COVANCE
THE DEVELOPMENT SERVICES COMPANY

AMENDMENT TO FINAL REPORT

Study Number:	2379-006	
Amendment Issue Date:	15 September 2008	
Amendment Number:	1	
Study Title:	SYN520453 EC (A15149AC): ACUTE 4-HOUR (NOSE-ONLY) INHALATION STUDY IN THE RAT	
Authorised By:	[signature]	15/9/08
	S L Keech Study Director	Date
Quality Assurance Audit:	[signature]	15/9/08
	L Earnshaw QA Representative	Date
Distribution:	Study Director, QA, Sponsor	

This amendment to final report contains 2 pages including this one.

Documentation

Section(s) amended and explanation for the change

The Task Number detailed on the front page of the study report was incorrect and was amended from TOI1363-06 to TOI1363-05 at the request of the Sponsor.

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SYN520453 EC

SYN520453 EC (A15149AC): ACUTE 4-HOUR (NOSE-ONLY) INHALATION STUDY IN THE RAT

AMENDED FINAL REPORT 1

DATA REQUIREMENT: OECD, Method 403 (1981)
EPA OPPTS 870 1300 (1998)
Annex V 67/548/EEC
JMAFF 12/8147 (2001)

AUTHOR: S Keech

STUDY COMPLETION DATE: 15 September 2008

TEST FACILITY: Covance Laboratories Ltd
Otley Road, Harrogate
North Yorkshire, HG3 IPY, UK

LABORATORY PROJECT ID: Report Number: 2379/006
Study Number: 2379/006
Task Number: TOI1363-05

SPONSOR: Syngenta Ltd
Jealott's Hill International Research Centre
Bracknell, Berkshire RG42 6EY, UK

COVANCE
THE DEVELOPMENT SERVICES COMPANY

SYN520453 EC

SYN520453 EC (A15149AC): ACUTE 4-HOUR (NOSE-ONLY) INHALATION STUDY IN THE RAT

FINAL REPORT

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TEST FACILITY: Covance Laboratories Ltd
Otley Road, Harrogate
North Yorkshire, HG3 1PY, UK

LABORATORY PROJECT ID: Report Number: 2379/006
Study Number: 2379/006
Task Number: T011363-06

SPONSOR: Syngenta Ltd
Jealott's Hill International Research Centre
Bracknell, Berkshire RG42 6EY, UK

STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

I the undersigned, hereby declare that the work described in this report was performed under my supervision as Study Director and that the report provides a true and accurate record of the results obtained.

The study was performed in accordance with the agreed protocol and with Covance Laboratories Limited Standard Operating Procedures. The work and generated data are scientifically acceptable and valid. This report provides a true and accurate record of the results obtained.

The study was conducted in compliance with the:

United Kingdom Statutory Instrument 1999 No. 3106, The Good Laboratory Practice Regulations 1999 as amended by the Good Laboratory Practice (Codification Amendments Etc.) Regulations 2004.

Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice (Revised 1997, issued Jan 1998) ENV/MC/CHEM(98)17.

The definitive protocol was signed on 1 February 2008. Consequently, pre-treatment procedures performed prior to this date were based on the Draft Protocol.

S Keech BSc (Hons) MSc
Study Director
Covance Laboratories Ltd

15 Sept 2008
Date

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

This study has been reviewed by the Quality Assurance Unit of Covance Laboratories Ltd. and the report accurately reflects the raw data. The following inspections were conducted and findings reported to the study director (SD) and associated management.

Critical procedures, which are performed routinely in an operational area, may be audited as part of a "process" inspection programme. This can be in addition to phases scheduled on an individual study basis. Selected process inspections conducted and considered applicable to this study are included below.

In addition to the inspection programmes detailed below, a facility inspection programme is also operated. Details of this programme, which covers all areas of the facility annually (at a minimum), are set out in standard operating procedures.

Inspection Dates			Date Reported to SD and SD
From	To	Phase	Management
11 Feb 2008	11 Feb 2008	Protocol Review	12 Feb 2008
20 Feb 2008	20 Feb 2008	Inhalation Exposure	20 Feb 2008
26 Feb 2008	26 Feb 2008	Protocol Amendment Review	26 Feb 2008
01 May 2008	07 May 2008	Draft Report and Data Review	07 May 2008
13 May 2008	13 May 2008	Protocol Amendment Review	13 May 2008
15 Sep 2008	15 Sep 2008	Final Report Review	15 Sep 2008

Process

Inspection Dates			Date Reported to SD and SD
From	To	Phase	Management
06 Feb 2008	06 Feb 2008	Necropsy - rat	06 Feb 2008

L Earnshaw — 15 September 2008

Lynn Earnshaw
Quality Assurance Unit

Date

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Title
S Keech	Study Director
I Tipping	Study Technician
P Smith	Study Reviewer
C Davies	Syngenta Study Manager

Study dates

Study initiation date: 01 February 2008
Experimental start date: 29 January 2008
First treatment – Preliminary study: 11 February 2008
First treatment – Main study: 20 February 2008
Study termination – Preliminary study: 20 February 2008
Study termination – Main study: 05 March 2008
Experimental termination date: 05 March 2008

The study completion date is the date the final report is signed by the Study Director.

Deviations from the guidelines

None.

Retention of samples

All primary data, or authenticated copies thereof, specimens and the original final report will be retained in the Covance archives Harrogate UK, for ten years after issue of the final report. At this time the Sponsor will be contacted to determine whether the data should be returned, retained or destroyed on their behalf and notified of the financial implications of each of these options.

Performing laboratory test substance reference number

CHD: 0082/08-2379

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Study design

1.1.1 Preliminary feasibility exposure

Prior to the conduct of the limit test, a preliminary study was conducted to evaluate the feasibility of conducting the main study at a concentration of 5 mg/L. One rat per sex (Crl:WI (Han)) was exposed, nose only, to the test article for a single period of two hours and one rat per sex was exposed for four hours to an aerosol concentration of 4.65 mg/L (target concentration of 5 mg/L) with a particle size distribution (MMAD ± GSD) of 3.38 ± 2.16. After exposure, the animals were observed for up to nine days after which these animals were sacrificed.

