Bicyclopyrone; PC Code 018986;
NOA449280; and SYN503780, CSCC163768 CSCD656831 SCD642512
ENVIRONMENTAL CHEMISTRY METHOD REVIEW REPORT

Residue Method for the Determination of NOA449280, and Metabolites SYN503780, CSCC163768, CSCD656831, and SCD642512 in Water.

Data Requirement: EPA Guideline: 850.6100
OECD Data Point: IIA 4.5

Reports:

Analytical Method: MRID 47842016. Braid, S. Richardson, M. and Eberhard Zietz. 2012. NOA449280 - Residue Method GRM030.06A for the Determination of NOA449280 and its metabolites SYN503780, CSCC163768, CSCD656832, CSCD642512 and CSAA806573 in Water. Analytical Method. Report No. GRM030.06A. Task no. T000995-08. Unpublished study prepared by Syngenta Ltd., Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK. Submitted by Syngenta Crop Protection, LLC, Greensboro, NC.

Independent Laboratory Validation: MRID 47841956. Zeitz, E. 2011. NOA449280 – Validation of an Analytical Method (DraftGRM030.06A) for the Determination of NOA449280 and its Metabolites SYN503780, CSCC163768, CSCD656832, CSCD642512 and CSAA806573 in Water. Method Validation. Report Number: IF-09/01378742. Study Number: IF-09/01378742. Task Number: TK0009384. Report Number: IF-09/01378742. Unpublished study prepared SGS INSTITUT FRESENIUS GmbH Im Maisel 14, D-65232 Taunusstein, Germany. Submitted by Syngenta Crop Protection, LLC, Greensboro, NC.

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Compliance Statements: These studies were conducted in compliance with GLP practices

Classification: This study is classified **Fully Reliable** (EPA classification: Acceptable). However, although this analytical method is valid for the determination of NOAA449280 and metabolites SYN503780, CSCC163768, CSCD656831 SCD642512, and CSAA806573 in water, the ILV data submitted do not qualify as an independent validation, as they are the same data as in the initial methods study. Thus, this study does not fully meet EPA data requirements, as it does not meet the independent method validation part of the data requirements with respect to the major degradates of bicyclopyrone. Additional studies (MRIDs 47841954, 47841955, and47842122) were submitted that do address the parent and one major metabolite of bicyclopyrone, but they also lacked sufficient ILV data.

PC Code: 018986

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Chemist (USEPA)
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Executive Summary

This analytical method,GRM030.06A, is designed for the quantitative determination of NOA449280 (parent bicyclopyrone; CAS# 352010-65-5) and metabolites SYN503780, CSCC163768, CSCD656831, and SCD642512 in water. The analytical chemistry method involves acidifying a well mixed water subsample and adding it to a Strata-X SPE cartridge, discarding the eluate. The analytes are sorbed to the column and subsequently quantitatively eluted with methanol, acetonitrile and formic acid, then evaporated to dryness. They are reconstituted in methanol/0.2%formic acid and are appropriately diluted for analysis by LC-MS/MS. Review of this analytical chemistry method indicated that it is acceptable. However, the Independent Laboratory Validation study is a repackaging of the original study data and is not acceptable as an ILV. Thus, the data requirement for two ILVs for the determination of the degradates in water has not been met.

Table 1. Analytical Method Summary

Analyte(s) by Pesticide	MRID		EPA Lab Review	Matrix	Method Date	Registrant	Analysis	Limit of Quantitation (LOQ)
	Environmental Chemistry Method	Independent Laboratory Validation						
NOA449280 SYN503780 CSCC163768 CSCD656831 CSCD642512 CSAA806573	47842016	47841956	None	Water	1/31/2012	Syngenta	LC/MS-MS	0.01µg/L

