Propamocarb (148)

The first draft was prepared by Dr Mi-Gyung Lee Andong National University Republic of Korea

EXPLANATION

Propamocarb is a systemic carbamate fungicide, which was first evaluated in 1984. It was evaluated under the periodic review program in 2005 for toxicology and 2006 for residues. The ADI and ARfD are established at 0–0.4 mg/kg bw and 2 mg/kg bw, respectively. The residue definition for plant and animal commodities is propamocarb (free base) for both enforcement of MRLs and dietary exposure assessment. The residue is not fat-soluble.

In 2014, the JMPR estimated maximum residue levels on new uses including kale and head cabbage, however, the maximum residue levels for mammalian commodities could not be estimated since a cattle feeding study did not encompass the estimated maximum cattle dietary burden. The 2014 Meeting recommended withdrawing the previous maximum residue level recommendations for mammalian commodities.

At the Forty-ninth Session of the CCPR (2017), propamocarb was scheduled for the evaluation of a new livestock feeding study by the 2018 JMPR and consideration of maximum residue levels for mammalian commodities. The Meeting received a dairy cow feeding study, analytical method and storage stability study from the manufacturer.

RESIDUE ANALYSIS

Analytical methods

A new method was developed for the determination of residues of propamocarb and its metabolites (propamocarb N-oxide, 2-hydroxypropyl propamocarb, propamocarb oxazolidinone and propamocarb glucuronide) in animal matrices [Kormos, 2014, report PR-002-A14-01 and PR-002-A14-02]. Residues in animal matrices were extracted with either 0.1% 1 N acetic acid in methanol for propamocarb glucuronide or acetonitrile for all other analytes. The extracts were filtered, and internal standards were added. The extracts were then cleaned by liquid extraction with hexane, brought to dryness, and reconstituted in 0.05% hydrochloric acid in water. Reconstituted samples were syringe filtered through a PTFE filter and analysed by LC-MS/MS. Information on mass transitions monitored are shown in Table 1.

The linearity in the range of 0.0625 ng/mL to 62.5 ng/mL was satisfactory (r^2= >0.99). No significant interferences from the specimen matrix were detected at the retention times corresponding to the analytes. The LOQ values for all analytes were 0.01 mg/kg in milk, cream and whey and 0.02 mg/kg in animal tissues (muscle, liver, kidney and fat), as parent equivalents. The LODs were determined from data obtained from control samples fortified at the respective analyte LOQs. The LOD was calculated by multiplying the standard deviation of recovery measurements at the LOQ, by $T_{0.99}$, the one-tailed Student's t statistic. In all tested matrices, mean recoveries of the analytes at the LOQ level and the higher levels were within the acceptable range of 70–118% and the RSDs were ≤18% except for propamocarb N-oxide in fat (21%). The recovery results and LOD/LOQ values are shown in Table 2.

Table 1 Quantification, confirmatory and internal standard mass transitions

	Mass transition used		Mass transition used for isotopically labelled internal standard (3rd MRM)
	Quantitation (1st MRM)	Confirmation (2nd MRM)	
Propamocarb	189.3>101.9	189.3>144.0	196.3>102.9
Propamocarb N-oxide	205.2>102.1	205.2>143.9	-
2-hydroxypropyl propamocarb	205>102.1	205>74.1	-
Propamocarb oxazolidinone	202.9>141.9	202.9>139.8	-
Propamocarb glucuronide	364.9>188.9	364.9>101.9	372.4>196.1

Table 2 Recoveries of propamocarb and its metabolites from cow's milk and tissues

Matrix	Analyte	Spike level (mg/kg)	Sample size (n)	Recoveries (%)		RSD	LOD, mg/kg parent equivalent	LOQ, mg/kg parent equivalent
				Range	Mean			
Milk	2-hydroxypropyl Propamocarb	0.010	19	71–87	79	6	0.0013	0.010
		0.200	3	92–94	93	1		
		0.300	3	92–110	100	9		
	Propamocarb	0.010	19	86–109	97	6	0.0015	0.010

