Report

[redacted]: Determination of Partition Coefficient

[redacted]

Version ID:	Final
Issue Date:	13 January 2017
Study Director:	R E Butler
Testing Facility:	Envigo Research Limited Shardlow Business Park London Road Shardlow Derbyshire DE72 2GD UK

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LIST OF APPENDICES

LIST OF ANNEXES

COMPLIANCE WITH GOOD LABORATORY PRACTICE

[redacted]: Determination of Partition Coefficient

With the exception detailed below, the study described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid.

- The UK Good Laboratory Practice Regulations (Statutory Instrument 1999 No. 3106, as amended by Statutory Instrument 2004 No. 994)
- OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17
- EC Commission Directive 2004/10/EC of 11 February 2004

These principles of Good Laboratory Practice are accepted by the members of the OECD Mutual Acceptance of Data including the European Community/United States of America and Japan.

Exception to Good Laboratory Practice includes:

- Partition coefficient estimate (Section 4.1.2.1)

R E Butler
Study Director
Envigo Research Limited

13 JAN 2017
Date

QUALITY ASSURANCE STATEMENT

[redacted]: Determination of Partition Coefficient

Study based activities at the Test Facility, Envigo, Shardlow were audited and inspected. The details of these audits and inspections are given below.

Type of Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Study Plan Verification	02 June 2016	02 June 2016
Study – based Partition coefficient	28 June 2016	28 June 2016
Report Audit	13 – 14 September 2016	14 September 2016

General facilities and activities where this study was conducted were inspected on an annual basis and results are reported to the relevant responsible person and Management.

Quality Assurance

13 JAN 2017

J Parker
QA Auditor
Envigo Research Limited

Date

1 SUMMARY

The partition coefficient of [redacted] has been determined using the HPLC method, designed to be compatible with Method A.8 Partition Coefficient of Commission Regulation (EC) No 440/2008 of 30 May 2008, Method 117 of the OECD Guidelines for Testing of Chemicals, 13 April 2004 and Method 830.7570 of the OCSPP Guidelines.

The partition coefficient has been determined to be in the range of less than 12.6 to greater than 1×10^{10}, $\log_{10} P_{ow}$ <1.1 to >10.

By area percentage normalization, 33.0% of the test item had a $\log_{10} P_{ow}$ <1.1 to 10 and 67.0% of the test item had a $\log_{10} P_{ow}$ >10.

The results are shown in the following table:

Peak number	Partition coefficient	$\text{Log}_{10}\ P_{ow}$	Mean Area %
1	<12.6	<1.1	1.67
2	<12.6	<1.1	1.00
3	94.5	2.98	3.17
4	1.15×10^4	4.06	2.61
5	5.18×10^4	4.72	3.18
6	2.58×10^5	5.41	4.85
7	4.23×10^5	5.63	0.20
8	7.77×10^5	5.89	1.60
9	1.43×10^6	6.16	0.18
10	2.19×10^6	6.34	0.79
11	1.43×10^7	7.16	4.18
12	4.37×10^7	7.64	0.75
13	1.88×10^8	8.27	6.80
14	5.71×10^8	8.76	0.41
15	1.92×10^9	9.28	1.17
16	2.77×10^9	9.44	0.52
17-31	$>1 \times 10^{10}$	>10	67.0

2 INTRODUCTION AND PURPOSE

The purpose of this study is to evaluate the partition coefficient of the test item.

2.1 Study Details

[redacted]

2.2 Study Schedule

Experimental starting date:	14 June 2016
Experimental completion date:	29 June 2016

2.3 Regulatory Testing Guidelines

The test methods described are designed to be compatible with the procedures indicated by the following internationally accepted guidelines and recommendations:

- Commission Regulation (EC) No 440/2008 (as amended) of 30 May 2008
- OECD Guidelines for Testing of Chemicals
- US EPA Office of Chemical Safety and Pollution Prevention (OCSPP) formerly the Office of Prevention, Pesticides and Toxic Substances (OPPTS), Series 830: Product Properties Test Guidelines and Series 835: Fate, Transport and Transformation Test Guidelines

3 MATERIALS

3.1 Test Item and Supporting Information

Information as provided by the Sponsor. The Certificate of Analysis provided by the Sponsor is presented as Annex 1.

[redacted]

Appearance/Physical state:	Yellow liquid

[redacted]

Purity:	UVCB
Expiry date:	21 April 2018
Storage conditions:	Room temperature, in the dark

4 TEST METHODS

4.1 Partition Coefficient (n-Octanol/Water)

4.1.1 Test System

The determination was carried out using the HPLC Method designed to be compatible with Method A.8 Partition Coefficient of Commission Regulation (EC) No 440/2008 of 30 May 2008 and Method 117 of the OECD Guidelines for Testing of Chemicals, 13 April 2004 and Method 830.7570 of the OCSPP Guidelines.

The test system consisted of a high performance liquid chromatograph with an appropriate detector. A reverse phase HPLC column with a very low percentage of polar groups was used.

4.1.2 Performance of the Test

4.1.2.1 Preliminary Estimate

A preliminary assessment of the partition coefficient was calculated using KOWWIN v1.68 (September 2010), © 2000 U.S. Environmental Protection Agency, based on information on the test item provided by the Sponsor.

The calculation method is based on the theoretical fragmentation of the molecule into substructures for which reliable log P_{ow} increments are known. The log P_{ow} is obtained by summing the fragment values and the correction terms for intramolecular interactions.

4.1.2.2 Definitive Test

Preparation of sample solution
Test item (0.5001 g) was diluted to 50 mL with methanol (MeOH) to give a concentration of 10.0 g/L.

