Renewal Assessment Report

under Regulation (EC) 1107/2009

Zoxamide

Zoxium 240 SC

Volume 3

Plant protection product
B.6 Toxicology and Metabolism data

Rapporteur Member State: Latvia
Co-Rapporteur Member State: France

Version History

When	What
July 2016	Initial RAR

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B.6. TOXICOLOGY AND METABOLISM DATA AND ASSESSMENT OF RISKS FOR HUMANS

Introduction
Zoxium 240 SC is a suspension concentrate (SC) formulation containing a nominal 240 g/L of zoxamide. The product is a fungicide intended for use on grapevines and potatoes.

B.6.1. ACUTE TOXICITY OF PLANT PROTECTION PRODUCT

ZOXIUM 240 SC is a fungicide belonging to the chemical family of benzamides. It is a non-systemic active ingredient, acting by inhibition of cell division, used to control Oomycete fungi infecting potatoes, table grapes and wine grapes. Zoxamide inhibits germ tube development and mycelium growth by inhibiting cell division. Germ tube elongation and mycelium growth is arrested concomitant with the first cycle of nuclear division, preventing fungal penetration of the host plant.

Table B.6.1-1: Summary of acute toxicity, primary irritation and sensitisation studies

Parameter [Reference]	Species	Result mg/kg or mg/m3 or effect	Classification
Acute oral LD_{50} [redacted (1999). Report No: 98R-026]	Rat	>5000 mg/kg	Not required
Acute oral LD_{50} [redacted (1999). Report No: 98R-031]	Mice	>5000 mg/kg	Not required
Acute dermal LD_{50} [redacted (1999). Report No: 98R-027]	Rat	>5000 mg/kg	Not required
Acute inhalation LC_{50} [redacted (1999) Report No: 98R-025]	Rat	>1.3 mg/L (highest achievable concentration)	Not required
Acute skin irritation [redacted (1999). Report No: 98R-028]	Rabbit	non irritant	Not required
Acute eye irritation [redacted (1999). Report No: 98R-029]	Rabbit	non irritant	Not required
Skin Sensitization [redacted (1999): Report No. 98R-030]	Guinea pig	no delayed contact hypersensitivity	Not Required

B.6.1.1. Oral

Report:	**KCP 7.1.1/01, [redacted] (1999).**
Title:	RH-117,281 2F (240 SC) Acute Oral Toxicity Study in Male and Female Rats
Document No:	98R-026
Guidelines:	OECD Guideline 401; US EPA 40 CFR Part 158 Guideline 81-1; Japan 59 NohSan Notification No. 4200; Acute Oral Toxicity Study EEC Directive 92/69/EEC B.1
GLP	Yes (self certification by the laboratory)

Material and Methods:

RH-117,281 2F (240SC) (Lot No. YS-1239) is a liquid containing the active substance Zoxamide (nominal concentration: 23.7 wt %, measured concentration: 22.35 wt %). A single administration of the undiluted test substance was administered by gavage to six male and six female Crl:CD®BR rats at 5000 mg/kg bw.

Table B.6.1.1-1: Acute oral toxicity in rats of RH-117,281 2F (240SC)

Dose (mg/kg)	**Toxicological results***	**Duration of signs**	**Time of death**	**LD_{50} (mg/kg) (14 days)**
male rats				
5000	0/0/6	-	-	> 5000
female rats				
5000	0/0/6	-	-	> 5000

* Number of animals which died/number of animals with clinical signs/number of animals used

Findings:

- No clinical signs and no deaths were observed during the study.
- There were no treatment-related effects on body weight.
- Necropsy revealed no gross changes in all the animals.

Conclusion/endpoint:

Under the experimental conditions, the oral LD_{50} of RH-117,281 2F (240SC) is higher than 5000 mg/kg in rats.

RMS: Study is acceptable. LD_{50} of RH-117,281 2F (240SC) is higher than 5000 mg/kg. No classification is required.

B.6.1.2. Dermal

Report:	**KCP 7.1.2/01, [redacted] (1999)**
Title:	RH-117,281 2F (240SC) Acute Dermal Toxicity Study in Males and Female Rats
Document No:	98R-027
Guidelines:	OECD Guideline 402 US EPA 40 CFR Part 158 Guideline 81-2 Japan 59 NohSan Notification No. 4200 Acute Dermal Toxicity Study EEC Directive 92/69/EEC B.3
GLP	Yes (self certification by the laboratory)

Material and Methods:

The acute dermal toxicity of RH-117,281 2F (240SC) (Lot No. YS-1239, Toxicology Department Sample No. 97-018, 22.35% active ingredient) was assessed in Crl:CD®BR rats.

The test substance was applied undiluted to the shaved intact skin of six male and six female rats at 5000 mg/kg body weight. The application sites were occluded for 24 hrs. After the 24-hr exposure, the application sites were wiped with paper towels saturated with tap water and blotted dry with paper towels.

Findings:

- No mortalities, clinical signs of systemic toxicity, or body weight effects were observed during the study.
- Necropsy revealed no gross changes in all the animals.

Conclusion/endpoint:

Under the experimental conditions, the acute dermal LD_{50} of RH-117,281 2F (240SC) is higher than 5000 mg/kg in male and female rats.

RMS: Study is acceptable. LD_{50} of RH-117,281 2F (240SC) is higher than 5000 mg/kg in male and female rats. No classification is required.

B.6.1.3. Inhalation

Report:	**KCP 7.1.3/01, [redacted] (1999)**
Title:	Acute Inhalation Toxicity Study in Rats
Document No:	98R-025

Guidelines:	OECD Guideline 403 EEC Directive 92/69/EEC B.2 US EPA OPPTS 870.1300, Acute Inhalation Toxicity Japan 59 NohSan Notification No. 4200, Acute Inhalation Toxicity Study
GLP	Yes (self certification by the laboratory)

Material and Methods:

The acute inhalation toxicity of RH-1 17,281 2F (240SC) (Lot No. YS-I 239, Toxicology Department Sample No. 98-1 13, 22.35% active ingredient) was assessed in CrI:CD®BR rats. Six male and six female rats received a single 4-hr nose-only inhalation exposure to RH- I 17,281 2F (240SC) at a maximum attainable aerosol concentration of 1.3 mg/L of air. The particle size distribution for the test material exposure was characterized by a mean mass median aerodynamic diameter (MMAD) of 7.2 ± 0.4 µm and a mean geometric standard deviation (OSD) of 3.3 ± 0.4. Approximately 26% of the particles were ≤4.0 µm. Due to the physical properties of the test material, the FIFRA particle size criteria of 1-4 µm could not be achieved.

Findings:

- No mortalities or clinical signs of systemic toxicity were noted during the 14-day observation period.
- There were no body weight effects in either sex when compared to historical control values.
- Necropsy revealed no gross changes.

Conclusion/endpoint:

Under the experimental conditions, the acute inhalation LC_{50} of the RH-117,281 2F (240SC) was greater than the maximum attainable concentration of 1.3 mg/L of air in male and female rats.

RMS: The study is acceptable. LC_{50} of the RH-117,281 2F (240SC) is > 1.3 mg/L (maximum attainable concentration).

B.6.1.4. Skin irritation

Report:	**KCP 7.1.4/01, [redacted] (1999)**
Title:	RH-117,281 2F (240SC) Skin Irritation Study in Rabbits
Document No:	98R-028
Guidelines:	OECD Guideline 404 US EPA 40 CFR Part 158; Guideline 81-5 Japan 59 NohSan No. 4200, Primary Dermal Irritation Study EEC Directive 92/69/EEC B.4
GLP	Yes (self certification by the laboratory)

Material and Methods:

The skin irritation potential of RH-117,281 2F (240SC) (Lot No. YS-1239, Toxicology Department Sample No. 97-018, 22.35% active ingredient) was assessed in New Zealand White rabbits. The test substance (0.5 ml, as received) was applied topically to the shaved intact skin of six male rabbits. The application sites were semi-occluded for 4 hrs. After the 4-hr exposure, the application site was wiped with paper towels saturated with tap water and blotted dry with paper towels. Skin irritation was evaluated according to Draize criteria at approximately 1, 24, 48, and 72 hrs after patch removal.

Findings:

- No mortalities or clinical signs of systemic toxicity were observed during the study.
- Very slight erythema was noted in two rabbits at 1 hr only.
- No edema was observed during the study.
- The Irritation Index (PH) were 0.0 (Erythema) and 0.0 (Edema).

