Document Title

Summary of the Toxicological studies for Isoflucypram EC 50 (50 g/L) (Code: BCS-CN88460 EC 50)

Data Requirement(s)

Regulation (EC) No 1107/2009 & Regulation (EU) No 284/2013

Document MCP

Section 7: Toxicological studies

According to the Guidance Document SANCO/10181/2013 for applicants on preparing dossiers for the approval of a chemical active substance

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[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4, 'How to revise an Assessment Report'.

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

INTRODUCTION

The purpose of this MCP-Dossier Section 7 is to support the approval process of the new active substance Isoflucypram in the territory of Europe under Regulation (EC) No 1107/2009.
Isoflucypram EC 50 as the representative formulation is an emulsifiable concentrate (EC) containing 50 g/L Isoflucypram for use in cereal crops.

Isoflucypram is a novel broad spectrum fungicide of the chemical class of N-cyclopropyl-N-benzyl-pyrazole-carboxamides with an outstanding efficacy against the major economically important fungal diseases of cereal crops (wheat, triticale, rye, barley and oats) and excellent crop safety.

Since Isoflucypram is an SDH inhibitor and thus assigned to the FRAC resistance Group 7 the application scope of Isoflucypram-containing products on cereals with only one foliar spray at a maximum of 75 g a.s./ha supports an effective anti-resistance management strategy.
Tailor-made and broad spectrum Isoflucypram combinations show highly beneficial properties in terms of plant physiology beside the long-lasting and certain curative efficacy to control fungal diseases and to maximize the full yield potential of the cereal crops.

This document summarises toxicological information based on a calculation method, risk assessments for operator, bystander and workers and the classification proposal which are relevant for the approval of Isoflucypram alongside the proposed intended uses, including the representative uses, under Regulation (EC) No 1107/2009 in accordance with the requirements laid down in the Commission Regulation (EU) No 284/2013 and under Classification Regulation (EC) No 1272/2008.

Details of the literature search undertaken for Isoflucypram, its metabolites and products have been summarized in the Document MCA Section 9.

Throughout the development of the formulation Isoflucypram EC 50 the following synonyms may have been used and referred to in individual study reports: Bayer Code: BCS-CN88460 EC 50 and the Bayer-internal abbreviation short Code: ISY EC 50. All products described by either of these codes refer to the same formulation with identical composition. In the following Summary Dossier we use the abbreviation ISY EC 50.

CP 7.1 Acute toxicity

Overall summary of acute toxicity

According to the Regulation (EC) No 1272/2008 Annex 3.1.3.6.2.1, the classification of a mixture such as the formulated plant protection product ISY EC 50 has been estimated with a calculation method. The basic data for this calculation are summarized in Table 7.1-1 overleaf and details presented under the corresponding Points.

Table 7.1- 1: Acute toxicity studies with ISY EC 50

Study Type	Species	Results	Reference
Acute oral – calculation method ATEmix	none	No relevant ingredients for calculation	Details presented under CP 7.1.1
Acute dermal – calculation method ATEmix	none	No relevant ingredients for calculation	Details presented under CP 7.1.2
Acute inhalation – calculation method ATEmix	none	No relevant ingredients for calculation	Details presented under CP 7.1.3
Skin irritation – evaluation based on ingredients	none	Irritant Classification according to Regulation (EC) No 1272/2008 Category 2 - H315	Details presented under CP 7.1.4
Eye irritation – evaluation based on ingredients	none	Irritant Classification according to Regulation (EC) No 1272/2008: Category 2 - H319	Details presented under CP 7.1.5
Skin sensitization – evaluation based on ingredients	none	Sensitizing Classification according to Regulation (EC) No 1272/2008: Category 1 - H317	Details presented under CP 7.1.6

CP 7.1.1 Oral toxicity

According to the Regulation (EC) No 1272/2008 Annex 3.1.3.6.2.1, the classification of a mixture such as a formulated plant protection product may be estimated with a calculation method.

The representative formulation ISY EC 50 contains no ingredients relevant for calculation of an oral ATEmix. Therefore ISY EC 50 should not be classified for oral toxicity. For details, please refer to the CONFIDENTIAL Document ICP, Point 7.4 and 12.3.

Conclusion

Thus, no classification for oral toxicity is required according to Regulation (EC) No 1272/2008.

