Committee for Risk Assessment
RAC

Annex 1
Background document
to the 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

30 November 2018

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Substance Name: 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]ethanon; Oxathiapiprolin (ISO)

EC Number: Not available

CAS Number: 1003318-67-9

Index Number: Not available

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Version number: 3 **Date:** FEB 2018

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Oxathiapiprolin
EC number:	Not available
CAS number:	1003318-67-9
Annex VI Index number:	Not available
Degree of purity:	≥950 g/kg
Impurities:	No relevant impurities for classification

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

Current entry in Annex VI, CLP Regulation	New active substance, no current classification in Annex VI
Current proposal for consideration by RAC	Aquatic toxicity classification and inclusion of M-factors. Aquatic Acute 1; H400 – Very toxic to aquatic life Acute M factor = 1 Aquatic Chronic 1, H410 – Very toxic to aquatic life with long lasting effects Chronic M factor = 1
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Aquatic Acute 1; H400 – Very toxic to aquatic life Acute M factor = 1 Aquatic Chronic 1, H410 – Very toxic to aquatic life with long lasting effects Chronic M factor = 1

1.3 Proposed harmonised classification and labelling based on CLP Regulation.

Table 3: Proposed classification according to the CLP Regulation

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 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

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	No classification	Not applicable	None	Conclusive but not sufficient for classification
2.2.	Flammable gases	No classification	Not applicable	None	Data lacking
2.3.	Flammable aerosols	No classification	Not applicable	None	Data lacking
2.4.	Oxidising gases	No classification	Not applicable	None	Data lacking
2.5.	Gases under pressure	No classification	Not applicable	None	Data lacking
2.6.	Flammable liquids	No classification	Not applicable	None	Data lacking
2.7.	Flammable solids	No classification	Not applicable	None	Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	No classification	Not applicable	None	Data lacking
2.9.	Pyrophoric liquids	No classification	Not applicable	None	Data lacking
2.10.	Pyrophoric solids	No classification	Not applicable	None	Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	No classification	Not applicable	None	Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	No classification	Not applicable	None	Conclusive but not sufficient for classification
2.13.	Oxidising liquids	No classification	Not applicable	None	Data lacking
2.14.	Oxidising solids	No classification	Not applicable	None	Conclusive but not sufficient for classification
2.15.	Organic peroxides	No classification	Not applicable	None	Data lacking
2.16.	Substance and mixtures corrosive to metals	No classification	Not applicable	None	Data lacking
3.1.	Acute toxicity - oral	No classification	Not applicable	None	Conclusive but not sufficient for classification
	Acute toxicity - dermal	No classification	Not applicable	None	Conclusive but not sufficient for classification

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
	Acute toxicity - inhalation	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	No classification	Not applicable	None	Data lacking
3.4.	Skin sensitisation	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.6.	Carcinogenicity	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	No classification	Not applicable	None	Conclusive but not sufficient for classification
3.10.	Aspiration hazard	No classification	Not applicable	None	Data lacking
4.1.	**Hazardous to the aquatic environment**	**Aquatic Acute 1; H400 – Very toxic to aquatic life** **Aquatic Chronic 1, H410 – Very toxic to aquatic life with long lasting effects**	**Acute M = 1** **Chronic M = 1**	**None**	
5.1.	Hazardous to the ozone layer	No classification	Not applicable	None	Data lacking

1) Including specific concentration limits (SCLs) and M-factors – new active substance, no current classification

2) Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Signal word: Warning

Hazard pictogram:

GHS09: Environment

Hazard statements:
H410: Very toxic to aquatic life with long lasting effects

Precautionary statements:

P273: Avoid release to the environment.

P391: Collect spillage.

P501: Dispose of contents/ container to an approved incineration plant.

Proposed notes assigned to an entry:

None

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Oxathiapiprolin (DPX-QGU42) is a fungicide from the piperidinyl thiazole isoxazoline class; it is a new active substance in the EU and has not previously been considered for harmonised classification and labelling. It is intended to be used as a plant protection product (PPP).

2.2 Short summary of the scientific justification for the CLH proposal

Oxathiapiprolin should not be classified for physical and chemical hazards.

Oxathiapiprolin should not be classified for acute toxicological properties.

Oxathiapiprolin is non-genotoxic; no toxicologically significant effects were found in repeated dose toxicity tests in rat, dog and mouse, and animal testing with oxathiapiprolin did not show any carcinogenic, teratogenic or reproductive toxicity effects.

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 2008/1272 EU a 48 hour EC_{50} (for crustacea) of 1mg a.s /L or less is sufficient for classification. Consequently, oxathiapiprolin is classified as Aquatic Acute 1 and assigned the hazard phrase H400 - *Very toxic to aquatic life*. A chronic study with the mysid shrimp (*Americamysis bahia*) resulted in a NOEC of 0.058 mg oxathiapiprolin/L; therefore oxathiapiprolin is classified as Aquatic Chronic Aquatic 1 and assigned the hazard phrase H410 - *Very toxic to aquatic life with long lasting effects*.

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

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Oxathiapiprolin is a new active substance. There is no current harmonised classification and labelling in Annex VI, Table 3.1 of the CLP regulation.

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Oxathiapiprolin is a new active substance. There is no current harmonised classification and labelling in Annex VI, Table 3.2 of the CLP regulation.

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Aquatic chronic 1, H410

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.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

No need for justification (cf. Article 36(3) CLP Regulation) as oxathiapiprolin is an active substance regulated by Regulation (EC) 1107/2009.

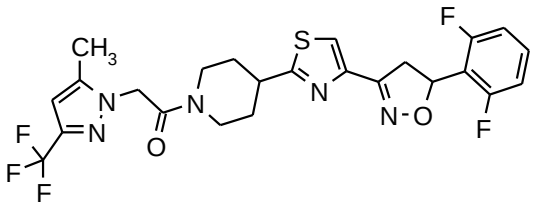
Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	Not assigned
EC name:	Oxathiapiprolin
CAS number (EC inventory):	Not available
CAS number:	1003318-67-9
CAS name:	Ethanone, 1-[4-[4-[5-(2,6-difluorophenyl)-4,5-dihydro-3-isoxazolyl]-2-thiazolyl]-1-piperidinyl]-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]
IUPAC name:	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
CLP Annex VI Index number:	New active substance – no current entry
Molecular formula:	$C_{24}H_{22}F_5N_5O_2S$
Molecular weight range:	539.53 g/mole
Structural formula:	

1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Oxathiapiprolin	≥950 g/kg	No range, since minimal purity stated	—

Current Annex VI entry: No current entry.

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
No relevant impurities for classification	—	Impurity identity and levels are confidential; see confidential annex of DAR/CAR.	Provisional specifications based on pre-commercial scale production have been submitted.

Current Annex VI entry: No current entry

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
No additives	—	—	—	—

Current Annex VI entry: No current entry

1.2.1 Composition of test material

The purity of the test substance is given in each test description when appropriate. Ranges are as follow:

Physico-chemical properties tests: 95.8 to 98.9%

Mammalian toxicology: 95.7 to ~99.5%

Ecotoxicology: 95.8 to 98.9%

The samples used for physico-chemical, toxicological and ecotoxicological testing are within the proposed specification for oxathiapiprolin. The minimum purity proposed for oxathiapiprolin, based on pre-commercial production, is 95.0%.

1.3 Physico-chemical properties

Table 8: Summary of physico - chemical properties

Property	**Value**	**Reference**	**Comment (*e.g.*, measured or estimated)**
State of the substance at 20°C and 101.3 kPa GLP	Both PAI and technical are off-white crystalline solids.	DuPont-32487, Revision No. 1 Moorthy, M.S., 2011 DuPont-32475 Moorthy, M.S., 2011	Lot #: QGU42-126, (98.9% purity, PAI) Lot #: QGU42-174 (95.8% purity, TGAI)
Melting/freezing point GLP	Melting point of oxathiapiprolin (PAI): 146.4 ± 0.19°C Melting point of oxathiapiprolin (TGAI): 138.7 ± 0.20°C	DuPont-32686 Svobodová, H., 2011 DuPont-32687 Svobodová, H., 2011	Lot #: QGU42-126, (98.9% purity, PAI) Lot #: QGU42-174 (95.8% purity, TGAI)
Boiling point GLP	No boiling point was noted by Differential Scanning Calorimeter (DSC), as decomposition occurred after melting.	DuPont-32686 Svobodová, H., 2011 DuPont-32687 Svobodová, H., 2011	Lot #: QGU42-126, (98.9% purity, PAI) Lot #: QGU42-174 (95.8% purity, TGAI)
Temperature of decomposition GLP	Decomposition temperature of oxathiapiprolin (PAI): 289.5 ± 0.42°C. Decomposition temperature of oxathiapiprolin (TGAI): 282.8 ± 0.43°C.	DuPont-32686 Svobodová, H., 2011 DuPont-32687 Svobodová, H., 2011	Lot #: QGU42-126, (98.9% purity, PAI) Lot #: QGU42-174 (95.8% purity, TGAI)
Relative density GLP	For oxathiapiprolin PAI: 1.4645 ± 0.007 at 20°C For oxathiapiprolin TGAI: 1.4684 ± 0.018 at 20ºC.	DuPont-32487, Revision No. 1 Moorthy, M.S., 2011 DuPont-32475 Moorthy, M.S., 2011	Lot #: QGU42-126, (98.9% purity, PAI) Lot #: QGU42-174 (95.8% purity, TGAI)
Vapour pressure GLP	1.141×10^{-6} Pa at 20°C (by extrapolation) 1.4055×10^{-6} Pa at 25°C 2.3592×10^{-6} Pa at 35°C 3.2804×10^{-6} Pa at 45°C	DuPont-31751 Moorthy, M.S., 2012	Lot #: QGU42-126, (98.9% purity, PAI)
Surface tension GLP	65.53 dynes/cm at 20.2 to 20.4°C	DuPont-32471 Kumar, S.V., 2011	Lot #: QGU42-174 (95.8% purity)
Water solubility GLP	Solubility at 20°C and Unbuffered distilled water: 0.1749 µg/mL pH 4: 0.2111 µg/mL pH 7: 0.1844 µg/mL pH 9: 0.2060 µg/mL	DuPont-29277, Revision No. 1 Saravanan, V., 2013	Lot #: QGU42-126, (98.9% purity, PAI) Oxathiapiprolin is slightly soluble in water at environmental pH values.

Property	**Value**	**Reference**	**Comment (*e.g.*, measured or estimated)**
Partition coefficient n-octanol/water GLP	Log octanol-water partition coefficient at 20°C and pH 4: 3.62 ± 0.02 pH 7: 3.67 ± 0.01 pH 9: 3.64 ± 0.03 Distilled water: 3.66 ± 0.02	DuPont-29274 Pushpalatha, K.G., 2011	Lot #: QGU42-126, (98.9% purity, PAI) The P_{ow} was independent of the concentration of oxathiapiprolin in either phase of the solvent system.
Flash point	Not applicable	Not tested	Not determined since oxathiapiprolin is not a liquid at temperatures <4°C.
Flammability GLP	The test material melted and discoloured to orange but did not ignite, did not support combustion, and is classified as not flammable.	DuPont-34870 Livingston, I., 2012	Lot #: QGU42-174 (95.8% purity)
Explosive properties GLP	Thermal sensitivity (effect of a flame): negative Mechanical sensitivity (shock): negative Mechanical sensitivity (friction): negative	DuPont-34870 Livingston, I., 2012	Lot #: QGU42-174 (95.8% purity)
Self-ignition temperature GLP	No self-ignition (auto-flammability). The test material melted prior to self-ignition.	DuPont-34870 Livingston, I., 2012	Lot #: QGU42-174 (95.8% purity)
Oxidising properties GLP	In the preliminary screening test the sample was observed to ignite and burn for 75 seconds before the flame extinguished. Only the very top of the cone had burned. The test substance did not give a positive result and is therefore not classified as an oxidising solid.	DuPont-34870 Livingston, I., 2012	Lot #: QGU42-174 (95.8% purity) The test material was not an oxidising agent. An assessment of the structure of oxathiapiprolin also indicates that it is not a reducing agent.
Granulometry	According to Regulation (EC) 1107/2009 granulometry is not required for active substances. Thus, no study or end-point has been provided.	Not required	

Property	**Value**	**Reference**	**Comment (*e.g.*, measured or estimated)**
Stability in organic solvents and identity of relevant degradation products GLP	No data on stability but solubility is given below. Solubilities of oxathiapiprolin (PAI) at 20°C: **Solvent** / **Solubility (g/L)** Acetonitrile 111.0 Methanol 13.0 Acetone 147.3 Ethyl acetate 31.7 Dichloromethane 347.3 o-Xylene 5.7 n-Octanol 0.04 n-Hexane 0.01 Solubilities of oxathiapiprolin (TGAI) at 20°C: **Solvent** / **Solubility (g/L)** Acetonitrile 129.9 Methanol 13.5 Acetone 162.8 Ethyl acetate 33.9 Dichloromethane 352.9 o-Xylene 5.8 n-Octanol 0.03 n-Hexane 0.01	DuPont-38201 Manikandan, K.N., 2013 DuPont-32486 Anand, H.S., 2012	Lot #: QGU42-126, (98.9% purity, PAI) Lot #: QGU42-174, (95.8% purity, TGAI)
Dissociation constant GLP	No dissociation at 20 ± 1ºC.	DuPont-32474 Kumar, S.V., 2011	Lot #: DPX-QGU42-126, (98.9% purity, PAI) Dissociation in water does not occur. Oxathiapiprolin is not a salt.
Viscosity	Not applicable		

Property	**Value**	**Reference**	**Comment (*e.g.*, measured or estimated)**
Stability in water Hydrolysis rate of purified a.s. GLP	Hydrolysis did not occur at a rapid rate across all pHs tested at 50°C. The hydrolytic half-life ($t_{1/2}$) at 25°C is considered to be >1 year at pH 4, 7, and 9.	DuPont-28424, Revision No. 1 Anand, H.S., 2010	The test was conducted with two radiolabeled forms of oxathiapiprolin at pH 4, 7 and 9 in sterilised buffered solutions at 50 ± 0.5°C. [Pyrazole-5-^{14}C] oxathiapiprolin Lot # 3504139, radiochemical purity 99.1%, specific activity 49 μCi/mg [Thiazole-5-^{14}C] oxathiapiprolin, Lot # 3614070, radiochemical purity 98.6%, specific activity 47.1 μCi/mg

Property	**Value**	**Reference**	**Comment (*e.g.*, measured or estimated)**
Stability in water Photochemical degradation of purified a.s Direct phototransformation GLP	Mass balance for the irradiated samples and the dark controls ranged from 90.19-110.87% AR in the pH 7 buffer and 93.93-107.78% AR in natural water. The photolysis half-life of oxathiapiprolin in sterile pH 7 buffer was 15.4 days under continuous irradiation. In sterile natural water the photolytic half-life was 20.2 days under continuous irradiation. Conversion to 12-hour sunlight days (Tranent, UK, 55°57'N 2°58'W) results in a half-life of 30.8 days in pH 7 buffer and 42 days in natural water.	DuPont-28074 Wardrope, L., 2011	The test was conducted with three radiolabeled forms of oxathiapiprolin. [Pyrazole-5-^{14}C], oxathiapiprolin Lot # 3504139, radiochemical purity 99.1%, specific activity 49 μCi/mg [Thiazole-5-^{14}C] oxathiapiprolin, Lot #. 3614070, radiochemical purity 98.6%, specific activity 47.1 μCi/mg [Isoxazoline-5-^{14}C] oxathiapiprolin, Lot # 3631021, radiochemical purity 98.7%, specific activity 45.8 μCi/mg The main photodegradation products were IN-RSA90, IN-RLD51, and IN-P3X26.
Quantum yield of direct photo-transformation in water GLP	Quantum yield of oxathiapiprolin in pH 7 buffer: $\Phi = 3.179 \times 10^{-6}$ molecules degraded/photon	DuPont-28074 Wardrope, L., 2011	The test was conducted with three radiolabeled forms of oxathiapiprolin. [Pyrazole-5-^{14}C], oxathiapiprolin Lot # 3504139, radiochemical purity 99.1%, specific activity 49 μCi/mg [Thiazole-5-^{14}C] oxathiapiprolin, Lot # 3614070, radiochemical purity 98.6%, specific activity 47.1 μCi/mg [Isoxazoline-5-^{14}C] oxathiapiprolin, Lot # 3631021, radiochemical purity 98.7%, specific activity 45.8 μCi/mg

Property	**Value**	**Reference**	**Comment (*e.g.*, measured or estimated)**
Stability in air, photochemical oxidative degradation Indirect photo-transformation	The overall OH rate constant is 38.8125×10^{-12} cm^3/molecule-sec. The half–life of oxathiapiprolin for reaction with average daily air concentrations of hydroxyl radicals (12-hr day; 1.5×10^6 OH radicals per cm^3) is 3.307 hours.	DuPont-34109 EU Hatzenbeler, C., 2013	Atkinson calculation
Spectra of purified a.s. GLP	IR: key bands are consistent with the structure of oxathiapiprolin. ^{13}C-NMR and ^{1}H-NMR spectra are consistent with the proposed chemical structure of oxathiapiprolin. MS confirmed the structure of oxathiapiprolin (molecular weight 539.5). UV/VIS spectra: λ_{max} under acidic conditions was 257 and 258 nm. ε = 14055 L mol^{-1} cm^{-1}. λ_{max} under basic conditions was 258 and 259 nm. ε = 16384 L mol^{-1} cm^{-1}. λ_{max} under neutral conditions was 256 and 257 nm. ε = 13863 L mol^{-1} cm^{-1}.	DuPont-32473, Revision No. 1 Anand, H.S., 2012	QGU42-126, (98.9% purity, PAI)
Henry's law	At 20°C: 3.521×10^{-3} Pa m^3/mol (3.474×10^{-8} atm m^3/mol)	DuPont-34110 Hatzenbeler, C., 2013	Calculation

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for classification and labelling.

2.2 Identified uses

Oxathiapiprolin (DPX-QGU42) is to be used in agriculture and viticulture as a fungicide. The product is suitable for field as well as for greenhouse usage.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

3.1 Physico-chemical properties

3.1.1 Summary and discussion of physico-chemical properties

None of the reported physico-chemical properties of oxathiapiprolin result in a requirement for classification using the criteria set out in the CLP Regulation.

3.1.2 Comparison with criteria

None of the reported physico-chemical results for oxathiapiprolin trigger classification using the CLP criteria.

Oxathiapiprolin does not meet any of the classification criteria for explosive properties (no explosion occurred at the conditions of the thermal, shock and friction test).

Oxathiapiprolin did not give a positive result in the preliminary screening test for oxidising properties.

Oxathiapiprolin does not meet any of the burning rate test classification criteria for flammable solids, as no propagation occurred during the duration of the flammability test.

Oxathiapiprolin does not meet any of the classification criteria for self-heating substances, as no self-ignition occurred.

3.1.3 Conclusions on classification and labelling

On the basis of the studies summarised in Table 8, oxathiapiprolin (as manufactured) is not self-igniting, not highly flammable, not explosive and not oxidising. Hence, classification for physical and chemical hazards according to CLP criteria is not warranted.

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**.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Table 9: Summary table of relevant toxicokinetics studies

Method	Results	Remarks	Reference
Single oral dose , rats OPPTS 870.7485 (1998), OECD 417 (2010), JMAFF 12-Nousan-8147 (2000) GLP compliant	Oxathiapiprolin and its metabolites were readily excreted by the rat with faecal excretion as the major route of elimination for all animals after low- and high-dose administration. Expiration as carbon dioxide or other volatile compounds was not a significant route of elimination.	Rat (Crl:CD®(SD)IGS BR) [isoxazoline-5-^{14}C]oxathiapiprolin or [pyrazole-5-^{14}C]oxathiapiprolin Lot #: QGU42-126, 98.9% purity	DuPont-28214, Revision 1 Himmelstein, M.W. 2013
Repeated dose, oral route in rats OPPTS 870.7485 (1998), OECD 417 (2010), JMAFF 12-Nousan-8147 (2000) GLP compliant		Rats (Crl:CD®(SD)) [pyrazole-5-^{14}C]oxathiapiprolin Lot #: QGU42-126, 98.9% purity	DuPont-32337 Himmelstein, M.W. 2013

The adsorption, distribution, metabolism and excretion of [^{14}C]oxathiapiprolin was investigated in rats after single low and high dose administration, and after multiple treatments at low doses. The results are summarised in Table 10 below.

Table 10
Summary of metabolism studies in rats

Absorption	Maximum absorption at the low dose (10 mg/kg bw) was 31–49% based on summation of residue in the bile, urine, and carcass (except GI contents), and declined to 5.4–7.7% at the high dose (200 mg/kg bw) due to saturation. Peak plasma concentrations occurred at 0.25–9.5 hours. Plasma ^{14}C residue concentrations showed steady-state kinetics in male and female rats after multiple low dose administration (10 mg/kg bw × 14 days).
Distribution	Maximum tissue concentrations at T_{max} occurred in the liver (~10 µg/g). Clearance was rapid (<0.01 to 0.1 µg/g) for liver and other tissues by 168 hours after dosing. All tissues at 168 hour including the carcass collectively retained ≤0.082% of the dose. The pattern of distribution was similar between sexes and single and multiple dose administration.
Potential for accumulation	The low percentage and concentration values in tissues indicate very low potential for accumulation.
Rate and extent of excretion	Plasma terminal elimination half-lives ranged from 40-51 hours following single or multiple low-dose ^{14}C administration. Shorter plasma half-lives were observed (5–14 hours) after single high-dose administration due to reduced absorption. Excretion in urine and faeces was >95% complete by 48 hours after single dosing. The pattern of excretion was similar after multiple dosing. Faecal excretion was the primary route of elimination (≥90.4%). Recovery in urine was much lower (≤2.44%). Essentially no excretion occurred by exhalation.
Metabolite profile	Oxathiapiprolin metabolism pathways mainly involved hydroxylation at various ring carbons resulting in formation of several mono-hydroxy and di-hydroxy-oxathiapiprolin metabolites. Hydroxylation at the pyrazole methyl carbon and further oxidation resulted in a carboxylic acid. Hydroxylation of piperidine ring followed by ring opening and further oxidation gave rise to another carboxylic acid. Isoxazoline ring hydroxylation and dehydration led to an unsaturated metabolite. Pyrazole-piperidine bridge cleavage reactions gave rise to pyrazole moiety metabolites. Defluorination and conjugation reactions at various positions were minor metabolic reactions. Un-metabolised test substance in faeces accounted for 17-87% of the dose for all dose groups.

4.1.2 Human information

No data available.

4.1.3 Summary and discussion on toxicokinetics

The toxicokinetics of oxathiapiprolin following oral administration have been investigated in single and repeat dose studies in rats. Oxathiapiprolin and its metabolites were readily excreted by the rat with faecal excretion as the major route of elimination. Expiration as carbon dioxide or other volatile compounds was not a significant route of elimination. Retention of oxathiapiprolin or its metabolites in tissues and blood was negligible indicating very low potential for bioaccumulation.

Oxathiapiprolin metabolism pathways mainly involved hydroxylation at various ring carbons and ring opening. Pyrazole-piperidine bridge cleavage also occurred.

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Oral, rat OECD 425 (2008) GLP compliant	LD_{50} >5000 mg/kg bw	Rats (Sprague-Dawley derived, albino) Lot #: QGU42-136, 96.2% purity	DuPont-29441, Revision No. 1 Oley, S.D., 2010
Inhalation, rat OECD Part 403 (2009), EEC Method B.2 Directive 92/69/EEC (1992) GLP compliant	LC_{50} >5 mg/L	Rats (Crl:CD(SD)) Lot #: QGU42-175, 95.7% purity	DuPont-30260 Kegelman, T.A., 2010
Dermal, rat OECD Part 402 (1987), EEC Method B.3 Directive 92/69/EEC (1992) GLP compliant	LD_{50} >5000 mg/kg bw	Rats (Crl:CD(SD)) Lot #: QGU42-175, 95.7% purity	DuPont-30259 Carpenter, C., 2010

4.2.1 Non-human information

Oxathiapiprolin demonstrated no significant acute toxicity *via* the oral, dermal, and inhalation routes of exposure.

4.2.1.1 Acute toxicity: oral

A single oral dose of oxathiapiprolin, suspended in a 0.1% solution of Tween 80 in 0.5% aqueous methylcellulose, was administered by oral gavage to six fasted female rats at a dose of 175, 550, 1750, or 5000 mg/kg body weight.

No mortalities were observed. No clinical signs of toxicity were observed. There were no body weight effects noted. No gross lesions were observed at necropsy.

Under the conditions of this study, the oral LD_{50} for oxathiapiprolin was greater than 5000 mg/kg bw for female rats.

4.2.1.2 Acute toxicity: inhalation

Rats were exposed nose-only for a single four-hour period to oxathiapiprolin suspended in air. One group of 5 male and 5 female rats was exposed to 5.1 ± 0.24 mg/L of the test substance.

No mortalities were observed. Body weight losses were observed in all male rats (from 2.7 to 4.7%) and all female rats (1.4 to 4.9%) the day after exposure. There were no other body weight losses observed in any rats throughout the 14-day recovery period. There were no clinical signs of toxicity observed after the rats were removed from their restrainers or at any time through the 14-day recovery period.

The acute inhalation LC_{50} for oxathiapiprolin in rats was greater than 5 mg/L for males and females.

4.2.1.3 Acute toxicity: dermal

In a limit test, a single dose of oxathiapiprolin, moistened with 1.5 mL of deionised water, was applied to the shaved, intact skin of 5 male and 5 female rats at a dose of 5000 mg/kg body weight. The

application site covered approximately 10% of each animal's body surface area. The application site was semi-occluded for 24 hours after which the test substance was removed.

No mortalities were observed. No clinical signs of toxicity were observed. The animals exhibited no dermal irritation throughout the study. Body weight loss of approximately 4% of the test Day 7 weight occurred in one female rat by test Day 14; the remaining rats exhibited no test substance-related body weight effects. No test substance-related gross lesions were observed at necropsy

The dermal LD_{50} for oxathiapiprolin was greater than 5000 mg/kg body weight for both male and female rats.

4.2.1.4 Acute toxicity: other routes

No data.

4.2.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin

4.2.3 Summary and discussion of acute toxicity

Oxathiapiprolin demonstrated no significant acute toxicity *via* the oral, dermal, and inhalation routes of exposure.

4.2.4 Comparison with criteria

The results of the various acute toxicity studies yielded values above the classification limits of CLP Regulation ([EC] 1272/2008; 2000 mg/kg bw for acute oral and dermal toxicity, 5 mg/L for acute inhalation toxicity). Thus no classification for acute oral, dermal or inhalation toxicity is proposed.

4.2.5 Conclusions on classification and labelling

No classification is warranted for acute toxicity by oral, dermal or inhalation routes.

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.**

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

No findings indicating STOT-SE concerns were reported following administration by oral, dermal and inhalation routes. Additionally, no findings suggestive of target organ toxicity were observed in the acute neurotoxicity study summarized in section 4.12.1.1.

4.3.2 Comparison with criteria

There were no functional disturbances or morphological changes or severe toxicity impacting on health, observed in any of the acute animal studies. There was no toxicological basis to compare with guidance value ranges for STOT SE category 1 or 2 as set out in section 3.8.2.2.1 of the CLP guidance. Similarly, there was no evidence or indication of transient respiratory tract irritation or narcosis nor was there any human data relating to these effects. The criteria for STOT SE category 3 were not met. Classification for STOT SE is not supported.

4.3.3 Conclusions on classification and labelling

No classification is required with regard to specific target organ toxicity following a single exposure *via* the oral, dermal or inhalation route.

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**.

4.4 Irritation

4.4.1 Skin irritation

Table 12: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
Dermal irritation, rabbit OECD 404 (2002) GLP compliant	No signs of erythema, oedema or other evidence of skin irritation in any of the animals at 1, 24, 48 and 72 h after patch removal, at either the treated or the control site. All individual scores were 0.	Rabbit (New Zealand White) Lot #: QGU42-175, 95.7% purity	DuPont-30262 Lowe, C., 2010

4.4.1.1 Non-human information

Oxathiapiprolin was applied as a single 0.5 g dermal dose to the shaved intact skin of three young adult New Zealand White rabbits (one male and two females). The rabbits were exposed to the test substance for 4 hours after which the test substance was removed. Test sites were evaluated using the criteria of Draize (1959) for signs of dermal irritation immediately after test substance removal and 30–60 minutes and 24, 48, and 72 hours after test substance removal.

There was no dermal irritation noted for any treated dose site during the study. There were no body weight effects or clinical signs noted.

4.4.1.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.4.1.3 Summary and discussion of skin irritation

Oxathiapiprolin produced no skin irritation in rabbits at 24 to 72 hours following a 4 hour dermal exposure.

4.4.1.4 Comparison with criteria

Following the criteria of the CLP Regulation ([EC] No. 1272/2008), classification of oxathiapiprolin as a skin irritant is not required.

4.4.1.5 Conclusions on classification and labelling

No classification for skin irritation is required.

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.**

4.4.2 Eye irritation

Table 13: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
Eye irritation, rabbit OECD 405 (2002) GLP compliant	Individual animal mean scores for 24, 48 and 72 hours Corneal opacity: 0, 0, 0 Iritis: 0, 0, 0 Conjunctival redness: 0.3, 0.3, 0.7 Conjunctival chemiosis: 0, 0, 0	Rabbit (New Zealand White) Lot #: QGU42-175, 95.7% purity	DuPont-30261 Lowe, C., 2010

4.4.2.1 Non-human information

A single dose of 0.07 g (equivalent to 0.1 mL) of oxathiapiprolin was administered into the conjunctival sac of the right eye of one female young adult New Zealand White rabbit. In the absence of significant irritation in this animal, two additional female animals were tested to confirm the result. The eyes remained unwashed after treatment. The conjunctiva, iris, and cornea of each treated eye were evaluated for evidence of irritation approximately 1, 24, 48, and 72 hours following administration of the test substance.

The test substance did not produce corneal opacity or iritis in any treated eye during the study. The test substance produced conjunctival redness (score of 1) and discharge (score of 1 or 2) in 3 rabbits and conjunctival chemosis (score of 1) in one rabbit. Signs of irritation completely resolved in all rabbits by 72 hours.

4.4.2.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.4.2.3 Summary and discussion of eye irritation

Oxathiapiprolin produced only slight symptoms of eye irritation in rabbits (conjunctiva redness), which had cleared by 72 hours.

4.4.2.4 Comparison with criteria

Following the criteria of the CLP Regulation ([EC] No. 1272/2008), classification of oxathiapiprolin as an eye irritant is not required.

4.4.2.5 Conclusions on classification and labelling

No classification for eye irritation is required.

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.**

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

No data available. There were no indications of respiratory tract irritation in the acute inhalation toxicity study (see section 4.2.1.2).

4.4.3.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.4.3.3 Summary and discussion of respiratory tract irritation

No indications of respiratory tract irritation were observed following inhalation exposure.

4.4.3.4 Comparison with criteria

There were no indications of respiratory tract irritation following inhalation exposure that would require classification following the criteria of the CLP ([EC] Regulation No 1272/2008).

4.4.3.5 Conclusions on classification and labelling

No classification is indicated as no respiratory tract irritation was observed.

4.5 Corrosivity

Table 14: **Summary table of relevant corrosivity studies**

Method	Results	Remarks	Reference
Not applicable	Not applicable	Not applicable	Not applicable

4.5.1 Non-human information

There were no indications of a corrosive response in any of the reported studies in 4.4.1 (skin irritation) or 4.4.2 (eye irritation). Oxathiapiprolin is not an irritant after contact with the skin or the eyes and is not expected to be corrosive under single or repeated exposure scenarios.

4.5.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.5.3 Summary and discussion of corrosivity

No specific data available

4.5.4 Comparison with criteria

There is no data requiring consideration for corrosivity using the criteria of the CLP regulation.

4.5.5 Conclusions on classification and labelling

Oxathiapiprolin does not require classification for corrosivity.

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 15: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
Dermal sensitisation, guinea pig Magnusson-Kligman Maximisation Method OECD 406 (1992) GLP compliant	No positive reaction at 24 and/or 48 hours for test article animals challenged with 18% w/w or 6% w/w test substance.	Guinea Pig (Hartley albino) Lot #: QGU42-175 95.7% purity	DuPont-30221 Lowe, C., 2010

4.6.1.1 Non-human information

The dermal sensitisation potential of oxathiapiprolin was evaluated by the Magnusson-Kligman Maximisation method in male Hartley albino guinea pigs. Preliminary irritation testing was performed on 12 animals to determine appropriate concentrations of test substance to be used for both the intradermal and topical induction and the topical challenge. Based on the results of preliminary irritation testing, 20 animals were intradermally induced on Day 1 with pairs of injections of the test substance (5% w/w mixture in mineral oil), test substance combined with Freund's Complete Adjuvant (5% w/w mixture of test substance in Adjuvant), and Adjuvant alone (50% v/v Adjuvant in distilled water). Approximately one week later, animals were topically induced with 0.5 g of test substance in mineral oil (70%). Animals were challenged on test Day 22 with 0.5 mL of an 18% w/w mixture of the test substance in mineral oil and 0.5 mL of a 6% w/w mixture of the test substance in mineral oil on two separate test sites. Approximately 24 and 48 hours after the challenge phase, the test sites were evaluated for signs of elicited sensitisation.

In the intradermal induction phase, test animals administered an emulsion of Freund's Adjuvant Complete [50% v/v in distilled water]) exhibited moderate erythema (scores of 2) for all test sites 24 and 48 hours after intradermal injections. Blanching was evident at one dose site. Test animals administered a 5% w/w mixture of the test substance in mineral oil exhibited faint to moderate erythema (1–2) for all test sites 24 and 48 hours after intradermal injections. Test animals administered a 5% w/w mixture of the test substance in an emulsion of Freund's Adjuvant Complete [50% v/v in distilled water]) exhibited very faint to moderate erythema (0.5–2) for all test sites 24 and 48 hours after intradermal injections. Test vehicle control animals administered an emulsion of Freund's Adjuvant Complete [50% v/v in distilled water]) exhibited faint to moderate erythema (1-2) for all test vehicle control sites 24 and 48 hours after intradermal injections. Test vehicle control animals administered 100% mineral oil exhibited very faint erythema (0.5) for all test vehicle control sites at 24 and 48 hours after intradermal injections. Test vehicle control animals administered a 50% w/w mixture of mineral oil in an emulsion of Freund's Adjuvant Complete [50% v/v in distilled water]) exhibited faint erythema (1) for all test sites 24 and 48 hours after intradermal injections. Moderate erythema (2) was noted for one site 48 hours after injection. In the topical induction phase, test animals administered a 70% w/w mixture of the test substance in mineral oil exhibited faint to moderate erythema (1–2) for all test sites one hour after patch removal. Test vehicle control animals administered 100% mineral oil exhibited no dermal irritation for any vehicle control site one hour after patch removal.

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 of test substance was 0%; the percentage of animals responding at 24 and/or 48 hours for the test article animals challenged with 6% w/w of test substance was 0%. No responses were noted in the vehicle control animals. Appropriate historical control data using alpha-hexylcinnamaldehyde technical (HCA) demonstrated a positive response.

Under the conditions of this Maximisation test in guinea pigs, oxathiapiprolin did not produce a positive dermal sensitisation response.

4.6.1.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.6.1.3 Summary and discussion of skin sensitisation

Oxathiapiprolin did not cause skin sensitisation under the conditions of the Maximisation test.

4.6.1.4 Comparison with criteria

A positive reaction in 30% of the test group is required in a maximisation test to indicate a sensitisation potential according to CLP criteria. There were no such positive reactions in the guinea pig study conducted with oxathiapiprolin. According to these criteria oxathiapiprolin does not warrant classification for skin sensitisation.

4.6.1.5 Conclusions on classification and labelling

Testing for sensitising properties by the method of Magnusson & Kligman did not show an allergenic potential. No classification is required for skin sensitisation.

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.**

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

No data available.

4.6.2.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.6.2.3 Summary and discussion of respiratory sensitisation

No data available to assess respiratory sensitisation potential.

4.6.2.4 Comparison with criteria

No data available to assess respiratory sensitisation potential.

4.6.2.5 Conclusions on classification and labelling

No data available to assess classification. No classification for respiratory sensitisation is proposed.

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.

4.7 Repeated dose toxicity

Information on repeated dose toxicity is available from ten studies: one 14 day oral study (in the rat), three 28-day oral studies (in the rat, mouse, and dog), three 90-day oral studies (in the rat, mouse and dog), two chronic 1-year oral study (one in the rat as a part of the chronic/cancer study and one in the dog), and one 28-day dermal study (in the rat).

