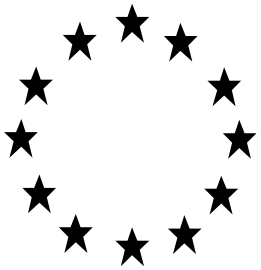
Competent Authority Report

According to Directive 98/8/EC



Copper pyrithione

CAS 14915-37-8

Active substance in Biocidal Products

Product Type 21 (Antifouling products)

Applicant: Arch Chemicals Inc.

DOCUMENT III A

Section 4: Analytical Methods for Identification and Detection

Rapporteur Member State: Sweden

Final CAR September 2014

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

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Section A.4 Analytical Methods for Detection and Identification

Section A4.1/01 Determination of the pure active substance and impurities in the technical material

Annex Point IIA, IV.4.1 **Active substance**

			Official use only
		1. REFERENCE	
1.1	**Reference**	**Document IV ARCPT 4010-001** [redacted] (2006) Copper Pyrithione – 5 Batch characterisation, ITS Testing Services (UK) Ltd. Study Number 1298506 (unpublished)	
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2. GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	OPPTS 830.1700	
2.2	**GLP**	Yes	
2.3	**Deviations**	None	
		3. MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	Enrichment	[redacted]	
3.1.2	Cleanup	[redacted]	
3.2	**Detection**		
3.2.1	Separation method	[redacted]	
3.2.2	Detector	[redacted]	
3.2.3	Standard	[redacted]	
3.2.4	Interfering substance	[redacted]	
3.3	**Linearity**		
3.3.1	Calibration range	[redacted]	X1
3.3.2	Number of	[redacted]	

Section A4.1/01 Determination of the pure active substance and impurities in the technical material

Annex Point IIA, IV.4.1 **Active substance**

	measurements		
3.3.3	Linearity	[redacted]	
3.4	**Specifity: interfering substances**	[redacted]	
3.5	**Recovery rates at different levels**	[redacted]	X2
3.5.1	Relative standard deviation	[redacted]	X3
3.6	**Limit of determination**	[redacted]	
3.7	**Precision**		
3.7.1	Repeatability	[redacted]	
3.7.2	Independent laboratory validation	[redacted]	

4. APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	[redacted]
4.2	**Conclusion**	The method may be used to assay TGAI copper pyrithione
4.2.1	Reliability	[redacted]
4.2.2	Deficiencies	No

Section A4.1/01 Determination of the pure active substance and impurities in the technical material

Annex Point IIA, IV.4.1 **Active substance**

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Section A4.1/02 Determination of the pure active substance and impurities in the technical material

Annex Point IIA, IV.4.1 **Impurities**

The validation data for the analysis of impurities in the technical copper pyrithione is confidential information and is presented in the Annex Confidential Data and Information

Section A4.1/03 Determination of the pure active substance and impurities in the technical material

Annex Point IIA, IV.4.1 **Assay of TGAI in AF formulations**

			Official use only
		1. REFERENCE	
1.1	**Reference**	**Document IV ARCPT 4011-003** [redacted] (2003) Validation of analytical method: HPLC determination of copper pyrithione in marine antifouling paints, Arch Chemicals, Inc. Cheshire, CT, Report No. CASR-03-2003 (unpublished)	X1
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2. GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3. MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	Enrichment	[redacted]	
3.1.2	Cleanup	[redacted]	
3.2	**Detection**		
3.2.1	Separation method	[redacted]	
3.2.2	Detector	[redacted]	
3.2.3	Standard	[redacted]	
3.2.4	Interfering substance	[redacted]	
3.3	**Linearity**		
3.3.1	Calibration range	[redacted]	X2
3.3.2	Number of measurements	[redacted]	

Section A4.1/03 Determination of the pure active substance and impurities in the technical material

Annex Point IIA, IV.4.1 **Assay of TGAI in AF formulations**

3.3.3 Linearity [redacted] X3

3.4 Specifity: interfering substances [redacted] X4

3.5 Recovery rates at different levels [redacted]

3.5.1 Relative standard deviation [redacted]

[redacted]