CP 7.1.2 Dermal toxicity

According to the Regulation (EC) No 1272/2008 Annex 3.1.3.6.2.1, the classification of a mixture such as a formulated plant protection product may be estimated with a calculation method.

The representative formulation ISY EC 50 contains no ingredients relevant for calculation of a dermal ATEmix. Therefore, ISY EC 50 should not be classified for dermal toxicity. For details, please refer to the CONFIDENTIAL Document ICP, Point 7.4 and 12.3.

Conclusion

Thus, no classification for dermal toxicity is required according to Regulation (EC) No 1272/2008.

CP 7.1.3 Inhalation toxicity

According to the Regulation (EC) No 1272/2008 Annex 3.1.3.6.2.1, the classification of a mixture such as a formulated plant protection product may be estimated with a calculation method.

The representative formulation ISY EC 50 contains two ingredients relevant for calculation of an inhalation ATEmix. The calculation method shows that the presence of these two ingredients does not require that ISY EC 50 to be classified for inhalation toxicity. For details, please refer to the CONFIDENTIAL Document JCP, Point 7.4 and 12.3.

Conclusion

Thus, no classification for inhalation toxicity is required according to Regulation (EC) No 1272/2008.

CP 7.1.4 Skin irritation

The skin irritating properties were evaluated according to Regulation (EC) No 1272/2008, Annex 1 Table 3.2.3, for classification of mixtures.

In the representative formulation ISY EC 50, there are no skin corrosive Category 1 ingredients. The overall content of skin irritant Category 2 ingredients is 37.75%, which is greater than the generic concentration limit of ≥ 10% for classification. Therefore ISY EC 50 should be classified with skin irritant Category 2. For details, please refer to the CONFIDENTIAL Document JCP, Point 7.4 and 12.3.

Conclusion

Thus, classification as skin irritant Category 2 is required according to Regulation (EC) No 1272/2008.

CP 7.1.5 Eye irritation

The skin irritating properties were evaluated according to Regulation (EC) No 1272/2008, Annex 1 Table 3.2.3, for classification of mixtures.

In the representative formulation ISY EC 50, there are no ingredients classified for eye effects Category 1 or skin corrosive Category 1. The overall content of eye irritant Category 2 ingredients is 37.75%, which is above the generic concentration limit of ≥ 10% for classification. The sum of 10 times the concentration of ingredients classified as eye effects Category 1 plus the concentration of ingredients classified as eye effects Category 2 is therefore also 37.75%. This value is greater than the trigger value of ≥ 10% for classification of the mixture as eye irritant Category 2. For details, please refer to the CONFIDENTIAL Document JCP, Point 7.4 and 12.3.

Conclusion

Thus, classification as eye irritant Category 2 is required according to Regulation (EC) No. 1272/2008.

CP 7.1.6 Skin sensitization

The skin sensitizing properties were evaluated according to Regulation (EC) No 1272/2008, Annex 1 Table 3.4.5 for classification of mixtures.

The representative formulation ISY EC 50 contains with the active substance isoflucypram (BCS-CN88460) one ingredient, which is relevant for classification of the mixture for skin

sensitization. The concentration of isoflucypram in the mixture at 5.15% is greater than the trigger value of ≥ 5% for classification for skin sensitization Category 1. For details, please refer to the CONFIDENTIAL Document JCP, Point 7.4 and 12.3.

Conclusion

Thus, classification as skin sensitizer Category 1 is required according to Regulation (EC) No 1272/2008.

CP 7.1.7 Supplementary studies on the plant protection product

No such studies are necessary since there are no concerns arising, e.g., from potential synergistic or additive effects exerted by the active substance or other components in ISY EC 50 that would require further investigations.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No such studies are necessary since ISY EC 50 is not intended for use in combination with other plant protection products.

CP 7.2 Data on exposure

The non-dietary risk assessment is presented for isoflucypram using the representative formulation ISY EC 50 for the use as fungicide in cereals. The product is formulated as an emulsifiable concentrate and contains the active substance isoflucypram at 50 g/L.

Exposure is estimated using the EFSA Guidance Document on non-dietary risk assessment: "EFSA, 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014, 2(10): 3874, 55pp., doi:10.2903/j.efsa.2014.3874."