1.1.2 Main study

Five male and five female (Crl:WI (Han)) rats were exposed to the test article, nose only, for a single four hour period at a target aerosol concentration of 2.8 mg/L. The target dose was selected due to mortality in the preliminary study. Following exposure, the animals were retained without treatment for 14 days.

The test aerosol concentration and particle size distribution were determined gravimetrically for SYN520453 EC (A15149AC) periodically throughout the exposure period. Clinical observations and bodyweights were recorded throughout the study and at the end of the scheduled period the animals were killed and subjected to a gross examination *post mortem*.

1.2 Results

The achieved aerosol concentration for the main study had the following characteristics:

Target aerosol concentration (mg/L)	Achieved concentration (mg/L)	MMAD[1] (µm)	GSD[2]
2.8	2.71	3.98	1.99

[1] Mass Median Aerodynamic Diameter (µm)
[2] Geometric Standard Deviation

Mortality occurred in both the preliminary study (one female) and the main study (one female). In the preliminary feasibility exposure the female exposed for 4 hours had decreased breathing rate throughout the exposure and when removed from the exposure chamber was comatose and as a consequence was sacrificed on the grounds of animal welfare.

In the main study, one female was observed as having decreased breathing rate and decreased activity during exposure. Observations of this animal made post-exposure included decreased breathing rate, cyanosis, hunched posture, hypothermia, closed eyes, piloerection, prone position and rales. The animal was found dead approximately 4 hours after the end of the exposure period.

Clinical signs noted post dosing in the main study included, but were not limited to, abnormal gait, hunched posture, closed eyes, gasping, hypothermia, piloerection, tremor, cyanosis, prone, rales and vocalisation. These observations were most predominant on the day of exposure, but some did persist for up to 5 days post dose. A transient body weight loss was also noted post dose where animals did not return to their pre-dose body weight for approximately 6 days, though is a common observation in inhalation studies due to the restraint procedures required for the exposure. There were no significant findings noted at necropsy in any animal including the decedents.

1.3 Conclusion

A single 4 hour (nose only) inhalation exposure to SYN520453 EC (A15149AC) at a mean aerosol concentration of 2.71 mg/L resulted in the death of one female. Clinical observations of limited incidence and severity and a transient loss in body weight were the only significant effects observed post dosing in all other surviving animals. However, the surviving animals had significantly improved the day following dosing and continued to do so throughout the observation phase of the study.

In conclusion, following a single 4 hour inhalation (nose only) exposure to SYN520453 EC (A15149AC), the LC_{50} can be considered greater than 2.71 mg/L.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to determine the limit dose of the test article, SYN520453 EC (A15149AC), following a single 4-hour inhalation exposure (nose-only) to rats with an observation period of at least 14 days.

2.2 Justification for route of administration

The inhalation route of administration was chosen because it is a possible route of human exposure.

2.3 Justification for the selection of aerosol concentrations

The aerosol concentration targeted for the preliminary feasibility exposure was 5 mg/L, which was selected based on criteria for European hazard classification.

The target aerosol concentration for the main study was 2.8 mg/L as mortality and significant clinical signs were observed in the preliminary study when rats were exposed to an aerosol concentration of 4.65 mg/L.

2.4 Justification for chosen species

The rat was used because it is one of the species generally accepted for the assessment of toxicity. The Crl:WI (Han) strain of rat was used because of the background data available for this strain in this laboratory. The rat is a rodent species accepted by various regulatory authorities.

3.0 MATERIALS AND METHODS

3.1 Test and control articles

The test article, a brown liquid, was identified as A15149AC and was received at Covance as follows:

Covance lot number	Batch number	Quantity supplied (mL)	Purity #	Expiry Date	Date of receipt at Covance
1	J8092/056	1500	13.4% (w/w) (4.1% (w/w) as SYN534968 & 9.3% (w/w) as SYN534969)	31 December 2009	23 January 2008

When not in use, the test article was stored in a sealed container, at room temperature (<30ºC), protected from light.

The Sponsor provided a certificate of analysis for the test article dated 15 January 2008, which is presented in APPENDIX 1.

3.2 Test article formulation

3.2.1 Preparation

The test article was generated as supplied.

3.2.2 Storage

When not in use, the test article was stored in a sealed container at room temperature (<30°C), protected from light.

3.2.3 Analysis of formulations

As the test article was used as supplied by the Sponsor, no chemical analysis was performed on this study.

3.3 Experimental design

3.3.1 Regulatory test guidelines

The study was designed to meet the following regulatory requirements:

- OECD Guidelines for Testing of Chemicals, Method 403 (adopted 12 May 1981).
- US Environmental Protection Agency, Health Effects Test Guidelines OPPTS 870.1300, 1998, Acute Inhalation Toxicity 1998.

- Annex V to Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, published in the Seventeenth Adaptation to Technical Progress, Commission Directive 92/69/EEC (OJEC, L383A, 117-120, 1992; B.2. Acute Toxicity Inhalation), corrected in the Eighteen Adaptation to Technical Progress, Commission Directive 93/21/EEC (OJEC L110 20-21, 1993).

- Japanese MAFF Agrochemical Test Guidelines 12 Nohsan 8147 (2-1-12, 24 November 2000 and revision of 24 June 2001).

3.3.2 Test article administration

The test article was administered in a single exposure by nose only inhalation in both the preliminary and main study phases.

3.3.2.1 Preliminary study

Prior to the conduct of the main study, a preliminary feasibility exposure was conducted to evaluate the effect of the test article. For this, four animals were exposed as follows:

Group number	Group description	Target exposure level (mg/L)	Duration of exposure (hours)	Animal numbers Male	Female
2	Preliminary	5[#]	2 4	11 13	12 14

[#] 5 mg/L or maximum practical concentration

After exposure, these animals were observed for up to nine days, after which surviving animals were sacrificed and discarded without any further investigations being conducted.