[redacted]

3.6 Limit of determination [redacted]

3.7 Precision

3.7.1 Repeatability [redacted]

3.7.2 Independent [redacted]

Section A4.1/03 Determination of the pure active substance and impurities in the technical material

Annex Point IIA, IV.4.1 **Assay of TGAI in AF formulations**

laboratory validation

4. APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	**[CONFIDENTIAL INFORMATION EXCLUDED]**.	X5
4.2	**Conclusion**	The method may be used for analysis of copper pyrithione in paint in the range of 0.5% – 7.5%.	
4.2.1	Reliability	[redacted]	X6
4.2.2	Deficiencies	No	

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date [redacted]

Materials and methods [redacted]

Conclusion [redacted]

Reliability [redacted]

Section A4.1/03 Determination of the pure active substance and impurities in the technical material

Annex Point IIA, IV.4.1 **Assay of TGAI in AF formulations**

[redacted]

Acceptability [redacted]

Remarks [redacted]

Section A4.2(a)/01 Determination of residues in soil

Annex Point IIA, IV.4.2(a) [redacted]

			Official use only
		1 REFERENCE	
1.1	**Reference**	**Document IV ARCPT 4020-001** [redacted] (2004) Method for the analysis of pyrithione in sediment by HPLC with MS/MS detection. Arch Chemicals, Inc. Cheshire, CT, USA, Report No. CASR-01-2004 (unpublished)	
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	Enrichment	[redacted]	X1
3.1.2	Cleanup	[redacted]	X1
3.2	**Detection**		
3.2.1	Separation method	[redacted]	
3.2.2	Detector	[redacted]	

Section A4.2(a)/01 Determination of residues in soil

Annex Point IIA, IV.4.2(a) **Zinc pyrithione**

[redacted]

3.2.3	Standard(s)	[redacted]	
3.2.4	Interfering substance(s)	[redacted]	
3.3	**Linearity**		
3.3.1	Calibration range	[redacted]	X2
3.3.2	Number of measurements	[redacted]	
3.3.3	Linearity	[redacted]	X3
3.4	**Specifity: interfering substances**	[redacted]	X1
		[redacted]	X4
3.5	**Recovery rates at different levels**	[redacted]	X5
3.5.1	Relative standard deviation	[redacted]	
3.6	**Limit of determination**	[redacted]	
3.7	**Precision**		
3.7.1	Repeatability	[redacted]	
3.7.2	Independent laboratory validation	[redacted]	

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	[redacted]	
		[redacted]	X6

Section A4.2(a)/01 Determination of residues in soil

Annex Point IIA, IV.4.2(a) [redacted]

[redacted] X1

4.2 Conclusion

The method was validated with sediment, but also applies to analysis of pyrithione in soils since the matrix is similar and variations in extraction efficiency are compensated for by the internal standard.

Pyrithione forms strong complexes with various metal ions (e.g., zinc, copper, and iron) and may also complex with metallic or other cationic sites in the sediment. Although the concentration of pyrithione in sediment or soil may be expressed for convenience as the equivalent concentration of [redacted] it is important to understand that at low concentrations in sediment (and the similar matrix, soil) [redacted] do not exist as a single compounds. This may be deduced from the general chemistry of chelation compounds. As discussed in the section on fate and behavior in water, experimental data exist that show [redacted] in water readily transchelates to copper pyrithione in the presence of copper(II). Soil and sediment are much more complex matrices, containing a variety of charged sites and various metal ions at concentrations much higher those predicted for pyrithione. Evidence that both compounds dissociate and interact with the sediment to form a common set of pyrithione complexes was obtained from aquatic metabolism studies conducted with [redacted] which showed that both compounds degraded at the same rate and the degradation products exhibited the same pattern of formation and decline.

