FENAZAQUIN (297)

First draft prepared by Dr M Doherty, Environmental Protection Agency, Washington, USA

EXPLANATION

Fenazaquin is a quinazoline insecticide/acaricide that exhibits contact and ovicidal activity against a broad spectrum of mites in grapes, pome fruit, citrus, peaches, cucurbits, tomatoes, cotton and ornamentals. It was first evaluated by JMPR in 2017 for toxicology and residues.

The 2017 JMPR established an ADI for fenazaquin of 0–0.05 mg/kg bw and an ARfD of 0.1 mg/kg bw. The residue definition for compliance with the MRL and dietary risk assessment for plant commodities is parent fenazaquin. As listed in the 2017 Report, the residue definition for compliance with the MRL and dietary risk assessment for animal commodities is the sum of fenazaquin and the metabolites 2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid (2-hydroxy-fenazaquin acid) and quinazolin-4-ol and 3,4-dihydroquinazolin-4-one (4-hydroxyquinazoline), expressed as fenazaquin equivalents. The residue is fat soluble.

The 2017 Meeting determined that the submitted storage stability data were inadequate to support the recommendation of a maximum residue level for almonds. At the Fiftieth Session of the CCPR (2018), fenazaquin was scheduled for a follow-up evaluation of additional uses by the 2019 Extra JMPR. The Meeting received additional storage stability and residue trial data for almond, an analytical method for fenazaquin residues in animal commodities, and a cattle-feeding study.

In this document, values in text are rounded to two significant figures; values in tables are generally presented to the level of precision provided by the sponsor.

RESIDUE ANALYSIS

Analytical Methods

No new methods of analysis of fenazaquin residues in plants were submitted to the Meeting. The analytical method used in the storage stability study and the crop field trials was ANADIAG R A4167, which is the same LC-MS/MS method that was reviewed and deemed acceptable by the 2017 Meeting for analysis of residues in several plant commodities. Validation data for almond nutmeat and almond shells (S. Carringer, 2015, Report TCI-12-349) submitted to the current Meeting are summarized in Table 1 (fenazaquin) and Table 2 (*p*-tert-butylphenylethanol (TBPE) and 4-hydroxyquinazoline (4-OHQ) metabolites). The Meeting noted that the shell is the fibrous material between the nutmeat and the hull, not the hull itself.

Table 1 Method validation for residues of fenazaquin in almond commodities

Matrix	Fortified Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%) ± std. dev.	RSD (%)
Almond Nutmeat	0.01	5	88, 85, 80, 83, 81	83 ± 3.2	3.8
	0.50	5	78, 72, 73, 70, 76	74 ± 3.2	4.3
Almond Shells	0.01	5	80, 97, 88, 87, 102	91 ± 8.7	9.6
	0.50	5	92, 86, 90, 84, 82	87 ± 4.1	4.8

Table 2 Method validation for residues of metabolites TBPE and 4-OHQ in almond commodities

Matrix	Analyte	Fortified Level (ppm)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)	RSD (%)
Almond Nutmeat	TBPE	0.01	5	93, 84, 71, 83, 70	80	12
		0.10	5	84, 86, 91, 77, 90	86	6.5
	4-OHQ	0.01	5	103, 114, 105, 116, 102	108	6.0
		0.10	5	90, 94, 94, 92, 90	92	2.2

Matrix	Analyte	Fortified Level (ppm)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)	RSD (%)
Almond Shells	TBPE	0.01	5	94, 90, 89, 100, 100	95	5.6
		0.50	5	75, 73, 78, 73, 81	76	4.6
	4-OHQ	0.01	5	88, 93, 86, 90, 85	88	3.6
		0.50	5	80, 84, 83, 82, 80	82	2.2

The Meeting received a cattle-feeding study with a description and validation of a method for the analysis of fenazaquin in milk, kidney, liver, and muscle, and 2-hydroxyfenazaquin acid in kidney, liver, and muscle (L. Ferguson, 2015, Report 029280). The method consists of extraction of residues sequentially into acetone and acetonitrile:water (4:1, v/v). Extracts are cleaned-up by solid-phase extraction on HLB sorbent and then residues were analysed by LC-MS/MS.

Table 3 Recovery of fenazaquin and 2-hydroxyfenazaquin acid from cattle matrices in the livestock feeding study