I. PRINCIPLE OF THE METHOD

This method starts with a 10 ml sample of thoroughly mixed water. The 10 ml aliquot is then placed in a centrifuge tube and 200 ul of formic acid is added to each sample (pH must be <2, checked with suitable indicator paper) Use one Strata-X SPE cartridge per sample. Place in a vacuum manifold. Add 2ml methanol percolate or draw through column to level of top frit discarding the eluate. Add samples to column allowing flow thru rate of 1-2 ml per minute to level of top frit. analytes are retained on column. At no time should column be allowed to dry. Rinse tube with ultra pure water plus 2ml of 2% formic acid and add to column. Elute as before. Elution of analytes is accomplished adding 5 ml of 0.1%formic acid in methanol that is percolated or drawn through the column under low vacuum collecting the column eluate , Eluate is evaporated to dryness with clean air. Immediately upon dryness methanol (200 ul) is added and the sample ultrsonicated. Add 900 ul of 0.2% formic acid in ultra-pure water and mix well. Immediately prior to analysis dilute an aliquot of the sample twofold and add to auto-sampler vial. Analysis is by LC-MS/MS.

II. RECOVERY FINDINGS

Table 2. Initial Validation Method Recoveries for Analytes in Drinking Water

Analyte	Fortification Level (ug/L)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%)	Relative Standard Deviation (%)
NOA449280 Primary transition	0.01	5	91-109	101	n/a	6.8
	0.1	5	92-101	98	n/a	3.4
SYN503780 Primary transition	0.01	5	87-102	95	n/a	6.7
	0.1	5	92-99	95	n/a	2.9
CSCC163768 Primary transition	0.01	5	87-98	93	n/a	4.6
	0.1	5	96-98	97	n/a	0.7
NCSCD656832 Primary transition	0.01	5	73-107	91	n/a	13.8
	0.1	5	75-83	84	n/a	4.7
CSCD642512 Primary transition	0.01	5	86-100	93	n/a	5.6
	0.1	5	98-107	101	n/a	3.5
CSAA806573	0.1	5	82-94	90	n/a	5.2

Primary transition	0.01	5	90-96	94	n/a	2.4
NOA449280	0.01	5	89-99	93	n/a	4.3
Confirmatory transition	0.1	5	91-96	93	n/a	2.0
SYN503780	0.01	5	102-110	106	n/a	3.2
Confirmatory transition	0.1	5	88-102	97	n/a	6.8
CSCC163768	0.01	5	92-102	99	n/a	4.6
Confirmatory transition	0.1	5	95-101	98	n/a	2.3
CSCD656832	0.01	5	85-92	89	n/a	3.5
Confirmatory transition	0.1	5	78-83	81	n/a	2.4
CSCD642512	0.01	5	80-106	95	n/a	11.4
Confirmatory transition	0.1	5	92-109	97	n/a	6.9
CSCD806573	0.01	5	91-94	92	n/a	1.6
Confirmatory transition	0.1	5	90-96	94	n/a	2.2

Table 3. Initial Validation Method Recoveries for Analytes in Surface Water

Analyte	Fortification Level (ug/L)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%)	Relative Standard Deviation (%)
NOA449280	0.01	5	78-88	85	n/a	4.7
Primary transition	0.1	5	85-97	92	n/a	4.8
SYN503780	0.01	5	89-95	92	n/a	2.7
Primary transition	0.1	5	91-95	94	n/a	2.1
CSCC163768	0.01	5	91-95	94	n/a	1.6
Primary transition	0.1	5	92-98	95		2.6
NCSCD656832	0.01	5	75-81	81	n/a	2.6
Primary transition	0.1	5	79-84	84	n/a	4.7
CSCD642512	0.01	5	87-109	93	n/a	10.0
Primary transition	0.1	5	88-94	91	n/a	3.1
CSAA806573	0.1	5	90-95	92	n/a	2.4
Primary transition	0.01	5	88-95	92	n/a	3.2
NOA449280	0.01	5	92-110	103	n/a	7.5
Confirmatory transition	0.1	5	92-98	95	n/a	2.4
SYN503780	0.01	5	80-86	82	n/a	3.3
Confirmatory transition	0.1	5	86-92	88	n/a	3.0
CSCC163768	0.01	5	100-108	102	n/a	3.5
Confirmatory transition	0.1	5	90-102	96	n/a	5.0
CSCD656832	0.01	5	89-101	96	n/a	4.8
Confirmatory transition	0.1	5	75-93	84	n/a	7.6
CSCD642512	0.01	5	81-92	89	n/a	5.1
Confirmatory transition	0.1	5	83-90	87	n/a	3.3
CSAA806573	0.01	5	85-100	91	n/a	7.2
Confirmatory transition	0.1	5	92-95	93	n/a	1.5

