

**Analytical method for mandestrobin (S-2200) and its products DX-CA-S-2200, 2-COOH-S-2200, 5-COOH-S-2200, 2-CONH2-S-2200, and 5-CONH2-S-2200 in soil**

**Reports:** ECM: EPA MRID No.: 49068570 (pages 255-273). Bitter, J. (p. 264). 2012. DETERMINATION OF S-2200 AND METABOLITES IN SOIL, METHOD RM-48S-3. Valent Analytical Report No.: VP-37959. Report prepared, sponsored and submitted by Valent U.S.A. Corporation, Dublin, California; 19 pages. Method dated October 11, 2012; final approval issued November 5, 2012 (pp. 255, 264).  
ILV: EPA MRID No. 49068638. Pernell, M. 2013. S-2200: Independent Laboratory Validation of Valent Method RM-48S-3, Determination of S-2200 and Metabolites in Soil. Critical Path Services, LLC (CPS). CPS Study No.: 13-CPS-002. Report prepared by Critical Path Services, LLC, Garnet Valley, Pennsylvania, sponsored and submitted by Valent U.S.A. Corporation, Walnut Creek, California; 138 pages. Final report issued February 15, 2013.

**PC Code:** 036603

**MRID:** MRIDs 49068570 (pages 255-273) & 49068638

**PMRA:** PMRA #s 2377958 & 2377849

**Guideline:** 850.6100

**GLP:** ECM: Data Confidentiality, Good Laboratory Practice (GLP), Quality Assurance, and Authenticity Certification statements were not provided. A signature page was included (p. 264).  
ILV: The study was conducted in compliance with USEPA GLP standards (p. 3). Signed and dated No Claim of Confidentiality, GLP, and Quality Assurance statements were provided (pp. 2-3, 5). An Authenticity Certification statement was not provided.

**Reviewer:** Richard Shamblen  
U.S. EPA

**Signature:**  
**Date:** February 20, 2015

Kim Davis  
PMRA

**Signature:2181**  
**Date:** March 30, 2015

**Study Classification**

This analytical method is classified as **Acceptable** (USEPA)/ **Acceptable** (PMRA). The registrant failed to establish that the soil matrix used in the ILV (loamy sand soil) was either an equivalent, or more difficult, analytical sample condition as that used in the ECM (uncharacterized soil). The determinations of the LOQ and LOD were not based on scientifically acceptable procedures. The soil used in the ECM was not characterized.

**Page citations refer to the page numbers located in the bottom center of MRID 49068638 (ILV, since this report contains the ECM), unless noted otherwise.**

## Executive Summary

This analytical method, Valent Method RM-48S-3, is designed for the quantitative determination of mandestrobin and its products DX-CA-S-2200, 2-COOH-S-2200, 5-COOH-S-2200, 2-CONH2-S-2200, and 5-CONH2-S-2200 in soil using HPLC/MS/MS. The method is quantitative for mandestrobin and its products at the stated LOQ of 0.02 mg/kg. The LOQ is less than the lowest toxicological level of concern in soil (NOAEC = 560 g ai/ ha; equivalent to 0.44 mg ai/ kg). The independent laboratory validated the method after two trials. No major modifications were made by the independent laboratory. The registrant failed to establish that the soil matrix used in the ILV (loamy sand soil) was either an equivalent, or more difficult, analytical sample condition as that used in the ECM (uncharacterized soil).

**Table 1. Analytical Method Summary**

Analyte(s) by Pesticide	MRID		EPA Review	Matrix	Method Date (dd/mm/yyyy)	Registrant	Analysis	Limit of Quantitation (LOQ)
	Environmental Chemistry Method	Independent Laboratory Validation						
Mandestrobin (S-2200)	49068570 (pp. 255-273)	49068638		Soil	Dated 11/10/2012, final approval 05/11/2012	Valent	HPLC/MS/MS	0.02 mg/kg
DX-CA-S-2200								
2-COOH-S-2200								
5-COOH-S-2200								
2-CONH2-S-2200								
5-CONH2-S-2200								

See attachment 1 for the chemical names and structures of the analytes.