			Recovery, %			
			Primary (*m/z* 307.0→161.2)		Confirmatory (*m/z* 307.0→147.2)	
Analyte	Matrix	Fortification, mg/kg	Individual	Mean ± RSD	Individual	Mean ± RSD
Fenazaquin	Milk	0.01	73.5, 83.3, 77.5	78 ± 6.3	71.8, 81.8, 70.4	75 ± 8.3
		0.2	76.2, 78.5, 83.9	80 ± 5.0	77.2, 78.4, 82.4	79 ± 3.4
		2	78.6, 84.0, 81.3	81 ± 3.3	80.9, 85.4, 81.5	83 ± 2.9
	Liver	0.01	92.3, 95.3, 93.0	94 ± 1.7	94.5, 87.9, 92.3	92 ± 3.7
		0.2	87.9, 86.4, 87.7	87 ± 0.92	88.3, 87.9, 86.4	88 ± 1.1
		2	84.5, 87.0, 86.8	86 ± 1.6	86.6, 86.0, 87.5	87 ± 0.92
	Kidney	0.01	80.1, 81.7, 88.0	83 ± 5.0	79.1, 84.8, 81.8	82 ± 3.5
		0.2	84.8, 127.0, 85.4	99 ± 24	82.3, 128.0, 82.0	97 ± 27
		2	86.0, 83.2, 82.6	84 ± 2.1	86.3, 85.5, 82.3	85 ± 2.5
	Muscle	0.01	85.9, 88.3, 88.7	88 ± 1.7	81.0, 90.2, 85.4	86 ± 5.4
		0.2	83.1, 85.0, 83.1	84 ± 1.3	82.2, 83.8, 83.0	83 ± 0.96
		2	81.1, 83.8, 83.2	83 ± 1.7	80.6, 83.5, 81.9	82 ± 1.8
	Fat	0.01	85.2, 86.3, 89.2	87 ± 2.4	84.3, 97.6, 90.0	91 ± 7.4
		0.2	74.9, 68.6, 83.2	76 ± 9.7	74.1, 69.5, 82.9	76 ± 9.0
		2	79.3, 82.5, 82.6	82 ± 2.3	78.0, 82.2, 79.0	80 ± 2.8
2-OH-Fenazaquin acid	Liver	0.01	83.0, 84.8, 80.2	83 ± 2.8	90.5, 85.8, 76.4	84 ± 8.6
		0.2	82.8, 77.9, 93.2	85 ± 9.2	82.4, 76.8, 93.1	84 ± 9.9
		2	86.0, 91.8, 93.2	90 ± 4.2	85.8, 92.7, 91.9	90 ± 4.2
	Kidney	0.01	85.9, 77.5, 84.0	82 ± 5.3	83.7, 74.2, 84.8	81 ± 7.2
		0.2	70.4, 73.6, 81.9	75 ± 7.8	72.1, 75.1, 83.7	77 ± 7.8
		2	70.2, 82.2, 82.3	78 ± 9.0	71.0, 82.9, 82.3	79 ± 8.5
	Muscle	0.01	92.4, 93.2, 96.2	94 ± 2.1	97.9, 93.9, 99.4	97 ± 2.9
		0.2	97.2, 96.6, 92.9	96 ± 2.4	96.8, 95.0, 90.4	94 ± 3.5
		2	90.7, 103.0, 89.2	94 ± 8.1	92.2, 103.0, 88.2	94 ± 8.1

The methods described above are suitable for the analysis of fenazaquin, TBPE, and 4-OHQ in almond commodities and for fenazaquin and 2-hydroxyfenazaquin acid in animal matrices. Recovery of analytes consistently fell within the range of 70 to 120% and relative standard deviations were less than 20%.

Stability of pesticide residues in stored analytical samples

A new storage stability study on almond was submitted to the Meeting. In the study (Report TCI-12-349, Carringer, 2015), almond nutmeats and shells were fortified with fenazaquin, TBPE, or 4-OHQ at 0.5 mg/kg and placed into frozen storage (-25 to -10 °C) for approximately 1 and 8 (TBPE and 4-OHQ) or 17 (fenazaquin) months prior to analysis by the method cited above; 0-day samples were also analysed. Results from storage stability samples are summarized in Table 4.

Table 4 Summary of storage stability results for almond commodities submitted to the current Meeting. Fortification level = 0.5 mg/kg.

Analyte	Matrix	Storage time, months	Residues remaining, mg/kg		% residues remaining, mg/kg	Average % remaining (normalized to 0-day)
			Procedural sample	Stored sample		
Fenazaquin	Nutmeat	0	--	0.392, 0.362, 0.364, 0.350, 0.378	78, 72, 73, 70, 76	100
		1	0.374, 0.360	0.362, 0.366	72, 73	99
		17	0.427, 0.442	0.396, 0.398	79, 80	108
	Shells	0	--	0.458, 0.432, 0.448, 0.418, 0.408	92, 86, 90, 84, 82	100
		1	0.370, 0.348	0.320, 0.302	64, 60	72
		17	0.464, 0.455	0.502, 0.495	100, 99	115
TBPE	Nutmeat	0	--	0.422, 0.455	84, 91	100
		1	0.387, 0.424	0.425, 0.504	85, 101	106
		8	0.460, 0.418	0.399, 0.446	80, 89	96
	Shells	0	--	0.348, 0.364	70, 73	100
		1	0.402, 0.438	0.393, 0.462	79, 92	120
4-OHQ	Nutmeat	0	--	0.446, 0.453	89, 91	100
		1	0.476, 0.520	0.541, 0.520	108, 104	118
		8	0.488, 0.484	0.490, 0.491	98, 98	109
	Shells	0	--	0.425, 0.441	85, 88	100
		1	0.452, 0.464	0.454, 0.424	91, 85	101

The Meeting received new storage stability data as part of the cattle feeding study. Control matrices were fortified at 0.2 mg/kg fenazaquin and stored frozen (ca. -20 °C) for 0, 0.5, 1, 2, and 4 months; data on the stability of 2-OH fenazaquin acid were not provided. Residues of fenazaquin were determined using the method described above. Concurrent recoveries at 0.2 mg/kg ranged from 79 to 98%, with most recoveries being >80%. Residues of fenazaquin in the storage stability samples are summarized in Table 5.

