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Office of Pollution Prevention and Toxics
US Environmental Protection Agency
1201 Constitution Ave., NW
Washington, DC 20460

RPW

The chemical identity of the substance is:
CAS Registry Number: 3188-75-8
Oxirane,2-[(bicyclo[2.2.1]hept-5-en-2-ylmethoxy)methyl]-

8(e) Submission: [epoxide substituted bicyclic olefin]

[ ]

Dear 8(e) Coordinator:

This letter is to inform you of the results of a Skin Sensitization Local Lymph Node Assay in the Mouse (LLNA), OECD No. 429, which is a test of Skin Sensitization.

The LLNA showed the substance to be a sensitizer under the conditions of the test. The data are being reported in accordance with EPA's 8(e) Reporting Guide (1991).

The report and a sanitized letter and report are attached herein. If I can be of any assistance, please contact me at [ ].

Yours very truly,

[

]

8EHQ-09-17682

Company Sanitized

MR# 322094

harlan™

[ ]

LOCAL LYMPH NODE ASSAY IN THE MOUSE

PROJECT NUMBER: [ ]

AUTHOR: A Sanders

STUDY SPONSOR:

[ ]

[ ]

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QUALITY ASSURANCE REPORT

This study type is classed as short-term. The standard test method for this study type ("General Study Plan" in OECD terminology) was reviewed for compliance once only on initial production. Inspection of the routine and repetitive procedures that constitute the study is carried out as a continuous process designed to encompass the major phases at or about the time this study was in progress. In addition, inspection of general facilities not specifically related to this study are done monthly or annually in accordance with QA Standard Procedure.

This report has been audited by the Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

	23 April 2007	Standard Test Method Compliance Audit
	03 August 2009	Test Material Preparation
	24 August 2009	Test System Preparation
	27 August 2009	Animal Preparation
	03 August 2009	Dosing
	13 August 2009	Assessment of Response
§	18 September 2009	Draft Report Audit
§	Date of QA Signature	Final Report Audit
§	Evaluation specific to this study	

..... DATE: 28 SEP 2009

For the Quality Assurance Unit*

***Authorised QA Signatures:**

Manager, Quality Assurance: J G Riley BSc (Hons) MRQA
Deputy Head of Department: JM Crowther MIScT MRQA
Senior Audit Staff: G Wren ONC MRQA

GLP COMPLIANCE STATEMENT

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106 as amended by SI 2004/0994)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 2004/9/EC and 2004/10/EC.

This report fully and accurately reflects the procedures used and data generated.

..... DATE: 28 SEP 2009

A Sanders
Study Director

This report may be presented in final form as a digital (pdf) document. Such documents are prepared by scanning the paper original, and are considered of equivalent integrity and authenticity to versions produced by optical photocopy. However, in all cases the hand-signed paper original, held in secure archives, is the definitive document.

CONTENTS

QUALITY ASSURANCE REPORT		**2**
GLP COMPLIANCE STATEMENT		**3**
CONTENTS		**4**
SUMMARY		**5**
1.	**INTRODUCTION**	**6**
2.	**TEST MATERIAL**	**7**
2.1	Description, Identification and Storage Conditions	7
2.2	Preparation of Test Material	7
3.	**METHODS**	**7**
3.1	Animals and Animal Husbandry	7
3.2	Procedure	8
3.3	Statistical Analysis	10
3.4	Interpretation of Results	11
4.	**ARCHIVES**	**11**
5.	**RESULTS**	**12**
5.1	Preliminary Screening Test	12
5.2	Main Test	12
6.	**CONCLUSION**	**13**
Table 1	Clinical Observations, Bodyweight and Mortality Data – Preliminary Screening Test	14
Table 2	Individual Disintegrations per Minute and Stimulation Indices	15
Table 3	Individual Clinical Observations and Mortality Data	16
Table 4	Individual Bodyweights and Bodyweight Changes	17
Appendix 1	Current Positive Control Study for the Local Lymph Node Assay	18
Appendix 2	Summary of Positive Control Data for the Local Lymph Node Assay	19
Appendix 3	Vehicle Determination Record	20
Appendix 4	Statement of GLP Compliance in Accordance with Directive 2004/9/EC	21