Table 4. Initial Validation Method Recoveries for Analytes in Ground Water

Analyte	Fortification Level (ug/L)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%)	Relative Standard Deviation (%)
NOA449280 Primary transition	0.01	5	82-90	86	n/a	3.9
	0.1	5	86-93	91	n/a	3.6
SYN503780 Primary transition	0.01	5	94-109	102	n/a	6.1
	0.1	5	96-98	97	n/a	0.8
CSCC163768 Primary transition	0.01	5	92-97	95	n/a	2.0
	0.1	5	92-94	93	n/a	1.2
NCSCD656832 Primary transition	0.01	5	80-87	85	n/a	3.1
	0.1	5	75-84	79	n/a	4.9
CSCD642512 Primary transition	0.01	5	86-101	95	n/a	6.1
	0.1	5	86-92	89	n/a	3.2
CSAA806573 Primary transition	0.1	5	90-95	92	n/a	2.4
	0.01	5	88-95	92	n/a	3.2
NOA449280 Confirmatory transition	0.01	5	98-108	103	n/a	5.1
	0.1	5	85-97	90	n/a	5.0
SYN503780 Confirmatory transition	0.01	5	101-105	103	n/a	2.1
	0.1	5	91-99	94	n/a	3.5
CSCC163768 Confirmatory transition	0.01	5	88-106	99	n/a	6.9
	0.1	5	88-97	92	n/a	3.9
CSCD656832 Confirmatory transition	0.01	5	85-94	91	n/a	2.3
	0.1	5	72-77	75	n/a	3.2
CSCD642512 Confirmatory transition	0.01	5	90-104	99	n/a	6.0
	0.1	5	82-105	94	n/a	9.7
CSAA806573 Confirmatory transition	0.01	5	98-100	98	n/a	1.1
	0.1	5	86-93	90		3.0

III. METHOD CHARACTERISTICS

Table 5. Method Characteristics

	NOA449280	SYN503780	CSCC163768	CSCD656832	CSCD642512	CSAA806573
Limit of Quantitation (LOQ)*	0.01 µg/L	0.01 µg/L	0.01 µg/L	0.01 µg/L	0.01 µg/L	0.01 µg/L
Limit of Detection (LOD) primary ion	0.0003 µg/L	0.0007 µg/L	0.0005 µg/L	0.001 µg/L	0.0004 µg/L	0.0008 µg/L
Limit of Detection (LOD) confirmatory ion	0.005 µg/L	0.005 µg/L	n/a	n/a	n/a	n/a
Linearity (calibration curve r^2 and concentration range)	$r^2 = 0.99$ 0.05ng/ mL– #10ngm/L	$r^2 = 0.99$ 0.05ng/ mL– #10ngm/	$r^2 = 0.99$ 0.05ng/ mL– #10ngm/L	$r^2 = 0.99$ 0.05ng/ mL– #10ngm/L	$r^2 = 0.99$ 0.05ng/ mL– #10ngm/L	$r^2 = 0.99$ 0.05ng/ mL– #10ngm/L
Repeatable	Yes	Yes	Yes	Yes	Yes	Yes
Reproducible	Yes	Yes	Yes	Yes	Yes	Yes
Specific	Yes	Yes	Yes	Yes	Yes	Yes

* The limit of quantitation of the method is defined as the lowest analyte concentration in a sample at which the methodology has been validated and a mean recovery of 70-110% with a relative standard deviation of ≤ 20% has been obtained.

IV. METHOD DEFICIENCIES AND REVIEWER'S COMMENTS

The data submitted as independent laboratory validation data are the same data reported for the analytical method validation and, as they were not determined by an independent laboratory, are classified **not acceptable**.

