Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

oxathiapiprolin (ISO); 1-(4-{4-[5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone

EC Number: -
CAS Number: 1003318-67-9

CLH-O-0000001412-86-246/F

Adopted

30 November 2018

30 November 2018

CLH-O-0000001412-86-246/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **oxathiapiprolin (ISO); 1-(4-{4-[5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone**

EC Number: **-**

CAS Number: **1003318-67-9**

The proposal was submitted by **Ireland** and received by RAC on **14 February 2018.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Ireland has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **12 March 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **11 May 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Julie Séba**

Co-Rapporteur, appointed by RAC: **Pietro Paris**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **30 November 2018** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	oxathiapiprolin (ISO); 1-(4-{4-[5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone	not assigned	1003318-67-9	Aquatic Chronic 1	H410	GHS09 Wng	H410	-	M = 1 M = 1	-
RAC opinion	TBD	oxathiapiprolin (ISO); 1-(4-{4-[5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone	not assigned	1003318-67-9	Aquatic Chronic 1	H410	GHS09 Wng	H410	-	M = 1	-
Resulting Annex VI entry if agreed by COM	TBD	oxathiapiprolin (ISO); 1-(4-{4-[5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone	not assigned	1003318-67-9	Aquatic Chronic 1	H410	GHS09 Wng	H410	-	M = 1	-

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Oxathiapiprolin (DPX-QGU42) is a fungicide from the piperidinyl thiazole isoxazoline class; it is a new active substance in the EU and there is no current harmonised classification and labelling according to the CLP Regulation.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

The DS concluded that none of the reported physico-chemical properties of oxathiapiprolin result in a requirement for classification using the criteria set out in the CLP Regulation.

Comments received during public consultation

One MSCA agreed with the conclusion of the DS.

Assessment and comparison with the classification criteria

Oxathiapiprolin does not meet any of the classification criteria for explosive properties, oxidising properties, flammable solids or self-heating substances. Therefore, **no classification is warranted for physical hazards**.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Oral Route

One OECD TG 425 study is available for the oral route. Under the conditions of the study, the acute oral LD_{50} for oxathiapiprolin was greater than 5000 mg/kg bw for female rats. No mortalities were observed.

The DS did not propose to classify oxathiapiprolin for acute oral toxicity.

Inhalation Route

One OECD TG 403 study is available for the inhalation route. Under the conditions of the study, the acute inhalatory LC_{50} for oxathiapiprolin was greater than 5 mg/L for female and male rats. No mortalities were observed.

The DS did not propose to classify oxathiapiprolin for acute inhalatory toxicity.

Dermal Route

One OECD TG 402 study is available for the dermal route. Under the conditions of the study, the acute dermal LD_{50} for oxathiapiprolin was greater than 5000 mg/kg bw for female and male rats. No mortalities were observed.

The DS did not propose to classify oxathiapiprolin for acute dermal toxicity.

Comments received during public consultation

Two MSCA supported the DS proposal not to classify oxathiapiprolin for acute oral, dermal and inhalation toxicity.

Assessment and comparison with the classification criteria

Oral Route

In a GLP OECD TG 425 acute oral study, oxathiapiprolin (purity 96.2 %) was administered as a dose of 175, 550, 1750 or 5000 mg/kg bw, suspended as a 20% w/w mixture in 0.1% solution of Tween 80 in 0.5% aqueous methylcellulose, to the stomach of 6 female Sprague-Dawley rats (DuPont-29441, 2010). All doses were administered in a single administration with the exception of the top dose which was divided in two equal portions administered two hours apart due to the high volume of test suspension (22.87 mL/kg).

No mortalities occurred during the course of this study at any dose. No clinical signs or body weight loss was noted during the study. At the end of the 14-day observation period, no gross abnormalities were noted for any of the animals when necropsied.

The oral LD_{50} for rats was greater than 5000 mg/kg bw.

Since the relevant criteria in the CLP Regulation were not met RAC agrees with the DS proposal for **no classification of oxathiapiprolin for acute oral toxicity.**

Inhalation Route

In a GLP compliant acute inhalation study partially consistent with OECD TG 403, oxathiapiprolin (purity 95.7 %) was administered via the inhalation route at a concentration of 5.1 mg/L to 5 males and 5 females (Crl:CD(SD) rats for a single 4 hour period (DuPont-30260, 2010). The mean mass median aerodynamic diameter (MMAD) was 2.7 µm +/- 2.0 µm.

No mortality was reported during the 4-h exposure neither at the end of the two-week post-exposure period. The day after exposure, body weight losses were observed in all male rats (from 2.7 to 4.7%) and all female rats (from 1.4 to 4.9%). There were no other body weight losses observed in any rats throughout the 14-day recovery period. There were no gross lesions observed at necropsy.

The inhalatory LC_{50} for rats was greater than 5 mg/L.

Since the relevant criteria in the CLP Regulation were not met RAC agrees with the DS proposal for **no classification of oxathiapiprolin for acute inhalation toxicity.**

Dermal Route

In a GLP compliant acute dermal study partially consistent with OECD TG 402, oxathiapiprolin (purity 95.7 %) was administered as a single dose of 5000 mg/kg bw, moistened with 1.5 mL of deionized water, directly to the skin of 5 male and 5 female Crl:CD(SD) rats, covering 10% of each animal's body surface area with a semi-occluded dressing, for 24 hours (DuPont-30259,

DAR B.6.2.2.1 - 2010). All animals survived. With the exception of one female (4% body weight loss), the animals exhibited no clinical signs of toxicity, dermal irritation (no erythema or oedema observed), or abnormal behaviour.

The dermal LD_{50} for rats was greater than 5000 mg/kg bw. Since relevant criteria in the CLP Regulation were not met, RAC agrees with the DS proposal for **no classification of oxathiapiprolin for acute dermal toxicity.**

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

The DS did not propose to classify oxathiapiprolin for specific target organ toxicity after single exposure due to the absence of findings indicating STOT-SE concerns following a single administration by oral, dermal or inhalation route nor in an acute neurotoxicity study.

Comments received during public consultation

Two MSCA supported the DS proposal to not classify oxathiapiprolin for STOT SE.

Assessment and comparison with the classification criteria

No functional disturbances, morphological changes or severe toxicity were reported in any of the acute animal studies through oral, dermal or inhalation exposure.

In a GLP compliant acute neurotoxicity study, partially consistent with OECD TG 424, Crl:CD(SD) rats (12/sex/dose) were administered a single oral dose of oxathiapiprolin (0, 200, 1000 or 2000 mg/kg bw, purity 96.2%) by gavage (DuPont-29440, 2010). The NOAEL was 2000 mg/kg based on the absence of toxicity. No findings suggestive of target organ toxicity were observed in this study.

Therefore, RAC is of the opinion that **classification for STOT SE is not warranted**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The DS proposed no classification for oxathiapiprolin as a skin irritant based on negative results in a GLP compliant OECD TG 404 study in New Zealand White (NZW) rabbits. Oxathiapiprolin produced no skin irritation in rabbits at 24 and 72 hours following a 4 hour dermal exposure. All individual scores were 0.

Comments received during public consultation

Two MSCA supported the DS proposal not to classify oxathiapiprolin for skin irritation/corrosion.

Assessment and comparison with the classification criteria

In a GLP compliant OECD TG 404 study, oxathiapiprolin (purity 95.7%) was applied as a single 500 mg dermal dose to the skin of two females and one male NZW rabbits (DuPont-30262, DAR B.6.2.4.1 - 2010). The test substance (moistened with mineral oil in a 70% w/w mixture for the first animal, and with distilled water in a 70% w/w mixture for the second and third animals) was placed on the skin and covered with a semi-occlusive dressing.

After 4 hours exposure, the test substance was removed. No signs of erythema, oedema or other evidence of skin irritation were reported in any of the animals at 1, 24, 48 and 72h after patch removal, at either the treated or the control site. No signs of any systemic toxicity were reported in any of the treated animals.

Since relevant criteria in the CLP Regulation were not met RAC agrees with the DS proposal for **no classification of oxathiapiprolin for skin irritation.**

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS proposed no classification for oxathiapiprolin as an eye irritant based on an OECD TG 405 study in rabbit. Results showed that oxathiapiprolin produced only slight conjunctival redness in rabbits, which had cleared by 72 hours.

Comments received during public consultation

Two MSCA supported the DS proposal to not classify oxathiapiprolin for eye irritation/corrosion.

Assessment and comparison with the classification criteria

In a GLP compliant OECD TG 405 eye irritation study, oxathiapiprolin (purity 95.7%) was applied as a single dose of 0.07g (equivalent to 0.1 mL) into the conjunctival sac of the right eye of 3 female NZW rabbits (DuPont-30261, DAR B.6.2.5.1 - 2010). The eyes remained unwashed after treatment.

No signs of corneal opacity or iritis were reported in any of the animals at 1, 24, 48 and 72h following administration of the test substance. Slight conjunctival redness (score of 1) and discharge (score of 1 or 2) were observed in all treated animals and conjunctival chemosis (score 1) was noted in one rabbit after 1h. Mean individual scores (according to Draize (1944) methodology) are presented in the table below. All effects reversed by 72h.

***Table**: Mean individual eye irritation scores according to Draize in an irritation study in rabbits*

Animal Number	Corneal opacity[a]	Iritis[a]	Conjunctival redness[a]	Conjunctival chemosis[a]
3401 (F)	0.00	0.00	0.3	0.00
3402 (F)	0.00	0.00	0.3	0.00
3403 (F)	0.00	0.00	0.7	0.00

[a] Mean of 24, 48 and 72 h readings

Since only slight conjunctival redness was observed in at least 2 of 3 tested animals with a mean Draize score lower than 2, relevant criteria for serious eye damage and eye irritation are not met.

RAC therefore agrees with the DS proposal for **no classification of oxathiapiprolin for serious eye damage/irritation.**

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

No data was available regarding respiratory sensitisation. Therefore no classification for this hazard class was proposed by the DS.

Comments received during public consultation

Two MSCA supported the DS proposal not to classify oxathiapiprolin for respiratory sensitisation.

Assessment and comparison with the classification criteria

In the absence of available data, RAC is of the opinion that oxathiapiprolin **does not warrant classification for respiratory sensitisation**, as concluded by the DS.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

No classification was proposed for oxathiapiprolin as a skin sensitiser on the basis of a Magnusson-Kligman Maximisation study in guinea pigs (GPMT). The DS concluded that under the conditions of this GPMT, oxathiapiprolin did not produce a positive dermal sensitisation response.

Comments received during public consultation

Two MSCA supported the DS proposal to not classify oxathiapiprolin for skin sensitisation.

Assessment and comparison with the classification criteria

The dermal sensitisation potential of oxathiapiprolin (purity 95.7%) was evaluated by a GLP compliant OECD TG 406 GPMT in male Hartley albino guinea pigs (DuPont-30221, DAR B.6.2.6.1 - 2010).