Table B.6.1.4-1: Skin Irritation Scores and Primary Irritation Index

Animal Number	Erythema				Edema			
	Hour				Hour			
	1	24	48	72	1	24	48	72
98-27017	1	0	0	0	0	0	0	0
98-27019	0	0	0	0	0	0	0	0
98-27021	1	0	0	0	0	0	0	0
98-27044	0	0	0	0	0	0	0	0
98-27045	0	0	0	0	0	0	0	0
98-27026	0	0	0	0	0	0	0	0

Conclusion: No skin irritation was noted. RH-117,281 2F (240SC) was not irritating to the rabbit skin.

RMS: The study is acceptable. No classification is required under the harmonised classification Regulation 1272/2008.

B.6.1.5. Eye irritation

Report:	**KCP 7.1.5/01, [redacted] (1999)**
Title:	RH-117,281 2F (240SC) Eye Irritation Study in Rabbits
Document No:	98R-029
Guidelines:	OECD Guideline 405 US EPA 40 CFR PART 158; Guideline 81-4 Japan 59 NohSan Notification No. 4200, Primary Eye Irritation Study EEC Directive 92/69/EEC B.5
GLP	Yes (self certification by the laboratory)

Material and Methods:

The eye irritation potential of RH-117,281 2F (240SC) (Lot No. YS-1239, Toxicology Department Sample No. 97-018, 22.35% active ingredient) was assessed in New Zealand White rabbits. The test substance (0.1 ml, as received) was applied into the conjunctival sac of six male rabbits. Eye irritation was evaluated according to Draize criteria at approximately 1, 24, 48 and 72 hrs after dosing. After the 24-hr observation, each eye (treated and control) was irrigated with0.9% saline for approximately 60 seconds.

Findings:

- No mortalities or clinical signs of systemic toxicity were observed.
- No ocular effects were evident during the study.
- No corneal, iridal or conjunctival effects were evident during the study.

Table B.6.1.5-1: Eye irritation scores

Animal numbers	**98-27056**			**98-270059**			**98-27061**			**98-27062**			**98-27063**			**98-27064**			**Mean***
Time (hr)	**24**	**48**	**72**	**24**	**48**	**72**	**24**	**48**	**72**	**24**	**48**	**72**	**24**	**48**	**72**	**24**	**48**	**72**	
Corneal Opacity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0.0**
Iris Lesions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0.0**
Conjuctival Redness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0.0**

Conjuctival Chemosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0.0**

* Mean of 24-, 48,- 72-hr Draize scores for all six animals

Conclusion/endpoint:

No eye irritation was noted. RH-117,281 2F (240SC) was not irritating to the rabbit eye.

RMS: The study is acceptable. No classification is required under the harmonised classification Regulation 1272/2008.

B.6.1.6. Skin sensitization

Report:	**KCP 7.1.6/01, [redacted] (1999)**
Title:	RH-117,281 2F (240SC): Delayed Contact Hypersensitivity Study in Guinea Pigs
Document No:	98R-030
Guidelines:	US EPA 40 CFR Part 158; Guideline 81-6 OECD Guideline 406 EEC Directive 92/69/EEC B.6 Japan 59 NohSan No. 4200, Dermal Sensitization Study
GLP	Yes (self certification by the laboratory)

Material and Methods:

The delayed contact hypersensitivity (DCH) potential of RH-117,281 2F (240SC) (Toxicology Department Sample Number 98-043, Lot Number TB 0335, 22.42% active ingredient) was tested in young adult male Hartley guinea pigs using the Buehler closed patch procedure. One group of 20 guinea pigs (Group 3) received three 6-hr induction doses (1 dose/week for 3 consecutive weeks) of 0.4 ml of undiluted RH-117,281 2F (240SC). An additional group of 10 guinea pigs (Group 2) received three 6-hr induction doses of 0.35 ml of undiluted hexylcinnamaldehyde (HCA) [Toxicology Department Sample Number 98-083, Lot Number 10021HF, containing 85% a.i.] and served as the positive control. Two weeks after the last induction dose, Group 3 animals were challenged with 0.4 ml of undiluted RH-117,281 2F (240SC). The positive control group was challenged with 0.35 ml of HCA at a concentration of 45% (w/w) in mineral oil. A naive control group of 10 guinea pigs (Group 1) was challenged at one site with 0.4 ml of undiluted RH-117,281 2F (240SC) and at a separate site with 0.35 ml of 45% (w/w) HCA in mineral oil. Dosing sites in each group were evaluated for erythema response at 24 and 48 hrs after challenge.

Findings:

- One out of ten animals in the non-induced (naive) control group displayed grade 1 erythema in response to the challenge application of undiluted RH-117,281 2F (240SC).
- Two out of 10 animals in the naive control group displayed grade 1 erythema in response to the challenge application of 45% (w/w) HCA in mineral oil.
- A 90% (9/10) incidence of erythema was observed in the HCA positive control group.

Conclusion/endpoint:

These results verify that the animals on test responded to a known sensitizer. No significant erythema (0/20) was observed in guinea pigs induced and challenged with undiluted RH-117,281 2F (240SC).

RMS: The study is acceptable. No classification is required under the harmonized classification Regulation 1272/2008.

There was slight disagreement with co-RMS France which indicated that Buehler test with 3 applications in not considered sensitive enough. However, it is still validated test guideline and widely used in EU. RMS is on the opinion, that the study is acceptable.

B.6.1.7. Supplementary studies on the plant protection product

No supplementary studies were performed on the plant protection product.

B.6.1.8. Supplementary studies for combinations of plant protection products

No supplementary studies were performed for combinations of plant protection products. No combination of plant protection products was recommended by the applicant.

B.6.2. DERMAL ABSORPTION

An *in vitro* dermal absorption study was conducted using Zoxium 240 SC.

Report:	**KCP 7.3/01, Craig, S., (2014)**
Title:	Zoxamide: The In Vitro Percutaneous Absorption of Radiolabelled Zoxamide in the Concentrate and Two In Use Spray Dilutions Through Human Skin
Document No:	Charles River Study number 794002
Guidelines:	OECD 428
GLP	Yes

Executive Summary

This study was conducted to assess the rate and extent of dermal absorption of Zoxamide from Zoxium concentrate and two in-use dilutions. An additional spray dilution was included in the study, as a surrogate of the 1:600 dilution foreseen for a second SC formulation containing Zoxamide at ca 180 g/L in addition to another active ingredient. As this formulation is not the one supported in this application, results will be not reported or discussed in the following summary.

The formulation concentrate was prepared by incorporating [^{14}C] Zoxamide into the blank formulation to achieve a final concentration of ca 240 g/L. The in use spray dilution was produced by mixing [^{14}C] Zoxamide with blank formulation and then diluting with water to give final test item concentration of 0.15 g/L (in-use spray dilution for Zoxium.

Split thickness human skin membranes were mounted into flow through diffusion cells. The receptor fluid was tissue culture medium supplemented with polyoxyethylene 20 oleyl ether (PEG oleyl ether?,

6% w/v). A tritiated water barrier integrity test was performed and any human skin sample exhibiting absorption greater than 0.6% of the applied dose was excluded from subsequent absorption measurements.

The test preparations (concentrate and in use spray dilution) were applied to the split thickness human skin membranes at an application rate of 10 µL/cm^2.

Percutaneous absorption was assessed by collecting receptor fluid in hourly fractions from 0 to 8 h post application and then in 2 hourly fractions from 8 to 24 h post application. At 8 h post application, exposure was terminated by washing the skin surface with a concentrated commercial hand wash soap followed by rinsing with a dilute soap solution and drying the skin surface with tissue paper (tissue swabs). At 24 h post application (termination), the underside of the skin was rinsed with receptor fluid.

The skin was then removed from the flow through diffusion cells and dried. The stratum corneum was removed with 20 successive tape strips. The remaining skin was divided into exposed and unexposed skin and solubilised with tissue solubiliser. All samples were analysed by liquid scintillation counting.

For none of the Test Preparations was absorption considered to be "complete" (as defined in the Guidance Document on Dermal Absorption (EFSA Journal 2011,9(7):2294)), because less than 75% of the absorption occurred within the first half of the study.

In conclusion, the dermal penetration value for Zoxium 240SC concentrate is estimated to be 4%, whilst the value for the 1:1000 in use dilution (0.15 g/L) was estimated at 10%.

