

Evaluation Report for Category A, Subcategory 1.3 Application

Application Number: 2016-4648
Application: New Active Ingredient – Maximum Residue Limits (MRL) only
Product: Isopyrazam Technical
Registration Number: NA
Active ingredient (a.i.): Isopyrazam
PMRA Document Number: 2877386

Background

Maximum residue limit(s) (MRLs) for isopyrazam were previously established for imported bananas, peanuts and apples. Please refer to the Evaluation Report under Application No. 2010-3110 and 2013-6735 available in the Pesticides and Pest Management section of Health Canada's website (<http://pr-rp.hc-sc.gc.ca/pi-ip/index-eng.php>), under Public Registry, Pesticide Product Information Database.

Purpose of Application

The purpose of this application was to establish maximum residue limits (MRLs) for isopyrazam in/on imported bell peppers, Crop Subgroup 8-09A (tomatoes) and Crop Subgroup 9A (melon).

Chemistry Assessment

A detailed review of the chemistry database for isopyrazam was previously conducted. Please refer to the Evaluation Report for Application No. 2010-3110. A summary is presented below.

Active substance Isopyrazam

Function Fungicide

Chemical name

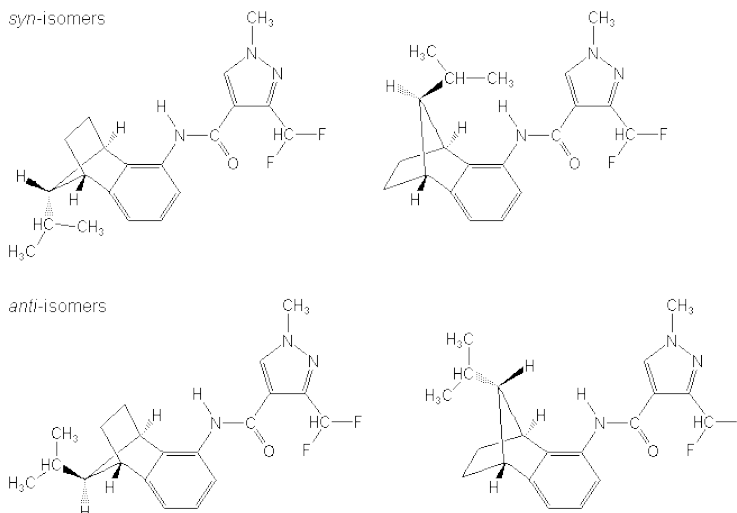
- 1. International Union of Pure and Applied Chemistry (IUPAC)** mixture of 2 *syn*-isomers 3-(difluoromethyl)-1-methyl-*N*-[(1*RS*,4*SR*,9*RS*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]pyrazole-4-carboxamide and 2 *anti*-isomers 3-(difluoromethyl)-1-methyl-*N*-[(1*RS*,4*SR*,9*SR*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]pyrazole-4-carboxamide
- 2. Chemical Abstracts Service (CAS)** 3-(difluoromethyl)-1-methyl-*N*-[1,2,3,4-tetrahydro-9-(1-methylethyl)-1,4-methanonaphthalen-5-yl]-1*H*-pyrazole-4-carboxamide

CAS number 881685-58-1

Molecular formula C₂₀H₂₃F₂N₃O

Molecular weight 359.4

Structural formula



Purity of the active ingredient 94.7%

Technical Product—Isopyrazam Technical

Property	Result									
Colour and physical state	Off-white crystalline powder									
Odour	Odourless									
Melting range	144.5°C for the <i>anti</i> -isomer 130.2°C for the <i>syn</i> -isomer									
Boiling point or range	N/A									
Density	1.332 g/cm ³									
Vapour pressure at 20°C	<table><thead><tr><th></th><th><i>anti</i>- isomer</th><th><i>syn</i>-isomer</th></tr></thead><tbody><tr><td>at 20°C</td><td>2.2 × 10⁻⁸ Pa</td><td>2.4 × 10⁻⁷ Pa</td></tr><tr><td>at 25°C</td><td>5.7 × 10⁻⁸ Pa</td><td>5.6 × 10⁻⁷ Pa</td></tr></tbody></table>		<i>anti</i> - isomer	<i>syn</i> -isomer	at 20°C	2.2 × 10 ⁻⁸ Pa	2.4 × 10 ⁻⁷ Pa	at 25°C	5.7 × 10 ⁻⁸ Pa	5.6 × 10 ⁻⁷ Pa
	<i>anti</i> - isomer	<i>syn</i> -isomer								
at 20°C	2.2 × 10 ⁻⁸ Pa	2.4 × 10 ⁻⁷ Pa								
at 25°C	5.7 × 10 ⁻⁸ Pa	5.6 × 10 ⁻⁷ Pa								
Ultraviolet (UV)-visible spectrum	For both <i>syn</i> and <i>anti</i> - isomers: λ _{max} < 300 nm in neutral, acidic and basic solutions.									
Solubility in water at 25°C	0.55 mg/L for <i>anti</i> -isomer 1.05 mg/L for <i>syn</i> -isomer									

