

5.10 FLUPYRADIFURONE (285)

RESIDUE AND ANALYTICAL ASPECTS

Flupyradifurone, is an insecticide with the structure of butenolides. It acts as an agonist of the nicotinic acetylcholine receptor.

Flupyradifurone was first evaluated by the Meeting for toxicology in 2015 as a new compound. It was evaluated for residues in 2016 and 2017.

The 2015 Meeting established an ADI of 0–0.08 mg/kg bw and an ARfD of 0.2 mg/kg bw.

The 2016 and 2017 Meeting recommended the following residue definitions:

Definition of the residue (for compliance with the MRL) for plant commodities:
Flupyradifurone

Definition of the residue (for dietary risk assessment) for plant commodities: *Sum of flupyradifurone, difluoroacetic acid (DFA) and 6-chloronicotinic acid (6-CNA), expressed as parent equivalents*

Definition of the residue (for compliance with the MRL and dietary risk assessment) for animal commodities: *Sum of flupyradifurone and difluoroacetic acid, expressed as parent equivalents*

The residue is not fat-soluble.

On a basis of the above residue definitions, the Meeting estimated maximum residue levels for a wide range of commodities.

Flupyradifurone was listed by the Forty-ninth CCPR for evaluation of additional uses by the current Meeting. The present Meeting received information on analytical methods, storage stability, use pattern, supervised residue trials and processing in support of estimation of maximum residue levels for blackberry, raspberry, avocado, pomegranate, cacao beans, coffee beans, and hops.

Methods of analysis

A number of analytical methods for plant and animal matrices were submitted to and evaluated by the 2016 Meeting. The current Meeting received information on new analytical methods (modified methods of those already reviewed) using HPLC-MS/MS together with validation data for residues of flupyradifurone. They were validated with the LOQs ranging from 0.01–0.5 mg eq/kg for flupyradifurone, DFA and 6-CNA in the plant commodities for which supervised trial or processing study data were submitted to this Meeting.

The Meeting evaluated in 2016 and 2017 storage stability data on flupyradifurone residues in various plant matrices stored frozen. The 2017 Meeting concluded that flupyradifurone, DFA and 6-CNA are stable for at least 52 months (1556 to 1572 days) in high water, high acid, high oil, high protein, and high starch content matrices, when stored frozen at approximately -18 °C. The frozen storage periods of samples in the trial studies submitted to the current Meeting were, at the longest, 841 days.

Results of supervised residue trials on crops

The current Meeting received information on supervised trials using foliar sprays of flupyradifurone conducted in support of estimating maximum residue levels for the following commodities: cane berries (blackberry and raspberry), avocado, pomegranate, cacao beans, coffee beans (drench and foliar applications) and hops, dry.

For the calculation of the sum of flupyradifurone, DFA and 6-CNA, expressed as parent equivalents (total residues), the Meeting used the approach agreed at the 2016 JMPR:

“Where parent or DFA residues were not detected or were less than the LOQ (*i.e.* < 0.01 mg/kg for parent or 0.05 mg/kg for DFA) the LOQ value was utilized for maximum residue estimation and

dietary exposure assessment. For 6-CNA, values less than the LOQ were not added for calculation of total residues of flupyradifurone.”

The table below on how the total residues were calculated for each trial was copied from the Evaluation of the 2016 JMPR for easy reference.

Parent	DFA	6-CNA	Total
<0.01	0.05	0.01	0.07
0.01	<0.05	0.01	0.07
<0.01	<0.05	<0.01	<0.06
0.01	0.05	<0.01	0.06
0.01	0.05	0.01	0.07

All expressed in parent equivalents (concentrations are described in mg eq/kg in this evaluation).

Cane berries (Blackberry and raspberry)

Critical GAP in the USA for the cane berry crop sub-group allows two foliar applications at a maximum rate of 205 g ai/ha with an interval of 7 days, and PHI of 0 days.

Four field trials were conducted on blackberries in Canada and the USA in the 2012–2014 growing seasons.