I. MATERIALS AND METHODS

A. MATERIALS

1. Non-radiolabeled substances:

Zoxamide working standard

Description:	
Lot/Batch #:	Batch no. 2010041301
Chemical purity:	98%
Expiry date:	30 April 2014

2. Radiolabeled substances:

[^{14}C]-Zoxamide

Batch #:	Batch No. 76045 06 35
Specific activity:	151.76 µCi/mg
Radiochemical purity:	99.3%
Storage/Expiry date:	N/A – repurified immediately prior to use
Structure:	

o

3. Blank formulation:

Batch #:	
Description:	03052013
Chemical content:	Blank formulation
Expiry date:	No zoxamide 03 May 2015

4. Test system

Human skin
Six samples of full-thickness human skin (4 abdomen, 1 breast and 1 abdomen/back) were obtained from female donors aged 31 to 62 years old. On arrival at the testing facility the samples were placed into self-sealing plastic bags and stored in a freezer set to maintain a temperature of 20°C until used in the study.

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 in a freezer set to maintain a temperature of -20ºC for a maximum period of 2 months.

5. Flow-through diffusion cells and receptor fluid

An automated flow through diffusion cell apparatus (Scott/Dick, Newcastle University, UK) was used. The flow through diffusion cells were placed in a steel manifold heated via a circulating water bath to maintain the skin surface temperature at 32ºC ± 1ºC. The cells were connected to multichannel 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 cm2. The receptor chamber volume was 0.25 mL. The peristaltic pumps were calibrated to maintain a flow-rate of 1.5 mL/h ± 0.15 mL/h.

A tissue culture medium (MEME) supplemented with polyoxyethylene 20 oleyl ether (PEG oleyl ether?, 6% w/v), was used as the receptor fluid. The solubility of zoxamide in the receptor fluid was experimentally determined as follows.

[^{14}C]-Zoxamide was transferred into two 25 mL volumetric flasks. The solvent was dried off and the flasks were then filled to the 25 mL line with either Receptor Fluid or acetone (as a positive control). The solutions were mixed and heated for 1 h at *ca* 32°C and then centrifuged at 2000 *g* for 5 min. Duplicate aliquots (1 mL) of the resultant supernatant were taken, and analysed by liquid scintillation counting.

The results are provided in the following table:

Sample Type	Concentration of Zoxamide in Solution (g/L)	% of Target Zoxamide Concentration (1.024 g/L)
Receptor Fluid	0.117	11.4
Acetone	1.07	105

The data demonstrated that the entire applied dose of [^{14}C]-Zoxamide from the concentrate formulation would dissolve in 9 mL of receptor fluid (*i.e.* within 6 h). Therefore, this receptor fluid was not considered to be rate limiting for solubility. This solubility was considered to be the highest achievable concentration in the most suitable receptor fluid that would not interfere with the test system.

B. STUDY DESIGN AND METHODS:

1. Experimental phase: 20 November 2013 to 27 February 2014

2. Skin integrity assessment and treatment

Tritiated water was used to assess integrity. Any human skin sample exhibiting greater than 0.6% absorption was excluded from subsequent absorption measurements. Tritiated water was removed and the skin surface was rinsed with deionised water and dried with a tissue swab.

Preparation of [^{14}C]-Zoxamide Radiodilution

[^{14}C]-Zoxamide in Test Preparation 1

The Test Preparation 1, corresponding to the commercial formulation Zoxium 240 SC, was prepared by adding the blank formulation to an appropriate amount of [^{14}C]-Zoxamide.
By radioactivity, the concentration of [^{14}C]-Zoxamide was determined to be 248 g/L. This was 104% of the target concentration of 240 g/L. The [^{14}C] Zoxamide was homogenously distributed within the test preparation, with a CV of 0.77%. Therefore, Test Preparation 1 was accepted for dosing.

[^{14}C]-Zoxamide in Test Preparation 2

The Test Preparation 2, corresponding to the in-use spray dilution of Zoxium 240 SC, was prepared by adding the blank formulation and diluting with water to obtain the target concentration of 0.15 g/L. By radioactivity, the concentration of [^{14}C]-Zoxamide was determined to be 0.152 g/L. This was 101.52% of the target concentration of 0.15 g/L. The [^{14}C]-Zoxamide was homogenously distributed within the test preparation. Therefore, Test Preparation 2 was accepted for dosing.

Application of Test Preparations to Human Skin

[^{14}C]-Zoxamide in Test Preparation 1 was applied over the stratum corneum surface of the exposed skin of 10 split-thickness samples using a positive displacement pipette set to deliver 10 µL/cm^2. Cells were left open to the atmosphere. Seven representative aliquots of each test preparation were collected into scintillation vials at the time of dosing and actual concentrations (241 mg/mL and 0.161 mg/mL), as well as homogeneity (CV% 0.74 and 1.31, respectively), were confirmed.

3. Collection of Mass balance samples

Receptor Fluid Sampling

Receptor fluid was collected in hourly fractions from 0 to 8 h, then 2 hourly until 24 h post dose. All the receptor fluid samples were analysed by liquid scintillation counting.

Terminal Exposure (8 h Post Dose)

At 8 h post dose, the exposure period was terminated by applying commercial hand wash soap and gently rubbing into the skin surface using a tissue swab. The skin was then rinsed with ten aliquots of an aqueous dilution of commercial soap solution (2% in water, v/v). Each aliquot was aspirated with the pipette. The skin was dried with a tissue swab. This process was repeated and the skin was dried with an additional tissue swab. The soap solution (skin wash) was pooled into a single pre-weighed vial and acetone was added. Duplicate aliquots were removed from each skin wash vial, and analysed by liquid scintillation counting. The tissue swabs were pooled into a single vial, and analysed by liquid scintillation counting. The tip was cut in two, and analysed by liquid scintillation counting.

Terminal Exposure (24 h Post Dose)

At 24 h post dose, *i.e.* after a 16 h monitoring period, each flow-through cell was disconnected from the receptor fluid pump lines. The underside of the skin was rinsed (receptor rinse) with receptor fluid and analysed by liquid scintillation counting. The receptor rinse represented the absorbed test item, which was in the receptor chamber, but had not been collected into the 22 to 24 h receptor fluid fraction.

The donor and receptor chambers were dismantled and the skin removed. The donor and receptor chambers were transferred into separate pre-weighed pots (receptor chamber wash and donor chamber wash) containing a weighed amount of acetone:water (1:1 v/v). Skin was placed on a piece of tissue to remove any remaining receptor fluid from the underside of the skin. These pieces of tissue were then placed into the cell-specific receptor wash pots. The samples were left to extract the test item during which time they were sonicated for *ca* 10 min. The donor and receptor chambers were removed from the pots and duplicate aliquots (2 mL) were removed, and analysed by liquid scintillation counting.

The stratum corneum was removed with 20 successive tape strips. The skin was rotated *ca* 90° after each tape strip. Each tape was placed into a separate vial and the samples analysed by liquid scintillation counting.

The skin under the cell flange (unexposed skin) was cut away from the exposed skin using scissors. The unexposed and exposed skin samples were placed into individual scintillation vials containing Solvable® (1 mL) to solubilise the skin. Vials were incubated in a water bath (*ca* 60-65°C) until skin fully dissolved. Stannous chloride solution was added prior to liquid scintillation counting analysis.

Quantification of Total Radioactivity

All samples were counted together with representative blanks using suitable liquid scintillation media and a Packard 2100-TR liquid scintillation analyser with automatic quench correction by external standard. Representative blank sample values were subtracted from sample count rates to give net d.p.m. per sample. Prior to analysis, samples were allowed to stabilise with regard to light and temperature.

II. RESULTS

The distribution of radioactivity at 24 h post dose is provided in Table 6.2-1.

Test Preparation 1 (commercial formulation "Zoxium" - 240 g/L

The mean mass balance was 98.14% of the applied dose at 24 h post dose. The potentially absorbable dose was 2.54 ± 1.83%, and was the sum of radioactivity in the receptor fluid, receptor chamber rinse, receptor chamber wash (0.10%), exposed skin (0.24%) and tape strips 3-20 (2.19%). Tape strips 3-20 are included because absorption was not considered to be "complete" (i.e. <75% of the of the absorption into the receptor fluid occurred in the first 12 h of the study) as per the EFSA Guidance Document on Dermal Absorption (EFSA Journal 2011,9(7):2294). Absorption is defined as complete if greater than 75% of the absorption occurs within the first half of the study.

The dermal absorption value for use in risk assessment is taken as the potentially absorbable value. In this case, because the standard deviation is >25% of the mean value it is added to the mean to get the final estimate, in accordance with the EFSA guidance. Therefore the dermal penetration value for the concentrate is taken at 2.54 + 1.83 = 4% (rounding to the nearest whole number).

The flux peaked at 5 µg equiv./cm^2/h at 5-10 hours.