4.2.1 Reliability [redacted]

4.2.2 Deficiencies No

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Section A4.2(a)/01 Determination of residues in soil

Annex Point IIA, IV.4.2(a) [redacted]

Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Table A4.2(a)/01: Characteristics of the sediment (loamy-sand) used in the validation (Ritter, 2004)

Section A4.2(b)/01 Determination of residues in air

Annex Point IIA, IV.4.2(b) [redacted]

			Official use only
		1. REFERENCE	
1.1	**Reference**	**Document IV ARCPT 4020-002** [redacted] (2001) Analysis of [redacted] on sample collection media in support of an application occupational exposure study. Arch Chemicals, Inc., Study Number 73-00B10CuPT (unpublished)	X1
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2. GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3. MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	Extraction	[redacted]	X1
3.1.2	Cleanup	[redacted]	
3.2	**Detection**		
3.2.1	Separation method	[redacted]	

Section A4.2(b)/01 **Determination of residues in air**

Annex Point IIA, IV.4.2(b) **Copper pyrithione**

[redacted]

3.2.2	Detector	[redacted]	
3.2.3	Standard(s)	[redacted]	
3.2.4	Interfering substance(s)	[redacted]	
3.3	**Linearity**		
3.3.1	Calibration range	[redacted]	
3.3.2	Number of measurements	[redacted]	
3.3.3	Linearity	[redacted]	
3.4	**Specificity: interfering substances**	[redacted]	
3.5	**Recovery rates at different levels**	[redacted]	
3.5.1	Relative standard deviation	[redacted]	
3.6	**Limit of determination**	[redacted]	X2
3.7	**Precision**		
3.7.1	Repeatability	[redacted]	
3.7.2	Independent laboratory validation	[redacted]	

4. APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	**[CONFIDENTIAL INFORMATION EXCLUDED]**.

Section A4.2(b)/01 Determination of residues in air

Annex Point IIA, IV.4.2(b) **Copper pyrithione**

4.2	**Conclusion**	The method is applicable for quantitation of copper pyrithione in the range of 0.5 µg to 200 µg collected on the sampling filters.	X1
4.2.1	Reliability	[redacted]	X2
4.2.2	Deficiencies	None	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

Section A4.2(b)/02 Determination of residues in air

Annex Point IIA, IV.4.2(b) [redacted]

Official use only

1 REFERENCE

1.1 Reference

Document IV EZPTF 4020-006

[redacted] (2007) Analytical method validation for the determination of [redacted] in air sampling collection media, Arch Chemicals, Inc., Cheshire, CT, USA, Identification No. CASR-05-2007 (unpublished).

1.2 Data protection [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study Not applicable

2.2 GLP Yes

2.3 Deviations No

3 MATERIALS AND METHODS

3.1 Preliminary treatment

3.1.1 Enrichment [redacted]

3.1.2 Cleanup [redacted]

3.2 Detection

3.2.1 Separation method [redacted]

3.2.2 Detector [redacted]

3.2.3 Standard(s) [redacted]

Section A4.2(b)/02 Determination of residues in air

Annex Point IIA, IV.4.2(b) [redacted]

3.2.4	Interfering substance(s)	[redacted]	X1
3.3	**Linearity**		X2
3.3.1	Calibration range	[redacted]	
3.3.2	Number of measurements	[redacted]	
3.3.3	Linearity	[redacted]	
3.4	**Specificity: interfering substances**	[redacted]	X1
3.5	**Recovery rates at different levels**	[redacted]	X3
3.5.1	Relative standard deviation	[redacted]	X3
3.6	**Limit of determination**	[redacted]	X4
3.7	**Precision**		
3.7.1	Repeatability	[redacted]	
3.7.2	Independent laboratory validation	[redacted]	

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	[redacted]	
4.2	**Conclusion**	This method is suitable for measurement of [redacted] concentrations in air using air sampling filters. The limit of quantitation is 0.2 µg collected on the filter. The corresponding air concentration depends on the volume of air sampled. No breakthrough occurred at a flow rate of 1.5 L/minute for 5 hours, corresponding to	X5

Section A4.2(b)/02 Determination of residues in air

Annex Point IIA, IV.4.2(b) [redacted]

