Health Canada Santé Canada

Evaluation Report for Category A, Subcategory 1.3 Application

Application Number: 2010-3110
Application: New Active Ingredient – Maximum Residue Limits (MRL)s only
Product: Isopyrazam Technical
Registration Number: n/a
Active ingredients (a.i.): Isopyrazam [IPR]
PMRA Document Number: 2213794

Purpose of Application

The purpose of this application was to establish a maximum residue limit (MRL) for the new active ingredient, isopyrazam, to cover residues in/on imported bananas. Isopyrazam is registered for use on bananas in Columbia.

1.0 Chemistry Assessment

Isopyrazam

The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

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	$C_{20}H_{23}F_2N_3O$
Molecular weight	359.4

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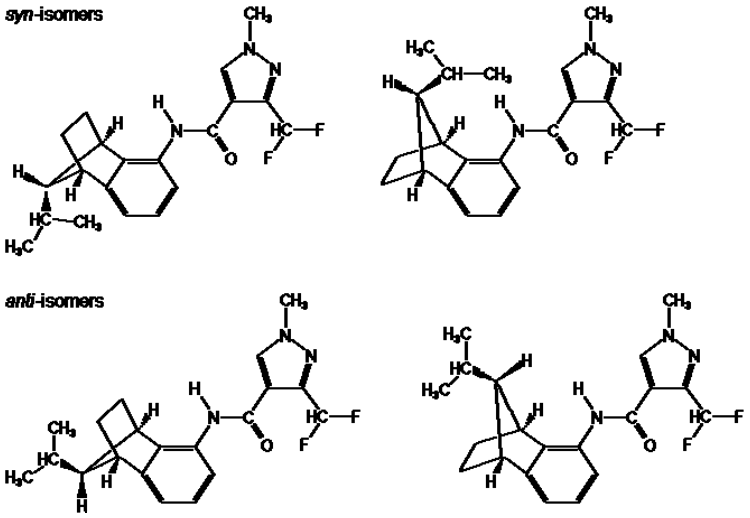
Structural formula



Purity of the active ingredient 94.7%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Isopyrazam Technical

Property	Result
Colour and physical state	Off-white crystalline powder
Odour	Odourless
Melting range	144.5°C for the *anti*-isomer 130.2°C for the *syn*-isomer
Boiling point or range	N/A
Density	1.332 g/cm^3
Vapour pressure at 20°C	<u>*anti*- isomer</u> <u>*syn*-isomer</u> 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 *syn* and *anti*- isomers: λ_{max} < 300 nm in neutral, acidic and basic solutions.
Solubility in water at 25°C	0.55 mg/L for *anti*-isomer 1.05 mg/L for *syn*-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
n-Octanol-water partition coefficient (K_{OW}) at 25°C	Log K_{ow} = 4.4 for *anti*-isomer Log K_{ow} = 4.1 for *syn*-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 54ºC. The technical grade active ingredient (TGAI) is not likely to be sensitive to sunlight since λ_{max} for both isomers (*syn* and *anti)* is < 300 nm.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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.

2.2 Methods for Residue Analysis

A liquid chromatography with tandem mass spectrometry (LC-MS/MS) method was developed and proposed for data generation and enforcement purposes in plant commodities. This method fulfilled the requirements with regards to specificity, accuracy and precision at the limit of quantitation of the method. Acceptable recoveries (70-120%) were obtained in plant matrices. The method was successfully validated by an independent laboratory. Extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method.

3.0 Health Assessments

3.1 Toxicology Summary

A detailed review of the toxicological database for isopyrazam was conducted. 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. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to isopyrazam. As isopyrazam is a mixture of two epimers (syn and anti), additional data were provided to compare the toxicity of the individual components and various mixtures of the two. Twelve toxicity studies on metabolites of isopyrazam were submitted (genotoxicity, acute oral, short term dietary and a developmental toxicity study).

Absorption and excretion of single or repeat low oral doses of radiolabeled isopyrazam were extensive and rapid in both sexes of rats. Females showed some evidence of faster absorption and distribution than males. Most of the administered dose (AD) was eliminated in the excreta within 48 hours, with elimination essentially completed by 7 days (95.6-106.3% of AD). The fecal route was the predominant route of excretion at 77-83% of AD, primarily via bile. Urinary excretion was 13-29% of AD. The half-life of elimination was 4.6-8.7 hours. Total terminal residues 7 days post-administration accounted for trace amounts of the administered dose with the highest radiolabel found in the liver, kidneys and adrenals of both sexes and also fat, pancreas, ovaries and uterus in females. Single or repeat dosing did not alter elimination profiles.

A large number of metabolites were isolated from urine and feces, created through hydroxylation and conjugation metabolic mechanisms.

The TGAI isopyrazam was of high acute toxicity by the oral route in rats. The anti epimer was the source of the toxicity while the syn epimer was found to be of low acute oral toxicity.

Short-term repeat dose feeding studies in mice, rats and dogs with isopyrazam technical revealed the liver to be the principal target organ of toxicity. Mice and rats treated with isopyrazam displayed liver toxicity (increased weight and altered cellular activity). In these studies, both mice and rats exhibited decreases in body weight and/or body weight gain, usually with corresponding decreases in food consumption. Oral treatment of dogs with technical isopyrazam revealed a reduction in body weight gain and food consumption, with limited and temporary effects on salivation, and behavioural clinical signs.

Technical isopyrazam was administered in the diet of mice and rats in long-term studies. In the mouse study, decreased body weight, body weight gains and food efficiency were noted along with increased liver weight, hepatocellular hypertrophy and eye/nasolacrimal effects. There were no treatment-related tumours in mice. In the rat study, administration of technical isopyrazam resulted in reduced body weights and body weight gains as well as liver histopathology, blood and clinical chemistry alterations and brown pigments in kidney tubules. Thyroid follicular cell and testicular interstitial cell tumours were found in males and hepatocellular and uterine endometrial tumours were found in females.

No evidence of mutagenic or clastogenic potential of technical isopyrazam was observed in the database. Two Ames assays, two mouse lymphoma clastogenicity assays, two human lymphocyte chromosome aberration assays, and two in vivo rat studies (a clastogenicity assay and an unscheduled DNA synthesis assay) were all negative. The weight of evidence suggested that isopyrazam was not genotoxic.

In a dietary multi-generation rat reproduction study, decreased body weight, body weight gain and food consumption were noted in the parental generations. The offspring exhibited similar body weight effects at higher dose levels. An increased time to sexual maturity was observed in both sexes of offspring, which may be secondary to the body weight effects. In the reproductive toxicity study, isopyrazam did not show sensitivity of the young in rats.

In rat oral developmental toxicity studies, isopyrazam produced decreased body weight, body weight gain and food consumption in the dams. Two dams were killed in extremis at a high dose level, though one of the deaths was considered unrelated to the test substance. At that same dose level, post-implantation loss was increased. Decreased fetal weights likely led to the multiple sites of delayed ossification in both rat studies. There was a slight increase in the number of supernumerary ribs in one of the studies. There was no evidence of sensitivity of the young in rats. The rabbit oral developmental toxicity study produced toxicity in dams in the form of reduced food consumption, liver toxicity and a death at the highest dose tested. At the same dose level, a single fetus had microphthalmia, which was also present at an even higher dose level in a range finding study. This serious effect (microphthalmia) occurred in the presence of maternal toxicity.

The acute and short-term neurotoxic potential of isopyrazam was examined in rats. Decreased activity at 1 hour post-dosing, decreased body weight gain and food consumption as well as weak appearance in females were the only adverse effects noted in the acute study. Decreased body weight gain and food consumption were the only effects observed in the short term study. There was no evidence of neurotoxicity following administration of isopyrazam.

For the two metabolites tested, CSCD465008 and CSCD459488, all six genotoxicity studies gave negative results. Both were of low acute oral toxicity. In short term oral toxicity studies, CSCD465008 produced no adverse effects while CSCD459488 caused increased liver weights, liver enzyme activity, hepatocyte hypertrophy and minimal follicular cell hypertrophy in the thyroid.

