

**FINAL REGISTRATION REPORT**

**Part B**

**Section 6**

**Mammalian Toxicology**

Detailed summary of the risk assessment

Product code: **102000037599**

Product name(s): (Active substance(s)) **Prohexadione-Ca OD 75 (75 g/L)**

**Central Zone**

Zonal Rapporteur Member State: **Poland**

**CORE ASSESSMENT**

**(Authorisation)**

Applicant: **Bayer Crop Science Division**

**MS Finalisation date: 29/04/2022**

## Version history

When	What
April 2021	Original Bayer submission
July 2021	Dossier sent for evaluation
January 2022	zRMS finalised evaluation
April 2022	Final version prepared by zRMS after Commenting period

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Evaluator comments:

The text highlighted in grey was provided by the evaluator.

## 6 Mammalian Toxicology (KCP 7)

### 6.1 Summary

**Table 6.1-1: Information on PRL OD 75 \***


Product name and code	Prohexadione-Ca OD 75 (75 g/L) PRL OD 75 102000037599
Formulation type	OD (Oil dispersion)
Active substance(s) (incl. content)	75 g/L Prohexadione-Ca OD
Function	Plant growth regulator
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 PRL OD 75 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 PRL OD 75 according to Regulation (EC) No 1272/2008**

Hazard class(es), categories:	Skin sensitisation: Category 1 Skin irritation: Category 2 Eye irritation: Category 2 Specific target organ toxicity - single exposure: Category 3
Hazard pictograms:	 GHS07
Signal word:	Warning
Hazard statement(s):	<b>H317</b> May cause an allergic skin reaction. <b>H315</b> Causes skin irritation. <b>H319</b> Causes serious eye irritation. <b>H335</b> May cause respiratory irritation. <b>EUH401</b> To avoid risks to human health and the environment, comply with the instructions
Precautionary statement(s):	<b>P261</b> Avoid breathing dust/fume/gas/mist/vapours/spray. <b>P264</b> Wash hands thoroughly after handling. <b>P272</b> Contaminated work clothing should not be allowed out of the workplace. <b>P280</b> Wear protective gloves/ protective clothing/ eye protection/ face protection. <b>P308 + P311</b> IF exposed or concerned: Call a POISON CENTER/ doctor/ physician.

	<b>P391</b> Collect spillage. <b>P501</b> Dispose of contents/container in accordance with local regulation.
Additional labelling phrases:	-

Comments of zRMS:	The proposed classification of the formulation Prohexadione-Ca OD 75 regarding human health is acceptable.
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**Table 6.1-3: Summary of risk assessment for operators, workers, bystanders and residents for PRL OD 75**

	Result	PPE / Risk mitigation measures
Operators	Acceptable	No PPE necessary according to the exposure assessment. Work wear - arms, body and legs covered Protective clothing, protective gloves, face/eye protection during handling, mixing and loading and when handling contaminated surfaces during application due to hazard characterisation.
Workers	Acceptable	None. Work wear - arms, body and legs covered
Bystanders	Acceptable	None
Residents	Acceptable	None

No unacceptable risk for operators, workers, bystanders and residents was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in Table 6.1-3 are applied.

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and bystanders/residents 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, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks:  (e.g. safener/synergist (L/ha))  critical gap for operator, worker, bystander or resident 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 kg as/ha  a) PRL b) -	Water L/ha  min / max			Operator	Worker	Bystander	Residents
1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20	Rape, winter (BRSNW)  (BBCH 12-18 or 30-59)	F	spraying (broadcast, overall)  LCTM	1	a) PRL 0.09	100 – 400	as per growth stage	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874	A	A	A	A

PRL: Prohexadione-Calcium

\* 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"

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

## Data gaps

Noticed data gaps are:

## 6.2 Toxicological Information on Active Substance(s)

Information regarding classification of the active substances and on EU endpoints and critical areas of concern identified during the EU review are given in the Tables below.

**Table 6.2-1: Information on active substance Prohexadione-Calcium**

Common Name	Prohexadione Calcium
CAS-No.	127277-53-6
<b>Classification and proposed labelling</b>	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes (s), categories: Aquatic chronic, Category 2 Code(s) for hazard pictogram(s): GHS09 Signal word: None assigned Hazard statement(s): Toxic to aquatic life with long lasting effects (H411). Precautionary statement(s): Avoid release to the environment (P273). Collect spillages Dispose of contents/container to an authorised waste collection point (P501)
Additional C&L proposal	None
<b>Agreed EU endpoints</b>	
AOEL systemic	0.35 mg/kg bw/d
Reference	EFSA Conclusion (EFSA Journal 2010; 8(3):1555), SANCO/11023/2011 Rev 2
<b>Conditions to take into account/critical areas of concern with regard to toxicology</b>	
Review Report/EFSA Conclusion for active substance	None

## 6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for PRL OD 75 is given in the following tables. Acute Toxicity Calculations (ATE) were performed on the formulation PRL OD 75 according to the Regulation (EC) No. 1272/2008 Annex I 3.1.3.3. The skin and eye irritating properties were evaluated based on the additivity approach according to Commission Regulation (EC) No 1272/2008, Annex I 3.2.3.3, table 3.2.3 and Annex I 3.3.3.3, table 3.3.3 for classification of mixtures. The skin sensitising properties were evaluated according



to the Commission Regulation (EC) No 1272/2008<sup>1</sup>, Annex I 3.4.3.3, table 3.4.5 for classification of mixtures.

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 PRL OD 75**

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
Acute oral toxicity Calculation method ATE <sub>mix</sub>  LD <sub>50</sub> oral, rat (OECD 425)	No ingredients relevant for calculation  >2000 mg/kg bw	Yes	None	For details please refer to Part C, Appendix 2 KCP 7.1.1  <a href="#">XXXX; 2020; M-690665-01-1</a>
Acute dermal toxicity Calculation method ATE <sub>mix</sub>  LD <sub>50</sub> dermal, rat (OECD 402)	No ingredients relevant for calculation  >2000 mg/kg bw	Yes	None	For details please refer to Part C, Appendix 2 KCP 7.1.2  <a href="#">XXXX; 2020; M-753937-01-1</a>
Acute inhalation toxicity Calculation method ATE <sub>mix</sub>  LC <sub>50</sub> inhalation, rat (OECD 403)	No ingredients relevant for calculation  >2.37 mg/L air (maximum attainable concentration)	Yes	None	For details please refer to Part C, Appendix 2 KCP 7.1.3  <a href="#">XXXX.; 2021; M-760383-01-1</a>
or e.g. Not submitted, not necessary. Justification presented in Appendix 2)				
Skin irritation Evaluation based on ingredients  Skin irritation and corrosivity, <i>in vitro</i> (OECD 439/431)  Skin irritation, rabbit (OECD 404)	Irritant  Non-corrosive but irritant  mild Irritant	Yes	Skin Irrit. 2, H315	For details please refer to Part C, Appendix 2 KCP 7.1.4 <a href="#">XXXX.; 2020; M-754958-01-1</a>  <a href="#">XXXX.; 2020; M-757433-01-1</a>
Eye irritation Evaluation based on ingredients  Eye irritation, <i>in vitro</i> (OECD 438)	<del>Irritant</del> Eye damage  Non-irritant (however loosening of the	Yes	Eye Irrit. 2 H319	For details please refer to Part C, Appendix 2 KCP 7.1.5 <a href="#">XXXX.; 2020; M-689659-01-1</a>

<sup>1</sup> As amended in Commission Regulation (EU) No 286/2011

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
Eye irritation, rabbit (OECD 405)	corneal epithelium was observed) Irritant			<a href="#">XXXX; 2020; M-757432-01-1</a>
Skin sensitisation Evaluation based on ingredients	Non-sensitising	Yes	Skin sens.1 H317	For details please refer to Part C, Appendix 2 KCP 7.1.6
Skin sensitisation, mouse (OECD 429, LLNA)	Sensitising			<a href="#">XXXX; 2020; 20/102-037E; M-758174-01-1</a>
Specific target organ toxicity single (STOT) Evaluation based on ingredients	Specific target organ toxicant	Yes	STOT SE 3 (RTI) H335	For details please refer to comments of zRMS in Part C and Appendix 2 KCP 7.1.7
Supplementary studies for combinations of plant protection products	No data – not required			

**Table 6.3-2: Additional toxicological information relevant for classification/labelling of PRL OD 75**

	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)	Prohexadione-calcium CAS No. 127277-53-6, 7.28 % (w/w)	Not classified	Reg. 1272/2008 MSDS**	
Toxicological properties of non-active substance(s) (relevant for classification of product)	N,N-Dimethyl decanamide CAS No. 14433-76-2, > 20.0 - < 30.0% (w/w)	Skin Irrit. 2, H315 Eye Irrit. 2, H319 STOT SE 3, H335	Reg. 1272/2008 MSDS**	Skin Irrit. 2, H315 STOT SE 3, H335
	Poly(oxy-1,2-ethanediyl), α-tridecyl-ω-hydroxy-, phosphate CAS No. 9046-01-9, > 3.0 - < 10.0% (w/w)	Eye Dam. 1, H318 Skin Irrit. 2, H315	Reg. 1272/2008 MSDS**	Eye Dam. 1, H318 Skin Irrit. 2, H315
	Hexanedioic acid CAS No. 124-04-9, > 1.0 - < 5.0% (w/w)	Eye Dam. 1, H318 ***	Reg. 1272/2008 MSDS**	Eye Dam. 1, H318
	Polyoxyethylene tridecyl ether phosphate CAS No. 9046-01-9,	Eye Dam. 1, H318 Skin Irrit. 2, H315	Reg. 1272/2008 MSDS**	Eye Dam. 1, H318 Skin Irrit. 2, H315

	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)
	> 1.0 - < 3.0% (w/w)			
Further toxicological information	No data – not required			

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

\*\* Material safety data sheet by the applicant

\*\*\* According to Regulation (EC) No 1272/2008 [CLP] Eye Dam. /Irrit. 2, H319; however according to the MSDS based on the supplier's knowledge Eye Dam. 1, H318 is required

## 6.4 Toxicological Evaluation of Groundwater Metabolites

Comments of zRMS:	No groundwater metabolites assessment is required.
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### 6.4.1 Prohexadione-Ca

No groundwater assessment is required.