A preliminary irritation test was performed on 12 animals to determine appropriate concentrations of the test substance to be used for both the intradermal and topical induction and the topical challenge. The concentration selected for the intradermal induction was a 5% w/w mixture in mineral oil. A concentration of 70% was found to produce faint to moderate dermal irritation and was selected for the topical induction phase and 18% did not produce dermal irritation and was selected as the challenge dose.

Based on the results of this preliminary irritation testing, 20 animals were induced by pairs of intradermal injections of the test substance (5% w/w mixture in mineral oil) or test substance combined with Freund's Complete Adjuvant (5% w/w mixture of test substance in Adjuvant). For the test vehicle control, 10 animals were induced with the Adjuvant alone (50% v/v Adjuvant in

distilled water). One week later, animals were topically induced with 0.5 g of test substance (70% w/w mixture in mineral oil).

Animals were challenged on test day 22 with occlusive applications of 18% w/w mixture of the test substance in mineral oil or a 6% w/w mixture of the test substance in mineral oil (0.5 mL). The percentage of animals responding with a positive reaction at 24 and/or 48 hours for the test article animals challenged with 18% w/w or 6% w/w of test substance was 0%.

No animal showed a positive reaction. Based on the results of this study, oxathiapiprolin was not considered to be a skin sensitiser.

A second GLP-compliant OECD TG 406 GPMT was conducted with Hartley albino guinea pigs to determine the potential for oxathiapiprolin to cause dermal skin sensitisation reactions (DuPont, 2014). Preliminary irritation testing was performed on 12 animals to determine appropriate concentrations of the test substance that could be used for both intradermal and topical induction as well as topical challenge.

Faint to moderate irritation (scores 1-2) was present at the intradermal induction sites injected with 5% w/w mixture in mineral oil, but the mixture was concluded too viscous to be administered properly. The concentration which produced very faint (score 0.5) irritation, which was selected for the topical induction, was a 65% w/w mixture in mineral oil. The highest concentration that produced responses (in four guinea pigs) two scores of 0.5 and two scores of zero was a 65% w/w mixture in mineral oil.

During the induction phase, 20 animals were induced by 6 pairs of intradermal injections of the test substance (3% w/w mixture in mineral oil), test substance combined with Freund's Complete Adjuvant (3% w/w mixture of test substance in Adjuvant) as well as an emulsion of Freund's Adjuvant Complete alone. For the vehicle control, 10 animals were induced with the Adjuvant alone (50% v/v Adjuvant in distilled water) or Freund's Adjuvant Complete alone. One week later, all animals received a pre-treatment of sodium dodecyl sulfate prior to test substance application due to a lack of significant irritation having been produced during preliminary testing. Animals were then topically induced with a 65% w/w mixture in mineral oil for 48h. Approximately two weeks later, a primary challenge consisting of three occluded applications of 65% w/w or 22% mixture in mineral oil was conducted on each animal for approximately 24 hours.

Very faint erythema (0.5) was noted in 3/20 sites 24 hours after 65% w/w mixture challenge and in 2/20 sites after 22% w/w mixture challenge. Irritation cleared from all affected sites by 48 hours. Based on the results of this study, oxathiapiprolin was considered not to be a skin sensitizer.

RAC notes that there was no concurrent positive control in both studies. However, alpha-hexylcinnamaldehyde (75% w/w mixture in mineral oil) is periodically tested in the laboratory and has been shown to demonstrate a positive response, in accordance with the OECD 406 guideline.

No animal showed positive reaction in the GPMT. Therefore since relevant criteria were not met, RAC agrees with the DS proposal for **no classification of oxathiapiprolin for skin sensitisation.**

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The DS assessed the repeated dose toxicity studies in rats (two-week, 28-day and 90-day studies by the oral route, a 28-day study by the dermal route and a combined chronic toxicity/oncogenicity study), in mice (28-day and 90-day studies by the oral route) and in dogs (28-day, 90-day and 1-year studies by the oral route). Liver was identified as a potential target-organ of oxathiapiprolin in dogs but the observed effects occurred outside the guidance values for STOT RE classification. In rats, minimal increases in cholesterol and adrenal weights were considered to be non-adverse. Therefore, the DS concluded that no classification was warranted.

Comments received during public consultation

Two MSCA supported the DS proposal not to classify oxathiapiprolin for STOT RE.

Assessment and comparison with the classification criteria

The Table below summarises the available oral and dermal repeated-dose toxicity studies with animals.

***Table**: Summary table for oral repeated dose toxicity studies in animals with oxathiapiprolin.*

Method	Results	Reference
Guideline not specified **Non-GLP study** 14 days Crl:CD(SD) Rat 8 animals/sex/dose (Control : 5 animals/sex) Oral, gavage Vehicle : 0,5% methycellulose and 0,1% Tween 80 0, 25, 300 and 1000 mg/kg bw/day Purity: 99% ***Guidance value level for warranting classification as category 2: 600 mg/kg bw/day***	**<u>1000 mg/kg bw/day</u>** ***Males*** Cholesterol increase (+55%) Triglycerides increase (+55%) CYP2B1 increase (332% of controls) ***Females*** CYP2B1 increase (215% of controls) **<u>300 mg/kg bw/day</u>** ***Males*** Cholesterol increase (+23%) **NOAEL = 1000 mg/kg bw/day** **LOAEL > 1000 mg/kg bw/day**	DuPont-24634 (2008)
OECD 407 **Non-GLP study** 28 days Crl:CD(SD) Rat 5 animals/sex/dose	**<u>20000 ppm</u>** *(1774/1657 mg/kg bw/day)* ***Females*** Cholesterol increase (+47%) **<u>7500 ppm</u>** *(580/588 mg/kg bw/day)*	1 DuPont-28294 (2010) DuPont-28294, Supplement No. 1 (2011)

Oral, diet 0, 500, 2000, 7500 and 20000 ppm equivalent to 0, 37, 153, 580 and 1657; and 0, 40, 159, 588 and 1774 mg/kg bw/day in males and females, respectively Purity 99.5% ***Guidance value level for warranting classification as category 2: 300 mg/kg bw/day***	***Females*** Increase in mean adrenal weight (+43%) **NOAEL = 1657/1774 mg/kg bw/day** **LOAEL > 1657/1774 mg/kg bw/day**	
OECD 407 **Non-GLP study** 28 days Crl:CD-1(ICR) mouse 10 animals/sex/dose Oral, diet 0, 200, 800, 3500 and 7000 ppm, equivalent to 0, 32, 129, 597 and 1151; and 0, 41, 175, 745 and 1440 mg/kg bw/day in males and females, respectively Purity: 99.5% ***Guidance value level for warranting classification as category 2: 300 mg/kg bw/day***	**<u>7000 ppm</u>** *(1151/1440 mg/kg bw/day in females)* ***Males*** CYP4A1/2/3 increase (+58%) **NOAEL = 1151/1440 mg/kg bw/day** **LOAEL > 1151/1440 mg/kg bw/day**	DuPont-28295 Revision No. 1 (2011) DuPont-28295, Supplement No. 1, Revision No. 1 (2013)
Non-guideline **Non-GLP study** 28 days Beagle dogs 2 animals/sex/dose Oral, diet 0, 1000, 10000 and 40000 ppm, equivalent to 0, 30, 352 and 1368; and 0, 31, 331 and 1346 mg/kg bw/day in males and females, respectively Purity: 99.5% ***Guidance value level for warranting classification***	**<u>40000 ppm</u>** *(1368/1346 mg/kg bw/day)* ***Males*** Relative liver + gallbladder weight increase (+39%) Absolute liver + gallbladder weight increase (+30%) Mild hepatocellular vacuolation ***Females*** Relative liver + gallbladder weight increase (+39%) in one female Absolute liver + gallbladder weight increase (+30%) in one female Mild hepatocellular vacuolation **<u>10000 ppm</u>** *(352/331 mg/kg bw/day)* ***Males*** Relative liver + gallbladder weight increase (+22%) Absolute liver + gallbladder weight increase (+19%) Mild hepatocellular vacuolation	DuPont-28296 DuPont-28296, Supplement No.1

as category 2: 300 mg/kg bw/day	**<u>1000 ppm</u>** *(30/31 mg/kg bw/day)* ***Males*** Relative liver + gallbladder weight increase (+18%) Absolute liver + gallbladder weight increase (+8%) **NOAEL = 30/31 mg/kg bw/day** **LOAEL = 352/331 mg/kg bw/day**	
OECD 408 **GLP study** 90 days Crl:CD(SD) rat 10 animals/sex/dose (toxicology groups) + 5 animals/sex/dose (neuropathology groups) Oral, diet 0, 500, 2000, 6000 and 18000 ppm, equivalent to 0, 29, 117, 359 and 1096; and 0, 36, 145, 433 and 1300 mg/kg bw/day in males and females, respectively Purity: 96.2% ***Guidance value level for warranting classification as category 2: 100 mg/kg bw/day***	There were no deaths or treatment-related clinical signs of toxicity observed in any dose group. **<u>18000 ppm</u>** *(1096/1300 mg/kg bw/day)* ***Females*** Bilirubin increase (+25%) Cholesterol increase (+22%) **<u>6000 ppm</u>** *(359/433 mg/kg bw/day)* ***Females*** Cholesterol increase (+25%) **<u>2000 ppm</u>** *(29/36 mg/kg bw/day)* ***Females*** Cholesterol increase (+30%) **NOAEL = 1096/1300 mg/kg bw/day** **LOAEL > 1096/1300 mg/kg bw/day**	DuPont-28947 (2011)
OECD 408 **GLP study** 90 days Crlj:CD1(ICR) mouse 10 animals/sex/dose Oral, diet 0, 200, 800, 3500 and 7500 ppm, equivalent to 0, 28.5, 118.6, 490.6 and 1058; and 0, 35.3, 155.4, 660.1 and 1468 mg/kg bw/day in males and females, respectively Purity: 96.2% ***Guidance value level for warranting classification as category 2: 100 mg/kg bw/day***	No adverse effect at any dose **NOAEL= 1058/1468 mg/kg bw/day** **LOAEL > 1058/1468 mg/kg bw/day**	DuPont-28946 (2012)