Test Preparation 2 (Zoxium in-use spray dilution - 0.15 g/L)

The mean mass balance was 101.22% of the applied dose at 24 h post dose. The potentially absorbable dose was 7.01 ± 2.59%, and was the sum of radioactivity in the receptor fluid, receptor chamber rinse, receptor chamber wash (0.45%), exposed skin (2.15%) and tape strips 3-20 (4.40). Tape strips 3-20 are included because absorption was not considered to be "complete" (i.e. <75% of the of the absorption into the receptor fluid occurred in the first 12 h of the study) as per the EFSA Guidance Document on Dermal Absorption (EFSA Journal 2011,9(7):2294). Two receptor fluid collections (22 h and 24 h) were incomplete for Cell 52. The data for Cell 52 has been included in the mean and SD.

The dermal absorption value for use in risk assessment is taken as the potentially absorbable value. In this case, because the standard deviation is >25% of the mean value it is added to the mean to get the final estimate, in accordance with the EFSA guidance. Therefore the dermal penetration value for the in-use spray dilution is taken at 7.01 + 2.59 = 10% (rounding to the nearest whole number).

The flux peaked at 0.32 µg equiv./cm^2/h at 8 hours.

Table 6.2-1: Results of the *in vitro* dermal absorption study of [^{14}C] through human skin (Percentage of dose - %, mean ± SD; n=6)

Test Preparation	**1**		**2**	
Target Zoxamide Concentration (g/L)	240		0.15	
Actual Zoxamide Concentration by Radioactivity (g/L)	241		0.161	
Application Rate of Test Preparation (µL/cm^2)	10.2		9.80	
Application Rate of Zoxamide (µg equiv/cm^2)	2458		1.58	
Time of maximal flux (hours)	5-10		8	
Maximum flux (µg equiv./cm^2/h)	5	3	0.32	0.22
	Mean n = 10	SD	Mean n = 10	SD
Skin Wash 8 h	49.24	12.65	23.55	5.88
Tissue Swab 8 h	42.91	15.81	67.66	6.91
Pipette Tip 8 h	0.09	0.17	0.03	°0.03
Dislodgeable Dose 8 h	92.24	3.82	91.23	3.36
Donor Wash	1.66	0.87	0.72	0.47
Tissue Swab 24 h	0.24	0.14	0.09	°0.06
Total Dislodgeable Dose	94.00	3.31	92.01	3.07
Stratum Corneum 1-2	1.60	0.84	2.16	0.84
Stratum Corneum 3-5	1.03	0.85	1.72	0.65
Stratum Corneum 6-10	0.80	0.85	1.62	0.77
Stratum Corneum 11-15	0.25	0.17	0.69	0.42
Stratum Corneum 16-20	0.11	0.08	0.38	0.24
Sum Strips 3-20	2.19	1.74	4.40	1.90
Sum Strip 1-20	3.79	2.38	6.57	2.43
Unexposed Skin	0.01	0.03	0.03	0.05
Exposed Skin	0.24	0.19	2.15	1.52
Receptor Fluid	0.02	0.01	0.39	0.16
Receptor chamber Rinse	°0.00	°0.00	°0.01	°0.00
Receptor chamber Wash	°0.08	°0.12	°0.06	°0.03
Total Absorbed in the fluid	0.10	0.12	0.45	0.19
Mass Balance	98.14	2.82	101.22	1.57

III. CONCLUSIONS

The dermal penetration value for Zoxium 240SC concentrate is 4%, whilst the value for the 1:1000 in use dilution (0.15 g/L) was estimated at 10%.

RMS: The study is acceptable. The dermal penetration value for Zoxium 240SC concentrate is 4%, whilst the value for the 1:1000 in use dilution (0.15 g/L) is 10%.

B.6.3. AVAILABLE TOXICOLOGICAL DATA RELATING TO CO-FORMULANTS

Please refer to Volume 4.

B.6.4. EXPOSURE DATA

Zoxium 240 SC is a suspension concentrate (SC) formulation containing a nominal 240 g/L of zoxamide. The product is a fungicide intended for use on grapevines and potatoes. The representative GAPs for the purposes of the AIR process are summarised in Table 6.4-1.

Table 6.4-1: Summary of the representative uses of Zoxium 240 SC

Crop Zone	**Pests or Group of pests controlled**	**Application**				**Application rate per treatment**		**PHI** days
		method kind	growth stage & season	number min max	interval between applications (min)	water l/ha min max	kg as/ha min max	
Potato All zones	Foliar fungi Late blight	Foliar spraying	BBCH 20-80	Max. 5	8 days	1000	0.15 - 0.18	7
Table and wine grapes Central and Southern EU	Foliar fungi Downy mildew	Foliar spraying	BBCH 15-79	Max.5	8 days	1000	0.15 - 0.18	28

B.6.4.1. Operator exposure

Risk assessment for operators

Operator exposure was assessed using the following standard approaches:

- Uniform Principles for Safeguarding the Health of applicators of Plant Protection Products (Uniform Principles for Operator Protection), Mitteilungen aus der Biologischen Bundesanstalt für Land-und Forstwirtschaft, Berlin-Dahlem, Heft 277, 1992. ("German model");

- Revised UK-POEM Model, (Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 1.0, (UK MAFF), 1992. ("UK model")).

Operator exposure was assessed against the AOEL of 0.3 mg/kg bw/day, which was agreed for the first inclusion of zoxamide in Annex I to Directive 91/414/EEC and listed in the Review Report for zoxamide (SANCO/10297/2003-Final).

Dermal absorption values are derived from an *in vitro* percutaneous absorption study with human skin (Craig, S., 2014). The values used in the exposure assessment are as follows:

Endpoint	Proposed endpoint
AOEL (mg/kg bw/day)	0.3
Dermal absorption of concentrate	4.0% (SC formulation, 240 g/L)
Dermal absorption of in-use dilution	10% (1/1000 dilution, 0.15 g/L)
Oral absorption	60%

The resulting exposure estimates are summarised in Tables 6.4.1-1 and 6.4.1-2

Table 6.4.1-1: Estimated operator exposure to Zoxium 240 SC using the German model and UK POEM for application to potatoes

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of AOEL (0.3 mg/kg bw/day)
Tractor boom sprayer application outdoors to low crops (Potatoes) *0.75 L of product/ha (equivalent to 180 g zoxamide/ha)*			
German Model • 20 ha/day • 70 kg operator	No PPE	0.016	5
UK POEM • 50 ha/day, 6 h/day • 1000 L/ha • 60 kg operator • 10 L with 63 mm closure	No PPE	0.045	15

Table 6.4.1-2: Estimated operator exposure to Zoxium 240 SC using the German model and UK POEM for application to Grapevine

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of AOEL
Tractor broadcast air-assisted sprayer application outdoors to high crops (Grapevines) *0.75 L of product/ha (equivalent to 180 g zoxamide/ha)*			
German Model • 8 ha/day • 70 kg operator	No PPE	0.026	9
UK POEM • 15 ha/day, 6 h/day • 1000 L/ha • 60 kg operator • 10 L with 63 mm closure	No PPE	0.053	18

Conclusion

The estimated level of exposure using the German Model and UK POEM are less than the AOEL for zoxamide when no personal protective equipment are worn. Therefore, according to the model calculations it can be concluded that the risk for the operator using Zoxium 240 SC for the proposed uses is acceptable without the use of PPE.

Estimation of operator exposure

Operator exposure estimates were calculated using the German Model (geometric mean) and UK POEM. Exposure was assessed on the basis of application to grapevines by broadcast air-assisted sprayer and to potatoes using a conventional tractor mounted boom sprayer. The worst-case scenario for the German model is given if the maximum dose rate is used. The worst-case scenario for UK POEM is given if the maximum dose rate and minimum water volume are used. For crops intended to be treated with Zoxium 240 SC, the critical GAPs are therefore:

Crop	Maximum application rate		Minimum water volume
Grapevines	0.75 L product/ha	180 g a.s./ha	1000 L/ha
Potatoes	0.75 L product/ha	180 g a.s./ha	1000 L/ha

The input parameters used in the models are listed below:

Input parameters for tractor-mounted application to potatoes

Equipment: Tractor-mounted boom sprayer
Formulation type: SC
Treated area: 50 ha/day (UK POEM), 20 ha/day (German Model)
Max. dose rate: 0.75 L product/ha
Min. water volume: 1000 L/ha
Body weight: 70 kg (German Model), 60 kg (UK POEM).

Input parameters for tractor-mounted application to grapevines

Equipment: Tractor-mounted broadcast air-assisted sprayer
Formulation type: SC
Treated area: 15 ha/day (UK POEM), 8 ha/day (German Model)
Max. dose rate: 0.75 L product/ha
Min. water volume: 1000 L/ha
Body weight: 70 kg (German Model), 60 kg (UK POEM).

The results taking into account the above mentioned input parameters are presented in Table 6.4.1-3. Detailed exposure calculations are also provided in Appendix 1.