Solubility in organic solvents at 20°C (g/L)	<u>Solvent</u>	<u>Solubility</u>
	acetone	314
	dichloromethane	330
	ethyl acetate	179
	n-hexane	1.17
	methanol	119
	n-octanol	44.1
	toluene	77.1
<i>n</i> -Octanol-water partition coefficient (K_{ow}) at 25°C	Log K_{ow} = 4.4 for <i>anti</i> -isomer Log K_{ow} = 4.1 for <i>syn</i> -isomer	
Dissociation constant (pK_a)	N/A	
Stability (temperature, metal)	This compound was not found to be corrosive when exposed to tin plate, galvanized sheet metal and stainless steel and slightly corrosive to sheet steel for seven days when stored at 54°C. The technical grade active ingredient (TGAI) is not likely to be sensitive to sunlight since λ_{max} for both isomers (<i>syn</i> and <i>anti</i>) is < 300 nm.	

Methods of Analysis

The methods provided for the analysis of the active ingredient and the impurities in Isopyrazam Technical have been validated and assessed to be acceptable for the determinations.

Methods for Residue Analysis

Please refer to the Evaluation Report for Application No. 2010-3110 for residue analytical methods used for data generation and enforcement purposes.

Health Assessments

Toxicology Summary

A detailed review of the toxicological database for isopyrazam was conducted previously for the purpose of establishing import MRLs and was summarised in the Evaluation Report for Application Number 2010-3110. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. An additional 90-day dietary toxicity study in rats was submitted for the current application. Overall, the scientific quality of the data is high and the database is considered adequate to characterize potential health hazards associated with isopyrazam.

In the newly-submitted 90-day dietary toxicity study in rats, the effects observed included decreased body weight, and increased liver weight and incidence of hepatocellular hypertrophy. These effects are similar to those which were observed at lower dose levels in the previously-reviewed 90-day dietary toxicity studies (Appendix I, Table 1). As such, the submitted study does not alter the previously selected toxicology reference values.

Please see the Evaluation Report for Application Number 2010-3110 for a summary of the toxicology database for Isopyrazam and the established toxicology reference values.

Incident Reports

As of March 14, 2018, no incidents were reported for humans, domestic animals or the environment in any US databases. Isopyrazam is not registered for use in Canada.

Occupational and Residential Risk Assessment

Occupational or residential risk assessments were not required.

Food Residues Exposure Assessment

Residues in Plant Foodstuffs

Please refer to the Evaluation Report for Application No. 2010-3110 for a summary of the previously reviewed data and the rationale for the regulatory decision.

The information captured herein relates to field trial and processed commodity data provided to support the establishment of MRLs on imported tomatoes (crop subgroup 8-09A), bell peppers and melons (crop subgroup 9A), and to the update of the dietary exposure assessments to include these commodities.

Tomatoes were processed and isopyrazam residues concentrated in tomato puree (4.8x), tomato paste (6.7x) and dried tomatoes (10.8x). Field trials conducted in Europe using end-use products containing isopyrazam at slightly exaggerated rates in or on tomatoes, bell peppers and cantaloupes are sufficient to support the proposed MRLs.

Dietary Risk Assessment

Acute, non-cancer chronic and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID), which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/WWEIA) dietary survey available through CDC's National Center for Health Statistics (NCHS).

Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined non-cancer chronic and cancer analyses for isopyrazam: combined residues of isopyrazam (i.e., isopyrazam, the sum of the two isomers SYN534968 (*anti*) and SYN534969 (*syn*) plus metabolite CSCD459488, expressed as parent

equivalents) based on supervised trial median residue (STMdR) values from European field trial studies; default and experimental processing factors (when available); 100% crop treated; and percent crops imported from exporting countries.