## 6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in PRL OD 75 are presented in the following table.

**Table 6.5-1: Dermal absorption rates for active substances in PRL OD 75**

	Prohexadione-Ca	
	Value	Reference
Concentrate	25 %	Guidance on dermal absorption, EFSA Journal 2017;15(6):4873
Dilution (1.2 L/prod/400L wa- ter: 1:333.3)	70 %	Guidance on dermal absorption, EFSA Journal 2017;15(6):4873

### 6.5.1 Justification for proposed values - Prohexadione-Ca

No data on dermal absorption for Prohexadione-Ca in PRL OD 75 is available. 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 Prohexadione-Ca**

	Value	Justification for value	Acceptability of justification
Concentrate	25 %	Page 19 table 2 of Guidance: Default values to be used in the absence of experimental data	Yes
Dilution	70 %	Page 19 table 2 of Guidance: Default values to be used in the absence of experimental data	Yes

Proposed dermal absorption rates for Prohexadione-Ca are based on the guidance on dermal absorption studies.

## 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	PRL OD 75					
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.					
Active substance(s) (incl. content)	Substance Concentration [g/L or g/kg]	AOEL <sub>systemic</sub> (RVNAS) [mg/kg bw/d]	Inhalation absorption [%]	Oral absorption [%]	Dermal absorption*	
					Concentrate [%]	Dilution [%]
Prohexadione (PRL)	75	0.35	100	100	25	70

\*For more information please refer to chapter 6.5

### 6.6.1 Selection of critical use(s) and justification

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

#### Justification

The chosen GAPS cover the worst-case scenarios with regard to application rates and dilution for the intended uses in the scope of operator, worker and resident/bystander exposure.

### 6.6.2 Operator exposure (KCP 7.2.1)

Comments of zRMS:	<p>The predicted longer term systemic exposure for operator without PPE (wearing work wear - arms, body and legs covered) calculated for Prohexadione-Ca OD 75 using the EFSA model is below of AOEL.</p> <p>Although the calculated operator exposure value is below of AOEL, due to hazard characterization of Prohexadione-Ca OD 75 <b>protective clothing, protective gloves, face/eye protection</b> are recommended during <b>handling, mixing/loading and application</b> of the product.</p>
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No acute non-dietary risk assessment is included in this submission. Lack of scientific guidance or methodology is an acceptable reason for waiving according to Guidance of the European Commission<sup>2</sup>. The absence of such guidance on derivation of an appropriate reference dose (“AAOEL”) was recognized by

<sup>2</sup> Guidance Document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013. SANCO/10181/2013, May 2013

- the European Food Safety Authority<sup>3</sup>, and
- the European Commission Standing Committee<sup>4</sup>.

Therefore, this waiver is presented in line with the Guidance of the European Commission.

This applies for the same degree with regard to acute operator exposure estimates.

### 6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for the estimation of operator exposure to the active substance(s) during application of Prohexadione OD 75 according to the critical use(s) is presented in the following table. Detailed calculations are presented in Appendix 3.

**Table 6.6-2: Exposure models for intended uses**

Critical use(s)	1.2 L product/ha for Oilseeds
Model(s)	<i>Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874</i>

The outcome of the estimation is presented in the following table(s).

**Table 6.6-2: Estimated operator exposure, Prohexadione, Oilseeds**

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL <sup>1</sup> (RVNAS)
Outdoor, Downward spraying, Vehicle-mounted Application rate: 0.09 kg a.s./ha			
<b>EFSA Operator Model</b> (75 <sup>th</sup> quantile regression)	no PPE <sup>2</sup>	0.074	21.42
	with PPE <sup>3</sup>	0.00334 0.010	0.945 2.85

<sup>1</sup> AOEL (RVNAS) of PRL: 0.35 mg/kg bw/day

<sup>2</sup> no PPE: Work wear - arms, body and legs covered

<sup>3</sup> with PPE: Work wear - arms, body and legs covered. In addition gloves during mixing ~~and loading and when handling contaminated surfaces during application.~~

### 6.6.2.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

<sup>3</sup> Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874

<sup>4</sup> Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. SANTE-10832-2015 rev.1.7, 24 January 2017

### 6.6.3 Worker exposure (KCP 7.2.3)

Comments of zRMS:	<p>The predicted worker exposure calculated for Prohexadione-Ca OD 75 using the EFSA model is below of AOEL assuming worker is wearing work wear - arms, body and legs covered.</p> <p>As a standard rule, crops treated by Prohexadione-Ca OD 75 should not be re-entered before spray deposit on leaf surfaces has completely dried.</p>
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#### 6.6.3.1 Estimation of worker exposure

A summary of the exposure models used for the estimation of worker exposure with default DFR (= 3 µg/cm<sup>2</sup>) to the active substance(s) after entry into a previously treated area or handling a crop treated with PRL OD 75 is presented in the following table. Detailed calculations are presented in Appendix 3.

**Table 6.6-3: Exposure models for intended uses**

Critical use(s)	1.2 L product/ha for Oilseeds
Model	<i>Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874</i>

The following table shows the crop groups with their respective transfer coefficients (TC) and task duration relevant for the estimation of worker exposure after the intended use of Prohexadione OD 75. Worker exposures for all intended uses within the zone/ EU given in Part B, Section 0 are covered by that.

**Table 6.6-4: Relevant parameters used for the worker exposure assessment**

Crop / Crop Group	N° of applications	Interval (Days)	TC <sup>1</sup> (cm <sup>2</sup> /hour)	Task Duration (hours)
Oilseeds	1	365	1400 <sup>2</sup>	2

<sup>1</sup> TC = transfer coefficients

<sup>2</sup> TC assuming arms, body and legs covered.

<sup>3</sup> TC assuming hands, arms, body and legs covered.

The outcome of the estimation is presented in the following tables.

**Table 6.6-5: Estimated worker exposure for re-entry in Oilseeds**

Active substance	Application rate (kg a.s./ha)	Total absorbed dose <sup>2</sup> (mg/kg/day)	% of systemic AOEL <sup>1</sup> (RVNAS)
PRL	0.09	0.00882	2.52

<sup>1</sup> AOEL (RVNAS) of PRL: 0.35 mg/kg bw/day

<sup>2</sup> Assuming arms, body and legs covered (workwear, bare hands)

#### 6.6.4 Refinement of generic DFR value (KCP 7.2)

Since the worker exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) will not be exceeded under conditions of intended uses a study to provide measurements of worker exposure was not necessary and was therefore not performed.

#### **6.6.4.1 Measurement of worker exposure**

Since the worker exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) will not be exceeded under conditions of intended uses a study to provide measurements of worker exposure was not necessary and was therefore not performed.

#### **6.6.5 Bystander and resident exposure (KCP 7.2.2)**

Comments of zRMS:	<u>Resident exposure:</u>
	The predicted resident exposure (child and adult) calculated for Prohexadione-Ca OD 75 using the EFSA model is below of AOEL.
	<u>Bystander exposure:</u>
	As no AAOEL value was established for active substance prohexadione calcium, bystander's exposure is covered by resident's exposure assessment.

According to EFSA longer term exposure of bystanders is covered by the resident scenario.

#### **6.6.5.1 Estimation of resident exposure (long term exposure)**

A summary of the exposure models used for the estimation of resident exposure to the active substance(s) during application of Prohexadione OD 75 according to the critical use(s) is presented in the following table. Detailed calculations are presented in Appendix 3.

**Table 6.6-6: Exposure models for intended uses**

Critical use(s)	1.2 L product/ha for Oilseeds
Model	<i>Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874</i>

Regarding the resident exposure to direct drift, exposure calculations are performed for ground boom sprayer (for low crops) and broadcast air assisted applications (for high crops) separately, when relevant. The outcome of the estimation is presented in the following table(s).

**Table 6.6-7: Estimated resident exposure, Prohexadione, Oilseeds**

	Adult <sup>2</sup>			Child <sup>2</sup>		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.09 kg a.s./ha, 365 days interval, Minimum water volume: 100 L/ha						
Routes of exposure	75 <sup>th</sup> centile (mg/kg bw/day)	in % of AOEL <sup>1</sup> (RVNAS)	Mean (mg/kg bw/day)	75 <sup>th</sup> centile (mg/kg bw/day)	in % of AOEL <sup>1</sup> (RVNAS)	Mean (mg/kg bw/day)
Spray drift <sup>3</sup>	0.00405	1.16	0.00192	0.0169	4.83	0.00931
Vapour	0.00023	0.0657	0.00023	0.00107	0.306	0.00107
Surface deposits	0.000429	0.123	0.000314	0.00099	0.283	0.000725
Entry into treated crops <sup>4</sup>	0.00591	1.69	0.00471	0.0106	3.04	0.00848
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00718 (2.05%)			0.0196 (5.6%)

<sup>1</sup> AOEL (RVNAS) of PRL: 0.35 mg/kg bw/day

<sup>2</sup> Considered bodyweight: adult = 60 kg, child = 10 kg

<sup>3</sup> Exposure at 2-3 m distance

<sup>4</sup> Default DFR = 3

#### 6.6.5.2 Measurement of bystander and/or resident exposure

Since the bystander/resident exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) will not be exceeded under conditions of intended uses a study to provide measurements of bystander/resident exposure to spray drift, vapour, surface deposits or entry into treated crops was not necessary and was therefore not performed.