LOCAL LYMPH NODE ASSAY IN THE MOUSE

SUMMARY

Introduction. A study was performed to assess the skin sensitisation potential of the test material in the CBA/Ca strain mouse following topical application to the dorsal surface of the ear. The method was designed to meet the requirements of the following:

- OECD Guideline for the Testing of Chemicals No. 429 "Skin Sensitisation: Local Lymph Node Assay" (adopted 24 April 2002)
- Method B42 Skin Sensitisation (Local Lymph Node Assay) of Commission Regulation (EC) No. 440/2008
- United States Environmental Protection Agency Health Effects Test Guidelines OPPTS 870.2600 Skin Sensitisation March 2003

Methods. Following a preliminary screening test in which no clinical signs of toxicity were noted at a concentration of 25% v/v, this concentration was selected as the highest dose investigated in the main test of the Local Lymph Node Assay. Three groups, each of five animals, were treated with 50 µl (25 µl per ear) of the test material as a solution in acetone/olive oil 4:1 at concentrations of 25%, 10% or 5% v/v. A further group of five animals was treated with acetone/olive oil 4:1 alone.

Results. The Stimulation Index expressed as the mean radioactive incorporation for each treatment group divided by the mean radioactive incorporation of the vehicle control group are as follows:

Concentration (% v/v) in acetone/olive oil 4:1	Stimulation Index	Result
5	11.63	Positive
10	13.97	Positive
25	23.12	Positive

Conclusion. The test material was considered to be a sensitiser under the conditions of the test.

LOCAL LYMPH NODE ASSAY IN THE MOUSE

1. INTRODUCTION

A study was performed to assess the skin sensitisation potential of the test material in the CBA/Ca strain mouse following topical application to the dorsal surface of the ear. The method was designed to meet the requirements of the following:

- OECD Guideline for the Testing of Chemicals No. 429 "Skin Sensitisation: Local Lymph Node Assay" (adopted 24 April 2002)
- Method B42 Skin Sensitisation (Local Lymph Node Assay) of Commission Regulation (EC) No. 440/2008
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The assay has undergone extensive inter-laboratory validation and has been shown to reliably detect test materials that are moderate to strong sensitisers.

The strain of mouse used in these laboratories has been shown to produce satisfactory responses using known sensitisers and non-sensitisers during the in-house validation. The results of routine positive control studies are shown in Appendix 1 and Appendix 2. The results of the study are believed to be of value in predicting the sensitisation potential of the test material to man.

The study was performed between 21 July 2009 and 25 August 2009.

2. TEST MATERIAL

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	[ ]
Description	:	clear colourless liquid
Batch number	:	08C10938
Date received	:	04 August 2008
Storage conditions	:	approximately 4°C in the dark under nitrogen

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the study, the test material was used undiluted and freshly prepared as a solution in acetone/olive oil 4:1. This vehicle was chosen as it produced the most suitable formulation at the required concentration. The concentrations used are given in the procedure section. The vehicle determination record is included as Appendix 3.

Determination, by analysis, of the concentration, homogeneity and stability of the test material preparations was not appropriate because it was not specified in the Study Plan and is not a requirement of the Test Guideline.

3. METHODS

3.1 Animals and Animal Husbandry

Female CBA/Ca (CBA/CaOlaHsd) strain mice were supplied by Harlan Laboratories UK Limited, Bicester, Oxon, UK. On receipt the animals were randomly allocated to cages. The animals were nulliparous and non-pregnant. After an acclimatisation period of at least five days the animals were selected at random and given a number unique within the study by indelible ink-marking on the tail and a number written on a cage card. At the start of the study the animals were in the weight range of 15 to 23 g, and were eight to twelve weeks old.

The animals were individually housed in suspended solid-floor polypropylene cages furnished with softwood woodflakes. Free access to mains tap water and food (2014 Teklad Global Rodent diet supplied by Harlan Teklad, Blackthorn, Bicester, Oxon, UK) was allowed throughout the study.

The temperature and relative humidity were controlled to remain within target ranges of 19 to 25°C and 30 to 70%, respectively. Any occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was approximately fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light (06.00 to 18.00) and twelve hours darkness.

The animals were provided with environmental enrichment items which were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

3.2 Procedure

Animals in which any adverse effects were noted that were considered to approach the moderate severity limit set forth in the UK Home Office Project Licence, were humanely killed.