## I. Principle of the Method

Samples (2.5 g) of soil were extracted twice with 25 mL of acetone:0.05M HCl (80:20, v:v) by shaking (reciprocating shaker, speed not specified) for 1 hour (Appendix 5, p. 117). Soil and extract were separated by centrifugation (*ca.* 2,000 rpm, 5 minutes). Extracts were decanted into a separatory funnel, treated with 5% sodium chloride solution (50 mL), then partitioned twice with methylene chloride (2 x 50 mL). Organic phases were combined, taken to dryness (rotary evaporation,  $\leq 40^{\circ}\text{C}$ ), and the resulting residues reconstituted in 0.05% formic acid in methanol:0.05% formic acid in HPLC water (1:1, v:v; 20 mL).

Samples were analyzed for mandestrobin (S-2200) and its products DX-CA-S-2200, 2-COOH-S-2200, 5-COOH-S-2200, 2-CONH2-S-2200, and 5-CONH2-S-2200 by HPLC (Agilent Eclipse XDB-C18, 4.6 mm x 150 mm, 5  $\mu\text{m}$  column,  $20 \pm 1^{\circ}\text{C}$ ) using a mobile phase of (A) aqueous 0.05% formic acid and (B) 0.05% formic acid in methanol [percent A:B at 0.0-2.0 min. 50:50, 8.0-20.0

min. 10:90, 22.5-30.0 min. 50:50] with MS/MS-ESI (electrospray ionization, positive ion mode) detection and multiple reaction monitoring (MRM; Appendix 5, pp. 118-119). Injection volume was 10  $\mu$ L. Mandestrobin and its products were identified and quantified using one ion transition. Ion transitions monitored were as follows:  $m/z$  314 $\rightarrow$ 192 for mandestrobin,  $m/z$  224 $\rightarrow$ 146 for DX-CA-S-2200,  $m/z$  344 $\rightarrow$ 192 for 2-COOH-S-2200 and 5-COOH-S-2200, and  $m/z$  343 $\rightarrow$ 192 for 2-CONH<sub>2</sub>-S-2200 and 5-CONH<sub>2</sub>-S-2200. A confirmatory method was not reported.

The ILV performed the method as written, with minor instrument parameter modifications (pp. 14, 18-19; Tables 13-14, pp. 38-39; Appendix 5, pp. 117-119).

LOQs and LODs for all analytes were the same in the ECM and ILV at 0.02 mg/kg and 0.01 mg/kg, respectively (p. 17; Appendix 5, p. 121).

## II. Recovery Findings

ECM (MRID 49068570, pages 255-273): Mean recoveries and relative standard deviations (RSDs) were within guideline requirements (mean 70-120%; RSD  $\leq$ 20%) for analysis of mandestrobin (S-2200) and its products DX-CA-S-2200, 2-COOH-S-2200, 5-COOH-S-2200, 2-CONH<sub>2</sub>-S-2200, and 5-CONH<sub>2</sub>-S-2200 in soil (uncharacterized) at fortification levels of 0.02 mg/kg (LOQ) and 0.2 mg/kg (10x LOQ, DER Attachment 2). Analytes were identified and quantified using a single ion transition; a confirmatory method was not used.

ILV (MRID 49068638): Mean recoveries and relative standard deviations (RSDs) were within guideline requirements (mean 70-120%; RSD  $\leq$ 20%) for analysis of mandestrobin and its products in loamy sand soil at fortification levels of 0.02 mg/kg (LOQ) and 0.2 mg/kg (10x LOQ; Tables 7-12, pp. 32-37). Analytes were identified and quantified using a single ion transition. The method was validated for all analytes at both fortification levels after two trials, with minor instrument parameter modifications (pp. 14, 18-19, 23; Tables 13-14, pp. 38-39; Appendix 5, pp. 117-119). The soil was fully characterized and screened for interferences prior to use (pp. 17, 20; Appendix 6, p. 132). The loamy sand soil was obtained from Georgia and supplied by Valent (V-37953-UTC 0-30cm; p. 16; Appendix 6, p. 132). Valent did not specify if the loamy sand soil was either an equivalent, or more difficult, analytical sample condition as that used in the ECM (uncharacterized soil).

