

REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: A22773A

Product name(s): ORONDIS EVO

Chemical active substances:

Azoxystrobin, 250 g/L

Oxathiapiprolin, 12 g/L

Interzonal

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(New authorization)

Applicant: Syngenta

Submission date: November 2021

MS Finalisation date: June 2022 (initial Core Assessment)

June 2023 (final Core Assessment)

Version history

When	What
November 2021	Applicant submission
June 2022	<p>Initial assessment by the iZ RMS</p> <p>The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are struck through and shaded for transparency.</p>
June 2023	<p>Final report (Core Assessment updated following the commenting period)</p> <p>Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow.</p>

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Reviewer summary:

This part of dossier summarizes data related to the toxicological and NDE assessment for the plant protection product ORONDIS EVO (product code A22773A an SC formulation containing 250 g/L azoxystrobin and 12 g/L oxathiapiprolin) which has been submitted to support registration according art. 33 of 1107/2009 in Poland also for zonal registration and interzonal for which PL was designated zRMS/izRMS. Intended use of PPP is as a fungicide on vegetables, solanacea and hops. For the current product registration, Syngenta provided an assessment of the toxicological potential based on *in vivo* and *in vitro* studies.

ORONDIS EVO (A22773A) is a new plant protection product, which is intended to be authorized in Member States for the first time. There is no duplication of vertebrate studies and extrapolation to data of similar formulations is not possible. The testing strategy considered by the Applicant takes into account methods compliant with the 3R concept for refinement, reduction and replacement of animal testing where applicable and acceptable. Since the fact that A22773A is a new plant protection product, thus there is no EU derogation allowing for these data points to be addressed by extrapolation from existing data; therefore in order to obtain approval new tests were required and the study reports are provided. Thus, zRMS/izRMS PL accept existing *in vivo* tests. The data is sufficient to indicate the time course and characteristics of the effect with full details of behavioural changes and possible gross pathological findings at post-mortem also allow to identify of effects following a single exposure to the plant protection product can be established.

Regarding submitted *in vitro* skin irritating study (xxxxxx 2021, VV-902652) zRMS/izRMS decided not to take it into account due to the following information available in TG OECD 439 rev. 14 June 2021 INITIAL CONSIDERATIONS AND LIMITATIONS Subsection 8: p.2 (...) *data indicates a lack of applicability of the RhE based in vitro skin irritation test for agrochemical formulations* (47). (...)

See also: Kolle S.N, van Ravenzwaay B. and Landsiedel R. (2017). Regulatory accepted but out of domain: In vitro skin irritation tests for agrochemical formulations. Regul. Toxicol. Pharmacol 89, 125-130.

Regarding submitted *in vitro* eye irritating study (xxxxxx 2021, VV-902426) zRMS/izRMS decided not to take it into account due to the following information available in TG OECD 438 rev. 25 June 2018:

(...) *The ICE test method is not recommended for the identification of test chemicals that should be classified as irritating to eyes (i.e., UN GHS Category 2 or Category 2A) or test chemicals that should be classified as mildly irritating to eyes (UN GHS Category 2B) due to the considerable number of UN GHS Category 1 chemicals underclassified as UN GHS Category 2, 2A or 2B and UN GHS No Category chemicals overclassified as UN GHS Category 2, 2A or 2B. For this purpose, further information and if needed, additional testing with another suitable method may be required.* (...).

Thus, considering mentioned above information's zRMS/izRMS decided to conclude assessment for the A22773A on this hazard categories (skin and eye irritating tests) based on *in vivo* studies.

NDE assessment for operator, workers and B&R has been calculated using the AOEM model (EFSA calculator), Dutch Greenhouse model, Southern European Glasshouse Model Greenhouse model v_2.1 (20101223) with Southern European Green-house Model and considering the worst-case exposure scenario to cover all the intended uses (highest application rate per application as well as the highest application rate per year with the shorter interval between each application).

Note: The Netherlands consider that it may be possible for active substances to be released from greenhouses. Therefore, an assessment of the possible bystander / resident exposure has been included using an approach adopted by the Netherlands. (refer Lee Side turbulence model ((Lijwervel model)). Duyzer, J., van der Staay, M., Weststrate, H., Boertjes, B., Hollander, K. and Verhagen, H., 2004. *De blootstelling van omwonenden van kassen aan gewasbeschermingsmiddelen via de lucht. TNO-rapport, R 2004/517: 72 pp.*). Proposed approach has been accepted by the iZ RMS PL.

All NDE calculations provided for operator, workers and B&R resulting from use of PPP, considering all tasks according to the critical use(s), identify safe use of the product ORONDIS EVO (A22773A).

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on A22773A *

Product name and code	A22773A
Formulation type	Suspension Concentrate (SC)
Active substance(s) (incl. content)	Azoxystrobin (250 g/L), oxathiapiprolin (12 g/L)
Function	Fungicide
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	No
Product previously evaluated in another MS according to Uniform Principles	No

* Information on the detailed composition of A22773A can be found in the confidential dRR Part C.

Justified proposals for classification and labelling

According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification and labelling with regard to toxicological data is proposed for the preparation:

Table 6.1-2: Justified proposals for classification and labelling for A22773A according to Regulation (EC) No 1272/2008

Hazard class(es), categories	None
Hazard pictograms or Code(s) for hazard pictogram(s)	None
Signal word	None
Hazard statement(s)	None
Precautionary statement(s)	Response: P391 Collect spillage. Disposal: P501 Dispose of contents/container to an approved waste disposal plant.
Additional labelling phrases	EUH208: Contains 1,2-benzisothiazol-3-one. May produce an allergic reaction. EUH401: To avoid risks to human health and the environment, comply with the instructions for use.
	This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher. Toxicological information: The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for A22773A

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Gloves for mixing/loading and gloves and impermeable coveralls for application • <i>Operator must wear adequate work clothing during both mixing/loading and application. The use of gloves is recommended.</i>
Workers	Acceptable	None • <i>Treated area should not be entered before spray deposits have completely dried. In case a worker enters the treated area, long trousers, and long-sleeved shirt should be worn. The use of gloves is recommended.</i>
Residents	Acceptable	None
Bystanders	Acceptable	None

* Considering comments made by the cMS during commenting period iZ RMS provide additional information regarding RMM. Taking into account the exposure estimates for operator (Dutch greenhouse model & ECPA Southern Greenhouse model – standard) and the worker exposure estimates (EFSA Calculator) and the labelling of the product (EUH208), phrases highlighted in yellow shading (see Table 6.1-3) should be included in the product label

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended. No specific PPE is necessary.

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and residents/bystanders is presented in the following table.

Table 6.1-4 Critical uses and overall conclusion of exposure assessment

1	2	3	4	5	6	7	8	9	10			
Use- No.*	Crops and situa- tion (e.g. growth stage of crop)****	F, Fn, Fpn G, Gpn or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safener/syn- ergist (L/ha)) critical gap for operator, worker, resident or by- stander exposure based on [Expo- sure model]	Acceptability of exposure assess- ment			
			Method / Kind (incl. applica- tion technique ***	Max. number (min. interval between appli- cations) a) per use b) per crop/ season	Max. application rate kg as/ha a) azoxystrobin b) oxathiapiprolin	Water L/ha min / max			Operator	Worker	Residents	Bystander
PL- 42	Cucumber	G	Spraying, LCHH	a) 2 (7 days)	a) 0.250 b) 0.012	200 - 1000	3	Guidance on the assessment of ex- posure of opera- tors, workers, resi- dents and bystand- ers in risk assess- ment for plant pro- tection products; EFSA Journal 2014;12(10):3874				
PL- 53 to PL- 55	Pepper	G	Spraying, HCHH	a) 2 (7 days)	a) 0.250 b) 0.012	200 - 1500	3	Dutch Greenhouse model [Dutch model for manual application in glasshouses. van Hemmen, 1992; van Golstein Brouwers et al., 1996; Snippe R J et al., 2002] Southern Euro- pean Glasshouse Model				

1	2	3	4	5	6	7	8	9	10
								Greenhouse model v_2.1 (20101223) with Southern European Greenhouse Model Overview. Members of the European Crop Protection Association. Occupational & Bystander Exposure Expert Group. October 2010 (Revision 9). ECPA, European Crop Protection Association, aisbl 6, Avenue E. Van Nieuwenhuysse, B-1160 Brussels, Belgium.	

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1. Uses listed for Poland only as they represent the most critical GAP. The justification of the critical use selection can be found in section 6.6.1.

** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application

*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Explanation for column 10 "Acceptability of exposure assessment"

A	Exposure acceptable without PPE / risk mitigation measures
R	Further refinement and/or risk mitigation measures required
N	Exposure not acceptable/ Evaluation not possible

Data gaps

There is no data gap.

6.2 Toxicological Information on Active Substance(s)

Information regarding classification of the active substances and on EU endpoints and critical areas of concern identified during the EU review are given in Table 6.2-1.

Table 6.2-1: Information on active substance(s)

	Azoxystrobin	Oxathiapiprolin
Common Name	Azoxystrobin	Oxathiapiprolin
CAS-No.	131860-33-8	1003318-67-9
Classification and proposed labelling		
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes (s), categories: Acute toxicity, Category 3 Code(s) for hazard pictogram(s): GHS06 Signal word: Danger Hazard statement(s): H331: Toxic if inhaled. Precautionary statement(s): Prevention: P261 Avoid breathing dust/ fume/ gas/ mist/ vapours/ spray. P273 Avoid release to the environment. Response: P304 + P340 + P311 IF INHALED: Remove person to fresh air and	Hazard classes (s), categories: n/a Code(s) for hazard pictogram(s): n/a Signal word: n/a Hazard statement(s): n/a Precautionary statement(s): n/a

	Azoxystrobin	Oxathiapiprolin
	keep comfortable for breathing. Call a POISON CENTER/doctor. P391 Collect spillage. Storage: P403 + P233 Store in a well-ventilated place. Keep container tightly closed. Disposal: P501 Dispose of contents/ container to an approved waste disposal plant.	
Additional C&L proposal	This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher. May form combustible dust concentrations in air.	This substance is not considered to be very persistent, bioaccumulating and toxic (PBT). This substance is not considered to be very persistent and very bioaccumulating (vPvB).
Agreed EU endpoints		
AOEL systemic	0.2 mg/kg bw/d (corrected for 100X UF, no correction for oral absorption needed)	0.04 mg/kg bw/d (corrected for 100X UF and 30% oral absorption)
Reference	EFSA Journal 2010; 8(4):1542	EFSA Journal 2016;14(7):4504
Conditions to take into account/critical areas of concern with regard to toxicology		
Review Report/EFSA Conclusion for active substance	<p>The technical specification as agreed in the Annex I inclusion is not covered by the toxicological assessment. From a toxicological point of view, it should comply with the rapporteur Member State's proposal from May 2009; the proposal made by the notifier for the Annex I renewal procedure which reduces the levels of a number of impurities compared to the specification agreed for Annex I inclusion, is also not covered by the toxicological assessment with respect to two impurities. None of these new proposals could be agreed on by the section on the identity, physical, chemical and technical properties (see sections 1 and 2).</p> <p>The potential for groundwater exposure by the metabolite of Azoxystrobin R234886 above the concentration of µg/L is predicted to be high over a wide range of geoclimatic conditions represented by the FOCUS groundwater scenarios. In case of Brassicae, 2 (FOCUS PELMO) or 3 (FOCUS PEARL) out of 7 scenarios; in case of spring cereals, 1 out of 6 scenarios; in case of winter cereals, 1 out of 9 scenarios were identified, where the concentration of 10 µg/L was exceeded by this non-relevant metabolite (in case of cereals all with FOCUS PEARL).</p>	None.