Preparation of dead time solution
The dead time was determined by measuring the retention time of thiourea (purity[*] >99%, 25 mg/L solution in MeOH:H_2O, 85:15 v/v).

Preparation of reference standard solution
A solution of reference standards (see following table) was prepared in MeOH.

---

[*] Value quoted by supplier

Table 1

Standard	Purity (%)[*]	Concentration (mg/L)
Benzoyl alcohol	99.9	60.0
Triphenylamine	99+	150
DDT	98.7	158
Nonylbenzene	97	1.01×10^3
Phenylundecane	99	1.01×10^3
Phenyldodecane	97	1.03×10^3
Phenyltridecane	99	1.00×10^3
Phenyltetradacane	97	1.02×10^3

Determination of retention time

The sample, dead time and reference standard solutions were injected in duplicate using the following HPLC parameters:

HPLC System	:	Agilent Technologies 1100 Series
Detector type	:	Ultraviolet (UV)
Column	:	Kinetex EVO C18 5µm (150 x 4.6 mm id)
Column temperature	:	30 ºC
Mobile phase	:	85:15 MeOH:H_2O ramped to 100% solvent after 55 mins
pH of mobile phase	:	7.2
Flow-rate	:	1.0 mL/min
Injection volume	:	10 µL
UV detector wavelength	:	210 nm

Typical chromatography is presented in Appendix 2.

4.1.3 Calculations

Construction of calibration curve

A calibration curve was constructed from the retention time data of the dead time and reference standard solutions (Figure 1). The capacity factors (k′) for the reference standards were calculated using Equation 1. $\text{Log}_{10}\ P_{ow}$ values of the reference standards are those quoted in Method 117 of the OECD Guidelines for Testing of Chemicals, 13 April 2004.

Partition coefficient of sample

The capacity factor was calculated using Equation 1 and the $\log_{10} P_{ow}$ value determined using Equation 2 with reference to the calibration curve (Figure 1).

---

[*] Value quoted by supplier

4.1.3.1 Capacity factor

The capacity factor was determined using the following equation:

Equation 1

$$k' = \frac{t_r - t_0}{t_0}$$

where:

k' = capacity factor
t_r = retention time (min)
t_0 = dead time (min)

A correlation of log k' versus log P_{ow} of the reference items was plotted using linear regression.

4.1.3.2 Partition Coefficient

The partition coefficient was calculated using the following equation:

Equation 2

$$\mathrm{Log}_{10}\ P_{ow} = \frac{\mathrm{Log}_{10}\ k'\text{-}A}{B}$$

where:

P_{ow} = partition coefficient
k' = capacity factor
A = intercept of the calibration curve (Figure 1)
B = slope of the calibration curve (Figure 1)

4.1.4 Results

4.1.4.1 Preliminary Estimate

The $\log_{10} P_{ow}$ was calculated to be: 15.3

The full KOWWIN calculation is presented in Appendix 1.

4.1.4.2 Definitive Test

Calibration
The retention times of the dead time and the retention times, capacity factors (k') and $\log_{10} P_{ow}$ values for the reference standards are shown in the following tables:

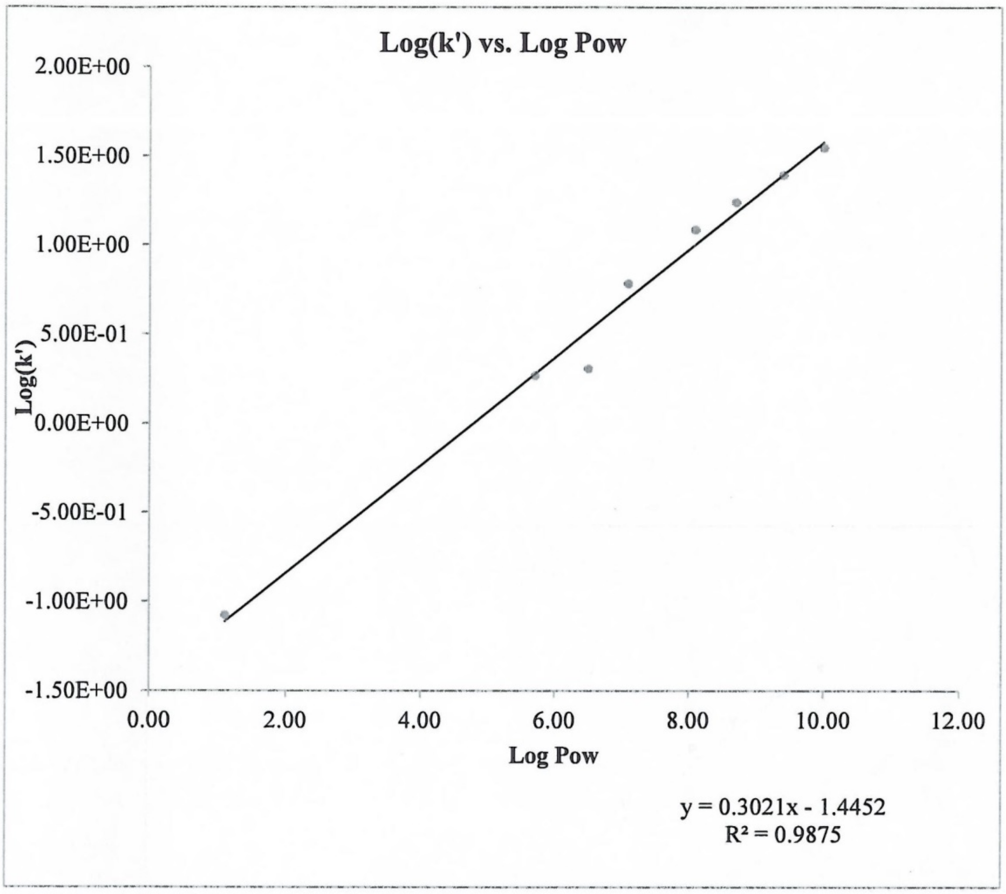
Table 2

Dead time	Retention Time (mins)		Mean retention time (mins)
	Injection 1	Injection 2	
Thiourea	1.331	1.336	1.334