3.3.2.2 Main study

An aerosol concentration of 2.8 mg/L was targeted. A total of five male and five female rats were exposed simultaneously to the aerosol for four hours. The animals were identified as follows:

Group number	Group description	Target aerosol concentration (mg/L)	Animal numbers Male	Female
1	High	2.8	1-5	6-10

Animals were observed for up to 14 days after the exposure for signs of clinical toxicity and morbidity.

3.4 Test aerosols

3.4.1 Development/validation of a test aerosol (technical trial)

Prior to the start of animal exposure, the Inhalation Technology section at Covance developed respirable aerosols of the test article at the target aerosol concentrations using a Sachsse atomiser. This technical trial assessed the stability of the aerosol concentration using the proposed system settings prior to the start of the study. Data generated during the development/validation has not been reported but is retained in the study records.

3.4.2 Aerosol generation and exposure

A representative schematic diagram of the exposure system is given in FIGURE 1.

The test aerosol was generated into the top of a nose-only, flow through (ADG Type) exposure chamber using a Sachsse atomiser together with clean dry air in order to achieve the target aerosol concentration. The chamber was exhausted from the bottom of the chamber to ensure a dynamic flow of fresh aerosol through the chamber during exposure. Full details of the operational settings are retained in the study records.

3.4.3 Air-flow

The air-flow rate through the exposure chamber was monitored continuously and recorded hourly during the exposure. The air-flow through the chamber provided a minimum of 12 air changes/hour.

3.4.4 Exposure concentration

The aerosol concentration in the exposure chamber was measured gravimetrically at approximately half-hourly intervals throughout the exposure.

The chamber aerosol concentration was sampled on to weighted glass-fibre filters. After sampling (ca 1 L/min), the filters were re-weighed. During the preliminary study the filters were then allowed to dry at room temperature overnight in a dessicator then dried at 50°C for 2 hours and re-weighed. For the main study the filters were dried at 50°C for 144 hours and re-weighed. Using the collected weight and volume of air sampled, the gravimetric chamber aerosol concentration was calculated.

The achieved chamber aerosol concentration was calculated using the following equation:

$$\text{Aerosol concentration (mg/L)} = \frac{\text{weight of test article collected (mg)}}{\text{air flow (L/min) x duration (min)}}$$

3.4.5 Nominal concentration

The weight of test article contained within the reservoir was recorded before and after exposure and together with the volume of air passing through the chamber, the nominal aerosol concentration was determined as follows:

$$\text{Nominal concentration (mg/L)} = \frac{\text{weight of test article used (g)}}{\text{air flow (L/min) x duration (min)}} \times \left[10^3\right]$$

3.4.6 Particle size

The particle size distribution of the aerosol was measured gravimetrically using a Marple 298 Cascade Impactor by sampling the aerosol from inside the chamber at a flow rate of 2 L/min. The weight of test article collected on each weighed substrate was used to calculate the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). Three samples were collected during exposure.

3.5 Animals

3.5.1 Species, strain and supplier

A sufficient number of rats of the Crl:WI (Han) strain was obtained from Charles River UK Ltd., Margate, in order to provide two healthy animals of each sex for the preliminary feasibility exposure phase of the study and five healthy animals of each sex for the main study.

3.5.2 Specification

The animals were obtained as young adults of about 7 to 8 weeks of age on arrival.

For the preliminary study, males weighed between 226 g and 228 g, females weighed between 173 g and 207 g and the animals were approximately 9 to 10 weeks old prior to exposure on day 1.

For the main study, males weighed between 259 g and 286 g, females weighed between 193 g and 211 g and the animals were approximately 10 to 11 weeks old prior to exposure on day 1.

3.5.3 Environment

The animals were routinely kept in the following environment except for short periods of time where experimental procedures dictated otherwise. The animals were routinely housed in a single room, air conditioned to provide a minimum of 15 air changes/hour. The temperature and relative humidity ranges were 19 to 25°C and 40 to 70% respectively.

Fluorescent lighting was controlled automatically to give a cycle of 12 hours light and 12 hours dark.

The animals were housed in cages that conform to the 'Code of Practice for the Housing and Care of Animals Used in Scientific Procedures' (Home Office, London, 1989).

Preliminary study animals were housed in groups of two during the acclimatisation period and were housed singly following exposure for 3 days after which they were returned to group housing. Main study animals were housed in groups of five during the acclimatisation period. From the day prior to dosing (Day –1), each rat was individually housed in a similar cage until after completion of the day 3 observations. After this time the animals were returned to group housing.

3.5.4 Environmental enrichment

Throughout the study, animals were provided with wooden 'Aspen' chew blocks (Datesand Ltd, Manchester) in order to enrich both the environment and the welfare of the animals.

3.5.5 Diet, water and bedding

Throughout the study, the animals had access *ad libitum* to SQC Rat and Mouse Maintenance Diet No 1, Expanded, (Special Diets Services Ltd, Witham). Each batch of diet is routinely analysed for specific constituents and contaminants.

Mains water was provided *ad libitum* via water bottles. The water is periodically analysed for specific contaminants.

Fresh clean bedding was provided on a weekly basis to each cage in the form of 'Aspen' wood chips (Datesand Ltd, Manchester). The bedding is routinely analysed for specific contaminants.

No contaminants were present in diet, water or bedding at levels that might have interfered with achieving the objective of the study. Results of diet, water and bedding analyses are retained on file at Covance Laboratories Ltd, Harrogate.

3.6 Pre-experimental procedures

3.6.1 Acclimatisation and health procedures

All animals were given a clinical inspection for ill health on arrival. Preliminary study animals were acclimatised to the laboratory environment for 13 days and main study animals for 22 days. A veterinary inspection was performed prior to the start of dosing to ensure the animals suitability for the study.

During the week prior to exposure, animals were acclimatised to the restraint procedures. Each animal was placed into a restraint tube, initially for a short period, and then gradually increasing the duration of restraint on a daily basis, until the day prior to exposure. The animals were eventually acclimatised to restraint for a period equivalent to that of the actual exposure.

