

REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product name(s): **INTUITY PLUS**

(Mandestrobin 40 SC)

Chemical active substance:

Mandestrobin 400 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: XXXX

Submission date: February 2024

Evaluation date: January 2025

Finalisation date: August 2025

Version history

When	What
February 2024	Article 33 submission – Initial Applicant’s version
May 2024	- Update of the cover page with the product trade name ‘Intuity Plus’. Mandestrobin 40 SC is the internal unique name. The internal name Mandestrobin 40 SC is the one used across the dRR content. - Update of Appendix 1: studies source and owner updated
January 2025	zRMS-PL evaluation
August 2025	Version revised to take into account cMSs’s and applicant’s comments

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6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on Mandestrobin 40SC *

Product name and code	Mandestrobin 40SC
Formulation type	SC
Active substance(s) (incl. content)	Mandestrobin Pure: 400 g/L Technical: 421 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 Mandestrobin 40SC 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 Mandestrobin 40SC according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Skin Sens. 1A; H317
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS07
Signal word	Warning
Hazard statement(s)	H317: May cause an allergic skin reaction
Precautionary statement(s)	P261 Avoid breathing mist/vapours/spray P280: Wear protective gloves/ protective clothing/eye protection/face protection. P302 + P352 - IF ON SKIN: Wash with plenty of water. P361 P362 + P364 - Take off immediately all contaminated clothing and wash it before reuse. P501 - Dispose of contents and container in accordance with all local, regional, national and international regulations.
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401] Contains: 1,2-benzisothiazolin-3-one. ¹

¹ Based on rules for labelling of CLP Regulation (Annex II, section 2.8)

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for Mandestrobin 40SC

	Result	PPE / Risk mitigation measures
Operators	Acceptable	None required according to the risk assessment. Due to classification of the product with Skin Sens. 1A; H317 protective gloves, protective clothing and eye protection/face protection should be worn when mixing and loading.
Workers	Acceptable	None required
Residents	Acceptable	None required
Bystanders	Acceptable	None required

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended. Due to the classification of the product with Skin Sens. 1A; H317, protective gloves, protective clothing and eye protection/face protection should be worn when mixing and loading.

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 situation (e.g. growth stage of crop)	F, F _n , F _{pn} G, G _n , G _{pn} or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safener/synergist (L/ha)) critical gap for operator, worker, resident or bystander exposure based on [Exposure model]	Acceptability of exposure assessment			
			Method / Kind (incl. application technique ***	Max. number (min. interval between applications) a) per use b) per crop/season	Max. application rate Product L/ha	Water L/ha min / max			Operator	Worker	Residents	Bystander
1	Winter oil seed rape (BBCH 60-69)	F	Spraying, LCTM	a) 1 b) 1	0.5	100-300	-	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032	A	A	A	A

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 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

Noticed data gaps are:

- none

6.2 Toxicological Information on Active Substance

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

	Mandestrobin
Common Name	Mandestrobin
CAS-No.	173662-97-0
Classification and proposed labelling	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	None Based on Conclusion on the peer review of the pesticide risk assessment of the active substance mandestrobin (EFSA Journal 2015;13(5):4100) no classification is proposed with regard to toxicological data
Additional C&L proposal	None
Agreed EU endpoints	
AOEL systemic	0.19 mg/kg bw/d
Reference	EFSA Journal 2015;13(5):4100
Conditions to take into account/critical areas of concern with regard to toxicology	
According to Review Report/EFSA Conclusion for active substance	<p>None</p> <p>According to the EFSA conclusion on Mandestrobin (EFSA Journal 2015;13(5):4100): <i>In the area of mammalian toxicology, one data gap was identified in relationship with the assessment of the toxicological relevance of all the impurities. Assessment of the (eco)toxicological relevance of the impurities (relevant for all representative uses evaluated) cannot be concluded (data gap).</i></p> <p>According to the Addendum to Review Report on Mandestrobin (SANTE/11647/2015/rev 3, 25 March 2021) <i>Assessment of the (eco)toxicological relevance of the impurities. As the specification is based on pilot plant production and needs to be confirmed following commercial scale production, the equivalence of the final specification with the batches used in the toxicological assessment should be confirmed at this stage including the relevance of impurities. This is requested as confirmatory information.</i></p>

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for Mandestrobin 40SC 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 Mandestrobin 40SC

Type of test, species, model system (Guideline)	Result of calculation method acc. to the criteria in CLP Reg.	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD ₅₀ oral, rat (calculation method)	> 2000 mg/kg	Yes the results of calculation method according to CLP Reg. is accepted	None	A 2.2 (KCP 7.1.1)
LD ₅₀ dermal, rat (calculation method)	> 2000 mg/kg		None	A 2.3 (KCP 7.1.2)
LC ₅₀ inhalation, rat (calculation method)	> 5 mg/L		None	A 2.4 (KCP 7.1.3)
Skin irritation (calculation method)	Non-irritant		None	A 2.5 (KCP 7.1.4)
Eye irritation (calculation method)	Non-irritant		None	A 2.6 (KCP 7.1.5)
Skin sensitisation (calculation method)	Sensitising		Skin Sens. 1A; H317: May cause an allergic skin reaction	A 2.7 (KCP 7.1.6)
Supplementary studies for combinations of plant protection products	-	-	-	-

Table 6.3-2: Additional toxicological information relevant for classification/labelling of Mandestrobin 40SC

	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)	Mandestrobin (38.99% (w/w))	None	EFSA conclusion 2015	None
Toxicological properties of non-active substance(s) (relevant for classification of product)	1,2-Benzisothiazolin-3-one (CAS 2634-33-5, >0.036 - <1% (w/w))*	Skin Sens. 1A; H317: May cause an allergic skin reaction (≥ 0.01% (w/w))*	Reg. 1272/2008 / MSDS**	Skin Sens. 1A; H317: May cause an allergic skin reaction
Further toxicological information	-	-	-	-

* 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

The following data on metabolites with the potential to reach the groundwater in concentrations above 0.1 µg/L and requiring relevance assessment were submitted. Note that the relevance assessment of the metabolites is reported in Part B.10.