The refined non-cancer chronic dietary exposure from all supported isopyrazam-treated imported food uses (alone) for the total population, including infants and children, and all representative population subgroups ranged from <0.1 to 0.2% of the acceptable daily intake (ADI), which is not of health concern. Exposure from food alone is considered acceptable in the context of a submission for specifying MRLs on imported crop commodities. The highest exposure and risk estimate is for children of 1 – 2 years old at 0.2% (0.000094 mg/kg bw/day) of the ADI.

The refined chronic cancer risk assessment was conducted with the same criteria used for the chronic non-cancer assessment. The lifetime cancer risk from exposure to isopyrazam in food (alone) was estimated to be 1.5×10^{-7} for the general population, which is not of health concern.

Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for isopyrazam: residues in/on crops at MRL levels, default processing factors and 100% crop treated. The basic acute dietary exposure from all supported isopyrazam-treated imported food uses (alone) is estimated to be 3.7% (0.007316 mg/kg bw/day) of the acute reference dose (ARfD) for the general population (95th percentile, deterministic). The highest exposed subpopulation is children 1-2 years of age at 17.0% (0.034074 mg/kg bw/day) of the ARfD, which is not of health concern.

Aggregate Exposure and Risk

An aggregate risk analysis for isopyrazam was not conducted as exposure is from food only and there are no residential uses. Drinking water sources are not affected as there are no registered Canadian uses.

Maximum Residue Limits

The recommendation for MRLs for isopyrazam was based upon the submitted field trial data from the exporting countries, and the guidance provided in the [OECD MRL Calculator](#). MRLs to cover residues of isopyrazam [i.e., sum of SYN534968 (*anti*) and SYN534969 (*syn*)] in/on crops and processed commodities are proposed as shown in the table below. Residues in processed commodities not listed in the table below are covered under the proposed MRLs for the raw agricultural commodities (RACs).

Summary of Field Trial and Processing Data Used to Support Maximum Residue Limits (MRLs) in/on Isopyrazam

Commodity	Application Method/ Total Application Rate (g a.i./ha)	PHI (days)	Total Isopyrazam Residues (ppm)		Experimental Processing Factor	Recommended MRL (ppm)
			LAFT	HAFT		
Cherry tomatoes (greenhouse)	Ground foliar broadcast spray/ 250 – 263	1	0.017	0.191	Tomato juice: 0.5x	0.5 ppm in/on tomatoes (crop subgroup 8-09A)
Tomatoes (field-grown)	Ground foliar broadcast spray/ 249 – 274	7	≤ 0.010	0.047	Canned tomatoes: 0.2x Tomato puree: 4.8x Tomato paste: 6.7x Dried tomatoes: 10.8x	
Bell peppers (greenhouse)	Ground foliar broadcast spray/ 246 – 282	3	≤ 0.010	0.041	Not required	
Bell peppers (field-grown)	Ground foliar broadcast spray/ 247 – 259	3	0.018	0.251		
Cantaloupes (greenhouse)	Ground foliar broadcast spray/ 238 – 260	7	0.012	0.101	Not required	0.3 ppm in/on melons (crop subgroup 9A)
Cantaloupes (field-grown)	Ground foliar broadcast spray/ 237 – 265	7	0.011	0.162		

Note: a.i. = active ingredient; ha = hectare; PHI = preharvest interval; total isopyrazam residues = sum of the SYN534968 (*anti*) and SYN534969 (*syn*) isomers; ppm = parts per million; LAFT = Lowest Average Field Trial; HAFT = Highest Average Field Trial.

Please refer to the [Maximum Residue Limit Database](http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php) in the Pesticides and Pest Management section of Health Canada's website (<http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php>) for the established MRLs for isopyrazam.

Environmental and Value Assessments

Environmental and value assessments were not required for this application.

Conclusion

The nature of the residues in plants is adequately understood. The residue definition for enforcement is isopyrazam [SYN534968 (*anti*) + SYN534969 (*syn*)] in plant products. The importation to Canada of isopyrazam-treated tomatoes (crop subgroup 8-09A), bell peppers and melons (crop subgroup 9A) from European countries does not constitute a health risk of concern for chronic or acute dietary exposure (food alone) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs in/on imported commodities. The PMRA recommends that the following MRLs be specified for residues of isopyrazam.