#### 6.6.6 Combined exposure

Not relevant as 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
KCP 7.1.1 / 01 ... also filed: KCP 10.1.2.1 / 01	XXXX	2020	Prohexadione-calcium OD 75 (75 g/L): Acute oral toxicity study in rats (up and down procedure) Report No.: 20/102-001P, Edition Number: <a href="#">M-690665-01-1</a> XXXX, Hungary GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.1.2 / 01	XXXX	2020	Prohexadione-calcium OD 75 (75 g/L): Acute dermal toxicity study in rats Report No.: 20/102-002P, Edition Number: <a href="#">M-753937-01-1</a> XXXX, Hungary GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.1.3 / 01	XXXX.	2021	Prohexadione-calcium OD 75 (75 g/L): Acute inhalation toxicity study (nose-only) in the rat Report No.: 20/102-004P, Edition Number: <a href="#">M-760383-01-1</a> XXXX, Hungary GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.1.4 / 01	XXXX.	2020	Prohexadione-calcium OD 75 (75 g/L): In vitro skin corrosivity and irritation test using the Epi-Derm™ model Report No.: 20/102-051B, Edition Number: <a href="#">M-754958-01-1</a> XXXX, Hungary GLP/GEP: Yes unpublished	No	Bayer
KCP 7.1.4 / 02	XXXX.	2020	Prohexadione-calcium OD 75 (75 g/L): Acute skin irritation study in rabbits Report No.: 20/102-006N, Edition Number: <a href="#">M-757433-01-1</a> XXXX, Hungary GLP/GEP: Yes unpublished	Yes	Bayer

<b>Data point</b>	<b>Author(s)</b>	<b>Year</b>	<b>Title Company Report No. Source (where different from company) GLP or GEP status Published or not</b>	<b>Vertebrate study Y/N</b>	<b>Owner</b>
KCP 7.1.5 / 01	XXXX.	2020	Prohexadione-calcium OD 75 (75 g/L): In vitro eye irritation test in isolated chicken eyes Report No.: 20/102-038CS, Edition Number: <a href="#">M-689659-01-1</a> XXXX, Hungary GLP/GEP: Yes unpublished	No	Bayer
KCP 7.1.5 / 02	XXXX.	2020	Prohexadione-calcium OD 75 (75 g/L): Acute eye irritation study in rabbits Report No.: 20/102-005N, Edition Number: <a href="#">M-757432-01-1</a> XXXX, Hungary GLP/GEP: Yes unpublished	Yes	Bayer
KCP 7.1.6 / 01	XXXX	2020	Prohexadione-calcium OD 75 (75 g/L): Local lymph node assay in the mouse Report No.: 20/102-037E, Edition Number: <a href="#">M-758174-01-1</a> XXXX, Hungary GLP/GEP: Yes unpublished	Yes	Bayer

## Appendix 2 Detailed evaluation of the studies relied upon

### A 2.1 Statement on bridging possibilities

The toxicological evaluation of the formulation PRL OD 75 was based on the ingredients. For registration in a country outside of Europe a complete data package was required and conducted with the formulation PRL OD 75.

### A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	<p>The approach of Applicant is acceptable.</p> <p>Acute oral toxicity of Prohexadione-Ca OD 75 was determined using the calculation method in accordance with CLP taking into consideration valid data available for each component of the mixture. The formulation contains no ingredients relevant for calculation of an oral ATE<sub>mix</sub>, therefore no classification for acute oral toxicity is required.</p> <p>In addition, Applicant submitted the result of the study <i>Prohexadione-calcium OD 75 (75g/L): Acute Oral Toxicity Study in Rats (Up and Down procedure)</i> (XXXX; 2020; 20/102-001P) conducted for a country outside of Europe. Although, according to the Regulation (EC) No 1107/2009 animal testing for the purpose of the registration plant protection product should be performed as a last resort, in the case of the available alternative CLP calculation method there is a concern for the underestimation of adverse effects for more toxic products (<i>A comparative assessment of the CLP calculation method and in vivo testing for the classification of plant protection products</i>, D. Kurth et al., Regulatory Toxicology and Pharmacology 101 (2019) 79–90). This additivity approach assumes a similar mode of action for all ingredients in a mixture and although it is often a worst-case estimation of chemical interaction, it does not take into account the influence of co-formulants on the toxicokinetic properties of the active substance(s). Therefore, both calculation method and submitted study were evaluated.</p> <p>Acute oral toxicity was examined according to the OECD Test Guideline 425 (2008); US EPA OPPTS 870.1100 (2002) and Commission Regulation (EC) No. 440/2008, B.1 tris (2008) in compliance with Principles of Good Laboratory Practice (GLP). No deviation was occurred during the study.</p> <p>The study was conducted with 4 female animals (CrI:WI Wistar rats), which were treated with a single oral (gavage) dose of Prohexadione-calcium OD 75, followed by a 14-day observation period. No mortality was observed and there were no effects on body weight or body weight gain. Animals were symptom-free from Day 1 until the end of the study. Also there was no evidence of any macroscopic observation at necropsy. The study results indicate that the estimated acute oral median lethal dose (LD<sub>50</sub>) of the Prohexadione-calcium OD 75 was found to be greater than 2000 mg/kg bw, therefore no classification for acute oral toxicity is required.</p> <p>Concluding, taking into consideration both results, no classification for acute oral toxicity is required according to the Regulation (EC) No. 1272/2008.</p>
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According to the Regulation (EC) No. 1272/2008 Annex 3.1.3.6.2.1 the classification of the mixture may be estimated with a calculation method.

The formulation contains no ingredients relevant for calculation of an oral ATE<sub>mix</sub>. For details please refer to Part C.

In addition, for a country outside of Europe an acute oral toxicity study was conducted with the formulation itself which revealed a LD<sub>50</sub> greater than 2000 mg/kg bw confirming that classification for acute oral toxicity is not warranted.

Reference:	<b>KCP 7.1.1/01</b>
Title:	Prohexadione-calcium OD 75 (75 g/L): Acute oral toxicity study in rats (up and down procedure)
Report:	<a href="#">XXXX; 2020; 20/102-001P; M-690665-01-1</a>
Authority registration No:	
Guideline(s):	OECD 425 (2008); US-EPA 712-C-02-190, OPPTS 870.1100 (2002); Commission Regulation (EC) 440/2008, B.1 tris (2008)
Deviations:	None
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	No

## Materials and methods

<b>Test material (Lot/Batch No.)</b>	Prohexadione-calcium OD 75 (75 g/L) Synonym(s): KUH-833 Batch number: 2020-001264
<b>Species</b>	CrI:WI Wistar rats
<b>No. of animals (group size)</b>	4 females (1+3)
<b>Dose(s)</b>	550 mg/kg bw and 2000 mg/kg bw
<b>Exposure</b>	Once by gavage
<b>Vehicle/Dilution</b>	Distilled water
<b>Post exposure observation period</b>	14 days
<b>Remarks</b>	Initially one animal was dosed at 550 mg/kg bw. Single animals were dosed sequentially following a surviving interval of at least approximately 48 hours. When the outcome for each animal was established, then the next individual animal was treated at the next appropriate dose.

## Results and discussions

**Table A 1: Results of acute oral toxicity study in rats of Prohexadione-calcium OD 75 (75 g/L)**

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Female rats				
550	0/0/1	-	-	> 2000
2000	0/1/3	2-6h	-	

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

**Table A 2: Summary of findings of acute oral toxicity study in rats of Prohexadione-calcium OD 75 (75 g/L)**

<b>Mortality:</b>	No mortality occurred.
<b>Clinical signs:</b>	At dose level of 2000 mg/kg bw one animal had hunched back on Day 0. Animals were symptomfree from Day 1 until the end of the study.
<b>Body weight:</b>	There was no treatment related effect on body weight or body weight gain in the animals.
<b>Macroscopic examination:</b>	There was no evidence of any macroscopic observation in four females given 550 or 2000 mg/kg bw.