Table 3

Standard	Retention time (mins)			Capacity factor (k')	Log_{10} k'	Log_{10} P_{ow}
	Injection 1	Injection 2	Mean			
Benzoyl alcohol	1.448	1.443	1.446	0.084	-1.07	1.1
Triphenylamine	3.800	3.800	3.800	1.85	0.267	5.7
DDT	4.028	4.028	4.028	2.02	0.305	6.5
Nonylbenzene	9.402	9.397	9.400	6.05	0.782	7.1
Phenylundecane	17.541	17.532	17.536	12.1	1.08	8.1
Phenyldodecane	24.393	24.378	24.385	17.3	1.24	8.7
Phenyltridecane	34.174	34.125	34.150	24.6	1.39	9.4
Phenyltetradacane	48.173	48.086	48.129	35.1	1.55	10.0

Figure 1 Calibration Curve



Partition coefficient of sample

The retention times, capacity factor, $\log_{10} P_{ow}$, partition coefficient and area % values determined for the sample are shown in the following table:

Table 4

Peak	**Injection**	**Retention time (mins)**	**Capacity factor (k′)**	**Log_{10} k'**	**Mean $\text{Log}_{10} P_{ow}$**	**Mean partition coefficient**	**Mean area %**
1	1	1.254	-6.01×10^{-2}	-	<1.1	<12.6	1.67
	2	1.254	-6.01×10^{-2}	-			
2	1	1.385	3.83×10^{-2}	-1.42	<1.1	<12.6	1.00
	2	1.375	3.83×10^{-2}	-1.51			
3	1	1.715	0.286	-0.544	2.98	945	3.17
	2	1.710	0.282	-0.549			
4	1	2.143	0.607	-0.217	4.06	1.15×10^{4}	2.61
	2	2.138	0.603	-0.220			
5	1	2.609	0.956	-1.94×10^{-2}	4.72	5.18×10^{4}	3.18
	2	2.600	0.949	-2.27×10^{-2}			
6	1	3.401	1.55	0.190	5.41	2.58×10^{5}	4.85
	2	3.392	1.54	0.188			
7	1	3.737	1.80	0.256	5.63	4.23×10^{5}	0.20
	2	3.722	1.79	0.253			
8	1	4.223	2.17	0.336	5.89	7.77×10^{5}	1.60
	2	4.203	2.15	0.333			
9	1	4.806	2.60	0.415	6.16	1.43×10^{6}	0.18
	2	4.786	2.59	0.413			
10	1	5.282	2.96	0.471	6.34	2.19×10^{6}	0.79
	2	5.258	2.94	0.469			
11	1	8.294	5.22	0.718	7.16	1.43×10^{7}	4.18
	2	8.246	5.18	0.715			
12	1	11.088	7.31	0.864	7.64	4.37×10^{7}	0.75
	2	11.025	7.27	0.861			
13	1	16.477	11.4	1.06	8.27	1.88×10^{8}	6.80
	2	16.385	11.3	1.05			
14	1	22.556	15.9	1.20	8.76	5.71×10^{8}	0.41
	2	22.366	15.8	1.20			
15	1	31.939	22.9	1.36	9.28	1.92×10^{9}	1.17
	2	31.662	22.7	1.36			
16	1	35.534	25.6	1.41	9.44	2.77×10^{9}	0.52
	2	35.267	25.4	1.41			
17	1	54.684	40.0	1.60	>10	$>1 \times 10^{10}$	67.0
	2	54.116	39.6	1.60			
18-31	-	>55	>40	>1.60	>10		

Log$_{10}$ P$_{ow}$: <1.1 to greater than 10
Partition coefficient: <12.6 to greater than 1 x 10^{10}

4.1.5 Discussion

The calculated estimate of the partition coefficient indicated that the HPLC method was suitable for determination of partition coefficient for this test item.

Weighted average partition coefficients may be applied to a substance which contains a homologous series of constituents. For substances which are mixtures and where substances have a significant proportion of the test item outside the reporting limits, the weighted average would not provide a reliable value. In addition, a gradient elution was applied to the system which prevents a meaningful weighted average value being calculated.

4.1.6 Conclusion

The partition coefficient has been determined to be in the range of less than 12.6 to greater than 1 x 10^{10}, log$_{10}$ P$_{ow}$ <1.1 to >10.

By area percentage normalization, 33.0% of the test item had a log$_{10}$ P$_{ow}$ <1.1 to 10 and 67.0% of the test item had a log$_{10}$ P$_{ow}$ >10).