Matrix	Analyte	Spike level (mg/kg)	Sample size (n)	Recoveries (%)		RSD	LOD, mg/kg parent equivalent	LOQ, mg/kg parent equivalent
				Range	Mean			
	glucuronide	0.200	3	110–118	114	4		
	Propamocarb N-oxide	0.010	19	74– 95	83	8	0.0012	0.010
		0.200	3	95–100	97	2		
		0.300	3	100–109	105	5		
	Propamocarb oxazolidinone	0.010	19	62–101	84	12	0.0037	0.010
		0.200	3	83–88	85	4		
		0.300	3	78–87	83	6		
	Propamocarb	0.010	19	80–106	90	8	0.0010	0.010
		0.200	3	103–105	104	1		
		0.300	3	99–106	104	4		
Cream	2-hydroxypropyl Propamocarb	0.010	3	86–113	101	13	0.0013	0.010
		0.300	3	98–113	103	9		
	Propamocarb glucuronide	0.010	3	94–97	96	1	0.0015	0.010
	Propamocarb N-oxide	0.010	3	84–103	95	11	0.0012	0.010
		0.300	3	106–117	110	5		
	Propamocarb oxazolidinone	0.010	3	100–117	109	8	0.0037	0.010
		0.300	3	89–103	95	8		
	Propamocarb	0.010	3	103–107	104	2	0.0010	0.010
		0.300	3	102–111	106	5		
Whey	2-hydroxypropyl Propamocarb	0.010	3	78–88	83	6	0.0013	0.010
		0.300	3	89–95	92	3		
	Propamocarb glucuronide	0.010	3	90–96	94	3	0.0015	0.010
	Propamocarb N-oxide	0.010	3	87–90	89	1	0.0012	0.010
		0.300	3	102–107	105	2		
	Propamocarb oxazolidinone	0.010	3	82–98	93	10	0.0037	0.010
		0.300	3	83–86	84	2		
	Propamocarb	0.010	3	95–101	98	3	0.0010	0.010
		0.300	3	96–103	100	3		
Fat	2-hydroxypropyl Propamocarb	0.020	9	72–122	91	18	0.0084	0.020
		0.200	3	89–105	98	8		
		0.500	3	70–82	77	8		
	Propamocarb glucuronide	0.020	10	93–105	99	4	0.0027	0.020
		0.200	3	105–107	106	1		
	Propamocarb N-oxide	0.020	9	77–126	92	21	0.0026	0.020
		0.200	3	92–99	96	3		
		0.500	3	97–107	102	5		
	Propamocarb oxazolidinone	0.020	9	62–100	82	15	0.0067	0.020
		0.200	3	80–95	88	9		
		0.500	2	69–71	70	-		
	Propamocarb	0.020	9	98–123	107	8	0.0022	0.020
		0.200	3	110–112	111	1		
		0.500	3	110–116	112	4		
Kidney	2-hydroxypropyl Propamocarb	0.020	9	74–116	88	14	0.0030	0.020
		0.200	3	91–106	98	7		
		4.000	3	96–111	102	8		
	Propamocarb	0.020	9	95–107	100	5	0.0024	0.020

Matrix	Analyte	Spike level (mg/kg)	Sample size (n)	Recoveries (%)		RSD	LOD, mg/kg parent equivalent	LOQ, mg/kg parent equivalent
				Range	Mean			
	glucuronide	0.200	3	110–116	112	3		
		0.300	3	110–113	111	2		
	Propamocarb N-oxide	0.020	9	85–92	90	3	0.0013	0.020
		0.200	3	96–103	100	3		
		4.000	3	99–113	105	7		
	Propamocarb oxazolidinone	0.020	9	75–115	90	13	0.0047	0.020
		0.200	3	84–94	89	6		
		4.000	3	98–113	106	8		
	Propamocarb	0.020	9	95–127	103	10	0.0020	0.020
		0.200	3	110–111	111	0		
		4.000	3	102–107	104	2		
Liver	2-hydroxypropyl Propamocarb	0.020	9	79–89	85	5	0.0024	0.020
		0.200	3	78–92	86	8		
		1.400	3	80–87	84	5		
	Propamocarb glucuronide	0.020	9	95–114	99	7	0.0022	0.020
		0.200	3	113–117	115	2		
		3.000	3	96–100	98	2		
	Propamocarb N-oxide	0.020	9	67–85	80	8	0.0040	0.020
		0.200	3	90–92	91	1		
		1.400	3	82–87	86	3		
	Propamocarb oxazolidinone	0.020	9	70–84	76	7	0.0027	0.020
		0.200	3	68–82	75	9		
		1.400	3	77–83	80	4		
	Propamocarb	0.020	9	92–126	107	10	0.0042	0.020
		0.200	3	105–107	106	1		
		1.400	3	106–114	111	5		
Muscle	2-hydroxypropyl Propamocarb	0.020	9	70– 98	85	11	0.0045	0.020
		0.200	3	94–99	97	2		
		0.500	3	88–97	93	5		
	Propamocarb glucuronide	0.020	10	97–106	103	3	0.0021	0.020
		0.200	3	117–121	118	3		
	Propamocarb N-oxide	0.020	9	82–104	87	9	0.0019	0.020
		0.200	3	88–92	90	2		
		0.500	3	100–105	102	3		
	Propamocarb oxazolidinone	0.020	9	71–87	79	8	0.0036	0.020
		0.200	3	84–87	86	1		
		0.500	3	78–83	80	3		
	Propamocarb	0.020	9	92–115	98	7	0.0020	0.020
		0.200	3	108–110	109	1		
		0.500	3	100–102	101	1		

This table includes concurrent recoveries generated in the lactating cow feeding study evaluated by this JMPR.