Table 6.4.1-3: Summary of operator exposure for Zoxium 240 SC using the German model and UK POEM and the assuming application to potatoes and no personal protective equipment

Method	Application technique	Predicted systemic exposure [mg/kg bw/day]	% of AOEL*
German Model	Tractor-mounted/trailed boom sprayer	0.016	5
UK POEM	Tractor-mounted/trailed boom sprayer	0.045	15

*Compared to the systemic AOEL of 0.3 mg/kg bw/day for zoxamide.

Table 6.4.1-4: Summary of operator exposure for Zoxium 240 SC using the German model and UK POEM and the assuming application to grapevines and no personal protective equipment

Method	Application technique	Predicted systemic exposure [mg/kg bw/day]	% of AOEL*
German Model	Tractor-mounted/trailed broadcast air-assisted sprayer	0.026	9
UK POEM	Tractor-mounted/trailed broadcast air-assisted sprayer	0.053	18

*Compared to the systemic AOEL of 0.3 mg/kg bw/day for zoxamide.

Conclusion

The estimated level of exposure using the German Model and UK POEM are less than the AOEL for zoxamide when no PPE are worn. Therefore, further refinement of the exposure scenario is not required.

Measurement of operator exposure

Measurements of operator exposure are not required since estimated levels of exposure using UK POEM and the German Model demonstrate an acceptable risk.

B.6.4.2. Bystander and resident exposure

Risk assessment for bystander and resident

The GAP used for the assessment of bystander exposure was a single application of Zoxium 240 SC to grapevines by tractor-mounted/trailed broadcast air-assisted sprayer using 0.75 L product/ha (equivalent to 180 g zoxamide/ha). This approach assumed the minimum water volume requested (1000 L/ha), a dermal absorption of 10%, 5% spray drift onto a bystander with a 2 m^2 body surface together with inhalation exposure of 0.06 mL spray liquid per hour for an exposure duration of 1 hour. Assessment of bystander exposure using the EUROPOEM II model (Report of the bystander working group (Dec 2002)"[1]) is presented below. Table 7.2.2-1 lists the overall results with the detailed calculations appearing under Appendix 1.

An assessment of the exposure of residents has been made in accordance with the approach set out by Martin *et al*.[2]. The results of the assessment of residential exposure to zoxamide resulting from the use of Zoxium 240 SC on grapevines are summarised in Table 7.2.2-1.

As levels of spray drift from broadcast air-assisted sprayers are higher than from field crop (boom) sprayers this scenario represents the worst case for bystanders and residents).

Table 6.4.2-1: Summary of bystander and residents exposure from application of Zoxium 240 SC to grapevines via broadcast air-assisted sprayer

Exposure Scenario	Predicted exposure (mg/kg bw/day)	% of AOEL (0.3 mg/kg bw/day)
Bystander Exposure		
Adult	0.0032	1.1
Resident exposure		
Adult	0.00039	0.1
Child	0.00076	0.3

Conclusion

The total systemic exposure of a bystander walking along a field as it is being sprayed is estimated to be 1.1% of the AOEL. The total systemic exposure of a resident exposed to zoxamide during and following local application of Zoxium 240 SC is estimated to be less than 1% of the AOEL. The risk to bystanders and residents following the application of Zoxium 240 SC is considered to be acceptable.

Estimation of bystander and resident exposure

Bystander exposure

According to the recommendations made in the report from the EUROPOEM II project "Report of the bystander working group (Dec 2002)"[3], the worst case is given by treatment of grapevines with

[1] Gilbert A., Krebs B., Maasfeld W. and Philips J., 2002. Bystander exposure to pesticides – Report of the bystander working group. EUROPOEM II PROJECT FAIR3 CT96-1406.

[2] Martin S, Westphal D, Erdtmann-Vourliotis M, Dechet F, Schulze-Rosario C, Stauber F, Wicke H, Chester G, 2008. Guidance for exposure and risk evaluation for bystanders and residents exposed to plant protection products during and after application J. Verbr. Lebensm. 3 (2008): 272 – 281.

[3] Gilbert A., Krebs B., Maasfeld W. and Philips J., 2002. Bystander exposure to pesticides – Report of the bystander working group. EUROPOEM II PROJECT FAIR3 CT96-1406.

Zoxium240 SC at 0.75 L product/ha as levels of spray drift from broadcast air-assisted sprayers are assumed in the model to be 10X higher than from applications made by field crop (boom) sprayers.

The following parameters were used in the bystander assessment with detailed exposure calculations are provided in Appendix 1:

Dermal exposure model (spray drift)

AR: Application rate – 0.18 kg zoxamide/ha (equivalent to 18 mg/m^2)

D: drift fallout value, i.e. 5% from orchard sprayer applications, 90th percentile value for bystanders

BSA: body surface area – 2 m²

DA: Dermal Absorption – 10%

BW: body weight – 60 kg

Inhalation exposure model (Spray drift)

I*A: Specific inhalation exposure – 0.06 mL/hour

T: Exposure duration – 1 hour

SC: Application rate – 0.18 mg a.s./mL (180 g zoxamide/ha in 1000 L water/ha)

IA: Inhalation absorption – 100%

Residential exposure

According to the exposure model of Martin *et al*, the worst case for residents results from multiple treatment of grapevines with Zoxium240 SC at 0.75 L product/ha. For repeated applications, it is conservatively assumed that the spray deposit on surfaces adjacent to the area sprayed does not decline between multiple applications and exposure occurs to the maximum total dose (3.75 L product/ha equivalent to 0.9 kg zoxamide/ha), which represent the theoretical worst case. As five applications are applied the % drift is based on 82nd percentile values. The following parameters were used in the resident assessment with detailed exposure calculations are provided in Appendix 3:

Dermal exposure model (via deposits caused by spray drift)

AR: Field application rate – five applications of 0.18 kg/ha (equivalent to 0.009 mg/cm^2)

D: drift fallout value, i.e. 1.07% from broadcast air-assisted sprayer applications to grapevine, 82nd percentile value for residents

TTR: turf transferable residues (%) – the EPA default value of 5% is assumed

TC: transfer coefficient (cm^2/hr) – default values of 7300 cm^2/hr for adults and 2600 cm^2/hr for children (values for 2 hours exposure, US EPA, 2001)

H: exposure duration for a typical day (hours) – this has been assumed to be 2 hours which matches the 75th percentile for toddlers playing on grass in the EPA Exposure Factors Handbook

DA: Percent dermal absorption – 10%

BW: body weight – 16.15 kg for children aged 2 to <5years and 60 kg for adults

Inhalation exposure model (vapour drift)

The vapour pressure of zoxamide is 1.3×10^{-7} Pa at 25°C therefore zoxamide is considered as semi-volatile by the exposure model.

Child Oral Exposure (children's hand to mouth transfer exposure model)

AR: Field application rate – five applications of 0.18 kg/ha (equivalent to 0.009 mg/cm^2)

D: drift fallout value, i.e. 1.07% from broadcast air-assisted sprayer applications to grapevine, 82nd percentile value for residents

TTR: turf transferable residues (%) – the EPA default value of 5% derived from transferability studies with wet hands.

SE: saliva extraction factor (%) – the default value of 50% is assumed

SA: surface area of the hands (cm^2) – the assumption used here is that 20 cm^2 of skin area is contacted each time a child puts a hand in his or her mouth (this is equivalent to the palmer surface of three figures and is also related to the next parameter)

Freq: frequency of hand to mouth (events/hour) – for short term exposures the value of 20 events/hours is used, this is the 90th percentile of observations that ranges from 0 to 70 events/hour

H: exposure duration (hours) – this has been assumed to be 2 hours which matches the 75th percentile for toddlers playing on grass in the EPA Exposure Factors Handbook

OA: oral absorption (%) - assumed to be 60% (based on recovery in bilecannulated rats, within 48h).

BW: body weight – 16.15 kg for children aged 2 to <5 years.

Child Oral Exposure (children's object-to-mouth transfer exposure model)

AR: Field application rate – five applications of 0.18 kg/ha (equivalent to 0.009 mg/cm^2)

D: drift fallout value, i.e. 1.07% from broadcast air-assisted sprayer applications to grapevine, 82nd percentile value for residents

DFR: dislodgeable foliar residues (%), a default value of 20% transferability from object to mouth assessments is recommended

IgR: ingestion rate for mouthing grass/day (cm^2) – this was assumed to be equivalent to 25 cm^2 of grass/day

OA: oral absorption (%) - assumed to be 60% (based on recovery in bilecannulated rats, within 48h).

