Renewal Assessment Report

under Regulation (EC) 1107/2009

Zoxamide

Volume 1

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

Version history

Date	Subject
July 2016	**Initial RAR**

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STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1 STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1 CONTEXT IN WHICH THE DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1 Purpose for which the draft assessment report was prepared

This renewal assessment report (RAR) has been prepared in accordance with Commission Regulation (EC) No 844/2012 and provides a discussion of relevant studies submitted for the original EU evaluation for Annex I inclusion as well as relevant new studies and information generated since the Annex I inclusion of Zoxamide in 2004. Where necessary, studies submitted for the original EU evaluation for Annex I inclusion have been reevaluated to allow risk assessment along current standards, and to validate previous conclusions and/or calculations.

1.1.2 Arrangements between rapporteur Member State and co-rapporteur Member State

According to Commission Regulation (EU) No 686/2012 Latvia was assigned RMS and France was assigned Co-Rapporteur Member State (Co-RMS). RMS evaluated all aspects of the renewal dossier via a draft RAR which was the subject of a peer review by the Co-RMS. There were no deviating views on critical issues between RMS and Co-RMS.

1.1.3 EU Regulatory history for use in Plant Protection Products

Zoxamide was included as a new active substance in Annex I of EU Council Directive 91/414/EEC on 01 April 2004 (Commission Directive 2003/119/EC of 5 December 2003). The Commission presented a Review Report (SANCO/10297/2003-final 04 February 2004) in support to the consideration of Annex I inclusion. No EFSA Conclusion was prepared at that time.

Rohm and Haas France S.A (Dow AgroSciences) was the data submitter in support of Annex I inclusion. The United Kingdom acted as the RMS. There was no request for confirmatory data to be submitted after the inclusion in Annex I of EU Council Directive 91/414/EEC.

The maximum residue levels (MRLs) for zoxamide have been set in by Regulation (EC) No 396/2005, and Commission Regulations (EC) No 149/2008 and 520/2011 thereof.

Since the initial Annex I inclusion of Zoxamide the ownsership of the active substance data has been transferred from Dow AgroSciences to Gowan Comercio Internacional e Servicos Limitada. Gowan Comercio Internacional e Servicos Limitada is the sole data submitter in support of the current evaluation in the scope of active substance renewal procedure under Commission Regulation (EC) No. 1107/2009.

1.1.4 Evaluations carried out under other regulatory contexts

The RMS is not aware of any other relevant EU-evaluations of zoxamide carried out in the framework of other relevant EU-legislation (e.g. biocides, flavourings, food additives, cosmetics).

1.2 APPLICANT(S) INFORMATION

1.2.1 Name and address of applicant(s) for approval of the active substance

Name: Gowan Comercio Internacional e Servicos Limitada

Address: Rua Ivens, no. 3-B
Edif D, Mécia Building, 6th Floor
9000-046 Funchal,
Madeira
Portugal

Contact: [redacted]

Telephone number: [redacted]
Fax number: [redacted]
E-mail: [redacted]

1.2.2 Producer or producers of the active substance

Refer to confidential volume 4.

1.2.3 Information relating to the collective provision of dossiers

Not relevant as Gowan is the only applicant for the European evaluation.

1.3 IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms (IIA 1.3)	Zoxamide

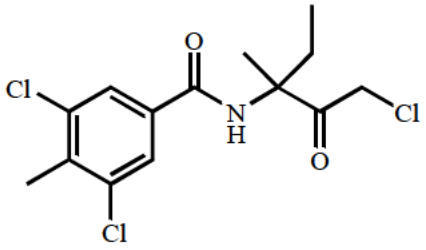
1.3.2. Chemical name (IUPAC and CA nomenclature) (IIA 1.4)

IUPAC	3,5-Dichloro-N-(3-chloro-1-ethyl-1-methylacetonyl)-p-tolumamide
CA	3,5-Dichloro-N-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide
1.3.3. Producer's development code numbers	Previous development codes were: RH-117,281 and RH-7281

1.3.4. CAS, EEC and CIPAC numbers

CAS	156052-68-5
EEC	Not assigned
CIPAC	640

1.3.5. Molecular and structural formulae, molecular mass

Molecular formula	$C_{14}H_{16}NO_2Cl_3$
Structural formula	 The technical active ingredient consists of a single racemic compound containing one chiral center. Both enantiomers are present in equal quantities.
Molecular mass	336.65 g/L
1.3.6. Method of manufacture (synthesis pathway) of the active substance	Refer to confidential volume 4
1.3.7. Specification of purity of the active substance in g/kg	Minimum purity of active substance: 950 g/kg

1.3.8. Identity and content of additives (such as stabilisers) and impurities

1.3.8.1. Additives	Refer to confidential volume 4
1.3.8.2. Significant impurities	Refer to confidential volume 4
1.3.8.3. Relevant impurities	Not contain relevant impurities
1.3.9. Analytical profile of batches	Refer to confidential volume 4

1.4 INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1 Applicant	**Gowan Comercio Internacional e Servicos Limitada** Rua Ivens, no. 3-B Edif D, Mécia Building, 6th Floor

	9000-046 Funchal, Madeira Portugal Contact : [redacted] Tel: + [redacted] Fax : + [redacted] Telephone number: [redacted] Fax number: [redacted] E-mail: [redacted]
1.4.2 Producer of the plant protection product	Sipcam S.p.A SBM Formulation Irca Sevice S.p.A
1.4.3 Trade name or proposed trade name and producer's development code number of the plant protection product	ZOXIUM 240 SC Code : RH-117,281 2F (240SC), GF-1045

1.4.4 Detailed quantitative and qualitative information on the composition of the plant protection product

1.4.4.1. Composition of the plant protection product	Confidential data, see volume 4
1.4.4.2. Information on the active substances	252.6 g/L of technical active substance 240 g/L of pure active substance
1.4.4.3. Information on safeners, synergists and co-formulants	Confidential data, see volume 4
1.4.5 Type and code of the plant protection product	Suspension concentrate (SC)
1.4.6 Function	Fungicide
1.4.7 Field of use envisaged	Agriculture. Foliar spray. Crops: potato, grapes.
1.4.8 Effects on harmful organisms	Contact fungicide, protective. Acting on the fungus class of "oomycetes".

1.5 DETAILED USES OF THE PLANT PROTECTION PRODUCT (TO BE INCLUDED FOR EACH PREPARATION FOR WHICH DOCUMENTATION WAS SUBMITTED)

1.5.1 Details of representative uses

The following representative uses of fungicide Zoxium 240 SC are supported for the renewal of approval of zoxamide:

1	2	3	4	5	6	7	8	10	11	12	13	14
Use-No.	**Zone(s)**	**Crop and/ or situation** **(crop destination / purpose of crop)**	**F G or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	**Application**			**Application rate**			**PHI** (days)	**Remarks:** e.g. safener/synergist per ha e.g. recommended or mandatory tank mixtures
					Method / Kind	Timing / Growth stage of crop & season	Max. number (min. interval between applications)	L product / ha a) max. rate per appl. b) max. total rate per crop/season	g as/ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		
1	Central South	Wine grapes	F	grape downy mildew *Plasmopara viticola*	3-d broadcast with mist blower	BBCH 15-79	5 (8)	a) 0.75 b) 3.75	a) 180 b) 900	1000	28	Maximum 3 consecutive applications of PPP's containing zoxamide. Always apply product in mix with downy mildewcides having different target site and mode of Action
2	Central South	Table grapes	F	grape downy mildew *Plasmopara viticola*	3-d broadcast with mist blower	BBCH 15-79	5 (8)	a) 0.75 b) 3.75	a) 180 b) 900	1000	28	
3	North, Central South	Potato	F	potato late blight *Phytophtora infestans* Mont. De Bary	broadcast with spray boom	BBCH 20-80	5 (8)	a) 0.75 b) 3.75	a) 180 b) 900	1000	7	

1.5.2 Further information on representative uses

Zoxamide is a non-systemic fungicide belonging to the benzamide group of compounds. It is claimed to have protectant properties and is intended to protect against oomycete diseases such as *Phytophthora infestans* (late blight of potato) and *Plasmopara viticola* (downy mildew of grapevines). Zoxamide inhibits germ tube development and mycelium growth by inhibiting cell division. As a result, the fungal organism dies.

The representative formulation supporting the application for renewal of approval is Zoxium 240 SC, containing 240 g zoxamide/L. The representative uses includes grapes in Central and Southern EU and potatoes in Northern, Central and Southern EU.

The maximum number of sprays with Zoxium 240 SC is limited to 5 per growing season, with a maximum of 3 consecutive applications. The active substance is applied at a maximum rate of 180 g / ha per application.

1.5.3 Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

Not relevant.

1.5.4 Overview on authorisations in EU Member States

Since the initial Annex I inclusion of zoxamide in 2004, authorisations for a range of different formulations have been achieved in Europe.

Country	**Since**	**Reg. No.**	**Product**	**Crop(s)**	**Maximum individual dose** g/ a.s./ha	**Maximum number of treatments**
Austria	28/11/2006	2882	Electis	Potatoes Vines	150 240	3 4
Belgium	16/05/2001	9258P/B	Unikat Pro	Vines, Potatoes, Tabac, Ornamentals	83 150 166 15 g/L	2 10 3 1
Bulgaria	4/02/2009	583	Electis 75WG	Vines.	150	Not available
Cyprus	25/05/2009	2457	Electis 75WG	Vines, Potatoes	150	Not Available
Czech Republic	21/09/2011	4470-9	Unikat Pro	Potato Grape,	150	3 3
Denmark	28/01/2011	572-2	Electis	Potato	150	10
Estonia	24/11/2010	249	Electis	Potato	150	8
Finland	18/02/2003	1,964	Electis	Potato	150	
France	--/--/2002	2020110	Electis Pro	Grape	123	3
France	12/06/2002	2000294	Roxam Combi	Grape	123	3
France	--/--/2002	2020110	Unikat	Grape	123	3

Country	**Since**	**Reg. No.**	**Product**	**Crop(s)**	**Maximum individual dose** g/ a.s./ha	**Maximum number of treatments**
France	11/08/2002	2000338	Aderio	Potato	150	4
France	04/04/2003	2030147	Ozys,	Potato	150	4
France	11/08/2002	2000338	Gavel	Potato	150	4
Germany	16/04/2004	4957	Electis	Potatoes Vines	150 239	3 4
Greece	29/07/2010	60284	Electis 750WG	Vines. Potatoes. Tomatoes	150	4 3 3
Hungary	2/05/2010	04.2/2924-2/2012 NÉBIH	Roxam 75 WG	Grape Potato Tomato	150 150 124	4 8 2
Hungary	15/11/2001	04.2/2771-1/2012 NÉBIH	Electis 75 WG	Grape Potato Tomato	150 150 124	4 8 2
Ireland	21/03/2003	PCS 01821	Electis 75WG	Potato (seed) Potato (ware)	180	10
Italy	18/10/2007	12827	Electis R	Grapes	150	5
Italy	30/04/2009	14546	Premier R	Grapes Tomatoes	150	5
Italy	27/08/2009	14348	Agron	Grapes Tomatoes	150	5
Italy	18/10/2007	12202	Zemix R	Grapes Tomatoes	150	5
Italy	15/10/2009	14803	Electis ZR	Grapes Tomatoes	150	5
Italy	28/01/2014	15744	Reboot	Tomato, Eggplant Potato Grape (table and wine)	150	3
Italy	25/02/2011	14510	Electis Trio	Grapes	180	5
Italy	22/03/2005	12564	Electis MZ	Grapes Potatoes Tomatoes	166 166 166	5
Italy	22/03/2005	14545	Premier MZ	Grapes Potatoes Tomatoes	166 166 166	5
Italy	14/06/2012	14419	Zoram	Grapes	85	3
Italy	10/05/2012	14062	Zoxium	Grapes Tomatoes Potatoes	180	5
Italy	14/06/2012	15188	Astro	Grapes Tomatoes Potatoes	180	5
Italy	08/10/2012	15572	Zominex	Grapes Tomatoes Potatoes	180	5
Latvia	04/05/2001	0179	Elektis 75 dg.	Potato	150	8
Lithuania	11/12/2001	0206/09	Electis 75 WG	Potato	150	8

Country	**Since**	**Reg. No.**	**Product**	**Crop(s)**	**Maximum individual dose** g/ a.s./ha	**Maximum number of treatments**
Luxemb-urg	02/04/2004	1607-117	Electis Pro	Grape Potato Tabac	166 150 166	3
Nether-lands	27/01/2006	12783	Uniakat Pro	Potato	150	-
Portugal	05/03/2004 (by Dow); 04/06/2009 (by Gowan)	3565	Aderio	Potato and grapevine (table and for vinification)	180	3
Romania	11/04/2011	2102	Electis 75WG Fungicide (GF-GWN-1045)	Tomatoes, Potatoes, Cucumbers. Grapevines,	150	3
Slovenia	5/5/2009	327-02-304/2003/15	Electis 75WG	Vines Potatoes	150	Not available
Spain	05/11/2013	ES-00007	Electis CX	Tomato, Eggplant Potato	150	3
Spain	05/25/05	23055	Electis	Potato Grapevine	166 150	3 2
UK	04/26/2012	MAPP 14200	Unikat 75WG	Potato Wine grapes	150	8 4
UK	03/30/2012	MAPP 14195	Electis 75WG	Potato Wine grapes	150	8 4
UK	04/26/2012	MAPP 14191	Roxam 75WG	Potato Wine grapes	150	8 4

VOLUME 1

LEVEL 2

ZOXAMIDE

SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

2 SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

2.1 IDENTITY

The active substance is manufactured one producer (refer to volume 4).

The active substance is manufactured with a minimum purity of 950 g/kg and does not contain any relevant impurities.

The details of the significant impurities remain the same at the previous review and indicated in the volume 4. The manufacturing process is currently under review/development. Analytical methods for the determination of active substance and impurities in the technical active substance are validated at the previous EU review.

The formulation Zoxium 240 SC is a suspension concentrate (SC) containing 240 g/L of pure zoxamide.

The integral composition of the formulation is confidential and can be found in the volume 4.

Analytical method for the determination of active substance in the formulation is available and validated.

2.2 PHYSICAL AND CHEMICAL PROPERTIES

2.2.1 Summary of physical and chemical properties of the active substance

Zoxamide is a white powder with a melting point of 159.5 – 160.5°C. No boiling point was determined as decomposition begins at the melting point. It is neither flammable nor auto-flammable and is not classified as explosive or oxidising. It has a very low vapour pressure of $< 1.3 \times 10^{-5}$ Pa at 25°C and a low solubility in water (0.681 mg/L at 20°C), but is more readily soluble in organic solvents (0.038 – >55.7 g/L). Zoxamide does not dissociate and the log Pow (octanol/ water partition coefficient) is 3.76, indicating a potential for bioaccumulation.

2.2.2 Summary of physical and chemical properties of the plant protection product

Zoxium 240 SC is a suspension concentrate containing 22.8% w/w of the active substance zoxamide. The product is neither flammable nor autoflammable and does not possess oxidizing or explosive properties. It has a relative density of 1.11 and the pH of a 1% dilution is 6.61. The product has good pourability, wet sieving, suspensibility and dispersion characteristics and does not produce excessive amounts of foam. In stability studies at 54°C for 14 days and two years at room temperature, the content of the active substance remained stable and no significant changes were seen in any other property. The product was demonstrated to be stable to low temperatures. The packaging of the product remained free from any corrosion or degradation for the duration of the two year study and the shelf life of the product is 24 months. The technical properties of Zoxium 240 SC indicate that no particular problems are expected, when used as recommended.

2.3 DATA ON APPLICATION AND EFFICACY

2.3.1 Summary of effectiveness

The active ingredient acts against fungus from the class of Oomycetes, especially against downy mildews (e.g. *Phytophtora infestans*). It works protective and needs to be applied before the disease attack.

Depending on the disease pressure, a good protection against the disease can be expected over a period of 7 to 10 days. The product will be used as a contact fungicide with the first application to be made when warning systems forecast significant disease attack situations.

2.3.2 Summary of information on the development of resistance

Zoxamide belongs to the chemical family of benzamides and works by disrupting mitosis and cell division (FRAC target site B3) through inhibition of β-tubulin assembly (FRAC code 22) and has specific biological activity on the oomycetes group of microorganisms, which include the proposed targets *Plasmopara viticola* and *Phytophtora infestans.* The Fungicide Resistance Action Committee (FRAC) considers that there is a low to medium risk of resistance developing and that resistance management is required for this group of chemistry. FRAC also consider that *Plasmopara viticola* and *Phytophtora infestans* are of high and medium risk respectively of developing resistance to this chemistry. The combined fungicide-pathogen risk is therefore considered to be medium.

For the first inclusion of zoxamide in Annex I to Directive 91/414/EEC, baseline responses of *Phytophtora infestans* to zoxamide were established which showed that the variation in sensitivity of naturally occurring and laboratory isolates was similar. **Note:** Although the potential for *Plasmopara viticola* to develop resistance to zoxamide was investigated, *Phytophtora infestans* was chosen to assess the possibility of fungicide resistance as it was considered to possess key attributes for the rapid development of resistance.

There was no indication of any cross-resistance between phenylamide resistance and sensitivity to zoxamide. In addition, no cross-resistance was found to other commonly used benzimidazoles which have a similar mode of action to zoxamide.

The *Phytophtora infestans* sensitivity study and lack of success at producing zoxamide cross-resistant strains in laboratory mutagenesis studies with *Phytophtora infestans*, suggest the risk of resistance development to zoxamide is low. However, it is considered that the disease has a high resistance risk because of its history, the life cycle of the disease and the large number of applications made to the crop.

As of January 2013, FRAC have stated that no resistance to zoxamide has been reported for any pathogen.

In light of the potential risk of resistance developing and to ensure the continued effectiveness of this active substance, the following risk management strategy is in place:

1. A limited number of repeated applications on the crop;
2. A program of disease management based on co-formulation with active substances with different modes of action and product alternation.
3. A respect of recommended product dose rate, timing and spray interval.
4. A rigorous program of stewardship

2.3.3 Summary of adverse effects on treated crops

The applicant informs that no adverse effects on treated crops have been observed.
Zoxamide based products have been registered in many EU countries based on detailed national assessments of the efficacy package. More detailed consideration will be fully assessed in the context of subsequent applications for products authorization.

2.3.4 Summary of observations on other undesirable or unintended side-effects

The applicant informs that no undesirable or unintended side-effects have ever been reported or observed.
Zoxamide based products have been registered in many EU countries based on detailed national assessments of the efficacy package. More detailed consideration will be fully assessed in the context of subsequent applications for products authorization.

2.4 FURTHER INFORMATION

2.4.1 Summary of methods and precautions concerning handling, storage, transport or fire

Active substance - Zoxamide

Handling procedures
This material is a potential skin sensitizer. Chemical-resistant (Neoprene, butyl rubber) gloves should be worn whenever this material is handled. Rinse and remove gloves immediately after use.

Storage conditions
Store this material in cool (minimum 0°C – max. 43 °C), dry, dark and well ventilated area.

Transport classification :

Shipping Name	ENVIRONMENTALLY HAZARDOUS SUBSTANCE SOLID NOS
Identification Number	3077
Packing Group	III
Label	Substance dangerous for the environment
ADR Class	9,12 C
IMO Class	9
EMS No.	NA
MFAG No.	NA
Marine Pollutant	Marine Pollutant (P)
IATA Class	NA

Fire fighting measures :
Combustion generates toxic fumes as nitrogen oxides or hydrogen chloride. Use carbon dioxide, dry chemical or water spray as extinguishing agents. Fight larger fires with water spray or alcohol resistant foam.

Plant Protection Product – Zoxium 240 SC

Handling procedures
Keep locked up and out of the reach of children.
Keep away from food, drink and animal feedingstuff.
When handling, do not eat, drink or smoke.
Wear suitable protective clothing (coveralls), suitable protective gloves and rubber boots when using low volumes in a knapsack sprayer or making cut stump treatments
Wash all protective clothing thoroughly after use, especially the insides of gloves.
Wash hands and exposed skin before meals and after work.
Wear suitable gloves and face protection (face shield) and mask when handling the concentrate.
Do not contaminate water with the product or its container [Do not clean application equipment near surface water/Avoid contamination via drains from farmyards and roads].
Avoid release to the environment. Refer to special instructions/safety data sheets.

Storage conditions
The product must be stored only in the unopened, original packaging and out of reach of children. It is not to be stored in gangways or stair wells. The product is to be protected from frost.

Transport classification :

Shipping Name	ENVIRONMENTALLY HAZARDOUS SUBSTANCE LIQUID N.O.S.
Identification Number	NA
Packing Group	III
Label	Substance dangerous for the environment
ADR Class	9
IMO Class	9
EMS No.	F-A, S-F
MFAG No.	NA
Marine Pollutant	Marine Pollutant (P)
IATA Class	9

2.4.2 Summary of procedures for destruction or decontamination

Active substance - Zoxamide

Controlled incineration
Content of halogen in this material is less than 60 %.
For disposal, incinerate liquid and contaminated solids at a facility which complies with local regulations.

Plant Protection Product – Zoxium 240 SC

Controlled incineration
Since the halogen content of the active ingredient and the co-formulants are less than 60 %, combustion of Zoxium 240 SC in a waste incinerator plant does not raise concern about the formation of halogenated dibenzodioxins/-furans.

2.4.3 Summary of emergency measures in case of an accident

Active substance - Zoxamide

Personal precautions, protective equipment and emergency procedures:
Not required

Environmental precautions:
Do not allow product to reach sewage system or any water course.
Inform respective authorities in case of seepage into water course or sewage system.
Do not allow to enter sewers/ surface or ground water.

Methods and material for containment and cleaning up:
Pick up mechanically.

Plant Protection Product – Zoxium 240 SC

Personal precautions, protective equipment and emergency procedures:
Not required

Environmental precautions:
Do not allow product to reach sewage system or any water course.
Inform respective authorities in case of seepage into water course or sewage system.
Do not allow to enter sewers/ surface or ground water.

Methods and material for containment and cleaning up:
Stop leaks if this can be achieved without risk. Contain or absorb leaking liquid with sand or earth or

other suitable material. Consult an expert. Prevent liquid entering water courses and sewers. If substance has entered a water course or sewer or has been spilled on soil or vegetation, advise police. Do not flush road with water.

2.5 METHODS OF ANALYSIS

2.5.1 Methods used for the generation of pre-authorisation data

2.5.1.1 Analysis of the active substance as manufactured

Technical grade zoxamide is analysed by high performance liquid chromatography with ultra-violet detection (HPLC-UV) at 210 nm. Quantification is performed using external standard solutions. Information on the analysis of impurities in technical zoxamide is considered to be confidential information and is discussed in Volume 4 of the RAR.

2.5.1.2 Formulation analysis

Zoxamide was determined in the formulated product by HPLC-UV and the method is considered to be sufficiently validated.

Zoxium 240 SC only contains one active substance. The formulation does not contain any relevant impurities or coformulants. Therefore, no other methods are required for formulation analysis.

2.5.1.3 Methods for Risk Assessment

Plants and plant products

Zoxamide was determined in potatoes, white table grape and black wine grape using HPLC-MS/MS and the method validation meets EU requirements in all respects. The LOQ is 0.005 mg/kg for potatoes and 0.01 mg/kg for white table grape and black wine grapes.

Zoxamide metabolites RH-141452 and RH-141455 were determined in potatoes and processing fractions using HPLC-MS/MS and the method validation meets EU requirements in all respects. The LOQ is 0.01 mg/kg for potato (tuber) and 0.05 mg/kg for potato (chips and flakes).

Zoxamide metabolite RH-150721 was determined in grapes and processing fractions using HPLC-MS/MS and the method validation meets EU requirements in all respects. The LOQ is 0.01 mg/kg for grapes and processing fractions.

Food of animal origin

Dietary burden calculations are presented for poultry, ruminant and pigs which show that dietary burdens are all below 0.1 mg/kg diet and also below 0.004 mg/kg bw/day, and therefore livestock feeding studies are not required. Therefore, analytical methods for food of animal origin are not necessary.

Soil

No new ecotoxicology studies with soil dwelling organisms are submitted with the supplementary dossier and therefore no additional analytical methods for residues in soil were required in support of renewal of active substance.

Zoxamide was determined in soil by extraction with acetonitrile and analysis using gas chromatography with ECD or MS detection.

Water

Zoxamide (RH-117,281) was determined in saltwater after a 96 hour flow-through acute toxicity test and in saltwater after a flow-through life-cycle toxicity test by HPLC-UV and the method validation meets EU requirements in all respects. The LOQ is 0.016 mg/L for saltwater after a 96 hour flow-through acute toxicity test and 20 µg/L for saltwater after a flow-through life-cycle toxicity test.