**Table 2. Initial Validation Method Recoveries for Mandestrobin and Its Products in Soil<sup>1</sup>**

Analyte	Fortification Level (mg/kg)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%)	Relative Standard Deviation (%)
Mandestrobin (S-2200)	0.02 (LOQ)	5	89.5-93.3	92.0	1.5	1.6
	0.2	5	86.6-96.3	91.5	3.7	4.1
DX-CA-S-2200	0.02 (LOQ)	5	90.7-99.7	94.0	3.7	3.9
	0.2	5	96.0-105.4	101.1	4.1	4.1
2-COOH-S-2200	0.02 (LOQ)	5	77.5-97.4	89.7	8.6	9.6
	0.2	5	92.9-101.1	97.1	3.5	3.6
5-COOH-S-2200	0.02 (LOQ)	5	71.3-93.3	78.2	9.8	12.5
	0.2	5	90.5-100.6	96.8	4.1	4.2
2-CONH2-S-2200	0.02 (LOQ)	5	87.6-96.0	91.1	3.1	3.4
	0.2	5	91.4-99.0	95.0	3.2	3.4
5-CONH2-S-2200	0.02 (LOQ)	5	74.1-87.9	82.2	7.1	8.6
	0.2	5	94.6-98.7	97.6	1.8	1.8

Data (% Recovery) were obtained from Appendix 5, pp. 126-131; means, standard deviations, and relative standard deviations per fortification level were reviewer-calculated (DER Attachment 2). It could not be determined whether or not the recovery results were corrected for any residues in the matrix control samples.

<sup>1</sup> The soil matrix was uncharacterized.

**Table 3. Independent Validation Method Recoveries for Mandestrobin and Its Products in Loamy Sand Soil<sup>1</sup>**

Analyte	Fortification Level (mg/kg)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%)	Relative Standard Deviation (%)
Mandestrobin (S-2200)	0.02 (LOQ)	5	101-113	107	4.74	4.43
	0.2	5	99.0-103	101	1.79	1.77
DX-CA-S-2200	0.02 (LOQ)	5	98.5-108	104	4.04	3.88
	0.2	5	98.5-103	101	1.80	1.78
2-COOH-S-2200	0.02 (LOQ)	5	105-117	111	5.77	5.20
	0.2	5	99.5-105	102	2.07	2.03
5-COOH-S-2200	0.02 (LOQ)	5	103-113	108	3.54	3.28
	0.2	5	101-105	103	1.48	1.44
2-CONH2-S-2200	0.02 (LOQ)	5	103-115	110	5.68	5.16
	0.2	5	100-105	102	1.82	1.78
5-CONH2-S-2200	0.02 (LOQ)	5	104-116	111	5.89	5.31
	0.2	5	101-105	103	1.52	1.48

Data were obtained from Tables 7-12, pp. 32-37. Although not specified, residue data sheets and example calculations indicate recovery results were uncorrected (Appendix 1, pp. 97-102; Appendix 2, p. 103).

<sup>1</sup> Control Soil No.: GS-13-3-1 was fully characterized (Appendix 6, p. 132).

### III. Method Characteristics

In the ECM and ILV, the LOQ and LOD for all analytes were 0.02 mg/kg and 0.01 mg/kg, respectively (p. 17; Appendix 5, p. 121). The ECM defined the LOQ as the concentration of the analyte successfully tested ("validated"; Appendix 5, p. 121). The LOD was estimated by dividing the lowest calibration standard concentration by the effective matrix concentration in the sample extracts.

**Table 4. Method Characteristics<sup>1</sup>**

	Mandestrobin	DX-CA-S-2200	2-COOH-S-2200	5-COOH-S-2200	2-CONH2-S-2200	5-CONH2-S-2200
Limit of Quantitation (LOQ)	0.02 mg/kg					
Limit of Detection (LOD)	0.01 mg/kg <sup>2</sup>					
Linearity (calibration curve r <sup>2</sup> and concentration range) <sup>3</sup>	r <sup>2</sup> = 0.9981	r <sup>2</sup> = 1.0	r <sup>2</sup> = 0.9994	r <sup>2</sup> = 0.9995	r <sup>2</sup> = 0.9997	r <sup>2</sup> = 0.9986
	(1.25-50 ng/mL)					
Repeatable	Yes					
Reproducible	Yes					
Specific <sup>4</sup>	Yes					

Data were obtained from pp. 17, 23; Tables 7-12, pp. 32-37; Appendix 1, pp. 97-102; and DER Attachment 2 (r<sup>2</sup>).