6.3 Toxicological Evaluation of Plant Protection Product

Acute Toxicity Estimate (ATE) calculations have been conducted and are provided in the Part C document. Syngenta has also conducted acute toxicity studies on the formulation as these studies are required for registration in other countries (Russia, Ukraine, Belarus, and Israel). Where classification proposals have varied between the ATE calculation approach and the animal data generated it is Syngenta's approach

to base the product classification on the animal data, in accordance with CLP guidance. A summary of the toxicological evaluation for A22773A is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for A22773A

Reviewer comment: Since that the provisions of Regulation 1272/2008 indicate that the *in vivo* tests are overriding the estimation of the calculation method (ATE, Additivity method) also due to fact that mentioned below *in vitro* tests (e.g. OECD 439, 438 are not suitable for agrochemical, see our detailed comment in the Preface p. 5), iZ RMS PL decided to summarize assessment of toxicological hazards for A22773A considering available *in vivo* tests.

Type of test, species, model system (Guideline)	Result	ATE & Additivity Calculation Result	Acceptability	Classification ¹ (acc. to the criteria in Reg. 1272/2008)	Reference
LD ₅₀ oral, rat (OECD 425)	> 2000 mg/kg bw	>2000 mg/kg Not-classified	Yes	None	xxxxxx 2020, VV-892044
LD ₅₀ dermal, rat (OECD 402)	>2000 mg/kg bw	>2000 mg/kg Not-classified	Yes	None	xxxxxx 2021, VV-910770
LC ₅₀ inhalation, rat (OECD 403)	> 2.14 mg/L air (maximum attainable concentration)	3.05 mg/L Category 4, H332	Yes	None	xxxxxx 2021, VV-899756
Skin irritation, <i>in vitro</i> (OECD 439)	Non-irritant		No	None n/a	xxxxxxx 2021, VV-902652
Skin irritation, rabbit (OECD 404)	Non-irritant	n/a Not-classified	Yes	None	xxxxxx 2020, VV-895236
Eye irritation, <i>in vitro</i> (OECD 438)	Non-irritant		No	None n/a	xxxxxx 2021, VV-902426
Eye irritation, rabbit (OECD 405)	Non-irritant	n/a Category 2, H319	Yes	None	xxxxxxx 2021, VV-896673
Skin sensitisation mouse (OECD 429, LLNA)	Non-sensitising	n/a Not-classified	Yes	None	xxxxxxx, 2020, VV-876976
Supplementary studies for combinations of plant protection products	No data – not required				

¹ Proposed acute toxicity classifications are based on A22773 study results.

Table 6.3-2: Additional toxicological information relevant for classification/labelling of A22773A

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of active substance(s) (relevant for classification of product)	Azoxystrobin (ISO) (>= 20 - < 25% (w/w))	Hazard statement Acute Tox. 3; H331	MSDS**	Hazard statement(s) n/a EUH208: Contains 1,2-benzisothiazol-
	Oxathiapiprolin (>= 1 - < 2.5% (w/w))	Hazard statement n/a		

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of non-active substance(s) (relevant for classification of product)	Residues (petroleum), catalytic reformer fractionator, sulfonated, polymers with formaldehyde, sodium salts (CAS No. 68425-94-5, >= 1 - < 10% (w/w))*	Hazard statements Skin Irrit. 2; H315 Eye Dam. 1; H318		3(2H)-one: May produce an allergic reaction.
	1,2-benzisothiazol-3(2H)-one (CAS No. 2634-33-5, ≥ 0.025- <0.05% (w/w))*	Hazard statements Acute Tox. 4; H302 Skin Irrit. 2; H315 Eye Dam. 1; H318 Skin Sens. 1; H317		
	Bronopol (INN) (CAS No. 52-51-7, >= 0.025 - < 0.1% (w/w))*	Hazard statements Acute Tox. 4; H302 Acute Tox. 4; H312 Skin Irrit. 2; H315 Eye Dam. 1; H318 STOT SE 3; H335		
Further toxicological information	No data – not required			

* Please use concentration range or concentration limit (e.g. 1-10% or > 1%) as provided in MSDS.

** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

6.4.1 Azoxystrobin metabolite R234886

An overview of the results of the accepted toxicological studies for groundwater metabolite R234886 is given in the following table. No detailed summaries are provided as the studies have already been assessed and accepted at EU level.

Table 6.4-1: Summary of the results of toxicity studies for R234886

Type of test, species (Guideline)	Result	Acceptability	Reference*
Acute Oral (OECD 425)	>5000 mg/kg	Yes	EFSA Journal 2010; 8(4):1542, Straube, E., 2005; RCC A12284*
Bacterial Reverse Mutation Assay (Ames Test) (OECD 471)	Non-mutagenic	Yes	EFSA Journal 2010; 8(4):1542, Callander, R., 2005; YV7083-REG *

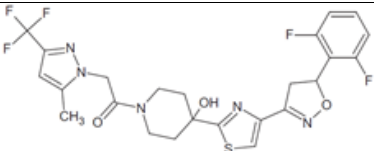
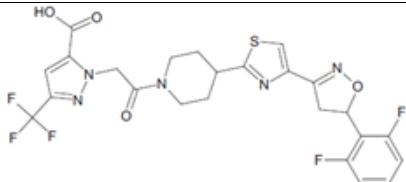
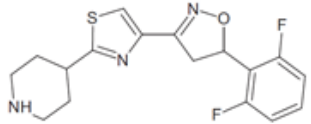
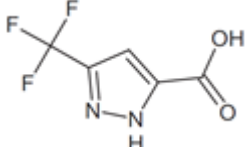
* indicates that a study was reviewed at EU level

6.4.2 Oxathiapiprolin metabolites IN-RDT31, IN-RAB06, IN-QPS10 & IN-E8S72

The oxathiapiprolin metabolites IN-RDT31, IN-RAB06 and IN-QPS10 are predicted to occur in groundwater at concentrations below 0.1 µg/L. The metabolite IN-E8S72 is predicted to occur in groundwater at concentrations >0.75 µg/L but <10 µg/L (see Chapter 8.8 of the dRR Part B, Section 8). Only assessment of the relevance of metabolite IN-E8S72 according to the stepwise procedure of the EC guidance document SANCO/221/2000 – rev.10 is therefore required.

General information on the metabolites are provided in Table 6.4-2. The impact of the relevance assessment on whether a particular GAP use leads to acceptable risk or not is presented in the summary of the cGAP evaluation in Chapter 8.1 of the dRR Part B, Section 8 (Environmental fate and behaviour).

Table 6.4-2: General information on metabolites IN-RDT31, IN-RAB06, IN-QPS10 & IN-E8S72

Name of active substance	Metabolite name and code	Structure/molecular formula	Trigger for relevance assessment	
Oxathiapiroline	IN-RDT31		Max PEC _{gw}	<0.001 µg/L
			Based on:	All models and all scenarios
Oxathiapiroline	IN-RAB06		Max PEC _{gw}	<0.001 µg/L
			Based on:	All models and all scenarios
Oxathiapiroline	IN-QPS10		Max PEC _{gw}	<0.001 µg/L
			Based on:	All models and all scenarios
Oxathiapiroline	IN-E8S72		Max PEC _{gw}	<3.11 µg/L
			Based on:	FOCUS PEARL v4.4.4 / Hamburg scenario; cabbage, 2 x 12 g a.s./ha

6.4.2.1 Relevance assessment of the oxathiapiroline metabolite IN-E8S72

The relevance of the groundwater metabolite IN-E8S72 has already been assessed and the assessment agreed at EU level (see Oxathiapiroline, EFSA Journal 2016;14(7):4504), and the relevance assessment is applicable as well for the GAP and groundwater scenarios considered in this dRR (i.e., the conclusions reached at Step 4 and 5 of the relevance assessment made at the EU-level are valid also with regard to the PEC_{GW} calculated for the GAP and groundwater scenarios considered in this dRR). IN-E8S72 is not considered relevant according to the criteria laid down in the EC guidance document SANCO/221/2000 – rev.10. A summary of the relevance assessment is provided in Chapter 10.3 of dRR Part B, Section 10.

The following table summarises the studies conducted with metabolite IN-E8S72, which have been evaluated in the Oxathiapiroline DAR (**Oxathiapiroline Volume 3 – Annex B.6 (AS) 2015**).

Table 6.4-3: Summary of the results of toxicity studies for IN-E8S72

Type of test, species (Guideline)	Result	Acceptability	Reference*
Ames test (OECD 471)	Non-genotoxic	Yes	DuPont-35559*
Gene mutation test in mammalian cells	Positive	Yes	DuPont-35560*
In vitro chromosome aberration	Non-genotoxic	Yes	DuPont-35561*
In vivo micronucleus	Non-genotoxic	Yes	DuPont-36720*
28-day feeding study in rats	NOAEL 1157 mg/kg bw/day	Yes	DuPont-35562*

* indicates that a study was reviewed at EU level

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in A22773A are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in A22773A

	Azoxystrobin		Oxathiapiprolin	
	Value	Reference	Value	Reference
Concentrate (AZT 250 g/L, OXTP 12 g/L)	0.42%	New study reported in Appendix 2	0.19%	New study reported in Appendix 2
Dilution 1 (AZT 0.167 g/L, OXTP 0.008 g/L)	3.3%	New study reported in Appendix 2	4.6%	New study reported in Appendix 2
Dilution 2 (AZT 0.076 g/L, OXTP 0.0036 g/L)	4.6%	New study reported in Appendix 2	5.8%	New study reported in Appendix 2

6.5.1 Justification for proposed values - Azoxystrobin

Proposed dermal absorption rates for Azoxystrobin are based on a dermal absorption study conducted with the current product. The study results are summarized in the following table. Full summaries of the study on the dermal absorption of Azoxystrobin/A22773A are described in detail in Appendix 2.

Table 6.5-2: Summary of the results of submitted dermal absorption studies for Azoxystrobin

Test	Concentrate (250 g/L)	Spray dilution (0.167 g/L)	Spray dilution (0.076 g/L)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	0.42%	3.3%	4.6%	A22773A	Yes	Not required	n/a	Dickson, L and Ogunrinola, D, 2021, VV-912717

* indicates that a study was reviewed at EU level

6.5.2 Justification for proposed values - Oxathiapiprolin

Proposed dermal absorption rates for Oxathiapiprolin are based on a dermal absorption study conducted with the current product/formulation. The study results are summarized in the following table. Full summaries of the study on the dermal absorption of Oxathiapiprolin/A22773A are described in detail in Appendix 2.

Table 6.5-3: Summary of the results of submitted dermal absorption studies for Oxathiapiprolin

Test	Concentrate (12 g/L)	Spray dilution (0.008 g/L)	Spray dilution (0.0036 g/L)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	0.19%	4.6%	5.8%	A22773A/Orondis Evo	Yes	Not required	n/a	Dickson, L and

Test	Concentrate (12 g/L)	Spray dilution (0.008 g/L)	Spray dilution (0.0036 g/L)	Formulation in study	Acceptability of study	Justification provided on representativity of study formu- lation for cur- rent product	Acceptability of justifica- tion	Reference*
								Ogunrinola, D, 2021, VV-912717

* indicates that a study was reviewed at EU level

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Table 6.6-1: Product information and toxicological reference values used for exposure assessment

Product name and code	A22773A	
Formulation type	Suspension Concentrate (SC)	
Category	Fungicide	
Active substance(s) (incl. content)	Azoxystrobin 250 g/L	Oxathiapiprolin 12 g/L
AOEL systemic	0.2 mg/kg bw/d ¹	0.04 mg/kg bw/d ²
Inhalation absorption	100%	100%
Oral absorption	80%	30%
Dermal absorption	Concentrate: 0.42% (250 g/L) Dilution (1 in 1500): 3.3% (0.167 g/L) Dilution (1 in 3300): 4.6% (0.076 g/L)	Concentrate: 0.19% (12 g/L) Dilution (1 in 1500): 4.6% (0.008 g/L) Dilution (1 in 3300): 5.8% (0.0036 g/L)

6.6.1 Selection of critical use(s) and justification

The critical GAPs used for the exposure assessment of the plant protection product are shown in Table 6.1-4. A list of all intended uses within the zone is given in Part B, Section 0.

