop-ethyl and Quizalofop-P-tefuryl (Third edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

Quizalofop-ethyl and Quizalofop-P-tefuryl have the different structures of the ester part, and toxicity studies were conducted for each. For this reason, it is not possible to assess them as one compound. Therefore, the FSCJ assessed each separately and conducted a group assessment considering the similarity of metabolic pathway in *in vivo* animals and plants of Quizalofop-ethyl and Quizalofop-P-tefuryl.[1]

Abstract of each substance is described below.

(1) Quizalofop-ethyl

The FSCJ conducted a risk assessment of a phenoxypropionic acid herbicide, Quizalofop-ethyl (CAS No.76578-14-8), based on the various documents. In this revision of the third edition, the additional results of the following studies were submitted by the Ministry of Health, Labour and Welfare (MHLW): residues in crops (domestic: broccoli, burdock, etc., overseas: barley and wheat); metabolism in livestock (goats and chickens); and residues in livestock products (cattle and chickens).

The test results used for the assessment include the data on metabolism in plant (soybean, sugar beet, etc.), residues in crops, metabolism in livestock (goats and chickens), residues in livestock products, fate in animals (rats, mice and dogs), subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and others.

The major adverse effects of Quizalofop-ethyl were observed in the liver (hypertrophy of hepatocytes) and testes (atrophy). Carcinogenicity, effects on fertility, teratogenicity and genotoxicity were not observed.

Based on these results, Quizalofop-ethyl and metabolites B were identified as the relevant substances for the residue definition of dietary risk assessment in agricultural and aquatic animals, and Quizalofop-ethyl and metabolites B (including metabolites to be converted into metabolites B by hydrolysis) were identified as the relevant substances for the residue definition of dietary risk assessment in livestock products.

[1] Details of each assessment are described in Part 1 and Part 2 of the Japanese full assessment report.

The lowest value of the no-observed-adverse-effect level (NOAEL) obtained from all studies was 0.9mg/kg bw per day in two-year combined chronic toxicity/carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.009 mg/kg bw per day applying a safety factor of 100 to this NOAEL.

The lowest-observed-adverse-effect-level (LOAEL) for potential adverse effects of a single oral administration of Quizalofop-ethyl was 833 mg/kg bw in an acute toxicity study in rats. Although no NOAEL was identified from the test result, it was considered to be above the cut-off level (500 mg/kg bw) after a comprehensive evaluation of all test results, thus it was deemed unnecessary to specify an acute reference dose (ARfD).

(2) Quizalofop-P-tefuryl

The FSCJ conducted a risk assessment of a phenoxyprophonic acid herbicide, Quizalofop-P-tefuryl (CAS No. 119738-06-6), referring to the evaluation documents of overseas food safety agencies [EU(EFSA) and Australia (APVMA)].

The test results used for the assessment include the data on metabolism in plant (soybean, potato, etc.), residues in crops, metabolism in livestock (goats and chickens), fate in animals (rats), subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/ carcinogenicity (rats), carcinogenicity (mice), acute neurotoxicity (rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and others.

The major adverse effects of Quizalofop-P-tefuryl were observed in the liver (hypertrophy of hepatocytes, etc.), testis (decreased weight, etc.) and blood (anemia). Neurotoxicity and genotoxicity were not observed.

In the carcinogenicity study using rats, an increased incidence of nephromal cellomics carcinoma, Leydig cell tumor and hepatocellular adenoma and carcinoma were observed. However, the mode of action was considered non-genotoxic, and it was deemed possible to establish a threshold for evaluation.

In the two-generation reproductive toxicity study in rats, decreases of conception rate and numbers of offspring surviving were observed.

In the developmental toxicity study in rats, cleft palate and tail abnormalities were found at dose that cause adverse effects on dams. No teratogenicity was observed in rabbits.

Based on these results, Quizalofop-P-tefuryl and metabolite B were identified as the relevant substances for the residue definition of dietary risk assessment in agricultural products.

The lowest value of the NOAEL obtained from all studies was 1.3 mg/kg bw per day in the two-year combined chronic toxicity/carcinogenicity study in rats. The FSCJ specified an acceptable daily intake (ADI) of 0.013 mg/kg bw per day applying the safety factor of 100 to this NOAEL.

Meanwhile, the lowest value of the NOAEL for potential adverse effects of a single administration of Quizalofop-P-tefuryl was 30 mg/kg bw per day in developmental toxicity study in rats. The FSCJ specified an acute reference dose (ARfD) of 0.3 mg/kg by applying a safety factor of 100 to this NOAEL.

(3) Group assessment

After overall evaluation of these results, the FSCJ specified the group ADI of 0.009 mg/kg bw per day, the lower value between Quizalofop-ethyl ADI (0.009 mg/kg) and Quizalofop-P-tefuryl ADI (0.013 mg/kg), to Quizalofop-ethyl and Quizalofop-P-tefuryl.

The FSCJ determined that it would not be necessary to set an ARfD for Quizalofop-ethyl. Meanwhile, an ARfD for Quizalofop-P-tefuryl was set at 0.3 mg/kg bw. Accordingly, the FSCJ concluded that 0.3 mg/kg bw, the value of Quizalofop-P-tefuryl ARfD, should be the group ARfD of Quizalofop-ethyl and Quizalofop-P-tefuryl.

The FSCJ identified Quizalofop-ethyl, Quizalofop-P-tefuryl and metabolite B as the relevant substances for the residue definition of dietary risk assessment in agricultural products. Further, the FSCJ identified Quizalofop-ethyl and metabolite B (including metabolite to be converted to metabolite B by hydrolysis) as the relevant substances for the residue definition of dietary risk assessment in livestock products. In aquatic animals, Quizalofop-ethyl and metabolite B were identified as the relevant substances for the residue definition of dietary risk assessment.

<Group ADI and ARfD of Quizalofop-ethyl and Quizalofop-P-tefuryl>

ADI	0.009 mg/kg bw per day
The critical study for setting ADI	Combined chronic toxicity and carcinogenicity studies (Quizalofop-ethyl)
Species	Rat
Term	Two years
Route of administration	Dietary administration
NOAEL	0.9 mg/kg bw per day
Safety Factor	100

ARfD	0.3 mg/kg bw
The critical study for setting ARfD	Developmental toxicity study (Quizalofop -P-tefuryl)
Species	Rat
Term	6-15 days pregnant
Route of administration	Gavage administration
NOAEL	30 mg/kg bw per day
Safety Factor	100