OECD 409 GLP study 90 days Beagle dog 4 animals/sex/dose Oral, diet 0, 40 (males only), 400, 4000 and 36000 ppm, equivalent to 0, 1.6, 16.6, 166.8 and 1415; and 0, 16.1, 172.1 and 1429 mg/kg bw/day in males and females, respectively Purity: 97.6% ***Guidance value level for warranting classification as category 2: 100 mg/kg bw/day***	No adverse effect at any dose **NOAEL= 1415/1429 mg/kg bw/day** **LOAEL > 1415/1429 mg/kg bw/day**	DuPont-30047 (2012) DuPont-30047 Supplement No. 1 (2013)
OECD 453 GLP Combined chronic toxicity/oncogenicity study 1 year CD[Crl:CD (SD)] rat 10 animals/sex/dose Oral, diet 0, 500, 2000, 6000/7500 and 18000 ppm, equivalent to 0, 24, 92, 346 and 846; and 0, 32, 128, 460 and 1147 mg/kg bw/day in males and females, respectively Purity: 95.7% ***Guidance value level for warranting classification as category 2: 25 mg/kg bw/day***	**<u>18000 ppm</u>** *(846/1147 mg/kg bw/day)* **Females** Cholesterol increase (+45 and +26% at the 6- and 12-month samplings). **<u>6000/7000 ppm</u>** *(346/460 mg/kg bw/day)* **Females** Cholesterol increase (+37 and +15% at the 6- and 12-month samplings). **NOAEL= 846/1147 mg/kg bw/day** **LOAEL > 846/1147 mg/kg bw/day**	DuPont-30180 (2013)
OECD 452 GLP study 1 year Beagle dog 4 animals/sex/dose Oral, diet 0, 40, 400, 4000 and 36000 ppm	**<u>36000 ppm</u>** *(1242/1461 mg/kg bw/day)* ***Males*** Absolute liver weight + gallbladder increased (+28%) Relative liver weight + gallbladder increased (+16%) ***Females*** Absolute liver weight + gallbladder increased (+31%) Relative liver weight + gallbladder increased (+35%) **<u>4000 ppm</u>** *(148/137 mg/kg bw/day)*	DuPont-30254 (2013)

equivalent to 0, 1.4, 13.6, 148.0 and 1242.2; and 0, 1.4, 13.8, 137 and 1461 mg/kg bw/day in males and females, respectively Purity: 95.7% ***Guidance value level for warranting classification as category 2: 25 mg/kg bw/day***	***Males*** Absolute liver weight + gallbladder increased (+29%) Relative liver weight + gallbladder increased (+13%) ***Females*** Absolute liver weight + gallbladder increased (+41%) Relative liver weight + gallbladder increased (+40%) **NOAEL = 13.6/13.8 mg/kg bw/day** **LOAEL = 148/137 mg/kg bw/day**	
OECD 410 **GLP study** 28-days Sprague-Dawley rat 10 animals/sex/dose Dermal 0, 150, 450 and 1000 mg/kg/day 6h/day Purity: 95.7% ***Guidance value level for warranting classification as category 2: 600 mg/kg bw/day***	There were no deaths or treatment-related systemic signs of toxicity observed in any dose group. **<u>1000 mg/kg bw/day</u>** **Males** Very slight erythema (1/10) **<u>450 mg/kg bw/day</u>** **Males** Very slight erythema (1/10) **Females** Very slight erythema (1/10) **<u>150 mg/kg bw/day</u>** **Males** Very slight erythema (1/10) **NOAEL = 1000 mg/kg bw/day** **LOAEL > 1000 mg/kg bw/day**	DuPont-32338 (2012)

Oral repeated-dose toxicity studies

<u>Oral short-term studies</u>

In a 14 day gavage study, oxathiapiprolin was administered to male and female rats at doses of 0, 25, 300 or 1000 mg/kg bw/day. Significant effects in serum cholesterol increases were reported in males given the mid dose and high dose (+23% and +55% respectively) and triglycerides (+55%) at the high dose only.

In a 28-day feeding rat study, cholesterol was increased to 147% of control in females at the top dose. Female adrenal weights were slightly elevated, but only the increase at 7500 ppm was statistically significant (mean adrenal weight relative to body weight as a % of control: 114%, 129%, 143% and 132% at 500, 2000, 7500 and 20000 ppm, respectively).

In mice, a 28-day study showed minimal increase in liver + gallbladder weight relative to body weight, without a dose-related trend (+2%, 8%, 2% and 9% in females and +11, 7, 9 and 6% in males at 200, 800 3500 and 7000 ppm, respectively). An increase in liver cytochrome P450 4A1/2/2 activity was reported in males, being only statistically significant at the highest dose (+58%). Slight increases were also observed in female mice. No effect was reported on CYP 2B1/2 activity.

With the exception of the increased cholesterol in the rat 14-day study at mid dose, all the effects described above were out of the range for STOT RE classification.

In dogs, oxathiapiprolin was administered during 28 days at concentrations of 0, 1000, 10000 and 40000 ppm. There was a trend for a dose-dependent increase in the absolute and relative liver weights (+ gallbladder) in the males, as summarised in the Table below. One female also reported an increase in absolute and relative liver + gallbladder weight of 130% and 139% of controls, respectively, at the highest dose. A dose-dependent increase in cytochrome P450 isozyme 2B1/2 was observed in 1000, 10000 and 40000 ppm males, and only at the highest dose in females. Mild hepatocellular vacuolation was reported in males at 1000, 10000 and 40000 ppm, which was considered to be an indication of higher glycogen levels in treated males relative to the controls.

The effects occurring in the range of guidance values for STOT RE 2 classification were limited to a minimal increase in absolute and relative liver + gallbladder weights in males only, of 118% and 108% of controls, respectively, associated with mild hepatocellular vacuolation and increased CYP P450 2B1/2 activity. There was no evidence of hepatocellular degeneration or necrosis and no alteration in hepatic enzymes indicative of liver toxicity.

***Table**: Summary of liver/gallbladder weight in a 28-day dog oral toxicity study*

	0 ppm	**1000 ppm**	**10000 ppm**	**40000 ppm**
Males (2/group)				
Absolute liver (+gallbladder) w/ g (% of control)	259.9	305.3 (+18%)	309.6 (+19%)	360.8 (+39%)
Relative liver (+gallbladder) w/bw % (% of control)	2.75	2.96 (+8%)	3.34 (+22%)	3.58 (+30%)
Females (2/group)				
Absolute liver (+gallbladder) w/ g (% of control)	278.5	239.0 (-14%)	299.9 (+8%)	329.2 (+18%)
Relative liver (+gallbladder) w/bw % (% of control)	3.39	2.74 (-19%)	2.92 (-14%)	3.47 (+2%)

Note : No statistical test performed as there were only 2 dogs/sex/dose in this study

Oral 90-day studies

Oxathiapiprolin was offered in the diet for 91 or 92 consecutive days to four toxicology groups and four neuropathology groups of rats. Dose levels were 0, 500, 2000, 6000, and 18000 ppm, respectively. Total bilirubin was minimally higher in the 18000 ppm-group female rats (125% of control). Slight, non-statistically significant and non-dose dependant increases in cholesterol occurred in females (mean values of 130%, 125% and 122% of control, at 2000, 6000 and 18000 ppm, respectively) but remained within the range of HCD.

In a mouse 90-day feeding study, oxathiapiprolin was administered at concentrations of 0, 200, 800, 3500 or 7500 ppm. Non-adverse minimal elevations in relative liver + gallbladder were reported in males at the mid and top doses, outside the range of guidance values for STOT RE classification.

In a dog 90-day feeding study, mean absolute and relative (to brain weight) liver weight plus gallbladder weights were increased compared to controls in some exposure groups, without a dose-dependent trend. When compared to body weight, there were no differences in the relative mean liver plus gallbladder weight between control and treated dogs (Table below). Overall, the effects seen in the range of guidance values for STOT RE classification are not considered relevant for classification.

***Table**: Summary of liver/gallbladder weight in a 90-day dog oral toxicity study*

	0 ppm	40 ppm	400 ppm	4000 ppm	36000 ppm
Males (4/group)					
Absolute liver (+gallbladder) w/ g (% of control)	209	215 (+3%)	254 (+22%)	239 (+14%)	275 (+32%)
Relative liver (+gallbladder) w/bw % (% of control)	3.21	2.98 (-7%)	2.92 (-9%)	3.06 (-5%)	3.19 (-1%)
Females (4/group)					
Absolute liver (+gallbladder) w/ g (% of control)	174	-	229 (+32%)	209 (+20%)	198 (+14%)
Relative liver (+gallbladder) w/bw % (% of control)	2.68	-	3.12 (+16%)	2.85 (+6%)	2.79 (+4%)

Oral long-term chronic toxicity studies

As part of a 2-year chronic toxicity and carcinogenicity oral study, 10 rats were sacrificed after approximately 1 year to assess chronic toxicity. Mean cholesterol levels were increased at 6000/7000 ppm and 18000 ppm. In females, minimal changes in adrenal weight relative to body weight as a percent of control values at 1 year at 500, 2000, 6000/7500 and 18000 ppm were 120%, 119%, 122% and 117%, respectively; and at 2 years: 105%, 119%, 119% and 107%, respectively.

After a 2 year-exposure, several statistically significant increases in non-neoplastic lesions were reported in males at the highest dose, including adrenal gland cortical angiectasis/cystic degeneration, cortical hypertrophy and medullary hyperplasia, kidney transitional cell hyperplasia, lung alveolar histiocytosis and pituitary gland cysts, all outside the range of guidance values for STOT RE classification.

In a 1 year feeding study, oxathiapiprolin was administered to male and female beagle dogs at concentrations of 0, 40, 400, 4000 or 36000 ppm (DuPont-30254 DAR B.6.2.4 2013). There was a trend for increased relative liver weight, which was more pronounced in females. Absolute and relative liver weight increases in the range of 20% to 40% were noted at doses of 4000 ppm and 36000 ppm (Table below). The effects seen in the range of guidance values for STOT RE classification were considered to be minimal.

***Table**: Summary of liver/gallbladder weight in a 1-year dog oral toxicity study*

	0 ppm	40 ppm	400 ppm	4000 ppm	36000 ppm
Males (4/group)					
Absolute liver (+gallbladder) w/ g (% of control)	208.1	220.8 (+6%)	213.2 (+2%)	269.0 (+29%)	267 (+28%)
Relative liver (+gallbladder) w/bw % (% of control)	2.59	2.65 (+2%)	2.64 (+2%)	2.94 (+13%)	3.00 (+16%)
Females (4/group)					
Absolute liver (+gallbladder) w/ g (% of control)	173.9	204.7 (+18%)	182.3 (+5%)	228.1 (+31%)	245.0 (+41%)
Relative liver (+gallbladder) w/bw % (% of control)	2.49	2.86 (+15%)	2.73 (+10%)	3.35 (+35%)	3.48 (+40%)

Not statistically significant

Dermal repeated-dose toxicity studies

In a 28-day dermal study, oxathiapiprolin was applied to the dorsal skin of male and female Sprague Dawley SD rats. The test substance was applied for 29 daily applications, 6 h per day at 0, 150, 450, or 1000 mg/kg bw/day. No systemic effects were reported. Very slight erythema was observed on day 1 at all dose groups. RAC is of the opinion that these effects do not trigger classification for STOT RE.

Conclusion

Oral repeated dose toxicity studies with oxathiapiprolin were conducted in rats, mice and dogs and a dermal 28-day study is available in rats.

In the dog 28-day study, there was a dose-dependent increase in the absolute and relative liver weights (+ gallbladder) in the males. Effects on liver (+ gallbladder) were also observed in the 90-day and 1-year studies, although the findings were graded as minimal at doses that were within the range of guidance values for STOT RE classification and there was no clear dose-dependence. These liver weight alterations were not accompanied by major clinical chemistry or histopathological changes indicative of liver toxicity. Therefore, RAC is of the opinion that the effects seen on the liver in dogs are not sufficient to classify oxathiapiprolin for STOT RE.