3.2.1 Preliminary Screening Test

Using available information regarding the systemic toxicity/irritancy potential of the test material, a preliminary screening test was performed using three mice, one per test material concentration. The mice were treated by daily application of 25 µl of the undiluted test material or the test material at concentrations of 50% or 25% v/v in acetone/olive oil 4:1, to the dorsal surface of each ear for up to three consecutive days (Days 1, 2, 3). The mice were observed twice daily on Days 1 and 2 and pre-dose on Day 3. The surviving mice were observed post-dose on Day 3 and once daily on Days 4 and 5. The surviving mouse was observed once on Day 6. Any signs of toxicity or excessive local irritation noted during this period were recorded. The bodyweight of each mouse was recorded on Day 1 (prior to dosing) and of the surviving mouse on Day 6. The bodyweights of the mice that were humanely killed were recorded immediately prior to termination.

3.2.2 Main Test

3.2.2.1 Test Material Administration

Groups of five mice were treated with the test material at concentrations of 25%, 10% or 5% v/v in acetone/olive oil 4:1. The preliminary screening test suggested that the test material would not produce systemic toxicity or excessive local irritation at the highest suitable concentration. The mice were treated by daily application of 25 µl of the appropriate concentration of the test material to the dorsal surface of each ear for three consecutive days (Days 1, 2, 3). The test material formulation was administered using an automatic micropipette and spread over the dorsal surface of the ear using the tip of the pipette.

A further group of five mice received the vehicle alone in the same manner.

3.2.2.2 ^{3}H-Methyl Thymidine Administration

Five days following the first topical application of the test material (Day 6) all mice were injected via the tail vein with 250 µl of phosphate buffered saline (PBS) containing ^{3}H-methyl thymidine (^{3}HTdR:80µCi/ml, specific activity 2.0 Ci/mmol, GE Healthcare UK Ltd) giving a total of 20 µCi to each mouse.

3.2.2.3 Observations

Clinical Observations: All animals were observed twice daily on Days 1, 2 and 3 and on a daily basis on Days 4, 5 and 6. Any signs of toxicity or signs of ill health during the test were recorded.

Bodyweights: The bodyweight of each mouse was recorded on Day 1 (prior to dosing) and Day 6 (prior to termination).

3.2.2.4 Terminal Procedures

Termination: Five hours following the administration of ^{3}HTdR all mice were killed by carbon dioxide asphyxiation. For each individual animal of each group the draining auricular lymph nodes were excised and processed. For each individual animal 1 ml of PBS was added to the lymph nodes.

Preparation of Single Cell Suspension: A single cell suspension of the lymph node cells for each individual animal was prepared by gentle mechanical disaggregation through a 200-mesh stainless steel gauze. The lymph node cells were rinsed through the gauze with 4 ml of PBS into a petri dish labelled with the project number and dose concentration. The lymph node cells suspension was transferred to a centrifuge tube. The petri dish was washed with an additional 5 ml of PBS to remove all remaining lymph node cells and these were added to the centrifuge tube. The lymph node cells were pelleted at 1400 rpm (approximately 190 *g*) for ten minutes. The pellet was resuspended in 10 ml of PBS and re-pelleted. To precipitate out the radioactive material, the pellet was resuspended in 3 ml of 5% Trichloroacetic acid (TCA).

Determination of ^{3}HTdR Incorporation: After approximately eighteen hours incubation at approximately 4°C, the precipitates were recovered by centrifugation at 2100 rpm (approximately 450 *g*) for ten minutes, resuspended in 1 ml of TCA and transferred to 10 ml of scintillation fluid (Optiphase 'Trisafe'). ^{3}HTdR incorporation was measured by β-scintillation counting. The "Poly Q™" vials containing the samples and scintillation fluid were placed in the sample changer of the scintillator and left for approximately twenty minutes. The purpose of this period of time in darkness was to reduce the risk of luminescence, which has been shown to affect the reliability of the results. After approximately twenty minutes, the vials were shaken vigorously. The number of radioactive disintegrations per minute was then measured using the Beckman LS6500 scintillation system (Beckman Instruments Inc, Fullerton, CA, USA).