Stability of residues in stored analytical samples

In the cow feeding study described in the next section, the analyses for propamocarb glucuronide were performed after samples had been in storage for longer than one month, thus the stability of propamocarb glucuronide was tested in cow's milk and tissues (kidney, liver, fat and muscle) kept in a freezer set at -20 °C [Tauber, 2004, report B004898]. Milk samples were fortified at 0.1 mg/kg, while tissue samples were fortified at 0.05 mg/kg and stored at approximately -10 °C to -27 °C for up to 12 months. For the

analysis of propamocarb glucuronide, the residue in milk and tissues was extracted by homogenization with 1% hydrochloric acid in methanol. The extract was purified by hexane partitioning and the analyte was determined by LC-MS/MS (mass transition: *m/z* 365.0>189.0). This analytical method has been used in the cow feeding study evaluated by the 2014 JMPR.

In the recovery test of propamocarb glucuronide conducted prior to the analysis of stored samples, the results were satisfactory, n=2 at each fortification level: 83–108% (total n=4) in milk samples fortified at 0.01 and 0.1 mg/kg; 73–108% (total n=16) in tissues, each fortified at 0.05 and 0.5 mg/kg.

Storage stability results are shown in Table 3. The data demonstrated that propamocarb glucuronide is stable in cow's milk, kidney, liver, fat and muscle when stored at -10 °C to -27 °C for at least 12 months.

Table 3 Storage stability results of propamocarb glucuronide in cow's milk and tissues

Matrix	Storage days	Fortification (mg/kg)	Residue level in stored samples (mg/kg)		Procedural recovery (%)
			Concentration (mg/kg)	Average recovery (%)	
Milk	0	0.1	0.088, 0.11	99	
	32	0.1	0.10, 0.11	108	107, 118
	91	0.1	0.091, 0.11	102	92, 107
	187	0.1	0.095, 0.098	97	83, 92
	371	0.1	0.090, 0.095	88	91, 91
Kidney	0	0.5	0.48, 0.59	107	
	30	0.5	0.46, 0.48	94	87, 98
	90	0.5	0.48, 0.56	103	91, 99
	184	0.5	0.41, 0.43	84	93, 97
	367	0.5	0.50, 0.51	101	98, 104
Liver	0	0.5	0.47, 0.51	98	
	30	0.5	0.52, 0.54	106	100, 102
	91	0.5	0.49, 0.49	98	95, 102
	183	0.5	0.50, 0.50	100	95, 102
	368	0.5	0.39, 0.40	79	96, 118
Fat	0	0.5	0.44, 0.45	89	
	32	0.5	0.46, 0.47	93	96, 98
	91	0.5	0.46, 0.45	92	88, 92
	184	0.5	0.45, 0.45	90	88, 89
	367	0.5	0.45, 0.46	92	104, 106
Muscle	0	0.5	0.36, 0.46	82	
	32	0.5	0.42, 0.47	90	95, 110
	91	0.5	0.50, 0.50	100	79, 101
	185	0.5	0.45, 0.46	91	85, 95
	367	0.5	0.45, 0.47	93	88, 93

RESIDUES IN ANIMAL COMMODITIES

Livestock feeding studies

A feeding study on Holstein dairy cows (*Bos Taurus*) was conducted [Kormos and Jerkins, 2015, report RAPRN023]. The dairy cattle were dosed for 29 consecutive days (morning dosing) via oral capsules containing propamocarb in the form of propamocarb-hydrochloride. Target doses (propamocarb equivalents, not propamocarb-HCl) were 15, 30 and 150 ppm dry matter feed.

Table 4 Propamocarb dose administration on dairy cow

Dose group	Dose level (mg/kg bw/day)	Number of cows (n)	Target dose (ppm feed)	Actual dose (ppm feed)
Control	0.0	3	0.0	0.0
Treated groups	0.545	3	15	13.6
	1.091	3	30	26.3
	5.455	6	150	138

Dose values are in terms of propamocarb equivalents, not propamocarb-HCl equivalents.