Increased cholesterol levels were noted in rats in various studies at doses within the range of guidance values for STOT RE classification. However, in the absence of other clinical or histopathological modifications, this effect was not considered adverse.

Finally, a minimal adrenal weight increase (20%) was reported in rats at 24/32 mg/kg bw/day after 1 year of exposure. After 2 years of exposure, the increase was limited to 5% at the same dose and no dose-dependence was demonstrated. Although adrenal gland cortical angiectasis/cystic degeneration was reported at the highest dose, no microscopic findings were reported at doses relevant for STOT RE classification.

In conclusion, RAC acknowledges that liver is a target-organ after oxathiapiprolin exposure. However, RAC considers that the observed changes observed in rats, mice and dogs either occurred outside the STOT RE guidance values or were not sufficiently adverse to trigger classification. Therefore, RAC agrees with the DS proposal for **no classification of oxathiapiprolin for STOT RE.**

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Oxathiapiprolin was negative in a complete battery of *in vitro* genotoxicity tests with or without metabolic activation. An *in vivo* mouse micronucleus study was also negative.

The *in vitro* studies included one bacterial mutation assays (DuPont-30255, 2011), a mammalian chromosome aberration test in human lymphocytes (DuPont-30256, 2010) and a mammalian cell gene mutation (HGPRT) test in Chinese hamster ovary cells (DuPont-30257, 2010). All studies were performed under GLP in accordance with OECD-guidelines.

In vivo, oxathiapiprolin did not induce micronuclei in bone marrow cells in a GLP mouse micronucleus test nor in a supportive rat micronucleus study.

Comments received during public consultation

Two MSCA supported the DS proposal to not classify oxathiapiprolin for germ cell mutagenicity.

One MSCA argued that no conclusion can be drawn on the *in vivo* genotoxic potential of oxathiapiprolin due to the absence of target cell toxicity in the *in vivo* studies.

Assessment and comparison with the classification criteria

In vitro studies

Oxathiapiprolin did not cause gene mutations or chromosome aberrations in a battery of *in vitro* genotoxicity studies conducted with and without exogenous metabolic activation system.

In a Bacterial Reverse Mutation Test (GLP, OECD TG 471 compliant), oxathiapiprolin (95.7% purity) was evaluated for mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and in *E. coli* strain WP2 uvrA at nominal concentrations of 33.3, 66.7, 100, 333, 667, 1000, 3333, and 5000 µg/plate (DuPont-30255, DAR B.6.4.1 - 2011). No positive mutagenic responses were observed with any of the tested strains with or without S9 metabolic activation. Precipitate was observed from 667 µg per plate and no appreciable toxicity was observed at doses up to and including 5000 µg per plate.

The clastogenic potential of oxathiapiprolin (95.7 % purity) was tested in the Mammalian Chromosome Aberration Test (GLP, OECD TG 473 compliant) using human peripheral blood lymphocytes (DuPont-30256, DAR B.6.4.1.2 - 2010). Based on the findings of a preliminary cytotoxicity assay, the chosen doses for the chromosome aberration assay ranged from 25 to 5000 µg/mL for the non-activated 4- and 20-hour treatment groups, and from 50 to 2000 µg/mL for the activated 4-hour treatment. At the highest test concentrations mitotic inhibition was comprised between 48-51% relative to the solvent control. No statistically significant increases in structural chromosome aberrations or polyploidy were observed at any of the concentrations evaluated.

A CHO/HGPRT mutation assay (GLP, OECD TG 476 compliant) was performed with and without exogenous metabolic activation (DuPont-30257 Rev No. 1, DAR B.6.4.1.3 - 2010). CHO-K1 cells were exposed for 5 h to oxathiapiprolin (95.7% purity) at concentrations of 5.0, 10, 25, 50, and 100 µg/mL, based on a preliminary toxicity assay. There was no indication of gene mutation for oxathiapiprolin in the presence and absence of an exogenous metabolic activation system in the *in vitro* CHO (HPRT) cell gene mutation assay.

In vivo studies

Treatment with oxathiapiprolin did not result in increases in micronucleated erythrocytes in two *in vivo* mouse genotoxicity studies.

In vivo, a mouse micronucleus assay (GLP, OECD TG 474 compliant) was performed in the bone marrow of male and female Crl:CD1 (ICR) mice (DuPont-31004, DAR B.6.4.1.4 - 2010). A single dose of vehicle, or 500, 1000 or 2000 mg oxathiapiprolin/kg bw (purity 95.7%) was given by oral gavage (10 animals/sex/dose at the low and mid doses, but 14/sex at the highest dose). Cyclophosphamide (CP) (40 mg/kg bw) was administered as the positive control to 5 animals/sex.

Bone marrow was removed approximately 24 hours after dosing at all dose levels. Additionally, high-dose mice were sampled at 48 h. No significant decrease in the PCE/NCE ratio was found at any dose level or sacrifice time, indicating an absence of target cell toxicity. No statistically significant or biologically relevant increases in micro-nucleated polychromatic erythrocyte frequency were observed at any time point up to the limit dose of 2000 mg/kg bw oxathiapiprolin.

In a supportive non-GLP 14-day study, oxathiapiprolin was administered to Crl:CD(SD) rats (5/sex/dose) at 0, 25, 300 or 1000 mg/kg bw/day for 12 days or were given a single dose of 2000 mg/kg bw/day (DuPont-24634, 2008). Cyclophosphamide was used as a positive control. No increase in micronuclei was observed at the highest dose after 12 days of treatment or after the single dose of 2000 mg/kg bw/day. The intermediate doses were not analysed for genotoxicity.

Conclusion

All the available *in vitro* and *in vivo* mutagenicity studies showed negative results. Therefore, since the relevant criteria were not met RAC agrees with the DS proposal for **no classification of oxathiapiprolin for germ cell mutagenicity.**

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

Based on the results of oral carcinogenicity studies in rats and mice, the DS concluded that oxathiapiprolin was not carcinogenic in either species and therefore proposed no classification.

A slight increase of pancreatic islet cell tumours (4/60) occurred in female rats at top dose (957 mg/kg bw/day) but this was within the laboratory historical control range and considered by the DS not to be compound related. In female mice, histiocytic sarcoma (2/60) and vaginal stromal polyps (2/60) were noted at the highest dose (1106 mg/kg bw/day), remaining within internal HCD.

No study was available regarding carcinogenicity after inhalation or dermal exposure.

Comments received during public consultation

Two MSCA supported the DS proposal to not classify oxathiapiprolin for carcinogenicity.

Assessment and comparison with the classification criteria

In a 2-year chronic toxicity and carcinogenicity feeding study, oxathiapiprolin (purity 95.7%) was administered to approximately 70 male and female CD[Crl:CD(SD)] rats/sex/dose (DuPont-30180, DAR B.6.5.1 - 2013). Concentrations in feed were 0, 500, 2000, 6000/7500, and 18000 ppm (6000 ppm for the first three weeks and 7500 ppm for weeks 4 through 105 in group 4). The mean daily intakes for male and female rats were respectively 0, 21, 84, 309, and 735 mg/kg bw/day and 0, 27, 109, 378, and 957 mg/kg bw/day.

A statistically significantly increased trend in pancreatic islet cell adenomas occurred in females with an incidence of 0/59, 0/39, 0/43, 1/43, and 4/60 (6.7%) in the 0, 500, 2000, 6000/7500, and 18000 ppm groups, respectively (Table below). Although statistically significant at the top dose, this finding remained within the internal historical control range (0-8.3%) and occurred in one sex only. Moreover, pancreatic islet cell adenomas are benign tumours. They occurred at very low incidence and no progression to malignancy was observed. In addition, no associated pre-neoplastic lesions were reported and no related neoplastic findings were reported in mouse. Therefore it was considered to represent the spontaneous occurrence of a benign neoplasm commonly seen in rats of this strain and age. RAC is of the opinion that this neoplastic finding is not relevant for classification.

***Table**: Occurrence of neoplastic pancreatic lesions in female rats in a 2-year chronic toxicity and carcinogenicity feeding study*

Dose (ppm)	0	500	2000	6000/7000	18000
Adenoma, islet cell, benign	0/59	0/39	0/43	1/43	4/60# (6.67%)
Carcinoma, islet cell, malignant	1/59	0/39	0/43	1/43	1/60
Benign/malignant combined	1/59	0/39	0/43	2/43	5/60# (8.33%)

: Cochran-Armitage Trend Test, P<0.05

In an 18 month carcinogenicity feeding study, oxathiapiprolin was administered to male and female Crlj:CD1(ICR) mice (60 mice/sex/concentration) at concentrations of 0, 200, 800, 3500, and 7000 ppm (DuPont-30263, DAR B.6.5.2 - 2013). The mean daily intakes in male and female mice were, respectively, 0, 27, 110, 468, and 948 mg/kg bw/day and 0, 30, 125, 529, and 1106 mg/kg bw/day.

The incidence of histiocytic sarcoma in the haemolymphatic system was slightly increased in females of the high dose group (2/60 females or 3.3%) but remained within the in-house historical control ranges (1.7 – 3.3%). This tumour occurred at the highest dose at very low incidence, in one sex only and was not observed in rat. RAC therefore considers that this finding is not relevant for classification.

A slight but statistically significantly increased incidence of stromal polyps in the vagina (2/60 or 3.3%) was also noted in females fed at 7000 ppm. The very low incidence in this study is comparable to historical control ranges for polyps of the vagina and cervix in this strain of mouse (0.78–3.3%) and are a typical spontaneous age-related lesion in mice. Moreover, stromal polyps are benign tumours and no progression to malignancy was observed. These tumours were also not reported in rats. These findings are therefore considered not to be relevant for classification.

All the neoplastic findings occurred in one sex in one species at very low incidence, only at the high dose and remained within the range of the internal historical control data. Two types are benign tumours observed without associated pre-neoplastic lesions and did not progress to malignancy. Overall RAC considers that **classification for carcinogenicity is not warranted.**

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The evaluation of reproductive toxicity after exposure to oxathiapiprolin is based on a non-guideline non-GLP range-finding one-generation study and a two-generation OECD TG 416 GLP-compliant reproductive toxicity study in rats and on two OECD TG 414 GLP-compliant developmental toxicity studies in rats and NZW rabbits. Furthermore, 3 studies investigated the hormonal activity of oxathiapiprolin.

In the one-generation study, during lactation, a decrease in F1 male and female pup body weights was observed at 20000 ppm during lactation and early post-weaning period. The decrease was statistically significant in males at different time points, in comparison with controls. A delay of roughly 3 days was reported in balanopreputial separation in F1 males at 20000 ppm. The DS concluded that the delayed balanopreputial separation was due to the decreased body weight in F1 males.

In the 2-generation study, the adverse effects consisted of reduced mean pup weights, for F1 litters at 17000/10000 ppm during lactation and developmental delays in F1 and F2 adult males at 6000/3500 and 17000/10000 ppm.

No adverse effect linked to maternal or developmental toxicity was observed in two OECD TG 414 developmental toxicity studies conducted on rats and rabbits.

Based on these results, the DS did not propose classification for reproductive toxicity for oxathiapiprolin.