3.3 Statistical Analysis

Data was processed to give group mean values for disintegrations per minute and standard deviations where appropriate. Individual and group mean disintegrations per minute values were assessed for dose response relationships by analysis of homogeneity of variance followed by one way analysis of variance (ANOVA). In the event of a significant result from the ANOVA, pairwise comparisons were performed between control and treated groups. For homogenous datasets Dunnett's Multiple Comparison test was used and for non-homogenous datasets Dunnett's T3 Multiple Comparison Method was used.

Probability values (p) are presented as follows:

$P<0.001$	***
$P<0.01$	**
$P<0.05$	*
$P\geq0.05$	(not significant)

3.4 Interpretation of Results

The proliferation response of lymph node cells was expressed as the number of radioactive disintegrations per minute per lymph nodes from each individual animal and as the ratio of ^{3}HTdR incorporation into lymph node cells of test nodes relative to that recorded for the control nodes (Stimulation Index).

The test material will be regarded as a sensitiser if at least one concentration of the test material results in a threefold or greater increase in ^{3}HTdR incorporation compared to control values. Any test material failing to produce a threefold or greater increase in ^{3}HTdR incorporation will be classified as a "non-sensitiser".

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Harlan Laboratories Ltd, Shardlow, UK archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

5.1 Preliminary Screening Test

Clinical observations, bodyweight and mortality data are given in Table 1.

The animal treated with the undiluted test material or the test material at a concentration of 50% v/v in acetone/olive oil 4:1 were humanely killed, pre-dose on Day 3 or on Day 5, due to the occurrence of clinical signs of toxicity that approached the moderate severity limit set forth in the UK Home Office Project Licence. Signs of systemic toxicity noted were hunched posture, lethargy, splayed gait, pilo erection and fasciculations. Bodyweight loss was also noted in these two animals.

No signs of systemic toxicity were noted in the animal treated with the test material at a concentration of 25% v/v in acetone/olive oil 4:1.

Based on this information the dose levels selected for the main test were 25%, 10% and 5% v/v in acetone/olive oil 4:1.

5.2 Main Test

5.2.1 Estimation of the Proliferative Response of Lymph Node Cells

The radioactive disintegrations per minute per lymph nodes for each individual animal and the stimulation index are given in Table 2.

The Stimulation Index expressed as the mean radioactive incorporation for each treatment group divided by the mean radioactive incorporation of the vehicle control group are as follows:

Concentration (% v/v) in acetone/olive oil 4:1	Stimulation Index	Result
5	11.63	Positive
10	13.97	Positive
25	23.12	Positive

5.2.2 Clinical Observations and Mortality Data

Individual clinical observations and mortality data for test and control animals are given in Table 3.

There were no deaths. No signs of systemic toxicity were noted in the test or control animals during the test.

5.2.3 Bodyweight

Individual bodyweights and bodyweight changes for test and control animals are given in Table 4.

Bodyweight changes of the test animals between Day 1 and Day 6 were comparable to those observed in the corresponding control group animals over the same period.

6. CONCLUSION

The test material was considered to be a sensitiser under the conditions of the test.

Table 1 Clinical Observations, Bodyweight and Mortality Data – Preliminary Screening Test

Concentration (% v/v) in acetone/olive oil 4:1	Animal Number	Bodyweight (g)		Day								
				1		2		3		4	5	6
		Day 1	Day 6	Pre-Dose	Post Dose	Pre-Dose	Post Dose	Pre-Dose	Post Dose			
100	S-1	17	-	0	0	0	0	HL WsP ∇K				
50	S-2	21	-	0	0	0	0	0	0	0	HL FaΔ K	
25	S-3	20	20	0	0	0	0	0	0	0	0	0

0 = No signs of systemic toxicity
H = Hunched posture
L = Lethargy
Ws = Splayed gait
P = Pilo-erection
Fa = Fasciculations
∇ = Bodyweight loss noted (3 g) animal weighed 14 g
Δ = Bodyweight loss noted (3 g) animal weighed 18 g
K = Animal humanely killed due to the occurrence of clinical signs of toxicity that approached the moderate severity limit set forth in the UK Home Office Project Licence