3.6.2 Allocation to treatment group

The animals were assigned arbitrarily from the delivery boxes and were allocated to the appropriate number of cages using a method that reduces selective bias. Individual male and female body weights were within ± 20% of, respectively, the mean male and mean female body weights of rats on the study.

3.6.3 Identification of the test system

Individual animal numbers were marked on the tails of the animals with indelible ink (in deviation from the protocol, which stated that animals would be identified by a subcutaneous electronic transponder). Individual cages were appropriately identified with study information including study number and animal numbers. This change in animal identification methodology had no adverse impact upon the study outcome.

3.7 Experimental observations

3.7.1 Clinical signs

All animals were observed daily for signs of ill health or overt toxicity. An individual record was maintained of the clinical condition of each animal. Animals were observed approximately hourly during the exposure period and for the remainder of the exposure day. The animals were observed at least once daily during the remainder of the study.

3.7.2 Routine health checks

All animals were observed at the beginning and the end of the working day to ensure that they were in good health.

3.7.3 Body weights

Individual body weights were recorded before and after exposure on day 1 and on days 2, 3, 4, 5, 6, 7, 8, 10 and 15.

3.8 Terminal Procedures

3.8.1 Necropsy and tissue preservation

An overdose of sodium pentobarbitone was administered by intraperitoneal injection and once a suitably deep plane of anaesthesia had been established, the animal was exsanguinated. A full macroscopic examination was performed under the general supervision of a pathologist and all abnormal lesions were recorded. The necropsy procedure included, but was not limited to, an inspection of the nasal cavity and respiratory tract.

Representative samples of macroscopic changes found at necropsy were retained in 10% neutral buffered formalin pending instructions from the Sponsor.

With the exception of the decedent female, the preliminary feasibility exposure phase animals were killed and discarded without further investigations.

All main study animals were subjected to a terminal necropsy and a gross macroscopic examination.

4.0 COMPUTER SYSTEMS

Scheduling	CMS (Covance Management System)
Aerosol sample analysis	Empower
Post-life data collection	Xybion
Report generation	Costar/Office 97

Version numbers of the systems will be held on file at Covance

5.0 DATA EVALUATION

The data generated in this study was evaluated on its own merit and no statistical methods have been applied to the evaluation of the data.

6.0 RESULTS

6.1 Aerosol concentration

(TABLE 1)
For the preliminary study, the mean achieved aerosol concentration over the 4 hour aerosol generation period was 4.65 mg/L. The aerosol concentration ranged from 3.42 to 5.34 mg/L during the 4 hour aerosol generation period. The average aerosol concentration delivered to animals exposed for 2 hours was 4.57 mg/L and the average delivered to animals exposed for 4 hours was 4.65 mg/L.

For the main study the mean achieved aerosol concentration over the 4 hour exposure period was 2.71 mg/L. The aerosol concentration ranged from 2.52 to 2.95 mg/L during exposure.

6.2 Nominal concentration

(TABLE 1)

The nominal aerosol concentration during the 4 hour exposure period was 29.9 mg/L for the preliminary feasibility exposure and 40.1 mg/L for the limit study.

6.3 Particle size

(TABLE 1)

The mean particle size distribution (MMAD ± GSD) during the 4 hour exposure was 3.38 µm ± 2.16 for the preliminary study and 3.98 µm ± 1.99 for the main study.

6.4 Temperature, relative humidity and oxygen concentration

(TABLE 1)

During exposure in the main study, the actual temperature and relative humidity ranges within the exposure chamber were 20.0 to 20.7°C and 11.2 to 14.0%, respectively. The relative humidity values were outside the ranges stated in the protocol (30 to 70 %), however, this was considered to be due to the nature of the test article and in the opinion of the Study Director, to have had no adverse effect on the outcome of the study. Oxygen concentration ranged from 20.6% to 21.0% (v/v) during animal exposure. The data for the preliminary feasibility exposure has not been reported.

6.5 Mortality

Mortality occurred in both the preliminary and the main study phases.

In the preliminary study, the female that was exposed for 4 hours was observed as having a decreased breathing rate throughout the exposure and was comatose immediately after dosing and as a consequence the animal was sacrificed on the grounds of animal welfare.

In the main study, one female was observed as having decreased activity and a decreased breathing rate during exposure. Observations made post dosing included decreased breathing, cyanosis, hunched posture, hypothermia, closed eyes, piloerection, prone position and rales. The animal was found dead approximately 4 hours after the end of the exposure period.

6.6 Clinical signs

(APPENDIX 2)

Clinical signs from the female sacrificed after the preliminary feasibility exposure and the female found dead in the main study are discussed in the mortality section of the report and are not discussed here.

6.6.1 Preliminary study

In the 2 hour preliminary feasibility exposure, observations noted up to 5 hours post dosing in one and/or both animals included abnormal gait, reduced breathing rate, hunched posture, lethargy, closed eyes, piloerection and tremor. Reduced breathing rate was also noted during exposure in both animals. Lethargy, rhinorrhoea and vocalisation were each observed on up to 2 occasions in the male up to day 6. Clinical signs were noted up to 5 hours post dosing in the surviving animal that was exposed for 4 hours which included abnormal gait, reduced breathing rate (also noted during exposure), hunched posture, hypothermia, lethargy, closed eyes, piloerection, sore mouth and chin and tremor. With the exception of reduced breathing rate, hypothermia, tremor and sore mouth/chin, all other signs were noted on one or more occasion from day 2 up to the day of necropsy.

6.6.2 Main study

On one or more occasions during dosing and on one or more occasions during the 5 hour observation period post dosing, reduced breathing rate and decreased activity were noted in all animals.

Post-exposure observations were noted in the majority of animals on the day of dosing and included abnormal gait, hunched posture and closed eyes. In addition, clinical signs observed in two or more females included gasping, hypothermia, piloerection, tremor (on one or more occasion), cyanosis (noted on one occasion in one female) and one female was observed as being prone on one occasion. Rales (3 males) and vocalisation (1 male) were also noted post exposure.