Zoxamide was determined in Daphnia/fish medium by HPLC-UV and the method validations meet EU requirements in all respects. The LOQ is 0.12 mg/L in Daphnia/fish medium.

Air

No new studies requiring an analytical method for residues in air have been performed. Air samples of zoxamide were unalysed using capillary gas chromatography with ECD detection, confirmed by a GC-MS metod.

2.5.2 Methods for post control and monitoring purposes

Plants and plant products

Zoxamide was determined in commodities with high water, high acid, high oil and high starch/high protein, by HPLC-MS/MS. Method validation meets EU requirements in all respects and the methods are considered suitable for monitoring purposes. The LOQ is 0.01 mg/kg in all matrices. Independent laboratory validations were also successfully conducted.

The efficiency of the extraction procedure (QuEChERS) used in the monitoring methods detailed above was demonstrated using radio-labelled samples from the pea metabolism study. Recoveries of 98.4% and 68.4% were achieved for immature whole plant and dry peas respectively.

Food of animal origin

Dietary burden calculations are presented for poultry, ruminant and pigs which show that dietary burdens are all below 0.1 mg/kg diet and also below 0.004 mg/kg bw/day, and therefore, analytical methods for post-authorisation control and monitoring of residues in food of animal origin are not necessary.

Soil

Zoxamide was determined in soil using HPLC-MS/MS. Method validation meets EU requirements in all respects and the method is considered suitable for monitoring purposes. The LOQ is 0.05 mg/kg in soil.

Water

Zoxamide was determined in surface water and drinking water by HPLC-MS/MS. Method validation meets EU requirements in all respects and the method is considered suitable for monitoring purposes. The LOQ is 0.1µg/L in both surface water and drinking water. Independent laboratory validations were also successfully conducted.

Air

Zoxamide was determined in air by HPLC-MS/MS. Method validation meets EU requirements in all respects and the method is considered suitable for monitoring purposes. The LOQ is 90 $\mu g/m^3$ in air.

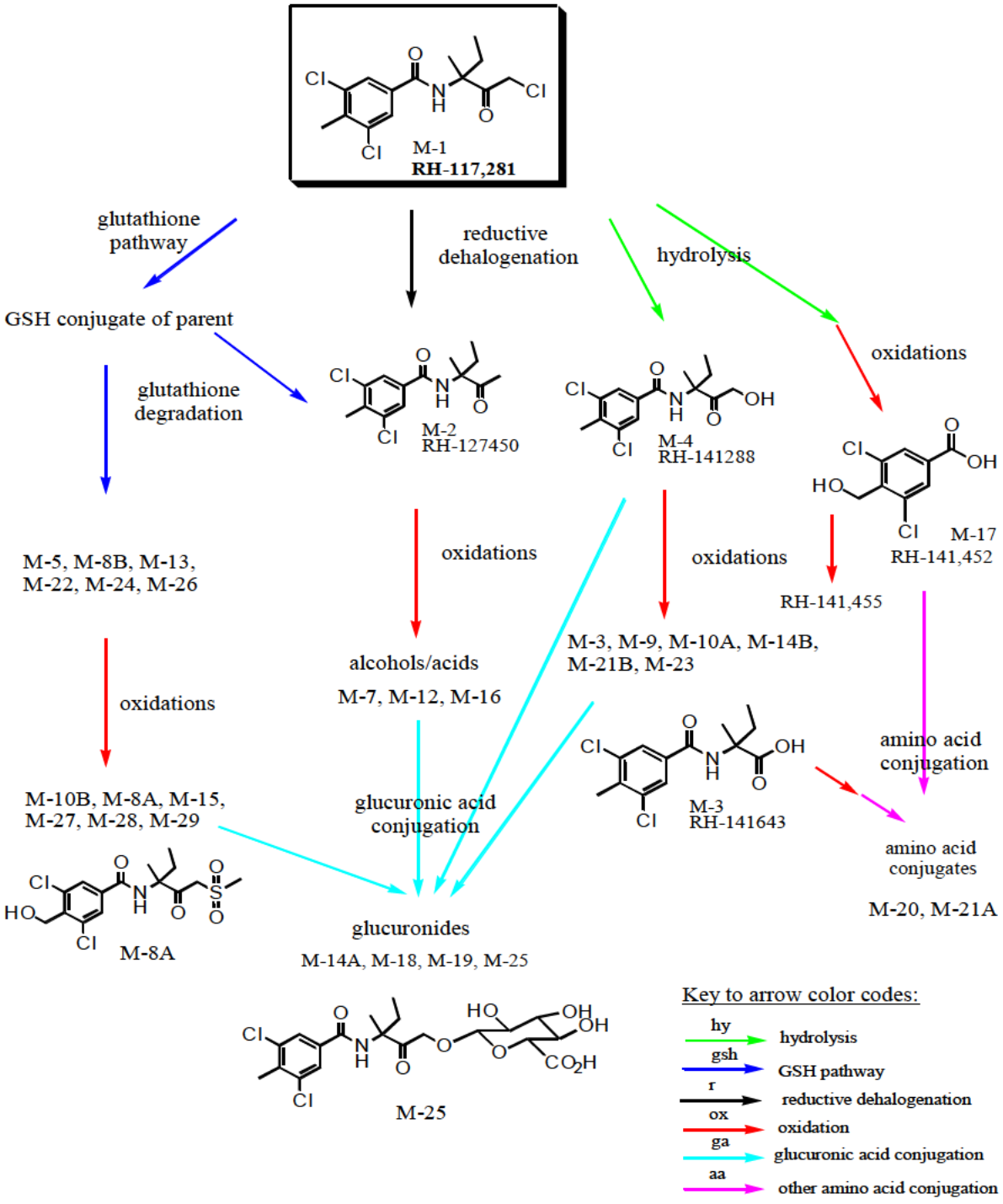
2.6 EFFECTS ON HUMAN AND ANIMAL HEALTH

2.6.1 Summary of absorption, distribution, metabolism and excretion in mammals

Zoxamide was moderately rapidly absorbed after an oral dose (60% becoming systemically available) and was widely distributed. Metabolism was extensive, with 32 metabolites identified (metabolism occurred mainly by hydrolysis, oxidation, reductive dehalogenation and conjugation). Excretion was rapid (over 85 % of the administered radioactivity was excreted during the first 24 -48 hours after dosing). Biliary excretion was the primary route of excretion. No potential for accumulation was apparent. In an in vitro comparative metabolism study with human, mouse, rat and dog hepatocytes, all metabolites detected in human were also seen in other species.

A summary of the metabolism of zoxamide in the rat is presented in Figure 2.6.1-1.

Figure 2.6.1-1. Proposed metabolism pathways of zoxamide, RH-117,281



2.6.2 Summary of acute toxicity

Zoxamide was not acutely toxic by any route of administration. There was very limited evidence of toxicity after a single oral dose in rats and mice (LD50 > 5,000 mg/kg bw) or dermal application to rats (LD50 > 2, 000 mg/kg bw) or after a 4-hr inhalation exposure (LC50 of > 5.3 mg/L, the highest attainable concentration). It is considered to be a primary eye irritant, while the potential for skin irritation was not evident. Zoxamide produced delayed contact hypersensitivity in the guinea pig in both the M&K and Buehler skin sensitisation tests. Very low dilutions were shown to be not sensitising to the skin of the guinea

pig. Because of the UV absorbing properties of zoxamide, a phototoxicity study was conducted. The findings show that the active substance is not phototoxic. Summary of the results of acute toxicity studies is presented in Table 2.6.2-1.

Table 2.6.2-1: Overview of the acute toxicity of zoxamide

Species	**Sex**	**Route/Study**	**Comments**	**Classification (EU Regulation EC 1272/2008)**
Rat	M F	Oral	LD_{50} > 5000 mg/kg bw for both sexes	Not classified
Mouse	M F	Oral	LD_{50} >5000 mg/kg bw for both sexes	Not classified
Rat	M F	Dermal	LD_{50} >5000 mg/kg bw for both sexes	Not classified
Rat	M F	Inhalation	LC_{50} > 5.3 mg/l for both sexes	Not classified
Rat	M/F	Intraperitoneal	Not determined or required	-
Rabbit	M/F	Skin irritation	No significant dermal responses over 24 - 72 h period.	Not classified
Rabbit	M/F	Eye irritation	Irritant	H319 - Causes serious eye irritation
Guinea pig	M/F	Skin sensitisation M&K method	Clear evidence of moderate skin sensitisation	H317 1A - May cause an allergic skin reaction.
Guinea pig	F	Skin sensitisation Buehler method	Clear evidence of moderate skin sensitisation	H317 1A - May cause an allergic skin reaction
3T3 Swiss mouse embryo cells	-	Phototoxicity (3T3 Neural Red Uptake)	Not phototoxic	Not classified

2.6.3 Summary of short-term toxicity

In short-term toxicity studies, there was no distinct evidence of systemic toxicity in the rat after an oral dose of 20000 ppm (ca. 1500 mg/kg bw/day) or a dermal dose of 1000 mg/kg bw/day. Zoxamide was shown to be a skin sensitiser and dermal effects and apparent changes in albumin and globulin levels were the main findings. The only observable change in mice was reduced body weight gain in females that received a dose of 7000 ppm (ca. 1606 mg/kg bw/day). The dog appeared to be the most sensitive species and the main target organs at high dosages were the liver, red blood cell parameters and the thyroid. The effects in the thyroid were considered to be secondary to that of the liver, based on published evidence. Body weight development was also affected in dogs at high dosages. Summary is presented in Table 2.6.3-1.

Table 2.6.3-1: Overview of short-term toxicity of zoxamide

Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kgbw/day)	Effects at LOAEL	Reference
90-day oral study in the rat at 0, 1000, 5000 & 20000 ppm	20000 ppm (ca. 1509 mg/kg bw/day)	>20000 ppm (1509 mg/kg bw/day)	No evidence of systemic toxicity at the highest test dose	[redacted] 1996a
90-day oral study in mice at 0, 70, 700, 2500 & 7000 ppm	2500 ppm (ca. 574 mg/kg bw/day)	7000 ppm (1606 mg/kg bw/day)	Reduced body weight gain and body weight in females	[redacted] 1996
4-week oral study in dogs at 0, 500, 15000, or 30000 ppm	30000 ppm (ca 1045 mg/kg bw/day)	>30000 ppm (ca 1045 mg/kg bw/day	Absence of systemic toxicity excepting soft faeces at the highest test dose	[redacted] 1996
90-day oral study in dogs at 0, 1500, 7500 or 30000 ppm	1500 ppm (ca. 50 mg/kg bw/day)	7500 ppm (ca. 281 mg/kg bw/day)	Reduction in body weight and in body weight gain in both sexes, changes in red blood cell parameters in females, increase in absolute and relative liver weights of the liver and evidence of liver hypertrophy and thyroid hypertrophy in both sexes	[redacted] 1997
12-month oral study in the dog at 0, 1500, 7500 or 30000 ppm	1500 ppm (ca. 50 mg/kg bw/day)	30000 (ca. 255 mg/kg bw/day	Reduction in body weight gain, reduction in albumin levels and increased alkaline phosphatase, increase in the absolute and relative liver and thyroid weights, and increased incidence of liver hypertrophy in both sexes	[redacted] 1998c

Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kgbw/day)	Effects at LOAEL	Reference
28-day dermal study in the rat at 0, 150, 400 or 1000 mg/kg bw/day	1000 mg/kg bw/day (systemic effects)	>1000 mg/kg bw/day (systemic effects)	Limited evidence of systemic toxicity. Dermal effects at treated skin sites and changes in albumin and globulin at ≥ 150 mg/kg bw/day was noted	[redacted] 1998d

2.6.4 Summary of genotoxicity

Zoxamide was not genotoxic in the Ames test or a mammalian cell mutation assay. Zoxamide was not genotoxic or clastogenic in the in vivo micronucleus study in mice. However, in the study for the induction of chromosome aberrations in cultured Chinese hamster ovary cells, mitotic accumulation was observed at concentrations, which inhibited cell growth in tests with and without metabolic activation. A statistically significant increase in the frequency of cells with numerical aberrations at the delayed sampling time (44 hours) was observed in the repeat test, Experiment 2, in tests both with and without metabolic activation and was observed to exceed the normal or historical control range. Sporadic frequencies of cells with numerical aberrations exceeding the normal range were also observed in cultures from other treatments. The increases observed in all cultures were noted to be predominantly due to increases in the frequency of cells with polyploidy.

It is noted that the 44 hour test was conducted only in Experiment 2 and the increases were present in a single sample each which leaves a degree of uncertainty in the reproducibility of the findings. However, noting that the mode of action of zoxamide involves an antitubulin activity this finding is considered to be positive.

On the basis of the overall evidence from in vitro and in vivo studies, zoxamide is not considered to be a genotoxic compound.Summary of genotoxicity studies is presented in table 2.6.4-1.

Table 2.6.4-1: Summary of genotoxicity

Study	Result	Reference
Bacterial Mutation Assay	Negative	Sames, J.S., Ciaccio, P.C. (1996a)
RH-117,281: Test for chemical induction of chromosome aberrations in cultured Chinese hamster	Positive	Riley, S. (1998)
Test for chemical induction of gene mutation at the HGPT locus in cultured Chinese hamster ovary cells with and without metabolic activation	Negative	Pant, K. (1994)
Technical: micronucleus assay in CD-1 mouse bone marrow cells	Negative	Sames, J.S., Vandenberghe, Y.L. (1996b)

Mammalian Erythrocyte Test with the Kinetochore Analyses	Negative	Gudi, R and Krsmanovic, L . (2002)

2.6.5 Summary of long-term toxicity and carcinogenicity

Zoxamide was not carcinogenic in studies in rats and mice. The NOAEL in the rat was 1000 ppm (50 mg/kg bw/day) and in mice 7000 ppm (1021 mg/kg bw/day) based on the absence of treatment-related toxicity at the highest test dose in both species. In the rat an increase in relative liver weight was observed at > 5000 ppm but there was no corroborative evidence of toxicity. Summary of long term toxicity and carcinogenicity is presented in tabele 2.6.5-1.

Table 2.6.5-1: Summary of long term toxicity and carcinogenicity

Study	NOEL/NOAEL (mg/kg bw/day)	LOEL/LOAEL (mg/kg bw/day)	Effects at LOAEL	Reference
2-year rat study at 0, 1000, 5000 and 20000 ppm	1000 ppm (50 mg/kg bw/day)	5000 ppm (260mg/kg bw/day)	Absence of significant toxicity at the highest test dose	[redacted] 1998a
2-year study in mice at 0, 350, 1750 and 7000 ppm	7000 ppm (ca. 1021 mg/kg bw/day)	7000 ppm (ca. 1021 mg/kg bw/day)	Absence of significant toxicity at the highest test dose	[redacted], 1998c

2.6.6 Summary of reproductive toxicity

In a multigeneration reproductive toxicity study, there were no adverse reproductive effects in rats following the administration of RH-117,281. Relevant parental and offspring NOAELof 360mg/kg is proposed.

There was no evidence of toxicity in the rat or rabbit in developmental toxicity studies. The NOAEL in both studies was 1000 mg/kg bw/day based on the absence of toxicity to dams or fetuses at the highest test dose. Zoxamide was not teratogenic in the rat or rabbit. Summary of reproductive toxicity is presented table 2.6.6-1.

Table 2.6.6-1: Summary of reproductive toxicity

Study	NOEL/NOAEL (mg/kg bw/day)	LOEL/LOAEL (mg/kg bw/day)	Effects at LOAEL	Reference
Multigeneration study in rats at 0,1000, 5000 & 20000	Parental NOAEL: 5000 ppm (360 mg/kg bw/day)	20000 ppm (1474 mg/kg bw/day)	Decreased body weight gain of P1 females during the pre-mating period and liver effects in males at 2000 ppm.	[redacted], 1998
	Reproductive NOAEL: 20000ppm (1474 mg/kg bw/day)	>20000ppm	No adverse effects on reproduction	
	Offspring NOAEL: 5000 ppm (360 mg/kg bw/day)	20000 ppm (1474 mg/kg bw/day)	Decreased body weight gain in F1a, F1b and F2a.	
Developmental toxicity in rabbits at 0, 100, 300 & 1000 mg/kg bw/day	1000 mg/kg bw/day	>1000 mg/kg bw/day	No evidence of toxicity at the highest test dose	[redacted], 1997
Developmental toxicity in rats at 0, 100, 300 & 1000 mg/kg bw/day.	1000 mg/kg bw/day	>1000 mg/kg bw/day	No evidence of toxicity at the highest test dose	[redacted], 1995b

2.6.7 Summary of neurotoxicity

The NOAEL in the acute neuroxicity study in the rat was 2000 mg/kg bw the highest test dose level. In a subchronic neurotoxicity study in the rat, the NOAEL was 20000 ppm (1509 mg/kg bw/day) based on the absence of toxicity at the highest test dose. Summary of neurotoxicity is presented in table 2.6.7-1.

Table 2.6.7-1: Summary of neurotoxicity

Study	NOEL/NOAEL (mg/kg bw/day)	LOEL/LOAEL (mg/kg bw/day)	Effects at LOAEL	Reference

Study	NOEL/NOAEL (mg/kg bw/day)	LOEL/LOAEL (mg/kg bw/day)	Effects at LOAEL	Reference
Neurotoxicity studies in rodents 0 (control), 125, 500 and 2000 mg /kg bw.	2000 mg/kg bw	> 2000 mg/kg bw	No evidence of neurotoxicty	[redacted] (1997)
Three-month dietary toxicity/neurotoxicity study in rats 0 (control), 1000, 5000, and 20,000 ppm.	20,000 ppm	> 20,000 ppm	No evidence of neurotoxicty	[redacted] (1996a

2.6.8 Summary of further toxicological studies on the active substance

In a series of experiments, the antitubulin benzamide (ATB) compounds RH-117,281 and RH-54032 inhibited nuclear division in the Oomycete fungus Phytophthora capsici by disruption of cellular microtubules as the result of a highly specific covalent binding to the ß-subunit of tubulin. In plants, RH-54032 reportedly caused morphological effects of leaf cupping and club-shaped roots which are considered typical of antimicrotubule agents. More detailed studies in tobacco suspension-cultured cells demonstrated covalent binding of RH-54032 to ß-subunit of tubulin, and an accumulation of cells in arrested metaphase. Mouse lymphoma cells were shown to be less sensitive than P. capsici and tobacco to RH-117,281 and RH-54032, however an accumulation of metaphase cells and covalent binding to ß -tubulin was also demonstrated. In vitro microtubule assembly assays demonstrated an inhibition of assembly by RH-117,281 and RH-54032, which was noted to be unusual in requiring a prolonged incubation with tubulin. RH-117,281 was comparable in potency to carbendazim in inhibiting microtubule assembly and the growth of mouse lymphoma cells, and was considerably less active than colchicine and vinblastine. Consistent with whole cell labelling experiments, the binding of radiolabeled RH-54032 to isolated bovine tubulin was shown to involve the ß-subunit. Since binding of radiolabeled RH-54032 to isolated tubulin was strongly inhibited by colchicine, podophyllotoxin and nocodazole, but not by vinblastine, it was considered likely that the ATBs bind at or near the colchicine binding site of tubulin. Summary is presented in table 2.6.8-1

Table 2.6.8-1: Summary of further toxicological studies on the active substance

Study	Species/system	Dose levels/concentrations	Result/Interpretation	Reference

Mechanistic study	Mouse	-	Consistent with whole cell labelling experiments, the binding of radiolabeled RH-54032 to isolated bovine tubulin was shown to involve the ß-subunit. Since binding of radiolabeled RH-54032 to isolated tubulin was strongly inhibited by colchicine, podophyllotoxin	*Young, D.H. (1998)*

2.6.9 Summary of toxicological data on impurities and metabolites

For the first inclusion of zoxamide in Annex I to Directive 91/414/EEC, data on some metabolites was evaluated and is summarised below. The data is considered satisfactory, and sufficient for the purposes of reregistration. No changes to the original conclusions are proposed.

In studies on the metabolite RH-145,452, the acute oral LD50 for RH-141,452 in male and female mice was > 5000 mg/kg bw. RH-141,452 was not mutagenic in the Salmonella gene mutation assay under the conditions of the study. In studies on the metabolite RH-141,455, the acute oral LD50 for RH-141,455 in male and female mice was greater than 5000 mg/kg bw. RH-141,455 was not mutagenic in an Ames test, a mammalian cell mutation assay and an in vitro micronucleus assay. The metabolite studies showed that the metabolites RH-145,452 and RH-141,455 were not of greater toxicity than parent RH-117,281.

A non-common plant metabolite RH-150,721, was evaluated for mutagenic potential in an Ames test, a mammalian cell mutation assay, and a mammalian cytogenetics assay, and further surveyed for toxicological hazard relative to parent using QSAR software (DEREK NEXUS). Although it's stated that this is an intermediate metabolite, in the result it could not be concluded whether this metabolite is less toxic than parent zoxamide. It can be concluded that metabolite RH-150,721 is not mutagenic in Ames test, a mammalian cell mutation assay and in mammalian cytogenetic assay. For further surveyed for toxicological hazard DEREK NEXUS software analysis was submitted where no new areas of toxicological concern were found. RMS is on the opinion that because of high amount of metabolite RH-150,721 in wine, genotoxic and carcinogenic potential could not be excluded. RMS believes that DEREK analysis is reliable in the results regarding mutagenicity rather than for genotoxicity or carcinogenicity. Overall conclusion is that it could not be concluded whether metabolite RH-150721 is less toxic than parent zoxamide

A comparative QSAR analysis of zoxamide against potential impurities in the technical material using OECD QSAR Toolbox, did not highlight any new areas of significant toxicological concern over parent. Summary is presented below.

Table 2.6.9-1: Overview of toxicity studies performed with metabolites

Study	Species/system	Dose levels/concentrations	Result/Interpretation	Reference
14C-RH-141,452Rat metabolism study, TieI testing	rat	1000 mg/kg body weight	The absorption, distribution, metabolism and elimination of [14C]-RH-141,452 was investigated in male rats. The majority of RH-141,452 was eliminated unchanged through urine, accounting for >94% of the administered dose. Three minor conjugates, M-2, M-3 (glucuronide conjugates), and M-4 (glycine conjugate) were also found in the urine samples, accounting for approximately 3% of the administered dose. An additional 1.6% of the administered radioactivity was excreted in the faeces as the parent chemical.	[redacted] *(1998a)*
RH-141,452: Acute oral toxicity study	mice	5000 mg/kg bw (20 ml/kg)	The acute oral LD50 of RH-141,452 in male and female mice was > 5000 mg/kg bw	[redacted] *(1998d)*
RH-141,452: Salmonella typhimurium gene mutation assay (Ames test)	Salmonella typhimurium	-	RH-141,452 was not mutagenic in the Salmonella gene mutation assay under the conditions of this study.	*Sames, J.L., Ciaccio, P.J.(1998a)*

14C-RH-141,455: Rat metabolism study, Tier I testing	Rat	1000 mg/kg bw	Greater than 96% of radioactivity excreted from faeces and urine was identified to be unchanged RH-141,455. Some very minor metabolites were also observed in urine samples but were not identified due to their extremely low percentage of dose.	[redacted] *(1998b)*
RH-141,455: Acute oral toxicity study in male and female mice.	Mice	5000 mg/kg bw (10 ml/kg)	The acute oral LD50 for RH-141,455 in male and female mice was greater than 5000 mg/kg bw.	[redacted] *(1998b)*
RH-141455: In Vitro Micronucleus Test In Human Lymphocytes	Human Lymphocytes	-	It is concluded that RH-141,455 administered for 3 hours in both the absence and presence of S9 mix and for 20 hours in the absence of S9 mix only, at concentrations of up to 587.5 µg/mL, did not show any evidence of causing an increase in the induction of micronuclei in cultured human lymphocytes in this in vitro test system under the experimental conditions described.	*Woods, I. (2014b)*
RH-141455: In Vitro Mutation Test Using Mouse Lymphoma L5178Y Cells	Mouse Lymphoma L5178Y Cells	-	It was concluded that RH-141455 did not demonstrate mutagenic potential in this in vitro cell mutation assay, under the experimental conditions described.	*Woods, I. (2014a)*

RH-141455: Salmonella typhimurium gene mutation assay (Ames test).	Salmonella typhimurium	-	RH-141,455 was not mutagenic in this Ames test.	*Sames, J.L., Ciaccio, P.J. (1998b)*
RH-150,721: Salmonella typhimurium reverse mutation assay potential in this in vitro cell mutation assay, under the experimental conditions described.	Salmonella typhimurium	-	RH150721 was not mutagenic under the conditions of this bacterial reverse mutation assay.	*Sokolowski, A. (2013)*
DEREK evaluation of the toxicities of zoxamide and metabolite RH-150,721	-	-	Overall conclusion is that it could not be concluded whether metabolite RH-150721 is less toxic than parent zoxamide	*Thandi, A. (2013)*

2.6.10 Summary of medical data and information

No studies were evaluated in the original DAR (2001) and no additional studies were submitted for the purpose of renewal

2.6.11 Toxicological end point for assessment of risk following long-term dietary exposure - ADI

As already agreed (Review report (SANCO/10297/2003-Final, 4 February 2004), the ADI is set at 0**.5 mg/kg bw/day** based on the 1-year study in dog and considering a safety factor of 100.