[illegible] LOCAL LYMPH NODE ASSAY IN THE MOUSE

Table 2 Individual Disintegrations per Minute and Stimulation Indices

Concentration (% v/v) in acetone/olive oil 4:1	Animal Number	dpm/ Animal [a]	Mean dpm/Animal (Standard Deviation)	Stimulation Index [b]	Result
Vehicle	1-1	1548.58	1783.18 (±658.89)	N/A	N/A
	1-2	2266.19			
	1-3	914.03			
	1-4	2593.60			
	1-5	1593.49			
5	2-1	20569.00	20729.62*** (±5285.91)	11.63	Positive
	2-2	18106.49			
	2-3	14372.55			
	2-4	21933.47			
	2-5	28666.58			
10	3-1	33477.26	24902.37*** (±8079.26)	13.97	Positive
	3-2	13051.32			
	3-3	24879.09			
	3-4	31117.06			
	3-5	21987.11			
25	4-1	39433.80	41231.50*** (±6964.89)	23.12	Positive
	4-2	49908.39			
	4-3	30784.62			
	4-4	43107.86			
	4-5	42922.81			

dpm = Disintegrations per minute
a = Total number of lymph nodes per animal is 2
b = Stimulation Index of 3.0 or greater indicates a positive result
N/A = Not applicable
*** = Significantly different from control group $p<0.001$

[ ] LOCAL LYMPH NODE ASSAY IN THE MOUSE

Table 3 Individual Clinical Observations and Mortality Data

Concentration (% v/v) in acetone/olive oil 4:1	Animal Number	Day 1		Day 2		Day 3		Day 4	Day 5	Day 6
		Pre-Dose	Post Dose	Pre-Dose	Post Dose	Pre-Dose	Post Dose			
Vehicle	1-1	0	0	0	0	0	0	0	0	0
	1-2	0	0	0	0	0	0	0	0	0
	1-3	0	0	0	0	0	0	0	0	0
	1-4	0	0	0	0	0	0	0	0	0
	1-5	0	0	0	0	0	0	0	0	0
5	2-1	0	0	0	0	0	0	0	0	0
	2-2	0	0	0	0	0	0	0	0	0
	2-3	0	0	0	0	0	0	0	0	0
	2-4	0	0	0	0	0	0	0	0	0
	2-5	0	0	0	0	0	0	0	0	0
10	3-1	0	0	0	0	0	0	0	0	0
	3-2	0	0	0	0	0	0	0	0	0
	3-3	0	0	0	0	0	0	0	0	0
	3-4	0	0	0	0	0	0	0	0	0
	3-5	0	0	0	0	0	0	0	0	0
25	4-1	0	0	0	0	0	0	0	0	0
	4-2	0	0	0	0	0	0	0	0	0
	4-3	0	0	0	0	0	0	0	0	0
	4-4	0	0	0	0	0	0	0	0	0
	4-5	0	0	0	0	0	0	0	0	0

0 = No signs of systemic toxicity

[ ] LOCAL LYMPH NODE ASSAY IN THE MOUSE

Table 4 Individual Bodyweights and Bodyweight Changes

Concentration (% v/v) in acetone/olive oil 4:1	Animal Number	Bodyweight (g)		Bodyweight Change (g)
		Day 1	Day 6	
Vehicle	1-1	18	17	–1
	1-2	18	18	0
	1-3	18	18	0
	1-4	19	19	0
	1-5	19	19	0
5	2-1	19	20	1
	2-2	19	20	1
	2-3	18	19	1
	2-4	19	19	0
	2-5	19	19	0
10	3-1	19	17	–2
	3-2	19	20	1
	3-3	19	19	0
	3-4	19	19	0
	3-5	18	19	1
25	4-1	17	16	–1
	4-2	19	19	0
	4-3	18	18	0
	4-4	19	20	1
	4-5	18	19	1

Appendix 1 Current Positive Control Study for the Local Lymph Node Assay

Introduction. A study was performed to assess the sensitivity of the strain of mouse used at these laboratories to a known sensitiser. The methodology for the LLNA is detailed in the OECD Guideline for the Testing of Chemicals, No. 429, and Method B.42 of Commission Regulation (EC) No. 440/2008. The study described in this document is based on these test methods but has been refined in order to reduce the number of animals required to demonstrate absence of skin sensitisation potential. The reduced LLNA (rLLNA) has been endorsed by the non-Commission members of the European Centre of the Validation of Alternative Method (ECVAM) Scientific Advisory Committee (ESAC) at its 26th meeting held on 26 – 27 April 2007 at ECVAM, Ispra, Italy.