Milk was collected twice daily from all dose groups, morning and evening. Doses were administered after the morning milking. Milk samples were collected on study days 0, 2, 4, 7, 10, 14, 17, 21, 25 and 28. In addition, a portion of the day 25 milk sample from the 150 ppm dose group was separated into cream (milk fat) and whey (skim milk) for analysis. On Day 29 (3 to 7 hours after the final dose), all of the 15 and 30 ppm dose group cows, and 3 of the 150 ppm cows were killed.

The remaining 3 cows in the 150 ppm dose group entered the depuration phase of the study. The depuration study cows were killed 7, 14, and 28 days following the last administered dose (days 36, 43, and 57). Additional milk samples were collected from the 150 ppm dose depuration cows on days 31, 35, 38, 42, 47, 52, and 56. All collected milk and tissue (fat, kidney, liver and muscle) samples were stored frozen at -15 °C to -20 °C or on dry ice during shipment.

Residues of propamocarb and its metabolites (propamocarb glucuronide, propamocarb N-oxide, 2-hydroxypropyl propamocarb, and propamocarb oxazolidinone) in milk and tissue samples were analyzed using the validated LC-MS/MS method described in the analytical method section above. All samples were analysed within 21 days of collection, except propamocarb glucuronide analysed within 33 days. The storage stability period of propamocarb glucuronide in cow's milk and tissues was demonstrated for 12 months, when stored at -10 °C to -27 °C (see storage stability section above).

Table 5 Residue concentrations detected in cow's milk following 29 consecutive days of dosing with propamocarb-HCl

Sampling day	Residue concentration in milk, mg/kg propamocarb equivalent, average value in parentheses				
	Propamocarb N-oxide	Propamocarb	Propamocarb oxazolidinone	2-hydroxypropyl Propamocarb	Propamocarb glucuronide
Dose: 13.6 ppm propamocarb equivalents					
Day 0	nd, nd, nd	nd, nd, nd	nd, nd, nd	nd, nd, nd	nd, nd, nd
Day 2	<0.01, <0.01,0.011 (0.010)	nd, nd, nd	nd, nd, nd	0.014, 0.017, 0.027 (0.019)	nd, nd, nd
Day 4	<0.01, <0.01, 0.012 (0.011)	nd, nd, nd	nd, nd, nd	0.016, 0.028, 0.025 (0.023)	nd, nd, nd
Day 7	<0.01, <0.01, 0.025 (0.015)	nd, nd, nd	nd, nd, nd	0.017, 0.020, 0.050 (0.029)	nd, nd, nd
Day 10	<0.01, <0.01, <0.01	nd, nd, nd	nd, nd, nd	0.017, 0.019, 0.020 (0.019)	nd, nd, nd
Day 14	0.011, <0.01, 0.011 (0.011)	nd, nd, nd	nd, nd, nd	0.014, 0.019, 0.020 (0.018)	nd, nd, nd
Day 17	<0.01, <0.01, <0.01	nd, nd, nd	nd, nd, nd	0.020, 0.020, 0.020 (0.020)	nd, nd, nd
Day 21	<0.01, <0.01, 0.011 (0.010)	nd, nd, nd	nd, nd, nd	0.017, 0.019, 0.017 (0.018)	nd, nd, nd
Day 25	<0.01, <0.01, 0.014 (0.011)	nd, nd, nd	nd, nd, nd	0.020, 0.021, 0.026 (0.022)	nd, nd, nd
Day 28	<0.01, 0.011, 0.028 (0.016)	nd, nd, <0.01	nd, nd, <0.01	0.018, 0.023, 0.045 (0.029)	nd, nd, nd
Dose: 26.3 ppm propamocarb equivalents					
Day 0	nd, nd, nd	nd, nd, nd	nd, nd, nd	nd, nd, nd	nd, nd, nd
Day 2	0.027, 0.020, 0.012 (0.019)	<0.01, nd, nd	nd, nd, nd	0.052, 0.038, 0.026 (0.038)	nd, nd, nd
Day 4	0.023, 0.019, <0.01 (0.017)	<0.01, <0.01, nd	nd, nd, nd	0.050, 0.049, 0.021 (0.040)	nd, nd, nd
Day 7	0.021, 0.019, 0.012 (0.017)	<0.01, nd, nd	nd, nd, nd	0.057, 0.039, 0.034 (0.043)	nd, nd, nd
Day 10	0.020, 0.022, 0.014 (0.019)	<0.01, <0.01, nd	nd, nd, nd	0.046, 0.046, 0.032 (0.041)	nd, nd, nd
Day 14	0.024, 0.021, 0.011 (0.019)	nd, nd, nd	nd, nd, nd	0.048, 0.041, 0.025 (0.038)	nd, nd, nd
Day 17	0.024, 0.021, 0.014 (0.020)	<0.01, nd, nd	nd, nd, nd	0.049, 0.039, 0.032 (0.040)	nd, nd, nd
Day 21	0.020, 0.017, 0.014 (0.017)	<0.01, nd, nd	nd, nd, nd	0.043, 0.034, 0.035 (0.038)	nd, nd, nd
Day 25	0.021, 0.021, 0.014 (0.019)	nd, nd, nd	nd, nd, nd	0.039, 0.043, 0.034 (0.039)	nd, nd, nd
Day 28	0.028, 0.025, 0.019 (0.024)	<0.01, <0.01, nd	nd, nd, nd	0.054, 0.049, 0.029 (0.044)	nd, nd, nd
Dose: 138 ppm propamocarb equivalents					