In addition, toxicological data available on metabolite DX-CA-S-2200 are presented in Appendix 2.

6.4.1 2-COOH-S-2200

An overview of the results of the accepted toxicological studies for groundwater metabolite 2-COOH-S-2200 is given in the following table.

Table 6.4-1: Summary of the results of toxicity studies for 2-COOH-S-2200

Type of test, species (Guideline)	Result	Acceptability	Reference*
Acute oral (OECD 423)	LD ₅₀ > 2000 mg/kg bw	Yes	XXXX, 2012a*
Ames test (OECD 471)	Negative	Yes	XXXX, 2012a*
<i>In vitro</i> chromosomal aberration test (OECD 473)	positive without S9 at cytotoxic levels	Yes	XXXX, 2012b*
<i>In vitro</i> mammalian gene mutation assay (OECD 476)	Negative	Yes	XXXX., 2011a*
<i>In vivo</i> micronucleus assay (OECD 474)	Negative	Yes	XXXX, 2012*#

* indicates that a study was reviewed at EU level (EFSA Journal 2015;13(5):4100)

Based on DE comment provided during MSs consultation period:

In vivo micronucleus assay (XXXX., 2012):

There are some deviations from the current OECD TG 474, 2016 identified:

- Only 2000 polychromatic erythrocytes were counted instead of 4000.

ADME data in rats with the active substance is used to demonstrate bone marrow exposure. Explanations are provided as to why it is reasonable to assume that the metabolite behaves similarly to the active substance in terms of toxicokinetics. However, the *in vivo* micronucleus assay was performed in mice and the transfer of ADME data between species appears to be difficult. Therefore, we consider that bone marrow exposure requires further consideration, as described by EFSA [EFSA Journal 2017;15(12):5113].

zRMS:

The above issue should be considered at EU level during a renewal assessment of Mandestrobin.

6.4.2 5-COOH-S-2200

An overview of the results of the accepted toxicological studies for groundwater metabolite 5-COOH-S-2200 is given in the following table.

Table 6.4-2: Summary of the results of toxicity studies for 5-COOH-S-2200

Type of test, species (Guideline)	Result	Acceptability	Reference*
Acute oral (OECD 423)	300 > LD ₅₀ > 2000 mg/kg bw	Yes	XXXX, 2012b*
Ames test (OECD 471)	Negative	Yes	XXXX, 2012c*
<i>In vitro</i> chromosomal aberration test (OECD 473)	Negative	Yes	XXXX, 2012d*#
<i>In vitro</i> mammalian gene mutation assay (OECD 476)	Negative	Yes	XXXX, 2011b*

* indicates that a study was reviewed at EU level (EFSA Journal 2015;13(5):4100)

Based on DE comment provided during MSs consultation period:

In vitro chromosomal aberration test (XXXX., 2012):

The following deviation from the current OECD TG 473, 2016 is identified:

Only 200 metaphases are counted instead of 300.

zRMS:

The above issue should be considered at EU level during a renewal assessment of Mandestrobin.

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in Mandestrobin 40SC are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in Mandestrobin 40SC

	Mandestrobin	
	Value	Reference
Concentrate	10%	Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873)
Dilution	50%	Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873)

6.5.1 Justification for proposed values - mandestrobin

Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for mandestrobin

	Value	Justification for value	Acceptability of justification
Concentrate	10%	Default value for a SC formulation	Justification accepted. Endpoint can be used for current product.
Dilution	50%	Default value for a SC formulation	Justification accepted. Endpoint can be used for current product.

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	Mandestrobin 40SC
Formulation type	SC
Category	Fungicide
Active substance(s) (incl. content)	Mandestrobin Pure: 400g/L Technical: 421g/L
AOEL systemic	0.19 mg/kg bw/d
Inhalation absorption	100%
Oral absorption	100%
Dermal absorption	Concentrate: 10% Dilution: 50%) (Default values)

6.6.1 Selection of critical use(s) and justification

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

Justification

Mandestrobin 40SC is a fungicide applied as spray in winter and spring oilseed rape. All applications are done via tractor-mounted downward spraying. The highest application rate of 0.5 L prod./ha in a minimum water volume of 100 L/ha.

Exposure assessments have been conducted using the active substance technical content of Mandestrobin 40SC (421 g/L mandestrobin) as is specified in the EFSA 2022 exposure calculator.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of Mandestrobin 40SC according to the critical uses 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 Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Winter and spring oilseed rape (max. 0.5 L product/ha)
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032 calculator version: 1.0.1

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

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Field crops/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
Mandestrobin	Number of applications and application rate: 1 x 0.2105 kg a.s./ha Dermal absorption (concentrate): 10 % Dermal absorption (in-use dilution): 50 %		
	M/L: None App: None	0.1	61.9
	M/L: Workwear App: Workwear	0.08	40.1

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

Błąd! Nie można odnaleźć źródła odwołania. shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with Mandestrobin 40SC according to the critical use(s). Outcome of the estimation is presented in Table 6.6-5 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	Winter and spring oilseed rape (max. 0.5 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032 calculator version: 1.0.1

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

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: NA Body weight: 60 kg TC (potential): 12500 cm ² /h TC (workwear (arms, body and legs covered)): 1400 cm ² /h TC (workwear (arms, body and legs covered) and gloves): 1250 cm ² /h TC (gloves): NA cm ² /h			
Number of applications & application rate: 1 x 0.2105 kg a.s./ha Dermal absorption: 50 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Potential	0.1	69.2	0
Workwear	0.01	7.8	0
Workwear and gloves	0.01	6.9	0

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not required.

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

No bystander risk assessment is required for PPPs that do not have significant acute toxicity or the potential to exert toxic effects after a single exposure. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days. Therefore, exposure assessment for residents also covers bystander exposure.

At this time, no acute AOEL has been set for mandestrobin. Consequently no acute (bystander) risk assessment has been provided.