Table 5 Stability of fenazaquin in animal matrices during frozen storage.

Matrix	Storage time, months	Mean concurrent recovery, %	Fenazaquin, mg/kg	Mean fenazaquin, mg/kg	Mean % remaining
Milk	0	81	0.166, 0.160, 0.162	0.163	81
	0.5	89	0.173, 0.177, 0.173	0.174	87
	1	88	0.184, 0.178, 0.172	0.178	89
	2	85	0.170, 0.172, 0.176	0.173	86
	4	87	0.166, 0.170, 0.171	0.169	84
Liver	0	88	0.189, 0.179, 0.185	0.184	92
	0.5	91	0.169, 0.174, 0.169	0.171	85
	1	82	0.168, 0.161, 0.161	0.163	82
	2	92	0.168, 0.156, 0.160	0.161	81
	4	98	0.160, 0.149, 0.156	0.155	77
Kidney	0	89	0.181, 0.189, 0.184	0.185	92
	0.5	80	0.147, 0.155, 0.139	0.147	74
	1	86	0.165, 0.160, 0.168	0.164	82
	2	84	0.170, 0.168, 0.160	0.166	83
	4	83	0.161, 0.168, 0.160	0.163	82
Muscle	0	85	0.170, 0.172, 0.176	0.173	86

Matrix	Storage time, months	Mean concurrent recovery, %	Fenazaquin, mg/kg	Mean fenazaquin, mg/kg	Mean % remaining
	0.5	88	0.184, 0.180, 0.181	0.182	91
	1	92	0.183, 0.172, 0.180	0.178	89
	2	92	0.174, 0.186, 0.181	0.180	90
	4	94	0.176, 0.181, 0.180	0.179	90
Fat	0	79	0.154, 0.161, 0.155	0.157	78
	0.5	87	0.180, 0.174, 0.174	0.176	88
	1	86	0.166, 0.172, 0.173	0.171	85
	2	84	0.166, 0.170, 0.169	0.168	84
	4	91	0.175, 0.176, 0.174	0.175	87

USE PATTERN

Information on the registered uses of fenazaquin was provided to the 2017 Meeting. Information relevant to almond is presented below (Table 6).

Table 5 Registered use of fenazaquin on almond

Country	End-use product	Application			Application rate per treatment			PHI (days)
		Method	No. per crop	Application interval (days)	kg ai/hL max	Water L/ha	kg ai/ha max	
TREE NUTS								
USA a	Soluble concentrate	Broadcast ground spray/ airblast	1	N/A	Not specified	935 (minimum recommended)	0.504	7

[a] In the USA, the registration is for US Crop Group 14-12, which includes African nut-tree, almond, beechnut, Brazil nut, Brazilian pine, bunya, bur oak, butternut, cajou nut, candlenut, cashew, chestnut, chinquapin, coconut, coquito nut, dika nut, ginkgo, Guiana chestnut, hazelnut (filbert), heartnut, hickory nut, Japanese horsechestnut, macadamia nut, mongongo nut, monkey-pot, monkey puzzle nut, okari nut, pachira nut, peach palm nut, pecan, pequi, pili nut, pine nut, pistachio, sapucaia nut, tropical almond, black walnut, English walnut, and yellowhorn.

RESULTS OF SUPERVISED RESIDUE TRIALS ON CROPS

The Meeting received data from supervised residue trials conducted on almond.

The field trial reports included method validation data, as recoveries from spiked samples at levels reflecting those observed in the field trial samples; dates from critical events during the study, including application, harvest, storage, and analysis; as well as detailed information on the field site and treatment parameters. Analytical reports were sufficiently detailed and included sample sizes, example chromatograms and example calculations. Samples were analysed by the method described above.

All harvested commodities were maintained whole in the field and not homogenized until they reached the analytical laboratory.

In the summary tables, values used for making maximum residue level recommendations are underlined. Where there is more than one sample per field trial, the highest individual values for estimating dietary intake are bolded. When calculating averages, residues reported as <0.01 mg/kg were assumed to be at 0.01 mg/kg. Analytical results described in the text are rounded to two significant figures according to ISO standards; values in tables appear as reported by the sponsor. In the summary tables, residue values leading to maximum residue estimations are double underlined, residues used for dietary risk estimation are underlined, and the highest individual values selected for estimating dietary exposure are bolded.

The field trial study designs included control plots. Data from field trials evaluated by the 2017 meeting are summarized separately from studies evaluated by the current Meeting.

Supervised trials for fenazaquin:

Category	Crop	Table
Tree nuts	Almond nutmeat (TN 0660)	7
	Almond and pecan nutmeat (TN 0660 and TN 0672) from 2017 JMPR	8

Tree nuts

Almond

Four trials were conducted in the USA during the 2012 growing season (S. Carringer, 2015, Study Report TCI-12-349). At each location, one control and one treated plot were established. The treated plot received a single application of fenazaquin by airblast sprayer as a soluble concentrate. The nominal application rate was 0.5 kg ai/ha; applications were made in 524 to 627 L/ha for concentrated sprays and in 1412–1543 L/ha for dilute sprays. All trials included a non-ionic surfactant in the tank mix. Samples consisted of at least 1 kg of tree nuts and 0.3 to 1.1 kg for shells. Samples were placed into freezers within 3.5 hours of harvest and were maintained frozen until analysis. Samples were homogenized in the presence of dry ice at the analytical facility. Average concurrent recoveries across all three analytes and across fortifications of 0.01 and 0.5 ranged from 87 to 121% with standard deviations ranging from 2.1 to 14%. Almond nutmeat samples were in frozen storage for a maximum of 438 days prior to analysis for fenazaquin and for a maximum of 605 days prior to analysis of TBPE and 4-OHQ. Since almond shells are neither a human food nor a livestock feed, residue levels have not been reported herein.