The results are shown in the following table:

Table 5

Peak number	Partition coefficient	Log$_{10}$ P$_{ow}$	Mean area %
1	<12.6	<1.1	1.67
2	<12.6	<1.1	1.00
3	94.5	2.98	3.17
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7	4.23 x 10^5	5.63	0.20
8	7.77 x 10^5	5.89	1.60
9	1.43 x 10^6	6.16	0.18
10	2.19 x 10^6	6.34	0.79
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15	1.92 x 10^9	9.28	1.17
16	2.77 x 10^9	9.44	0.52
17-31	>1 x 10^{10}	>10	67.0

5 MAJOR COMPUTERIZED SYSTEMS

System	**Test**
EZChrom Elite	Partition coefficient

6 DEVIATIONS FROM STUDY PLAN

There were no deviations from study plan.

7 ARCHIVING

Records and documentation relating to this study (including electronic records) will be maintained in the archives of Envigo Research Limited for a period of 10 years from the date on which the Study Director signs the final report. This will include study plan, raw data and final report that support the reconstruction of the study.

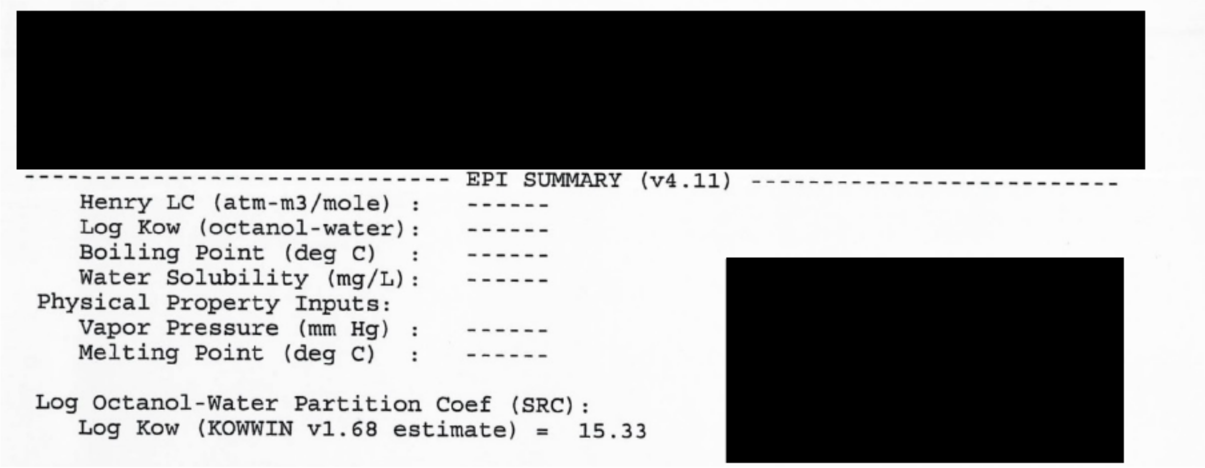
At termination of the aforementioned period, the Sponsor will be contacted in order to determine the final disposition of these records and materials. After the specified period, the Sponsor is responsible for all costs associated with the retention, retrieval, onward transfer or destruction/disposal of these materials. If the Sponsor is unresponsive the records will be destroyed in accordance with the Envigo Research Limited Standard Operating Procedure. An electronic copy of data will be transferred to the Sponsor upon request.

In case records are transferred, the Sponsor should ensure that the materials and records in support of regulatory studies are retained and maintained under conditions that guarantee their integrity and continued access according to archiving requirements of the principles of GLP. The Sponsor should also ensure that such materials and records are retained for as long as required by relevant authorities.

Envigo Research Limited will retain in its archive the study plan and final report, and any amendments indefinitely.

APPENDICES

Appendix 1 Partition Coefficient Estimate



[redacted]

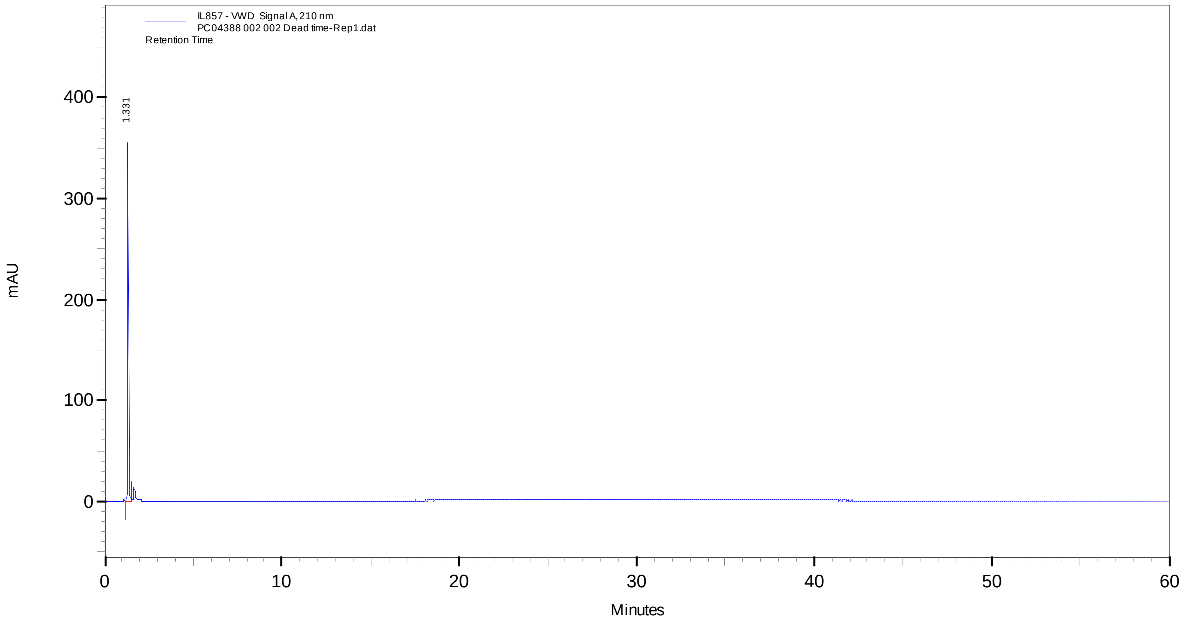
```
------------------------------ EPI SUMMARY (v4.11) -------------------------
    Henry LC (atm-m3/mole) :   ------
    Log Kow (octanol-water):   ------
    Boiling Point (deg C)  :   ------
    Water Solubility (mg/L):   ------
 Physical Property Inputs:
    Vapor Pressure (mm Hg) :   ------
    Melting Point (deg C)  :   ------

 Log Octanol-Water Partition Coef (SRC):
    Log Kow (KOWWIN v1.68 estimate) =  15.33
```

