REGISTRATION REPORT

Part B
Section 3: Mammalian Toxicity

Detailed summary of the risk assessment

CLOSER (GF-2626)

120 g/L Sulfoxaflor

All Zones

Zonal Rapporteur Member State: France

(Greenhouse G)

CORE ASSESSMENT

Applicant: DOW AgroSciences

Date: October 2017

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TOXICOLOGICAL STUDIES

Sulfoxaflor is a new active substance which is listed in Annex I of Directive 91/414. Ireland (Pesticide Registration and Control Division, PRCD) is the rapporteur Member State (RMS). A dossier for the active substance was submitted by Dow AgroSciences, under Regulation (EC) 1107/2009, to the RMS in July 2011. The evaluation of the dossier and review report (i.e. full report) including an outline of the technical questions was finalised May 29th, 2015. A Commission decision following Annex I inclusion was published August 18th, 2015 (Reg. (EU) 2015/1295).

The active substance submission followed a zonal approach where the evaluation was shared by four Member States participating under a work-share umbrella as follows: Ireland - RMS, lead reviewer for the sections Toxicology, Residues and Metabolism along with coordination of the work-share project. France: Lead reviewer for the sections Identity/Physical-Chemical properties, Methods of Analysis and Efficacy/Biology. Poland: Lead reviewer for the section Environmental Fate. Czech Republic: Lead reviewer for the section Ecotoxicology.

The Draft Assessment Report (DAR) on sulfoxaflor was finalised and distributed by Ireland in November 2012, with a recommendation for approval of the active substance according to Regulation (EC) 1107/2009. The EFSA peer review process was conducted and the EFSA conclusion was published in May 2014.

Dow AgroSciences submitted an EU MRL dossier to the RMS, Ireland, in April 2011. The EU MRL evaluation was integrated with the active substance evaluation under 1107/2009. The adoption of MRL/Import tolerances was therefore aligned with the same timing as that of the active substance approval.

There were two representative formulations for the EU active approval submission. These were GF-2372 (500 g/kg WG) and GF-2626 (120 g/L SC).

This current submission is for one of these two formulations, GF-2626. This is the first submission for authorisation of plant protection products containing sulfoxaflor in EU Member States. The proposed zonal RMS for Central Zone and Southern Zone are Ireland and France respectively.

Where appropriate, this document refers to the conclusions of the EFSA review report (EFSA Journal 2014; 12(5):3692) of sulfoxaflor. This will be where: the active substance data are relied upon in the risk assessment of the formulation; or when the EU review concluded that additional data/information should be considered at national registration.

This Part B document only reviews data (active substance or plant protection product) and additional information that has not previously been considered within the EU review process, as part of the active approval decision. Studies for the active substance which have already been evaluated during the approval process are not summarised. New active substance data are only included if they are considered essential for the evaluation and a full study summary is provided.

Details of the active substance, the active approval Regulation and the Commission Review Report are provided in Table #-1.

Table #-1: Details for the active substance

Active Substance	Approval Regulation	Commission Review Report	EFSA Scientific Report
Sulfoxaflor	Regulation (EU) 2015/129 (18 August 2015)	SANTE/10665/2015 rev 2, 29 May 2015	EFSA Journal 2014; 12(5):3692

The review report for sulfoxaflor (SANTE/10665/2015 rev 2, 29 May 2015) is considered to provide the relevant review information or a reference to where such information as considered appropriate for this application can be found. The following table provides the EU endpoints to be used in the evaluation.

Active substance	Acceptable Daily Intake (ADI) mg/kg bw/d	Acute reference dose (ARfD) mg/kg bw	Acceptable operator exposure level (AOEL) mg/kg bw/d	Classification
Sulfoxaflor approved	**0.04 (2-years rat oral study, SF 100)**	**0.25 (90-day rat oral study, 90-day dog study and 1-year dog study, SF 100)**	**0.06 (Rat acute neurotoxicity study, SF 100)**	Cat4 H302 Cat1 H400 Cat1 H410
Origin	UE, 2015	UE, 2015	UE, 2015	CEE

The active approval Regulation for sulfoxaflor provides specific provisions which need to be considered by the applicant in the preparation of their product submissions and by the Member States prior to granting an authorisation:

For sulfoxaflor, Member States shall pay particular attention to [to be defined].

These concerns have been addressed within the current submission.

NOTE
Sulfoxaflor is also referred to as manufacture's code numbers X11422208, XR-208, XDE-208 and DE-208 in the section.

IIIA 7.1 Acute toxicity

Acute toxicity studies have not been conducted on GF-2626 on the basis of animal welfare. It is possible to bridge from a similar formulation, GF-2032, which is a suspension concentrate (SC) containing 240 g/L sulfoxaflor. The nominal compositions of GF-2626 and GF-2032 could be found in part C.

The nominal compositions of GF-2626 and GF-2032 are considered similar enough to allow GF-2032 acute toxicity data to be used as a surrogate in the absence of GF-2626. Because the concentration of sulfoxaflor in GF-2032 is double that in GF-2626, it can be considered a worst-case scenario.

Overall Summary

Table 7.1-1: GF-2032 Acute toxicity data

Parameter	Species (sex)	Result	EU Classification	Reference
Acute oral	Rat/ Fischer 344 (both)	LD_{50} >5000 mg/kg	None	[redacted] 2008a
Acute dermal	Rat/ Fischer 344 (both)	LD_{50} >5000 mg/kg	None	[redacted] 2008a
Acute inhalation	Rat/ Fischer 344 (both)	LC_{50} >2.21 mg/L	None	[redacted], 2012
Skin irritation	Rabbit/ NZW (female)	Minimal Irritation	None	[redacted] 2008b
Eye irritation	Rabbit/ NZW (female)	Slight Irritation	None	[redacted] 2008c
Skin sensitisation	Mouse/ CBA/J (female)	No Sensitization	None	[redacted] 2008

Overall Conclusions: IIIA 7.1 Acute toxicity

GF-2032 exhibited low acute oral and dermal toxicity in the male and female rat with LD50 values > 5000 mg/kg bw. GF-2032 exhibited low acute inhalation toxicity in the male and female rat with an LC50 value > 2.21 mg/L. Skin and eye irritation studies in the NZW rabbit showed minimal to slight irritation and all effects resolved by 72 hours. No skin sensitization potential was evident in a mouse local lymph node assay. These results should be viewed as a worse-case surrogate in the absence of direct GF-2626 data.

Classification in accordance with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, as follows:

- Unclassified

The package should be labeled "EUH208: Contains 1,2-benzisothiazol-3(2H)-one (CAS No. 2634-33-5). May produce an allergic reaction"

IIIA 7.1.1 **Acute oral toxicity**

Report	KIIIA1 7.1.1/01, [redacted] (2008)
Title	Acute Oral Acute Toxic Class Method in Rats. [redacted] February 25, 2009, Unpublished
Document No	EPSL Study Number 26524, Dow Study Number 080049
Guideline	Acute Oral Toxicity – Rat; OPPTS 870.1100; OECD 423
GLP	Yes

EXECUTIVE SUMMARY: An acute oral toxicity test (Acute Toxic Class Method) was conducted with Fischer 344 rats to determine the potential for GF-2032 to produce toxicity from a single dose via the oral route.

An initial dose of 5,000 mg/kg was administered to one healthy female rat by oral gavage. Due to the absence of mortality in this animal, three additional females received the same dose level, simultaneously. Since these animals survived, four males received a 5,000 mg/kg dose simultaneously. All animals were observed for mortality, signs of gross toxicity, and behavioural changes at least once daily for 14 days after dosing. Body weights were recorded prior to administration, and on Days 7 and 14 (termination) following dosing. Necropsies were performed on all animals at sacrifice.

All animals survived test substance administration and gained body weight during the study. Apart from ano-genital staining noted for one female and three males on Days 1 and/or 2 after dosing, all animals appeared active and healthy over the course of the study. There were no other signs of gross toxicity, adverse clinical signs, or abnormal behavior. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

Under the conditions of this study, the acute oral LD_{50} of GF-2032 was greater than 5,000

mg/kg of body weight in female and male rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1.	**Test Material:**	GF-2032
	Description:	Liquid suspension, tan
	Lot #:	E2198-52
	Test Substance Number	018439-0011
	Purity:	242 g/L XDE-208

2. Vehicle and/or positive control: None

3.	**Test animals:**		
	Species:	Rat	
	Strain:	Fischer 344	
	Age/weight at dosing:	9-10 weeks/males: 118-135 and females: 175-190 grams at experimental start	
	Source:	[redacted]	
	Housing:	Singly housed in suspended stainless steel caging with mesh floors	
	Diet:	Purina Certified Rodent Diet, PMI #5002 *ad libitum*	
	Water:	Filtered tap water *ad libitum*	
	Environmental conditions:	**Temperature:** **Humidity:** **Air changes:** **Photoperiod:**	19-21ºC 15-60%RH 19/hr 12 hrs dark/12 hrs light
	Acclimation period:	8-13 days	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: January 14, 2009 End: February 2, 2009

2. Animal assignment and treatment - Animals were assigned to the test group as noted in Table 7.1.1/1-1. Following an overnight fast, rats were given a single dose of GF-2032 by gavage then observed (first several hours post-dosing and at least once daily thereafter) and weighed prior to test substance administration (initial) and again on Days 7 and 14 (termination) following dosing. All rats were euthanized via CO_2 inhalation at the end of the 14-day observation period. Gross necropsies were performed on all animals. The external surface of the body and all orifices, tissues, and organs of the thoracic and abdominal cavities were examined.

II. RESULTS AND DISCUSSION:

A. Mortality is given below in Table 7.1.1/1-1.

Table 7.1.1/1-1. Doses, mortality/animals treated

Dose (mg/kg bw)	Females	Males
5,000	0/4	0/4

B. Clinical observations - All animals survived test substance administration. Apart from ano-genital staining noted for one female and three males on Days 1 and/or 2 after dosing, all animals appeared active and healthy over the course of the study. There were no other signs of gross toxicity, adverse clinical signs, or abnormal behavior.

C. Body Weight - All animals gained body weight throughout the 14-day observation period.

D. Necropsy - No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

E. Applicant's Conclusions: Under the conditions of this study, the acute oral LD_{50} of GF-2032 was greater than 5,000 mg/kg of body weight in female and male rats.

IIIA1 7.1.1/01 Study comments	The study is acceptable.
IIIA1 7.1.1/01 Agreed endpoint	Acute oral LD_{50} > 5000 mg/kg bw in the rat. According to the classification criteria of **CLP Regulation (EC) No. 1272/2008**, the test material **does not require classification** for acute oral toxicity.

IIIA 7.1.2 **Acute percutaneous (dermal) toxicity**

Report	KIIIA1 7.1.2/01 [redacted] 2008a)
Title	Acute Dermal Toxicity in Rats. [redacted] January 14, 2009
Document No	PSL Study Number 26459, Dow Study Number 080050
Guideline	Acute Dermal Toxicity - Rat; OPPTS 870.1200; OECD 402
GLP	Yes

EXECUTIVE SUMMARY: An acute dermal toxicity test was conducted with Fischer 344 rats to determine the potential for GF-2032 to produce toxicity from a single topical application.

Five thousand milligrams of the test substance per kilogram of body weight was applied to the skin of ten healthy rats for 24 hours. The animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days. Body weights were recorded prior to application and again on Days 7 and 14 (termination). Necropsies were performed on all animals at sacrifice.

All animals survived, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, dermal irritation, adverse clinical signs, or abnormal behavior. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

Under the conditions of this study, the single dose acute dermal LD_{50} of the test substance was

greater than 5,000 mg/kg of body weight in male and female rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1.	**Test Material:**	GF-2032
	Description:	Liquid suspension, Tan
	Lot #:	E2198-52
	Test Substance Number	018439-0011
	Purity:	XDE-208 – 22.0 wt%

2. Vehicle and/or positive control: None

3.	**Test animals:**		
	Species:	Rat	
	Strain:	Fischer 344	
	Age/weight at dosing:	11 weeks/ males: 220-228 grams and females: 128-136 grams at experimental start	
	Source:	[redacted]	
	Housing:	Singly housed in suspended stainless steel caging with mesh floors	
	Diet:	Purina Certified Rodent Diet, PMI #5002 *ad libitum*	
	Water:	Filtered tap water *ad libitum*	
	Environmental conditions:	**Temperature:** **Humidity:** **Air changes/Hour:** **Photoperiod:**	18-21ºC 30-67%RH 19/hr 12 hrs dark/12 hrs light
	Acclimation period:	19 days	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: November 18, 2008 End: December 2, 2008

2. Animal assignment and treatment - Animals were assigned to the test groups noted in Table 7.1.2/1-1. On the day prior to application, a group of animals was prepared by clipping the dorsal area and the trunk. Five thousand mg/kg of body weight of the test substance was applied evenly over a dose area of approximately 2 inches x 3 inches (approximately 10% of the body surface) on each animal and covered with a 2-inch x 3-inch, 4-ply gauze pad. The gauze pad and entire trunk of each animal were then wrapped with 3-inch Durapore tape to avoid dislocation of the pad and to minimize loss of the test substance. The rats were then returned to their designated cages. The day of application was considered Day 0 of the study. All animals were observed during the first several hours after application and at least once daily thereafter for 14 days and weighed prior to test substance application (initial) and again

on Days 7 and 14 (termination). All rats were euthanized via CO_2 inhalation at the end of the 14-day observation period. Gross necropsies were performed on all animals. The external surface of the body and all orifices, tissues, and organs of the thoracic and abdominal cavities were examined.

3. Statistics – Not applicable.

II. RESULTS AND DISCUSSION:

A. Mortality is given below in (Table 7.1.2/1-1).

Table 7.1.2/1-1. Doses, mortality/animals treated

Dose (mg/kg bw)	Males	Females	Combined
5,000	0/5	0/5	0/10

B. Clinical observations – All animals survived and appeared active and healthy during the study. There were no signs of gross toxicity, dermal irritation, adverse clinical signs, or abnormal behaviour

C. Body Weight – All animals gained body weight over the entire 14 day observation period.

D. Necropsy - No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

E. Applicant's Conclusions:

The dermal LD_{50} of GF-2032 was greater than 5,000 mg/kg of body weight in male and female rats.

IIIA1 7.1.2/01 Study comments	The study is acceptable.
IIIA1 7.1.2/01 Agreed endpoint	Acute dermal LD_{50} > 5000 mg/kg bw in the rat. According to the classification criteria of **CLP Regulation (EC) No. 1272/2008**, the test material **does not require classification** for acute dermal toxicity.

IIIA 7.1.3 **Acute inhalation toxicity**

Report	[redacted]
Title	[redacted]

Document No	[redacted]
Guideline	[redacted]
GLP	[redacted]

STUDY TYPE: Acute Inhalation Toxicity – (rats); OPPTS 870.1300; OECD 403; JMAFF (2000), EEC (2008).

TEST MATERIAL (PURITY): GF-2032 (A formulation containing N-(methyloxido(1-(6-(trifluoromethyl)-3-pyridinyl)ethyl)-λ^4-sulfanylidene)-cyanamide (XDE-208 or Sulfoxaflor)) (21.7% by weight Sulfoxaflor (a.i.)).

SYNONYMS: None.

CITATION: [redacted] (2012). GF-2032: Acute Aerosol Inhalation Toxicity Study in F344/DuCrl Rats. [redacted]

Study ID: 081191, (13 January 2012). MRID (no hyphen). Unpublished.

SPONSOR: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, Indiana.

EXECUTIVE SUMMARY: This study was conducted to determine the acute inhalation toxicological properties of GF-2032. Groups of five rats/sex were exposed for four hours, using a nose-only inhalation exposure system, to a maximum attainable respirable time-weighted average chamber concentration of 2.21 mg GF-2032 per liter of air. The mass median aerodynamic diameter (MMAD) of particulate GF-2032 present in the exposure chamber test atmosphere averaged 3.53 microns with an average geometric standard deviation of 1.76 microns.

All animals survived the four-hour exposure to the test material as well as the two-week post-exposure period. Clinical effects noted during the four-hour exposure period were limited to soiling of the haircoat in two male and two female rats. In-life observations noted post-exposure were limited to perineal and/or abdominal soiling in two male and four female rats. All rats appeared normal by test day 3. Mean body weight losses of 2.4% and 1.4% were noted for male and female rats, respectively, on test day 2. Pre-exposure mean body weight values were exceeded on test day 4. There were no visible treatment-related lesions noted in any of the rats exposed to GF-2032 at the test day 15-scheduled necropsy.

Based on these data, the four-hour LC_{50} of inhaled particulate GF-2032 is greater than the maximum attainable respirable concentration of 2.21 mg/L for male and female F344/DuCrl

rats.

This study is acceptable and satisfies the guideline requirement for a Acute Inhalation Toxicity – (rats); OPPTS 870.1300; OECD 403, JMAFF, EEC.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1.	**Test Material:**	GF-2032
	Lot/Batch #:	Lot # E3460-38, TSN018439-0031
	Purity:	21.7% by weight Sulfoxaflor (a.i.)
	CAS #:	Sulfoxaflor: 946578-00-3

2. Vehicle and/or positive control: Not Applicable

3.	**Test animals:**		
	Species:	Rats	
	Strain:	F344/DuCrl	
	Age/weight at dosing:	Animals were seven weeks at arrival and 8 weeks at the time of exposure.	
	Source:	[redacted]	
	Housing:	After assignment, animals were housed two-three per cage in stainless steel cages. Cages had wire mesh floors and were suspended above absorbent paper. Non-woven gauze was placed in the cages to provide a cushion from the flooring for the rodents' feet. The gauze also provided environmental enrichment. Cages contained a hanging feeder and a pressure activated lixit valve-type watering system. The following environmental conditions were maintained in the animal room.	
	Environmental conditions:	**Temperature:** **Humidity:** **Air changes:** **Photoperiod:**	22°C with a tolerance of ± 1°C (and a maximum permissible excursion of ± 3°C) 40-70% 12-15 times/hour (average) Photoperiod: 12-hour light/dark (on at 6:00 a.m. and off at 6:00 p.m.)

	Food and Water:	Animals were provided LabDiet Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, Missouri) in pelleted form. Feed and municipal water were provided *ad libitum* except during the 2-hour acclimation period the day prior to exposure and during the 4-hour exposure period. Drinking water obtained from the municipal water source was periodically analyzed for chemical parameters and biological contaminants by the municipal water department.
	Acclimation period:	During the acclimation period each animal was evaluated by a laboratory veterinarian, or a trained animal/toxicology technician under the direct supervision of a laboratory veterinarian, to determine the general health status and acceptability for study purposes (fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International - AAALAC International). The animals were housed two-three per cage in stainless steel cages, in rooms designed to maintain adequate environmental conditions (temperature, humidity, and photocycle), prior to randomization. Animals were acclimated to the laboratory for at least one week prior to the start of the study. Animals were acclimated to the nose cones for at least two hours on the day preceding exposure to the test material.