Table 7 Results of 2012 fenazaquin residue trials in almond provided to the current Meeting

Report Trial No. Location	Crop (Variety)	Application			Matrix	DALA	Residues [mean] (mg/kg)		
		No.	L/ha	kg ai/ha			Fenazaquin	TBPE	4-OHQ
Critical GAP [US]	Tree nuts	1	935 [a]	0.504	--	7	--	--	--
TCI-12-349 01 [b] Terra Bella, CA, US	Almond (Nonpareil)	1	627	0.511	Nutmeat	7	<0.01, <0.01 [<u>≤0.01</u>]	ND, ND [ND]	ND, ND [ND]
TCI-12-349 04 [b] Strathmore, CA, US	Almond (Fritz)	1	1543	0.506	Nutmeat	7	<0.01, <0.01 [<u>≤0.01</u>]	ND, ND [ND]	ND, ND [ND]
TCI-12-349 02 Wasco, CA, US	Almond (Non Pareil)	1	524	0.512	Nutmeat	7	<0.01, <0.01 [<u>≤0.01</u>]	ND, ND [ND]	ND, ND [ND]
TCI-12-349 03 Fresno, CA, US	Almond (Butte)	1	1412	0.507	Nutmeat	7	<0.01, 0.0113 [<u>0.011</u>]	ND, ND [ND]	ND, ND [ND]

[a] Minimum recommended on the label; not specified as part of GAP.

[b] Separated by approx. 20 km; application and harvest dates are offset by approximately 30 days

Almond and Pecan (Evaluated by 2017 Meeting)

Residues from field trials with almond and pecan evaluated by the 2017 Meeting are provided in Table 8.

Table 8 Summary of 2008 field trials residues in almond and pecan reviewed by the 2017 Meeting

Report Trial No. Location	Crop (Variety)	Application			Matrix	DALA	Residues [mean] (mg/kg) Fenazaquin
		No.	L/ha	kg ai/ha			
Critical GAP [USA]	Tree nuts	1	935	0.504	--	7	--
TCI-08-219 06 [a] Terra Bella, CA, US	Almond (Nonpareil)	1	571	0.500	Nutmeat	1	0.047, 0.023 [0.035]
						7	<0.01, 0.012 [0.011]
						14	<0.01, <0.01 [<0.01]
						21	**0.016**, <0.01 [0.013]
TCI-08-219 09 [a] Strathmore, CA, US	Almond (Nonpareil)	1	1104	0.520	Nutmeat	7	<0.01, <0.01 [<0.01]
TCI-08-219 07 Dinuba, CA, US	Almond (Carmel)	1	1151	0.490	Nutmeat	7	<0.01, <0.01 [<0.01]
TCI-08-219 08 [b] Wasco, CA, US	Almond (Price)	1	655	0.500	Nutmeat	7	<0.01, <0.01 [<0.01]
TCI-08-219 10 [b] Wasco, CA, US	Almond (Nonpareil)	1	589	0.530	Nutmeat	7	<0.01, <0.01 [<0.01]
TCI-08-219 01 Girard, GA, US	Pecan (Desirables)	1	963	0.520	Nutmeat	6	<0.01, <0.01 [<0.01]
TCI-08-219 02 Montezuma, GA, US	Pecan (Money Makers)	1	1600	0.500	Nutmeat	7	<0.01, <0.01 [<0.01]
TCI-08-219 03 Alexandria, LA, US	Pecan (Creek)	1	1001	0.490	Nutmeat	0	0.017, 0.019 [0.018]
						7	<0.01, <0.01 [<0.01]
						14	<0.01, <0.01 [<0.01]
						21	<0.01, <0.01 [<0.01]
TCI-08-219 04 Pearsall, TX, US	Pecan (Wichita)	1	561	0.490	Nutmeat	7	<0.01, <0.01 [<0.01]
TCI-08-219 05 Anton, TX, US	Pecan (Western Schley)	1	645	0.490	Nutmeat	7	0.013, 0.015 [0.014]

[a] Trials are separated by approximately 25 km.

[b] Application and harvest dates are offset by approximately 30 days

PRIMARY FEED COMMODITIES OF PLANT ORIGIN

Almond hulls (Evaluated by 2017 Meeting)

Residues from field trials with almond evaluated by the 2017 Meeting are provided in Table 9.