Results of the toxicology studies conducted on laboratory animals with the varying ratios of syn and anti isopyrazam and two metabolites are summarized in Appendix I, Table 1. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 2.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the Pest Management Regulatory Agency (PMRA) within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched for isopyrazam, and any additional information submitted by the applicant during the review process was considered. As of June 28, 2012, there were no health-related incident reports for this active in either jurisdiction.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* (PCPA) requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for isopyrazam. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of offspring compared to parental animals in the reproductive toxicity study. There were increased incidences of skeletal variations in the rat developmental toxicity study and delayed sexual maturation in the reproductive toxicity study. Both of those effects are likely secondary to decreased body weight seen in the fetuses and pups and occurred in the presence of maternal toxicity. A single incidence of microphthalmia was observed at the highest dose in the main rabbit developmental toxicity study in the presence of maternal toxicity. Although this effect is within the historical control range, there were higher incidences observed in a range finding study at higher doses and therefore it cannot be discounted.

Overall, the database is adequate for determining the sensitivity of the young. Effects on the young are well-characterized. The fetal microphthalmia in rabbits was considered a serious endpoint, although the concern was tempered by the presence of maternal toxicity. The PCPA factor was reduced to 3-fold for scenarios in which this endpoint was relevant. For all other scenarios, the PCPA factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

Acute Reference Dose (all populations)

To estimate acute dietary risk (1 day) in all populations, the rat developmental toxicity study with a no observed adverse effect level (NOAEL) of 20 mg/kg bw/day was selected for risk assessment. At the lowest observed adverse effect level (LOAEL) of 75 mg/kg bw/day, body weight gain and food consumption were significantly reduced in the dams starting the day after dosing commenced. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor has been reduced to 1-fold. **The composite assessment factor (CAF) is 100.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{20 \text{ mg/kg bw}}{100} = 0.2 \text{ mg/kg bw of isopyrazam}$$

This ARfD provides a margin of 750 to the NOAEL for microphthalmia in the rabbit developmental toxicity study.

3.3 Acceptable Daily Intake (ADI)

To estimate dietary risk from repeated dietary exposure, the rat chronic toxicity/oncogenicity study with a NOAEL of 5.5 mg/kg bw/day was selected for risk assessment. At the LOAEL of 27.6 mg/kg bw/day, liver histopathology, clinical chemistry alterations, brown pigment in kidney tubules and decreased body weight and body weight gains were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor has been reduced to 1-fold. **The CAF is 100**.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5.5 \text{ mg/kg bw/day}}{100} = 0.06 \text{ mg/kg bw/day of isopyrazam}$$

The ADI provides a margin of 2500 to the NOAEL for microphthalmia in the rabbit developmental toxicity study.

Cancer Assessment

There were no treatment-related tumours found in mice. In rats, thyroid follicular cell and testicular interstitial cell tumours were found in males and hepatocellular and uterine endometrial tumours were found in females. No mode of action data were provided to address the relevance of these tumours, therefore linear low dose extrapolations were generated for all four tumour types with the most conservative value of 7.36×10^{-3} $(\text{mg/kg bw/day})^{-1}$ from the uterine endometrial adenocarcinomas being used for the risk assessment.

3.4 Occupational and Residential Risk Assessment

As this is an import MRL application, no occupational or residential risk assessment was required.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition in plant products is isopyrazam for enforcement purposes, and isopyrazam and metabolite CSCD459488 for risk assessment. The LC-MS/MS enforcement analytical method is valid for the quantification of isopyrazam residues in plant commodities. The residues of isopyrazam are stable when stored in a freezer at ≤-18°C for up to 8 months in spinach, 13 months in tomatoes and potatoes, 14 months in lentils, 15 months in barley grain, barley straw and ryegrass, and 16 months in rapeseed. There are no processed crop commodities associated with the use of isopyrazam. There are no animal feed items associated with the use of isopyrazam, and quantifiable residues are not expected to occur in livestock matrices. Supervised residue trials conducted throughout Latin America using end-use products containing isopyrazam at label rates in or on bananas are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic analysis: 100% crop treated, default processing factors, residues of isopyrazam in bananas at MRL values. The basic chronic dietary exposure from all supported isopyrazam food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 1% of the ADI. Exposure from food is considered acceptable. The PMRA estimates that chronic dietary exposure to isopyrazam from food is <0.1% (0.000018 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 0.2% (0.000092 mg/kg bw/day) of the ADI.

The basic 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 was estimated to be 1.3×10^{-7} for the general population, which is considered acceptable.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following criteria were applied to the basic acute analysis: 100% crop treated, default processing factors, residues of isopyrazam in/on bananas at MRL levels. The basic acute dietary exposure from all supported isopyrazam food uses was estimated to be <0.1% of the ARfD for the general population (95^{th} percentile, deterministic). Specifically, an acute dietary exposure of <0.1% to 0.24% of the ARfD was obtained for all population subgroups, with the highest exposed population subgroup being children 1-2 years old.

3.5.3 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.

3.5.4 Maximum Residue Limits

Table 3.5.4 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Bananas	0.05

For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant matrices, analytical methodology, field trial data, and the acute, chronic and cancer dietary risk estimates are summarized in Appendix I, Tables 3, 4 and 5.

4.0 Environmental and Value Assessments

Environmental and value assessments were not required for this application.

5.0 Conclusion

The Pest Management Regulatory Agency has completed an assessment of the information provided in support of the product, Isopyrazam Technical, and has found the information sufficient to establish an MRL for imported bananas.

List of Abbreviations

A:G	albumin/globulin
AD	administered dose
ADI	acceptable daily intake
a.i.	active ingredient
ALAT	alanine aminotransferase
ALK	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ARfD	acute reference dose
ASAT	aspartate aminotransferase
AUC	area under the curve
BBCH	Biologishe Bundesanstalt, Bundessortenamt and Chemical industry
BROD	benzyloxyresorufin
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Services
cm	centimetre(s)
DALA	days after last application
DNA	deoxyribonucleic acid
EROD	ethoxyresorufin-O-deethylase
F_1	first generation
F_2	second generation
fc	food consumption
fe	food efficiency
g	gram(s)
GD	gestation day
GGT	gamma glutamyltransferase
GI	gastrointestinal
ha	hectare(s)
HGB	hemoglobin
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
LSC	liquid scintillation counting
mg	milligram(s)
MRL	maximum residue limit
NA	not applicable
nm	nanometre(s)
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effect level
P450	cytochrome P450 family of enzymes
Pa	pascals
PCPA	*Pest Control Product Act*

PHI	preharvest interval
pKa	p*K*a dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PROD	pentoxyresorufin-O-deethylase
q_1*	cancer potency factor
RBC	red blood cells
RTI	retreatment interval
STMdR	supervised trial median residue
STMR	supervised trial mean residue
TGAI	technical grade active ingredient
$T_{1/2}$	half life
TLC	thin layer chromatography
TRR	total radioactive residue
UK	United Kingdom
US	United States
UV	ultra violet
WBC	white blood cells
Wt	weight