Table 16: Summary table of relevant repeated dose toxicity studies

Species / Test Method	**Test substance/purity Doses tested (mg/kg bw/day)**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**Target organs / principal effects**	**Reference**
2-week rat oral gavage study Strain: Crl:CD(SD) Guidelines not specified Non-GLP	Lot #: QGU42-020 99% purity Males and females: 0, 25, 300, and 1000	Males and females: 1000	Males and females: >1000	No adverse effects minimal increase in cholesterol in males at 300 and 1000 mg/kg, minimal increase in triglycerides at 1000 mg/kg in males, CYP2B1 increase at 1000 mg/kg in males and females	DuPont-24634 Nabb, D., 2008
28-day rat feeding study Strain: Crl:CD(SD) OECD 407 Section 4 (2008), EEC Method B.7 (1988) Non-GLP	Lot #: QGU42-123 99.5% purity Males: 0, 37, 153, 580, and 1657 Females: 0, 40, 159, 588, and 1774 [dietary concentrations of 0, 500, 2000, 7500, and 20000 ppm]	Males: 1657 Females: 1774	Males: >1657 Females: >1774	No adverse effects; minimal increase in cholesterol in females at top dose	DuPont-28294 Carpenter, C., 2010 DuPont-28294, Supplement No. 1 Mawn, M.P., 2011
28-day mouse feeding study Strain: Crl:CD-1(ICR) OECD 407 Section 4 (2008), EEC Method Part B7 Directive 96/54/EC (1988) Non-GLP	Lot #: QGU42-123 99.5% purity Males: 0, 32, 129, 597, and 1151 Females: 0, 41, 175, 745, and 1440 [dietary concentrations of 0, 200, 800, 3500, and 7000 ppm]	Males: 1151 Females: 1440	Males: >1151 Females: >1440	No adverse effects; statistically significant increase in P450 4A1/2/3 at top dose in males	DuPont-28295, Revision No. 1 Carpenter, C., 2011 DuPont-28295, Supplement No. 1, Revision No. 1 Mawn, M.P., 2013
28-day dog feeding study	Lot #: QGU42-123 99.5% purity Males: 0, 30, 352, and 1368 Females: 0, 31, 331, and 1346 [dietary concentrations of 0, 1000, 10000 and 40000 ppm]	m/f : 1000 ppm males: 30 females: 31	m/f : 10000 ppm males: 352 females: 331	Absolute and relative liver weight increases of 20 to 30% when compared to controls Increased P450 2B1/2 in males; increase in P450 2B1/2 in females at top dose only, no test-substance related histological changes	DuPont-28296 DuPont-28296, Supplement No. 1

Species / Test Method	**Test substance/purity Doses tested (mg/kg bw/day)**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**Target organs / principal effects**	**Reference**
90-day rat feeding study Strain: Crl:CD(SD) EEC Method B.26 (2001), OECD 408 GLP compliant	Lot #: QGU42-136 96.2% purity Males: 0, 29, 117, 359, and 1096 Females: 0, 36, 145, 433, and 1300 [dietary concentrations of 0, 500, 2000, 6000, and 18000 ppm]	Males: 1096 Females: 1300	Males: >1096 Females: >1300	No adverse effects; possible test substance-related increase in cholesterol in females at ≥2000 ppm (1300 mg/kg)	DuPont-28947 Haas, M.C., 2011
90-day mouse feeding study Strain: Crlj:CD1(ICR) OECD 408 (1998), EEC Method B.26 (2001) GLP compliant	Lot #: QGU42-136 96.2% purity Males: 0, 28.5, 118.6, 490.6, and 1058.4 Females: 0, 35.3, 155.4, 660.1, and 1468.0 [dietary concentrations of 0, 200, 800, 3500, and 7500 ppm]	Males: 1058 Females: 1468	Males: >1058 Females: >1468	No adverse effects	DuPont-28946 Park, S-Y., 2012
90-day dog feeding study Strain: Beagle OECD 409 (1998) GLP compliant	Lot #: QGU42-166 97.6% purity Males: 0, 1.6, 16.6, 166.8, and 1415.3 Females: 0, 16.1, 172.1, and 1428.6 [dietary concentrations of 0, 40 (males only), 400, 4000, and 36000 ppm]	Males: 1415 Females: 1429	Males: >1415 Females: >1429	No adverse effects	DuPont-30047 Han, S-C., 2012 DuPont-30047, Supplement No. 1 Han, S-C., 2013
Combined chronic toxicity/oncogenicity feeding study in rats Strain: Rat (CD® [Crl:CD® (SD)]) OECD 453 (2009) GLP compliant	Lot #: QGU42-175 95.7% purity Males: 0, 24, 92, 346, and 846 Females: 0, 32, 128, 460, and 1147 [dietary concentrations of 0, 500, 2000, 6000/7500, and 18000 ppm]	Males: 846 Females: 1147	Males: >846 Females: >1147	No adverse effects; minimal increases in cholesterol at ≥6000/7500 ppm (460 mg/kg/day) in females	DuPont-30180 Craig, L., 2013

Species / Test Method	Test substance/purity Doses tested (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Target organs / principal effects	Reference
1-year dog feeding study Strain: Beagle OECD 452 (2009) GLP compliant	Lot #: QGU42-175 95.7% purity Males: 0, 1.4, 13.6, 148.0, and 1242.2 Females: 0, 1.4, 13.8, 136.9, and 1460.6 [dietary concentrations of 0, 40, 400, 4000 and36000 ppm]	m/f : 400 ppm males: 13.6 females: 13.8	m/f : 4000 ppm males: 148 females: 136.9	Absolute and relative liver weight increases of 20 to 40% when compared to controls	DuPont-30254 Han, K-H., 2013
28-day rat dermal study Strain: Sprague-Dawley SD OECD 410 (1981) GLP compliant	Lot #: QGU42-175 95.7% purity Male and females: 0, 150, 450, and 1000 mg/kg/day	Males and females: 1000	Males and females: >1000	No adverse effects	DuPont-32338 Bauter, M.R., 2012

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

2-week rat oral gavage study - rat

In a 14-day gavage study, oxathiapiprolin technical was administered to male and female Crl:CD(SD) rats at doses of 0 (5 animals/sex), 25 (8 animals/sex), 300 (8 animals/sex), or 1000 (8 animals/sex) mg/kg bw/day. In addition, animals designated for a genetic toxicity component (two groups of 5 animals/sex/dose level) were dosed once with oxathiapiprolin at 2000 mg/kg bw or with a positive control. The vehicle was 0.5% methylcellulose and 0.1% Tween 80. Parameters evaluated included clinical signs, body weight, body weight gain, haematology, clinical chemistry, urinalysis, gross pathology, organ weights, pharmacokinetics, and histopathology.

No deaths occurred during the study. No adverse changes in body weight, body weight gain, clinical signs, haematology (including coagulation), clinical chemistry parameters, urinalysis, gross findings, organ weights or histopathology were observed during the study. Group mean cholesterol and triglyceride values were minimally increased in male rats dosed with 1000 mg/kg, but not in females. Mean cholesterol was also elevated at 300 mg/kg in males. An increase in CYP2B1 was observed at 1000 mg/kg in males and females. The genetic toxicity results (micronucleus test) for the treated group (1000 mg/kg) were negative and there was no indication of target cell toxicity.

The NOAEL for males and females was 1000 mg/kg bw/day. This NOAEL was based on a lack of any adverse finding in this study.

28-day repeated dose (oral) study in rats

In a 28-day feeding study, oxathiapiprolin technical was administered to male and female Crl:CD(SD) rats (5 animals/sex/concentration) at concentrations of 0, 500, 2000, 7500, and 20000 ppm. The mean daily intakes for males were 0, 37, 153, 580, and 1657 mg/kg bw/day. The mean daily intakes for females were 0, 40, 159, 588, and 1774 mg/kg bw/day. The overall mean daily intake of test substance in the 0, 500, 2000, 7500, or 20000 ppm groups was 0, 37, 153, 580, or 1657 mg/kg/day, respectively,

for male rats and 0, 40, 159, 588, or 1774 mg/kg/day, respectively, for female rats. Parameters evaluated included body weights, food consumption, clinical signs, biochemical, gross and microscopic pathology, organ weights, haematology, clinical chemistry, coagulation, and urinalysis. Blood was collected on test Day 21 for analysis of plasma concentrations of oxathiapiprolin and metabolites.

No deaths occurred during the study. No treatment-related changes in body weight, body weight gain, food consumption, food efficiency, clinical signs, ophthalmology evaluations, haematology (including coagulation), clinical chemistry parameters, urinalysis, gross findings, organ weights or histopathology were observed during the study. No clear changes in liver biochemistry parameters were observed.

The NOAEL for males and females was 20000 ppm. This NOAEL was based on a lack of adverse test substance-related effects on any in-life, clinical pathology, anatomic pathology, or biochemical parameter in males and females at concentrations up to 20000 ppm.

28-day repeated dose (oral) study in mouse

In a 28-day feeding study, oxathiapiprolin was administered to male and female Crl:CD1(ICR) mice (10 animals/sex/concentration) at concentrations of 0, 200, 800, 3500, and 7000 ppm. The mean daily intakes for males were 0, 32, 129, 597, and 1151 mg/kg bw/day. The mean daily intakes for females were 0, 41, 175, 745, and 1440 mg/kg bw/day. Parameters evaluated included body weight, food consumption, clinical signs, gross and microscopic pathology, organ weights, biochemical, haematology, clinical chemistry. Blood was collected on test Day 21 for analysis of plasma concentrations of oxathiapiprolin and metabolites.

No deaths occurred during the study. No treatment-related changes in body weight, body weight gain, food consumption, food efficiency, clinical signs, ophthalmology evaluations, haematology, clinical chemistry parameters, gross findings, organ weights or histopathology were observed during the study. A statistically significant test substance-related increase in liver cytochrome P450 4A1/2/3 was observed in male mice at 7000 ppm. Increased cytochrome P450 4A1/2/3 was observed at lower doses in males and in treated females, but due to the high variability in the data, these changes were considered inconclusive for males and not treatment-related in females.

The NOAEL for males and females was 7000 ppm. This NOAEL was based on a lack of adverse test substance-related effects on any in-life, clinical pathology, anatomic pathology, or biochemical parameters in male and female mice at concentrations up to 7000 ppm.

28-day repeated dose (oral) study – dog

In a 28-day feeding study, oxathiapiprolin was administered to male and female beagle dogs (2 animals/sex/concentration) at concentrations of 0, 1000, 10000 and 40000 ppm. The mean daily intakes for males were 0, 30, 352, and 1368 mg/kg bw/day. The mean daily intakes for females were 0, 31, 331, and 1346 mg/kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, haematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. Blood was collected on test Day 21 for analysis of plasma concentrations of oxathiapiprolin and metabolites.

No deaths were observed. No adverse changes in body weight, body weight gain, food consumption, food efficiency, clinical signs, ophthalmology evaluations, haematology, clinical chemistry parameters, gross findings, organ weights or histopathology were observed during the study. Mild changes in absolute and relative (to body weight) liver plus gall bladder weights were observed in males and in one high dose female, but due to the low number of animals and variability in the data, the significance of this finding, especially in females, was difficult to assess (see Table 17 in section 4.1.7.1). While there also appeared to be possible changes in liver plus gall bladder weight relative to brain weight, in the absence of body weight effects, this endpoint was not considered relevant according to studies in the literature (compare Sellers, R.S. *et al*., 2007, *Toxicologic Pathology*, 35, 751-755, and Bailey, S.A. *et al*., 2004, *Toxicologic Pathology*, 32, 448-466.

Conclusions

Oxathiapiprolin was well tolerated in dogs up to 40000 ppm. However, absolute and relative liver weight increases in the range of 20 to 30% were noted at the mid and top doses equating to 352, and 1368 mg/kg bw/day. These liver weight increases were not accompanied by clinical chemistry or histopathological changes but their magnitude was great enough for them to be regarded as adverse in their own right. Based on these liver weight increases the mid dose was chosen as the LOAEL with the lowest dose of 30 mg/kg bw/day considered the NOAEL.

90-day repeated dose (oral) study in rat

Oxathiapiprolin technical was offered *ad libitum* in the diet for 91 or 92 consecutive days to four toxicology groups (Groups 2-5) and four neuropathology groups (Groups 2A-5A) of Crl:CD(SD) rats. Dose levels were 500, 2000, 6000, and 18000 ppm, respectively. Concurrent control groups (Groups 1 and 1A) received the basal diet on a comparable regimen. Each toxicology group consisted of 10 animals/sex, and each neuropathology group consisted of 5 animals/sex. The mean daily intakes for male rats were 0, 29, 117, 359, and 1096 mg/kg/day. The mean daily intakes for female rats were 0, 36, 145, 433, and 1300 mg/kg/day. Parameters evaluated included survival (all groups), clinical observations (all groups), body weight and body weight gain (all groups), food consumption and food efficiency (all groups), functional observational battery assessments (FOB, all 5 from the neuropathology groups and 5/sex/dose from toxicology groups), locomotor activity (all 5 from the neuropathology groups and 5/sex/dose from toxicology groups), haematology (toxicology groups), serum chemistry (toxicology groups), urinalysis (toxicology groups), serum collection (all groups), ophthalmic examinations (toxicology groups), macroscopic examination (toxicology groups), organ weights (toxicology groups), slide preparation and microscopic examination (toxicology groups), macroscopic examination and brain measurements (neuropathology groups), and slide preparation and microscopic examination (neuropathology groups).

Based on the results of this study, there were no adverse test substance-related effects of oxathiapiprolin when administered to Crl:CD(SD) rats for 91 or 92 consecutive days at 500, 2000, 6000, and 18000 ppm. Therefore, the no-observed-adverse-effect level (NOAEL) for oxathiapiprolin was 18000 ppm, the highest concentration tested, equivalent to 1096 and 1300 mg/kg/day for male and female rats, respectively.

90-day repeated dose (oral) study in mouse

In a 90-day feeding study, oxathiapiprolin technical (DPX-QGU42) was administered to male and female Crlj:CD1(ICR) mice (10 mice/sex/concentration) at concentrations of 0, 200, 800, 3500, or 7500 ppm. The mean daily intakes for male mice were 0, 28.5, 118.6, 490.6, and 1058.4 mg/kg bw/day. The mean daily intakes for female mice were 0, 35.3, 155.4, 660.1, and 1468.0 mg/kg bw/day.

Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, haematology, clinical chemistry, ophthalmology, organ weights, and gross and microscopic pathology.

There were no treatment-related changes or findings in mortality, body weight or nutritional parameters, clinical signs, ophthalmology, clinical pathology parameters, causes of death, organ weights, gross pathology, or microscopic pathology in either sex.

The no-observed-adverse-effect-level (NOAEL) for males and females was 7500 ppm (1058.4 and 1468.0 mg/kg bw/day, respectively) based on the absence of any treatment-related changes or findings in the study.

90-day repeated dose (oral) study in beagle dogs

In a 90-day feeding study, oxathiapiprolin technical (DPX-QGU42) was administered to male and female beagle dogs (four dogs/sex/concentration) at concentrations of 0, 40 (males only), 400, 4000, or 36000 ppm in the diet. The mean daily intakes for male dogs were 0, 1.6, 16.6, 166.8, and 1415.3 mg/kg bw/day. The mean daily intakes for female dogs were 0, 16.1, 172.1, and 1428.6 mg/kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, haematology, clinical chemistry, ophthalmology, organ weights, urinalysis, and gross and histopathology.

No deaths occurred during the study. No treatment-related adverse changes in body weight, body weight gain, food consumption, food efficiency, clinical signs, ophthalmology evaluation, haematology (including coagulation), clinical chemistry, urinalysis, gross findings, organ weights or histopathology were observed during the study. The changes in liver plus gall bladder weight relative to body weight observed in the 28-day dog study were not repeated in this study.

Conclusions

There were no adverse findings on treatment of dogs with up to 36000 ppm of the test substance for 13 weeks. The NOAEL for male and female dogs was 3600 ppm (1415 and 1429 mg/kg bw/day, respectively). This NOAEL was based on the absence of any treatment related adverse findings in the study.

1-year repeated dose (oral) study in rats (chronic toxicity portion of OECD Guideline 453)

As part of the 2-year chronic toxicity and carcinogenicity feeding study in rats (summarised in section 4.10.1), oxathiapiprolin technical was administered to male and female CD[Crl:CD (SD)] rats (approximately 70 rats/sex/concentration). Concentrations were 0, 500, 2000, 6000, and 18000 ppm for the first three weeks and 500, 2000, 7500, and 18000 ppm for Weeks 4 through 105. Ten rats per group were sacrificed after approximately 1 year on study to assess chronic toxicity. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, clinical pathology, ophthalmology, organ weights, and gross and microscopic pathology. The mean daily intakes over the first year on study were 23.7, 92.5, 346.1, and 845.8 mg/kg/day, respectively, for males and 32.2, 127.9, 460.2, and 1147.0 mg/kg/day for females at 500, 2000, 7500, and 18000 ppm, respectively. Exposure to the test substance produced no effects on body weight or food intake parameters in either sex. There were no test substance-related gross findings, organ weight changes, or histopathological changes in interim sacrificed (1-year) male or female rats at any concentration. Minimal increases in cholesterol were observed in females at ≥6000/7500 ppm. In this regard, mean cholesterol levels were increased to 137 and 115% of control values at the 6- and 12-month samplings at 6000/7500 ppm, respectively, with only the result at the 6 month being statistically significant. At 18000 ppm, female cholesterol levels were increased to 145 and 126% of control at the 6- and 12-month samplings, respectively. The no-observed-adverse-effect level (NOAEL) was 18000 ppm for males and females (846 and 1147 mg/kg bw/day, respectively). This NOAEL was based on a lack of adverse effects in males and females at any concentration.

1-year repeated dose (oral) study in beagle dogs

In a 1-year feeding study, oxathiapiprolin technical was administered to male and female beagle dogs (4 dogs/sex/concentration) at concentrations of 0, 40, 400, 4000 or 36000 ppm. The mean daily intakes for male dogs were 0, 1.4, 13.6, 148.0, and 1242.2 mg/kg body weight (bw)/day. The mean daily intakes for female dogs were 0, 1.4, 13.8, 136.9, and 1460.6 mg/kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, haematology, clinical chemistry, ophthalmology, organ weights, and gross and microscopic pathology.

No deaths occurred during the study. No adverse changes in body weight, body weight gain, food consumption, food efficiency, clinical signs, ophthalmology evaluation, haematology (including

coagulation), clinical chemistry, urinalysis, gross findings, organ weights, or histopathology were observed during the study. There was a trend for increased liver weight relative to body weight with dose; however, in contrast to the 28-day study, it was more pronounced in females (see Table 19).

Oxathiapiprolin was well tolerated in dogs up to 36000 ppm. However, absolute and relative liver weight increases in the range of 20 to 40% were noted at doses of 4,000ppm and 36,000ppm equating to 148.0, and 1242.2 mg/kg body weight (bw)/day. These liver weight increases were not accompanied by clinical chemistry or histopathological changes but their magnitude was great enough for them to be regarded as adverse in their own right. Based on these liver weight increases 4000ppm (148 mg/kg bw/day) was chosen as the LOAEL with the second lowest dose of 13.6 mg/kg bw/day considered the NOAEL.

4.7.1.2 Repeated dose toxicity: inhalation

No study available.

Due to the low acute inhalation toxicity, the overall toxicity profile of the compound and the expected exposure conditions, this study was not conducted and will likely not be required.

4.7.1.3 Repeated dose toxicity: dermal

28-day repeated dose (dermal) study in rats

In a 28-day dermal study, oxathiapiprolin technical was applied to the clipped, intact dorsal skin of male and female Sprague-Dawley SD rats (10/sex/dose). The test substance was applied for 29 daily (consecutive) applications. The rats were exposed to the test substance for 6 hours per day. Exposure doses were 0, 150, 450, or 1000 mg/kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, evaluations for dermal irritation, clinical signs, clinical pathology, organ weights, and gross and microscopic pathology.

No deaths occurred during the study. No treatment-related changes in body weight, body weight gain, food consumption, food efficiency, clinical signs, ophthalmology evaluations, haematology (including coagulation), clinical chemistry parameters, urinalysis, gross findings, organ weights or histopathology were observed during the study.

No oedema was noted for any treated group male or female rats. Very slight erythema was observed at the site of test substance application in one of ten male rats in all dosed groups on study Day 1 only. One female at 450 mg/kg exhibited very slight erythema on study Day 1. No erythema or oedema was observed in male or female control rats. Dermal irritation was considered to be incidental, non-adverse, and not associated with test substance administration.

The no-observed-adverse-effect level (NOAEL) for this study was 1000 mg/kg/day oxathiapiprolin in males and females based on the lack of adverse effects at any dose.

4.7.1.4 Repeated dose toxicity: other routes

No data available.

4.7.1.5 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.7.1.6 Other relevant information

No data available.

4.7.1.7 Summary and discussion of repeated dose toxicity

Repeated dose toxicity studies with oxathiapiprolin were conducted in rats, mice and dogs. In addition to oral feeding studies with durations of up to 90 days in rats, mice and dogs, and up to one year in rats and dogs, two other studies were performed in rats: a 14-day oral gavage study (conducted in discovery) and a 28-day dermal study. No adverse effects were observed in any rodent studies.

However,in the dog 28 day and 1 year studies, absolute and relative liver weight increases in the range of 20 to 40% were noted when compared to controls. These liver weight increases were not accompanied by clinical chemistry or histopathological changes but their magnitude was great enough for them to be regarded as adverse in their own right. Based on these liver weight increases 30 mg/kg bw/day was considered the NOAEL in the 28 day dog study with 13.6 mg/kg bw/day taken as the NOAEL in the 1 year dog study.

Non-adverse findings observed in these studies were limited to changes in organ weights, clinical chemistry parameters and liver cytochrome P450 isozymes.

No test substance-related body weight changes were observed in any of the rat, mouse or dog studies. There were no test substance related-changes in liver weights or in liver histopathology in any of repeated dose studies in rats (including studies up to 2 years). In the 28-day mouse study, mean liver + gall bladder weight relative to body weight was sometimes increased relative to controls, but there was no dose-related trend for either sex (in males elevated to 102, 108, 102 and 109% of control at 200, 800, 3500 and 7000 ppm; in females 111, 107, 109 and 106 % of control at 200, 800, 3500 and 7000 ppm, respectively). Mean liver + gall bladder weight relative to body weight was slightly elevated in both sexes of the 90-day mouse study (maximum increase to 108% of control in females at 7500 ppm), but the changes were not considered remarkable in the study as they were minimal. In dogs, there was a trend for increased liver + gall bladder weight with dose in males in the 28-day study, with the change in mean liver + gall bladder weight relative to body weight increased to 130%[1] of control at the top dose of 36000 ppm (elevations in liver + gall bladder weight relative to brain weight were observed in this study, but did not correlate with changes in liver + gall bladder weight relative to body weight; in the absence of test substance-related body weight effects, the liver + gall bladder weight relative to body weight is a more appropriate endpoint to assess weight changes[2]). In contrast to males, in females from this study, decreases in mean liver + gall bladder weight relative to body weight were seen at some doses; however, these changes are probably spurious given that no trend with dose was seen. In the 90-day dog study, there was no test substance-related trend in mean liver + gall bladder weight relative to body weight in either sex. Liver + gall bladder weight relative to brain weight at the top dose (36000 ppm) in male dogs was elevated to 125% of the control value and was statistically significant; however, the lack of relevance of this measurement in the absence of body weight effects, and additionally, the lack of any effect on liver + gall bladder weight relative to body weight in this study, strongly suggests that this finding was spurious. Finally, in the one-year dog study, increases in liver + gall bladder weight relative to body weight were observed at ≥4000 ppm in females. A possible explanation for the increased liver + gall bladder weight relative to body weight in the one-year females may be that the one-year control dogs merely had smaller livers and gall bladders relative to their body size. In this regard, when comparing the female liver + gall bladder weight relative to body weight across controls of the 28-day, 90-day and one-year dog studies, the one-year female controls had the lowest mean weight of the three studies (female control mean liver + gall bladder weights: 3.39, 2.68 and 2.49 percent of the body weight in the 28-day, 90-day and one-year studies, respectively). Further support for the one-year female controls having smaller liver and gall bladders comes from the fact that the mean final female control body weight in the 90-day study was 6585 g and in the one-year study was 7184 g, but the mean female liver + gall bladder weight in both studies was 174 g. Thus, while female liver + gall

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

2 Sellers, R.S. *et al*., (2007). *Toxicologic Pathology*, 35, 751-755, and Bailey, S.A. *et al*., (2004). *Toxicologic Pathology*, 32, 448-466.

bladder weights relative to body weight were elevated at ≥4000 ppm at one year, it is not clear if this is a test substance related-finding.

Based on the above, it could be regarded as difficult to draw a strong conclusion on the changes in liver + gall bladder weight in the dog when assessing all three dog studies together, given the small sample size in each study and the inconsistency in the results across studies (28-day, 90-day and one-year). If it is test substance-related, it should be pointed out that there were no adverse changes in liver or gall bladder histopathology observed in any of the repeat dose dog studies. In the 28-day study a non-adverse increase in liver glycogen was noted in treated males which was diagnosed as a mild increase in hepatocellular vacuolation. Given the small group size (2 dogs/sex/dose) in the 28-day study and the normal variability in liver glycogen in nonfasted dogs, the glycogen accumulation observed in the treated males was not outside the range expected to occur spuriously. This position is supported by the results of subsequent studies in dogs with larger group sizes and longer exposure durations where there were no test substance-related differences in liver glycogen content noted in any treated group relative to controls.

Changes in liver cytochrome P450 in the 14-day rat study consisted of increases in cytochrome P450 2B1 (332 and 215% of controls, in males and females, respectively) in samples from rats gavaged with oxathiapiprolin at doses of 1000 mg/kg bw/day. Total P450 was not changed. A similar increase in cytochrome P450 2B1/2 was not seen in male rats in the 28-day dietary study, and western blots from females were too faint to assess from this study. The lack of this finding in the males of the 28-day study suggest the transient nature of this enzyme or differences in toxicokinetics between dosing by gavage *versus* feeding. In mice from the 28-day feeding study, there was an increase in liver cytochrome 450 4A1/2/3 in males, with increases reaching 158% of control values and statistically significant ($p < 0.05$) at 7000 ppm (highest dose tested). There were slight increases in CYP 4A1/2/3 in female mice for which it was unclear if it was test substance-related; however, CYP 2B1/2 was not elevated in either sex. Total cytochrome P450 was not elevated in mice. In the 28-day feeding study in dogs there was a dose-dependant increase in liver cytochrome P450 2B1/2 in males. In female dogs, this isozyme was only increased at the top dose. Based on the findings in males, the increase in cytochrome P450 2B1/2 at the top dose in female dogs was likely test substance-related. The increases in cytochrome P450 2B1/2 in dogs might be potentially related to the increases in liver weights mentioned above. While this cannot be ruled out, there were no test substance-related in changes in liver hypertrophy in any of the dogs studies, a finding that typically correlates with increases in liver cytochrome P450. This lack of hypertrophy is consistent with the fact that the increase in total liver cytochrome P450 in the 28-day dog study was inconclusive in males (increased 130% over controls at the highest dose tested) and was not elevated in females.

Adrenal weights in the female rats of the 14-day gavage study showed no test substance-related effect. In the 28-day feeding study the female adrenal weights were elevated, but not in a dose-related manner (adrenal weight relative to body weight as % of control: 114, 129, 143 and 132% at 500, 2000, 7500 and 20000 ppm, respectively). The report mentioned a statistically significant increase in mean adrenal weight relative to body weight in females at the next to highest dose (increased to143% of control at 7500 ppm) in the 28-day study, but it was considered spurious since the value at the highest dose was lower (132% of controls). No remarkable changes in adrenal weights of females were observed in the 90-day feeding study in rats (adrenal weight relative to body weight as % of control: 83, 109, 104 and 109% of control at 500, 2000, 6000 and 18000 ppm, respectively). Nor was a consistent pattern observed at the one year sacrifice in the 2-year rat study, also tested up to dietary levels 18000 ppm. Increases in adrenal weights were observed in the P_1 and F_1 adult female rats in the multigeneneration reproduction study (study details in section 4.11) at dietary levels of 1500 ppm and above. Mean absolute adrenal weights were increased 15.5, 15.5, and 15.5% in the 1500, 6000, and 17000 ppm dose groups in P_1 females, respectively. Mean relative values (% brain wt. and % body wt.) were similarly increased, and all differences, absolute and relative, were statistically significant ($p<0.05$). The relative to brain weight increases compared to controls in P_1 females were 16, 16, and 15% and the relative to body weight increases were 19, 14, and 19%, at 1500, 6000 and 17000 ppm, respectively. Likewise, F_1

adult female mean adrenal weights were mildly increased compared to the control at dietary exposures of ≥1500 ppm. Mean absolute adrenal weights were increased by 13, 21, and 24% in the 1500, 6000, and 17000 ppm dose groups, respectively. Relative weights (% brain weight and % body weight) were similarly increased, and all differences, absolute and relative, were statistically significant ($p<0.05$). Relative to brain weight increases compared to controls in F_1 females were up by 13, 21, and 24% and the relative to body weight increases were up by 9, 14, and 18%, at 1500, 6000 and 17000 ppm, respectively. Since there were no associated morphological changes, including degenerative or hyperplastic lesions, the increased adrenal weights in the P_1 and F_1 adult females were interpreted as non-adverse and a possible transient, stress-related effect on the adrenal glands. Taking all studies together, these findings are not adverse since they appear inconsistently, and no treatment-related histological changes were observed.

Table 17
28-Day Dog Study: Liver (+ gall bladder) weights

ppm	Initial bw	Final bw	Absolute liver wt	% of Control	Liver wt relative to bw	% of Control	Liver wt relative to brain wt	% of Control
Males								
0	9465	9485	259.881	—	2.7487	—	3.3795	—
100	9775	10290	305.311	118	2.9637	108	3.8661	114
10000	9365	9310	309.584	119	3.3415	122	3.6072	107
40000	9715	10075	360.785	139	3.5810	130	4.5748	135
Females								
0	8005	8210	278.476	—	3.3900	—	3.6767	—
100	8880	8720	239.053	86	2.7419	81	3.5186	96
10000	10255	10255	299.945	108	2.9231	86	3.8822	106
40000	9575	9575	329.245	118	3.4722	102	4.3579	119

Table 18
90-Day Dog Study: Liver (+ gall bladder) weights

ppm	Initial bw	Final bw	Absolute liver wt	% of Control	Liver wt relative to bw	% of Control	Liver wt relative to brain wt	% of Control
Males								
0	5450	6755	209	—	3.21	—	287	—
40	5757	7215	215	103	2.98	93	300	105
400	6498	8712	254	122	2.92	91	312	109
4000	5963	7917	239	114	3.06	95	333	116
36000	7108	8627	275	132	3.19	99	359*	125
Females								
0	5724	6585	174	—	2.678	—	255	—
40	—	—	—	—	—	—	—	—
400	5958	7308	229	132	3.119	116	319	125
4000	5987	7382	209	120	2.852	106	287	113
36000	6037	7138	198	114	2.790	104	277	109

Table 19
1-Year Dog Study: Liver (+ gall bladder) weights

ppm	Initial bw	Final bw	Absolute liver wt	% of Control	Liver wt relative to bw	% of Control	Liver wt relative to brain wt	% of Control
Males								
0	6621.8	8246.0	208.080	—	2.595	—	281.890	—
40	6853.0	8343.8	220.844	106	2.655	102	308.951	110
400	6917.3	8156.5	213.248	102	2.637	102	283.871	101
4000	6920.3	9416.8	268.989*	129	2.936	113	344.616	122
36000	7215.5	9220.8	266.878	128	3.001	116	344.190	122
Females								
0	5797.8	7184.8	173.935	—	2.486	—	253.506	—
40	5536.3	7369.5	204.683	118	2.863	115	292.106	115
400	6048.0	6835.8	182.318	105	2.734	110	254.789	100
4000	5898.3	6981.8	228.101	131	3.355	135	331.215	130
36000	6096.3	7267.8	245.029	141	3.477	140	351.652*	139

***** significant difference from control

Minimal to mild changes in clinical chemistry parameters were noted in the repeated dose studies. In the 14-day rat study, group mean cholesterol values were increased in male and female rats dosed by gavage at ≥300 mg/kg bw oxathiapiprolin. The increase in cholesterol was statistically significant only in males at 1000 mg/kg (155% of control). A minimal increase in females at ≥300 mg/kg may have been test substance-related; however, the result was not as remarkable as what was observed in males. In males, there was also a statistically significant increase in triglyceride values (155% of control) at 1000 mg/kg, but triglycerides values were not remarkably elevated at any other dose in males and no changes were observed in females. In the 28-day feeding study in rats, the mean cholesterol level was significantly ($p < 0.05$) increased to 147% of control values in females at 20000 ppm oxathiapiprolin. This may have been test-substance related, given the changes in the 14-day study; however, only one of the five females had a value outside the laboratories 95% reference interval. In the 90-day dietary study in rats, no differences in group mean cholesterol values in male or female rats were noted; however, values in females were slightly elevated at ≥2000 ppm (increased by 122 to 130% of control, not dose-dependent and not statistically significant). Finally, minimal increases in cholesterol were observed in female rats at ≥6000/7500 ppm in the 2-year rat study. In this regard, mean cholesterol levels were increased to 137 and 115% of control values at the 6- and 12-month samplings at 6000/7500 ppm (460 mg/kg bw), respectively, with the result at 6 months statistically significant. At 18000 ppm, female cholesterol levels were increased to 145 and 126% of control at the 6 and 12 month samplings. All of these changes in cholesterol in rats were likely test substance-related, but were not considered adverse, as changes in cholesterol of a low magnitude generally do not impact the health of the animals.[3] The increase in triglycerides in the 14-day study may have been spurious, as no similar finding was seen in other rat studies, or may have been due to differences in dosing regimens in subsequent studies. There were no consistent or remarkable test substance-related changes in clinical chemistry parameters in the repeated dose mouse or dog studies with oxathiapiprolin. While triglycerides were statistically significantly higher than controls at 36000 ppm in male dogs on test Day 91 in the 90-day study, similar findings were not observed in the one-year dog study, and most notably not at the Day 84 sampling. Thus, this finding is considered to spurious as it was not reproducible.

[3] Hall, R.L. (2001). Principles of Clinical Pathology for Toxicology Studies. *In* (A.W. Hayes, ed.), Principles and Methods of Toxicology, 4th Edition, pp 1030. Taylor & Francis, Philadelphia.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

Under the CLP Regulation, STOT RE may be assigned on the basis of a substance demonstrating evidence of significant or severe specific organ toxicity, at or below a guidance value of 100 mg/kg bw/d (for classification in Category 2) obtained in a 90 day oral study. This guidance value is adjusted to take into account studies of different durations. 'Significant' toxicity is taken to mean changes that clearly indicate functional disturbance or morphological changes that are toxicologically relevant. 'Severe' toxicity is considered to be more profound or serious and indicates changes that are of a considerably adverse nature with a significant impact on health. Repeated dose toxicity has been evaluated in 14-day, 28-day and 13-week oral studies in the rat, mouse and dog, 52-week oral studies in the rat and dog, and in a 28-day dermal study in the rat.

In a 28 day study in dogs, absolute and relative liver weight increases in the range of 20 to 30% were noted at the mid and top doses equating to 352, and 1368 mg/kg bw/day. These liver weight increases were not accompanied by clinical chemistry or histopathological changes but their magnitude was great enough for them to be regarded as adverse in their own right. Based on these liver weight increases the mid dose was chosen as the LOAEL with the lowest dose of 30 mg/kg bw/day considered the NOAEL.

In a one year study in dogs, absolute and relative liver weight increases in the range of 20 to 40% were noted at doses of 4,000ppm and 36,000ppm equating to 148.0, and 1242.2 mg/kg body weight (bw)/day. These liver weight increases were not accompanied by clinical chemistry or histopathological changes but their magnitude was great enough for them to be regarded as adverse in their own right. Based on these liver weight increases 4000ppm (148 mg/kg bw/day) was chosen as the LOAEL with the second lowest dose of 13.6 mg/kg bw/day considered the NOAEL.

Effects on liver weight were noted in dog studies over 28 days and 1 year exposure to Oxathiapiprolin. However, the concentrations at which effects were seen were 352, and 148 mg/kg bw/day respectively. Effects at these concentrations do not precipitate STOT RE classification.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

There was no evidence for any adverse findings, or serious target organ toxicity in studies in rats, mice or dogs at or below the applicable guidance values for repeated dose toxicity classification of the CLP. The most frequent non-adverse effects observed were minimal increases in cholesterol (rats), mild increases in adrenal weights (female rats), and mild increase in liver + gall bladder weight in dogs.

Effects on liver weight were noted in dog studies over 28 days and 1 year exposure to Oxathiapiprolin. However, the concentrations at which effects were seen were 352, and 148 mg/kg bw/day respectively. Effects at these concentrations do not precipitate STOT RE classification (100 mg/kg bw/day for 90-day study using the CLP criteria). Therefore, no classification for STOT RE is proposed.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

No adverse findings occurred at or below the guidance values for repeated dose toxicity classification according to the CLP in the studies with oxathiapiprolin. Therefore, no classification for repeated dose toxicity is proposed according to the criteria of the CLP.

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 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***	**<u>20000 ppm</u>** *(1774/1657 mg/kg bw/day)* ***Females*** Cholesterol increase (+47%) **<u>7500 ppm</u>** *(580/588 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**	1 DuPont-28294 (2010) DuPont-28294, Supplement No. 1 (2011)
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	**<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	DuPont-28296 DuPont-28296, Supplement No.1

Purity: 99.5% ***Guidance value level for warranting classification as category 2: 300 mg/kg bw/day***	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 **<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	No adverse effect at any dose **NOAEL= 1058/1468 mg/kg bw/day**	DuPont-28946 (2012)

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***	**LOAEL > 1058/1468 mg/kg bw/day**	
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 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***	**<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)* ***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**	DuPont-30254 (2013)
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

Oral short-term studies

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.**

4.9 Germ cell mutagenicity (Mutagenicity)

Table 20: Summary table of relevant *in vitro* and *in vivo* mutagenicity studies

Method	Results	Test substance/purity Concentration range tested	Reference
In vitro bacterial mutagenicity (Ames) *Salmonella typhimurium* and *Escherichia coli* OECD 471 (1998), EC Directive 2000/32/EC Annex 4D-B.13/14 Number L 136 GLP compliant	Negative (± S9)	Lot #: QGU42-175, 95.7% purity 0-5000 µg/plate (with and without S9)	DuPont-30255 Myhre, A., 2011
In vitro mammalian chromosome aberration test (clastogenicity) Human lymphocytes OECD 473 (1998), EC Directive 2000/32/EC Annex 4A-B10 Number L 136 GLP compliant	Negative (± S9)	Lot #: QGU42-175, 95.7% purity 0-2000 µg/mL (with S9) 0-5000 µg/mL (without S9)	DuPont-30256 Madraymootoo, W., Jois, M., 2010
In vitro mammalian cell gene mutation test (CHO/HGPRT assay) CHO cells EC Directive 2000/32/EC Annex 4E Number L 136, OECD 476 (1998) GLP compliant	Negative (± S9)	Lot #: QGU42-175, 95.7% purity 0–100 µg/plate (with and without S9)	DuPont-30257, Revision No. 1 Clarke, J.J., 2010
In vivo micronucleus Mouse bone marrow OECD 474 (1998), EC Directive 2000/32/EC Annex 4C-B12 Number L 136 GLP compliant	Negative	Lot #: QGU42-175, 95.7% purity male: 0-5000 mg/kg bw female: 0-5000 mg/kg bw	DuPont-31004 Donner, E.M., 2010
In vivo micronucleus test in rats after single or multiple dosing by gavage (see **Table 16** above) Non-GLP	Negative	Lot #: QGU42-020, 99% purity Males: 0-1000 mg/bw 12-doses or single dose of 2000 mg/kg bw Females: 0-1000 mg/bw 12-doses or single dose of 2000 mg/kg bw	DuPont-24634 Nabb, D., 2008

4.9.1 Non-human information

4.9.1.1 *In vitro* data

Bacterial reverse mutation

Oxathiapiprolin technical (DPX-QGU42, 95.7% purity) was evaluated for mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and in *Escherichia coli* strain WP2*uvr*A with and without an exogenous metabolic activation system (Aroclor-induced rat liver S9). An initial toxicity-mutation assay was used to establish the dose range for the confirmatory mutagenicity assay and to provide a preliminary mutagenicity evaluation. A confirmatory mutagenicity assay was used to

evaluate and confirm the mutagenic potential of the test substance. The plate incorporation method was used for both assays. A correction factor based on the percent active substance was used for preparation of the dosing concentrations.