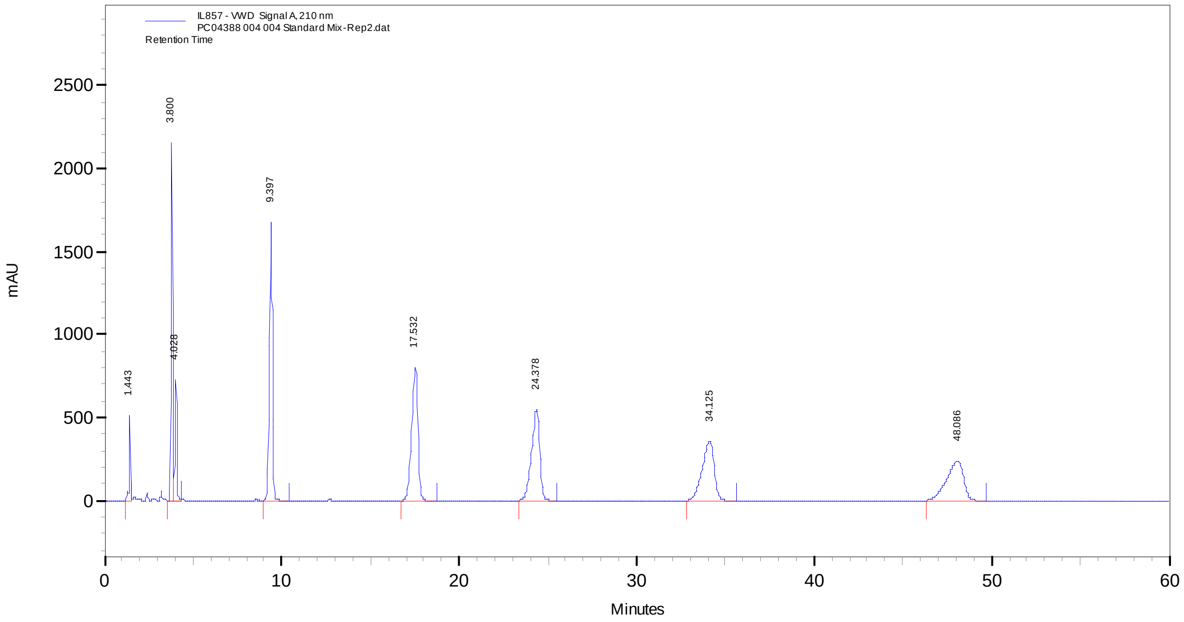
[redacted]