BW: body weight – 16.15 kg for children aged 2 to <5 years

Measurement of bystander and resident exposure

A study to measure bystander and resident exposure to zoxamide under practical conditions of the use of Zoxium 240 SC was not conducted since the estimates of exposure under worst case assumptions demonstrated that there is an acceptable margin of safety between the estimated exposure levels and the systemic AOEL for the active substance zoxamide.

B.6.4.3. Worker exposure

Risk assessment for worker

Worker exposure was estimated using the approach recommended by the EUROPOEM II re-entry group (van Hemmen *et al.* (2002))[4]. It is considered that the harvesting of grapes treated with Zoxium 240 SC would be the worst case scenario for re-entry workers and therefore, an exposure assessment is given for this activity. For completeness an assessment is also given for workers re-entering treated potato crops to perform scouting/crop-inspection tasks.

The exposure assessment assumes a work duration of 2 hours, together with a transfer coefficient (TC) value of 2,500 cm^2/person/hour for scouting activities in potatoes and a work duration of 8 hours, together with a transfer coefficient (TC) value of 4,500 cm^2/person/hour for hand harvesting activities in grapes. The TC value selected for crop scouting in potatoes is the recommended EUROPOEM value for workers hand harvesting vegetables and is based on workers cutting and tying cucumbers in glasshouses. This may therefore be regarded as a precautionary TC value for workers inspecting potato crop. The TC value selected for a worker hand harvesting grapes is the recommended EUROPOEM value for workers hand harvesting pome fruit; European practice is to prune foliage from vines prior to harvesting grapes in order to facilitate the ripening of the grapes. The intensity and frequency of contact with the crop for workers involved in hand harvesting grapes is therefore not expected to exceed that of workers hand harvesting tree fruit. The GAP used for the exposure assessment considers multiple applications where five applications of Zoxium 240 SC are made. For a Tier 1 assessment the scenario considers there is no decline in foliar residues of zoxamide between treatments, and exposure occurs to the maximum total dose (3.75 L product/ha equivalent to 0.9 kg zoxamide/ha). This represents the theoretical worse case.

Table 6.4-3: Estimated exposure to zoxamide from the proposed use of Zoxium 240 SC for re-entry workers

Active substance	AOEL [mg/kg bw/day]	Crop	PPE	Absorbed dose [mg/kg bw/day]	% of AOEL
Zoxamide	0.3	Potato	None[a]	0.023	7.5
		Vines	None[a]	0.162	54

a) Worker wearing shoes, socks, long-sleeved shirt, and long trousers

Conclusion

The estimated exposure is less than the AOEL for the worker wearing adequate work clothing but no PPE and assuming no dissipation of DFR between or following applications. As a standard rule, it should be mentioned on the product label that treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried.

[4] van Hemmen *et al.* (2002). Post-application exposure of workers to pesticides in agriculture. Report of the re-entry working group, EUROPOEM II project: FAIR3-CT96-. Policy paper on agricultural transfer coefficients.

Estimation of worker exposure

Exposure scenario: scouting activities in potato crops

Estimates of dermal exposure for workers are based on the exposure model proposed in the EUROPOEM II Re-entry Working Group report. The EUROPOEM re-entry model assumes dislodgeable foliar residues of 3 µg a.s./cm^2 per kg a.s./ha. The assessment assumes calculation of DFR at re-entry is based on the highest maximum total dose of 3.75 L product/ha. The transfer coefficient (TC) assumed for workers handling performing scouting activities is 2,500 cm^2/person/hour. Systemic exposure is predicted assuming a dermal absorption of 10%, an exposure duration of 2 hours and a 60 kg worker body weight. Exposure for workers may be calculated as follows:

D	=	DFR	×	AR	×	TC	×	WR	×	DA
	=	3	×	0.9	×	2,500	×	2	×	10%
	=	1.35 mg/person/d								
	=	0.0225 mg/kg bw/d (based on 60 kg person)								
	=	7.5% AOEL								

Where:

- D = Dermal exposure (mg/person/day)
- DFR = Dislodgeable foliar residues (3 µg/cm^2 per kg a.s./ha)
- AR = Application Rate five applications of 0.75 L product/ha (0.18 kg zoxamide/ha)
- TC = transfer factor for harvesting vegetable (2,500 cm^2/person/hour)
- WR = Working time (2 hours/day)
- D = Dermal absorption zoxamide (10%)

Exposure scenario: hand-harvesting grapes

Estimates of dermal exposure for workers are based on the exposure model proposed in the EUROPOEM II Re-entry Working Group report. The EUROPOEM re-entry model assumes dislodgeable foliar residues of 3 µg a.s./cm^2 per kg a.s./ha. The assessment assumes calculation of DFR at re-entry is based on the highest maximum total dose of 3.75 L product/ha. The transfer coefficient (TC) assumed for workers hand harvesting grapes is 4,500 cm^2/person/hour. Systemic exposure is predicted assuming a dermal absorption of 10%, an exposure duration of 8 hours and a 60 kg worker body weight. Exposure for workers may be calculated as follows:

D	=	DFR	×	AR	×	TC	×	WR	×	DA
	=	3	×	0.9	×	4,500	×	8	×	10%
	=	9.72 mg/person/d								
	=	0.162 mg/kg bw/d (based on 60 kg person)								
	=	54% AOEL								

Where:

- D = Dermal exposure (mg/person/day)
- DFR = Dislodgeable foliar residues (3 µg/cm^2 per kg a.s./ha)
- AR = Application Rate five applications of 0.75 L product/ha (0.18 kg zoxamide/ha)
- TC = transfer factor for harvesting tree fruit (4,500 cm^2/person/hour)
- WR = Working time (8 hours/day)
- D = Dermal absorption zoxamide (10%)

Measurement of worker exposure

The predicted worker exposure assuming no personal protective equipment is within the AOEL. Therefore, no further assessment is therefore required.

B.6.5. REFERENCES RELIED ON

New studies

Data point	Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Vertebrate study Y/N	Data protection claimed (Y/N)	Justification if data protection claimed	Owner
KCP 7.1.1/01	[redacted]	1999	RH-117,281 2F (240 SC): Acute oral toxicity study in male and female rats [redacted] Report N:° 98R-026 GLP, Unpublished	Y	Y	Data to support new representative formulation	Gowan
KCP 7.1.1/02	[redacted]	1999	RH-117,281 2F (240 SC): Acute oral toxicity study in male and female mice [redacted] Report N:° 98R-031 GLP, Unpublished	Y	Y	Data to support new representative formulation	Gowan
KCP 7.1.2/01	[redacted]	1999	RH-117,281 2F (240SC): Acute dermal toxicity study in male and female rats [redacted] Report N:° 98R-027 GLP, Unpublished	Y	Y	Data to support new representative formulation	Gowan

Data point	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Vertebrate study Y/N**	**Data protection claimed (Y/N)**	**Justification if data protection claimed**	**Owner**
KCP 7.1.3/01	[redacted]	1999	Acute Inhalation Toxicity Study in Rats Report N:° 98R-025 [redacted] GLP, Unpublished	Y	Y	Data to support new representative formulation	Gowan
KCP 7.1.4/01	[redacted]	1999	RH-117,281 2F (240SC): Skin irritation study in rabbits [redacted] Report N:° 98R-028 GLP, Unpublished	Y	Y	Data to support new representative formulation	Gowan
KCP 7.1.5/01	[redacted]	1999	RH-117,281 2F (240SC): Eye irritation study in rabbits [redacted] Report N:° 98R-029 GLP, Unpublished	Y	Y	Data to support new representative formulation	Gowan
KCP, 7.1.6/01	[redacted]	1999	RH-117,281 2F (240SC): Delayed contact hypersensitivity study in guinea pigs [redacted] Report N:° 98R-030 GLP, Unpublished	Y	Y	Data to support new representative formulation	Gowan

Data point	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Vertebrate study Y/N**	**Data protection claimed (Y/N)**	**Justification if data protection claimed**	**Owner**
KCP, 7.3	Craig, S.	2014	Zoxamide: The In Vitro Percutaneous Absorption of Radiolabelled Zoxamide in the Concentrate and Two In Use Spray Dilutions Through Human Skin. Charles River, Tranent, Edinburgh, UK Study No. 794002, Report No. 35303 GLP, Unpublished	N	Y	Data to support new representative formulation	Gowan

Studies relied on for the first inclusion of zoxamide in Annex I to Directive 91/414/EEC and for renewal of approval under Regulation (EC) 1107/2009.

None.