## Conclusion

Under the experimental conditions, the oral LD<sub>50</sub> of Prohexadione-calcium OD 75 (75 g/L) is higher than 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

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

Comments of zRMS:	<p>The approach of Applicant is acceptable.</p> <p>Acute dermal toxicity of Prohexadione-Ca OD 75 was determined using the calculation method in accordance with CLP taking into consideration valid data available for each component of the mixture. The formulation contains no ingredients relevant for calculation of a dermal ATE<sub>mix</sub>, therefore no classification for acute dermal toxicity is required.</p> <p>In addition, Applicant submitted the result of the study <i>Prohexadione-calcium OD 75 (75g/L): Acute Dermal Toxicity Study in Rats</i> (XXXX; 2020; 20/102-002P) conducted for a country outside of Europe. Although, according to the Regulation (EC) No 1107/2009 animal testing for the purpose of the registration plant protection product should be performed as a last resort, in the case of the available alternative CLP calculation method there is a concern for the underestimation of adverse effects for more toxic products (<i>A comparative assessment of the CLP calculation method and in vivo testing for the classification of plant protection products</i>, D. Kurth et al., Regulatory Toxicology and Pharmacology 101 (2019) 79–90). This additivity approach assumes a similar mode of action for all ingredients in a mixture and although it is often a worst-case estimation of chemical interaction, it does not take into account the influence of co-formulants on the toxicokinetic properties of the active substance(s). Therefore, both calculation method and submitted study were evaluated.</p> <p>Acute dermal toxicity was examined according to the OECD Test Guideline 402 (2017); Commission Regulation (EC) No. 440/2008, B.3 (2008) and US EPA OPPTS 870.1200 (1998) in compliance with Principles of Good Laboratory Practice (GLP). No deviation was occurred during the study.</p> <p>The study was conducted with three female CRL:(WI) Wistar rats, which were treated with a single 24-hour semi-occlusive dermal application of Prohexadione-Ca OD 75 followed by a 14-day observation period. A limit test was carried out at 2000 mg/kg bw in one female rat and the main test was carried out on another two animals. No mortality occurred during the study. As systemic clinical signs hunched back was observed from Day 1 until Day 4 (1/3) and scales/crust were observed from Day 2 until Day 7 (1/3) or Day 9 (2/3). Body weight gain was considered to be normal and there was no evidence of any gross observations at necropsy. The study results indicate that the median lethal dose (LD<sub>50</sub>) of Prohexadione-calcium OD 75 after a single dermal administration was found to be greater than 2000</p>
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	mg/kg, therefore no classification for acute dermal toxicity is required. Concluding, taking into consideration both results, no classification for acute dermal toxicity is required according to the Regulation (EC) No. 1272/2008.
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According to the Regulation (EC) No. 1272/2008 Annex 3.1.3.6.2.1 the classification of the mixture may be estimated with a calculation method.

The formulation contains no ingredients relevant for calculation of a dermal ATE<sub>mix</sub>. For details please refer to Part C.

In addition, for a country outside of Europe an acute dermal toxicity study was conducted with the formulation itself which revealed a LD<sub>50</sub> greater than 2000 mg/kg bw confirming that classification for acute dermal toxicity is not warranted.

Reference:	<b>KCP 7.1.2/01</b>
Title:	Prohexadione-calcium OD 75 (75 g/L): Acute dermal toxicity study in rats
Report:	<a href="#">XXXX; 2020; 20/102-002P; M-753937-01-1</a>
Authority registration No:	
Guideline(s):	OECD 402 (2017); Commission Regulation (EC) No 440/2008, B.3 (2008); US-EPA 712-C-98-192, OPPTS 870.1200 (1998)
Deviations:	None
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	No

## Materials and methods

<b>Test material (Lot/Batch No.)</b>	Prohexadione-calcium OD 75 (75 g/L) Synonym(s): KUH-833 Batch number: 2020-001264
<b>Species</b>	Crl:WI Wistar rats
<b>No. of animals (group size)</b>	Range finding study: 1 female Main study: 2 females
<b>Dose(s)</b>	2000 mg/kg bw
<b>Exposure</b>	24 hours (dermal, semi-occlusive)
<b>Vehicle/Dilution</b>	None
<b>Post exposure observation period</b>	14 days
<b>Remarks</b>	Initially, one animal was dosed at the selected limit dose (2000 mg/kg bw). As the animal survived, the second and third animal received the same dose.

## Results and discussions

**Table A 3: Results of acute dermal toxicity study in rats of Prohexadione-calcium OD 75 (75 g/L)**

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Female rats				

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
2000	0/3/3	Day1-9	--	> 2000

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

**Table A 4: Summary of findings of acute dermal toxicity study in rats of Prohexadione-calcium OD 75 (75 g/L)**

<b>Mortality:</b>	No mortality occurred.
<b>Clinical signs:</b>	Hunched back was observed from Day 1 until Day 4 (1/3) and scales / crust were observed from Day 2 until Day 7 (1/3) or Day 9 (2/3)
<b>Body weight:</b>	Body weight gain was considered to be normal.
<b>Macroscopic examination:</b>	The necropsies performed at the end of the study revealed no apparent findings.

## Conclusion

Under the experimental conditions, the dermal LD<sub>50</sub> of Prohexadione-calcium OD 75 (75 g/L) is higher than 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

## A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	<p>The approach of Applicant is acceptable.</p> <p>Acute inhalation toxicity of Prohexadione-Ca OD 75 was determined using the calculation method in accordance with CLP taking into consideration valid data available for each component of the mixture. The formulation contains no ingredients relevant for calculation of an inhalation ATE<sub>mix</sub>, therefore no classification for acute inhalation toxicity is required.</p> <p>In addition, Applicant submitted the result of the study <i>Prohexadione-calcium OD 75 (75g/L): Acute Inhalation Toxicity Study (Nose-only) in the Rat</i> (XXXX.; 2021; 20/102-004P) conducted for a country outside of Europe. Although, according to the Regulation (EC) No 1107/2009 animal testing for the purpose of the registration plant protection product should be performed as a last resort, in the case of the available alternative CLP calculation method there is a concern for the underestimation of adverse effects for more toxic products (<i>A comparative assessment of the CLP calculation method and in vivo testing for the classification of plant protection products</i>, D. Kurth et al., Regulatory Toxicology and Pharmacology 101 (2019) 79–90). This additivity approach assumes a similar mode of action for all ingredients in a mixture and although it is often a worst-case estimation of chemical interaction, it does not take into account the influence of co-formulants on the toxicokinetic properties of the active substance(s). Therefore, both calculation method and submitted study were evaluated.</p> <p>Acute inhalation toxicity was examined according to the OECD Test Guideline 403 (2009); US EPA OPPTS 870.1300 (1998) and Commission Regulation (EC) No. 440/2008, B.2 (2008) in compliance with Principles of Good Laboratory Practice (GLP). Deviations indicated in study report were considered to have no impact on the outcome of the study and interpretation of the results.</p> <p>The study was conducted with CRL:(WI) Wistar rats - 1/sex for sighting exposure (maximum achievable concentration 2.63 mg/L) and 5/sex in main study</p>
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	<p>(maximum achievable concentration 2.37 mg/L). In both study phases, the animals were exposed to the test atmosphere for 4 hours using a nose-only exposure system. Clinical observations were performed on all animals during exposure at hourly intervals, following removal from restraint, approximately 1 hour after exposure, and daily for 14 days thereafter. Body weight was measured on Days 0 (before the exposure), 1, 3, 7 and 14. Gross necropsy was performed on all animals on Day 14. Under the experimental conditions of this study, one male animal (1/5) in main study was found dead after being exposed to a test atmosphere concentration of 2.37 mg/L. The acute inhalation median lethal concentration (LC<sub>50</sub>) of Prohexadione-calcium OD 75 in male and female CrI:WI rats was considered to be above the maximum attainable concentration of 2.37 mg/L.</p> <p>Concluding, taking into consideration both results, no classification for acute inhalation toxicity is required according to the Regulation (EC) No. 1272/2008.</p>
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According to the Regulation (EC) No. 1272/2008 Annex 3.1.3.6.2.1 the classification of the mixture may be estimated with a calculation method.

The formulation contains no ingredients relevant for calculation of an inhalation ATE<sub>mix</sub>. For details please refer to Part C.

In addition, for a country outside of Europe an acute inhalation toxicity study was conducted with the formulation itself which revealed a LC<sub>50</sub> greater than 2.37 mg/L air (maximum attainable concentration) confirming that classification for acute inhalation toxicity is not warranted.

Reference:	<b>KCP 7.1.3/01</b>
Title:	Prohexadione-calcium OD 75 (75 g/L): Acute inhalation toxicity study (nose-only) in the rat
Report:	<a href="#">XXXX.; 2021; 20/102-004P; M-760383-01-1</a>
Authority registration No:	
Guideline(s):	OECD 403 (2009); US-EPA OPPTS 870.1300 (1998); Commission Regulation (EC) 440/2008, B.2 (2008)
Deviations:	None
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	No

## Materials and methods

<b>Test material (Lot/Batch No.)</b>	Prohexadione-calcium OD 75 (75 g/L) Synonym(s): KUH-833 Batch number: 2020-001264
<b>Species</b>	CrI:WI Wistar rats
<b>No. of animals (group size)</b>	5/sex in group 1 (main study) (and 1/sex for sighting exposure)
<b>Concentration(s)</b>	2.37 mg/L air ( maximum attainable)
<b>Exposure</b>	4 hours (nose only)
<b>Vehicle/Dilution</b>	None
<b>Post exposure observation period</b>	14 days
<b>Remarks</b>	None



## Results and discussions

**Table A 5: Concentration(s) and exposure conditions**

Target conc. (mg/L air)	or	Nominal conc. (mg/L air)	Actual conc. (mg/L air)	MMAD * (µm)	GSD ** (µm)
Maximum attainable		63.49	2.37	3.12	2.01

\* MMAD = Mass Median Aerodynamic Diameter

\*\* GSD = Geometric Standard Deviation

**Table A 6: Results of acute inhalation toxicity study in rats of Prohexadione-calcium OD 75 (75 g/L)**

Concentration (mg/L air)	Toxicological results *	Duration of signs	Time of death	LC <sub>50</sub> (mg/L air) (14 days)
female				
2.37	0/5/5	Day 0-1	-	> 2.37
male				
2.37	1/5/5	Day 0-3	Day 0	> 2.37

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

**Table A 7: Summary of findings of acute inhalation toxicity study in rats of Prohexadione-calcium OD 75 (75 g/L)**

<b>Mortality:</b>	One male animal (1/5) was found dead during the exposure on Day 0.
<b>Clinical signs:</b>	In the male animals, laboured respiration (slight), noisy respiration (slight), increased respiratory rate (slight), gasping respiration, sneezing, decreased activity (slight), lack of grooming, red brown staining on the nose and cranium, fur staining by test item on the head and wet fur on the whole body were recorded from Day 0 up to Day 3. All surviving male animals were symptom-free from Day 4. In the female animals, laboured respiration (slight), increased respiratory rate (slight), lack of grooming, fur staining by test item on the head and wet fur on the whole body were recorded from Day 0 up to Day 1. All female animals were symptom-free from Day 2. Red-brown staining (as chromodacryorrhea), fur staining by test item and wet fur in the animals were considered to be related to the restraint and exposure procedures or discomfort of the animals but not to be toxicologically significant.
<b>Body weight:</b>	In the surviving male animals, slight body weight losses were recorded on Days 0-1. The body weight gains were normal between Days 1-14. In the female animals, slight body weight losses were recorded on Days 0-1. The body weight gains were normal between Days 1-14.
<b>Macroscopic examination:</b>	There was no evidence of any test item-related gross changes at necropsy in surviving animals. In the found dead male animal of the main study, diffuse dark red discoloration of lungs, dilatation in stomach with gas and clear liquid at the perioral and perinasal region were observed.