Post-exposure clinical signs observed from day 2 onwards included rales (1 male and 1 female), vocalisation (1 male and 4 females), decreased activity (1 male and 2 females), hunched posture (all females), piloerection (2 females), cyanosis (1 female) and rhinorrhea (1 female). The clinical signs observed were sporadic and of low incidence and, with the exception of rales in the female (day 7 and 9) and rhinorrhea in the female (day 7), were present between days 2 and 5 only.

Other clinical observations that were noted in the majority of animals included wet fur, unkempt appearance, stained head/snout and, in a few animals, hair loss. These signs are considered to have resulted from the method of exposure and/or restraint used in inhalation studies or to be incidental and were not considered to be related to treatment with the test article.

6.7 Body weight

(APPENDIX 3, APPENDIX 4)

All animals lost weight during the 4 hour exposure period in both the preliminary feasibility exposure phase and the main study. This loss of body weight was considered to be due to the removal of food and water and/or the method of restraint used during exposure in inhalation studies and not treatment related.

In the preliminary study, all surviving animals had regained their pre-dose weight by day 6.

In the main study, on day 2, the body weight of one male was lower than its day 1 post exposure weight and one female lost weight for 2 consecutive days (days 2 and 3) when compared to the day 1 post exposure body weight. However, all males had returned to their pre-dose body weight by day 4 and surviving females by day 5.

6.8 Macroscopic findings

(APPENDIX 5)

All lobes of the lung were described as moderately red with a few dark areas (1-2 mm in diameter) in the animal that was sacrificed during the preliminary study.

No adverse treatment related effects were noted at necropsy in any animal from the main study.

7.0 DISCUSSION

In the preliminary study, the 4 hour exposure resulted in the death of 1 female.

In the main study, administration of the test article via the inhalation route for 4 hours at an aerosol concentration of 2.71 mg/L resulted in the death of 1 female. However, in all other

animals, effects were generally limited to clinical signs, predominantly observed on the day of exposure, although some did persist for up to 5 days post exposure coupled with a transient loss in body weight.

8.0 CONCLUSIONS

A single 4 hour (nose only) inhalation exposure to SYN520453 EC (A15149AC) at a mean aerosol concentration of 2.71 mg/L resulted in the death of one female. Clinical observations of limited incidence and severity and a transient loss in body weight were the only significant effects observed post dosing in all other surviving animals. All surviving animals had significantly improved the day following exposure and continued to do so throughout the 14 day observation phase of the study.

In conclusion, following a single 4 hour inhalation (nose only) exposure to SYN520453 EC (A15149AC), the LC50 can be considered greater than 2.71 mg/L.

TABLES SECTION

TABLE 1 Aerosol Concentration

Preliminary study

Time sample taken (mins)	Aerosol concentration (mg/L)	Particle size distribution	
		MMAD (µm)	GSD
37	5.34		
64	3.42		
99	4.88		
120		2.70	2.44
124	4.64		
153	4.59		
160		3.11	2.19
194	4.64		
220	4.78		
223		4.32	1.84
250	4.92		
Mean	4.65	3.38	2.16
SD	0.552	-	-
CV	12	-	-

MMAD = Mass median aerodynamic diameter
GSD = Geometric standard deviation

TABLE 1 Aerosol Concentration (cont.)

Main study

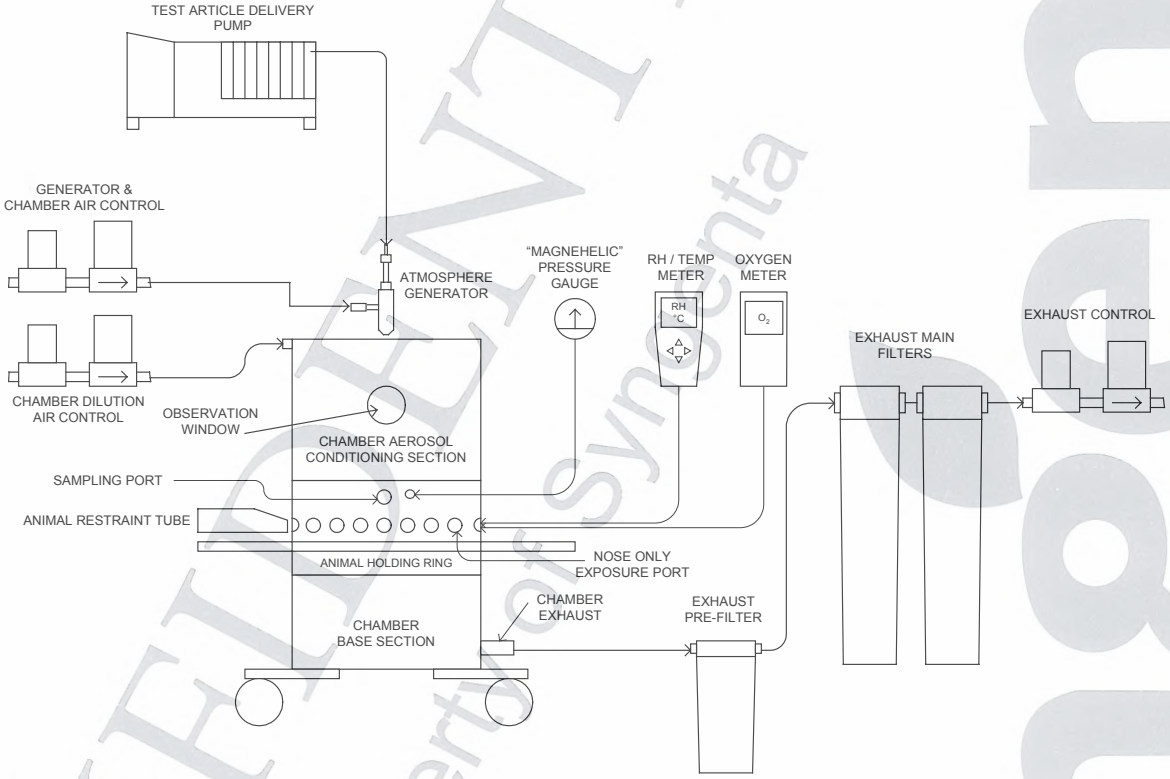
Time sample taken (mins)	Aerosol concentration (gravimetric) (mg/L)	Particle size MMAD (µm)	Particle size GSD	Generator Air flow (L/min)	Air flow (L/min) Dilution	Air flow (L/min) Exhaust	Temperature (°C)	Humidity (% RH)	Oxygen concentration (% v/v)
0#				10.0	4.1	14.1	20.0	42.2	21.0
31	2.65								
60	2.68								
62				10.0	4.1	14.1	20.7	14.0	20.6
80		4.36	1.90						
87	2.52								
122				10.1	4.1	14.1	20.5	12.1	20.6
125	2.95								
157		4.61	1.77						
158	*								
180	2.70								
183				10.1	4.1	14.1	20.5	12.6	20.6
216		2.98	2.30						
217	2.53								
243				10.1	4.1	14.1	20.5	11.3	20.6
245	2.88								
255				10.1	4.1	14.2	20.5	11.2	20.9
Mean	2.71	3.98	1.99	-	-	-	20.5	12.2	20.7
SD	0.153						0.089	1.14	0.134
CV%	6						-	-	-