Table 6.6-6 shows the exposure model used for estimation of resident and bystander exposure to mandestrobin. The outcome of the estimation is presented in Table 6.6-7 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Winter and spring oilseed rape (max. 0.5 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032 calculator version: 1.0.1

Table 6.6-7: Estimated resident exposure (longer term exposure)

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: NA Minimum volume of water: 100 l			
Number of applications and application rate: 1 x 0.2105 kg a.s./ha Dermal absorption: 50 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Mandestrobin	Drift (75th perc.)	0.03	15
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.002	0.9
	Re-entry (75th perc.)	0.02	9.3
	Sum (mean)	0.03	16.7
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.007	3.6
	Vapour (75th perc.)	0.0003	0.1

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
	Deposits (75th perc.)	0.0007	0.4
	Re-entry (75th perc.)	0.01	5.2
	Sum (mean)	0.01	6.2

6.6.4.2 Measurement of resident and/or bystander exposure

Since the resident and/or bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for mandestrobin will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

6.6.5 Combined exposure

Not relevant. The product contains only one active substance.

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
KCA 5.8.1/01	XXXX	2017	Acute oral toxicity study of DX-CA-S-2200 in rats Report No. ROT-0093 XXXX, GLP Unpublished	Y	XXXX
KCA 5.8.1/02	XXXX	2017	DX-CA-S-2200: Bacterial reverse mutation test Report No. ROT-0094 XXXX, GLP Unpublished	N	XXXX
KCA 5.8.1/03	XXXX	2017	DX-CA-S-2200: Chromosome aberration test in cultured mammalian cells Report No. ROT-0095 XXXX, GLP Unpublished	N	XXXX
KCA 5.8.1/04	XXXX	2017	DX-CA-S-2200: Gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) Report No. ROT-0096 XXXX, GLP Unpublished	N	XXXX

* XXXX).

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
KCA 5.8.1	XXXX	2012a	Acute Oral Toxicity Study of 2-COOH-S-2200 in Rats Report No. ROT-0043 GLP Unpublished.	Y	XXXX
KCA 5.8.1	Kitamoto, S.	2012a	Reverse Mutation Test of 2-COOH-S-2200 in Bacterial Systems Report No. ROT-0041 GLP Unpublished	N	XXXX
KCA 5.8.1	XXXX	2012b	<i>In vitro</i> Chromosomal Aberration Test on 2-COOH-S-2200 in Chinese Hamster Lung Cells (CHL/IU) Report No. ROT-0046 GLP Unpublished	N	XXXX
KCA 5.8.1	XXXX	2011a	Gene Mutation Assay in Chinese Hamster V79 Cells <i>in vitro</i> (V79/HPRT) with 2-COOH-S-2200 Report No. ROT-0033 XXXX GLP Unpublished	N	XXXX
KCA 5.8.1	XXXX	2012	Micronucleus Assay of 2-COOH-S-2200 in Mice Report No. ROT-0040 XXXX GLP Unpublished	Y	XXXX
KCA 5.8.1	XXXX	2012b	Acute Oral Toxicity Study of 5-COOH-S-2200 in Rats Report No. ROT-0044 GLP Unpublished	Y	XXXX

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
KCA 5.8.1	Kitamoto, S.	2012c	Reverse Mutation Test of 5-COOH-S-2200 in Bacterial Systems Report No. ROT-0042 GLP Unpublished	N	XXXX
KCA 5.8.1	XXXX	2012d	<i>In vitro</i> Chromosomal Aberration Test on 5-COOH-S-2200 in Chinese Hamster Lung Cells (CHL/IU) Report No. ROT-0047 GLP Unpublished	N	XXXX
KCA 5.8.1	XXXX	2011b	Gene Mutation Assay in Chinese Hamster V79 Cells <i>in vitro</i> (V79/HPRT) with 5-COOH-S-2200 Report No. ROT-0034 XXXX GLP Unpublished	N	XXXX

* XXXX).

The following tables are to be completed by MS

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
KCA 5.8.1/01	XXXX	2017	Acute oral toxicity study of DX-CA-S-2200 in rats Report No. ROT-0093 XXXX. GLP Unpublished	Y	XXXX

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
KCA 5.8.1/02	XXXX	2017	DX-CA-S-2200: Bacterial reverse mutation test Report No. ROT-0094 XXXX. GLP Unpublished	N	XXXX
KCA 5.8.1/03	XXXX	2017	DX-CA-S-2200: Chromosome aberration test in cultured mammalian cells Report No. ROT-0095 XXXX. GLP Unpublished	N	XXXX
KCA 5.8.1/04	XXXX	2017	DX-CA-S-2200: Gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) Report No. ROT-0096 XXXX. GLP Unpublished	N	XXXX
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	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
KCP XX	Author	YYYY	Title Company Report N	Y/N	Owner

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
			Source GLP/non GLP/GEP/non GEP Published/Unpublished		

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

In the first instance, classification using an alternative method based on the complete composition of the plant protection product is taken into account for classification purpose. Classification via the application of bridging principles is not necessary.

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	The assessment of acute oral toxicity based on the criteria of CLP Regulation. Accepted
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Acute oral toxicity has been calculated using the method described in Regulation (EC) No 1272/2008 section 3.1.3.6. For more details refer to Part C Section 1.3.2.

One ingredient in Mandestrobin 40SC is classified for acute oral toxicity (category 4). The calculated ATE_{mix} for acute oral toxicity is >2000 mg/kg and 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 zRMS:	The assessment of acute dermal toxicity based on the criteria of CLP Regulation. Accepted
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Acute dermal toxicity has been calculated using the method described in Regulation (EC) No 1272/2008 section 3.1.3.6. For more details refer to Part C Section 1.3.2.

No ingredients in Mandestrobin 40SC are classified for acute dermal toxicity. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	The assessment of acute inhalation toxicity based on the criteria of CLP Regulation. Accepted
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Acute inhalation toxicity has been calculated using the method described in Regulation (EC) No 1272/2008 section 3.1.3.6. For more details refer to Part C Section 1.3.2.

