

## 5.24 ISOPYRAZAM (249)

### RESIDUE AND ANALYTICAL ASPECTS

Isopyrazam is a broad-spectrum foliar fungicide belonging to the chemical class of ortho-substituted phenyl amides. It controls a wide range of fungal pathogens. Isopyrazam was first evaluated by the JMPR as a new compound in 2011. An ADI of 0–0.06 mg/kg bw/day and an ARfD of 0.3 mg/kg bw were established. The residue definitions were established: for compliance with MRLs for plant commodities: *Isopyrazam (sum of syn-isomer and anti-isomer)*; for risk assessment for plant commodities: *Sum of isopyrazam and 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid [9-(1-hydroxyl-1-methylethyl)-(1RS, 4RS, 9RS)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl] amide(CSCD459488 ), expressed as isopyrazam*; for animal commodities (enforcement and risk assessment): *Isopyrazam (sum of syn-isomer and anti-isomer)*. The residue is fat-soluble.

Isopyrazam was scheduled by the 48<sup>th</sup> Session of the CCPR for evaluation by the 2017 JMPR for additional MRLs. The Meeting received information on registered labels and supporting residue trials data for pome fruits, stone fruits, cucurbits, peppers, tomato, carrot, barley, wheat, rape seed and peanut as well as studies on the storage stability of CSCD459488 and processing studies.

#### *Methods of analysis*

The analytical methods used in the trials (GRM006.01B, GRM006.03A) were reviewed by the 2011 JMPR and considered suitable as data collection methods. In general, the methods employ extraction by homogenization with a mixture of acetonitrile and water (mostly 80:20 v/v), clean-up with solid phase extraction or a process of centrifugation and dilution, and determination of analytes using LC-MS/MS or GC-MS/MS.

#### *Stability of residues in stored analytical samples*

The stability of residues of isopyrazam (both isomers) and metabolites CSCD459488, CSCD 459489, CSCD465008, and CSAA 798670 during frozen storage (-15 to -20 °C) was evaluated by the 2011 JMPR. The stability of residues of each analyte spiked at 0.5 mg/kg was investigated in tomato, oilseed rape seeds, lentil seeds, potato tubers, barley grain and straw, ryegrass forage and spinach leaves and the animal commodities milk, eggs, liver, kidney, muscle and fat. Isopyrazam (both isomers) was stable for at least 24 months in all plant matrices. CSCD459488 and other metabolites were stable for at least 11 months during frozen storage. Both isomers of isopyrazam were stable for at least 14 months in animal commodities, the metabolites hydrolysable to CSAA798670 were stable for at least 12 months.

The current Meeting received information on the stability of metabolite CSCD459488 in wheat grain and straw, rape seed, apple fruit, lentils, orange fruit, spinach and carrot stored at a temperature of -20±5 °C. The residues of CSCD459488 spiked at a level of 0.5 mg/kg were stable in all tested commodities in storage for at least 28 months. The tested commodities covered representatives of all five crop sample types i.e., high water, high acid, high oil, high protein and high starch containing materials. Therefore, residues of CSCD459488 are expected to be stable in all crop commodities, when stored at -20±5 °C, for at least 28 months.

#### *Results of supervised residue trials on crops*

The Meeting received supervised trial data for isopyrazam on apple, apricot, peach, cucumber and summer squash, melon, peppers (sweet), cherry tomato, carrot, barley, wheat, rape seed (canola) and peanut.

*Pome fruits**Apple*

The GAP for on pome fruit in Chile is 2 foliar applications of 150 g ai/ha with a PHI of 21 days. In trials conducted in Europe matching the Chilean GAP, residues of isopyrazam in apples were (n=16): 0.026, 0.031, 0.047, 0.050, 0.062, 0.092, 0.093, 0.11, 0.12, 0.12, 0.14, 0.15, 0.17, 0.19, 0.20 and 0.24 mg/kg. For dietary assessment, total residues (isopyrazam plus CSCD459488, expressed as isopyrazam) were (n=16): 0.031, 0.036, 0.052, 0.055, 0.067, 0.097, 0.098, 0.12, 0.12, 0.13, 0.15, 0.16, 0.18, 0.19, 0.21 and 0.24 mg/kg.

The Meeting estimated a maximum residue level of 0.4 mg/kg based on residues of isopyrazam, estimated an STMR of 0.12 mg/kg and an HR of 0.24 mg/kg based on total residues. The Meeting estimated a median residue for animal burden calculations of 0.115 mg/kg based on residues of parent. As the Chile GAP is for pome fruit, the Meeting agreed to extrapolate the maximum residue level, STMR and HR of apples to pome fruits.