B. STUDY DESIGN AND METHODS:

1. In life dates: 9 November 2011 to 23 November 2011

2. Exposure conditions: Exposure room temperature, chamber temperature, humidity and airflow were monitored continuously and recorded approximately every 30 minutes during the exposure period.

3. Animal assignment and treatment: Before administration of test material began, animals were stratified by body weight and then randomly assigned to the treatment group using a computer program designed to increase the probability of uniform group mean weights and standard deviations at the start of the study. Animals placed on study were uniquely identified via subcutaneously implanted transponders (BioMedic Data Systems, Seaford, Delaware) that were correlated to unique alphanumeric identification numbers.

Rats were exposed to GF-2032 by nose only exposure for 4 hours.

Animals were observed daily and weighed on test days 1, 2, 4, 8, 11, and 15.

Detailed clinical observations (DCO) were conducted pre-exposure, twice following exposure (test day 1), and daily thereafter. The DCO were conducted at approximately the same time each examination day, according to an established format. The examination

included cage-side, hand-held and open-field observations, which were recorded categorically or using explicitly defined scales (ranks).

All surviving animals were necropsied on test day 15. Non-fasted rats submitted alive for necropsy were anesthetized by the inhalation of CO2, their tracheas were exposed and clamped, and the animals were euthanized by decapitation.

A complete necropsy was conducted on all animals by a veterinary pathologist or by a trained technologist qualified to recognize common lesions. The necropsy included an examination of the external tissues and all orifices. The head was removed, the cranial cavity opened and the brain, pituitary and adjacent cervical tissues was examined. The head was split longitudinally to facilitate examination of the nasal passage. The eyes were examined in situ by application of a moistened microscope slide to each cornea. The skin was reflected from the carcass, the thoracic and abdominal cavities were opened and the viscera examined. All visceral tissues were dissected from the carcass, re-examined and selected tissues were incised. Tissues were not saved and histopathologic examination was not performed unless deemed meaningful on selected tissues based on results of gross pathological examination.

TABLE 1. Concentrations, exposure conditions, mortality/animals treated

Nominal Conc. (mg/L)	Gravimetric Conc. (mg/L)	MMAD µm	GSD	Mortality (# dead/total)		
				Males	Females	Combined
10.5	2.21	3.53	1.76	0/5	0/5	0/10

4. Generation of the test atmosphere / chamber description:

Exposure: The exposures occurred under dynamic airflow conditions.

Chambers: A 42-liter, Dow-modified ADG nose-only chamber [30 centimeters (cm) in diameter by 60 cm high] was used for the study. Compressed filtered air supplied to the chamber was at ambient temperature. Airflow through the chamber was determined with a manometer which measured the pressure drop across a calibrated orifice plate and was maintained at approximately 20 liters per minute, which was sufficient to provide the normal concentration of oxygen to the animals and approximately 29 air changes per hour. The manometer was calibrated with a gas meter (Model DTM-115, Singer Aluminum Diaphragm Meter, American Meter Division, Philadelphia, Pennsylvania) prior to the start of the study. The chamber was operated at a slightly positive pressure relative to the surrounding area and was contained within a secondary vented area. Chamber and exposure room temperature were recorded from two thermocouples attached to an electronic digital thermometer (Control Company, Friendswood, Texas), one thermocouple extended into the exposure chamber and the second was stationed next to the chamber. Chamber relative humidity was monitored by a hygrometer (Airguide, Sturtevant, Wisconsin) stationed in the interior of the chamber.

Based on the 20 liter per minute flow rate, the theoretical equilibrium time to 99% (T_{99}) of the target concentration was 9.7 minutes. The animals were placed on the chamber after the T_{99} had elapsed and were removed after 240 minutes of exposure.

Generation System: A liquid aerosol of GF-2032 was generated by metering the test material with a FMI pump (Fluid Metering, Inc., Oyster Bay, New York) into a stainless steel ¼-J spray nozzle (Spraying Systems Co., Wheaton, Illinois). The test material was mixed with compressed air in the spray nozzle and aerosol was sprayed into the chamber. Since the formulation contained materials of varying vapor pressures, the test material was not recycled.

Exposure Concentration: The mass concentration of aerosol present in the chamber was determined gravimetrically three times during each exposure period. Samples were taken by drawing air, at 1 L/minute, through a sampling probe located in the

breathing zone of the animals. Aerosol particles were collected on pre-weighed glass fiber filters (PALL Corporation, Ann Arbor, Michigan). Since a substantial portion of the exposure chamber atmosphere consisted of water and inert vapor, silica sorbent tubes were used in-line with, and down-stream of the glass fiber filter. After each atmosphere sampling, the filter was reweighed to obtain the total wet weight of the particles. The filters were then air-dried to a stable weight (24 hours as determined during preliminary chamber work) and the time-weighted average (TWA) exposure concentration was calculated from the net dry weight gravimetric analysis and the percent solids in the total formulation (21.7%). Background measurements of the chamber were taken prior to starting the exposure.

The nominal concentration was calculated based on the amount of test material fed into the generation system divided by the total chamber airflow during the exposure period.

Particle Size: The aerodynamic particle size was determined twice during the exposure period by drawing samples from within the animal breathing zone, at a set rate using a constant flow air sampling pump through a multi-stage mercer-style cascade impactor. The MMAD and geometric standard deviation (GSD) were determined for each sample as well as the average of the samples.

5. **Statistics:** Means and standard deviations were calculated for descriptive purposes for chamber concentration (mean only), animal body weights, exposure room temperature and chamber temperature, humidity, and airflow.

II. RESULTS AND DISCUSSION:

A. **Chamber Summary Data:** The resulting time-weighted average concentration was 2.21 mg/L; the nominal concentration was 10.5 mg/L. The difference between the gravimetric and the nominal concentration was due to the loss of test material coating the walls of the generation apparatus and exposure chamber, and the inefficiency of the generation system employed.

The average chamber temperature and relative humidity were 20.1 ± 0.1°C and 49.0 ± 10.1%, respectively. The average exposure room temperature was 22.1 ± 0.3°C. The chamber O_2 level was determined to be 20.8% and the CO_2 level was determined to be 415 ppm. Airflow was maintained at 20 liters per minute.

Based on two determinations, the mean MMAD of the particles was 3.53 microns with an average geometric standard deviation of 1.76 microns. Approximately 18% of the particle mass was contained in a size fraction with an aerodynamic diameter less than 1 micron. Approximately 84% of the particulate mass was present in size fractions with an

aerodynamic diameter less than 6 microns

B. **Mortality:** All animals survived the four-hour exposure to the test material as well as the two-week post-exposure period.

C. **Clinical observations:** Clinical effects noted during the four-hour exposure period were limited to soiling of the haircoat in two male and two female rats.

In-life observations noted post-exposure were limited to perineal and/or abdominal soiling in two male and four female rats. All rats appeared normal by test day 3.

D. **Body Weight:** Mean body weight losses of 2.4% and 1.4% were noted for male and female rats, respectively, on test day 2. Pre-exposure mean body weight values were exceeded on test day 4.

E. **Necropsy:** There were no treatment-related visible lesions noted in any of the rats exposed to GF-2032 at the test day 15-scheduled necropsy.

F. **Applicant's Conclusions:** Based on these data, the four-hour LC_{50} of inhaled GF-2032 is greater than the maximum attainable respirable concentration of 2.21 mg/L for male and female F344/DuCrl rats.

IIIA1 7.1.3/01 Study comments	The study is acceptable.
IIIA1 7.1.3/01 Agreed endpoint	Acute inhalation LC_{50} >2.21 mg/L in the rat, the maximum attainable concentration. According to the classification criteria of **CLP Regulation (EC) No. 1272/2008**, the test material **does not require classification** for acute inhalative toxicity.

IIIA 7.1.4 **Skin irritation**

Report	KIIIA1 7.1.4/01 [redacted] 2008b)
Title	Primary Skin Irritation in Rabbits. [redacted] January 14, 2009
Document No	EPSL Study Number 26461, Dow Study Number 080051
Guideline	Primary Dermal Irritation - Rabbit; OPPTS 870.2500: OECD 404
GLP	Yes

EXECUTIVE SUMMARY: A primary skin irritation test was conducted with New Zealand albino rabbits to determine the potential for GF-2032 to produce irritation after a single topical application. Five-tenths of a milliliter of the test substance was applied to the skin of three healthy rabbits for 4 hours. Following exposure, dermal irritation was evaluated by the

method of Draize *et al.*[1].

There was no edema observed at any treated site during this study. Within one hour of patch removal, one treated site exhibited very slight erythema. Irritation cleared from this site by 24 hours.

Under the conditions of this study, GF-2032 caused very slight erythema, which cleared within 24 hours.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1.	**Test Material:**	GF-2032
	Description:	Liquid suspension, Tan
	Lot #:	E2198-52
	Test Substance Number	018439-0011
	Purity:	XDE-208 – 22.0 wt%

2. Vehicle and/or positive control: Not applicable

3.	**Test animals:**		
	Species:	Rabbit	
	Strain:	New Zealand, albino	
	Age/weight at treatment:	Young Adult	
	Source:	[redacted]	
	Housing:	Singly housed in suspended stainless steel caging with mesh floors	
	Diet:	Purina Certified High Fiber Rabbit Diet (PMI #5325) *ad libitum*	
	Water:	Filtered tap water *ad libitum* by an automatic water dispensing system.	
	Environmental conditions:	**Temperature:** **Humidity:** **Air changes/Hour:** **Photoperiod:**	19-21°C 34-64%, RH 12/hr 12 hrs dark/12 hrs light
	Acclimation period:	6 days	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: November 18, 2008 End: November 21, 2008

2. Animal assignment and treatment - Five-tenths of a milliliter of the test substance was applied to one 6-cm^2 intact dose site on each animal and covered with a 1-inch x 1-inch, 4-ply gauze pad. The pad and entire trunk of each animal were then wrapped with semi-occlusive 3-inch Micropore tape to avoid dislocation of the pad. Elizabethan collars were placed on each

[1] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390.

rabbit and they were returned to their designated cages.

After 4 hours of exposure to the test substance, the pads and collars were removed and the test sites were gently cleansed with a 3% soap solution then tap water and a clean towel to remove any residual test substance.

Individual dose sites were scored according to the Draize scoring system[2] at approximately 30-60 minutes, 24, 48, and 72 hours after patch removal.

All animals were observed for signs of gross toxicity and behavioral changes at least once daily during the test period. Body weights of the animals were recorded prior to test substance administration (initial) and again at study termination.

II. RESULTS AND DISCUSSION:

A. Results:

All animals gained body weight and appeared active and healthy during the study. Apart from the skin irritation noted (Table 7.1.4/1-1), there were no other signs of gross toxicity, adverse clinical signs, or abnormal behavior.

There was no edema observed at any treated site during this study. Within one hour of patch removal, one treated site exhibited very slight erythema. Irritation cleared from this site by 24 hours.

Table 7.1.4/1-1: Mean of scores for skin irritation at 24, 48 and 72 hours

Animal	Erythema	Oedema
1	0	0
2	0	0
3	0	0
EC trigger values	≥ 2.3, ≤ 4.0*	≥ 2.3, ≤ 4.0*

*Any irreversible effect in 2/3 animals d14

B. Applicant's Conclusions:

Under the conditions of this study, GF-2032 caused very slight erythema, which cleared within 24 hours.

[2] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390.

IIIA1 7.1.4/01 Study comments	The study is acceptable.
IIIA1 7.1.4/01 Agreed endpoint	Under the conditions of this study, GF-2032 caused very slight erythema, which cleared within 24 hours. According to the classification criteria of **CLP Regulation (EC) No. 1272/2008**, the test material **does not require classification** for dermal irritancy.

IIIA 7.1.5 **Eye irritation**

Report	KIIIA1 7.1.5/01, [redacted] 2008c)
Title	Primary Eye Irritation in Rabbits. [redacted] January 14, 2009
Document No	EPSL Study Number 26460, Dow Study Number 080052
Guideline	Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405
GLP	Yes

EXECUTIVE SUMMARY: A primary eye irritation test was conducted with New Zealand albino rabbits to determine the potential for GF-2032 to produce irritation from a single instillation via the ocular route. One-tenth of a milliliter of the test substance was instilled into the right eye of three healthy rabbits. The left eye remained untreated and served as a control. Ocular irritation was evaluated by the method of Draize *et al.*[3].

There was no corneal opacity observed in any treated eye during this study. One hour after test substance instillation, two treated eyes exhibited iritis and all three treated eyes exhibited conjunctivitis. The overall incidence and severity of irritation decreased with time. All animals were free of ocular irritation by 72 hours.

Under the conditions of this study, GF-2032 caused iritis and conjunctival irritation, which cleared within 72 hours.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1.	**Test Material:**	GF-2032
	Description:	Liquid suspension, Tan
	Lot #:	E2198-52
	Test Substance Number	018439-0011
	Purity:	XDE-208 – 22.0 wt%

[3] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390.

2. Vehicle and/or positive control: None

3.	**Test animals:**		
	Species:	Rabbit	
	Strain:	New Zealand, albino	
	Age/weight at dosing:	Young Adult	
	Source:	[redacted]	
	Housing:	Singly housed in suspended stainless steel caging with mesh floors	
	Diet:	Purina Certified High Fiber Rabbit Diet (PMI #5325) *ad libitum*	
	Water:	Filtered tap water *ad libitum* by an automatic water dispensing system.	
	Environmental conditions:	**Temperature:** **Humidity:** **Air changes:** **Photoperiod:**	20-22ºC 37-65%RH 12/hr 12 hrs dark/12 hrs light
	Acclimation period:	12 days	

B. STUDY DESIGN and METHODS:

1. In life dates - Start: December 1, 2008 End: December 4, 2008

2. Animal assignment and treatment - One-tenth of a milliliter of the test substance was instilled into the conjunctival sac of the right eye of each rabbit by pulling the lower lid away from the eyeball. The upper and lower lids were then gently held together for about one second before releasing to minimize loss of the test substance. The other eye of each rabbit remained untreated with the test substance and served as a control. The rabbits were then returned to their designated cages.

Ocular irritation was evaluated using a high-intensity white light (Mag Lite) in accordance with Draize *et al*.[4] at 1, 24, 48, and 72 hours post-instillation. The fluorescein dye evaluation procedure described in Section 5.A. was used in the treated eye at 24 hours to verify the absence of corneal damage. Individual scores were recorded for each animal. In addition to observations of the cornea, iris, and conjunctivae, any other observed lesions were noted. The average score for all rabbits at each scoring period was calculated to aid in data interpretation.

The animals were observed for signs of gross toxicity and behavioral changes at least once daily during the test period. Individual body weights of the animals were recorded prior to test substance instillation (initial) and again on study termination following scoring.

II. RESULTS AND DISCUSSION:

A. All animals appeared active and healthy during the study. Apart from the eye irritation noted (Table 7.1.5/1-1), there were no other signs of gross toxicity, adverse clinical signs, or

[4] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390.

abnormal behavior.

There was no corneal opacity observed in any treated eye during this study. One hour after test substance instillation, two treated eyes exhibited iritis and all three treated eyes exhibited conjunctivitis. The overall incidence and severity of irritation decreased with time. All animals were free of ocular irritation by 72 hours.

Table 7.1.5/1-1: Mean values for ocular lesions 24, 48 and 72 hours after instillation

Animals	Corneal	Iridial	Conjunctival	
	Opacity	Lesions	Redness	Chemosis
1	0.0	0.0	0.0	0.0
2	0.0	0.0	0.66	0.0
3	0.0	0.33	0.66	0.0
EC trigger values*: (H319)	≥ 1	≥ 1.0	≥ 2	≥ 2.0
EC trigger values*: (H318)**	≥ 3	≥ 1.5	na	na

**Classification triggered if any EC value is attained by two or more animals*
*** Any Irriversible effect in 1/3 animals d21*
H318also triggered by corneal or iris effects present at the end of the test in any animal
na not applicable

B. <u>Applicant's Conclusions</u>: The GF-2032 caused iritis and conjunctival irritation, which cleared within 72 hours.

IIIA1 7.1.5/01 Study comments	The study is acceptable.
IIIA1 7.1.5/01 Agreed endpoint	Under the conditions of this study, GF-2032 caused very slight erythema, which cleared within 24 hours. According to the classification criteria of **CLP Regulation (EC) No. 1272/2008**, the test material **does not require classification** for dermal irritancy.

IIIA 7.1.6 **Skin sensitisation**

Report	KIIIA1 7.1.6/01 [redacted] (2008).
Title	GF-2032: Local Lymph Node Assay in CBA/J Mice. [redacted] December 2008).
Document No	Study ID: 081180
Guideline	Dermal sensitization via the local lymph node assay [mice]; OPPTS 870; OECD 429, and EC B.42

GLP	Yes

EXECUTIVE SUMMARY: The Local Lymph Node Assay (LLNA) was conducted to assess the potential of GF-2032 to cause contact sensitization by measuring lymphocyte proliferative responses from auricular lymph nodes following topical application of the test material to the mouse ear.

Screening Study: Three daily topical applications of 1%, 5%, 25%, 50%, 75% or 100% GF-2032 were given to one animal at each dose level. Erythema was absent and body weights were unaffected in all dose groups. Results from this study were used to determine the dosing concentrations for GF-2032 in the LLNA.

LLNA: Six female mice/group received 5%, 25%, or 100% GF-2032, or vehicle (1% L92) or 30% α-hexylcinnamaldehyde (HCA; positive control) on days 1-3. On day 6, uptake of ^{3}H-thymidine into the auricular lymph nodes draining the site of chemical application was measured five hours post administration. Proper conduct of the LLNA was confirmed via a positive response using 30% α-hexylcinnamaldehyde (HCA), a moderate contact sensitizer, which elicited proliferation that was 4.3 in comparison to vehicle-treated mice.

Erythema was absent and body weights were unaffected in all dose groups.

GF-2032 at doses of 5%, 25%, or 100% elicited proliferative responses with stimulation indices (SI) that were 0.6, 0.5, and 0.7, respectively, in comparison to vehicle-treated mice. GF-2032 did not demonstrate dermal sensitization potential in the mouse LLNA as the lymph nodes draining the area of topical application did not demonstrate a 3-fold proliferation when compared to vehicle-treated mice.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1.	**Radioisotope**	
	Radioisotope :	^{3}H-Thymidine
	Purity of Radioisotope :	96.5%
	Date of Isotope Activity Assay	May 27, 2008

2.	**Test Material:**	GF-2032
	Description:	Liquid, tan
	Lot/Batch #:	Lot # E2198-52, TSN018439-0011
	Purity:	22.0% wt. XDE-208
	Compound Stability:	Not Applicable
	CAS #:	946578-00-3

3.	**Test Animals:**		
	Species:	Mice	
	Strain:	CBA/J	
	Age at study initiation:	Approximately 9-12 weeks	
	Source:	[redacted]	
	Housing:	Animals were housed up to six per cage in filter tubs containing corncob bedding, food pellets and a water bottle. On the day the animals were euthanized and following the injection of ^{3}H-thymidine, each treatment group of mice was housed in shoebox cages containing corncob bedding, food pellets, and a crock filled with water. The mice were euthanized five hours later.	
	Feed and Water:	Animals were provided LabDiet Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, Missouri) in pelleted form. Feed and municipal water was provided *ad libitum*. Drinking water obtained from the municipal water source was periodically analyzed for chemical parameters and biological contaminants by the municipal water department.	
	Environmental conditions:	Temperature: Humidity: Air changes: Photoperiod:	22 ± 1°C with a tolerance of ± 1°C (and a maximum permissible excursion of ± 3°C). 40-70% 12-15 times/hour 12-hour light/dark (on at 6:00 a.m. and off at 6:00 p.m.)
	Acclimation period:	For at least one week prior to the start of the study.	