Nominal concentrations of 33.3, 66.7, 100, 333, 667, 1000, 3333, and 5000 μg/plate were used in the toxicity-mutation assay. The highest dose level in the mutagenicity assay was set based on the OECD 471 limit dose for this test system. In the toxicity mutation assay, no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. Precipitate was observed beginning at 667 μg per plate. No appreciable toxicity was observed.

In the mutagenicity assay, the dose levels tested were 333, 667, 1000, 3333, and 5000 μg/plate. In the mutagenicity assay, no positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. Precipitate was observed beginning at 667 μg per plate. No appreciable toxicity was observed.

Dimethyl sulfoxide (DMSO) was chosen as the dosing vehicle based on the solubility of the test substance and compatibility with the target cells. The test substance was soluble in DMSO at 50 mg/mL, the highest stock concentration that was prepared for use on this study.

Under the conditions of this study, oxathiapiprolin was negative for mutagenic activity in non-activated and S9-activated test systems.

***In vitro* mammalian chromosome aberration test**

Oxathiapiprolin was tested in the *in vitro* mammalian chromosome aberration test using human peripheral blood lymphocytes (HPBL) both with and without an exogenous metabolic activation system (Aroclor-induced rat liver S9). In the preliminary toxicity assay, the cells were exposed to nine concentrations of the test substance ranging from 0.5 to 5000 μg/mL, as well as a control vehicle. Visible precipitate was observed in treatment medium at does levels ≥150 μg/mL and dose levels ≤50 μg/mL were soluble in treatment medium at the beginning of the test period. Substantial toxicity (at least 50% reduction in mitotic index relative to the solvent control) was observed at any dose level in the non-activated 4- and 20-hour exposure groups. Substantial toxicity was observed at dose levels of 500 and 1500 μg/mL in the S9-activated 4-hour exposure group. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 25 to 5000 μg/mL for the non-activated 4- and 20-hour treatment groups, and ranged from 50 to 2000 μg/mL for the S9-activated 4-hour treatment group. In the chromosome aberration assay, visible precipitate was observed in treatment medium at dose levels ≥200 μg/mL, and dose levels ≤100 μg/mL were soluble in treatment medium at the beginning and conclusion of the treatment period. The test substance formed a workable suspension in dimethyl sulfoxide (DMSO) at a concentration of 500 mg/mL, the maximum concentration prepared for the preliminary toxicity assay and was soluble in DMSO up to 250 mg/mL. HPBL were treated for 4 hours (activated and non-activated test system) and 20 hours (non-activated test system). After exposure to Colcemid®, metaphase cells were harvested approximately 20 hours following the initiation of treatment. Cells were evaluated for toxicity (mitotic inhibition) then structural and numerical chromosome aberrations. The positive and solvent controls fulfilled the requirements for a valid test.

No statistically significant increases in structural chromosome aberrations were observed in either trial at any of the concentrations evaluated. In addition, no statistically significant increases in polyploidy were observed. Positive controls induced the appropriate response.

Based on the findings of this study, oxathiapiprolin was concluded to be negative for the induction of structural and numerical chromosome aberrations in cultured human peripheral blood lymphocytes with and without an exogenous metabolic activation system.

***In vitro* mammalian cell gene mutation test (CHO/HGPRT assay)**

Oxathiapiprolin was tested in the CHO/HGPRT mutation assay with and without an exogenous metabolic activation system (Aroclor®-induced rat liver S9). Both an initial and an independent repeat trial were conducted. Following a preliminary toxicity assay, duplicate flasks of exponentially growing CHO-K_1 cells were exposed for 5 hours at 37 ± 1°C to the test substance at concentrations of 5.0, 10, 25, 50, and 100 µg/mL. The highest dose level was set based on insolubility of the test substance at higher doses in a range finding experiment. Cells were then independently subcultured for assessment of cytotoxicity (cloning efficiency) and for expression and selection of the 6-thioguanine (2-amino-6-mercaptopurine)-resistant phenotype. The test substance was dissolved in dimethylsulfoxide (DMSO) at a maximum concentration of 100 mg/mL. Ethyl methanesulfonate (EMS) and benzo(a)pyrene (B(a)P) were used as positive controls for the non-activated and activated test systems, respectively. Toxicity was defined as a cloning efficiency of ≤50% of the concurrent vehicle controls. The assay was considered positive when a dose-dependent increase in mutation frequencies occurred with at least 2 consecutive doses having mutation frequencies of greater than 40 mutants per 10^6 clonable cells. The positive and solvent controls fulfilled the requirements for a valid test.

There were no positive responses and no evidence of toxicity in any of the assays at any of the concentrations of the test substance evaluated.

Oxathiapiprolin was negative in the non-activated and S9-activated test systems in the CHO/HGPRT mutation assay.

4.9.1.2 *In vivo* data

Mouse bone marrow micronucleus test

Oxathiapiprolin was evaluated for its ability to induce micronucleated polychromatic erythrocytes (MNPCEs) in the bone marrow of male and female Crl:CD1 (ICR) mice. Based on range-finding results, doses of 0, 500, 1000, or 2000 mg/kg/bw of the test substance were selected for the main study. The highest dose level was set based on the limit dose. The test substance vehicle was aqueous methylcellulose (0.5%). Cyclophosphamide (CP) (40 mg/kg bw) was used as the positive control. In-life observations included clinical signs and body weight determinations. Bone marrow smears were prepared approximately 24 and 48 hours after dosing. Two thousand polychromatic erythrocytes (PCEs) per animal were scored for micronuclei. The number of PCEs per 1000 erythrocytes was also recorded to assess toxic effects on the bone marrow. The 500 and 1000 mg/kg bw dose groups were not evaluated at the 48 hour time point since there were no positive responses observed in the 2000 mg/kg bw group. The positive and vehicle controls fulfilled the requirements for a valid test.

There were no statistically significant increases in MNPCE frequency in male or female mice administered oxathiapiprolin. In addition, no statistically significant depressions in the proportion of PCEs among 1000 erythrocytes were observed.

There were no clinical signs of toxicity observed at any time point in any dose level in male and female mice. No mortalities occurred during the study. There were no statistically significant body weight losses.

Under the conditions of this study, oxathiapiprolin did not exhibit *in vivo* mammalian genotoxicity in mouse bone marrow cells.

2-Week repeated-dose study in rats

As described in section 4.7.1.1, a 14-day study was conducted in rats by oral gavage that included a genetic toxicity endpoint. Oxathiapiprolin technical was administered to male and female Crl:CD(SD) rats (5 animals/sex/dose level) at 0, 25, 300, or 1000 mg/kg bw/day for 12 days or with a single dose of 2000 mg/kg bw. A positive control (10 mg/kg cyclophosphamide) was also included. Micronuclei in

peripheral blood were evaluated by flow cytometry in 20,000 immature reticulocytes. Since there was no indication of positive results at the highest dose level after 12 days of treatment or after a single dose of 2000 mg/kg, the intermediate doses were not analysed. No increase in micronuclei was observed.

4.9.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.9.3 Other relevant information

No further information is available.

4.9.4 Summary and discussion of mutagenicity

A battery of *in vitro* and *in vivo* genetic toxicity studies was conducted with oxathiapiprolin. These studies demonstrate that oxathiapiprolin is not genotoxic. Oxathiapiprolin was negative for gene mutations in bacteria and mammalian cells *in vitro* and clastogenicity in an *in vitro* cytogenetic assay using human peripheral blood lymphocytes. Oxathiapiprolin was not clastogenic (by evaluation of micronuclei) in mouse bone marrow cells following single-dose oral gavage of 2000 mg/kg bw, nor was it clastogenic in rats after repeated dosing of up to 1000 mg/kg bw or after a single dose of 2000 mg/kg bw. Collectively, these results provide sufficient evidence to conclude that oxathiapiprolin is neither inherently genotoxic nor does it have genotoxic potential in the whole animal.

4.9.5 Comparison with criteria

Based on the full battery of genetic toxicology studies that have been conducted with oxathiapiprolin, this material does not cause genetic damage and, therefore, does not pose a mutagenic risk. Oxathiapiprolin does not meet the criteria specified in the CLP regulation for classification as a mutagen.

4.9.6 Conclusions on classification and labelling

Classification is not proposed.

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.**

4.10 Carcinogenicity

Table 21: Summary table of relevant carcinogenicity studies

Method/type of test/ test species	Test substance/purity Doses tested (mg/kg bw/day)	NOAEL (mg/kg/day)	Target organs and effects	Reference
Oral (Feeding), 2-year Rat (CD® [Crl:CD® (SD)]) GLP compliant	Lot #: QGU42-175 95.7% purity Males: 0, 21, 84, 309, and 735 Females: 0, 27, 109, 378, and 957 [dietary concentrations of 0, 500, 2000, 6000/7500, and 18000 ppm]	Males: 735 Females: 957	No adverse effects; minimal increases in cholesterol at ≥6000/7500 ppm (957 mg/kg/day) in females	DuPont-30180 Craig, L., 2013
Oral (Feeding), 18-month Mouse (Crlj:CD1(ICR)) GLP compliant	Lot #: QGU42-175 95.7% purity Males: 0, 27, 110, 468, and 948 Females: 0, 30, 125, 529, and 1106 [dietary concentrations of 0, 200, 800, 3500, and 7000 ppm]	Males: 948 Females: 1106	No adverse effects; a marginal increase in liver weights occurred at 3500 and 7000 ppm (529 and 1106 mg/g/day) in females, no histological correlates identified	DuPont-30263 Moon, K.S., 2013

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Rats:

In a 2-year chronic toxicity and carcinogenicity feeding study, oxathiapiprolin technical was administered to male and female CD®[Crl:CD® (SD)] rats (approximately 70 rats/sex/concentration). Concentrations were 500, 2000, 6000, and 18000 ppm for the first three weeks and 500, 2000, 7500, and 18000 ppm for Weeks 4 through 105. The mean daily intakes for male rats were 21, 84, 309, and 735 mg/kg bw/day. The mean daily intakes for female rats were 27, 109, 378, and 957 mg/kg bw/day. Ten rats per group were sacrificed after approximately 1 year on study, and all surviving rats were sacrificed after approximately 2 years on study. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, clinical pathology, ophthalmology, organ weights, and gross and microscopic pathology.

Exposure to the test substance produced no effects on body weight or food intake parameters in either sex. There were no test substance-related gross findings, organ weight changes, or histopathological changes in interim or terminal male or female rats at any concentration.

No test substance-related gross lesions were observed at necropsy. There were no test substance-related microscopic findings in the male or female any dose groups. All histopathological observations in this study were consistent with normal background lesions of rats of this age and strain. There were no test article-related increases in the incidence of any tumour type among males or females in any oxathiapiprolin treatment group by pairwise comparison. No evidence of carcinogenicity was observed.

A statistically significant increased trend in pancreatic islet cell tumours occurred in females, but was considered to represent the spontaneous occurrence of a neoplasm commonly seen in rats of this strain and age, as it was not statistically significant by pairwise comparison and was within the laboratories historical control range. Islet cell adenomas occurred 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. The combined incidences of islet cell adenoma and carcinoma were 1/59, 0/39, 0/43, 2/43, and 5/60 (8.3%) in the 0, 500, 2000, 6000/7500, and 18000 ppm groups, respectively. The increased incidences of islet cell adenoma and combined islet cell adenoma and carcinoma at 18000 ppm were statistically significant by the Cochran-Armitage trend test only, but were not statistically significant by pairwise comparisons to the control using the Fisher Exact test, and both incidences were within the laboratory's historical control ranges for islet cell adenomas (0-8.3%) and combined adenomas and carcinomas (0-10.8%) (Details are given in Annex 1). The incidence of islet cell carcinoma was not increased in females (1/59, 0/39, 0/43, 1/43, and 1/60 for 0, 500, 2000, 6000/7500, and 18000 ppm, respectively) and there was no statistical significance at any dose. Therefore, this finding was not considered to be test article related.

There were several statistically significant increases in non-neoplastic lesions in males for which the p-value in the Cochran-Armitage trend test and/or Fisher's Exact test was less than 0.05, but for which the findings were not considered to be related to treatment since they were within the laboratory historical control range. In this regard, the percentages of adrenal gland cortical angiectasis/cystic degeneration, cortical hypertrophy and medullary hyperplasia at 18000 ppm were 30% (18/60), 6.7% (4/60) and 31.7% (19/60), respectively; however, the laboratory historical control ranges were 7-36%, 0-47% and 3-32% for these adrenal lesions, respectively. The percent of kidney transitional cell hyperplasia was 6.7% (4/60) at 18000 ppm; however, the laboratory historical control range was 0-20%. The incidence of lung alveolar histiocytosis was 43.3% (26/60) at 18000 ppm, but the laboratory historical control range was 8-80%. Finally, the percentage of pituitary gland cysts was 6.7% (4/60) at 18000 ppm, with the laboratory's historical control range at 0-12%. All of these findings were considered spurious.

The no-observed-adverse-effect level (NOAEL) was 18000 ppm for males and females (735 and 957 mg/kg bw/day, respectively). This NOAEL was based on no effects in males at any concentration and no effects in females at any concentration.

Under the conditions of this study oxathiapiprolin was not a carcinogen.

Mice:

In an 18-month carcinogenicity feeding study, oxathiapiprolin technical (DPX-QGU42) was administered to male and female Crlj:CD1(ICR) mice (60 mice/sex/concentration) at concentrations of 0, 200, 800, 3500, and 7000 ppm. The mean daily intakes in male mice were 0, 27, 110, 468, and 948 mg/kg bw/day. The mean daily intakes in female mice were 0, 30, 125, 529, and 1106 mg/kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, clinical pathology, ophthalmology, organ weights, and gross and microscopic pathology.

No adverse test substance-related changes were observed in the following observations in male and female mice fed up to 7000 ppm oxathiapiprolin: body weight, body weight gain, food consumption, food efficiency, clinical signs, clinical pathology, ophthalmology, organ weights, and gross and microscopic pathology. Mild increases in liver weight were observed at 3500 and 7000 ppm in females. At 3500 ppm absolute and relative (to body weight) liver weights were up by 10 and 6%, respectively, with the difference in absolute weight being statistically significant. At 7000 ppm absolute and relative (to body weight) liver weights were up by 15 and 13%, respectively, with both differences statistically significant. There were no treatment-related gross or histological changes observed in the liver, and no similar weight changes occurred in males. While these liver weight changes in females were of uncertain significance, they were clearly considered non-adverse.

There were no statistically significant, test article-related increases in the incidence of any tumour type among males or females in any oxathiapiprolin treatment group by pairwise comparison to the controls. The incidence of histiocytic sarcoma in the haemolymphatic system was statistically increased ($p < 0.05$) by the Cochran-Armitage trend test in the 7000 ppm female group (2/60 females or 3.3%); however, it was not statistically significant by the Fisher's exact test. This neoplasm was not considered to be test substance-related as the very low incidence in this study was not statistically significant by the Fisher's exact test and was within the historical control ranges for both the institutional historical control range (1.7–3.3%) and the published historical control range (1.67-18.33%, 1.67-11.67%) for this tumour in the female ICR mouse.

The incidence of stromal polyps in the vagina (2/60 or 3.3%) was statistically increased ($p < 0.05$) by the Cochran-Armitage trend test in females fed 7000 ppm; however, it was not statistically significant by the Fisher's exact test. These polyps were identified in the vagina on cut section; however, the base of the polyp was not identifiable within the vagina, and the polyps were presumed to originate from further cranially within the reproductive tract. Polyps of the female reproductive tract are a typical spontaneous age-related lesion in mice, and 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%). This finding was not considered to be test substance-related.

In males fed 7000 ppm, the incidences of hyperplasia of the Harderian glands, mineralisation and papillary fibrosis in the kidneys, vascular mineralisation in the pancreas and lymphoid infiltration in the urinary bladder were statistically increased ($p < 0.05$) by the Cochran-Armitage trend test, but none of these changes were statistically significant by the Fisher's exact test. In females fed 7000 ppm. the incidences of cortical hypertrophy/hyperplasia in the adrenal gland, arteritis in the heart, bile duct hyperplasia, granulomatous inflammation and single cell necrosis in the liver, vascular mineralisation in the lung and stromal hyperplasia in the uterus/cervix were statistically increased ($p < 0.05$) by the Cochran-Armitage trend test, but none of these changes were statistically significant by the Fisher's exact test. All of these changes were present at low incidences, are common, spontaneous, age-related

changes in mice of this strain and were interpreted as spurious and not indicative of a test substance-related effect. The incidences of epidermal hyperplasia and ulcer of the skin of the neck were statistically increased ($p < 0.05$) in 800, 3500, and 7000 ppm groups males by the Cochran-Armitage trend test, but not by the Fisher's exact test. These lesions are histological correlates to gross findings and clinical observations. Grossly and clinically, there were no indications that skin observations were related to test substance administration. When all incidences of epidermal hyperplasia and ulcer were combined regardless of location, there was no clear dose response. These findings were interpreted as spurious and not indicative of a test substance-related effect.

The no-observed-adverse-effect level (NOAEL) was 7000 ppm for males and females (948 and 1106 mg/kg bw/day, respectively). This NOAEL was based on a lack of any adverse test substance-related effects on any parameter in males and females at 7000 ppm (948 and 1106 mg/kg bw/day).

Under the conditions of this study, oxathiapiprolin was not a carcinogen.

4.10.1.2 Carcinogenicity: inhalation

No data available.

4.10.1.3 Carcinogenicity: dermal

No data available.

4.10.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.10.3 Other relevant information

No further data.

4.10.4 Summary and discussion of carcinogenicity

The chronic toxicity and potential carcinogenicity of oxathiapiprolin was tested in long-term dietary feeding studies in rats and mice. Oxathiapiprolin was not carcinogenic in rats or mice.

No test substance-related adverse findings were identified in the 2-year study in rats at dietary intakes of oxathiapiprolin of up to 18000 ppm. There were no test substance-related, statistically significant increases in tumours between treated and control groups by pairwise comparison. A statistically significant increased trend in pancreatic islet cell tumours occurred in female rats, but was considered to represent a spontaneous neoplasm commonly seen in rats of this strain and age, as it was not significant by pairwise comparison and was within the laboratories historical control range. There were several statistically significant increases in non-neoplastic lesions in males for which the p-value in the Cochran-Armitage trend test and/or Fisher's exact test was less than 0.05, but for which the findings were not considered to be related to treatment, as they were within the laboratory historical control range. The overall NOAEL in this 2-year study in rats was 18000 ppm (735 and 957 mg/kg bw in males and females, respectively), the highest dose tested.

No adverse findings occurred in male mice which received dietary levels of oxathiapiprolin of up to 7000 ppm for up to 18 months. In female mice exposed to 7000 ppm of the test substance for 18 months, mean absolute and mean relative (% body weight) liver plus gallbladder weights were increased approximately 15 and 13%, respectively, when compared to controls. The differences in mean absolute and mean relative (% body weight) liver weights at 7000 ppm were statistically significant. In 3500 ppm females, mean absolute and relative (% body weight) liver weights were increased approximately

10 and 6%, respectively. The difference in mean absolute liver weights was statistically significant, however, with the exception of two to three animals, individual liver weights in the 3500 and 7000 ppm females were within the range of study controls. No associated gross or microscopic liver or gall bladder pathology findings were observed. Thus, these liver plus gall bladder weight changes may have been test substance-related, but were considered non-adverse. There were no test-substance related statistically significant increases in tumours between treated and control groups by pairwise comparison. The incidence of histiocytic sarcoma in the haemolymphatic system was statistically increased by the Cochran-Armitage trend test in the 7000 ppm female group; however, it was considered spurious as it was at a very low incidence and it was not statistically significant by pairwise comparison to the control. Several non-neoplastic lesions occurred with statistical significance by trend analysis, but were interpreted as spurious and not indicative of a test substance-related effect as they occurred at a low incidence typical in aging mice. The NOAEL in this 18-month study in mice was 7000 ppm (948 and 1106 mg/kg bw in males and females, respectively), the highest dose tested.

4.10.5 Comparison with criteria

No evidence of carcinogenicity was seen in chronic studies conducted with oxathiapiprolin in rats and mice. Oxathiapiprolin does not meet the criteria specified in the CLP regulation for classification as a carcinogen.

4.10.6 Conclusions on classification and labelling

Oxathiapiprolin is not classified with regards to carcinogenicity.

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.**

4.11 Toxicity for reproduction

A one-generation range-finding reproductive study, followed by a two-generation reproduction study were conducted in rats with oxathiapiprolin. Developmental toxicity studies in rats and rabbits were also conducted.

Table 22: Summary table of relevant reproductive toxicity studies

Method/type of test/ test species	**Test substance/purity Doses/concentrations tested**	**NOAEL**	**Reference**
One-generation reproduction toxicity study, oral route, range finding Non-guideline Rat (Crl:CD(SD)) Non-GLP; however, all work was done in a GLP facility.	Lot #s: QGU42-123 99.5% purity and QGU42-136 96.23% purity Dietary concentrations of 0, 2000, 10000, and 20000 ppm	Parental/Repro/Fertility: 20000 ppm (1321 mg/kg/day for parental males, and 1507, 1389, and 3089 mg/kg/day for parental females during premating, gestation, and lactation, respectively) Offspring: 10000 ppm (1655 mg/kg/day for dams during lactation; 1251, 914, and 701 mg/kg/day for F1 males, and 1257, 978, and 806 mg/kg/day for F1 females on PNDs[4] 28-42, 28-70, and 28-112, respectively)	DuPont-28631, Revision No. 1 Edwards, T.L., 2011
Two-generation reproduction toxicity study, oral route OECD Part 416 (2001), Directive 87/302/EEC Part B (1987) Rat (Crl:CD(SD)) GLP compliant	Lot #: QGU42-175 95.7% purity Dietary concentrations of 0, 500, 1500, 6000, and 17000 ppm, adjusted to 0, 300, 900, 3500, and 10000 ppm, respectively, on PND 0 to 42 (during lactation and F_1 and F_2 post weaning/adults)	Parental/Repro/Fertility: 17000/10000 ppm (1013 mg/kg bw/day for P_1 males and 1210, 1113, and 1374 mg/kg bw/day for P_1 females during premating, gestation, and lactation, respectively; for F_1 males, 1228 (up to PND 42) and 1196 (PND 42-91) mg/kg bw/day, and for F_1 females 1243 (up to PND 42), 1364 (PND 42-91), 1149, and 1417 mg/kg bw/day during premating, gestation, and lactation, respectively) Offspring body weights: 6000/3500 ppm (494 mg/kg/day based on intakes by F_1 dams during lactation) Offspring other effects: 1500/900 ppm due to slight developmental delays in F_1 and F_2 adult males (F_1 males 104 to 108 mg/kg bw/day; F_2 males 111 to 131 mg/kg bw/day)	DuPont-30258 Lewis, J.M., 2013 DuPont-30258, Supplement No. 1 Lewis, J.M., 2013
Developmental toxicity, oral route OECD 414 Section 4 (2001), Directive 87/302/EEC Part B (1987) Rat (Crl:CD(SD)) GLP compliant	Lot #: QGU42-175 95.7% purity 0, 100, 300, and 1000 mg/kg/day by gavage	Maternal: 1000 mg/kg bw/day Foetal: 1000 mg/kg	DuPont-30253, Revision No. 1 Munley, S.M., 2013

Method/type of test/ test species	**Test substance/purity Doses/concentrations tested**	**NOAEL**	**Reference**
Developmental toxicity study, oral route OECD 414 (2001) 440/2008/ED Method B.31 (2008) Rabbit (New Zealand White (Hra:[NZW]SPF female rabbits)) GLP compliant	Lot #: QGU42-175 95.7% purity 0, 100, 300, and 1000 mg/kg/day by gavage	Maternal: 1000 mg/kg bw/day Foetal: 1000 mg/kg	DuPont-32357 Charlap, J.H., 2012

Table 23: Studies investigating hormonal activity

Method/type of test/ test species	**Test substance/purity Doses/concentrations tested**	**NOAEL**	**Reference**
5-Day uterotrophic assay for detecting endocrine activity Non-Guideline Rat – female (Crl:CD(SD)) Non- GLP However, all experiments were done according to GLP standards	Lot #: QGU42-123 99.5% purity 0, 500 and 1000 mg/kg/day by gavage	1000 mg/kg/day Oxathiapiprolin did not induce estrogenic effects in ovariectomised adult female rats administered 500 or 1000 mg/kg of the test substance for 4 consecutive days	DuPont-28579, Revision No. 1 Snajdr, S.I., 2012
15-Day intact male assay for detecting endocrine activity Non-Guideline Rat (Crl:CD(SD)) Non-GLP However, all experiments were done according to GLP standards	Lot #: QGU42-123 99.5% purity 0, 500 and 1000 mg/kg/day by gavage	1000 mg/kg/day Oxathiapiprolin did not induce alterations that were consistent with endocrine-modulating activity in adult male rats	DuPont-27827, Revision No. 1 Snajdr, S.I., 2012
H295R steroidogenesis assay OECD 456 (2011) Human cells *in vitro* GLP compliant	Lot #: QGU42-175 95.7% purity 7.9×10^{-6} to 7.9×10^{-9} M	Oxathiapiprolin was negative for statistically significant effects on testosterone and estradiol at the exposure concentrations evaluated	DuPont-37042 Wagner, H., 2013

[4] PNDs = post-natal dayss

4.11.1 Effects on fertility

4.11.1.1 Non-human information

One-generation reproductive toxicity study

Three groups of male and female Crl:CD(SD) rats (10/sex/group) were administered either basal diet (control) or the test substance, oxathiapiprolin, continuously in the diet for 28 consecutive days prior to mating. Target test substance concentrations were 0, 2000, 10000 and 20000 ppm for the F_0[5] and F_1 generations. The F_0 males were offered the test substance in the diet for 28 days prior to mating, throughout mating, and continuing through the day of euthanasia. The F_0 females were offered the test substance diet for 28 days prior to mating, throughout mating, gestation, and lactation, and through the day of euthanasia. For the F_1 generation, eight pups per litter (four per sex, when possible) were selected on postnatal day (PND) 4 to reduce the variability among the litters. The offspring were able to access and ingest the test diet during the latter portion of the lactation period. The test diet was then exclusively offered to the offspring following weaning (beginning on PND 21) through the day of euthanasia. All offspring from the pairing of the F_0 animals continued on study until euthanasia on PND 70 or PND 119–133. F_0 males and females were exposed to the test substance for 44 and 71-84 consecutive days, respectively, and F_1 males and females were directly exposed after lactation for 50 or 99-112 consecutive days, respectively.

F_0 mean test substance consumption was 129, 653, and 1321 mg/kg/day for males and 150, 715, and 1507 mg/kg/day for females in the 2000, 10000, and 20000 ppm groups, respectively, during Study Days 0–27. F_0 female mean test substance consumption was 140, 676, and 1389 mg/kg/day during Gestation Days 0–20 and 316, 1655, and 3089 mg/kg/day during Lactation Days 1–21 in the same respective groups.

Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, reproductive indices, oestrous cyclicity, spermatogenic endpoints, developmental landmarks, gross pathology, organ weights, and histopathology.

All F_0 males and females survived to the scheduled necropsy. There were no test substance-related clinical findings.

A test substance-related lower mean body weight gain was noted in the 20000 ppm group F_0 females during the first week of test diet administration (Study Days 0–7) without correspondingly lower food consumption. Because this transient reduction was not of a sufficient magnitude to result in significantly lower mean body weights, the lower mean body weight gain in these F_0 females was not considered adverse. No test substance-related effects on mean F_0 body weights or body weight gains were noted in males at any dietary concentration or in females at 2000 and 10000 ppm. Mean F_0 gestation and lactation body weights and body weight gains were not affected by test diet administration at any concentration. No test substance-related effects on mean male and female food consumption or food efficiency were noted throughout the F_0 generation, with the following exceptions. Lower mean food efficiency was noted in the 20000 ppm group females during Study Days 0–7 and the overall pre-mating period (Study Days 0–27).

There were no test substance-related effects on F_0 male and female reproductive performance, the number of days between pairing and coitus, or the process of parturition.

There were no test substance-related macroscopic findings in the F_0 males and females. The mean numbers of implantation sites and sites that were not accounted for in the test substance-exposure group females were similar to the control group.

[5] The designation F_0 in this study is equivalent to P_1 in the multigeneration reproduction study, both of which refer to the first parental generation.

No test substance-related effects on organ weights were noted in the F_0 males and females.

All F_0 microscopic findings in this study were consistent with normal background lesions that occur in rats of this age and strain.

There were no test substance-related effects observed on the mean number of F_1 pups born, live litter size on PND 0, the percentage of males born, postnatal survival, general physical condition, or macroscopic findings for the pups that were found dead. Mean F_1 pup birth weights (PND 1) in the 2000, 10000, and 20000 ppm groups were similar to the control group. However, markedly lower mean body weight gains in the 20000 ppm group F_1 males and females resulted in mean body weights that were up to 20.0 and 16.5% lower, respectively, during the remainder of the pre-weaning period.

Mean F_1 test substance consumption during PND 28–70 was 185, 914, and 1948 mg/kg/day in the males and 199, 978, and 1978 mg/kg/day for the females in the 2000, 10000, and 20000 ppm groups, respectively. Mean F_1 test substance consumption during PND 28–112 was 140, 701, and 1461 mg/kg/day for the males and 161, 806, and 1609 mg/kg/day for the females in the same respective groups.

There were no test substance-related mortalities in the F_1 generation at any dietary concentration. No test substance-related clinical findings were noted at the daily examinations or the detailed clinical observations conducted weekly from PND 21–56.

The decrements in the 20000 ppm F_1 group mean male and female body weights observed in the pre-weaning period continued into the post-weaning period. Lower mean body weight gains, food consumption, and food efficiency were noted in the males in this group through PND 35, resulting in lower mean body weight gain for the overall intervals through necropsy (PND 21–70 and PND 21-119). The 20000 ppm group F_1 males did not fully recover from the effects on mean body weights prior to the final necropsy at the minimum age of 119 days. Mean body weights remained 6.9% and 8.3% lower in these males on PND 70 and 119, respectively. Mean body weight gains in the 20000 ppm group F_1 females were similar to the control group during the post-weaning period, resulting in an improvement in the effects on body weights by PND 49. Slightly lower mean food consumption (g/animal/day) in the 20000 ppm group F_1 females was a result of the lower mean body weights noted in this group as evidenced by higher mean food efficiency. No test substance-related effects on mean body weights, body weight gains, food consumption, or food efficiency were noted in the F_1 males and females in the 2000 and 10000 ppm groups.

At the time of reporting, the lower mean body weights observed in the 20000 ppm group were thought to be the cause for the delay in the mean age of balanopreputial separation in F_1 males (delayed approximately 3 days). No other effects on F_1 developmental landmarks were noted at any dietary concentration.

No test substance-related effects on F_1 spermatogenic endpoints occurred at any dietary concentration. There were no test substance-related F_1 macroscopic findings in animals that were found dead, euthanised *in extremis*, or examined at the scheduled necropsy. No test substance-related effects on F_1 organ weights were noted at any dietary concentration.

All F_1 microscopic findings in this study were consistent with normal background lesions that occur in rats of this age and strain.

The no-observed-adverse-effect-level (NOAEL) for F_0 systemic toxicity and reproductive performance in both males and females was 20000 ppm (1321 mg/kg/day for F_0 males and 1507, 1389, and 3089 mg/kg/day for F_0 females during pre-mating, gestation, and lactation periods, respectively) based on the lack of adverse effects observed on the F_0 generation. The NOAEL for F_1 growth and development in both males and females was 10000 ppm (1251, 914, and 701 mg/kg/day for F_1 males

and 1257, 978, and 806 mg/kg/day for F_1 females on PNDs 28–42, 28-70, and 28–112, respectively) based on decreases in mean body weight gain during pre-weaning and post-weaning periods at 20000 ppm.

Multigeneration reproduction study in rats

In a two-generation reproduction study, oxathiapiprolin technical was administered in the diet to male and female Crl:CD(SD) rats (30 rats/sex/concentration for both the P_1 and F_1 generations). Concentrations were 0, 500, 1500, 6000, and 17000 ppm. During the lactation period (P_1 and F_1 adults), and up to postnatal Day (PND) 42 for F_1 adults and F_2 adult males, the concentrations were adjusted to 0, 300, 900, 3500, and 10000 ppm, respectively, to achieve targeted concentration intakes. The P_1 rats were bred within their treatment groups to produce F_1 litters after at least 70 days on test. The F_1 rats were bred within their respective treatment groups to produce F_2 litters at least 70 days after weaning. Parameters evaluated included clinical observations, body weight, body weight gain, food consumption, food efficiency, gestation length, organ weight, implantation site numbers, post implantation loss (%), implantation efficiency, mean number of pups per litter, percent born alive, 0–4 day viability, viability index, lactation index, precoital interval, vaginal patency, preputial separation, oestrous cycle parameters, sperm parameters, ovarian follicle counts, sex ratio, mean pup weights, anogenital distance, mating index, fertility index, gestation index, and litter survival.

Table 24 shows the mean daily intakes of oxathiapiprolin during the various phases of the study.

Table 24
Multigeneration study: mean daily intakes in mg/kg body weight/day

Dietary concentration	500/300 ppm	1500/900 ppm	6,000/3500 ppm	17000/10000 ppm
P_1 males	29	86	346	1013
P_1 females premating	34	106	430	1210
Gestation	31	95	383	1113
Lactation	41	119	483	1374
F_1 males to PND 42	37	108	422	1228
F_1 males PND 42-91	34	104	411	1196
F_1 females to PND 42	37	109	426	1243
F_1 females PND 42-91	41	116	465	1364
Gestation	32	98	390	1149
Lactation	41	127	494	1417
F_2 males to PND 42	37	111	430	1278
F_2 males PND 42-60	44	131	519	1519

There were no test substance-related deaths, increases in any clinical observations, or effects on body weight, body weight gain, food consumption, or food efficiency reported throughout the study for the P_1 and F_1 parental rats. A mild increase in mean adrenal weight parameters was observed in the P_1 and F_1 adult females at 1500 ppm and above (details given in section 4.7.1.7). Since there were no associated morphological changes, including degenerative or hyperplastic lesions, the increased adrenal weights in the P_1 and F_1 adult females were interpreted as non-adverse and a possible transient, stress-related effect on the adrenal glands. There were no test substance-related causes of death or gross observations among any generations in this study. There were no test substance-related microscopic findings in the reproductive organs of the F_2 adult males. Microscopic examination of reproductive organs did not demonstrate any test substance-related cause for reproductive failure in the 13 P_1 and 6 F_1 adult pairs that failed to produce litters.

There were no treatment-related effects observed on sperm parameters in P_1 or F_1 males at any concentration tested. There was a statistically significant reduction in the number of sperm per gram

testis observed in F_1 males at 17000/10000 ppm (*i.e.*, mean daily intakes of *ca*. 1200 mg/kg bw/day[6]); however, this effect was not considered to be treatment-related since the value observed (89.9) was within the testing facility's historical control range (range 89.2 to 113.2 for 17 studies from the previous 5 years, mean 100.0). Also, there were no corresponding effects on fertility indices in F_1 males, nor were there any effects on histopathology for any reproductive organs examined in this study. Nor was there a similar effect in the one generation reproduction study that tested rats at dietary levels of up to 20000 ppm. There were no effects on oestrous cyclicity at any dietary level tested for both P_1 and F_1 females. While there was a statistically significant increase in post implantation loss observed at 17000/10000 ppm in P_1 females that was outside of the DuPont Haskell historical control range (mean 5.3%, range of means 1.0 to 10.1%; 17 studies, 2006 to 2011), there was no similar finding in the subsequent F_1 adult females at any dose level, nor were there any effects noted for this endpoint in a one generation reproductive toxicity study in rats tested at a higher dietary concentration (20000 ppm). Thus, although this increase was statistically significant and outside of the historical control range, the fact that it did not occur in a dose-dependent manner, did not repeat in the subsequent generation and was not observed at a higher dose level in a separate study, all support that this was a spurious finding.

There were no test substance-related clinical observations in either F_1 or F_2 offspring at any dietary level tested. There were no treatment-related mean pup weight effects noted at any level tested for P_1 litters. Mean pup weights at 17000/10000 ppm (equivalent to lactational intakes of 1417 mg/kg bw/day) in F_1 litters were 8% lower (statistically significant) than controls on PND 21 (*i.e.*, after the end of lactation). In addition, mean pup weights were 7 to 8% lower than controls (not statistically significant) from lactation Days 4 through 14 at 17000/10000 ppm. On lactation Day 21, selected pups were randomly assigned to serve as the parental generation for production of the second (F_2) generation. Thus, lactation Day 21 was equal to test Day 0 for the F_2 generation adults. Despite the fact that the lactation Day 21 offspring weights of the whole 17000/10000 ppm group were lower, the weight of a subset (1/sex/litter) of these offspring selected as the F_2 generation adults on the same day (now designated as Day 0 of the F_2 generation) was generally comparable to controls at 17000/10000 ppm.