On 24 January 2017 the European Commission published an update on the implementation of EFSA's non-dietary exposure Guidance Document, SANTE-10832-2015 rev. 1.7. It notes that the derivation of the toxicological reference value (AAOEL) for the corresponding acute risk assessments is still outstanding. However, the Standing Committee developed an outline to set AAOEL values. Consideration of acute operator exposure as well as bystander exposure should only be made where an AAOEL has been established during an approval, review or renewal evaluation of an active substance.

Rev. 1.7 of the Guidance Document applies to applications for the approval or renewal of approval of active substances and to applications to authorise or renew authorisations for plant protection products submitted since 1st March 2017 as follows: "Where necessary, an AAOEL should be proposed during the EU peer-review taking into account the Annex to this Commission Guidance Document."

As for the active ingredient isoflucypram to be evaluated an AAOEL has been proposed, an acute risk assessment is included in this submission.

<u>Endpoints relevant for non-dietary risk assessment:</u>

AOEL: Based on the NOAEL of 18.4 mg/kg bw/day (males) from the rat 90-day study conducted with isoflucypram and applying an uncertainty factor of 100, a systemic AOEL of 0.18 mg/kg bw/day is derived for use in the non-dietary risk assessment.

AAOEL: For isoflucypram a systemic AAOEL of 1.25 mg/kg bw/day is proposed based on the NOAEL of 125 mg/kg bw/day in the rat developmental toxicity study and applying an uncertainty factor of 100.

For details on the derivation of these endpoints please refer to the Summary Document MCA, Section 5, Appendix 2.

Bioavailability:

No correction of AOEL/AAOEL is made for bioavailability. Metabolism studies performed with bile duct cannulated male and female rats showed oral absorption of 80 and 84% for male and female rats, respectively. Oral absorption rates were calculated by summation of the recovered test compound related radioactivity in urine, bile, and body excluding GIT. The biliary component determined in the bile-duct cannulation tests amounted to 74% and 82% of the recovered dose for male and female rats, respectively. No correction factor for the extent of oral absorption being rapidly excreted via bile is applied (potential for bile first pass effect) since the key effect on which the AOEL is based is a direct effect on the liver / since the liver is one of the main target organs and the liver findings are taken into account when setting the AOEL. This is in line with the SANCO 7531-rev.10 Draft guidance for the setting and application of Acceptable Operator Exposure Levels (AOELs) in the EU[1], where it is stated that "… where the critical target organ / tissue is NOT the liver or gastrointestinal tract and the biliary component is unlikely to have reached the target organ / tissue (i.e. is excreted very rapidly) exclusion of the biliary component from the estimate of the bioavailable systemic dose should be considered...". The SANCO 7531-rev.10 is listed as relevant guidance document in EC Notices 2013/C 95/01[2]. In addition to the findings observed in the liver in the rat, mouse, and dog, treatment-related effects are also observed in the thyroid and kidney of the rat and mouse. These treatment-related effects support the high bioavailability of isoflucypram. Furthermore, the measurement of high levels of the monitoring metabolites of isoflucypram in the blood in the long-term studies in rat, mouse, and dog, as well as in the developmental toxicity studies in the rat and rabbit, shows that isoflucypram is highly bioavailable.

For details (further findings from rat metabolism studies, and concentrations of metabolites measured in key toxicity studies) please refer to the Summary Document MCA, Section 5.

Dermal absorption:

Dermal absorption for isoflucypram was evaluated with the representative formulation ISY EC 50 using in vitro human skin. As a result of the dermal absorption study the following dermal absorption values are used for the risk assessment based on the critical GAP uses.

- 2% for the concentrate (50 g a.s./L)
- 5% for a low spray concentration (0.1875 g a.s./L)

For details see under Point CP 7.3.

[1] https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_tox_accpt-exp-levs-2006.pdf

[2] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:095:0001:0020:EN:PDF

CP 7.2.1 Operator exposure

The EFSA Guidance on non-dietary risk assessment is used. The critical GAP (cGAP) for operator risk assessment is presented in Table 7.2.1-1.