Table 9 Summary of 2008 field trials residues in almond hulls reviewed by the 2017 Meeting

Report Trial No. Location	Crop (Variety)	Application			Matrix	DALA	Fenazaquin Residues [average], mg/kg
		No.	L/ha	kg ai/ha			
Critical GAP [USA]	Almond	1	935	0.504	--	7	--
TCI-08-219 06 [a] Terra Bella, CA, US	Almond (Nonpareil)	1	571	0.500	Hulls	1	1.80, 1.91 [1.86]
						7	1.01, 1.17 [1.09]
						14	1.23, 1.52 [1.38]
						21	1.33, 1.22 [1.28]

Report Trial No. Location	Crop (Variety)	Application			Matrix	DALA	Fenazaquin Residues [average], mg/kg
		No.	L/ha	kg ai/ha			
TCI-08-219 09 [a] Strathmore, CA, US	Almond (Nonpareil)	1	1104	0.520	Hulls	7	1.28, 1.12 [1.20]
TCI-08-219 07 Dinuba, CA, US	Almond (Carmel)	1	1151	0.490	Hulls	7	1.67, 1.27 [1.47]
TCI-08-219 08 [b] Wasco, CA, US	Almond (Price)	1	655	0.500	Hulls	7	0.312, 0.461 [0.387]
TCI-08-219 10 [b] Wasco, CA, US	Almond (Nonpareil)	1	589	0.530	Hulls	7	0.217, 0.315 [0.268]

[a] Trials are separated by approximately 25 km.

[b] Application and harvest dates are offset by approximately 30 days

RESIDUES IN ANIMAL COMMODITIES

Farm animal feeding studies

In a feeding study conducted in lactating Holstein cows with fenazaquin (Ferguson, 2015, Report 029280), test animals were dosed with fenazaquin by capsule for 28 days. Holstein cows were dosed at 0 (2 cows), 12.5 ppm (3 cows), 37.5 ppm (3 cows), or 125 ppm (6 cows). Milk samples were collected twice daily and pooled. Skim milk and cream were obtained from the Day-25 milk sample. Other than the cows retained to study residue depuration, the test animals were sacrificed at the end of the dosing period and tissues were collected within approximately 8 hours of the final dose. Samples of liver, muscle, kidney, fat (perirenal, mesenterial, subcutaneous) were collected and immediately placed into frozen (-22 to -10 °C) storage. Samples were homogenized in the presence of dry ice and placed back into frozen storage prior to analysis. Analysis for fenazaquin and 2-OH fenazaquin acid was done using the method described above.

Residues of fenazaquin in milk plateaued in milk by Day 3 of dosing and declined to < 0.01 mg/kg at Depuration Day 3. Residues of fenazaquin in milk were <LOQ at all time points from the 37.5 ppm dose; residues of 2-OH fenazaquin acid were not measured and samples from the 12.5 ppm dose level were not analysed. Fenazaquin residues in milk from the 125 ppm dose group averaged 0.035 mg/kg, with a maximum of 0.046 mg/kg (Table 10). Residues of fenazaquin in skim milk were <0.01 mg/kg at all feeding levels. Quantifiable residues occurred in cream from the 37.5-ppm and 125-ppm dose groups at 0.037 mg/kg and 0.12 mg/kg, respectively.

Table 10 Residues of fenazaquin in milk from the 125 ppm dose group

Dosing Day	Fenazaquin, mg/kg						
Test animal	1	2	3	4	5	6	Mean
1	<0.01	0.017	<0.01	0.020	0.022	0.020	0.016
3	0.018	0.043	0.026	0.044	0.068	0.051	0.042
7	0.013	0.037	0.022	0.033	0.044	0.053	0.034
10	0.022	0.037	0.022	0.041	0.045	0.055	0.037
13	0.016	0.030	0.017	0.036	0.046	0.041	0.031
16	0.016	0.042	0.017	0.042	0.050	0.055	0.037
19	0.016	0.029	0.021	0.029	0.047	0.040	0.030
22	0.022	0.043	0.024	0.046	0.080	0.060	0.046
25	0.017	0.036	0.016	0.034	0.030	0.051	0.031
28	0.017	0.022	0.017	0.032	0.038	0.049	0.029
Depuration 1	0.018	0.036	0.030				0.028
Depuration 3	<0.01	<0.01	<0.01				<0.01
Depuration 7	<0.01	<0.01	<0.01				<0.01
Depuration 10	<0.01						<0.01
Depuration 14	<0.01						<0.01

Residues of fenazaquin in tissues were highest in fat and lower in liver and kidney. Residues in muscle were <LOQ at the highest dose. Similarly, residues of 2-OH fenazaquin acid were <LOQ in muscle; the highest levels of 2-OH fenazaquin acid were found in liver, with lesser amounts in kidney (Table 11).