Appendix 2 Typical Chromatography

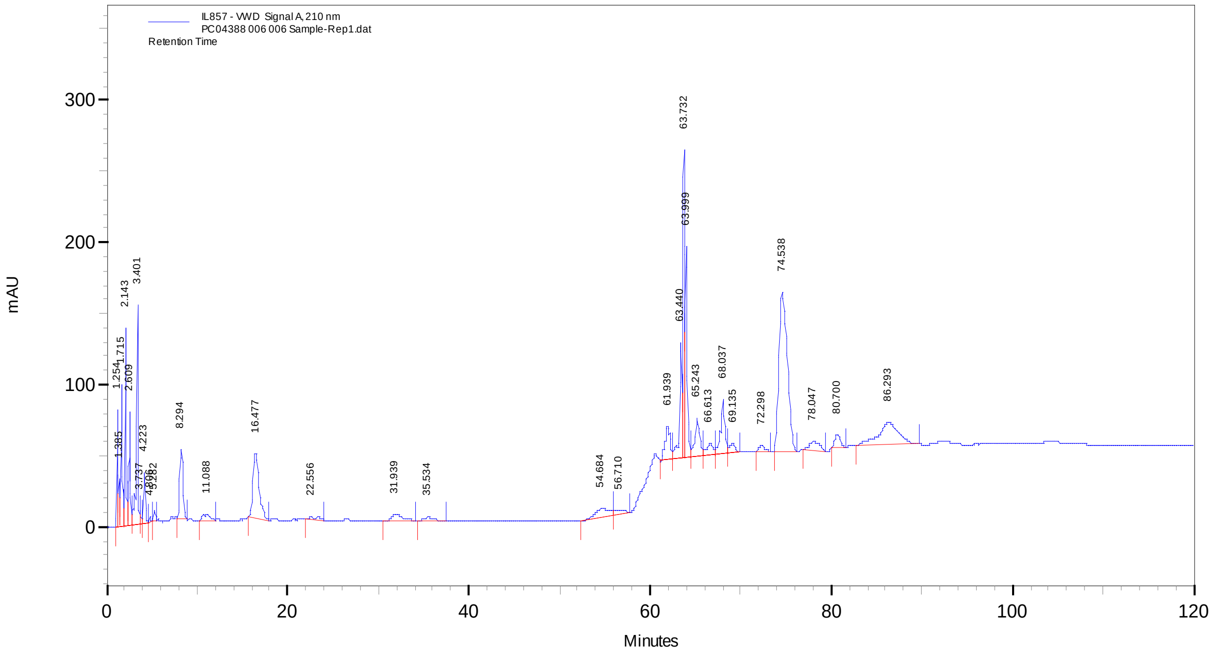
Dead Time



Standard References



Sample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PC04388 006 006 Sample-Rep1.dat
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200
100
0
1.254
1.385
1.715
2.143
2.609
3.401
3.737
4.223
4.806
5.282
8.294
11.088
16.477
22.556
31.939
35.534
54.684
56.710
61.939
63.440
63.732
63.999
65.243
66.613
68.037
69.135
72.298
74.538
78.047
80.700
86.293
0
20
40
60
80
100
120
Minutes

ANNEXES

Annex 1 Certificate of Analysis

[redacted]

Annex 2 Copy of Study Plan

Study Specific Supplement

To General Study Plan: [redacted]

[redacted]: Determination of Partition Coeffcient (n-Octanol/water)

[redacted]

Version ID:	Final
Issue Date:	01 June 2016
Study Director:	R E Butler
Testing Facility:	Envigo Research Limited Shardlow Business Park London Road, Shardlow Derbyshire DE72 2GD UK

Proposed Schedule

Experimental Starting Date:	01 June 2016
Experimental Completion Date:	31 July 2016
Draft Report Date:	31 August 2016

Test Item

Information as provided by the Sponsor.

Identification: [redacted]

Special Conditions

Quality Assurance: At least one study based inspection will be performed.

Archiving will be for a period of 10 years.

Section 4.3.2. Reference standards up to a highest log Pow value of 10 will be used.

Contact Details

In temporary absence of the Study Director, formal GLP responsibilities will be assumed by Management.

[redacted]

Study Director

R E Butler
Tel: 44 (0) 1332 792896
Email: Roger.Butler@Envigo.com

Signatures

-1 JUN 2016

Study Director
R E Butler
Envigo

Date

01 JUN 2016

Facility Management
D F White
Envigo

Date

[redacted]

1 JUN 2016

Date

Note: These signatures also acknowledge the procedures described in the corresponding General Study Plan.

General Study Plan: [redacted]

Determination of Partition Coefficient (n-Octanol/water)

Testing Facility

Envigo Research Limited
Shardlow Business Park
London Road, Shardlow
Derbyshire
DE72 2GD

[redacted]

Table of Contents

[redacted]

1. Introduction and Purpose

The purpose of this study is to evaluate the partition coefficient of the test item.

2. Regulatory Information

2.1 Good Laboratory Practice

The study will be conducted in compliance with principles of Good Laboratory Practice Standards as set forth in:

- The UK Good Laboratory Practice Regulations (Statutory Instrument 1999 No. 3106, as amended by Statutory Instrument 2004 No. 994)
- OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17
- EC Commission Directive 2004/10/EC (Official Journal No L 50/44)

These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

2.2 Regulatory Testing Guidelines

The study will be performed in compliance with the following regulations or guidelines:

- Commission Regulation (EC) No 440/2008 (as amended) of 30 May 2008.
- OECD Guidelines for Testing of Chemicals.
- REACH Regulation (EC) No 1907/2006 of the European Parliament and of the Council.
- Regulation (EU) No. 528/2012 of the European Parliament and of the Council.
- US EPA Office of Chemical Safety and Pollution Prevention (OCSPP), Series 830: Product Properties Test Guidelines.
- Commission Regulation (EU) No 283/2013 and 284/2013 of 01 March 2013 implementing Regulation No 1107/2009.

3. Test Item and Supporting Information

The test item will be supplied by or on behalf of the Sponsor including the following information if known; description, batch, purity, expiry / retest date, storage conditions and safety precautions to be taken.

[redacted]

4. Partition Coefficient (n-Octanol/Water)

4.1 Guidelines / Regulations

The procedure outlined in this document has been designed to be compatible with the following guidelines and recommendations:

- EC Method A.8
- OECD Method 107 or OECD Method 117
- OPPTS 830.7550 or OPPTS 830.7570

Where testing is conducted to satisfy the requirements of specific guidelines and/or regulations, this will be documented and reflected in the final report.

4.2 Principle of the Test

In principle, the log P_{ow} can be determined by the shake flask method (log P_{ow} between -2 and 4), or alternatively, by the HPLC method (log P_{ow} between 0 and 6). The selection of the method depends on the analytical method available for the determination of the test item and on the chemical properties of the test item. Limitations of both methods are described in the relevant guidelines. If the methods are inapplicable an estimate of the partition coefficient will be provided using a computer-based, atom fragment contribution method.

4.3 Performance of the Test

A preliminary estimate of the partition coefficient of the test item will be generated to aid in the decision of which method will be used. This may be obtained from the ratio of the approximate solubilities of the test item in n-octanol and water (by visual assessment) or calculated using appropriate modeling software.

4.3.1 The Shake Flask Method

In order to determine a partition coefficient, equilibrium between all interacting components of the system must be achieved, and the equilibrium concentrations of the items dissolved in the two phases must be determined.

Before the partition coefficient can be determined, the two individual phases will be pre-saturated by shaking both n-octanol and water with a sufficient quantity of the opposite phase. A stock solution of the test item will be prepared in either n-octanol saturated water or water saturated n-octanol. The actual mass concentration of this stock solution will be determined using a suitable analytical method.