The GAP for leafy vegetables and fruiting vegetables for SEU countries presents a split option on drained soils and non-drained soils, driven by the environmental fate assessment. For human safety exposure assessment, the GAP for non-drained soils was selected, as it is the most critical. This matches the GAP for CEU countries. GAP for drained soil is covered by assessment on non-drained soil GAP.

Justification

For operators, the critical GAP is dependent on the amount of product handled and the application method. A22773A is to be applied to indoor cucumber and peppers using hand-held sprayers:

- The critical GAP for cucumber also covers uses on crops which are commonly sprayed downward (LCHH): cucurbits (gherkin, melon, pumpkin, squash, watermelon, zucchini) and leafy vegetables (lettuce, salad plants, garden purslane, spinach and similar leaves, sweet basil).
- The critical GAP for pepper also covers uses on other fruiting vegetables (tomato, eggplant, okra) grown vertically on trellis which are sprayed upward manually only (HCHH) as per common agricultural practice.

The application methods identified for the critical GAPs are considered suitable to cover the variability of vertical-high crop and horizontal-low crop spraying for the intended uses of A22773A.

The critical GAP has been defined for these uses based on the highest amount of active substance applied.

¹ Conclusion on the peer review of the pesticide risk assessment of the active substance azoxystrobin, EFSA Journal 2010; 8(4):1542

² Peer review of the pesticide risk assessment of the active substance oxathiapiprolin European Food Safety Authority, EFSA Journal 2016;14(7):4504

For workers, the critical GAP depends on the task being carried out (i.e. the amount of contact between the worker and the crop), the time taken, the amount of product applied and where more than one treatment is applied, the length of the interval between treatments. The relevant re-entry scenario for application of A22773A to cucumber and peppers are handling/hand harvesting.

A22773A is to be applied in greenhouses. Therefore, bystander / resident exposure is normally considered to be negligible, however an assessment of the possible bystander / resident exposure has been included using an approach adopted by the Netherlands using the Lee Side turbulence model.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

<p>Comments of izRMS:</p>	<p>NDE calculations performed by the applicant are acceptable and zRMS agrees to the conclusions.</p> <p>The risk for operators is acceptable under conditions of intended uses and considering below mentioned risk mitigation measures such as: Work wear (arms, body and legs covered) plus PPE: gloves during M, L and A.</p> <p>Hand-held application indoors to low crops –cucumber:</p> <p>1) Spray application indoor (Southern European Glasshouse Model; 75th percentile) Low crop, standard; Body weight: 60 kg: Work wear (arms, body and legs covered) M/L and A</p> <p>2) Spray application indoor (Southern European Glasshouse Model; 75th percentile) Low crop, intensive; Body weight: 60 kg: Work wear (arms, body and legs covered) M/L and A</p> <p>3) Spray application indoor (Dutch Greenhouse Model); Body weight: 60 kg: Work wear (arms, body and legs covered) M/L and A</p> <p>Hand-held application indoors to high crops – peppers:</p> <p>1) Spray application indoor; (Southern European Glasshouse Model; 75th percentile) High crop, standard; Body weight: 60 kg: Work wear (arms, body and legs covered) M/L and A</p> <p>2) Spray application indoor (Southern European Glasshouse Model; 75th percentile) High crop, intensive; Body weight: 60 kg: Gloves for mixing/loading and gloves and impermeable coveralls for application</p>
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A summary of the exposure models used for estimation of operator exposure to the active substances during application of A22773A according to the critical use(s) is presented in Table 6.6-2. The outcome of the estimation is presented in

Table 6.6-3 (longer term exposure). Detailed calculations are in 0.

At this time, no acute AOELs have been set for azoxystrobin and oxathiapiprolin. Consequently, no acute risk assessment has been provided for these active substances.

Indoor foliar spray application is applied using hand-held sprayers (including trolley/pipe-train sprayer), automated sprayers and tractor. For applications using automated sprayers, there is no operator interaction during spray application and therefore operator exposure only occurs during mixing and loading. Operator exposure through tractor mounted sprayers is expected to be no more than application through hand-held

sprayers and therefore the risk assessment for hand-held sprayers provides a worst-case scenario for each application method.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Protected cucumber (max.1 L product/ha) Protected pepper (max. 1 L product/ha) The maximum application volume is 1500 L/ha for pepper, equivalent to 0.167 g azoxystrobin/L and 0.008 g oxathiapiprolin/L. The most relevant dermal absorption for the dilution is 3.2% and 4.5% for azoxystrobin and oxathiapiprolin, respectively for the worst-case scenario. These dermal absorption values are also applicable to the lower water volumes of 1000L/ha and 800L/ha which are represented in the GAP for other crops (cucurbits including cucumber presented below, solanaceae, leafy vegetables).
Model(s)	Dutch Greenhouse model [Dutch model for manual application in glasshouses. van Hemmen, 1992; van Golstein Brouwers <i>et al.</i> , 1996; Snippe R J <i>et al.</i> , 2002] Southern European Glasshouse Model Greenhouse model v_2.1 (20101223) with Southern European Greenhouse Model Overview. Members of the European Crop Protection Association. Occupational & Bystander Exposure Expert Group. October 2010 (Revision 9). ECPA, European Crop Protection Association, aisle 6, Avenue E. Van Nieuwenhuysse, B-1160 Brussels, Belgium.

Table 6.6-3: Estimated operator exposure (longer term exposure)

Table 6.6-3: Estimated operator exposure (longer term exposure)					
		Azoxystrobin		Oxathiapiprolin	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AAOEL	Total absorbed dose (mg/kg/day)	% of systemic AAOEL
Hand-held application indoors to low crops –cucumber					
Application rate		0.25 kg a.s./ha		0.012 kg a.s./ha	
Spray application indoor (Dutch Greenhouse Model) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.0317	15.8	0.002	5.1
	Work wear (arms, body and legs covered) and gloves M/L and A	0.0069	3.5	0.00038	0.96
Spray application indoor (Southern European Glasshouse Model; 75 th percentile) Low crop, standard Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.0027	1.4	0.00015	0.4
Spray application indoor (Southern European Glasshouse Model; 75 th percentile) Low crop, intensive Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.052	26.1	0.0034	8.4
Hand-held application indoors to high crops – peppers					
Application rate		0.25 kg a.s./ha		0.012 kg a.s./ha	
Spray application indoor (Dutch Greenhouse Model) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	Model prediction not given. This will be identical to that given for use on low crops as the Dutch greenhouse model covers applications made to high and low crops using hand-held equipment.			

Spray application indoor (Southern European Glasshouse Model; 75 th percentile) High crop, standard Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.0088	4.4	0.00053	1.3
Spray application indoor (Southern European Glasshouse Model; 75 th percentile) High crop, intensive Body weight: 60 kg	Gloves for mixing/loading and gloves and impermeable coveralls for application	0.004	2.0	0.0002	0.5

6.6.2.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and consideration of the above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

6.6.3 Worker exposure (KCP 7.2.3)

6.6.3.1 Estimation of worker exposure

Comments of izRMS:	<p>NDE calculations performed by the applicant are acceptable and zRMS agrees to the conclusions.</p> <p>Exposure for workers (entry into a previously treated area or handling a crop according to the critical uses) is acceptable under conditions of intended uses considering below mentioned risk mitigation measures such as: Work wear, (arms, body and legs covered) plus PPE: gloves are used.</p> <p>Hand-held application indoors – cucumber and pepper: (EFSA Model; 75th percentile): Work wear (arms, body and legs covered) (TC: 2500 cm²/person/h)</p>
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Table 6.6 4 shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with A22773A according to the critical uses. Outcome of the estimation is presented in

Table 6.6-5 (longer term exposure). Detailed calculations are in 0.

At this time, no acute AOELs have been set for azoxystrobin and oxathiapiprolin and as there is no available model within the EFSA re-entry model for assessing acute exposure, an acute risk assessment for re-entry workers has not been performed.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	Protected cucumber (max. 2 × 1 L product/ha) Protected pepper (max. 2 × 1 L product/ha) The maximum application volume is 1500 L/ha, equivalent to 0.167 g azoxystrobin/L and 0.008 g oxathiapiprolin/L. The most relevant dermal absorption for the dilution is 3.3% and 4.6% for azoxystrobin and oxathiapiprolin, respectively for the worst-case scenario.
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 calculator version: 30/03/2015

Table 6.6-5: Estimated worker exposure (longer term exposure)

		Azoxystrobin		Oxathiapiprolin	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Hand harvesting cucumber and peppers Indoor Work rate: 8 hours/day, DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 7 days					
Number of applications and application rate		2 × 0.25 kg a.s./ha		2 × 0.012 kg a.s./ha	
Body weight: 60 kg	Potential TC: 5800 cm ² /person/h	0.035	17.7	0.0024	5.93
	Work wear (arms, body and legs covered) TC: 2500 cm ² /person/h	0.015	7.63	0.001	2.55
	Work wear (arms, body and legs covered) and gloves TC: 580 cm ² /person/h	0.0035	1.77	0.00024	0.59

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

6.6.3.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mention PPE, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

Comments of iZ RMS:	The currently enforced guidance on the assessment of exposure of operators, workers, residents and bystanders (EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874) considers the exposure to resident and bystander negligible following application in greenhouses. To this date it is therefore not necessary to cover the risks to resident and bystander for greenhouse uses. However, a pragmatic approach exists: the Lee Side Turbulence model which has been adopted by Ctgb NL: https://english.ctgb.nl/documents/assessment-framework-ppp/2016/10/27/calculation-model-resident-lee-side-turbulence-model . This model is based on actual emissions data that has been measured out of a greenhouse. iZ RMS agree with applicant position that discussed (see above) model was deemed as it is based on actual data and doesn't rely on overconservative approaches. The data shows
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	<p>the inherent nature of a greenhouse structure to be protective and a great barrier to limit exposure to resident and bystander, as opposed to field application where no protection is available to people nearby. The tiered approach is pragmatic and help prove negligible exposure for formulations that have low risks of exposure.</p> <p>In the case of Orondis EVO/ A22773A, the first-tier risk assessment of the Lee side turbulence model for azoxystrobin and oxathiapiprolin shows a ratio ADI/ application rate well above 2.14, therefore there is no need to use the 2nd tier risk assessment. The results demonstrate that the risk to residents and bystanders is very low and well within acceptable limits.</p>
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A22773A is to be applied in greenhouses. Therefore, bystander / resident exposure is normally considered to be negligible. The Netherlands consider that it may be possible for active substances to be released from greenhouses. Therefore, an assessment of the possible bystander / resident exposure has been included using an approach adopted by the Netherlands.

At this time, no acute AOELs have been set for azoxystrobin and oxathiapiprolin. Consequently, no acute risk assessment has been provided for these active substances.

Table 6.6-6: Exposure models for intended uses

Critical use	Foliar application to cucumber and pepper (1 L product/ha)
Model	Lee Side turbulence model ((Lijwervel model)). Duyzer, J., van der Staay, M., Weststrate, H., Boertjes, B., Hollander, K. and Verhagen, H., 2004. De blootstelling van omwonenden van kassen aan gewasbeschermingsmiddelen via de lucht. TNO-rapport, R 2004/517: 72 pp.

The Netherlands require an assessment of bystander and resident exposure to be carried out according to Duyzer *et al* (2004). The emission of Plant Protection Products out of greenhouses can lead to transiently increased concentrations of the active substance in the air in the vicinity of the greenhouse. The concentration of the active substance outside the greenhouse during and after application is dependent on several factors, such as physical chemical properties of the active substance, the application method used, specific characteristics of the greenhouse, the position of the greenhouse to other buildings and climatological conditions.