Appendix I Tables and Figures

Table 1 **Toxicity Profile of Technical Isopyrazam and Some Metabolites**
(Effects are known or assumed to occur in both sexes unless otherwise noted; 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 and PMRA No.	**Study Results**
Metabolism and pharmacokinetics PMRA 1932107, -08, -09, -10, -11, -13, -14, -15	Absorption and excretion of single oral doses (1 or 75 mg/kg bw in corn oil) was extensive and rapid in male and female Wistar rats. No radioactivity was collected in expired air at 48 hours. Average recovery from the excretion/mass balance experiment was greater than 92% administered dose (AD) by 2 days and greater than 95% AD by 7 days. Feces provided the highest recoveries at 77-83% AD. For urine, 13-27% of AD was recovered with female values tending to be higher than males. The most significant trace residues were found in the GI tract, liver and kidney. Bile cannulation resulted in 48-58% recovery of AD at 48 hours with feces at 21-36% and urine at 7-16%. These values suggest 63-73% absorption of test substance within 48 hours. Dosing with the individual isomers produced similar results. Absorption and elimination were also similar following repeat dosing. Maximum plasma concentration was attained within 3-6 hours post dose. The AUC analysis showed that females had a greater systemic exposure at 1.3-2.5 times the male values. The systemic exposure of both sexes scaled proportionally with the dose level. The terminal elimination $T_{1/2}$ was 4.6-8.7 hours. At 6 hours, the highest tissue concentrations of radioactivity occurred in the liver, kidney and adrenals of both sexes plus fat, pancreas, ovaries and uterus in females. Again, higher levels of radioactivity were found in the tissues of females at 6 hours suggesting faster absorption and distribution. In all dose groups, [^{14}C]SYN520453 was extensively metabolized by rats via oxidation of the isopropyl and bicycle moieties giving rise to a range of hydroxy, dihydroxy, acid and hydroxy acid metabolites, along with their glucuronide and sulfate conjugates. Oxidation of the demethylated metabolite of SYN520453 produced an equivalent range of oxidized demethylated metabolites. No cleavage of the parent molecule was observed. The major routes of biotransformation were generally independent of dose level and sex, and were similar for the syn and anti isomers. Metabolism of the syn isomer also appeared to be similar following either a single dose or repeated dosing.
Acute Oral Toxicity (gavage) Wistar rats PMRA 1932042	LD_{50} pure syn > 2000 mg/kg bw LD_{50} pure anti = 310.2 mg/kg bw LD_{50} 50:50 syn:anti = 310.2 mg/kg bw **High toxicity**

Acute Oral Toxicity (gavage) 70:30 – syn:anti Wistar rats PMRA 1932045	LD_{50} between 550 and 2000 mg/kg bw
Acute Oral Toxicity (gavage) 93:7 – syn:anti Wistar rats PMRA 1932046	LD_{50} > 2000 mg/kg bw
28-Day Oral Toxicity (diet) CD-1 mice PMRA 1932057 MRID 47746830	Range-finding, NOAEL not established **≥ 287.8 mg/kg/bw/day:** ↑ liver wt, hepatocellular hypertrophy, ↑ PROD, EROD, BROD, total P450 activity **1125.8 mg/kg bw/day:** ↑ bilirubin, ↑ plasma protein, ↓ A:G
90-Day Oral Toxicity (diet) CD-1 mice PMRA 1932050 MRID 47746832	NOAEL = 76.5 mg/kg bw/day **≥ 390.8 mg/kg bw/day:** ↓ bw, bwg, fe, ↑ liver wt with hepatocellular hypertrophy
28-Day Oral Toxicity (diet) Wistar rats PMRA 1932056 MRID 47746831	Range-finding, NOAEL not established **≥ 390.1 mg/kg/bw/day:** ↓ bw, ↑ liver wt, centrilobular hepatocyte hypertrophy, altered clin chem parameters (↓ triglycerides ♂; ↑ urea, cholesterol, phosphorus ♀)
28-Day Oral Toxicity (diet) Wistar rats PMRA 1932058 MRID 47746826	Range-finding, NOAEL not established **≥ 46 mg/kg/bw/day:** ↑ liver wt, ↑ PROD ♀ **175 mg/kg bw/day:** centrilobular hepatocellular hypertrophy, ↑ P450, EROD; ↓ WBC, ↓ triglycerides, ↑ creatine kinase and creatinine, ↑ liver wt ♂, ↑ PROD; ↓ bw, fc, ↑ APTT ♀

28-Day Oral Toxicity (diet) Wistar rats PMRA 1932059 MRID 47746829	Supplementary, NOAEL not established 50:50 mixture **≥ 45 mg/kg/bw/day:** ↑ liver wt with hepatocellular hypertrophy, ↑ P450, PROD, EROD **≥ 180 mg/kg bw/day:** ↓ bw, ↑ cholesterol **≥ 420 mg/kg bw/day:** ↓ fc, hunched posture and piloerection, ↑ RBC, ↓ APTT, ↓ albumin, ↓ total protein Syn epimer **≥ 45 mg/kg/bw/day:** ↑ liver wt with hepatocellular hypertrohpy, ↑ P450, PROD, EROD **≥ 420 mg/kg bw/day:** ↓ bw, ↑ cholesterol, ↓ ALK, ↑ calcium, ↑ P450, ↓ platelets, lymphocytes, basophils Anti epimer **≥ 45 mg/kg/bw/day:** ↑ liver wt with hepatocellular hypertrophy, ↑ P450, PROD, EROD, ↓ APTT **≥ 180 mg/kg bw/day:** ↓ bw, fc, piloerection, ↓ albumin, total protein, triglycerides, ↑ cholesterol, ↓ basophils **≥ 420 mg/kg bw/day:** hunched posture, ↑ potassium, phosphorus, ↑ plasma enzymes, ↑ HGB, hematocrit, RBC, prothrombin time
90-Day Oral Toxicity (diet) Wistar rats PMRA 1932047 MRID 47746834	NOAEL = 21.3 mg/kg bw/day **≥ 106.3 mg/kg bw/day:** altered clin chem parameters (↓ triglycerides and ↑ plasma enzymes and ions), ↑ liver wt with hepatocellular hypertrophy; ↓ bw, bwg, fc, fe ♀
90-Day Oral Toxicity (diet) Wistar rats PMRA 1932048 MRID 47746833	NOAEL = 20.3 mg/kg bw/day (from 93:7 syn:anti mixture) **≥ 158.7 mg/kg bw/day:** ↓ bw, bwg, fe, altered clin chem parameters (↓ ALAT, alk phos ♂♀, ↑ cholesterol ♀), ↑ liver wt with centrilobular hypertrophy and midzonal vacuolation, ↑ thyroid wt The two mixtures were toxicologically equivalent
28-Day Oral Toxicity (capsule) Beagle dogs PMRA 1932062	Range-finding, NOAEL not established **≥ 100 mg/kg bw/day:** ↓ bwg, fc ♀ **300 mg/kg bw/day:** salivation, ↑ GGT, hepatocellular hypertrophy; ↑ liver wt ♀

28-Day Oral Toxicity (capsule) Beagle dogs PMRA 1932063	Range-finding, NOAEL not established **≥ 150 mg/kg bw/day:** ↓ fc, ↓ monocyte count ♂; ↑ liver wt ♀ **400 mg/kg bw/day:** ↓ bw, bwg, decreased activity, regurgitation, salivation, ↑ alk phos, GGT, ↑ liver wt; reduced stability, vomitting, ↑ platelets, ↓ WBC, ↑ triglycerides, ALT, cholesterol, creatine kinase, ↑ eosinophilia and hypertrophy of periportal hepatocytes ♂; splayed gait, thin appearance ♀
90-Day Oral Toxicity (capsule) Beagle dogs PMRA 1932051 MRID 477746835	NOAEL = 30 mg/kg bw/day **≥ 250 mg/kg bw/day:** ↓ bwg, fc, ↑ salivation; ↑ adverse behavioural clinical signs in one ♂; ↓ bw ♀
90-Day Oral Toxicity (capsule) Beagle dogs PMRA 1932053 MRID 477746836	NOAEL = 30 mg/kg bw/day **≥ 100 mg/kg bw/day:** ↓ bwg, ↑ altered clin chem parameters (↑ alk phos, ↓ plasma albumin, total protein, cholesterol); head wobble and abnormal activity levels in one ♂ **300 mg/kg bw/day:** ↓ bw, fc, ↑ liver wt; ↑ platelets, ↓ stability, abnormal activity levels, fearfulness and vocalization ♂; urinary specific gravity ♀
12-Month Oral Toxicity (capsule) Beagle dogs PMRA 1932055 MRID 477746848	NOAEL = 25 mg/kg bw/day **≥ 100 mg/kg bw/day:** ↓ bwg, ↑ altered clin chem parameters (↑ alk phos, ↓ plasma albumin, ↓ bilirubin), ↑ liver wt ♂
18-Month Carcinogenicity (diet) CD-1 mice PMRA 1932067 MRID 47746849	NOAEL = 56.2 mg/kg bw/day **≥ 432.6 mg/kg bw/day:** ↓ bw, bwg, fe, ↑ liver wt, hepatocellular hypertrophy, eye discharge, nasolacrimal duct effects **No evidence of carcinogenicity**