*Stone fruits**Apricot and Peach*

The GAP for apricot and peach in Turkey is 2 foliar applications of 10 g ai/hL with a PHI of 7 days for peach and 21 days for apricot. In trials conducted in France, Italy and Spain matching the Turkish GAP, the residues of isopyrazam in peach fruit were (n=4): 0.080, 0.18, 0.25 and 0.39 mg/kg, the total residues were (n=4): 0.085, 0.18, 0.26 and 0.40 mg/kg. The Meeting concluded that four trials were insufficient for the estimation of a maximum residue level.

*Fruiting vegetables, Cucurbits**Cucumber*

The GAP for cucumber and summer squash (protected) in the UK is 2 foliar applications at a rate of 12.5 g ai/hL, up to 1000 L/ha (maximum of 125 g ai/ha) with a PHI of 1 day. In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in protected cucumber were (n=8): < 0.010, 0.010, 0.012, 0.013, 0.015, 0.017, 0.025 and 0.036 mg/kg. The total residues in cucumber were (n=8): 0.021, 0.022, 0.023(2), 0.024(2), 0.030 and 0.041 mg/kg.

The Meeting estimated the maximum residue level of 0.06 mg/kg, STMR of 0.0235 mg/kg and HR of 0.041 mg/kg for cucumber.

*Melons*

The GAP for melon and watermelon (protected) in the UK is 2 foliar applications at rate of 12.5 g ai/hL, up to 1000 L/ha (maximum of 125 g ai/ha) with a PHI of 7 days. In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in protected melon (whole fruit) were (n=8): 0.012, 0.013, 0.014, 0.017(2), 0.022, 0.031 and 0.10 mg/kg, the total residues in melon flesh were (n=8): < 0.015(8) mg/kg.

The Meeting estimated the maximum residue level of 0.15 mg/kg for melons except watermelon, STMR of 0.015 mg/kg and HR of 0.015 mg/kg for melon flesh.

*Fruit vegetable, other than Cucurbits**Peppers*

The GAP for on protected sweet peppers and chili peppers in the UK is 2 foliar applications at rate of 12.5 g ai/hL, up to 1000 L/ha (maximum of 125 g ai/ha) with a PHI of 3 days. In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in sweet peppers were (n=8): < 0.010,

0.019, 0.021, 0.023, 0.039, 0.028, 0.036 and 0.045 mg/kg, the total residues in sweet peppers were (n=8): < 0.015, 0.024, 0.026, 0.028, 0.033, 0.041, 0.044 and 0.050 mg/kg.

The Meeting agreed to recommend the maximum residue level of 0.09 mg/kg, STMR of 0.0305 mg/kg and HR of 0.050 mg/kg for sweet peppers.

#### *Tomato*

The GAP for tomato and eggplant (protected) in the UK allows 2 foliar applications at rate of 12.5 g ai/hL, up to 1000 L/ha (maximum of 125 g ai/ha) with a PHI of 1 day. In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in cherry tomato were (n=8): 0.017, 0.018, 0.025, 0.048, 0.049, 0.13, 0.19 and 0.23 mg/kg, and the total residues in cherry tomato were (n=8): 0.022, 0.023, 0.030, 0.053, 0.054, 0.14, 0.20 and 0.23 mg/kg.

The Meeting estimated the maximum residue level of 0.4 mg/kg, STMR of 0.0535 mg/kg and HR of 0.23 mg/kg for cherry tomato. The Meeting estimated a median residue of 0.0485 mg/kg for animal burden calculation. The Meeting noted residues in cherry tomato are normally higher than tomato, and agreed to extrapolate the MRL, STMR and HR to tomato and to the subgroup of eggplants.

#### *Root and tuber vegetables*

##### *Carrot*

The GAP for carrot in the UK is 2 foliar applications at rate of 125 g ai/ha with a PHI of 14 days. In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in carrot root were (n=16): < 0.010(4), 0.010(2), 0.011, 0.015, 0.019, 0.025, 0.029, 0.037, 0.054, 0.055, 0.075 and 0.099 mg/kg, and the total residues in carrot root were (n=16): < 0.015(4), 0.015(2), 0.016, 0.020, 0.024, 0.030, 0.034, 0.042, 0.059, 0.060, 0.080 and 0.10 mg/kg.

The Meeting estimated the maximum residue level of 0.15 mg/kg, STMR of 0.022 mg/kg and HR of 0.10 mg/kg for carrot.