As a worse case the Lee Side turbulence model estimates the acute exposure of persons outside a greenhouse at a distance of 20 m over 24 hours. The concentration at the lee side of the greenhouse will decrease only very slightly over the first 20-30 meters.

The model considers 5 scenarios dependant on application techniques:

1. Volatility > 10 mPa, independent of application technique.
2. Low Volume Misting (LVM) (volatility between 0.01 and 10 mPa)
3. High volume techniques (volatility between 0.01 and 10 mPa)
4. Low volume techniques (volatility between 0.01 and 10 mPa)
5. Volatility < 0.01 mPa, independent of application technique

In line with the recommendations given in the Lee Side Turbulence model (Lijwervel model), estimates of exposure are to be compared to the substances ADI. The ADI of azoxystrobin is 0.2 mg/kg bw/day¹ and oxathiapiprolin is 0.14 mg/kg bw/day².

It is firstly assumed that if the ADI (in µg/kg bw/day) divided by the application rate (in kg a.s./ha) is > 2.14 then safe use can be demonstrated for each scenario when considering exposure to bystanders positioned near a glasshouse.

	Azoxystrobin	Oxathiapiprolin
Exposure ratio	$= \frac{\text{ADI } (\mu\text{g/kg bw/day})}{\text{Application rate (kg a.s./ha)}}$	
Exposure ratio	$= \frac{200 \mu\text{g/kg bw/day}}{0.25 \text{ kg a.s./ha}}$	$= \frac{140 \mu\text{g/kg bw/day}}{0.012 \text{ kg a.s./ha}}$
Exposure ratio	800	11667

Assuming an application of 0.25 kg azoxystrobin/ha and 0.012 kg oxathiapiprolin/ha, no protection from clothing and 100% inhalation, retention and absorption of potential inhalation exposure (PIE), the estimated bystander exposure ratio is > 2.14 which demonstrates risk to bystanders and residents are within acceptable levels.

6.6.4.2 Measurement of resident and/or bystander exposure

Since the estimated bystander exposure carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses, a study to provide bystander and/or resident exposure was not necessary and was therefore not performed.

6.6.5 Combined exposure

6.6.5.1 Exposure assessment of azoxystrobin and oxathiapiprolin in A22773A

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL is converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-7: Risk assessment from combined exposure (longer term exposure)

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Operators – NL Greenhouse model. Low and high crop scenario. No PPE	Azoxystrobin	0.158
	Oxathiapiprolin	0.051
	Cumulative risk operators (HI)	0.209
Operators – SEGM low crop, standard. No PPE	Azoxystrobin	0.014
	Oxathiapiprolin	0.004
	Cumulative risk operators (HI)	0.018
Operators – SEGM low crop, intensive. No PPE	Azoxystrobin	0.261
	Oxathiapiprolin	0.084
	Cumulative risk operators (HI)	0.345
Operators – SEGM high crop, standard. No PPE	Azoxystrobin	0.044
	Oxathiapiprolin	0.013
	Cumulative risk operators (HI)	0.057
Operators – SEGM high crop, intensive. Gloves M/L and gloves and coveralls A	Azoxystrobin	0.020
	Oxathiapiprolin	0.005
	Cumulative risk operators (HI)	0.025

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Workers – hand harvesting with standard workwear.	Azoxystrobin	0.076
	Oxathiapiprolin	0.026
	Cumulative risk workers (HI)	0.102
Workers – hand harvesting with standard workwear and gloves.	Azoxystrobin	0.0177
	Oxathiapiprolin	0.0059
	Cumulative risk workers (HI)	0.0236

The Hazard Index is < 1. Thus, combined exposure to all active substances in A22773A is not expected to present a risk for operators, workers, residents and bystanders. No further refinement of the assessment is required.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP 7.1.1	xxxxxx	11/02/2021	Azoxystrobin/Oxathiapiprolin SC (A22773A) - Acute Oral Toxicity Study in Rats (Up and Down Procedure) Report No. 20/130-001P Document No. VV-892044 Test Facility xxxxxx GLP Unpublished	Y	SYN
KCP 7.1.2	xxxxxx	09/07/2021	Azoxystrobin/Oxathiapiprolin SC (A22773A) – Acute Dermal Toxicity Study in Rats Report No. 20/130-002P Document No. VV-910770 Test Facility xxxxxx GLP Unpublished	Y	SYN
KCP 7.1.3	xxxxxx	23/04/2021	Azoxystrobin/Oxathiapiprolin SC (A22773A) – Acute Inhalation Toxicity Study (Nose-Only) in Rats Report No. 20/130-004P Document No. VV-899756 Test Facility xxxxxx GLP Unpublished	Y	SYN
KCP 7.1.4	xxxxxx	11/03/2021	Azoxystrobin/Oxathiapiprolin SC (A22773A) - Primary Skin Irritation Study in Rabbits Report No. 20/130-006N Document No. VV-895236 Test Facility xxxxxx GLP Unpublished	Y	SYN

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP 7.1.4	xxxxxx	13/05/2021	Azoxystrobin/Oxathiapiprolin SC (A22773A) – In Vitro Skin Irritation Test in the EPISKIN™ Model Report No. 20/130-043B Document No. VV-902652 Test Facility xxxxxx GLP Unpublished	N	SYN
KCP 7.1.5	xxxxxx	22/03/2021	Azoxystrobin/Oxathiapiprolin SC (A22773A) - Acute Eye Irritation Study in Rabbits Report No. 20/130-005N Document No. VV-896673 Test Facility xxxxxx GLP Unpublished	Y	SYN
KCP 7.1.5	xxxxxx	12/05/2021	Azoxystrobin/Oxathiapiprolin SC (A22773A) – In Vitro Eye Irritation Test in Isolated Chicken Eyes Report No. 20/130-038CS Document No. VV-902426 Test Facility xxxxxx GLP Unpublished	N	SYN
KCP 7.1.6	xxxxxx	20/10/2020	Azoxystrobin/Oxathiapiprolin SC (A22773A) – Skin Sensitisation Local Lymph Node Assay Report No. 2119600 Document No. VV-876976 Test Facility xxxxxx GLP Unpublished	Y	SYN
KCP 7.3	Dickson, L. Ogunrinola, D.	15/07/2021	Azoxystrobin/Oxathiapiprolin SC (A22773A) - The In Vitro Percutaneous Absorption of Radiolabelled Azoxystrobin and Radiolabelled Oxathiapiprolin in Concentrate Formulation and Two In-Use Dilutions Through Human Split-Thickness Skin Report No. 787332 Document No. VV-912717 Test Facility Charles River Laboratories Edinburgh, Ltd. GLP Unpublished	N	SYN

List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
-	-	-	-	-	-

List of data submitted by the applicant and not relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
-	-	-	-	-	-

List of data relied on not submitted by the applicant but necessary for evaluation

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
-	-	-	-	-	-

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Acute Toxicity Estimate (ATE) and Additivity calculations have been conducted and are provided in the Part C document. Syngenta has also conducted acute toxicity studies on the formulation as at the time of the initial registration these studies were required for registration in Russia, Ukraine, Belarus, and Israel. The data from these studies has been used to populate the safety data sheet, therefore classification proposals may vary between the ATE calculation approach and the safety data sheet. It is Syngenta's approach to base the product classification on the animal data. Summaries of the acute toxicity studies are included in this document

Comments of izRMS:	<i>In vivo</i> studies submitted by the applicant to support registration of the product A22773A has been conducted on the same formulation thus bridging approach is not applicable for this registration process. Due to the fact that zRMS PL accept all <i>in vivo</i> studies as background to hazard assessment, that is why mentioned above by the applicant Acute Toxicity Estimate (ATE) and Additivity calculations has not been taken into account in the final conclusions regarding toxicity potential by the zRMS PL.
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A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of izRMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol. The OECD 425 procedure implements the 3R rules thus study is in line with the suggestions of point 5 of Regulation 284/2013. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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A 2.2.1 Study 1

Reference	KCP 7.1.1
Report	Azoxystrobin/oxathiapiprolin SC (A22773A)- Acute Oral Toxicity Study in Rats (Up and Down Procedure). xxxxxx 2020 20/130-001P, VV-892044
Guideline(s)	Yes. Acute Oral Toxicity (rat): OECD Test Guideline 425 (2008): EPA OPPTS 870.1100 (2002)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A22773A/Orondix Evo (SFI003-174-001)
Species	Rat, CrI:WI
No. of animals (group size)	5 rats (female)

Dose(s)	2000 mg/kg bw
Exposure	Once by gavage
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of A22773A/Orondis Evo

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD₅₀ (mg/kg bw) (14 days)
Female rats				
2000	0/3/5	Day 1	Day 14	> 2000

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

Table A 2: Summary of findings of acute oral toxicity study in rats of A22773A/Orondis Evo

Mortality	No mortality occurred.
Clinical signs	Yes. Hunched back (3/5 animals) was observed from 1 hour after treatment until 3 hours after treatment or at 6 hours after treatment. From Day 1 all animals were symptom free.
Body weight	Reduced (e.g. significantly reduced between days xxx and xxx) / Body weight gain was considered to be normal.
Macroscopic examination	The necropsies performed at the end of the study revealed no apparent findings. / Apparent abnormalities in xxx animals (if yes, describe kind of abnormalities)

Conclusion

Under the experimental conditions, the oral LD₅₀ of A22773A/Orondis Evo is higher than 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.3 Acute percutaneous (dermal) toxicity (KCP 7.1.2)

Comments of iZ RMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. OECD 402 procedure is still valid and acceptable. Noted deviation from the study protocol has no impact on the final outcome of the study. Results of the study and conclusions are reliable for risk assessment and classification purpose. Study accepted.
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A 2.3.1 Study 1

Reference:	KCP 7.1.2/01
Report	Azoxystrobin/Oxathiapiprolin SC (A22773A) - Acute Dermal Toxicity Study in Rats, xxxxxx 2021 Report No. 20/130-002P VV-910770
Guideline(s):	OECD 402 (2017); EPA 870.1200 (1998); EC No. 440/2008 (2008)
Deviations:	Due to technical error, humidity value (maximum of 80%) outside the expected range of 30-70% was recorded during the study. This deviation has no effect on the outcome of the study.
GLP:	Yes
Acceptability:	Yes

Duplication No
(if vertebrate study)

Materials and methods

Test material (Lot/Batch No.)	A22773A/ Orondis Evo (SFI003-174-001)
Species	Rat, CrI:WI
No. of animals (group size)	3 rats/female
Dose(s)	2000 mg/kg bw
Exposure	24 hours (dermal, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 3: Results of acute dermal toxicity study in rats of A22773A/Orondis Evo

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD ₅₀ (mg/kg bw) (14 days)
Female rats				
2000	0/0/3	-	Day 14	>2000

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

Table A 4: Summary of findings of acute dermal toxicity study in rats of A22773A/Orondis Evo

Mortality:	No mortality occurred.
Clinical signs:	No clinical signs of toxicity were observed.
Body weight:	Body weight gain was considered to be normal.
Macroscopic examination:	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the dermal LD₅₀ of A22773A/Orondis Evo is higher than 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of iZ RMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 403 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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A 2.4.1 Study 1

Reference KCP 7.1.3
Report Azoxystrobin/oxathiapiprolin SC (A22773A) – Acute Inhalation Toxicity Study (Nose-Only) in Rats.
xxxxxx 2021
20/130-004P, VV-899756
Guideline(s) Yes.

Acute Inhalation Toxicity (rat): OECD 403 (2009); EPA 870.1300 (1998); EC 440/2008, B.2 (2008).

Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A22773A / Orondis Evo (SFI003-174-001)
Species	Rat, CrI: (WI) Wistar
No. of animals (group size)	10 rats (5 male & 5 female)
Concentration(s)	2.14 mg/L air
Exposure	4 hours (nose only)
Vehicle/Dilution	50% (w/w) aqueous formulation
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 5: Concentration(s) and exposure conditions

Group	Maximum achievable mean concentration (mg/L air)	Mean Mass Median Aerodynamic Diameter MMAD * (µm)	Geometric Standard Deviation GSD ** (µm)
0.1 (sighting exposure)	2.41	3.24	2.03
1 (main study)	2.14	3.21	2.06

* MMAD = Mass Median Aerodynamic Diameter

** GSD = Geometric Standard Deviation

Table A 6: Results of acute inhalation toxicity study in rats of A22773A / Orondis Evo

Concentration (mg/L air)	Toxicological results *	Duration of signs	Time of death	LC ₅₀ (mg/L air) (14 days)
Male rats				
2.14	*/x/5 0/5/5	*** from Day 0 up to Day 3. All male animals were symptom-free from Day 4	*** Not applicable	> 2.14
Female rats				
2.14	*/x/5 0/5/5	*** from Day 0 up to Day 2. All male animals were symptom-free from Day 3	*** Not applicable	> 2.14

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

Table A 7: Summary of findings of acute inhalation toxicity study in rats of A22773A / Orondis Evo

Mortality	No mortality occurred.
Clinical signs	<p><i>Group 0.1 (Sighting Exposure – 2.41 mg/L)</i> In the male animals, decreased activity (1/2) (slight), laboured respiration (2/2) (slight to moderate), noisy respiration (2/2) (slight to moderate), red-brown staining (on the head and on the nose) and wet fur (on the whole body) were observed from Day 0 up to Day 1. All male animals were symptom-free from Day 2.</p> <p>In the female animals, laboured respiration (2/2) (slight to moderate), noisy respiration (2/2) (moderate), red-brown staining (on the head) and wet fur (on the whole body) were observed from Day 0 up to Day 1. All female animals were symptom-free from Day 2.</p> <p><i>Group 1 (Main Exposure – 2.14 mg/L)</i> In the male animals, laboured respiration (5/5) (slight to moderate), noisy respiration (5/5) (slight), red-brown staining (on the head) and wet fur (on the whole body) were observed from Day up to Day 3. All male animals were symptom-free from Day 4.</p> <p>In the female animals, laboured respiration (5/5) (slight to moderate), noisy respiration (5/5) (slight), red-brown staining (on the head) and wet fur (on the whole body) were observed from Day up to Day 2. All male animals were symptom-free from Day 3.</p> <p>Wet fur and red-brown staining (as chromodacryorrhea) in the animals were considered to be related to the restraint and exposure procedures or discomfort of the animals but not to be toxicologically significant.</p>
Body weight	<p><i>Group 0.1 (Sighting Exposure – 2.41 mg/L)</i> In the male animals, slight body weight losses were noted on Day 0-3. The body weight gain was normal from Day 3.</p> <p>In the female animals, slight body weight losses were noted on Day 0-3. The body weight gain was normal from Day 3.</p> <p><i>Group 1 (Main Exposure – 2.14 mg/L)</i> In the male animals, slight body weight losses were noted on Day 0-1. The body weight gain was normal from Day 3.</p> <p>In the female animals, slight body weight losses were noted on Day 0-3. The body weight gain was normal from Day 3.</p>
Macroscopic examination	<p><i>Group 1 (Main Exposure – 2.14 mg/L)</i> There was no evidence of any test item-related internal changes in animals at a dose level of 2.14 mg/L (with particle size at 1 to 4 µm) at necropsy.</p>

Conclusion

Under the experimental conditions, no mortality occurred in a group of ten rats and the inhalation LC₅₀ of A22773A / Orondis Evo was higher than 2.14 mg/L (maximum achievable mean concentration) air in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of izRMS:	<p>As we mentioned in the preface to this report zRMS PL recognized this <i>in vitro</i> study as a not applicable for agrochemicals:</p> <p>TG OECD 439 rev. 14 June 2021 INITIAL CONSIDERATIONS AND LIMITATIONS Subsection 8: p.2 (..) <i>data indicates a lack of applicability of the RhE based in vitro skin irritation test for agrochemical formulations</i> (47). (..)</p> <p>See also: Kolle S.N, van Ravenzwaay B. and Landsiedel R. (2017). Regulatory accepted but out of domain: In vitro skin irritation tests for agrochemical formulations. Regul. Toxicol. Pharmacol 89, 125-130.</p> <p>Thus for this end point “Skin irritation” Reviewer consider an <i>in vivo</i> study A.2.5.2 xxxxx, 2020 20/130-006N, VV-895236 as background for hazard and risk assessment.</p>
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A 2.5.1 Study 1 (*in-vitro*)

Reference	KCP 7.1.4
Report	<p>Azoxystrobin/Oxathiapiprolin SC (A22773A) – In Vitro Skin Irritation Test in the EPISKINTM Model, xxxxxxx, 2021</p> <p>20/130-043B, VV-902652</p>

Guideline(s)	OECD 439 (2020), EC No 440/2008, B.46 (2008)
Deviations	No
GLP	Yes
Acceptability	No

Materials and methods

For this test to be considered valid the following validity criteria need to be met.

The mean OD value of the three negative control tissues should be between 0.6 and 1.5, and the standard deviation value (SD) of the % viability values should be ≤ 18 .

The acceptable mean percentage viability range for positive controls is 0-40% and the standard deviation value (SD) of the % viability values should be ≤ 18 .

The SD calculated from individual % tissue viability values of the three test item treated replicates should be <18 .

The mean OD value of the blank samples (acidified isopropanol) should be <0.1 .

Test material (Lot/Batch No.)	Azoxystrobin/oxathiapiprolin SC (A22773A)
Test system	EpiSkin™ Small Model
No. of replicate wells	3 units
Test item application	10 µL
Test exposure time	15 minutes at room temperature
Vehicle/dilution	None
Remarks	None

Results and discussions

Table A 8: Optical Density (OD) and the Calculated Relative Viability % of the Samples

Substance	Optical Density (OD)			Viability (% RV)	Standard Deviation (SD)
		Measured	Blank corrected		
Negative Control: Phosphate buffered saline	1	1.269	1.223	96.0	--
	2	1.306	1.260	98.9	--
	3	1.385	1.340	105.1	--
	mean	--	1.275	100.0	4.7
Positive Control: 5% (w/v) SDS solution	1	0.156	0.110	8.7	--
	2	0.095	0.049	3.9	--
	3	0.266	0.221	17.3	--
	mean	--	0.127	10.0	6.8
Test Item: Azoxystrobin/oxathiapiprolin SC (A22773A)	1	1.441	1.395	109.5	--
	2	1.413	1.367	107.3	--
	3	1.290	1.244	97.6	--
	mean	--	1.336	104.8	6.3

Notes:

- Mean blank value was 0.045.
- Optical density means the mean value of the duplicate wells for each sample (rounded to three decimal places)
- The mean optical density of NSC_{living} was 0.008, non-specific colour percent was calculated as 0.6%. This value was below 5%, therefore an additional data calculation to account for non-specific colouring was not necessary.

All the parameters met the acceptability criteria, therefore the study was considered to be valid.

Criteria for In Vitro interpretation	Classification
	UN GHS
Mean tissue viability % is \leq 50 %	Category 2 or Category 1
Mean tissue viability % is $>$ 50 %	Non-Irritant*

* Note: If there is clear evidence that the test item is not corrosive, then it can be determined as No Category according to the UN GHS. It is plausible that some weaker corrosives could be classified as non-irritant in this *in vitro* assay.

Conclusion

In conclusion, under the conditions of this *in vitro* EpiSkin™ irritation assay conducted on azoxystrobin/oxathiapiprolin SC (A22773A), the results indicate that the test item is non-irritant to skin.

Comments of izRMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 404 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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A 2.5.2 Study 2 (*n-vivo*)

Reference	KCP 7.1.4
Report	Azoxystrobin/oxathiapiprolin SC (A22773A) - Primary Skin Irritation Study in Rabbits. xxxxxx 2020 20/130-006N, VV-895236
Guideline(s)	Yes. Acute Skin Irritation (rabbit) OECD 404 (2015); OPPTS 870.2500 (1998); EC No 440/2008, B.4 (2008).
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A22773A / Orondis Evo (SFI003-174-001)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 (male)
Initial test using one animal	Yes
Exposure	0.5 mL (4 hours, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	3 days
Remarks	None

Results and discussions

Table A 9: Skin irritation of A22773A / Orondis Evo

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
3321	Erythema	0	0	0	0	0	-
	Oedema	0	0	0	0	0	-
3336	Erythema	0	0	0	0	0	-
	Oedema	0	0	0	0	0	-
3324	Erythema	0	0	0	0	0	-
	Oedema	0	0	0	0	0	-

* scores in the range of 0 to 4

Clinical signs:	No clinical signs of toxicity were observed.
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Conclusion

Under the experimental conditions, A22773A / Orondis Evo is not a skin irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of iZ RMS:	<p>As we mentioned in the preface to this report zRMS PL recognized this <i>in vitro</i> study as a not suitable for agrochemicals: TG OECD 438 rev. 25 June 2018 (..)The ICE test method is not recommended for the identification of test chemicals <u>that should be classified as irritating to eyes (i.e., UN GHS Category 2 or Category 2A) or test chemicals that should be classified as mildly irritating to eyes (UN GHS Category 2B) due to the considerable number of UN GHS Category 1 chemicals underclassified as UN GHS Category 2, 2A or 2B and UN GHS No Category chemicals overclassified as UN GHS Category 2, 2A or 2B. For this purpose, further information and if needed, additional testing with another suitable method may be required. (..).</u> Thus for this end point “eye irritation” Reviewer consider an <i>in vivo</i> study A.2.6.2 xxxxxx 2021 20/130-005N, VV-896673 as valid study for hazard and risk assessment.</p>
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A 2.6.1 Study 1 (*in-vitro*)

Reference	KCP 7.1.5
Report	<p>Azoxystrobin/Oxathiapiprolin SC (A22773A) – In Vitro Eye Irritation Test in Isolated Chicken Eyes xxxxxx, 2021 20/130-038CS VV-902426</p>
Guideline(s)	<p>Yes. OECD 438 (2013) EPA OPPTS 870.2400 (1998) EC No 440/2008, B.48 (2008)</p>
Deviations	No
GLP	Yes
Acceptability	No

Materials and methods

Test material (Lot/Batch No.)	Azoxystrobin/oxathiapiprolin SC (A22773A)
Species	Chicken eyes (COBB 500)
No. of eyes per group (group size)	Nine to Twelve
Test item application	30 µL (applied to the entire surface of the cornea)
Irrigation (time point)	Yes. Cornea surface was rinsed thoroughly with 20 mL physiological saline.
Vehicle/Dilution	None
Post exposure observation period	4 hours
Remarks	None

Results and discussions

Table A 10: Eye irritation of A22773A

Observation	Value	ICE Class*
Mean maximum corneal swelling at up to 75 min	-1.6%	I
Mean maximum corneal swelling at up to 240 min	-3.8%	I
Mean maximum corneal opacity change	0.83	II
Mean fluorescein retention change	0.50	I
Other Observations	Minimal amount of test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were not cleared at 240 minutes after the post-treatment rinse. The cornea surfaces were considered clean.	
Overall ICE Class	2xI 1xII	

* I = none, II = slight, III = moderate, IV = severe

Table A 11: Positive control 5 % (w/v) Benzalkonium chloride solution

Observation	Value	ICE Class*
Mean maximum corneal swelling at up to 75 min	9.4 %	II
Mean maximum corneal swelling at up to 240 min	22.2 %	III
Mean maximum corneal opacity change	4.00	IV
Mean fluorescein retention change	3.00	IV
Other Observations	None	
Overall ICE Class	1xIII 2xIV	

* I = none, II = slight, III = moderate, IV = severe

The positive control 5 % (w/v) Benzalkonium chloride solution was classified as severely irritating.