Sampling day	Residue concentration in milk, mg/kg propamocarb equivalent, average value in parentheses				
	Propamocarb N-oxide	Propamocarb	Propamocarb oxazolidinone	2-hydroxypropyl Propamocarb	Propamocarb glucuronide
Day 0	nd, nd, nd	nd, nd, nd, <0.01, nd, nd	nd, nd, nd, nd, nd, nd	nd, nd, nd, nd, nd, nd	nd, nd, nd, nd, nd, nd
Day 2	0.11, 0.10, 0.11, 0.090, 0.13, 0.16 (0.12)	<0.01, <0.01, 0.017 0.013, 0.017, 0.015 (0.014)	<0.01, <0.01, <0.01, <0.01, <0.01, <0.01	0.15, 0.16, 0.23, 0.13, 0.23, 0.18 (0.18)	nd, nd, nd, nd, nd, nd
Day 4	0.096, 0.091, 0.095, 0.087, 0.11, 0.16 (0.11)	0.013, 0.014, 0.015, 0.019, 0.012, 0.019 (0.015)	<0.01, <0.01, <0.01, <0.01, <0.01, <0.01	0.17, 0.20, 0.24, 0.17, 0.15, 0.21, (0.19)	nd, nd, nd, nd, nd, nd
Day 7	0.084, 0.10, 0.10, 0.086, 0.12, 0.17 (0.11)	<0.01, 0.013, 0.012, 0.019, 0.016, 0.017 (0.015)	nd, <0.01, <0.01, <0.01, <0.01, <0.01	0.14, 0.18, 0.17, 0.15, 0.19, 0.19 (0.17)	nd, nd, nd, nd, nd, nd
Day 10	0.077, 0.090, 0.11, 0.095, 0.12, 0.16 (0.11)	<0.01, <0.01, 0.015, 0.022, <0.01, 0.020 (0.015)	nd, <0.01, <0.01, <0.01, <0.01, <0.01	0.13, 0.14, 0.20, 0.16, 0.16, 0.22 (0.17)	nd, nd, nd, nd, nd, nd
Day 14	0.079, 0.098, 0.10, 0.094, 0.12, 0.17 (0.11)	<0.01, <0.01, 0.016 0.022, 0.012, 0.020 (0.015)	nd, <0.01, <0.01, <0.01, <0.01, <0.01	0.12, 0.17, 0.19, 0.15, 0.18, 0.22 (0.17)	nd, nd, nd, nd, nd, nd
Day 17	0.084, 0.099, 0.10, 0.094, 0.12, 0.19 (0.11)	<0.01, <0.01, 0.014 0.011, <0.01, 0.014 (0.012)	nd, <0.01, <0.01, nd, <0.01, <0.01	0.12, 0.14, 0.17, 0.099, 0.14, 0.16 (0.14)	nd, nd, nd, nd, nd, nd
Day 21	0.088, 0.093, 0.10, 0.089, 0.10, 0.16 (0.11)	<0.01, <0.01, 0.019 0.017, 0.014, 0.019 (0.015)	nd, nd, <0.01, nd, <0.01, <0.01	0.097, 0.11, 0.19, 0.12, 0.15, 0.18 (0.14)	nd, nd, nd, nd, nd, nd
Day 25	0.11, 0.10, 0.13, 0.12, 0.12, 0.19 (0.13)	<0.01, 0.015, 0.017 0.019, 0.012, 0.021 (0.016)	nd, <0.01, <0.01, <0.01, <0.01, <0.01	0.12, 0.15, 0.18, 0.14, 0.16, 0.20 (0.16)	nd, nd, nd, nd, nd, nd
Day 28	0.11, 0.10, 0.12, 0.12, 0.12, 0.18 (0.13)	0.010, 0.017, 0.018, 0.022, 0.012, 0.021 (0.017)	<0.01, <0.01, 0.010, <0.01, <0.01, <0.01	0.15, 0.16, 0.22, 0.17, 0.16, 0.21, (0.18)	nd, nd, nd, nd, nd, nd
Cream Day 25	nd, nd, nd	0.033, 0.050, 0.043 (0.042)	nd, nd, <0.01	0.075, 0.11, 0.092 (0.093)	nd, nd, nd
Whey Day 25	nd, nd, nd	0.088, 0.11, 0.10 (0.10)	nd, <0.01, <0.01	0.18, 0.24, 0.18 (0.20)	nd, nd, nd