Flupyradifurone residues from independent trials on blackberry following the above GAP were in rank order (n=2): 0.81 and 1.6 mg/kg.

In other two trials, application rates were 95–115 g ai/ha, lower than the critical GAP rate, and residues from these trials were in rank order (n=2): 0.49 and 2.1 mg/kg.

The Meeting decided to apply the proportionality principle to the residues from trials conducted with rates about half of the critical GAP rate.

The residues from the trials following the GAP and with the lower application rates, after scaling to the critical GAP rate of 205 g ai/ha, were in rank order (n=4): 0.81, 0.96, 1.6 and 3.9 mg/kg.

Corresponding total residues from the trials following the US GAP were (n=2): 0.84 and 1.7 mg/kg. Total residues from the trials using the application rates (95-115 g ai/ha) lower than the critical GAP rate were (n=2): 0.55 and 2.2 mg/kg.

The total residues from the trials following the GAP and with the lower application rates, after scaling to the GAP rate of 205 g ai/ha were: 0.84, 1.1, 1.7 and 4.1 mg/kg (highest individual residue: 4.3 mg/kg).

Seven field trials were conducted on raspberries in Canada and the USA in the 2012 growing seasons.

Flupyradifurone residues from independent trials on raspberry following the US GAP were in rank order (n=6): 0.84, 1.0, 1.1, 2.2, 2.5 and 2.5 mg/kg.

Corresponding total residues were: 0.86, 1.0, 1.1, 2.2, 2.5 and 2.5 mg/kg (highest individual residue: 2.8 mg/kg).

The US GAP is for the cane berry crop sub-group including blackberry and raspberry, and blackberry or raspberry is a representative commodity for the cane berries sub-group in the Codex classification. As the Mann-Whitney U-test on the residue populations of blackberry and raspberry indicated that these populations were not significantly different, the Meeting decided to combine these two populations to estimate a maximum residue level, STMR and HR for the subgroup of cane berries.

Combined flupyradifurone residues in rank order were (n=10): 0.81, 0.84, 0.96, 1.0, 1.1, 1.6, 2.2, 2.5, 2.5 and 3.9 mg/kg.

The Meeting estimated a maximum residue level of 6 mg/kg for the cane berries sub-group.

Corresponding combined total residues were in rank order (n=10): 0.84, 0.86, 1.0, 1.1, 1.1, 1.7, 2.2, 2.5, 2.5, and 4.1 mg/kg (highest individual residue: 4.3 mg/kg).

The Meeting estimated a STMR and HR of 1.4 mg/kg and 4.3 mg/kg, expressed in parent equivalents, respectively for the cane berries sub-group.

Avocado

Critical GAP in the USA for avocado, in the group of “tropical and subtropical, medium to large fruit, smooth, inedible peel”, allows two foliar applications at a maximum individual rate of 205 g ai/ha with an interval of 14 days, and a PHI of 1 day. Four supervised trials were conducted on avocado in the USA in 2013.

Flupyradifurone residues from independent trials on avocado following the above GAP were in rank order (n=4): 0.026, 0.19, 0.22 and 0.24 mg/kg.

The Meeting estimated a maximum residue level of 0.6 mg/kg for avocado.

The Corresponding total residues were: 0.076, 0.27, 0.29 and 0.31 mg/kg (highest individual residue: 0.36 mg/kg).

The Meeting estimated a STMR and HR of 0.28 mg/kg and 0.36 mg/kg, expressed in parent equivalents, respectively for avocado.

Pomegranate

Critical GAP in the USA for pomegranate, in the group of “tropical and subtropical, medium to large fruit, smooth, inedible peel”, allows two foliar applications at a maximum individual rate of 205 g ai/ha with an interval of 7 days, and a PHI of 0 days. Four supervised trials were conducted on pomegranate in the USA in 2012. Two trials were conducted in close proximity to each other with the application timing only a few days apart. Since other differences in the trial parameters would not affect the residue concentrations significantly, the Meeting considered that these trials were not independent.