Table A 12: Negative control Physiological saline (Salsol solution, NaCl 0.9% w/v)

Observation	Value	ICE Class*
Mean maximum corneal swelling at up to 75 min	0.0%	I
Mean maximum corneal swelling at up to 240 min	-1.6%	I
Mean maximum corneal opacity change	0.00	I
Mean fluorescein retention change	0.00	I
Other Observations	None	
Overall ICE Class	3xI	

* I = none, II = slight, III = moderate, IV = severe

The negative control Physiological saline (Salsol solution, NaCl 0.9% w/v) was classed as non-irritating.

Table A 13: Assessment of the General In Vitro Eye Irritancy and Regulatory GHS Classification

UN GHS Classification	Combinations of the three ICE Classes
No Category	3xI 2xI, 1xII 2xII, 1xI
No prediction can be made	Other combinations
Category 1	3xIV 2xIV, 1xIII 2xIV, 1xII* 2xIV, 1xI* Corneal opacity ≥ 3 at 30 min (in at least 2 eyes) Corneal opacity = 4 at any time point (in at least 2 eyes) Severe loosening of epithelium (in at least 1 eye)

Morphological signs on the test item treated eyes	none
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Conclusion

Based on this *in vitro* eye irritation study on isolated chicken eyes with azoxystrobin/oxathiapiprolin SC (A22773A), the test item is non-irritant.

Comments of izRMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 405 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted. (for more explanations regarding acceptability of this study refer izRMS comment point A 2.6.1)
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A 2.6.2 Study 2 (*in-vivo*)

Reference	KCP 7.1.5/01
Report	Azoxystrobin/oxathiapiprolin SC (A22773A) - Acute Eye Irritation Study in Rabbits. xxxxxx 2021 20/130-005N, VV-896673
Guideline(s)	Yes. Acute Eye Irritation (rabbit) OECD Test Guideline 405 (2017), EPA 870.2400 (1998), EC No 2127/735, B.5 (2017) amending EC No 440/2008.
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A22773A / Orondis Evo (SFI003-174-001)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 (male)
Initial test using one animal	Yes
Exposure	0.1 (conjunctival sac of the left eye)
Irrigation (time point)	Physiological saline solution following fluorescein control: 24 hours after test item application as part of the fluorescein observation process.

Vehicle/Dilution	None
Post exposure observation period	3 days
Remarks	None

Results and discussions

Table A 14: Eye irritation of A22773A / Orondis Evo

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
4245	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	1	0	0	0	0	1
	Chemosis conjunctivae	0	0	0	0	0	-
4244	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	1	0	0	0	0	1
	Chemosis conjunctivae	0	0	0	0	0	-
4241	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	1	0	0	0	0	1
	Chemosis conjunctivae	0	0	0	0	0	-

* scores in the range of 0 to 4 for cornea opacity and chemosis, 0 to 3 for redness of conjunctivae and 0 to 2 for iritis

Clinical signs:	No clinical signs of toxicity were observed.
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Conclusion

Under the experimental conditions, A22773A / Orondis Evo is not an eye irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of iZ RMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 429 procedure is valid and acceptable. Study is in line with the suggestions of point 5 of Regulation 284/2013 and Annex VII to REACH REG (EC) No 1907/2006. Results of the study and conclusions are reliable for risk assessment and classification purpose. Study accepted.
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A 2.7.1 Study 1

Reference	KCP 7.1.6
Report	Azoxystrobin/Oxathiapiprolin SC (A22773A) – Skin Sensitisation Local Lymph Node Assay. xxxxxxx 2020 2119600, VV-876976
Guideline(s)	Yes. Skin Sensitisation Local Lymph Node Assay OECD 429 (2010)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A22773A/Orondis Evo (SFI003-174-001)
Species	Mouse, CBA/CaOlaHsd
No. of animals (group size)	Pre-test: 2 female mice Main Study: 16 female mice
Range finding	No
Exposure (concentration(s), no. of applications)	Topical induction - concentrations of 25 and 50% in 1% aqueous Pluronic®, or 100% (undiluted test substance)
Vehicle	1% aqueous Pluronic®
Pretreatment prior to topical application	No
Reliability check	α -hexyl cinnamaldehyde dissolved in acetone/olive oil (4+1 v/v)
Remarks	None

Results and discussions

Table A 15: Results of skin sensitisation study of A22773A/Orondis Evo

Test substance concentration	Group Calculation		
	Mean DPM per animal (2 lymph nodes) ^a	SD S.I.	SD S.I.
Vehicle Control Group (1% aqueous Pluronic®)	1189.8	561.8	1.0
25% Azoxystrobin/Oxathiapiprolin SC (A22773A)	1423.2	457.4	1.2
50% Azoxystrobin/Oxathiapiprolin SC (A22773A)	1183.5	189.7	1.0
100% Azoxystrobin/Oxathiapiprolin SC (A22773A)	1540.0	426.4	1.0

Mean DPM/animal was determined by dividing the sum of the measured values from lymph nodes of all animals within a group by the number of animals in that group (5 animals)

Clinical signs:	No clinical signs of toxicity were observed.
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Conclusion

Under the experimental conditions, A22773A/Orondis Evo is not a skin sensitiser. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.8 Supplementary studies for combinations of plant protection products (KCP 7.1.7)

Not relevant.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co-formulant

Information regarding material safety data sheets of the co-formulants can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.9.2 Available toxicological data for each co-formulant

Available toxicological data for each co-formulant can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.10 Studies on dermal absorption (KCP 7.3)

A 2.10.1 Study 1 – Azoxystrobin/Oxathiapiprolin in A22773A / Orondis Evo

Comparative dermal absorption, in vitro using rat and human skin

Comments of iZ RMS:	Study is considered to be acceptable and dermal absorption for a.s. azoxystrobin/oxathiapiprolin are covered by this study. DA values obtained from the study are reliable and can be used for risk assessment. Values of the tested doses and proposed ones in the GAP (applications rate, spray dilution) are comparable thus Pro-rata correction is not needed.
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Reference	KCP 7.3
Report	Azoxystrobin/Oxathiapiprolin SC (A22773A) - The In Vitro Percutaneous Absorption of Radiolabelled Azoxystrobin and Radiolabelled Oxathiapiprolin in Concentrate Formulation and Two In Use Dilutions Through Human Split Thickness Skin, Dickson, L., Ogunrinola, D., 2021, 787332, VV-912717
Guideline(s)	OECD 428 (2004)
Deviations	None
GLP	Yes
Acceptability	Yes

Materials and methods

Test material	Name (Batch No.)	[¹⁴ C]-Azoxystrobin (ATS-21-2046)
	Test preparation	radioformulation
	Specific activity	102.2 µCi/mg
	Radiochemical purity	99.6%
	Name (Batch No.)	[¹⁴ C]-Oxathiapiprolin (ZA0-175900-036)
	Test preparation	radioformulation
	Specific activity	48.0 µCi/mg
	Radiochemical purity	98.5%
Product	Name (Batch No.)	A22773A (SFI003-174-001)
	Alternative Name	Azoxystrobin/Oxathiapiprolin SC (250/012)
	Concentration a.s.	247 g/L Azoxystrobin and 11.2 g/L Oxathiapiprolin
Blank product	Name (Batch No.)	EXF16235A (SFI003-162-003)

Test system		
Diffusion cell	Cell type	Dynamic
	(if dynamic) Flow rate	1.5 mL/h ± 0.15 mL/h (0.75 mL/h ± 0.15 mL/h when testing [¹⁴ C]-Oxathiapiprolin in spray dilution 1 and 2)
	Exposed skin area	0.64 cm ²
	Cover	Not occluded
Membrane	Skin type	dermatomed
	Skin thickness range	360-400 µm
	Skin donors age	28-67
	Skin donors sex	M + F
	Location	Abdomen

	Source	ex vivo
	Integrity test	Electrical resistance (> 7.7 kΩ)
Receptor	Receptor medium	phosphate buffered saline containing polyoxyethylene 20 oleyl ether (PEG, ca 6%, w/v), sodium azide (ca 0.01%, w/v), streptomycin (ca 0.1 mg/mL) and penicillin (ca 100 units/mL), pH 7.30-7.46
	Solubility in receptor medium	Y
Sample Time	Exposure time	6 h
	Observation time	24 h
Sampling	Sample intervals	[¹⁴ C]-Azoxystrobin formulation concentrate, spray dilution 1 and spray dilution 2 and [¹⁴ C]-Oxathiapiprolin formulation concentrate; 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22 h and 24 h [¹⁴ C]-Oxathiapiprolin spray dilution 1 and spray dilution 2 : 4, 8, 12, 16, 20 h and 24 h
Washing		6h and 24 h
Final Procedure	Tape stripping	20
	TS1-2 analysed separately	N
Remarks:		

	[¹⁴ C]-Azoxystrobin			[¹⁴ C]-Oxathiapiprolin		
Tested doses	FC	SD1	SD2	FC	SD1	SD2
Target concentration [g/L]	250	0.167	0.076	12	0.008	0.0036
Area dose Occasion 1 [µg/cm²]	2551	1.72	0.665	122	0.0737	0.0329
Area dose Occasion 2 [µg/cm²]	N/A	1.82	0.770	N/A	N/A	N/A
Total dose [µL/cm²]	10	10	10	10	10	10
Specific activity [µCi/mg]	0.531	102.2	102.2	15.69	48.0	48.0
No. of donors	4	8	8	4	4	4
No of cells used/valid cells*	8	12/8*	12/9*	8	8/7*	8/6*

*Cells 9 -12 Excluded due to low mass balance

Cells 20, 21 and 23 Excluded due to low mass balance

Cell 33 rejected due to suspected leakage

Cells 44 and 47 rejected due to contamination at 24h skin wash

N/A = Not Applicable

Results and discussions

Table A 16: In-vitro dermal penetration of [¹⁴C] Azoxystrobin and [¹⁴C] Oxathiapiprolin as A22773A through human skin - Recovery data

Dose group	[¹⁴ C]-Azoxystrobin			[¹⁴ C]-Oxathiapiprolin		
	FC	SD1	SD2	FC	SD1	SD2
Target concentration [g/L]	250	0.167	0.076	12	0.008	0.0036
Mean actual applied concentration [g/L] Occasion 1	255	0.172	0.067	12.2	0.00737	0.00329
Mean actual applied concentration [g/L] Occasion 2	N/A	0.182	0.077	N/A	N/A	N/A
Recovery [%]						
Mean ± SD						
Dislodgeable dose	99.42 ± 3.04	98.13 ± 1.86	98.83 ± 6.67	96.54 ± 2.87	106.23 ± 7.05	111.48 ± 10.33
Skin washing after 6 h	98.85	95.30	95.47	96.21	98.98	100.08
Skin washing after 24 h	0.42	2.66	3.21	0.16	6.55	10.29
Donor chamber wash	0.15	0.17	0.16	0.17	0.70	1.11
Dose associated to skin						

Tape strips 1 - 2	0.02	0.11	0.13	0.03	0.07	0.20
Tape strips 3 - 20	0.05	0.37	0.34	0.06	0.73	1.27
Exposed skin	0.18	1.03	1.40	0.05	1.31	0.99
Unexposed skin	0.01	0.06	0.09	<0.01	0.07	0.13
Absorbed dose	0.07 ± 0.09	0.99 ± 0.45	1.43 ± 0.83	0.02 ± 0.02	1.81 ± 0.59	1.95 ± 0.95
Receptor fluid	0.01	0.84	1.16	<0.01	0.98	0.90
Receptor chamber wash	0.06	0.13	0.25	0.02	0.74	0.98
Receptor Rinse	0.00	0.02	0.03	0.00	0.10	0.07
Total recovery¹	99.73 ± 3.05	100.68 ± 1.27	102.22 ± 5.88	96.70 ± 2.92	110.22 ± 7.25	116.02 ± 10.73
Absorption essentially complete at end of study (>75% absorption within half the study duration) [% Absorption at t _{0.5}] ²	N 67.21	N 74.03	N 70.62	N 67.17	N 70.86	N 65.95
If no: Absorption estimates = absorbed dose + exposed skin + tape strips 3-20	0.29 ± 0.16	2.38 ± 1.05	3.17 ± 1.89	0.13 ± 0.07	3.85 ± 0.85	4.22 ± 1.53
If yes: Absorption estimates = absorbed dose + exposed skin	N/A	N/A	N/A	N/A	N/A	N/A
Absorption estimate normalised ³	N	N	N	N	N	N
k	0.84	0.84	0.77	0.84	0.92	1.0
Mean + k*SD	0.424	3.26	4.63	0.189	4.62	5.75
Absorption estimates used for risk assessment⁴	0.42	3.3	4.6	0.19	4.6	5.8

¹ Values may not calculate exactly due to rounding of figures

² In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study. Finally, the skin preparation is also considered potentially absorbable.