Three ratios of the two phases will be carried out, each in duplicate, as detailed in the method guidelines. Ratio selection will be based on the characteristics of the test item and analytical methodology, but will contain both twice and half the n-octanol to water ratio of the middle ratio.

[redacted]

The test solutions will be partitioned and phase separation performed by centrifugation before analysis to determine the concentration of the test item in the initial stock solution and in both phases. The total quantity of test item present in both phases will be calculated and compared with the quantity of the test item originally introduced (derived from the analyzed stock solution concentration).

The test item concentration will be determined using a suitable analytical method. Details of the analytical method will be given in the raw data and the final report.

4.3.2 The High Performance Liquid Chromatography Method

HPLC grade methanol and high purity water will be used to prepare the eluting solvent. Isocratic elution will be employed with a minimum water content in the eluent of 25%. If necessary other organic solvent-water mixtures may also be used. If it is not possible to elute the test item with an eluent containing at least 25% aqueous phase, a gradient to a higher organic solvent content will be employed to demonstrate that the log Pow of the test item is above 6.5 (log P_{ow} of the highest reference item).

Measurements on ionizable items will be made only in their non-ionized form if possible (free acid or free base) produced by manipulation of the mobile phase pH. No additives such as ion pair reagents will be used.

The reference items will be selected from the list published in the guideline(s) according to the expected partition coefficient of the test item (other reference standards may be used if considered appropriate). At least 6 reference items will be used, with at least one above and one below the expected log Pow of the test item, if possible. The reference items will be injected in duplicate and their retention times will be determined to allow calculation of the capacity factor (k').

The dead time of the HPLC system will be determined by injecting a solution of a substance (e.g. thiourea or formamide), which will not be retained by the column, in duplicate.

A solution of the test item will be prepared in an appropriate solvent and injected in duplicate.

4.4 Evaluation of Data

The partition coefficient (P_{ow}) is defined as the ratio of the equilibrium concentrations (c) of a dissolved test item in a two-phase system consisting of two largely immiscible solvents. The partition coefficient therefore is the quotient of two concentrations (no dimension) and is usually given in the form of its logarithm to base ten (log P_{ow}).

In the HPLC method the partition coefficient is deduced from the capacity factor. The capacity factors will be calculated from the dead time and retention times of the selected reference items. A calibration graph of the log k' data versus log P_{ow} for the used reference items will be plotted. The corresponding logarithms of the capacity factors will be calculated and then plotted as a function of the retention time versus the log P_{ow} mean values given in the guideline(s). For very low and very high partition coefficients, a limit value may be necessary.

If the test item is insoluble in n-octanol, water and typical reverse phase HPLC solvents, the test will not be undertaken. The methods may also be inapplicable to strong acids and bases, metal complexes and surface-active materials. If the methods are inapplicable an estimate of the partition coefficient will be provided using a computer-based, atom fragment contribution method.

All observations which may be used to interpret the results of the tests will be documented.

Where appropriate, mean values and standard deviation will be calculated and linear regression analysis (least square method) will be applied.

Calculations performed will be presented in the study report.

5. Major Computerized Systems

Chemstation

EZChrom Elite

Openlab – Chemstation Edition

UV Winlab ES

Shimadzu GC-MS Solutions

Openlab Enterprise Content Manager

Mass Hunter

6. Quality Assurance

The following will be inspected or audited in relation to this study.

Study Plan	Study Plan and any amendments.
Process based inspections	Procedures will be inspected on representative studies, not necessarily on this study
Report Audit	The draft report and study data will be audited

QA findings will be reported to the Study Director and Test Facility Management promptly on completion of each action, except for process based inspections which will be reported to appropriate Test Facility Management with the Study Director being informed of any related findings.

7. Study Plan Amendment and Deviation

Any intended change to the study plan will result in an amendment to study plan approved by the Study Director, test facility management and the Sponsor. Amendments will be distributed to all recipients of the study plan.

[redacted]

Deviations (unplanned changes) from the study plan will be documented and acknowledged by the Study Director.

8. Reporting

Draft Report	A GLP compliant report will be prepared. Following experimental completion an audited draft report will be provided to the Sponsor for their review. The draft report will be provided electronically in PDF (non-hyperlinked) format.
Final Report	The final report will be provided electronically in eCTD compliant fully hyperlinked PDF format. After receipt and review of the Sponsor's comments, appropriate changes will be made and revisions provided to the Sponsor. Once authorized by the Sponsor, the audited, signed final report will be issued. Any additions or corrections to an authorized final report will be documented as a formal addendum/amendment to the final report.

In the absence of ongoing communications and after notification in writing to the Sponsor, Envigo reserves the right to finalize, sign and issue the final report from this study three months after the issue of the draft. Any subsequent requests for modifications, corrections or additions to the final report will be the subject of a formal report amendment (or new study, as appropriate) and will be subject to additional cost.

9. Archiving

Records and documentation relating to this study (including electronic records) will be maintained in the archives of Envigo – Shardlow for a period of 2 years from the date on which the Study Director signs the final report. This will include study plan, raw data and final report that support the reconstruction of the study.

At termination of the aforementioned period, the Sponsor will be contacted in order to determine the final disposition of these records and materials. After the specified period, the Sponsor is responsible for all costs associated with the retention, retrieval, onward transfer or destruction/disposal of these materials. If the Sponsor is unresponsive the records will be destroyed in accordance with the Envigo – Shardlow Standard Operating Procedure. An electronic copy of data will be transferred to the Sponsor upon request.