B. STUDY DESIGN:

1. In life dates: 22 October 2008 to 3 November 2008.

2. Animal assignment: Before administration of test material began, animals were stratified by body weight and then randomly assigned to treatment groups using a computer program designed to increase the probability of uniform group mean weights and standard deviations at the start of the study. Animals placed on study were uniquely identified via subcutaneously implanted transponders (BioMedic Data Systems, Seaford, Delaware) that were correlated to unique alphanumeric identification numbers.

3. Dose selection: The dermal route is a relevant route for evaluation of skin contact allergy potential and is consistent with the animal model developed by Kimber and Weisenberger (1989) to predict dermal sensitization potential using the mouse LLNA.

Concentrations tested for the irritancy screen were selected based upon maximum miscibility or solubility in an appropriate LLNA vehicle while maintaining a solution suitable for application. Toxicity data regarding irritation potential and lethality doses were also taken into consideration.

Concentrations tested in the LLNA were based on this information and previous dermal sensitization data.

4. Statistics:

1. The Stimulation Index (SI) was calculated for each mouse using the following equation:

$$SI = \frac{\text{Disintegration per minute (dpm) of individual mouse}}{}$$

Average dpm of the VH control mice

2. EC_3 Calculation:

$$EC_3 = X_L + [(3-Y_L)/(Y_h-Y_L)](X_h-X_L)$$

Where, Y_L = SI value below 3
X_L = chemical concentration that elicits Y_L
Y_h = SI value above 3
X_h = chemical concentration that elicits Y_h

Means and standard deviation (SD) were generated for body weight data (absolute and gain) and the LLNA response (dpm & SI values).

These body weight and dpm data were analyzed by a one-way analysis of variance (Steele and Torrie, 1960). When differences were indicated by the ANOVA, a comparison of treated vs. control groups was done using a Dunnett's t-test (Steele and Torrie, 1960). The alpha level at which all tests were conducted was 0.05. The final interpretation of the biological significance of the responses was based on both statistical outcome and scientific judgment.

C. METHODS:

1. Observations: Twice each day a cage-side examination was conducted by animal care personnel, and to the extent possible the following parameters were evaluated: skin, fur, mucous membranes, respiration, nervous system function (including tremors and convulsions), animal behavior, morbidity, mortality, and the availability of feed and water. The ears were evaluated for erythema prior to application of test material solutions and ^{3}H-thymidine injections as follows:

Table 7.1.6/1-1. Erythema Evaluation

	Value
No visual effect	0
Slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Eschar	4

2. Body weight: The initial and terminal body weights were obtained and recorded.

3. Sacrifice and Pathology: Approximately five hours post administration, the mice were euthanized via CO_2 asphyxiation and both auricular lymph nodes located at the bifurcation of the jugular veins were excised and placed in PBS.

a. Gross necropsy: N/A

b. Tissue preparation/histopathology: A single cell suspension of the auricular lymph

nodes from one mouse was prepared by gentle mechanical disaggregation using a tissue homogenizer (Stomacher 80 Lab System, Seward Ltd., London, United Kingdom). The cells were washed two times and were suspended in 3 ml of 5% trichloroacetic acid (TCA) for approximately 18 hours. The suspended precipitates were centrifuged (200 x g for 10 minutes) and the supernatant removed. The pellet from each mouse was reconstituted in 1 ml of 5% TCA and subsequently transferred to a scintillation vial containing 10 ml of Aquasol-2 scintillation cocktail (Packard Instrument Company, Meridan, Connecticut). Two additional 2 ml aliquots of water were used to rinse the tubes and the rinses were added to the scintillation vials containing the 1 ml of pellet in TCA and cocktail. The radioactivity in each precipitate was measured using a β-scintillation counter and reported as disintegrations per minute (dpm) per mouse.

II. RESULTS During the screening study, the mice were treated with three daily applications 1%, 5%, 25%, 50%, 75% or 100% GF-2032. Erythema was absent and body weights were unaffected in all dose group.

Based on the results of the screen, 100% GF-2032 was tested in the LLNA along with 25% and 5% to characterize the dose response. Erythema was absent (Table 7.1.6/1-2), and body weights were unaffected (Table 7.1.6/1-3).in all dose groups.

Proper conduct of the LLNA was demonstrated via the positive response from the positive control, 30% HCA which elicited a stimulation index (SI) that was 4.3 in comparison to vehicle-treated mice (Table 7.1.6/1-4).

GF-2032 at doses of 5%, 25% or 100% elicited proliferative responses with stimulation indices (SI) that were 0.6, 0.5, and 0.7, respectively, in comparison to vehicle-treated mice (Table 7.1.6/1-4). GF-2032 did not demonstrate dermal sensitization potential in the mouse LLNA as the lymph nodes draining the area of topical application did not demonstrate a 3-fold proliferation when compared to vehicle-treated mice.

A. Observations:

1. Clinical signs of toxicity: Not Applicable

Table 7.1.6/1-2. Individual Erythema Scores of Animals Treated with Vehicle (1% L92), 30% α-hexylcinnamaldehyde (HCA) or 5%, 25%, and 100% GF-2032.

DOSE %	ANIMAL NUMBER	DAYS ON TEST 1	2	3	6
VH (1% L92)	8646	0	0	0	0
	8647	0	0	0	0
	8648	0	0	0	0
	8649	0	0	0	0
	8650	0	0	0	0
	8651	0	0	0	0
5% GF-2032	8658	0	0	0	0
	8659	0	0	0	0
	8660	0	0	0	0

	8661	0	0	0	0
	8662	0	0	0	0
	8663	0	0	0	0
25% GF-2032	8664	0	0	0	0
	8665	0	0	0	0
	8666	0	0	0	0
	8667	0	0	0	0
	8668	0	0	0	0
	8669	0	0	0	0
100% GF-2032	8670	0	0	0	0
	8671	0	0	0	0
	8672	0	0	0	0
	8673	0	0	0	0
	8674	0	0	0	0
	8675	0	0	0	0
30% HCA	8652	0	0	2	1
	8653	0	1	2	1
	8654	0	1	2	1
	8655	0	1	2	1
	8656	0	1	1	1
	8657	0	1	2	1

Table 7.1.6/1-3. ***Individual Body Weights (g) and Body Weight Gain (g) of Animals Treated with Vehicle (1% L92), 30% α-hexylcinnamaldehyde (HCA) or 5%, 25%, and 100% GF-2032***

DOSE %	ANIMAL NUMBER	DAYS ON TEST 1	6	GAIN
VH (1% L92)	8646	22.7	22.4	-0.3
	8647	24.1	22.6	-1.5
	8648	23.5	22.7	-0.8
	8649	24.2	24.5	0.3
	8650	23.3	23.3	0.0
	8651	23.1	22.1	-1.0
	MEAN	23.5	22.9	-0.6&
	S.D.	0.6	0.9	0.7
	N=	6	6	6
5% GF-2032	8658	24.0	24.1	0.1
	8659	22.1	22.1	0.0
	8660	22.8	24.2	1.4
	8661	24.7	25.8	1.1
	8662	23.6	24.6	1.0
	8663	22.1	21.5	-0.6
	MEAN	23.2	23.7	0.5&
	S.D.	1.1	1.6	0.8
	N=	6	6	6
25% GF-2032	8664	25.1	25.9	0.8
	8665	24.6	24.3	-0.3
	8666	24.5	24.1	-0.4
	8667	25.1	23.2	-1.9
	8668	24.5	23.2	-1.3
	8669	24.0	24.9	0.9
	MEAN	24.6	24.3	-0.4&
	S.D.	0.4	1.0	1.1
	N=	6	6	6
100% GF-2032	8670	24.6	24.6	0.0
	8671	24.7	24.6	-0.1
	8672	22.9	22.8	-0.1
	8673	21.8	22.3	0.5
	8674	22.0	22.5	0.5
	8675	22.3	23.1	0.8
	MEAN	23.1	23.3	0.3&
	S.D.	1.3	1.0	0.4
	N=	6	6	6
30% HCA	8652	23.7	24.2	0.5
	8653	21.2	21.3	0.1
	8654	23.9	23.8	-0.1
	8655	22.5	23.6	1.1
	8656	22.6	23.0	0.4
	8657	25.8	24.7	-1.1
	MEAN	23.3	23.4	0.2&
	S.D.	1.6	1.2	0.7
	N=	6	6	6

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

Table 7.1.6/1-4. ***Disintegrations Per Minute (DPM) and Stimulation Indices (SI) of Animals Treated with Vehicle (1% L92), 30% α-hexylcinnamaldehyde (HCA) or 5%, 25%, and 100% GF-2032***

DOSE %	ANIMAL NUMBER	DPM	SI
VH (1% L92)	8646	917.00	0.8
	8647	1748.0	1.5
	8648	1207.0	1.1
	8649	1149.0	1.0
	8650	524.00	0.5
	8651	1254.0	1.1
	MEAN	1133.2	1.0&
	S.D.	404.01	0.3
	N=	6	6
5% GF-2032	8658	527.00	0.5
	8659	944.00	0.8
	8660	754.00	0.7
	8661	809.00	0.7
	8662^	2227.0	1.9
	8663	485.00	0.4
	MEAN	703.80	0.6&
	S.D.	193.92	0.2
	N=	5	5
25% GF-2032	8664	796.00	0.7
	8665	645.00	0.6
	8666	1077.0	1.0
	8667	270.00	0.2
	8668	257.00	0.2
	8669	315.00	0.3
	MEAN	560.00	0.5&
	S.D.	336.49	0.3
	N=	6	6
100% GF-2032	8670	1368.0	1.2
	8671	588.00	0.5
	8672	913.00	0.8
	8673	1098.0	1.0
	8674	485.00	0.4
	8675	456.00	0.4
	MEAN	818.00	0.7&
	S.D.	370.07	0.3
	N=	6	6
30% HCA	8652	5402.0	4.8
	8653	5939.0	5.2
	8654	3761.0	3.3
	8655	4959.0	4.4
	8656	3160.0	2.8
	8657	5649.0	5.0
	MEAN	4811.7*	4.3&
	S.D.	1111.2	1.0
	N=	6	6

^ STATISTICAL OUTLIER NOT INCLUDED IN CALCULATION
& INDICATES NO STATISTICAL COMPARISON OF MEANS.
* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

III. DISCUSSION

A. Investigator's conclusions: GF-2032 did not elicit a stimulation index (SI) that met the 3X threshold, thus indicating a lack of dermal sensitization potential in the mouse LLNA.

IIIA1 7.1.6/01 Study comments	The study is acceptable.
IIIA1 7.1.6/01 Agreed endpoint	Under the conditions of this study, GF-2032 indicates a lack of dermal sensitisation potential in the mouse LLNA, which cleared within 24 hours. According to the classification criteria of **CLP Regulation (EC) No. 1272/2008**, the test material **does not require classification** for skin sensitisation.

IIIA 7.1.7 Supplementary studies for combinations of plant protection products

This formulation contains a single active, therefore additional data are not required

IIIA 7.2 Short-term toxicity studies

This is not an EC data requirement according to Regulation (EC) No. 1107/2009.

IIIA 7.3 Operator exposure

GF-2626 is a suspension concentrate (SC) insecticidal formulation containing a nominal 120 g/L sulfoxaflor as the active ingredient. Details of intended uses and packaging of GF-2626 in the European Union are contained in IIIA 3 and IIIA 4 of this dossier.

A single application of GF-2626 to fruiting vegetables and ornamentals (see Table 7.3-1 for details) will be made using a hand lance with nurse tank/atomizer (greenhouse crops). Water is the intended diluent/carrier.

Sulfoxaflor has a low vapour pressure (*ca.* $\leq 2.5 \times 10^{-6}$ Pa @ 25°C). This means that any additional exposure from inhalation exposure would be negligible.

Information pertinent to operator exposure is summarized in Table 7.3-1, Table 7.3-2 and 7.3-3.

Table 7.3-1: Summary of application information for GF-2626

Crop	Conc. in product g/L	Application rate		Spray volume L/ha	Pack size L
		Product L/ha	Active substance kg/ha		
Fruiting vegetables: Cucurbits (Edible and non-edible peel)[1], Solanaceous vegetables[2]	120	0.2-0.4	0.024-**0.048**	**500**-1500	0.25-20
Ornamentals (Bulbs, Ornamentals, Flowers)			0.024-**0.048**	**200**-2000	

1	Edible peel – cucumbers, courgettes, gherkins; inedible peel – melons, pumpkins/ squash, zuccini, watermelons
2	Tomatoes, peppers (incl. chilli pepper), aubergines (incl. pepinos)

Table 7.3-2: Summary of critical use patterns (i.e. worst case)

Crop	Application rate		Spray volume L/ha	Pack size L
	Product L/ha	Active substance kg/ha		
Ornamentals	0.4	0.048	**200**-2000	1

Table 7.3-2: EU endpoints for non-dietary human exposure

Endpoint		**EU agreed endpoint[1]**	**Endpoint used in risk assessment**
		Value	
Dermal absorption			
Active	Concentrate	0.8%	0.8%
	Spray dilution	6%	12%
AOEL			
Sulfoxaflor		0.06 mg/kg bw/day (EFSA, 2014)	
Default body weights (kg):		UK POEM	60
		German/Greenhouse Model	70
Application parameters:		Area treated (UK POEM)	1 ha per day
		Area treated (German Model)	1 ha per day
		Duration of spraying (UK POEM)	6 hours
		Duration of Spraying (German Model)	N/A

[1] *EFSA Journal 2014; 12(5):3692*

IIIA 7.3.1 **Estimation of operator exposure without personal protection**

Estimations of potential operator exposure to sulfoxaflor associated with application of GF-2626 were made using the UK POEM and the German model assuming the maximum proposed application rate for each crop group detailed in Table 7.3.1. The German Model handheld data are applicable to high crops only and the UK POEM handheld data is applicable to low crops only, therefore, the crop could be low or high depending on growth stage and/or growing method being utilised and both models are presented.

Predicted systemic exposures are summarised in Table 7.3.1-1. Individual spreadsheets are presented in Appendix 3, Tables 1 and 2.

Table 7.3.1-1: Estimation of operator exposure for GF-2626 assuming PPE is not used*

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of AOEL
Hand held sprayer application indoors to high crops (ornamentals) *Application rate: 0.048 kg* sulfoxaflor */ha*			
German Model 1 ha/day 70 kg operator	no PPE	0.0047	**7.8**
Hand held sprayer application indoors to low crops (ornamentals) *Application rate: 0.048 kg* sulfoxaflor/*ha*			
UK POEM 1 ha/day, 6 h/day 200 L/ha 1 L any closure 60 kg operator	no PPE	0.0517	**86.1**

No PPE German Model: Operator wearing long work wear (coverall) but no gloves.
UK POEM: Operator wearing long sleeved shirt, long trousers ("permeable") but no gloves

An additional evaluation has been performed with the German model with similar entry parameters in the model as presented in the dRR; however taking into account a protection factor of 90% for the working coverall. With this consideration the estimation of operator exposure, when GF-2626 is applied on:

- Ornamentals using a lance to high crops represented 1.5 % of the AOEL of sulfoxaflor with working coverall and with gloves during mixing/loading and application.
- Ornamentals using a lance to high crops represented 24.8 % of the AOEL of sulfoxaflor with working coverall and with gloves during mixing/loading and application.

IIIA 7.3.2 Estimation of operator exposure using personal protective equipment

Estimation of operator exposure assuming PPE is used is required when the AOEL may be exceeded in the absence of PPE, or based on hazard classification requirements.

Exposure based on no PPE indicates that PPE will not be required for use of GF-2626 on greenhouse fruiting vegetables, and ornamentals according to predicted exposures using the German, UK and Greenhouse models.

In addition, GF-2626 is not classified for acute toxicity in accordance with criteria in Council Directive 1272/2008/EC (Classification, labelling and packaging of substances and mixtures) and 99/45/EEC (Dangerous Preparations Directive).

Therefore, an estimation of operator exposure assuming PPE is used is not required and has not been performed.

IIIA 7.3.3 Measurement of operator exposure

Measurement of operator exposure is required where, based on estimated exposure, the AOEL may be exceeded. Estimations of operator exposure indicate that the AOEL will not be exceeded by the proposed uses of GF-2626 during mixing, loading and application.
Therefore, measurement of operator exposure is not required and has not been performed.

IIIA 7.4 Bystander and resident exposure

Bystander exposure
Sulfoxaflor is a new active substance developed by Dow AgroSciences. GF-2626, containing sulfoxaflor is the representative formulation for the EU registration of sulfoxaflor.
All relevant data and risk assessments are provided and are considered adequate.

The Plant Protection Product GF-2626 containing 120 g/L sulfoxaflor is intended to be used indoors (or in greenhouses) on vegetables crops and ornamentals crops as an insecticide.

Since GF-2626 is only intended to be used indoor in professional facilities, it is reasonable to assume that bystanders, i.e. persons that are not involved in the application of pesticides, are present. Therefore, bystander exposure is not relevant.

Residential exposure
Sulfoxaflor is a new active substance developed by Dow AgroSciences. GF-2626, containing sulfoxaflor is the representative formulation for the EU registration of sulfoxaflor.
All relevant data and risk assessments are provided and are considered adequate.

The Plant Protection Product GF-2626 containing 120 g/L sulfoxaflor is intended to be used indoors (or in greenhouses) on vegetables crops and ornamentals crops as an insecticide.

Since GF-2626 is only intended for indoor use, it is reasonable to assume that residents are not exposed during and after application. Therefore, resident exposure is not relevant.

IIIA 7.4.1 Estimation of bystander exposure

Not applicable.

Total bystander exposure to sulfoxaflor from spray drift following application is acceptable according to EUROPOEM II.

It is concluded that there is no significant risk to incidental bystanders (adults or children) from sulfoxaflor in the formulation GF-2626 for the commercial uses/rates illustrated in the GAP when applied via hand held sprayer.

IIIA 7.4.2 Estimation of resident exposure

Not applicable.

IIIA 7.5 Worker exposure

Re-entry worker exposure to GF-2626 was evaluated as part of the EU review of sulfoxaflor. Therefore, all relevant data and risk assessments are provided here and are considered adequate. Table 7.3-1 summarizes the GAPs evaluated for re-entry worker exposure assessment.

Workers may have to enter treated areas after treatment for crop inspection or harvest activities. Consequently, estimation of worker exposure was calculated according to the EUROPOEM II model.