2.6.12 Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

The establishment of ARfD is not considered to be necessary for zoxamide due to the toxicological profile of this active substance.

2.6.13 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL

As already agreed (Review report (SANCO/10297/2003-Final, 4 February 2004), the AOEL is set at **0.3 mg/kg bw/day** based on the 90-day study in dog and considering a safety factor of 100 and oral absorbtion of 60 %.

2.6.14 Summary of product exposure and risk assessment

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.2.6.14-1: 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

2.6.14.1 Operator Exposure

Operator exposure was evaluated using German BBA and UK POEM exposure models and dermal absorption values of 4% and 10% for mixing/loading and for application respectively.

According to the model calculations, it can be concluded that the risk for the operator using Zoxium 240 SC on potatos and grapevines is acceptable without the use of personal protective equipment.

For potatoes:

BBA model predictions result in a maximal exposure estimate of 0.016 mg/kg bw/day corresponding to 5% of the AOEL of zoxamide.

UK POEM predictions result in a maximal exposure estimate of 0.045 mg/kg bw/day corresponding to 15% of the AOEL of zoxamide.

For grapevines:

BBA model predictions result in a maximal exposure estimate of 0.026 mg/kg bw/day corresponding to 9 % of the AOEL of zoxamide.

UK POEM predictions result in a maximal exposure estimate of 0.053 mg/kg bw/day corresponding to 18% of the AOEL of zoxamide.

2.6.14.2 Bystander and Resident Exposure

Bystander exposure has been evaluated according to the EUROPOEM II model:

Estimated exposure to bystander upon incidental exposure to zoxamide during the application of Zoxium 240 SC is below the AOEL and represents 1.1 % of the AOEL of zoxamide (0.0032 mg/kg bw/day). Therefore, the risk for bystander is considered to be acceptable based on EUROPOEM II data.

Resident exposure has been evaluated according to the Martin (2008) model:

Estimated exposure to resident upon exposure to zoxamide during the application of Zoxium 240 SC is below the AOEL and represents 0.1 % of the AOEL of zoxamide (0.00039 mg/kg bw/day) for adults and 0.3 % of the AOEL of zoxamide (0.00076 mg/kg bw/day). Therefore, the risk for resident is considered to be acceptable based on Martin (2008) data.

2.6.14.3 Workers

Estimations of potential worker exposure have been done according to the EUROPOEM II model.

It is concluded that there is no unacceptable risk anticipated for the unprotected worker wearing adequate work clothing (but no PPE) when re-entering potato and grapevine crops treated with Zoxium 240 SC.

Dislodgeable foliar residue (DFR) studies with the Zoxium 240 SC were not available. Using the conservative DFR default value of 3 µg/cm2, the predicted systemic exposure for an unprotected worker corresponds to 7.5% of the AOEL of zoxamide (0.023 mg/kg bw/day) for potato and 54% of the AOEL of zoxamide (0.162 mg/kg bw/day) for grapevines.

2.7 RESIDUES

2.7.1 Summary of storage stability of residues

Storage stability of zoxamide (RH-7281) residues was shown to be acceptable for up to 24 months in potatoes, grape juice, raisins and wine, and for up to 18 months in grapes.

Residues of RH-150721 were shown to be stable for at least 18 months in grape berries and at least 24 months in wine when stored frozen at ≤ -18°C.

Storage stability of the metabolites RH-141452 and RH-141455 in potatoes was demonstrated over a period of 24 months when stored frozen at ≤-18°C.

Studies to determine the stability of residues in commodities of animal origin are not required as studies on the metabolism and residues in livestock are not required due to low residues in contributing feed items.

2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

Plant

Metabolism studies are presented for three crop groups: fruit (grape, tomato and cucumber), root crop (potato) and pulses and oilseeds group (peas).

Zoxamide is of low systemicity, therefore following foliar application to crops, most of the applied material remains on the surface of the plants. In the metabolism studies conducted in grapes, tomato, cucumber and peas, the major component of the residue is unchanged zoxamide (RH-7281). Degradation is by photolysis on the crop surface and hydrolysis or oxidation, and results in a number of minor metabolites.

In the potato metabolism study, no parent zoxamide was found in potato tubers as the tubers were not in direct contact with the spray, and zoxamide is minimally translocated. The main components of the residue in potato tubers were the metabolites RH-141452 and RH-141455, probably as a result of uptake of residues from the soil.

In the pea metabolism study, low residues of zoxamide were found in fresh and dry peas as the pea seed was protected by the pods and therefore not in direct contact with the spray. The remainder of the residue in fresh and dry peas comprised unidentified polar residues and unextractable residues that were characterised as being associated with starch, protein, pectin, lignin, hemicellulose and cellulose.

Livestock

The representative uses on potatoes and grapevines do not result in significant residues (above 0.1 mg/kg total diet) occurring in the diet of poultry, ruminants, therefore no data on poultry or ruminant metabolism are required. Nevertheless, a goat metabolism study is available, which showed that zoxamide was extensively metabolised and readily eliminated following oral administration. No parent zoxamide was found in any tissue or milk sample. A number of metabolites were detected, of which RH-127450 was the most abundant metabolite, found at 0.13 mg/kg (65% TRR) in fat. At the maximum calculated dietary burden, no significant residues are likely to occur in any edible tissue or milk.

The representative uses on potatoes and grapevines do not result in significant residues occurring in the diet of pigs, and the metabolism of zoxamide is qualitatively similar in the goat and the rat, and therefore a pig metabolism study is not required.

Zoxamide has a log P_{OW} of 3.76, and therefore has potential to bioaccumulate. However, residues of zoxamide in fish feed arising from the representative uses on potatoes and grapevines are <0.01 mg/kg diet, and therefore a fish metabolism study is not required. A metabolism study in Bluegill sunfish (*Lepomis macrochirus*) is available which showed that metabolism was extensive and no parent zoxamide was found in fillet or viscera. RH-127450 was the major metabolite detected.

New studies evaluated in the RAR do not change the conclusion with regard to the main degradation pathway.

2.7.3 Definition of the residue

For fruit and pulses and oilseeds group the residue definition is parent zoxamide, for both risk assessment and monitoring.

For potato the residue definition is parent zoxamide and its metabolites RH-141455 and RH-141452, for both risk assessment and monitoring.

It is proposed that no definition of residue is required for animal products for risk assessment and monitoring.

Residue definition for wine – parent zoxamide is generally not present (<0.01mg/kg), however the metabolite/degradite RH-150721 is found at significant levels (>10% TRR in wine in the radiolabelled vinification study, and up to 0.49mg/kg in processing studies). Although it's stated that this is an intermediate metabolite, in the result it could not be concluded whether this metabolite is less toxic than parent zoxamide. It can be concluded that metabolite RH-150721 is not mutagenic in AMES test, a mammalian cell mutation assay and in mammalian cytogenetic assay. For further surveyed for toxicological hazard DEREK NEXUS software analysis was submitted where no new areas of toxicological concern were found. RMS is on the opinion that because of high amount of metabolite RH-150721 in wine, genotoxic and carcinogenic potential could not be excluded. RMS believes that DEREK analysis is reliable in the results regarding mutagenicity rather than for genotoxicity or carcinogenicity. Overall conclusion is that it could not be concluded whether metabolite RH-150721 is less toxic than parent zoxamide. Therefore RMS is not able to conclude on residue definition for wine for both monitoring and risk assessment.

2.7.4 Summary of residue trials in plants and identification of critical GAP

The critical GAP for potatoes is 5 applications at 180 g as/ha, minimum application interval of 8 days, PHI 7 days.

The critical GAP for table and wine grapes is 5 applications at 180 g as/ha, minimum application interval of 8 days, PHI 28 days.

Sufficient residue trials are presented for potato which show that residues of zoxamide, and the metabolites RH-141452 and RH-141455, are <0.02 mg/kg. Two additional trials performed in southern Europe with the representative formulation, Zoxium 240 SC, confirmed the zero-residue situation for potatoes.

Sufficient residue trials are presented for grapes which show that residues of zoxamide are below the current EU MRL of 5 mg/kg. Two additional trials performed in southern Europe with the representative formulation, Zoxium 240 SC, confirmed that residues in grapes are below the MRL level. For the 2F

(240 SC) formulation, residues in grapes were 0.47-2.65 mg/kg in northern Europe and 0.22-1.86 mg/kg in southern Europe.

Table 2.7.4-1: Critical GAP for representative intended use of zoxamide

Crop	Zone	Outdoor/ Protected	Growth stage	Maximum Number of Applications	Min. Interval (days)	Maximum		Min. PHI (days)
						Rate g as/ha	Water L/ha	
Wine grapes	Central South	O	BBCH 15-79	5	8	180	1000	28
Table grapes	Central South	O	BBCH 15-79	5	8	180	1000	28
Potato	North Central South	O	BBCH 20-80	5	8	180	1000	7

2.7.5 Summary of feeding studies in poultry, ruminants, pigs and fish

Dietary burden calculations are presented for poultry, ruminant and pigs which show that dietary burdens are all below 0.004 mg/kg bw/day, and therefore livestock feeding studies are not required.

Grapes are not used for the preparation of fish feedstuffs. Root and tuber vegetables are used only in small quantities for fish feedstuffs, and potato protein comprises a maximum of 3% of the diet for carp, and is not used in trout feed. Residues of zoxamide (and the metabolites RH-141455 and RH-141452) in potatoes are <LOQ, therefore residues in fish feed will be <0.01 mg/kg. Zoxamide has a log P_{OW} of 3.76, and therefore has potential to bioaccumulate, however as residues of zoxamide in fish feed will be <0.01 mg/kg, fish feeding studies are not required.

2.7.6 Summary of effects of processing

Processing studies are not required for potato as residues of zoxamide (and the metabolites RH-141455 and RH-141452) are <0.02 mg/kg (<LOQ) in studies for AnnexI inclusion and <0.005mg/kg (<LOQ) in studies performed in 2010 using the product Zoxium 240 SC according to the representative GAP in this submission.

The nature of residues following processing of grapes was investigated in a radiolabelled vinification study. This study showed that the only significant residue in grape juice was parent zoxamide (RH-7281), while in wine the residue comprised mainly parent zoxamide (RH-7281) and the metabolite RH-150721.

No studies simulating hydrolytic conditions for industrial processing (pasteurisation, baking, brewing, boiling, sterilisation) are submitted. Such studies are required according to EU Regulation No 283/2013 and OECD document 507 „Nature of the pesticide residues in processed commodities – high temperature hydrolysis". Therefore RMS is not able to conclude on nature of residues for processed commodities. It is not possible to conclude about processing factors and magnitude of residues in processed commodities as long as nature of residues in processed commodities is not clearly demonstrated.

2.7.7 Summary of residues in rotational crops

A confined crop rotation study was previously evaluated for Annex I inclusion. Study showed minimal translocation of zoxamide residues from soil into crops. Parent zoxamide was not detected in following

crops. The crop metabolite RH-141452 was found at trace levels in following crops. No detectable residues of zoxamide or related metabolites are expected in rotational crops.

2.7.8 Summary of other studies

A radiovalidation study has been performed to determine the extraction efficiency of the QuEChERS method extraction. The study used immature whole plant and dry pea seed samples containing radiolabelled incurred residues from the pea metabolism study. The amount of zoxamide extracted using the QuEChERS extraction method and the metabolism study extraction method was found to be in good agreement.

No other studies are deemed necessary.

2.7.9 Estimation of the potential and actual exposure through diet and other sources

TMDI (chronic) calculations have been performed using the EFSA PRIMo model, rev 2.0, and compared to an Acceptable Daily Intake (ADI) of 0.5 mg/kg bw/day.

The TMDI values have been calculated based on the current EU MRLs for zoxamide in grapes (5 mg/kg) and potatoes (0.02* mg/kg).

As no determinable residues of zoxamide are likely in animal products, and MRLs are not currently set on products of animal origin, these commodities have not been included in the dietary risk assessment.

The summary of the chronic intake calculation is presented in following table.

Zoxamide

Status of the active substance		Code no.	
LOQ (mg/kg bw)		proposed LOQ	
Toxicological end points			
ADI (mg/kg bw/day)	**0.5**	ARfD (mg/kg bw)	**n.n.**
Source of ADI	**Review Rep**	Source of ARfD	
Year of evaluation	**2004**	Year of evaluation	

Prepare workbook for refined calculations

Undo refined calculations

The risk assessment has been performed on the basis of the MRLs collected from Member States in April 2006. For each pesticide/commodity the highest national MRL was identified (proposed temporary MRL pTMRL).
The pTMRLs have been submitted to EFSA in September 2006.

Chronic risk assessment

TMDI (range) in % of ADI
minimum - maximum
4

No of diets exceeding ADI: ---

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of AD)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
4.1	FR a l population	4.1	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
2.8	PT General population	2.8	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
2.2	WHO Cluster diet B	2.1	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
1.8	WHO cluster diet E	1.8	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
1.5	DK adult	1.5	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
1.3	DE child	1.3	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
1.2	IE adult	1.2	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
1.1	UK Adult	1.1	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.9	UK vegetarian	0.9	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.9	NL general	0.9	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.8	NL child	0.8	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.7	WHO Cluster diet F	0.7	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.6	WHO cluster diet D	0.6	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.5	ES adult	0.5	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.4	WHO regional European diet	0.4	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.3	PL general population	0.3	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.3	FI adult	0.3	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.3	UK Toddler	0.3	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.2	SE general population 90th percentile	0.2	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.2	FR toddler	0.2	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.2	DK child	0.2	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.1	IT adult	0.1	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.1	IT kids/toddler	0.1	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.1	FR infant	0.1	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.1	UK Infant	0.0	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.0	ES child	0.0	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	
0.0	LT adult	0.0	Table and wine grapes	0.0	Potatoes		FRUIT (FRESH OR FROZEN)	

Conclusion:
The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.
A long-term intake of residues of Zoxamide is unlikely to present a public health concern.

Using this model, the chronic risk assessment ranges from 0 to 4.1% of the ADI. The diet with the highest TMDI is "FR All Population" with 4.1% of the ADI. The results indicate that the proposed uses of

zoxamide on grapes and potatoes result in no unacceptable chronic risk to human health from the consumption of treated commodities.

An Acute Reference Dose is not necessary, and therefore an acute dietary exposure calculation (NESTI) has not been performed.

2.7.10 Proposed MRLs and compliance with existing MRLs

Code Number	Crops	Current EU MRLs Reg(EU) 520/2011	Proposed MRL
0151010	Table grapes	5.0	5.0
0151020	Wine grapes	5.0	5.0
0211000	Potatoes	0.02*	0.02*

It is proposed that the current MRLs of 0.02* mg/kg for potato and 5 mg/kg for grapes remain unchanged.

(*) At the LOQ of the analytical method.

2.7.11 Proposed import tolerances and compliance with existing import tolerances

Not applicable.

2.8 FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1 Summary of fate and behaviour in soil

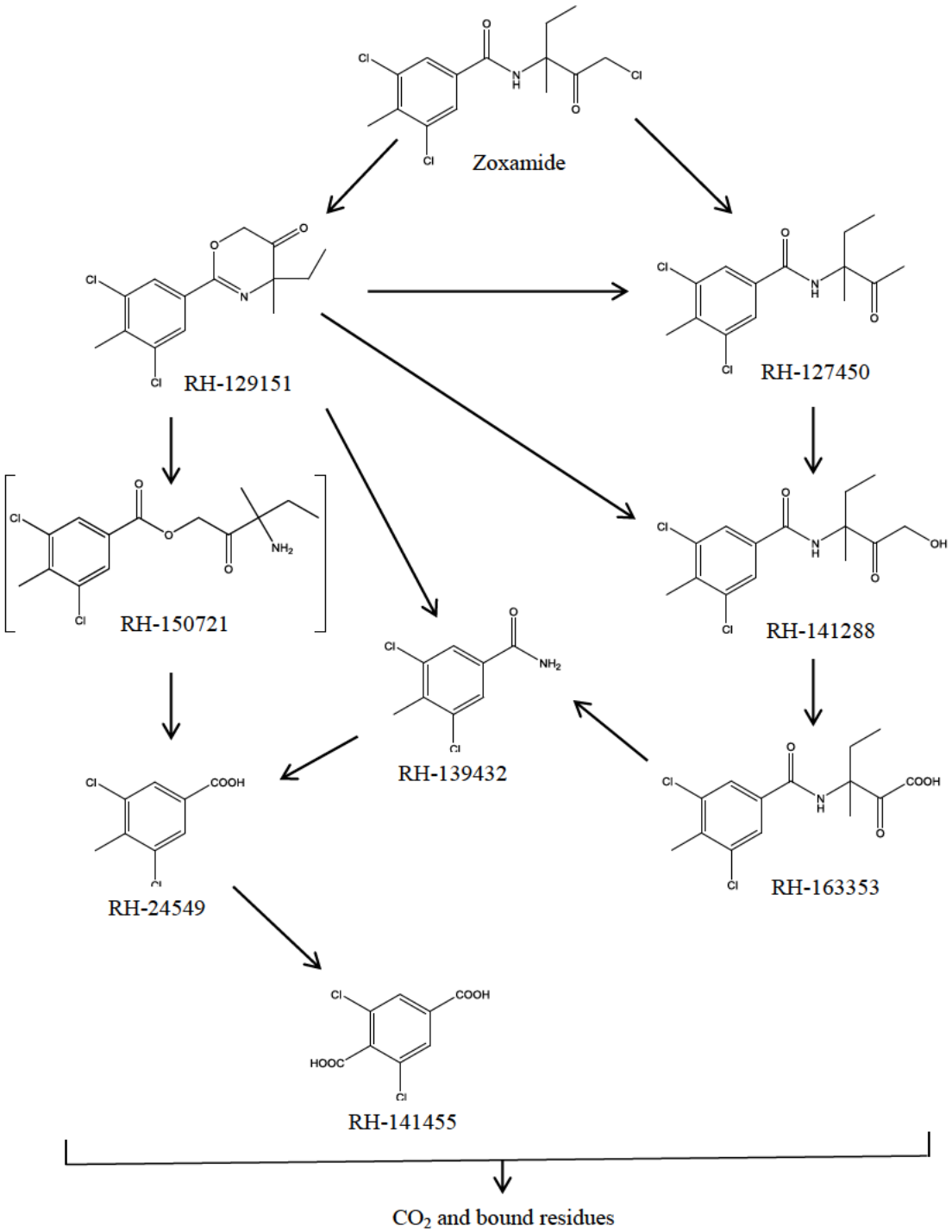
Route of degradation in soil

In the original review the route of degradation of zoxamide in aerobic soil was studied in six soils (pH 5.0-8.1, 0.8-2.4 %oc), besides one soil (Germany, sandy loam) was investigated considering three different incubation conditions. Up to 23 degradates were detected. Major metabolites exceeding 10% AR were RH-127450 (de-chlorinated product, 8.1-15.1% AR), RH 24549 (benzoic acid derivative, 5.5-33.8% AR) and RH-163353 (acid, 7.9-15% AR). Maximum levels of these metabolites at 20°C and 10°C were found on days 3-7 and 7-14 respectively. Mineralisation of zoxamide was significant (34.4-57.8% AR by days 120-122), although non-extractable residues accounted for maximums of 25.6-39.1-% AR (days 28-120). Of the unextracted residues, 9.2-17.5% AR and <0.1-12.7% AR was associated with fulvic and humic acid fractions respectively and 2.8-22.7% AR was associated with humins. Although there was no significant difference in metabolite levels found at different temperatures, mineralisation was slower at 10°C. Mineralisation of non-extracted residues over the study period was slow. Aerobic metabolism of zoxamide in soil is similar to that observed during hydrolysis studies in water and proceeds by cyclisation and de-chlorination, followed by oxazine ring-opening, by hydrolysis leading to amination or hydroxylation and subsequent cleavage at the epoxyimino- and epidioxy- bridges (Figure 2.8.1-1).

Since the original review, the guidelines for evaluating the relevance of metabolites have changed. Metabolites occurring at >5% on two or more consecutive occasions should be considered as well as those which reach their maximum at the final timepoint of the study. The previously submitted studies were examined for any other metabolites meeting these lower thresholds. In the soil degradation and metabolism study (Burgener, 1998a), metabolite RH-141455 was detected at levels above 5% on more than two occasions (Maximum was 8%), therefore this metabolite also requires further consideration.

The anaerobic degradation of zoxamide was examined in two soils (soil pH 6.9-7.4, 1.2-2.4 %oc, 20-25°C). In the first study, anaerobic conditions were established before introduction of the test material, however in the second study, aerobic metabolism was allowed to take place for 21 days before anaerobic conditions were introduced. Up to 22 degradates were identified. Major metabolites exceeding 10% AR were RH-127450 and RH-24549. Near-maximum concentrations occurred in soils around days 14-56 and were continually maintained under anaerobic conditions, as were levels of CO2 (4.6-5.1% AR), indicating that although metabolites were formed under both aerobic and anaerobic conditions, their degradation was slower under anaerobic conditions. Levels of RH-127450 increased from 0.2% AR (day 1) to 30.2% AR (day 28), declining slowly to 23.7% AR by day 120. Levels of RH-24549 increased from 0.3% AR (day 1) to 23.7% AR (day 120). Non-extractable residues accounted for maximums of 25.6-39.1% AR and were associated primarily with humic and fulvic acids and humins. The possibility that anaerobic conditions are encountered after application is unlikely as the proposed applications to potatoes and grapes will occur during the summer months.

Figure 2.8.1-1: Proposed route of degradation of zoxamide in soil



In a soil photolysis study, degradation was observed in both the irradiated and dark control samples. Similar metabolites were identified as in the aerobic and anaerobic soil degradation studies, suggesting that degradation is primarily hydrolytic or microbial, rather than photolytic.

Rate of degradation in soil

For the first EU review DT50s of 2.0-10 days and DT90s of 6.7-110 days (1st order at 10-20°C and root 1st order at 25°C) were calculated for zoxamide. It was concluded that there was no clear effect of temperature on degradation rate within the range of studies undertaken and no significant effect of soil type/properties on degradation rates. DT50s under anaerobic conditions were 7 to 14 days. Degradation rates for the metabolites, RH-127450, RH-24549 and RH-163353 were calculated to be 4.0-17.8 days, 5.5-19 days and 7.5-13 days respectively under aerobic conditions at 20°C. Results suggest their degradation may be slower under anaerobic conditions, however it was not possible to estimate DT50s.

Since the first review, the guidelines for evaluating the relevance of metabolites have changed. Metabolites occurring at >5% on two or more consecutive occasions should be considered as well as those which reach their maximum at the final time point of the study. In the soil degradation and metabolism study (Burgener, 1998a), metabolite RH-141455 was detected at levels above 5% on more than two occasions (Maximum was 8%), therefore data on the degradation of this metabolite in soil are provided.

The rates of degradation in the aerobic soil degradation studies of Smalley and Reynolds (1997) and Burgerer (1998) have been re-evaluated according to the recommendations of the FOCUS Kinetics Group (FOCUS 2006). The SFO model satisfactorily describes the decline of zoxamide in all soils incubated in the study of Burgener (1998a). However, for soils incubated in the study of Smalley *et al* (1997) DFOP kinetics provides a better fit to the data. Persistence endpoints of DT50s of 2.03 to 13.75 days at 10 to 25°C and modelling endpoints of DT50s 2.03 to 41.3 days at 10 to 25°C were obtained.

For the metabolites, although in many instances the chi2 % error is >15%, P values are generally <0.1 and visual fits are acceptable with only an unacceptable fit identified for two of the metabolites in two soils. Persistence and modelling DT50s were 1.99 to 11.69 days at 20°C (17.8 days at 10°C) for RH-127450, 3.05 to 16.23 days at 20 to 25°C for RH-24549, 5.62 to 53.65 days at 20°C (55.5 days at 10°C) for RH-163353 and 195.2 days at 20°C for RH-141455. In the new study with RH-141455 DT50s were 11.1 to 31.7 days at 20°C. The slower DT50 for RH-141455 in the study with the parent is largely due to the low detections of the metabolite in this study.