Flupyradifurone residues from independent trials on pomegranate following the above GAP were in rank order (n=3): 0.18, 0.20 and 0.23 mg/kg.

The corresponding total residues were: 0.20, 0.22 and 0.25 mg/kg

According to the Codex document on minor crops, pomegranate requires 4 trials for estimating maximum residue level. The Meeting concluded that the data from 3 trials were insufficient to estimate a maximum residue level for pomegranate.

Cacao beans

The critical GAP is from Ghana, which allows 4 foliar applications in August, September, October and December at a maximum rate of 15 g ai/ha each with a PHI of 7 days. A total of nine supervised trials were conducted on cacao in Côte d’Ivoire and Ghana in 2014 and 2015.

Flupyradifurone residues dried cacao bean from trials approximating the GAP in Ghana were (n=7) all < 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.01(*) mg/kg for cacao beans.

Among nine decline trials, the total residue concentrations increased in two trials up to the longest days after the last application (DALA) interval, while in the others the total residue concentrations seemed to reach a peak or plateau. The Meeting considered that the dataset of total residues, regardless of DALA, would adequately cover the expected residues.

The total residues from trials approximating the GAP were (n=7): 0.051, 0.059, 0.070, 0.071, 0.087, 0.099 and 0.11 mg/kg.

The Meeting estimated a STMR of 0.071 mg/kg, expressed in parent equivalents, for cacao beans.

Coffee beans

Critical GAP in Brazil for coffee allows one drench application at 600 g ai/ha and three foliar spray applications at an application rate of 200 g ai/ha each with an interval of 15 days between foliar applications, and a PHI of 21 days. The drench application should be approximately 90 days before the spray applications. The total annual application rate for drench or foliar applications is 600 g ai/ha. A total of 16 supervised trials were conducted on coffee in Brazil, Colombia, Guatemala and Mexico in 2011 and 2012 following the GAP in Brazil.

Flupyradifurone residues in dried coffee bean, green, from independent trials on coffee following the above GAP were in rank order (n=16): < 0.01 (2), 0.02, 0.05, 0.065, 0.08, 0.14, 0.14, 0.14, 0.16, 0.20, 0.21, 0.22, 0.35, 0.55 and 0.60 mg/kg.

The Meeting estimated a maximum residue level of 0.9 mg/kg for coffee beans.

Among the 12 decline trials, the total residue concentrations steadily increased in four trials up to the longest DALA, while in the others the total residue concentrations seemed to reach a peak or plateau. The Meeting considered that the dataset of total residues, regardless of DALA, would adequately cover the expected residues.

The total residues in these trials were (n=16): < 0.06, < 0.06, 0.10, 0.10, 0.19, 0.20, 0.24, 0.29, 0.30, 0.30, 0.41, 0.49, 0.56, 0.61, 0.77 and 0.87 mg/kg.

The Meeting estimated a STMR of 0.295 mg/kg, expressed in parent equivalents, for coffee beans.

Hops, dry

A total of 12 trials were conducted on hops in Germany and the USA.

Critical GAP in the Netherlands allows one foliar application at a rate of 150 g ai/ha and a PHI of 21 days. Eight residue trials were conducted on hops in the 2010 (4) and 2011 (4) seasons in Germany.

In four trials, 6-CNA residues were detected above the LOQ in control samples of dried hop cone. Among them, in three trials, the levels were more than 25% of the total residues, and the Meeting did not use these trials in the evaluation.

Flupyradifurone residues from trials on hops in Germany approximating the GAP in the Netherlands were in rank order (n=5): 0.31, 0.43, 1.1, 1.8 and 2.0 mg/kg.

Corresponding total residues from the German trials were (n=5): 0.63, 0.73, 1.7, 2.3 and 2.4 mg/kg.

Critical GAP in the USA on hops allows one foliar application at an application rate of 154 g ai/ha and a PHI of 21 days. Four field trials were conducted on hops in the USA following the US GAP in 2011 (three trials) and 2015 (one trial).