## Conclusion

Under the experimental conditions, the inhalation LC<sub>50</sub> of Prohexadione-calcium OD 75 (75 g/L) is above 2.37 mg/L (maximum attainable concentration) in male and female rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

## A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	<p>The approach of Applicant is acceptable.</p> <p>Skin irritation property of Prohexadione-Ca OD 75 was determined using the calculation method in accordance with CLP taking into consideration valid data available for each component of the mixture. The overall content of ingredients classified as Skin Irrit. 2 is above the generic concentration limit of 10%, therefore the formulation Prohexadione-Ca OD 75 should be classified as Skin Irrit. 2 with the hazard statement H315.</p> <p>The calculation result was confirmed by the <i>in vitro</i> study <i>Prohexadione-calcium OD 75 (75g/L): In Vitro Skin Corrosivity and Irritation Test using EpiDerm™ Model</i> (Tóth-Gönczöl, K.; 2020; 20/102-051B) conducted according to the OECD Test Guideline 439 (2019); OECD Test Guideline 431 (2019); Commission Regulation (EC) No. 440/2008, Annex Part B, B.40; Commission Regulation (EC) No. 761/2009, ANNEX III, B.46 (2009) in compliance with Principles of Good Laboratory Practice (GLP). No deviations occurred during this study. The study results revealed that Prohexadione-calcium OD 75 is non-corrosive but irritant to the skin - following exposure with Prohexadione-calcium OD 75, the mean cell viability was 2.0% compared to the negative control. This is below the threshold of 50%, therefore the test item was considered as being irritant to skin (Category 2). This result is consistent with the calculation result.</p>
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The skin irritating properties were evaluated according to Regulation (EC) No. 1272/2008, Annex I table 3.2.3, for classification of mixtures.

In the current formulation the sum of ingredients classified as Skin corrosive Category 1 is below the generic concentration limits of  $\geq 5\%$  and  $\geq 1\%$  for classification as Skin corrosive Category 1 or Skin irritant Category 2, respectively.

The overall content of Skin irritant Category 2 ingredients is above the generic concentration limit of  $\geq 10\%$  for classification. For details please refer to Part C.

An *in vitro* skin irritation study was conducted with the current formulation. According to this *in vitro* skin irritation test the current formulation is irritant.

In addition, for a country outside of Europe a skin irritation study conducted with the formulation itself confirmed that classification for skin irritation is warranted.

Reference:	<b>KCP 7.1.4/01</b>
Title:	Prohexadione-calcium OD 75 (75 g/L): In vitro skin corrosivity and irritation test using the EpiDerm™ model
Report:	<a href="#">XXXX.; 2020; 20/102-051B; M-754958-01-1</a>
Authority registration No:	
Guideline(s):	OECD 439 (2019); OECD 431 (2019); Commission Regulation (EC) No 440/2008, Annex Part B, B.40. (2008); Commission Regulation (EC) No 761/2009, ANNEX III, B.46. (2009); US-EPA OCSPP 870.SUPP
Deviations:	None
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	

## Materials and methods

<b>Test material (Lot/Batch No.)</b>	Prohexadione-calcium OD 75 (75 g/L) Synonym(s): KUH 833 Batch number: 2020-001264
<b>Test system</b>	EpiDerm™ Model (EPI-200-SIT) and (EPI-200-SCT) (human-derived epidermal keratinocytes (NHEK) / multilayered, highly differentiated model of the human epidermis)
<b>No. of replicates (corrosivity / irritation)</b>	2 for each tested substance (test item, negative control, positive control) / 3 for each tested substance (test item, negative control, positive control)
<b>Exposure (corrosivity / irritation)</b>	Test item: 50 µL(corrosion) for 1h or 3min / 30 µL (irritation) for 1h Controls: 50 µL(corrosion) for 1h or 3min / 30 µL (irritation) for 1h
<b>Controls (corrosivity/irritation)</b>	Positive: 8M Potassium hydroxide solution (KOH) / 5% (w/v) SDS Negative: distilled water / DPBS
<b>Vehicle/Dilution</b>	None for the test item (distilled water for the preparation of the positive control)
<b>Post exposure observation period</b>	42 hours (± 2 h) after application and rinsing + 3 hours for the MTT test
<b>Remarks</b>	As the test item was coloured, two additional test item-treated living tissues were used for the non-specific OD evaluation. These tissues followed the same test item application and all steps as for the other tissues, except for the MTT step: MTT incubation was replaced by incubation with fresh Assay Medium to mimic the amount of colour from the test item that may be present in the test disks. OD reading was conducted following the same conditions as for the other tissues.

SDS= Sodium Dodecyl Sulfate; DPBS=Dulbecco's Phosphate Buffered Saline

## Results and discussions

**Table A 8: Results of in vitro skin irritation of Prohexadione-calcium OD 75 (75 g/L)**

Treatment	Optical Density (OD)			% Relative Viability (±SD)
	Replicate Number	Measured	Blank corrected	
Negative Control	1	1.720	1.674	101.0
	2	1.717	1.671	100.8
	3	1.673	1.627	98.1
	Mean	--	<b>1.657</b>	<b>100.0 ± 1.6</b>
Positive Control	1	0.090	0.044	2.6
	2	0.079	0.033	2.0
	3	0.086	0.040	2.4
	Mean	--	<b>0.039</b>	<b>2.3± 0.3</b>
Test Item	1	0.078	0.032	1.9
	2	0.079	0.033	2.0
	3	0.079	0.033	2.0
	Mean	--	<b>0.033</b>	<b>2.0 ± 0.0</b>

Notes:

- Mean blank value was 0.046
- Optical density means the mean value of the duplicate wells for each sample (rounded to three decimal places).

Criteria for in vitro interpretation	UN GHS classification
% mean tissue viability ≤ 50 %	Cat 2
% mean tissue viability > 50 %	Non-Irritant*

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

**Table A 9: Results of in vitro skin corrosion of Prohexadione-calcium OD 75 (75 g/L) after 3 minutes exposure**

Treatment 3 min	Optical Density (OD)			% Relative Viability (±CV)
	Replicate Number	Measured	Blank corrected	
Negative Control	1	1.861	1.815	100.8
	2	1.833	1.787	99.2
	Mean	--	<b>1.801</b>	<b>100.0 ± 1.1</b>
Positive Control	1	0.432	0.386	21.4
	2	0.278	0.232	12.9
	Mean	--	<b>0.309</b>	<b>17.2 ± 35.2</b>
Test Item	1	1.897	1.851	102.8
	2	1.563	1.517	84.2
	Mean	--	<b>1.684</b>	<b>93.5 ± 14.0</b>

Notes:

1. Mean blank value was 0.046
2. Optical density means the mean value of the duplicate wells for each sample (rounded to three decimal places).
3. CV = Coefficient of Variation (CV % = Standard Deviation / mean viability \* 100)

**Table A 10: Results of in vitro skin corrosion of Prohexadione-calcium OD 75 (75 g/L) after 1 hour exposure**

Treatment 1h	Optical Density (OD)			% Relative Viability (±CV)
	Replicate Number	Measured	Blank corrected	
Negative Control	1	1.855	1.809	95.4
	2	2.030	1.984	104.6
	Mean	--	<b>1.896</b>	<b>100.0 ± 6.5</b>
Positive Control	1	0.195	0.149	7.8
	2	0.182	0.136	7.2
	Mean	--	<b>0.142</b>	<b>7.5 ± 6.2</b>
Test Item	1	1.146	1.100	58.0
	2	1.350	1.304	68.7
	Mean	--	<b>1.202</b>	<b>63.4 ± 12.0</b>

Notes:

1. Mean blank value was 0.046
2. Optical density means the mean value of the duplicate wells for each sample (rounded to three decimal places).
3. CV = Coefficient of Variation (CV % = Standard Deviation / mean viability \* 100)

Criteria for in vitro interpretation	prediction
% mean tissue viability 3min < 50 %	corrosive
% mean tissue viability 3 min < 25%	Sub-category 1A
% mean tissue viability 3 min ≥ 25%	Sub-categories 1B and 1C
% mean tissue viability 3 min ≥ 50 % and 1 hour <15%	corrosive
% mean tissue viability 3 min ≥ 50 % and 1 hour ≥ 15%	non-corrosive

<b>Additional controls:</b>	<p>As no colour change was observed after one hour of incubation of the test item in MTT medium, the test material did not interact with MTT. Therefore, additional controls and data calculations were not necessary. The false estimation of viability can be excluded.</p> <p>As the test item was coloured (light yellow), two additional test item-treated living tissues were used for the non-specific OD evaluation for both corrosivity and irritation testing. The NSC<sub>living</sub> % values for the test item compared to negative control were below 5%, therefore an additional data calculation to account for non-specific colouring was not</p>
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	necessary.
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## Conclusion

Under the experimental conditions, Prohexadione-calcium OD 75 (75 g/L) is non-corrosive but irritant to the skin.