The rates of degradation of zoxamide and its metabolites are summarised in Table 2.8.1-1.

Table 2.8.1-1: Summary of the rates of degradation of zoxamide and its metabolites

Study	Soil	Model	DT_{50} (days)	DT_{90} (days)	FF[1]
Zoxamide					
Burgener 1998	England silt loam 20°C 50%MWHC	SFO (persistence & modelling)	4.16	13.8	-
	France loam 20°C 50%MWHC	SFO (persistence & modelling)	2.03	6.7	-
	Germany sandy loam 20°C 50%MWHC	SFO (persistence & modelling)	2.7	9.0	-
	Italy clay loam 20°C 50%MWHC	SFO (persistence & modelling)	2.38	7.9	-
	Germany sandy loam 10°C 50%MWHC	SFO (persistence & modelling)	7.73	25.7	-
	Germany sandy loam 20°C 100%FC	SFO (persistence & modelling)	2.27	7.6	-
Smalley et al (1997)	Pennsylvania silt loam 25°C 75%FC	DFOP (persistence)	7.75	98.1	-
		DFOP (modelling)*	39.2	-	-
	Ohio loamy sand 25°C 75%FC	DFOP (persistence)	13.75	107.1	-
		DFOP (modelling)*	41.3	-	-
RH-127450					
Burgener	England silt loam 20°C 50%MWHC	SFO (persistence & modelling)	11.69	38.84	0.26

1998	France loam 20°C 50%MWHC	SFO (persistence & modelling))	3.78	12.57	0.21
	Germany sandy loam 20°C 50%MWHC	SFO (persistence & modelling)	6.66	22.14	0.18
	Italy clay loam 20°C 50%MWHC	SFO (persistence & modelling)	1.99	6.6	0.21
	Germany sandy loam 10°C 50%MWHC	SFO (persistence & modelling)	17.8	59.05	0.17
	Germany sandy loam 20°C 100%FC	SFO (persistence & modelling)	5.76	19.13	0.20
RH-24549					
Burgener 1998	France loam 20°C 50%MWHC	SFO (persistence & modelling)	6.29	20.89	0.19
	Germany sandy loam 20°C 50%MWHC	SFO (persistence & modelling)	5.35	17.77	0.17
	Italy clay loam 20°C 50%MWHC	SFO (persistence & modelling)	8.44	28.03	0.47
	Germany sandy loam 20°C 100%FC	SFO (persistence & modelling)	3.05	10.15	0.28
Smalley et al (1997)	Ohio loamy sand 25°C 75%FC	SFO (persistence & modelling)	16.23	53.9	0.17
RH-163353					
Burgener 1998	England silt loam 20°C 50%MWHC	SFO (persistence & modelling)	53.65	178.23	0.09
	France loam 20°C 50%MWHC	SFO (persistence & modelling)	6.62	21.99	0.20
	Germany sandy loam 20°C 50%MWHC	SFO (persistence & modelling)	5.62	18.67	0.29
	Italy clay loam 20°C 50%MWHC	SFO (persistence & modelling)	6.39	21.24	0.23
	Germany sandy loam 10°C 50%MWHC	SFO (persistence & modelling)	55.5	184.36	0.15
	Germany sandy loam 20°C 100%FC	SFO (persistence & modelling)	9.9	32.9	0.185
RH-141455					
Burgener 1998	Germany sandy loam 20°C 50%MWHC	SFO (persistence & modelling)	195.2	648.5	0.50[2]
Van den Bosch (2013)	Speyer 2.2 20°C 40%MWHC	SFO (persistence & modelling)	12.0	40.0	-[3]
	Speyer 2.3 20°C 40%MWHC	SFO (persistence & modelling)	11.1	36.9	-[3]
	Speyer 6S 20°C 40%MWHC	SFO (persistence & modelling)	31.7	105.3	-[3]

[1] formation fraction [2] from RH-24549 [3] study conducted with metabolite (RH-141455)

Mobility in soil

For the first EU evaluation, adsorption studies for zoxamide on a range of five soils (pH 4.8-7.2, 0.26-1.77%oc) gave Koc values of 815-1431, classifying zoxamide as slightly mobile using the SSLRC scale.

The adsorption behaviour for the metabolites RH-24549, RH-127450 and RH-163353, was also examined, each in a range of 3 soils (RH-24549: pH 5.2-7.6, 1.3-2.4%oc; RH-127450: pH 5-7.3, 1.0-4.0%oc; RH-163353: pH 5.4-7.2, 1.2-4.8 %oc). Koc values obtained were as follows: RH-24549: 90.5-307.4 ml/g; RH-127450: 404-1156 ml/g and RH-163353: 75-79 ml/g. RH-24549 and RH-163353 are therefore classified as moderately mobile and RH-127450 as slightly to moderately mobile (BCPC monograph 47).

No clear relationships were observed between pH and Kfoc or between % clay content and Kfoc for zoxamide or any of the metabolites, except for RH-24549 which showed tendency of pH dependence. The role of pH or % clay content in determining the mobility of zoxamide is limited, as expected from the lack of a pKa and the non-dependency of water solubility on pH under environmentally relevant conditions.

A 3-day aged column leaching study, performed in one sandy loam soil with 59.1% sand content and relatively low %oc content (pH 7.4, 1.2 %oc) showed 68.6-74.4 %AR in the top 0-5 cm layer and only 1.8-2.3 %AR in the leachate. Zoxamide and major metabolite RH-127450 were only detectable in the 0-5 and 0-10 cm layers respectively. Results indicate a slightly greater potential for leaching of metabolites RH-24549 and RH-163353, however levels were <10% AR in the 0-5 cm layer and non-detectable in the 20-30cm layers.

Due to the short half-lives of zoxamide and major soil metabolites RH-24549, RH-127450 and RH-163353, and the low to moderate mobility through soil, it is considered highly unlikely that these

compounds will leach to groundwater. This is confirmed in simulation modelling summarised within Volume 3 CP – B8 of RAR.

Since the original review, the guidelines for evaluating the relevance of metabolites have changed. Metabolites occurring at >5% on two or more consecutive occasions should be considered as well as those which reach their maximum at the final time-point of the study. In the soil degradation and metabolism study (Burgener, 1998a), metabolite RH-141455 was detected at levels above 5% on more than two occasions (Maximum was 8%), therefore data on the adsorption of this metabolite have been provided. Adsorption of RH-141455 was examined in three soils (0.94 to 1.87%oc, pH 5.5 to 7.1) and was found to be very low with Koc values of 2.1 to 3.3 ml/g (Kd 0.03 to 0.06). As adsorption was so low, Freundlich isotherms were not determined.
The data on the adsorption of zoxamide and its metabolites are summarised in Table 2.8.1-2.

Table B.2.8.1-2: Kfoc values for zoxamide and its metabolites

Compound	Soil	%oc	pH	Kf	1/n	Koc	Kom
Zoxamide	Loam, Huntsburg, Ohio, USA	1.27	7.2	10.35	0.896	815	473
	Sandy loam, Madera, CA., USA	0.26	5.6	3.36	0.986	1294	751
	Silty clay loam, Concord, Ohio, USA	1.77	4.8	25.33	0.963	1431	830
	Sandy loam, Madison, Ohio, USA	1.1	6.7	15.23	0.953	1385	803
	Silty loam, Newtown, Pennsylvania, USA	1.04	6.8	12.44	1.067	1196	694
	Mean / Geometric mean				**0.973**	**1224 / 1201**	**710 / 697**
RH-127450	Loamy sand, Borstel/Germany	1.05	6.1	12.14	0.519	1156	671
	Clay, Egerkingen/ Switzerland	2.82	5.0	11.4	0.603	404	234
	Silt loam, Vetroz/Switzerland	4.05	7.3	18.12	0.448	447	259
	Mean / Geometric mean				**0.523**[1]	**669 / 593**	**388 / 344**
RH-24549	Sandy loam, Iowa/USA	1.3	5.2	4.0	0.791	307.43	178
	Silty clay loam, Illinois/USA	2.4	7.3	3.6	0.833	150.16	87
	Silt loam, Ohio/USA	2.0	7.6	1.8	0.811	90.55	53
	Mean / Geometric mean				**0.811**	**183 / 161**	**106 / 94**
RH-163353	Loamy sand, Borstel/Germany	1.22	6.1	0.6	1.0[2]	50[2]	29
	Clay, Egerkingen/ Switzerland	3.17	5.4	2.4	0.833	75	44
	Silt loam, Vetroz/Switzerland	4.79	7.2	3.8	0.844	79	46
	Mean / Geometric mean				**0.892**	**68 / 67**	**39 / 39**
RH-141455	Speyer 2.2, loamy sand	1.87	5.5	0.06[3]	1.0[2]	3.1[2,4]	1.8
	Speyer 2.3, sandy loam	0.94	6.8	0.03[3]	1.0[2]	3.3[2,4]	1.9
	Speyer 6S, clay	1.64	7.1	0.03[3]	1.0[2]	2.1[2,4]	1.2
	Mean / Geometric mean				**1.0**	**2.8 / 2.8**	**1.6 / 1.6**

[1]low value not considered reliable [2]Kfoc/Koc derived from a Kf/Kd from the screening study, therefore a 1/n value of 1.0 was assumed [3]represents Kd [4]represents Koc

2.8.2 Summary of fate and behaviour in water and sediment

For the first EU evaluation of zoxamide, it was concluded that the active substance hydrolyses in the pH range 4-9 in the absence of light under sterile conditions, with first-order DT50s of 8 (pH 9) and 16 (pHs 4,7) days. Major metabolites exceeding 10% AR were RH-129151 (re-arranged cyclic product), RH-150721 (amine), RH-24549 (benzoic acid derivative) and RH-141288 (alcohol). The hydrolytic stability of zoxamide decreases as temperature and pH increase. Hydrolysis of zoxamide proceeds by de-chlorination and cyclisation to RH-129151, followed by oxazine ring-opening, amination, hydroxylation

and subsequent cleavage at the epoxyimino- and epidioxy- bridges. Degradation rate constants were calculated for the major metabolites at each pH, assuming first order kinetics using linear and non-linear compartmental regression analysis. DT50s were estimated to be 2 and 9 days (RH-129151, at pH 9 and 7 respectively) and 18 days (RH-150721, at pH 4). RH-24549 and RH-141288 were stable (concentrations were still increasing during the study).

The aqueous photolysis of zoxamide was studied at pH 4 to minimise any effects of hydrolysis. When irradiated with a xenon lamp (equivalent light intensity of New Jersey summer sunlight, 42^{o}N) the half-life corresponding to natural irradiation with a 12 hour photoperiod was 8 days. However degradation of zoxamide also occurred in dark controls with a calculated half-life of 22 days. The major degradates occurring at >10% AR, RH-24549 and RH-150721, were not photo-products, reaching similar or greater concentrations in the dark control as in the irradiated samples and were also major hydrolysis degradates. RH-139432 (amide, occurring at a maximum of 42.4%AR) was the only major photo-product in the study and was photolytically stable. The other major metabolites did not degrade under the conditions of this study.

The ready biodegradability of zoxamide was assessed using a method suitable for poorly soluble compounds. Zoxamide was not inhibitory to the microbial innoculum and was only biodegraded by 8% in 29 days, indicating that it is not readily biodegradable under these conditions.

In Rhine river and Rheinfelden pond water/sediment studies conducted at 20 and 10^{o}C, zoxamide degraded in the whole system with first order DT50s of 3.6-11 days (river) and 7.6-16 days (pond) respectively. Zoxamide dissipated from water with 1st order DT50s of 3-6 days (river) and 3-11 days (pond), at 20 and 10^{o}C respectively. A slightly higher proportion of applied radioactivity partitioned into the pond sediment (maximum 80.6% AR) compared to the river sediment (maximum 64.5% AR, however the pond sediment had a higher %oc content than the river sediment. In sediment, zoxamide increased to account for a maximum of 13-26% AR (river, day 7-14) and 23-30 % AR (pond, day 7), then declined with DT50s of 0.8-16 days (river) and 10-19 days (pond).

Preliminary metabolites were identical to those generated during hydrolysis studies. However, the extent of metabolism was greater in natural systems. Metabolites were similar to those found in soil and levels were all <10% AR except for RH-127450 (max. 17% AR (day 28) and 23% AR (day 56) in water and sediment respectively) and RH-163353 (max 16% AR (day 28) and 13.8% AR (day 106) in water and sediment respectively). RH-127450 and RH-163353 were first detected on days 2-14 and dissipated from water with DT50s calculated under the first review of <39 days and <89 days respectively. Levels of major metabolites in sediment were slightly higher in systems incubated at 10^{o}C than at 20^{o}C. Of the non-extractable radioactivity in sediment, 16-20% AR was fulvic acid-associated (soluble at low pH), 8-13% AR was humic acid-associated (soluble at high pH) and 9-10% AR was found in the insoluble humin fraction. Therefore a higher proportion was incorporated into the less mobile sediment organic matter. The extent of mineralisation was similar in river and pond systems and was higher at 20^{o}C (20-22% AR) than at 10^{o}C (4-6.5% AR).

The first EU evaluation concluded that in natural waters, the major dissipation routes of zoxamide will be hydrolysis, microbial degradation and partitioning to sediment, although photolysis may play a minor role. In sediment, zoxamide dissipated moderately rapidly. Significant levels of non-extracted residues are formed, a high proportion being associated with the less mobile humin/humic acid fraction. In water/sediment systems, RH-127450 and RH-163353 were the major metabolites. These metabolites dissipated from water and appeared to be more stable in sediment (levels either continued to increase throughout a study, or peaked on day 56 and declined slowly). Lifetimes of these metabolites in natural aquatic systems are likely to be controlled by biological and chemical degradation rather than by photochemical degradation.

In an aquatic mineralisation study conducted to OECD guideline 309, zoxamide degraded rapidly to non-detectable levels after 28 days with SFO DT50s of 7.6 to 8.4 days. The metabolites RH-141455, RH-139432, RH-141288, RH-163353, RH-24549 and M-7 were detected at >5% on two consecutive occasions at respective maximums of 10.5% AR, 21.4% AR, 22.1% AR, 47.9% AR, 22.7% AR and 9.1% AR. Further experimental work is ongoing to identify M-1, M-2, M-5 and M-7.

The rates of degradation in the sediment/water study of Morgenroth (1998) have been re-evaluated according to the recommendations of the FOCUS Kinetics Group (FOCUS 2006). Zoxamide degraded with DT50s of 6.3 to 6.4 days at 20°C and 10.4 to 19.4 days at 10°C. RH-127450 degraded with DT50s of 88.9 to 326.1 days at 20°C and 123 days at 10°C. DT50s for RH-163353 could not be calculated. The calculated DT50s are given in Table 2.8.2-1.

Table B.2.8.2-1: Calculated DT_{50}s for zoxamide and its metabolites in sediment water systems

Parameter	**River system**		**Pond system**	
	20°C	**10°C**	**20°C**	**10°C**
	SFO	**SFO**	**SFO**	**SFO**
	Zoxamide			
DT_{50} (days)	6.4	10.4	6.3	19.4
DT_{90} (days)	21.1	34.7	20.9	64.6
	RH-127450			
DT_{50} (days)	148.4	-	326.1	123
DT_{90} (days)	493.1	-	1083.3	408.7

2.8.3 Summary of fate and behaviour in air

Adequate data to assess the route and rate of degradation of zoxamide in air were evaluated during the first EU review and no further data are considered necessary.

The vapour pressure of zoxamide is 1.33 x 10^{-5} Pa at 25°C and the water solubility at 20°C is 0.68 mg/l (pH 4-9). Using these values a Henry's Law constant of <6.59 x 10^{-3} Pa/mol·m^3 was derived. These figures suggest that zoxamide is only very slightly volatile. Volatilisation of zoxamide from soil and leaf surfaces under standardised climatic conditions was investigated. Losses were very low with losses of 5.1% AR from leaf surfaces and 3.9% AR from soil after 24 hours. Concentrations of zoxamide in air will therefore be negligible.

A theoretical calculation of the photo-oxidation of zoxamide in the atmosphere, using the method of Atkinson (1988), gave a DT_{50} of 7.5 hours. Therefore in the unlikely event of residues entering air, they will be rapidly degraded.

2.8.4 Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

No data are submitted and are not considered to be necessary.

2.8.5 Definition of the residues in the environment requiring further assessment

Soil

Zoxamide, RH-127450, RH-24549, RH-163353 and RH-141455.

Groundwater

Zoxamide, RH-127450, RH-24549, RH-163353 and RH-141455.

Surface water

Zoxamide, RH-127450 (>10% in soil & water), RH-163353 (>10% in soil & water), RH-141288 (>5% on 2 consecutive occasions in water), RH-24549 (>10% in soil only), RH-141455 (>5% of 2 or more consecutive occasions in soil) and photodegradate RH-139432 (>10% in water).

Air

Zoxamide.

2.8.6 Summary of exposure calculations and product assessment

Environmental fate studies using the formulation Zoxium 240 SC were not conducted as data from studies with the active substance, zoxamide, are available and adequate to enable extrapolation to the behaviour of the formulated product in the environment.

Soil

Zoxium 240 SC is used in vines and potatoes at a maximum application rate of 0.18 kg a.s./ha. Up to a maximum of five applications may be made at a minimum interval of 8 days. PECs for Zoxium 240 SC in soil have been calculated according to FOCUS (1997) using crop interception values from FOCUS (2012). The initial predicted environmental concentration of zoxamide in soil (**PECsoil**) was estimated to be 0.467 mg/kg in potatoes assuming 50% crop interception and 0.374 mg/kg in vines assuming 60% crop interception. The predicted environmental concentrations decrease to 0.087 and 0.070 mg/kg soil after 100 days after application to potatoes and vines respectively.

The metabolites RH-127450, RH-24549, RH-163353 and RH-141455, were detected at >5% AR at maximums of 15.1%, 33.8%, 15% and 8% AR respectively, therefore PECs in soil have been calculated for these metabolites. The initial PECsoil values for RH-127450 were estimated to be 0.039 (potatoes) and 0.031 (vines) mg/kg soil. The initial PECsoil values for RH-24549 were estimated to be 0.07 and 0.056 mg/kg soil. The initial PECsoil values for RH-163353 were estimated to be 0.073 and 0.058 mg/kg soil. The initial PECsoil values for RH-141455 were estimated to be 0.032 and 0.025 mg/kg soil.

In addition, as the metabolite RH-141455 is persistent in soil (DT_{90} > 365 d), accumulation calculations were undertaken. The PECs for RH-141455 were estimated to be 0.050 and 0.040 mg/kg soil when no tillage was considered and 0.037 and 0.029 mg/kg soil considering tillage (0-20 cm).

Groundwater

PECgw have been calculated using the FOCUS groundwater scenarios and the PEARL and PELMO models assuming use of Zoxium 240 SC in potatoes and vines at a maximum of 5 applications of 0.18 kg a.s./ha. Predicted environmental concentrations in groundwater of zoxamide, RH-24549, RH-163353 and RH-127450 were << 0.1 µg/l in all scenarios for the different crops using both models. Predicted environmental concentrations of RH-141455 were above the threshold value of 0.1 µg/L in all scenarios for vines using both models. The values were from 0.356 to 2.596 µg/l. For potatoes, using application every year, the PEC values were above 0.1 µg/l in all scenarios, except for the Sevilla scenario, with both models. The values were from 0.041 to 3.478 µg/l. For potatoes, using application every 3 years, the PEC values were above 0.1 µg/L in all scenarios, except for the Porto, Sevilla and Thiva scenarios, with the PELMO model. The values were from 0.032 to 1.014 µg/l. With the PEARL model, the PEC values did not exceed the threshold value in the Porto and Sevilla scenarios, and only marginally exceeded this threshold in the Thiva scenario. The values were from 0.022 to 1.201 µg/l. The calculated values for zoxamide, RH-24549, RH-163353 and RH-127450 are lower than 0.1 µg/l and though PECgw for RH-141455 exceed this threshold, PECgw for this metabolite are <10 µg/l and data are available which demonstrate the metabolite to be non-relevant. There is therefore a negligible risk to groundwater from the proposed use.

An assessment of the relevance of RH-141455 in groundwater is presented at Section 2.11.

Surface water

PECsw and **PECsed** have been calculated for zoxamide and the metabolites RH-127450, RH-24549, RH-163353, RH-141455,RH-141288 and RH-139432. Use of Zoxium 240 SC in potatoes and vines at a maximum of 5 applications of 0.18 kg a.s./ha was assumed. The initial Step 1 PECsw for zoxamide were 122.3 to 138.1 µg/L. The Step 2 PECsw were 3.09 to 6.8 µg/L (N and S EU). At FOCUS Step 3 these PECsw declined to 0.035 to 3.54 µg/L. Spray drift was the main route of exposure in most scenarios but drainage and run-off were the main route of exposure in some scenarios. FOCUS Step 4 simulations were therefore run with a 10 or 20 m buffer zone. These gave initial PECsw of 0.018 to 1.579 µg/L. The initial FOCUS Step 3 PECsed for zoxamide were 0.018 to 9.184 µg/kg.

The initial FOCUS Step 1 PECsw for RH-127450, RH-24549, RH-163353, RH-141455,RH-141288 and RH-139432 were 24.3 to 30.0 µg/L, 50.8 to 53.0 µg/L, 44.5 to 52.1 µg/L, 17.3 to 18.5 µg/L,1.69 to 5.03 µg/L and 10.87 to 14.98 µg/L respectively. At FOCUS Step 2 these declined to 1.43 to 4.73 µg/L for RH-127450, 1.91 to 3.92 µg/L for RH-24549, 3.76 to 10.0 µg/L for RH-163353, 1.37 to 2.88 µg/L for RH-141455,1.1 to 4.08 µg/L for RH-141288 and 2.22 to 5.78 µg/L for RH-139432. Initial FOCUS Step 2 PECsed for RH-127450, RH-24549, RH-163353, RH-141455,RH-141288 and RH-139432 were 8.39 to 25.2 µg/kg, 3.42 to 7.06 µg/kg, 2.51 to 6.63 µg/kg, 0.04 to 0.08 µg/kg,0.11 to 0.4 µg/kg and 0.22 to 0.58 µg/kg respectively.

For all other PEC values refer to Volume 3 CP – Section B.8, Point B.8.5.

2.9 EFFECTS ON NON-TARGET SPECIES

2.9.1 Summary of effects on birds and other terrestrial vertebrates

Avian toxicity data submitted under the previous EU review of zoxamide consisted of an acute oral toxicity study with bobwhite quail, short-term dietary toxicity studies and reproductive toxicity studies with bobwhite quail and mallard duck.

Table 2.9.1-1: Summary of effects of zoxamide to birds

Test species	Test System	Duration of exposure	Results	Reference
Bobwhite quail *Colinus virginianus*	Acute	single appl.	LD_{50}: >2000 mg a.s./kg bw	IIA 8.1.1/01 [redacted] 1997a *
Bobwhite quail *Colinus virginianus*	short-term	8 days	LC_{50}: >5250 ppm LD_{50}: >1415.9 mg/kg bw/day**	IIA 8.1.2/01 [redacted] 1997b *
Mallard duck *Anas plathyrhynchos*	short-term	8 days	LC_{50}: >5250 ppm LD_{50}: > 1167 mg/kg bw/day**	IIA 8.1.2/02 [redacted] 1997c *
Mallard duck *Anas plathyrhynchos*	reproduction	20 weeks	NOEC: 1000 mg a.s./kg food NOEL: 114.3 mg/kg bw/day**	IIA 8.1.3/02 [redacted] 1998 *
Bobwhite quail *Colinus virginianus*	reproduction	20 weeks	NOEC: 1000 mg a.s./kg food NOEL: 158.2 mg/kg bw/day**	IIA 8.1.3/01 [redacted] 1998 *

* Already assessed in the DAR

** Conversion as calculated by the RMS based on study data

Table 2.9.1-2: Summary of effects of Zoxium 240 SC to mammals

Test species	Test System	Results[1]	Reference
Rat	Acute	LD_{50}: >5000 mg/kg bw	KCP 7.1.1/01/01 [redacted] (1999)

[1] As listed in the EC Review Report (2004)

Table 2.9.1-3: Summary of effects of zoxamide to mammals

Test species	Test System	Endpoints[1]	Reference
Rat	Parental	**NOAEL: 5000 ppm (360 mg/kg bw/day)**	CA 5.6.1/01, [redacted] (1998)
Rat	Reproductive	NOAEL: > 20 000ppm (1474 mg/kg bw/day)	CA 5.6.1/01, [redacted] (1998)
Rat	Offspring	**NOAEL: 5000 ppm (360 mg/kg bw/day)**	CA 5.6.1/01, [redacted] (1998)
Rabbit	Development	NOAEL: 1000 mg/kg bw/day)	CA 5.6.2/02, [redacted]., (1997)
Rat	Development	NOAEL: 1000mg/kg bw/day)	CA 5.6.2/01, [redacted]

			(1995b)

[1] Updates from toxicology section Vol. 3 A.S. B6
Values in **bold** are used in risk assessment.