One worst-case scenario has been identified to assess potential worker exposure. This is the application of GF-2626 to ornamental crop at a rate of 0.4 L product/ha (equivalent to 0.048 kg sulfoxaflor/ha) in a water volume of 200 L/ha. Usage information pertinent to operator exposure is summarised in Table 7.5-1 and Table 7.5-2.

Table 7.5 -1: Usage scenarios for which worker exposure has been considered

Crop (field use)	Application rate (kg a.s./ha)	Minimum water volume (L/ha)	Re-entry activities
Ornamentals	0.048	200	Harvesting activities

Table 7.5-2: Parameters applied for the assessment of worker exposure

Estimation of worker exposure was calculated according to the following formula (proposed by EUROPOEM II):

Parameters and units	Sulfoxaflor

DFR	Dislodgeable Foliar Residues (µg/cm²/kg a.i./ha) (default value)	3
AR	Application rate (kg a.i./ha)	0.048
TC	Transfer coefficient (cm²/ person/h)	14000
T	Task duration (h)	8
BW	Body weight (kg)	60
DA	Dermal absorption (worst-case between diluted and undiluted formulations)	12%
TSF	Transfer Specific Factor (%)	0.01
PPE	Personal Protection Equipment	1 or 0.1

The potential dermal exposure of a worker is calculated by the following approach:

D (mg/person/d) = 0.001 x DFR (µg/cm²/kg a.i./ha) x AR (kg a.i./ha) x TC (cm²/person/h) x T (h/day)

The potential inhalation exposure of a worker is calculated by the following approach:

I (mg/person/d) = AR (kg a.i./ha) x TSF (%) x T (h/day)

The worker total systemic exposure is calculated as follows:

$$\textbf{Total systemic exposure}\ (\text{mg/kg bw/d}) = \frac{D\ (\text{mg/person/d}) \times DA\ (\%) + I\ (\text{mg/person/d})}{BW\ (\text{kg})}$$

Table 7.5-2: Estimated worker exposure to GF-2626 and % of the AOEL

Uses	Personal Protective Equipment	% A.O.E.L. Sulfoxaflor (0.06 mg/kg bw/day)
Ornamental	Without PPE	**53.9**
	With PPE	**5.5**

Total worker exposure to sulfoxaflor from spray drift following application is acceptable according to EUROPOEM II.

IIIA 7.5.1 **Estimation of worker exposure without personal protective equipment**

See IIIA 7.5.

IIIA 7.5.2 **Estimation of worker exposure with personal protective equipment**

See IIIA 7.5.

IIIA 7.5.3 **Measurement of worker exposure**

Measurement of worker exposure is required where, on the basis of estimated exposure, the AOEL may be exceeded. Estimations of worker exposure indicate that the AOEL of sulfoxaflor will not be exceeded by proposed uses of GF-2626 and therefore measurement of worker exposure is not required and has not been conducted.

IIIA 7.6 Dermal absorption

Dermal absorption of fluxapyroxad formulated in the Suspension Concentrate (SC) GF-2032 was evaluated as part of the EU review. Therefore, all relevant data and risk assessments are provided here and are considered adequate.

No dermal absorption studies have been conducted on the sulfoxaflor liquid suspension concentrate (SC) formulation GF-2626 (120 g/L). This test preparation can be adequately represented by the sulfoxaflor SC formulation, GF-2032, which had already been extensively tested for dermal absorption in a rat in vivo study and a rat/human in vitro study. Based on GAP, spray dilutions of GF-2032 are comparable surrogates for those of GF-2626. Details of the studies on GF-2032 are supplied in this dossier.

Table 7.6-1: Dermal absorption end-points for the risk assessment

End-Point	
Dermal absorption	Concentrate: 0.8 % Dilution: 12%

IIIA 7.6.1 **Dermal absorption, *in vivo*, in the rat**

Report:	KIIIA 7.6.1/01, [redacted] June 2010)
Title:	XDE-208: The *In Vivo* Percutaneous Absorption of Radiolabelled XDE-208 in Formulation (GF-2032) and Two In-Use Spray Dilutions in the Rat (OECD 427). [redacted]
Document No:	No. 191168
Guidelines:	*In Vivo* Dermal Absorption – *Rat Sprague Dawley*; OECD 427
GLP	Yes

EXECUTIVE SUMMARY:

GF-2032 is a suspension concentrate (SC) formulation containing the active substance XDE-208, an experimental insecticide under development by Dow AgroSciences. The nominal concentration of the active substance in GF-2032 is 240 g per litre. The highest in-use spray dilution concentration is produced by mixing 0.4 L of formulation with 200 L of water to give 0.48 g XDE-208/L. The lowest in-use spray dilution concentration is produced by mixing 0.1 L of formulation with 1000 L of water to give 0.024 g XDE-208/L.

As part of the safety evaluation of XDE-208, this study was designed to assess its rate and extent of absorption through rat skin following topical application of the formulation and two typical in-use spray dilutions that cover the concentration range of these sprays.

The study was divided into 3 phases, each phase corresponded to one of the test preparations studied (i.e. undiluted formulation, highest and lowest spray dilutions concentrations),

For each test preparation five groups of four male CD rats were tested. The contact time was 10 hours, in order to be consistent with the US EPA Guideline 870.7600 and the first group was killed at 24 h and the remaining groups at 48, 96, 144 and 192 h post dose to provide additional data on the stratum corneum reservoir/application site and long term absorption, distribution and excretion of XDE-208.

Following dose administration, the application site, which was protected by an O-ring that enclosed the treated area, was then covered with a protective dressing. The animals were placed in all-glass metabowls designed specifically for the quantitative collection of urine and faeces. Urine and faeces were quantitatively collected for the periods predose, 0-10 and 10-24 h then daily up to termination. Cages were washed with water at the time of each collection and the wash retained. At 10 h post dose, the dressing was removed and retained for analysis. The exposed area was gently wiped clean using a single cotton wool swab soaked in handwash soap concentrate followed by 3 cotton wool swabs soaked in lukewarm soapy water. The skin was dried with a further 3 cotton wool swabs. The washing process was repeated once. The washes and cotton wool were retained. A new protective dressing was then applied.

A terminal blood sample (*ca* 5-10 mL) was taken from the *vena cava* or by cardiac puncture into tubes containing lithium heparin. A sample of whole blood (*ca* 0.5 mL) was retained separately for analysis. Plasma was separated by centrifugation and the blood cells discarded. The exposed area of skin was washed as described above prior to being clipped and the hair clippings retained along with the dressings. The stratum corneum was removed by 20 successive tape strips and each tape strip was retained separately. The exposed area was dissected out and retained. The remaining carcass and gastrointestinal tract were retained.

Each sample retained was analysed for total radioactivity.

The mass balance was complete for [^{14}C]-XDE-208 from all three test preparations and across all time

points was (99%, 95% and 94%, of the applied dose, respectively).

The results for the test preparations can be expressed as *absorbed*, (excreted dose plus dose retained in the body, excluding the application site), or as the *dermal delivery* (excreted dose plus dose retained in the body, plus the *absorbable dose* (residue remaining at the application site).

As this study design incorporated the separation of the stratum corneum from the application site, the definition of the *dermal delivery* was refined to exclude the stratum corneum. The inclusion of the stratum corneum was covered by an additional definition of *potential absorbable dose*.

This study was designed to determine the dermal absorption and the fate of that residual material (application site), in particular the portion absorbed and the rate at which it is absorbed (EPA 870/7600).

For all three test preparations (formulation , highest and lowest spray dilutions concentrations), the amount of the applied dose removed across all time points, by washing the skin at 10 h post dose; was 96%, 71% and 67% of the applied dose, respectively.

Formulation (GF-2032)

At 24 h following topical application of [^{14}C]-XDE-208 in GF-2032, the *absorbed dose* of was 1.5% (42.61 µg equiv./cm^2) and at subsequent sampling times (48, 96,144 at 192 hours), the absorbed dose was 1.7 % (49.35 µg equiv./cm^2), 1.1% (37.20 µg equiv./cm^2), 1.4% (42.44 µg equiv./cm^2) and 1.2% (43.47 µg equiv./cm^2 indicating that absorbed dose was low and complete by 24 hours with a maximum absorbed dose of 1.7%

Highest Concentration Spray Dilution (0.48g/L)

At 24 h following topical application of [^{14}C]-XDE-208 in highest concentration in-use dilution (0.48 g/L), the absorbed dose of [^{14}C]-XDE-208 was 2.01% (98.89 ng equiv./cm^2) and at subsequent sampling times (48, 96, 144 at 192 hours), the absorbed dose was 2.88 % (132.94 ng equiv./cm^2), 8.16% (392.91 ng equiv./cm^2), 11.24% (549.82 ng equiv./cm^2) and 11.35% (555.56 ng equiv./cm^2).

This indicates that absorption was initially increasing until reaching a plateau at 144 h to give a dermal absorption value of ca. 11%.

Lowest Concentration Spray Dilution (0.024g/L)

At 24 h following topical application of [^{14}C]-XDE-208 in lowest concentration in-use dilution (0.024 g/L), the absorbed dose of [^{14}C]-XDE-208 was 2.50% (6.50 ng equiv./cm^2) and at subsequent sampling times (48, 96, 144 at 192 hours), the absorbed dose was 1.25 % (4.42 ng equiv./cm^2), 6.02% (16.05 ng equiv./cm^2), 12.51% (34.31 ng equiv./cm^2) and 10.77% (29.87 ng equiv./cm^2).

This indicates that absorption was initially increasing until reaching a plateau at 12.5 % at 144 h.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Preparations:

Three test preparations were tested.

Test Preparation 1: Radiolabelled Formulation GF-2032, (240g/L)

[^{14}C]-XDE-208 in GF-2032 (1.5 mL) was added to unlabeled GF-2032 (4.5 mL) and stirred until visually confirmed as homogenous. This adjustment was required to ensure an appropriate dose in terms of MBq per rat. The homogeneity and radioactive concentration were confirmed by removing nine 10 µL weighed aliquots (3 from the top, 3 from the middle and 3 from the bottom) from the test preparation and analyzed by liquid scintillation counting. The concentration of XDE-208 in the test preparation was calculated to be 236.3 g/L (1.63 MBq/g).

Test Preparation 2: Spray Dilution Formulation of Lowest In-Use Spray Dilution/ Highest Concentration (ca 0.48 g/L)

XDE-208 (10.49 mg) was transferred into a vial. GF-2032 formulation blank (105 µL) was added. The sample was mixed and the new concentration of XDE-208 was calculated to be 81.51 mg/g. The [^{14}C]-XDE-208 (100 µCi, 3.7 MBq) was removed from *ca* -20°C freezer storage and allowed to reach ambient temperature. An aliquot (22 µL, 21.13 mg) of the 81.51 mg/g formulation was added to the [^{14}C]-XDE-208. Water (pH 7, 4.98 mL, 4.96503 g) was added and the sample mixed by vortex and sonication. The homogeneity, radioactive concentration and concentration of XDE-208 were determined by removing nine 10 µL aliquots (3 from the top, 3 from the middle and 3 from the bottom) from the test preparation and analysed by liquid scintillation counting.

The concentration of XDE-208 in the test preparation was calculated to be 0.48 g/L (0.8 MBq/g).

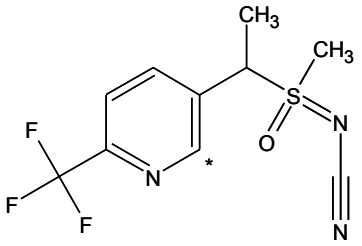
Test Preparation 3: Formulation of Highest In-Use Spray Dilution/ Lowest Concentration (*ca* 0.024 g/L)

The [^{14}C]-XDE-208 (20 µCi, 0.74 MBq) was removed from *ca* -20°C freezer storage and allowed to reach ambient temperature. An aliquot (10 µL, 9.62 mg) of GF-2032 formulation blank was added to the [^{14}C]-XDE-208. Water (pH 7, 4.50 mL, 4.47170 g) was added and the sample stirred until visually confirmed as homogenous. The homogeneity, radioactive concentration and concentration of XDE-208 were determined by removing nine 10 µL aliquots from the test preparation and analysed by liquid scintillation counting. The results of this analysis showed that the sample concentration was too low. Therefore the sample was stirred and sonicated again. Two 10 µL aliquots were taken and analysed and the concentration calculated. This concentration was found to be too high. Therefore, an aliquot (3.15 mL) of the resultant sample was taken, water (1.3 mL) was added and the sample mixed. Six aliquots (10 µL) were taken from the test preparation (at random and not from top, middle and bottom) and analysed by liquid scintillation counting.

The concentration of XDE-208 in the test preparation was calculated to be 0.025 g/L (0.15 MBq/g).

Radiolabelled GF-2032:	[^{14}C]-XDE-208, batch no. XS9-37562-34
Radiochemical purity	97% [determined by HPLC,]
Specific Activity	1.63 Mbq/g
Lot/Batch #:	E3026-33

Radiolabelled XDE 208	[^{14}C]-XDE-208, batch no. XS9-37562-34
Radiochemical purity	99.3% [determined by HPLC,]
Specific Activity	45.2 McI/mmo;
Lot/Batch #:	Batch no. XS9-37562-34
Non-Radiolabelled Test Material:	XDE-208
Description:	Analytical Standard
Lot/Batch #:	TSN105878
Purity:	99.8%
Contaminants:	n/a
CAS #:	946578-00-3



* - position of ^{14}-C [2-^{14}C]

Vehicle and/or positive control: not appropriate

3. Test animals:

Species:	Rat
Strain:	Spraque Dawley (male selected as the elimination rate is slower compared to female)
Age/weight at study initiation:	6-8 Weeks 200-300g
Source:	[redacted]
Housing:	The animals were multiply housed in polypropylene and stainless steel cages with wood shavings as bedding during pre-trial periods. For collection of pre-dose urine samples and immediately following dose administration, animals were housed in all-glass metabowls designed specifically for the quantitative collection of urine and faeces. Each animal was uniquely identified by tail marking.
Feed and Water:	A complete diet of known formulation (SDS Rat and Mouse Maintenance Diet No. 1, Special Diet Services, 1 Stepfield, Witham, Essex, UK) was offered *ad libitum* to the animals. Domestic mains quality water was available *ad libitum*
Environmental conditions:	**Temperature:** 19-21ºC **Humidity:** 35-76%
Acclimation period:	

4. Preparation of dosing solutions:

Refer to section I. MATERIALS AND METHODS for preparation of dose

B. STUDY DESIGN AND METHODS:

1. Group Arrangements: 4 rats per time point Sacrifice at 24, 48, 96, 144 and 192 hours.

2. Dosing and sample collection:

A single 100 µL dose of the concentrate and in-use spray dilution was applied within the exposed area (O-ring) onto the skin on the back of the animal. The test preparation was evenly applied over the area defined within the O-ring using the pipette tip used to apply the test preparation. The pipette was weighed before and after dosing to calculate the weight of test preparation delivered to the skin surface. A pervious protective dressing (Micropore® tape) was wrapped around the animal to protect the exposed area of the skin.

Approximately 24 h prior to dose application, the fur was clipped from the back of each animal and the area wiped with lukewarm water. Care was taken not to abrade the skin. Any animal whose skin was observed to be damaged was rejected from the study and replaced.

Approximately 1 h prior to dosing, a rubber O-ring of internal area *ca* 10 cm^2 was glued, using acrylic glue, to the back of each animal.
Following dose administration, the animals were placed in all-glass metabowls designed specifically for the quantitative collection of urine and faeces. Urine and faeces were quantitatively collected for the periods predose, 0-10, 10-24 h then daily up to 192 h post dose (or up until termination). Cages were washed with water at the time of each collection and the wash retained.

At 10 h post dose, the pervious dressing was removed and retained for analysis. The expose area was gently wiped clean using a single cotton wool swab soaked in handwash soap concentrate followed by 3 cotton wool swabs soaked in lukewarm soapy water. The skin was dried with a further 3 cotton wool swabs. The washing process was repeated once. The washes and cotton wool were retained. A new pervious protective dressing was then placed on the animals.

Groups of four male rats were humanely killed (CO_2 narcosis) at 24, 48, 96, 144 and 192 h post dose administration. A terminal blood sample (*ca* 5-10 mL) was taken from the *vena cava* or by cardiac puncture into tubes containing lithium heparin.

A sample of whole blood (*ca* 0.5 mL) was retained separately for analysis. Plasma was separated by centrifugation and the blood cells discarded.

The exposed area of skin was washed as described above prior to being clipped and the hair clippings retained along with the dressings. The stratum corneum was removed by 20 successive tape strips and each tape strip was retained separately. The exposed area was dissected out and retained. The remaining carcass and gastrointestinal tract were retained.

3. Statistics:

Individual date was collected and the mean values summarised.

II. RESULTS

The report contains a summary table for each test preparation, detailed tables for each test preparation, distribution of the dose for each sacrifice time point for each individual rat. The data is presented as % of dose applied and s absolute mass (µg equiv /cm^2). In addition the distribution through the Stratum Corneum is reported by the analysis of the individual tape strips. The data is also presented graphically.

The overall summary of the data is presented in Table 1

Table 1: Summary of the Results Following a Single Percutaneous Administration of [^{14}C]-XDE-208 for each Test Preparation Studied Results expressed as % administered dose

Test Preparation	Concentrate				
Target XDE-208 Concentration	240 g/L				
XDE-208 Concentration in Test Preparation by Radioactivity	236 g/L				
Application Site	Dermal				
Time	24 h	48 h	96 h	144 h	192 h
Dislodgeable Dose 10 h	94.44	95.16	93.09	98.06	98.86
Total Dislodgeable Dose	95.66	97.44	94.38	98.96	99.69
Unabsorbed Dose	95.78	97.63	94.65	99.30	99.99

Absorbed Dose	1.50	1.66	1.05	1.41	1.22
Dermal Delivery	1.91	2.03	1.27	1.61	1.35
Potentially Absorbable Dose	1.95	2.11	1.36	1.72	1.52
Mass Balance	97.70	99.80	96.10	101.00	101.30

Test Preparation	Highest In-Use Concentration				
Target XDE-208 Concentration	0.48 g/L				
XDE-208 Concentration in Test Preparation by Radioactivity	0.48 g/L				
Application Site	Dermal				
Time	24 h	48 h	96 h	144 h	192 h
Dislodgeable Dose 10 h	61.70	78.81	66.03	71.62	75.81
Total Dislodgeable Dose	73.75	84.50	71.21	74.22	78.02
Unabsorbed Dose	77.81	89.61	79.22	80.21	81.41
Absorbed Dose	2.01	2.88	8.16	11.24	11.35
Dermal Delivery	11.72	10.41	12.16	16.01	17.71
Potentially Absorbable Dose	13.40	13.59	15.53	17.95	18.86
Mass Balance	89.60	100.03	91.33	96.20	99.10

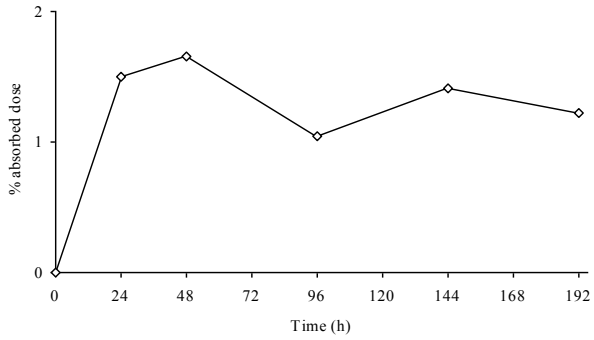
Test Preparation	Lowest In-Use Concentration				
Target XDE-208 Concentration	0.024 g/L				
XDE-208 Concentration in Test Preparation by Radioactivity	0.025 g/L				
Application Site	Dermal				
Time	24 h	48 h	96 h	144 h	192 h
Dislodgeable Dose 10 h	67.40	64.42	70.52	63.01	70.80
Total Dislodgeable Dose	76.75	73.51	76.12	67.17	71.59
Unabsorbed Dose	82.88	83.36	83.83	74.45	79.49
Absorbed Dose	2.50	1.25	6.02	12.51	10.77
Dermal Delivery	9.09	7.05	11.23	19.16	16.87
Potentially Absorbable Dose	10.05	8.66	14.50	20.51	20.11
Mass Balance	92.00	90.37	96.10	95.40	96.40

Detailed analysis for each preparation was undertaken.

