FINAL REPORT

Study Title:	Solubility in Organic Solvents of MK 244
Purpose of the Study:	Determination of physico-chemical properties: solubility in organic solvents
Study Director:	Dr. R. Kettner
Sponsor:	N. Burkhard Novartis Crop Protection AG CH-4002 Basel
Test Facility:	GLP Testing Facility EZA Novartis Crop Protection Münchwilen AG CH-4333 Münchwilen
Study Completion Date:	10-DEC-1999
Study Number:	79454

Test Item	: MK 244 tech.
Other Test Item Identification(s)	: Emamectin Benzoate tech.
Batch	: FL 971780/1 (technical grade active ingredient, TGAI, assay: 96·1 %)
Principal Investigator(s)	: ----
Study Initiation Date	: 25-NOV-1999
Experimental Starting Date	: 29-NOV-1999
Experimental Termination Date	: 06-DEC-1999
Archive	: GLP Testing Facility EZA, Novartis Crop Protection Münchwilen AG, CH-4333 Münchwilen. Study plan, all raw data and final report are archived.

Statement of GLP Compliance:
This study was performed in compliance with Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986, issued by the Federal Department of the Interior and the Intercantonal Office for the Control of Medicaments, Switzerland.
These procedures are based on the OECD Principles of Good Laboratory Practice, adopted May 12, 1981 by Decision of the OECD Council [C (81) 30 (Final)] concerning Mutual Acceptance of Data in the Assessment of Chemicals.

Date of Signature : 10 December 1999

Signature of Study Director :

1. Summary and Conclusion

The solubility of MK 244 has been determined in 7 organic solvents. As there is no general method available for the determination of the solubility in organic solvents, a procedure similar to that described in CIPAC method MT 157.3 (water solubility) was used for the determination of the solubility.

The solubilities, determined at 25 °C, are as follows:

Acetone	140	g/l
Dichloromethane	> 500	g/l
Ethyl Acetate	81	g/l
Hexane	77	mg/l
Methanol	270	g/l
Octanol	48	g/l
Toluene	26	g/l

The results have been quoted correct to two significant figures, where appropriate.

2. Results

Technical grade active ingredient, TGAI, batch: FL 971780/1, with an assay of 96·1 % was used in this study. The final average solubilities have been quoted correct to two significant figures, where appropriate.

Experimental data:

Solvent	B1a			B1b			MK 244 (= B1a + B1b)
	Equilibration time at 25 °C			Equilibration time at 25 °C			
	1 day	2 days	average	1 day	2 days	average	
Acetone:	20·7 g of test substance dispersed in 30·0 ml						
results in g/l	130·128 130·001	132·146 132·442	131·179	11·668 11·574	11·605 11·660	11·627	140
Dichloromethane:	20·6 g of test substance dissolved in 20·0 ml						
results in g/l	544·427 553·176		548·802	28·957 29·153		29·055	> 500
Ethyl Acetate:	20·8 g of test substance dispersed in 25·0 ml						
results in g/l	71·300 71·728	73·403 73·157	72·397	7·942 8·021	8·256 8·327	8·137	81
Hexane:	1·7 g of test substance dispersed in 50·0 ml						
results in mg/l	72·121 72·666	75·077 74·978	73·711	3·160 3·221	3·720 3·450	3·388	77
Methanol:	10·3 g of test substance dispersed in 25·0 ml						
results in g/l	260·665 259·827	259·611 265·845	261·487	13·224 13·318	13·668 13·312	13·381	270
Octanol:	10·0 g of test substance dispersed in 25·0 ml						
results in g/l	45·263 45·162	44·055 44·241	44·680	3·435 3·430	3·190 3·185	3·310	48
Toluene:	4·7 g of test substance dispersed in 25·0 ml						
results in g/l	23·991 23·938	24·826 24·922	24·419	1·957 1·949	2·026 2·031	1·991	26

3. Description of Test Methods

3.1. Description of the procedure

Mixtures of the test substance with each of the solvents were prepared in glass volumetric flasks. Apart from dichloromethane, sufficient substance was added to ensure that saturation was achieved. The contents of each flask were stirred continuously at the test temperature of 25·0 °C (± 0·5 °C) in a thermostatically controlled water bath throughout the duration of the experiment. One and two days (except for dichloromethane) after preparation of the saturated solutions, a representative aliquot from each flask was transferred to a stainless steel centrifuge tube. These tubes were then centrifuged for 40 minutes at 50000 G in a centrifuge, thermostated at 25 °C.

After centrifugation, for all solvents apart from dichloromethane, each centrifuge tube contained a clear supernatant liquid - saturated solution - with a residue of undissolved, excess test substance still present. An aliquot from each clear, saturated solution was subsequently analysed by high performance liquid chromatography to determine the concentration of the test substance therein.

After one day a clear solution was obtained for dichloromethane. This clear solution was also centrifuged and an aliquot from the still clear solution was subsequently analysed. A concentration in excess of 500 g/l was determined, indicating that the solubility in dichloromethane must also exceed 500 g/l. The experiment was discontinued at this point.