2.9.2 Summary of effects on aquatic organisms

Zoxamide

The data on zoxamide are taken from the previous EU review and the endpoints reflect the values agreed in the EC Review Report (2004) or from the DAR (2001) and its subsequent amendments. Additional data on the saltwater species *Mysidopsis bahia* were submitted in support of the renewal of the active substance.

Table 2.9.2-1: Summary of the toxicity of zoxamide to aquatic organisms

Test species	Test system	Endpoint (mg a.s./L)	Reference
Acute fish			
Oncorhynchus mykiss	96h – flow-through	LC_{50}: **0.16** (mean measured)	IIA 8.2.1/01 [redacted] 1995a
Lepomis macrochirus	96h – flow through	LC_{50}: >0.79 (mean measured)	IIA 8.2.1/02 [redacted] 1995b
Pimephales promelas	96h – flow-through	LC_{50}: >0.208 (mean measured)	IIA 8.2.1/03 (IIA 8.2.2.3/01) [redacted] 1998d
Brachydanio rerio	96h – flow through	LC_{50}: >0.73 (mean measured)	IIA 8.2.1/04 [redacted] 1998a
Cyprinodon variegatus	96h – flow-through	LC_{50}: >0.85 (mean measured)	IIA 8.2.1/05 [redacted] 1997
Long-term fish			
Oncorhynchus mykiss	95 d – flow-through, ELS	NOEC: **0.00348** (mean measured)	IIA 8.2.2.2/01 [redacted] 1996
Pimephales promelas	202 d – flow-through, FLC	NOEC: 0.06 (mean measured)	IIA 8.2.1/03 (IIA 8.2.2.3/01) [redacted] 1998d
Lepomis macrochirus	28 day – flow-through, bioaccumulation	BCF: 95-136	IIA 8.2.3/01 [redacted] 1998
Acute aquatic invertebrates			
Daphnia magna	48h – flow-through	EC_{50}: >0.78 (mean measured)	IIA 8.2.4/01 Sword, M.C., Gardner, C. 1995c
Mysidopsis bahia	96h - flow-through	LC_{50}: **0.076** (mean measured)	MCA 8.2.4.2 Roberts, C.A., Swigert, J.P. 1997
Long-term aquatic invertebrates			
Daphnia magna	21d – flow through	NOEC: **0.039** (mean measured)	IIA 8.2.5/01 Murrell, H., Rhodes, J.E., Stewart, S. 1997

Test species	Test system	Endpoint (mg a.s./L)	Reference
Chironomus riparius	28d– flow through	NOEC: **0.45** (nominal)	IIA 8.2.7/01 van der Kolk, J. 1998a
Mysidopsis bahia	27d- flow-through	NOEC: **0.0072** (mean measured)	MCA 8.2.5.2 Drottar, K.R., Krueger, H.O. 1998
Algae			
Selenastrum capricornutum	120h - static	E_bC_{50}: 0.023 E_rC_{50}: 0.048 (mean measured)	IIA 8.2.6/01 Ziegler, T.A., Stewart, S. 1996
Anabaena flos-aquae	96h - static	E_bC_{50}: >0.86 E_rC_{50}: >0.86 (mean measured)	IIA 8.2.6/02 Drottar, K.R., Sutherland, C.A., Krueger, H.O. 1998e
Scenedesmus subspicatus	96h - static	E_bC_{50}: **0.011** E_rC_{50}: 0.018 (mean measured)	IIA 8.2.6/03 Drottar, K.R., Sutherland, C.A., Krueger, H.O. 1998f
Navicula pelliculosa	96h - static	E_bC_{50}: >0.93 E_rC_{50}: >0.93 (mean measured)	IIA 8.2.6/04 Drottar, K.R., Sutherland, C.A., Krueger, H.O. 1998g
Skeletonema costatum	96h - static	E_bC_{50}: >0.91 E_rC_{50}: >0.91 (mean measured)	IIA 8.2.6/05 Drottar, K.R., Krueger, H.O. 1998c
Aquatic plants			
Lemna gibba	14d – static renewal	7d-EC_{50}: >0.018 14d-EC_{50}: **0.017** (mean measured)	IIA 8.2.6/01 Ziegler, T.A., Stewart, S. 1996

The endpoints for use in the risk assessment are highlighted in **bold**

Table 2.9.2-2: Summary of the toxicity of Zoxium 240 SC to aquatic organisms

Test species	Test system	Endpoint (mg/L)	Reference
Acute fish			
Danio rerio	96h – static	LC_{50}: 0.184 mg a.s./L (0.865 mg formulation/L)	CP 10.2.1.1 [redacted] 2010
Acute aquatic invertebrates			
Daphnia magna	48h – static	EC_{50}: **>0.69 mg a.s./L** (>3.0 mg formulation/L)	CP 10.2.1.2 Mantilacci, S. 2010
Algae			
*Selenastrum capricornutum***	96h– static	E_bC_{50}: 0.24 mg formulation/L (0.0514 mg a.s./L)* E_rC_{50}: 0.274 mg formulation/L (0.0582 mg a.s./L)*	CP 10.2.1.3 Ward, G.S., Murdock, C. W. 1998

*endpoints expressed as mg formulation/L are converted to mg a.s./L considering the purity of the formulation (21.24%)

** Study was performed with RH-117,281 2F, a very similar formulation to Zoxium 240 SC. Refer to Document J-CP for details of both formulations.
The endpoints for use in the risk assessment are highlighted in **bold**

Metabolites

The metabolites identified as relevant are RH-127450, RH-24549, RH-141455, RH-163353 and RH-141288. Aquatic toxicity tests were previously performed with metabolite RH-139432 as it was included in the first EU review in the definition of the residues in water based on its formation in the aquatic photolysis study (Vo.3 Part B.8). RH-139432 is now no longer identified as relevant for the aquatic risk assessment.

Aquatic toxicity data are available for RH-127450, RH-163353 (algae only) and RH-139432. Aquatic ecotoxicity tests for metabolites RH-24549, RH-141455 and RH-141288 have not been conducted but their toxicity is addressed by read across to other structurally similar metabolites for which data are available (Vol.3 Part B.8 more information on structure of metabolites and degradation scheme see Vol.3 part B.8 AS point B.8.2.2. and Figure B.8.2.2.3-3). Considering the structure of the metabolites RH-24549 and RH-141455 it can be concluded that the active part (haloketone toxophore) which is found in the parent molecule is no longer intact, therefore, it is very unlikely that they could exhibit an increased toxicity compared to the active substance. RH-141455 has been shown not to be fungicidal. This reduction in toxicity is confirmed by the aquatic toxicity data on the metabolite RH-139432. RH-139432 is structurally similar to RH-24549 and RH-141455, and therefore it can be assumed that the toxicity will also be reduced for these metabolites compared to the parent molecule. Moreover, both RH-24549 and RH-141455 are soil metabolites formed at the end of the metabolic pathway.

The metabolite RH-141288 is structurally very similar to the major metabolite RH-127450 but more polar and hydrophilic and therefore it is considered that the potential risks posed by RH-141288 to aquatic organisms are covered by the risk assessment for RH-127450 for which data are available and the calculated PEC_{sw} values for RH-127450 are higher than for RH-141288.

For the metabolite RH-163353 no toxicity data on fish and *Daphnia* are available. However, this metabolite is also structurally similar to RH-127450 but more polar and hydrophilic, while being less toxic to algae than RH-127450. It is therefore considered acceptable to use the available acute fish and *Daphnia* toxicity data on metabolite RH-127450 in order to assess the potential risk to these organisms from the metabolite RH-163353.

Table 2.9.2-3: Summary of the toxicity of RH-127450 to aquatic organisms

Test species	Test system	Endpoint (mg/L)	Reference
Acute fish			
Oncorhynchus mykiss	96h – static	LC_{50}: >5 (nominal)	IIA 8.2.1/06 [redacted] 1998a
Acute aquatic invertebrates			
Daphnia magna	48h – semi-static	EC_{50}: >5 (nominal)	IIA 8.2.4/02 Rhodes, J.E., Williams, S. 1998b
Algae			
Selenastrum capricornutum	96h - static	EC_{50}: 3.2 **E_bC_{50}: 2.8** E_rC_{50}: 4.1 (mean measured)	IIA 8.2.6/07 Rhodes, J.E., Williams, S. 1998c

The endpoints for use in the risk assessment are highlighted in **bold**

Table 2.9.2-4: Summary of the toxicity of RH-139432 to aquatic organisms

Test species	Test system	Endpoint (mg/L)	Reference
Acute fish			
Oncorhynchus mykiss	96h – flow-through	LC_{50}: 2 (nominal)	IIA 8.2.6/10 [redacted] 2002
Acute aquatic invertebrates			
Daphnia magna	48h – semi-static	EC_{50}: 17 (nominal)	IIA 8.2.6/09 Caferella, M.A. 2002
Algae			
Scenedesmus subspicatus	96h - static	EC_{50}: **21** 72h-E_bC_{50}: 26 72h-E_rC_{50}: >30 (mean measured)	IIA 8.2.6/11 Hoberg, J.R. 2002

The endpoints for use in the risk assessment are highlighted in **bold**

Table 2.9.2-5: Summary of the toxicity of RH-163353 to aquatic organisms

Test species	Test system	Endpoint (mg/L)	Reference
Algae			
Selenastrum capricornutum	96h - static	E_bC_{50}: >23 E_rC_{50}: >23 (mean measured)	IIA 8.2.6/08 Rhodes, J.E., Williams, S. 1999

2.9.3 Summary of effects on arthropods

Bees

Adequate data to assess the effects of zoxamide on bees were evaluated during the previous EU review. Zoxamide is of low toxicity to bees with a 48 h LD_{50} value for contact toxicity being > 100 µg a.s./bee. No oral toxicity data were available for the active substance alone but two studies with the representative formulation were evaluated during the previous EU review.

In line with the new data requirements under Regulation (EC) No 1107/2009, a 10 day chronic study on adult bees and a bee larvae study are required. These studies have been finalised and indicate no concern.

Table 2.9.3-1: Summary of bee toxicity data

Test species	Time scale/method	Test material	Endpoint	Author, year & Doc ID
Apis mellifera	48 hr/oral (adult)	RH-117,281 2F	**48 hr LD_{50}: >147 µg formulation/bee (corresponding to >33 µg a.s./bee)**	IIA 8.3.1.1/02 Engelhard, E.K.. 1998
	48 hr/contact (adult)	Zoxamide	48 hr LD_{50}: >100 µg a.s./bee	IIA 8.3.1.1/01 Kirkland, R.L.. 1993
		RH-117,281 2F	**48 hr LD_{50}: >200 µg formulation/bee (corresponding to >43.2 µg a.s./bee)**	IIA 8.3.1.1/02 Engelhard, E.K.. 1998
	10 day/chronic (adult)	Zoxium 240 SC	10-day LC_{50}: >5000 mg a.s./kg feed 10-day LD_{50}: 174.8 µg a.s./bee/day	CP 10.3.1.2 Schmitzer, S., 2014a
	Semi-field bee brood test	Zoxium 240 SC	No effects on bee brood development up to 3.47 g Zoxium 240 SC/L feeding solution corresponding to 0.75 g a.s./L feeding solution	CP 10.3.1.3 Schmitzer, S., 2014b

Note: endpoints in **bold** used in the following risk assessment

Non-target arthropods other than bees

During the previous EU review of zoxamide a range of tests on toxicity to non-target terrestrial arthropods were submitted which were conducted using the representative formulation Zoxium 240 SC containing 240 g/L zoxamide.

The Annex I renewal of zoxamide is based on the same formulation. A summary of the existing endpoints is provided in Table B.2.9.3-2. No further data are considered necessary.

Table 2.9.3-2: Summary of data on the toxicity of Zoxium 240 SC to non-target arthropods

Test species	Test system	Endpoint	Reference
Zoxium 240 SC			
Aphidius rhopalosiphi	48h – glass plate	LR_{50}: >300 g a.s./ha ER_{50} (reproduction): >300 g a.s./ha	IIIA 10.5.1/01 Engelhard, E.K. 1998b
Typhlodromus pyri	14d – glass plate	LR_{50}: >300 g a.s./ha ER_{50} (reproduction): >300 g a.s./ha	IIIA 10.5.1/02 Engelhard, E.K. 1998c
Amblyseius andersoni	14d – glass plate	LR_{50}: >300 g a.s./ha ER_{50} (reproduction): >300 g a.s./ha	IIIA 10.5.1/03 Engelhard, E.K. 1998d
Pardosa sp.	1 spray application with spiders present (14 d post-treatment observation) – sand substrate	LR_{50}: >300 g a.s./ha ER_{50} (feeding): >300 g a.s./ha	IIIA 10.5.1/04 Engelhard, E.K. 1998e
Poecilus cupreus	1 spray application with beetles present (14 d post-treatment observation) – sand substrate	LR_{50}: >300 g a.s./ha ER_{50} (feeding): >300 g a.s./ha	IIIA 10.5.1/05 Engelhard, E.K. 1998f
Chrysoperla carnea	28d – glass plate	LR_{50}: >300 g a.s./ha ER_{50} (reproduction): >300 g a.s./ha	IIIA 10.5.1/06 Engelhard, E.K. 1998g
Orius insidiosus	9d – glass cells	LR_{50}: >300 g a.s./ha ER_{50} (reproduction): >300 g a.s./ha	IIIA 10.5.1/07 Engelhard, E.K. 1998h

2.9.4 Summary of effects on non-target soil meso- and macrofauna

Earthworms

During the previous EU review for Annex I inclusion an acute earthworm toxicity and two long-term earthworm toxicity studies for zoxamide were deemed sufficient to address the risk for the active substance. Zoxamide was shown to be of low toxicity to earthworms with a 14-day LC_{50} of > 1070 mg a.s./kg d.w. soil. An acute toxicity study on the soil metabolite RH-127450 was evaluated during the previous EU review.

A summary of the existing endpoints is provided in Table B.2.9.4-1.

Table 2.9.4-1: Summary of data on the toxicity of zoxamide and metabolites to earthworms

Test species	Test system	Endpoint	Reference
Zoxamide			
Eisenia foetida	14d – artificial soil	**14d-LC_{50}: >1070 mg a.s./kg soil dw** 14d-NOEC (mortality): 66.7 mg a.s./kg soil dw	IIA 8.4.1/01 Downing, J. 1995
Eisenia foetida	56d – artificial soil	28d-LC_{50}: >20 mg a.s./kg soil dw 28d-NOEC (mortality): 20 mg a.s./kg soil dw **56d-NOEC (reproduction): 1.0 mg a.s./kg soil dw**	IIA 8.4.2/01 Nienstedt, K. 1999
Eisenia foetida	56d – natural soil	28d-LC_{50}: >10 mg a.s./kg soil dw 28d-NOEC (mortality, growth, cocoons laid): 10 mg a.s./kg soil dw **56d-NOEC (reproduction): 7.0 mg a.s./kg soil dw**	IIA 8.4.2/01 Nienstedt, K. 2001
RH-127450			
Eisenia foetida	14d – artificial soil	14d-LC_{50}: >1000 mg a.s./kg soil dw 14d-NOEC (mortality): 1000 mg a.s./kg soil dw	IIA 8.4.1/02 Bryan, R.L., Porch, J.R., Krueger, H.O. 2000

Soil microorganisms

For the first EU review for Annex I inclusion additional testing on non-target soil meso- and macro-organisms was not required due to the fact that field and laboratory study DT_{90} values for zoxamide were <100 days. Please refer to the DAR dated May 2001, Point B.9.7 for further details.

In addition, data are available on both *Aphidius rhopalosiphi* and *Typhlodromus pyri* and these have been used in an initial risk assessment. As no concern is raised with either species tested and as the product is not applied directly to soil data on *Folsomia candida* and *Hypoaspis aculeifer* are not required.

2.9.5 Summary of effects on soil nitrogen transformation

For the first EU review it was concluded that zoxamide had no impact on soil respiration and nitrogen mineralisation at soil concentrations equivalent to a rate of 1.5 kg a.s./ha (2 mg a.s./kg soil).

Table 2.9.5-1: Summary of data on the toxicity of zoxamide to soil nitrogen transformation

Test	Endpoint	Reference
Zoxamide		
Nitrogen mineralisation	<25% after 42 days at 2 mg a.s./kg soil	IIA 8.5/01 van der Kolk, J. 1998b
Carbon transformation	<25% after 28 days at 2 mg a.s./kg soil	

2.9.6 Summary of effects on terrestrial non-target higher plants

For the first EU review, only screening test data on terrestrial vascular plants were presented. No adverse effects were seen at dose rates up to 500 g a.s./ha. Therefore, no studies on seedling emergence and vegetative vigour were required. Please refer to the DAR dated May 2001, Point B.9.9.1 (IIA 8.6/01 Nunez, M.V., 1998a; IIA 8.6/02 Nunez, M.V. 1998b) for further details.

As the active substance is not a herbicide and/or plant growth regulator additional studies examining the effects on seedling emergence and vegetative vigour are not required

2.9.7 Summary of effects on other terrestrial organisms (flora and fauna)

No data on other terrestrial organisms have been generated with Zoxium 240 SC. During the previous EU review adequate data were submitted to assess the potential impact of the active substance zoxamide on a range of insect species (screening data). No adverse effects on insects (2 species of *Lepidoptera*, 1 species of mite, 2 species of *Homoptera*) were seen at dose rates up to 600 g a.s./ha. On a third species of *Homoptera* 40% mortality was seen at the same rates and when applied to soil, zoxamide was harmless to one species of *Coleoptera* at 11.4 kg a.s./ha. Please refer to the DAR dated May 2001, Point B.9.9.1 (IIA 8.6/03 Sames, B.A., 1998) for further details.

No further data are considered necessary.

2.9.8 Summary of effects on biological methods for sewage treatment

During the previous EU review adequate data were submitted to assess the potential impact of zoxamide on activated sludge (ready biodegradability, CO_2 evolution test). Please refer to the DAR dated May 2001, Point B.9.10 (IIA 8.7/01 Barnes, S., 1998) for further details.

No further data are considered necessary.

2.9.9 Summary of product exposure and risk assessment

2.9.9.1 Birds and other terrestrial vertebrates

Birds

Dietary risk assessment

Table 2.9.9.1-1: Screening step – estimates of acute exposure to zoxamide for application in potatoes at 180 g a.s./ha [5 applications]

Acute risk assessment screening step	**Indicator species**	**Short cut value**	**Daily Dietary Dose (single)**	**MAF (90)**	**Daily Dietary Dose (Multiple)**	**TER**
	Small omnivorous bird	158,8	28,58	1,7	48,59	41,2

Table 2.9.9.1-2: Screening step – estimates of long-term exposure to zoxamide for application in potatoes at 180 g a.s./ha [5 applications]

Acute risk assessment screening step	**Indicator species**	**Short cut value**	**Daily Dietary Dose (single)**	**MAF mean**	**Daily Dietary Dose (Multiple)**	**TER**
	Small omnivorous bird	64,8	11,66	2,2	13,60	8,4

Table 2.9.9.1-3: Screening step – estimates of acute exposure to zoxamide for application in grapevines at 180 g a.s./ha [5 applications]

Acute risk assessment screening step	**Indicator species**	**Short cut value**	**Daily Dietary Dose (single)**	**MAF (90)**	**Daily Dietary Dose (Multiple)**	**TER**
	Small omnivorous bird	95,3	17,15	1,7	29,16	68,6

Table 2.9.9.1-4: Screening step – estimates of long-term exposure to zoxamide for application in grapevines at 180 g a.s./ha [5 applications]

Acute risk assessment screening step	**Indicator species**	**Short cut value**	**Daily Dietary Dose (single)**	**MAF mean**	**Daily Dietary Dose (Multiple)**	**TER**
	Small omnivorous bird	38,9	7,00	2,2	8,16	14,0

The calculated acute and reproductive screening TER values are above the trigger value, indicating an acceptable acute and reproductive risk to birds from the proposed uses of Zoxium 240 SC in potatoes and grapes.

Mammals

Dietary risk assessment

Table 2.9.9.1-5: Screening step – estimates of acute exposure to zoxamide for application in potatoes at 180 g a.s./ha [5 applications]

Acute risk assessment screening step	**Indicator species**	**Short cut value**	**Daily Dietary Dose (single)**	**MAF (90)**	**Daily Dietary Dose (Multiple)**	**TER**
	Small herbivorous mammal	118,4	21,31	1,7	36,23	138,0

Table 2.9.9.1-6: Screening step – estimates of long-term exposure to zoxamide for application in potatoes at 180 g a.s./ha [5 applications]

Acute risk assessment screening step	**Indicator species**	**Short cut value**	**Daily Dietary Dose (single)**	**MAF mean**	**Daily Dietary Dose (Multiple)**	**TER**
	Small herbivorous mammal	48,3	8,69	2,2	10,14	35,51

Table 2.9.9.1-7: Screening step – estimates of acute exposure to zoxamide for application in grapevines at 180 g a.s./ha [5 applications]

Acute risk assessment screening step	**Indicator species**	**Short cut value**	**Daily Dietary Dose (single)**	**MAF (90)**	**Daily Dietary Dose (Multiple)**	**TER**
	Small herbivorous mammal	136,4	24,55	1,7	41,74	119,8

Table 2.9.9.1-8: Screening step – estimates of long-term exposure to zoxamide for application in grapevines at 180 g a.s./ha [5 applications]

Acute risk assessment screening step	**Indicator species**	**Short cut value**	**Daily Dietary Dose (single)**	**MAF mean**	**Daily Dietary Dose (Multiple)**	**TER**
	Small herbivorous mammal	72,3	13,01	2,2	15,17	23,72

The calculated acute and reproductive screening TER values are above the trigger value, indicating an acceptable acute and reproductive risk to mammals from the proposed uses of Zoxium 240 SC in potatoes and grapes.

Drinking water risk assessment

Table 2.9.9.1-9: Risk for birds and mammals through drinking water

Data from Data_Entry worksheet	Concentration of the spray solution - C Spray (g/L)	Organic adsorption coefficient - KOC (mL/g)	Application rate (mg/m^2)	Birds LD50	Birds Reproductive End Point (mg/kg bw/d)	Mammals LD50	Mammals Reproductive End Point (mg/kg bw/d)
	0,18	1224,00	18	2000,0	114,3	5000,0	360,0
Leaf senario							
Acute risk assessment - Leaf senario	**PEC pool (mg/L)**	**DWR for small granivorous bird (15.3g bw) in L/kg bw/d**	**TER birds**	**DWR for small granivorous mammal (21.7g bw) in L/kg bw/d**	**TER mammals**	**No refinement step required**	
	36	0,46	120,8	0,24	578,7		
Puddle senario							
Calculate predicted enviromental	**pore water term**	**soil term**	**MAF mean**	**PEC puddle (mg/L)**			
	0,02	0,0015	2,2	0,02134			
Acute risk assessment - Puddle senario	**DWR for small granivorous bird (15.3g bw) in L/kg bw/d**	**TER birds**	**DWR for small granivorous mammal (21.7g bw) in L/kg bw/d**	**TER mammals**	**No refinement step required**		
	0,46	203776,9	0,24	976431,0			
Reproductive risk assessment - Puddle senario	**DWR for small granivorous bird (15.3g bw) in L/kg bw/d**	**TER birds**	**DWR for small granivorous mammal (21.7g bw) in L/kg bw/d**	**TER mammals**	**No refinement step required**		
	0,46	11645,8	0,24	70303,0			

Effects on secondary poisioning

As the log Kow of zoxamide is greater than three (3.76) an assessment of secondary poisoning to earthworm-eating and fish-eating birds and mammals are required.

Table 2.9.9.1-10: Food chain from earthworm to earthworm-eating birds and mammals

Food chain from earthworm to earthworm-eating birds and mammals								
Dry soil approach	**Foc (organic carbon content of soil)**	**BCF earthworm**	**PEC earthworm**	**DDD birds (based on 100g bird eating 104.6g worms per day)**	**TER Birds**	**DDD mammals (based on 10g mammal eating 12.8g worms per day)**	**TER Mammals**	**No refinement step required**
	0,02	0,04	0,02	0,02	6446,9	0,02	16656,54	

Table 2.9.9.1-11: Food chain from fish to fish-eating birds and mammals

Food chain from fish to fish-eating birds and mammals						
Calculate predicted environmental concentration of active substance in fish	**PEC fish**	**DDD birds (based on 1000g bird eating 159g fish per day)**	**TER Birds**	**DDD mammals (based on 3000g mammal eating 425g fish per day)**	**TER Mammals**	**No refinement step required**
	1,72	0,15	787,44	0,13	2777,05	

Conclusion: The acute and long-term risk of zoxamide is acceptable for small omnivorous and herbivorous birds following the intended uses of Zoxium 240 SC in potatoes and grapes.