Comments received during public consultation

One MSCA agreed with the proposal for no classification. Two other MSCA commented on this endpoint.

One MSCA highlighted that a classification as Repr. 2 may be warranted considering the adverse developmental effects seen in the 2-generation toxicity study, such as a dose-dependent delay in preputial separation.

The other MSCA suggested considering classification for effects on or via lactation based on delayed growth and preputial separation as well as effects on body weights and body weight gains appearing during the lactation period.

Assessment and comparison with the classification criteria

Fertility

The Table below summarises the available studies investigating fertility in animals.

Table**: Summary table for fertility studies in animals with oxathiapiprolin.

Method	Exposure	Doses tested	NOAELs/LOAELs	Reference
One-generation reproduction toxicity study Non-guideline Non-GLP Oral, feeding Rat (Crl:CD(SD)) 10/sex/group Purity 99.5% and 96.23% (two different batches)	28 days prior to mating, throughout mating, and continuing through the end of the study	0, 2000, 10000 and 20000 ppm dietary	**Adults:** NOAEL 20000 ppm (No LOAEL) **Offspring**: NOAEL 10000 ppm LOAEL 20000 ppm based on decreased body weight during lactation and post-weaning period + delayed balanopreputial separation **Reproduction:** NOAEL 20000 ppm (No LOAEL)	DuPont-28631, Revision No. 1 (2011) Supportive

Two-generation reproduction study OECD Part 416 (2001) GLP Oral, feeding Rat (Crl:CD(SD)) 30/sex/dose Purity 95.7%	70 days prior to mating, throughout mating, and continuing through the end of the study	0, 500, 1500, 6000 and 17000 ppm dietary, Adjusted to 0, 300, 900, 3500 and 10000 ppm respectively for PND 0 to 42 (lactation and post-weaning)	**Adults:** NOAEL 17000/10000 ppm No LOAEL **Offspring**: NOAEL 1500/900 ppm LOAEL 6000/3500 ppm due to delayed preputial separation in F1 offspring. **Reproduction:** NOAEL 17000/10000 ppm (No LOAEL)	DuPont-30258 (2013) DuPont-30258, Supplement No. 1 (2013) Key-study

In a non-guideline non-GLP one-generation study, oxathiapiprolin was given via the diet to 10 Crl:CD(SD) rats/sex/dose. Dietary concentrations were 0, 2000, 10000 and 20000 ppm for the F0 and F1 generations (Table below).

***Table**: Mean daily intakes (mg/kg body weight/day) in a one-generation reproduction study*

Dietary concentrations	2000 ppm	10000 ppm	20000 ppm
F0 males (D 0-27)	129	653	1321
F0 females (D 0-27)	150	715	1507
Gestation	140	676	1389
Lactation	316	1655	3089

Exposure levels were based on the results seen on a repeated-dose 28-day oral toxicity study in rats, where no adverse effects were noted up to 20000 ppm and a previous developmental screening study in rat showing no toxicity at exposure levels up to 1000 mg/kg bw/day.

Parental effects

A statistically significantly lower mean body weight gain was noted in F0 females in the 20000 ppm group during Days 0–7 which was associated with lower mean food efficiency. Mean body weight gain in these females was generally similar to the control group during the remainder of the pre-mating period (Days 7–27).

Mean absolute and relative (to final body weight) seminal vesicle and coagulating gland weights in the 20000 ppm group P males were statistically significantly higher than in the concurrent control group (+14% and +17% of control, respectively). However, they remained within the range of the WIL historical control data.

There were no test-substance related effects on P male and female reproductive parameters.

F1 litters effects

In the 20000 ppm group, 17 of 19 pups out of a single litter were found dead or missing on PND 0-2, affecting the postnatal survival index.

F1 pup body weights were similar to controls at birth in all test-groups and no maternal toxicity was reported at any dose. However, during the lactation period, test substance-related lower mean body weight gains were noted in the 20000 ppm group F1 pups compared to the control,

without maternal toxicity. Mean body weights in the 20000 ppm group were up to 20.0% (F1 males) and 16.5% (F1 females) lower than in the control group during PND 7-21.

Post-weaning, significantly lower mean body weights were noted in the 20000 ppm group F1 males throughout the post-weaning period. At the end of the study, the body weights of these males remained 8% lower than in the control group. F1 females also showed lower body weights during the first 2 weeks of the post-weaning period. Thereafter, mean body weight in these females was generally similar to the control group.

Decreased food consumption and food efficiency were also noted in 20000 ppm F1 males through PND 28-35. The lower mean food consumption in this group was attributed to the residual effect of the lower mean body weights from the pre-weaning period.

The F1 mean age of attainment of balanopreputial separation in the high dose group was statistically significantly increased (+3.1 days) compared to the concurrent control group value and was shown to correlate with the test substance-related reduction in offspring body weight (Table below).

***Table** : Balanopreputial separation in F1 rats in a one-generation reproductive study*

F1 males				
Mean Balanopreputial separation (PND) *SD (N)*	0 ppm 45.8 *2.64 (10)*	2000 ppm 45.4 *2.81 (10)*	10000 ppm 45.1 *1.86 (10)*	20000 ppm 48.9* *2.35 (9)*
Mean Body weight (g) *SD (N)*	0 ppm 236.7 *22.72 (10)*	2000 ppm 228.5 *17.10 (10)*	10000 ppm 227.8 *13.25 (10)*	20000 ppm 229.3 *17.50 (9)*

* Significantly different from control by Dunnett's test criteria, at $p < 0.05$

No significant effects were observed on spermatogenic endpoints or organ weights in F1 males. Slight, non-statistically significant decreases in absolute and relative weights (to brain weight) of epididymides (11% and 8%, respectively) and testes (11% and 9%, respectively) were however noted in F1 males at the highest dose.

Mean ages of attainment of F1 vaginal patency were unaffected by test substance exposure. The mean ages of attainment of vaginal patency were 32.8, 32.6, 32.9, and 33.0 days in the control, 2000, 10000, and 20000 ppm groups, respectively. F1 stages of oestrous cycles were similar in all tested groups and the controls.

The NOAEL for F0 systemic toxicity and reproductive performance in both males and females was 20000 ppm based on the lack of adverse effects observed on the F0 generation. The developmental NOAEL for F1 in both males and females was 10000 ppm, based on the decreases in mean body weight gain during pre-weaning and post-weaning periods at 20000 ppm.

In an OECD TG 416 and GLP compliant two-generation reproductive toxicity study in Crl:CD(SD) rats, oxathiapiprolin was administered in the diet to 30 rats/sex/dose (both the P1 and F1 generations) at concentrations of 0, 500, 1500, 6000 and 17000 ppm in the diet. During lactation (P1 and F1 adults) and up to PND42, the dietary concentrations were adjusted to 0, 300, 900, 3500 and 10000 ppm to achieve the targeted mean daily intakes (Table below).

***Table**: Mean daily intakes (mg/kg body weight/day) in a rat multigeneration study*

Dietary concentration	500/300 ppm	1500/900 ppm	6000/3500 ppm	17000/10000 ppm
P1 males	29	86	346	1013
P1 females premating	34	106	430	1210
Gestation	31	95	383	1113
Lactation	41	119	483	1374
F1 males to PND42	37	108	422	1228
F1 males PND42-91	34	104	411	1196
F1 females to PND42	37	109	426	1243
F1 females PND42-91	41	116	465	1364
Gestation	32	98	390	1149
Lactation	41	127	494	1417
F2 males to PND 42	37	111	430	1278
F2 males PND 42-60	44	131	519	1519

Parental effects

A mild increase in mean adrenal weight was observed in the P1 and F1 adult females at ≥1500 ppm. Since there were no associated morphological changes, the increased adrenal weights in the P1 and F1 adult females were interpreted as non-adverse and a possible transient, stress-related, or adaptive effect on the adrenal glands. In F1 females, mean absolute and relative kidney weights were statistically significantly increased from 1500 ppm (range 7-13%), but without dose-dependence and remaining within the HCD range.

There was a statistically significant reduction in the number of sperm per gram testis observed in F1 males at the highest dose (89.9), but remaining within the HCD range (89.2 – 113.2). No corresponding effects on fertility indices or effects on histopathology were observed.

A statistically significant increase in post-implantation loss was reported at the highest dose in P1 females (14.8% vs 5.4% for the control group), which was outside the laboratory HCD range. No similar finding was observed in the F1 adult females at any dose level.

Offspring effects

Mean body weights at 17000/10000 ppm for F1 litters were 7 to 8% lower than controls from lactation days 4 through 14; F1 litter body weights were 8% lower than controls (statistically significant) on PND 21.

A statistically significant delay of 2.0 and 2.4 days, respectively, was observed in the preputial separation in F1 males exposed to 6000/3500 and 17000/10000 ppm, compared to controls. Also, a statistically significant delay of 2.4 days in preputial separation was reported in F2 males when exposed to 17000/10000 ppm. At 6000/3500 ppm, a delay of 1.6 days was found not to be statistically significant. These findings were demonstrated to not be correlated to pup weight

as the associated preputial separation body weights were increased compared to the controls (Table below).

***Table**: Mean number of days to achieve preputial separation in a rat two-generation study*

Dietary concentrations	0 ppm	500/300 ppm	1500/900 ppm	6000/3500 ppm	17000/10000 ppm
F1 males					
PS (SD)	41.5 (3.2)	41.1 (1.8)	42.1 (2.4)	43.5* (2.7)	43.9* (2.8)
mean PS bw (g)	222.1	211.7	227.3	236.7	238.9#
F2 males					
PS (SD)	43.8 (2.8)	44.4 (2.4)	44.0 (1.8)	45.4 (2.9)	46.2* (2.3)
mean PS bw (g)	238.4	242.0	245.4	255.5#	255.7#

*statistically significant : Dunnett Non-Parametric 2 Sided p < 0,05
statistically significant : Dunnett 2 Sided p < 0,05

There was no test substance-related effects on timing for achievement of vaginal patency in F1 females nor on anogenital distance in F1 and F2 pups.

The NOAEL for offspring was 1500/900 ppm due to delays in preputial separation at 6000/3500 and 17000/10000 ppm in F1 and F2 adult males, and the reduced F1 offspring weight at 17000/10000 ppm. The NOAEL for reproductive performance and systemic toxicity was 17000/10000 ppm, the highest concentration tested.

Conclusion on fertility

In the range-finding one-generation reproductive toxicity study, comparable birth weights were observed in all F1 male and female pups. However during lactation, lower mean body weights (up to 20%) were noted in the high dose-group F1 male pups compared to the control group. These lower body weights were correlated with a delay in preputial separation (+3.1 days).