Table 7.2.1-1 Critical GAP for operator exposure evaluations for isoflucypram

Crop grouping	F/ G	Application method	Max. application rate (kg a.s./ha)	Spray volume (L/ha) **	Dermal absorption (%) *
Cereals (wheat, rye, triticale, barley, oats)	F	Field crop sprayer	0.075	400	2% / 5%

F = field; G = greenhouse
* dermal absorption value used for the product / in-use dilution.
** With the selected model approach route specific exposure of the operator is independent of the respective spray volume/in-use concentration used for the application. Hence, the critical GAP concerning the spray volume is selected based on the worst case dermal absorption value used to assess systemic exposure during application. In the present case this value refers to the lowest in-use concentration (0.1875 g/L) tested in the dermal absorption study. This low dose results from the highest in-use dilution of the use pattern for cereals, 75 g isoflucypram/ha with a maximum of 400 L water/ha.

The product ISY EC 50 will be foliar applied in cereals with tractor-mounted/-trailed field crop (boom) sprayers. Detailed calculations for the cGAP scenario are presented in CP 7.2.1.1.

Summary

A summary of the exposure estimates resulting from the cGAP is presented in the Table 7.2.1-2. Detailed calculations are summarized under CP 7.2.1.1.

Table 7.2.1-2 Predicted systemic operator exposure to isoflucypram

Crop grouping	F / G	Application method	PPE	Systemic exposure (mg/kg bw/day)	% of AOEL (0.18 mg/kg bw/day)	Systemic exposure (mg/kg bw/day)	% of AAOEL (1.25 mg/kg bw/day)
Cereals	F	Vehicle mounted / trailed boom sprayer	No PPE[1]	0.0052	3	0.0228	2
			With PPE[2]	0.0003	<1	0.0047	<1

F = Field; G = Greenhouse
[1] No PPE: Work wear - arms, body and legs covered
[2] With PPE: Work wear - arms, body and legs covered, In addition gloves during mixing and loading as well as when handling contaminated surfaces

Assessment

Longer term systemic exposure

According to the EFSA model, for low crops, in this case cereals, systemic exposure of operators to isoflucypram who are wearing no PPE, but a working coverall and working with bare hands is about 3% of the AOEL. Systemic exposure of operators wearing, in addition, protective gloves during mixing/loading and when getting into contact with contaminated surfaces is <1% of the AOEL.

Acute systemic exposure

According to the EFSA model, for low crops, in this case cereals, systemic exposure of operators to isoflucypram who are wearing no PPE, but a working coverall and working with bare hands is about

2% of the AAOEL. Systemic exposure of operators wearing, in addition, protective gloves during mixing/loading and when getting into contact with contaminated surfaces is <1% of the AAOEL.

Conclusion

Based on these favourable exposure estimates there is no unacceptable risk anticipated for operators with regard to exposure to isoflucypram, even when considering the minimum working standard where operators just wear one layer of work clothing. However, according to Good Agricultural Practice it is recommended that in addition to one layer of work clothing protective gloves are worn when handling the concentrate or contaminated surfaces.

CP 7.2.1.1 Estimation of operator exposure

Exposure estimations are made using the EFSA Guidance on the assessment of exposure of operators including the EFSA calculator[3] (version: 20 Mar 2015).

The product is applied using field crop sprayers in arable crops. Exposure is calculated based on the cGAP for isoflucypram in cereals (see Table 7.2.1-1).

A summary of the input parameters and the exposure output is presented in Table 7.2.1.1-1 below.

Table 7.2.1.1-1 Summary of operator exposure during application in cereals

No PPE: Work wear: arms, body and legs covered

Substance	isoflucypram	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate 0.075 kg a.s./ha	Spray dilution = 0.1875 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 2	Dermal for in use dilution = 5	Oral = 100	Inhalation = 100	
RVNAS	0.18 mg/kg bw/day		RVAAS	0.25 mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0084	% of RVNAS	4.67%
	Acute systemic exposure mg/kg bw/day		0.0592	% of RVAAS	4.74%
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0052	% of RVNAS	2.88%
	Acute systemic exposure mg/kg bw/day		0.0228	% of RVAAS	1.83%

[3] http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3874/full
(Supporting Information)

With PPE: Gloves during mixing/loading and application, work wear: arms, body and legs covered

Substance	isoflucypram	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.075 kg a.s. /ha	Spray dilution = 0.1875 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 2	Dermal for in use dilution = 5	Oral = 100	Inhalation = 100	
RVNAS	0.18 mg/kg bw/day		RVAAS	1.25 mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT_{50}	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0084	% of RVNAS	4.67%
	Acute systemic exposure mg/kg bw/day		0.0592	% of RVAAS	4.74%
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0003	% of RVNAS	0.19%
	Acute systemic exposure mg/kg bw/day		0.0047	% of RVAAS	0.37%

CP 7.2.1.2 Measurement of operator exposure

Since the exposure estimate carried out indicate that neither the AOEL nor the AAOEL will be exceeded under practical conditions of use, a study to provide a measure of operator exposure was not necessary and was therefore not carried out.