Two ingredients in Mandestrobin 40SC are classified for acute inhalation toxicity. One ingredient is classified Acute Tox. 2 and the other ingredient is classified Acute Tox. 4. The calculated ATE_{mix} for acute inhalation toxicity is >5 mg/L and thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	The assessment of skin corrosion/irritation properties of the product Intuity Plus based on the criteria of CLP Regulation. Accepted
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Skin irritation has been calculated using the method described in Regulation (EC) No 1272/2008 section 3.2.3. For more details refer to Part C Section 1.3.2.

Three ingredients in Mandestrobin 40SC are classified for skin irritation (Skin Irrit. 2) and one ingredient is classified for skin corrosion (Skin Corr. 1A). The sum of the classified ingredients in Mandestrobin 40SC is below the generic or specific concentration limit for skin corrosion and irritation and thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	The assessment of eye damage/irritation properties of the product Intuity Plus based on the criteria of CLP Regulation. Accepted
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Eye irritation has been calculated using the method described in Regulation (EC) No 1272/2008 section 3.3.3. For more details refer to Part C Section 1.3.2.

One ingredient in Mandestrobin 40SC is classified for skin corrosion (Skin Corr. 1A), other one for eye damage ~~irritation~~ (category 1) and two ingredients are classified for eye irritation (category 2). The sum of the classified ingredients in Mandestrobin 40SC is below the generic or specific concentration limit for eye irritation and thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	The assessment of skin sensitising properties of the product Intuity Plus based on the criteria of CLP Regulation. The CLP classification of the product as Skin Sens. 1; H317 is warranted.
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Skin sensitisation has been calculated using the method described in Regulation (EC) No 1272/2008 section 3.4.3. For more details refer to Part C Section 1.3.2.

One ingredient in Mandestrobin 40SC is classified for skin sensitisation (Skin Sens. 1A). The ingredient is present in Mandestrobin 40SC at a concentration above the specific concentration limit and therefore classification of Mandestrobin 40SC is required according to Regulation (EC) No. 1272/2008 as Skin Sens. 1A; H317.

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)

No studies submitted.

A 2.11 Other/Special Studies

A 2.11.1 Acute oral toxicity study (KCA 5.8.1)

Comments of zRMS:	The metabolite DX-CA-S-2200 is predicted to occur in groundwater at maximum concentration below 0.1 µg/L Therefore a relevance assessment according to SANCO/221/2000 is not required. The study was not used to evaluation of the relevance of metabolites in groundwater and therefore was not assessed here. This study should be evaluated at EU peer review process for active substance mandestrobin.
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Reference:	KCA 5.8.1/01
Report	Acute oral toxicity study of DX-CA-S-2200 in rats, XXXX. 2017, Report No. ROT-0093
Guideline(s):	Yes. JMAFF 12 Nousan No 8147 (2000 / 2014), OECD 423 “acute toxic class method” (2001), EC No. 440 B.1 tris (2008)
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.), purity	DX-CA-S-2200 (089-160803-1), 99.9%
Species	Rat [RccHan:WIST]
No. of animals (group size)	6 females (3 animals per group, Group 1 and 2 tested separately)
Dose(s)	2000 mg/kg bw (both Groups 1 and 2)
Exposure	Once by gavage

Vehicle/Dilution	0.5% (w/v) methylcellulose aqueous solution
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 12: Results of acute oral toxicity study in rats of DX-CA-S-2200

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD ₅₀ (mg/kg bw) (14 days)
Female rats				
2000	0/0/6	-	-	> 2000

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

Table A 13: Summary of findings of acute oral toxicity study in rats of DX-CA-S-2200

Mortality:	No deaths occurred.
Clinical signs:	No clinical signs were observed.
Body weight:	Body weight and body weight were 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 oral LD₅₀ of DX-CA-S-2200 is higher than 2000 mg/kg bw in female rats.

A 2.11.2 Bacterial reverse mutation test (KCA 5.8.1)

Comments of zRMS:	The metabolite DX-CA-S-2200 is predicted to occur in groundwater at maximum concentration below 0.1 µg/L Therefore a relevance assessment according to SANCO/221/2000 is not required. The study was not used to evaluation of the relevance of metabolites in groundwater and therefore was not assessed here. This study should be evaluated at EU peer review process for active substance mandestrobin.
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Reference:	KCA 5.8.1/02
Report	DX-CA-S-2200: Bacterial reverse mutation test, XXXX. 2017, Report No. ROT-0094
Guideline(s):	Yes. JMAFF 12 Nousan No 8147, 2-1-19-1 (2000), EPA OPPTS (870.5100, 1998), OECD 471 (1997), EU No 440, Method B.13/14 (2008)
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	Not a vertebrate study

Materials and methods

Test material (Lot/Batch No.), purity	DX-CA-S-2200 (089-160803-1), 99.9%
Control materials	Negative (solvent) control Dimethyl sulfoxide (DMSO) Positive controls without activation 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2): 0.01 µg/plate TA100, WP2 <i>uvrA</i> ; 0.1 µg/plate TA98 Sodium azide (NaN ₃): 0.5 µg/plate TA1535 9-aminoacridine hydrochloride hydrate (9-AA): 80 µg/plate TA1537 Positive controls with activation Benzo[a]pyrene (B[a]P): 5 µg/plate TA100, TA98 2-aminoanthracene (2-AA): 2 µg/plate TA1535, TA1537; 10 µg/plate WP2 <i>uvrA</i>
Mammalian metabolic system	S9 mix 8 mM MgCl ₂ 33 mM KCl 5 mM glucose-6-phosphate 4 mM NADH 4 mM NADPH 100 mM sodium phosphate buffer (pH 7.4) S9 10% (v/v) Rat liver induced with phenobarbital and 5,6-benzoflavone (Kikkoman Biochemifa Company, Tokyo, Japan)
Test system	<i>Salmonella typhimurium</i> TA100, TA1535, TA98, TA1537 <i>Escherichia coli</i> WP2 <i>uvrA</i>
Test concentrations	Experiment I (dose range finding) 5.0, 15, 50, 150, 500, 1500 and 5000 µg/plate, +/- S9 Experiment II (main test) 313, 625, 1250, 2500 and 5000 µg/plate, +/- S9 Triplicate plates also for solvent control and positive control groups.
Remarks	None