Comments of zRMS:	<p>In addition to the CLP calculation method and <i>in vitro</i> testing of skin corrosive and irritant properties of Prohexadione-calcium OD 75, Applicant submitted the result of the study: <i>Prohexadione-calcium OD 75 (75g/L): Acute Skin Irritation Study in Rabbit</i> (XXXX.; 2020; 20/102-006N) conducted for a country outside of Europe. Although, according to the Regulation (EC) No 1107/2009 animal testing for the purpose of the registration plant protection product should be performed as a last resort, in the case of the available alternative CLP calculation method there is a concern for the underestimation of adverse effects for more toxic products (<i>A comparative assessment of the CLP calculation method and in vivo testing for the classification of plant protection products</i>, D. Kurth et al., Regulatory Toxicology and Pharmacology 101 (2019) 79–90). This additivity approach assumes a similar mode of action for all ingredients in a mixture and although it is often a worst-case estimation of chemical interaction, it does not take into account the influence of co-formulants on the toxicokinetic properties of the active substance(s). Therefore the study was evaluated and accepted.</p> <p>Acute Skin Irritation was examined according to the OECD Test Guideline 404 (2015); Commission Regulation (EC) No. 440/2008, B.4 (2008) and US EPA OPPTS 870.2500 (1998) in compliance with Principles of Good Laboratory Practice (GLP). Deviations indicated in study report were considered to have no impact on the outcome of the study and interpretation of the results.</p> <p>The study was conducted with three young adult male New Zealand White rabbits, which were treated by topical semi-occlusive application of 0.5 mL test item to the intact shaved dorsal area of the trunk (4 hours). No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred. The body weights of all rabbits were considered to be within the normal range of variability. The mean scores for erythema and oedema were below 2.3 in all animals. Results were interpreted according to CLP and GHS and classification system based on the scheme devised by Draize. It was concluded that Prohexadione-calcium OD 75 is "mild irritant" to the skin of rabbits according to the Draize classification system with a recovery period of 3 weeks.</p> <p>Concluding, taking into consideration all available information (result from calculation method, result from <i>in vitro</i> study and fact that <i>in vivo</i> study there was erythema in all animals after 48h) the formulation Prohexadione-Ca OD 75 should be classified as Skin Irrit. 2 (H315) according to the Regulation (EC) No. 1272/2008.</p>
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Reference:	<b>KCP 7.1.4/02</b>
Title:	Prohexadione-calcium OD 75 (75 g/L): Acute skin irritation study in rabbits
Report:	<a href="#">XXXX.: 2020; 20/102-006N; M-757433-01-1</a>
Authority registration No:	
Guideline(s):	OECD 404 (2015); Commission Regulation (EC) No 440/2008, B.4 (2008); US-EPA OPPTS 712-C-98-196, 870.2500 (1998)
Deviations:	None
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	No

## Materials and methods

Test material (Lot/Batch No.)	Prohexadione-calcium OD 75 (75 g/L) Synonym(s): KUH-833 Batch number: 2020-001264
Species	Rabbit, New Zealand White
No. of animals (group size)	3 males
Initial test using one animal	Yes
Exposure	0.5 mL (4 hours, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	3 weeks
Remarks	None

## Results and discussions

**Table A 11: Skin irritation of Prohexadione-calcium OD 75 (75 g/L)**

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Erythema	0	0	2	2	1.33	21
	Oedema	0	0	1	1	0.67	7
2	Erythema	0	0	1	1	0.67	21
	Oedema	0	0	0	1	0.33	7
3	Erythema	0	0	1	2	1.00	21
	Oedema	0	0	0	1	0.33	7

\* scores in the range of 0 to 4

<b>Clinical signs:</b>	No clinical signs of toxicity were observed.
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## Conclusion

Under the experimental conditions, Prohexadione-calcium OD 75 (75 g/L) is “mild” skin irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

## A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	Eye irritation property of Prohexadione-Ca OD 75 was determined using the
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	<p>calculation method in accordance with CLP taking into consideration valid data available for each component of the mixture. The sum of ingredients classified as Eye effects Category 1 is 10.48 % and thereby above the generic concentration limits of 3 % triggering classification of the mixture as Eye effects Category 1.</p> <p>Applicant submitted also result of the <i>in vitro</i> study <i>Prohexadione-calcium OD 75 (75g/L): In Vitro Eye Irritation Test in Isolated Chicken Eyes</i> (Tóth-Gönczöl, K.; 2020; 20/102-038CS) conducted according to the OECD Test Guideline 438 (2018); Commission Regulation (EC) 2017/735 (2017) in compliance with Principles of Good Laboratory Practice (GLP). No deviations occurred during this study. The study results revealed that based on <i>in vitro</i> eye irritation tests in isolated chicken eyes, the numerical scores indicate that the test item Prohexadione-calcium OD 75 is Non-Irritant. This result is contrary to the result of calculation method. However, in <i>in vitro</i> study there was loosening of the corneal epithelium, which should be also taken in account. It suggests that more information is required for classification of the mixture tested.</p> <p>In addition to the CLP calculation method and <i>in vitro</i> testing of eye corrosive and irritant properties of Prohexadione-calcium OD 75, Applicant submitted also the result of the <i>in vivo</i> eye irritation study evaluated below, which was taken into consideration during the final classification of the mixture.</p>
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The eye irritating properties were evaluated according to Regulation (EC) No. 1272/2008, Annex I table 3.3.3, for classification of mixtures.

In the current formulation the sum of ingredients classified as Eye effects Category 1 or Skin corrosive Category 1 is above the generic concentration limits of  $\geq 3$  % for classification as Eye effects Category 1.

The overall content of Eye irritant Category 2 ingredients is above the generic concentration limit of  $\geq 10$  % for classification. For details please refer to Part C.

An *in vitro* eye irritation study was conducted with the current formulation. According to this *in vitro* eye irritation test in isolated chicken eyes the current formulation is not irritant, however a loosening of the corneal epithelium was observed, which should be also taken in account in final classification.

In addition, for a country outside of Europe an eye irritation study conducted with the formulation itself confirmed that classification for eye irritation is warranted.

Reference:	<b>KCP 7.1.5/01</b>
Title:	Prohexadione-calcium OD 75 (75 g/L): In vitro eye irritation test in isolated chicken eyes
Report:	<a href="#">XXXX.; 2020; 20/102-038CS; M-689659-01-1</a>
Authority registration No:	
Guideline(s):	OECD 438 (2018); EU Commission Regulation (EC) No 1272/2008 (2008); EU Commission Regulation (EU) 2017/735 (2017); US-EPA OCSPP 870.SUPP
Deviations:	None
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	

## Materials and methods

Test material (Lot/Batch No.)	Prohexadione-calcium OD 75 (75 g/L)
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	Synonym(s): KUH 833 Batch number: 2020-001264
<b>Test System</b>	Isolated chicken eyes
<b>No. of replicates</b>	3 for the test item, 3 for the positive control and 1 for the negative control (for each Experiment (I+II))
<b>Exposure</b>	30 µL for 10 seconds
<b>Controls</b>	Positive: 5% (w/v) Benzalkonium chloride solution Negative: physiological saline
<b>Irrigation (time point)</b>	After the exposure period the cornea surface was rinsed thoroughly with 20 mL physiological saline
<b>Vehicle/Dilution</b>	None for the test item (distilled water for the preparation of the positive control)
<b>Post exposure observation time points</b>	Approx. 30, 75, 120, 180 and 240 minutes after the post-treatment rinse
<b>Remarks</b>	None

## Results and discussions

**Table A 12: Results of in vitro eye irritation of Prohexadione-calcium OD 75 (75 g/L) Experiment I**

Treatment	Observations							
	75 Mins		240 Mins		Corneal Opacity		Flourescein Retention	
	Mean Max. Swelling (%)	ICE Class	Mean Max. Swelling (%)	ICE Class	Mean Max. Corneal Opacity	ICE Class	Mean Flourescein Retention	ICE Class
Negative Control	0.0	I	-1.6	I	0.00	I	0.00	I
Positive Control	9.2	II	21.1	III	4.00	IV	2.83	IV
Test Item	1.6*	I	6.0	II	0.17	I	0.83	II
* The maximum change up to 75 minutes mean is -0.5%, but as the change at 30 minutes observation mean is 1.6%, this is considered as the Maximum change up to 75 minutes.								