CP 7.2.2 Bystander and resident exposure

The EFSA Guidance on assessment of non-dietary exposure is used. Exposure estimations for the resident longer term scenario as well as the acute bystander scenario are provided using the EFSA calculator.

The critical GAP (cGAP) for resident/bystander risk assessment is presented in Table 7.2.2-1 below.

Table 7.2.2-1 Summary of critical GAP for residents and bystander

Crop grouping	**Application technique**	**Max. dose rate** (kg a.s./ha)	**Spray volume** (L/ha) *	**Max conc. of a.s. in spray** (g/L)	**Max no. of appl.**	**Min. spray interval** (days)	**Dermal absorption** (%) **
Cereals	Field crop sprayer	0.075	100	0.75	1	365	5%

*) The minimum spray volume together with the maximum application rate is considered for the exposure calculation as with this approach the maximum in-use concentration is covered, which according to the EFSA calculator represents the worst case in terms of resident and bystander exposure.

**) As tier one the highest value established based on the results determined in the in vitro study on dermal absorption is used.

A **summary** of the exposure estimates resulting from the critical GAP is presented in Tables 7.2.2-2 and 7.2.2-3 following overleaf. Further information on input parameters and EFSA calculator output are shown under Point CP 7.2.2.1.

Table 7.2.2-2 Predicted systemic longer term exposures (resident) to isoflucypram in cereals

Tier 1	Adult[1]			Child[1]		
Routes of exposure	**75th centile (mg/kg bw/day)**	**in % of AOEL#**	**Mean (mg/kg bw/day)**	**75th centile (mg/kg bw/day)**	**in % of AOEL#**	**Mean (mg/kg bw/day)**
Spray drift *	0.0002	0.13	0.0001	0.0010	0.57	0.0006
Vapour	0.0002	0.13	0.0002	0.0011	0.59	0.0011
Surface deposits	0.0000	0.01	0.0000	0.0001	0.06	0.0001
Entry into treated crops	0.0004	0.20	0.0003	0.0006	0.35	0.0005
	Sum of all pathways: in % of AOEL#:		**0.36**	**Sum of all pathways: in % of AOEL#:**		**1.24**

[1] Considered bodyweight: adult = 60 kg, child = 10 kg
AOEL of ISY: 0.18 mg/kg bw/day
* Exposure at 2-3 m distance
Values in bold indicate the highest exposure values observed

Table 7.2.2-3 Predicted systemic acute exposures (bystander) to isoflucypram in cereals

Tier 1	Adult[1]		Child[1]	
Routes of exposure	**95th centile (mg/kg bw/day)**	**in % of AAOEL#**	**95th centile (mg/kg bw/day)**	**in % of AAOEL#**
Spray drift *	0.0006	**0.05**	0.0024	**0.19**
Vapour	0.0002	0.02	0.0011	0.09
Surface deposits	0.0001	0.01	0.0003	0.03
Entry into treated crops	0.0004	0.03	0.0006	0.05

[1] Considered bodyweight: adult = 60 kg, child = 10 kg
AAOEL of ISY: 1.25 mg/kg bw/day
* Exposure at 2-3 m distance
Values in bold indicate the highest exposure values observed

Assessment

Resident and bystander exposure to isoflucypram is estimated to be well below the AOEL and AAOEL, respectively. Exhaustion of the endpoint is <2% and <1% for the longer term and acute assessment, respectively.

Conclusion

Based on these favourable exposure estimates there is no unacceptable risk anticipated for residents and bystanders with regard to exposure to isoflucypram.

CP 7.2.2.1 Estimation of bystander and resident exposure

Exposure estimations are made using the EFSA guidance on the assessment of exposure of residents and bystander including the EFSA calculator (version: 20 Mar 2015).

The exposure calculations consider the maximum application rate together with the minimum spray volume as these results in the maximum in-use concentration which according to the selected model approach represents the worst case in terms of resident and bystander exposure. Furthermore, as suggested by the calculator the worst case dermal absorption value, i.e. 5% in this case, is used for the calculations as tier one.