<sup>1</sup> The ILV was performed using a loamy sand soil supplied by Valent (p. 16; Appendix 6, p. 132). Valent did not specify if the loamy sand soil was either an equivalent, or more difficult, analytical sample condition as that used in the ECM (uncharacterized soil).

<sup>2</sup> LOD was estimated based on lowest calibration standard and effective matrix concentration in sample extracts (Appendix 5, p. 121).

<sup>3</sup> Reviewer-calculated r<sup>2</sup> values (linear regression) for the provided ILV calibration standards (Appendix 1, pp. 97-102; DER Attachment 2). The ILV reported r values (quadratic, 1/x weighting) of 0.9994-0.9999 (Figures 1-6, pp. 41-46). The ECM did not provide calibration curves.

<sup>4</sup> A confirmation method was not used; however, OCSPP 850.6100 guidelines specify that a confirmatory procedure is not typically necessary where GC/MS and LC/MS methods are used as the primary method(s) to generate study data.

#### IV. Method Deficiencies and Reviewer's Comments

1. The soil ECM, with performance data, was submitted as part of a terrestrial field dissipation study submission (MRID 49068570), with only pages 255-273 of the document pertaining to the ECM.
2. The registrant failed to establish that the soil matrix used in the ILV was either an equivalent, or more difficult, analytical sample condition as that used in the ECM. The ILV was performed using loamy sand soil obtained from Georgia and supplied by Valent (V-37953-UTC 0-30cm); matrix characterization was provided (p. 16; Appendix 6, p. 132). The soil used in the ECM validation performed by Valent was not characterized (Appendix 5, pp. 113-131).

For a given sample matrix, the registrant should select the most difficult analytical sample condition (*e.g.*, high organic content versus low organic content in a soil matrix) for use in the ILV to demonstrate how well the method performs.

3. The determination of the LOQ and LOD were not based on scientifically acceptable procedures. In the ECM and ILV, the LOQ and LOD for all analytes were 0.02 mg/kg and 0.01 mg/kg, respectively (p. 17; Appendix 5, p. 121). The ECM defined the LOQ as the concentration of the analyte successfully tested ("validated"; Appendix 5, p. 121). The LOD was estimated by dividing the lowest calibration standard concentration by the effective matrix concentration in the sample extracts.

Detection limits should not be based on the arbitrarily selected lowest concentration in the spiked samples. Additionally, the lowest toxicological level of concern in soil was not

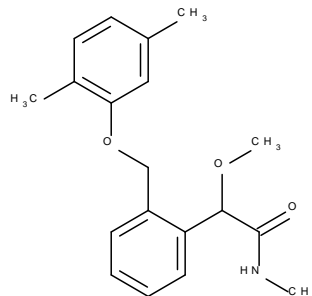
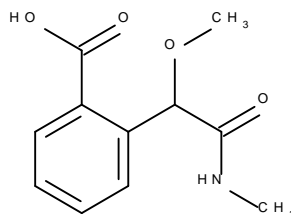
- reported. An LOQ above toxicological levels of concern results in an unacceptable method classification.
4. A confirmatory method was not used. However, OCSPP 850.6100 guidelines specify that a confirmatory procedure is not typically necessary where GC/MS and LC/MS methods are used as the primary method(s) to generate study data.
  5. For the ECM, it could not be determined whether or not reported recovery values were corrected for reagent blanks, matrix blanks, or other recoveries. The method calculations specify correcting recovery results for any residues detected in the matrix control samples (Appendix 5, p. 121). The example calculation for 2-CONH2-S-2200 show no residues were detected in the matrix control sample. However, results for the matrix control samples were not presented with the performance data (Appendix 5, pp. 126-131), and raw data were not provided.
  6. For the ECM, the purities of the analytes (mandestrobin, DX-CA-S-2200, 2-COOH-S-2200, 5-COOH-S-2200, 2-CONH2-S-2200, and 5-CONH2-S-2200) used for the fortifications were not reported.
  7. For the ECM, standard curves, chromatograms of reagent blank samples, and chromatograms of samples fortified at the LOQ were not provided.
  8. It was reported for the ILV that extraction and analysis time for one set of thirteen samples (one reagent blank, two matrix control samples, and ten fortified samples) required approximately 2.6 days; *ca.* 8 hours for extraction, plus *ca.* 12.5 hours for analysis (p. 23).