**Table A 13: Results of in vitro eye irritation of Prohexadione-calcium OD 75 (75 g/L) Experiment II**

Treatment	Observations							
	75 Mins		240 Mins		Corneal Opacity		Flourescein Retention	
	Mean Max. Swelling (%)	ICE Class	Mean Max. Swelling (%)	ICE Class	Mean Max. Corneal Opacity	ICE Class	Mean Flourescein Retention	ICE Class
Negative Control	1.6	I	1.6	I	0.00	I	0.00	I
Positive Control	8.7	II	21.2	III	4.00	IV	3.00	IV
Test Item	0.5*	I	0.5*	I	0.67	II	0.83	II

\* The maximum change up to 75 and 240 minutes mean is 0.0%, but as the change at 30 minute observation mean is 0.5%, this is considered as the Maximum change up to 75 and 240 minutes.



Treatment	Other observations/Morphological effects	Overall ICE Class
<b>Negative Control</b>	Experiment I: None Experiment II: None	3xI 3xI
<b>Positive Control</b>	Experiment I: Severe loosening of epithelium was observed in one eye at 75 minutes after the post treatment rinse. Experiment II: None	1xIII 2xIV 1xIII 2xIV
<b>Test Item</b>	Experiment I: Slight loosening of epithelium was observed in one eye at 30 minutes and severe loosening of epithelium was observed in one eye at 75 minutes after the post-treatment rinse. Test item was stuck on all cornea surfaces after the post-treatment rinse. The cornea surfaces (3/3) were cleared at 75 minutes after the post-treatment rinse. Experiment II: Slight loosening of epithelium was observed in one eye at 30 minutes after the post-treatment rinse.	1xI 2xII  1xI 2xII

## Conclusion

Based on these in vitro eye irritation tests in isolated chicken eyes, the numerical scores indicate that the Prohexadione-calcium OD 75 (75 g/L) is Non-Irritant. However, there was loosening of the corneal epithelium, which suggests that a more suitable conclusion is that more information is required before a full classification can be made.

Comments of zRMS:	<p>In addition to the CLP calculation method and <i>in vitro</i> testing of eye corrosive and irritant properties of Prohexadione-calcium OD 75 (contrary results), Applicant submitted the result of the study: <i>Prohexadione-calcium OD 75 (75 g/L): Acute Eye Irritation Study in Rabbits</i> (XXXX.; 2020; 20/102-005N) conducted for a country outside of Europe.</p> <p>Acute <b>Skin Eye</b> Irritation was examined according to the OECD Test Guideline 405 (2017); Commission Regulation (EU) No. 2017/735, B.5 (2017) and US EPA OPPTS 870.2400 (1998) in compliance with Principles of Good Laboratory Practice (GLP). No deviations occurred during this study.</p> <p>The study was conducted with three male New Zealand White rabbits. The test item was placed into the conjunctival sac of the left eye of each animal. The untreated right eye served as control. The test item was administered as an instillation of 0.1 mL as a single dose. The eyes were examined at 1 (±5 min) hour, 24 (±30 min), 48 (±1 h), 72 (±1 h) hours, at 1 week after application in three animals and 2 weeks after application in the first and second animal. The irritation effects of the test item were evaluated according to the Draize method (OECD No.: 405, 2017). There were no clinical signs of systemic toxicity. The general state and behaviour of the animals were normal throughout the experimental period. It was concluded that Prohexadione-calcium OD 75 applied to the rabbits' eye mucosa, caused conjunctival effects and corneal effects for a maximum of 1 week, which were fully reversible within a maximum of 2 weeks.</p> <p>Concluding, according to the result of study performed with the formulation Prohexadione-Ca OD 75, this mixture should be finally classified as Eye Irrit. 2 (H319) according to the Regulation (EC) No. 1272/2008.</p>
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Reference:	<b>KCP 7.1.5/02</b>
Title:	Prohexadione-calcium OD 75 (75 g/L): Acute eye irritation study in rabbits
Report:	<a href="#">XXXX.: 2020; 20/102-005N; M-757432-01-1</a>
Authority registration No:	
Guideline(s):	OECD 405 (2017); Commission Regulation (EU) No 2017/735, B.5 (2017); US-EPA 712-C-98-195, OPPTS 870.2400 (1998)
Deviations:	None
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	No

## Materials and methods

<b>Test material (Lot/Batch No.)</b>	Prohexadione-calcium OD 75 (75 g/L) Synonym: KUH 833 Batch number: 2020-001264
<b>Species</b>	Rabbit, New Zealand White
<b>No. of animals (group size)</b>	3 males
<b>Initial test using one animal</b>	Yes
<b>Exposure</b>	0.1 mL (single instillation in conjunctival sac)
<b>Irrigation (time point)</b>	Saline (0.9% NaCl) 1 hour after treatment
<b>Vehicle/Dilution</b>	None
<b>Post exposure observation period</b>	7 to 14 days
<b>Remarks</b>	Based on the results from the in vitro eye irritation study in the Isolated Chicken Eyes model with the test item, the test item is non-irritant. It is concluded that an in vivo study is required for proper classification and regulatory purposes.

## Results and discussions

**Table A 14: Eye irritation of Prohexadione-calcium OD 75 (75 g/L)**

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	1	1	1	1	1.00	14
	Iritis	0	0	0	0	0.00	na
	Redness conjunctivae	2	2	2	2	2.00	14
	Chemosis conjunctivae	3	2	1	1	1.33	7
	Discharge	3	1	0	0	0.33	2
2	Corneal opacity	1	1	1	1	1.00	14
	Iritis	0	0	0	0	0.00	na
	Redness conjunctivae	3	2	2	2	2.00	14
	Chemosis conjunctivae	3	2	1	1	1.33	7
	Discharge	2	3	0	0	1.00	2
3	Corneal opacity	1	1	1	1	1.00	7
	Iritis	0	0	0	0	0.00	na
	Redness conjunctivae	2	2	2	1	1.67	7
	Chemosis conjunctivae	3	2	1	0	1.00	3
	Discharge	3	3	1	0	1.33	3

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

na not applicable

<b>Clinical signs:</b>	No clinical signs of toxicity were observed.
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## Conclusion

Under the experimental conditions, Prohexadione-calcium OD 75 (75 g/L) is an eye irritant. Thus, classification is required according to Regulation (EC) No. 1272/2008.

## A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	<p>The approach of Applicant is acceptable.</p> <p>Skin sensitisation potential of Prohexadione-Ca OD 75 was determined using the calculation method in accordance with CLP taking into consideration valid data available for each component of the mixture. The formulation contains no ingredients triggering classification of the mixture for skin sensitisation.</p> <p>In addition, Applicant submitted the result of the study <i>Prohexadione-calcium OD 75 (75g/L): Local Lymph Node Assay in the Mouse</i> (XXXX; 2020; 20/102-037E) conducted for a country outside of Europe.</p> <p>Although, according to the Regulation (EC) No 1107/2009 animal testing for the purpose of the registration plant protection product should be performed as a last resort, in the case of the available alternative CLP calculation method there is a concern for the underestimation of adverse effects for more toxic products (<i>A comparative assessment of the CLP calculation method and in vivo testing for the classification of plant protection products</i>, D. Kurth et al., Regulatory Toxicology and Pharmacology 101 (2019) 79–90). This additivity approach assumes a similar mode of action for all ingredients in a mixture and although it is often a worst-case estimation of chemical interaction, it does not take into account the influence of co-formulants on the toxicokinetic properties of the active substance(s). It is also noted that <i>in vitro</i> alternatives to the skin sensitization testing methods are not fully regulatory available. Therefore, both calculation method and submitted study were evaluated.</p> <p>Skin sensitization potential was examined according to the OECD Test Guideline 429 (2010); Commission Regulation (EC) No. 640/2012 (2012) amending 440/2008 Method B 42 and US EPA OPPTS 870.2600 (2003) in compliance with Principles of Good Laboratory Practice (GLP). Deviations indicated in study report were considered not to adversely affect the results or integrity of the study.</p> <p>The study was conducted with the minimum number of animals corresponding to the regulatory guidelines. Prohexadione-calcium OD 75, tested in 1% Pluronic as vehicle at 25% (w/v) 50% (w/v), and at 100% (undiluted) concentrations was shown to have skin sensitisation potential (sensitiser) in the Local Lymph Node Assay. The EC3 (estimated concentration of a test substance needed to produce a stimulation index of three, which is considered as the threshold ratio to characterise a positive response vs. the concurrent vehicle control group) was extrapolated to give an EC3 value of Prohexadione-calcium OD 75 of 20.91% (w/v). This result triggered classification of the tested formulation as Skin Sens. 1 according to the Regulation (EC) No. 1272/2008.</p> <p>Concluding, taking into consideration both results, the formulation Prohexadione-Ca OD 75 should be classified as Skin Sens. 1 (H317) according to the Regulation (EC) No. 1272/2008.</p>
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The skin sensitising properties were evaluated according to Regulation (EC) No. 1272/2008, Annex I table 3.4.5, for classification of mixtures.

The current formulation contains no ingredients triggering classification of the mixture for skin sensitization. However, a skin sensitization study was conducted with the formulation itself for a country outside of Europe which revealed a positive response requiring classification for skin sensitization.