Combined 12/24-Month Oral Toxicity and Carcinogenicity (diet) Wistar rats PMRA 1932069 MRID 47746851	NOAEL = 5.5 mg/kg bw/day **≥ 27.6 mg/kg bw/day:** liver histopathology (hypertrophy, vacuolation, pigmentation, bile duct hyperplasia and fibrosis, eosinophilic altered hepatocytes), ↓ alk phos, ↑ ASAT; ↑ GGT ♂; ↓ bw, ↓ bwg, ↓ plasma triglycerides and bilirubin, brown pigment in kidney tubules ♀ **Evidence of carcinogenicity** Thyroid follicular cell adenoma ♂ 1, 4, 2, 7 Thyroid follicular cell carcinoma ♂ 0, 0, 5, 0 Testicular interstitial cell adenoma ♂ 3, 2, 1, 7 Hepatocellular adenoma ♀ 0, 0, 1, 11 Hepatocellular adenoma ♀ 0, 0, 0, 1 Uterine endometrial adenoma ♀ 1, 0, 1, 0 Uterine endometrial adenocarcinoma ♀1, 2, 3, 15
1-Generation Reproductive Toxicity (diet) Wistar rats PMRA 1932071 MRID 47746846	Range-finding, NOAEL not established Parental Toxicity **≥ 76.1 mg/kg bw/day:** ↑ liver wt **≥ 151.6 mg/kg bw/day:** ↓ bw, bwg, fc Offspring Toxicity **≥ 76.1 mg/kg bw/day:** ↑ liver wt **≥ 151.6 mg/kg bw/day:** ↓ bw Reproductive Toxicity No effects
2-Generation Reproductive Toxicity (diet) Wistar rats PMRA 1932070 MRID 47746847	Parental Toxicity NOAEL = 8.9 mg/kg bw/day **≥ 44.5 mg/kg bw/day:** ↓ bw, bwg, fc F_1 ♀ Offspring Toxicity NOAEL = 44.5 mg/kg bw/day **269.3 mg/kg bw/day:** ↓ bw, bwg F_1, F_2, delayed sexual maturation Reproductive Toxicity NOAEL = 269.3 mg/kg bw/day **No evidence of sensitivity of the young**

Developmental Toxicity (gavage) Wistar rats PMRA 1932080 MRID 47746844	Range-finding, NOAEL not established Parental Toxicity **≥ 60 mg/kg bw/day:** ↓ bwg **≥ 125 mg/kg bw/day:** ↓ bw, fc, ↑ quietness, ventral recumbency **250 mg/kg bw/day:** Uncoordinated movements, ruffled fur Developmental Toxicity **≥ 125 mg/kg bw/day:** ↓ fetal wt, multiple sites of delayed ossification
Developmental Toxicity (gavage) Wistar rats PMRA 1932072 MRID 47746843	Parental Toxicity NOAEL = 20 mg/kg bw/day **≥ 75 mg/kg bw/day:** ↓ bw, bwg, fc Developmental Toxicity NOAEL = 20 mg/kg bw/day **≥ 75 mg/kg bw/day:** ↓ fetal weights, multiple sites of delayed ossification (cervical vertebrae, sternum and limbs) **No evidence of sensitivity of the young**
Developmental Toxicity (gavage) Wistar rats PMRA 1932077 MRID 47746845	Parental Toxicity NOAEL = 75 mg/kg bw/day **≥ 250 mg/kg bw/day:** one dam sacrificed due to morbidity, ↓ bw, bwg, fc, ↑ post-implantation loss (8.4 vs. 1.6 control) Developmental Toxicity NOAEL = 75 mg/kg bw/day **≥ 250 mg/kg bw/day:** ↓ fetal weights, multiple sites of delayed ossification (cervical centra, caudal arches, costal cartilage, limbs), ↑ post-implantation loss (8.4 vs. 1.6 control) **No evidence of sensitivity of the young**
Developmental Toxicity (gavage) Wistar rats PMRA 1932075 MRID 47746839	Range-finding, NOAEL not established Parental Toxicity **≥ 200 mg/kg bw/day:** ↓ bw, fc, ↑ liver wt **≥ 350 mg/kg bw/day:** centrilobular hepatocyte hypertrophy, slight ↑ post-implantation loss **500 mg/kg bw/day:** All dams sacrificed GD 11 due to ↓ bw, fc and clinical signs Developmental Toxicity **≥ 350 mg/kg bw/day:** slight ↑ post-implantation loss, ↓ fetal wt

Developmental Toxicity (gavage) NZW rabbits PMRA 1932082 MRID 47746838	Range-finding, NOAEL not established Parental Toxicity **≥ 400 mg/kg bw/day:** One moribund sacrifice at mid and high doses, ↓ bwg, fc, defecation, gravid uterine weight, ↑ liver wt with hepatocellular vacuolation and hypertrophy, ↑ serum GGT **1000 mg/kg bw/day:** ↑ early resorptions and post implantation loss Developmental Toxicity **1000 mg/kg bw/day:** ↑ early resorptions and post implantation loss, ↓ fetal wt, microphthalmia (5 fetuses, 2 litters vs. 1/1 in control), hemorrhagic ring around the iris and/or reddened eyes or dark red areas on the eye, absent or small gall bladders
Developmental Toxicity (gavage) NZW rabbits PMRA 1932081 MRID 47746840	Parental Toxicity NOAEL = 150 mg/kg bw/day **500 mg/kg bw/day:** ↓ fc, a single death, ↑ liver wt with hypertrophy and vacuolation Developmental Toxicity NOAEL = 150 mg/kg bw/day **500 mg/kg bw/day:** Single incidence of microphthalmia **Serious effect in the presence of maternal toxicity**
Developmental Toxicity (gavage) Himalayan rabbits PMRA 1932083 MRID 47746841	Range-finding, NOAEL not established Parental Toxicity **1000 mg/kg bw/day:** ↓ fc Developmental Toxicity **≥ 600 mg/kg bw/day:** ↑ small eye (variation) and microphthalmia
Developmental Toxicity (gavage) Himalayan rabbits PMRA 1932087 MRID 47746842	Range-finding, NOAEL not established Parental Toxicity **400 mg/kg bw/day:** ↓ fc Developmental Toxicity **400 mg/kg bw/day:** ↑ small eye (variation)
Acute neurotoxicity Wistar rats PMRA 1932116 MRID 47746866	NOAEL = 30 mg/kg bw/day **250 mg/kg bw/day:** ↓ activity 1h post-dosing; ↓ bwg, fc (first week), weak appearance ♀

Short term neurotoxicity Wistar rats PMRA 1932117 MRID 47746865	NOAEL = 98 mg/kg bw/day **382 mg/kg bw/day:** ↓ bwg; ↓ fc ♀
Bacterial Reverse Mutation Assay PMRA 1932090 MRID 47746854	**Negative**
Bacterial Reverse Mutation Assay PMRA 1932092 MRID 47746855	**Negative**
In Vitro Mammalian Clastogenicity PMRA 1932097 MRID 47746859	**Negative**
In Vitro Mammalian Clastogenicity PMRA 1932098 MRID 47746858	**Negative**
In Vitro Chromosome Aberration PMRA 1932101 MRID 47746863	**Negative**
In Vitro Chromosome Aberration PMRA 1932104 MRID 47746862	**Negative**
In Vivo Mammalian Clastogenicity PMRA 1932105 MRID 47746864	**Negative**
In Vivo Unscheduled DNA Synthesis PMRA 1932106 MRID N/A	**Negative**