The F_1 males in the 6000/3500 and 17000/10000 ppm group had a slight increase in the number of days to achieve preputial separation compared to control males (43.5 and 43.9 days for 6000/3500 and 17000/10000 ppm males, respectively, compared to 41.5 days for controls) (summarised in Table 25). There was also a statistically significant increase in body weights on the day of developmental achievement at 17000/10000 ppm as a result of the lack of an effect on growth post weaning. A similar effect was noted on F_2 adult males at the same respective levels. For the F_2 generation there was a statistically significant increase in the number of days to achieve preputial separation compared to controls (means of 45.4 and 46.2 days for 6000/3500 and 17000/10000 ppm males, respectively, compared to 43.8 days for controls) that corresponded to a significantly increased body weight on day of achievement for the same reasons mentioned for F_1 adults. The values observed in the 6000/3500 (45.4 days) and 17000/10000 ppm (46.2 days) F_2 males were outside the performing laboratory's historical control range obtained within the last 5 years when the in-life phase for this study ended (mean 43.4 days; range of means 42.7 to 44.6 days; 17 studies; 2006 to 2011). The magnitude of the delay in achievement at 17000/10000 ppm for F_2 males may have been impacted, in part, by the slight reduction in mean body weights on PND 21 (test Day 0) as compared to control values since body weight decreases are known to impact this endpoint. There were no test substance-related effects on timing for achievement of vaginal patency in F_1 offspring at any dietary level tested. There were no test substance-related effects on anogenital distance observed in F_1 litters evaluated on lactation Day 0. There were no changes in the number of pups born alive and the number of pups alive on Day 4 (pre-culling) of lactation, survival indices, sex ratio, or litters sizes observed in P_1 or F_1 litters at any concentration tested. A statistically significant reduction in the number of pups born alive and the number of pups alive on Day 4 (pre-culling) of lactation was observed in P_1 litters at 17000/10000 ppm. This statistically significantly decrease in the number of pups observed at 17000/10000 ppm in P_1 females was not considered treatment-related and was a direct result of the increase in post

[6] Dietary intakes immediately after lactation to PND 42 = 1228 mg/kg bw/day and PND 42 to PND 91 = 1196 mg/kg bw/day

implantation loss observed in P_1 females at this dose mentioned above. Statistically significant decreases in the number of pups born, born alive, and alive on Day 4 (pre-culling) observed in P_1 litters at 1500 ppm were not dose-related and were considered spurious. The statistically significant effect on sex ratio that occurred in F_1 litters at 1500 ppm was considered spurious since it was not dose-dependent (not observed at 6000/3500 or 17000/10000 ppm). There were no test substance-related causes of death or gross observations.

Table 25
Preputial separation - day of achievement

Generation	Control	500/300 ppm	1500/900 ppm	6000/3500 ppm	17000/10000 ppm
F1	41.5	41.1	42.1	43.5*	43.9*
F2	43.8	44.4	44.0	45.4*	46.2*

* statistically significant

The NOAELs in the two-generation reproduction study in rats were:

Reproductive performance and parental toxicity:	17000/10000 ppm [equivalent to 1013 mg/kg body weight/day for P_1 males and 1210, 1113, and 1374 mg/kg body weight/day for P_1 females during premating, gestation, and lactation, respectively; for F_1 males, 1228 (up to PND 42) and 1196 (PND 42 through 91) mg/kg body weight/day, and for F_1 females 1243 (up to PND 42), 1364 (PND 42 through 91), 1149, and 1417 mg/kg body weight/day during premating, gestation, and lactation, respectively].
Pup growth and development:	1500/900 ppm, based on delays in preputial separation at 6000/3500 and 17000/10000 ppm in F_1 and F_2 adult males and reduced offspring weight at 17000/10000 ppm. The 1500/900 ppm exposure level for F_1 males was equivalent to mean daily intakes of 108 (up to PND 42) and 104 (PND 42 and thereafter) mg/kg body weight/day. This exposure level was equivalent to mean daily intakes of 111 (up to PND 42) and 131 (PND 42 through 60) mg/kg body weight/day for F_2 males.

4.11.1.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Developmental toxicity study in rats

In a developmental toxicity study, oxathiapiprolin technical was administered by oral gavage to time-mated Crl:CD(SD) female rats (22/dose group) on gestation Days 6–20. Gavage doses in 0.5% methylcellulose with 0.1% Tween 80 were administered to deliver doses of 0, 100, 300, and 1000 mg/kg body weight/day. The dose volume was 10 mL/kg. Clinical observations, body weights, and food consumption were recorded at appropriate intervals. On gestation Day 21, a

laparohysterectomy was performed on each female. The uteri, placentae, and ovaries were examined, and the numbers of foetuses, early and late resorptions, total implantations, and *corpora lutea* were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The foetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations and variations.

There was no test substance-related mortalities at any level tested; all animals survived until scheduled euthanasia.

There were no test substance-related clinical observations at any level tested; the observations that were recorded were unremarkable and occurred infrequently.

There were no adverse test substance-related effects on maternal body weight parameters at any level tested. Mean absolute and adjusted final body weights were within 4% of the respective control mean for all doses tested.

At 1000 mg/kg/day, there was a slight (4%), statistically significant increase in mean maternal body weight on gestation Day 19. At 100, 300, and 1000 mg/kg/day, there were significant increases in mean maternal body weight gain (17 to 21%) from gestation Days 18 to 20. These transient increases were considered neither test substance-related nor were they considered adverse.

There were no adverse test substance-related effects on maternal food consumption at any level tested. At 300 and 1000 mg/kg/day, mean food consumption was significantly increased over several intervals. Consequently, mean cumulative food consumption values were up to 6% higher than the respective control group means at 300 and 1000 mg/kg/day. These increases are consistent with the slightly increased body weights discussed previously and are considered not test substance-related or adverse.

There were no test substance-related maternal gross post-mortem observations at any level tested. The single observation that was recorded was liver discoloration in a control group female. All other animals on study had no visible lesions.

There were no test substance-related effects on reproductive outcome or quantitative litter data. The mean number of implantation sites, resorptions, live foetuses, as well as mean foetal weight and sex ratio were comparable across all groups tested.

There were no test substance-related foetal malformations or variations observed at any dose level tested.

The foetal alterations that were observed were unremarkable and occurred with low frequency across the dose levels tested.

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 no-observed-effect level (NOAEL) for maternal and developmental toxicity was considered to be 1000 mg oxathiapiprolin/kg body weight/day.

Developmental toxicity study in rabbit

In a developmental toxicity study, oxathiapiprolin technical was administered by oral gavage to time-mated New Zealand White (Hra:[NZW]SPF) female rabbits (22/dose group) on gestation Days 7–28. Gavage doses in 0.5% methylcellulose with 0.1% Tween® 80 were 0, 100, 300, and 1000 mg/kg body weight/day. The dose volume was 10 mL/kg. Clinical observations, body weights, and food consumption were recorded at appropriate intervals. On gestation Day 29, a laparohysterectomy was performed on each surviving female. The uteri, placentae, and ovaries were examined, and the numbers of foetuses, early and late resorptions, total implantations, and *corpora lutea* were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The

foetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations and developmental variations.

One female in each of the 1000 and 100 mg/kg/day groups aborted on gestation Days 24 and 27, respectively. One female in each of the control and 100 mg/kg/day groups were found dead on gestation Days 25 and 10, respectively, following respiratory clinical observations. One female in the 300 mg/kg/day group delivered on gestation Day 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 dosage level, and the abortions, deliveries, and deaths did not occur in a dose-dependent manner, they were not considered to be related to test substance administration.

All other females in the control, 100, 300, and 1000 mg/kg/day groups survived to the scheduled necropsy on gestation Day 29. A slightly increased incidence of soft stool was noted in the 1000 mg/kg/day group generally throughout the treatment period, which was attributed to test substance administration, but was not considered to be adverse as there were no corresponding adverse effects on body weight or food consumption. There were no test substance-related clinical findings noted in the 100 and 300 mg/kg/day groups.

Mean body weight, body weight gains, gravid uterine weights, and food consumption in the 100, 300, and 1000 mg/kg/day groups were unaffected by test substance administration.

There were no test substance-related maternal macroscopic findings noted at the scheduled necropsy.

Intrauterine growth and survival were unaffected by test substance administration at all dosage levels tested. There were no test substance-related external, visceral, or skeletal malformations or developmental variations observed at any dosage level tested.

There were no adverse test substance-related effects on maternal survival, clinical or macroscopic findings, body weight, or food consumption at any dosage level. In addition, there was no developmental toxicity observed in the 100, 300, or 1000 mg/kg/day groups. Based on these results, a dosage level of 1000 mg/kg body weight/day, the highest dosage level evaluated, was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity when oxathiapiprolin was administered orally by gavage to time-mated New Zealand White rabbits.

4.11.2.2 Human information

No illnesses have been attributed to exposure associated with the handling, testing or manufacturing of oxathiapiprolin.

4.11.3 Other relevant information

Studies which investigated hormonal effects are summarised here. Two of these studies (5-day uterotrophic assay and intact male assay) were conducted as screening tests and were conducted under non-GLP conditions (in a GLP-compliant facility). The other study (*in vitro* steroidogenesis) was a guideline compliant, GLP study. The results of these studies do not provide evidence for endocrine activity by oxathiapiprolin.

5-Day uterotrophic assay for detecting endocrine activity

Oxathiapiprolin technical was evaluated for its ability to induce oestrogen-like effects in ovariectomised adult female Crl:CD(SD) rats. Based on a previous study, doses of 500 and 1000 mg/kg body weight of the test substance were selected for the study. A concurrent control group was administered the vehicle (0.1% Tween® 80 in 0.5% methylcellulose). The experimental groups consisted of 15 rats/dose. All rats were administered the test substance or vehicle by oral gavage for 4 consecutive days and then sacrificed on test Day 5, approximately 24 hours after the last administered dose. The endpoints

evaluated included body weights, vaginal cytology (conversion out of dioestrous), and organ weights (liver and uterus).

No mortality or adverse clinical signs were observed throughout the in-life phase of the study. There were no effects on mean body weight, body weight gain, food consumption, or food efficiency when compared to the control group.

There were no test substance-related gross observations or effects on organ weights. No ovarian tissue was observed in the microscopic evaluation of the ovarian stumps for any animals in any dose group.

There were no effects on vaginal cytology (conversion out of dioestrous) when compared to the control group.

Under the conditions of this study, oxathiapiprolin did not induce estrogenic effects in ovariectomised adult female rats administered 500 or 1000 mg/kg of the test substance for 4 consecutive days.

15-Day intact male assay for detecting endocrine activity

Oxathiapiprolin technical was evaluated for its ability to alter endocrine homeostasis in intact adult male Crl:CD(SD) rats. Based on a previous study, doses of 500 and 1000 mg/kg body weight of the test substance were selected for the main study. A concurrent control group was administered the vehicle control (0.1% Tween® 80 in 0.5% methylcellulose). The experimental groups consisted of 15 rats/dose. All rats were administered the test substance by oral gavage for 15 consecutive days and then sacrificed on test Day 15, approximately 2–3 hours after the last administered dose. At the terminal sacrifice, selected organs were weighed (liver, thyroid, adrenals, testes, epididymides, seminal vesicles, prostate, accessory sex gland unit). Blood was collected, and serum was prepared for hormonal analyses by radioimmunoassay (testosterone, dihydrotestosterone [DHT], oestradiol, luteinising hormone [LH], follicle stimulating hormone [FSH], prolactin, thyroid stimulating hormone [TSH], thyroxine [T4], and triiodothyronine[T3]). The thyroid, testes, and epididymides were saved for microscopic evaluation.

No mortality or adverse clinical signs were observed throughout the in-life phase of the study. There were no effects on mean body weight, body weight gain, food consumption, or food efficiency when compared to the control group.

There were no test substance-related effects on organ weights. Gross and microscopic evaluation of the testes, epididymides, and thyroid gland also did not demonstrate any test substance-related effects.

There were no effects on the serum concentrations of testosterone, DHT, oestradiol, prolactin, LH, or TSH. Serum FSH concentrations appeared to be affected (decreased) at 500 and 1000 mg/kg/day. In this regard, the FSH level was 81% of control levels at 500 mg/kg and the decrease was not statistically significant. At 1000 mg/kg, the level was 72% of control and was statistically significant. To clarify if this was a test substance-related effect, a second study was performed to further investigate a possible effect on FSH, in which the test substance was administered to two groups of intact adult male rats maintained in two different barriers. A dose of 1000 mg/kg body weight of the test substance was selected for the repeat study along with a concurrent control group administered the vehicle. The in-life conditions were the same as the main study. At the terminal sacrifice, blood was collected and serum was prepared for hormonal analyses by radioimmunoassay (FSH) and thyroid, testes, and epididymides were saved but not evaluated microscopically. For the repeat study, there were no effects on serum FSH concentrations in rats from either barrier. The level of FSH in the two different 1000 mg/kg dose groups was 98 and 85% of control values. Neither result was statistically different from the control.

The decrease in serum FSH concentrations observed in the main study was considered to be spurious since it was not replicated in the repeat study, nor were there any effects on the other reproductive hormone concentrations, organ weights, or histopathology at 500 or 1000 mg/kg/day in the main study.

Under the conditions of this study, oxathiapiprolin did not induce alterations that were consistent with endocrine-modulating activity in adult male rats administered 500 or 1000 mg/kg of the test substance. The no-observed-effect level (NOEL) for oxathiapiprolin was 1000 mg/kg body weight/day for male rats.

H295R steroidogenesis assay

Oxathiapiprolin technical was evaluated for its potential to interact with the steroidogenic pathway beginning with the sequence of reactions occurring after the gonadotropin hormone receptors (follicle stimulating hormone [FSHR] and luteinising hormone [LHR]) through the production of testosterone and oestradiol/oestrone using the H295R steroidogenesis assay. This is an *in vitro* steroidogenesis assay using the human cell line, H295R, a human adrenocortical carcinoma cell line that expresses genes that encode for all the key enzymes for steroidogenesis.

In this steroidogenesis assay, H295R cells cultured *in vitro* in 48-well plates were incubated with oxathiapiprolin at concentrations of 7.9×10^{-6}, 2.5×10^{-6}, 7.9×10^{-7}, 2.5×10^{-7}, 7.9×10^{-8}, 2.5×10^{-8}, and 7.9×10^{-9} M in replicates of six per plate for 48 hours. The test chemical's vehicle was dimethyl sulfoxide (DMSO), and its final concentration was 0.05%. The concentrations of oxathiapiprolin tested were based on viability tests.

Testosterone and oestradiol levels were measured by high pressure liquid chromatography/mass spectrometry/mass spectrometry (HPLC/MS/MS). Two independent runs were performed. A Quality Control (QC) plate was included with each independent run of the test chemical to demonstrate that the assay responded properly to the positive control agents at two concentration levels. Positive controls included a known inducer (forskolin) and inhibitor (prochloraz) of testosterone and oestradiol synthesis.

Oxathiapiprolin did not cause statistically significant or biologically relevant changes in testosterone or oestradiol levels relative to the vehicle control in two independent experimental runs. As expected, forskolin showed effects consistent with testosterone and oestradiol induction, and prochloraz showed effects consistent with testosterone and oestradiol inhibition. Performance criteria for a valid assay were met.

Under the conditions of this study, the test substance was judged to be negative for statistically significant effects on testosterone and oestradiol at the exposure concentrations evaluated in two independent runs in this H295R assay.

4.11.4 Summary and discussion of reproductive toxicity

Both one- and two-generation reproduction toxicity studies were conducted with oxathiapiprolin. In the one-generation study oxathiapiprolin was given *via* the diet to 10 rats/sex/dose. Dietary concentrations were 0, 2000, 10000 and 20000 ppm for the F_0[7] and F_1 generations. No parental effects or effects on fertility were noted at any dose. No effects on offspring were observed at 2000 and 10000 ppm. Pup body weights at 20000 ppm were similar to controls at birth, but were then decreased by 20.0% (F_1 males) and 16.5% (F_1 females) below controls during lactation when the dams mean daily dietary intakes were 3089 mg/kg bw/day. Consequently, lower mean body weight gains were noted in 20000 ppm pups during lactation. The body weight decreases at 20000 ppm were statistically significant ($p \leq 0.05$) in males at several timepoints during lactation. Post weaning, lower mean body weight gains, food consumption, and food efficiency were also noted in 20000 ppm males through PND 35, resulting in lower mean body weight gains for the overall intervals through necropsy (PND 21–70 and PND 21–119). The 20000 ppm group F_1 males did not fully recover from the effects on mean body weights prior to the final necropsy at the approximate age of 119 days. Mean body weights remained 6.9% and 8.3% lower in 20000 ppm males on PND 70 and 119, respectively. The mean daily dietary intakes at 20000 ppm for F_1 males were 2725, 1948, and 1461 mg/kg bw/day over the PND

[7] F_0 in this study is equivalent to P_1 in the multigeneration reproduction study, both of which refer to the first parental generation.

intervals 28-42, 28-70, and 28-112, respectively. Mean body weight gains in the 20000 ppm F_1 females were similar to controls during the post weaning period, resulting in an improvement of weight by PND 49. The mean daily dietary intakes at 20000 ppm for F_1 females were 2599, 1978, and 1609 mg/kg bw/day over the PND intervals 28-42, 28-70, and 28-112, respectively.

When the report was written, the lower mean body weights observed in the 20000 ppm F_1 males were interpreted as the cause of the delay (3 days) in the mean age of preputial separation. While the decreases in offspring weight may have exacerbated this finding, dose spacing in the subsequent multigeneration study allowed for the observation of delays in preputial separation in the absence of body weight effects. No effects on F_1 developmental landmarks were noted in females at any dose in the one generation study.

In the multigeneration reproduction toxicity study in rats, oxathiapiprolin was administered in the diet to male and females at concentrations of up to 17000 ppm. During lactation (P_1 and F_1 adults), and up to postnatal Day (PND) 42 the dietary concentrations were adjusted to a maximum of 10000 ppm. There were no test substance related deaths, increases in clinical observations, or effects on body weight, body weight gain, food consumption, or food efficiency reported for P_1 and F_1 parental rats. A mild increase in mean adrenal weight was observed in the P_1 and F_1 adult females at ≥1500 ppm (details in section 4.7.1.7). Since there were no associated morphological (gross or microscopic) changes, including degenerative or hyperplastic lesions, the increased adrenal weights in the P_1 and F_1 adult females were interpreted as non-adverse and a possible transient, stress-related, or adaptive effect on the adrenal glands. There were no treatment-related effects observed on sperm parameters in P_1 or F_1 males at any concentration tested. There was a statistically significant reduction in the number of sperm per gram testis observed in F_1 males at 17000/10000 ppm; however, this effect was not considered treatment related, since the values were within the testing facility's historical control range and there were no corresponding effects on fertility indices in F_1 males, nor were there any effects on histopathology for any reproductive organs examined in this study. Furthermore, no changes in sperm parameters were observed in the one-generation reproduction study F_1 males which tested to an even higher level (20000 ppm). There were no effects on oestrous cyclicity at any dietary level tested for both P_1 and F_1 females. While there was a statistically significant increase in post implantation loss at 17000/10000 ppm in P_1 females that was outside the laboratory historical control range, there was no similar finding in the subsequent F1 adult females at any dose level, nor were there any effects noted for this endpoint in the one-generation reproductive toxicity study in rats which tested at a higher dietary concentration (20000 ppm). Thus, although this increase was statistically significant and outside of the historical control range, the fact that it did not occur in a dose-dependent manner, did not repeat in the subsequent generation and was not observed at a higher dose level in a separate study, all support that this was a spurious finding. There were no test substance related clinical observations in either F_1 or F_2 offspring at any dietary level. There were no treatment-related mean pup weight effects noted at any level tested for P_1 litters. Mean pup weights at 17000/10000 ppm (dietary intakes of 1417 mg/kg bw/day for dams during lactation) for F_1 litters were 7 to 8% lower than controls (not statistically significant) from lactation Days 4 through 14; pup weights were 8% lower than controls (statistically significant) on PND 21. F_1 males in the 6000/3500 and 17000/10000 ppm groups had a slight increase in the number of days required to achieve preputial separation compared to controls (mean of 43.5 and 43.9 days for 6000/3500 and 17000/10000 ppm males, respectively, compared to 41.5 days in controls). Likewise, there was a statistically significant increase in the number of days to achieve preputial separation for the 6000/3500 and 17000/10000 ppm F_2 males when compared to controls (means of 45.4 and 46.2 days at 6000/3500 and 17000/10000 ppm, respectively, compared to 43.8 days for controls). It is interesting to observe that the mean day of achievement for the F_1 males at the top dose is essentially the same value as the controls for the F_2 males (day 43.9 versus 43.8), which lend support to the fact that these changes are relatively minimal. The magnitude of the delay in preputial separation at 17000/10000 ppm for F_2 males may have been impacted, in part, by the reduction in mean body weights during lactation, as was observed in the first reproduction study. There were no effects on anogenital distance in either sex or on vaginal opening in females at any dose. Adverse test substance-related effects consisted of reduced mean pup weights for F_1 litters at 17000/10000 ppm during lactation and developmental delays

in F_1 and F_2 adult males at 6000/3500 and 17000/10000 ppm. There were no systemic adverse test substance-related effects observed at any dietary level tested in this study. Thus, the NOAEL for offspring was 1500/900 ppm due to delays in preputial separation at 6000/3500 and 17000/10000 ppm in F_1 and F_2 adult males, and the reduced F_1 offspring weight at 17000/10000 ppm. The NOAEL for reproductive performance and systemic toxicity was 17000/10000 ppm, the highest concentration tested.

Developmental toxicity studies were conducted with oxathiapiprolin in rats and rabbits. Oxathiapiprolin was not teratogenic and was not uniquely toxic to the rat or rabbit conceptus. In the developmental toxicity study in rats, the NOAEL for both maternal and foetal effects was 1000 mg/kg body weight based on a lack of any adverse effects at any dose level. In the developmental study conducted in rabbits, both the maternal and foetal NOAEL was 1000 mg/kg body weight based on a lack of any adverse effects at any dose level.

Investigational studies were conducted in male (intact male assay) and female (uterotropic assay) rats that showed no adverse effects on hormones or male and female sex organs. The slight delay in maturation observed in male rats in the reproduction studies may be exacerbated by weight effects; however, the data suggest that other factors are involved. Investigational studies did not reveal any adverse effects on androgens by oxathiapiprolin in rats. In addition to these *in vivo* studies, an *in vitro* study in the human H295R cell line tested the ability of oxathiapiprolin to affect steroidogenesis by investigating the levels of oestradiol and testosterone after treatment. Oxathiapiprolin did not cause any biologically relevant changes in testosterone or oestradiol levels in this study.

4.11.5 Comparison with criteria

The available studies are adequate for the assessment of the classification of oxathiapiprolin for reproductive toxicity. In guideline complaint studies there is no data to support the classification of oxathiapiprolin for adverse effects on sexual function or fertility. Nor was there evidence to support classification of oxathiapiprolin for toxicity on development. While delays in maturation (delays in preputial separation) were observed in rats, these changes can be considered small differences in postnatal developmental assessment which by themselves do not merit classification.

While decreases in pup body weights occurred during lactation in both reproduction studies, oxathiapiprolin does not meet the requirement to be classified as a substance causing effects on or *via* lactation according to the criteria of Regulation No. 1272/2008 (the CLP), given that in both studies, this finding occurred at doses well in excess of the guideline maximum recommended dose (i.e. at 3089 mg/kg bw/day in the one-generation study and 1417 mg/kg bw/day in the multigeneration study).

4.11.6 Conclusions on classification and labelling

Classification for reproductive toxicity is not proposed.

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

<u>Conclusion of RAC on developmental toxicity</u>

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*

Conclusion of RAC on lactation

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.

Supplemental information - In depth analyses by RAC

The effects of oxathiapiprolin on hormonal activity was investigated in various studies, showing equivocal or negative results.

In vitro, the ability of oxathiapiprolin to affect the steroidogenic pathway was assessed using H295R human adrenocortical carcinoma cells without metabolic activation (DuPont-37042, 2013). The exposure concentrations were chosen based on solubility and cytotoxicity results and were the following : $7{,}9.10^{-6}$; $2{,}5.10^{-6}$; $7{,}9.10^{-7}$; $2{,}5.10^{-7}$; $7{,}9.10^{-8}$; $2{,}5.10^{-8}$ and $7{,}9.10^{-9}$ M during approximately 48 hours exposure in two independent runs. No statistically significant increases or decreases in testosterone or estradiol were observed after oxathiapiprolin in the conditions of the study.

A 5-day uterotrophic assay was also performed to detect the ability of oxathiapiprolin to induce estrogen-like effects in ovariectomised adult female Crl:CD(SD) rats (DuPont-28579 Rev.1, 2011). Doses of 0, 500 or 1000 mg/kg bw/day were administered by oral gavage for 4 consecutive days. No mortality or clinical signs were observed at any dose. No effects were reported on vaginal cytology, liver or uterus weight. Under the conditions of this study, oxathiapiprolin did not induce estrogenic effects in ovariectomised rats.

Finally, the endocrine activity of oxathiapiprolin was investigated in a 15-Day Intact Male Assay (DuPont-27827 Rev. 1, 2012). Crl:CD(SD) rats were administered 500, 1000 mg/kg bw or the concurrent control by oral gavage for 15 consecutive days and then sacrificed 2-3 hours after the last administered dose. Serum FSH concentration were statistically significantly decreased at 1000 mg/kg bw/day (72% of control), accompanied by a non-statistically significantly decrease in serum FSH concentrations at 500 mg/kg bw/day (81% of control). A repeated dose study (15 days) investigating serum FSH concentration only was therefore performed at 0 and 1000 mg/kg bw/day in two different groups. A non-statistically significant decrease was observed in serum FSH concentration in one group (85% of control). No difference in serum FSH concentration was observed in the second group. No other alterations in hormonal concentrations or organ weights were observed in adult male rats under the conditions of this study.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Table 26: Summary table of relevant neurotoxicity toxicity studies

Method/type of test/ test species	Test substance/purity Doses/concentrations tested	NOEL/NOAEL	Reference
Acute neurotoxicity OECD Part 424 (1997), EEC Method B.43 Directive 2004/73/EC (2004) Rat (Crl:CD(SD)) GLP compliant	Lot #s: QGU42-136 96.2% purity 0, 200, 1000, and 2000 mg/kg bw by oral gavage	Both NOEL and NOAEL 2000 mg/kg bw based on absence of toxicity	DuPont-29440 Malley, L.A. (2010)

In an acute neurotoxicity study, oxathiapiprolin technical was administered to male and female Crl:CD(SD) rats (12 rats/sex/dose) by a single oral gavage dose in 0.5% methylcellulose and 0.1% Tween®. Doses were 0, 200, 1000, or 2000 mg/kg body weight for both male and female rats. The dose volume was 10 mL/kg body weight for males and females. A neurobehavioral test battery, consisting of functional observational battery (FOB) and motor activity (MA) assessments, was conducted on all study rats prior to dosing, 2 hours after dosing (Day 1), and on Days 8 and 15. Other parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, and gross pathology. On test Day 19, six rats per sex per group were perfused *in situ* with fixative. A microscopic neuropathological evaluation of the peripheral and central nervous systems and selected muscle tissues from the control and high dose rats was conducted.

The no-observed-effect level (NOEL) and no-observed-adverse-effect-level (NOAEL) for neurotoxicity were 2000 mg oxathiapiprolin/kg bw, based on the absence of toxicity observed at any dose level in males or females.

4.12.1.2 Immunotoxicity

Table 27: Summary table of relevant immunotoxicity toxicity studies

Method/type of test/ test species	Test substance/purity Doses/concentrations tested	NOAEL	Reference
28-day immunotoxicity OPPTS 870.7800 (1998) Mouse (Crl:CD1(ICR)) GLP compliant	Lot #s: QGU42-175 95.7% purity 0, 200, 800, 3500, and 7000 ppm	7000ppm (1432 mg a.s./kg bw/day) Based on lack of adverse test substance-related effects on any in-life or anatomic pathology parameter or on the humoral immune response in female mice fed up to 7000 ppm	DuPont-30252 Hoban, D. (2012)

In a 28-day feeding study, oxathiapiprolin was administered to female Crl:CD1(ICR) mice (10 animals/concentration) at concentrations of 200, 800, 3500, and 7000 ppm. The mean daily intakes for females were 0, 38, 151, 645, and 1432 mg a.s./kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, gross pathology, humoral immune function, and organ weights.

There were no adverse effects on body weight or nutritional parameters in female mice fed 0, 200, 800, 3500, and 7000 ppm oxathiapiprolin. No clinical signs of systemic toxicity were observed. No test substance-related effects were observed on 1) gross pathology; 2) absolute and relative brain, spleen, and thymus weights; or 3) humoral immune response.

The no-observed-adverse-effect level (NOAEL) for female mice was 7000 ppm (1432 mg a.s./kg bw/day). The NOAEL is based on lack of adverse test substance-related effects on any in-life or anatomic pathology parameter or on the humoral immune response in female mice fed up to 7000 ppm.

4.12.1.3 Specific investigations: other studies

4.12.1.4 Human information

No data available.

4.12.2 Summary and discussion

No adverse effects were observed in the neurotoxicity study in rats or the immunotoxicity study in mice at the dose level tested.

4.12.3 Comparison with criteria

Oxathiapiprolin showed no neurotoxic or immunotoxic effects, and thus, does not trigger any classification criteria.

4.12.4 Conclusions on classification and labelling

Not required.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 28: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Stability Hydrolysis OECD 111 (2004), OPPTS 835.2120 (2008) GLP compliant	Hydrolysis at: pH 4: Stable pH 7: Stable pH 9: Stable	[Pyrazole-5-^{14}C] oxathiapiprolin: 49 µCi/mg, radiochemical purity 99.1% [Thiazole-5-^{14}C] oxathiapiprolin: 47.1 µCi/mg, radiochemical purity 98.6%	DuPont-28424, Revision No. 1 Anand, H.S., 2010
Aqueous photolysis SETAC Europe (1995), OPPTS 835.2240 (2008), OECD 316 (2008) GLP compliant	Photolytic degradation of active substance and metabolites >10%: pH 7 buffer, DT_{50}: 15.4 days Natural light, DT_{50}: 20.2 days IN-P3X26: 14.03% AR (15 d) Quantum yield of direct phototransformation in water at $\sum$ >290 nm: 3.179×10^{-6} molecules degraded/photon	[Pyrazole-5-^{14}C] oxathiapiprolin: 49.0 µCi/mg, radiochemical purity 99.1% [Thiazole-5-^{14}C] oxathiapiprolin: 47.1 µCi/mg, radiochemical purity 98.6% [Isoxazoline-5-^{14}C] oxathiapiprolin: 45.8 µCi/mg, radiochemical purity 98.7%	DuPont-28074 Wardrope, L., 2011
Soil photolysis OPPTS 835.2410, SETAC Europe (1995), Draft OECD Soil Photolysis January (2002) GLP compliant	Oxathiapiprolin transformed into several minor metabolites over the course of the 15 day study. The majority of the degradation products were at levels at or below 5% AR. Relevant metabolites and % of applied: IN-E8S72 – 6.42% at 15 d (n = 1) IN-RAB06 – 5.18% at 15 d (n = 1) IN-RDT31 – 5.71% at 10 d (n = 1)	[Pyrazole-5-^{14}C] oxathiapiprolin: 49 µCi/mg, radiochemical purity 99.1% [Isoxazoline-5-^{14}C] oxathiapiprolin: 45.8 µCi/mg, radiochemical purity 98.7%	DuPont-28075, Revision No. 1 Cleland, H., 2013
Biodegradation Ready biodegradability EEC C.4, OECD 301B GLP compliant	Not readily biodegradable.	Lot #: QGU42-174 95.8% purity	DuPont-34408 Piriyadarsini, J.R., 2013

Method	Results	Remarks	Reference
Aerobic water sediment OECD 308 (2002), SETAC Pesticides (1995), U.S. EPA 162-4 (1982) GLP compliant	Oxathiapiprolin degraded in aerobic water/sediment systems with DT_{50} values of 18.6–44.9 days and DT_{90} values of 149.2–267.9 days in the total system. In the water phase DT_{50} values were5.5–13.6 days and DT_{90} values were 38.3-45.1 days.	[Pyrazole-5-^{14}C] oxathiapiprolin: 49 µCi/mg, radiochemical purity 99.1% [Thiazole-5-^{14}C] oxathiapiprolin: 47.1 µCi/mg, radiochemical purity 98.6%	DuPont-28073 Cleland, H., 2012 DuPont-31671 Khanijo, I. *et.al.* 2013
Aerobic mineralisation OECD 309 (2004) GLP compliant	Oxathiapiprolin did not mineralise significantly during the 60-day study. The results of the study showed that oxathiapiprolin 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 labels, respectively.	[Pyrazole-5-^{14}C] oxathiapiprolin: 32.58 µCi/mg, radiochemical purity 95.85% [Isoxazoline-5-^{14}C] oxathiapiprolin: 45.8 µCi/mg, radiochemical purity 97.37%	DuPont-32709 Wardrope, L., 2012
Aerobic soil degradation rate- laboratory study SETAC Europe (1995), OECD 307 (2002), OPPTS 835.4100 (2008) GLP compliant	DT_{50} values range from 18.2–134.4 days DT_{90} values range from 197.2–1224 days DT_{50} in soil standardised to 20°C pF2 / 10kPa = 59.4–217.3 days, Geometric mean = 121.2 days	[Pyrazole-5-^{14}C] oxathiapiprolin: 49 µCi/mg, radiochemical purity 99.1% [Thiazole-5-^{14}C] oxathiapiprolin: 47.1 µCi/mg, radiochemical purity 98.6%	DuPont-28072 Manjunatha, S., 2011 DuPont-28071, Revision No. 1 Cleland, H., 2013 DuPont-29443, Revision No. 1 McCorquodale, G., 2013 DuPont-31761 Khanijo, I. *et.al.* 2013

Method	Results	Remarks	Reference
Aerobic soil metabolism U.S. EPA 162-1, OPPTS 835.4100, SETAC Europe (1995), OECD 307 (2002) GLP compliant	Mineralisation after 100 days: <LOQ-11.81% after 120 d, [^{14}C-thiazole]–label (n = 5) <LOQ-6.58% after 120 d, [^{14}C-pyrazole]–label (n = 6) 3.95% after 120 d, [^{14}C-isoxazoline]-label (n = 1) Non-extractable residues after 100 days: 6.7-38.2% after 120 d, [^{14}C-thiazole]–label (n = 5) 9.88-34.2% after 120 d, [^{14}C-pyrazole]–label (n = 6) 8.24% after 120 d, [^{14}C-isoxazoline]--label (n = 1) Relevant metabolites: 20°C (n = 6) [^{14}C-thiazole], [^{14}C-pyrazole] & [^{14}C-isoxazoline] IN-RAB06 – 4.4-13.5% at 7-120 d (maximum 13.5% at 90 d) IN-RDT31 – 5.1-9.4% at 7-120 d (maximum 9.4% at 120 d) 20°C (n = 6) [^{14}C-pyrazole] IN-E8S72 – nd-6.72% at 30-120 d (maximum 6.72% at 120 d) 20°C (n = 6) [^{14}C-thiazole], and [^{14}C-isoxazoline] IN-QPS10 – nd-8.7% at 7-120 d (maximum 8.7% at 60 d)	[Pyrazole-5-^{14}C] oxathiapiprolin: 49 µCi/mg, radiochemical purity 99.1% [Thiazole-5-^{14}C] oxathiapiprolin: 47.1 µCi/mg, radiochemical purity 98.6% [Isoxazoline-5-^{14}C] oxathiapiprolin: 45.8 µCi/mg, radiochemical purity 98.7%	DuPont-28072 Manjunatha, S., 2011 DuPont-28071, Revision No. 1 Cleland, H., 2013 DuPont-29443, Revision No. 1 McCorquodale, G., 2013
Anaerobic soil metabolism U.S. EPA 162-2, OPPTS 835.4200, OECD 307 (2002), SETAC Europe (1995) GLP compliant	Mineralisation after 100 days: 1.5% after 120 d, [^{14}C-pyrazole] (n = 1) 2.97% after 120 d, [^{14}C-isoxazoline] (n = 1) Non-extractable residues after 100 days: 5.89% after 120 d, [^{14}C-pyrazole] (n = 1) 7.65% after 120 d, [^{14}C-isoxazoline] (n = 1) Relevant metabolites: IN-E8S72 – 4.91% at 120 d (n = 1)	[Pyrazole-5-^{14}C] oxathiapiprolin: 32.58 µCi/mg, radiochemical purity 95.85% [Isoxazoline-5-^{14}C] oxathiapiprolin: 45.8 µCi/mg, radiochemical purity 97.37%	DuPont-31137 Anderson, C., Wardrope, L., 2012

Method	Results	Remarks	Reference
Soil degradation study – field EU 1607/VI/97 rev. 1 (1997), EU 7029/VI/95 rev. 5 (1997), SETAC Europe (1995), SANCO/3029/99 rev. 4 (2000), U.S. EPA 164-1 (1982), North American Free Trade Agreement Guidance Document for Conducting Terrestrial Field Studies (1996) OPPTS 835.6100 (2008) GLP compliant	4 field soil degradation studies were conducted in Europe. Measured DT_{50} values range from 5.5. – 101 days Measured DT_{90} values range from 178.5 – 556.7 days Normalised DT_{50} values range from 72.3 – 93.7 days	Oxathiapiprolin 100 g/L OD	DuPont-27404 Doig, A., Just, G., 2012 DuPont-27214 Doig, A., Just, G., 2012 DuPont-29820 Doig, A., Just, G., McConnell, K., 2012 DuPont-29819 Doig, A., Just, G., McConnell, K., 2012 DuPont-31761 Khanijo, I. *et.al.* 2013
Soil degradation study – field OPPTS 835.6100 (2008) GLP compliant	4 field soil dissipation studies were conducted in the USA and 2 in Canada. Measured DT_{50} values range from 3.9. – 205.3 days Measured DT_{90} values range from 75.8 – 682 days Normalised DT_{50} values range from 48.8 – 180 days	Oxathiapiprolin 100 g/L OD	DuPont-29813 Rice, F., 2012 DuPont-29818 Rice, F., 2012 DuPont-29817 Rice, F., 2012 DuPont-29823 Rice, F., 2012 DuPont-29814 Vincent, T.P., 2012 DuPont-29816 Vincent, T.P., 2013 DuPont-31761 Khanijo, I. *et.al.* 2013

nd Not detected

5.1.1 Stability

Aquatic hydrolysis

The hydrolysis of oxathiapiprolin in sterile buffer solutions was slow. In pH 4, 7 and 9 buffer solutions, <10% degradation occurred at 50°C indicating that the DT_{50} in sterile buffers was >1 year. It was concluded that oxathiapiprolin is hydrolytically stable in the whole range of environmental conditions.