Results and discussions

Table A 24: Mean revertant counts following treatment with DX-CA-S-2200

Metabolic activation	Concentration (µg/plate)		Number of revertant colonies/plate (mean ±SD)				
			TA100	TA1535	WP2 <i>uvrA</i>	TA98	TA 1537
Experiment I (dose range finding)							
Without activation	DMSO		107 ± 7	6 ± 3	19 ± 2	13 ± 4	7 ± 2
	DX-CA-S-2200	5	121 ± 11	6 ± 1	18 ± 3	12 ± 3	5 ± 3
		15	115 ± 1	6 ± 2	14 ± 4	14 ± 3	5 ± 3
		50	116 ± 4	6 ± 1	21 ± 3	14 ± 6	8 ± 1
		150	114 ± 9	4 ± 3	19 ± 2	16 ± 4	7 ± 3
		500	118 ± 1	6 ± 4	20 ± 1	11 ± 4	5 ± 2
		1500	108 ± 8	6 ± 4	19 ± 6	13 ± 2	5 ± 4
		5000	124 ± 17	7 ± 3	18 ± 3	12 ± 3	7 ± 1
	AF-2	0.01	583 ± 10		165 ± 7		
	NaN ₃	0.5		432 ± 11			
AF-2	0.1				444 ±21		
9-AA	80					582 ± 155	
With activation	DMSO		109 ± 5	8 ± 0	27 ± 10	21 ± 8	10 ± 2
	DX-CA-S-2200	5	118 ± 5	5 ± 2	17 ± 4	21 ± 4	10 ± 4
		15	112 ± 9	8 ± 3	22 ± 7	17 ± 3	9 ± 4
		50	128 ± 13	5 ± 1	20 ± 9	26 ± 1	11 ± 1
		150	114 ± 7	7 ± 1	16 ± 4	25 ± 8	10 ± 2
		500	104 ± 1	6 ± 1	18 ± 4	21 ± 6	12 ± 3
		1500	115 ± 8	3 ± 1	20 ± 3	15 ± 1	8 ± 1
		5000	118 ± 11	6 ± 2	21 ± 5	27 ± 5	8 ± 2
	B[a]P	5	1163 ± 53			242 ± 25	
	2-AA	2		106 ± 2			56 ± 5
2-AA	10			217 ± 39			
Experiment II (main study)							
Without activation	DMSO		104 ± 10	9 ± 2	16 ± 3	16 ± 1	7 ± 3
	DX-CA-S-2200	313	112 ± 8	6 ± 1	13 ± 6	16 ± 3	3 ± 2
		625	103 ± 13	6 ± 2	21 ± 4	14 ± 2	6 ± 4
		1250	95 ± 9	10 ± 1	19 ± 7	13 ± 3	6 ± 2
		2500	103 ± 13	6 ± 3	19 ± 3	17 ± 2	7 ± 2
		5000	103 ± 5	8 ± 2	20 ± 3	14 ± 3	5 ± 3
	AF-2	0.01	582 ± 31		162 ± 28		
	NaN ₃	0.5		465 ± 20			
	AF-2	0.1				422 ± 2	
9-AA	80					397 ± 161	
With activation	DMSO		103 ± 16	7 ± 5	23 ± 1	18 ± 6	10 ± 3
	DX-CA-S-2200	313	106 ± 8	10 ± 2	20 ± 4	22 ± 10	10 ± 5
		625	94 ± 7	6 ± 4	18 ± 3	21 ± 2	9 ± 3
		1250	94 ± 9	8 ± 3	19 ± 3	24 ± 8	9 ± 2
		2500	94 ± 7	7 ± 1	16 ± 3	22 ± 7	8 ± 4
		5000	85 ± 14	4 ± 3	23 ± 1	15 ± 4	11 ± 1
	B[a]P	5	1431 ± 70			256 ± 33	
	2-AA	2		111 ± 3			66 ± 6
2-AA	10			275 ± 44			

AF-2 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide
NaN₃ Sodium azide
9-AA 9-aminoacridine hydrochloride hydrate
B[a]P benzo[a]pyrene
2-AA 2-aminoanthracene

Table A 15: Summary of findings of bacterial reverse mutation test on DX-CA-S-2200

Cytotoxicity & precipitation:	Neither precipitation of the test substance nor cytotoxicity to bacteria was observed at any test concentration in any of the tester strains with or without metabolic activation in both the dose range finding study and the main test.
Number of revertant colonies:	A two-fold or more increase above solvent control in the number of revertant colonies was not observed in any of the strains treated with the test substance, either with or without metabolic activation in both the dose range finding study and the main test.

Conclusion

DX-CA-S-2200 does not induce gene mutations in the genome of *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537 or in the genome of *Escherichia coli* strain WP2 *uvrA*, under the conditions of the test.

A 2.11.3 Chromosome aberration test (KCA 5.8.1)

Comments of zRMS:	The metabolite DX-CA-S-2200 is predicted to occur in groundwater at maximum concentration below 0.1 µg/L Therefore a relevance assessment according to SANCO/221/2000 is not required. The study was not used to evaluation of the relevance of metabolites in groundwater and therefore was not assessed here. This study should be evaluated at EU peer review process for active substance mandestrobin.
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Reference:	KCA 5.8.1/03
Report	DX-CA-S-2200: Chromosome aberration test in cultured mammalian cells, XXXX. 2017, Report No. ROT-0095
Guideline(s):	Yes. JMAFF 12 Nousan No 8147, 2-1-19-2 (2000), EPA OPPTS 870.5375 (1998), OECD 473 (2016), EU No 440, Method B.10 (2008)
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	Not a vertebrate study