CSCD465008 Acute Oral Toxicity (gavage) Wistar rats PMRA 1932043	LD_{50} > 2000 mg/kg bw **2000 mg/kg bw:** ruffled fur, sedation, hunched posture
CSCD459488 Acute Oral Toxicity (gavage) Wistar rats PMRA 1932044	LD_{50} > 2000 mg/kg bw No toxicity
CSCD465008 14-Day Oral Toxicity (diet) Wistar rats PMRA 1932065	Supplemental, NOAEL not established No adverse effects observed
CSCD465008 28-Day Oral Toxicity (diet) Wistar rats PMRA 1932060 MRID 47746827	Supplemental, NOAEL not established No adverse effects observed
CSCD459488 28-Day Oral Toxicity (diet) Wistar rats PMRA 1932061 MRID 47746828	Supplemental, NOAEL not established **≥ 27 mg/kg bw/day:** ↑ EROD; ↑ PROD ♀ **≥ 370 mg/kg bw/day:** ↑ liver wt, ↑ centrilobular hepatocyte hypertrophy; ↑ total hepatic cytochrome P450, ↑ PROD, minimal follicular cell hypertrophy in thyroid ♂
CSCD459488 Developmental Toxicity (gavage) NZW rabbits PMRA 1932085 MRID 47746837	Supplemental, NOAEL not established Parental Toxicity **≥ 150 mg/kg bw/day:** ↑ liver wt **No evidence of sensitivity of the young**

CSCD465008 R958945 Bacterial Reverse Mutation Assay PMRA 1932094 MRID 47746852	**Negative**
CSCD459488 SYN545364 Bacterial Reverse Mutation Assay PMRA 1932096 MRID 47746853	**Negative**
CSCD465008 In Vitro Mammalian Clastogenicity PMRA 1932099 MRID 47746856	**Negative**
CSCD459488 SYN545364 In Vitro Mammalian Clastogenicity PMRA 1932100 MRID 47746857	**Negative**
CSCD465008 In Vitro Chromosome Aberration PMRA 1932102 MRID 47746860	**Negative**
CSCD459488 SYN545364 In Vitro Chromosome Aberration PMRA 1932103 MRID 47746861	**Negative**

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Isopyrazam

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1]
Acute dietary general population	Rat developmental toxicity	NOAEL = 20 mg/kg bw Decreased body weight gain and food consumption in dams following the first dose	100
	ARfD = 0.2 mg/kg bw		
Repeated dietary	Rat chronic/oncogenicity	NOAEL = 5.5 mg/kg bw/day Decreased body weight, body weight gain, increased liver weight with pale spots and/or masses, increased clinical chemistry and hematology alterations	100
	ADI = 0.06 mg/kg bw/day		
q_1*	7.36×10^{-3} (mg/kg bw/day)$^{-1}$		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments

Table 3 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Plant	GRM006.01B Enforcement method	Isopyrazam as isomers SYN534968 (*anti*) & SYN534969 (*syn*)	LC-MS/MS (liquid chromatography with tandem mass spectrometry)	0.005 ppm per analyte	Barley (grain, forage, straw), apple, carrot, spinach, potato, canola seed, lentils, tomato, bran, bread, beer	PMRA # 1932127, 1932132
	GRM006.03A	Metabolites CSCD459489 (*anti*) & CSCD459488 (*syn*)		0.005 ppm per analyte	Barley (grain, forage, straw), lentils; spinach, potato, tomato, canola seed, apple	PMRA # 1932131

Table 4 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN WHEAT			**PMRA# 1932119**
Radiolabel Position	**[Phenyl-U-^{14}C] (syn:anti, 96:4)**	**[Pyrazole-5-^{14}C] (syn:anti, 96:4)**	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**
Test Site	Wheat plants grown and treated in pots of sandy loam soil under glasshouse conditions		
Treatment	Broadcast foliar spray applications at BBCH 31, 39 and 69		
Rate	3 x 125 g a.i./ha for a total rate of 375 g a.i./ha		
End-use product	EC100 (AC14421C) – emulsion concentrate		
Preharvest interval	Forage: 13 days after 2nd application (BBCH 55-59) Straw and grain: 46-48 days after 3rd application (at maturity)		

Matrix	PHI (days)	[Phenyl-U-^{14}C] (syn:anti, 96:4)	[Pyrazole-5-^{14}C] (syn:anti, 96:4)	[Phenyl-U-^{14}C] (syn:anti, 70:30)
		TRR (ppm)	TRR (ppm)	TRR (ppm)
Forage	13 (after 2nd appl)	7.088	6.175	4.749
Straw (including husks)	46-48	20.844	20.189	14.083
Grain	46-48	0.058	0.059	0.031

Metabolites Identified	Major Metabolites (> 10% TRR)	Minor Metabolites (< 10% TRR)
Radiolabel Position	**[Phenyl-U-^{14}C] (syn:anti, 96:4)**	
Forage	Isopyrazam	CSCD459488, CSCD563692, CSCD563691, CSCD539372, dihydroxy-isopyrazam
Straw	Isopyrazam	CSCD459488, CSCD563692, CSCD563691, CSCD539372, CSCD539391, dihydroxy-isopyrazam
Grain	Isopyrazam	CSCD459488
	[Pyrazole-5-^{14}C] (syn:anti, 96:4)	
Forage	Isopyrazam	CSCD459488, CSCD563692, CSCD563691, CSAA798670, CSCC230729, dihydroxy-isopyrazam
Straw	Isopyrazam	CSCD459488, CSCD563692, CSCD563691, CSAA798670, CSCC230729, dihydroxy-isopyrazam
Grain	Isopyrazam	CSCD459488, CSCD563692, dihydroxy-isopyrazam
	[Phenyl-U-^{14}C] (syn:anti, 70:30)	
Forage	Isopyrazam (64% SYN534969 (syn), 27% SYN534968 (anti)	CSCD459488, CSCD563692, CSCD563691, CSCD539372, CSCD539391, dihydroxy-isopyrazam
Straw	Isopyrazam	CSCD459488, CSCD563692, CSCD563691, CSCD539372, CSCC230729, dihydroxy-isopyrazam
Grain	Isopyrazam	CSCD459488, CSCD563692

Extractable residues represented >95% of the total radioactive residues (TRRs) in wheat forage and straw (including husks), and 79-89% of the TRRs in wheat grain. All samples were analysed by liquid scintillation counting (LSC) following combustion. The samples were extracted sequentially with acetonitrile, acetonitrile/water, water and acetone. The resulting extracts were analysed by LSC, thin layer chromatography (TLC), high performance liquid chromatography (HPLC) and liquid chromatography with tandem mass spectrometry (LC-MS/MS). The resulting unextractable material was combusted and analysed by LSC. Nuclear magnetic resonance (NMR) spectroscopy was used to confirm the structure of some metabolites.

There were no significant differences between the metabolic profiles of the three radiolabelled experiments. The proposed metabolic pathways for isopyrazam in wheat involve hydroxylation of the isopropyl group or hydroxylation of the bicyclic ring (Figure 1). Trace levels of the half molecule pyrazole acid, CSAA798670, were observed in this study indicating some cleavage of the amide bond between the two aromatic rings.

To address the possibility of racemisation, the syn:anti ratio was determined in forage samples from the phenyl study (syn:anti, 70:30). The syn:anti ratio had not changed, remaining at 70:30, 13 days after the second application to the wheat.

NATURE OF THE RESIDUE IN GRAPE			**PMRA# 1932120**	
Radiolabel Position	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**		**[Pyrazole-5-^{14}C] (syn:anti, 70:30)**	
Test Site	Field-based established grape vines in the UK			
Treatment	Foliar spray application			
Rate	1 x 400 g a.i./ha			
End-use product	SC 250 (A15309E) – suspension concentrate			
Preharvest interval	21 days			
Matrix	**PHI (days)**	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**	**[Pyrazole-5-^{14}C] (syn:anti, 70:30)**	
		TRR (ppm)	**TRR (ppm)**	
Grapes	21	0.156	0.147	
Foliage	21	10.973	3.768	
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**	**[Pyrazole-5-^{14}C] (syn:anti, 70:30)**	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**	**[Pyrazole-5-^{14}C] (syn:anti, 70:30)**
Grape	Isopyrazam	Isopyrazam	CSCD459488, CSCD563692, CSCD610195	CSCD459488, CSCD563692/610195, CSCD465008, CSAA798670

Foliage	Isopyrazam	Isopyrazam	CSCD459488, CSCD459489, CSCD563692, CSCD610195, CSCD539391/539372, CSCD656800	CSCD459488, CSCD459489, CSCD563692/610195, CSCD539391/539372, CSCD656800, CSCD465008

Extractable residues represented >98% of the TRRs in grapes and leaves. All samples were analysed by LSC following combustion. The samples were also extracted sequentially with acetonitrile (leaves only), acetonitrile/water and water (leaves only). The resulting extracts were analysed by LSC, TLC and HPLC. The resulting unextractable material was combusted and analysed by LSC.