		450 liters sampled. The LOD in air is therefore at least 0.44 µg/m³. The instrumentation required to perform the analysis is available in most well equipped analytical laboratories. No toxic or hazardous reagents are required to prepare the samples, and all of the sample preparation equipment is commercially available. The method does not require the use of untreated commodity to correct for recoveries. The method uses [redacted] as the external calibration standard, but the derivative reacts with the pyrithione portion of the molecule. The method is therefore applicable to measurement of NaPT and CuPT as well as ZnPT. Results expressed as ZnPT concentration can be converted to CuPT or NaPT concentrations by applying the appropriate molecular weight ratio. NaPT concentration = [redacted] concentration) x (2) x (149.15) / (317.67) CuPT concentration = ([redacted] concentration) x (315.86) / (317.67)	
4.2.1	Reliability	[redacted]	X6
4.2.2	Deficiencies	No	

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date [redacted]

Materials and methods [redacted]

Section A4.2(b)/02 Determination of residues in air

Annex Point IIA, IV.4.2(b) [redacted]

[redacted]

Section A4.2(b)/02 Determination of residues in air

Annex Point IIA, IV.4.2(b) [redacted]

[redacted]

Conclusion

[redacted]

Reliability

[redacted]

Acceptability

[redacted]

Remarks

[redacted]

Section A4.2(c)/01 Determination of residues in water (fresh water)

Annex Point IIA, IV.4.2(c) [redacted]

			Official use only
		1. REFERENCE	
1.1	**Reference**	**Document IV ARCPT 4020-003** [redacted] (2003) Determination of copper pyrithione in freshwater by high performance liquid chromatography. Method validation at 0.1 µg/L concentration. Arch Chemicals, Inc. Cheshire, CT, USA, Report No. CASR-02-2003 (unpublished)	
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2. GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3. MATERIALS AND METHODS	
3.1	**Preliminary treatment**		
3.1.1	Extraction	[redacted]	
3.1.2	Cleanup	[redacted]	
3.2	**Detection**		
3.2.1	Separation method	[redacted]	X1

Section A4.2(c)/01 Determination of residues in water (fresh water)

Annex Point IIA, IV.4.2(c) [redacted]

3.2.2	Detector	[redacted]	
3.2.3	Standard(s)	[redacted]	
3.2.4	Interfering substance(s)	[redacted]	X2
3.3	**Linearity**		
3.3.1	Calibration range	[redacted]	X3
3.3.2	Number of measurements	[redacted]	
3.3.3	Linearity	[redacted]	
3.4	**Specificity: interfering substances**	[redacted]	
3.5	**Recovery rates at different levels**	[redacted]	X4
3.5.1	Relative standard deviation	[redacted]	
3.6	**Limit of determination**	[redacted]	X5
3.7	**Precision**		
3.7.1	Repeatability	[redacted]	
3.7.2	Independent laboratory validation	[redacted]	

4. APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

[CONFIDENTIAL INFORMATION EXCLUDED].

4.2 Conclusion

This method is suitable for use by regulatory agencies to detect pyrithione in surface and drinking water. The instrumentation required to perform the analysis is available in most well equipped analytical laboratories. No toxic or hazardous reagents are required to prepare the samples, and all of the sample preparation equipment is commercially available. The method does not require the use of untreated commodity to correct for recoveries.

Section A4.2(c)/01 Determination of residues in water (fresh water)

Annex Point IIA, IV.4.2(c) [redacted]

4.2.1 Reliability	[redacted]	X6
4.2.2 Deficiencies	No	

Evaluation by Competent Authorities	
Date	[redacted]
Materials and methods	[redacted]
Conclusion	[redacted]
Reliability	[redacted]

Section A4.2(c)/01 Determination of residues in water (fresh water)

Annex Point IIA, IV.4.2(c) [redacted]

Acceptability	[redacted]
Remarks	[redacted]

Section A4.2(c)/02 Determination of residues in water (drinking)