In an OECD TG 416 two-generation reproductive toxicity study, no significant difference was noted in F1 and F2 male pup body weights during the lactation and post-weaning periods. Delays in the mean age of preputial separation were, however, reported in F1 males at 6000/3500 ppm (+2.0 days), corresponding to a daily intake in the range of 483-519 mg/kg bw/day and at 17000/10000 ppm (+2.4 days), corresponding to 1196-1519 mg/kg bw/day. In the F2 generation, a statistically significant delay in preputial separation was also noted at the highest dose (+2.4 days). Finally, a slight and non-statistically significant delay in PS was noted at 6000/3500 ppm (+1.6 days) in the F2 pups. This delay was however associated with a statistically significantly increased PS body weight. Although a correlation between reduced body weight in F1 pups and delayed preputial separation was seen in the supportive one-generation study, this relationship was not evident in F2 offspring in the key two-generation study. A slightly reduced body weight was observed in F1 litters at the highest dose (up to 8% reduction) during lactation. However, no difference was observed in body weights of F1 and F2 males compared to control groups in either the lactation or post-weaning periods. The delay in preputial separation seen in F1 and F2 males at 6000/3500 ppm and 17000/10000 ppm can therefore not be formally correlated to delayed growth in the two-generation study.

Regarding the exposures, statistically significant effects on preputial separation were observed at maternal exposure levels of 390-519 to 3089 mg/kg bw/day. Although some dose levels were higher than the recommended limit-doses, in particular in the two-generation study, RAC considers that a dose of 6000/3500 ppm (390-519 mg/kg bw/day) should not be seen as excessive.

Preputial separation is usually seen as a marker of puberty in males and is known to be androgen-dependent. Although balanopreputial separation is well known to be correlated with body weight, other determining factors can disrupt normal development of this landmark. In the absence of changes in body weight, differences in the timing of balanopreputial separation of two days or greater are commonly considered to be treatment-related (Hood, 2016).

The endocrine disrupting potential of oxathiapiprolin has therefore been investigated in three different studies, as developed in the supplemental information below. All studies were negative, with the exception of equivocal results on serum FSH concentrations in a 15-Day Intact Male Assay. However, an effect on the androgen-dependent pathway mediated by a toxic metabolite of oxathiapiprolin cannot be formally ruled out, in particular through breast milk.

Regarding the reproductive performance of the offspring affected by delayed puberty, a statistically significant reduction in the number of sperm per gram testis was only observed at the highest dose in F1 males in the key two-generation study, although this remained within the HCD. This endpoint was not investigated in the F2 offspring affected by a delayed preputial separation in the same study. In the one-generation study, no effect on sperm was reported at any dose.

Overall, RAC is of the opinion that the delay in preputial separation seen in males in two different studies should be considered treatment-related. However, the observed delays were of low severity or occurred at very high doses. Moreover, some inconsistencies were noted by RAC between the F1 and F2 preputial separation days in the two-generation study. Finally, no clear effect on reproductive performance/parameters or organ weight were noted.

In conclusion, no significant effects were observed on reproductive parameters or developmental landmarks, with the exception of a treatment-related delayed preputial separation in F1 and F2 males occurring at high doses or with low severity. Without other substantial information, this delay in puberty is considered by RAC as not sufficient to trigger classification. Therefore, RAC is of the opinion that **classification for fertility is not warranted.**

Developmental toxicity

The Table below summarises the available developmental toxicity studies with animals.

Table*: Summary table for developmental toxicity studies in animals with oxathiapiprolin***.**

Method	**Doses Exposure**	**NOAELs/LOAELs**	**Reference**
Developmental toxicity study OECD 414 section 4 GLP Oral gavage Crl:CD(SD) rat 22 females /dose	0, 100, 300 or 1000 mg/kg bw/day Purity 95.7% GD 6-20	*Maternal*: The NOAEL for maternal toxicity was 1000 mg/kg bw/day (No LOAEL) *Embryotoxicity/teratogenicity*: The NOAEL for developmental toxicity was 1000 mg/kg bw/day (No LOAEL)	DuPont-30253 Revision No. 1 (2013)

Developmental toxicity study OECD 414 GLP Oral gavage New Zealand White rabbit 22 females /dose	0, 100, 300 or 1000 mg/kg bw/day Purity 95.7% GD 7- 28	*Maternal*: The NOAEL for maternal toxicity was 1000 mg/kg bw/day (No LOAEL) *Embryotoxicity/teratogenicity*: The NOAEL for developmental toxicity was 1000 mg/kg bw/day (No LOAEL)	DuPont-32357 (2012)

In an OECD TG 414 developmental toxicity study, time-mated Crl:CD(SD) female rats (22/dose) were orally exposed to oxathiapiprolin on gestation days (GD) 6–20 (DuPont30253, 2013). Gavage doses, in 0.5% methylcellulose with 0.1% Tween 80, were administered to achieve doses of 0, 100, 300, and 1000 mg/kg body weight/day (dose volume of 10 mL/kg).

At 100, 300, and 1000 mg/kg/day, there were statistically significant increases in mean maternal body weight gain (17 to 21 %) from GD 18 to 20. Mean food consumption was also significantly increased over several intervals from 300 mg/kg bw/day.

Under the conditions of this study, there was no evidence of either maternal or developmental toxicity at doses up to 1000 mg/kg/day. Therefore, the NOAEL for maternal and developmental toxicity was considered to be 1000 mg/kg bw/day.

In an OECD TG 414 developmental toxicity study, oxathiapiprolin was orally administered to time-mated New Zealand White (Hra:[NZW]SPF) female rabbits (22/dose group) on GD 7–28 (DuPont-32357, 2012). Gavage doses were prepared in 0.5% methylcellulose with 0.1% Tween 80 to achieve 0, 100, 300, and 1000 mg/kg body weight/day (the dose volume was 10 mL/kg).

One female each in the 1000 and 100 mg/kg/day groups aborted on GD 24 and 27, respectively. One female each in the control and 100 mg/kg/day groups were found dead on GD 25 and 10, respectively, following respiratory clinical observations. One female in the 300 mg/kg/day group delivered on GD 29 following several days of reduced food consumption and body weight loss. Since there were no other indications of toxicity observed in surviving animals at any dose level, and the abortions, deliveries, and deaths did not occur in a dose-dependent manner, they were considered not treatment-related.

A dose level of 1000 mg/kg body weight/day, the highest dose evaluated, was considered to be the NOAEL.

Conclusion of RAC on developmental toxicity

No effects were seen on developmental toxicity studies in rats or rabbits. RAC notes that no maternal toxicity was observed at the highest dose in either study. However, the compound is slightly toxic (no acute toxicity up to 5000 mg/kg bw/day in rats, little evidence of target organ toxicity) and the dosing reached 1000 mg/kg bw/day for both studies.

In a rat range-finding one generation reproduction study, F1 offspring demonstrated the same birth weight in all dose-groups. During the lactation period, reduced body weight were observed in F1 males and females from PND 7 at an exposure dose of 3089 mg/kg bw/day. The reduced body weight was correlated with delayed preputial separation in males. During the post-weaning period, the difference in body weight between high dose pups and controls reduced in a dose-dependent manner. No significant difference between F1 females and controls was seen from

PND 56 until the end of the study. At the end of the study, the F1 males in the high dose group was only 8% lower than controls (statistically significant).

In a rat two-generation reproductive toxicity study, no significant difference was noted in F1 and F2 pup body weights during the lactation and post-weaning periods, with the exception of an 8% decrease in body weight in F1 litters during the lactation period. Delays in the mean age of preputial separation were, however, observed in F2 males at 6000/3500 ppm (45.4 vs 43.8 days), corresponding to a daily intake in the range of 483-519 mg/kg bw/day and at 17000/10000 ppm, corresponding to 1196-1519 mg/kg bw/day (45.4 and 46.2 vs 43.8 days in controls, respectively).

Overall, the effects seen on body weight at the end of the one-generation study were minimal in males at the highest dose, and no major effect on body weight were seen in the developmental study and the multigeneration study. Although treatment-related, the delay in preputial separation is not clearly correlated with lower body weight in the multigeneration study. This effect is therefore not clearly associated with an altered growth. RAC considers that **classification for developmental toxicity is not warranted.**

Lactation

In a rat non-guideline non-GLP one-generation study, F1 pups showed similar body weights to controls at birth in all test-groups and no maternal toxicity was reported at any dose. During the lactation period, test substance-related lower mean body weight gains were noted in the 20000 ppm group F1 pups compared to the control, without maternal toxicity. Mean body weights in the 20000 ppm group were up to 20.0% (F1 males) and 16.5% (F1 females) lower than the control group during PND 7-21 (Table below).

***Table**: Mean F1 rat offspring body weights (g) in a one-generation reproductive toxicity study*

F1 male rats				
Days	**0 ppm**	**2000 ppm**	**10000 ppm**	**20000 ppm**
PND 1	6.8	6.8	6.9	6.6
PND 4	9.6	9.2	9.6	8.2
PND 7	15.5	14.7	15.4	12.4*
PND 14	32.1	30.4	31.3	26.0*
PND 21	49.9	47.6	49.2	40.2*
F1 female rats				
Days	**0 ppm**	**2000 ppm**	**10000 ppm**	**20000 ppm**
PND 1	6.3	6.3	6.5	6.2
PND 4	8.9	8.6	9.2	7.9
PND 7	14.3	13.6	14.8	12
PND 14	30.3	28.9	30.4	25.3
PND 21	46.6	44.5	46.6	38.9

* Significantly different from control by Dunnett's test criteria, at $p < 0.05$

During the post-weaning period, the difference in body weight between high dose pups and controls reduced in a dose-dependent manner. At the end of the study, the body weights of these males remained 8% lower than in the control group. F1 females also showed lower body weights during the first 2 weeks of the post-weaning period (13% on PND 21 to 11% on PND 35). Thereafter, mean body weights in these females were generally similar to the control group.

These lower body weights were associated with a delay in preputial separation (48.9 days vs. 45.8 days in controls) in F1 males. Effects occurred at the highest dose of 20000 ppm, which corresponds to 3089 mg/kg bw/day.

Decreased food consumption and food efficiency were also noted in 20000 ppm F1 males through PND 28-35. Thereafter, food consumption (g/animal/day) and food efficiency in these males were generally similar to the control group. Mean food consumption was also slightly (1-2 g/animal/day) lower in the 20000 ppm group F1 females than the control group during PND 28–63. The lower mean food consumption in this group was attributed to the residual effect of the lower mean body weights from the pre-weaning period.

In an OECD TG 416 and GLP compliant two-generation reproductive toxicity study, mean pup weights at 17000/10000 ppm for F1 litters were 7 to 8% lower than controls from lactation Days 4 through 21, being only statistically significant on PND 21 (Table below). Exposure level corresponds to 1374 mg/kg bw/day.

***Table**: Mean F1 pup weight during lactation period in a two-generation reproduction study in rat.*

	0 ppm	**300 ppm**	**900 ppm**	**3500 ppm**	**10000 ppm**
PND 0	6.6	6.7	6.6	6.7	6.8
PND 4	10.7	10.5	10.4	10.7	10.0
PND 7	17.5	17.0	17.2	17.0	16.0
PND 14	35.9	35.2	35.5	35.1	33.4
PND 21	57.2	55.9	56.4	55.1	52.5*

<u>Conclusion of RAC on lactation</u>

In the one-generation reproductive toxicity study, similar birth weights were observed in all F1 male and female pups. However during the lactation period, lower mean body weights (up 20%) were noted in the high dose-group F1 male pups compared to the control group. These lower body weights were associated with a delay in preputial separation (48.9 days vs. 45.8 days in controls). In F1 females, lower body weights were also noted during the lactation period. Effects occurred at the highest dose of 20000 ppm, which corresponds to 3089 mg/kg bw/day.