2.9.9.2 Aquatic organisms

Acute risk assessment for fish

Table 2.9.9.2-1: Acute TER values for fish from the proposed worst-case uses of Zoxium 240 SC using the maximum initial FOCUS Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	160	170	100
D4 Pond	Drift	0.047[2]		3404	
D4 Stream	Drift	0.709[1]		226	
D6 Ditch (1st)	Drift	0.937[1]		171	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		117	
R1 Pond	Run-off	0.534[2]		300	
R1 Stream	Run-off	2.415[2]		**66.3**	
R2 Stream	Drift	0.877[1]		182	
R3 Stream	Run-off	0.961[2]		166	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	160	109	100
R1 Pond	Drift	0.126[2]		1270	
R1 Stream	Drift	1.666[2]		**96**	
R2 Stream	Drift	0.984[1]		163	
R3 Stream	Drift	1.043[1]		153	
R4 Stream	Run-off	3.145[2]		**50.9**	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	160	**45.1**	100
R1 Pond	Drift	0.308[2]		519	
R1 Stream	Drift	2.264[1]		**70.7**	
R2 Stream	Drift	3.034[1]		**52.7**	
R3 Stream	Drift	3.190[1]		**50.1**	
R4 Stream	Run-off	2.263[1]		**70.7**	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme.
TER values below the trigger are highlighted **in bold**

Table 2.9.9.2-2: Acute TER values for fish from the proposed worst-case uses of Zoxium 240 SC using the maximum initial FOCUS Step 4 PEC_{sw} values

Scenario	Maximum initial Step 4 PEC_{sw} (µg a.s./L)		Acute endpoint (µg a.s./L)	TER	Trigger value
	10 m *	10 m **			
Potatoes:					
R1 Stream	1.028	0.368	160	156	100
Grapevines (early application):					
R1 Stream	-	0.733†	160	218	100
R4 Stream	-	1.428†		112	100
Grapevines (late application):					
D6 Ditch	0.776	-	160	206	100
R1 Stream	0.597	-		268	
R2 Stream	0.801	-		200	
R3 Stream	1.564	-		102	
R4 Stream	0.950†	-		168	

10 m *: Mitigation (spray drift): 10 m buffer zone

10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip

† Run-off is the main route of entry when this mitigation is considered.

Table 2.9.9.2-3: Acute TER values for fish from the proposed worst-case uses of Zoxium 240 SC using the maximum initial FOCUS Step 1 PEC_{sw} values for surface water metabolites of zoxamide

Crops	Maximum initial Step 1 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
RH-127450				
Potatoes	24.4	>5000	>205	100
Grapevines	30.0		>167	100
RH-24549				
Potatoes	50.8	2000[1]	**39.3**	100
Grapevines	53.0		**37.7**	100
RH-141455				
Potatoes	17.3	2000[1]	116	100
Grapevines	18.5		108	100
RH-163353				
Potatoes	44.6	>5000[2]	>112	100
Grapevines	52.1		**>96**	100

[1] Acute fish toxicity data for metabolite RH-139432

[2] Acute fish toxicity data for metabolite RH-127450

TER values below the trigger are highlighted **in bold**

Table 2.9.9.2-4: Acute TER values for fish from the proposed worst-case uses of Zoxium 240 SC using the maximum FOCUS Step 2 PEC_{sw} values for surface water metabolites of zoxamide

Crops	Maximum initial Step 2 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
RH-24549				
Potatoes	2.55	2000[1]	784	100
Grapevines	3.92		510	100
RH-163353				
Grapevines	10.0	>5000[2]	>500	100

[1] Acute fish toxicity data for metabolite RH-139432
[2] Acute fish toxicity data for metabolite RH-127450

The calculated TER_A values for RH-24549 and RH-163353 greater than the trigger value indicating an acceptable acute risk from the proposed uses of Zoxium 240 SC in both potatoes and grapevines.

Long term risk assessment for fish

Table 2.9.9.2-5: Long-term TER values for fish from the proposed worst-case uses of Zoxium 240 SC using the maximum initial FOCUS Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Long-term endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	3.48	**3.69**	10
D4 Pond	Drift	0.047[2]		74.0	
D4 Stream	Drift	0.709[1]		**4.91**	
D6 Ditch (1st)	Drift	0.937[1]		**3.71**	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		**2.55**	
R1 Pond	Run-off	0.534[2]		**6.52**	
R1 Stream	Run-off	2.415[2]		**1.44**	
R2 Stream	Drift	0.877[1]		**3.97**	
R3 Stream	Run-off	0.961[2]		**3.62**	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	3.48	**2.37**	10
R1 Pond	Drift	0.126[2]		28	
R1 Stream	Drift	1.666[2]		**2.1**	
R2 Stream	Drift	0.984[1]		**3.54**	
R3 Stream	Drift	1.043[1]		**3.34**	
R4 Stream	Run-off	3.145[2]		**1.11**	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	3.48	**0.98**	10
R1 Pond	Drift	0.308[2]		11.3	
R1 Stream	Drift	2.264[1]		**1.54**	
R2 Stream	Drift	3.034[1]		**1.15**	

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Long-term endpoint (µg a.s./L)	TER	Trigger value
R3 Stream	Drift	3.190[1]		**1.09**	
R4 Stream	Run-off	2.263[1]		**1.54**	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme.
TER values below the trigger are highlighted **in bold**

Table 2.9.9.2-6: Long-term TER values for fish the proposed worst-case uses of Zoxium 240 SC using the maximum FOCUS Step 4 PEC_{sw} values

Scenario	Maximum Step 4 PEC_{sw} (µg a.s./L)				Long-term endpoint (µg a.s./L)	TER	Trigger value
	10 m*	10 m**	20 m*	20 m**			
Potatoes:							
D3 Ditch	0.164	-	-	-	3.48	21.2	10
D4 Stream	0.159	-	-	-		21.9	
D6 Ditch (1st)	0.163	-	-	-		21.3	
D6 Ditch (2nd) [1]	-	1.367	-	-		**2.55**	
R1 Pond	0.235	0.103	-	-		14.81	
R1 Stream	1.028	0.368	0.539	**0.0477**		**6.47**	
R2 Stream	0.312	-	-	-		11.1	
R3 Stream	0.618†	0.282	-	**0.230**		15.1	
Grapevines (early application):							
D6 Ditch	0.303	-	-	-	3.48	11.5	10
R1 Stream	-	**0.733**†	-	**0.397**		**8.77**	
R2 Stream	0.403†	**0.199**‡	-	-		**8.64**	
R3 Stream	0.265	-	-	-		13.1	
R4 Stream	0.674†	0.305	-	-		**5.16**	
Grapevines (late application):							
D6 Ditch	0.776	-	**0.272**	-	3.48	12.8	10
R1 Stream	0.597	-	**0.209**	-		16.6	
R2 Stream	0.801	-	**0.281**	-		12.4	
R3 Stream	1.579†	0.707†	0.368†	**0.235**‡		**9.46**	
R4 Stream	0.950†	0.482‡	-	**0.494**†		**7.04**	

[1]Drainage: no mitigation measures can be applied
10 m *: Mitigation (spray drift): 10 m buffer zone
10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip
20 m *: Mitigation (spray drift): 20 m buffer zone
20 m **: Mitigation (spray drift and run-off): 20 m buffer zone and 20 m vegetative filter strip
PECsw values highlighted **in bold** have been used in the calculation of TER values
† Run-off is the main route of entry when this mitigation is considered.
‡ No mitigation can be performed for drainage within the programme.
TER values below the trigger are highlighted **in bold**

Except for the D6 (ditch 2nd) and R1 (stream) for potatoes and R1 (stream), R2 (stream) and R4 (steam) for grapevines (early application) and R3 (stream) and R4 (stream) for grapevines (late application), the calculated TER_{LT} values are greater than the trigger value indicating an acceptable long-term risk to fish from the proposed worst-case use of Zoxium 240 SC for these scenarios. For failing scenarios, further refinements have been performed to demonstrate an acceptable risk. However, it is noted that for failing scenarios except D6 (ditch 2nd), i.e. R3 Stream for application in potatoes, R1 (stream), R2 (stream) and R4 (steam) for grapevines (early application) and R2 stream and R3 Stream for late applications in grapevines if FOCUS Step 4 PEC_{sw} values are calculated using the VFSmod module and not the manual module (see Volume 3, CP, B.8 point 8.5 for details) then the TER values are greater than the trigger value.

Table 2.9.9.2-7: Long-term TER values for fish the proposed worst-case uses of Zoxium 240 SC using the maximum FOCUS Step 4 PEC_{sw} values calculated by utilising the VFSmod module

Scenario	Maximum Step 4 PEC_{sw} (µg a.s./L)				Long-term endpoint (µg a.s./L)	TER	Trigger value
	10 m*	10 m**	20 m*	20 m**			
Potatoes:							
R1 Stream	-	0.368	-	**0.047**	3.48	74.0	10
Grapevines (late application):							
R3 Stream	1.564	0.680	1.564	**0.235**	3.48	14.8	10
R4 Stream	-	0.482	-	**0.167**		20.8	

10 m *: Mitigation (spray drift): 10 m buffer zone
10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip (VFSmod)
20 m *: Mitigation (spray drift): 20 m buffer zone
20 m **: Mitigation (spray drift and run-off): 20 m buffer zone and 20 m vegetative filter strip (VFSmod)
PECsw values highlighted **in bold** have been used in the calculation of TER values
TER values below the trigger are highlighted **in bold**

However, the risk assessment performed using the worst-case PEC_{sw} values calculated by the manual module has also been refined to demonstrate safe use.

Further refinement is based on the use of time weighted average (TWA) PEC_{sw} values which is deemed appropriate due to the following reasons.

The endpoint used in the long-term risk assessment for fish is derived from a flow-through 95 day study during which effects (survival of fry) were observed in fish after 69 days of exposure (35 days post-hatch) (Downing, et al., 1996). The study meets certain conditions which have been presented in the EFSA Guidance (2013)[1] and this allows the use of a TWA-PEC_{sw} exposure value:

- The exposure was maintained in the system and the endpoint was expressed in mean measured concentration (ranging from 106 to 118% of the nominal concentrations).

- The effect endpoint (survival of fry) is not based on a developmental process during a specific sensitive life stage that may last a short time only.

- The effect endpoint (survival of fry) is not based on mortality occurring early in the test, which would have indicated an acute effect. Reduced numbers of surviving fry were first observed at the highest concentration tested 16 days post-hatching of the eggs which is equivalent to a total duration of exposure of 52 days of eggs and fry to the test item.

[1] Guidance of tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013; 11(7):3290.

- There is no indication from the toxic mode of action of the active substance or substances with a similar toxic mode of action that latency of effects may occur.

As suggested by the EFSA Guidance (2013) a default 7-day TWA time window of the TWA-PEC_{sw} should be used if no further information on the relation between exposure pattern and time-to-onset of the relevant effect is provided.

TER_{LT} values following applications of Zoxium 240 SC to potatoes and grapevines for fish have been re-calculated using the FOCUS Step 3 7-d TWA-PEC_{sw} values (see Volume 3, CP, B.8, Point 8.5 for details) and the long-term toxicity endpoint for the active substance.

Table 2.9.9.2-8: Refined long-term TER values for fish from the proposed worst-case uses of Zoxium 240 SC using the maximum FOCUS Step 3 7-day TWA-PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum Step 3 7-d TWA-PEC_{sw} (µg a.s./L)	Long-term endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.158[1]	3.48	22.02	10
D4 Pond	Drift	0.078 [2]		46.6	
D4 Stream	Drift	0.011[2]		316.4	
D6 Ditch (1st)	Drift	0.083[1]		42	
D6 Ditch (2nd)	Drainage	0.233[2]		15	
R1 Pond	Run-off	0.503[2]		**6.92**	
R1 Stream	Run-off	0.344[2]		10.1	
R2 Stream	Drift	0.071[2]		49.0	
R3 Stream	Run-off	0.150[2]		23.2	
Grapevines (early application):					
D6 Ditch	Drift	0.985[2]	3.48	**3.53**	10
R1 Pond	Drift	0.119[2]		29.2	
R1 Stream	Drift	0.206[2]		16.9	
R2 Stream	Drift	0.061[2]		57	
R3 Stream	Drift	0.097[2]		35.9	
R4 Stream	Run-off	0.738[2]		**4.72**	
Grapevines (late application):					
D6 Ditch	Drift	**2.372[2]**	3.48	**1.47**	10
R1 Pond	Drift	0.290[2]		12	
R1 Stream	Drift	0.070 [1]		49.7	
R2 Stream	Drift	0.048[1]		72.5	
R3 Stream	Drift	**0.497[2]**		**7**	
R4 Stream	Drift	0.337[2]		10.3	

[1] Calculated for a single application in potatoes;
[2] Calculated for multiple applications in potatoes;
[3] Calculated for late single applications in grapevines;
[4] Calculated for late multiple application in grapevines
TER values below the trigger are highlighted **in bold**

A step-wise approach has been taken in applying risk mitigation measures to refine the failing scenarios using the 7-d TWA Step 4 PEC_{sw} values. The refinement steps taken and the subsequently calculated TER_{LT} values are summarised in Table B.9.2.16-9.

Table 2.9.9.2-9: Refined long-term TER values for fish the proposed worst-case uses of Zoxium 240 SC using the maximum Step 4 7-d TWA-PEC_{sw} FOCUS values

Scenario	Maximum Step 4 7-d TWA-PEC_{sw} (µg a.s./L)			Long-term endpoint (µg a.s./L)	TER	Trigger value
	10 m *	10 m **	20 m *			
Potatoes:						
R1 Pond	**0.223**	**0.100**	-	3.48	15.6	10
Grapevines (early application):						
D6 Ditch	**0.223**	-	-	3.48	15.6	10
R4 Stream	-	**0.326**	**0.168**		10.7	
Grapevines (late application):						
D6 Ditch	0.529	-	**0.191**	3.48	18.2	10
R3 Stream	0.197	**0.039**	0.096		17.7	

10 m *: Mitigation (spray drift): 10 m buffer zone
10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip
20 m *: Mitigation (spray drift): 20 m buffer zone
PECsw values highlighted **in bold** have been used in the calculation of TER values

The calculated TER_{LT} values using the worst case Step 4 7-day TWA-PEC_{sw} values are greater than the trigger indicating an acceptable long-term risk from the proposed uses of Zoxium 240 SC in grapevines and potatoes when risk mitigation measures of a 20 m buffer zone with a 10 m vegetative filter strip (VFS) are implemented.

Acute risk assessment for aquatic invertebrates:

Daphnia magna

Table 2.9.9.2-10: Acute TER values for *Daphnia* from the proposed worst-case uses of Zoxium 240 SC using the maximum initial FOCUS Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	>690	>732	100
D4 Pond	Drift	0.047[2]		>14681	
D4 Stream	Drift	0.709[1]		>973	
D6 Ditch (1st)	Drift	0.937[1]		>736	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		>505	
R1 Pond	Run-off	0.534[2]		>1292	
R1 Stream	Run-off	2.415[2]		>286	
R2 Stream	Drift	0.877[1]		>787	
R3 Stream	Run-off	0.961[2]		>719	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	>690	>469	100

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
R1 Pond	Drift	0.126[2]		>5476	
R1 Stream	Drift	1.666[2]		>414	
R2 Stream	Drift	0.984[1]		>701	
R3 Stream	Drift	1.043[1]		>662	
R4 Stream	Run-off	3.145[2]		>219	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	>690	>195	100
R1 Pond	Drift	0.308[2]		>2240	
R1 Stream	Drift	2.264[1]		>305	
R2 Stream	Drift	3.034[1]		>227	
R3 Stream	Drift	3.190[1]		>216	
R4 Stream	Run-off	2.263[1]		>305	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme.

The calculated TER_A values are greater than the trigger value indicating an acceptable acute risk to *Daphnia* from the proposed uses of Zoxium 240 SC in both potatoes and grapevines.

Mysidopsis bahia

Table 2.9.9.2-11: Acute TER values for *Mysidopsis bahia* from the proposed worst-case uses of Zoxium 240 SC using the maximum initial Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	76	**80.6**	100
D4 Pond	Drift	0.047[2]		1617	
D4 Stream	Drift	0.709[1]		107	
D6 Ditch (1st)	Drift	0.937[1]		**81.1**	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		**55.6**	
R1 Pond	Run-off	0.534[2]		142	
R1 Stream	Run-off	2.415[2]		**31.5**	
R2 Stream	Drift	0.877[1]		**86.7**	
R3 Stream	Run-off	0.961[2]		**79.1**	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	76	**51.7**	100
R1 Pond	Drift	0.126[2]		603.2	
R1 Stream	Drift	1.666[2]		**45.6**	
R2 Stream	Drift	0.984[1]		**77.2**	

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
R3 Stream	Drift	1.043[1]		**72.9**	
R4 Stream	Run-off	3.145[2]		**24.2**	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	76	**21.4**	100
R1 Pond	Drift	0.308[2]		247	
R1 Stream	Drift	2.264[1]		**33.6**	
R2 Stream	Drift	3.034[1]		**25.0**	
R3 Stream	Drift	3.190[1]		**23.8**	
R4 Stream	Run-off	2.263[1]		**33.6**	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme
TER values below the trigger are highlighted **in bold**

Table 2.9.9.2 -12: Acute TER values for *Mysidopsis bahia* the proposed worst-case uses of Zoxium 240 SC using the maximum FOCUS Step 4 PEC_{sw} values

Scenario	Maximum Step 4 PEC_{sw} (µg a.s./L)			Acute endpoint (µg a.s./L)	TER	Trigger value
	10 m *	10 m**	20 m **			
Potatoes:						
D3 Ditch	0.164	-	-	76	463	100
D6 Ditch (1st)	0.163	-	-		466	
D6 Ditch (2nd)	1.367[1]				**55.6**	
R1 Stream	-	1.027	**0.539**		141	
R2 Stream	0.312	-	-		243	
R3 Stream	0.618‡	-	-		123	
Grapevines (early application):						
D6 Ditch	0.213	-	-	76	357	100
R1 Stream	0.733‡	-	-		103.7	
R2 Stream	0.403	-	-		189	
R3 Stream	0.265	-	-		287	
R4 Stream	0.674	-	-		113	
Grapevines (late application):						
D6 Ditch	0.776	-	0.272	76	279	100
R1 Stream	0.597	-	-		127	
R2 Stream	0.801		**0.281**		270	
R3 Stream	1.579	**0.700**	-		108	
R4 Stream	-	0.950	**0.494**		154	

[1]Drainage: no mitigation measures can be applied; value remains as calculated at Step 3
10 m *: Mitigation (spray drift): 10 m buffer zone
10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip

20 m **: Mitigation (spray drift and run-off): 20 m buffer zone and 20 m vegetative filter strip
‡ No mitigation can be performed for drainage within the programme
PECsw values highlighted **in bold** have been used in the calculation of TER values
TER values below the trigger are highlighted **in bold**

The TER_A values for all scenarios except D6 Ditch (2^{nd}) scenario for application to potatoes are higher than the trigger demonstrating an acceptable risk to the marine crustacean *Mysidopsis bahia* when risk mitigation measures of a 20 m buffer with a 20 m VFS are implemented.

A refined risk assessment for the D6 Ditch (2^{nd}) scenario is performed using the geomean approach as described in EFSA Guidance (2013). In this approach, the geomean LC_{50} value for species belonging to the same taxonomic group is calculated. In this case, a geomean LC_{50} value is calculated for crustaceans using the LC_{50} values of zoxamide for *Daphnia magna* and *Mysidopsis bahia*. This is considered appropriate as it has been indicated that sensitivity distributions of taxonomically similar freshwater and marine species to organic plant protection products do not differ significantly and thus the data can be combined (EFSA Guidance, 2013). In addition, the resulting geomean LC_{50} (229 µg a.s./L) is less than an order of magnitude greater than the LC_{50} of the most sensitive species LC_{50}; therefore, it is considered that the geomean approach in this case is not biased by using data on insensitive species.

Using this refined LC_{50} value the resulting TER_A for the D6 Ditch (2^{nd}) scenario is 167.5 (trigger = 100), therefore indicating that the acute risks to aquatic invertebrates from the uses of Zoxium 240 SC are acceptable even for this exposure scenario for which risk mitigation measures such as buffer zones or vegetative filter strip zones have no effect.

Table 2.9.9.2-13: Acute TER values for *Daphnia* from the proposed worst-case uses of Zoxium 240 SC using the maximum initial FOCUS Step 1 PEC_{sw} values for surface water metabolites of zoxamide

Crops	Maximum initial Step 1 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
RH-127450				
Potatoes	24.4	>5000	>205	100
Grapevines	30.0		>167	100
RH-24549				
Potatoes	50.8	17000[1]	335	100
Grapevines	53.0		321	100
RH-141455				
Potatoes	17.3	17000[1]	983	100
Grapevines	18.5		919	100
RH-163353				
Potatoes	44.6	>5000[2]	>112	100
Grapevines	52.1		**>96**	100

[1] Acute *Daphnia* toxicity data for metabolite RH-139432
[2] Acute *Daphnia* toxicity data for metabolite RH-127450
TER values below the trigger are highlighted **in bold**

The calculated TER_A values for RH-127450, RH-24549 and RH-141455 are greater than the trigger value indicating an acceptable acute risk from the proposed uses of Zoxium 240 SC in both potatoes and grapevines. However, the TER_A value for RH-163353 (for grapevines) is lower than the trigger value

indicating a potential concern. For this scenario the acute TER value for *Daphnia* has been calculated using the maximum FOCUS Step 2 PEC_{sw} value.

Table 2.9.9.2-14: Acute TER value for *Daphnia* from the proposed worst-case uses of Zoxium 240 SC using the maximum initial FOCUS Step 2 PEC_{sw} values for surface water metabolites of zoxamide

Crops	Maximum initial Step 2 PEC_{sw} (µg a.s./L)	Acute endpoint (µg a.s./L)	TER	Trigger value
RH-163353				
Grapevines	10.0	>5000[1]	>500	100

[1] Acute *Daphnia* toxicity data for metabolite RH-127450

The calculated TER_A value for RH-163353 is greater than the trigger value indicating an acceptable acute risk from the proposed uses of Zoxium 240 SC in grapevines.

Long-term risk assessment for aquatic invertebrates:

Daphnia magna

Table 2.9.9.2-15: Long-term TER values for *Daphnia* from the proposed worst-case uses of Zoxium 240 SC using the maximum initial Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Long-term endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	39	41.4	10
D4 Pond	Drift	0.047[2]		830	
D4 Stream	Drift	0.709[1]		55.0	
D6 Ditch (1st)	Drift	0.937[1]		41.6	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		28.5	
R1 Pond	Run-off	0.534[2]		73	
R1 Stream	Run-off	2.415[2]		16.1	
R2 Stream	Drift	0.877[1]		44.5	
R3 Stream	Run-off	0.961[2]		40.6	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	39	26.5	10
R1 Pond	Drift	0.126[2]		312	
R1 Stream	Drift	1.666[2]		23.4	
R2 Stream	Drift	0.984[1]		39.6	
R3 Stream	Drift	1.043[1]		37.4	
R4 Stream	Run-off	3.145[2]		12.4	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	39	11	10
R1 Pond	Drift	0.308[2]		127	
R1 Stream	Drift	2.264[1]		17.2	
R2 Stream	Drift	3.034[1]		12.8	
R3 Stream	Drift	3.190[1]		12.2	

R4 Stream	Run-off	2.263[1]		17.2	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme

The calculated TER_{LT} values are greater than the trigger value indicating an acceptable long-term risk to *Daphnia* from the proposed uses of Zoxium 240 SC in both potatoes and grapevines, without the need for risk mitigation.