Commodity	Recommended MRL (ppm)
Bell Peppers, Tomatoes (Crop Subgroup 8-09A)	0.5
Melons (Crop subgroup 9A)	0.3

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the [Residue Chemistry Crop Groups](#) webpage in the Pesticides and Pest Management section of Health Canada's website.

List of Abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Services
DEEM-FCID	Dietary Exposure Evaluation Model - Food Commodity Intake Database
g	gram(s)
HAFT	highest average field trial
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K _{ow}	<i>n</i> -octanol-water partition coefficient
L	litre(s)
LAFT	lowest average field trial
LOAEL	lowest observed adverse effect level
mg	milligram(s)
MRL	maximum residue limit
NA	not applicable
NHANES	National Health and Nutritional Examination Survey
NCHS	National Center for Health Statistics
NOAEL	no observed adverse effect level
OECD	Organization for Economic Co-operation and Development
PHI	preharvest interval
pKa	pKa dissociation constant
RAC	raw agricultural commodity
STMdR	supervised trial median residue
TGAI	technical grade active ingredient
US	United States
UV	ultraviolet
WWEIA	What We Eat in America

Appendix I

Table 1 Additional Toxicity data for Technical Isopyrazam

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted

Study Type/Animal/PMRA #	Study Results
90-day dietary toxicity (diet) Wistar rats PMRA # 2204255	NOAEL = 74/ 85 mg/kg bw/day (♂/♀) LOAEL ♂/♀= 315/341 mg/kg bw/day (♂/♀). Effects at the LOAEL include increased liver weight and incidence of hepatocellular hypertrophy, decreased body weight, body weight gain, food consumption and food efficiency (♂); decreased heart weight (♀).

References

PMRA Document Number	Reference
1932031	2009, Isopyrazam Technical (SYN520453) - Manufacturing Process Description and Supporting Data, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4, 2.12.1, 2.12.2, 2.13.1, 2.13.2, 2.13.3, 2.13.4, 2.4, 2.5, 2.6, 2.7, 2.8,2.9 CBI
1932032	2010, SYN520453 Technical - Analysis of [CBI Removed] In Five Representative Batches Produced At Munchwilen Ag, DACO: 2.13.1, 2.13.2, 2.13.3 CBI
1932033	2010, SYN520453 Technical -Analysis of [CBI Removed] In Five Representative Batches Produced At Munchwilen Ag, DACO: 2.13.1, 2.13.2, 2.13.3 CBI
1932034	2009, Isopyrazam Technical (SYN520453) - Physical and Chemical Properties, DACO: 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9 CBI
1932035	2009, A15149W SYN520453 125 g/L EC Document M-III, Section 1 Identity, Physical and Chemical Properties, Further Information and Proposed Classification, DACO: 2.1, 2.2, 2.3, 2.3.1, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.2, 3.5.3, 3.5.4, 3.5.5
1973842	2010, Isopyrazam (SYN520453) - Manufacturing Process Description and Supporting Data, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4, 2.12.1, 2.13.1, 2.13.2, 2.13.3, 2.4 CBI
1973845	2008, Confirmation of structures of by-products for isopyrazam (SYN520453) by mass spectroscopy, DACO: 2.13.2 CBI
1973847	2008, Confirmation of the structure of the by-product SYN546208 for isopyrazam (SYN520453) by mass spectroscopy, DACO: 2.13.2 CBI
2051521	2011, 2.11.3-1 Manufacturing Process (Detailed) SYN520453 - Isopyrazam, DACO: 2.11.3 CBI
2051522	2011, 2.11.4-1 Statement - Isopyrazam – [CBI REMOVED] Content, DACO: 2.11.4 CBI
2051524	2011, 2.13.1-1 Isopyrazam (SYN520453) Statement on Linearity for the Validation of SA-39/1, DACO: 2.13.1 CBI
2051525	2011, 2.13.1-2 Isopyrazam (SYN520453) Statement on Linearity for the Validation of SB-39/2, DACO: 2.13.1 CBI
2051526	2011, 2.13.1-3 Addendum to Study TK0011956 - SYN520453 Technical Analysis of [CBI REMOVED] in Five Representative Batches Produced at Munchwilen AG, DACO: 2.13.1 CBI
2051527	1999, Validation of Analytical Method AG-1229, DACO: 2.13.1 CBI
2051528	2008, 2.13.2-1 SYN534968 AND SYN534969 Spectra Final Report, DACO: 2.13.2 CBI
2051529	2011, 2.13.2-2 Isopyrazam (SYN520452) Statement on configuration of syn- and anti-epimers, DACO: 2.13.2 CBI
2051530	2006, 2.13.2-3 Isopyrazam - Certificate of Analyses (USA and Switzerland), DACO: 2.13.2 CBI
2118654	2011, 2.11.4 – [CBI REMOVED] - Clarification, DACO: 2.11.4 CBI
2118655	2011, 2.11.4 – [CBI REMOVED] - Clarification, DACO: 2.11.4 CBI