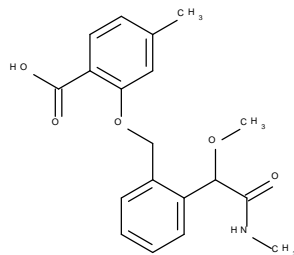
**Conclusion:**

The results of the method validation study demonstrated that the HPLC/MS/MS analytical method can be performed successfully on soil samples for mandestrobin and its transformation products, DX-CA-S-2200, 2-COOH-S-2200, 5-COOH-S-2200, 2-CONH2-S-2200, and 5-CONH2-S-2200, down to a level of 0.02 mg/kg with a limit of detection at 0.01 mg/kg. This method was assessed to be acceptable as a post registration monitoring method.

**V. References**

- U.S. Environmental Protection Agency. 2012. Ecological Effects Test Guidelines, OCSPP 850.6100, Environmental Chemistry Methods and Associated Independent Laboratory Validation. Office of Chemical Safety and Pollution Prevention, Washington, DC. EPA 712-C-001.
- 40 CFR Part 136. Appendix B. Definition and Procedure for the Determination of the Method Detection Limit-Revision 1.11, pp. 317-319.

**Attachment 1: Chemical Names and Structures****Mandestrobin (S-2200)****IUPAC Name:** (RS)-2-methoxy-N-methyl-2-[ $\alpha$ -(2,5-xilyloxy)-o-tolyl]acetamide**CAS Name:** 2-[(2,5-Dimethylphenoxy)methyl]- $\alpha$ -methoxy-N-methylbenzeneacetamide**CAS Number:** 173662-97-0**SMILES String:** Cc1ccc(c(c1)OCc2ccccc2C(C(=O)NC)OC)C**DX-CA-S-2200****IUPAC Name:** (RS)-2-(N-methylcarbamoyl-methoxymethyl)benzoic acid**CAS Name:** Not reported**CAS Number:** Not reported**SMILES String:** CNC(=O)C(c1ccccc1C(=O)O)OC**2-COOH-S-2200****IUPAC Name:** (RS)-2-{2-[1-methoxy-1-(N-methylcarbamoyl)methyl]benzyloxy}-4-methylbenzoic acid**CAS Name:** Not reported**CAS Number:** Not reported**SMILES String:** Cc1ccc(c(c1)OCc2ccccc2C(C(=O)NC)OC)C(=O)O

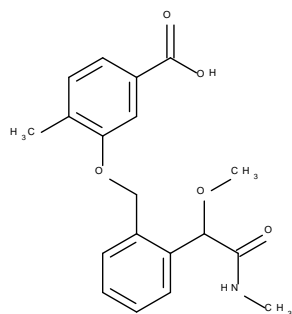
**5-COOH-S-2200**

**IUPAC Name:** (RS)-3-{2-[1-methoxy-1-(N-methylcarbamoyl)methyl]benzyloxy}-4-methylbenzoic acid

**CAS Name:** Not reported

**CAS Number:** Not reported

**SMILES String:** Cc1ccc(cc1OCc2ccccc2C(C(=O)NC)OC)C(=O)O

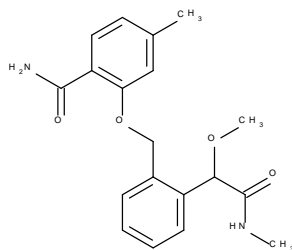
**2-CONH2-S-2200 (2-amide-S-2200)**

**IUPAC Name:** 2-({2-[1-Methoxy-2-(methylamino)-2-oxoethyl]benzyl}oxy)-4-methylbenzamide

**CAS Name:** Not reported

**CAS Number:** Not reported

**SMILES String:** Cc1ccc(c(c1)OCc2ccccc2C(C(=O)NC)OC)C(=O)N

**5-CONH2-S-2200 (5-amide-S-2200)**

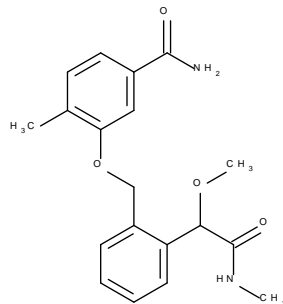
**IUPAC Name:** 3-({2-[1-Methoxy-2-(methylamino)-2-oxoethyl]benzyl}oxy)-4-methylbenzamide