Materials and methods

Test material (Lot/Batch No.), purity	DX-CA-S-2200 (089-160803-1), 99.9%
Control materials	Negative (solvent) control Dimethyl sulfoxide (DMSO) at 1% (v/v) Short-term treatment Positive control absence of S9 Mitomycin C (MMC), 0.1 µg/mL Positive control presence of S9 Benzo[a]pyrene (B[a]P), 10 µg/mL Continuous treatment Positive control Mitomycin C (MMC): 0.1 µg/mL
Mammalian metabolic system	S9 mix 8 mM MgCl ₂

	33 mM KCl 5 mM glucose-6-phosphate 4 mM NADH 4 mM NADPH 100 mM sodium phosphate buffer (pH 7.4) S9 30% (v/v) Rat liver induced with phenobarbital and 5,6-benzoflavone (Kikkoman Biochemifa Company, Tokyo, Japan)
Test system	Mammalian cells in culture Chinese hamster lung (CHL/IU) cells Culture medium and conditions MEM supplemented with 10% inactivated newborn calf serum, penicillin-streptomycin (100 IU/mL-100 µg/mL) and L-glutamine (2 mM). Cells sub-cultured using 0.25% trypsin solution. 37°C, humidified atmosphere, 5% CO ₂ .
Test concentrations	Short-term treatment 6 hours without S9 mix 250, 500*, 1000* and 2000* µg/mL 6 hours with S9 mix (18 hour culture) 250, 500*, 1000* and 2000* µg/mL Continuous treatment 24 hours without S9 mix 250, 500*, 1000* and 2000* µg/mL * selected after cytotoxicity and test substance precipitation observations
Remarks	None

Results and discussions

Table A 36: Percentage of cells with aberrations or polyploidy following treatment with DX-CA-S-2200

Experiment	Treatment	No cells examined	RICC (%)	% cells with aberrations [#]	Polyloid cells (%)	HCD [†] mean ± SD [min to max]
Short-term treatment -S9, 6-18 h ⁽ⁱ⁾	Solvent control	150	100	0.7	0.7	a) 0.80 ± 0.94 [0.0 to 5.0]; b) 0.40 ± 0.46 [0.0 to 2.0]
	DX-CA-S-2200					
	500 µg/mL	150	93	1.0	0	
	1000 µg/mL	150	94	0.7	0.3	
	2000 µg/mL	150	85	0.7	0	
	Positive control 0.1 µg/mL MMC	150	40	53.3**	0	a) 34.8 ± 9.5 [18.5 to 54.5]
Short-term treatment +S9, 6-18 h ⁽ⁱⁱ⁾	Solvent control	150	100	0.3	0.3	a) 0.76 ± 0.74 [0.0 to 3.0]; b) 0.36 ± 0.39 [0.0 to 1.5]
	DX-CA-S-2200					
	500 µg/mL	150	105	0	0	
	1000 µg/mL	150	102	0.3	0	
	2000 µg/mL	150	94	0.7	0	
	Positive control (10 µg/mL B[a]P)	150	49	22.3**	0	a) 20.3 ± 3.4 [14.0 to 26.7]

Experiment	Treatment	No cells examined	RICC (%)	% cells with aberrations [#]	Polyloid cells (%)	HCD [†] mean ± SD [min to max]
Continuous-treatment -S9, 24 h ⁽ⁱⁱⁱ⁾	Solvent control	150	100	0.3	0.7	a) 0.71 ± 0.64 [0.0 to 3.5]; b) 0.38 ± 0.56 [0.0 to 3.0]
	DX-CA-S-2200					
	500 µg/mL	150	94	0.7	0	
	1000 µg/mL	150	87	1.0	0	
	2000 µg/mL	150	78	1.3	0.3	
	Positive control (0.1 µg/mL MMC)	150	45	59.7**	0	a) 53.0 ± 11.3 [24.0 to 84.0]

** Significantly different from the solvent control: $p \leq 0.01$

(i) Cells treated with test substance for 6 hours -S9 and then cultured in fresh medium for a further 18 hours

(ii) Cells treated with test substance for 6 hours +S9 and then cultured in fresh medium for a further 18 hours

(iii) Cells treated with test substance continuously for 24 hours -S9

RICC Relative Increase in Cell Count; MMC: mitomycin C; B[a]P: benzo[a]pyrene

[#] Excluding gaps

[†] HCD: historical control data

a) structurally aberrant cells (%), excluding gaps; b) polyloid cells (%), negative control only.

Negative control data for solvents dimethyl sulfoxide, physiological saline or carboxymethylcellulose sodium salt (1988-2015). Positive control data for Mitomycin C (1988-2015) and benzo[a]pyrene (November 2014-December 2015).

Conclusion

In both the short-term and continuous treatments, no significant increases in the frequency of structurally or numerically aberrant metaphases were found in the DX-CA-S-2200-treated groups.

Under the conditions of this study the clastogenic potential of DX-CA-S-2200 was negative in cultured Chinese hamster CHL/IU cells in the presence and absence of metabolic activation.

A 2.11.4 Gene mutation assay in Chinese Hamster V79 cells *in vitro* (KCA 5.8.1)

Comments of zRMS:	The metabolite DX-CA-S-2200 is predicted to occur in groundwater at maximum concentration below 0.1 µg/L Therefore a relevance assessment according to SANCO/221/2000 is not required. The study was not used to evaluation of the relevance of metabolites in groundwater and therefore was not assessed here. This study should be evaluated at EU peer review process for active substance mandestrobin.
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Reference: KCA 5.8.1/04

Report DX-CA-S-2200: Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79/HPRT), XXXX. 2017, Report No. ROT-0096

Guideline(s): Yes. EPA OPPTS 870.5300 (1998), OECD 476 (2016), EU No 440, Method B.17 (2008)

Deviations: No

GLP: Yes

Acceptability: Yes

Duplication Not a vertebrate study
(if vertebrate study)