Dissociation constant

No dissociation at pH 1.0 to 9.1.

Aqueous photolysis

Oxathiapiprolin has the potential to photolyse in irradiated sterile pH 7 buffer solutions and in natural water.

The photolysis half-life of oxathiapiprolin in sterile pH 7 buffer was 15.4 days under continuous irradiation. The quantum yield for oxathiapiprolin was calculated as 3.179×10^{-6} molecules degraded/photon.

In sterile natural water the photolytic half-life was 20.2 days under continuous irradiation.

Soil photolysis

Only two metabolites were formed in soil treated with either [pyrazole-5-^{14}C]oxathiapiprolin or [isoxazoline-5-^{14}C]oxathiapiprolin and irradiated for 15 days at >5% AR. IN-RDT31 and IN-RAB06 both formed at >5% AR but <10% AR. Both are known aerobic soil metabolites. Numerous minor metabolites were observed, though none exceeded 10% AR at any sample interval or 5% AR at any two consecutive sample intervals or increasing and >5% at the end of the study.

Oxathiapiprolin data showed a DT_{50} value of 28.2 days and a DT_{90} value of 93.5 days in moist irradiated soils. Oxathiapiprolin data showed a DT_{50} value of 36.3 days and a DT_{90} value of 120.7 days in dry irradiated soils.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

An estimation of biodegradation is not required as studies are available.

5.1.2.2 Screening tests

Ready biodegradability

The test substance, oxathiapiprolin, was added to duplicate glass bioreactors, containing aqueous nutrient medium inoculated with activated sewage sludge (30 mg solids/L). The bioreactors were incubated for 28 days at a nominal temperature range of 18–22°C. The amount of carbon dioxide (CO_2), produced per bioreactor was determined at intervals to assess the percent biodegradation. Inoculated nutrient medium was used as a negative control to assess background CO_2 and sodium benzoate was used as a positive control.

Oxathiapiprolin exhibited only minimal degradation at a loading rate of 10 mg/L. It did not attain the criteria for ready biodegradation of greater than 60% biodegradation within 10 days of reaching 10% biodegradation. Therefore, the test substance cannot be classified as “ready biodegradable”. However results of the aerobic soil metabolism and water sediment studies clearly show degradation of the test material in the environment. Results of the experiment which contained both oxathiapiprolin and sodium benzoate indicate that at these concentrations oxathiapiprolin may have an inhibitory effect on the microorganisms.

5.1.2.3 Simulation tests

Water/sediment systems

The degradation of oxathiapiprolin in two aerobic aquatic systems obtained from natural sources involved multiple processes. Over 15 extractable metabolites were observed in either the water phase or the sediment extracts. Oxathiapiprolin degraded to five major degradation products: the two isomeric forms of IN-RYJ52, IN-RSE01, IN-S2K66, and IN-Q7D41, as defined by greater than 10% AR at any sampling interval, greater than 5% AR at two consecutive sampling intervals or increasing and greater than 5% AR at the end of the study. IN-RAB06 was also observed as a minor metabolite. The major route of degradation involved opening of the isoxazoline ring to form IN-RSE01. Reduction of IN-RSE01 resulted in the formation of the two isomers of IN-RYJ52 which underwent further degradation to form IN-S2K66.

Degradation values were recalculated using a revised kinetic analysis. 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.

Aerobic aquatic mineralisation

Oxathiapiprolin did not mineralise significantly during the 60-day study. The results of the study showed that oxathiapiprolin 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 showed one identified degradation product, IN-S2K66, reaching maximums of 6.95 and 3.24% AR in the pyrazole and isoxazoline labels, respectively. The reference item was readily mineralised confirming the validity of the system.

Aerobic soil degradation rate

The rate of aerobic degradation of oxathiapiprolin in the laboratory was measured in five different soils. Under laboratory conditions, the DT_{50} values ranged from 18.2 to 134.4 days at 20°C. No correlation was observed between the rate of degradation of oxathiapiprolin and soil pH. In addition, laboratory studies show that the degradation of oxathiapiprolin in soil results in the formation of several metabolites, including CO_2 and non-extractable residue.

Soil metabolism

The route of degradation of oxathiapiprolin involves multiple primarily biotic processes which included mineralisation to CO_2. The route of degradation does not show a pH dependence.

The route of degradation of oxathiapiprolin was studied in a loamy sand at pH 5.3, using test substance radiolabelled in either the pyridine, thiazole or isoxazoline ring.

Degradation of oxathiapiprolin in dark aerobic soil proceeded along multiple pathways which included the following.

- Cleavage of the pyrazole ring to form IN-QPS10 and IN-E8S72.

- The formation of $^{14}CO_2$ from the thiazole label demonstrated cleavage of the thiazole ring generating CO2 and multiple minor metabolites which would have included IN-RLD51 which was never observed above 5% AR. IN-RLD51 undergoes rapid oxidation to form IN-WR791 which was also never observed above 5% AR. IN-WR791 undergoes hydroxylation and multiple oxidations to form IN-E8S72.

- Hydroxylation of the methyl group on the pyrazole ring followed by oxidation results in the formation of IN-RAB06. The studies conducted using IN-RAB06 as parent using test material radiolabeled in the 5-position of the thiazole and pyrazole rings showed almost no formation of IN-QPS10 and IN-E8S72. However significant amounts of $^{14}CO_2$ were generated from both radiolabeled forms of IN-RAB06.

- Hydroxalation at the 4-position of the piperidine ring results in the formation of IN-RDT31. IN-RDT31 undergoes cleavage of the piperidine to form IN-WR791 which then degrades to IN-E8S72.

Degradation of oxathiapiprolin in dark anaerobic soil preceded along the same multiple pathways as the aerobic soil although at a much slower rate. No principle metabolites were formed in soil treated with either [pyrazole-5-^{14}C] oxathiapiprolin or [isoxazoline-5-^{14}C] oxathiapiprolin. Numerous minor metabolites were observed, though none exceeded 10% AR at any sample interval or 5% AR at any two

consecutive sample intervals. Metabolites identified were IN-QPS10, IN-E8S72, IN-RDT31, and IN-RAB06.

Oxathiapiprolin degrades slowly under anaerobic conditions in the sandy loam soil tested with DT_{50} and DT_{90} values of 1505 and 4998 days, respectively.

Degradation of oxathiapiprolin by photolysis in soil proceeded along the multiple minor pathways. It is believed that photolysis does not contribute significantly to the degradation of oxathiapiprolin under field conditions as demonstrated in the Florida, USA field study which was conduct in two adjacent plots (one covered with soil and one uncovered) which showed similar rates of degradation.

Based on the information generated from aerobic soil metabolism, soil photolysis and rate of degradation in soil, the major degradation products of oxathiapiprolin greater than 10% of applied at any sampling interval or >5% of applied at two consecutive sampling intervals or increasing and >5% at the end or the study were IN-RDT31, IN-RAB06, IN-QPS10 and IN-E8S72. No other degradation products exceeded 10% of applied radiolabel at any sampling interval, exceeded 5% of applied radiolabel at two consecutive sampling intervals or were increasing and exceeded 5% at the end of the study. Ultimately oxathiapiprolin and its degradation products degrade to CO_2 and bound residues.

Field soil dissipation

The dissipation behaviour of oxathiapiprolin was investigated at four field sites in the EU using Oxathiapiprolin 100 g/L OD formulation. In all studies application was made to bare ground in the summer (June) at a nominal rate of 200 g a.s./ha. Soil cores were collected to a depth of 90 cm up to *ca*. 18–21 months following application.

The following conclusions can be drawn based on the data collected in each study:

Lentzke, Germany

- There were no abnormal circumstances with respect to test site management, climate conditions, or analysis which would compromise the conclusions drawn or the data collected.

- Averaged residue of oxathiapiprolin in 0–5 cm soil on Day 0 of 166.0 g peq/ha in the three replicate soil cores, represented 83% of the nominal applied amount and verified the application rate.

- Oxathiapiprolin declined rapidly to approximately half of the amount applied, 86.1 g peq/ha by Day 29 and to about 5% of applied (10.7 g peq/ha) by the end of the study (Day 427).

- Three of the metabolites monitored were detected at some sampling intervals during this study. IN-RDT31, IN-RAB06, and IN-E8S72 were detected. IN-QPS10 was not detected.

- Oxathiapiprolin and its degradation products IN-RDT31 and IN-RAB06 remained primarily in the upper 5 cm of soil.

- IN-E8S72 remained in the upper 30 cm of soil. There were no detections below 30 cm for any individual component at any sampling interval.

- The revised kinetic analysis of the data resulted in calculated best fit DT_{50} and DT_{90} for oxathiapiprolin using the DFOP model of 23.9 and 556.7 days respectively.

- A Limit of Quantification (LOQ) of 1.0 ppb for all analytes was sufficiently low to account for ≥0.4% of the applied amount in the sampled soil segments.

Lyon, France

- There were no abnormal circumstances with respect to test site management and analysis which would compromise the conclusions drawn or data collected.
- Averaged residue of oxathiapiprolin in 0–5 cm soil on Day 0 of 215.3 g peq/ha in the three replicate soil cores, represented 107.6% of the nominal applied amount and verified the application rate.
- Oxathiapiprolin declined rapidly to approximately 50% of the amount applied, 117.0 g peq/ha by Day 5 and to about 3% of applied (6.5 g peq/ha) by the end of the study (Day 443).
- All metabolites monitored were detected at some sampling intervals during this study.
- IN-RDT31 was found almost immediately after the application. IN-RDT31 reached an average peak level of 11.8 g peq/ha by Day 5 and declined to an average level of 1.9 g peq/ha by the end of the study (Day 443).
- IN-E8S72 reached an average peak level of approximately 15.6 g peq/ha on Day 205 and then declined to 1.6 g peq/ha at Day 443.
- Oxathiapiprolin and its degradation products IN-RAB06, IN-RDT31, and IN-QPS10 remained primarily in the upper 15 cm of soil. IN-E8S72 remained in the upper 30 cm of soil. There were no detections below 30 cm for any individual component at any sampling interval.
- The revised kinetic analysis of the data resulted in calculated best fit DT_{50} and DT_{90} for oxathiapiprolin using the DFOP model of 5.5 and 178.5 days, respectively.
- A Limit of Quantification (LOQ) of 1.0 ppb for all analytes was sufficiently low to account for ≥0.3% of the applied amount in the sampled soil segments.

Sevilla, Spain

- There were no abnormal circumstances with respect to test site management and analysis which would compromise the conclusions drawn or data collected.
- Averaged residue of oxathiapiprolin on Day 0 of 178.0 g peq/ha in the three replicate soil cores, represented 89.0% of the nominal applied amount and verified the application rate.
- Oxathiapiprolin declined rapidly to less than half of the amount applied, 80.0 g peq/ha by Day 8 in the 0–5cm soil segment and to about 5% of applied (10.9 g peq/ha) in all soil segments by the last analysed sampling interval (Day 253).
- Three of the metabolites monitored were detected at some sampling intervals during this study. IN-RDT31, IN-RAB06, and IN-E8S72 were all detected, whereas IN-QPS10 was not detected.
- IN-RDT31 was found almost immediately after the application. IN-RDT31 reached an average peak level of 14.6 g peq/ha by Day 50 and declined to an average level of 5.1 g peq/ha by the last analysed sampling interval (Day 253).
- IN-RAB06 was found at average levels of 0.5 g peq/ha or less at only three sampling intervals.
- IN-E8S72 reached an average peak level of 11.8 g peq/ha, Day 15 and declined to an average level of 2.8 g peq/ha by the last analysed sampling interval (Day 253).

- The revised kinetic analysis of the data resulted in calculated best fit DT_{50} and DT_{90} for oxathiapiprolin using the DFOP model of 8.1 and 211.5 days, respectively.

- Almost all oxathiapiprolin and its degradation products remained in the upper 15 cm of soil. Detections below 15 cm for any individual component at any sampling interval were infrequent.

- A Limit of Quantification (LOQ) of 1.0 ppb for all analytes was sufficiently low to account for ≥0.3% of the applied amount in the sampled soil segments.

Cambridgeshire, UK

- There were no abnormal circumstances with respect to test site management and analysis which would compromise the conclusions drawn or data collected.

- Averaged residue of oxathiapiprolin on Day 0 of 217.1 g peq/ha in the three replicate soil cores, represented 108.5% of the nominal applied amount and verified the application rate.

- Oxathiapiprolin declined to approximately half of the amount applied, 109.7 g peq/ha by Day 102 and to approximately 10% of applied (21.2 g peq/ha) in all soil segments by the end of the study (Day 538), excluding three samples which were considered outliers.[8]

- All of the metabolites monitored were detected at some sampling intervals during this study.

- IN-RDT31 reached an average peak level of 5.2 g peq/ha by Day 102 and declined to an average level of 1.9 g peq/ha by the last analysed sampling interval (Day 538), excluding three samples which were considered outliers.[8]

- IN-E8S72 reached an average peak level of 12.5 g peq/ha by Day 153 and declined to an average level of 6.0 g peq/ha by the last analysed sampling interval (Day 538), excluding three samples which were considered outliers.[8]

- IN-RAB06 and IN-QPS10 were only observed at very low average peak levels of 2.7 g peq/ha and below at any sampling interval, excluding three samples which were considered outliers.

- Oxathiapiprolin and its degradation products remained in the upper 30 cm of soil, excluding the outlier sample from Day 278, plot II, 30–50 cm segment.

- The revised kinetic analysis of the data resulted in calculated best fit DT_{50} and DT_{90} for oxathiapiprolin using the DFOP model of 101.0 and 524.5 days, respectively.

- A Limit of Quantification (LOQ) of 1.0 ppb for all analytes was sufficiently low to account for ≥0.2% of the applied amount in the sampled soil segments.

In addition, a further four field dissipation studies were conducted in the U.S and two in Canada. The rate of degradation observed across all studies was similar.

5.1.3 Summary and discussion of degradation

The hydrolysis of oxathiapiprolin in sterile buffer solutions was slow. In pH 4, 7 and 9 buffer solutions, <10% degradation occurred at 50°C indicating that the DT_{50} in sterile buffers was >1year. However degradation was observed in irradiated sterile pH 7 buffer solutions and in natural water at 25°C under simulated sunlight (xenon arc light, continuous irradiation). The photolysis half-life of oxathiapiprolin

[8] Day 193, plot III ,0-5 cm segment; Day 278 ,plot II, 30-50 cm segment; and Day 307, plot II, 15-30 cm segment

in sterile pH 7 buffer was 15.4 days under continuous irradiation. The quantum yield for oxathiapiprolin was calculated as 3.179×10^{-6} molecules degraded/photon. In natural water /sediment systems oxathiapiprolin partitioned from the water into the sediment phase where it underwent further degradation. The DT_{50} and DT_{90} values for oxathiapiprolin in the water phase of the aerobic sediment systems ranged from 5.5 to 13.6 days and 38.3 to 45.1 days in the two water/sediment systems. The DT_{50} and DT_{90} values for oxathiapiprolin in the extracts ranged from 112.7 to 249.2 days and 374.3 to 827.9 days in the two water/sediment systems. For the total system, the DT_{50} and DT_{90} values for oxathiapiprolin ranged from 18.6 to 44.9 days and 267.9 to 149.2 days, respectively in the two water/sediment systems. Based on the results of these studies, oxathiapiprolin and its metabolites would dissipate from water sediment systems in the environment.

Oxathiapiprolin degraded in aerobic soil with laboratory DT_{50} values ranging from 18.2 to 134.4 days at 20°C. No correlation was observed between the rate of degradation of oxathiapiprolin and soil pH. In addition, laboratory studies show that the degradation of oxathiapiprolin in soil results in the formation of several metabolites, including CO_2 and non-extractable residue.

Degradation under field conditions in Europe was slightly faster with DT_{50} values ranging from 5.5 to 101 days (measured) which equates to 72.3–93.7 days (normalised).

Oxathiapiprolin did not meet the criteria to be classified as "ready biodegradable" in the 28-day ready biodegradation study; however it does degrade in the environment under natural condition although the rate of degradation does not meet the CLP criteria to be considered as rapidly degradable.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

The adsorption/desorption characteristics of oxathiapiprolin was studied in six soils (pH range of 5.0 to 7.7, organic carbon range of 0.8 to 2.9%) from the U.S. and European countries in a batch equilibrium experiment. The adsorption phase of the study was carried out by equilibrating air-dried soil with solutions of [thiazole-5-^{14}C] or [isoxazoline-5-^{14}C] oxathiapiprolin at 0.00065, 0.005, 0.01, 0.03, and 0.065 µg/mL in dark at 20°C for 24 hours. Two desorption cycles were performed on samples treated at the highest test concentration.

A 1:20 (w/v) soil-to-solution ratio was used in the definitive testing. The sorption coefficients K_d, K_{om}, and K_{oc} were calculated for each soil at each concentration of the test item. A summary of the average sorption coefficients for each soil is given in the table below:

Soil	**OC (%)**	**pH [0.01 M $CaCl_2$ (1:2)]**	**K_d (mL/g)**	**K_{om} (mL/g)**	**K_{oc} (mL/g)**
Drummer	2.9	6.0	518	10354	17852
Gross-Umstadt	1.2	7.1	61.5	3074	5123
Nambsheim	1.4	7.5	86.0	3583	6142
Lleida	1.8	7.7	113	3631	6254
Sassafras #16	1.2	5.0	97.8	4892	8153
Porterville	0.8	7.4	116	8935	11038
Average			**165**	**5745**	**9094**

The values for the Freundlich adsorption isotherm parameter K_F, K_{Fom}, K_{Foc}, and 1/n were derived from the linear form of the Freundlich equation for all soils. A summary of the adsorption isotherm parameters for each soil is given in the table below:

Soil	K_F	K_{Fom}	K_{Foc}	1/n	r^2
Drummer	1322	26440	45586	1.1207	0.9948
Gross-Umstadt	52.2	2610	4350	0.9741	0.9941
Nambsheim	102	4250	7286	1.0294	0.9865
Lleida	100	3226	5556	0.9833	0.9938
Sassafras # 16	87.4	4370	7283	0.9851	0.9838
Porterville	53.9	4146	6738	0.8877	0.9914
Average	**286**	**7507**	**12800**	**0.9967**	**0.9907**

The desorption coefficients, K_{d1}, K_{d2}, $K_{d1,om}$, $K_{d1,oc}$, $K_{d2,om}$ and $K_{d2,oc}$ were calculated for each soil at the highest test concentration. A summary of the average desorption coefficients for each soil is given in the table below:

Soil	K_{d1} (mL/g)	$K_{d1,om}$ (mL/g)	$K_{d1,oc}$ (mL/g)	K_{d2} (mL/g)	$K_{d2,om}$ (mL/g)	$K_{d2,oc}$ (mL/g)
Drummer	718	14350	24741	858	17160	29587
Gross-Umstadt	68.6	3428	5713	115	5725	9542
Nambsheim	91.8	3823	6554	147	6105	10464
Lleida	114	3661	6306	179	5775	9945
Sassafras # 16	96.8	4838	8063	151	7550	12584
Porterville	142	10924	17750	120	9321	15000
Average	**205**	**6837**	**11521**	**262**	**8606**	**14520**

The percent [^{14}C]oxathiapiprolin desorbed from the soils during two desorption intervals (D_1 and D_2) was calculated and totalled (D_T) for all soils at the highest test solution concentration. The D_T values ranged from 4.8% in the Drummer soil to 32.8% in the Gross-Umstadt soil. In general, lower desorption values were observed in second desorption interval for all soils. In both desorption intervals, highest desorption was observed in Gross-Umstadt soil and the lowest desorption was observed in Drummer soil. A summary of the average percent desorption for each soil is given in the table below:

Soil	D_1 (%)	D_2 (%)	D_T (%)
Drummer	2.7	2.2	4.8
Gross-Umstadt	21.7	11.1	32.8
Nambsheim	17.6	9.4	27.0
Lleida	14.2	8.0	22.2
Sassafras # 16	16.1	9.1	25.1
Porterville	11.1	12.0	23.1

The mass balance was determined by summing the amount of test item recovered in the adsorption solution, the two desorption solutions and the combusted soil and ranged from 92.6 to 105.5%.

The adsorption constants for oxathiapiprolin appeared to correlate with the organic carbon content of the soils tested. The adsorption constants did not appear to correlate with pH. K_{Foc} values ranged from 4350 to 45586 mL/g with an average of 12800 mL/g with 1/n values ranging from 0.8877 to 1.1207 with an average of 0.9967.

The percent of oxathiapiprolin desorbed from the soil during two desorption intervals (D_1 and D_2) was calculated and totalled (D_T) for all soils at the highest test solution concentration. Total desorption levels ranged from 4.8% in Drummer soil to 32.8% in Gross-Umstadt soil.

5.2.2 Volatilisation

Neither oxathiapiprolin nor any of its principal degradation products have significant volatility. The vapour pressure of oxathiapiprolin was 1.141×10^{-6} Pa. There is no guidance currently available for conducting meaningful studies regarding the potential breakdown of oxathiapiprolin or its degradation products in air.

Further, the Henry's law constant of oxathiapiprolin is 3.521×10^{-3} Pa m^3/mol, suggesting little potential for volatilisation in the environment. Henry's law constants below 3.04×10^{-2} Pa m^3/mol show that the compound is less volatile than water and can be considered essentially non-volatile.

5.2.3 Distribution modelling

Not relevant to classification

5.3 Aquatic bioaccumulation

Table 29: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
Trout hepatocyte screen No Guideline Non-GLP	The modelled BCF (with k_{Met}) was calculated to be 501 L/kg (wet weight).	Lot #: QGU42-126, 98.9% purity	DuPont-29276, Revision No. 2 Nabb, D.L., 2013
Fish bioaccumulation OECD 305 (1996), OPPTS 850.1730 (1996) Bluegill GLP compliant	Steady State Bioconcentration factor (BCF) = (mean tissue concentration / mean water concentration); Edible (11), non-edible (98) and whole fish (62)	Lot #.: QGU42-174, 95.8% purity Radiolabeled test material: [Isoxazoline-5-^{14}C] oxathiapiprolin. Specific activity 33.88 µCi/mg, radiochemical purity 98.3%	DuPont-32483 Thomas, S.T., Kendall, T.Z., Martin, K.H., Gallagher, S.P., Krueger, H.O., 2013

5.3.1 Aquatic bioaccumulation

Oxathiapiprolin is applied in some cases more than 2 times in a season. Oxathiapiprolin has a log P_{ow} >3. Based on the log P_{ow}, and the likelihood of continuous and repeated exposure, a study on bioconcentration potential of the active substance in fish was conducted. In addition, for the active substance oxathiapiprolin, an *in vitro* bioconcentration estimate and clearance assay *via* the use of rainbow trout liver hepatocytes was also conducted. Based on the results from this *in vitro* test a modelled BCF value, considering the metabolism in liver hepatocyte cells, was estimated using the model presented by Han *et al*. (2007).[9] The results from the *in vitro* test support the ones from the BCF test and verify that the *in vitro* test can be effectively used to determine the bioaccumulation potential of the test material. For the active substance oxathiapiprolin, the whole fish BCF is 62, whereas the modelled BCF (with metabolism k_{Met} in liver hepatocyte cells) was calculated to be 501 L/kg (wet weight). Both values are <1000 indicating low potential for bioaccumulation. As a proof of concept, the BCF values in the whole fish assay are lower than the calculated BCF value in the *in vitro* test, indicating that the test material is being processed in other areas of the body than the liver alone.

[9] Han, X., Nabb, D.L., Mingoia, R.T., and Yang, C.H. (2007) Determination of Xenobiotic Intrinsic Clearance in Freshly Isolated Hepatocytes from Rainbow Trout (*Oncorhynchus mykiss*) and Rat and Its Application in Bioaccumulation Assessment. *Environ. Sci. Technol*. **41**, 3269–3276

5.3.1.1 Bioaccumulation estimation

A study was conducted to estimate the metabolic clearance rate and predict the bioconcentration factor (BCF) of oxathiapiprolin using isolated rainbow trout hepatocytes. The metabolic clearance of oxathiapiprolin in trout hepatocytes was estimated, and results extrapolated to the whole animal, using a test concentration of 2.158 ppm. Hepatocyte suspensions were exposed to oxathiapiprolin for approximately 4 hours.

Significant metabolism was observed within 4 hours of incubation. The results for the positive control reaction indicated that the cells were functioning properly at the time of the experiment. The modelled BCF (with k_{Met}) was calculated to be 501 L/kg (wet weight).

5.3.1.2 Measured bioaccumulation data

The bioconcentration potential of [isoxazoline-^{14}C]oxathiapiprolin in bluegill (*Lepomis macrochirus)* was determined in an aerated, flow-through, 70-day test. The test was conducted in accordance with the U.S. Environmental Protection Agency Series 850 – Ecological Effects Test Guidelines, OPPTS Guideline 850.1730, (Draft, 1996) and OECD Guideline for Testing of Chemicals 305. Treatments consisted of a solvent (dimethylformamide) control and two nominal oxathiapiprolin concentrations of 10 and 100 µg a.s./L. The corresponding mean, measured concentrations based on total radioactive residues were 9.2 and 94 µg a.s./L, respectively. The steady-state BCF values for the edible, non-edible and whole fish tissue in the low concentration were 10, 84 and 53, respectively. The steady-state BCF values for the edible, non-edible and whole fish tissue in the high concentration were 11, 98 and 62, respectively. The kinetic BCF (BCFK) values in the edible, non-edible, and whole fish tissues in the low concentration were 14, 126, and 80, respectively and in the high concentration were 15, 137, and 87, respectively. Lipid normalised steady-state BCF values for the low and high level whole fish tissue were 41 and 35, respectively. The lipid normalised kinetic BCF values for the low and high level whole fish tissue were 63 and 49, respectively.

5.3.2 Summary and discussion of aquatic bioaccumulation

The measured bioconcentration factor for oxathiapiprolin in fish was 62, which is less than 500, the value considered as indicative of the potential to bioconcentrate for classification purposes according to the CLP regulation.

5.4 Aquatic toxicity

Oxathiapiprolin has low water solubility, 0.184 mg/L, therefore all aquatic testing was conducted at or slightly above the water solubility limit.

Table 30: Summary of relevant information on aquatic toxicity

Method	Endpoint	Remarks	Reference
96-hour static acute toxicity test with the rainbow trout (*Oncorhynchus mykiss*) OECD 203 (1992), OPPTS 850.1075 (1996) GLP compliant	LC_{50} >0.69 mg a.s./L the highest concentration tested, based on mean, measured concentrations and mortality	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.057, 0.11, 0.23, 0.45, and 0.69 mg a.s./L	DuPont-32481, Revision No. 1 Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2012
96-hour static acute toxicity test with the bluegill sunfish (*Lepomis macrochirus*) OECD 203 (1992), OPPTS 850.1075 (1996) GLP compliant	LC_{50} >0.72 mg a.s./L the highest concentration tested, based on mean, measured concentrations and mortality	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.060, 0.12, 0.22, 0.45 and 0.72 mg a.s./L	DuPont-32818 Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2011
96-hour static acute toxicity test with the sheepshead minnow (*Cyprinodon variegatus*) OPPTS 850.1075 (1996) GLP compliant	LC_{50} >0.65 mg a.s./L the highest concentration tested, based on mean, measured concentrations and mortality	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.048, 0.068, 0.19, 0.41 and 0.65 mg a.s./L	DuPont-32819 Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2011
Early life-stage toxicity test with the sheepshead minnow (*Cyprinodon variegatus*) Unaerated flow-through, 35 days OPPTS 850.1400 GLP compliant	NOEC = 0.34 mg a.s./L LOEC = >0.34 mg a.s./L the highest concentration tested, based on mean, measured concentrations hatching success, survival and growth	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.031, 0.059, 0.12, 0.23 and 0.34 mg a.s./L	DuPont-32820 Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2012
Early life-stage toxicity test with the rainbow trout (*Oncorhynchus mykiss*) Unaerated, flow-through, 88 days OECD 210 (1992), OPPTS 850.1400 (1996) GLP compliant	NOEC = 0.46 mg a.s./L LOEC = 0.74 mg a.s./L based on mean, measured concentrations and growth	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.060, 0.12, 0.23, 0.46 and 0.74 mg a.s./L	DuPont-32482 Minderhout, T., Kendall, T.Z., Krueger, H.O., 2012
48-hour static acute toxicity test with the cladoceran (*Daphnia magna*) OECD 202 (2004), OPPTS 850.1010 (1996) GLP campliant	EC_{50} = 0.67 mg a.s./L based on mean, measured concentrations and immobility data	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.060, 0.12, 0.24, 0.44 and 0.78 mg a.s./L	DuPont-32484 Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2011
96-hour static acute toxicity test with the saltwater mysid (*Americamysis bahia*) OPPTS 850.1025 (1996) GLP compliant	EC_{50} >0.64 mg a.s./L the highest concentration tested, based on mean, measured concentrations and mortality	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.065, 0.12, 0.25, 0.41 and 0.64 mg a.s./L	DuPont-32485 Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2011

Method	Endpoint	Remarks	Reference
96-hour shell deposition test with the eastern oyster (*Crassostrea virginica*) Flow-through OPPTS 850.1025 (1996) GLP compliant	EC_{50} >0.33 mg a.s./L the highest concentration tested, based on mean, measured concentrations and shell deposition	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.028, 0.056, 0.11, 0.21 and 0.33 mg a.s./L	DuPont-32453 Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2012
Semi-static life-cycle toxicity test with the cladoceran (*Daphnia magna*) 21-day test OECD 211 (2008), OPPTS 850.1300 (1996) GLP compliant	NOEC = 0.75 mg a.s./L LOEC = >0.75 mg a.s./L the highest concentration tested, based on mean, measured concentrations, adult survival, reproduction and growth (total length and dry weight)	Lot #.: QGU42-174, 95.8% purity Mean, measured concentrations of 0.057, 0.12, 0.24, 0.45 and 0.75 mg a.s./L	DuPont-32455 Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2011
Flow-through life-cycle toxicity test with the saltwater mysid (*Americamysis bahia*) Unaerated, flow-through, 32-day OPPTS 850.1350 (1996) GLP compliant	NOEC = 0.058 mg a.s./L LOEC = 0.12 mg a.s./L based on mean, measured concentrations and reproduction	Lot #.: QGU42-174, 95.8% purity Mean, measured concentrations of 0.029, 0.058, 0.12, 0.21 and 0.30 mg a.s./L	DuPont-32456 Claude, M.B., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2012
96-hour toxicity test with the marine diatom (*Skeletonema costatum*) Static OECD 201 (2006), OCSPP 850.4500 (2012) GLP compliant	96-hour values: E_rC_{50} >351 µg a.s./L (>0.351 mg a.s./L) E_yC_{50} = 351 µg a.s./L (0.351 mg a.s./L) the highest concentration tested, based on mean, measured concentration	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 13, 42, 96, 141, and 351 µg a.s./L	DuPont-35834 Arnie, J.R., Kendall, T.Z., Porch, J.R., 2013
96-hour toxicity test with the freshwater diatom (*Navicula pelliculosa*) Static OECD 201 (2006), OCSPP 850.4500 (2012) GLP compliant	96-hour values: E_rC_{50} >163 µg a.s./L (>0.163 mg a.s./L) E_yC_{50} >163 µg a.s./L (>0.163 mg a.s./L) the highest concentration tested, based on geometric mean, measured concentrations	Lot #: QGU42-174, 95.8% purity Geometric mean, measured concentrations of 16, 23, 47, 26 and 163 µg a.s./L	DuPont-35843 Arnie, J.R., Kendall, T.Z., Porch, J.R., 2013

Method	Endpoint	Remarks	Reference
Effects on growth to the green algae *Pseudokirchneriella subcapitata* in a static test 96-hour OECD 201 (2006), EPA 712-C-96-164 (1996) GLP compliant	96-hour values: E_rC_{50} >142 µg a.s./L (>0.142 mg a.s./L) E_yC_{50} >142 µg a.s./L (>0.142 mg a.s./L) the highest concentration tested, based on mean, measured concentrations	Lot #: QGU42-126, 98.9% purity Mean, measured concentrations of 10, 20, 36, 70, and 142 µg a.s./L	DuPont-29275 Kley, A., Deierling, T., 2010
Effects on growth to the blue-green algae *Anabaena flos-aquae* in a static test 96-hour OECD 201 (2006), EPA 712-C-96-164 (1996) GLP compliant	96-hour values: E_rC_{50} >193 µg a.s./L (>0.193 mg a.s./L) E_yC_{50} >193 µg a.s./L (>0.193 mg a.s./L) the highest concentration tested, based on mean, measured concentrations	Lot #: QGU42-126, 98.9% purity Mean, measured concentrations of 6, 13, 24, 45, 96, and 193 µg a.s./L	DuPont-29320 Kley, A., Deierling, T., 2010
7-day static-renewal toxicity test with duckweed (*Lemna gibba* G3) OPPTS 850.4400 (1996) GLP compliant	EC_{50} >0.79 mg a.s./L the highest concentration tested, based on mean, measured concentrations, frond count, frond count yield, biomass, biomass yield, and growth rate based on both frond count and biomass	Lot #: QGU42-174, 95.8% purity Nominal concentrations of 0.0625, 0.125, 0.25, 0.5 and 1.0 mg a.s./L	DuPont-32480 Porch, J.R., Kendall, T.Z., Krueger, H.O., 2011
48-hour static acute toxicity test with *Chironomus riparius* OECD 235 (2011), ASTM Standard E729-96 (1996) GLP compliant	EC_{50} >0.56 mg a.s./L the highest concentration tested, based on mean, measured concentrations and immobility data	Lot #: QGU42-174, 95.8% purity Mean, measured concentrations of 0.04, 0.08, 0.17, 0.32 and 0.56 mg a.s./L	DuPont-32454 Thomas, S.T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O., 2012
Prolonged sediment toxicity test with *Chironomus riparius* using spiked sediment 28 –day, static OECD 218 (2004) GLP compliant	NOEC = 2.8 mg a.s./kg based on emergence ratios	Lot #: QGU42-174, 95.8% purity [Isoxazoline-5-^{14}C] oxathiapiprolin: 33.88 µCi/mg, radiochemical purity 98.3% Mean, measured concentrations in sediment of 0.69, 2.8, 8.0, 29 and 96 mg a.s./kg	DuPont-35835 Thomas, S.T., Kendall, T.Z., Martin, K.H., Gallagher, S.P., Krueger, H.O., 2013

Method	Endpoint	Remarks	Reference
Prolonged sediment toxicity test with *Chironomus riparius* using spiked water 28-day, static OECD 219 (2004) GLP compliant	NOEC = 0.11 mg a.s./L based on emergence ratios	Lot #: QGU42-174, 95.8% purity [Isoxazoline-5-^{14}C] oxathiapiprolin: 33.88 µCi/mg, radiochemical purity 98.3% Mean, measured concentrations of 0.011, 0.033, 0.11, 0.36 and 1.1 mg a.s./L	DuPont-36043 Thomas, S.T., Kendall, T.Z., Martin, K.H., Gallagher, S.P., Krueger, H.O., 2013

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Report: Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2012a); DPX-QGU42 technical: A 96-hour static acute toxicity test with the rainbow trout (*Oncorhynchus mykiss*)

Report No.: DuPont-32481, Revision No. 1

Guidelines: OECD 203 (1992), OPPTS 850.1075 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Controls:	Dilution water (laboratory well water)
Test vehicle:	Dimethylformamide (DMF)
Toxic reference:	Not applicable
Test organism:	Rainbow trout
Species:	*Oncorhynchus mykiss*
Age/life stage at dosing:	Juveniles (hatch date 18 July 2011)
Control weight at termination:	0.38–0.51 g
Control length at termination	3.5–3.9 cm
Test chamber:	Stainless steel aquaria (38 L) holding 30 L of test solution (23.5 cm liquid depth)
Environmental conditions:	Dissolved oxygen: ≥7.8 mg/L (≥72% of saturation); pH: 8.3–8.6
Temperature:	11.8–12.0°C in test chambers; 11.8–12.3°C measured continuously in the negative control.
Photoperiod:	16 hr light (670 lux at initiation) and 8 hr dark including 30 min transitional period preceding and following the 16-hr light interval.

The acute toxicity of oxathiapiprolin to unfed juvenile rainbow trout, *Oncorhynchus mykiss*, was determined in an unaerated, static, 96-hour dose response test. Treatments consisted of a dilution water control, a solvent control (0.1 mL/L dimethylformamide) and five nominal concentrations of 0.063, 0.13, 0.25, 0.50 and 1.0 mg oxathiapiprolin/L. A single replicate test chamber was maintained in each treatment and control group, with seven fish each (total of seven fish in the dilution water control, solvent control and in each test concentration).

Observations

Mortality and behavioural observations were made at approximately 2 hours and every 24 hours following initiation of exposure (±1 hour).

Statistics

No analysis performed as no mortality observed.

FINDINGS

Nominal concentrations of oxathiapiprolin were 0.063, 0.13, 0.25, 0.50 and 1.0 mg oxathiapiprolin/L. Mean, measured concentrations of oxathiapiprolin ranged from 69 to 92% of nominal concentrations during the test. No sublethal effects were observed. No mortalities were observed.

CONCLUSION

The 96-hour LC_{50} for rainbow trout was greater than 0.69 mg oxathiapiprolin/L, the highest concentration tested, based on mean, measured concentrations of oxathiapiprolin and mortality. The highest mean, measured concentration causing no mortality was 0.69 mg oxathiapiprolin/L. The lowest mean, measured concentration causing 100% mortality was greater than 0.69 mg oxathiapiprolin/L.

Report: Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2011a); DPX-QGU42 technical a 96-hour static acute toxicity test with the bluegill (*Lepomis macrochirus*)

Report No.: DuPont-32818

Guidelines: OECD 203 (1992), OPPTS 850.1075 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Controls:	Dilution water (laboratory well water) control Solvent control (0.1 mL/L dimethylformamide)
Test vehicle:	Solvent dimethylformamide (0.1 mL/L dimethylformamide)
Toxic reference:	Not applicable
Test organism:	Bluegill
Species:	*Lepomis macrochirus*
Age/life stage at dosing:	Juvenile (estimated hatch date 08 May 2011)
Initial population:	7 fish test chamber
Diet:	Unfed during test
Test chamber:	38-L stainless steel aquaria containing 15 L of test solution (12-cm test solution depth)
Environmental conditions:	Dissolved oxygen: ≥7.0 mg/L (≥81% of saturation) pH: 8.4 to 8.6
Temperature:	21.5 to 21.9°C in test chambers; 21.2 to 22.3°C measured continuously in a negative control
Photoperiod:	16 hr light (559 lux at initiation) and 8 hr dark including 30 min transitional period preceding and following the 16-hr light interval.

