Fenpyroximate (193)

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EXPLANATION

The current Meeting identified an error in a table in the 2017 evaluation of fenpyroximate that was relied upon is setting the residue definitions for livestock commodities by the 2017 JMPR. Columns in Table 39 on lactating goat metabolism were incorrectly labelled leading the 2017 JMPR to include (*E*)-4-{[(1,3-dimethyl-5-(4-hydroxyphenoxy)pyrazol-4-yl]methyleneaminooxymethyl}benzoic acid (M-5) and its conjugates in the residue definition for risk assessment for animal commodities. The current Meeting re-evaluated the lactating goat metabolism studies and the residue definitions for livestock commodities.

In goats, the residue profile varied by matrix. The Fen-OH metabolite was consistently observed as a major residue in milk, muscle and fat (27% TRR milk, 74% TRR muscle, 35% TRR fat) and detected in liver and kidney (5% TRR liver, and 3% TRR kidney). Additional residues observed across multiple matrices at greater than 10% TRR were fenpyroximate (26% TRR milk, 36% TRR fat), N-desmethyl M-3 (20% TRR liver, 26% TRR kidney), M-3 (33% TRR muscle, 14% TRR fat, 59% TRR liver, 47% TRR kidney) and M-21 (26–55% TRR in milk). A QuEChERS method was validated for analysis of fenpyroximate and M-3 in milk, fat, muscle, and offal. Based on structural similarities between fenpyroximate, M-3 and Fen-OH, the Meeting noted that the method is likely to be suitable for analysis of Fen-OH. The Meeting confirmed that the sum of fenpyroximate, Fen-OH and M-3, expressed as fenpyroximate is a suitable marker for compliance in livestock commodities.

In addition to the residues for compliance, dietary exposure from consumption of livestock commodities may occur for the sum of M-5 and M-5-glucuronide for liver (6% TRR, 0.065 mg eq/kg) and kidney (10% TRR, 0.213 mg eq/kg), for M-21 in milk (55% TRR, 0.015 mg eq/kg), and M-22 in liver and kidney (4–9% TRR, 0.053–0.14 mg eq/kg). The toxicity of M-5, M-5-glucuronide, M-21 and M-22 are covered by parent fenpyroximate. M-5 and its conjugates were only detected in liver and kidney and only at ≤10% TRR. As such M-5 and its conjugates are expected to make a negligible contribution to overall long-term dietary exposure. Since M-21, M-22 and desmethyl-M3 were not detected in the dairy cow feeding study, the Meeting decided that they do not need to be included for assessing dietary exposure. There was no evidence in the goat metabolism study of significant levels of *Z*-isomers and it is not necessary to include *Z*-isomers in the residue definition. The Meeting decided that definition for dietary risk assessment should be revised to the sum of fenpyroximate, Fen-OH and M-3, expressed as fenpyroximate, in livestock commodities.

In summary, the fenpyroximate residue definition, for compliance with the MRL and dietary risk assessment, for animal commodities is: *sum of fenpyroximate, 2-hydroxymethyl-2-propyl (E)-4-[(1,3-dimethyl-5- phenoxypyrazol-4-yl)-methylenaminooxymethyl]benzoate (Fen-OH), and (E)-4-[(1,3-dimethyl-5-phenoxypyrazol-4-yl)methyleneaminooxymethyl]benzoic acid (M-3), expressed as fenpyroximate.*

Maximum residue levels for livestock commodities need to be revisted in light of the amended residue definitions. The dietary burdens are the same as reported by the 2017 JMPR.

Animal commodity maximum residue levels

The calculation used to estimate highest total residues for use in estimating maximum residue levels, STMR and HR values for cattle matrices is shown below.

	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Residues (mg/kg)			
				Muscle	Liver	Kidney	Fat
MRL beef or dairy cattle							
Feeding study [a]	3	0.005	3	0.017	0.42	0.36	0.083
	10	0.013	10	0.059	0.91	0.459	0.169
Dietary burden and high residue	3.503	0.0056	3.503	0.02	0.455	0.367	0.089
STMR beef or dairy cattle							
Feeding study [b]	1	0	1	< 0.01	0.19	0.20	0.015
	3	0.005	3	0.015	0.37	0.29	0.063
Dietary burden and median residue	1.595	0.0015	1.595	0.011	0.247	0.229	0.029

[a] Highest residues for tissues and mean residues for milk

[b] Mean residues for tissues and milk

For liver and kidney, the compounds measured in the feeding study and reported as the residue were the sum of fenpyroximate and M-3 while the residue definition for dietary risk assessment also includes Fen-OH. The lactating goat metabolism studies can be used to calculate scaling factors for conversion of residues measured as the sum of fenpyroximate and M-3 to the sum of fenpyroximate, Fen-OH and M-3. The scaling factors, calculated as the mean factors from the benzyl and pyrazole label experiments, are kidney 1.04 and liver 1.08. A conservative scaling factor of 1.1 is applied to the estimates for liver and kidney to give highest residues of 0.501 and 0.404 mg/kg for liver and kidney respectively and median residues of 0.272 and 0.252 mg/kg respectively.