Test Material:	α-Hexylcinnamaldehyde
Project number:	0039/1080
Study dates:	24 April 2009 to 30 April 2009

Methods. A group of five animals was treated with 50 µl (25 µl per ear) of α-Hexylcinnamaldehyde as a solution in acetone/olive oil 4:1 at a concentration of 15% v/v. A further control group of five animals was treated with acetone/olive oil 4:1 alone.

Results. The Stimulation Index expressed as the mean radioactive incorporation for each treatment group divided by the mean radioactive incorporation of the vehicle control group is as follows:

Concentration (% v/v) in acetone/olive oil 4:1	Stimulation Index	Result
15	8.34	Positive

Conclusion. α-Hexylcinnamaldehyde was considered to be a sensitiser under the conditions of the test.

Appendix 2 Summary of Positive Control Data for the Local Lymph Node Assay

Project Number	Start Date	Finish Date	Test Material	Concentration	Vehicle	Stimulation Index[a]	Classification[b]
0039/1059	29/10/08	04/11/08	α-Hexylcinnamaldehyde	15% v/v	butanone	4.05	Positive
0039/1060	05/11/08	17/12/08	α-Hexylcinnamaldehyde	15% v/v	dimethyl sulphoxide	5.73	Positive
0039/1061	05/11/08	11/11/08	α-Hexylcinnamaldehyde	15% v/v	acetone	4.21	Positive
0039/1062	05/11/08	11/11/08	α-Hexylcinnamaldehyde	15% v/v	ethanol/distilled water 7:3	9.49	Positive
0039/1078	18/03/09	24/03/09	2,4-Dinitrobenzenesulfonic acid, sodium salt	10% w/w	1% pluronic L92 in distilled water	13.71	Positive
0039/1079	20/03/09	26/03/09	Phenylacetaldehyde (90%)	2.5% v/v	propylene glycol	8.00	Positive
0039/1080	24/04/09	30/04/09	α-Hexylcinnamaldehyde	15% v/v	acetone/olive oil 4:1	8.34	Positive
0039/1081	30/04/09	06/05/09	α-Hexylcinnamaldehyde	15% v/v	dimethyl formamide	4.24	Positive
0039/1082	17/04/09	23/04/09	α-Hexylcinnamaldehyde	50% v/v	cotton seed oil	6.54	Positive
0039/1083	16/04/09	22/04/09	α-Hexylcinnamaldehyde	15% v/v	butanone	4.08	Positive
0039/1084	17/04/09	23/04/09	α-Hexylcinnamaldehyde	15% v/v	dimethyl sulphoxide	4.60	Positive
0039/1091	25/06/09	01/07/09	α-Hexylcinnamaldehyde	15% v/v	ethanol/distilled water 7:3	10.68	Positive
0039/1092	25/06/09	01/07/09	α-Hexylcinnamaldehyde	15% v/v	acetone	10.72	Positive
0039/1099	08/07/09	14/07/09	α-Hexylcinnamaldehyde	5%, 10% 25% v/v	1% pluronic L92 in distilled water	1.30, 2.37, 8.14	Positive

a = Ratio of test to control lymphocyte proliferation
b = Stimulation index greater than 3.0 indicates a positive result

Appendix 3 Vehicle Determination Record

Vehicle	Concentration	Method of Preparation	Description of Formulation	Suitability*
acetone/olive oil (4:1)	50% 0.5 ml test material + 0.5 ml vehicle	Vortex mixer	solution	suitable for dosing

* = Suitable for dosing if formulation is a solution or fine homogenous suspension which can be administered via a micropipette

Appendix 4 Statement of GLP Compliance in Accordance with Directive 2004/9/EC

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	TEST TYPE
Harlan Laboratories Ltd. Shardlow Business Park London Road Shardlow Derby DE72 2GD	Analytical/Clinical Chemistry Environmental Fate Environmental Toxicology Mutagenicity Phys/Chem Toxicology

DATE OF INSPECTION

19th August 2008

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

At the time of inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

4/3/09

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

MHRA