#### *Cereal grains*

##### *Barley*

The GAP for barley in the UK is 2 foliar applications at rate of 125 g ai/ha before beginning of flowering (first anthers visible, BBCH 61). In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in barley grains were (n=13): < 0.010, 0.014, 0.015, 0.016, 0.024(2), 0.026, 0.035, 0.046, 0.15, 0.17, 0.27 and 0.41 mg/kg, and the total residues in barley grains were (n=13): 0.018, 0.020(2), 0.031, 0.042, 0.047, 0.051, 0.057, 0.061, 0.20, 0.22, 0.36 and 0.43 mg/kg.

The Meeting estimated a maximum residue level of 0.6 mg/kg to replace the previous recommendation of 0.07 mg/kg, an STMR of 0.051 mg/kg, and a median residue of 0.026 mg/kg for the calculation of animal burden for barley.

##### *Wheat*

The GAP for wheat, rye and triticale in the UK is 2 foliar applications at a rate of 125 g ai/ha before grain watery ripe stage (BBCH 71). In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in wheat grain were (n=8): < 0.010(5), 0.010, 0.013, 0.014 mg/kg, the total residues were < 0.015(5), 0.015, 0.018 and 0.019 mg/kg.

The Meeting confirmed the previous maximum residue level recommendation of 0.03 mg/kg, STMR of 0.015 mg/kg and median residues of 0.01 mg/kg for wheat, triticale and rye.

*Oil seeds**Rape seed (canola)*

The GAP for oilseed rape in the UK allows 1 foliar application at rate of 125 g ai/ha up to the end of flowering (BBCH 71). In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in rape seed were (n=20): < 0.010(3), 0.010, 0.012, 0.013(2), 0.016, 0.033, 0.035, 0.038, 0.052, 0.055, 0.058, 0.068(3), 0.086, 0.090 and 0.094 mg/kg, the total residues in rape seed were (n=20): < 0.015, 0.015, 0.018(3), 0.021, 0.023, 0.038(2), 0.040, 0.043, 0.060, 0.063, 0.073(2), 0.075, 0.091, 0.095, 0.099 and 0.292 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.0415 mg/kg mg/kg for rape seed.

*Peanut*

The GAP for peanut in Nicaragua allows 2 foliar application at rate of 100–125 g ai/ha with PHI of 7 days. In trials conducted in Nicaragua (3 application at 125 g ai/ha), the residues of isopyrazam in peanuts were (n=4): < 0.010(4) mg/kg, and the total residues in peanut seeds were (n=4): < 0.015(4) mg/kg.

The Meeting estimated a maximum residue level of 0.01\* mg/kg and an STMR of 0.015 mg/kg mg/kg for peanut.

*Animal feedstuffs**Cereal forage*

The GAP for barley (up to BBCH 61), wheat, rye and triticale (up to BBCH 71) in UK allows 2 foliar applications at rate of 125 g ai/ha. As no livestock feeding withholding periods are specified. The Meeting used the residue values from 0-day whole plant samples to estimate median and highest residues. In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in barley forages were (n=9): 2.1, 2.3, 2.9, 3.1, 3.5, 3.5, 3.9, 5.0 and 5.5 mg/kg. Residues of isopyrazam in wheat forages were (n=4): 1.9, 2.1, 2.1, 2.3 mg/kg.

Based on the combined data sets for the wheat and barley forage (1.9, 2.1, 2.1, 2.1, 2.3, 2.3, 2.9, 3.1, 3.5, 3.5, 3.9, 5.0 and 5.5 mg/kg), the Meeting estimated a median residues of 2.9 mg/kg and highest residues of 5.5 mg/kg for wheat and barley forage, and agreed to extrapolate these estimates to rye, and triticale forage, and to replace previous recommendation.

*Cereal straw and fodder, dry*

The GAP for barley (application up to BBCH 61), wheat, rye and triticale (application up to BBCH 71) in the UK allows for 2 foliar applications at a rate of 125 g ai/ha. No livestock feeding withholding periods are specified. In trials conducted in Europe matching the UK GAP, the residues of isopyrazam in barley straw were (n=13): 0.13, 0.13, 0.15, 0.26, 0.35, 0.45, 0.84, 1.1, 1.4, 2.5, 3.5, 5.9 and 6.9 mg/kg. Residues of isopyrazam in wheat straw were (n=8): 0.051, 0.29, 0.62, 0.75, 0.97, 3.6, 4.2 and 5.5 mg/kg.