The Meeting estimated a maximum residue level of 0.01 mg/kg for fenpyroximate for milk, of 0.1 mg/kg for mammalian meat (fat), of 0.5 mg/kg for edible offal (mammalian) and 0.1 mg/kg for mammalian fats confirming its previous recommendations. The Meeting estimated STMRs of 0.0015 mg/kg for milk, of 0.011 mg/kg for mammalian meat, 0.272 mg/kg for edible offal (mammalian) and 0.029 mg/kg for mammalian fat.

There were no changes to the conclusions of the dietary risk assessment. A corrigenda was prepared for the monograph.

CORRIGENDA

Pesticide Residues in Food 2017. Evaluations Part 1 – Residues. FAO Plant Production and Protection Paper, 233, 2018.

Changes are shown in bold

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Table 39 Metabolite levels mg equiv/kg) detected in tissues and milk of goat administered [benzyl-U-^{14}C]-fenpyroximate at a dose of 0.3 mg fenpyroximate/kg body weight/day for 3 consecutive days

Sample (times given in hours)	Distribution of metabolites (expressed as mg/kg, %TRR in parenthesis)									
	Total radio-active residue	Fenp	M-1	N-desmethyl M-3 acid	M-5	N-desmethyl M-3	M-5 glucuronide	M-3	Fen-OH	M-22
0-8 milk	0.008	NA	NA	NA	NA	NA	NA	NA	NA	NA
8-24 milk	0.013	0.003 (23)	0.005 (39)	0.000	0.000	0.000	0.000	0.000	0.003 (23)	0.000
24-32 milk	0.024	0.006 (25)	0.000	0.000	0.000	0.000	0.000	0.002 (8)	0.006 (25)	0.000
32-48 milk	0.025	0.004 (16)	0.000	0.000	0.000	0.000	0.000	0.000	0.004 (16)	0.000
48-56 milk	0.031	0.008 (26)	0.000	0.000	0.000	0.000	0.000	0.000	0.007 (23)	0.000
56-sac milk	0.022	0.003 (14)	0.000	0.000	0.000	0.000	0.000	0.000	0.006 (27)	0.000
Muscle	0.027	0.002 (7)	0.000	0.000	0.000	0.000	0.000	0.009 (33)	0.020 (74)	0.000
Fat	0.138	0.049 (36)	0.000	0.000	0.000	0.003 (2)	0.000	0.019 (14)	0.024 (17)	0.000
Kidney	2.082	0.022 (1)	0.000	0.060 (3)	0.111 (5)	0.550 (26)	0.102 (5)	0.984 (47)	0.054 (3)	0.140 (5)
Liver	1.253	0.000	0.070 (6)	0.014 (1)	0.036 (3)	0.250 (20)	0.000	0.741 (59)	0.068 (5)	0.073 (6)

Note: Values < 0.0005 mg equiv/kg are reported as 0.000 mg equiv/kg; values in parentheses represent % of total radioactive residues;

NA – not analysed due to the low total radioactive residue level (0.004 mg equiv/kg)

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[***Note***: Separate lines were included for fenpyroximate in liver and kidney in Table 235 and the explanation paragraph was modified. The GC method used for milk, muscle, fat converts fenpyroximate and Fen-OH to M-3 which is converted to the methyl ester for analysis so measure the sum of fenpyroximate and Fen-OH. The LC-MS/MS method used for liver and kidney measured fenpyroximate, M-3, N-desmethyl M-3 and M-22 separately. Fen-OH was not monitored.

In addition, the description of the lactating dairy cow feeding study has been expanded to clarify the compounds monitored in liver and kidney. The following updates the description of the lactating dairy cow feeding study including table 235.]