Materials and methods

Test material (Lot/Batch No.), purity	DX-CA-S-2200 (089-160803-1), 99.9%
Control materials	Concurrent (negative) control Untreated cells cultivated without interruption throughout the assay. Solvent control Dimethyl sulfoxide (DMSO) Positive control without activation Ethylmethane sulfonate (EMS): 300 µg/mL Positive control with activation 7,12-dimethylbenz(a)anthracene (DMBA): 2.3 µg/mL
Mammalian metabolic system	S9 derived Rat liver induced with phenobarbital/β-naphthoflavone (Envigo). S9 mix 8 mM MgCl ₂ 33 mM KCl 5 mM glucose-6-phosphate 4 mM NADP 100 mM sodium ortho-phosphate buffer (pH 7.4) Protein concentration of S9, pre-experiment: 28.1 mg/mL; experiment I and II: 30.1 mg/mL
Test system	Chinese hamster cell line V79 Complete culture medium was MEM (minimal essential medium) containing Hank's salts, neomycin (5 µg/mL), 10% foetal bovine serum (FBS) and amphotericin B (1 %). All cultures were incubated at 37°C with 1.5% carbon dioxide in humidified air (98.5% air). Locus examined: hypoxanthine-guanine phosphoribosyl transferase (HPRT) Selective agent: 6-thioguanine (TG)
Test concentrations	Experiment I and II 31.3, 62.5, 125, 250, 500, 1000 and 2000 µg/mL (4 hours with and without S9)
Remarks	None

Results and discussions

Table A 47: Mean number of mutant colonies following treatment with DX-CA-S-2200

Concentration	μg/mL	S9 mix	Culture I		Culture II		HCD† mean ± SD [min to max]
			% relative adjusted cloning efficiency	mutants/ 10 ⁶ cells	% relative adjusted cloning efficiency	mutants/ 10 ⁶ cells	
Experiment I / 4 hour treatment							
Neg. control ^(a)		-	124.3	20.7	109.8	28.2	
Solvent control ^(b)		-	100.0	18.0	100.0	<u>30.7</u>	15.9 ± 7.1 [3.4-41.0]
Pos. control EMS ^(c)	300	-	69.2	192.1	74.6	325.8	190.3 ± 88.4 [53.9-872.3]
DX-CA-S-2200	31.3	-	114.4	#	77.5	#	95% confidence interval‡: 1.7-30.2
DX-CA-S-2200	62.5	-	102.4	#	77.2	#	
DX-CA-S-2200	125	-	72.7	25.1	73.0	29.3	
DX-CA-S-2200	250	-	122.4	16.1	82.6	<u>34.9</u>	
DX-CA-S-2200	500	-	87.4	24.5	73.1	<u>30.8</u>	
DX-CA-S-2200	1000	-	72.0	23.8	73.8	<u>30.9</u>	
DX-CA-S-2200	2000^P	-	90.5	<u>30.6</u>	83.4	24.6	
Linear regression				p = 0.072		p = 0.099	
Neg. control ^(a)		+	104.8	22.6	98.8	32.1	

Concentration	µg/mL	S9 mix	Culture I		Culture II		HCD† mean ± SD [min to max]
			% relative adjusted cloning ef- ficiency	mutants/ 10 ⁶ cells	% relative adjusted cloning effi- ciency	mutants/ 10 ⁶ cells	
Solvent control ^(b)		+	100.0	21.8	100.0	<u>31.1</u>	15.7 ± 6.8 [2.4-39.2]
Pos. control DMBA ^(c)	2.3	+	56.4	137.8	82.8	144.4	215.8 ± 110.9 [56.7-739.9]
DX-CA-S-2200	31.3	+	69.7	#	83.3	#	95% confi- dence interval‡: 2.0-29.4
DX-CA-S-2200	62.5	+	103.7	#	89.7	#	
DX-CA-S-2200	125	+	87.6	19.6	77.4	<u>34.0</u>	
DX-CA-S-2200	250	+	70.0	27.1	85.6	24.6	
DX-CA-S-2200	500	+	65.0	17.7	79.2	<u>34.8</u>	
DX-CA-S-2200	1000	+	74.2	16.6	86.0	24.3	
DX-CA-S-2200	2000 ^P	+	65.0	19.7	81.7	<u>33.5</u>	
Linear regression				p = 0.485		p = 0.886	
Experiment II / 4 hour treatment							
Neg. control ^(a)		-	69.1	9.6	100.5	7.7	
Solvent control ^(b)		-	100.0	11.6	100.0	14.1	15.9 ± 7.1 [3.4-41.0]
Pos. control EMS ^(c)	300	-	44.5	354.7	90.3	211.3	190.3 ± 88.4 [53.9-872.3]
DX-CA-S-2200	31.3	-	#	#	#	#	95% confi- dence interval‡: 1.7-30.2
DX-CA-S-2200	62.5	-	#	#	#	#	
DX-CA-S-2200	125	-	45.0	12.8	75.9	12.7	
DX-CA-S-2200	250	-	49.5	10.5	76.5	11.2	
DX-CA-S-2200	500	-	64.2	13.5	82.0	12.4	
DX-CA-S-2200	1000	-	44.3	14.7	86.3	9.8	
DX-CA-S-2200	2000 ^P	-	27.5	11.0	92.9	13.1	
Linear regression				p = 0.955		p = 0.803	
Neg. control ^(a)		+	135.1	16.1	106.0	12.3	
Solvent control ^(b)		+	100.0	8.9	100.0	14.6	15.7 ± 6.8 [2.4-39.2]
Pos. control DMBA ^(c)	2.3	+	108.4	141.2	80.1	138.4	215.8 ± 110.9 [56.7-739.9]
DX-CA-S-2200	31.3	+	#	#	#	#	95% confi- dence interval‡: 2.0-29.4
DX-CA-S-2200	62.5	+	#	#	#	#	
DX-CA-S-2200	125	+	81.3	9.4	71.5	9.4	
DX-CA-S-2200	250	+	111.4	14.3	78.5	6.6	
DX-CA-S-2200	500	+	78.3	12.7	73.3	14.7	
DX-CA-S-2200	1000	+	87.3	16.3	94.1	10.8	
DX-CA-S-2200	2000 ^P	+	104.3	8.2	84.0	1.1	
Linear regression				p = 0.846		p = 0.115	

(a): negative control with medium; (b): solvent control with DMSO; (c): Positive control with EMS (ethyl methane sulfonate) or DMBA (7,12-dimethylbenz(a)anthracene).