Based on the combined data sets for the wheat and barley straw (0.051, 0.13, 0.13, 0.15, 0.26, 0.29, 0.35, 0.45, 0.62, 0.75, 0.84, 0.97, 1.1, 1.4, 2.5, 3.5, 3.6, 4.2, 5.5, 5.9, 6.9 mg/kg), the Meeting estimated a maximum residue level of 15 mg/kg dw), median residues of 0.84 mg/kg and highest residues of 6.9 mg/kg for wheat and barley straw, and agreed to extrapolate these estimates to rye and triticale straw, and to replace previous recommendation of 3 mg/kg.

*Fate of residues during processing*

The Meeting received information on processing of apple, tomato, carrot and rape seed. Processing factors were calculated for the corresponding processed food commodities and are shown in the table below, together with those calculated by the 2011 JMPR for the commodities considered at this

Meeting. STMR-Ps or HR-Ps were calculated for the processed corresponding commodities which are consumed as foods.

Crop	Commodity	Mean/Median Processing factor		STMR or STMR-P*** mg/kg	HP or HR-P mg/kg
		Isopyrazam*	Isopyrazam and CSCD459488**		
Barley (2011 JMPR)	RAC			0.051	
	Malt	0.55	0.59	0.03	
	Beer	< 0.13	< 0.12	0.061	
	Pot barley	0.37	0.33	0.17	
Wheat (2011 JMPR)				0.015	
	Bran (unprocessed)	4.07	4.39	0.066	
	White flour	0.20	0.23	0.0035	
	Whole meal flour	0.73	0.81	0.012	
	Whole meal bread	0.50	0.55	0.0083	
	Wheat germ	0.19	0.25	0.0038	
Apple	RAC			0.12	0.24
	Washed fruit	0.77	0.77	0.092	0.18
	Sauce	0.18	0.19	0.023	
	Juice	0.02	0.03	0.0036	
	Canned fruit	0.05	0.06	0.0071	0.014
	Dried fruit	6.03	5.95	0.71	1.4
Tomato	RAC			0.0535	0.23
	Juice	0.5	NC		
	Puree	5.1	NC		
	Paste	6.4	NC		
	Canned tomato	0.19	NC		
	Ketchup	4.2	NC		
	Sun-dried tomato	11	NC		
Rape seed	RAC			0.042	
	Pressed crude oil	1.59	0.75	0.032	
	Refined oil	1.81	0.9	0.038	

\* - According to the residue definition for enforcement (anti-isomer + syn-isomer).

\*\* - According to the residue definition for risk assessment (anti-isomer + syn-isomer + CSCD459488).

\*\*\*STMR-P is calculated with processing factor of isopyrazam and CSCD459488.

NC - Not calculable.

Processing factors were calculated for the corresponding processed commodities used for feed and are shown in the table below for the commodities considered at this Meeting. Processed Median Residue or Highest residue were calculated for the processed corresponding commodities which were used for the calculation of animal burdens.

Crop	Commodity	Mean/Median Processing factor	Median Residue -P** mg/kg
		Isopyrazam*	
Apple	RAC		0.115
	Wet pomace	2.49	0.28
	Dry pomace	5.51	0.63
Tomato	RAC		0.0485
	Wet pomace	3.1	0.15
	Dry pomace	32	1.6

\* - According to the residue definition for animal commodities (anti-isomer + syn-isomer).

\*\* Processed Median Residues and highest Residues are calculated with processing factor of isopyrazam.

As residues in apple dried fruit are higher than residues in apple fruit, the Meeting estimated a maximum residue level of 3 mg/kg for apple, dried by multiplying the maximum residue level for apple fruit (0.4 mg/kg) by 6.03.

As residues in sun-dry tomato are higher than residues in tomato fruit, the Meeting estimated a maximum residue level of 5 mg/kg for dry tomato by multiplying the maximum residue level for tomato fruit (0.4 mg/kg) by 11.

### *Residues in animal commodities*

#### *Farm animal dietary burden*

Potential cattle feed items include: grain, straw and forage of barley, wheat, rye and triticale, apple pomace, tomato pomace and carrot culls that may be fed to dairy cattle, beef cattle, broilers and layers. The maximum and mean dietary burden were calculated using the highest residues or median residue of isopyrazam estimated using the OECD diets listed in Appendix IX of the 2016 edition of the FAO Manual.