Table 11 Residues of fenazaquin in cattle tissues

Tissue	Dose level, ppm	Residues, mg eq/kg [a]				
		Fenazaquin	2-OH fenazaquin acid	4-OH quinazoline [b]	Fenazaquin + 2-OH fenazaquin acid	Fenazaquin + 2-OH fenazaquin acid + 4-OH quinazoline
Liver	12.5	Not analysed	0.011, 0.017, 0.015 [0.014]	0.0083, 0.018, 0.018 [0.011]	0.021, 0.027, 0.025 [0.024]	0.029, 0.045, 0.043 [0.039]
	37.5	<0.01, <0.01, <0.01 [<0.01]	0.052, 0.046, 0.049 [0.049]	0.039, 0.034, 0.037 [0.037]	0.062, 0.056, 0.059 [0.059]	0.10, 0.090, 0.096 [0.096]
	125	0.059, 0.029, 0.012 [0.033]	0.15, 0.10, 0.12 [0.13]	0.12, 0.076, 0.091 [0.094]	0.21, 0.13, 0.13 [0.16]	0.33, 0.21, 0.22 [0.25]
Kidney	12.5	Not analysed	<0.009, 0.009, <0.009 [0.009]	<0.002, <0.002, <0.002 [<0.002]	<0.019, <0.019, <0.019 [<0.019]	<0.021, <0.021, <0.021 [<0.021]
	37.5	<0.01, <0.01, <0.01 [<0.01]	0.027, 0.026, 0.019 [0.024]	0.018, 0.018, 0.018 [0.01]	0.037, 0.036, 0.029 [0.034]	0.055, 0.054, 0.047 [0.052]
	125	<0.01, 0.022, 0.011 [0.013]	0.061, 0.052, 0.056 [0.056]	0.018, 0.018, 0.018 [0.014]	0.071, 0.074, 0.067 [0.071]	0.089, 0.092, 0.085 [0.089]
Muscle	12.5	Not analysed	<0.009, <0.009, <0.009 [<0.009]	Assumed 0	<0.019, <0.019, <0.019 [<0.019]	<0.019, <0.019, <0.019 [<0.019]
	37.5	Not analysed	<0.009, <0.009, <0.009 [<0.009]	Assumed 0	<0.019, <0.019, <0.019 [<0.019]	<0.019, <0.019, <0.019 [<0.019]
	125	<0.01, <0.01, <0.01 [<0.01]	<0.009, <0.009, <0.009 [<0.009]	Assumed 0	<0.019, <0.019, <0.019 [<0.019]	<0.019, <0.019, <0.019 [<0.019]
Perirenal Fat	12.5	0.028, 0.056, 0.052 [0.045]	Not analysed	Assumed 0	0.028, 0.056, 0.052 [0.045]	0.028, 0.056, 0.052 [0.045]
	37.5	0.12, 0.11, 0.091 [0.11]			0.12, 0.11, 0.091 [0.11]	0.12, 0.11, 0.091 [0.11]
	125	0.32, 0.42, 0.18 [0.31]			0.32, 0.42, 0.18 [0.31]	0.32, 0.42, 0.18 [0.31]
Mesenterial fat	12.5	0.020, 0.031, 0.044 [0.032]			0.020, 0.031, 0.044 [0.032]	0.020, 0.031, 0.044 [0.032]
	37.5	0.10, 0.11, 0.083 [0.098]			0.10, 0.11, 0.083 [0.098]	0.10, 0.11, 0.083 [0.098]
	125	0.26, 0.41, 0.11 [0.26]			0.26, 0.41, 0.11 [0.26]	0.26, 0.41, 0.11 [0.26]
Subcutaneous fat	12.5	<0.01, <0.01, 0.034 [0.014]			<0.01, <0.01, 0.034 [0.014]	<0.01, <0.01, 0.034 [0.014]
	37.5	0.042, 0.048, 0.046 [0.045]			0.042, 0.048, 0.046 [0.045]	0.042, 0.048, 0.046 [0.045]
	125	0.20, 0.20, <0.01 [0.13]			0.20, 0.20, <0.01 [0.13]	0.20, 0.20, <0.01 [0.13]

[a] For fenazaquin and 2-OH fenazaquin acid reported as not analysed or <LOQ mg/kg, residues were assumed to be 0.01 mg/kg and combined residues are listed as <combined fenazaquin-equivalent LOQs only when all residues were reported as <0.01 mg/kg.

[b] Calculated from 2-OH fenazaquin acid by a factor of 0.75 (liver) or 0.25 (milk) from the goat metabolism study evaluated by the 2017 JMPR. Residues in fat were assumed to be zero.

APPRAISAL

Fenazaquin is a quinazoline insecticide/acaricide that exhibits contact and ovicidal activity against a broad spectrum of mites in grapes, pome fruit, citrus, peaches, cucurbits, tomatoes, cotton and ornamentals. It was first evaluated by JMPR in 2017 for toxicology and residues.

The 2017 JMPR established an ADI for fenazaquin of 0–0.05 mg/kg bw and an ARfD of 0.1 mg/kg bw. The residue definition for compliance with the MRL and dietary risk assessment for plant commodities is parent fenazaquin. The residue definition for compliance with the MRL and dietary risk assessment for animal commodities is the sum of fenazaquin and the metabolites 2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid (2-hydroxy-fenazaquin acid) and quinazolin-4-ol and 3,4-dihydroquinazolin-4-one (4-hydroxyquinazoline), expressed as fenazaquin equivalents. The residue is fat soluble.

The 2017 Meeting determined that the submitted storage stability data were inadequate to support the recommendation of a maximum residue level for almonds. At the Fiftieth Session of the CCPR (2018), fenazaquin was scheduled for a follow-up evaluation of additional uses by the 2019 Extra JMPR Meeting. The Meeting received additional storage stability and residue trial data for almond nutmeat and shells (the fibrous material between the nutmeat and the hull), an analytical method for the analysis of fenazaquin, 2-hydroxyfenazaquin acid, and 2-hydroxyfenazaquin-N-oxide in bovine matrices, and a cattle-feeding study.