Emamectin is a mixture of two homologues, B1a and B1b. The final solubility figure is, therefore, given as the sum of these two species.

3.2. Analytical Method

Aliquots from the clear, saturated, solutions were analysed by HPLC using external standard calibration. The method is sufficiently sensitive and reproducible and is specific with respect to potential degradation products.

The more important parameters are given below.

Parameters

Detector Wavelength:	245 nm
Column:	Nucleosil C_{18} (5 µm), length 250 mm, i.d. 4·0 mm
Column temperature:	room temperature
Injection volume:	10 µl (sample loop) of the reference and test solutions
Typical Retention times:	7·7 minutes for the B1b homologue, 9·5 minutes for the B1a homologue
Chromatographic run time:	12 minutes
Flow rate:	1·0 ml / min
Mobile phase:	acetonitrile / 0·1 % aqueous trifluoroacetic acid : 60 / 40

Preparation of the Reference Solutions

Concentrations (accurately known) of about 120 mg/l and 60 mg/l were prepared from stock solutions of the reference material in methanol, appropriately diluted with the mobile phase.

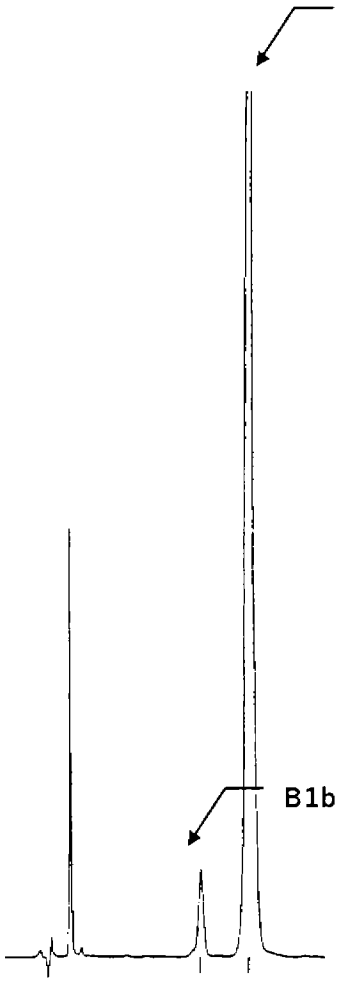
Preparation of the Test Solutions

Aliquots of the clear, centrifuged, solutions were diluted similarly to the reference solutions. The final concentrations of the test solutions were in a range, similar to that of the reference solutions.

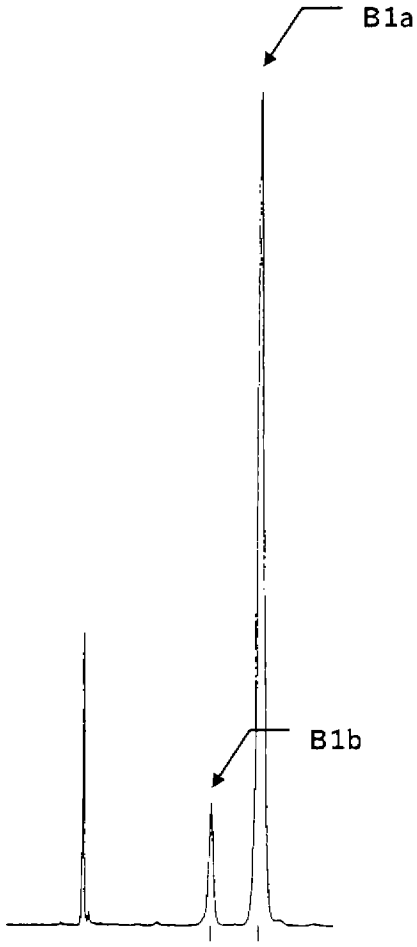
Reference Material

Pure active ingredient, PAI, AMS 921/2, with a purity of 96·6 % was used for the preparation of the reference solutions.

3.3. *Typical Chromatograms*



reference solution



test solution (ethyl acetate)

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Quality Assurance Statement

Novartis Crop Protection AG, GLP Quality Assurance, Prod. Safety Services, 4002 Basel

Study Number	**79454**
Test Item	**MK 244**
Study Title	**Solubility in Organic Solvents of MK 244**
Study Director	**Dr. Robert Kettner**
QA Inspector	**Wally W. Hartmann**

It is herewith confirmed that the following Quality Assurance activities were performed:

Activity	Performed	Reported
Facility-Based Inspection	May 5, 1999	May 17, 1999
Process Based Inspection	October 27, 1999	October 27, 1999
Study Plan Check	November 26, 1999	November 26, 1999
Final Report Inspection	December 9, 1999	December 9, 1999

December 14, 1999

Date

Form. QSSTAT01

D. Baltisberger

Dieter Baltisberger, subst.
Quality Assurance Inspector