nd: not detected

In milk, parent compound was found only at the high dose (138 ppm) at the level of 0.015 mg/kg (<0.01 mg/kg at the medium dose, 26.3 ppm). A plateau in residue concentrations of parent was observed by Day 4. Parent did not concentrate in cream.

In tissues, mean (maximum) concentrations of parent were at the lowest, medium and high doses, respectively: for muscle, <0.02 (<0.02) mg/kg, 0.02 (0.020) mg/kg and 0.077 (0.088) mg/kg; for fat, <0.02 (<0.02) mg/kg, <0.02 (<0.02) mg/kg and 0.029 (0.042) mg/kg; for liver, 0.23 (0.28) mg/kg, 0.38 (0.50) mg/kg and 1.3 (1.3) mg/kg; for kidney, 0.49 (0.57) mg/kg, 0.92 (1.1) mg/kg and 3.4 (3.7) mg/kg.

Metabolite propamocarb N-oxide was found in milk, at the lowest dose, at the level of 0.012 mg eq/kg. For muscle, fat, liver and kidney, the compound was present at maximum concentrations of 0.051, 0.082, <0.02 (0.038 mg eq/kg at 138 ppm) and 0.13 mg eq/kg, respectively, at the lowest dose.

Metabolite 2-hydroxypropyl propamocarb was found in milk, at the lowest dose, at the level of 0.022 mg eq/kg. In muscle, fat, liver and kidney, the maximum concentrations were 0.023 mg eq/kg (26.3 ppm), 0.044 mg eq/kg (138 ppm), 0.15 mg eq/kg (13.6 ppm) and 0.18 mg eq/kg (13.6 ppm), respectively.

Propamocarb oxazolidinone was found at above LOQ values only in liver and kidney at the high dose.

Propamocarb glucuronide was found only in liver and kidney and the maximm concentrations at the lowest dose were 0.51 and 0.040 mg eq/kg, respectively.

Table 6 Residue concentrations detected in cow tissues following 29 consecutive days of administration with propamocarb-HCl

Tissue	Residue concentration in tissues, mg/kg propamocarb equivalent, average value in parentheses				
	Propamocarb N-oxide	Propamocarb	Propamocarb oxazolidinone	2-hydroxypropyl Propamocarb	Propamocarb glucuronide
Dose: 13.6 ppm propamocarb equivalents					
Muscle	0.034, 0.039, 0.051 (0.041)	<0.02, <0.02, <0.02	nd, nd, nd	<0.02, <0.02, <0.02	nd, nd, nd
Fat	0.082, 0.042, 0.028 (0.051)	<0.02, nd, nd	nd, nd, nd	nd, nd, nd	nd, nd, nd
Liver	<0.02, <0.02, <0.02	0.20, 0.20, 0.28 (0.23)	<0.02, <0.02, <0.02	0.074, 0.090, 0.15 (0.10)	0.37, 0.46, 0.51 (0.45)
Kidney	0.13, 0.10, 0.13 (0.12)	0.57, 0.38, 0.51 (0.49)	nd, nd, <0.02	0.13, 0.12, 0.18 (0.14)	<0.02, 0.022, 0.040 (0.027)
Dose: 26.3 ppm propamocarb equivalents					
Muscle	0.087, 0.066, 0.073 (0.075)	0.020, <0.02, <0.02	nd, nd, nd	0.023, <0.02, 0.021 (0.021)	nd, nd, nd
Fat	0.13, 0.058, 0.071 (0.088)	<0.02, nd, nd	nd, nd, nd	<0.02, nd, nd	nd, nd, nd
Liver	<0.02, <0.02, <0.02	0.50, 0.39, 0.26 (0.38)	<0.02, <0.02, <0.02	0.16, 0.15, 0.13 (0.15)	0.69, 0.65, 0.73 (0.69)
Kidney	0.20, 0.10, 0.14 (0.15)	1.1, 0.91, 0.73 (0.92)	<0.02, <0.02, <0.02	0.29, 0.20, 0.22 (0.24)	0.051, 0.033, 0.042 (0.042)
Dose: 138 ppm propamocarb equivalents					
Muscle	0.27, 0.35, 0.35 (0.32)	0.070, 0.073, 0.088 (0.077)	<0.02, <0.02, <0.02	0.11, 0.12, 0.10 (0.11)	nd, nd, nd
Fat	0.22, 0.45, 0.36 (0.34)	0.026, 0.042, <0.02 (0.029)	nd, nd, nd	0.029, 0.044, 0.027 (0.033)	nd, nd, nd
Liver	0.038, 0.030, 0.022 (0.030)	1.3, 1.3, 1.2 (1.3)	<0.02, 0.026, <0.02 (0.022)	0.53, 0.60, 0.40 (0.51)	1.9, 2.4, 2.9 (2.4)
Kidney	0.30, 0.23, 0.61 (0.38)	3.0, 3.6, 3.7 (3.4)	0.029, 0.041, 0.037 (0.036)	0.89, 1.1, 1.0 (1.0)	0.13, 0.21, 0.25 (0.20)