2204255 SYN520453: 90 Day Dietary Toxicity Study In Rats DACO 4.3.1

2669405 2011, Isopyrazam - Residue Study on Protected Pepper in Italy in 2010, DACO: 7.4.1

2669407 2011, Isopyrazam - Residue Study on Protected Cherry Tomatoes in Spain in 2010, DACO: 7.4.1

2669408 2011, Isopyrazam - Residue Study on Protected Melon in Spain in 2010, DACO: 7.4.1

2669409 2011, Isopyrazam - Residue Study on Protected Cherry Tomatoes in Northern France in 2010, DACO: 7.4.1

2669410 2012, Isopyrazam - Residue Study on Melon in Italy and Spain in 2011, DACO: 7.4.1

2669412 2012, Isopyrazam - Residue Study on Melon in Germany and Northern France in 2011, DACO: 7.4.1

2669415 2012, Isopyrazam - Residue Study on Protected Pepper in the United Kingdom and Northern France in 2011, DACO: 7.4.1

2669416 2012, Isopyrazam - Residue Study on Protected Pepper in Italy and Spain in 2011, DACO: 7.4.1

2669417 2011, Isopyrazam - Residue Study on Protected Melon in Northern France in 2010, DACO: 7.4.1

2669418 2012, Isopyrazam - Residue Study on Melon in Northern France in 2013, DACO: 7.4.1

2669419 2012, Isopyrazam - Residue Study on Field Melon in Germany and Northern France During 2012, DACO: 7.4.1

2669420 2012, Isopyrazam - Residue Study on Field Tomato in Northern France in 2011, DACO: 7.4.1

2669421 2013, Isopyrazam - Residue Study on Field Melon in Germany and Northern France During 2012, DACO: 7.4.1

2669422 2012, Isopyrazam - Residue Study on Protected Cherry Tomato in Italy in 2013, DACO: 7.4.1

2669423 2013, Isopyrazam - Residue Study on Field Melon in Spain and Southern France During 2012, DACO: 7.4.1

2669424 2012, Isopyrazam - Residue Study on Field Pepper in Northern France in 2011, DACO: 7.4.1

2669425 2012, Isopyrazam - Residue Study on Field Pepper in Spain in 2011, DACO: 7.4.1

2669426 2012, Isopyrazam - Residue Study on Protected Melon in Northern France in 2011, DACO: 7.4.1

2669427 2012, Isopyrazam - Residue Study on Protected Cherry Tomato in the United Kingdom and Northern France in 2011, DACO: 7.4.1

2669428 2012, Isopyrazam - Residue Study on Field Tomato in Italy and Spain in 2011, DACO: 7.4.1

2669429 2012, Isopyrazam - Residue Study on Protected Melon in Southern France and Italy in 2011, DACO: 7.4.1

2669430 2012, Isopyrazam - Residue Study on Protected Cherry Tomato in Southern France, Spain and Italy in 2011, DACO: 7.4.1

2691442 2012, Isopyrazam and Cyprodinil - Residue Study on Tomatoes and Processed Products in France (South) in 2009, DACO: 7.4.5

- 2709467 2010, SYN520453 - Storage Stability of Metabolite CSCD459488 Residues in Crops Stored Deep Frozen for up to 28 Months Final Report, DACO: 7.3
- 2709468 2010, SYN520453 - Storage Stability in Various Crops Stored Deep Frozen for up to Two Years Final Report Amendment 1, DACO: 7.3
- 2709958 2010, SYN520453 - Storage Stability of Metabolite CSCD459489 Residues in Crops Stored Deep Frozen for up to 28 Months, DACO: 7.3

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