LIVESTOCK FEEDING STUDIES

The Meeting received the information on a lactating dairy cow feeding study (Baker F.C., Bacher R. and Gibson N., 1999, report No. R-4113). Holstein dairy cows were treated orally with gelatine capsules fortified with fenpyroximate once daily for 29 consecutive days. Groups of cows were dosed at three dose levels (3 cows/dose group) equal to 1.0, 3.0 and 10.0 ppm fenpyroximate equivalents in the diet (dry weight basis) for the low (1×), medium (3×) and high (10×) dose groups, corresponded to 0.03, 0.10 and 0.35 mg ai/kg body weight. Milk samples were collected twice a day (morning and evening) on dose days 0, 1, 3, 7, 11, 14, 18, 21, 24 and 28. Milk samples were composited as a proportion of the level of morning and evening milk production, and stored frozen prior to analysis. Cows were sacrificed between 15 and 22 hours after their last dose. Animals were examined for gross tissue abnormalities and the tissue samples of liver, kidney, composite muscle (round and loin) and composite fat (perirenal and omental) were collected, homogenised in a frozen state with dry ice and stored frozen prior to analysis. Samples were extracted with acetone, purified and subsequently analysed by ***GC-NPD (milk, muscle, fat) or LC-MS/MS (liver, kidney***). The limit of quantification for each ***analytes monitored using GC-NPD*** (fenpyroximate/Fen-OH, M-21, M-22, M-3, N-desmethyl-M-3) was 0.005 ***mg/kg*** in milk and 0.01 ***mg/kg in muscle and fat***. The limit of detection for milk, muscle and fat method (GC-NPD) was approximately 0.1 µg/mL. ***The LOQ for the analytes monitored in liver and kidney using LC-MS/MS (fenpyroximate, M-3, N-desmethyl M-3, M-22) was 0.01 mg/kg***. The limit of detection for the LC-MS/MS analysis of liver and kidney was approximately 0.005 µg/mL. All residue values were corrected for recovery of concurrent fortification samples under 100%. In addition storage stability studies were conducted to evaluate the stability of the analytes when stored frozen up to 82 days before extraction.

Milk results indicate that the mean daily fenpyroximate/Fen-OH residues in high dose milk reached a maximum level of 0.017 ***mg/kg*** 1 day and 3 days after the first dose. Mean daily residues of fenpyroximate/Fen-OH appeared to decline gradually over the remainder of the study except for an outlier at day 21 (0.016 ***mg/kg***). High dose milk contained 0.010 ***mg/kg*** at day 28. Medium dose milk contained < 0.005 mg/kg fenpyroximate/Fen-OH at day 3, 0.008 ***mg/kg*** at day 14 and 0.005 ***mg/kg*** at day 21. Metabolite M-21 was detected below the method LOQ (< 0.005 ***mg/kg***) in some high dose milk samples throughout the study. M-21 was not detected in day 3 medium dose milk and was < 0.005 ***mg/kg*** in day 14 and day 21 milk. Low dose milk was not analysed because of the low, or undetectable, residues observed in medium dose samples. Result are summarised in Table 234.

Muscle from animals receiving a high dose of fenpyroximate contained an average of 0.038 ***mg/kg*** fenpyroximate/Fen-OH and < 0.010 ***mg/kg*** of M-3. Muscle from medium dose animals contained 0.015 ***mg/kg*** fenpyroximate/Fen-OH; M-3 was undetectable. The latter result was confirmed in one sample by LC-MS/MS analysis, which allowed a lower limit of detectability. Low dose muscle contained < 0.010 ***mg/kg*** fenpyroximate/Fen-OH.

Fat from high dose animals contained an average of 0.105 ***mg/kg*** fenpyroximate/Fen-OH. Residues of M-3 were < 0.01 ***mg/kg***. Fat from animals receiving a medium dose of fenpyroximate contained an average of ***0.056 mg/kg*** fenpyroximate/Fen-OH and < 0.020 ***mg/kg*** of M-3. The absence, or low level, of M-3 in medium dose fat was confirmed in one sample by LC-MS/MS analysis. Fat from animals receiving a low dose of fenpyroximate contained 0.015 ***mg/kg*** fenpyroximate/Fen-OH.

Liver from high dose animals contained an average of < 0.010 ***mg/kg*** fenpyroximate, N-desmethyl-M-3 and M-22. M-3 residues averaged 0.80 ***mg/kg***. Liver from animals receiving a medium dose of fenpyroximate contained 0.37 ***mg/kg*** M-3; other metabolite residues were undetectable. Low dose liver contained 0.19 ***mg/kg*** M-3 and undetectable levels of other metabolites.

Kidney from high dose animals also contained a significant residue of M-3 (0.40 ***mg/kg***), a lesser amount of fenpyroximate (0.014 ***mg/kg***) and undetectable residues of N-desmethyl-M-3 and M-22. Kidney from medium dose animals contained 0.29 ***mg/kg*** M-3, < 0.01 mg/kg fenpyroximate, and undetectable levels of N-desmethyl-M-3 and M-22. Low dose kidney samples contained 0.20 ***mg/kg*** M-3; other residues were not detected.