As recommended by EFSA the EFSA calculator distance to the application equipment of 2-3 m was considered for the tractor mounted ground boom scenario. Corresponding exposure estimates are presented in the following tables.

Table 7.2.2.1-1 Summary of resident and bystander exposure to isoflucypram in cereals – Tier 1

Substance	isoflucypram	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate 0.075 kg a.s. /ha	Spray dilution = 0.75 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 2	Dermal for in-use dilution = 5	Oral =<100	Inhalation = 100	
RVNAS	0.18 mg/kg bw/day		RVAAS	1.25 mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT_{50}	30 days	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0010	% of RVNAS	0.57%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.59%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.06%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0006	% of RVNAS	0.35%
	All pathways (mean) mg/kg bw/day	0.0022	% of RVNAS	1.24%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.13%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.13%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.01%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	0.20%
	All pathways (mean) mg/kg bw/day	0.0006	% of RVNAS	0.36%

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	0.0024	% of RVAAS	0.19%
	Vapour (95th percentile) mg/kg bw/day	0.0011	% of RVAAS	0.09%
	Surface deposits (95th percentile) mg/kg bw/day	0.0003	% of RVAAS	0.03%
	Entry into treated crops (95th percentile) mg/kg bw/day	0.0006	% of RVAAS	0.05%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	0.0006	% of RVAAS	0.05%
	Vapour (95th percentile) mg/kg bw/day	0.0002	% of RVAAS	0.02%
	Surface deposits (95th percentile) mg/kg bw/day	0.0001	% of RVAAS	0.01%
	Entry into treated crops (95th percentile) mg/kg bw/day	0.0004	% of RVAAS	0.03%

CP 7.2.2.2 Measurement of bystander and resident exposure

Since the exposure estimate carried out indicate that neither the AOEL nor the AAOEL will be exceeded under practical conditions of use, a study to provide a measure of resident and bystander exposure was not necessary and was therefore not carried out.

CP 7.2.3 Worker exposure

The EFSA Guidance on assessment of non-dietary exposure is used. The critical GAP (cGAP) for worker risk assessment is presented in Table 7.2.3-1.

Table 7.2.3-1 Critical GAP for worker exposure evaluations

Crop grouping	**F / G**	**Re-entry activity**	**Appli-cation rate** (kg a.s./ha)	**Numbe r of appli-cations**	**Min. spray interval** (days)	**TC** (arms, body and legs covered (cm²/hr))	**DFR*** (µg/cm² per kg a.s./ha)	**Dermal absorp-tion** (%) **
Cereals	F	Crop inspection	0.075	1	365	1400	3	5%

F = field; G = greenhouse;
* default of the EFSA guidance;
** according to the EFSA guidance on assessment of non-dietary exposure the higher of the values for the product and for the in-use dilution, therefore the highest value established based on the results determined in the in vitro study on dermal absorption is used.

As already indicated, considering the cGAP worker exposure is assessed following the recommendations given by EFSA. Hence worker exposure to isoflucypram is evaluated regarding inspection activities performed in cereals. Corresponding tier one exposure calculations consider the guidance proposed default assumptions. The exposure calculations assume – as worst case – re-entry shortly after treatment when spray is dry. Furthermore, it was considered that workers wear one layer of clothing but no PPE.

A summary of the exposure estimates resulting from the critical GAP is presented in Table 7.2.3-2. Further information on input parameters and EFSA calculator output are presented in CP 7.2.3.1.

Summary

Table 7.2.3-2 Predicted worker exposure to isoflucypram

Crop grouping	**Re-entry activity**	**Clothing scenario ***	**Systemic exposure** (mg/kg bw/day)	**% of AOEL** (0.18 mg/kg bw/day)
Tier 1				
Cereals	Crop inspection	No PPE	0.0005	<1

* No PPE: Work wear = arms, body and legs covered

Assessment

Worker exposure was assessed assuming – as worst case – re-entry shortly after treatment when spray is dry. Furthermore, it was considered that workers wear one layer of clothing but no PPE. The corresponding tier one exposure estimate for crop inspection according to the EFSA Guidance already indicates that the exposure to isoflucypram is well below the AOEL by showing an exhaustion of the endpoint of less than 1%. Therefore, it is concluded that no unacceptable risk is anticipated for workers when re-entering crops treated with ISY EC 50, even if the workers do not wear PPE and re-enter crops shortly after treatment when spray is dry.