Methods of analysis

Residue analysis for all almond sample results submitted to the 2019 Extra Meeting was done using Method ANADIAG R A4167. This LC-MS/MS method was found acceptable by the 2017 JMPR for analysis of residues in multiple plant commodities. The current meeting received validation data for residues of fenazaquin in almond nutmeat and almond shells.

For both matrices, validation data generated concurrently with the analysis of field trial samples demonstrated adequate method performance for residues of fenazaquin. The LOQ was 0.01 mg/kg for all analytes and matrices.

The Meeting received information on an analytical method that was validated in conjunction with a cattle-feeding study. Average recoveries of fenazaquin at fortification levels of 0.01, 0.2, or 2 mg/kg ranged from 76–99%. The RSDs were <10% with the exception of kidney fortified at 0.2 mg/kg, for which the RSD was 24%. The Meeting considered this to be a minor deviation. The LOQs were 0.01 mg/kg for both fenazaquin and 2-OH fenazaquin acid in all matrices.

Stability of residues in stored analytical samples

The 2017 Meeting could not conclude that stability of fenazaquin in stored almonds was adequately demonstrated based on the inconsistent percent remaining residues with increasing storage time in the previously submitted study.

Stability of fenazaquin was investigated in parallel with the field trial study submitted to the current meeting. Samples of almond nutmeat and shells were fortified with each analyte separately at 0.5 mg/kg each, stored frozen (-25 to -10 °C), and analysed using the method cited above. Residues were stable for all analytes in both matrices for at least 17 months.

Based on the results of the new study, the Meeting concluded that the new data are sufficient to support the field trials conducted in 2008 and 2012.

Definition of the residue

The current Meeting noted that there are discrepancies in the residue definitions for animal commodities provided in the 2017 report.

In examining the 2017 report for clarification, the Meeting specifically noted the following points taken from the residue definition section pertaining to residues in animals:

> "The Meeting concluded that fenazaquin and 2-hydroxy-fenazaquin acid are suitable markers for enforcement of MRLs for livestock commodities."
>
> "The metabolite 4-hydroxyquinazoline is predominantly found in milk accounting for 1.5-fold the fenazaquin residues. In tissues, 4-hydroxyquinazoline was either not detected or detected at lower levels than those of the metabolite 2-hydroxy-fenazaquin acid. The Meeting concluded

that the 2-hydroxy-fenazaquin acid and 4-hydroxyquinazoline metabolites are not likely to be more toxic than the parent fenazaquin."

The current Meeting recommended that the residue definitions for animal commodities be corrected as follows:

For compliance with the MRL: The sum of fenazaquin and the metabolite 2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid (2-hydroxy-fenazaquin acid) expressed as fenazaquin equivalents.

For estimation of dietary risk: The sum of fenazaquin and the metabolites 2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid (2-hydroxy-fenazaquin acid) and quinazolin-4-ol and 3,4-dihydroquinazolin-4-one (tautomeric forms of 4-hydroxyquinazoline), expressed as fenazaquin equivalents.

The residue is fat soluble.

As there were no recommendations made by the 2017 Meeting involving animal commodities, the previous recommendations are not affected by this correction.

Results of supervised residue trials on crops

The current Meeting received supervised trial data reflecting applications of fenazaquin to almond; these data are in addition to data reviewed by the 2017 Meeting for almond. The demonstrated period of stability of fenazaquin residues (17 months) covers the storage period for that analyte in nutmeats for the previously submitted trials (maximum storage period of 2 months) and the new trials (maximum storage period of 14 months).

A label for the end-use product containing fenazaquin was available from the USA describing the registered use of fenazaquin on the USA tree nuts crop group.

Tree nuts

The cGAP for tree nuts in the USA is a single application at up to 0.504 kg ai/ha with a 7-day PHI.

Nine trials in almonds, approximating the cGAP, were conducted in the USA. Residues of fenazaquin were (n=9): < 0.01(7), 0.011, and 0.013 mg/kg.

Five independent trials in pecan, approximating the cGAP, were conducted in the USA. Residues of fenazaquin were (n=5): < 0.01 (4), and 0.014 mg/kg.

Based on the observed similarity in residue levels for almond and pecan, the Meeting decided to use both data sets to mutually support a recommendation for tree nuts, except coconut. The combined dataset is (n=14): < 0.01(11), 0.011, 0.013 and 0.014 mg/kg.

The Meeting estimated a maximum residue level of 0.02 mg/kg, STMR of 0.01 mg/kg and HR of 0.016 mg/kg (based on highest individual value) for fenazaquin in Tree nuts (except coconut).

Animal feeds

Almond hulls

Residue data for fenazaquin in almond hulls were reviewed by the 2017 Meeting; however, that Meeting was unable to make residue estimates due to the lack of supporting storage stability data. The current Meeting decided to apply the new storage stability data for almond nutmeat and shells to the almond hull data reviewed previously.

Residues of fenazaquin in almond hulls from trials approximating cGAP were (n=5): 0.27, 0.39, 1.2, 1.4, and 1.5 mg/kg.

The Meeting estimated a maximum residue level of 4 mg/kg for almond hulls (dry; based on a dry matter content of 90% as per the OECD feed table), with a corresponding median residue of 1.2 mg/kg (as received).