³ According to the EFSA Guidance on Dermal Absorption, cells with insufficient recovery (< 95%) can be corrected by normalisation of absorption estimate to 100% recovery; explanation should be included.

⁴ Relevant absorption estimate was rounded to the required number of significant figures.

N/A: not applicable

Remarks

Cells 9 -12 and Cells 20, 21 and 23 were excluded due to low mass balance. Cell 33 was rejected due to suspected leakage. Cells 44 and 47 rejected from the dataset due to contamination at 24h skin wash.

Conclusion/endpoint:

The study demonstrated that the amount of azoxystrobin absorbed through human split-thickness skin membranes over 24 h (following a 6 h exposure) from the formulation concentrate (250 g/L) and the intended in-use concentrations (0.167 g/L and 0.076 g/L) was 0.07%, 0.99%, and 1.43% of the applied dose, respectively, as measured in the receptor fluid, receptor rinse and receptor chamber wash. The dermal penetration estimates to be used for risk assessment were set at 0.42%, 3.3% and 4.6% for the formulation concentrate, spray dilution 1 and spray dilution 2 respectively based on the EFSA Guidance on Dermal Absorption (2017) criteria.

The study demonstrated that the amount of oxathiapiprolin absorbed through human split-thickness skin membranes over 24 h (following a 6 h exposure) from the formulation concentrate (12 g/L) and the intended in-use dilutions (0.008 g/L and 0.0036 g/L) was 0.02%, 1.81%, and 1.95% of the applied dose, respectively, as measured in the receptor fluid, receptor rinse and receptor chamber wash. The dermal penetration estimates to be used for risk assessment were set at 0.19%, 4.6% and 5.8% for the formulation concentrate,

spray dilution 1 and spray dilution 2 respectively based on the EFSA Guidance on Dermal Absorption (2017) criteria.

A 2.11 Other/Special Studies

No other studies are submitted with this application.

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for azoxystrobin

Table A 17: Input parameters and estimation of longer term operator exposure towards azoxystrobin using the Dutch Greenhouse Model

OPERATOR EXPOSURE			DUTCH GREENHOUSE MODEL	
form	A22773A		Application including mixing and loading	
a.s.	Azoxystrobin			
Parameter		Value	Unit	References, comments
MANUAL SPRAYING in greenhouses				
AR	Application rate	0.25	kg a.s./ha	summary of intended uses
A	Area treated	1	ha/ day	Dutch model
Inhalation Exposure				without PPE
SV	Surrogate Exposure Value	1	mg a.s./ kg a.s.	Dutch model
Inhalation Exposure (without PPE)		0.25	mg a.s./ day	IE = SV x AR x A
Inhalation Exposure (with PPE)				with PPE
	PPE-factor	1		reduction factor
Inhalation Exposure (with PPE)		0.25	mg a.s./ day	IE(PPE) = PPE factor x IE
Dermal Exposure				without PPE
SV	Surrogate Exposure Value	200	mg a.s./ kg a.s.	Dutch model
Dermal Exposure		50	mg a.s./ day	DE = SV x AR x A
Dermal Exposure (with PPE)				with PPE
	PPE-factor	0.1		reduction factor
Dermal Exposure (with PPE)		5	mg a.s./ day	DE(PPE) = PPE-factor x DE
Internal exposure				
IA	Inhalation Absorption	100	%	
DA	Dermal Absorption	3.3	%	
	AOEL	12	mg a.s./ day	based on 60 kg bw
		Without PPE	With PPE	
	Internal exposure	[mg a.s. / day]	[mg a.s. / day]	
	Inhalation	0.25	0.25	IE(int) = IE x (IA/100)
	Dermal	1.65	0.165	DE(int) = DE x (DA/100)
	Total	1.9	0.415	sum
	% AOEL			
	Inhalation	2.1	2.1	%AOEL = 100 x IE(int) / AOEL
	Dermal	13.8	1.4	%AOEL = 100 x DE(int) / AOEL
	Total	15.83	3.46	sum

Table A 18: Estimation of longer term operator exposure towards azoxystrobin using the SEGM – low crop standard

Operator exposure estimate: Greenhouse model. Low crop, standard							
Product:	A22773A						
Active substance:	Azoxystrobin		a.s. concentration:	250	[g/l or kg]		
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None		
Dose [l or kg/ha product] :	1.0			Hands:	Gloves		
Work rate [ha/day]:	1		PPE during application:	Respiration:	None		
Body weight [kg]:	60			Hands:	Gloves		
Inhalation absorption [%]	100			Head:	None		
Dermal absorption [%]	0.42	(concentrate)		Body:	Coverall		
	3.3	(dilution)					
Calculation of route exposure:							
Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]			
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected	
I _M =	0.000049		0.250	0.00000021			I = Inhalation
D _{M(H)} =	2.007001	0.022309	0.250	0.00836250		0.00009295	D = Dermal
I _A =	0.443296		0.250	0.00184707			M = Mix/Loading
D _{A(C)} =	0.011494		0.250	0.00004789			A = Application
D _{A(H)} =	5.710485	0.000237	0.250	0.0237937		0.0000010	C = Head
D _{A(B)} =	0.372960		0.250	0.001554			H = Hands
							B = Body
Absorbed dose:							
Route		Absorption [%]	Unprotected		Protected		
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	
Dermal:	Mix/Loading	0.4	0.008363	0.0000351	0.000093	0.000000	
	Application	3.3	0.025396	0.000838	0.001603	0.0000529	
Inhalation:	Mix/Loading	100	0.00000021	0.00000021	0.00000021	0.00000021	
	Application	100	0.001847	0.001847	0.001847	0.001847	
	Total =			0.00272		0.001901	

Table A 19: Estimation of longer term operator exposure towards azoxystrobin using the SEGM – low crop intensive

Operator exposure estimate: Greenhouse model. Low crop, intensive contact with treated crop						
Product:	A22773A					
Active substance:	Azoxystrobin		a.s. concentration:	250	[g/l or kg]	
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha product]:	1.0			Hands:	Gloves	
Work rate [ha/day]:	1		PPE during application:	Respiration:	None	
Body weight [kg]:	60			Hands:	Gloves	
Inhalation absorption [%]	100			Head:	None	
Dermal absorption [%]	0.42	(concentrate)		Body:	Impervious clothing	
	3.3	(dilution)				
Calculation of route exposure:						
Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]		
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected
I = Inhalation						
D = Dermal						
M = Mix/Loading						
A = Application						
C = Head						
H = Hands						
B = Body						
Absorbed dose:						
Route		Absorption [%]	Unprotected		Protected	
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.4	0.008363	0.0000351	0.000093	0.000000
	Application	3.3	1.392830	0.045963	0.008381	0.0002766
Inhalation:	Mix/Loading	100	0.00000021	0.00000021	0.00000021	0.00000021
	Application	100	0.006105	0.006105	0.006105	0.006105
Total =				0.052104		0.006382

Crop standard				
Operator exposure estimate: Greenhouse model. High crop, standard				

Product:	A22773A						
Active substance:	Azoxystrobin		a.s. concentration:	250	[g/l or kg]		
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None		
Dose [l or kg/ha product]:	1.0			Hands:	Gloves		
Work rate [ha/day]:	1		PPE during application:	Respiration:	None		
Body weight [kg]:	60			Hands:	Gloves		
Inhalation absorption [%]	100			Head:	None		
Dermal absorption [%]	0.42	(concentrate)		Body:	Impervious clothing		
	3.3	(dilution)					
Calculation of route exposure:							
Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]			
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected	
I _M =	0.000049		0.250	0.00000021			I = Inhalation
D _{M(H)} =	2.007001	0.022309	0.250	0.00836250		0.00009295	D = Dermal
I _A =	0.676955		0.250	0.00282065			M = Mix/Loading
D _{A(C)} =	0.806061		0.250	0.00335859			A = Application
D _{A(H)} =	25.190386	0.021652	0.250	0.1049599		0.0000902	C = Head
D _{A(B)} =	17.084126	465.0184268	0.250	0.071184	0.005	0.009688	H = Hands
		See footnote for explanation					B = Body
Absorbed dose:							
Route		Absorption [%]	Unprotected		Protected		
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	
Dermal:	Mix/Loading	0.4	0.008363	0.000035	0.000093	0.000000	
	Application	3.3	0.179502	0.005924	0.013137	0.0004335	
Inhalation:	Mix/Loading	100	0.00000021	0.00000021	0.00000021	0.00000021	
	Application	100	0.002821	0.002821	0.002821	0.002821	
		Total =		0.00878		0.003255	
N.B.							

Table A 21: Estimation of longer term operator exposure towards azoxystrobin using the SEGM – high crop intensive

Operator exposure estimate: Greenhouse model. High crop, intensive contact with treated crop						
Product:	A22773A					
Active substance:	Azoxystrobin		a.s. concentration:	250	[g/l or kg]	
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha product]:	1.0			Hands:	Gloves	
Work rate [ha/day]:	1		PPE during application:	Respiration:	None	
Body weight [kg]:	60			Hands:	Gloves	
Inhalation absorption [%]	100			Head:	None	
Dermal absorption [%]	0.42	(concentrate)		Body:	Impervious clothing	
	3.3	(dilution)				
Calculation of route exposure:						
Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]		
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected
I _M =	0.000049		0.250	0.00000021		
D _{M(H)} =	2.007001	0.022309	0.250	0.00836250		0.00009295
I _A =	0.824467		0.250	0.00343528		
D _{A(C)} =	1.066230		0.250	0.00444262		
D _{A(H)} =	not applicable	1.051509	0.250			0.0043813
D _{A(B)} =	not applicable	2.17365615	0.250			0.009057
Absorbed dose:						
Route		Absorption [%]	Unprotected		Protected	
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.4	0.008363	0.0000351	0.000093	0.000000
	Application	3.3			0.017881	0.0005901
Inhalation:	Mix/Loading	100	0.00000021	0.00000021	0.00000021	0.00000021
	Application	100	0.003435	0.003435	0.003435	0.003435
Total =						0.004026

I = Inhalation
D = Dermal
M = Mix/Loading
A = Application
C = Head
H = Hands
B = Body

A 3.1.2 Calculations for oxathiapiprolin

Table A 22: Input parameters and estimation of longer term operator exposure towards oxathiapiprolin using the Dutch Greenhouse Model