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Table 235 Mean and range of recovery corrected residue levels found in milk and tissues of cows fed fenpyroximate at dose levels of 0.003, 0.10 and 0.35 mg/kg bw over 29 consecutive days

Analyte	Mean and (range) residue level (mg/kg)				
	Milk	Liver	Kidney	Muscle	Fat
High dose (10 ppm)					
Fenpyroximate/Fen-OH [a]	0.013* (0.006-0.022) [101.5%]	-	-	0.038 (0.024-0.049) [76.1%]	0.105 (0.046-0.159) [53.5%]
Fenpyroximate	-	< 0.010 (< 0.010-0.011) [87%]	0.014 (0.009-0.019) [77%]	-	-
M-21	< 0.005 (ND-< 0.005) [73.7%]	NA	NA	NA	NA
M-3	NA	0.80 (0.70-0.90) [103%]	0.40 (0.35-0.44) [90%]	< 0.010 (ND-< 0.010) [56.3%]	< 0.010 (ND-< 0.010) [55.2%]
N-desmethyl-M-3	NA	< 0.010 (ND-	ND	NA	NA

Analyte	Mean and (range) residue level (mg/kg)				
	Milk	Liver	Kidney	Muscle	Fat
		< 0.010) [83%]			
M-22	NA	< 0.010 (ND-0.010) [94%]	ND	NA	NA
Medium dose (3 ppm)					
Fenpyroximate/Fen-OH [a]	0.005 (< 0.005-0.011) [101.5%]	-	-	0.015 (0.012-0.017) [76.1%]	0.056 (0.025-0.073) [53.5%]
Fenpyroximate	-	ND	< 0.01 (ND-< 0.01) [77%]	-	-
M-21	< 0.005 (ND-< 0.005) [73.7%]	NA	NA	NA	NA
M-3	NA	0.37 (0.28-0.42) [103%]	0.29 (0.23-0.35) [90%]	ND	< 0.010 (ND-< 0.01) [55.2%]
N-desmethyl-M-3	NA	ND	ND	NA	NA
M-22	NA	ND	ND	NA	NA
Low dose (1 ppm)					
Fenpyroximate/Fen-OH [a]	-	-	-	< 0.010 (all < 0.010) [76.1%]	0.015 (0.010-0.018) [53.5%]
Fenpyroximate	-	ND	ND	-	-
M-21	-	NA	NA	NA	NA
M-3	NA	0.19 (0.16-0.22) [103%]	0.20 (0.18-0.23) [90%]	-	-
N-desmethyl-M-3	NA	ND	ND	NA	NA
M-22	NA	ND	ND	NA	NA

[a] ***combined residues of fenpyroximate and Fen-OH expressed as fenpyroximate mg/kg corrected for recoveries of fortifications <100%.***

NA–Not applicable;

ND–Not detected ;

- Not analysed ;

* - Does not include day 0

Recovery % is in [ ].

Animal metabolism

Lactating goats

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More than 85% of the TRR in milk and tissues was extracted with solvent. The residues of fenpyroximate in milk were 0.003–0.008 mg eq/kg (13–26% TRR). The major metabolites in milk were Fen-OH (0.003–0.007 mg eq/kg, 16–27% TRR). M-3 was detected only in milk (0.002 mg eq/kg, 8% TRR) at 23–32 hour and M-1 (0.005 mg eq/kg, 38% TRR) was only detected in milk at 8–24 hours. The residues of fenpyroximate ***were*** highest in fat (0.049 mg eq/kg, 36% TRR), followed by kidney (0.022 mg eq/kg, 1% TRR) and muscle (0.002 mg eq/kg, 7% TRR). N-desmethyl M3 (0.25-0.55 mg eq/kg, 20-26% TRR), M3 (0.741-0.98 mg eq/kg, 47-59% TRR) were the major metabolites in kidney and liver, ***Fen-OH (0.020 mg eq/kg, 74% TRR), M-3 (0.009 mg eq/kg, 33% TRR) were major metabolites in muscle. M-3 (0.019 mg eq/kg, 14% TRR) and Fen-OH (0.024 mg eq/kg, 17% TRR) were detected in fat***. M-22 was detected in kidney (0.140 mg eq/kg, 5% TRR) and liver (0.073 mg eq/kg, 6% TRR). Other metabolites detected were less than 10% TRR in tissues.