APPENDIX 1: ADDITIONAL INFORMATION PROVIDED BY THE APPLICANT (E.G. DETAILED MODELLING DATA)

Appendix 1-1: German BBA model - Exposure to zoxamide during tractor-mounted boom spraying; no PPE

Input parameters considered for the estimation of operator exposure:

Formulation type:	Liquid		**Application technique:**	Field Crops, Tractor Mounted (FCTM)	
Application rate (AR):	0.18	kg			
Area treated per day (A):	20	ha	**Dermal hands m/l ($D_{M(H)}$):**	2.4	mg/person/kg a.s.
Dermal absorption (DA):	4	% (concentr.)	**Dermal hands appl. ($D_{A(H)}$):**	0.38	mg/person/kg a.s.
	10	% (dilution)	**Dermal body appl. ($D_{A(B)}$):**	1.6	mg/person/kg a.s.
Inhalation absorption (IA):	100	%	**Dermal head appl. ($D_{A(C)}$):**	0.06	mg/person/kg a.s.
Body weight (BW):	70	kg/person	**Inhalation m/l (I_M):**	0.0006	mg/person/kg a.s.
AOEL	0.3	mg/kg bw/d	**Inhalation appl. (I_A):**	0.001	mg/person/kg a.s.

Operator exposure towards zoxamide		
Without PPE		
Operators: Systemic dermal exposure after application in		
Dermal exposure during mixing/loading		
Hands		
$SDE_{OM(H)} = (D_{M(H)} \times AR \times A \times DA) / BW$		
(2.4 x 0.18 x 20 x 4%) / 70		
External dermal exposure	8.64	mg/person
External dermal exposure	0.1234286	mg/kg bw/d
Systemic dermal exposure	**0.004937**	**mg/kg bw/d**
Dermal exposure during application		
Hands		
$SDE_{OA(H)} = (D_{A(H)} \times AR \times A \times DA) / BW$		
(0.38 x 0.18 x 20 x 10%) / 70		
External dermal exposure	1.368	mg/person
External dermal exposure	0.0195429	mg/kg bw/d
Systemic dermal exposure	**0.001954**	**mg/kg bw/d**
Body		
$SDE_{OA(B)} = (D_{A(B)} \times AR \times A \times DA) / BW$		
(1.6 x 0.18 x 20 x 10%) / 70		
External dermal exposure	5.76	mg/person
External dermal exposure	0.0822857	mg/kg bw/d
Systemic dermal exposure	**0.008229**	**mg/kg bw/d**
Head		
$SDE_{OA(C)} = (D_{A(C)} \times AR \times A \times DA) / BW$		
(0.06 x 0.18 x 20 x 10%) / 70		
External dermal exposure	0.216	mg/person
External dermal exposure	0.0030857	mg/kg bw/d
Systemic dermal exposure	**0.000309**	**mg/kg bw/d**
Total systemic dermal exposure: $SDE_O = SDE_{OM(H)} + SDE_{OA(H)} + SDE_{OA(B)} + SDE_{OA(C)}$		
Total external dermal exposure	15.984	mg/person
Total external dermal exposure	0.2283429	mg/kg bw/d
Total systemic dermal exposure	**0.01543**	**mg/kg bw/d**

Operators: Systemic inhalation exposure after application		
Inhalation exposure during mixing/loading		
$SIE_{OM} = (I_M \times AR \times A \times IA) / BW$		
(0.0006 x 0.18 x 20 x 100%) / 70		
External inhalation exposure	0.00216	mg/person
External inhalation exposure	3.086E-05	mg/kg bw/d
Systemic inhalation exposure	**0.000031**	**mg/kg bw/d**
Inhalation exposure during application		
$SIE_{OA} = (I_A \times AR \times A \times IA) / BW$		
(0.001 x 0.18 x 20 x 100%) / 70		
External inhalation exposure	0.0036	mg/person
External inhalation exposure	5.143E-05	mg/kg bw/d
Systemic inhalation exposure	**0.000051**	**mg/kg bw/d**
Total systemic inhalation exposure: $SIE_O = SIE_{OM} + SIE_{OA}$		
Total external inhalation exposure	0.005760	mg/person
Total external inhalation exposure	0.000082	mg/kg bw/d
Total systemic inhalation exposure	**0.000082**	**mg/kg bw/d**
Total systemic exposure: $SE_O = SDE_O + SIE_O$		
Total systemic exposure	1.08576	mg/person
Total systemic exposure	**0.015511**	**mg/kg bw/d**
% of AOEL	**5.2**	**%**

Appendix 1-2: UK POEM - Exposure to zoxamide during tractor-mounted boom spraying; no PPE

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method					
Product	Zoxium 240 SC		Active substance	Zoxamide	
Formulation type			a.s. concentration	240	mg/ml
Dermal absorption from product	4	%	Dermal absorption from spray	10	%
Container					
PPE during mix/loading			PPE during application		
Dose	0.75	l/ha	Work rate/day	50	ha
Application volume	1000	l/ha	Duration of spraying	6	h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	0.75	litres product/ha
Work rate	50	ha/day
Number of operations	4	/day
Hand contamination	0.2	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0.2	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	1000	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	5%	15%	
Dermal exposure	6.5	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.55	ml/day		

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.2	ml/day	41.55	ml/day
Concen. of a.s. product or spray	240	mg/ml	0.18	mg/ml
Dermal exposure to a.s.	48	mg/day	7.479	mg/day
Percent absorbed	4	%	10	%
Absorbed dose	1.92	mg/day	0.7479	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.18	mg/ml
Inhalation exposure to a.s.	0.0108	mg/day
Percent absorbed	100	%
Absorbed dose	0.0108	mg/day

PREDICTED EXPOSURE

Total absorbed dose	2.6787	mg/day
Operator body weight	60	kg
Operator exposure	0.044645	mg/kg bw/day
AOEL	0.3	mg/kg bw/day
%AOEL	15%	

Appendix 1-3: German BBA model - Exposure to zoxamide during broadcast air-assisted spraying; no PPE

Input parameters considered for the estimation of operator exposure:

Formulation type:	Liquid		**Application technique:**	High Crops, Tractor Mounted (HCTM)	
Application rate (AR):	0.18	kg			
Area treated per day (A):	8	ha	**Dermal hands m/l ($D_{M(H)}$):**	2.4	mg/person/kg a.s.
Dermal absorption (DA):	4	% (concentr.)	**Dermal hands appl. ($D_{A(H)}$):**	0.7	mg/person/kg a.s.
	10	% (dilution)	**Dermal body appl. ($D_{A(B)}$):**	9.6	mg/person/kg a.s.
Inhalation absorption (IA):	100	%	**Dermal head appl. ($D_{A(C)}$):**	1.2	mg/person/kg a.s.
Body weight (BW):	70	kg/person	**Inhalation m/l (I_M):**	0.0006	mg/person/kg a.s.
AOEL	0.3	mg/kg bw/d	**Inhalation appl. (I_A):**	0.018	mg/person/kg a.s.

Operator exposure towards zoxamide		
Without PPE		
Operators: Systemic dermal exposure after application in		
Dermal exposure during mixing/loading		
Hands		
$SDE_{OM(H)} = (D_{M(H)} \times AR \times A \times DA) / BW$		
(2.4 x 0.18 x 8 x 4%) / 70		
External dermal exposure	3.456	mg/person
External dermal exposure	0.0493714	mg/kg bw/d
Systemic dermal exposure	**0.001975**	**mg/kg bw/d**
Dermal exposure during application		
Hands		
$SDE_{OA(H)} = (D_{A(H)} \times AR \times A \times DA) / BW$		
(0.7 x 0.18 x 8 x 10%) / 70		
External dermal exposure	1.008	mg/person
External dermal exposure	0.0144	mg/kg bw/d
Systemic dermal exposure	**0.001440**	**mg/kg bw/d**
Body		
$SDE_{OA(B)} = (D_{A(B)} \times AR \times A \times DA) / BW$		
(9.6 x 0.18 x 8 x 10%) / 70		
External dermal exposure	13.824	mg/person
External dermal exposure	0.1974857	mg/kg bw/d
Systemic dermal exposure	**0.019749**	**mg/kg bw/d**
Head		
$SDE_{OA(C)} = (D_{A(C)} \times AR \times A \times DA) / BW$		
(1.2 x 0.18 x 8 x 10%) / 70		
External dermal exposure	1.728	mg/person
External dermal exposure	0.0246857	mg/kg bw/d
Systemic dermal exposure	**0.002469**	**mg/kg bw/d**
Total systemic dermal exposure: $SDE_O = SDE_{OM(H)} + SDE_{OA(H)} + SDE_{OA(B)} + SDE_{OA(C)}$		
Total external dermal exposure	20.016	mg/person
Total external dermal exposure	0.2859429	mg/kg bw/d
Total systemic dermal exposure	**0.02563**	**mg/kg bw/d**