Residues in animal commodities

Almond hulls are the only potential livestock feed item relevant to fenazaquin. Based on a median residue of 1.2 mg/kg, the maximum and mean dietary burdens are both 0.133 ppm. The burden is the same for beef and dairy cattle in both Australia and Canada/USA. In the feeding study, residues of fenazaquin were measured in milk and fenazaquin and 2-OH fenazaquin acids were measured in tissues. Measured residues of 2-OH fenazaquin acid were converted to fenazaquin-equivalents using the molecular weight factor of 0.869. The Meeting used results from the goat metabolism study to estimate unmeasured residues as follows:

Milk:2-OH fenazaquin acid = 0.25 × fenazaquin

4-OH quinazoline = 1.5 × fenazaquin

Liver: 4-OH quinazoline = 0.75 × 2-OH fenazaquin acid

Kidney:4-OH quinazoline = 0.25 × 2-OH fenazaquin acid

Muscle:4-OH quinazoline not detected, assumed to be zero

Fat:4-OH quinazoline not detected, assumed to be zero

Fenazaquin feeding study	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Residues (mg eq/kg)			
				Muscle	Liver	Kidney	Fat
MRL beef or dairy cattle							
Feeding study	12.5	<LOQ	12.5	<LOQ	0.027	<0.019	0.056
Dietary burden and high residue	0.133	<0.02	0.133	<0.02	<0.02	<0.02	<0.02
STMR beef or dairy cattle							
Feeding study	12.5	<0.01	12.5	<0.019	0.039	<0.019	0.045
Dietary burden and residue estimate	0.133	<0.0001	0.133	<0.0002	0.00041	<0.0002	0.00048
HR beef or dairy cattle							
Feeding study	12.5	<0.01	12.5	<0.019	0.045	<0.019	0.056
Dietary burden and residue estimate	0.133	<0.0001	0.133	<0.0002	0.00048	<0.0002	0.00060

Based on the anticipated residues, the Meeting estimated maximum residue levels of 0.02(*) mg/kg for edible offal (mammalian), mammalian fats (except milk fats), meat (from mammals other than marine mammals; as fat), milks, and milk fats. Corresponding STMRs and HRs are 0 mg/kg.

RECOMMENDATIONS

On the basis of the available data, the Meeting concluded that the residue levels listed below are suitable for establishing maximum residue levels and for IEDI and IESTI assessments.

The definition of the residue for compliance with the MRL and for dietary risk assessment for plant commodities is *fenazaquin*.

The definition of the residue for compliance with the MRL for animal commodities is *the sum of fenazaquin and the metabolite 2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid (2-hydroxy-fenazaquin acid) expressed as fenazaquin equivalents*.

The definition of the residue for dietary risk assessment for animal commodities is *the sum of fenazaquin and the metabolites 2-(4-{2-[(2-hydroxyquinazolin-4-yl)oxy]ethyl}phenyl)-2-methylpropanoic acid (2-hydroxy-fenazaquin acid) and quinazolin-4-ol and 3,4-dihydroquinazolin-4-one (tautomeric forms of 4-hydroxyquinazoline), expressed as fenazaquin equivalents*.

The residue is fat soluble.

Commodity		Recommended MRL, mg/kg		STMR or STMR-P, mg/kg	HR or HR-P, mg/kg
CCN	Name	New	Previous		
TN 0085	Tree nuts, except coconut	0.02	--	0.01	0.016
AM 0660	Almond hulls	4 (dw)	--	Median: 1.2 (as)	--
MO 0105	Edible offal (mammalian)	0.02*	--	0	0
MF 0100	Mammalian fats (except milk fats)	0.02*	--	0	0
MM 0095	Meat (from mammals other than marine mammals)	0.02* (fat)	--	Muscle: 0 Fat: 0	Muscle: 0 Fat: 0
ML 0106	Milks	0.02*	--	0	0
FM 0183	Milk fats	0.02*	--	0	0

(as) – as received; (dw) – dry weight

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for fenazaquin is 0–0.05 mg/kg bw. The International Estimated Daily Intakes (IEDIs) for fenazaquin were estimated for the 17 GEMS/Food Consumption Cluster Diets using the STMR or STMR-P values estimated by the JMPR. The results are shown in Annex 3 of the 2019 Extra JMPR Report.

The IEDIs were 0% of the maximum ADI. The Meeting concluded that long-term dietary exposure to residues of fenazaquin from uses considered by the JMPR is unlikely to present a public health concern.

Acute dietary exposure

The ARfD for fenazaquin is 0.1 mg/kg bw. The International Estimate of Short-Term Intakes (IESTIs) for fenazaquin were calculated for the food commodities and their processed 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 were 0% of the ARfD for children and for the general population. The Meeting concluded that acute dietary exposure to residues of fenazaquin from uses considered by the present Meeting is unlikely to present a public health concern.

REFERENCES

Report	Author	Year	Title
TCI-12-349	Carringer, S.J.	2015	Residues of Fenazaquin in or on Almonds Following One Application of GWN-1708 1.67 SC (2012)
029280	Ferguson, L-J.	2015	Magnitude of the Residue of Fenazaquin and Metabolite M29 N-Oxide in Bovine Tissues and Milk from a 28-Day Feeding Study