Summary of livestock dietary burden (ppm isopyrazam equivalents of dry matter diet)

	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	mean	max	Mean	max	Mean
Beef cattle	0.80	0.11	6.52	3.47	<b>22<sup>a</sup></b>	<b>11.6<sup>c</sup></b>	0.021	0.021
Dairy cattle	4.57	2.42	6.44	3.40	<b>14.09<sup>b</sup></b>	7.14 <sup>c</sup>	0.012	0.012
Broilers	0.022	0.022	0.103	0.035	0.004	0.004	0.003	0.003
Layers	0.022	0.022	<b>2.307<sup>ef</sup></b>	<b>1.202<sup>ef</sup></b>	0.004	0.004	-	-

<sup>A</sup> Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat

<sup>B</sup> Highest maximum dairy cattle dietary burden suitable for MRL estimates for mammalian milk

<sup>C</sup> Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.

<sup>D</sup> Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

<sup>E</sup> Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs

<sup>F</sup> Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs

#### *Residues in milk and cattle tissues*

Feeding study on lactating dairy cow were evaluated by 2011 JMPR, the residues of isopyrazam in milk from all dose group (15, 42 and 137 ppm in diet) were less than 0.01 mg/kg. The residues in low and median dose groups were: < 0.01–0.01 for muscle, 0.01–0.036 for liver, < 0.01–0.012 for kidney, < 0.01–0.053 for fat.

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	Residues (mg/kg) in cream	Feed level (ppm) for tissue residues	Residue (mg/kg)			
					Muscle	liver	Kidney	Fat
<b>MRL (mg/kg); beef or dairy cattle</b>								
Feeding study	15	< 0.01	0.01	15	< 0.01	0.01	< 0.01	< 0.01
				42	0.01	0.036	0.012	0.053
Dietary burden and high residue estimation	14.09	< 0.01	< 0.01	22	< 0.01	0.017	0.0106	0.0211
<b>STMR (mg/kg). beef or dairy cattle</b>								
Feeding study	15	< 0.01	0.01	15	< 0.01	0.01	< 0.01	< 0.01
Dietary burden and median residue estimated	7.14	< 0.01	< 0.01	11.63	< 0.01	< 0.01	< 0.01	< 0.01

The Meeting estimated a maximum residue level of 0.03 mg/kg for mammalian fat, a maximum residue level of 0.03 mg/kg (fat) for mammalian meat, to replace the previous recommendation (0.01\* mg/kg for fat, 0.01\* mg/kg for meat), and confirmed a maximum residue level of 0.02 mg/kg for edible offal (mammalian) and milk fat, and a maximum residue level of 0.01\* mg/kg for isopyrazam in milk. The Meeting estimated an STMR of 0.01 mg/kg respectively for milk, mammalian meat, edible offal (mammalian) and mammalian fat and milk fat.

#### *Residues in eggs and poultry tissues*

No feeding study on laying hens was available. In a hen metabolism study conducted at a dose of 11 ppm dry matter in feed, the residues in extracts of egg white, egg yolk, meat, liver, skin and attached fat, and peritoneal fat were less than 0.004 mg/kg. The calculated maximum and mean dietary burdens for poultry were 2.31 and 1.20 ppm, significantly higher than the burdens calculated by the 2011 JMPR, but significantly lower than 11ppm, the Meeting confirmed the maximum residue levels of 0.01\*mg/kg and STMRs of 0.01 mg/kg for isopyrazam in eggs, poultry meat, edible offal of poultry and fat.

### RECOMMENDATION

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI/IESTI assessment.

The definition of the residue (for compliance with MRLs) for plant commodities: *Isopyrazam (sum of syn-isomer and anti-isomer)*.

The definition of the residue (for estimation of dietary intake) for plant commodities: *Sum of isopyrazam and 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid [9-(1-hydroxyl-1-methylethyl)-(1RS, 4RS, 9RS)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl] amide(CSCD459488), expressed as isopyrazam;*

The definition of the residue (for compliance with the MRLs and estimation of dietary intake) for animal commodities: *Isopyrazam (sum of syn-isomer and anti-isomer)*.

*The residue is fat-soluble.*

### DIETARY RISK ASSESSMENT

#### *Long-term dietary exposure*

The IEDI of isopyrazam based on the STMRs estimated by this and previous Meetings for the 17 GEMS/Food regional diets were 0–1% of the maximum ADI of 0.06 mg/kg bw. The Meeting concluded that the long-term dietary exposure to residues of isopyrazam is unlikely to present a public health concern.

#### *Short-term dietary exposure*

The ARfD for isopyrazam is 0.3 mg/kg bw. The Meeting estimated the International Estimated Short-Term Intake (IESTI) of isopyrazam for commodities for which STMR, HR and maximum residue levels were estimated by the current Meeting. The IESTI represented a maximum of 6–10% of the ARfD. The Meeting concluded that the short-term dietary exposure to isopyrazam residues from uses considered by the current Meeting is unlikely to present a public health concern.