The acute toxicity of oxathiapiprolin to unfed bluegill (juvenile) was determined in an unaerated, static, 96-hour test. Treatments consisted of a dilution water control, solvent control (0.1 mL/L dimethylformamide) and mean

measured test concentrations of 0.060, 0.12, 0.22, 0.45 and 0.72 mg oxathiapiprolin/L. Seven fish were used per test concentration and controls.

Observations

Mortality and behavioural observations were made at approximately 3.5 hours and every 24 hours (±1 hour) following initiation of exposure.

Statistics

No analysis performed as no mortality observed.

FINDINGS

Nominal test concentrations of oxathiapiprolin were 0.063, 0.13, 0.25, 0.50 and 1.0 mg oxathiapiprolin/L. Mean measured concentrations of oxathiapiprolin were 0.060, 0.12, 0.22, 0.45 and 0.72 mg oxathiapiprolin/L and ranged from 72 to 95% of nominal concentrations. No sublethal effects were observed. No mortalities were observed.

CONCLUSION

The 96-hour LC_{50} value, based on the mean, measured test concentrations of oxathiapiprolin and mortality, was estimated to be greater than 0.72 mg oxathiapiprolin/L. The highest mean, measured test concentration causing no immobility at test end was 0.72 mg oxathiapiprolin/L. The lowest mean, measured test concentration causing 100% immobility at test end was greater than 0.72 mg oxathiapiprolin/L.

Report: Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2011b); DPX-QGU42 technical: A 96-hour static acute toxicity test with the sheepshead minnow

DuPont Report No.: DuPont-32819

Guidelines: OPPTS 850.1075 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Controls:	Dilution water (filtered saltwater) control Solvent control (0.1 mL/L dimethylformamide)
Test vehicle:	Solvent dimethylformamide (0.1 mL/L dimethylformamide)
Toxic reference:	Not applicable
Test organism:	Sheepshead minnow
Species:	*Cyprinodon variegatus*
Age/life stage at dosing:	Juvenile (estimated hatch date 22 June 2011)
Diet:	Unfed during test
Test chamber:	25-L stainless steel aquaria containing 15 L of test solution (18.2-cm test solution depth)
Environmental conditions:	Dissolved oxygen: ≥4.7 mg/L (≥60% of saturation) pH: 7.8 to 8.1
Temperature:	21.1 to 22.2°C in test chambers; 21 to 22°C measured continuously in the negative control
Photoperiod:	16 hr light (238 lux at initiation) and 8 hr dark including 30 min transitional period preceding and following the 16-hr light interval.

The acute toxicity of oxathiapiprolin to unfed sheepshead minnow (juvenile) was determined in an unaerated, static, 96-hour test. Treatments consisted of a dilution water control, solvent control (0.1 mL/L dimethylformamide) and mean measured test concentrations of 0.048, 0.068, 0.19, 0.41 and 0.65 mg oxathiapiprolin/L. Seven fish were used per test concentration and controls.

Observations

Mortality and behavioural observations were made at approximately 3 hours and every 24 hours (±1 hour) following initiation of exposure.

FINDINGS

Nominal test concentrations of oxathiapiprolin were 0.063, 0.13, 0.25, 0.50 and 1.0 mg oxathiapiprolin/L. Mean measured concentrations of oxathiapiprolin were 0.048, 0.068, 0.19, 0.41 and 0.65 mg oxathiapiprolin/L and ranged from 52 to 82% of nominal concentrations. It is unclear why the recovery observed at the 0.13 mg oxathiapiprolin/L was lower than the recoveries seen in other test concentrations; however, since no adverse effects were observed in any of the oxathiapiprolin treatment levels, the low recovery had no impact on the interpretation of the study results. Although the overall recoveries were slightly low, they were consistent throughout the test. No sublethal effects were observed. No mortalities were observed.

Statistics

No analysis performed as no mortality observed.

CONCLUSION

The 96-hour LC_{50} value, based on the mean, measured test concentrations of oxathiapiprolin and mortality, was estimated to be greater than 0.65 mg oxathiapiprolin/L. The highest mean, measured test concentration causing no immobility at test end was 0.65 mg oxathiapiprolin/L. The lowest mean, measured test concentration causing 100% immobility at test end was greater than 0.65 mg oxathiapiprolin/L.

5.4.1.2 Long-term toxicity to fish

Report: Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2012b); DPX-QGU42 technical: An early life-stage toxicity test with the sheepshead minnow (*Cyprinodon variegatus*)

DuPont Report No.: DuPont-32820

Guidelines: OPPTS 850.1400 **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Controls:	Dilution water (filtered saltwater) Solvent control (0.1 mL/L dimethylformamide)
Test vehicle:	Solvent dimethylformamide (0.1 mL/L DMF)
Toxic reference:	None
Test organism:	Sheepshead minnow
Species:	*Cyprinodon variegatus*
Age/life stage at dosing:	Embryos ~ 24 hours
Initial population:	20 embryos per egg cup and test chamber, 80 embryos per concentration and control
Diet:	Brine shrimp nauplii (*Artemia sp.*), 2-3 times daily
Test chamber:	9-L glass aquaria containing approximately 7 L of test solution (15.5-cm test solution depth)
Environmental conditions:	Dissolved oxygen: ≥6.8 mg/L (≥93% of saturation) pH: 7.9–8.1
Temperature:	24.4 to 25.9°C in test chambers; 24 to 26°C measured continuously in a negative control replicate.
Photoperiod:	16 hr light (118 lux at initiation) and 8 hr dark including 30 min transitional period preceding and following the 16-hr light interval.

The effects of oxathiapiprolin on the early life stages (time to hatch, hatching success, survival and growth) of sheepshead minnow was determined in a flow-through, 35-day test. The test system was unaerated throughout the test. Treatments consisted of a dilution water control, a solvent control (0.1 mL/L HPLC-grade dimethylformamide) and five nominal oxathiapiprolin concentrations of 0.031, 0.063, 0.13, 0.25 and 0.50 mg a.s./L (mean, measured concentrations of 0.031, 0.059, 0.12, 0.23 and 0.34 mg a.s./L). Four incubation cups, each containing 20 embryos, were placed in each of four replicate test chambers per treatment and the control groups (total of 80 embryos per test group). Test concentrations were maintained by a continuous-flow diluter.

Observations

The following parameters were observed and recorded: first and last day of hatching, hatching success, and survival and abnormalities from hatch to test termination. Fish total lengths, wet and dry weights were measured at test termination.

Statistics

Test endpoints analysed statistically were time to beginning and end of hatch, hatching success, larval survival and growth (total length, wet weight and dry weight) for the juvenile fish. Data from the negative and solvent control groups for each parameter were compared using a t-test. Since no differences were detected between the two control groups ($p > 0.05$) for hatching success, survival, total length or wet weight, the control data for these parameters were pooled for comparison among the treatment groups. When statistically significant difference was found between the two controls ($p \leq 0.05$) for dry weight, the treatment data were compared to the negative control and solvent control data separately. The effect on time to hatch was determined by visual interpreting the data. Hatching success and survival data were considered to be discrete-variable data, while growth data were considered continuous-variable data. Discrete-variable data were analysed using Chi-square and Fisher's exact test to identify treatment groups that showed a statistically significant difference ($p \leq 0.05$) from the pooled controls. All continuous-variable data were evaluated for normality using Shapiro-Wilk's test, and for homogeneity of variance using Levene's test ($p = 0.01$). Since the data passed the assumptions of normality and homogeneity, those treatments that were significantly different from the control means were identified using Dunnett's one-tailed test ($p \leq 0.05$). All statistical tests were performed using a personal computer with SAS software.

The results of the statistical analyses were used to aid in the determination of the NOEC, LOEC and MATC. The NOEC was defined as the highest test concentration that produced no significant treatment-related effects on hatching success, survival or growth. The LOEC was defined as the lowest test concentration that produced a significant

treatment-related effect on hatching success, survival or growth. The MATC was calculated as the geometric mean of the NOEC and LOEC.

FINDINGS

Analytical verification of oxathiapiprolin concentrations was made on test solutions sampled on Day 0 and at regular intervals during the study. Mean, measured concentrations of oxathiapiprolin were 0.031, 0.059, 0.12, 0.23 and 0.34 mg a.s./L, representing 100, 94, 92, 92 and 68% of nominal concentrations. All chemical and physical parameters for the 35-day study were within acceptable ranges. All validity criteria were met for the study.

A summary of percent hatching success, survival, and growth of surviving minnows is shown in Table 31.

Table 31
Summary of effects following exposure of sheepshead minnow to oxathiapiprolin for 35 days

Mean, measured oxathiapiprolin concentration (mg a.s./L)	Mean % hatch[a,d]	Mean % Survival [b,d]	Mean term length (mm)[d]	Mean term wet weight (mg)[d]	Mean term dry weight (mg)[d]
Negative Control (0.0)	90	99	21.2	122.7	30.2
Solvent Control (0.0)	94	97	21.0	116.6	26.4
Pooled Controls	92	98	21.1	119.6	--
0.031	95	97	21.0	116.2	26.8*, [e]
0.059	98	97	21.2	114.9	27.3
0.12	94	96	21.5	133.0	32.0
0.23	93	96[c]	21.4	127.1	31.2
0.34	98	96[c]	20.8	116.2	26.3*, [e]

* Indicates a statistically significant difference from the negative controls (dry weight: Dunnett's one-tailed test, alpha = 0.05).

[a] Percent hatched of live embryos

[b] Percent larvae survive to test termination.

[c] On Day 8 of the test, one fish from replicate D of the 0.23 mg a.s./L treatment group was assumed to be inadvertently transferred into replicate A of the 0.34 mg a.s./L treatment group. The misplaced fish was left in replicate A of the 0.34 mg a.s./L test chamber to test termination since it was impossible to distinguish the misplaced fish from the rest of the fish in the test chamber.

[d] No statistically significant differences from the pooled controls (Percent hatching success and survival: Fisher's Exact Test, alpha = 0.05; and length and wet weight: Dunnett's one-tailed test, alpha = 0.05). No statistically significant reductions in mean dry weight in any of the treatment groups in comparison to the solvent control (Dunnett's one-tailed test, alpha = 0.05).

[e] Since the reductions in mean dry weight did not follow a dose-response pattern and the mean dry weight at 0.34 mg a.s./L treatment group was comparable to the mean dry weight of the solvent control group, the statistically significant reductions in mean dry weight detected at the 0.031 and 0.34 mg a.s./L treatment groups in comparison to the negative control was not considered to be treatment related.

CONCLUSION

Sheepshead minnow (*Cyprinodon variegatus*) were exposed to mean, measured concentrations of oxathiapiprolin of 0.031 to 0.34 mg a.s./L under flow-through conditions for 35 days (a 6-day hatching period plus a 29-day post-hatch growth period). There were no statistically significant treatment-related effects on hatching success, survival or growth (total length, wet and dry weight) at concentrations ≤0.34 mg a.s./L. Consequently, the NOEC, based on mean, measured test concentrations, and hatching success, survival and growth was 0.34 mg a.s./L. The LOEC was greater than 0.34 mg a.s./L and the MATC was estimated to be greater than 0.34 mg a.s./L.

Report: Minderhout, T., Kendall, T.Z., Krueger, H.O. (2012); DPX-QGU42 technical: An early life-stage toxicity test with the rainbow trout (*Oncorhynchus mykiss*)

Report No.: DuPont-32482

Guidelines: OECD 210 (1992), OPPTS 850.1400 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Controls:	Dilution water (laboratory well water) control
Test vehicle:	Solvent (dimethylformamide, DMF)
Toxic reference:	None
Test organism:	Rainbow trout
Species:	*Oncorhynchus mykiss*
Age/life stage at dosing:	Embryos <24 hours
Initial population:	15 embryos per egg cup and 30 embryos per test chamber, 120 embryos per concentration and control, 30 embryos for fertilization rate
Diet:	Salmon-starter mash, 3 times daily during the first 7 days and 2-3 times daily, thereafter
Test chamber:	9-L glass aquaria containing 7 L of test solution (16-cm test solution depth)
Environmental conditions:	Dissolved oxygen: ≥6.5 mg/L (≥60% of saturation) pH: 7.9 to 8.2
Temperature:	11.5 to 12.3°C in test chambers; 11 to 14°C measured continuously in a negative control replicate A.
Photoperiod:	24 hr dark until one week after hatch. Thereafter, 16 hr light (128 lux at initiation) and 8 hr dark including 30 min transitional period preceding and following the 16-hr light interval.

The effects of oxathiapiprolin on the early life stages (time to hatch, hatching success, time to swim-up, survival and growth) of rainbow trout was determined in an unaerated, flow-through test system for 88 days. Treatments consisted of a dilution water control, a solvent control (0.1 mL DMF/L) and five nominal oxathiapiprolin concentrations of 0.063, 0.13, 0.25, 0.50 and 1.0 mg a.s./L (mean, measured concentrations of 0.060, 0.12, 0.23, 0.46 and 0.74 mg a.s./L). Two incubation cups, each containing 15 embryos, were placed in each of four replicate test chambers per treatment and the control (total of 120 embryos per test group). An additional 30 embryos were held in each of four extra incubation cups (120 embryos total) in dilution water and were sacrificed on Day 11 to evaluate fertilization success, which was 88.3%. On Day 17 of the test, the embryos in each replicate of each treatment and control group were reduced to 20 viable embryos when they reached the eyed stage (total of 80 embryos in each treatment and control group). Test concentrations were maintained by a continuous-flow diluter.

Observations

The following parameters were observed and recorded: Hatching success, time to swim-up (based on numbers of larvae reached swim-up stage when ≥95% of the larvae in the control groups reached swim-up and fish were thinned), first and last day of hatching, first day of swim-up, and survival and abnormalities from hatch to thinning and from thinning to test termination.

Fish lengths and fish wet and dry weights were measured at test termination.

Statistics

Hatching success, time to swim-up, percent survival of larvae prior to and after swim-up, fish length, and wet and dry weight of the juvenile fish at test termination were analysed statistically.

Data from the negative and solvent control groups for each parameter were compared using a t-test. When no differences were detected between the two control groups ($p \geq 0.05$) for hatching success, larval survival at

thinning, time to swim up, larval survival at test termination, fish total length wet and dry weights, the control data were pooled for comparison among the treatment groups.

Hatching success, time to swim-up and survival (discrete-variable data) were analysed using Chi-square and Fischer's Exact test to determine treatment groups that showed a statistically significant difference (p = 0.05) from the pooled control.

Total length, wet and dry weights (continuous variable data) were evaluated for normality using the Shapiro-Wilk's test and for homogeneity of variance using Levene's test (p = 0.01). Those treatments that were significantly different from the pooled controls means were identified using Dunnett's one-tailed test (p = 0.05).

The infrequent occurrence of deformed larvae and abnormal behaviour observed in fish preclude the statistical analyses of these endpoints.

FINDINGS

Analytical verification of oxathiapiprolin concentrations was made on test solutions sampled on Day 0 and at regular intervals during the study. Mean, measured concentrations of oxathiapiprolin were 0.060, 0.12, 0.23, 0.46 and 0.74 mg a.s./L, representing 95, 92, 92, 92 and 74% of nominal concentrations. All chemical and physical parameters for the 88-day study were within acceptable ranges. All validity criteria were met for the study.

A summary of percent hatching success, time to swim-up, survival, and growth of surviving trout is shown in Table 32.

Table 32
Summary of effects following exposure of rainbow trout to oxathiapiprolin for 88 days

Mean, measured oxathiapiprolin concentration (mg a.s./L)	Mean % hatch[a]	Mean % Swim-up[b]	Mean % survival from hatch to thinning[c,e]	Mean % survival from thinning to term[d,e]	Mean term length (mm)	Mean term wet weight (g)	Mean term dry weight (g)
Negative Control (0.0)	96	100	97	98	52.8	1.32	0.27
Solvent Control (0.0)	100	95	99	98	52.7	1.30	0.27
Pooled Controls	98	97	98	98	52.7	1.31	0.27
0.060	100	95	98	97	53.0	1.34	0.27
0.12	99	95	100	97	52.7	1.34	0.27
0.23	99	96	97	100	51.4	1.23	0.25
0.46	99	97	99	93	52.2	1.31	0.26
0.74	98	91	96	90*, [f]	49.1*	1.09*	0.22*

[a] Percent hatched of live embryos.

[b] Percent larvae reaching swim-up stage prior to thinning on Day 17 post-hatch.

[c] Percent larvae surviving to thinning on Day 17 post-hatch.

[d] Percent larvae surviving from thinning on Day 17 post-hatch to test termination on Day 60 post-hatch.

e No significant differences from the pooled controls (Fisher's Exact Test, p >0.05).

f A statistically significant difference from the pooled controls (Fisher's Exact Test, p ≤0.05). However, the statistically significant difference found at this treatment group was not considered significant since the percent survival in this treatment concentration was greater than the control validity criteria for post-hatch survival (>70%).

* There were statistically significant differences from the pooled controls (mean lengths, wet and dry weights: Dunnett's one-tailed test, p ≤0.05).

CONCLUSION

Growth, determined as mean total length, wet and dry weights at test termination, was the most sensitive end-points of the study. The 88-day NOEC and LOEC in rainbow trout, based on mean, measured concentrations of oxathiapiprolin and growth were 0.46 and 0.74 mg a.s./L, respectively. The MATC was estimated to be 0.58 mg a.s./L.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Report: Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2011e); DPX-QGU42 technical: A 48-hour static acute toxicity test with the cladoceran (*Daphnia magna*)

DuPont Report No.: DuPont-32484

Guidelines: OECD 202 (2004), OPPTS 850.1010 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Controls:	Dilution water (laboratory well water) control; Solvent (0.1 mL DMF/L) control
Toxic reference:	Not applicable
Test organism:	Cladoceran
Species:	*Daphnia magna*
Age/life stage at dosing:	<24 hours
Initial population:	Four replicate test chambers with 5 daphnids per test chamber
Diet:	Unfed during test
Test chamber:	250-mL glass beaker containing approximately 200 mL of test solution (5.7-cm test solution depth)
Environmental conditions:	Dissolved oxygen: ≥7.6 mg/L (≥84% of saturation) pH: 8.1 to 8.5
Temperature:	19.7 to 20.9°C in test chambers; 20 to 21°C measured continuously in an adjacent container of water.
Photoperiod:	16 hr light (529 lux at initiation) and 8 hr dark including 30 min transitional period preceding and following the 16-hr light interval.

The acute toxicity of oxathiapiprolin to unfed *Daphnia magna* (<24-hour old) was determined in an unaerated, static, 48-hour test. Treatments consisted of a dilution water control, solvent control (0.1 mL DMF/L) and mean, measured test concentrations of 0.060 to 0.78 mg a.s./L. Five daphnids were used per replicate with four replicates per test concentration and control.

Observations

Immobility and behavioural observations were made at approximately 1.5 hours, and at 24 and 48 hours (±1 hour) following initiation of exposure.

Statistics

The 48-hour mortality data were analysed using the computer program of C. E. Stephan. The program was designed to calculate the EC_{50} value and the 95% fiducial interval by probit analysis, the moving average method, and binomial probability with nonlinear interpolation. In this study, there was less than 50% immobility/mortality

in any of the oxathiapiprolin treatment groups at 24 hours, which precluded the statistical calculation of EC_{50} value; therefore, the 24-hour EC_{50} was estimated to be greater than the highest concentration tested. The 48-hour EC_{50} value was calculated using nonlinear interpolation. The 95% fiducial limits were estimated using binomial test. The highest test concentration causing no immobility at test end and the lowest test concentration causing 100% immobility at test end were assessed by visual observation of the immobility and observation data.

FINDINGS

Nominal test concentrations of oxathiapiprolin were 0.063, 0.13, 0.25, 0.50 and 1.0 mg a.s./L. The highest nominal test concentration of 1.0 mg a.s./L was slightly above the solubility limit of the test material in the test system. Mean, measured concentrations of oxathiapiprolin 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.

Table 33
Summary of observed immobility of unfed *Daphnia magna* exposed to oxathiapiprolin for 48 hours in an unaerated, static, acute test

Mean Measured Test Concentration (mg a.s./L)	Immobility (No. immobile/No. at test start) [b]							
	24 Hours [c]				48 Hours			
	A	B	C	D	A	B	C	D
Dilution water control (0.0)	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Solvent Control (0.0)[a]	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.060	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.12	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.24	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.44	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.78	2/5	2/5	1/5	2/5	2/5	3/5	1/5	2/5

[a] Solvent concentration: 0.1 mL DMF/L.

[b] A–D represent replicate test chambers containing 5 daphnids each at test start.

[c] There were no immobile daphnids noted at the 1.5-hour observation interval.

Table 34
Summary of sublethal effects of unfed *Daphnia magna* exposed to oxathiapiprolin for 48 hours in an unaerated, static, acute test

Mean Measured Test Concentration (mg a.s./L)	Number affected / Number alive [b]							
	24 Hours [c, d]				48 Hours [d]			
	A	B	C	D	A	B	C	D
Dilution Water Control (0.0)	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Solvent Control (0.0) [a]	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.060	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/4
0.12	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.24	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.44	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.78	3C/3	3C/3	4C/4	3C/3	1C/1	--/0	3C/3	1C/1

[a] Solvent concentration: 0.1 mL DMF/L.

[b] A–D represent replicate test chambers containing 5 daphnids each at test start.

[c] There were no sublethal effects noted at the 1.5-hour observation interval.

[d] All surviving daphnids in the 0.78 mg a.s./L treatment group appeared lethargic (C) at the 24- and 48-hour observations.

CONCLUSION

The 48-hour EC_{50} value, based on the mean, measured test concentrations of oxathiapiprolin and immobility, was estimated to be 0.67 mg a.s./L, with the 95% fiducial 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. The lowest mean measured test concentration causing 100% immobility at test end was >0.78 mg a.s./L.

Report: Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2011c); DPX-QGU42 technical: A 96-hour static acute toxicity test with the saltwater mysid (*Americamysis bahia*)

DuPont Report No.: DuPont-32485

Guidelines: OPPTS 850.1025 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Controls:	Dilution water (UV-sterilized, filtered saltwater) Solvent control (0.1 mL/L dimethylformamide)
Test carrier:	Solvent dimethylformamide (0.1 mL/L dimethylformamide)
Toxic reference:	None
Test organism:	Saltwater mysid
Species:	*Americamysis bahia*
Age/life stage at dosing:	Juveniles (<24 hours old)
Initial population:	10 mysids per test chamber
Acclimation period:	At least 14 days
Diet:	Pre-test (2 weeks): live brine shrimp nauplii (*Artemia* sp.), fed daily Test period: live brine shrimp nauplii (*Artemia* sp.), fed daily. The brine shrimp periodically were enriched with a nutrient enrichment
Test chamber:	Glass beaker (2 L) holding 1.0 L of test solution (7.0 cm liquid depth)
Water:	Natural seawater collected at Indian River Inlet, Delaware (filtered and diluted to approximately 20% with well water)
Environmental conditions:	
Temperature:	24.0 to 25.7°C in test chambers; 24.9 to 25.9°C measured continuously in a beaker of dilution water adjacent to the test chambers.
Photoperiod:	16 hr light (480 lux at initiation) and 8 hr dark including a 30 min transitional period preceding and following the 16-hr light interval.

The acute toxicity of oxathiapiprolin to juvenile saltwater mysids (*Americamysis bahia*), an aquatic marine invertebrate, was determined in an unaerated, static, 96-hour dose response test. Treatments consisted of a dilution water control, solvent control (0.1 mL/L dimethylformamide) and five nominal concentrations of 0.063, 0.13, 0.25, 0.50 and 1.0 mg a.s./L. The concentrations were selected based on the solubility limit of the test substance in the test system. Two replicate test chambers were maintained in each treatment and control group, with 10 mysids in each chamber for a total of 20 mysids per concentration.

Observations

Mortality and behaviour at approximately 3.5 hours and every 24 hours following initiation of exposure; dead mysids were removed from the test chambers when observed.

Statistics

No statistical analysis was performed as the mortality did not exceed 50% in any of the treatment groups.

FINDINGS

Mean, measured concentrations of oxathiapiprolin were 0.065, 0.12, 0.25, 0.41 and 0.64 mg a.s./L and ranged from 77.9 to 102% of nominal concentrations on Day 0 and from 46.0 to 110% of nominal concentrations at test end on Day 4. All validation criteria were met for the study. Summaries of cumulative mortality and sublethal effects are presented in Table 35 and Table 36, respectively.

Table 35
Observed mortality of saltwater mysids (*Americamysis bahia)* exposed to oxathiapiprolin for 96 hours in an unaerated, static, acute test

Mean, measured oxathiapiprolin concentration (mg a.s./L)	Cumulative mortality (No. dead/No. at test start)[a, b]				
	~3.5 h	24 h	48 h	72 h	96 h
Water Control (0.0)	0/20	0/20	0/20	0/20	0/20
Solvent Control (0.0)	0/20	0/20	0/20	0/20	0/20
0.065	0/20	0/20	0/20	0/20	0/20
0.12	0/20	0/20	0/20	0/20	0/20
0.25	0/20	0/20	0/20	0/20	0/20
0.41	0/20	0/20	0/20	0/20	0/20
0.64	0/20	1 MAD[b]/20	1/20	2/20	2/20

[a] Two replicate test chambers, each containing 10 mysids at test start, were tested at each concentration.

[b] MAD = missing, assumed dead.

Table 36
Observed sublethal effects of saltwater mysids (*Americamysis bahia)* exposed to oxathiapiprolin for 96 hours in an unaerated, static, acute test

Mean, measured oxathiapiprolin concentration (mg a.s./L)	Sublethal effects (Number affected / Number alive) [a]				
	~3.5 h	24 h	48 h	72 h	96 h
Water Control (0.0)	0/20	0/20	0/20	0/20	0/20
Solvent Control (0.0)	0/20	0/20	0/20	0/20	0/20
0.065	0/20	1[b]/20	0/20	0/20	0/20
0.12	0/20	0/20	0/20	0/20	0/20
0.25	0/20	0/20	0/20	0/20	0/20
0.41	0/20	0/20	0/20	0/20	0/20
0.64	0/20	0/20	0/19	0/18	0/18

[a] Two replicate test chambers, each containing 10 mysids at test start, were tested at each concentration.

[b] Mysid was observed to swim erratically.

CONCLUSION

The 96-hour LC_{50} for the saltwater mysid based on mean measured concentrations of oxathiapiprolin and mortality data was greater than 0.64 mg a.s./L. The highest mean, measured concentration causing no mortality at test end was 0.41 mg a.s./L and the lowest mean, measured concentration causing 100% mortality at test end was greater than 0.64 mg a.s./L.

Report: Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2012c); DPX-QGU42 technical: A 96-hour shell deposition test with the eastern oyster (*Crassostrea virginica*)

DuPont Report No.: DuPont-32453

Guidelines: OPPTS 850.1025 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Controls:	Dilution water (filtered saltwater) control Solvent control (0.1 mL/L dimethylformamide)
Test vehicle:	Solvent dimethylformamide (0.1 mL/L dimethylformamide)
Toxic reference:	Not applicable
Test organism:	Eastern oyster
Species:	*Crassostrea virginica*
Age/life stage at dosing:	Juveniles
Length at initiation:	30.2–37.9 mm
Acclimation period:	At least 10 days
Diet:	Pretest: suspension of marine microalgae 2.9×10^9 cells/oyster/day Test period: suspension of marine microalgae 5.8×10^9 cells/oyster/day
Test chamber:	Glass aquaria (54 L) holding approximately 27 L of test solution (14.2 cm liquid depth)
Water:	Natural seawater collected at Indian River Inlet, Delaware (filtered and diluted to 20% with well water)
Environmental conditions:	
Temperature:	18.9 to 19.0°C in test chambers; remained at 19°C measured continuously in the negative control.
Photoperiod:	16 hr light (318 lux at initiation) and 8 hr dark including a 30 min transitional period preceding and following the 16-hr light interval.

The acute toxicity of oxathiapiprolin to Eastern oyster (*Crassostrea virginica*), a marine mollusc, was determined in a flow-through, 96-hour dose response test. Treatments consisted of a dilution water control, a solvent (0.1 mL dimethylformamide/L), and nominal oxathiapiprolin concentrations of 0.031, 0.063, 0.13, 0.25, and 0.50 mg a.s./L. The concentrations were selected based on the solubility limit of the test substance in the test system. One test chamber, containing 20 oysters, was exposed to each treatment concentration and control (total of 20 oysters in the dilution water control, solvent control and 20 oysters in each test concentration).

Observations

Mortality and behavioural observations were made at approximately 4 hours and every 24 hours (±1 hour) following initiation of exposure.

Statistics

There was less than 50% inhibition of shell deposition in any treatment group in comparison to the pooled control. Therefore, the EC_{50} was estimated to be greater than the highest concentration tested. The shell deposition data were evaluated for normality and homogeneity of variance using the Chi-Square test and Levene's test, respectively. Data in the treatment groups then were compared to the pooled control data using analysis of variance (ANOVA) and Bonferroni's t-test to identify any significant differences. The no-observed-effect-concentration (NOEC) was determined from the statistical analysis of the data and an assessment of the concentration-response pattern. The highest mean, measured test concentration causing no mortality at test end and the lowest mean, measured test concentration causing 100% mortality at test end were assessed by visual observation of the mortality and observation data.

FINDINGS

Mean, measured concentrations of oxathiapiprolin were 0.028, 0.056, 0.11, 0.21, and 0.33 mg a.s./L and ranged from 66 to 90% of nominal concentrations. All validation criteria were met for the study. No sublethal effects were observed. No mortalities were observed. Summaries of mean shell deposition and shell growth inhibition are presented in Table 37.

Table 37
Mean shell deposition and shell growth inhibition for Eastern oyster (*Crassostrea virginica*) exposed to oxathiapiprolin for 96 hours in a flow-through, acute test

Mean, measured oxathiapiprolin concentration (mg a.s./L)	Shell Deposition Mean ± Standard Deviation (mm)	Shell Growth Inhibition vs. Pooled Controls (%)
Water Control (0.0)	2.9 ± 1.2	--
Solvent Control (0.0)	2.9 ± 1.2	--
Pooled Controls	2.9 ± 1.2	--
0.028	3.0 ± 1.7	-3.4
0.056	2.6 ± 1.2	10
0.11	2.3 ± 0.9	23
0.21	2.4 ± 1.2	17
0.33	2.4 ± 1.2	18

CONCLUSION

The 96-hour EC_{50} for *Crassostrea virginica* based on the mean, measured test concentrations of oxathiapiprolin and shell deposition was estimated to be greater than 0.33 mg a.s./L, the highest concentration tested. The NOEC was 0.33 mg a.s./L. The highest mean, measured test concentration causing no mortality at test end was 0.33 mg a.s./L. The lowest mean, measured test concentration causing 100% mortality at test end was greater than 0.33 mg a.s./L.

5.4.2.2 Long-term toxicity to aquatic invertebrates

Report: Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2011d); DPX-QGU42 technical: A semi-static life-cycle toxicity test with the cladoceran (*Daphnia magna*)

DuPont Report No.: DuPont-32455

Guidelines: OECD 211 (2008), OPPTS 850.1300 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Controls:	Dilution water (UV-sterilized, filtered wellwater) Solvent control (0.1 mL/L dimethylformamide)
Test vehicle:	Solvent dimethylformamide (0.1 mL/L DMF)
Toxic reference:	None
Test organism:	Cladoceran
Species:	*Daphnia magna*
Age/life stage at dosing:	<24 hours
Initial population:	1 daphnid per test chamber
Diet:	A mixture of yeast, cereal grass media, and trout chow (YCT), as well as a suspension of the freshwater green alga, *Pseudokirchneriella subcapitata*, daily. Each test chamber was fed 0.5 mL of YCT and 1.0 mL of algae at each feeding during the test.
Test chamber:	250-mL glass beaker containing approximately 200 mL of test solution (6.5-cm test solution depth)
Environmental conditions:	Dissolved oxygen: ≥6.4 mg/L (≥71% of saturation) pH: 8.1 to 8.6
Temperature:	19.1 to 21.0°C in test chambers; 20 to 21°C measured continuously in an adjacent container of water, measured to the nearest 1°C.
Photoperiod:	16 hr light (298 lux at initiation) and 8 hr dark including 30 min transitional period preceding and following the 16-hr light interval.

The effect of oxathiapiprolin on the survival, growth and reproduction of *Daphnia magna* was determined in an unaerated, semi-static, 21-day test. Treatments consisted of a dilution water control, solvent (0.1 mL/L dimethylformamide) control and five nominal oxathiapiprolin concentrations of 0.063, 0.13, 0.25, 0.50 and 1.0 mg a.s./L (mean, measured oxathiapiprolin concentrations of 0.057, 0.12, 0.24, 0.45 and 0.75 mg a.s./L). The concentrations were selected based on the solubility limit of the test substance in the test system. A total of 10 replicates, each containing one, <24-hour-old neonate, were tested per concentration (10 neonates/concentration). Each of the control groups consisted of twenty replicates. Test concentrations were renewed approximately every 48 to 72 hours, except for Week 1 when the longest renewal was 96 hours.

Observations

Observations were made daily of the number of surviving adult daphnids and occurrence of sublethal effects. With the onset of reproduction, live or immobile neonates produced were counted and then discarded at renewal on Monday, Wednesday, and Friday during the test and at test termination. The exception was on Day 20 of the test when the solution was not renewed in order to avoid disturbing the test organisms unnecessarily one day prior to test termination. Therefore, the neonates were counted at test end. Length and dry weight of surviving adult daphnids were determined at test end (21 days).

Statistics

Test endpoints analysed statistically for first-generation daphnids were survival, reproduction (the number of live young produced per 21-day surviving adult), and growth (length and dry weight).

Survival data (discrete-variable data) were analysed using Chi-square and Fisher's Exact test to determine treatment groups that showed a statistically significant difference ($p \leq 0.05$) from the control.

Reproduction and growth data (continuous variable data) were evaluated for normality using the Chi-square test or Shapiro-Wilk's test and for homogeneity of variance using Levene's test ($p = 0.01$).

Those treatments that were significantly different from the pooled controls means were identified using Bonferroni t-test or Dunnett's test ($p \leq 0.05$), since all data passed the assumptions of normality and homogeneity of variance.

The EC_{50} values based on the 21-day immobility and reproduction data were estimated to be greater than the highest concentration tested since there was less than 50% immobility or reduction in reproduction in any of the oxathiapiprolin treatment groups during the test, which precluded the statistical calculation of the EC_{50} values.

FINDINGS

Analytical verification of oxathiapiprolin concentrations was made on test solutions sampled on Day 0 and at regular intervals during the study. Mean, measured concentrations of oxathiapiprolin were 0.057, 0.12, 0.24, 0.45 and 0.75 mg a.s./L and ranged from 75 to 94% of nominal concentrations. All chemical and physical parameters for the 21-day study were within acceptable ranges. All validation criteria were met for the study.

A summary of percent adult survival, onset of reproduction, total live young produced per surviving female, and length and dry weight of surviving adults is shown in Table 38.

Table 38
Summary of effects following exposure of *Daphnia magna* to oxathiapiprolin for 21 days

Mean, measured oxathiapiprolin concentration (mg a.s./L)	Mean % adult survival[a,e,g]	First day of reproduction[b]	Mean total live young [c,g]	Mean total immobile young[d,f]	Mean adult length (mm)[e]	Mean adult dry weight (mg)[e]
Water Control (0.0)	85	7 to 8	291	0.29	5.0	1.12
Solvent Control (0.0)	80	7 to 8	280	0.063	5.1	1.07
0.057	100	7 to 8	281	0.10	5.1	0.99
0.12	80	7 to 8	300	0.00	5.0	1.03
0.24	70	7 to 9	245*	0.00	5.0	1.22
0.45	80	7 to 8	286	0.00	5.1	1.07
0.75	90	7 to 8	288	0.11	5.0	1.02

[a] Percent of adult daphnids alive at the end of the test.

[b] First day that reproduction was observed in each treatment group.

[c] Mean number of live young produced per surviving female.

[d] Mean number of immobile young produced per surviving female.

[e] There were no statistically significant differences in survival (Fisher's Exact test, $p > 0.05$), in mean total length (Bonferroni t-test, $p > 0.05$) or in mean dry weight (Dunnett's test, $p \leq 0.05$) from the pooled controls.

[f] The frequencies and the numbers of immobile neonates produced during the test were low; therefore, the statistical analysis of this endpoint was not performed.

[g] The 21-day EC_{50} value for adult immobility and the 21-day EC_{50} value for reproduction were both greater than 0.75 mg a.s./L, the highest mean, measured test concentration.

* Statistically significant reductions in reproduction (Dunnett's test, $p \leq 0.05$); however, it did not follow a dose responsive pattern.

CONCLUSION

The 21-day NOEC and LOEC values for *Daphnia magna* based on adult survival, reproduction and growth (total length and dry weight) and mean, measured concentrations of oxathiapiprolin were 0.75 and greater than 0.75 mg a.s./L, respectively. The MATC value was estimated to be greater than 0.75 mg a.s./L. The 21-day EC_{50} value for adult immobility and the 21-day EC_{50} value for reproduction were both greater than 0.75 mg a.s./L, the highest mean, measured test concentration.