nd: not detected

During the depuration phase for cows dosed at 138 ppm, residue levels of parent and its metabolites declined rapidly. In milk 3 days and tissues 7 days after the cessation of dosing, the residue levels of parent and its metabolites were all below LOQs.

APPRAISAL

Propamocarb is a systemic carbamate fungicide, which was first evaluated in 1984. It was evaluated under the periodic review program in 2005 for toxicology and 2006 for residues. It was last evaluated by the 2014 JMPR, which recommended maximum residue levels for additional uses. The ADI and ARfD are established as 0–0.4 mg/kg bw and 2 mg/kg bw, respectively. The residue definition for plant and animal commodities is propamocarb (free base) for both enforcement of MRLs and dietary exposure assessment. The residue is not fat-soluble.

At the Forty-ninth Session of the CCPR (2017), propamocarb was scheduled for the evaluation of a new livestock feeding study by the 2018 JMPR and consideration of maximum residue levels for mammalian commodities. The Meeting received a dairy cow feeding study, analytical method and storage stability study from the manufacturer.

Methods of analysis

The Meeting received a new analytical method for the determination of propamocarb and its metabolites (propamocarb N-oxide, 2-hydroxypropyl propamocarb, propamocarb oxazolidinone and propamocarb glucuronide) in animal matrices. For extraction of residues, either 0.1% 1 N acetic acid in methanol for propamocarb glucuronide or acetonitrile for all other analytes were used. LC-MS/MS was used for the determination of the analytes. This method was successfully validated and the LOQ levels achieved for all analytes were 0.010 mg/kg in milk and 0.020 mg/kg in tissues (muscle, fat, liver and kidney), as parent equivalents.

Stability of residues in stored analytical samples

Analysis for propamocarb was completed within one month of sampling.

Residues in animal commodities

Farm animal feeding studies

The Meeting received information on the residue levels in milk and tissues of dairy cows administered propamocarb (as propamocarb-HCl) at doses equivalent to of 13.6, 26.3 and 138 ppm in the feed for 29 consecutive days.

In milk, parent compound was found only at the highest dose (138 ppm) at the level of 0.015 mg/kg (< 0.01 mg/kg at the medium dose, 26.3 ppm).

In tissues, mean (maximum) concentrations of parent were at the lowest, medium and the highest doses, respectively: for muscle, < 0.02 (< 0.02) mg/kg, 0.02 (0.020) mg/kg and 0.077 (0.088) mg/kg; for fat, < 0.02 (< 0.02) mg/kg, < 0.02 (< 0.02) mg/kg and 0.029 (0.042) mg/kg; for liver, 0.23 (0.28) mg/kg, 0.38 (0.50) mg/kg and 1.3 (1.3) mg/kg; for kidney, 0.49 (0.57) mg/kg, 0.92 (1.1) mg/kg and 3.4 (3.7) mg/kg.

During the depuration phase for cows dosed at 138 ppm, residue levels of parent declined rapidly. In milk (3 days) and tissues (7 days) after the cessation of dosing, the residue levels of parent were all below LOQs.