Mysidopsis bahia

Table 2.9.9.2-16: Long-term TER values for *Mysidopsis bahia* from the proposed worst-case uses of Zoxium 240 SC using maximum initial Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Long-term endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	7.2	**7.64**	10
D4 Pond	Drift	0.047[2]		153	
D4 Stream	Drift	0.709[1]		10.1	
D6 Ditch (1st)	Drift	0.937[1]		**7.68**	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		**5.28**	
R1 Pond	Run-off	0.534[2]		13.5	
R1 Stream	Run-off	2.415[2]		**2.98**	
R2 Stream	Drift	0.877[1]		**8.21**	
R3 Stream	Run-off	0.961[2]		**7.49**	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	7.2	**4.89**	10
R1 Pond	Drift	0.126[2]		57	
R1 Stream	Drift	1.666[2]		**4.32**	
R2 Stream	Drift	0.984[1]		**7.32**	
R3 Stream	Drift	1.043[1]		**6.90**	
R4 Stream	Run-off	3.145[2]		**2.29**	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	7.2	**2.03**	10
R1 Pond	Drift	0.308[2]		23.4	
R1 Stream	Drift	2.264[1]		**3.18**	
R2 Stream	Drift	3.034[1]		**2.37**	
R3 Stream	Drift	3.190[1]		**2.26**	
R4 Stream	Run-off	2.263[1]		**3.18**	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme
TER values below the trigger are highlighted **in bold**

Table 2.9.9.2-17: Long-term TER values for *Mysidopsis bahia* the proposed worst-case uses of Zoxium 240 SC using the maximum FOCUS Step 4 PEC_{sw} values

Scenario	Maximum Step 4 PEC_{sw} (µg a.s./L)				Endpoint (µg a.s./L)	TER	Trigger value
	10 m *	10 m**	20 m*	20 m **			
Potatoes:							
D3 Ditch	0.164	-	-	-	7.2	43.9	10
D6 Ditch (1st)	0.163	-	-	-		44.1	
D6 Ditch (2nd)	1.367[1]					**5.27**	
R1 Stream	-	1.028	-	**0.539**		13.4	
R2 Stream	0.312	-	-	-		23.1	
R3 Stream	0.618	-	-	-		11.7	
Grapevines (early application):							
D6 Ditch	0.303	-	-	-	7.2	23.8	10
R1 Stream	0.733	-	0.379	-		19	
R2 Stream	0.403	-	-	-		17.9	
R3 Stream	0.265	-	-	-		27.2	
R4 Stream	0.674	-	-	-		10.7	
Grapevines (late application):							
D6 Ditch	0.776	-	0.272	-	7.2	26.8	10
R1 Stream	0.597	-	-	-		12.1	
R2 Stream	0.801	-	**0.281**	-		25.6	
R3 Stream	1.579	**0.707**	-	1.579		10.2	
R4 Stream	-	0.950	-	**0.494**		14.6	

[1]Drainage: no mitigation measures can be applied; value remains as calculated at Step 3
10 m *: Mitigation (spray drift): 10 m buffer zone
10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip
20 m *: Mitigation (spray drift): 20 m buffer zone
20 m **: Mitigation (spray drift and run-off): 20 m buffer zone and 20 m vegetative filter strip
PECsw values highlighted **in bold** have been used in the calculation of TER values
TER values below the trigger are highlighted **in bold**

The TER_{LT} values for all scenarios except D6 Ditch (2nd) are higher than the trigger demonstrating an acceptable risk to the marine crustacean *Mysidopsis bahia* when risk mitigation measures of a 20 m buffer with a 20 m VFS are implemented.

A refined risk assessment for the D6 Ditch (2nd) scenario is performed using the geomean approach as described in EFSA Guidance (2013). In this approach, the geomean NOEC value for species belonging to the same taxonomic group is calculated. In this case, a geomean NOEC value is calculated for crustaceans using the NOEC value of zoxamide for *Daphnia magna* and *Mysidopsis bahia*. This is considered appropriate as it has been indicated that sensitivity distributions of taxonomically similar freshwater and marine species to organic plant protection products do not differ significantly and thus the data can be combined. In addition, the endpoints used from the two studies are biologically comparable (reproduction) and the resulting geomean NOEC (16.7 µg a.s./L) is of the same order of magnitude with the NOEC of the most sensitive species; therefore, it is considered that the geomean approach in this case is not biased by using data on insensitive species.

Using this refined NOEC value the resulting TER_{LT} for the D6 Ditch (2nd) scenario is 12.2 (trigger = 10), therefore indicating that the long-term risks to aquatic invertebrates from the uses of Zoxium 240 SC is

acceptable even for this exposure scenario for which risk mitigation measures such as buffer zones or vegetative filter strip zones have no effect.

Sediment dwelling aquatic invertebrates - *Chironomus riparius*

TER_{LT} values following applications of Zoxium 240 SC to potatoes and grapevines for the sediment dwelling organism *Chironomus riparius* have been determined using the maximum initial FOCUS Step 3 PEC_{sw} from either a single or multiple application (see Volume 3, CP, B.8, Point 8.5 for details) and the acute toxicity endpoint for the active substance.

Table 2.9.9.2-18: Long-term TER values for *Chironomus riparius* from the proposed worst-case uses of Zoxium 240 SC using the maximum initial Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Long-term endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	450	477	10
D4 Pond	Drift	0.047[2]		9574	
D4 Stream	Drift	0.709[1]		634	
D6 Ditch (1st)	Drift	0.937[1]		480	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		329	
R1 Pond	Run-off	0.534[2]		843	
R1 Stream	Run-off	2.415[2]		186	
R2 Stream	Drift	0.877[1]		513	
R3 Stream	Run-off	0.961[2]		468	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	450	306	10
R1 Pond	Drift	0.126[2]		3571	
R1 Stream	Drift	1.666[2]		270	
R2 Stream	Drift	0.984[1]		457	
R3 Stream	Drift	1.043[1]		431	
R4 Stream	Run-off	3.145[2]		143	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	450	127	10
R1 Pond	Drift	0.308[2]		1461	
R1 Stream	Drift	2.264[1]		199	
R2 Stream	Drift	3.034[1]		148	
R3 Stream	Drift	3.190[1]		141	
R4 Stream	Run-off	2.263[1]		199	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme

The calculated TER_{LT} values are greater than the trigger value indicating an acceptable long-term risk to *Chironomus riparius* from the proposed uses of Zoxium 240 SC in both potatoes and grapevines, without the need for risk mitigation.

Toxicity exposure ratios (TER) for algae

Table 2.9.9.2-19: TER values for algae from the proposed worst-case uses of Zoxium 240 SC using the maximum initial Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	11	11.7	10
D4 Pond	Drift	0.047[2]		234	
D4 Stream	Drift	0.709[1]		15.5	
D6 Ditch (1st)	Drift	0.937[1]		11.7	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		**8.05**	
R1 Pond	Run-off	0.534[2]		20.6	
R1 Stream	Run-off	2.415[2]		**4.55**	
R2 Stream	Drift	0.877[1]		12.5	
R3 Stream	Run-off	0.961[2]		11.4	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	11	**7.48**	10
R1 Pond	Drift	0.126[2]		87	
R1 Stream	Drift	1.666[2]		6.60	
R2 Stream	Drift	0.984[1]		11.2	
R3 Stream	Drift	1.043[1]		10.5	
R4 Stream	Run-off	3.145[2]		**3.5**	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	11	**3.10**	10
R1 Pond	Drift	0.308[2]		35.7	
R1 Stream	Drift	2.264[1]		**4.86**	
R2 Stream	Drift	3.034[1]		**3.62**	
R3 Stream	Drift	3.190[1]		**3.45**	
R4 Stream	Run-off	2.263[1]		**4.86**	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme
TER values below the trigger are highlighted **in bold**

Table 2.9.9.2-20: TER values for algae from the proposed worst-case uses of Zoxium 240 SC using the maximum FOCUS Step 4 PEC_{sw} values

Scenario	Maximum Step 4 PEC_{sw} (µg a.s./L)		Endpoint (µg a.s./L)	TER	Trigger value
	10 m*	10 m**			
Potatoes:					
D6 Ditch (2nd)	1.367[1]		11	**8.05**	10
R1 Stream	-	1.028		10.7	
Grapevines (early application):					
R4 Stream	0.674	-	11	16.3	10
D6 Ditch	0.303	-		36.3	
Grapevines (late application):					

D6 Ditch	0.776	-	11	14.2	10
R1 Stream	0.597	-		18.4	
R2 Stream	0.801	-		13.7	
R3 Stream	1.579	0.707		15.6	
R4 Stream	-	0.950		11.6	

[1]Drainage: no mitigation measures can be applied; value remains as calculated at Step 3
10 m *: Mitigation (spray drift): 10 m buffer zone
10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip
TER values below the trigger are highlighted **in bold**

Except for the D6 (ditch 2nd) for potatoes the calculated TER values are greater than the trigger value indicating an acceptable risk to algae from the proposed worst-case use of Zoxium 240 SC in potatoes and grapevines (both early and late applications). Due to drainage being the main route of entry it is not possible to further refine the scenario D6 (ditch 2nd) using FOCUS.

The current risk assessment is based on the guidance document SANCO/3268/2001 (final 2002). More up to date guidance related to the selection and use of preferable endpoints from toxicity studies with algae and aquatic plants has not been considered so far. According to the OECD guideline 201 (revised in 2011) and also in line with the recently published EFSA Guidance (2013)[2] the preferred endpoint to be used in the risk assessment for algae at the first instance is the E_rC_{50} i.e. the EC_{50} value based on inhibition of growth rate, since it is more robust considering varying test conditions, and endpoints based on biomass or yield may be used if growth rate points are not provided. It is also stated that toxicity data based on specific growth rate are more informative and better suited than toxicity values based on biomass or yield for both algae and macrophytes. The reason is that direct use of the biomass concentration without logarithmic transformation cannot be applied to an analysis of result from a system in exponential growth. In addition, according to both EFSA Guidance (2013) and the OECD 201, EC_{50} values calculated for growth rate are usually greater than EC_{50} values calculated for biomass or yield for mathematical reasons, and this should not be interpreted as a difference in sensitivity between the response variables. It is also recommended that yield is not used for comparing the sensitivity to toxicants among algal or duckweed species. There is therefore a clear indication that endpoints based on biomass or yield are not necessarily more ecologically sensitive than endpoints based on growth rate.

On that basis it is considered appropriate to re-calculate the TER values for algae using the lowest available E_rC_{50} value of 18 µg a.s./L (Volume 3, CP, B.9, Point. B.9.2. Table B.9.2.16-1) and the maximum initial FOCUS Step 3 PEC_{sw} have been calculated.

Table 2.9.9.2-21: TER values for algae (based on E_rC_{50} toxicity endpoint) from the proposed worst-case uses of Zoxium 240 SC using the maximum initial Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	18	19.1	10
D4 Pond	Drift	0.047[2]		383	
D4 Stream	Drift	0.709[1]		25.4	
D6 Ditch (1st)	Drift	0.937[1]		20.3	
D6 Ditch (2nd)	Drainage	1.367‡ [2]		13.2	
R1 Pond	Run-off	0.534[2]		33.7	

[2] Guidance of tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013; 11(7):3290.

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Endpoint (µg a.s./L)	TER	Trigger value
R1 Stream	Run-off	2.415[2]		**7.45**	
R2 Stream	Drift	0.877[1]		20.5	
R3 Stream	Run-off	0.961[2]		18.8	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	18	12.24	10
R1 Pond	Drift	0.126[2]		143	
R1 Stream	Drift	1.666[2]		10.8	
R2 Stream	Drift	0.984[1]		18.3	
R3 Stream	Drift	1.043[1]		17.2	
R4 Stream	Run-off	3.145[2]		**5.72**	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	18	**5.08**	10
R1 Pond	Drift	0.308[2]		58	
R1 Stream	Drift	2.264[1]		**7.95**	
R2 Stream	Drift	3.034[1]		**5.93**	
R3 Stream	Drift	3.190[1]		**5.64**	
R4 Stream	Run-off	2.263[1]		**7.95**	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme
TER values below the trigger are highlighted **in bold**

Table 2.9.9.2-22: TER values for algae (based on E_rC_{50} toxicity endpoint) from the proposed worst-case of Zoxium 240 SC using maximum FOCUS Step 4 PEC_{sw} values

Scenario	Maximum Step 4 PEC_{sw} (µg a.s./L)		Endpoint (µg a.s./L)	TER	Trigger value
	10 m *	10 m **			
Potatoes:					
R1 Stream	-	1.028	18	17.5	10
Grapevines (early application):					
R4 Stream	0.674	0.305	18	27	10
Grapevines (late application):					
D6 Ditch	0.776	-	18	23.2	10
R1 Stream	0.597	-		30.1	
R2 Stream	0.801	-		22.5	
R3 Stream	1.579	-		11.4	
R4 Stream	-	0.950		19	

10 m *: Mitigation (spray drift): 10 m buffer zone
10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip

All calculated TER values are greater than the trigger value indicating an acceptable risk to algae from the proposed uses of Zoxium 240 SC in both potatoes and grapevines when risk mitigation measures of a 10 m buffer with a 10 m VFS are implemented.

Table 2.9.9.2-23: TER values for algae from the proposed worst-case of Zoxium 240 SC using maximum initial FOCUS Step 1 PEC_{sw} values for surface water metabolites of zoxamide

Crops	Maximum initial Step 1 PEC_{sw} (µg a.s./L)	Endpoint (µg a.s./L)	TER	Trigger value
RH-127450				
Potatoes	24.4	>2800	>115	100
Grapevines	30.0		>**93.3**	100
RH-24549				
Potatoes	50.8	>21000	>413	100
Grapevines	53.0		>396	100
RH-141455				
Potatoes	17.3	>21000	>1214	100
Grapevines	18.5		>1135	100
RH-163353				
Potatoes	44.6	>23000	>516	100
Grapevines	52.1		>441	100

TER values below the trigger are highlighted **in bold**

The calculated TER values for RH-127450 (only for potatoes) RH-24549, RH-141455 and RH-163353 are greater than the trigger value indicating an acceptable risk from the proposed uses of Zoxium 240 SC. However, the TER value for RH-127450 (for grapevines) is lower than the trigger value indicating a potential concern. For this scenario the TER value for algae has been calculated using maximum FOCUS Step 2 PEC_{sw} value.

Table 2.9.9.2-24: TER value for algae from the proposed worst-case use of Zoxium 240 SC using maximum initial FOCUS Step 2 PECsw values surface water metabolites of zoxamide

Crops	Maximum initial Step 2 PEC_{sw} (µg a.s./L)	Endpoint (µg a.s./L)	TER	Trigger value
RH-127450				
Grapevines	1.59	>2800	>17610	100

The calculated TER value for RH-127450 greater than the trigger value indicating an acceptable risk from the proposed uses of Zoxium 240 SC in grapevines.

Toxicity exposure ratios (TER) for *Lemna*

Table 2.9.9.2-25: TER values for *Lemna* from the proposed worst-case uses of Zoxium 240 SC using the maximum initial Step 3 PEC_{sw} values

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Endpoint (µg a.s./L)	TER	Trigger value
Potatoes:					
D3 Ditch	Drift	0.943[1]	17	18.0	10
D4 Pond	Drift	0.047[2]		362	
D4 Stream	Drift	0.709[1]		24.0	
D6 Ditch (1st)	Drift	0.937[1]		18.1	

Scenario	Main route of entry into water body at Step 3	Maximum initial Step 3 PEC_{sw} (µg a.s./L)	Endpoint (µg a.s./L)	TER	Trigger value
D6 Ditch (2nd)	Drainage	1.367‡ [2]		12.4	
R1 Pond	Run-off	0.534[2]		32	
R1 Stream	Drift	2.415[2]		**7.04**	
R2 Stream	Drift	0.877[1]		19.4	
R3 Stream	Run-off	0.961[2]		17.7	
Grapevines (early application):					
D6 Ditch	Drift	1.471[2]	17	11.6	10
R1 Pond	Drift	0.126[2]		135	
R1 Stream	Drift	1.666[2]		10.2	
R2 Stream	Drift	0.984[1]		17.3	
R3 Stream	Drift	1.043[1]		16.3	
R4 Stream	Run-off	3.145[2]		**5.40**	
Grapevines (late application):					
D6 Ditch	Drift	3.546[2]	17	**4.8**	10
R1 Pond	Drift	0.308[2]		55.2	
R1 Stream	Drift	2.264[1]		**7.51**	
R2 Stream	Drift	3.034[1]		**5.60**	
R3 Stream	Drift	3.190[1]		**5.33**	
R4 Stream	Drift	2.263[1]		**7.51**	

[1] Calculated for a single application
[2] Calculated for multiple applications
‡ No mitigation can be performed for drainage within the programme
TER values below the trigger are highlighted **in bold**

Table 2.9.9.2-26: TER values for *Lemna* the proposed worst-case uses of Zoxium 240 SC using the maximum FOCUS Step 4 PEC_{sw} values

Scenario	Maximum Step 4 PEC_{sw} (µg a.s./L)		Endpoint (µg a.s./L)	TER	Trigger value
	10 m*	10 m**			
Potatoes:					
R1 Stream	-	1.028	17	16.5	10
Grapevines (early application):					
R4 Stream	0.674	0.305	17	25.2	10
Grapevines (late application):					
D6 Ditch	0.776	-	17	21.9	10
R1 Stream	0.597	-		28.5	
R2 Stream	0.801	-		21.2	
R3 Stream	1.579	-		10.8	
R4 Stream	-	0.950		17.9	

10 m *: Mitigation (spray drift): 10 m buffer zone
10 m **: Mitigation (spray drift and run-off): 10 m buffer zone and 10 m vegetative filter strip

The calculated TER values are greater than the trigger value indicating an acceptable risk to *Lemna* from the proposed uses of Zoxium 240 SC in both potatoes and grapevines when risk mitigation measures of a 10 m buffer zone with a 10 m vegetative filter strip (VFS) are implemented.

Conclusion: The acute and long-term risk of zoxamide is acceptable for aquatic organisms following the intended uses of Zoxium 240 SC in potatoes using 20 m buffer zone with 20 m VFS and in grapes using 20 m buffer zone with 10 m VFS.

2.9.9.3 Bees

Table 2.9.9.3-1: Acute hazard quotients for the proposed uses of Zoxium 240 SC

Test substance	Route of exposure	Maximum single application rate	Endpoint	HQ	Trigger value
Zoxium 240 SC	Oral	180 g a.s./ha	>33 µg a.s./bee	< 5.4	50
Zoxium 240 SC	Contact	180 g a.s./ha	>43.2 µg a.s./bee	< 4.2	

Conclusion: The acute and long-term risk of zoxamide is acceptable for bees following the intended uses of Zoxium 240 SC in potatoes and grapes.

2.9.9.4 Non-target arthropods

Table 2.9.9.4-1: Estimated exposure levels from the proposed uses of Zoxium 240 SC

Crop	Application rate	MAF	In-field exposure	Drift rate	Off-field exposure
Potatoes	180 g a.s./ha	3.0	540 g a.s./ha	0.0175	9.45 g a.s./ha
Grapevines	180 g a.s./ha	3.0	540 g a.s./ha	0.0659	35.586 g a.s./ha

MAF: Multiple application factor (3.0 for 5 applications)

Table 2.9.9.4-2: In-field and off-field risk hazard quotient for terrestrial arthropods, from the proposed uses of Zoxium 240 SC

Species	Exposure		Endpoint	In-field HQ	Off-field HQ	Trigger value
	In-field	Off-field				
Potatoes:						
Aphidius rhopalosiphi	540 g a.s./ha	9.45 g a.s./ha	>300 g a.s./ha	<1.8	<0.0315	2
Typhlodromus pyri	540 g a.s./ha	9.45 g a.s./ha	>300 g a.s./ha	<1.8	<0.0315	
Grapevines:						
Aphidius rhopalosiphi	540 g a.s./ha	35.586 g a.s./ha	>300 g a.s./ha	<1.8	<0.119	2
Typhlodromus pyri	540 g a.s./ha	35.586 g a.s./ha	>300 g a.s./ha	<1.8	<0.119	

The resulting hazard quotients for both indicator species demonstrate that the risk to non-target arthropod species from the proposed uses of Zoxium 240 SC in potatoes and grapes is acceptable and no higher-tier risk assessment is required.

Conclusion: The acute and long-term risk of zoxamide is acceptable for non-target arthropods following the intended uses of Zoxium 240 SC in potatoes and grapes.

2.9.9.5 Earthworms

Table 2.9.9.5-1: Acute and chronic toxicity exposure ratios for the risk to earthworms from the proposed uses of Zoxium 240 SC

Species	Test substance	Toxicity endpoint (mg a.s./kg soil dw)	Maximum initial PEC_{soil} (mg/kg soil dw)***	TER	Trigger value
Acute					
Eisenia foetida	Zoxamide	>535*	0.467	1146	10
	RH-127450	>500	0.039	12820	
	RH-24549	>53.5**	0.070	764	
	RH-163353	>53.5**	0.073	733	
	RH-141455		PEC soil accumulation **(mg/kg soil dw)**		
		>53.5**	no tillage – potatoe 0.0505	1059.4	
		>53.5**	no tillage – vineyard 0.0404	1324.3	
		>53.5**	tillage – potatoe 0.0366	1461.7	
		>53.5**	tillage – vineyard 0.0293	1825.9	
Chronic					
Eisenia foetida	Zoxamide	0.5* (artificial soil)	0.467	**1.07**	5
		7* (natural soil)	0.467	15	
	RH-127450	0.7**	0.039	17.9	
	RH-24549	0.7**	0.070	10.0	
	RH-163353	0.7**	0.073	9.60	
	RH-141455		PEC soil accumulation **(mg/kg soil dw)**		
		0.7**	no tillage – potatoe 0.0505	13.9	
		0.7**	no tillage – vineyard 0.0404	17.3	
		0.7**	tillage – potatoe 0.0366	19.1	
		0.7**	tillage – vineyard 0.0293	23.9	

* Since zoxamide has a log P_{ow} of 3.76 (>2) it is necessary to reduce the LC_{50} and NOEC values by a factor of 2 for the studies conducted using artificial soil in line with EU Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002 of October 2002). For the natural soil study, no adjustment of the toxicity value is required because the natural soil used in this study is typical of agricultural soils and contained only 2.7% organic carbon.

** Acute and chronic toxicity endpoints used for metabolites assuming that each metabolite is 10 fold more toxic than the parent to earthworms
*** All maximum initial PEC_{soil} values were calculated for application in potatoes
Values in **bold** are below the trigger value

All resulting acute and chronic TERs (with consideration to earthworm exposure via natural soil) demonstrate that the risk to earthworms from the proposed uses of Zoxium 240 SC in potatoes and grapes is acceptable.

Conclusion: The acute and long-term risk of zoxamide is acceptable for earthworms following the intended uses of Zoxium 240 SC in potatoes and grapes.

2.10 CLASSIFICATION AND LABELLING

Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	-	-	-	-
2.2.	Flammable gases	-	-	-	-
2.3.	Flammable aerosols	-	-	-	-
2.4.	Oxidising gases	-	-	-	-
2.5.	Gases under pressure	-	-	-	-
2.6.	Flammable liquids	-	-	-	-
2.7.	Flammable solids	-	-	-	-
2.8.	Self-reactive substances and mixtures	-	-	-	-
2.9.	Pyrophoric liquids	-	-	-	-
2.10.	Pyrophoric solids	-	-	-	-
2.11.	Self-heating substances and mixtures	-	-	-	-
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	-
2.13.	Oxidising liquids	-	-	-	-
2.14.	Oxidising solids	-	-	-	-
2.15.	Organic peroxides	-	-	-	-
2.16.	Substance and mixtures corrosive to metals	-	-	-	-
3.1.	Acute toxicity - oral	-	-	-	-
	Acute toxicity - dermal	-	-	-	-
	Acute toxicity - inhalation	-	-	-	-
3.2.	Skin corrosion / irritation	-	-	-	-
3.3.	Serious eye damage / eye irritation	Eye Irrit. 2, H319: Causes serious eye irritation	-	-	-
3.4.	Respiratory sensitisation	-	-	-	-
3.4.	Skin sensitisation	Skin sens. 1, H317: May cause an allergic skin reaction	-	Skin sens. 1, H317: May cause an allergic skin reaction	-
3.5.	Germ cell mutagenicity	-	-	-	-
3.6.	Carcinogenicity	-	-	-	-

3.7.	Reproductive toxicity	-	-	-	-
3.8.	Specific target organ toxicity –single exposure	-	-	-	-
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	-
3.10.	Aspiration hazard	-	-	-	-
4.1.	Hazardous to the aquatic environment	Aquatic acute 1, H400: Very toxic to aquatic life Aquatic chronic 1, H410: Very toxic to aquatic life with long lasting effects	10	Aquatic acute 1, H400: Very toxic to aquatic life Aquatic chronic 1, H410: Very toxic to aquatic life with long lasting effects	-
5.1.	Hazardous to the ozone layer	-	-	-	-

[1)] Including specific concentration limits (SCLs) and M-factors

[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Warning

Hazard statements: H317, H319, H400/ H410

Precautionary statements:

Proposed notes assigned to an entry:

Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

2.11 RELEVANCE OF METABOLITES IN GROUNDWATER

2.11.1 STEP 1: Exclusion of degradation products of no concern

In soil, the major metabolites which either exceeded 10% AR on one occasion or 5% on more than 2 occasions were RH-127450 (8.1-15.1% AR), RH-24549 (5.5-33.8% AR), RH-163353 (7.9-15% AR) and RH-141455 (8%). None of these substances meet any of the conditions set out in guidance document "Sanco/221/2000 –rev.10- final, 25 February 2003" to be considered to be degradation products of no concern. Therefore, further consideration is necessary.