The proposed metabolic pathways for isopyrazam in grapes and vine leaves involve hydroxylation of the isopropyl group or hydroxylation of the bicyclic ring (Figure 1). A minor metabolic transformation observed is N-demethylation of the pyrazole ring.

To address the possibility of racemisation, the syn/anti ratio was determined in grape and leaf samples from the pyrazole and phenyl studies (syn:anti, 70:30). The syn:anti ratio had not changed significantly, remaining at 72:28, in grapes and 71:29 in leaves, 21 days after application to grapes.

NATURE OF THE RESIDUE IN LETTUCE			**PMRA# 1932124**	
Radiolabel Position	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**		**[Pyrazole-5-^{14}C] (syn:anti, 70:30)**	
Test Site	Lettuce plants grown in clay loam soil, under glasshouse conditions for 14 days, then transplanted into soil in test plots outdoors			
Treatment	Foliar spray applications at BBCH <40, 42 and 46			
Rate	3 x 125 g a.i./ha for a total rate of 375 g a.i./ha			
End-use product	EC100 (AC14421D) – emulsion concentrate			
Preharvest interval	3 and 14 days			
Matrix	**PHI (days)**	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**	**[Pyrazole-5-^{14}C] (syn:anti, 70:30)**	
		TRR (ppm)	**TRR (ppm)**	
Lettuce	3	1.555	1.538	
Lettuce	14	0.311	0.221	
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**	**[Pyrazole-5-^{14}C] (syn:anti, 70:30)**	**[Phenyl-U-^{14}C] (syn:anti, 70:30)**	**[Pyrazole-5-^{14}C] (syn:anti, 70:30)**
Lettuce (3 day PHI)	Isopyrazam	Isopyrazam	CSCD459488, CSCD610195/563692, CSCD539372, dihydroxy-isopyrazam	CSCD459488, CSCD610195/563692, CSCD539372, CSCD465008, dihydroxy-isopyrazam

Lettuce (14 day PHI)	Isopyrazam, CSCD459488	Isopyrazam, CSCD459488	CSCD610195/563692, CSCD573363, CSCD539372, CSCD120604, dihydroxy-isopyrazam	CSCD610195/563692, CSCD573363, CSCD539372, CSCD120604, CSCD465008, CSAA798670, dihydroxy-isopyrazam

Extractable residues represented >85% of the TRRs in immature and mature lettuce leaves. All samples were analysed by LSC following combustion. The samples were also extracted sequentially with acetontitrile and acetonitrile/water. The resulting extracts were analysed by LSC, TLC and HPLC. The resulting unextractable material was combusted and analysed by LSC, with the exception of the mature lettuce sample from the pyrazole label study, which was further extracted by acid hydrolysis, followed by combustion and analysed by LSC.

The proposed metabolic pathways for isopyrazam in lettuce involve hydroxylation of the isopropyl group or hydroxylation of the bicyclic ring (Figure 1). Minor metabolic transformations observed are N-demethylation of the pyrazole ring and cleavage of the amide bond.

Proposed Metabolism in Plants

Studies on wheat, grape and lettuce showed comparable metabolic pathways. Metabolism of isopyrazam in plants is proposed to result mainly from hydroxylation of the isopropyl group and hydroxylation of the bicyclic ring. Minor metabolism transformations are N-demethylation of the pyrazole ring and cleavage of the amide bond.

The metabolism of isopyrazam in plants is adequately documented. The metabolic pathways in three diverse crops (wheat, grape and lettuce) are similar. The residue definition in plant commodities is isopyrazam for enforcement purposes, and isopyrazam and the metabolite CSCD459488 for risk assessment purposes.

CONFINED ACCUMULATION IN ROTATIONAL CROPS

Not required as bananas are not rotational crops.

NATURE OF THE RESIDUE IN ANIMALS

Not required as there are no livestock feedstuffs associated with the use on bananas.

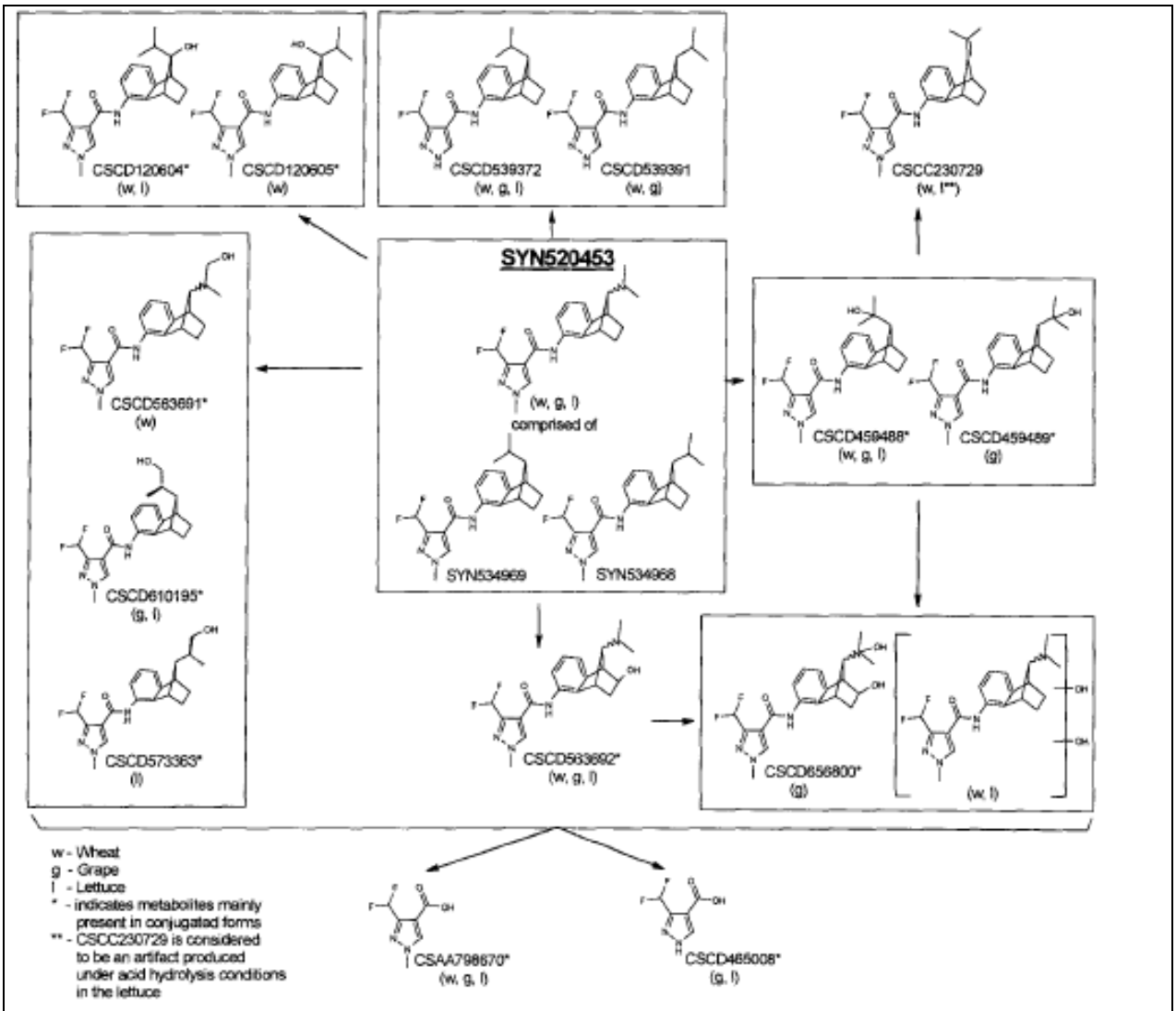


Figure 1. Proposed metabolic scheme for isopyrazam (SYN520453) in plants.