Flupyradifurone residues in the dried hop cone from independent trials in the USA on hops following the above GAP were in rank order (n=4): 2.4, 2.7, 2.7 and 4.7 mg/kg.

In one trial in the USA, 6-CNA was not analysed in dried hop cone. Assuming that the LOQ for 6-CNA was the same as for flupyradifurone and DFA (0.5 mg eq/kg), the Meeting agreed to add 0.5 mg eq/kg as 6-CNA to the sum of flupyradifurone and DFA residues to make a conservative estimate of the total residue.

The Corresponding total residues from the USA trials were (n=4): 3.4, 3.4, 3.7, 8.1 mg/kg.

Since the data from the USA trials would lead to a higher maximum residue level, the Meeting used these trials for the estimation of the maximum residue level for hops, dry.

The Meeting estimated a maximum residue level of 10 mg/kg and a STMR of 3.55 mg/kg, expressed in parent equivalents, for hops, dry.

Fate of residues during processing

The effects of processing on the concentrations of flupyradifurone residues were evaluated by the 2016 and 2017 JMPR for a wide range of commodities for which maximum residue levels were recommended.

The current Meeting received information on the processing of cacao beans, coffee beans and dried hops to processed commodities, relevant to the current evaluation.

The calculated processing factors for these commodities together with calculated STMR-Ps are summarized below.

Total Residues			
Processed commodity	Individual processing factor	Median or best estimate	STMR/STMR-P
Cacao dry bean (RAC)			0.071
Roasted cacao bean	0.58, 0.96	0.77	0.0547
Cocoa powder	1.05, 2.22	1.64	0.116
Chocolate	0.53, 0.87	0.70	0.0497
Coffee green bean (RAC)			0.295
Roasted coffee bean	0.63, 0.68, 0.75, 0.81	0.72	0.21
Instant coffee	1.6, 3.1, 3.2, 3.4	3.2	0.94
Hops, dry (RAC)			3.55
Beer (hops)	0.01, 0.01	0.01	0.0355

Animal commodity maximum residue levels

As none of the commodities evaluated, or their by-products, for which supervised trial data were submitted to the current Meeting are fed to animals, the Meeting concluded that there was no need to revisit the previous recommendations for flupyradifurone in animal commodities.

RECOMMENDATIONS

On the basis of the data from supervised trials, the Meeting concluded that the residue levels listed below are suitable for establishing maximum residue limits and for IEDI and IESTI assessment.

Definition of the residue for compliance with the MRL for plant commodities: *Flupyradifurone*.

Definition of the residue for dietary risk assessment for plant commodities: *Sum of flupyradifurone, difluoroacetic acid (DFA) and 6-chloronicotinic acid (6-CNA), expressed as parent equivalents.*

Definition of the residue for compliance with the MRL and for dietary risk assessment for animal commodities: *Sum of flupyradifurone and difluoroacetic acid, expressed as parent equivalents.*

The residue is not fat-soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for flupyradifurone is 0–0.08 mg/kg bw. The International Daily Intakes (IEDIs) for flupyradifurone were estimated for the 17 GEMS/Food Consumption Cluster Diets using the STMR and STMR-P values estimated by JMPR. The results are shown in Annex 3 of the 2019 Extra JMPR Report.

The IEDIs ranged from 6–20% of the maximum ADI. The Meeting concluded that long-term dietary exposure to residues of flupyradifurone from uses considered by JMPR is unlikely to present a public health concern.

Acute dietary exposure

The ARfD for flupyradifurone is 0.2 mg/kg bw. The international Estimate of Short-Term Intakes (IESTIs) for flupyradifurone were calculated for the food commodities and their processes commodities for which HRs/HR-Ps or STMRs/STMR-Ps were estimated by the present Meeting and for which consumption data were available. The results are shown in Annex 4 of the 2019 Extra JMPR report.

The IESTIs varied from 0–20% of the ARfD for the general population and for children. The Meeting concluded that acute dietary exposure to residues of flupyradifurone from uses considered by the present Meeting is unlikely to present a public health concern.