Values excluded from mean as taken in the stabilisation period
* Sample lost during drying period
MMAD = Mass median aerodynamic diameter
GSD = Geometric standard deviation

FIGURES SECTION

FIGURE 1 Schematic Representation of Exposure System

This diagram differs from the generalised schematic diagram in the protocol. The diagram shows in detail the system layout and specific generator that was used on this study.



APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

GLP Testing Facility JH
Analytical Development & Product Chemistry

Jealott's Hill International Research Centre,
Bracknell, Berkshire
RG42 6EY
United Kingdom

Certificate of Analysis

Formulated Material

SYN520453(125 g/L) EC

Batch Identification	**J8092/056**
Design Code	**A15149AC**
Other Product Code(s)	-

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredient(s)***	**confirmed**
– **Content of SYN520453 ***	**13.4% w/w corresponding to 128 g/L.**
	4.1% w/w SYN534968 corresponding to 39 g/L)
	9.3% w/w SYN534969 corresponding to 89 g/L))
Methodology used for Characterisation / Reanalysis	Capillary GC

The Active Ingredient(s) content is within the FAO limits.

Physical Analysis

– **Appearance**	**A uniform mobile clear brown liquid**
– **Density ***	**0.956 g/cm^3**

Stability:

– **Storage Temperature**	**0 < t < 40°C, keep away from direct sunlight**
– **Expiry date**	**December 2009 (Temperate and sub-tropical climates)**

The stability of this test substance will be controlled by reanalysis of material held in the inventory at Syngenta Crop Protection Muenchwilen AG at the appropriate time.

This Certificate of Analysis summarizes data which originates either from a single study or from several individual studies. Tests marked with an asterisk (*) have been conducted under GLP protocol. Raw data, documentation, study plans and reports pertaining to this/these study/studies are stored under the study number(s) referenced below within the archives of the GLP Testing Facility JH at Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY.

Study Number(s):	08AS001, NS00979
IDS Report Number(s):	10343850
Supplementary Information:	Initial characterisation January 2008.
	Where applicable, spray tank dilutions should be used within one working day.
	Handling of the material will follow the guidelines within the appropriate MSDS

Authorisation:

P. Clarke — P M Clarke

15 Jan 2008 — Date

APPENDIX 2 Individual Clinical Signs

Preliminary study
Day 1

Animal number /sex	Clinical sign	Sign noted during exposure (hours):					Sign noted post-exposure (hours):				
		Pre-exposure	0-1	1-2	2-3	3-4	0-1	1-2	2-3	3-4	4-5
11M	Abnormal gait						+				
	Bradypnoea		+	+			+	+			
	Hunched posture						+	+	+	+	+
	Lethargy								+	+	+
	Palpebral closure						+				
	Piloerection						+	+			
	Unkempt								+	+	+
	Wet fur						+	+			
13M	Abnormal gait						+	+	+	+	+
	Bradypnoea		+	+	+	+	+	+			
	Hunched posture						+	+	+	+	+
	Hypothermia						+	+			
	Lethargy						+	+	+	+	+
	Palpebral closure						+	+	+		
	Piloerection						+	+	+	+	+
	Sore mouth/chin						+	+	+	+	+
	Tremor								+	+	
	Unkempt								+	+	+
	Wet fur			+	+	+	+	+			
12F	Abnormal gait						+	+	+	+	+
	Bradypnoea		+	+			+	+			
	Hunched posture						+	+	+	+	+
	Palpebral closure						+				
	Piloerection						+	+			
	Tremor								+		
	Unkempt								+	+	+
	Wet fur			+			+	+			
14F	Bradypnoea		+	+	+	+	+				
	Wet fur			+	+	+	+				
	Comotose						+				
	Killed *in extremis*						+				

\+ sign present

APPENDIX 2 Individual Clinical Signs (cont.)

Preliminary study
Days 2-10

Animal number /sex	Clinical sign	Observation seen on Day: 2	3	4	5	6	7	8	9	10
11M	Lethargy	+	+							
	Rhinorrhoea			+						
	Snout stained		+							
	Unkempt	+								
	Vocalisation				+	+				
13M	Abnormal gait			+	+					
	Hunched posture	+	+	+	+	+	+	+		
	Lethargy	+	+	+	+	+	+	+	+	+
	Palpebral closure			+						
	Piloerection						+	+	+	+
	Rhinorrhoea		+							
	Stained head	+	+							
	Unkempt	+	+							
	Vocalisation		+							
12F	Hair loss - dorsal		+	+	+	+	+	+	+	+
	Stained head	+	+							
	Staining - dorsal								+	+
	Unkempt	+	+		+					

\+ sign present

APPENDIX 2 Individual Clinical Signs (cont.)