OPERATOR EXPOSURE			DUTCH GREENHOUSE MODEL	
form	A22773A		Application including mixing and loading	
a.s.	Oxathiapiprolin			
Parameter		Value	Unit	References, comments
MANUAL SPRAYING in greenhouses				
AR	Application rate	0.012	kg a.s./ha	summary of intended uses
A	Area treated	1	ha/ day	Dutch model
Inhalation Exposure				
SV	Surrogate Exposure Value	1	mg a.s./ kg a.s.	without PPE Dutch model
Inhalation Exposure (without PPE)		0.012	mg a.s./ day	IE = SV x AR x A
Inhalation Exposure (with PPE)				
	PPE-factor	1		with PPE reduction factor
Inhalation Exposure (with PPE)		0.012	mg a.s./ day	IE(PPE) = PPE factor x IE
Dermal Exposure				
SV	Surrogate Exposure Value	200	mg a.s./ kg a.s.	without PPE Dutch model
Dermal Exposure		2.4	mg a.s./ day	DE = SV x AR x A
Dermal Exposure (with PPE)				
	PPE-factor	0.1		with PPE reduction factor
Dermal Exposure (with PPE)		0.24	mg a.s./ day	DE(PPE) = PPE-factor x DE
Internal exposure				
IA	Inhalation Absorption	100	%	
DA	Dermal Absorption	4.6	%	
	AOEL	2.4	mg a.s./ day	based on 60 kg bw
		Without PPE	With PPE	
	Internal exposure	[mg a.s. / day]	[mg a.s. / day]	
	Inhalation	0.012	0.012	IE(int) = IE x (IA/100)
	Dermal	0.1104	0.01104	DE(int) = DE x (DA/100)
	Total	0.1224	0.02304	sum
	% AOEL			
	Inhalation	0.5	0.5	%AOEL = 100 x IE(int) / AOEL
	Dermal	4.6	0.5	%AOEL = 100 x DE(int) / AOEL
	Total	5.10	0.96	sum

Table A 23: Estimation of longer term operator exposure towards oxathiapiprolin using the SEGM – low crop standard

Operator exposure estimate: Greenhouse model. Low crop, standard							
Product:	A22773A						
Active substance:	Oxathiapiprolin		a.s. concentration:	12	[g/l or kg]		
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None		
Dose [l or kg/ha product] :	1.0			Hands:	Gloves		
Work rate [ha/day]:	1		PPE during application:	Respiration:	None		
Body weight [kg]:	60			Hands:	Gloves		
Inhalation absorption [%]	100			Head:	None		
Dermal absorption [%]	0.19	(concentrate)		Body:	Coverall		
	4.6	(dilution)					
Calculation of route exposure:							
Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]			
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected	
I _M =	0.000049		0.012	0.00000001			I = Inhalation
D _{M(H)} =	2.007001	0.022309	0.012	0.00040140		0.00000446	D = Dermal
I _A =	0.443296		0.012	0.00008866			M = Mix/Loading
D _{A(C)} =	0.011494		0.012	0.00000230			A = Application
D _{A(H)} =	5.710485	0.000237	0.012	0.0011421		0.0000000	C = Head
D _{A(B)} =	0.372960		0.012	0.000075			H = Hands
							B = Body
Absorbed dose:							
Route		Absorption [%]	Unprotected		Protected		
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	
Dermal:	Mix/Loading	0.2	0.000401	0.0000008	0.000004	0.000000	
	Application	4.6	0.001219	0.000056	0.000077	0.000035	
Inhalation:	Mix/Loading	100	0.00000001	0.00000001	0.00000001	0.00000001	
	Application	100	0.000089	0.000089	0.000089	0.000089	
		Total =		0.000146		0.000092	

Table A 24: Estimation of longer term operator exposure towards oxathiapiprolin using the SEGM – low crop intensive

Operator exposure estimate: Greenhouse model. Low crop, intensive contact with treated crop						
Product:	A22773A					
Active substance:	Oxathiapiprolin		a.s. concentration:	12	[g/l or kg]	
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha product]:	1.0			Hands:	Gloves	
Work rate [ha/day]:	1		PPE during application:	Respiration:	None	
Body weight [kg]:	60			Hands:	Gloves	
Inhalation absorption [%]	100			Head:	None	
Dermal absorption [%]	0.19	(concentrate)		Body:	Impervious clothing	
	4.6	(dilution)				
Calculation of route exposure:						
Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]		
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected
I _M =	0.000049		0.012	0.00000001		
D _{M(H)} =	2.007001	0.022309	0.012	0.00040140		0.00000446
I _A =	1.465226		0.012	0.00029305		
D _{A(C)} =	0.363874		0.012	0.00007277		
D _{A(H)} =	28.618020	0.038972	0.012	0.0057236		0.0000078
D _{A(B)} =	305.297355	1.60857197	0.012	0.061059		0.000322
Absorbed dose:						
Route		Absorption [%]	Unprotected		Protected	
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.2	0.000401	0.0000008	0.000004	0.000000
	Application	4.6	0.066856	0.003075	0.000402	0.0000185
Inhalation:	Mix/Loading	100	0.00000001	0.00000001	0.00000001	0.00000001
	Application	100	0.000293	0.000293	0.000293	0.000293
		Total =		0.003369		0.000312

Table A 25: Estimation of longer term operator exposure towards oxathiapiprolin using the SEGM – high crop standard

Operator exposure estimate: Greenhouse model, High crop, standard							
Product:	A22773A						
Active substance:	Oxathiapiprolin		a.s. concentration:	12	[g/l or kg]		
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None		
Dose [l or kg/ha product]:	1.0			Hands:	Gloves		
Work rate [ha/day]:	1		PPE during application:	Respiration:	None		
Body weight [kg]:	60			Hands:	Gloves		
Inhalation absorption [%]	100			Head:	None		
Dermal absorption [%]	0.19	(concentrate)		Body:	Impervious clothing		
	4.6	(dilution)					
Calculation of route exposure:							
Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]			
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected	
I _M =	0.000049		0.012	0.00000001			I = Inhalation
D _{M(H)} =	2.007001	0.022309	0.012	0.00040140		0.00000446	D = Dermal
I _A =	0.676955		0.012	0.00013539			M = Mix/Loading
D _{A(C)} =	0.806061		0.012	0.00016121			A = Application
D _{A(H)} =	25.190386	0.021652	0.012	0.0050381		0.0000043	C = Head
D _{A(B)} =	17.084126	465.0184268	0.012	0.003417	0.005	0.000465	H = Hands
		See footnote for explanation					B = Body
Absorbed dose:							
Route		Absorption [%]	Unprotected		Protected		
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	
Dermal:	Mix/Loading	0.2	0.000401	0.000001	0.000004	0.000000	
	Application	4.6	0.008616	0.000396	0.000631	0.0000290	
Inhalation:	Mix/Loading	100	0.00000001	0.00000001	0.00000001	0.00000001	
	Application	100	0.000135	0.000135	0.000135	0.000135	
		Total =		0.000533		0.000164	

N.B.

The following should be noted with respect to the use of the table entitled "Calculation of route exposure". There is an apparent anomaly concerning the intermediate, normalised values for dermal exposure to the body [D_{A(B)}] for "Unprotected" and "Protected" operators: the value for the protected body is higher (465.15 mg/kg a.s. in cell C21) than that for the unprotected operator (17.08 mg/kg a.s. in cell B21). The reason for this is that, for the unprotected operator, the actual dermal exposure of the body is taken from the relevant data set in the "Expo Appl" worksheet and this value is used without modification, i.e. by using an exposure reduction factor, in calculating the estimated dermal exposure (cell E21 in the "Calculation of route exposure" table). For the protected operator, the total potential dermal exposure value is taken from the "Expo Appl" worksheet and is modified using the exposure reduction factor in cell F21 (0.005) for use of impervious protective clothing (cell G21). The essential point to note is that the normalised data are intermediate values used in the calculation of the estimated, product-specific exposures, and the unprotected and protected scenarios are based on actual and potential dermal exposures, respectively.

Table A 26: Estimation of longer term operator exposure towards oxathiapiprolin using the SEGM – high crop intensive

Operator exposure estimate: Greenhouse model. High crop, intensive contact with treated crop						
Product:	A22773A					
Active substance:	Oxathiapiprolin		a.s. concentration:	12	[g/l or kg]	
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha product]:	1.0			Hands:	Gloves	
Work rate [ha/day]:	1		PPE during application:	Respiration:	None	
Body weight [kg]:	60			Hands:	Gloves	
Inhalation absorption [%]	100			Head:	None	
Dermal absorption [%]	0.19	(concentrate)		Body:	Impervious clothing	
	4.6	(dilution)				
Calculation of route exposure:						
Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]		
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected
I _M =	0.000049		0.012	0.00000001		
D _{M(H)} =	2.007001	0.022309	0.012	0.00040140		0.00000446
I _A =	0.824467		0.012	0.00016489		
D _{A(C)} =	1.066230		0.012	0.00021325		
D _{A(H)} =	not applicable	1.051509	0.012			0.0002103
D _{A(B)} =	not applicable	2.17365615	0.012			0.000435
Absorbed dose:						
Route		Absorption [%]	Unprotected		Protected	
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.2	0.000401	0.0000008	0.000004	0.000000
	Application	4.6			0.000858	0.0000395
Inhalation:	Mix/Loading	100	0.00000001	0.00000001	0.00000001	0.00000001
	Application	100	0.000165	0.000165	0.000165	0.000165
Total =						0.000204

I = Inhalation
D = Dermal
M = Mix/Loading
A = Application
C = Head
H = Hands
B = Body

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for azoxystrobin

Table A 27: Input parameters and estimation of worker exposure towards azoxystrobin according to EFSA guidance – cucumber and pepper

Worker exposure from residues on foliage for A22773A			
Crop type	Fruiting vegetables		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.25 kg a.s./ha		
Number of applications	2		
Interval between multiple applications	7 days		
Half-life of active substance	30 days		
Multiple application factor	1.9		
Dermal absorption of the product	0.42%		
Dermal absorption of the in-use dilution	3.30%		
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.75 µg a.s./cm ²		
Working hours	8 hr		
Dermal transfer coefficient - Total potential exposure	5800 cm ² /hr		
Dermal transfer coefficient - arms, body and legs covered	2500 cm ² /hr		
Dermal transfer coefficient - hands, arms, body and legs covered	580 cm ² /hr		
Inhalation transfer coefficient for automated applications	NA ha/hr*10 ^{^(-3)}		
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10 ^{^(-3)}		
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10 ^{^(-3)}		
1. Total			
	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves
Total systemic exposure (mg a.s./day)	2.1253062	0.9160802	0.2125306
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0354218	0.0152680	0.0035422
% of RVNAS	17.71%	7.63%	1.77%

A 3.2.2 Calculations for oxathiapiprolin

Table A 28: Input parameters and estimation of worker exposure towards oxathiapiprolin according to EFSA guidance – cucumber and pepper

Worker exposure from residues on foliage for A22773A			
Crop type	Fruiting vegetables		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.012 kg a.s./ha		
Number of applications	2		
Interval between multiple applications	7 days		
Half-life of active substance	30 days		
Multiple application factor	1.9		
Dermal absorption of the product	0.19%		
Dermal absorption of the in-use dilution	4.60%		
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.036 µg a.s./cm ²		
Working hours	8 hr		
Dermal transfer coefficient - Total potential exposure	5800 cm ² /hr		
Dermal transfer coefficient - arms, body and legs covered	2500 cm ² /hr		
Dermal transfer coefficient - hands, arms, body and legs covered	580 cm ² /hr		
Inhalation transfer coefficient for automated applications	NA ha/hr*10 ^{^(-3)}		
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10 ^{^(-3)}		
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10 ^{^(-3)}		
1. Total			
	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves
Total systemic exposure (mg a.s./day)	0.1422023	0.0612941	0.0142202
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0023700	0.0010216	0.0002370
% of RVNAS	5.93%	2.55%	0.59%