Preparation 1 (GF-2032)

The absorption of XDE 208 over the duration of the study is expressed in Table 1 and Figure 1.

Figure 1: % Absorption over the Study Period Following a Single Percutaneous Administration of [14C]-XDE-208 in the Concentrate Test Preparation



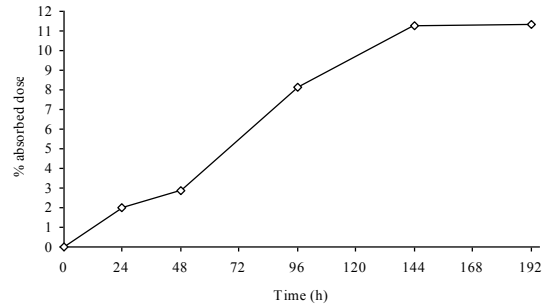
This indicates that absorption essentially ceased at 24 hours.

The concentration of total radioactivity in plasma (Table 63) gave a highest mean concentration at 24 h post application with a mean of 0.23 µg equiv./mL, decreasing to 0.21 µg equiv./mL at 48 h post application. The mean concentration of total radioactivity decreased to 0.01, 0.05 and 0.03 µg equiv./mL at 96, 144 and 192 h post application, respectively. The concentration of total radioactivity in whole blood (Table 64) was below the limit of reliable measurement at all times analysed.

The plasma data combined with the data obtained from the excretion rate profiles at 144 and 192 hrs (Figure 15 and 18), confirm that absorption had ceased by the end of the study and that the absorbed dose (1.7%) based on the sum of the urine (0.86%), faeces (0.20%), cage wash (0.24%), gastrointestinal tract (0.00%) and carcass (0.40%) at 48 hours is representative of the absorbed dose.

Preparation 2 (Spray Dilution) (*ca* 0.48 g/L)
The absorption of XDE 208 over the duration of the study is expressed in Table 1 Figure 2.

Figure 2: % Absorption over the Study Period Following a Single Percutaneous Administration of [^{14}C]-XDE-208 in the Highest In-Use Spray Dilution



This figure indicates that absorption has essentially ceased at 144 hours.

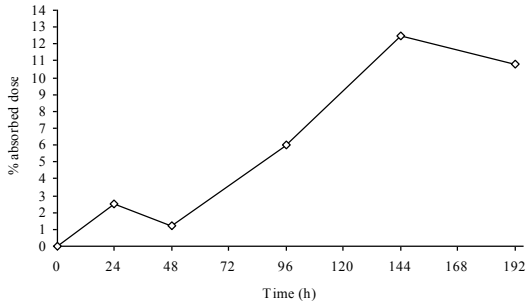
The concentration of total radioactivity in plasma and blood are presented in Table 65 and 66. The highest mean concentration was noted at 24 h post application with a mean of 2.0 ng equiv./mL, respectively, decreasing to 0.6 ng equiv./mL , respectively at 192hrs. It should be noted that these later low values were very close the background levels.

The plasma data combined with the data obtained from the excretion profiles at 144 and 192 hrs (Figure 30 and 33) confirm that the peak absorption had passed and the excreted dose particularly urine, was returning to pre dose values.

The absorbed (11.35%) was the sum of the urine (4.20%), faeces (4.73%), cage wash (2.38%), gastrointestinal tract (0.10%) and carcass (0.00%) at 192 hrs and is representative of the absorbed dose.

Preparation 3 (Spray Dilution) (*ca* 0.024 g/L)
The absorption of XDE 208 over the duration of the study is expressed in Figure 1.

Figure 3: % Absorption over the Study Period Following a Single Percutaneous Administration of [^{14}C]-XDE-208 in the Lowest In-Use Spray Dilution



This indicates that absorption essentially ceased at 144 hours.

The concentration of total radioactivity in plasma and blood following percutaneous administration of [^{14}C]-XDE-208 in the lowest in-use spray dilution is shown in Table 67 and 68. The mean concentration of total radioactivity in both was below the limit of reliable measurement at all times analysed.

The data obtained from the excretion profiles at 144 and 192 hrs (Figure 45 and 48) which confirm that the peak absorption had passed and the excreted dose, particularly urine was returning to pre dose values.

The absorbed dose (12.51%) was the sum of the urine (6.76%), faeces (2.18%), cage wash (3.58%), gastrointestinal tract (0.00%) and carcass (0.00%) at 144 hours is representative of the absorbed dose.

III. DISCUSSION

A. Applicants conclusions

The mass balance was complete for [^{14}C]-XDE-208 from all three test preparations and across all time points was (99%, 95% and 94%,of the applied dose, respectively).

For all dose groups following skin washing, some radioactivity remained in the skin at the application site and was therefore recognised as potentially absorbable. Because each skin site was tape-stripped, it was possible to discriminate between radioactivity present in the stratum corneum, which was subject either to loss from the skin surface by desquamation or to subsequent absorption, and radioactivity in the epidermis, which had translocated the stratum corneum and was therefore was potentially available for absorption, although it had not yet entered systemic circulation.

After 8 days, the excretion of the absorbed dose was minimal suggesting absorption of skin residues was no longer significant.

At each dose level, elimination of the absorbed dose in urine and faeces appeared to be fairly slow, with the greater proportion excreted *via* the urine. At the end of the collection period, excretion of radioactivity was considered to be essentially complete. However in some cases at 192 h once the

animals were removed from their cages an extensive final excreta collection gave a slight rise in the excretion value at this time. This rise was considered to be related to residues of excreta products from earlier timepoints rather than a sudden increase in elimination of absorbed components. This is supported by the low levels of radioactivity in the residual carcasses and gastrointestinal tract after 8 days which are entirely consistent with limited absorption in the latter stages of each experiment.

All radioactivity concentrations in blood were low throughout each experiment. After an initial early peak all values were near to or below the limit of detection, particularly in the low dose group (0.024 g/L).

Within each dose group there was some variance in individual results however group data were consistent across the study, with good recoveries of applied radioactivity, thereby providing confidence in these absorption values determined for each dose preparation.

To conclude, following a dermal exposure period of 10 h to XDE-208 formulation concentrate (240 g/L), *ca* 93-99% of the applied radioactivity was readily removed from the skin surface by a mild detergent wash. Approximately 1-2% of the applied dose was absorbed over the exposure interval and subsequent post exposure collection periods up to 192 h after exposure. The highest absorption was observed within the 48 hour group with 1.7%.

After a 10 h dermal exposure to the 0.48g/L spray dilution, the dosed material was not as readily removed from the skin surface with *ca* 62-79% of the applied radioactivity removed by a mild detergent wash. Approximately 2-3% of the applied radioactivity was absorbed after 24 h and 48 h, increasing to *ca* 8% at 96 h. By 144 h and 192 h the absorption levels were similar at *ca* 11%, indicating that absorption of the dose was essentially complete.

After a 10 hour dermal exposure to the 0.024g/L spray, the amount of dislodgeable dose was similar to the 0.48g/L spray dilution with *ca* 63-71% of the applied radioactivity removed from the skin surface by the detergent wash. Approximately 1-3% of the applied radioactivity was absorbed after 24 h and 48 h increasing to *ca* 6% at 96 h. By 144 h and 192 h the absorption levels were similar at *ca* 13% and *ca* 11%, respectively, indicating that absorption of the dose was essentially complete.

IIIA1 7.6.1/01 Study comments	The study was evaluated during the inclusion of the active substance. The study is not revalued.
IIIA1 7.6.1/01 Agreed endpoint	The results for the test preparations are expressed as: (1) **absorbed**, (excreted dose plus dose retained in the body, excluding the application site), (2) **dermal delivery,** (excreted dose plus dose retained in the body, plus the residue remaining at the application site excluding the *stratum corneum* (tape strips 2-20). (3) **potential absorbable dose,** (excreted dose plus dose retained in the body, plus residue remaining at the application site plus the *stratum corneum.* **Table 6.12.1-1: Summary of the Results Following a Single Percutaneous Administration of [^{14}C]-sulfoxaflor for each Test Preparation. (Expressed as mean values of % administered dose)** **Summary of the Results Following a Single Percutaneous Administration of [^{14}C]-sulfoxaflor for each**

Test Preparation. (Expressed as mean values of % administered dose)					
Test Preparation: 240 g/L					
Time	24 h	48 h	96 h	144 h	192 h
Dislodgeable Dose 10h	94.44	95.16	93.09	98.06	98.86
Total Dislodgeable Dose	95.66	97.44	94.38	98.96	99.69
Unabsorbed Dose	95.78	97.63	94.65	99.30	99.99
Absorbed Dose	1.50	1.66	1.05	1.41	1.22
Dermal Delivery	1.91	2.03	1.27	1.61	1.35
Potentially Absorbable Dose	1.95	***2.11***	1.36	1.72	1.52
Carcass	0.00	0.40	0.00	0.00	0.00
Urine + Cage Wash	1.17	1.10	0.85	1.04	1.14
Faeces	0.25	0.20	0.50	0.38	0.08
GI Tract	0.09	0.00	0.00	0.00	0.00
Plasma[a]	0.23	0.21	0.01	0.05	0.03
Whole Blood[a]	0.03	0.06	0.05	0.00	0.07
Mass Balance	97.70	99.80	96.10	101.00	101.30
Test Preparation: 0.48 g/L					
Dislodgeable Dose 10h	61.70	78.81	66.03	71.62	75.81
Total Dislodgeable Dose	73.75	84.50	71.21	74.22	78.02
Unabsorbed Dose	77.81	89.61	79.22	80.21	81.41
Absorbed Dose	2.01	2.88	8.16	11.24	11.35
Dermal Delivery	11.72	10.41	12.16	16.01	17.71
Potentially Absorbable Dose	13.40	13.59	15.53	17.95	***18.86***
Carcass	0.00	0.00	0.00	0.00	0.00
Urine + Cage Wash	1.58	2.16	4.02	7.39	6.58
Faeces	0.27	0.69	3.10	3.85	4.73
GI Tract	0.16	0.03	0.03	0.00	0.10
Plasma[a]	2.0	1.0	1.1	0.7	0.6
Whole Blood[a]	2.1	1.1	1.4	0.5	0.2
Mass Balance	89.60	100.03	91.33	96.20	99.10
Test Preparation: 0.024 g/L					
Dislodgeable Dose 10h	67.40	64.42	70.52	63.01	70.80
Total Dislodgeable Dose	76.75	73.51	76.12	67.17	71.59
Unabsorbed Dose	82.88	83.36	83.83	74.45	79.49
Absorbed Dose	2.50	1.25	6.02	12.51	10.77
Dermal Delivery	9.09	7.05	11.23	19.16	16.87
Potentially Absorbable Dose	10.05	8.66	14.50	***20.51***	20.11
Carcass	0.00	0.00	0.00	0.00	0.00
Urine + Cage Wash	2.41	1.25	5.14	10.34	8.85
Faeces	0.09	0.00	0.90	2.18	1.93
GI Tract	0.00	0.00	0.00	0.00	0.00
Plasma[a]	0.0	0.0	0.0	0.0	0.0
Whole Blood[a]	0.0	0.0	0.0	0.0	0.0
Mass Balance	92.00	90.37	96.10	95.40	96.40

[a]expressed as ng equiv./cm^2; numbers in ***bold italic*** indicate maximum dermal absorption. The maximum time to complete absorption was 48 for the concentrate and 144 to 192h for the two dilutions.

The mass balance for [^{14}C]-sulfoxaflor from all three test preparations and across all time points was (99%, 95% and 94%, of the applied dose, respectively). The inclusion of the *stratum corneum* in the calculations for the absorbed dose is found in the *potential absorbable dose*. Following the EFSA guidance on dermal absorption (2012), tape strips 2-20 (the *stratum corneum*), should always be included unless >75% of the total absorption occurs within half of the study duration. As this is not the case (see the following absorption profile figures) for the two dilutions tested in this study, the potentially Absorbable Dose represents the most appropriate estimate of the dermal absorption for sulfoxaflor in these two cases. The undiluted formulation shows a different absorption profile in that

	the majority of the total absorption occurs within 48h out of the 192h study duration so technically tape strips 2-20 can be discarded. In this case the dermal delivery value is more appropriate (it just lacks the amount of sulfoxaflor attributable to the tape strips). **Conclusion:** To conclude, following a dermal exposure period of 10 h to sulfoxaflor formulation concentrate (240 g/L), 93-99% of the applied radioactivity was readily removed from the skin surface by a mild detergent wash. Approximately 1-2% of the applied dose was absorbed over the exposure interval and subsequent post exposure collection periods up to 192 h after exposure. The highest absorption was observed within the 48 hour group with 2.03%. After a 10 h dermal exposure to the 0.48g/L spray dilution, the dosed material was not as readily removed from the skin surface with 62-79% of the applied radioactivity removed by a mild detergent wash. Approximately 13% of the applied radioactivity was absorbed after 24h and 48h, increasing to 15% at 96h. By 144h and 192h the absorption levels were similar at 18-19%, indicating that absorption of the dose was essentially complete near the end of the study. After a 10 hour dermal exposure to the 0.024g/L spray, the amount of dislodgeable dose was similar to the 0.48g/L spray dilution with 63-71% of the applied radioactivity removed from the skin surface by the detergent wash. Approximately 10% of the applied radioactivity was absorbed after 24 h and 48 h increasing to 14% at 96h. By 144h and 192h the absorption levels had peaked and were similar at 20.5% and 20.1%, respectively, indicating that absorption of the dose was essentially complete near the end of the study. The study finds dermal absorption values of 2.11%, 18.86% and 20.51% for the concentrate and two dilutions respectively. These values appear to correspond to appropriate time points for cessation of dermal absorption. In the case of the two dilutions, the values include the substance remaining on the skin in the *stratum corneum* as required by current guidance on dermal absorption (EFSA 2012). Guidance mandates the use of the *dermal delivery* value. Hence, dermal absorption values for the *in vivo* rat should be established as follows: **Formulation (GF-2032)** *Dermal delivery* (excreted dose plus dose retained in the body, plus the *absorbable dose* (residue remaining at the application site) **2.11%** **Highest Concentration Spray Dilution (0.48g/L)** *Dermal delivery* (excreted dose plus dose retained in the body, plus the *absorbable dose* (residue remaining at the application site) **18.86%** **Lowest Concentration Spray Dilution (0.024g/L)** *Dermal delivery* (excreted dose plus dose retained in the body, plus the *absorbable dose* (residue remaining at the application site) **20.51%**

IIIA 7.6.2 **Comparative dermal absorption, in vitro, using rat and human skin**

Report:	KIIIA 7.6.2/01, Clive S Roper BSc PhD CBiol MSB, 2010
Title:	XDE-208: The *In Vitro* Percutaneous Absorption of Radiolabelled XDE-208 in Formulation (GF-2032) and Two In-Use Spray Dilutions Through Rat and Human Skin (OECD 428).
Document No:	Report No 786740

Guidelines:	*In Vitro* Dermal Absorption – Isolated Rat Sprague Dawley/Human Skin; OECD 428
GLP	Yes

EXECUTIVE SUMMARY:

GF-2032 is a suspension concentrate (SC) formulation containing the active substance XDE-208, an experimental insecticide. The nominal concentration of the active substance in GF-2032 is 240 g per litre. The highest in-use spray dilution concentration is produced by mixing 0.4 L of formulation with 200 L of water to give *ca* 0.48 g XDE-208/L. The lowest in-use spray dilution concentration is produced by mixing 0.1 L of formulation with 1000 L of water to give *ca* 0.024 g XDE-208/L.

As part of the safety evaluation of XDE-208, a study was required to assess the rate and extent of absorption of XDE-208 following topical application of the formulation and two typical in-use spray dilutions to human and rat skin.

The experimental procedure is summarised as follows:

Split-thickness human and rat skin membranes were mounted into flow-through diffusion cells. Receptor fluid, a tissue culture medium containing polyoxyethylene 20-oleyl ether (PEG, *ca* 6%, w/v), sodium azide (*ca* 0.01%, w/v), glucose (*ca* 1%, w/v), streptomycin (*ca* 0.1 mg/mL) and penicillin G (*ca* 100 units/mL), was pumped underneath the skin at a flow rate of *ca* 1.5 mL/h. 5% CO_2 in air was bubbled over the surface of the receptor fluid reservoir. The skin surface temperature was maintained at *ca* 32°C throughout the experiment. A tritiated water barrier integrity test was performed and any human and rat skin sample exhibiting absorption greater than 0.6% of the applied tritiated water was excluded from subsequent absorption measurements.

Three test preparations containing [^{14}C]-XDE-208 were prepared and applied, at an application volume of 10 µL/cm^2, to human and rat split-thickness skin membranes mounted into flow-through diffusion cells *in vitro*.

Percutaneous absorption was assessed by collecting receptor fluid in hourly fractions from 0 to 6 h post application and then in 2-hourly fractions from 6 to 24 h post application. At 10 h post application, exposure was terminated by washing the skin surface with a concentrated commercial soap followed by rinsing with a dilute soap solution and drying the skin surface with tissue paper (tissue swabs). At 24 h post application (*ie* after a 14 h post exposure monitoring period), the underside of the skin was rinsed with receptor fluid (receptor rinse). The receptor rinse represented the absorbed test item, which was in the receptor chamber but had not been collected in the 22 to 24 h receptor fluid fraction. The skin surface receiving the dose was washed and dried again. The skin was then removed from the flow-through diffusion cells, dried and the stratum corneum was removed with 20 successive tape strips. The remaining skin was divided into exposed and unexposed skin and solubilised with Solvable® tissue solubiliser. All samples were analysed by liquid scintillation counting.