Animal commodity maximum residue levels

The 2014 JMPR estimated the propamocarb dietary burdens for the calculation of mammalian commodity maximum residue levels and STMRs as 31.55 ppm and 10.7 ppm, respectively. The calculations used to estimate maximum residue levels, STMR and HR values for cattle matrices (based on the dietary burdens and feeding study results described above) is shown below.

	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Propamocarb (mg/kg)			
				Muscle	Liver	Kidney	Fat
Maximum residue level (mg/kg), beef or dairy cattle							
Feeding study	26.3	< 0.01	26.3	0.020	0.50	1.1	0.02
	138	0.015	138	0.088	1.3	3.7	0.042
Dietary burden and high residue estimation	31.55	0.010	31.55	0.023	0.54	1.2	0.021
STMR (mg/kg), beef or dairy cattle							
Feeding study	13.6	< 0.01	13.6	0.020	0.28	0.57	0.02
Dietary burden and median residue estimation	10.7	< 0.01	10.7	0.016	0.22	0.45	0.016

The Meeting estimated a maximum residue level of 0.01(*) mg/kg and a STMR of 0 mg/kg for milks. For tissues, the Meeting estimated maximum residue levels of 0.03 mg/kg for meat (from mammals other than marine mammals) and mammalian fat (except milk fats) and 1.5 mg/kg for edible offal (mammalian) based on residues in kidney. The Meeting estimated STMR and HR values of 0.016 mg/kg and 0.023 mg/kg for muscle, 0.016 mg/kg and 0.021 mg/kg for fat and 0.45 mg/kg and 1.2 mg/kg for edible offal, respectively.

RECOMMENDATIONS

On the basis of the available data, 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 and dietary risk assessment for plant and animal commodities: *propamocarb.*

The residue is not fat-soluble.

Commodity		Recommended maximum residue level (mg/kg)		STMR or STMR-P (mg/kg)	HR or HR-P (mg /kg)
CCN	Name	New	Previous		
MO 0105	Edible offal (Mammalian)	1.5	0.01*	0.45	1.2

Commodity		Recommended maximum residue level (mg/kg)		STMR or STMR-P (mg/kg)	HR or HR-P (mg /kg)
CCN	Name	New	Previous		
MF 0100	Mammalian fats (except milk fats)	0.03	-	0.016	0.021
MM 0095	Meat from mammals (other than marine mammals)	0.03	0.01*	0.016 muscle	0.023 muscle
ML 0106	Milks	0.01*	0.01*	0	-

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for propamocarb is 0–0.4 mg/kg bw. The International Estimated Daily Intakes (IEDIs) for propamocarb 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 2018 JMPR Report. The IEDIs ranged from 0–2% of the maximum ADI.

The Meeting concluded that long-term dietary exposure to residues of propamocarb from uses considered by the JMPR is unlikely to present a public health concern.

Acute dietary exposure

The ARfD for propamocarb is 2 mg/kg bw. The International Estimate of Short Term Intakes (IESTIs) for propamocarb 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 2018 JMPR Report. The IESTIs were 0% of the ARfD for children and varied from 0–1% for the general population.

The Meeting concluded that acute dietary exposure to residues of propamocarb from uses considered by the current Meeting is unlikely to present a public health concern.

REFERENCES

Report number	Author(s)	Year	Study title
PR-002-A14-01	Kormos, T.	2015	An analytical method for the determination of residues of propamocarb and its metabolites propamocarb glucuronide, propamocarb N-oxide, 2-hydroxypropyl propamocarb, and propamocarb oxazolidinone in/on milk, muscle, liver, kidney, and fat using LC/MS/MS. Edition Number: M-509460-01-1. GLP/GEP: unpublished.
PR-002-A14-02	Kormos, T.	2014	An analytical method for the determination of residues of propamocarb and its metabolites propamocarb glucuronide, propamocarb N-oxide, 2-hydroxypropyl propamocarb, and propamocarb oxazolidinone in/on milk, muscle, liver, kidney, and fat using LC/MS/MS. Edition Number: M-509462-01-1.GLP/GEP: unpublished.
B004898	Tauber, R.	2004	Frozen storage stability for propamocarb glucuronide in cow milk, kidney, liver, fat and muscle using LC/MS/MS. Edition Number: M-243564-01-1. GLP/GEP: unpublished.
RAPRN023	Kormos, T., Jenkins, E.	2015	Propamocarb: Magnitude of residues in dairy cows. Edition Number: M-507614-01-1. GLP/GEP: unpublished.