Section A4.1/01 Analytical Methods for Detection and Identification

Annex Point IIA, IV.4.1 *Analytical method for detection of a.s.*

			Official use only
		1 REFERENCE	
1.1	**Reference**	Randel, G. (2011) ACTICIDE® OIT 100% - 5 Batch Analysis, Spectral Service AG, [redacted]	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Thor GmbH, Germany	
1.2.2	Companies with letter of access	None	
1.2.3	Criteria for data protection	Data submitted on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes. USP method 761, Ph.Eur. method 01/2009:20233, Ph.Eur. method 01/2008:20243, EC, 1999: SANCO/3030/99 rev.4 11/07/00, EPA 712-C-96-11, OPPTS 830.1700	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Preliminary treatment**	The test substance is a solidified melt. The substance was warmed up to 30-35°C before weighting. Dilution in $CDCl_3$ / MeOD (80/20).	
3.1.1	Extraction	None	
3.1.2	Cleanup	None	
3.2	**Detection**		
3.2.1	Separation method	Quantitative ^{1}H-NMR using internal standard method	
3.2.2	Detector	See 3.2.1	
3.2.3	Standard(s)	Response of the active substance OIT to the internal standard on three concentration levels with double measurement. 80%, 100% and 120% of the concentration in sample. An internal standard solution of butyl hydroxytoluene (BHT) was prepared by diluting about 375 mg BHT in $CDCl_3$ / MeOD (80/20, v/v). After further dilution 1.5 ml of this internal standard solution was added to each sample and calibration solution.	X
3.2.4	Interfering substance(s)	None	
3.3	**Linearity**	The integrals of the active substance signals at δ = 8.1, 6.25 and 3.7 ppm were plotted against the initial weight of the standard and assessed by linear regression.	X
3.3.1	Calibration range	80%, 100% and 120% of the concentration in sample, samples were dissolved in $CDCl_3$ / MeOD (80/20)	
3.3.2	Number of measurements	Standard solution were measured in duplicate	
3.3.3	Linearity	The graph obtained was linear and regression yielded a correlation	

		coefficient of $R^2 = 0.999$.	
3.4	**Specifity: interfering substances**	Given by the use of ^{1}H-NMR and ^{13}C NMR measurement	X
3.5	**Recovery rates at different levels**	Not required	
3.5.1	Relative standard deviation		
3.6	**Limit of determination**	Not required for the active substance.	
3.7	**Precision**		
3.7.1	Repeatability	Five individually prepared samples of test item were analysed for their content of active substance. Samples were dissolved in CDCl3 / MeOD (80/20) and quantified. The relative standard deviation of the results was [redacted] at a mean active substance content of [redacted] Intermediate precision (repeatability): Fivefold analysis of the same batch was repeated on a second day. The relative standard deviation of the results was [redacted] at a mean active substance content of [redacted].	
3.7.2	Independent laboratory validation	Not required	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	A validation of an analytical method using quantitative ^{1}H-NMR with internal standard method was carried out for the content determination of the active substance in 5 batches of the technical material ACTICIDE® OIT 100%.	
4.2	**Conclusion**	The validation of the analytical method for the active substance OIT is valid according to SANCO3030/99 rev.4.	
4.2.1	Reliability	1	
4.2.2	Deficiencies	No	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	30/01/12

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Materials and methods	
	3.2.3 Standard(s) and 3.3 linearity: Linearity has been based on the preparation of sample solutions containing different concentrations of technical material and hence containing different ratios of the active to the internal standard. A linear response of weight of the technical material versus the ^{1}H integrals was achieved. Clearly this approach does not address the linearity and would not normally be an acceptable approach. However, these data demonstrate that the detector has not been overload with sample and as NMR is an absolute technique and the NMR spectra clearly demonstrate there is no interference with signals from the solvent and internal standard then no further data on linearity are required. **3.4: Specifity: interfering substances** Example $^{1}HNMR$ spectra of the internal standard and solvent, the technical material and the technical material plus the internal standard were presented. These demonstrate that the ^{1}H signal for the active used for quantification was free of interference.
Conclusion	Adopt applicant´s version
Reliability	1
Acceptability	Acceptable. The method of analysis used has been fully validated and is therefore acceptable to support the batch analysis data. However, quantitative NMR is not a widely used technique. Therefore, while the method is acceptable to support the batch analysis data and the technical specification the method may not be accepted as a monitoring method for the technical material. It is noted that there is no specific technical issues preventing the use in this specific case of more traditional methods such as HPLC-MS etc.
Remarks	A more widely available method for monitoring the active in the TGAI may be required.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	