Operators: Systemic inhalation exposure after application		
Inhalation exposure during mixing/loading		
$SIE_{OM} = (I_M \times AR \times A \times IA) / BW$		
(0.0006 x 0.18 x 8 x 100%) / 70		
External inhalation exposure	0.000864	mg/person
External inhalation exposure	1.234E-05	mg/kg bw/d
Systemic inhalation exposure	**0.000012**	**mg/kg bw/d**
Inhalation exposure during application		
$SIE_{OA} = (I_A \times AR \times A \times IA) / BW$		
(0.018 x 0.18 x 8 x 100%) / 70		
External inhalation exposure	0.02592	mg/person
External inhalation exposure	0.0003703	mg/kg bw/d
Systemic inhalation exposure	**0.000370**	**mg/kg bw/d**
Total systemic inhalation exposure: $SIE_O = SIE_{OM} + SIE_{OA}$		
Total external inhalation exposure	0.026784	mg/person
Total external inhalation exposure	0.000383	mg/kg bw/d
Total systemic inhalation exposure	**0.000383**	**mg/kg bw/d**
Total systemic exposure: $SE_O = SDE_O + SIE_O$		
Total systemic exposure	1.82102	mg/person
Total systemic exposure	**0.026015**	**mg/kg bw/d**
% of AOEL	**8.7**	**%**

Appendix 1-4: UK POEM - Exposure to zoxamide during broadcast air-assisted spraying; no PPE

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method					
Product	Zoxium 240 SC		Active substance	Zoxamide	
Formulation type			a s. concentration	240	mg/ml
Dermal absorption from product	4	%	Dermal absorption from spray	10	%
Container					
PPE during mix/loading			PPE during application		
Dose	0.75	l/ha	Work rate/day	15	ha
Application volume	1000	l/ha	Duration of spraying	6	h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	0.75	litres product/ha
Work rate	15	ha/day
Number of operations	2	/day
Hand contamination	0.1	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0.1	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha			
Application volume	1000	spray/ha		
Volume of surface contamination	400	ml/h		
Distribution	Hands	Trunk	Legs	
	10%	65%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	2%	5%	
Dermal exposure	10	5.2	5	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	121.2	ml/day		

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.1	ml/day	121.2	ml/day
Concen. of a.s. product or spray	240	mg/ml	0.18	mg/ml
Dermal exposure to a s.	24	mg/day	21.816	mg/day
Percent absorbed	4	%	10	%
Absorbed dose	0.96	mg/day	2.1816	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.05	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.18	mg/ml
Inhalation exposure to a.s.	0.054	mg/day
Percent absorbed	100	%
Absorbed dose	0.054	mg/day

PREDICTED EXPOSURE

Total absorbed dose	3.1956	mg/day
Operator body weight	60	kg
Operator exposure	0.05326	mg/kg bw/day
AOEL	0.3	mg/kg bw/day
%AOEL	18%	

Appendix 1.5: Estimation of bystander exposure to zoxamide from use of Zoxium 240 SC on grapevine during broadcast air-assisted spraying

An estimate of bystander exposure has been made based on the recommendations made in the report from the EUROPOEM II project "Report of the bystander working group (Dec 2002)"[5]. The model assumes that bystanders will not be involved in the spray operation and their exposure can be considered to occur mainly to spray drift via the airborne route.

The EUROPOEM II report considered bystander exposure data generated by the Application Hazards Unit (AHU) of the Central Science Laboratory and compared these data against spray drift rate tables published by Ganzelmeier[6].

Indicative values as proposed by the EUROPOEM II report have been used, representing the 90th percentile exposure values for bystanders. A maximum of 5% of the application rate is assumed for dermal exposure via drift (surface contamination) on 2 m^2 body surface of a person passing a field at a distance of 7 m, where orchard sprayers are used. For inhalation exposure, the estimation is based on a bystander inhaling 0.06 mL spray solution per hour adjusted for an exposure duration of 1 hour.

Bystander exposure has been estimated based upon the above indicative exposure values and an application rate of 0.75 L product/ha applied via tractor-mounted/trailed broadcast air-assisted sprayer (equivalent to 0.18 kg zoxamide/ha (18 mg/m^2)). The minimum water volume sprayed is 1000 L/ha which leads to a maximum concentration in the spray solution of 0.18 mg zoxamide/mL. The potential bystander exposure may be calculated as follows:

Dermal exposure = Max. application rate (mg a.s./m^3) × % Drift × Bystander surface area (m^2) × Dermal absorption (%)
= 18 mg a.s./m^2 × 0.05 drift × 2 m^2
= 1.8 mg/person/d
= 0.03 mg/kg bw/d (assuming 60 kg body weight)
= 0.003 mg/kg bw/d (10% dermal absorption)
Inhalation exposure = Volume inhaled (mL/hr) × Exposure duration (hr) × × Spray concentration (mg a.s./mL)
= 0.06 mL/hr × 1 hr × 0.18 mg a.s./mL
= 0.0108 mg/person/d (assuming 1 hour exposure)
= 0.00018 mg/kg bw/d (assuming 60 kg body weight)
Total bystander exposure = **Dermal exposure + Inhalation exposure**
= 0.003 mg/kg bw/d + 0.00018 mg/kg bw/d
= 0.0032 mg/kg bw/d

[5] Gilbert A., Krebs B., Maasfeld W. and Philips J., 2002. Bystander exposure to pesticides – Report of the bystander working group. EUROPOEM II PROJECT FAIR3 CT96-1406.

[6] Ganzelmeier H (2000). Drift studies and Drift Reducing Sprayers – A German Approach. ASEA paper 001024, ASEA Meeting July 9-12, Milwaukee, Wisconsin

Appendix 1.6: Estimation of resident's exposure to zoxamide from use of Zoxium 240 SC on grapevine following broadcast air-assisted spraying

Estimation of resident exposure after application in High crops, tractor mounted (HCTM)

Input parameters considered for the estimation of resident exposure:

Intended use(s):	Grape Vine		**Drift (D):**	1.07	% (HCTM, 10 m)
Application rate (AR):	0.45	kg a.s./ha	**Transfer coefficient (TC):**	7300	cm^2/h (adults)
				2600	cm^2/h (children)
Number of applications (NA):	2		**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):**	0.001	mg/m3
Dermal absorption (DA):	10.00	% ('worst case')	**Inhalation Rate (IR):**	16.57	m^3/d (adults),
Inhalation absorption (IA):	100	%		8.31	m^3/d (children)
Oral absorption (OA)	60	%	**Saliva Extraction Factor (SE):**	50	%
AOEL	0.3	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 zoxamide					
Adults			**Children**		
Residents: Dermal exposure after application in Grape Vine (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		
(0.0045 x 2 x 1.07% x 5% x 7300 x 2 x 10%) / 60			(0.0045 x 2 x 1.07% x 5% x 2600 x 2 x 10%) / 16.15		
External exposure	0.070299	mg/person	External exposure	0.025038	mg/person
External exposure	0.00117165	mg/kg bw/d	External exposure	0.00155034	mg/kg bw/d
Absorbed dose:	**0.0001172**	**mg/kg bw/d**	**Absorbed dose:**	**0.0001550**	**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		
(0.001 x 16.57 x 100%) / 60			(0.001 x 8.31 x 100%) / 16.15		
External exposure	0.01657	mg/person	External exposure	0.00831	mg/person
External exposure	0.00027617	mg/kg bw/d	External exposure	0.00051455	mg/kg bw/d
Absorbed dose:	**0.0002762**	**mg/kg bw/d**	**Absorbed dose:**	**0.0005146**	**mg/kg bw/d**
The model does not accept more than 2 applications. To reflect the worst case the maximum total dose from 5 applications applied in 2 treatments of 0.45 kg a.s./ha has been assessed.			**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) /		
			(0.0045 x 2 x 1.07% x 5% x 50% x 20 x 20 x 2 x 60%) / 16.15		
			External exposure	0.001926	mg/person
			External exposure	0.00011926	mg/kg bw/d
			Absorbed dose	**0.0000716**	**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		
			(0.0045 x 2 x 1.07% x 20% x 25 x 60%) / 16.15		
			External exposure	0.0004815	mg/person
			External exposure	2.9814E-05	mg/kg bw/d
			Absorbed dose	**0.0000179**	**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)	0.0235999	mg/person	Total systemic exposure (absorbed dose)	0.0122583	mg/person
Total systemic exposure (absorbed dose)	**0.0003933**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0007590**	**mg/kg bw/d**
% of AOEL:	**0.131**	**%**	**% of AOEL:**	**0.25**	**%**