P: Precipitation (visible microscopically at the beginning and at the end of treatment)

#: Culture was not continued as a minimum of only four analysable concentrations is required

†: Historical control data (HCD) for 2014-2016 (111 studies without S9, 105 studies with S9). Number of mutant colonies per 10⁶ cells: solvent control (for medium, acetone, water, DMSO, ethanol, THF, EGDE); positive control for EMS (150 and 300 µg/mL) and DMBA (1.1 and 2.3 µg/mL)

‡: 95% confidence interval (solvent control): mean ± 2 × standard deviation. Underlined values of mutants/10⁶ cells are outside the relevant interval.

No relevant, reproducible increase in mutants/10⁶ cells was observed up to the maximum concentration. The 95% confidence interval was exceeded at certain concentrations in Experiment I (underlined values in Table A 17) however, considering the mean values, the 95% confidence interval was not exceeded for Experiment I, with or without metabolic activation. A t-test using values for both cultures, for concentrations where the confidence interval was exceeded, showed no significant response. In addition, the 95% confidence interval was not exceeded at any concentration with or without metabolic activation in Experiment II. The slight increases in mutants/10⁶ cells in Experiment I were therefore not considered relevant or indicative of a mutagenic effect.

Linear regression analysis of the mutation frequency data did not suggest a significant dose dependent

trend.

EMS and DMBA were used as positive controls and showed a distinct increase in the number of mutant colonies.

Conclusion

DX-CA-S-2200 does not induce gene mutations at the HPRT locus in V79 cells and therefore DX-CA-S-2200 is considered to be non-mutagenic under the experimental conditions of this HPRT assay.

Appendix 3 Exposure calculations

EFSA 2022 Model:



Mandestrobin 40SC_20230927_09h40_opex1.0.1.zip

EFSA 2022 Report:



Mandestrobin
40SC_20230927.docx

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for mandestrobin

Table A 5: Input parameters considered for the estimation of operator exposure

Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	Name of active sub- stance	Mandestrobin
Concentration of ac- tive substance [g a.s./l or kg]	421	Crops	Field crops
Area treated [ha/day]	50	Application method	Downward spraying
Dermal absorption [%] (concentrate)	10	Application technique	Vehicle-mounted
Dermal absorption [%] (dilution)	50	Indoor/outdoor	Outdoor
Oral absorption [%]	100	Drift reduction [%]	0
Inhalation absorption [%]	100	Type of cultivation	Normal
Body weight (kg)	60		
AOEL [mg/kg bw/day]	0.19		
AAOEL [mg/kg bw]			

Table A 6: Estimation of longer term operator exposure towards mandestrobin according to EFSA guidance

Activity	Systemic exposure per body part	With work- wear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	Hand protection	None	None
	Hands exposure	61.1	61.1
	Body protection	Workwear	Workwear
	Body exposure	0.4	0.4
	Head protection	None	None
	Head exposure	1.1	1.1

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
Application (µg/kg bw per day)	Inhalation protection	None	None
	Inhalation exposure	0.1	0.1
	Hand protection	None	None
	Hands exposure	13	13
	Body protection	Workwear	Workwear
	Body exposure	0.2	0.2
	Head protection	None	None
	Head exposure	0.3	0.3
	Inhalation protection	None	None
	Inhalation exposure	0.06	0.06
Total	Total systemic exposure [mg/kg bw per day]	0.08	0.08
	% of AOEL	40.1	40.1

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for mandestrobin

Table A 7: Input parameters considered for the estimation of worker exposure

Indoor/outdoor	Outdoor	AOEL [mg/kg bw/day]	0.19
Re-entry activity	Inspection, irrigation	Dermal transfer coefficient - Total potential exposure [cm²/h]	12500
Crops	Field crops	Dermal transfer coefficient - Arm, body and legs covered [cm²/h]	1400
Application method	Downward spraying	Dermal transfer coefficient - Hands, arm, body and legs covered [cm²/h]	1250
Application technique	Vehicle-mounted	Dermal transfer coefficient - Hands covered, no workwear [cm²/h]	
Max. application rate of the product [l or kg/ha]	0.5	DFR refined worker [µg/cm² foliage per kg a.s./ha]	3
Max. no. of applications	1	DT50 foliar worker [days]	30
Interval between multiple applications [days]	NA		
Multiple application factor	1		

Body weight (kg)	60
Name of active substance	Mandestrobin
Dermal absorption [%] (dilution)	50
Inhalation absorption [%]	100
Time [hours per day]	2

Table A 8: Estimation of longer term worker exposure towards mandestrobin according to EFSA guidance

Exposure route	Description	Potential	Work-wear	Workwear and gloves	Gloves
Dermal	Systemic dermal exposure [mg a.s. per day]	7.9	0.9	0.8	NA
Inhalation	Systemic inhalation exposure [mg a.s. per day]				NA
Total	Total systemic exposure [mg a.s. per day]	7.9	0.9	0.8	NA
	Total systemic exposure [mg/kg bw per day]	0.1	0.01	0.01	NA
	% of AOEL	69.2	7.8	6.9	NA

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for mandestrobin

Table A 9: Estimation of longer term resident exposure towards mandestrobin according to EFSA guidance

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: NA Minimum volume of water: 100 l			
Number of applications and application rate: 1 x 0.2105 kg a.s./ha Dermal absorption: 50 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Mandestrobin			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.03	15
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.002	0.9
	Re-entry (75th perc.)	0.02	9.3
	Sum (mean)	0.03	16.7
	Drift (75th perc.)	0.007	3.6

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Resident adult Body weight: 60 kg	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0007	0.4
	Re-entry (75th perc.)	0.01	5.2
	Sum (mean)	0.01	6.2

Appendix 4 Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)