During the post-weaning period, the difference in body weight between high dose pups and controls was reduced in a dose-dependent manner. No significant difference between F1 females and controls was seen from PND 56 until the end of the study. In F1 males, a difference of 19.5% in body weight was observed at weaning, which continued until PND 35. This difference was only of 13% at PND 42, reaching 7% at PND 56. At the end of the study, the F1 males did not fully recover compared to controls. This trend in F1 male and female body weights suggest that there was a recovery phase during the post-weaning period.

In a two-generation reproductive toxicity study, no significant difference was noted in F1 and F2 pup body weights during the lactation and post-weaning periods with the exception of a slight decrease in body weight in F1 pups at the highest dose of 10000 ppm (1374 mg/kg bw/day) during the lactation period (up to 8%).

No maternal toxicity was associated with any dose in either study, therefore no impaired nursing is assumed.

Regarding the exposures, statistically significant effects on body weight were observed from a maternal exposure level of 1374 to 3089 mg/kg bw/day. RAC acknowledges that these dose levels are higher than the limit-dose recommended in the OECD guideline. However, due to a lack of an appropriate toxicokinetic study, a substantiated estimate of the real exposure of pups

through breast milk, taking into consideration the percentages of absorption, metabolism and excretion in milk, cannot be performed. The possibility of pup exposure to a toxic metabolite occurring only in breast milk can also not be ruled out.

RAC is of the opinion that the effects observed in the offspring during lactation and the post-weaning period are compound-related. Although the offspring were able to access and ingest the test diet from the latter portion of the lactation period, the statistically significant effects on body weight gain at 20000 ppm appeared from PND 7 and increased in severity with time during lactation period. Moreover, mean body weight gain in these pups was generally similar to the control group in the latter part of the post-weaning period indicating a recovery phase. This trend suggests that the substance or its metabolite might be present at toxic levels for offspring in breast milk.

Nevertheless, the adverse effects are limited to a slight decrease in body weight in F1 pups at 10000 ppm and decreased body weight in F1 males and females in the range of 17-20% at 20000 ppm. Although delayed preputial separation was seen to be correlated with lower body weight at 20000 ppm, no effect on body weight was seen in males at 3500 and 10000 ppm in the two-generation study. The relevance of preputial separation for a lactation classification is therefore questionable without further mechanistic information.

According to the CLP Regulation, a lactation classification can be assigned based on the following:

(a) "Human evidence indicating a hazard to babies during the lactation period; and/or
(b) Results of one or two generations in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or
(c) Absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk."

Results of one or two-generation studies in rats demonstrated a decrease in body weight in F1 males and females which was limited to the lactation period. The difference in body weight between these pups and controls seemed to reduce during the early post-weaning period, suggesting a recovery phase. Considering that the delayed growth during lactation was of limited magnitude or occurring at high doses, and that no other adverse effect clearly related to lactation were demonstrated, **RAC is of the opinion that a classification for lactation is not warranted.**

Overall, RAC agrees that classification for toxicity to reproduction (sexual function and fertility, development and lactation) is not warranted.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The DS highlights that all the acute L(E)C_{50} values for aquatic organisms are above the water solubility of the technical which is 0.184 mg/L (<1 mg/L). However, *Daphnia magna* exposed to oxathiapiprolin for 48 hours in an unaerated, static, acute test showed immobility, at a concentration of 0.67 mg a.s./L. According to EU Regulation 2008/1272 (the CLP Regulation), a 48 hour EC_{50} (for crustacea) of 1mg a.s /L or less is sufficient for classification. Consequently, the DS proposes to classify oxathiapiprolin as Aquatic Acute 1, M=1.

Oxathiapiprolin does not meet the criteria to be considered as readily degradable it is not boiaccumulative.

A chronic study with the mysid shrimp (Americamysis bahia) resulted in a NOEC of 0.058 mg /L; therefore the DS proposes to classify oxathiapiprolin as Aquatic Chronic Aquatic 1, M=1.

Degradation

The hydrolysis of oxathiapiprolin was studied according to OECD TG 111 and in compliance with GLP. In pH 4, 7 and 9 buffer solutions, < 10% degradation occurred at 50°C indicating that the DT_{50} was > 1 year. Hence, oxathiapiprolin is stable to hydrolysis at environmentally relevant pH values.

The photodegradation of radio-labelled oxathiapiprolin was studied at a temperature of 25 ± 1ºC according to OECD TG 316 and in compliance with GLP. The photolysis half-life of oxathiapiprolin was 15.4 days in sterile pH 7 buffer and 20.2 days in sterile natural water under continuous irradiation.

The ready biodegradability was investigated following the method described in the 92/69/EEC C.4 and OECD TG 301B (carbon dioxide evolution test) and in compliance with GLP. Oxathiapiprolin was added to the duplicate glass bioreactors, containing aqueous nutrient medium inoculated with activated sewage sludge at a concentration of 30 mg solids/L for a period of 28 days at a nominal temperature range of 18-22 °C. The substance showed only minimal degradation at a loading rate of 10 mg/L. The test results indicate that oxathiapiprolin is not readily biodegradable.

A water simulation study conducted with radiolabelled test substance, performed according to OECD TG 309 and in compliance with GLP, showed that oxathiapiprolin did not mineralise significantly during the 60-day study and that it was binding significantly to any fine particulate material remaining in the surface water and to a lesser degree to the test vessels. HPLC analysis of the surface water identified one degradation product, IN-S2K66, reaching maximums of 6.95 and 3.24% AR in the pyrazole and isoxazoline fractions, respectively.

A water/sediment simulation study, carried out according to OECD TG 308 and in compliance with GLP, was run in the dark at 20 ± 2ºC using two aerobic aquatic systems obtained from natural sources. In both test systems, oxathiapiprolin partitioned from the water into the sediment phase and underwent further degradation in the sediment phase. In both water/sediment systems, there were no major metabolites formed in the water phase, but numerous minor degradation products were identified. In the sediment phase of the test systems, five major degradation products were observed. Dissipation of oxathiapiprolin from the overlying water from both systems was rapid, with DT_{50} values of 13.6 and 5.5 days for loamy sand and silt loam waters, respectively. Dissipation from the sediment was slower, with DT_{50} values of 112.7 and 249.2 days for the loamy sand and silt loam systems, respectively. For the total system, the DT_{50} ranged from 18.6 to 44.9 days. Volatile radioactivity identified as $^{14}CO_2$ at the end of the study represented 0.18 and 0.35% AR for the pyrazole fraction in the loamy sand and silt loam systems, respectively. The corresponding figures for the thiazole fraction were 7.19 and 6.78% AR.

Aerobic soil degradation of oxathiapiprolin was studied in five different soils according to OECD TG 307 and in compliance with GLP. Under laboratory conditions, the DT_{50} values ranged from 18.2 to 134.4 days at 20°C. The studies showed that the degradation of oxathiapiprolin results in the formation of several degradation products, including CO_2 and non-extractable residues.

Degradation under field conditions in Europe was slightly faster with DT_{50} values ranging from 5.5 to 101 days.

Based on the information above, the DS concluded that oxathiapiprolin is not considered to be rapidly degradable for the purpose of classification according to Regulation (EC) 1272/2008.

Bioaccumulation

Based on a measured log K_{ow} >3, a study on the bioconcentration potential of oxathiapiprolin in fish was performed in accordance following OECD TG 305.

In the bioaccumulation study, bluegill sunfish (*Lepomis Macrochirus*) were exposed to radio-labelled oxathiapiprolin at two nominal concentration of 0.01 and 0.1 mg/L for 70 days in an aerated flow-through system. At steady-state, the lipid normalised whole fish bioconcentration factor for the low and high concentration were 41 and 35 L/kg, respectively. The lipid normalised kinetic BCF values for the low and high level whole fish tissue were 63 and 49 L/kg, respectively.

A study was conducted to estimate the metabolic clearance rate and predict the bioconcentration factor of oxathiapiprolin using isolated rainbow trout hepatocytes. The metabolic clearance of oxathiapiprolin in trout hepatocytes was estimated, and results extrapolated to the whole animal. The modelled BCF (with kMet) was calculated to be 501 L/kg (wet weight). The method has not been assessed for regulatory use and in this case it appears to significantly over-estimate the BCF.

Based on the measured BCF, the DS concluded that oxathiapiprolin has no potential for bioconcentration and is unlikely to bioaccumulate in the environment.

Aquatic toxicity

Studies on acute and long-term aquatic toxicity of oxathiapiprolin for all three trophic levels are available. All aquatic testing was conducted at or slightly above the water solubility limit (0.184 mg/L).

The test results are summarised in the following table. The key tests forming the basis for classification are reported in bold.

Method	**Test organism**	**Test system**	**Results**			**Test conc.**	**Reference**
			Endpoint	**LC50/EC50 [mg/L]**	**NOEC [mg/L]**		
Fish							
OECD TG 203 (1992), OPPTS 580.1075 (1996) GLP	Oncorhynchus mykiss	Static 96h	Mortality	>0.69		mean measured highest concentration tested	DuPont-32481, rev. 1 (2012)
OECD TG 203 (1992), OPPTS 580.1075 (1996) GLP	Lepomis macrochirus	Static 96h	Mortality	>0.72		mean measured highest concentration tested	DuPont-32818 (2011)
OPPTS 580.1075 (1996) GLP	Cyprinodon variegatus	Static 96h	Mortality	>0.65		mean measured highest concentration tested	DuPont-32819 (2011)

OPPTS 850.1400 GLP	Cyprinodon variegatus	Flow-through 35d	Hatching success, survival and growth		0.34	mean measured highest concentration tested	DuPont-32820 (2012)
OECD TG 210 (1992), OPPTS 850.1400 (1996) GLP	Oncorhynchus mykiss	Flow-through 88d	Growth		0.46	mean measured	DuPont-32482 (2012)
Aquatic invertebrates							
OECD TG 202 (2004), OPPTS 850.1010 (1996) GLP	Daphnia magna	Static 48h	Immobility	0.67		mean measured	DuPont-32484 Minderhout et al. (2011)
OPPTS 850.1025 (1996) GLP	Americamysis bahia	Static 96h	Mortality	>0.64		mean measured highest concentration tested	DuPont-32485 Minderhout et al. (2011)
OPPTS 850.1025 (1996) GLP	Crassostrea virginica	Flow-through 96h	Shell Deposition	>0.33		mean measured highest concentration tested	DuPont-32453 Minderhout et al. (2012)
OECD TG 211 (2008), OPPTS 850.1300 (1996) GLP	Daphnia magna	Semi-static 21d	Adult survival, reproduction and growth		0.75	mean measured highest concentration tested	DuPont-32455 Minderhout et al. (2011)
OPPTS 850.1350 (1996) GLP	Americamysis bahia	Flow-through 32d	Reproduction		0.058	mean measured	DuPont-32456 Claude et al. (2012)
Algae and aquatic plants							
OECD TG 201 (2006), OCSPP 850.4500 (2012) GLP	Skeletonema costatum	Static 72ha	Growth rate	>0.351	0.141b	mean measured	DuPont-35834 Arnie et al. (2013)
OECD TG 201 (2006), OCSPP 850.4500 (2012) GLP	Navicula pelliculosa	Static 72ha	Growth rate	>0.163	0.163b	mean measured highest concentration tested	DuPont-35843 Arnie et al. (2013)
OECD TG 201 (2006), EPA 712-C-96-164 (1996) GLP	Pseudokirchneriella subcapitata	Static 72ha	Growth rate	>0.142	0.142b	mean measured highest concentration tested	DuPont-29275 Kley and Deierling (2010)
OECD TG 201 (2006), EPA 712-C-96-164 (1996) GLP	Anabaena flos-aquae	Static 72ha	Growth rate	>0.193	0.193b	mean measured highest concentration tested	DuPont-29320 Kley and Deierling (2010)