Annex Point IIA, IV.4.2 [redacted]

			Official use only
		1 REFERENCE	
1.1	**Reference**	**Document IV ARCPT 4020-003** [redacted] (2007) Method for the analysis of copper pyrithione in drinking water by HPLC with MS/MS detection. Arch Chemicals, Inc. Cheshire, CT, USA, Report No. CASR-07-2007 (unpublished)	
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted].	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	X1
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**	[redacted]	
3.1.1	Enrichment	[redacted]	
3.1.2	Cleanup	[redacted]	
3.2	**Detection**	[redacted]	
3.2.1	Separation method	[redacted]	
3.2.2	Detector	[redacted]	

Section A4.2(c)/02 Determination of residues in water (drinking)

Annex Point IIA, IV.4.2 [redacted]

		[redacted]	
3.2.3	Standard(s)	[redacted]	
3.2.4	Interfering substance(s)	[redacted]	X2
3.3	**Linearity**	[redacted]	
3.3.1	Calibration range	[redacted]	
3.3.2	Number of measurements	[redacted]	
3.3.3	Linearity	[redacted]	X3
3.4	**Specificity: interfering substances**	[redacted]	X4
3.5	**Recovery rates at different levels**	[redacted]	X5 X6
3.5.1	Relative standard deviation	[redacted]	X6
3.6	**Limit of determination**	[redacted]	X7
3.7	**Precision**		
3.7.1	Repeatability	[redacted]	
3.7.2	Independent laboratory validation	[redacted]	

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

Extenal standards are prepared at concentrations of 0.0498, 0.0996 0.249, 0.996, 2.49, and 9.96 µg/L in HPLC grade water. One milliter of each standard and each water sample are derivatized by addition of 10 ul of a 20-mg/ml solution of the derivatizing reagent [redacted] After a reaction time of 20 minutes at 65 dgerees C, 60 µL of each are injected onto the HPLC column. The pyrithione derivative elutes with a retention time of 3.9 – 4.0 minutes.

Section A4.2(c)/02 Determination of residues in water (drinking)

Annex Point IIA, IV.4.2 [redacted]

		A linear least squares analysis of the standards concentration vs. peak area (1/x weighting) is used to calculate the copper pyrithione concentration in the samples.	
4.2	**Conclusion**	The method was validated using residential well water. This method is suitable for use by regulatory agencies to detect copper pyrithione in surface and drinking water. The instrumentation required to perform the analysis is available in most well equipped analytical laboratories. No toxic or hazardous reagents are required to prepare the samples, and all of the sample preparation equipment is commercially available. The method does not require the use of untreated commodity to correct for recoveries.	X8
4.2.1	Reliability	[redacted]	
4.2.2	Deficiencies	no	

Evaluation by Competent Authorities

Date [redacted]

Materials and methods [redacted]

Section A4.2(c)/02 Determination of residues in water (drinking)

Annex Point IIA, IV.4.2 [redacted]

[redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

Section A4.2(c)/03 Determination of residues in water (seawater)

Annex Point IIA, IV.4.2 [redacted]

			Official use only
		1 REFERENCE	
1.1	**Reference**	**Document IV EZPTF 4020-008** [redacted] (2009) Method for the analysis of pyrithione in seawater by HPLC with MS/MS detection. Arch Chemicals, Inc. Cheshire, CT, USA, Report No. CASR-02-2009 (unpublished)	
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**	[redacted]	
3.1.1	Enrichment	[redacted]	
3.1.2	Cleanup	[redacted]	
3.2	**Detection**	[redacted]	
3.2.1	Separation method	[redacted]	X1
3.2.2	Detector	[redacted]	

Section A4.2(c)/03 Determination of residues in water (seawater)

Annex Point IIA, IV.4.2 [redacted]

[redacted]