**CAS Name:** Not reported

**CAS Number:** Not reported



**SMILES String:** Cc1ccc(cc1OCc2ccccc2C(C(=O)NC)OC)C(=O)N



**Attachment 2:**

**ECM Validation for Determination of Mandestrobin (S-2200) and its Products in Soil**

Chemical: Mandestrobin  
 PC: 036603  
 MRIDs: 49068570 (pages 255-273) & 49068638  
 Guideline: 850.6100

ECM Validation for Determination of Mandestrobin (S-2200) and its Products in Soil (uncharacterized)

Fortified (mg a.i./kg)	Mandestrobin (S-2200)							DX-CA-S-2200							2-COOH-S-2200							
	Recovery (%)	Mean (%)	SD <sup>1</sup> (%)	RSD <sup>2</sup> (%)	Max	Min	n =	Recovery (%)	Mean (%)	SD <sup>1</sup> (%)	RSD <sup>2</sup> (%)	Max	Min	n =	Recovery (%)	Mean (%)	SD <sup>1</sup> (%)	RSD <sup>2</sup> (%)	Max	Min	n =	
0.02	92.7							99.7							93.4							
LOQ	93.3							95.1							97.4							
	89.5							90.7							77.5							
	92.4							90.8							84.0							
	92.1	92.0	1.5	1.6	93.3	89.5	5	93.6	94.0	3.7	3.9	99.7	90.7	5	96.3	89.7	8.6	9.6	97.4	77.5	5	
0.2	89.2							100.2							98.1							
	93.2							105.4							101.1							
	96.3							105.2							99.5							
	92.3							96.0							92.9							
	86.6	91.5	3.7	4.1	96.3	86.6	5	98.6	101.1	4.1	4.1	105.4	96.0	5	94.1	97.1	3.5	3.6	101.1	92.9	5	
Fortified (mg a.i./kg)	5-COOH-S-2200							2-CONH2-S-2200							5-CONH2-S-2200							
Recovery (%)	Mean (%)	SD <sup>1</sup> (%)	RSD <sup>2</sup> (%)	Max	Min	n =	Recovery (%)	Mean (%)	SD <sup>1</sup> (%)	RSD <sup>2</sup> (%)	Max	Min	n =	Recovery (%)	Mean (%)	SD <sup>1</sup> (%)	RSD <sup>2</sup> (%)	Max	Min	n =		
0.02	83.0							90.5							87.5							
LOQ	93.3							96.0							87.9							
	71.3							87.6							74.1							
	71.6							90.1							74.8							
	71.7	78.2	9.8	12.5	93.3	71.3	5	91.3	91.1	3.1	3.4	96.0	87.6	5	86.8	82.2	7.1	8.6	87.9	74.1	5	
0.2	90.5							96.7							94.6							
	96.1							95.8							98.7							
	96.7							99.0							97.2							
	100.6							91.9							98.7							
	100.3	96.8	4.1	4.2	100.6	90.5	5	91.4	95.0	3.2	3.4	99.0	91.4	5	98.7	97.6	1.8	1.8	98.7	94.6	5	