Main study
Day 1

Animal number /sex	Clinical sign	Sign noted during exposure (hours): Pre-exposure	0-1	1-2	2-3	3-4	Sign noted post-exposure (hours): 0-1	1-2	2-3	3-4	4-5
1M	Abnormal gait								+		
	Bradypnoea		+	+	+	+	+				
	Decreased activity				+		+	+			
	Hunched posture							+	+	+	
	Snout stained							+			
	Unkempt							+	+	+	+
	Vocalisation						+				
	Wet fur			+	+	+	+				
2M	Abnormal gait								+		
	Bradypnoea		+	+	+	+	+				
	Decreased activity				+	+	+	+	+	+	+
	Hunched posture							+	+		
	Palpebral closure							+	+	+	
	Snout stained			+			+	+			+
	Unkempt							+	+	+	+
	Wet fur				+	+	+				
3M	Bradypnoea		+	+	+	+	+				
	Decreased activity				+	+	+	+	+		+
	Hunched posture							+			
	Palpebral closure							+			
	Rales						+	+			+
	Snout stained				+			+			
	Unkempt							+	+	+	+
	Wet fur			+	+	+	+				
4M	Abnormal gait								+	+	+
	Bradypnoea		+	+	+	+	+				
	Decreased activity				+	+	+	+	+	+	+
	Hunched posture							+			
	Rales							+			
	Stained head						+	+			
	Unkempt							+	+	+	+
	Wet fur			+	+	+	+				
5M	Bradypnoea		+	+	+	+	+				
	Decreased activity				+	+	+				
	Rales						+				
	Snout stained			+					+	+	
	Unkempt							+	+	+	+
	Wet fur				+	+	+				

+ sign present

APPENDIX 2 Individual Clinical Signs (cont.)

Main study
Day 1

Animal number /sex	Clinical sign	Sign noted during exposure (hours):					Sign noted post-exposure (hours):				
		Pre-exposure	0-1	1-2	2-3	3-4	0-1	1-2	2-3	3-4	4-5
6F	Abnormal gait						+	+	+	+	+
	Bradypnoea		+	+	+	+	+				
	Decreased activity				+	+	+	+		+	+
	Gasping								+		
	Hunched posture						+	+	+		+
	Hypothermia						+				
	Palpebral closure									+	
	Piloerection						+	+	+		
	Snout stained							+			
	Unkempt								+	+	+
	Wet fur				+	+	+	+			
7F#	Bradypnoea		+	+	+	+	+	+			
	Cyanosis							+	+		
	Decreased activity				+	+					
	Hunched posture						+				
	Hypothermia						+	+	+		
	Palpebral closure						+	+	+		
	Piloerection						+				
	Prone						+	+	+		
	Rales						+	+	+		
	Unkempt								+		
	Wet fur			+	+	+	+	+			
8F	Abnormal gait						+	+			
	Bradypnoea		+	+	+	+	+	+			
	Cyanosis						+	+	+	+	+
	Decreased activity				+	+	+	+	+	+	+
	Gasping							+	+		
	Hunched posture						+	+	+	+	+
	Palpebral closure						+	+			+
	Piloerection						+	+	+	+	+
	Snout stained						+				
	Unkempt							+	+	+	+
	Wet fur			+	+	+	+	+			

\+ sign present
\# animal dead at 3-4 hours observation

APPENDIX 2 Individual Clinical Signs (cont.)

Main study
Day 1

Animal number /sex	Clinical sign	Sign noted during exposure (hours):					Sign noted post-exposure (hours):				
		Pre-exposure	0-1	1-2	2-3	3-4	0-1	1-2	2-3	3-4	4-5
9F	Abnormal gait						+	+	+	+	+
	Bradypnoea		+	+	+	+	+	+			
	Decreased activity				+	+	+	+	+	+	+
	Hair loss - dorsal	+	+								
	Hunched posture						+	+	+	+	+
	Hypothermia						+				
	Palpebral closure						+	+	+	+	
	Piloerection						+	+	+	+	
	Tremor								+	+	+
	Unkempt							+			+
	Wet fur			+	+	+	+	+			
10F	Abnormal gait							+	+		+
	Bradypnoea		+	+	+	+	+	+	+		
	Decreased activity				+	+	+	+	+		+
	Hunched posture						+	+	+	+	+
	Hypothermia						+				
	Palpebral closure						+	+	+	+	+
	Piloerection						+	+	+	+	
	Prone									+	
	Tremor									+	
	Unkempt							+	+	+	+
	Wet fur			+	+	+	+				

+ sign present
# animal dead at 3-4 hours observation

APPENDIX 2 Individual Clinical Signs (cont.)

Main study
Days 2-15

Animal number /sex	Clinical sign	Observation seen on day: 2	3	4	5	6	7	8	9	10	11	12	13	14	15
1M	Unkempt	+													
2M	Unkempt	+													
3M	Rales	+	+												
	Unkempt	+	+												
	Vocalisation	+													
4M	Decreased activity	+	+	+	+										
	Unkempt	+	+												
6F	Hair loss - dorsal					+	+	+	+	+	+	+		+	+
	Hunched posture				+										
	Piloerection		+												
	Snout stained	+													
	Unkempt	+	+												
	Vocalisation	+													
8F	Cyanosis	+													
	Hair loss - head					+	+								
	Hunched posture		+												
	Rales						+		+						
	Rhinorrhoea						+								
	Snout stained						+								
	Stained head	+	+												
	Unkempt	+	+												
	Vocalisation		+												
9F	Decreased activity		+		+										
	Hair loss - dorsal		+	+	+	+	+	+	+						
	Hunched posture		+												
	Unkempt	+	+												
	Vocalisation	+	+	+	+										
10F	Decreased activity		+	+	+										
	Hair loss - dorsal					+	+	+	+	+	+	+			
	Hunched posture		+		+										
	Piloerection				+										
	Snout stained	+													
	Unkempt	+	+												
	Vocalisation	+	+	+	+										