3.2.3	Standard(s)	[redacted]	X2
3.2.4	Interfering substance(s)	[redacted]	
3.3	**Linearity**	[redacted]	
3.3.1	Calibration range	[redacted]	X3
3.3.2	Number of measurements	[redacted]	
3.3.3	Linearity	[redacted]	X4
3.4	**Specificity: interfering substances**	[redacted]	X5
3.5	**Recovery rates at different levels**	[redacted]	X6
3.5.1	Relative standard deviation	[redacted]	
3.6	**Limit of determination**	[redacted]	X7
3.7	**Precision**	[redacted]	
3.7.1	Repeatability	[redacted]	

Section A4.2(c)/03 Determination of residues in water (seawater)

Annex Point IIA, IV.4.2 [redacted]

3.7.2	Independent laboratory validation	[redacted]

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	The method uses internal standard calibration. Standards are prepared containing [redacted] at 5-6 concentration levels in the range of 0.05 to 10 µg/L in HPLC grade water. Three-milliliter aliquots of each standard and sample are spiked with [redacted] (internal standard) at a concentration of 0.4 ug/L and derivatized by addition of 15 µL of a 20-mg/ml solution of the derivatizing reagent [redacted] After a reaction time of 20 minutes at 65° C, 50 µL of each are analyzed by HPLC with detection by positive ion electrospray ionization mass spectrometry in the multiple reaction monitoring scan mode. The pyrithione derivative elutes with a retention time of [redacted] A linear least squares analysis (1/x weighting) of the standard concentration vs. the [redacted] /IS peak area ratio is used to calculate the [redacted] concentration in the samples.
4.2	**Conclusion**	The method was validated using seawater. The instrumentation required to perform the analysis is available in most well equipped analytical laboratories. No toxic or hazardous reagents are required to prepare the samples, and all of the sample preparation equipment is commercially available. The method does not require the use of untreated commodity to correct for recoveries.
4.2.1	Reliability	[redacted]
4.2.2	Deficiencies	no

Evaluation by Competent Authorities

Date	[redacted]
Materials and methods	[redacted]

Section A4.2(c)/03 Determination of residues in water (seawater)

Annex Point IIA, IV.4.2 [redacted]

[redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

Section A4.2(d)/01 Determination of residues in animal and human body fluids and tissues (plasma)

Annex Point IIA, IV.4.2(d) [redacted]

Official use only

1. REFERENCE

1.1 Reference

Document IV EZPTF 4020-004, EXPTF 4020-005

[redacted] (2002) Quantitation of total pyrithione in rat plasma via HPLC with MS/MS detection. PPD Development, Richmond, VA, USA, Method No. LCMSC 218 Version 1.00 (unpublished)

[redacted] (2003) Validation of a high-performance liquid chromatography/mass spectrometry method for the analysis of total pyrithjione in rat plasma. PPD Development, Richmond, VA, USA, Validation Report No. LCMSC 218 Version 1.00 (unpublished)

1.2 Data protection [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

2. GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study Not applicable

2.2 GLP Not applicable

2.3 Deviations Not applicable

3. MATERIALS AND METHODS

3.1 Preliminary treatment

3.1.1 Extraction [redacted]

3.1.2 Cleanup [redacted]

3.2 Detection

Section A4.2(d)/01 Determination of residues in animal and human body fluids and tissues (plasma)

Annex Point IIA, IV.4.2(d) [redacted]

3.2.1	Separation method	[redacted]	
3.2.2	Detector	[redacted]	
3.2.3	Standard(s)	[redacted]	
3.2.4	Interfering substance(s)	[redacted]	
3.3	**Linearity**		
3.3.1	Calibration range	[redacted]	X1
3.3.2	Number of measurements	[redacted]	X2
3.3.3	Linearity	[redacted]	X3
3.4	**Specificity: interfering substances**	[redacted]	X4

Section A4.2(d)/01 Determination of residues in animal and human body fluids and tissues (plasma)

Annex Point IIA, IV.4.2(d) [redacted]

[redacted]

3.5 Recovery rates at different levels

3.5.1 Relative standard deviation

[redacted] X5

[redacted]

3.6 Limit of determination

[redacted]

3.7 Precision

3.7.1 Repeatability

[redacted]

[redacted]

3.7.2 Independent laboratory validation

[redacted]

Section A4.2(d)/01 Determination of residues in animal and human body fluids and tissues (plasma)

Annex Point IIA, IV.4.2(d) [redacted]

4. APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

[CONFIDENTIAL INFORMATION EXCLUDED].