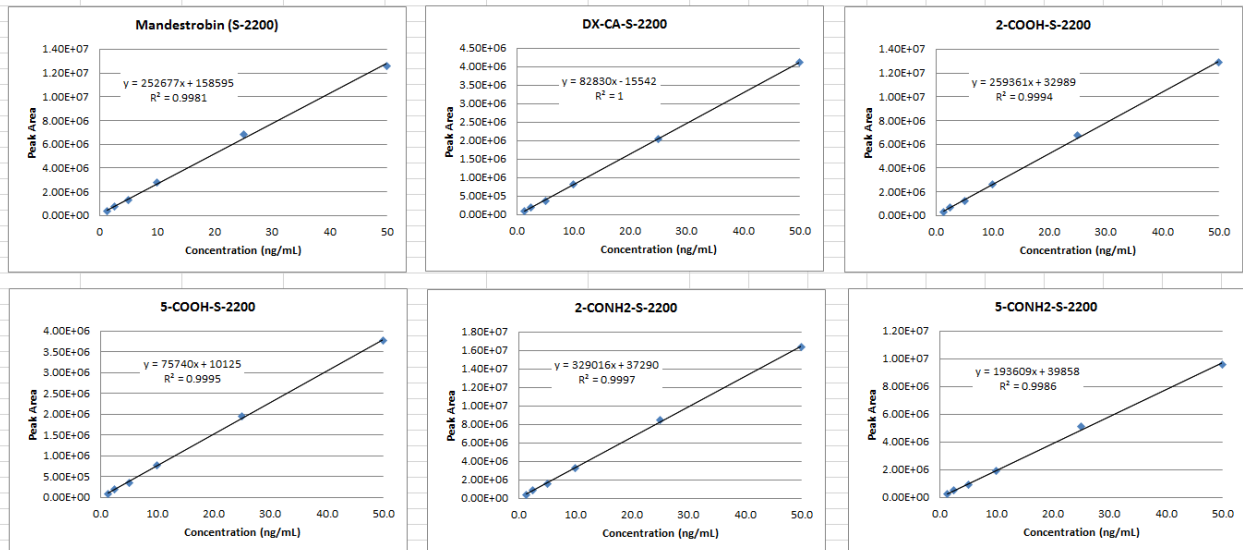
Results (% Recovery) from p. 268-273 of MRID 49068570 and Appendix 5, pp. 126-131 of MRID 49068638.  
 Calculation of recovery values in the ECM allowed for the correction of residues in the matrix control samples (p. 263). Raw data sheets were not provided to determine which recovery values, if any, were corrected.  
 Means and standard deviations calculated using Microsoft program functions =AVERAGE(A1:A2) and =STDEV(A1:A2).  
 Any discrepancies between reviewer calculated values and reported results most likely due to rounding.  
 1 SD = Standard Deviation; determined using the "unbiased" or "n-1" method.  
 2 RSD = Relative Standard Deviation; calculated as (SD/mean) x 100.

**ILV Calibration Curves**

Chemical: Mandestrobin  
 PC: 036603  
 MRIDs: 49068570 (pages 255-273) & 49068638  
 Guideline: 850.6100

Concentration (ng/mL)	Mandestrobin Peak Area counts	DX-CA-S-2200 Peak Area counts	2-COOH-S-2200 Peak Area counts	5-COOH-S-2200 Peak Area counts	2-CONH2-S-2200 Peak Area counts	5-CONH2-S-2200 Peak Area counts
1.25	3.67E+05	9.71E+04	3.33E+05	9.54E+04	4.23E+05	2.59E+05
2.50	7.33E+05	2.03E+05	6.70E+05	1.97E+05	8.56E+05	5.00E+05
5.00	1.31E+06	3.82E+05	1.25E+06	3.61E+05	1.62E+06	9.31E+05
10.0	2.77E+06	8.10E+05	2.62E+06	7.78E+05	3.31E+06	1.95E+06
25.0	6.86E+06	2.05E+06	6.74E+06	1.96E+06	8.46E+06	5.15E+06
50.0	1.26E+07	4.13E+06	1.29E+07	3.77E+06	1.64E+07	9.60E+06

Results (STD 1-6 Peak Area Counts) from Appendix 1, pp. 97-102 of MRID 49068638.



Test Material: Mandestrobin

MRID: 49068570 (pages 255-273)

Title: DETERMINATION OF S-2200 AND METABOLITES IN SOIL,  
METHOD RM-48S-3

MRID: 49068638

Title: S-2200: Independent Laboratory Validation of Valent Method RM-48S-3, Determination of S-2200 and Metabolites in Soil

EPA PC Code: 036603

OCSPP Guideline: 850.6100

**For CDM Smith**

**Primary Reviewer:** Lynne Binari

**Signature:** 

**Date:** 9/5/14

**Secondary Reviewer:** Lisa Muto

**Signature:** 

**Date:** 9/5/14

**QC/QA Manager:** Joan Gaidos

**Signature:** 

**Date:** 9/5/14