Any other animal, any other day - no signs present
+ sign present

APPENDIX 3 Individual and Group Mean Body Weights

Preliminary study

Group and sex	Animal number	Pre-exposure body weight (g)	Body weight (g) post-exposure	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
2M	11	226	216	215	221	224	231	246	243	247	247	257
	13	228	219	207	215	218	224	232	233	226	229	236
2F	12	173	168	175	179	178	178	185	189	186	180	188
	14	207	197	#	#	#	#	#	#	#	#	#

animal dead

Main study

Group and sex	Animal number	Pre-exposure body weight (g)	Body weight (g) post-exposure	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 15
1M	1	286	269	277	287	289	298	299	295	306	310	323
	2	284	272	269	276	286	295	301	297	304	314	338
	3	282	268	270	272	286	292	297	296	297	307	332
	4	259	242	246	253	258	263	268	259	268	273	287
	5	263	255	257	258	265	274	276	270	277	282	301
	Mean	**275**	**261**	**264**	**269**	**277**	**284**	**288**	**283**	**290**	**297**	**316**
	SD	**12.8**	**12.6**	**12.3**	**13.8**	**14.2**	**15.2**	**15.1**	**17.7**	**17.0**	**18.4**	**21.5**
1F	6	197	189	192	189	194	200	199	201	204	204	214
	7	210	205	#	#	#	#	#	#	#	#	#
	8	196	188	189	188	194	199	195	195	199	206	215
	9	211	201	203	208	218	220	215	220	224	219	231
	10	193	191	185	180	186	189	191	193	202	202	214
	Mean	**201**	**195**	**192**	**191**	**198**	**202**	**200**	**202**	**207**	**208**	**219**
	SD	**8.4**	**7.7**	**7.7**	**11.9**	**13.9**	**13.0**	**10.5**	**12.3**	**11.4**	**7.7**	**8.3**

animal dead

APPENDIX 4 Individual and Group Mean Body Weight Gains

Preliminary study

Group and sex	Animal number	Pre-exposure body weight (g)	Body weight gain relative to pre-exposure (g)									
			post-exposure	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
2M	11	226	-10	-11	-5	-2	5	20	17	21	21	31
	13	228	-9	-21	-13	-10	-4	4	5	-2	1	8
2F	12	173	-5	2	6	5	5	12	16	13	7	15
	14	207	-10	#	#	#	#	#	#	#	#	#

animal dead

Main study

Group and sex	Animal number	Pre-exposure body weight (g)	Body weight gain relative to pre-exposure (g)									
			post-exposure	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 15
1M	1	286	-17	-9	1	3	12	13	9	20	24	37
	2	284	-12	-15	-8	2	11	17	13	20	30	54
	3	282	-14	-12	-10	4	10	15	14	15	25	50
	4	259	-17	-13	-6	-1	4	9	0	9	14	28
	5	263	-8	-6	-5	2	11	13	7	14	19	38
	Mean	**275**	**-14**	**-11**	**-6**	**2**	**10**	**13**	**9**	**16**	**22**	**41**
	SD	**12.8**	**3.8**	**3.5**	**4.2**	**1.9**	**3.2**	**3.0**	**5.6**	**4.6**	**6.1**	**10.5**
1F	6	197	-8	-5	-8	-3	3	2	4	7	7	17
	7	210	-5	#	#	#	#	#	#	#	#	#
	8	196	-8	-7	-8	-2	3	-1	-1	3	10	19
	9	211	-10	-8	-3	7	9	4	9	13	8	20
	10	193	-2	-8	-13	-7	-4	-2	0	9	9	21
	Mean	**201**	**-7**	**-7**	**-8**	**-1**	**3**	**1**	**3**	**8**	**9**	**19**
	SD	**8.4**	**3.1**	**1.4**	**4.1**	**5.9**	**5.3**	**2.8**	**4.5**	**4.2**	**1.3**	**1.7**

animal dead

APPENDIX 5 Individual Macroscopic Data

COVANCE
HARROGATE, ENGLAND

PRINTED: 26-AUG-08
PAGE: 1

STUDY NUMBER: 2379006

ANIMAL NUMBER: 000001 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 323.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

ANIMAL NUMBER: 000002 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 338.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

ANIMAL NUMBER: 000003 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 332.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

ANIMAL NUMBER: 000004 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 287.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

ANIMAL NUMBER: 000005 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 301.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

ANIMAL NUMBER: 000006 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 214.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

Appendix 5

Individual animal macroscopic data

ANIMAL NUMBER: 000007 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: UNSCHEDULED (M)
DATE OF DEATH: 02/20/08 STUDY DAY OF DEATH: 1 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 205.0 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
KIDNEY	-PELVIC DILATATION, MODERATE	-LEFT, MINIMAL, RIGHT

Appendix 5

Individual animal macroscopic data

COVANCE
HARROGATE, ENGLAND

PRINTED: 26-AUG-08
PAGE: 8

STUDY NUMBER: 2379006

ANIMAL NUMBER: 000008 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 215.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

Appendix 5

Individual animal macroscopic data

COVANCE
HARROGATE, ENGLAND

PRINTED: 26-AUG-08
PAGE: 9

STUDY NUMBER: 2379006

ANIMAL NUMBER: 000009 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 231.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

ANIMAL NUMBER: 000010 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 03/05/08 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 214.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
ANIMAL	-NOT REMARKABLE	

APPENDIX 6 Good Laboratory Practice Statement

This Appendix consists of two pages, including this one

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

Covance Laboratories Ltd
Otley Road
Harrogate
North Yorkshire
HG3 1PY

Covance Clinical Research Unit Ltd
Springfield House
Hyde Street
Leeds
West Yorkshire
LS2 9LH

TEST TYPE

Analytical Chemistry
Ecosystems
Environmental Fate
Environmental Toxicity
Mutagenicity
Phys/chem Testing
Toxicology
Biosafety Testing

TK Data Analysis

DATE OF INSPECTION

3rd – 5th December 2007

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.

31/1/08

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

MHRA