FREEZER STORAGE STABILITY	**PMRA # 1932134, 1932133, 1932135, 1973848**
Residues of isopyrazam (SYN520453; as individual isomers SYN534968 and SYN534969) were shown to be stable at ≤-18°C for up to 8 months in spinach, 13 months in tomatoes and potatoes, 14 month in lentils, 15 months in barley grain, barley straw and ryegrass, and 16 months in rapeseed. Residues of CSCD459488 and CSCD459489 were shown to be stable at ≤-18°C for up to 11 months in wheat grain and wheat straw (barley straw for CSCD459489), rapeseed, apples, lentils, oranges, spinach and carrot roots. Isopyrazam and metabolites CSCD459488 and CSCD459489 were also shown to be stable in bananas under conditions at which the samples were stored during the field trials: ambient conditions (at ~35°C) over a period of 7 days followed by refrigeration (~5°C) over a period of 14 days.	
CROP FIELD TRIALS ON BANANAS	**PMRA # 1932136**

Twelve banana field trials were conducted in Latin America during 2008: Costa Rica (4 trials), Ecuador (3 trials), Guatemala (2 trials), Colombia (2 trials), and Honduras (1 trial).

Treated plots received five foliar broadcast applications of a 125 g a.i./L emulsifiable concentrate formulation (SYN520543 125EC) at an application rate of 75 g a.i./ha/application, for a total seasonal rate of 375 g a.i./ha. (Six applications were made in one trial, for a total rate of 450 g a.i./ha). Retreatment intervals (RTIs) were 10±2 days. Applications were made in spray volumes of 29-32 L/ha. The spray mix included spray oil and an emulsifier for all applications. Bananas were harvested at a PHI of 0 day, after allowing time for the spray to dry.

Commodity	Total Appl. Rate (g a.i./ha)	PHI (days)	Residue Levels* (ppm)						
			Analyte	n	Min.	Max.	Median (STMdR)	Mean (STMR)	Std. Dev.
Unbagged whole bananas	365-447	0	SYN 534968	12	<0.005	0.0136	0.0050	0.0061	0.0025
			SYN 534969	12	<0.005	0.0264	0.0081	0.0096	0.0061
			Total Isopyrazam	**12**	**<0.010**	**0.0400**	**0.0133**	**0.0157**	**0.0085**
			CSCD 459489	12	<0.005	<0.005	<0.005	<0.005	NA
			CSCD 459488	12	<0.005	0.0126	0.005	0.0070	0.0027

* Reported in terms of the analytes themselves.

RESIDUE DECLINE IN BANANAS	**PMRA # 1932136**

At two trial sites, samples of bananas were collected to assess residue decline at 0, 1 and 3 days after last application (DALA). At one trial, isopyrazam residues in/on unbagged whole fruit decreased slightly from 0.015 ppm on day 0 to 0.014 ppm on day 1, followed by a peak on day 3 (0.034 ppm). In the other trial, isopyrazam residues peaked on day 1 (0.011 ppm) and decreased to <LOQ on day 3.

PROCESSED FOOD AND FEED

Not required as there are no processed commodities associated with the use on bananas.

LIVESTOCK FEEDING

Not required as there are no livestock feedstuffs associated with the use on bananas.

Table 5 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops** **Rotational crops**	Isopyrazam NA
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**	Isopyrazam and metabolite CSCD459488 NA

METABOLIC PROFILE IN DIVERSE CROPS		Similar in wheat, grape and lettuce
ANIMAL STUDIES		
RESIDUE DEFINITION FOR ENFORCEMENT		NA
RESIDUE DEFINITION FOR RISK ASSESSMENT		NA
METABOLIC PROFILE IN ANIMALS		NA
FAT SOLUBLE RESIDUE		NA
DIETARY RISK FROM FOOD AND WATER		
Basic chronic non-cancer dietary risk **ADI = 0.06 mg/kg bw/day** **Estimated chronic drinking water concentration = NA**	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**
		Food Only
	All infants < 1 year	0.1
	Children 1-2 years	0.2
	Children 3-5 years	0.1
	Children 6-12 years	<0.1
	Youth 13-19 years	<0.1
	Adults 20-49 years	<0.1
	Adults 50+ years	<0.1
	Females 13-49 years	<0.1
	Total population	<0.1
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.2 mg/kg bw** **Estimated acute drinking water concentration = NA**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**
		Food Only
	All infants < 1 year	0.24
	Children 1-2 years	0.24
	Children 3-5 years	0.17

	Children 6-12 years	<0.1
	Youth 13-19 years	<0.1
	Adults 20-49 years	<0.1
	Adults 50+ years	<0.1
	Females 13-49 years	<0.1
	Total population	<0.1
Basic cancer dietary risk **q_1* = 7.36 x 10^{-3} (mg/kg bw/day)$^{-1}$** **Estimated chronic drinking water concentration = NA**	**POPULATION**	**ESTIMATED RISK** **Food Only**
	Total population	1.3 x 10^{-7}

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Canadian MRLs are the same as those currently established in the US. Codex MRLs have not been established.

Table 1 MRLs in Canada and Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Bananas	0.05	0.05	Not reviewed by Codex

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

Maximum residue levels may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

References

1.0 Chemistry

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, 3.5.6, 3.5.7, 3.5.8, 3.5.9
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 configution 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

2.0 Toxicology

PMRA Document Number	Reference
1932042	2006, SYN534969 (Pure Syn), SYN534968 (Pure Anti) and SYN520453 (50 Syn 50 Anti) - Acute Oral Toxicity Study in the Rat - Up and Down Procedure, DACO: 4.2.1
1932043	2008, CSCD465008 - Acute Oral Toxicity Study in the Rat (Up and Down Procedure), DACO: 4.2.1
1932044	2008, CSCD459488 - Acute Oral Toxicity Study in the Rat (Up and Down Procedure), DACO: 4.2.1
1932045	2008, SYN520453 - Acute Oral Toxicity Study in the Rat (Up and Down Procedure), DACO: 4.2.1
1932046	2007, SYN520453 - Acute Oral Toxicity Study in the Rat (Up and Down Procedure), DACO: 4.2.1
1932047	2007, 90 Day Dietary Toxicity Study in Rats, DACO: 4.3.1
1932048	2008, SYN520453 (89.5 Syn 6.9 Anti), SYN520453 (63.3 Syn 27.5 Anti) - 13 Week Comparative Dietary Toxicity Study in Rats, DACO: 4.3.1
1932050	2008, 90 Day Preliminary Carcinogenicity Study in the Mouse, DACO: 4.3.1
1932051	2008, SYN520453 - 13-Week Oral (Capsule) Toxicity Study in the Dog, DACO: 4.3.2
1932053	2007, 90 Day Oral Toxicity Study in Dogs, DACO: 4.3.2
1932055	2008, SYN520453 - 52-Week Oral (Capsule) Toxicity Study in the Beagle Dog, DACO: 4.3.2
1932056	2007, 28 Day Dietary Toxicity Study in Rats, DACO: 4.3.3
1932057	2007, 28 Day Dietary Toxicity Study in the Mouse, DACO: 4.3.3
1932058	2008, SYN520453 - 28-Day Dietary Toxicity Study in Rats, DACO: 4.3.3
1932059	2007, SYN520453 (49.5 Syn 48.7 Anti) and SYN534968 - 28 Day Comparative Study in the Rat, DACO: 4.3.3
1932060	2008, CSCD465008 - A 28-Day Oral (Dietary) Toxicity Study in Wistar Rats, DACO: 4.3.3
1932061	2009, CSCD459488 (Metabolite of SYN520453) - 28-Day Rat Dietary Toxicity Study, DACO: 4.3.3
1932062	2008, SYN520453 - 4-Week Oral (Capsule) Toxicity Study in the Dog, DACO: 4.3.3
1932063	2007, SYN520453 - Preliminary Oral Toxicity Study in Dogs, DACO: 4.3.8
1932065	2008, CSCD465008 - A 14-Day Oral (Dietary) Range-Finding Study in Wistar Rats, DACO: 4.3.8