The results for the test preparations can be expressed as absorbed dose (receptor fluid excluding the treated skin) or as the dermal delivery (receptor fluid plus the treated skin). This study incorporated the separation of the stratum corneum from the treated skin. The definition of the dermal delivery was refined to exclude the stratum corneum. The inclusion of the stratum corneum was covered by an additional definition of potentially absorbable dose.

A summary of the mean results are provided in the tables below:

Test Preparation	1			
Target XDE-208 Concentration	240 g/L			
XDE-208 Concentration in Test Preparation by Radioactivity	244.51 g/L			
Species	Human		Rat	
Distribution	% Applied Dose	µg equiv./cm^2	% Applied Dose	µg equiv./cm^2
Dislodgeable Dose 10 h	94.73	2287.15	95.00	2293.66
Total Dislodgeable Dose	95.06	2295.13	95.46	2304.65
Unabsorbed Dose	95.16	2297.60	95.66	2309.67
Absorbed Dose	0.26	6.26	1.30	31.33
Dermal Delivery	0.31	7.51	1.63	39.24
Potentially Absorbable Dose	0.35	8.39	1.67	40.34
Mass Balance	95.48	2305.12	97.29	2348.92

Test Preparation	2			
Target XDE-208 Concentration	0.48 g/L			
XDE-208 Concentration in Test Preparation by Radioactivity	0.47 g/L			
Species	Human		Rat	
Distribution	% Applied Dose	ng equiv./cm^2	% Applied Dose	ng equiv./cm^2
Dislodgeable Dose 10 h	92.28	4336.15	84.53	3971.95
Total Dislodgeable Dose	93.99	4416.65	87.52	4112.44
Unabsorbed Dose	94.62	4445.98	89.34	4198.01
Absorbed Dose	1.54	72.57	3.94	185.03
Dermal Delivery	1.93	90.59	7.63	358.68
Potentially Absorbable Dose	2.44	114.63	8.72	409.97
Mass Balance	96.54	4536.57	96.97	4556.68

Test Preparation	3			
Target XDE-208 Concentration	0.024 g/L			
XDE-208 Concentration in Test Preparation by Radioactivity	0.0255 g/L			
Species	Human		Rat	
Distribution	% Applied Dose	ng equiv./cm^2	% Applied Dose	ng equiv./cm^2
Dislodgeable Dose 10 h	92.69	236.44	85.35	217.73
Total Dislodgeable Dose	94.45	240.94	88.00	224.49
Unabsorbed Dose	95.05	242.45	89.07	227.21
Absorbed Dose	1.15	2.92	4.34	11.08
Dermal Delivery	1.94	4.94	7.21	18.38
Potentially Absorbable Dose	2.38	6.07	8.02	20.45
Mass Balance	96.98	247.40	96.27	245.59

In conclusion, the dermal delivery for [^{14}C]- XDE-208 from GF-2032 (240 g/L) essentially ceased after 8 to 12 hours. Comparing the mean results generated as µg equiv./cm^2 or percentage of dose, the dislodgeable and unabsorbed dose and the stratum corneum profiles for the rat and human were similar. The comparative absorbed dose was 0.26% (6.26 µg equiv./cm^2) and 1.30% (31.33 µg equiv./cm^2) for human and rat, respectively. The absorbed dose for the rat skin was greater than the human skin by a factor of 5-fold. A similar difference in this ratio was observed in the dermal delivery and potentially absorbable dose.

The dermal delivery of [^{14}C]-XDE-208 from the highest concentration in-use spray dilution (0.48 g/L) for rat and human skin based on the absorption profiles had a degree of similarity. However, there was a wash-in effect observed in the rat after the 10 h wash and not in the human. The absorption rate also reduced more evidently after washing in the rat than in the human skin. Absorption at 24 h was continuing although at a decreased rate. The dermal delivery was 1.93% (90.59 ng equiv./cm^2) and 7.63% (358.68 ng equiv./cm^2) for human and rat, respectively. The dermal delivery for the rat skin was greater than the human skin by a factor of 4-fold. A similar difference in this ratio was observed when the potentially absorbable doses were compared, but a lower ratio (2.5-fold) was observed for the absorbed dose.

The dermal delivery of [^{14}C]-XDE-208 from the lowest concentration in-use spray dilution (0.024 g/L) for rat and human skin based on the absorption profiles had a degree of similarity. However, the rate of absorption fell more evidently in the human than in the rat at *ca* 4 h post dose and the reduction in the rat was increased after washing at 10 h post dose. Absorption at 24 h was continuing although at a significantly decreased rate. The dermal delivery was 1.94% (4.94 ng equiv./cm^2) and 7.21% 18.38 ng equiv./cm^2) for human and rat, respectively; which indicated that the rat skin had absorbed more XDE-208 than human skin by a factor of 3.7-fold. A similar difference in this ratio was observed for the potentially absorbable dose and absorbed dose.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Preparations:

Three test preparations were tested.

Test Preparation 1: Radiolabelled Formulation GF-2032, (240g/L)

The supplied [^{14}C]-XDE-208 in GF-2032 was used as supplied. The homogeneity and radioactive concentration were confirmed by removing nine 6.4 µL weighed aliquots (3 from the top, 3 from the middle and 3 from the bottom) from the test preparation and analysed by liquid scintillation counting. The results of the homogeneity confirmation are provided in the Table below.

	Radioactive Concentration (µCi/g)		
Region	Mean	SD	CV (%)
Top	179.40	10.33	5.76
Middle	173.86	5.07	2.92
Bottom	173.95	2.04	1.17

This was considered to be acceptable for dosing.

Test Preparation 2: Spray Dilution Formulation of Lowest In-Use Spray Dilution/ Highest Concentration (*ca* 0.48 g/L)

The following work was performed, as per protocol, under Charles River Study No. 191168. XDE-208 (10.49 mg) was transferred into a vial. GF-2032 formulation blank (105 µL) was added. The sample was mixed and the new concentration of XDE-208 was calculated to be 81.51 mg/g.

The [^{14}C]-XDE-208 (100 µCi, 3.7 MBq) was removed from *ca* -20C freezer storage and allowed to reach ambient temperature. An aliquot (22 µL, 21.13 mg) of the 81.51 mg/g formulation was added to the [^{14}C]-XDE-208. Water (pH 7, 4.98 mL, 4.96503 g) was added and the sample mixed by vortex and sonication. The homogeneity, radioactive concentration and concentration of XDE-208 were determined by removing nine 10 µL aliquots (3 from the top, 3 from the middle and 3 from the bottom) from the test preparation and analysed by liquid scintillation counting. The results of the homogeneity confirmation are provided in the Table below.

Region	Radioactive Concentration (µCi/g)		CV (%)
	Mean	SD	
Top	17.97	0.09	0.48
Middle	18.33	0.40	2.16
Bottom	18.50	0.42	2.25

Note: one of the replicates from the bottom region was rejected, therefore, the results for the bottom region are reported from two aliquots only.

The mean concentration of XDE-208 in the test preparation was calculated to be 0.46 g/L. This was 95.07% of target concentration of 0.48 g/L. This was considered to be acceptable for dosing.

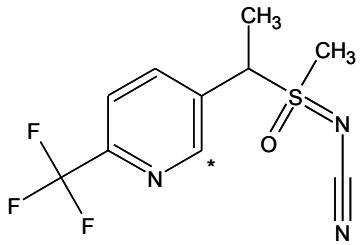
Test Preparation 3: Formulation of Highest In-Use Spray Dilution/ Lowest Concentration (*ca* 0.024 g/L)

The following work was performed, as per protocol, under Charles River Study No. 191168. The [^{14}C]-XDE-208 (20 µCi, 0.74 MBq) was removed from *ca* -20C freezer storage and allowed to reach ambient temperature. An aliquot (10 µL, 9.62 mg) of GF-2032 formulation blank was added to the [^{14}C]-XDE-208. Water (pH 7, 4.50 mL, 4.47170 g) was added and the sample mixed by vortex and sonication. The homogeneity, radioactive concentration and concentration of XDE-208 were determined by removing nine 10 µL aliquots from the test preparation and analysed by liquid scintillation counting. The results of this analysis showed that the sample concentration was too low. Therefore the sample was mixed by vortex and sonication again. Two 10 µL aliquots were taken and analysed and the concentration calculated. This concentration was found to be too high. Therefore, an aliquot (3.15 mL) of the resultant sample was taken, water (1.3 mL) was added and the sample mixed. Six aliquots (10 µL) were taken from the test preparation (at random and not from top, middle and bottom) and analysed by liquid scintillation counting.

The mean concentration of XDE-208 in the test preparation was calculated to be 0.0248 g/L with a CV of 0.71%. This was 103.28% of target concentration of 0.024 g/L. The mean (SD) radioactive concentration was 4.04 µCi/g (0.03 µCi/g). This was considered to be acceptable for dosing.

Radiolabelled GF-2032:	[^{14}C]-XDE-208, batch no. XS9-37562-34
Radiochemical purity	97% [determined by HPLC,]
Specific Activity	1.63 Mbq/g
Lot/Batch #:	E3026-33
Radiolabelled XDE 208	[^{14}C]-XDE-208, batch no. XS9-37562-34
Radiochemical purity	99.3% [determined by HPLC,]
Specific Activity	45.2 McI/mmo;

Lot/Batch #:	Batch no. XS9-37562-34
Non-Radiolabelled Test Material:	XDE-208
Description:	Analytical Standard
Lot/Batch #:	TSN105878
Purity:	99.8%
Contaminants:	n/a
CAS #:	946578-00-3



* - position of ^{14}-C [2-^{14}C]

. **Vehicle and/or positive control:** not appropriate

Test Species

3.

Species:	Rat/ Human skin
Preparation of Skin (Rat)	Eight male CD rats (Crl:CD(SD)), aged 35-42 days, weighing 190-200 g were obtained from Charles River UK Limited, Manston Road, Margate, Kent, CT9 4LT, UK. The animals were held in the animal rooms for 8 days. The dorsal hair on the animal was then clipped. The animals were then killed *ca* 25 h later by rising carbon dioxide narcosis with death confirmed by cervical dislocation. The weights of the carcass were determined and are provided in Appendix 8. All animals were within the desired age (6 to 8 weeks) and weight (200 g to 300 g) range when killed. The clipped area of the pelt was then removed using a scalpel. The pelts were divided into 2 along the mid lateral line, placed onto aluminium foil, placed onto self sealing bags and then stored at *ca* -20C until use.
Preparation of Skin (Human) :	A total of 10 samples of human skin, obtained from 5 different donors. The skin samples were removed from storage and allowed to thaw at ambient temperature. The thickness of the uncut skin membranes was measured using a micrometer. Split-thickness membranes were prepared by pinning the full-thickness skin, stratum corneum uppermost, onto a raised cork board and cutting at a setting equivalent to 200-400 µm depth using a Zimmer® electric dermatome. The membranes were then laid out onto aluminium foil and the thickness of the membranes measured using a micrometer. The split-thickness membranes were stored at *ca* -20°C. The thickness of the human and rat

full-thickness and split-thickness membranes is provided in Appendix 9.

Integrity Testing

The method as described by Meidan and Roper (2008) and modified by Runciman *et al.* (2009) was used. Tritiated water (250 µL, *ca* 100,000 disintegrations per minute [d.p.m.]) was applied to the surface of each skin sample and the donor chamber occluded. Penetration of tritiated water was assessed by collecting receptor fluid for 1 h and analysing the sample by liquid scintillation counting. The mean d.p.m. applied for the tritiated water was calculated from the seven mock tritiated water samples taken at the time of dosing. The percentage absorption was then calculated for each skin sample from the 1 h receptor fluid sample collected. Any human skin sample exhibiting a percentage absorption value greater than 0.6% was excluded from subsequent absorption measurements. A cross reference for skin cell number, donor number and % absorption is presented in Appendix 13. At the end of the 1 h period, residual tritiated water was removed from the skin surface by rinsing with water (*ca* 2 mL). The residual water was then removed from the skin surface using a plastic pastette, rinsed with water (*ca* 1 to 2 mL) and dried with tissue paper. An equilibration period of *ca* 90 min was allowed prior to collection of the pre-dose sample which was collected for *ca* 45 min.

Solubility in Receptor Fluid

Receptor fluid, tissue culture medium containing polyoxyethylene 20-oleyl (PEG, *ca* 6%, w/v), sodium azide (*ca* 0.01%, w/v), glucose (*ca* 1%, w/v), streptomycin (0.1 mg/mL) and penicillin G (100 units/mL) was used as the receptor fluid. 5% CO_2 in air was bubbled over the surface of the receptor fluid reservoir.

XDE-208 has a water solubility of *ca* 570 mg/L. For an application of 10 µL/cm^2 of the highest concentration formulation (GF-2032, 240 g/L) over a 0.64 cm^2 application area (*ca* 1536 µg/ 0.64 cm^2), if 100% was absorbed in 24 h (36 mL), then this was equivalent to 43 µg/mL (43 mg/L). Therefore, this receptor fluid was not considered to be rate limiting for solubility.

4. Preparation of dosing solutions:

Refer to section I. MATERIALS AND METHODS for preparation of dose

B. STUDY DESIGN AND METHODS:

1. Design:

An automated flow-through diffusion cell apparatus (Scott/Dick, University of Newcastle-upon-Tyne, UK) was used (see photograph overleaf). The flow-through cells were placed in a steel manifold heated *via* a circulating water bath to maintain the skin surface temperature at *ca* 32°C (Appendix 10). The cells were connected to multi-channel peristaltic pumps from their afferent ports, with the receptor fluid effluent dropping *via* fine bore tubing into scintillation vials on a fraction collector.

The surface area of exposed skin within the cells was 0.64 cm^2. The receptor chamber volume was 0.25 mL. The peristaltic pumps were adjusted to maintain a flow-rate of *ca* 1.5 mL/h

2. Dosing and sample collection:

Dosing

Test Preparation 1 (GF-2032) was applied over the surface of the stratum corneum of the exposed skin using a Gilson Microman positive displacement pipette set to deliver *ca* 6.4 µL (*ca* 10 µL/cm^2). The donor chambers were left open to the atmosphere. To accurately quantify the radioactivity applied to the skin samples, eight *ca* 6.4 µL aliquots of test preparation were taken and weighed. These samples were mixed with methanol (1 mL) and scintillant (10 mL) for analysis by liquid scintillation counting. Test Preparation 2 and Test Preparation 3 (in use dilutions of GF-2032) were applied to skin samples and analysed in a similar manner except that the representative dose confirmation samples were not weighed.

A summary of the cells to which each of the test preparations were applied are shown in the Table below.

Test Preparation No.	Cells Nos
1	28-37, 39-46 and 54
2	1-5, 7, 8, 10, 11, 13, 16-19 and 21-25
3	58-71, 73,76, 77, 79, 81 and 83

Sample Collection

Receptor fluid was collected in hourly fractions from 0 to 6 h post dose and then in 2 hourly fractions from 6 to 24 h post dose. All receptor fluid samples were mixed with scintillation fluid (10 mL) and analysed by liquid scintillation counting.

The exposure period was terminated at 10 h by applying concentrated commercial hand wash soap (*ca* 50 µL) to each cell which was rubbed in with a tissue swab. Each cell was then washed with commercial soap diluted in water (2%, v/v, 5 mL). Each aliquot was aspirated three times. The skin surface was dried with a tissue swab. This process was then repeated except that the skin surface was dried with two tissue swabs. The tissue swabs were retained in scintillation vials, mixed with methanol (1 mL) and scintillation fluid (10 mL) and analysed by liquid scintillation counting. The skin wash was pooled in one pre weighed skin wash vial per skin sample. Duplicate weighed aliquots (1 mL) were removed from each skin wash vial, mixed with scintillation fluid (10 mL) and analysed by liquid scintillation counting. The pipette tips were mixed with methanol (1 mL) and scintillation fluid (10 mL) and analysed directly by liquid scintillation counting.

At 24 h post dose, the diffusion cell was disconnected from the receptor fluid pump lines. The underside of the skin was washed (receptor rinse) with receptor fluid (1 to 2 mL), which was collected into vials, mixed with scintillation fluid (10 mL) and then analysed by liquid scintillation counting. The receptor rinse represented the absorbed test item, which was in the receptor chamber but had not been collected in the 22 to 24 h receptor fluid fraction. The skin was washed and dried as previously performed at 10 h post dose.

The cell was dismantled and the skin removed from the cell. The donor and receptor chambers were placed into pot containing ethanol (*ca* 20 mL and 40 mL, respectively). The solvent was then allowed to extract the test item for *ca* 30 min during this time, the sample were sonicated for *ca* 10 min. The equipment was then removed from the pots. Duplicate weighed aliquots (2 mL) were removed from each of the posts, mixed with scintillation fluid (10 mL) and analysed by liquid scintillation counting.

The stratum corneum was removed with 20 successive D-Squame® discs. Where a small piece of epidermis was removed, the tape strip number was recorded and the tape stripping process was stopped. These samples are provided in Appendix 15. The discs were placed into vial containing methanol (1 mL) and scintillant (10 mL) and analysed by liquid scintillation counting.

The skin under the cell flange (unexposed skin) was cut away from the exposed skin with scissors. The

samples were placed into individual vials containing Solvable® (1 mL) to dissolve the skin. The samples were placed into a water bath at *ca* 60-65°C for *ca* 2-5 h to aid tissue solubilisation. All samples were mixed with stannous chloride solution (0.2 g/mL, 50 µL) and scintillation fluid (10 mL) and analysed by liquid scintillation counting. Stannous chloride was added to reduce quenching of the liquid scintillant by Solvable®.

3. Statistics:

$$\text{Sample amount (µg equiv./cm}^2\text{)} = \frac{\text{sample radioactivity (d.p.m.)}}{\text{SA (d.p.m./µg equiv.) x exposure area (cm}^2\text{)}}$$

$$\text{Sample absorbed dose (\%)} = \frac{\text{sample radioactivity (d.p.m.)}}{\text{applied dose (d.p.m.)}} \times 100\%$$

II. RESULTS

The results for the test preparations can be expressed as absorbed dose (receptor fluid excluding the treated skin) or as the dermal delivery (receptor fluid plus the treated skin). This study incorporated the separation of the stratum corneum from the treated skin. The definition of the dermal delivery was refined to exclude the stratum corneum. The inclusion of the stratum corneum was covered by an additional definition of potentially absorbable dose.