4.2 Conclusion

This method is suitable for use by regulatory agencies to detect pyrithione in blood plasma and in principle may be adapted for analysis in other body fluids and tissues. Stable label [redacted] is used as the internal standard; however, the actual analyte after derivatization is the uncomplexed pyrithione molecule, which is the form that both [redacted] takes in biological fluids. The method is therefore applicable to copper pyrithione as well. The instrumentation required to perform the analysis is available in most well equipped analytical laboratories.

X6

4.2.1 Reliability [redacted]

X7

4.2.2 Deficiencies No

Evaluation by Competent Authorities

Date [redacted]

Materials and methods [redacted]

Section A4.2(d)/01 Determination of residues in animal and human body fluids and tissues (plasma)

Annex Point IIA, IV.4.2(d) [redacted]

[redacted]

[redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

Section A4.2(d)/02 Determination of residues in animal and human body fluids and tissues

Annex Point IIA, IV.4.2(d) [redacted]

JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
[redacted]	
Detailed justification: [redacted]	X1
[redacted]	

Evaluation by Competent Authorities	
Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	[redacted]

Section A4.3/01 Determination of residues in/on food or feedstuffs

Annex Point IIIA, IV.1. [redacted]

JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
[redacted]	
Detailed justification: [redacted]	
[redacted]	

Evaluation by Competent Authorities	
Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	[redacted]

Section A4.3/01 Analytical Methods for Detection and Identification Environmental Media – Residues in Fish and Shellfish

Annex Point IIIA, IV.1. [redacted]

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2009) Method for the Analysis of Pyrithione in Fish Muscle by HPLC with MS/MS Detection, Arch Chemicals, Inc. Cheshire, CT, Report No. CASR-02-2008 (unpublished).	
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	[redacted]	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**	[redacted]	
3.1.1	Enrichment	[redacted]	
3.1.2	Cleanup	[redacted]	X1
3.2	**Detection**	[redacted]	
3.2.1	Separation method	[redacted]	X2
3.2.2	Detector	[redacted]	

Section A4.3/01 Analytical Methods for Detection and Identification Environmental Media – Residues in Fish and Shellfish

Annex Point IIIA, IV.1. [redacted]

		[redacted]	
3.2.3	Standard(s)	[redacted]	
3.2.4	Interfering substance(s)	[redacted]	
3.3	**Linearity**	[redacted]	
3.3.1	Calibration range	[redacted]	X3
3.3.2	Number of measurements	[redacted]	X4
3.3.3	Linearity	[redacted]	X5
3.4	**Specificity: interfering substances**	[redacted]	X6
3.5	**Recovery rates at different levels**	[redacted]	X7
3.5.1	Relative standard deviation	[redacted]	X7
3.6	**Limit of determination**	[redacted]	X8
3.7	**Precision**	[redacted]	
3.7.1	Repeatability	[redacted]	
3.7.2	Independent laboratory validation	[redacted]	

Section A4.3/01 **Analytical Methods for Detection and Identification Environmental Media – Residues in Fish and Shellfish**

Annex Point IIIA, IV.1. [redacted]

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

[redacted]

4.2 Conclusion

The method is accuarate and specific for pyrithione in fish at concentrations equivalent to 0.5 to 5 ng/Kg of either copper or [redacted]

4.2.1 Reliability [redacted]

4.2.2 Deficiencies None

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date [redacted]

Materials and methods [redacted]

Section A4.3/01 Analytical Methods for Detection and Identification Environmental Media – Residues in Fish and Shellfish

Annex Point IIIA, IV.1. [redacted]

[redacted]

Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

Reference list of studies submitted by Section No.

See document I

Reference list of studies submitted by Author

See document I