OPPTS 850.4400 (1996) GLP	Lemna gibba G3	Static renewal 7d	Frond Count Growth Rate	>0.79	0.79b	mean measured highest concentration tested	DuPont-32480 Porch et al. (2011)
Other aquatic organisms (including sediment)							
OECD TG 235 (2011), ASTM Standard E729-96 (1996) GLP	Chironomus riparius	Static 48h	Immobility	>0.56		mean measured highest concentration tested	DuPont-32454 Thomas et al. (2012)
OECD TG 219 (2004) GLP	Chironomus riparius	Static 28d	Emergence ratios		2.8 mg/kg	mean measured in sediment	DuPont-35835 Thomas et al. (2013)
OECD TG 219 (2004) GLP	Chironomus riparius	Static 28d	Emergence ratios		0.11	mean measured	DuPont-36043 Thomas et al. (2013)

a) results are referred to 72h, based on MS sugestion in Public Consultation. In the summarising table of the CLH report, results were referred to 96h.

b) the NOEC results were added as suggested in the Public Consultaton.

Acute aquatic toxicity

All three tests on fish showed acute toxicity above the highest concentration tested and the water solubility of the substance of 0.184 mg/L. The also DS specifies that measured, acute LD_{50} values are greater than 0.69 mg/L (*Oncorhynchus mykiss*) and greater than 0.65 mg/L (*Cyprinodon variegatus*). In both cases, this also represents the apparent limit of solubility in the test system.

Three studies on invertebrates were provided (*Daphnia magna*, *Americamysis bahia,* and *Crassostrea virginica).* The most acutely sensitive species was *Daphnia magna* in an unaerated, static, 48-hour test (OECD TG 202 (2004)). Nominal test concentrations of oxathiapiprolin were 0.063, 0.13, 0.25, 0.50 and 1.0 mg a.s./L. The mean, measured concentrations were 0.060, 0.12, 0.24, 0.44 and 0.78 mg a.s./L and ranged from 78 to 96% of nominal concentrations. The 48-hour EC_{50} value was estimated to be 0.67 mg a.s./L, based on mean measured concentrations, with the 95% confidence interval of 0.44 to 0.78 mg a.s./L. The highest mean measured test concentration causing no immobility at test end was 0.44 mg a.s./L.

For the other two species, the EC_{50} was above the highest concentration tested. In all cases, acute toxicity to algae and aquatic plants was higher than the highest concentration tested and the water solubility of oxathiapiprolin. The same result was obtained with the midge *C. riparus*.

In summary, acute toxicity was only observed for *Daphnia magna,* based on the mean measured concentrations. The estimated EC_{50} value of 0.67 mg a.s./L, is above the water solubility of the technical which is 0.184 mg/L (<1 mg/L). However according to EU Regulation 2008/1272, a 48 hour EC_{50} (for crustacea) of 1mg a.s /L or less is sufficient for classification.

Consequently, the DS proposed to classify oxathiapiprolin as Aquatic Acute 1, M=1, based on the EC_{50}= 0.67 mg a.s./L (mean measured) for *Daphnia magna.*

Chronic aquatic toxicity

Two tests on fish were available, only for the study with *Oncorhynchus mykiss* there were effects observed below the highest concentration tested, resulting in a NOEC of 0.46 mg/L. The chronic

end-point was based on mean, measured concentrations of oxathiapiprolin and growth, after 88 days of exposure.

Two studies were available for invertebrates *(*on *Daphnia magna* and *Americamysis bahia*). For the species *Americamysis bahia*, a 32d-NOEC of 0.058 mg/L, mean measured (OPPTS 850.1350 (1996) was derived. For the *Daphnia magna* organism no effect was observed up to the highest concentration tested (0.75 mg/L) in a semi-static 21 day study (OECD TG 211).

The most sensitive chronic end-point for algae and aquatic plants was a 72h NOEC of 0.141 mg/L obtained with the marine diatom *Skeletonema costatum.* This was also the only algae test which showed effects below the highest concentration tested. The NOEC value was based on mean measured concentrations and algal growth inhibition calculated as growth rate.

The most sensitive chronic effect of the substance for sediment dwelling organisms was a NOEC of 0.11 mg/L obtained in a prolonged sediment toxicity test with *Chironomus riparius* using spiked water.

The DS proposed to classify oxathiapiprolin as Aquatic Chronic 1, M=1 based on a NOEC of 0.058 mg/L (for *Americamysis bahia*) and considering that oxathiapiprolin does not meet the criteria to be considered as readily degradable.

Comments received during public consultation

During Public Consultation, four MSCAs commented the Aquatic toxicity. Two of these supported explicitly the proposed environmental classification; one of these agreed to the proposed classification in the general comment section.

One MSCA asked for clarifications about potential physical effects in the test media for the *Daphnia magna* key study for acute classification (Minerhaut, Kendall, Gallagher and Krueger, 2011e), also pointing out that there wasn't a clear dose response curve and that effects were only observed at the highest treatment (0.78 mg/L). The DS clarified that the test solution was mixed by sonication for 30 minutes, followed by stirring for approximately 2 hours. All test solutions appeared clear and colourless with no visible precipitate. The concentration of the solvent dimethylformamide (DMF) was 0.1 ml/L. There were no further observations recorded for substance solubility.

Moreover, the same MSCA asked for a justification for the exposure period extension (32 day NOEC of 0.058 mg/L) for the chronic toxicity test on invertebrate *Americamysis bahia*. Indeed, the used protocol (US EPA Mysid Chronic Toxicity Test (OPPTS 850.1350)) foresees a 28 day exposure using juvenile mysids. The doubt of the MSCA was related to whether a 28 day endpoint would be within the same classification range. The DS answered that 32 days is the period to consider a complete life-cycle test, i.e. at least terminated when the last first-generation mysid dies.

Finally the same MSCA noted that no effects were observed in the 21 day chronic toxicity to *Daphnia magna* study resulting in a 21 day NOEC of 0.75 mg/l (mm) which is above the quoted acute EC_{50}. The DS answered that in the 21 day chronic toxicity to *Daphnia magna* study, the only effect noted at levels lower than the 48 hour EC_{50} was statistically significantly lower compared to control and observed at a concentration of 0.24 mg/L. However, two higher test concentrations (0.45 and 0.75 mg/L) showed no statistical difference. Therefore, it was not a dose responsive pattern. Both studies were performed according to GLP and OECD guidelines, no further information is available to explain these results.

An MSCA suggested adding in the summarising table the NOEC values available for the algae and aquatic plants as relevant endpoints for chronic classification. That was agreed by DS.

One MSCA supported the conclusion that oxathiapiprolin is neither rapidly degradable or potentially bioaccumulative but asked if there was indication for ultimate degradation in simulation studies since in CLH proposal it is stated that oxathiapiprolin degraded in the environment under natural conditions ultimately forming CO_2 and bound residues. The DS replied that oxathiapiprolin did not mineralize significantly based on the available studies.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS proposal to consider oxathiapiprolin as not rapidly degradable. The substance is hydrolytically stable under acidic, neutral and alkaline conditions and it is not readily biodegradable. In addition, oxathiapiprolin is demonstrated to be not ultimately degraded to a level greater than 70% in surface water, aquatic sediment and soil simulation tests.

Bioaccumulation

The measured BCF of oxathiapiprolin is below the CLP criterion (BCF ≥500). Therefore, RAC agrees with the DS proposal to consider that oxathiapiprolin is not bioaccumulative.

Acute aquatic hazard

The most sensitive trophic level is invertebrates. *Daphnia magna* with a Static 48h-EC_{50}=0.67 mg/L mean measured (OECD TG 202 (2004)) was proposed as the key data for classification. The measured value 0.67 mg/L is above the water solubility which is 0.184 mg/L (<1 mg/L).

According to the Guidance on the Application of CLP criteria, Annex I.4.2, for poorly soluble substances: "*Ideally, tests using appropriate dissolution techniques and with accurately measured concentrations within the range of water solubility should be used. Where such test data are available, they should be used in preference to other data*."

In the oxathiapiprolin case, a range of measured values (some below water solubility) are available due to its use of a solvent, i.e. it is possible to verify the actual exposure concentrations using measured data. However, RAC noted uncertainties in the overall EC_{50} estimation from the acute tests and lack of consistency with chronic effects for *Daphnia*. For example, effects in the acute Daphnia study were only seen in the highest treatment of 1 mg/L nominal (0.78 mg/L measured). No effects were reported at all at the next dose of 0.5 mg/L nominal (0.44 mg/L measured), which creates some uncertainty in the EC_{50} estimate.

The 21-d EC_{50} is >0.75 mg/L (measured) for parental immobility, corresponding to the same nominal concentration of 1 mg/L as used in the acute test. No effects were seen for any endpoint up to the highest test concentration in the chronic test. There is therefore a lack of consistency between apparent acute and chronic effects for Daphnia. No other species had acute effects.

The water solubility is reported to be around 0.2 mg/L, and it is noted that solubility in test media can be different. However, in this case, it is more appropriate to conclude that the acute effects only occur above the water solubility limit, and therefore no acute classification is necessary.

Therefore, contrary to the DS proposal, RAC concluded **not to classify oxathiapiprolin for aquatic acute hazard**.

Chronic aquatic hazard

The lowest value reported was a NOEC of 0.058 mg/L for the invertebrate *Americamysis bahia*.

In conclusion, the substance is considered to be not rapidly degradable according to provided data, and RAC agrees to classify oxathiapiprolin as **Aquatic Chronic 1, with an M-factor of 1**.

More details can be found in the Background Document.

Additional references

DuPont (2014). Oxathiapiprolin (DPX-QGU42) Technical: Dermal Sensitization Magnusson-Kligman Maximization Method

Draize JH, Woodard G, Calvery HO (1944). Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. Journal of Pharmacology and Experimental Therapeutics 82, 377-390

Hood RD (2016). Developmental and Reproductive Toxicology, A Practical Approach - CRC Press, Third Ed. 1168 p.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).