The overall summary of the data is presented in the following Table

Test Preparation	1			
Target XDE-208 Concentration XDE-208 Concentration in Test Preparation by Radioactivity	240 g/L 244.51 g/L			
Species	Human		Rat	
Distribution	% Applied Dose	µg equiv./cm^2	% Applied Dose	µg equiv./cm^2
Dislodgeable Dose 10 h	94.73	2287.15	95.00	2293.66
Total Dislodgeable Dose	95.06	2295.13	95.46	2304.65
Unabsorbed Dose	95.16	2297.60	95.66	2309.67
Absorbed Dose	0.26	6.26	1.30	31.33
Dermal Delivery	0.31	7.51	1.63	39.24
Potentially Absorbable Dose	0.35	8.39	1.67	40.34
Mass Balance	95.48	2305.12	97.29	2348.92

Test Preparation	2			
Target XDE-208 Concentration	0.48 g/L			
XDE-208 Concentration in Test Preparation by Radioactivity	0.47 g/L			
Species	Human		Rat	
Distribution	% Applied Dose	ng equiv./cm^2	% Applied Dose	ng equiv./cm^2
Dislodgeable Dose 10 h	92.28	4336.15	84.53	3971.95
Total Dislodgeable Dose	93.99	4416.65	87.52	4112.44
Unabsorbed Dose	94.62	4445.98	89.34	4198.01
Absorbed Dose	1.54	72.57	3.94	185.03
Dermal Delivery	1.93	90.59	7.63	358.68
Potentially Absorbable Dose	2.44	114.63	8.72	409.97
Mass Balance	96.54	4536.57	96.97	4556.68

Test Preparation	3			
Target XDE-208 Concentration	0.024 g/L			
XDE-208 Concentration in Test Preparation by Radioactivity	0.0255 g/L			
Species	Human		Rat	
Distribution	% Applied Dose	ng equiv./cm^2	% Applied Dose	ng equiv./cm^2
Dislodgeable Dose 10 h	92.69	236.44	85.35	217.73
Total Dislodgeable Dose	94.45	240.94	88.00	224.49
Unabsorbed Dose	95.05	242.45	89.07	227.21
Absorbed Dose	1.15	2.92	4.34	11.08
Dermal Delivery	1.94	4.94	7.21	18.38
Potentially Absorbable Dose	2.38	6.07	8.02	20.45
Mass Balance	96.98	247.40	96.27	245.59

The report contains detailed tables for each test preparation, distribution of the dose , dose /collection period and distribution through the stratum corneum . The data is presented as % of dose applied and s absolute mass (µg equiv /cm^2). In addition the distribution through the Stratum Corneum is reported by the analysis of the individual tape strips. The data is also presented graphically.

III. DISCUSSION

A. Applicants conclusions

In conclusion, the dermal delivery for [^{14}C]- XDE-208 from GF-2032 (240 g/L) essentially ceased after 8 to 12 hours. Comparing the mean results generated as µg equiv./cm^2 or percentage of dose, the dislodgeable and unabsorbed dose and the stratum corneum profiles for the rat and human were similar. The comparative absorbed dose was 0.26% (6.26 µg equiv./cm^2) and 1.30% (31.33 µg equiv./cm^2) for human and rat, respectively. The absorbed dose for the rat skin was greater than the human skin by a factor of 5-fold. A similar difference in this ratio was observed in the dermal delivery and potentially absorbable dose.

The dermal delivery of [^{14}C]-XDE-208 from the highest concentration in-use spray dilution (0.48 g/L) for rat and human skin based on the absorption profiles had a degree of similarity. However, there was a wash-in effect observed in the rat after the 10 h wash and not in the human. The absorption rate also reduced more evidently after washing in the rat than in the human skin. Absorption at 24 h was continuing although at a decreased rate. The dermal delivery was 1.93% (90.59 ng equiv./cm^2) and 7.63% (358.68 ng equiv./cm^2) for human and rat, respectively. The dermal delivery for the rat skin was

greater than the human skin by a factor of 4-fold. A similar difference in this ratio was observed when the potentially absorbable doses were compared, but a lower ratio (2.5-fold) was observed for the absorbed dose.

The dermal delivery of [^{14}C]-XDE-208 from the lowest concentration in-use spray dilution (0.024 g/L) for rat and human skin based on the absorption profiles had a degree of similarity. However, the rate of absorption fell more evidently in the human than in the rat at *ca* 4 h post dose and the reduction in the rat was increased after washing at 10 h post dose. Absorption at 24 h was continuing although at a significantly decreased rate. The dermal delivery was 1.94% (4.94 ng equiv./cm^2) and 7.21% 18.38 ng equiv./cm^2) for human and rat, respectively; which indicated that the rat skin had absorbed more XDE-208 than human skin by a factor of 3.7-fold. A similar difference in this ratio was observed for the potentially absorbable dose and absorbed dose.

IIIA1 7.6.2/01 Study comments	The study was evaluated during the inclusion of the active substance. The study is not revalued.
IIIA1 7.6.2/01 Agreed endpoint	In conclusion, the dermal delivery for [14C]- XDE-208 from GF-2032 (240 g/L) essentially ceased after 8 to 12 hours. Comparing the mean results generated as µg equiv./cm^2 or percentage of dose, the dislodgeable and unabsorbed dose and the stratum corneum profiles for the rat and human were similar. The dermal delivery was 0.35% (8.39 µg equiv./cm^2) and 1.67% (40.34 µg equiv./cm^2) for human and rat, respectively. The dermal delivery of [14C]-XDE-208 from the highest concentration in-use spray dilution (0.48 g/L) for rat and human skin based on the absorption profiles had a degree of similarity. However, there was a wash-in effect observed in the rat after the 10 h wash and not in the human. The absorption rate also reduced more evidently after washing in the rat than in the human skin. Absorption at 24 h was continuing although at a decreased rate. The dermal delivery was 2.44% (114.63 ng equiv./cm^2) and 8.72% (409.97 ng equiv./cm^2) for human and rat, respectively. The dermal delivery for the rat skin was greater than the human skin by a factor of 4-fold. A similar difference in this ratio was observed when the potentially absorbable doses were compared, but a lower ratio (2.5-fold) was observed for the absorbed dose. The dermal delivery of [14C]-XDE-208 from the lowest concentration in-use spray dilution (0.024 g/L) for rat and human skin based on the absorption profiles had a degree of similarity. However, the rate of absorption fell more evidently in the human than in the rat at *ca* 4 h post dose and the reduction in the rat was increased after washing at 10 h post dose. Absorption at 24 h was continuing although at a significantly decreased rate. The dermal delivery was 2.38% (6.07 ng equiv./cm^2) and 8.02% (20.45 ng equiv./cm^2) for human and rat, respectively; which indicated that the rat skin had absorbed more XDE-208 than human skin by a factor of 3.7-fold. A similar difference in this ratio was observed for the potentially absorbable dose and absorbed dose. **Overall Conclusions:** The *in vivo* rat dermal absorption for undiluted (240 g/L) was 1-2% of the applied dose measured for up to 192 h after exposure. The highest absorption was 2.11%, observed within the 48-hour group with skin included as per current guidance. For the most concentrated spray dilution (0.48 g/L spray dilution) absorption

increased to *ca* 18% at 144 - 192 h indicating that absorption was complete.
For the most dilute spray dilution (0.024 g/L spray), absorption increased to *ca* 20.5% at 144 h and was *ca* 20% at 192 h, indicating that absorption was complete.
Data from the study of absorption through rat and human skin ***in vitro*** gave a value for undiluted GF-2032 (240 g/L) of 1.67% for rat skin, which was very similar to the value of 1-2% for rat skin in the in vivo study. The corresponding value for human skin was 0.35%.
Dermal absorption of sulfoxaflor from the most concentrated spray dilution (0.48 g/L) was continuing for rat and human skin at 24 h although at a decreased rate. The potentially absorbable dose was 8.72% and 2.44% for rat and human skin, respectively.
Dermal absorption of sulfoxaflor from the most dilute spray dilution (0.024 g/L) was continuing for rat and human skin at 24 h although at a significantly decreased rate. The dermal delivery was 8.02% and 2.38% for rat and human skin, respectively.
The *in vivo* human equivalent values can be calculated from the *in vivo* rat data, by dividing the *in vivo* rat data by the *in vitro* rat/human ratio:

Suspension Concentration	(240 g/L)	(*in vivo* rat)/ (*in vitro rat/ in vitro* human) = 0.4 % (2.11)/(1.67/0.35)
Spray dilution	(0.48 g/L)	(*in vivo* rat)/ (*in vitro rat/ in vitro* human) = 5 % (18.86)/(8.72/2.44)
Spray dilution	(0.024 g/L)	(*in vivo* rat)/ (*in vitro rat/ in vitro* human) = 6 % (20.51)/(8.02/2.38)

Endpoints used in risk assessment

- Concentrate

As the highest concentration of sulfoxaflor (120 g/L) is below the concentration tested in that study (240 g/L), a pro rata adaption has to be performed (according to EFSA 2012) for the spray dilution, which results in a value of 0.8% (0.4% x 240 / 120) dermal absorption for the concentrate.

- Field dilution

As the lowest concentration of sulfoxaflor defined in the GAP (0.0096 g /L) is below the concentration tested in that study (0.024 g/L), a pro rata adaption has to be performed (according to EFSA 2012) for the spray dilution, which results in a value of 12 % (6% x 0.024 / 0.012) dermal absorption for the spray dilution.

Dermal penetration	Concentrate: 0.8% In-use dilution: 12%

IIIA 7.7 Dislodgeable residues

IIIA 7.7.1 Dislodgeable residues – foliar

IIIA 7.7.1/1 Dislodgeable residues – foliar – Broccoli

Citation: Rotondaro, A, McKellar, R. 2010. Dissipation of Dislodgeable Foliar Sulfoxaflor Residues from Treated Broccoli. Dow AgroSciences Report No. 101091. 09 July 2010.

Executive Summary

Three applications at 100 g/Ha of were made to evaluate the foliar dissipation of sulfoxaflor on broccoli in two growing regions of the United States. The trials were conducted in California and Georgia with the suspension concentrate (240SC) formulation in the spring of 2010. The samples were shipped to Dow AgroSciences LLC for analysis. Field fortifications were conducted a total of five times for both trials; two in California and three in Georgia. The recoveries ranged from 81.4% to 116% with an overall average of 99.8%. Dislodgeable residues at the California site ranged from 0.158 µg/cm2 at time zero after the first application to 0.00178 µg/cm2 at the 21 day sampling interval following the final application. Dislodgeable residues at the Georgia site ranged from 0.343 µg/cm2 at time zero after the first application to none detected at the 14 day sampling interval following the final application. The half life of sulfoxaflor on the leaf surface ranged from 1.0 day at the Georgia site to 3.0 days at the California site (Table 7). The average half life was determined to be 2.0 days.

IIIA1 7.7.1/1 Study comments	The study is acceptable.
IIIA1 7.7.1/1 Agreed endpoint	Nevertheless, the study was realized on the broccoli. Consequently, she cannot be used for the other claimed cultures. Furthermore, this study is judged not necessary.

IIIA 7.7.2 Dislodgeable residues – soil

This is not an EC data requirement in Regulation 1107/2009/EC.

IIIA 7.7.3 Dislodgeable residues – indoor surface and volatilisation

This is not an EC data requirement in Regulation 1107/2009/EC.

IIIA 7.8 Epidemiology

This is not an EC data requirement in Regulation 1107/2009/EC.

IIIA 7.9 Data on Formulants

IIIA 7.9.1 Material Safety Data Sheet for each formulant

Data on formulants are considered CONFIDENTIAL BUSINESS INFORMATION as public disclosure would compromise trade secrets regarding the composition of the formulation.

IIIA 7.9.2 Available toxicological data for each formulant

Data on formulants are considered CONFIDENTIAL BUSINESS INFORMATION as public disclosure would compromise trade secrets regarding the composition of the formulation.

IIIA 7.10 Domestic animal/livestock assessment

This is not an EC data requirement in Regulation 1107/2009/EC.

IIIA 7.11 Other/special studies

No other/special studies.

Appendix 1 List of data submitted in support of the application

Data protection statement
Dow AgroSciences is the first applicant for approval of this active substance. Data protection for the studies and tests indicated in the following reference list is claimed for a period of 10 years from the first authorisation of the formulation in each Member State in accordance with Article 59 of Regulation (EC) No 1107/2009.

These tests and studies are submitted to a Member State for first time and as such, all are considered necessary for the authorisation. Relevant studies (as listed in SanCo Guidance Document 7109/VI/1995) have been conducted in compliance with the principles of GLP or GEP.

Annex Point/ Reference Number	Author(s)	Year	Title Source (where different from the Company), Company, Report Number, GLP or GEP status (where relevant), Published or not	Data Protection claimed (Y/N)	Owner
KIIIA 7.1.1	[redacted]	2009	GF-2032: Acute Oral Toxic Class Method in Rats [redacted] Report No.: 080049 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIIA 7.1.2	[redacted]	2009a	GF-2032: Acute Dermal Toxicity Study in Rats [redacted] Report No.: 080050 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIIA 7.1.3	[redacted]	2012	GF-2032: Acute Liquid Aerosol Inhalation Toxicity Study in F344/Ducrl Rats [redacted] Report No.: 081191 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS

Annex Point/ Reference Number	Author(s)	Year	Title Source (where different from the Company), Company, Report Number, GLP or GEP status (where relevant), Published or not	Data Protection claimed (Y/N)	Owner
KIIIA 7.1.4	[redacted]	2009b	GF2032: Primary Skin Irritaton Study in Rabbits [redacted] Report No.: 080051 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIIA 7.1.5	[redacted]	2009c	GF-2032: Primary Eye Irritation Study in Rabbits [redacted] Report No.: 080052 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIIA 7.1.6	[redacted]	2008	GF-2032: Local Lymph Node Assay in CBA/J Mice [redacted] Report No.: 081180 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIIA 7.6.1	[redacted]	2010	XDE-208: The In Vivo Percutaneous Absorption of Radiolabelled XDE-208 in Formulation (GF-2032) and Two In-Use Spray Dilutions in the Rat (OECD 427) [redacted] Report No.: 191168 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS

Annex Point/ Reference Number	Author(s)	Year	Title Source (where different from the Company), Company, Report Number, GLP or GEP status (where relevant), Published or not	Data Protection claimed (Y/N)	Owner
KIIIA 7.6.2	[redacted]	2010	XDE-208: The *In Vitro* Percutaneous Absorption of Radiolabelled XDE-208 in Formulation (GF-2032) and Two In-Use Spray Dilutions through Rat and Human Skin (OECD 428) [redacted] Report No.: 786740 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIIA 7.7.1/2	[redacted]	2010b	Dissipation of Dislodgeable Foliar Sulfoxaflor Residues from Treated Broccoli [redacted] Report No.: 101091 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS

Appendix 2 Table of intended uses, GAP and justification for the risk envelope

Austria	Aubergines (incl. Pepinos), Bulbs, Ornamentals, Flowers, Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Pepper (incl. Chilli pepper), Tomatoes
Belgium	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers
Bulgaria	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers
Croatia	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos)
Cyprus	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos)
France	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon)
Germany	Aubergines (incl. Pepinos), Bulbs, Ornamentals, Flowers, Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Pepper (incl. Chilli pepper), Tomatoes
Greece	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers
Ireland	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers
Italy	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers
Malta	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos)
Netherlands	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers
Portugal	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers
Romania	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos)
Poland	Aubergines (incl. Pepinos), Bulbs, Ornamentals, Flowers, Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Pepper (incl. Chilli pepper), Tomatoes
Spain	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers
UK	Tomatoes, Pepper (incl. Chilli pepper), Aubergines (incl. Pepinos), Cucurbits (Cucumber, Water Melon, Zuccini, Melon), Bulbs, Ornamentals, Flowers

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number min max	Interval between applications (min)	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		
Aubergines (incl. Pepinos)	All zones (AT, BE, BG, HR,	GF-2626	G	Aphids, Whiteflies	SC	120 g/L	Ground applied foliar	BBCH 20-87 All year	1-2	7	0.0016-0.0096	500 - 1500	0.024-0.048 (see Remarks)	1	Aphids: One or two applications of 0.024 g a.s./ha. Two applications would be minimum 7

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application			Interval between applications (min)	Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number min max		kg as/hl min max	Water (l/ha) min max	kg as./ha min max		
	CY, FR, DE, EL, IE, IT, MA, NL, PT, RO, ES, UK, PL)						spray, broadcast								days interval. Whiteflies: Either two applications of 0.024 kg a.s./hawith a minimum 7 days interval or only one application of 0.048 g a.s./ha.
Bulbs, Ornamentals, Flowers	All zones (AT, BE, BG, FR, DE, EL, IE, IT, NL, PT, ES, UK, PL)	GF-2626	G	Aphids, Whiteflies	SC	120 g/L	Ground applied foliar spray, broadcast	BBCH 12-59 All year	1-2	7	0.0012-0.024	200 - 2000	0.024-0.048 (see Remarks)	1	Aphids: One or two applications of 0.024 g a.s./ha. Two applications would be minimum 7 days interval. Whiteflies: Either two applications of 0.024 kg a.s./hawith a minimum 7 days interval or only one application of 0.048 g a.s./ha.
Cucurbits (edible peel – cucumbers, courgettes, gherkins; inedible peel – melons, pumpkins/ squash, Zuccini, watermelons)	All zones (AT, BE, BG, FR, DE, EL, IE, IT, NL, PT, RO, ES, UK, PL)	GF-2626	G	Aphids, Whiteflies	SC	120 g/L	Ground applied foliar spray, broadcast	BBCH 20-87 All year	1-2	7	0.0016-0.0096	500 - 1500	0.024-0.048 (see Remarks)	1	Aphids: One or two applications of 0.024 g a.s./ha. Two applications would be minimum 7 days interval. Whiteflies: Either two applications of 0.024 kg a.s./hawith a minimum 7 days interval or only one application of 0.048 g a.s./ha.

Crop and/or situation (a)	Member State or Country	Product Name	F or G (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI days (k)	Remarks (l)
					Type (d-f)	Conc. of a.s. (i) g/L	Method Kind (f-h)	Growth stage (j)	Number min max	Interval between applications (min)	kg as/hl min max	Water (l/ha) min max	kg as./ha min max		
Pepper (incl. Chilli pepper)	All zones (AT, BE, BG, HR, CY, FR, DE, EL, IE, IT, MA, NL, PT, RO, ES, UK, PL)	GF-2626	G	Aphids, Whiteflies	SC	120 g/L	Ground applied foliar spray, broadcast	BBCH 20-87 All year	1-2	7	0.0016-0.0096	500 - 1500	0.024-0.048 (see Remarks)	1	Aphids: One or two applications of 0.024 g a.s./ha. Two applications would be minimum 7 days interval. Whiteflies: Either two applications of 0.024 kg a.s./hawith a minimum 7 days interval or only one application of 0.048 g a.s./ha.
Tomatoes	All zones (AT, BE, BG, HR, CY, FR, DE, EL, IE, IT, MA, NL, PT, RO, ES, UK, PL)	GF-2626	G	Aphids, Whiteflies	SC	120 g/L	Ground applied foliar spray, broadcast	BBCH 20-87 All year	1-2	7	0.0016-0.0096	500 - 1500	0.024-0.048 (see Remarks)	1	Aphids: One or two applications of 0.024 g a.s./ha. Two applications would be minimum 7 days interval. Whiteflies: Either two applications of 0.024 kg a.s./hawith a minimum 7 days interval or only one application of 0.048 g a.s./ha.