1932067	2008, SYN520453 - 80 Week Dietary Carcinogenicity Study in the Mouse, DACO: 4.4.3
1932068	2008, Han Wistar Rat Control Study up to 104 Weeks (Including Histological Extension to Rat Toxicity Study), DACO: 4.4.4
1932069	2008, SYN520453 - 2 Year Dietary Toxicity and Carcinogenicity Study in Rats, DACO: 4.4.4
1932070	2008, SYN520453 - Multigeneration Reproduction Toxicity Study in Rats, DACO: 4.5.1
1932071	2006, Effects on Post-Natal Survival and Development in the Rat following Dietary Administration, DACO: 4.5.1
1932072	2008, SYN520453 (63.3 Syn 27.5 Anti) - Prenatal Developmental Toxicity Study in the Han Wistar Rat, DACO: 4.5.2
1932075	2007, Preliminary Prenatal Developmental Toxicity Study in the Rat, DACO: 4.5.2
1932077	2007, Prenatal Developmental Toxicity Study in Rats, DACO: 4.5.2
1932080	2008, SYN520453 (63.3 Syn 27.5 Anti) - Dose Range-Finding Prenatal Developmental Toxicity Study in the Han Wistar Rat, DACO: 4.5.2
1932081	2008, SYN520453 - A Prenatal Developmental Toxicity Study in New Zealand White Rabbits, DACO: 4.5.3
1932082	2008, SYN520453 - A Dose Range-Finding Prenatal Developmental Toxicity Study in New Zealand White Rabbits, DACO: 4.5.3
1932083	2008, SYN520453 - Second Dose Range-Finding Prenatal Developmental Toxicity Study in the Himalayan Rabbit, DACO: 4.5.3
1932085	2009, CSCD459488 - A Dose Range-Finding Prenatal Developmental Toxicity Study in New Zealand White Rabbits, DACO: 4.5.3
1932087	2008, SYN520453 - Dose Range-Finding Prenatal Developmental Toxicity Study in the Himalayan Rabbit, DACO: 4.5.3
1932090	2008, Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay with SYN520453, DACO: 4.5.4
1932092	2006, Bacterial Mutation Assay in S.typhimurium and E.coli, DACO: 4.5.4
1932094	2008, CSCD465008 - Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay, DACO: 4.5.4
1932096	2008, CSCD459488 - Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay, DACO: 4.5.4
1932097	2008, SYN520453 - Cell Mutation Assay at the Thymidine Kinase Locus (TK +/-) in Mouse Lymphoma L5178Y Cells, DACO: 4.5.5
1932098	2006, SYN520453 - L5178Y TK +/- Mouse Lymphoma Mutation Assay, DACO: 4.5.5
1932099	2008, CSCD465008 - Cell Mutation Assay at the Thymidine Kinase Locus (TK+/-) in Mouse Lymphoma L5178Y Cells, DACO: 4.5.5
1932100	2008, CSCD459488 - Cell Mutation Assay at the Thymidine Kinase Locus (TK +/-) in Mouse Lymphoma L5178Y Cells, DACO: 4.5.5
1932101	2008, Chromosome Aberration Test in Human Lymphocytes in Vitro with SYN520453, DACO: 4.5.6
1932102	2008, CSCD465008 - Chromosome Aberration Test in Human Lymphocytes In Vitro, DACO: 4.5.6
1932103	2008, CSCD459488 - Chromosome Aberration Test in Human Lymphocytes In Vitro, DACO: 4.5.6

1932104	2006, SYN520453 - In Vitro Cytogenetic Assay in Human Lymphocytes, DACO: 4.5.6
1932105	2006, SYN520453 - Rat Bone Marrow Micronucleus Test, DACO: 4.5.7
1932106	2006, SYN520453 - In Vivo Rat Liver Unscheduled DNA Synthesis Assay, DACO: 4.5.7
1932107	2009, SYN520453 - Investigation of the Nature and Identity of Radiolabelled Metabolites Present in Plasma, Urine, Faeces and Bile Collected from Rats Following Oral Administration of [14C]SYN520453, DACO: 4.5.9
1932108	2008, SYN520453 - The Biliary Elimination of Total Radioactivity in the Rat Following Single Oral Administration of Syn or Anti [14C]-SYN520453 (2 mg/kg and 75 mg/kg), DACO: 4.5.9
1932109	2008, SYN520453 - The Tissue Depletion of [14C]-SYN520453 in the Rat Following a Single Oral Administration (1 and 75 mg/kg), DACO: 4.5.9
1932110	2007, SYN520453 - Whole Body Autoradiography and Expired Air Study in the Rat, DACO: 4.5.9
1932111	2008, SYN520453 - The Biliary Elimination of Total Radioactivity in the Rat Following Single Oral Administration of [14C]-SYN520453 (1mg/kg and 75 mg/kg), DACO: 4.5.9
1932113	2008, SYN520453 - The Tissue Distribution and Elimination of [14C]-SYN520453 in the Rat following Multiple Oral Administration (1 mg/kg/day), DACO: 4.5.9
1932114	2008, SYN520453 - The Excretion and Tissue Distribution of [14C]-SYN520453 in the Rat Following Single Oral Administration (1 mg/kg and 75 mg/kg), DACO: 4.5.9
1932115	2009, SYN520453 - Pharmacokinetics in the Rat Following Single Oral Administration of [14C]-SYN520453 (1 and 75 mg/kg), DACO: 4.5.9
1932116	2009, SYN520453 - Acute Oral (Gavage) Neurotoxicity Study in Rats, DACO: 4.5.12
1932117	2009, SYN520453 - 90-Day Neurotoxicity (Dietary) Study in the Rat, DACO: 4.5.13

3.0 Food Residue

PMRA Document Number	**Reference**
1932119	2007, SYN520453 - Metabolism in Wheat, DACO: 6.3
1932120	2008, SYN520453 - Metabolism in Grapes, DACO: 6.3
1932124	2008, SYN520453 - Metabolism in Lettuce, DACO: 6.3
1932127	2008, SYN520453 - Analytical Method for the Determination of Residues of SYN534968 and SYN534969 in Crops. Final Determination by LC-MS/MS, DACO: 7.2.1, 7.2.2, 7.2.3, 7.2.4, 7.2.5
1932129	2008, SYN520453 MRMT PAM Test, DACO: 7.2.1,7.2.2,7.2.3,7.2.4,7.2.5
1932131	2008, SYN520453 - Analytical Method for the Determination of Residues of the Metabolites CSCD459488 and CSCD459489 in Crops. Final Determination by LC-MS/MS, DACO: 7.2.1, 7.2.2, 7.2.3, 7.2.4, 7.2.5
1932132	2009, SYN520453 - Independent Laboratory Validation of Method GRM006.01B for Analysis of SYN534968 and SYN534969 isomers of SYN520453, in Crops by LC-MS/MS, DACO: 7.2.1, 7.2.2, 7.2.3, 7.2.4, 7.2.5
1932133	2008, SYN520453 - Storage Stability of Metabolite CSCD459488 Residues in Crops Stored Deep Frozen for up to Two Years, DACO: 7.3

1932134	2008, SYN520453 - Storage Stability in Various Crops Stored Deep Frozen for up to Two Years, DACO: 7.3
1932135	2008, SYN520453 - Storage Stability of Metabolite CSCD459489 Residues in Crops Stored Deep Frozen for up to Two Years, DACO: 7.3
1932136	2009, SYN520453 - Residues in or on Bananas for Import Tolerance, DACO: 7.4.1
1973848	2010, Storage Stability in Banana Under Ambient and Refrigerated Storage Conditions, DACO: 7.3

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