Definition of the residue

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In goats, the residue profile varied by matrix. The Fen-OH metabolite was consistently observed as a major residue ***in milk, muscle and fat (27%*** TRR milk, ***74%*** TRR muscle, 35% TRR fat) ***and detected in liver and kidney (5% TRR liver, and 3% TRR kidney)***. Additional residues observed across multiple matrices at greater than 10% TRR were fenpyroximate (26% TRR milk, 36% TRR fat), N-desmethyl M3 (20% TRR liver, 26% TRR kidney), M-3 (***33% TRR muscle, 14% TRR fat, 59% TRR liver, 47% TRR kidney) and M-21 (26–55% TRR in milk***). A QuEChERS method was validated for analysis of fenpyroximate and M-3 in milk, fat, muscle, and offal. Based on structural similarities between fenpyroximate, M-3 and Fen-OH, the Meeting noted that the method is likely to be suitable for analysis of Fen-OH. The Meeting decided that the sum of fenpyroximate, Fen-OH and M-3, expressed as fenpyroximate is a suitable marker for compliance in livestock commodities.

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In addition to the residues for compliance, dietary exposure from consumption of livestock commodities may occur for ***the sum of M-5 and*** M-5-glucuronide for liver (***6% TRR, 0.065*** mg eq/kg) and kidney (***10% TRR, 0.213 mg eq/kg***), for M-21 in milk (***55% TRR, 0.015 mg eq/kg***), and M-22 in ***liver and kidney (4-9% TRR, 0.053-0.14 mg eq/kg***). The toxicity of ***M-5***, M-5- glucuronide, M-21 and M-22 are covered by parent fenpyroximate. ***M-5 and its conjugates were only detected in liver and kidney and only at ≤10% TRR. As such M-5 and its conjugates are expected to make a negligible contribution to overall long-term dietary exposure***. Since M-21 and M-22 were not detected in the dairy cow feeding study, the Meeting decided that they do not need to be included for assessing dietary exposure. ***There was no evidence in the goat metabolism study of significant levels of Z-isomers and it is not necessary to include Z-isomers in the residue definition***. The Meeting decided that definition for dietary assessment is the sum of fenpyroximate, Fen-OH and M-3, expressed as fenpyroximate, in livestock commodities.

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Residue definition of fenpyroximate for animal commodities for compliance with MRL and for dietary risk assessment is sum of fenpyroximate, Fen-OH and M-3, expressed as fenpyroximate.

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Animal commodity maximum residue levels

The calculation used to estimate highest total residues for use in estimating maximum residue levels, STMR and HR values for cattle matrices is shown below.

	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Residues (mg/kg)			
				Muscle	Liver	Kidney	Fat
MRL beef or dairy cattle							
Feeding study [a]	3	0.005	3	0.017	0.42	0.36	0.083
	10	0.013	10	0.059	0.91	0.459	0.169
Dietary burden and high residue~~s~~	3.503	0.0056	3.503	0.02	0.455	0.367	0.089
STMR beef or dairy cattle							
Dietary burden and median residue	1	0	1	< 0.01	0.19	0.20	0.015
Feeding study [b]	3	0.005	3	0.015	0.37	0.29	0.063
Dietary burden and median residue	1.595	0.0015	1.595	0.011	0.247	0.229	0.029

[a] Highest residues for tissues and mean residues for milk

[b] mean residues for tissues and milk

For liver and kidney, the compounds measured in the feeding study and reported as the residue were the sum of fenpyroximate and M-3 while the residue definition for dietary risk assessment also includes Fen-OH. The lactating goat metabolism studies can be used to calculate scaling factors for conversion of residues measured as the sum of fenpyroximate and M-3 to the sum of fenpyroximate, Fen-OH and M-3. The scaling factors, calculated as the mean factors from the benzyl and pyrazole label experiments, are kidney 1.04 and liver 1.08. A conservative scaling factor of 1.1 is applied to the estimates for liver and kidney to give highest residues of 0.501 and 0.393 mg/kg for liver and kidney respectively and median residues of 0.272 and 0.252 mg/kg respectively.

The Meeting estimated a maximum residue level of 0.01* mg/kg for fenpyroximate for milk, of 0.1 mg/kg for mammalian meat (fat), of 0.5 mg/kg for edible offal (mammalian) and 0.1 mg/kg for mammalian fats. The Meeting estimated an STMR of 0.0015 mg/kg for milk, of 0.011 mg/ kg for mammalian meat, ***0.272*** mg/kg for edible offal (mammalian) and ***0.029*** mg/kg for mammalian fat.