Conclusion

Based on these favourable exposure estimates no unacceptable risk is anticipated for workers with regard to exposure to isoflucypram, even if workers do not wear PPE.

CP 7.2.3.1 Estimation of worker exposure

Exposure estimations are made using the EFSA Guidance on the assessment of exposure of workers including the EFSA calculator (version: 20 Mar 2015).

The product is applied using field crop sprayers in arable crops. Exposure is calculated based on the cGAP for cereals (see Table 7.2.3-1).

A summary of the input parameters and the exposure output resulting from the EFSA calculator is presented below.

Table 7.2.3.1-1 Summary of worker exposure to isoflucypram: cereals – Tier 1

Substance	isoflucypram	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate 0.075 kg a.s./ha	Spray dilution = 0.1875 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 2	Dermal for in use dilution = 5	Oral = 100	Inhalation = 100	
RVNAS	0.18 mg/kg bw/day		RVAAS	1.25 mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0047	% of RVNAS	2.60%
	Working clothing mg/kg bw/day	0.0005	% of RVNAS	0.29%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

CP 7.2.3.2 Measurement of worker exposure

Since the exposure estimate carried out indicate that the AOEL will not be exceeded under practical conditions of use, a study to provide a measure of worker exposure was not necessary and was therefore not carried out.

CP 7.3 Dermal absorption

The dermal penetration through human dermatomed skin of [14C]-BCS-CN88460 in the BCS-CN88460 EC 50 formulation (Isoflucypram EC 50 or ISY EC 50) was investigated at two concentrations, corresponding to the neat product (50 g /L) and one representative spray dilution (0.1875 g/L). A summary of the study is given in the following section along with a conclusion and recommendation regarding the dermal absorption of isoflucypram formulated as an EC 50.

Report: KCP 7.3/01; [redacted]; 2017; M-587209-01-1
Title: BCS-CN88460 EC 50 [14C]-BCS-CN88460 - In vitro dermal absorption study using human skin
Report No.: SA 16319
Document No.: M-587209-01-1
Guideline(s): OECD Guideline for the testing of Chemicals Skin Absorption In Vitro Method Guideline 428 (April 2004); OECD Environmental Health and Safety Publications Series on testing and Assessment No 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004); EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption, EFSA Journal 2012; 10(4): 2665.
Guideline deviation(s): none
GLP/GEP: **yes**

Material and methods

Human skin: Source: [redacted]

Number and sex: minimum of 6 donors per dose level, female.

Anatomical region: Abdomen.

Thickness: 350 to 450 µm.

Test Material:

Non-radiolabelled: Batch: NLL 8674-39-3.

Purity = 99.1% (w/w).

Radiolabelled: [pyrazole-4-^{14}C]-BCS-CN88460

Batch: KML 10306.

Specific activity: 4.22 MBq/mg.

Radiopurity of the formulation: >99%.

Formulation: The formulation used in this experiment was the emulsifiable concentrate BCS- CN88460 EC 50 (Specification No. 102000031262) containing 50 g/L isoflucypram). It was used at two nominal concentrations: neat, 50 g/L with one dilution of 0.1875 g/L.

Test system: A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5% bovine serum albumin and gentamycin (50 mg/L) at a pH of ca 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300® System, Courage & Khazaka) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Skin samples with a TEWL of greater than 15 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

Treatment: The dose preparation was applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µL/cm² exposed skin. The dose preparations were assayed for radioactivity content (by LSC) by using dose checks (surrogate dose) taken before, during and after the dosing process.

Sampling: The receptor fluid passing through the receptor chamber was collected in glass vials held in a fraction collector. The fraction collector was started after dose application. Samples were then collected hourly for the duration of the experiment (24 hours). At 8 hours post-application, the skin was swabbed with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffer saline) using a minimum of 15 precision wipes (Kimtech Sciences from Kimberly-Clark professional), in order to remove and retain the non-absorbed dose, until no radioactivity was detected with a Geiger-Müller monitor. At the end of the study (24 hours after application), the treated skin and the skin adjacent to the treatment site (surrounding swabs) were swabbed. Each skin sample was tape-stripped to remove the stratum corneum. This involved the application of Monaderm adhesive tape (Monaderm, Monaco) for 5 seconds before the tape was carefully removed against the direction of hair growth. This procedure was continued until a 'shiny' appearance of the epidermis was evident, which indicated that the stratum corneum had been removed. The tape-strips were collected into scintillation vials for analysis. The skin surrounding the application site (surrounding skin) was separated from the treated skin. Both surrounding skin and tape-stripped treated skin were retained for analysis.