Report: Claude, M.B., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2012); DPX-QGU42 technical: A follow-through life-cycle toxicity test with the saltwater mysid (*Americamysis bahia*)

DuPont Report No.: DuPont-32456

Guidelines: OPPTS 850.1350 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Controls:	Dilution water (UV-sterilized, filtered saltwater) Solvent control (0.02 mL/L dimethylformamide)
Test vehicle:	Solvent dimethylformamide (0.02 mL/L DMF)
Toxic reference:	None
Test organism:	Saltwater mysid
Species:	*Americamysis bahia*
Age/life stage at dosing:	<24 hours
Initial population:	15 mysids per test compartment per test chamber
Diet:	Live brine shrimp nauplii (*Aretmia sp.*) were fed to the mysids up to four times a day. Live brine shrimp enriched with A1 DHA Selco or Algamac 3050 was fed to the mysids as one of the feedings at the end of each day. Additionally, the mysids were also fed *Skeletonema costatum* as a supplement one time each day of the study. Feeding rates varied depending on the age of the mysids.
Test chamber:	Juvenile Phase: 9-L glass aquaria containing approximately 2.5 L of test solution. Juvenile compartments were 2-L glass containers measuring approximately 12 cm in diameter and 19 cm in height, with two nylon mesh-covered holes on opposite sides of the container. Adult Phase: 19-L glass aquaria filled with approximately 14.5 L of test solution, which contained a self-starting siphoning system to exchange test solution. Reproductive compartments were approximately 10-cm diameter glass petri dishes with sides of nylon mesh screen.
Environmental conditions:	Dissolved oxygen: ≥5.4 mg/L (≥74% of saturation) pH: 7.8 to 8.0
Temperature:	25.1 to 26.4°C in test chambers; 25 to 27°C measured continuously in the negative control replicate A, measured to the nearest 1°C.
Photoperiod:	14 hours light (108 lux at initiation) and 10 hours dark including 120 min transitional period preceding and following the 14-hr light interval.

The effects of oxathiapiprolin on the survival, growth and reproduction of *Americamysis bahia* were determined in an aerated, flow-through, 32-day test. Treatments consisted of a dilution water control, solvent (0.02 mL/L dimethylformamide) control and five nominal oxathiapiprolin concentrations of 0.031, 0.063, 0.13, 0.25 and 0.50 mg a.s./L (mean, measured oxathiapiprolin concentrations of 0.029, 0.058, 0.12, 0.21 and 0.30 mg a.s./L). The concentrations were selected based on the solubility limit of the test substance in the test system. A total of 4 replicates, each containing fifteen <24-hour-old neonates, were tested per compartment, one compartment per concentration and control group (60 neonates/concentration). On Day 15 of the test, after mysids attained sexual maturity, male and female adults were paired in each treatment and control group, with a maximum of five reproductive pairs per replicate. Test concentrations were maintained by a continuous-flow diluter.

Observations

Observations were made daily of the survival and behaviour of each first-generation mysid. After the mysids were sexually identified and paired, and with the onset of reproduction, young mysids that were produced were

counted, recorded and removed daily. Second-generation mysids were also observed for abnormal development and aberrant behaviour. Male and female total body length and dry weight of surviving adult mysids were determined at test end (32 days).

Statistics

Test endpoints analysed statistically for first-generation mysids were survival, reproduction (the number of young produced per reproductive day, the number of young per surviving female and the percent of surviving females that produced young), and growth (total body length and dry weight for male and female mysids).

Survival data and percent of surviving females producing young data (discrete-variable data) were analysed using Chi-square and Fisher's Exact test to determine treatment groups that showed a statistically significant difference ($p \leq 0.05$) from the pooled control.

Reproduction (number of young per reproductive day and number of young per surviving female) and growth data (continuous variable data) were evaluated for normality using Shapiro-Wilk's test and for homogeneity of variance using Levene's test ($p = 0.01$).

Those treatments that were significantly different from the pooled/negative controls means were identified using Dunnett's test ($p \leq 0.05$), since all data passed the assumptions of normality and homogeneity of variance.

FINDINGS

Analytical verification of oxathiapiprolin concentrations was made on test solutions sampled on Day 0 and at regular intervals during the study. Mean, measured concentrations of oxathiapiprolin were 0.029, 0.058, 0.12, 0.21 and 0.30 mg a.s./L and ranged from 60 to 94% of nominal concentrations. All chemical and physical parameters for the 32-day study were within acceptable ranges. All validity criteria were met for the study.

A summary of percent juvenile survival, adult survival, young per reproductive day, young produced per surviving female, percent of surviving females producing young, and male and female total body length and dry weight of surviving adults is shown in Table 39.

Table 39
Summary of effects following exposure of *Americamysis bahia* to oxathiapiprolin for 32 days

Mean, measured oxathiapiprolin concentration (mg a.s./L)	Mean % juvenile survival[a]	Mean % adult survival[b,d]	Mean number of young produced per reproductive day	Mean % of surviving females producing young[c]	Mean number of young per surviving female[c]	Mean male total length (mm)	Mean female total length (mm)	Mean male dry weight (mg)	Mean female dry weight (mg)
Water control (0.0)	95.0	82.7	0.719	100	12.4	7.83	8.20	0.88	1.27
Solvent control (0.0)	93.3	81.4	0.611	100	10.8	7.52	8.03	0.83	1.17
0.029	91.7	79.6	0.663	100	11.5	7.79	8.14	0.91	1.22
0.058	96.7	88.2	0.501	94.4	7.4	7.81	8.12	0.90	1.23
0.12	88.3	86.7	0.268*	100	4.6*	7.86	8.09	0.91	1.21
0.21	93.3	85.4	0.298*	94.7	5.1*	7.82	8.09	0.83	1.17
0.30	65.0*	96.8	0.122*	15.4*	2.1*	7.37	7.64*	0.74*	0.95*

[a] Percent of juvenile mysids alive at pairing on Day 15 of the test.

[b] Percent of adult mysids alive from Day 16 to the end of the test.

[c] Calculated based on the total number of surviving females present at test termination. Females that died prior to test termination and the young that they produced were excluded from the calculation of the mean percent of females producing young and the mean number of young per female.

[d] There were no statistically significant differences in adult survival (Fisher's Exact test, $p > 0.05$) from the pooled controls.

* Statistically significant reductions in reproduction (number of young per reproductive day and number of young per surviving female), mean total body length and dry weight (Dunnett's test, $p \leq 0.05$); juvenile survival and percent of surviving females producing young (Fisher's Exact test, $p \leq 0.05$).

CONCLUSION

The 32-day NOEC and LOEC values for *Americamysis bahia* based on reproduction, the most sensitive endpoint, and mean, measured concentrations of oxathiapiprolin were 0.058 and 0.12 mg a.s./L, respectively. The MATC value was calculated to be 0.083 mg a.s./L.

5.4.3 Algae and aquatic plants

Report: Arnie, J.R., Kendall, T.Z., Porch, J.R. (2013a); DPX-QGU42 technical: A 96-hour toxicity test with the marine diatom (*Skeletonema costatum*)

DuPont Report No.: DuPont-35834

Guidelines: OECD 201 (2006), OCSPP 850.4500 (2012) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Control:	Saltwater algal medium
Test vehicle:	None
Toxic reference:	None
Test organism:	Marine diatom
Species:	*Skeletonema costatum*
Initial population:	Approximately 10000 cells/mL
Growth medium:	Saltwater algal medium
Test chamber:	250-mL Erlenmeyer flask containing 100 mL of test solution and plugged with foam stoppers
Environmental conditions (in-life period):	
Temperature:	19.5 to 21.4°C (measured in a container of water located adjacent to the test)
Photoperiod:	14 hour photoperiod (5600 to 6510 lux)
pH	8.0 to 8.9 throughout the exposure period

A study was conducted to determine the effect of oxathiapiprolin on area under the growth curve, growth rate and yield of the marine diatom, *Skeletonema costatum*. The diatoms were exposed to an untreated blank control, and five mean, measured concentrations of 13, 42, 96, 141, and 351 µg a.s./L in saltwater algal medium for 96 hours, without test medium renewal. Four replicate test vessels were maintained in the treatment groups and blank control. An abiotic (stability) control was also included at the highest test concentration and was tested as a single unit (no replicates).

Observations

Test concentrations were measured on Day 0 and Day 4 (96 hours) to verify stability of the test item. Cell counts were recorded for samples collected approximately 24, 48, 72, and 96 hours after test initiation. Area under the growth curve, growth rate, and yield were recorded and expressed as percent inhibition relative to the blank control replicates following exposure to oxathiapiprolin for 96 hours.

Statistics

Area under the growth curve, growth rate and yield data were evaluated for normality and homogeneity of variance ($\alpha = 0.01$) using the Shapiro-Wilk's and Levene's tests, respectively. The 96-hour growth rate and yield data failed to meet assumptions of normal distribution. Log transformation of the data failed to resolve this issue. The treatment groups were compared to the blank control using ANOVA and Dunnett's test ($\alpha = 0.05$). Non-parametric analyses (Jonkheere-Terpstra Trend Test) were also conducted with the datasets that failed Shapiro-Wilk's test. The results of the statistical analyses, as well as an evaluation of the concentration-response pattern, were used to determine the NOEC relative to each parameter at 72 and 96 hours.

FINDINGS

Day 0 measured concentrations for the 31, 63, 125, 250, and 500 µg a.s./L treatment levels ranged from 51 to 95% of targeted nominal concentrations. Measured concentrations in the nominal 31 and 250 µg a.s./L treatment groups were 51 and 67% of nominal. On Day 4, measured concentrations of oxathiapiprolin in the biotic test solutions ranged from less than the limit of quantitation to 59% of nominal. Measured concentrations of oxathiapiprolin in the abiotic control solution at test initiation and at test termination were 92 and 48% of the nominal concentration, respectively. The untreated control solutions contained no detectable concentrations of the active substance on Day 0 or Day 4. The results of the study are based on mean, measured test concentrations.

A summary of algal growth inhibition following exposure of *S. costatum* to oxathiapiprolin for 72 and 96 hours is presented in the table that follows.

Table 40
Summary of algal growth inhibition following exposure of *Skeletonema costatum* to oxathiapiprolin for 72 hours

Mean measured oxathiapiprolin test concentration (µg a.s./L)	% Inhibition relative to blank control		
	Area under the growth curve	Growth rate	Yield
Blank Control (0.0)	—	—	—
13	-11	-3	-10
42	8	4	17
96	22	7	25
141	2	1	2
351	50*	23*	58*

* Treatment group response was significantly different when compared to the blank control mean (Dunnett's Test, $p \leq 0.05$)

Table 41
Summary of algal growth inhibition following exposure of *Skeletonema costatum* to oxathiapiprolin for 96 hours

Mean measured oxathiapiprolin test concentration (µg a.s./L)	% Inhibition relative to blank control		
	Area under the growth curve	Growth rate	Yield
Blank Control (0.0)	—	—	—
13	-11	-3	-13
42	7	0	-2
96	11	-2	-11
141	-4	-3	-15
351	42*	7	21

* Treatment group response was significantly different when compared to the blank control mean (Dunnett's Test, $p \leq 0.05$)

CONCLUSIONS

The effects of oxathiapiprolin on area under the growth curve, growth rate and yield of *Skeletonema costatum* as calculated using mean measured concentrations and day 0 measured concentrations were as follows:

	Based on mean measured oxathiapiprolin concentration	**Based on Day 0 measured oxathiapiprolin concentration**
Area Under the Growth Curve:	72-hr E_bC_{50} >351 µg a.s./L (confidence interval not applicable)	72-hr E_bC_{50} >460 µg a.s./L (confidence interval not applicable)
	72-hr E_bC_{25} = 199 µg a.s./L (93 to >351 µg a.s./L)	72-hr E_bC_{25} = 224 µg a.s./L (92 to >460 µg a.s./L)
	0-72-hr NOEC = 141 µg a.s./L	0-72-hr NOEC = 168 µg a.s./L
	96-hr E_bC_{50} >351 µg a.s./L (confidence interval not applicable)	96-hr E_bC_{50} >460 µg a.s./L (confidence interval not applicable)
	96-hr E_bC_{25} = 333 µg a.s./L (316 to 351 µg a.s./L)	96-hr E_bC_{25} = 431 µg a.s./L (404 to 459 µg a.s./L)
	0-96-hr NOEC = 141 µg a.s./L	0-96-hr NOEC = 168 µg a.s./L
Growth Rate:	72-hr E_rC_{50} >351 µg a.s./L (confidence interval not applicable)	72-hr E_rC_{50} >460 µg a.s./L (confidence interval not applicable)
	72-hr E_rC_{25} >351 µg a.s./L (confidence interval not applicable)	72-hr E_rC_{25} >460 µg a.s./L (confidence interval not applicable)
	0-72-hr NOEC = 141 µg a.s./L	0-72-hr NOEC = 168 µg a.s./L
	96-hr E_rC_{50} >351 µg a.s./L (confidence interval not applicable)	96-hr E_rC_{50} >460 µg a.s./L (confidence interval not applicable)
	96-hr E_rC_{25} >351 µg a.s./L (confidence interval not applicable)	96-hr E_rC_{25} >460 µg a.s./L (confidence interval not applicable)
	0-96-hr NOEC = 351 µg a.s./L	0-96-hr NOEC = 460 µg a.s./L
Yield:	72-hr E_yC_{50} = 348 µg a.s./L (337 to >351 µg a.s./L)	72-hr E_yC_{50} = 451 µg a.s./L (415 to >460 µg a.s./L)
	72-hr E_yC_{25} = 320 µg a.s./L (299 to 343 µg a.s./L)	72-hr E_yC_{25} = 420 µg a.s./L (392 to 449 µg a.s./L)
	0-72-hr NOEC = 141 µg a.s./L	0-72-hr NOEC = 168 µg a.s./L
	96-hr E_yC_{50} >351 µg a.s./L (confidence interval not applicable)	96-hr E_yC_{50} >460 µg a.s./L (confidence interval not applicable)
	96-hr E_yC_{25} = 349 µg a.s./L (332 to >351 µg a.s./L)	96-hr E_yC_{25} = 457 µg a.s./L (435 to >460 µg a.s./L)
	0-96-hr NOEC = 351 µg a.s./L	0-96-hr NOEC = 460 µg a.s./L

Report: Arnie, J.R., Kendall, T.Z., Porch, J.R. (2013b); DPX-QGU42 technical: A 96-hour toxicity test with the freshwater diatom (*Navicula pelliculosa*)

DuPont Report No.: DuPont-35843

Guidelines: OECD 201 (2006), OCSPP 850.4500 (2012) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Control:	Freshwater AAP medium with silica constituents
Test vehicle:	None
Toxic reference:	None
Test organism:	Freshwater diatom
Species:	*Navicula pelliculosa*
Initial population:	Approximately 5000 cells/mL
Growth medium:	Freshwater AAP medium with silica constituents
Test chamber:	250-mL Erlenmeyer flask containing 100 mL of test solution and plugged with foam stoppers
Environmental conditions (in-life period):	
Temperature:	22.6 to 23.4°C (measured in a container of water located adjacent to the test)
Photoperiod:	Continuous lighting (5700 to 6570 lux)
pH	7.3 to 9.5 throughout the exposure period

A study was conducted to determine the effect of oxathiapiprolin on area under the growth curve, growth rate and yield of the freshwater diatom, *Navicula pelliculosa*. The diatoms were exposed to an untreated blank control, and five nominal of 31, 63, 125, 250 and 500 µg a.s./L in freshwater AAP medium with silica constituents for 96 hours, without test medium renewal. Four replicate test vessels were maintained in the treatment groups and six replicate test vessels were included in the blank control. An abiotic (stability) control was also included at the highest test concentration and was tested as a single unit (no replicates).

Observations

Test concentrations were measured on Day 0 and Day 4 (96 hours) to verify stability of the test item. Cell counts were recorded for samples collected approximately 24, 48, 72, and 96 hours after test initiation. Area under the growth curve, growth rate and yield were calculated and expressed as percent inhibition relative to the blank control replicates following exposure to oxathiapiprolin for 96 hours.

Statistics

Area under the growth curve, growth rate and yield data were evaluated for normality and homogeneity of variance ($\alpha = 0.01$) using the Shapiro-Wilk's and Levene's tests, respectively. The 96-hour growth rate and yield data failed to meet assumptions of normal distribution. Log transformation of the data failed to resolve this issue. The treatment groups were compared to the blank control using ANOVA and Dunnett's test ($\alpha = 0.05$). The results of the statistical analyses, as well as an evaluation of the concentration-response pattern, were used to determine the NOEC relative to each parameter at 72 and 96 hours.

FINDINGS

Day 0 measured concentrations for the 31, 63, 125, 250, and 500 µg a.s./L treatment levels ranged from 27 to 86% of targeted nominal concentrations. Measured concentrations in the nominal 125, 250, and 500 µg a.s./L treatment groups were 72, 27, and 70% of nominal, respectively. The low analytical recovery for the 500 µg a.s./L treatment group was attributed to the solubility of the test substance in this particular matrix. The aberrant analytical recovery observed in the 250 µg a.s./L treatment group resulted in the data from that treatment level being excluded from statistical analyses. On Day 4, measured concentrations of oxathiapiprolin in the biotic test solutions ranged from less than the limit of quantitation to 20% of nominal. Measured concentrations of oxathiapiprolin in the abiotic control solution at test initiation and at test termination were 70 and 33% of the nominal concentration, respectively. The untreated control solutions contained no detectable concentrations of the active substance on Day 0 or Day 4. The results of the study are based on geometric mean, measured test concentrations.

Table 42
Summary of algal growth inhibition following exposure of *Navicula pelliculosa* to oxathiapiprolin for 72 hours

Geometric mean, measured oxathiapiprolin test concentration (μg a.s./L)	% Inhibition relative to blank control[a]		
	Area under the growth curve	Growth rate	Yield
Blank Control (0.0)	—	—	—
16	-12	-1	-3
23	-12	-2	-10
47	-18	-2	-12
26	-23	-2	-16
163	-7	-1	-4

[a] None of the treatment group responses were significantly reduced when compared to the blank control mean (Dunnett's Test, p >0.05). The 26 μg a.s./L treatment group was considered to be an outlier and was excluded from statistical analyses.

Table 43
Summary of algal growth inhibition following exposure of *Navicula pelliculosa* to oxathiapiprolin for 96 hours

Geometric mean, measured oxathiapiprolin test concentration (μg a.s./L)	% Inhibition relative to blank control[a]		
	Area under the growth curve	Growth rate	Yield
Blank Control (0.0)	—	—	—
16	-6	0	-2
23	-7	0	1
47	-8	0	3
26	-14	-1	-4
163	-2	1	5

[a] None of the treatment group responses were significantly reduced when compared to the blank control mean (Dunnett's Test, p >0.05). The 26 μg a.s./L treatment group was considered to be an outlier and was excluded from statistical analyses.

CONCLUSIONS

The effects of oxathiapiprolin on area under the growth curve, growth rate, and yield of *Navicula pelliculosa* as calculated using mean measured concentrations were as follows:

	Based on mean measured oxathiapiprolin concentration	**Based on Day 0 measured oxathiapiprolin concentration**
Area Under the Growth Curve:	72-hr E_bC_{50} >163 µg a.s./L (confidence interval not applicable)	72-hr E_bC_{50} >348 µg a.s./L (confidence interval not applicable)
	72-hr E_bC_{25} >163 µg a.s./L (confidence interval not applicable)	72-hr E_bC_{25} >348 µg a.s./L (confidence interval not applicable)
	0-72-hr NOEC = 163 µg a.s./L	0-72-hr NOEC = 348 µg a.s./L
	96-hr E_bC_{50} >163 µg a.s./L (confidence interval not applicable)	96-hr E_bC_{50} >348 µg a.s./L (confidence interval not applicable)
	96-hr E_bC_{25} >163 µg a.s./L (confidence interval not applicable)	96-hr E_bC_{25} >348 µg a.s./L (confidence interval not applicable)
	0-96-hr NOEC = 163 µg a.s./L	0-96-hr NOEC = 348 µg a.s./L
Growth Rate:	72-hr E_rC_{50} >163 µg a.s./L (confidence interval not applicable)	72-hr E_rC_{50} >348 µg a.s./L (confidence interval not applicable)
	72-hr E_rC_{25} >163 µg a.s./L (confidence interval not applicable)	72-hr E_rC_{25} >348 µg a.s./L (confidence interval not applicable)
	0-72-hr NOEC = 163 µg a.s./L	0-72-hr NOEC = 348 µg a.s./L
	96-hr E_rC_{50} >163 µg a.s./L (confidence interval not applicable)	96-hr E_rC_{50} >348 µg a.s./L (confidence interval not applicable)
	96-hr E_rC_{25} >163 µg a.s./L (confidence interval not applicable)	96-hr E_rC_{25} >348 µg a.s./L (confidence interval not applicable)
	0-96-hr NOEC = 163 µg a.s./L	0-96-hr NOEC = 348 µg a.s./L
Yield:	72-hr E_yC_{50} >163 µg a.s./L (confidence interval not applicable)	72-hr E_yC_{50} >348 µg a.s./L (confidence interval not applicable)
	72-hr E_yC_{25} >163 µg a.s./L (confidence interval not applicable)	72-hr E_yC_{25} >348 µg a.s./L (confidence interval not applicable)
	0-72-hr NOEC = 163 µg a.s./L	0-72-hr NOEC = 348 µg a.s./L
	96-hr E_yC_{50} >163 µg a.s./L (confidence interval not applicable)	96-hr E_yC_{50} >348 µg a.s./L (confidence interval not applicable)
	96-hr E_yC_{25} >163 µg a.s./L (confidence interval not applicable)	96-hr E_yC_{25} >348 µg a.s./L (confidence interval not applicable)
	0-96-hr NOEC = 163 µg a.s./L	0-96-hr NOEC = 348 µg a.s./L

Report: Kley, A., Deierling, T. (2010a); DPX-QGU42 technical: Effects on growth to the green algae *Pseudokirchneriella subcapitata* in a static test

DuPont Report No.: DuPont-29275

Guidelines: OECD 201 (2006), EPA 712-C-96-164 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-126
Purity:	98.9%
Control:	OECD medium
Test vehicle:	OECD medium
Toxic reference:	Potassium dichromate p.a.
Test organism:	Algae
Species:	*Pseudokirchneriella subcapitata*
Initial cell density:	10000 cells per mL
Growth medium:	OECD medium
Test chamber:	Erlenmeyer flasks of 50 mL volume with 50 mL of test medium.
Environmental conditions (in-life period):	
Water Temperature:	23 to 24°C
pH:	8.1 at test start and 9.5–9.6 at test end
Photoperiod:	24 hour photoperiod (4635 lux mean; range: 4510-4720 lux)

Toxicity of oxathiapiprolin to the unicellular green algal species *Pseudokirchneriella subcapitata* was determined in a static 96 hour test. The effect of oxathiapiprolin on *Pseudokirchneriella subcapitata* was determined in OECD medium. Treatments consisted of five mean measured test concentrations of 142, 70, 36, 20, and 10 µg a.s./L and a control. Each test concentration was tested as three and the control was tested as six replicates. At test start 10000 cells/mL were inoculated per mL test medium. Algae were incubated for 96 hours.

Observations

The cell densities in the samples were determined by spectrophotometrical measurement. Therefore defined volumes of the algal suspensions from all replicates and from the blanks were sampled after 24, 48, 72, and 96 hours of exposure, and were not replaced.

The algal cell densities were calculated by subtracting the absorption of the blanks, from each of the measured absorption of the test media (with algae).

The cell densities in a number of samples from one control replicate were counted by microscope after 96 hours of test duration. Out of this control five defined dilutions were prepared and measured spectrophotometrically. Based on the counted cell densities and the absorption of the control sample and the dilutions a linear regression was performed for the calculation of the cell densities in all other samples measured spectrophotometrically during the test.

To check for any effect of the test item on the morphology of the algal cells, one sample from a test item concentration with a reduced cell density was taken after the test period of 96 hours. The shape of the treated algal cells compared to the control was examined microscopically.

Statistics

Based on the calculated cell densities, the 72- and the 96-hour E_rC_{50} as well as the 72- and the 96-hour E_yC_{50} and where possible their 95%-confidence limits were calculated by Probit analysis.

For the determination of the 72- and the 96-hour LOEC as well as the 72- and the 96-hour NOEC, the calculated growth rates and yields at each test concentration were tested for significant differences compared to the control values by the Welch t-test (growth rate) and the Williams t-test (yield).

The software used to perform the statistical analysis was ToxRat Professional, Version 2.10, ToxRat® Solutions GmbH, 2009.

FINDINGS

The mean measured values of oxathiapiprolin ranged from 10 to 142 µg a.s./L. At each concentration level the relative standard deviation of oxathiapiprolin was less than 25%. The aged samples of the lowest concentrations

were below the LOQ of this method. Since the recoveries were in the expected range and standards in this range could be measured, the values were nevertheless used for calculation. Since a filtrate was tested and no nominal values are available, the biological endpoints refer to the mean, measured values.

Table 44
Yield (y) and percentage inhibition of yield during the test period

Mean measured concentration	Yield y [mg/L] and % inhibition of y											
	0 - 24 hours			0 - 48 hours			0 - 72 hours			0 - 96 hours		
[µg test item/L]	y	%		y	%		y	%		y	%	
Control	2.96	0.0		16.87	0.0		49.26	0.0		158.11	0.0	
9	2.36	20.1	*	16.89	-0.1	-	49.54	-0.6	-	150.94	4.5	*
18	1.81	38.8	*	13.96	17.2	-	45.31	8.0	-	151.97	3.9	*
36	2.80	5.4	*	15.66	7.2	-	49.14	0.2	-	153.48	2.9	-
70	1.73	41.5	*	17.36	-2.9	-	43.56	11.6	-	155.85	1.4	-
142	3.87	-30.8	-	19.50	-15.6	-	49.62	-0.7	-	160.36	-1.4	-

negative values in '% inhibition' indicate an increase in growth relative to that of the control

* mean value significantly different from the control (tested with Williams Test, $\alpha = 0.05$, one-sided)

Table 45
Growth rates (µ) and percentage inhibition of growth rates during the test period

Mean measured concentration	Growth rates µ [1/day] and % inhibition of µ											
	0 - 24 hours			0 - 48 hours			0 - 72 hours			0 - 96 hours		
[µg test item/L]	µ	%		µ	%		µ	%		µ	%	
Control	1.373	0.0		1.441	0.0		1.305	0.0		1.267	0.0	
9	1.197	12.8	-	1.442	-0.1	-	1.307	-0.2	-	1.256	0.9	-
18	1.026	25.3	-	1.351	6.2	-	1.278	2.0	-	1.258	0.8	-
36	1.331	3.1	-	1.406	2.4	-	1.303	0.1	-	1.260	0.6	-
70	0.992	27.8	-	1.451	-0.7	-	1.265	3.0	-	1.264	0.3	-
142	1.579	-15.0	-	1.510	-4.8	-	1.308	-0.3	-	1.271	-0.3	-

negative values in '% inhibition' indicate an increase in growth relative to that of the control

\- no significant difference compared to the control (tested with Welch t-test for inhomogeneous variances, $\alpha = 0.05$, one-sided)

CONCLUSIONS

Growth inhibition values based on mean measured test concentrations obtained with oxathiapiprolin on *Pseudokirchneriella subcapitata* were as follows:

Parameter	Yield	Growth rate
72-hour EC_{50}	>142 µg a.s./L	>142 µg a.s./L
96-hour EC_{50}	>142 µg a.s./L	>142 µg a.s./L
95% conf. limits	n.d.	n.d.
72-hour NOEC	≥142 µg a.s./L	≥142 µg a.s./L
96-hour NOEC	≥142 µg a.s./L	≥142 µg a.s./L
72-hour LOEC	>142 µg a.s./L	>142 µg a.s./L
96-hour LOEC	>142 µg a.s./L	>142 µg a.s./L

n.d. = not determinable

Values refer to mean measured test concentrations.

Report: Kley, A., Deierling, T. (2010b); DPX-QGU42 technical: Effects on growth to the blue-green algae *Anabaena flos-aquae* in a static test

DuPont Report No.: DuPont-29320

Guidelines: OECD 201 (2006), EPA 712-C-96-164 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-126
Purity:	98.9% by analysis
Control:	20X AAP nutrient medium
Test vehicle:	20X AAP nutrient medium
Toxic reference:	3,5-dichlorophenol
Test organism:	Algae
Species:	*Anabaena flos-aquae*
Initial cell density:	10000 cells per mL
Origin:	The algae were supplied by "The University of Texas at Austin, MCDB, Bio Labs311", Austin, TX 78712, USA.
Growth medium:	20X AAP nutrient medium
Test chamber:	Erlenmeyer flasks of 50 mL volume with 50 mL of test medium.
Environmental conditions (in-life period):	
Water temperature:	23 to 24°C
pH:	7.5 at test start and 8.9–9.0 at test end
Photoperiod:	24 hour photoperiod (2663 lux mean; range: 2430–2950 lux)

Toxicity of oxathiapiprolin to the freshwater blue-green algal species *Anabaena flos-aquae* was determined in a static 96-hour test. The effect of oxathiapiprolin on *Anabaena flos-aquae* was determined in 20X AAP nutrient medium. Treatments consisted of six mean measured test concentrations of 193, 96, 45, 24, 13, and 6 µg a.s./L and a control. Each test concentration was tested as three and the control as six replicates, respectively. At test start 10000 cells/mL were inoculated per mL test medium. Algae were incubated for 96 hours.

Observations

The cell densities in the samples were determined by spectrophotometrical measurement. Therefore defined volumes of the algal suspensions from all replicates and from the blanks were sampled after 24, 48, 72, and 96 hours of exposure, and were not replaced. The algal cell densities were calculated by subtracting the absorption of the blanks, from each of the measured absorption of the test media (with algae).

The cell densities in a number of samples from one control replicate were counted by microscope after 96 hours of test duration. Out of this control five defined dilutions were prepared and measured spectrophotometrically. Based on the counted cell densities and the absorption of the control sample and the dilutions a linear regression was performed for the calculation of the cell densities in all other samples measured spectrophotometrically during the test.

To check for any effect of the test item on the morphology of the algal cells, one sample from a test item concentration with a reduced cell density was taken after the test period of 96 hours. The shape of the treated algal cells compared to the control was examined microscopically.

Statistics

Based on the calculated cell densities, the 72- and the 96-hour E_rC_{50} as well as the 72- and the 96-hour E_yC_{50} and where possible their 95%-confidence limits were calculated by Probit analysis.

For the determination of the 72- and the 96-hour LOEC as well as the 72- and the 96-hour NOEC, the calculated growth rates and yields at each test concentration were tested for significant differences compared to the control values by the Williams Test (growth rate and yield), respectively.

The software used to perform the statistical analysis was ToxRat Professional, Version 2.10, ToxRat® Solutions GmbH, 2009.

FINDINGS

The mean measured values of oxathiapiprolin ranged from 5.7 to 192.6 µg a.s./L. At each concentration level the relative standard deviation of oxathiapiprolin was less than or equal to 18%. Since a filtrate was tested, and no nominal values are available, the biological endpoints refer to the mean measured values.

Table 46
Yield (y) and percentage inhibition of yield during the test period

Mean measured concentration [µg test item/L]	Yield y [mg/L] and % inhibition of y											
	0 - 24 hours			0 - 48 hours			0 - 72 hours			0 - 96 hours		
	y	%		y	%		y	%		y	%	
Control	2.75	0.0		6.62	0.0		16.82	0.0		44.10	0.0	
6	2.66	3.1	*	5.67	14.3	*	17.27	-2.7	-	43.48	1.4	-
13	2.77	-0.6	-	4.49	32.1	*	15.99	4.9	-	36.92	16.3	-
24	2.49	9.4	*	4.63	30.0	*	16.55	1.6	-	43.20	2.0	-
45	3.22	-17.0	-	4.53	31.6	*	17.58	-4.5	-	42.75	3.1	-
96	2.91	-5.7	-	3.35	49.3	*	19.07	-13.3	-	37.64	14.6	-
193	3.35	-22.0	-	4.29	35.2	*	18.20	-8.2	-	42.34	4.0	-

negative values in '% inhibition' indicate an increase in growth relative to that of the control

* mean value significantly different from the control (tested with Williams Test, $\alpha = 0.05$, one-sided)

Table 47
Growth rates (μ) and percentage inhibition of growth rate during the test period

Mean measured concentration [μg test item/L]	Growth rates μ [1/day] and % inhibition of μ											
	0 - 24 hours			0 - 48 hours			0 - 72 hours			0 - 96 hours		
	μ	%		μ	%		μ	%		μ	%	
Control	1.320	0.0		1.015	0.0		0.959	0.0		0.951	0.0	
6	1.298	1.6	-	0.948	6.6	*	0.968	-1.0	-	0.947	0.4	-
13	1.326	-0.4	-	0.850	16.3	*	0.944	1.6	-	0.908	4.5	-
24	1.239	6.1	-	0.862	15.1	*	0.953	0.7	-	0.946	0.5	-
45	1.402	-6.2	-	0.853	16.0	*	0.974	-1.5	-	0.944	0.7	-
96	1.362	-3.2	-	0.733	27.8	*	0.999	-4.1	-	0.913	4.0	-
193	1.471	-11.4	-	0.832	18.1	*	0.985	-2.7	-	0.938	1.3	-

negative values in '% inhibition' indicate an increase in growth relative to that of the control

* mean value significantly different from the control (tested with Williams Test, $\alpha = 0.05$, one-sided)

CONCLUSIONS

Growth inhibition values based on mean measured test concentrations obtained with oxathiapiprolin on *Anabaena flos-aquae* were as follows:

Parameter	Growth rate	Yield
72-hour EC_{50}	>193 μg a.s./L	>193 μg a.s./L
96-hour EC_{50}	>193 μg a.s./L	>193 μg a.s./L
95% conf. limits	n.d.	n.d.
72-hour NOEC	≥193 μg a.s./L	≥193 μg a.s./L
96-hour NOEC	≥193 μg a.s./L	≥193 μg a.s./L
72-hour LOEC	>193 μg a.s./L	>193 μg a.s./L
96-hour LOEC	>193 μg a.s./L	>193 μg a.s./L

n.d. = not determinable

Values refer to mean measured test concentrations.

Report: Porch, J.R., Kendall, T.Z., Krueger, H.O. (2011); DPX-QGU42 technical: A 7-day static-renewal toxicity test with duckweed (*Lemna gibba* G3)

DuPont Report No.: DuPont-32480

Guidelines: OPPTS 850.4400 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Control:	20X AAP nutrient medium
Test vehicle:	N,N-dimethylformamide (DMF) at 0.1 mL/L
Toxic reference:	None
Test organism:	Duckweed
Species:	*Lemna gibba* G3
Initial population:	4 plants, totaling 12 fronds
Growth medium:	20X AAP nutrient medium
Test chamber:	250-mL beaker containing approximately 100 mL of test solution and covered with a disposable petri dish lid to permit gas exchange
Environmental conditions (in-life period):	
Temperature:	22.8 to 24.3°C (Environmental growth chamber and surrogate vessel, during exposure period)
Photoperiod:	24-hr photoperiod (4260 to 5470 lux)
pH:	7.9 to 9.2 throughout the exposure period

Toxicity of oxathiapiprolin to the floating, freshwater vascular plant *Lemna gibba* G3 was determined in a static-renewal, 7-day test. The effect of oxathiapiprolin on *Lemna gibba* G3 was determined in 20X AAP nutrient medium. Treatments consisted of five nominal concentrations of 0.0625, 0.125, 0.25, 0.5 and 1.0 mg a.s./L, a blank control, a solvent control and an abiotic control. The concentrations were selected based on the solubility limit of the test substance in the test system. Each test concentration and the blank and solvent controls were tested as three replicates. The abiotic control was tested as a single unit. Three additional replicates at the highest two treatment levels and the negative control were designated for use, if needed, in the recovery test. Four plants totaling 12 fronds were used per replicate. Plants were incubated in an environmental chamber for 7 days, with renewal of test solutions on Day 3.

Observations

Test concentrations were measured on Days 0 (new), 3 (new and old), and 7 (old) to verify stability and concentrations of the test items. Frond counts were made on Days 0, 3, 5, and 7. Biomass was determined at the completion of the 7-day test. Growth rates were determined on Day 7 and were based on frond count and on biomass. Healthy frond count yield and biomass yield were determined by subtracting the initial frond count or biomass from the test end values. Healthy frond count, frond count yield, biomass, biomass yield, growth rate based on frond count, and growth rate based on biomass were expressed as percent inhibition relative to the solvent control.

Statistics

Day 7 EC_{50} values were estimated by visual inspection of the treatment response (frond count, frond count yield, biomass, biomass yield, and growth rates based on frond count and biomass) in treatment groups relative to the solvent control. Dead, chlorotic, and necrotic fronds were counted and combined in order to calculate the percentage of abnormal fronds relative to the total number of fronds present in each test chamber.

The data were evaluated for normality and homogeneity of variances ($\alpha = 0.01$) using the Shapiro-Wilk's and Levene's tests, respectively. The blank control and solvent control were compared for significant differences using a t-test. Treatment group means were compared to the means of the solvent control group ($\alpha = 0.05$) using analysis of variance (ANOVA) and Dunnett's t-test. Results of the statistical analyses, as well as an evaluation of the concentration-response pattern and other observations of effects, were used to determine the NOEC and LOEC. All calculations and statistical analyses were conducted using "Microsoft Excel 2000," or "The SAS System for Windows Version 8.2."

FINDINGS

The mean, measured concentrations of oxathiapiprolin in biological replicates were 0.0653, 0.126, 0.26, 0.47, and 0.79 mg a.s./L., which were 104, 101, 104, 94 and 79% of nominal, respectively. Recovery in the abiotic control replicate was 0.73 mg a.s./L (73% of nominal). Blank control and solvent control solutions showed no detectable concentrations of the active substance. The test item was determined to be stable over the course of the test. All validation criteria were met for the study.

Table 48
Summary of growth inhibition (frond count and biomass) following exposure of *Lemna gibba* G3 to oxathiapiprolin for 7 days

Mean, measured concentration (mg a.s./L)	Frond count		Biomass	
	7-Day mean frond count	% Inhibition[a] relative to solvent control	7-Day mean biomass (mg)	% Inhibition[a] relative to solvent control
Blank Control	185	—	24.1	—
Solvent Control	174	—	22.7	—
0.0653	182	-4	21.7	4
0.126	168	3	21.2	6
0.26	175	0	22.7	0
0.47	161	8	21.1	7
0.79	165	6	22.0	3

[a] Because there was no significant difference between the blank and solvent controls, the solvent control was used. No significant differences from solvent control were detected (Dunnett's test, p >0.05).