Reference:	<b>KCP 7.1.6/01</b>
Title:	Prohexadione-calcium OD 75 (75 g/L): Local lymph node assay in the mouse
Report:	<a href="#">XXXX; 2020; 20/102-037E; M-758174-01-1</a>
Authority registration No:	
Guideline(s):	OECD 429 (2010); EU Commission Regulation (EC) 640/2012 (2012); amending 440/2008 Method B 42.; US-EPA 712-C-03-197, OPPTS 870.2600 (March 2003)
Deviations:	None
GLP/GEP:	yes
Acceptability:	
Duplication (if vertebrate study):	No

## Materials and methods

<b>Test material (Lot/Batch No.)</b>	Prohexadione-calcium OD 75 (75 g/L) Synonym(s): KUH 833 Batch number: 2020-001264
<b>Species</b>	Mouse, CBA/CaOlaHsd
<b>No. of animals (group size)</b>	5 females/group
<b>Range finding:</b>	Yes (preliminary irritation/toxicity test)
<b>Exposure (concentration(s), no. of applications)</b>	25 µL at 100% (undiluted), 50% and 25%(w/v) in 1% Pluronic on the dorsal surface of each ear on three consecutive days.
<b>Vehicle</b>	1% Pluronic
<b>Pretreatment prior to topical application</b>	No
<b>Reliability check</b>	Negative control: 1% Pluronic Positive control: 15% (w/v) Formaldehyde
<b>Remarks</b>	None

## Results and discussions

**Table A 15: Results of skin sensitisation study of Prohexadione-calcium OD 75 (75 g/L)**

	<b>No. of animals</b>	<b>Concentration (%)</b>	<b>DPN / group</b>	<b>Stimulation index (SI)</b>
Test item	5	100	4363.4	6.4
	5	50	4699.4	6.9
	5	25	2563.9	3.8
Test Vehicle Control Group	5	N/A	678.0	1.0
Positive control	5	N/A	4558.5	6.7

<b>Clinical signs:</b>	No mortality or signs of systemic toxicity were observed during the study. Minimal amount of test item residue was observed on the ears of the animals at 100% (undiluted) on Days 2-
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	4. Very slight erythema (score 1) was observed in all animals of the 100% (undiluted) dose group on Days 2-4 and in all animals of the 50% (w/v) on Day 3 (after treatment). Well-defined erythema (score 2) was observed in all animals of the 100% (undiluted) dose group on Day 3 (after treatment).
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## Conclusion

Under the experimental conditions, Prohexadione-calcium OD 75 (75 g/L) is a skin sensitizer. Thus, classification is required according to Regulation (EC) No. 1272/2008.

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

Comments of zRMS:	Applicant did not provide an explanation for the classification of the formulation Prohexadione-calcium OD 75 as STOT-SE 3 (RTI), H335. According to the Safety Data Sheets one co-formulant is classified in this hazard class. Taking into account the concentration of this ingredient in the formulation (24.27%) and the generic concentration limit of ingredients of a mixture classified according to CLP as a specific target organ toxicant that trigger classification of the mixture as Category 3 (20%), the formulation Prohexadione-calcium OD 75 needs to be classified as STOT-SE 3 (RTI) with the hazard statement H335 (May cause respiratory irritation).
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## Supplementary studies for combinations of plant protection products (KCP 7.1.8)

Not required.

## 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)

Default values according to Guidance on dermal absorption<sup>5</sup> are used in this submission.

<sup>5</sup> Guidance on Dermal Absorption according to EFSA Journal 2017;15(6):4873. Doi: 10.2903/j.efsa.2017.4873

## **A 2.11                    Other/Special Studies**

Nothing submitted.

## Appendix 3 Exposure calculations

The following tables provide an overview of exposure calculations for all active substances, relevant crops and PPE scenarios as an outcome of the most updated version of the EFSA calculator.

### A 3.1 Operator exposure calculations (KCP 7.2.1.1)

**Table A-16: Operator exposure, Prohexadione, Oilseeds, no PPE / with PPE**

<b>Substance</b>	Prohexadione	<b>Formulation =</b> Soluble concentrates, emulsifiable concentrate, etc.	<b>Application rate =</b> 0.09 kg a.s. /ha	<b>Spray dilution =</b> 0.9 g a.s./l	<b>Vapour pressure =</b> low volatile substances having a vapour pressure of <5*10 <sup>-3</sup> Pa
<b>Scenario</b>	Oilseeds, Outdoor, Downward spraying, Vehicle-mounted			<b>Buffer =</b> 2-3 m	<b>Number of applications =</b> 1 <b>Application interval =</b> 365 days
<b>Percentage Absorption</b>	Dermal for product = 25%	<b>Dermal for in use dilution</b> = 70%	<b>Oral =</b> 100%	<b>Inhalation =</b> 100%	
RVNAS <sup>1</sup> (AOEL)	0.35 mg/kg bw/day		RVAAS <sup>2</sup>	- mg/kg bw/day	

<b>Operator Model</b>	Mixing, loading and application AOEM				
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.121	% of RVNAS <sup>1</sup>	34.5%	
	Acute systemic exposure mg/kg bw/day	-	% of RVAAS <sup>2</sup>	-%	
Mixing and Loading	<b>Gloves = Yes</b>	Clothing = Work wear - arms, body and legs covered	PPE = None	Soluble bags = No	
Application	<b>Gloves = Yes</b>	Clothing = Work wear - arms, body and legs covered	PPE = None	Closed cabin = No	
Exposure (Workwear)	Longer term systemic exposure mg/kg bw/day	<b>0.074</b>	% of RVNAS <sup>1</sup>	<b>21.1%</b>	
	Acute systemic exposure mg/kg bw/day	-	% of RVAAS <sup>2</sup>	-%	
Exposure (Including PPE options above)	Longer term systemic exposure mg/kg bw/day	<b>0.00331</b>	% of RVNAS <sup>1</sup>	<b>0.945%</b>	
	Acute systemic exposure mg/kg bw/day	-	% of RVAAS <sup>2</sup>	-%	

<sup>1</sup> RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

<sup>2</sup> RVAAS = Reference Value Acutely toxic active Substance

### A 3.2 Worker exposure calculations (KCP 7.2.3.1)

**Table A-17: Worker exposure, Prohexadione, Oilseeds**

<b>Substance</b>	Prohexadione	<b>Formulation =</b> Soluble concentrates, emulsifiable concentrate, etc.	<b>Application rate =</b> 0.09 kg a.s. /ha	<b>Spray dilution =</b> 0.9 g a.s./l	<b>Vapour pressure =</b> low volatile substances having a vapour pressure of <5*10 <sup>-3</sup> Pa
<b>Scenario</b>	Oilseeds, Outdoor, Downward spraying, Vehicle-mounted			<b>Buffer =</b> 2-3 m	<b>Number of applications =</b> 1 <b>Application interval =</b> 365 days
<b>Percentage Absorption</b>	Dermal for product = 25%	<b>Dermal for in use dilution</b> = 70%	<b>Oral =</b> 100%	<b>Inhalation =</b> 100%	
RVNAS <sup>1</sup> (AOEL)	0.35 mg/kg bw/day		RVAAS <sup>2</sup>	- mg/kg bw/day	
DFR	3 µg a.s./cm <sup>2</sup> per kg a.s./ha		DT50	30 days	
Worker – Inspection, irrigation	Potential exposure mg/kg bw/day		0.0788	% of RVNAS <sup>1</sup>	22.5%
	Working clothing mg/kg bw/day		0.00882	% of RVNAS <sup>1</sup>	2.52%
	Working clothing and gloves mg/kg bw/day		-	% of RVNAS <sup>1</sup>	-%

<sup>1</sup> RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

<sup>2</sup> RVAAS = Reference Value Acutely toxic active Substance

#### A 3.2.1 Calculations for the active substance(s)

Please refer to A 3.



### A 3.3 Bystander and resident exposure calculations (KCP 7.2.2.1)

**Table A-18: Bystander and resident exposure, Prohexadione, Oilseeds**

<b>Substance</b>	Prohexadione	<b>Formulation =</b> Soluble concentrates, emulsifiable concentrate, etc.	<b>Application rate =</b> 0.09 kg a.s. /ha	<b>Spray dilution =</b> 0.9 g a.s./l	<b>Vapour pressure =</b> low volatile substances having a vapour pressure of <5*10 <sup>-3</sup> Pa
<b>Scenario</b>	Oilseeds, Outdoor, Downward spraying, Vehicle-mounted			<b>Buffer =</b> 2-3 m	<b>Number of applications =</b> 1 <b>Application interval =</b> 365 days
<b>Percentage Absorption</b>	Dermal for product = 25%	<b>Dermal for in use dilution</b> = 70%	<b>Oral =</b> 100%	<b>Inhalation =</b> 100%	
<b>RVNAS<sup>1</sup> (AOEL)</b>	0.35 mg/kg bw/day		<b>RVAAS<sup>2</sup></b>	- mg/kg bw/day	
<b>DFR</b>	3 µg a.s./cm <sup>2</sup> per kg a.s./ha		<b>DT50</b>	30 days	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0169	% of RVNAS <sup>1</sup>	4.83%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS <sup>1</sup>	0.306%
	Surface deposits (75th percentile) mg/kg bw/day	0.00099	% of RVNAS <sup>1</sup>	0.283%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0106	% of RVNAS <sup>1</sup>	3.04%
	All pathways (mean) mg/kg bw/day	0.0196	% of RVNAS <sup>1</sup>	5.6%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00405	% of RVNAS <sup>1</sup>	1.16%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS <sup>1</sup>	0.0657%
	Surface deposits (75th percentile) mg/kg bw/day	0.000429	% of RVNAS <sup>1</sup>	0.123%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00591	% of RVNAS <sup>1</sup>	1.69%
	All pathways (mean) mg/kg bw/day	0.00718	% of RVNAS <sup>1</sup>	2.05%

<sup>1</sup> RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

<sup>2</sup> RVAAS = Reference Value Acutely toxic active Substance

#### A 3.3.1 Calculations for the active substance(s)

Please refer to Appendix 3.

### 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)

Not applicable.

#### A 4.1 Prohexadione-Ca

Not applicable.