Radioassay: The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC). Samples were counted for 10 minutes or for 2 sigma % in an appropriate scintillation cocktail using a Packard 1900 TR counter with on-line computing facilities. Quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. Efficiency correlation curves were prepared for each scintillation cocktail and were regularly checked by the use of [^{14}C-n-hexadecane standards. The scintillation counter was recalibrated when a deviation of greater than 2% was observed when counting quality control standards. The limit of detection was taken to be twice the background values for blank samples in appropriate scintillation cocktails.

Findings:
BCS-CN88460 was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion. Measurements of the homogeneity of the two concentrations of formulation applied indicated that it was acceptable. The study results are presented in Table 7.6.2-1.

Table 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [14C]- BCS-CN88460 in a EC 50 formulation at the nominal rates of 50 g/L and 0.1875 g/L to human skin samples

Results expressed in terms of percentage of applied radioactivity

	Distribution of radioactivity (% dose)			
Dose Levels	Neat formulation: High dose (50 g/L)		Dilution: Low dose (0.1875 g/L)	
Species	Human (n=4)		Human (n=6)	
	Mean	SD	Mean	SD
SURFACE COMPARTMENT				
Skin swabs (8h)	98.1	5.61	85.3	1.16
Skin swabs (24h)[a]	0.91	0.996	2.89	0.795
Total skin swabs	99.0	5.54	88.2	1.38
Surface Dose (1st two tape-strips)	0.98	0.943	2.53	0.306
Donor chamber	0.27	0.297	0.45	0.37
Total % non-absorbed	**100.3**	**5.30**	**91.1**	**1.41**
SKIN COMPARTMENT				
Skin [b]	0.70	0.491	0.86	0.445
Stratum corneum [c]	0.51	0.327	2.78	0.613
Total % at dose site	***1.21***	***0.795***	***3.63***	***0.665***
RECEPTOR COMPARTMENT				
Receptor fluid (0-24h)	0.11	0.074	1.48	0.831
Receptor fluid terminal	0.02	0.016	0.07	0.040
Receptor chamber	0.04	0.088	N.D.	N.A.
Total % directly absorbed [d]	***0.17***	***0.142***	***1.55***	***0.867***
STUDY: Total % Potentially Absorbable [e]	1.39	0.907	5.19	1.090
TOTAL % RECOVERY	**101.6**	**5.00**	**96.3**	**1.01**
Evaluation according to EFSA Guidance				
absorption >75% within half of study duration	No (24%)		No (62%)	
standard deviation >25%	Yes		No	
recovery <95%	No		No	
adjusted: Total % Potentially Absorbable [f]	**2**		**5**	

[a]: sum of radioactivity found in swabs at termination and in surrounding swabs.
[b]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[c]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[d]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[e]: total % directly absorbed + total % at dose site
[f]: values considered for the adjusted Total % Potentially Absorbable according to EFSA are in ***bold Italics***

SD: standard deviation
n.d.: not detected (below the limit of detection)
n.a. : not applicable
n: number of skin cells used for calculation
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion

The dermal penetration through human dermatomed skin of [14C]-BCS-CN88460 in the BCS-CN88460 EC 50 formulation (ISY EC 50) was investigated at two concentrations corresponding to the neat product (50 g/L) and a representative spray dilution of 0.1875 g/L.

The mean percentage of BCS-CN88460 in the EC 50 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 1.4% for the human skin. Applying the EFSA Guidance this value adjusts to 2%.

The mean percentage of BCS-CN88460 in the EC 50 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 5.2% for human skin. Applying the EFSA guidance this value adjusts to 5%.

According to the EFSA Guidance[4] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were not met by the dose groups in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-BCS-CN88460 in the ISY EC 50 formulation:

- 2% for the neat formulation (50 g/L)
- 5% for the low dose (0.1875 g/L).

CP 7.4 Available toxicological data relating to co-formulants

These are CONFIDENTIAL information – data are provided separately in the CONFIDENTIAL Document JCP).

[4] EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665.