In case records are transferred, the Sponsor should ensure that the materials and records in support of regulatory studies are retained and maintained under conditions that guarantee their integrity and continued access according to archiving requirements of the principles of GLP. The Sponsor should also ensure that such materials and records are retained for as long as required by relevant authorities.

[redacted]

Envigo will retain in its archive the study plan and final report, and any amendments indefinitely.

10. Signatures

Author

11 SEP 2015

Date

D A Tarran

Approved by Facility Management

11 SEP 2015

Date

D F White

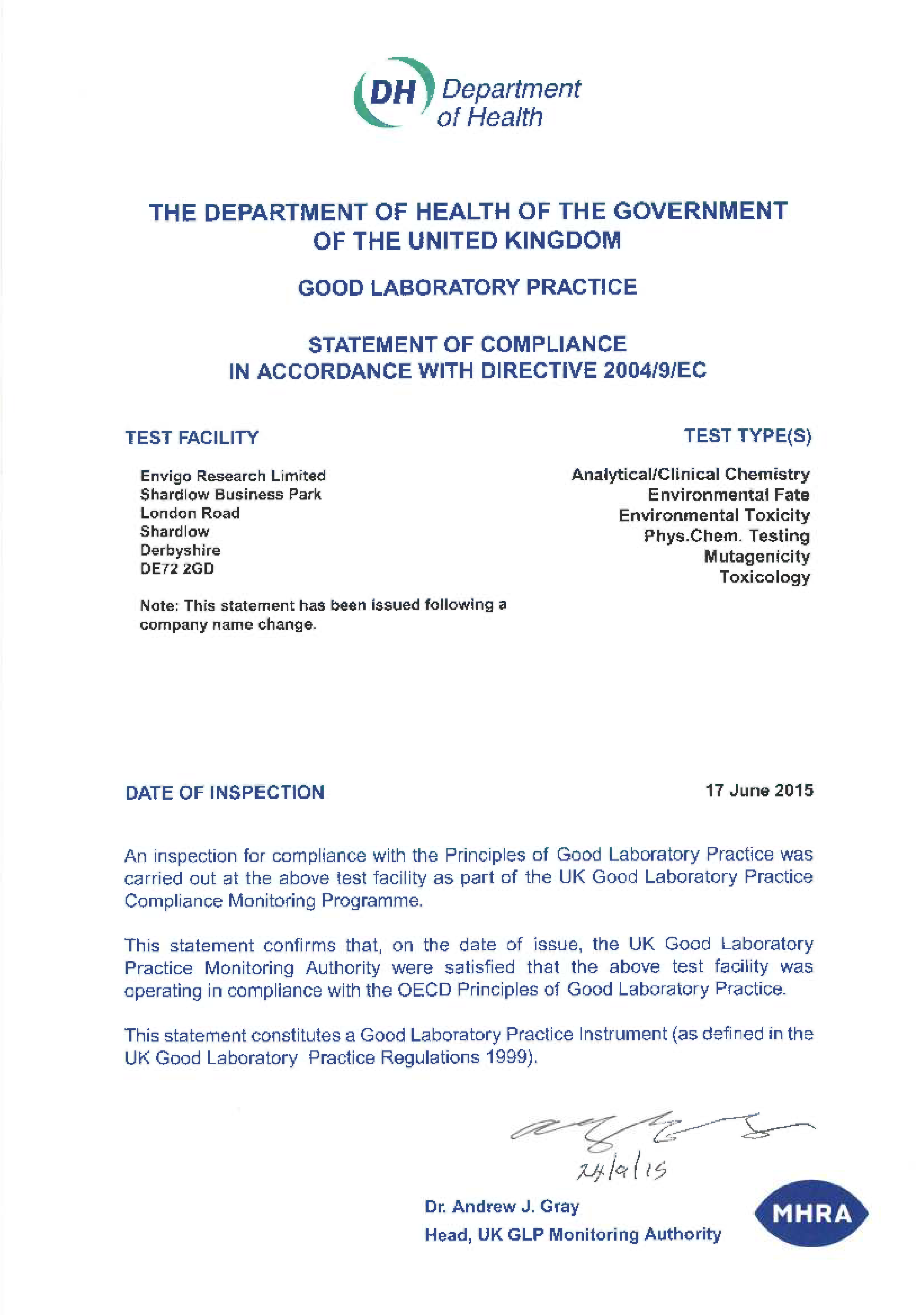
Reviewed by Quality Assurance

17 SEP 2015.

Date

A Mohamed

Annex 3 Monitoring Authority Statement of GLP Compliance



DH Department of Health

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE IN ACCORDANCE WITH DIRECTIVE 2004/9/EC

TEST FACILITY

Envigo Research Limited
Shardlow Business Park
London Road
Shardlow
Derbyshire
DE72 2GD

Note: This statement has been issued following a company name change.

TEST TYPE(S)

Analytical/Clinical Chemistry
Environmental Fate
Environmental Toxicity
Phys.Chem. Testing
Mutagenicity
Toxicology

DATE OF INSPECTION 17 June 2015

An inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above test facility as part of the UK Good Laboratory Practice Compliance Monitoring Programme.

This statement confirms that, on the date of issue, the UK Good Laboratory Practice Monitoring Authority were satisfied that the above test facility was operating in compliance with the OECD Principles of Good Laboratory Practice.

This statement constitutes a Good Laboratory Practice Instrument (as defined in the UK Good Laboratory Practice Regulations 1999).

24/9/15

Dr. Andrew J. Gray
Head, UK GLP Monitoring Authority

MHRA