Attachment 1: Chemical Names and Structures:

Figure 1 NOA449280

Compound Code Number	:	**NOA449280**
CAS Number	:	**352010-68-5**
IUPAC Name	:	**4-hydroxy-3-[2-(2-methoxy-ethoxymethyl)-6-(triflouro-methyl)-pyridine-3-carbonyl]-bicyclo[3.2.1]oct-3-en-2-one**
Molecular Formula	:	**$C_{19}H_{20}F_3NO_5$**
Molecular Weight	:	**399.4**

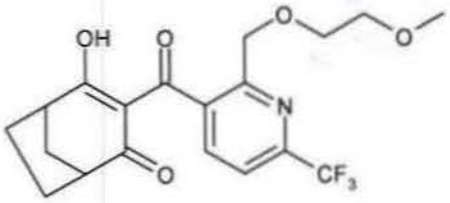


Figure 2 SYN503780

Compound Code Number	:	**SYN503780**
CAS Number	:	**380355-55-5**
IUPAC Name	:	**2-(2-methoxy-ethoxymethyl)-6-triflouromethyl-nicotinic acid**
Molecular Formula	:	**$C_{11}H_{12}F_3NO_4$**
Molecular Weight	:	**279.2**

Figure 3 CSCC163768

Compound Code Number	:	**CSCC163768**
CAS Number	:	**Not in registry**
IUPAC Name	:	**6-(trifluoromethyl)pyridine-2,3-dicarboxylic acid**
Molecular Formula	:	**$C_8H_4F_3NO_4$**
Molecular Weight	:	**235.1**

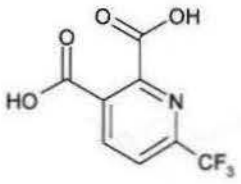


Figure 4 CSCD656832

Compound Code Number	:	**CSCD656832**
CAS Number	:	**Not in registry**
IUPAC Name	:	**6-(trifluoromethyl)pyridin-3-ol-2-carboxylic acid**
Molecular Formula	:	**$C_7H_4F_3NO_3$**
Molecular Weight	:	**207.1**

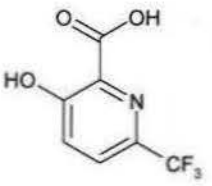


Figure 5 CSCD642512

Compound Code Number	:	**CSCD642512**
CAS Number	:	**Not in registry**
IUPAC Name	:	**Not known**

Molecular Formula	:	**$C_{18}H_{16}F_3NO_6$**
Molecular Weight	:	**399.3**

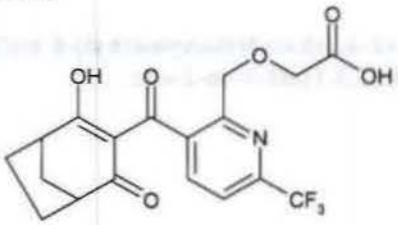
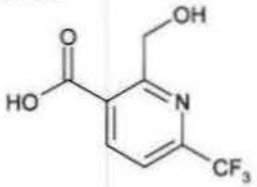


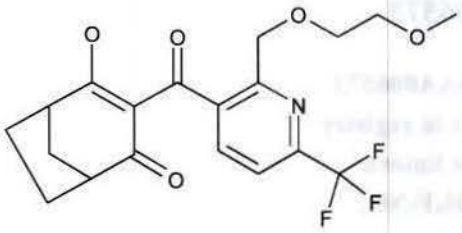
Figure 6 CSAA806573

Compound Code Number	:	**CSAA806573**
CAS Number	:	**Not in registry**
IUPAC Name	:	**Not known**
Molecular Formula	:	**$C_8H_6F_3NO_3$**
Molecular Weight	:	**221.1**



Attachment 1: Chemical Names and Structures:

IUPAC Name:	**4-Hydroxy-3-[2-(2-methoxy-ethoxymethyl)-6-trifluoromethyl-pyridine-3-carbonyl]-bicyclo[3.2.1]oct-3-en-2-one**
CAS Name:	N/A
CAS Number:	352010-65-5



IUPAC Name:	**2-(2-Methoxy-ethoxymethyl)-6-trifluoromethyl-nicotinic acid**
CAS Name:	**N/A**
CAS Number:	**None listed**