2.11.2 STEP 2: Quantification of potential groundwater contamination

Predicted Environmental Concentrations in groundwater have been calculated for the metabolites RH-24549, RH-163353, RH-127450 and RH-141455 using the FOCUS groundwater scenarios and the PELMO 5.5.3 and PEARL 4.4.4. models (refer to Volume 3, CP, B.8). Potatoes and grapevines (5 applications of 180 g a.s./ha) were used for the simulations. For vines, 60% crop interception was considered for all applications. For potatoes, 60% crop interception was considered for the first, second and third application with 85% for the fourth and fifth application. Application both every year and once every three years was considered for potatoes. Application was simulated from 28 days after emergence for both crops. DT_{50}s of 4.3 days, 7.5 days, 10.3 days and 23.9 days were assumed for RH-127450, RH-24549, RH-163353 and RH-141455 respectively. Respective K_{oc}s of 669 ml/g, 90.5 ml/g, 68 ml/g and 2.8 ml/g were used. Predicted environmental concentrations for RH-24549, RH-163353 and RH-127450 were << 0.1 µg/L in all scenarios for each crop using both models. However, for RH-141455, predicted environmental concentrations were above the threshold value of 0.1 µg/L in all scenarios for vines using both models. The values were from 0.356 to 2.596 µg/l. For potatoes, using application every year, the PEC values were above 0.1 µg/l in all scenarios, except for the Sevilla scenario, with both models. The values were from 0.041 to 3.478 µg/l. For potatoes, using application every 3 years, the PEC values were above 0.1 µg/L in all scenarios, except for the Porto, Sevilla and Thiva scenarios, with the PELMO model. The values were from 0.032 to 1.014 µg/l. With the PEARL model, the PEC values did not exceed the threshold value in the Porto and Sevilla scenarios, and only marginally exceeded this threshold in the Thiva scenario. The values were from 0.022 to 1.201 µg/l.

Therefore, only for metabolite RH-141455 is further consideration necessary.

2.11.3 STEP 3: Hazard assessment – identification of relevant metabolites

2.11.3.1 STEP 3, Stage 1: screening for biological activity

A fungicide secondary screen under greenhouse conditions was performed for the metabolite RH-141455 and the structurally similar metabolite, RH-141452.

For the screen, technical preparations of RH-141452 and RH-141455 were prepared by dissolving 30 mg of the technical metabolite in 2 ml of an acetone/methanol mixture (50:50). The solution was then further diluted to provide test solutions at two dilutions. The resulting preparations were sprayed onto test plants and one day later, plants were inoculated with the test pathogens.

The effectiveness of each preparation was assessed 5 to 12 days after inoculation depending on the disease. Disease assessment was made by visual comparison of infection on the untreated and treated plant leaves. Incremental control values of 0, 50, 75, 80, 85, 90, 95, 99 and 100 percent were used to differentiate activity between treatments, doses and the untreated controls.

Neither metabolite showed any fungicidal activity on a range of plant pathogens including tomato and potato late blight and grape downy mildew. Zoxamide showed high activity for the same pathogens. Refer to Table 2.11.3.1-1.

Table 2.11.3.1-1: Activity of zoxamide and the metabolites RH-141455 and RH-11452 against fungal pathogens

Percentage disease control					
Compound	Application rate (g/ha)	BOT	CPM	GDM	TLB
Zoxamide	300	75	100	99	99
	75	75	85	99	100
	19	0	80	9	99
RH-141455	300	0	0	0	0
	75	0	0	0	0
RH-141452	300	0	0	0	0
	75	0	0	0	0

BOT (*Botrytis cinerea*), CPM (*Sphaerotheca fulginea*), GDM (*Plasmopara viticola*), TLB (*Phytophthora infestans*).

2.11.3.2 STEP 3, Stage 2: screening for genotoxicity

The genotoxicty of RH-141455 has been assessed in three *in vitro* assays (refer to Volume 3, CA, B.6):

In a bacterial gene mutation assay (1998), histidine-dependent TA98, TA100, TA1535, TA1537, and TA102 strains of *Salmonella typhimurium* were exposed to the metabolite, RH-141455 (Lot number WJZ 4091B, purity 98.74%) dissolved in dimethyl sulfoxide at concentrations of 0 (solvent control) to 5000 µg/plate in the presence and absence of an Arochlor 1245-treated rat S-9 liver fraction. In the tests with metabolic activation, 2-anthramine was used as the positive control for all strains. In the tests without metabolic activation, the positive controls used were: 2- nitrofluorene (TA98), sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and mitomycin-c (TA102). The number of revertants was determined. The results were confirmed in an independent assay. The study was certified to be GLP compliant and satisfied the essential criteria of OECD guideline # 471. The metabolite, RH-141455 did not induce an increase in revertants compared to solvent controls. This was true for all tester strains both with and without metabolic activation. RH-141455 was not mutagenic in the *Salmonella* gene mutation assay under the conditions of this assay.

In an *in vitro* mutation test using mouse lymphoma L5178Y, RH-141455 did not demonstrate mutagenic potential in this *in vitro* cell mutation assay.

In an *in vitro* micronucleus test in cultured human lymphocytes, RH-141455 did not show any evidence of causing an increase in the induction of micronuclei.

Refer to Volume 3, CA, B.6 of RAR for further details.

2.11.3.3 STEP 3, Stage 3: screening for toxicity

The active substance, zoxamide is not classified on the basis of its toxicology. Although RH-141455 has not been confirmed as a metabolite in the rat, it is probable that it is formed during mammalian metabolism. Nevertheless, additional studies have been performed with RH-141455 to support the conclusion that it is not of toxicological concern.

The absorption, distribution, metabolism and elimination of [14C]- RH-141455 in male rats has been studied. Four male rats were administered a single oral dose of [14C]- RH-141455 in pH adjusted water at a nominal dose of 1000 mg/kg bw. At 168 hours post dose, the rats were sacrificed and the total

radiolabelled residues were determined. The study was certified to be GLP compliant and conducted in accordance with EPA guidelines. Greater than 96% of radioactivity excreted from faeces and urine was identified to be unchanged RH-141455. Some very minor metabolites were also observed in urine samples but were not identified due to their extremely low percentage of dose. (Refer to DAR, UK, 2001, Section B.6.1.3 for details).

In an acute oral toxicity study (1998), six male and six female Crl:CD-1®(ICR)BR mice were administered by gavage a limit dose of 5000 mg/kg bw (10 ml/kg) of the metabolite RH-141455. The study was certified to be GLP compliant and satisfied the essential criteria of OECD guideline # 401.

There were no mortalities or effects on body weight when compared with historical control data. Scant faeces was noted in males and/or females on days 1 and 2. Necropsy revealed no gross changes. The acute oral LD50 for RH-141455 in male and female mice was greater than 5000 mg/kg bw. (Refer to DAR, UK, 2001, Section B.6.8.2 for details).

Therefore, the metabolite RH-141455 is not expected to be more toxic than parent zoxamide.

2.11.4 STEP 4: Exposure assessment – threshold of concern approach

Not applicable, the PECgw values for metabolite RH-141455 are greater than 0.75 µg/L.

2.11.5 STEP 5: Refined risk assessment

The available data show that the metabolite RH-141455 does not have fungicidal activity, that it is not genotoxic and is no more toxic than the active substance. The ADI for zoxamide is 0.5 mg/kg bw/day and for the first EU approval of zoxamide, it was concluded that it was not necessary to allocate an ARfD. As a conservative approach to the refined risk assessment, an additional assessment factor of 10 is applied to the ADI for zoxamide to establish an ADI for the metabolite RH-141455 of 0.05 mg/kg bw/day (50 µg/kg bw/day).

In accordance with Sanco/221/2000 –rev.10- final, 25 February 2003, it is assumed that an individual has a daily water consumption of 2 L/day.

The maximum PECgw value calculated for RH-141455 is 3.48 µg/L. This would be equivalent to a daily consumption of 7 µg/person/day, or 0.12 µg/kg bw/day for a person weighing 60 kg, considerably lower that the proposed ADI for RH-141455.
RH-141455 is also a metabolite found in potatoes. However, in supervised field trials with potatoes performed in accordance with the intended GAP, residues in potato tubers were < 0.02 mg/kg (The LOQ for the analytical method). Therefore, the contribution to the dietary intake of RH-141455 made by potatoes is predicted to be negligible.

2.11.6 Overall conclusion

In accordance with the guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC (Sanco/221/2000 –rev.10-final, 25 February 2003), the metabolite RH-141455 is considered **not** to be relevant.

2.12 CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.12.1 Identity and physical chemical properties

The zoxamide molecule contains a single chiral carbon atom and is manufactured as a racemic mixture of R and S isomers. Both enantiomers are present in equal quantities. The fungicidal activity of zoxamide resides in the S isomer (Development code RH-116949). However, the manufacture of the RH-116949 presents significant technical challenges and is determined to be prohibitively expensive. Therefore, it was decided to develop racemic (R,S) zoxamide.

All tests on physical and chemical properties are performed on racemic zoxamide. Generally, racemic isomers of a compound have identical physical and chemical properties. The exception being the rotation of plane polarised light, where the R and S isomers would have opposite optical rotations. As racemic zoxamide would have an optical rotation of zero, in accordance with Commission Regulation (EU) No 283/2013, the optical purity of zoxamide was not determined.

2.12.2 Methods of analysis

All analytical methods have been developed for racemic zoxamide. No stereoselective methods have been developed for the determination of either enantiomer of zoxamide. Chiral columns are available for the separation and analysis of enantiomeric isomers. However, these are expensive and not suitable for the routine analysis of most matrices.

2.12.3 Mammalian toxicity

All tests are performed on racemic zoxamide. No information is available on either enantiomer of zoxamide. However, zoxamide is metabolised rapidly in mammals. The results of an *in vitro* comparative metabolism study (Volume 3, CA, B.6) indicates that 70 to 90% of parent is metabolised within 2 hours. This indicates that there is no significant preferential metabolism of one isomer and that therefore, the existing data on racemic zoxamide can be read across to either enantiomer and there is no need to add additional assessment factors for the derivation of toxicological reference values.

2.12.4 Operator, Worker, Bystander and Resident exposure

All exposure estimates have been calculated for racemic zoxamide. Given the available information on the physical and chemical properties of racemic zoxamide and the evidence of rapid metabolism in mammals, these estimates are considered to be appropriate and to address the risk from either enantiomer or both in combination.

2.12.5 Residues and Consumer risk assessment

No analytical methods have been developed for the determination of either enantiomer of zoxamide in treated crops or food products of animal origin. All residue determinations were for racemic zoxamide and all estimates of consumer exposure are for total (racemic) zoxamide. The available information on residues and consumer risk assessment are considered to cover exposure and risk to either enantiomer of zoxamide as well as racemic zoxamide for the following reasons:

- Residues in potatoes are very low and consist of metabolites that have lost the chiral centre.
- Residues in grapes consist primarily of unchanged parent.
- All livestock intakes are calculated to be below 0.004 mg/kg bw/day.

- Metabolism by mammals is rapid, the available toxicology data and toxicological reference values are considered to cover either enantiomer or both.

2.12.6 Environmental fate

All studies have been performed using racemic zoxamide. No information is available on either enantiomer of zoxamide.

In soil, zoxamide degrades very rapidly with a laboratory DT50 of 2 – 4 days. In water / sediment systems, zoxamide also degrades rapidly (DT50 is 3 days in the water phase and 3.6 – 8 days in the whole system). Therefore, it is unlikely that there is significant preferential degradation of either enantiomer and it is not necessary to generate data on the rate and route of degradation of R or S zoxamide in the environment.

2.12.7 Ecotoxciology

All studies have been performed using racemic zoxamide. No information is available on either enantiomer of zoxamide.

Zoxamide is a non-systemic fungicide belonging to the benzamide group of compounds. It is intended to protect against late blight on potato (Phytophthora infestans) and downy mildew on grape (Plasmopara viticola). The mode of action of zoxamide involves the inhibition of germ tube development and mycelium growth by inhibiting cell division. Given this mode of action, it is unlikely that the toxicity of R and S zoxamide to non-target organisms will differ significantly and therefore ecotoxicology data on R or S zoxamide is not required.

In addition, zoxamide degrades rapidly in the environment and there is no evidence to suggest that there is preferential degradation of either R or S-zoxamide.

2.12.8 Efficacy

Zoxamide is a racemic mixture of R and S isomers. The efficacy data on the activity of the racemic zoxamide and S-zoxamide (RH-116949) against foliar blight indicate that the S-enantiomer has double the potency of racemic zoxamide and is the active component within zoxamide.

2.13 RESIDUE DEFINITIONS

2.13.1 Definition of residues for exposure/risk assessment

Food of plant origin: Zoxamide

Food of animal origin: Zoxamide

Soil: Zoxamide, RH-127450, RH-24549, RH-163353 and RH-141455.

Groundwater: Zoxamide, RH-127450, RH-24549, RH-163353 and RH-141455.

Surface water: Zoxamide, RH-127450 (>10% in soil & water), RH-163353 (>10% in soil & water), RH-141288 (>10% in water), RH-24549 (>10% in soil only) and RH-141455 (>5% of 2 or more consecutive occasions in soil).

Air: Zoxamide.

2.13.2 Definition of residues for monitoring

Food of plant origin: Zoxamide

Food of animal origin: Zoxamide

Soil: Zoxamide

Groundwater: Zoxamide

Surface water: Zoxamide

Air: Zoxamide

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LEVEL 3

ZOXAMIDE

PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3 PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1 BACKGROUND TO THE PROPOSED DECISION

3.1.1 Proposal on acceptability against the approval criteria – Article 4 and Annex II of Regulation (EC) No 1107/2009

3.1.1.1 Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	X		It is considered that Article 4 of Regulation(EC) No 1107/2009 is complied with zoxamide for the representative uses (please refer to Section 1.5.1, Level 1 for details of representative uses)
3.1.1.2 Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.			Please refer to Section 3.1.4.
3.1.1.3 Restrictions on approval				
		Yes	No	

	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.		X	
3.1.1.4 Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		The data submitted are sufficient to establish an Acceptable Daily Intake (ADI) and Acceptable Operator Exposure Level (AOEL). Results from the toxicological studies do not raise the need for setting an Acute Reference Dose (ARfD).
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.	X		Yes, however see Volume 1, Level 2, Section 2.7 and Volume 1, Level 3, Section 3.1.5.

	It is considered that the dossier submitted is sufficient to dermine, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	X		The dossier contains sufficient information to determine the fate and distribution of the active substance in the environment, and its impact on non-target species.
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	X		Sufficient information on efficacy of zoxamide was provided. Please see Volume 1, Level 2, Section 2.3.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	X		No studies simulating hydrolytic conditions for industrial processing (pasteurisation, baking, brewing, boiling, sterilisation) are submitted. Therefore RMS is not able to conclude on nature of residues for processed commodities. See Volume 1, Level 2, Section 2.7.6.
Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	X		The active substance is manufactured with a minimum purity of 950 g/kg and does not contain any relevant impurities.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where		X	FAO specification not available.

	such specification exists.			
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted		X	FAO specification not available.
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	X		The relevant analytical methods have been provided and are sufficiently validated.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	X		The relevant analytical methods have been provided and are sufficiently validated.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		The relevant analytical methods have been provided and are sufficiently validated.
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD	X		The ADI is set at 0.5 mg/kg bw/day based on the 1-year study in dog

	can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.			and considering a safety factor of 100. See Volume 1, Level 2, Section 2.6.11. The establishment of ARfD is not considered to be necessary for zoxamide due to the toxicological profile of this active substance. See Volume 1, Level 2, Section 2.6.12. The AOEL is set at 0.3 mg/kg bw/day based on the 90-day study in dog and considering a safety factor of 100 and oral absorbtion of 60 %. See Volume 1, Level 2, Section 2.6.13.
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		X	Zoxamide was not genotoxic in the Ames test or a mammalian cell mutation assay, and not genotoxic or clastogenic in the *in vivo* micronucleus study in mice. However, in the study for the induction of chromosome aberrations in cultured Chinese hamster ovary cells, mitotic accumulation was observed at concentrations, which inhibited cell growth in tests with and without metabolic activation. On the basis of the overall evidence from in vitro and in vivo studies, zoxamide is not considered to be a genotoxic compound.Summary of genotoxicity studies is presented in Volume 1, Level 2, Section 2.6.4.
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in		X	Zoxamide was not carcinogenic in studies in rats and mice. See Volume 1, Level 2, Section 2.6.5.

	accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**			
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.	-		Not applicable, the active substance is not carcinogenic.
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**		X	In a multigeneration reproductive toxicity study, there were no adverse reproductive effects in rats. There was no evidence of toxicity in the rat or rabbit in developmental toxicity studies. See Volume 1, Level 2, Section 2.6.6.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of	-		Not applicable, the active substance is not classified as toxic for reproduction.

	Regulation (EC) No 396/2005.			
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**		X	Zoxamide is not classified for carcinogenicity or reproductive toxicity. Furthermore, the available toxicity data on zoxamide demonstrate that there are no adverse effects on endocrine tissues or any evidence of perturbation of endocrine function.
ii)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties**		X	Zoxamide is not proposed to be classified as toxic for reproduction. Furthermore, the available toxicity data on zoxamide demonstrate that there are no adverse effects on endocrine tissues or any evidence of perturbation of endocrine function.
iii)	Linked to either i) or ii) immediately above. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.	-		Not applicable. The active substance is not expected to have endocrine disrupting properties.
Fate and behaviour in the environment				
Persistent organic pollutant (POP)				

		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		X	Zoxamide does not fulfil the criteria of a persistent organic pollutant (POP): 1) DT50 values in water, soil, and sediment do not exceed the threshold values; 2) bio-concentration factor in aquatic species is 136, i.e., below the threshold value of 5000, and the partition coefficient n-octanol/water is 3.76, below the threshold value of 5; 3) zoxamide is very slightly volatile (vapour pressure of 1.33 x 10^{-5} Pa at 25°C) with an estimated half-life in atmosphere of 7.5 hours. Therefore, the active substance does not have potential for long-range transport via air.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		X	Zoxamide does not fulfil the PBT criteria: 1) Persistence: DT50 values in water, soil, and sediment do not exceed the threshold values; 2) Bioaccumulation: the bioaccumulation criteria are not fulfiled; 3) Toxicity: The substance is not classified as carcinogenic, mutagenic, or toxic to reproduction, and there is no evidence of chronic toxicity that requires classifications STOT RE 1 or STOT RE 2 pursuant to Regulation (EC) No 1272/2008. However, the long-term NOEC for aquatic organisms is less than 0.01 mg/L. Therefore, only the toxicity criteria (T) have been fulfilled.
Very persistent and very bioaccumulative substance (vPvB).				

		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	Zoxamide does not fulfil the criteria of a vPvB substance: 1) the bioaccumulation criteria are not fulfiled; 2) DT50 values in water, soil, and sediment do not exceed the threshold values.
Ecotoxicology				
		Yes	No	
	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.	X		For non-target aquatic organisms, the risk is considered acceptable when a 20 m buffer zone with 20 vegetative filter strip is applied. The risk for other non-target organisms is considered acceptable for all intended uses. See Volume 1, Level 2, Section 2.9 for more details.
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance **HAS** endocrine disrupting properties that may cause adverse effects on non-target organisms.		X	The active substance is not expected to exhibit endocrine disrupting properties.
	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.	X		The active substance is not expected to exhibit endocrine disrupting properties.

	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	X		The acute and long-term risk of zoxamide is acceptable for bees following the intended uses of Zoxium 240 SC for all intended uses. See Volume 1, Level 2, Section 2.9 for more details.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X		For commodities of plant and animal origin, the residue definition is parent zoxamide, for both risk assessment and monitoring. For wine, it is proposed to set residue definition as parent zoxamide only for both risk assessment and monitoring. See Volume 1, Level 2, Section 2.7 for more details.
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		Predicted Environmental Concentrations in groundwater have been calculated for the metabolites RH-24549, RH-163353, RH-127450 and RH-141455 using the FOCUS groundwater scenarios and the PELMO 5.5.3 and PEARL 4.4.4. models. Representative uses were considered for simulations. Predicted environmental concentrations for RH-24549, RH-163353 and RH-127450 were << 0.1 µg/L in all scenarios for each crop using both models.

				For RH-141455, predicted environmental concentrations were above the threshold value of 0.1 µg/L in all scenarios for vines using both models. The values were from 0.356 to 2.596 µg/l. For the use on potatoes, application both every year and once every three years was considered. Assuming application every year, the PEC values were above 0.1 µg/l in all scenarios, except for the Sevilla scenario, with both models. The values were from 0.041 to 3.478 µg/l. Assuming application every 3 years, the PEC values were above 0.1 µg/L in all scenarios, except for the Porto, Sevilla and Thiva scenarios, with the PELMO model. The values were from 0.032 to 1.014 µg/l. With the PEARL model, the PEC values did not exceed the threshold value in the Porto and Sevilla scenarios, and only marginally exceeded this threshold in the Thiva scenario. The values were from 0.022 to 1.201 µg/l. However, in accordance with the guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC (Sanco/221/2000 –rev.10- final, 25 February 2003), the metabolite RH-141455 is considered not to be relevant. See Volume 1, Level 2, Section 2.11 for more details.

3.1.2 Proposal - Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution		X	Zoxamide does not fulfill any of the criteria specified in point 4 of Annex II of Regulation (EC) No 1107/2009.

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		X	Zoxamide cannot be considered as a substance of low risk due to following reasons: - The substance is to proposed to be classified in accordance with Regulation (EC) No 1272/2008 as H400 / H410 (acute category 1, chronic category 1, very toxic to aquatic life with long lasting effects); - bio-concentration factor in aquatic species is 136.

3.1.4 List of studies to be generated, still ongoing or available but not evaluated

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1 Identity of the active substance or formulation				
-				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
-				
3.1.4.3 Data on uses and efficacy				
-				
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
-				
3.1.4.5 Methods of analysis				
-				
3.1.4.6 Toxicology and metabolism				
-				
3.1.4.7 Residue data				
Storage Stability of residues of Zoxamide, RH-150721, RH-1452 and RH-1455 in Grape			X	

and Processed Products and Potato				
3.1.4.8 Environmental fate and behaviour				
-				
3.1.4.9 Ecotoxicology				
-				

3.1.5 Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	**Relevance in relation to representative use(s)**
Toxicity of metabolite RH-150721, present in high amounts in wine	Grapes
Assessment of nature of residues for processed commodities could not be finalized	All prepresentative uses

3.1.6 Critical areas of concern

An issue is listed as a critical area of concern:

(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or

(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the

lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	**Relevance in relation to representative use(s)**
-	-

3.1.7 Overview table of the concerns identified for each representative use considered

If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.

All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		Use potatoes (X^1)	Use grapes (X^1)
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial vertebrates	Risk identified		
	Assessment not finalised		

Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised		
Risk to aquatic organisms	Risk identified		
	Assessment not finalised		
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10µg/L[(a)] breached		
	Assessment not finalised		
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

3.1.8 Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	Justification
-	-

3.1.9 Critical issues on which the Co-RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	Opinion of Co-RMS	Opinion of RMS

3.2 PROPOSED DECISION

[redacted]

3.3 RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH ANY APPROVAL OR AUTHORISATION(S), AS APPROPRIATE

3.3.1 Particular conditions proposed to be take into account to manage the risks identified

[redacted]

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APPENDICES

APPENDIX 1 GUIDANCE DOCUMENTS USED IN THIS ASSESSMENT

European Commission, 2012; Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (the Renewal Regulation). SANCO/2012/11251 - rev.1.2, July 2012:

European Chemical Agency; ECHA Guidance on the application of the CLP criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Version 4.1, June 2015

European Food Safety Authority, 2011; Guidance of EFSA - Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011; 9(2):209

Identity, Physical and chemical properties

European Commission, 2011; Guidance Document on the Assessment of the Equivalence of Technical Materials of Substances Regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003 – rev.9, 17 June 2011.

Methods of analysis

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