Remarks:
(a) For crops the EU and Codex classifications (both) should be used.
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) e.g. biting and sucking insects, soil borne insects, foliar fungi, weeds
(d) e.g. wettable powder (WP),emulsifiable concentrate (EC), granule (GR)
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants
(i) g/kg or g/l
(j) Growth stage at last treatment, including where relevant information on season at time of application

(e) GIFAP Codes - GIFAP Technical Monograph No. 2, 1989
(f) All abbreviations must be explained

(k) The minimum and maximum number of applications possible under practical conditions must be given
(l) PHI - Pre-harvest interval
(m) Remarks may include: Extent of use/ economic importance/restrictions (e.g. feeding/grazing)/minimal intervals between applications. Indicate uses not yet authorised.

Appendix 3 Operator and bystander calculations

Appendix 3 Table 1

Estimation of operator exposure to the active ingredient sulfoxaflor upon application of GF-2626 (ornamental, BBA model, glasshouse, hand held sprayer, no PPE)

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Hand-held sprayer: hydraulic nozzles. Outdoor, high level target					
Product	GF-2626		Active substance		Sulfoxaflor	
Formulation type	Liquid		a.s. concentration		120	g/l
Dermal absorption from product	0,8	%	Dermal absorption from spray		12	%
RPE during mix/loading	None		RPE during application		None	
PPE during mix/loading	None					
PPE during application: Head	None	Hands	None	Body	None	
Dose	0,4	l product/ha	Work rate/day		1	ha

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	205	mg/kg a.s.
Hand contamination/day	9,84	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	9,84	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,05	mg/kg a.s.
Inhalation exposure/day	0,0024	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0024	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique: Hand-held sprayer: hydraulic nozzles. Outdoor, high level target

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	4,8	10,6	25	
Dermal contamination/day	0,2304	0,5088	1,2	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	1,9392	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,3	mg/kg a.s.
Inhalation exposure/day	0,0144	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0,0144	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	9,84	mg/day	1,9392	mg/day
Percent absorbed	0,8	%	12	%
Absorbed dose (dermal route)	0,07872	mg/day	0,232704	mg/day
Inhalation exposure to a.s.	0,0024	mg/day	0,0144	mg/day
Total systemic exposure	0,08112	mg/day	0,247104	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0,328224	mg/day
Operator body weight	70	kg
Operator exposure	**0,004688914**	**mg/kg bw/day**

AOEL (mg/kg/day) =	0,0600
% of AOEL =	**7,8%**

Appendix 3 Table 2

Estimation of operator exposure to the active ingredient sulfoxaflor upon application of GF-2626 (ornamental, BBA model, glasshouse, hand held sprayer, no PPE)

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Hand-held sprayer (15 l tank): hydraulic nozzles. Outdoor, low level target				
Product	**GF-2626**		Active substance	**Sulfoxaflor**	
Formulation type	water-based		a.s. concentration	**120**	mg/ml
Dermal absorption from product	**0,8**	%	Dermal absorption from spray	**12**	%
Container	1 litre any closure				
PPE during mix/loading	None		PPE during application	None	
Dose	**0,4**	l/ha	Work rate/day	**1**	ha
Application volume	**200**	l/ha	Duration of spraying	**6**	h

EXPOSURE DURING MIXING AND LOADING

Container size	1	litres
Hand contamination/operation	0,01	ml
Application dose	0,4	litres product/ha
Work rate	1	ha/day
Number of operations	14	/day
Hand contamination	0,14	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0,14	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Hand-held sprayer (15 l tank): hydraulic nozzles. Outdoor, low level target			
Application volume	200			spray/ha
Volume of surface contamination	50			ml/h
Distribution	Hands	Trunk	Legs	
	25%	25%	50%	
Clothing	None	Permeable	Permeable	
Penetration	100%	20%	18%	
Dermal exposure	10	2,5	4,5	ml/h
Duration of exposure	6			h
Total dermal exposure to spray	102			ml/day

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0,14	ml/day	102	ml/day
Concen. of a.s. product or spray	120	mg/ml	0,24	mg/ml
Dermal exposure to a.s.	16,8	mg/day	24,48	mg/day
Percent absorbed	0,8	%	12	%
Absorbed dose	0,1344	mg/day	2,9376	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0,02	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0,24	mg/ml
Inhalation exposure to a.s.	0,0288	mg/day
Percent absorbed	100	%
Absorbed dose	0,0288	mg/day

PREDICTED EXPOSURE

Total absorbed dose	3,1008	mg/day
Operator body weight	60	kg
Operator exposure	0,05168	mg/kg bw/day

AOEL (mg/kg/day) =	0,0600
% of AOEL =	**86,1%**

Appendix 3 Table 3
Resident Exposure Estimation BfR Calculator – ornamentals

Estimation of bystander and resident exposure (adults and children)

Active substance (a.s.)		**Sulfoxaflor**
Product		**GF-2626**
Intended uses	**Ornamental**	**High crops, hand held (HCHH)**
Treated area per day (A)	**1**	**ha/d**
Application rate (AR)	**0,048**	kg a.s./ha
Number of applications (NA)	**1**	1)

1) Consideration of more than two applications are not necessary if degradation of the active substance on foliage of at least 50 % can be assumed between two applications (otherwise use multiple application factor).

Dermal absorption (DA)	**12**	% (worst case, e.g. during application)
Inhalation absorption (IA)	**100**	%
Oral absorption (OA)	**100**	%
Systemic AOEL	**0,06**	mg/kg bw/d
Body weight (BW)	**60**	kg/person (adults)
	16,15	kg/person (children)

Distance between application and bystander or resident:

Field crops not selected		m
HCTM/HCHH:	**Vegetables, ornamentals, berry fruits (> 50 cm)**	
	3	m
Home & garden not selected		
		m

Drift deposit (D) for 1 appl. based on appl. technique and distance: **8,02 % (HCHH, 3 m)**

Airborne vapour concentration (ACv) mg/m^3 2)

2) 1 µg/m^3 for semivolatile substances, i.e. vapour pressure (20 °C): ≥ 1x10^{-5} - < 5x10^{-3} Pa; 15 µg/m^3 for volatile substances, i.e. vapour pressure (20 °C): ≥ 5x10^{-3} Pa

Estimation of resident exposure after application in High crops, hand held (HCHH)

Input parameters considered for the estimation of resident exposure:

Intended use(s):	Ornamental		**Drift (D):**	8,02	% (HCHH, 3 m)
Application rate (AR):	0,048	kg a.s./ha	**Transfer coefficient (TC):**	7300	cm^2/h (adults)
				2600	cm^2/h (children)
Number of applications (NA):	1		**Turf Transferable Residues (TTR):**	5	%
Body weight (BW):	60	kg/person (adults)	**Exposure Duration (H):**	2	h
	16,15	kg/person (children)	**Airborne Concentration of Vapour (ACV):**	none	
Dermal absorption (DA):	12,00	% ('worst case')	**Inhalation Rate (IR):**	16,57	m^3/d (adults),
Inhalation absorption (IA):	100	%		8,31	m^3/d (children)
Oral absorption (OA)	100	%	**Saliva Extraction Factor (SE):**	50	%
AOEL	0,06	mg/kg bw/d	**Surface Area of Hands (SA):**	20	cm^2
			Frequency of Hand to Mouth (Freq):	20	events/h
			Dislodgeable foliar residues (DFR):	20	%
			Ingestion Rate for Mouthing of Grass/Day (IgR):	25	cm^2/d

Resident exposure towards Sulfoxaflor					
Adults			**Children**		
Residents: Dermal exposure after application in Ornamental (via deposits caused by spray drift)					
SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW			SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW		
(0,00048 x 1 x 8,02% x 5% x 7300 x 2 x 12%) / 60			(0,00048 x 1 x 8,02% x 5% x 2600 x 2 x 12%) / 16,15		
External exposure	0,02810208	mg/person	External exposure	0,01000896	mg/person
External exposure	0,00046837	mg/kg bw/d	External exposure	0,00061975	mg/kg bw/d
Absorbed dose:	**0,0000562**	**mg/kg bw/d**	**Absorbed dose:**	**0,0000744**	**mg/kg bw/d**
Residents: Inhalation exposure to vapour					
SIE_R = (AC_V x IR x IA) / BW			SIE_R = (AC_V x IR x IA) / BW		
(0 x 16,57 x 100%) / 60			(0 x 8,31 x 100%) / 16,15		
External exposure		mg/person	External exposure		mg/person
External exposure		mg/kg bw/d	External exposure		mg/kg bw/d
Absorbed dose:		**none**	**Absorbed dose:**		**none**
			Residents: Oral exposure (hand-to-mouth transfer)		
			SOE_H = (AR x NA x D x TTR x SE x SA x Freq x H x OA) /		
			(0,00048 x 1 x 8,02% x 5% x 50% x 20 x 20 x 2 x 100%) / 16,15		
			External exposure	0,00076992	mg/person
			External exposure	4,7673E-05	mg/kg bw/d
			Absorbed dose	**0,0000477**	**mg/kg bw/d**
			Residents: Oral exposure (object-to-mouth transfer)		
			SOE_O = (AR x NA x D x DFR x IgR x OA) / BW		
			(0,00048 x 1 x 8,02% x 20% x 25 x 100%) / 16,15		
			External exposure	0,00019248	mg/person
			External exposure	1,1918E-05	mg/kg bw/d
			Absorbed dose	**0,0000119**	**mg/kg bw/d**
Total systemic exposure: SE_R = SDE_R + SIE_R			Total systemic exposure: SE_R = SDE_R + SIE_R + SOE_H + SOE_O		
Total systemic exposure (absorbed dose)	0,00337225	mg/person	Total systemic exposure (absorbed dose)	0,00216348	mg/person
Total systemic exposure (absorbed dose)	**0,0000562**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0,0001340**	**mg/kg bw/d**
% of AOEL:	**0,09**	**%**	**% of AOEL:**	**0,22**	**%**

Appendix 4 : Applicant's assessment

IIIA 7.3.1 Estimation of operator exposure without personal protection

Estimations of potential operator exposure to sulfoxaflor associated with application of GF-2626 were made using the UK POEM and the German model and Southern European Greenhouse (EOEM) greenhouse model v. 2.1 for greenhouse crops assuming the maximum proposed application rate for each crop group detailed in Table 7.3.1. The German Model handheld data are applicable to high crops only and the UK POEM handheld data is applicable to low crops only, therefore, the crop could be low or high depending on growth stage and/or growing method being utilised and both models are presented.

The Greenhouse Model is based on data derived from handlance applications and, therefore, may be regarded as more relevant to predict exposures for the supported uses of GF-2626. The Greenhouse Model contains 4 application scenarios, standard low crop, intensive low crop, standard high crop and intensive high crop. The intensive scenarios are when crops are grown in narrow or no rows and direct contact with treated foliage cannot be avoided. All 4 scenarios are considered due to the wide range of supported crops that GF-2626 may be applied to and the wide range of growing systems that may be used across the EU.

Predicted systemic exposures are summarised in Table 7.3.1-2. Individual spreadsheets are presented in Appendix 3, Tables 1, 2, 2a and 4.

Table 7.3.1-2: Estimation of operator exposure for GF-2626 assuming PPE is not used*

Crop	Application rate		Spray volume L/ha	Model	Total systemic exposure as % AOEL
	Product L/ha	**Active substance** kg/ha			
Fruiting vegetables: Cucurbits (Edible and non-edible peel), Solanaceous vegetables	0.2-0.4	0.024-**0.048**	**500**-1500	German*	**5** (Table 1)
				UK	**26** (Table 2)
Ornamentals (Bulbs, Ornamentals, Flowers)	0.2-0.4	0.024-0.**048**	**200**-2000	German*	**5** (Table 1)
				UK	**45** (Table 2a)
Greenhouse Model[#] – Handlance applications					
All Crops	Low standard	0.024-0.**048**	NA	Greenhouse Model	**1** (Table 4)
	Low intensive				**25** (Table 4)
	High standard				**4** (Table 4)
	High intensive				**No data** (Table 4)

* The Notifier and Agrochemical Industry, in agreement with SANCO/6895/2009 rev. 1, does not believe that the scenario of T-shirts and shorts is appropriate attire for professional applicators and, therefore, has included the coverall giving additional consistency with the clothing of the UK POEM.

[#] Applications in greenhouses can be made to high >0.5m or low <0.5m crops. Data is presented for both options and includes a scenario for standard and l intensive contact with treated crop. For the intensive high crop contact scenario gloves and impervious clothing are mandatory. Therefore, an estimation of exposure for intensive scenarios assuming no PPE is not performed.

NA = Not Applicable.

IIIA 7.3.2 Estimation of operator exposure with personal protection

Estimation of operator exposure assuming PPE is used is required when the AOEL may be exceeded in the absence of PPE, or based on hazard classification requirements.

Exposure based on no PPE indicates that PPE will not be required for use of GF-2626 on greenhouse fruiting vegetables, and ornamentals according to predicted exposures using the German, UK and Greenhouse models.

In addition, GF-2626 is not classified for acute toxicity in accordance with criteria in Council Directive 1272/2008/EC (Classification, labelling and packaging of substances and mixtures) and 99/45/EEC (Dangerous Preparations Directive).

However for the application scenario "intensive contact with treated crop" gloves and impervious clothing are mandatory. Therefore an estimation of exposure with PPE for greenhouse applications is performed and presented below.

Predicted systemic exposures are summarised in Table 7.3.2-1. Individual spreadsheets are presented in Appendix 3, Tables 1, 3, 3a and 4.

Table 7.3.2-1: Estimation of operator exposure for GF-2626 assuming PPE[2] is used in greenhouse applications (gloves and impervious coverall for intensive contact scenario)

Crop	Application rate		Spray volume L/ha	Model	Total systemic exposure as % AOEL
	Product L/ha	**Active substance** kg/ha			
Greenhouse fruiting vegetables: Cucurbits, Solanaceous vegetables	0.2-0.4	0.024-**0.048**	**500**-2000	German*	**5** (Table 1)
				UK	**9** (Table 3)
Ornamentals (Bulbs, Ornamentals, Flowers)	0.2-0.4	0.024-0.**048**	**200**-2000	German*	**5** (Table 1)
				UK	**21** (Table 3a)
Greenhouse Model# – Handlance applications					
All Crops	Low standard	0.024-0.**048**	NA	Greenhouse Model	**1**[3] (Table 4)
	Low intensive				**2**[4] (Table 4)
	High standard				**2**[3] (Table 4)
	High intensive				**1**[5] (Table 4)

* The Notifier and Agrochemical Industry, in agreement with SANCO/6895/2009 rev. 1, does not believe that the scenario of T-shirts and shorts is appropriate attire for professional applicators and, therefore, has included the coverall giving additional consistency with the clothing of the UK POEM.

[2] PPE assumed – gloves for mixing, loading and application.
[3] PPE assumed – gloves for mixing/loading and application and a polycotton coverall during application.
[4] PPE assumed – gloves for mixing and loading and impervious trousers and gloves during application.
[5] PPE assumed – gloves for mixing/loading and gloves and an impermeable coverall during application.

Applications in greenhouses can be made to high >0.5m or low <0.5m crops. Data is presented for both options and includes a scenario for standard and l intensive contact with treated crop. For the intensive high crop contact scenario gloves and impervious clothing are mandatory. Therefore, an estimation of exposure for intensive scenarios assuming no PPE is not performed.

NA = Not Applicable.

Conclusion: Exposure of operators to from greenhouse applications of GF-2626 was estimated using the UK POEM and German models adapted for greenhouse applications. The models indicate that GF-2626 does not present an adverse risk to human health when applied to greenhouse fruiting vegetables and ornamental crops, even without PPE (≤ 45% of the AOEL for sulfoxaflor).

Exposure of operators to sulfoxaflor from greenhouse applications of GF-2626 was estimated using the Southern European (EOEM) greenhouse model. The model indicates that GF-2626 does not present an adverse risk to human health when applied to greenhouse crops when appropriate PPE is worn (≤ 2% of the AOEL for sulfoxaflor).

Greenhouse all crops – Southern European Greenhouse Model – with and without PPE

Data entry screen & summary calculation sheet — GREENHOUSE MODEL v_2.1

Product:	GF-2626	75th percentile			
Formulation:	Liquid				
Body weight [kg]:	70				
Active substance(s):	sulfoxaflor	Substance 2	Substance 3	Substance 4	Add substance
Concentration [g/l or kg]:	120	0	0	0	
Inhalation absorption [%]	100	0	0	0	
Dermal absorption [%]					Remove substance
Concentrate:	0.8	0.0	0.0	0.0	
Dilution:	6.0	0.0	0.0	0.0	
AOEL [mg/kg bw/day]	0.06	0.0	0.0	0.0	

Scenario 1:	Low crop, standard			Add application scenario
Application rate [l or kg product/ha]:	0.4			
Dose [kg a.s./ha]:	0.048	0.0	0.0	0.0
Work rate [ha/day]:	1.00			
		PPE during application:		
PPE during mix/loading:		Respiration:	None	
Respiration:	None	Hands:	Gloves	Remove application scenario
Hands:	Gloves	Head:	None	
		Body:	Coverall	

Scenario 2:	Low crop, intensive contact with treated crop			
Application rate [l or kg product/ha]:	0.4			
Dose [kg a.s./ha]:	0.048	0.0	0.0	0.0
Work rate [ha/day]:	1.00			
		PPE during application:		
PPE during mix/loading:		Respiration:	None	
Respiration:	None	Hands:	Gloves	
Hands:	Gloves	Head:	None	
		Body:	Impervious clothing	

Scenario 3:	High crop, standard			
Application rate [l or kg product/ha]:	0.4			
Dose [kg a.s./ha]:	0.048	0.0	0.0	0.0
Work rate [ha/day]:	1.00			
		PPE during application:		
PPE during mix/loading:		Respiration:	None	
Respiration:	None	Hands:	Gloves	
Hands:	Gloves	Head:	None	
		Body:	Coverall	

Scenario 4:	High crop, intensive contact with treated crop			
Application rate [l or kg product/ha]:	0.4			
Dose [kg a.s./ha]:	0.048	0.0	0.0	0.0
Work rate [ha/day]:	1.00			
		PPE during application:		
PPE during mix/loading:		Respiration:	None	
Respiration:	None	Hands:	Gloves	
Hands:	Gloves	Head:	None	
		Body:	Impervious clothing	

Appendix 3 Table 4 continued
Greenhouse all crops – Southern European Greenhouse Model – with and without PPE

Summary

Predicted systemic exposure as a percentage of the AOEL: Greenhouse Model

75th percentile

Active substance	Protection	Systemic exposure [mg/kg bw/day]	AOEL [mg/kg bw/day]	% of AOEL
Low crop, standard				
sulfoxaflor	None	0.00057	0.06	0.9
	With	0.00032		0.5
Low crop, intensive contact with treated crop				
sulfoxaflor	None	0.01477	0.06	24.6
	With	0.001088		1.8
High crop, standard				
sulfoxaflor	None	0.00225	0.06	3.7
	With	0.001201		2.0
High crop, intensive contact with treated crop				
sulfoxaflor	None		0.06	
	With	0.000742		1.2