Table 49
Summary of growth inhibition (frond count yield and biomass yield) following exposure of *Lemna gibba* G3 to oxathiapiprolin for 7 days

Mean, Measured concentration (mg a.s./L)	Frond count yield		Biomass yield	
	7-Day mean frond count yield	% Inhibition[a] relative to solvent control	7-Day mean biomass yield (mg)	% Inhibition[a] relative to solvent control
Blank Control	173	—	22.9	—
Solvent Control	162	—	21.5	—
0.0653	170	-5	20.6	4
0.126	156	4	20.0	7
0.26	163	0	21.5	0
0.47	149	8	20.0	7
0.79	153	6	20.8	3

[a] Because there was no significant difference between the blank and solvent controls, the solvent control was used. No significant differences from solvent control were detected (Dunnett's test, p >0.05).

Table 50
Summary of growth inhibition (growth rate) following exposure of *Lemna gibba* G3 to oxathiapiprolin for 7 days

Mean, Measured concentration (mg a.s./L)	0-7 day growth rate based on frond count		0-7 day growth rate based on biomass	
	0-7 day mean growth rate	% Inhibition[a] relative to solvent control	0-7 day mean growth rate	% Inhibition[a] relative to solvent control
Blank Control	0.390	—	0.432	—
Solvent Control	0.382	—	0.423	—
0.0653	0.388	-2	0.418	1
0.126	0.377	1	0.414	2
0.26	0.382	0	0.424	0
0.47	0.369	3	0.412	2
0.79	0.374	2	0.419	1

[a] Because there was no significant difference between the blank and solvent controls, the solvent control was used. No significant differences from solvent control were detected (Dunnett's test, p >0.05).

CONCLUSIONS

Growth inhibition values based on mean, measured concentrations obtained with oxathiapiprolin on *Lemna gibba* G3 were as follows:

7-Day Frond Count: EC_{50} >0.79 mg a.s./L
NOEC = 0.79 mg a.s./L
LOEC >0.79 mg a.s./L

7-Day Frond Count Yield: EC_{50} >0.79 mg a.s./L
NOEC = 0.79 mg a.s./L
LOEC >0.79 mg a.s./L

0-7 Day Frond Count Growth Rate: EC_{50} >0.79 mg a.s./L
NOEC = 0.79 mg a.s./L
LOEC >0.79 mg a.s./L

7-Day Biomass: EC_{50} >0.79 mg a.s./L
NOEC = 0.79 mg a.s./L
LOEC >0.79 mg a.s./L

7-Day Biomass Yield: EC_{50} >0.79 mg a.s./L
NOEC = 0.79 mg a.s./L
LOEC >0.79 mg a.s./L

0-7 Day Biomass Growth Rate: EC_{50} >0.79 mg a.s./L
NOEC = 0.79 mg a.s./L
LOEC >0.79 mg a.s./L

5.4.4 Other aquatic organisms (including sediment)

Report: Thomas, S.T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O. (2012); DPX-QGU42 technical: A 48-hour static acute toxicity test with *Chironomus riparius*

DuPont Report No.: DuPont-32454

Guidelines: OECD 235 (2011), ASTM Standard E729-96 (1996) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Controls:	Dilution water (laboratory well water) control. Solvent Control (0.02 mL solvent/L dilution water)
Test vehicle:	Dimethylformamide (DMF)
Toxic reference:	Not applicable
Test organism:	Midge
Species:	*Chironmous riparius*
Age/life stage at dosing:	First instar (1–4 days post hatch)
Initial population:	Four replicate test chambers with 5 larvae per test chamber
Diet:	Unfed during test
Test chamber:	250-mL glass beaker containing approximately 220 mL of test solution (6.6-cm test solution depth)
Environmental conditions:	Dissolved oxygen: ≥8.1 mg/L (≥90% of saturation) pH: 8.1 to 8.5
Temperature:	19.4 to 20.8°C in test chambers; 20 to 21°C measured continuously in an adjacent container of water.
Photoperiod:	16 hr light (300 lux at initiation) and 8 hr dark including 30 min transitional period preceding and following the 16-hr light interval.

The acute toxicity of oxathiapiprolin to unfed *Chironomus riparius* (1–4 days old) was determined in an unaerated, static, 48-hour test. Treatments consisted of a dilution water control a solvent control, and mean measured test concentrations of 0.04 to 0.56 mg a.s./L. The concentrations were selected based on the solubility limit of the test substance in the test system. Five midge larvae were used per replicate with four replicates per test concentration and control.

Observations

Immobility and behavioural observations were made at approximately 19 hours, and at 24 and 48 hours (±1 hour) following initiation of exposure.

Statistics

No statistical analysis as there was less than 50% immobility/mortality in all of the oxathiapiprolin treatment groups at 24 and 48 hours.

FINDINGS

Nominal test concentrations of oxathiapiprolin were 0.04, 0.09, 0.18, 0.35 and 0.70 mg a.s./L. The highest nominal test concentration of 0.70 mg a.s./L was approximately at the solubility limit of the test material in the test system. Mean measured concentrations of oxathiapiprolin were 0.04, 0.08, 0.17, 0.32 and 0.56 mg a.s./L, ranging from 80 to 100% of nominal concentrations. No sublethal effects were observed. No immobility/mortalities were observed.

CONCLUSION

The 48-hour EC_{50} value, based on the mean measured test concentrations of oxathiapiprolin and immobility, was estimated to be >0.56 mg a.s./L. The highest mean measured test concentration causing no immobility at test end was 0.56 mg a.s./L. The lowest mean measured concentration causing 100% immobility at test end was >0.56 mg a.s./L.

Report: Thomas, S.T., Kendall, T.Z., Martin, K.H., Gallagher, S.P., Krueger, H.O (2013b); ^{14}C DPX-QGU42: A prolonged sediment toxicity test with *Chironomus riparius* using spiked sediment

DuPont Report No.: DuPont-35835

Guidelines: OECD 218 (2004) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Non-radiolabeled test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Radiolabeled test material:	[Isoxazoline-5-^{14}C]oxathiapiprolin
Lot/Batch #:	1640597
Radiochemical purity:	98.3%
Specific activity:	33.88 µCi/mg, 18.26 mCi/mmol, 1.25 MBq/mg
Controls:	Negative control and solvent control
Test vehicle:	Solvent acetone (10 mL acetone/kg sediment – allowed to evaporate)
Toxic reference:	None
Test organism:	Midge
Species:	*Chironomus riparius*
Age/life stage at dosing:	1-4 days (first instar)
Initial population:	20 larvae per test chamber
Diet:	Rabbit Food supplied by Hartz, Secaucus, New Jersey during holding and TetraMin® Flake food supplied by Doctors Foster and Smith, Blacksburg, Virginia during the test.
Test chamber:	One-quart glass jars
Environmental conditions:	Dissolved oxygen: ≥7.5 mg/L (≥83% of saturation) pH: 8.2 to 8.6
Temperature:	20 ± 2°C in test chambers; and measured continuously in a beaker of water adjacent to the test chambers, measured to the nearest 1°C.
Photoperiod:	16 hours light (321 lux at test initiation) and 8 hours dark including 30 min transitional period preceding and following the 16-hr light interval.

The effects of sediment incorporated [isoxazoline-5-^{14}C]oxathiapiprolin on the midge (*Chironomus riparius)* were determined in an aerated, static, 28-day test. Treatments consisted of a negative and solvent (acetone) control and five nominal oxathiapiprolin technical concentrations of 0.95, 3.1, 9.8, 31 and 100 mg a.s./kg (mean, measured concentrations of 0.69, 2.8, 8.0, 29 and 96 mg a.s./kg based on total radioactive residues). Each treatment group had four replicates used for biological observations. Each replicate was initiated with 20 first instar larvae. Four additional replicates were included in the test design for analytical measurements. Each analytical replicate contained 20 organisms except for those being sampled on Day 0. At each sampling interval, an entire analytical replicate from each treatment group was sacrificed for the measurement of oxathiapiprolin in sediment, overlying water and pore water.

Observations

Observations were made daily of the survival and emergence of the midges.

Statistics

The 28-day LC_{50} was determined by analysing the number of organisms that failed to emerge during the study as well as the number of organisms that emerged and died using binomial probability with nonlinear interpolation. The NOEC and LOEC were determined by visual interpretation of the dose response pattern and statistical analyses of the mean development times, emergence ratios and development rates. The data were analysed to determine any statistical differences between the negative and solvent control groups. Since there were no differences, the controls were pooled and the treatment groups were compared to the pooled control using a Dunnett's test.

FINDINGS

Analytical verification of [isoxazoline-5-^{14}C]oxathiapiprolin concentrations was made in sediment, overlying water and pore water sampled on Days 0, 7 and 28 of the test. Mean measured concentrations of oxathiapiprolin in the sediment were 0.69, 2.8, 8.0, 29 and 96 mg a.s./kg, based on total radioactive residues. All chemical and physical parameters for the 28-day study were within acceptable ranges. All validity criteria were met for the study.

A summary of the 28-day LC_{50}, NOEC and LOEC is shown in Table 51.

Table 51
Summary of effects for oxathiapiprolin to the midge (*Chironomus riparius*) in a prolonged sediment toxicity test using spiked sediment

Endpoint	Mean Measured Concentration in Sediment Based on TRR	Effect
28-day LC_{50}	6.9 mg a.s./kg, 95% confidence interval of 2.8 and 29 mg a.s./kg	Based on number failing to emerge and number that emerged and died.
NOEC	2.8 mg a.s./kg	Based on emergence ratios, most sensitive endpoint.
LOEC	8.0 mg a.s./kg	Based on emergence ratios, most sensitive endpoint.

CONCLUSION

The 28-day LC_{50} value based on emergence and/or mortality of *Chironomus riparius* exposed to sediment-incorporated [isoxazoline-5-^{14}C]oxathiapiprolin was 6.9 mg a.s./kg, with 95% confidence limits of 2.8 and 29 mg a.s./kg. There were no treatment related effects observed on mean development time in any of the treatment groups when compared to the pooled control. There were treatment related effects observed for emergence ratios between the pooled control group and the 8.0, 29 and 96 mg a.s./kg treatment groups. There was also a treatment related effect observed for development rate between the pooled control and the 96 mg a.s./kg treatment group. Therefore, the 28-day LOEC was 8.0 mg a.s./kg and the NOEC was 2.8 mg a.s./kg.

Report: Thomas, S.T., Kendall, T.Z., Martin, K.H., Gallagher, S.P., Krueger, H.O (2013c); ^{14}C DPX-QGU42: A prolonged sediment toxicity test with *Chironomus riparius* using spiked water

DuPont Report No.: DuPont-36043

Guidelines: OECD 219 (2004) **Deviations:** None

GLP: Yes

MATERIALS AND METHODS

Non-radiolabeled test material:	Oxathiapiprolin technical
Lot/Batch #:	QGU42-174
Purity:	95.8%
Description:	Solid
Radiolabeled test material	[Isoxazoline-5-^{14}C]oxathiapiprolin
Lot/Batch #:	1640597
Radiochemical purity:	98.3%
Specific activity:	33.88 μCi/mg, 18.26 mCi/mmol, 1.25 MBq/mg
Controls:	Negative control and solvent control
Test vehicle:	Solvent acetone (0.10 mL acetone/L water)
Toxic reference:	None
Test organism:	Midge
Species:	*Chironomus riparius*
Age/life stage at dosing:	1-4 days (first instar)
Initial population:	20 larvae per test chamber
Source:	Environmental Consulting and Testing of Superior, Wisconsin
Diet:	Rabbit Food supplied by Hartz, Secaucus, New Jersey during holding and TetraMin® Flake food supplied by Doctors Foster and Smith, Blacksburg, Virginia during the test.
Test chamber:	One-quart glass jars
Environmental conditions:	Dissolved oxygen: ≥7.2 mg/L (≥80% of saturation) pH: 8.0 to 8.6
Temperature:	20 ± 2°C in test chambers; and measured continuously in a beaker of water adjacent to the test chambers, measured to the nearest 1°C.
Photoperiod:	16 hours light (283 lux at test initiation) and 8 hours dark including 30 min transitional period preceding and following the 16-hr light interval.

The effects of [isoxazoline-5-^{14}C]oxathiapiprolin administered in overlying water on the midge (*Chironomus riparius)* were determined in an aerated, static, 28-day test. Treatments consisted of a negative and solvent (acetone) control and five nominal oxathiapiprolin technical concentrations of 0.010, 0.032, 0.10, 0.33 and 1.0 mg a.s./L (mean, measured concentrations of 0.011, 0.033, 0.11, 0.36, and 1.1 mg a.s./L based on total radioactive residues). The concentrations were selected based on the solubility limit of the test substance in the test system. Each treatment group had four replicates used for biological observations. Each replicate was initiated with 20 first instar larvae. Four additional replicates were included in the test design for analytical measurements. Each analytical replicate contained 20 organisms except for those being sampled on Day 0. At each sampling interval, an entire analytical replicate from each treatment group was sacrificed for the measurement of oxathiapiprolin in sediment, overlying water and pore water.

Observations

Observations were made daily of the survival and emergence of the midges.

Statistics

The 28-day LC_{50} was determined by analysing the number of organisms that failed to emerge during the study as well as the number of organisms that emerged and died using binomial probability with nonlinear interpolation. The NOEC and LOEC were determined by visual interpretation of the dose-response pattern and statistical analyses of the mean development times, emergence ratios and development rates. The data were analysed to determine any statistical differences between the negative and solvent control groups. Since there were no differences, the controls were pooled and the treatment groups were compared to the pooled control using a Dunnett's test.

FINDINGS

Analytical verification of [isoxazoline-5-^{14}C] oxathiapiprolin concentrations was made in sediment, overlying water and pore water sampled on Days 0, 7, and 28 of the test. Mean measured concentrations of oxathiapiprolin in the overlying water were 0.011, 0.033, 0.11, 0.36, and 1.1 mg a.s./L, based on total radioactive residues. All chemical and physical parameters for the 28-day study were within acceptable ranges. All validity criteria were met for the study.

A summary of the 28-day LC_{50}, NOEC, and LOEC are shown in Table 52.

Table 52
Summary of effects for oxathiapiprolin to the midge (*Chironomus riparius*) in a prolonged sediment toxicity test using spiked water

Endpoint	Mean Measured Concentration in Sediment Based on TRR	Effect
28-day LC_{50}	0.179 mg a.s./L, 95% confidence interval of 0.11 and 0.36 mg a.s./L	Based on number failing to emerge and number that emerged and died.
NOEC	0.11 mg a.s./L	Based on emergence ratios, most sensitive endpoint.
LOEC	0.36 mg a.s./L	Based on emergence ratios, most sensitive endpoint.

CONCLUSION

The 28-day LC_{50} value based on emergence and/or mortality of *Chironomus riparius* exposed to [isoxazoline-5-^{14}C]oxathiapiprolin administered in overlying water was 0.179 mg a.s./L, with 95% confidence limits of 0.11 and 0.36 mg a.s./L. There were no treatment related effects observed on mean development time or mean development rate in any of the treatment groups when compared to the pooled control. There were treatment related effects observed for emergence ratios between the pooled control group and the 0.36 and 1.1 mg a.s./L treatment groups. Therefore, the 28-day LOEC was 0.36 mg a.s./L and the NOEC was 0.11 mg a.s./L.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

***Degradation**:* Oxathiapiprolin degrades in the environment under natural conditions ultimately forming CO_2 and bound residues. Under laboratory conditions, the DT_{50} values in soil ranged from 18.2 to 134.4 days at 20°C. In sterile buffer solutions oxathiapiprolin is stable to hydrolysis but degrades due to photolysis. In aerobic water/sediment systems the total system DT_{50} and DT_{90} values for oxathiapiprolin ranged from 18.6 to 44.9 days and 267.9 to 149.2 days, respectively in the two water/sediment systems whilst the water phase DT_{50} and DT_{90} values ranged from 5.5 to 13.6 days and 38.3 to 45.1 days

In the ready biodegradability test oxathiapiprolin exhibited only minimal degradation when applied at 10 mg/L, not attaining greater than 60% biodegradation within ten days of reaching 10% biodegradation.

The rate of degradation seen is less than the rate defined by the CLP regulation for a substance to be considered as readily biodegradable.

Environmental distribution: Oxathiapiprolin has low water solubility, 0.184 mg/L. The predicted concentrations of oxathiapiprolin and relevant soil and aquatic metabolites in surface water and sediment were calculated using FOCUS models. The aquatic modelling assessment for oxathiapiprolin demonstrates that the active substance is not likely to pose an unacceptable risk to aquatic organisms if oxathiapiprolin in Oxathiapiprolin 100 g/L OD is used in compliance with label recommendations.

Aquatic bioaccumulation: The experimentally determined BCF of oxathiapiprolin is less than the limit value of 500 as defined by the CLP regulation. Therefore oxathiapiprolin has a low potential to bioaccumulate.

Aquatic toxicity: Both acute and chronic toxicity tests were conducted for three trophic levels.

Freshwater and marine fish species show a similar sensitivity to oxathiapiprolin; 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 represents the highest mean, measured concentration tested, and also the apparent limit of solubility in that test system. The most sensitive chronic no observed effects concentration (NOEC) for freshwater fish is 0.46 mg/L (*Oncorhynchus mykiss*) and for marine fish is 0.34 mg/L (*Cyprinodon variegatus*).

Oxathiapiprolin has negligible acute and low chronic toxicity to aquatic invertebrates. The most sensitive acute freshwater and marine species EC_{50} values are 0.67 mg/L (*Daphnia magna*) and >0.33 mg/L (*Crassostrea virginica*), the highest mean, measured concentration tested and the apparent limit of solubility in that test system. The most sensitive chronic NOEC values are for brackish species 0.058 mg/L (*Americamysis bahia*) and for sediment dwelling organisms 0.11 mg/L (*Chironomus riparius*).

Oxathiapiprolin has negligible effects on algae and aquatic plants. The most sensitive ErC_{50} values for freshwater algae (*Pseudokirchneriella subcapitata*) and aquatic plants (*Lemna gibba*) were >0.142 and >0.79 mg/L, respectively; the highest concentration tested and also the apparent limit of solubility in that test system.

Acute aquatic toxicity values were less than the limit of solubility. 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 2008/1272 EU, a 48 hour EC_{50} (for crustacea) of 1mg a.s /L or less is sufficient for classification. Consequently, oxathiapiprolin is classified as Acute Aquatic Category 1 and assigned the hazard phrase H400 Very toxic to aquatic life. The chronic NOEC for the mysid shrimp (*Americamysis bahia*) resulted in a NOEC of 0.058 mg oxathiapiprolin/L, less than 1 mg/L the trigger value for classification as Chronic category 1 under the CLP regulation.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Oxathiapiprolin does not bioaccumulate, BCF <500.

Oxathiapiprolin does not meet the criteria to be considered as rapidly degradable.

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 2008/1272 EU a 48 hour EC_{50} (for crustacea) of 1mg a.s /L is sufficient for classification. Consequently, oxathiapiprolin is classified as Acute Aquatic Category 1 and assigned the hazard phrase H400 Very toxic to aquatic life. A chronic study with the mysid shrimp (*Americamysis bahia*) resulted in a NOEC of 0.058 mg oxathiapiprolin/L, therefore oxathiapiprolin is classified as Aquatic Chronic Category 1 and assigned the hazard phrase H410 Very toxic to aquatic life with long lasting effects.

Oxathiapiprolin is considered <u>not rapidly degradable.</u> The chronic NOEC of 0.058 mg/L is between 0.01 and 0.1 mg/L; therefore an M factor of 1 is applied. The acute EC50 value of 0.67 mg/L (*Daphnia magna*) is between 0.1 and 1.0 mg/L; therefore an M-factor of 1 is appropriate.

Proposed classification based on CLP:

Aquatic chronic 1
Chronic M factor = 1
H410: Very toxic to aquatic life with long lasting effects.

Acute Aquatic 1
Acute M factor = 1
H400 Very toxic to aquatic life

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 radiolablled 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	LC_{50}/EC_{50} [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 72h[a]	Growth rate	>0.351	0.141[b]	mean measured	DuPont-35834 Arnie *et al*. (2013)
OECD TG 201 (2006), OCSPP 850.4500 (2012) GLP	*Navicula pelliculosa*	Static 72h[a]	Growth rate	>0.163	0.163[b]	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 72h[a]	Growth rate	>0.142	0.142[b]	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 72h[a]	Growth rate	>0.193	0.193[b]	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	0.79[b]	mean measured highest concentration tested	DuPont-32480 Porch *et al*. (2011)
Other aquatic organisms (including sediment)							
OECD TG 235 (2011),	*Chironomus riparius*	Static 48h	Immobility	>0.56		mean measured	DuPont-32454

ASTM Standard E729-96 (1996) GLP						highest concentration tested	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 boiaccumulative..

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 at the Background Document.

Supplemental information - In depth analyses by RAC

In the following tables the study summaries are reported to provide elements for a more in depth analysis by RAC.

Table 33
Summary of observed immobility of unfed *Daphnia magna* exposed to oxathiapiprolin for 48 hours in an unaerated, static, acute test

Mean Measured Test Concentration (mg a.s./L)	Immobility (No. immobile/No. at test start) [b]							
	24 Hours [c]				48 Hours			
	A	B	C	D	A	B	C	D
Dilution water control (0.0)	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Solvent Control (0.0)[a]	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.060	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.12	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.24	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.44	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.78	2/5	2/5	1/5	2/5	2/5	3/5	1/5	2/5

[a] Solvent concentration: 0.1 mL DMF/L.
[b] A–D represent replicate test chambers containing 5 daphnids each at test start.
[c] There were no immobile daphnids noted at the 1.5-hour observation interval.

Table 34
Summary of sublethal effects of unfed *Daphnia magna* exposed to oxathiapiprolin for 48 hours in an unaerated, static, acute test

Mean Measured Test Concentration (mg a.s./L)	Number affected / Number alive [b]							
	24 Hours [c, d]				48 Hours [d]			
	A	B	C	D	A	B	C	D
Dilution Water Control (0.0)	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Solvent Control (0.0) [a]	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.060	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/4
0.12	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.24	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.44	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
0.78	3C/3	3C/3	4C/4	3C/3	1C/1	--/0	3C/3	1C/1

[a] Solvent concentration: 0.1 mL DMF/L.
[b] A–D represent replicate test chambers containing 5 daphnids each at test start.
[c] There were no sublethal effects noted at the 1.5-hour observation interval.
[d] All surviving daphnids in the 0.78 mg a.s./L treatment group appeared lethargic (C) at the 24- and 48-hour observations.

Table 38
Summary of effects following exposure of *Daphnia magna* to oxathiapiprolin for 21 days

Mean, measured oxathiapiprolin concentration (mg a.s./L)	Mean % adult survival[a,e,g]	First day of reproduction[b]	Mean total live young [c,g]	Mean total immobile young[d,f]	Mean adult length (mm)[e]	Mean adult dry weight (mg)[e]
Water Control (0.0)	85	7 to 8	291	0.29	5.0	1.12
Solvent Control (0.0)	80	7 to 8	280	0.063	5.1	1.07
0.057	100	7 to 8	281	0.10	5.1	0.99
0.12	80	7 to 8	300	0.00	5.0	1.03
0.24	70	7 to 9	245*	0.00	5.0	1.22
0.45	80	7 to 8	286	0.00	5.1	1.07
0.75	90	7 to 8	288	0.11	5.0	1.02

[a] Percent of adult daphnids alive at the end of the test.
[b] First day that reproduction was observed in each treatment group.
[c] Mean number of live young produced per surviving female.
[d] Mean number of immobile young produced per surviving female.
[e] There were no statistically significant differences in survival (Fisher's Exact test, $p > 0.05$), in mean total length (Bonferroni t-test, $p > 0.05$) or in mean dry weight (Dunnett's test, $p \leq 0.05$) from the pooled controls.
[f] The frequencies and the numbers of immobile neonates produced during the test were low; therefore, the statistical analysis of this endpoint was not performed.
[g] The 21-day EC_{50} value for adult immobility and the 21-day EC_{50} value for reproduction were both greater than 0.75 mg a.s./L, the highest mean, measured test concentration.
* Statistically significant reductions in reproduction (Dunnett's test, $p \leq 0.05$); however, it did not follow a dose responsive pattern.

In the acute test for *Daphnia magna*, effects were only seen in the highest treatment of 1 mg/L nominal (0.78 mg/L measured), based on immobility (Table above). As the reported ratio of cumulative number of immobile Daphnia with respect to the number at the start of the test is 8/20, a robust EC_{50} value cannot be derived from the data presented in the Table above, where effects were only seen at the highest concentration tested.

In the same acute test for *Daphnia magna* (see Table above), using sublethal effects (lethargy) as the monitored effects endpoint, inconsistencies were also noted relating to the number of "dead" Daphnia at test termination (15/20), in that these do not coincide with the number of immobile Daphnia (8/20) at test termination. According to OECD TG 202, immobilization should be considered as a surrogate for death.

In addition to the uncertainties raised above referring to the only acute study that shows effects, there is also an apparent lack of consistency both between the acute and chronic *Daphnia magna* studies and between the different aquatic invertebrate species, with *Americamysis bahia* evidently orders of magnitude more sensitive than *Daphnia magna*.

6 OTHER INFORMATION

No other data available for consideration in determining the classification of oxathiapiprolin.

7 REFERENCES

Physico-chemical References

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Anand, H.S.	2012a	DPX-QGU42: Laboratory study of recording UV-VIS absorption spectra, IR, NMR and mass spectra Advinus Therapeutics Limited DuPont-32473, Revision No. 1 GLP: Yes Published: No	Y	DuPont
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Hatzenbeler, C.	2013a	Photochemical oxidative degradation of DPX-QGU42 DuPont Stine-Haskell Research Center DuPont-34109 EU GLP: No Published: No	N	DuPont
Hatzenbeler, C.	2013b	Henry's law constant for DPX-QGU42 DuPont Stine-Haskell Research Center DuPont-34110 GLP: No Published: No	N	DuPont
Kumar, S.V.	2011a	DPX-QGU42: Laboratory study of surface tension Advinus Therapeutics Limited DuPont-32471 GLP: Yes Published: No	Y	DuPont
Kumar, S.V.	2011b	DPX-QGU42: Laboratory study of dissociation constants in water Advinus Therapeutics Limited DuPont-32474 GLP: Yes Published: No	Y	DuPont
Livingston, I.	2012	DPX-QGU42 (technical): Laboratory study of flammability, autoflammability, oxidizing and explosive properties Chilworth Technology Limited DuPont-34870 GLP: Yes Published: No	Y	DuPont

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
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Moorthy, M.S.	2011a	DPX-QGU42: Laboratory study of physicochemical properties for color, odor, physical state, relative density and pH Advinus Therapeutics Limited DuPont-32475 GLP: Yes Published: No	Y	DuPont
Moorthy, M.S.	2011b	DPX-QGU42 (PAI): Laboratory study of physicochemical properties for color, odor, physical state, relative density and pH Advinus Therapeutics Limited DuPont-32487, Revision No. 1 GLP: Yes Published: No	Y	DuPont
Moorthy, M.S.	2012	DPX-QGU42: Laboratory study of vapour pressure Advinus Therapeutics Limited DuPont-31751 GLP: Yes Published: No	Y	DuPont
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Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
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Wardrope, L.	2011	DPX-QGU42: Photodegradation in pH 7 buffer and natural water Charles River Laboratories (UK) DuPont-28074 GLP: Yes Published: No	Y	DuPont

Mammalian Toxicology References

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
Bauter, M.R.	2012	DPX-QGU42 technical: 28-Day repeat dermal application study in rats Product Safety Labs DuPont-32338 GLP: Yes Published: No	Y	DuPont
Carpenter, C.	2010a	DPX-QGU42 technical: Repeated-dose oral toxicity 28-day feeding study in rats DuPont Haskell Laboratory DuPont-28294 GLP: No Published: No	N	DuPont
Carpenter, C.	2010b	DPX-QGU42 technical: Acute dermal toxicity study in rats DuPont Haskell Laboratory DuPont-30259 GLP: Yes Published: No	Y	DuPont
Carpenter, C.	2011	DPX-QGU42 technical: Repeated-dose oral toxicity 28-day feeding study in mice DuPont Haskell Laboratory DuPont-28295, Revision No. 1 GLP: No Published: No	N	DuPont
Charlap, J.H.	2012	DPX-QGU42 technical: An oral (gavage) prenatal developmental toxicity study in rabbits WIL Research Laboratories, Inc. (USA) DuPont-32357 GLP: Yes Published: No	Y	DuPont
Clarke, J.J.	2010	DPX-QGU42 technical: *In vitro* mammalian cell gene mutation test (CHO/HGPRT assay) BioReliance DuPont-30257, Revision No. 1 GLP: Yes Published: No	Y	DuPont
Craig, L.	2013	DPX-QGU42 technical: Combined chronic toxicity/oncogenicity study 2-year feeding study in rats MPI Research, Inc. DuPont-30180 GLP: Yes Published: No	Y	DuPont

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
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Edwards, T.L.	2011	A dietary range-finding one-generation reproductive toxicity study of DPX-QGU42 technical in rats WIL Research Laboratories, Inc. (USA) DuPont-28631, Revision No. 1 GLP: No Published: No	N	DuPont
Haas, M.C.	2011	DPX-QGU42 technical: Subchronic toxicity 90-day feeding study in rats WIL Research Laboratories, Inc. (USA) DuPont-28947 GLP: Yes Published: No	Y	DuPont
Han, K-H.	2013	DPX-QGU42 technical: Chronic oral toxicity one-year feeding study in beagle dogs Korea Institute of Toxicology (KIT) DuPont-30254 GLP: Yes Published: No	Y	DuPont
Han, S-C.	2012	DPX-QGU42 technical: Subchronic oral toxicity ninety-day feeding study in beagle dogs Korea Institute of Toxicology (KIT) DuPont-30047 GLP: Yes Published: No	Y	DuPont
Han, S-C.	2013	DPX-QGU42 technical: Subchronic oral toxicity ninety-day feeding study in beagle dogs Korea Institute of Toxicology (KIT) DuPont-30047, Supplement No. 1 GLP: Yes Published: No	Y	DuPont
Himmelstein, M.W.	2013a	^{14}C-DPX-QGU42: Absorption, distribution, metabolism, and elimination in the Sprague-Dawley rat DuPont Haskell Laboratory DuPont-28214, Revision No. 1 GLP: Yes Published: No	Y	DuPont

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
Himmelstein, M.W.	2013b	^{14}C-DPX-QGU42: Disposition in male and female rats during and after multiple dose administration DuPont Haskell Laboratory; Charles River Laboratories (UK) DuPont-32337 GLP: Yes Published: No	Y	DuPont
Hoban, D.	2012	DPX-QGU42 technical: 28-Day immunotoxicity feeding study in mice DuPont Haskell Laboratory DuPont-30252 GLP: Yes Published: No	Y	DuPont
Kegelman, T.A.	2010	DPX-QGU42 technical: Inhalation median lethal concentration (LC_{50}) study in rats DuPont Haskell Laboratory DuPont-30260 GLP: Yes Published: No	Y	DuPont
Lewis, J.M.	2013a	DPX-QGU42 technical: Multigeneration reproduction study in rats DuPont Haskell Laboratory DuPont-30258 GLP: Yes Published: No	Y	DuPont
Lewis, J.M.	2013b	DPX-QGU42 technical: Multigeneration reproduction study in rats DuPont Haskell Laboratory DuPont-30258, Supplement No. 1 GLP: Yes Published: No	Y	DuPont
Lowe, C.	2010a	DPX-QGU42 technical: Dermal sensitization - Magnusson-Kligman maximization method Eurofins Product Safety Laboratories DuPont-30221 GLP: Yes Published: No	Y	DuPont
Lowe, C.	2010b	DPX-QGU42 technical: Primary eye irritation in rabbits Eurofins Product Safety Laboratories DuPont-30261 GLP: Yes Published: No	Y	DuPont

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
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Madraymootoo, W., Jois, M.	2010	DPX-QGU42 technical: *In vitro* mammalian chromosome aberration test BioReliance DuPont-30256 GLP: Yes Published: No	Y	DuPont
Malley, L.A.	2010	DPX-QGU42 technical: Acute oral neurotoxicity study in rats DuPont Haskell Laboratory DuPont-29440 GLP: Yes Published: No	Y	DuPont
Mawn, M.P.	2011	DPX-QGU42 technical: Repeated-dose oral toxicity 28-day feeding study in rats DuPont Haskell Laboratory DuPont-28294, Supplement No. 1 GLP: No Published: No	N	DuPont
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Moon, K.S.	2013	DPX-QGU42 technical: Oncogenicity 18-month feeding study in mice Korea Institute of Toxicology (KIT) DuPont-30263 GLP: Yes Published: No	Y	DuPont
Munley, S.M.	2013	DPX-QGU42 technical: Developmental toxicity study in rats DuPont Haskell Laboratory DuPont-30253, Revision No. 1 GLP: Yes Published: No	Y	DuPont
Myhre, A.	2011	DPX-QGU42 technical: Bacterial reverse mutation test DuPont Haskell Laboratory DuPont-30255 GLP: Yes Published: No	Y	DuPont

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Nabb, D.	2008	2-Week repeat dose oral gavage – IN-QGU42-020 DuPont Haskell Laboratory DuPont-24634 GLP: No Published: No	N	DuPont
Oley, S.D.	2010	DPX-QGU42 technical: Acute oral toxicity – up-and-down procedure in rats Eurofins Product Safety Laboratories DuPont-29441, Revision No. 1 GLP: Yes Published: No	Y	DuPont
Park, S-Y.	2012	DPX-QGU42 technical: Subchronic toxicity 90-day feeding study in mice Korea Institute of Toxicology (KIT) DuPont-28946 GLP: Yes Published: No	Y	DuPont
Snajdr, S.I.	2012a	DPX-QGU42 technical: 5-Day uterotrophic assay for detecting endocrine activity DuPont Haskell Laboratory DuPont-28579, Revision No. 1 GLP: No Published: No	N	DuPont
Snajdr, S.I.	2012b	DPX-QGU42 technical: 15-Day intact male assay for detecting endocrine activity DuPont Haskell Laboratory DuPont-27827, Revision No. 1 GLP: No Published: No	N	DuPont
Wagner, H.	2013	DPX-QGU42: H295R steroidogenesis assay CeeTox, Inc. DuPont-37042 GLP: Yes Published: No	Y	DuPont

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Anderson, C., Wardrope, L.	2012	DPX-QGU42: Anaerobic soil metabolism Charles River Laboratories (UK) DuPont-31137 GLP: Yes Published: No	Y	DuPont
Cleland, H.	2012	[^{14}C]-DPX-QGU42: Degradability and fate in the water/sediment system Charles River Laboratories (UK) DuPont-28073 GLP: Yes Published: No	Y	DuPont
Cleland, H.	2013a	Aerobic soil metabolism of DPX-QGU42 Charles River Laboratories (UK) DuPont-28071, Revision No. 1 GLP: Yes Published: No	Y	DuPont
Cleland, H.	2013b	Photodegradation of [^{14}C]-DPX-QGU42 on moist and dry soil Charles River Laboratories (UK) DuPont-28075, Revision No. 1 GLP: Yes Published: No	Y	DuPont
Doig, A., Just, G.	2012a	Terrestrial field dissipation study of DPX-QGU42 following a single application to bare ground - Germany, 2009 Charles River Laboratories (UK) DuPont-27404 GLP: Yes Published: No	Y	DuPont
Doig, A., Just, G.	2012b	Terrestrial field dissipation study of DPX-QGU42 following a single application to bare ground - Lyon France 2009 Charles River Laboratories (UK) DuPont-27214 GLP: Yes Published: No	Y	DuPont
Doig, A., Just, G., McConnell, K.	2012a	Terrestrial field dissipation study of DPX-QGU42 following a single application to bare ground - Sevilla, Spain, 2010 Charles River Laboratories (UK) DuPont-29820 GLP: Yes Published: No	Y	DuPont

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
Doig, A., Just, G., McConnell, K.	2012b	The field soil dissipation of DPX-QGU42 following a single application to bare ground - UK Charles River Laboratories (UK) DuPont-29819 GLP: Yes Published: No	Y	DuPont
Manjunatha, S.	2010	^{14}C-DPX-QGU42: Batch equilibrium (adsorption/desorption) in five soils Advinus Therapeutics Private Limited DuPont-28425 GLP: Yes Published: No	Y	DuPont
Manjunatha, S.	2011	Rate of degradation of ^{14}C-DPX-QGU42 in four aerobic soils Advinus Therapeutics Limited DuPont-28072 GLP: Yes Published: No	Y	DuPont
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McCorquodale, G.	2013	DPX-QGU42: Aerobic soil metabolism Charles River Laboratories (UK) DuPont-29443, Revision No. 1 GLP: Yes Published: No	Y	DuPont
Piriyadarsini, J.R.	2013	DPX-QGU42: Laboratory study of ready biodegradability International Institute of Biotechnology and Toxicology (IIBAT) DuPont-34408 GLP: Yes Published: No	Y	DuPont
Rice, F.	2012a	Terrestrial field dissipation of DPX-QGU42 fungicide on bare soil in California, 2010, USA ABC Laboratories, Inc. (Missouri) DuPont-29823 GLP: Yes Published: No	Y	DuPont
Rice, F.	2012b	Terrestrial field dissipation of DPX-QGU42 fungicide on bare soil in New York, 2010, USA ABC Laboratories, Inc. (Missouri) DuPont-29813 GLP: Yes Published: No	Y	DuPont

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
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Rice, F.	2012d	Terrestrial field dissipation of DPX-QGU42 fungicide on bare soil and bare soil under covered conditions in Florida, 2010, USA ABC Laboratories, Inc. (Missouri) DuPont-29817 GLP: Yes Published: No	Y	DuPont
Vincent, T.P.	2012	Terrestrial field dissipation of DPX-QGU42 fungicide on bare soil in Manitoba, 2010, Canada ABC Laboratories, Inc. (Missouri) DuPont-29814 GLP: Yes Published: No	Y	DuPont
Vincent, T.P.	2013	Terrestrial field dissipation of DPX-QGU42 on bare soil in British Columbia, 2010, Canada ABC Laboratories, Inc. (Missouri) DuPont-29816 GLP: Yes Published: No	Y	DuPont
Wardrope, L.	2011	DPX-QGU42: Photodegradation in pH 7 buffer and natural water Charles River Laboratories (UK) DuPont-28074 GLP: Yes Published: No	Y	DuPont
Wardrope, L.	2012	DPX-QGU42: Aerobic mineralisation in surface water Charles River Laboratories (UK) DuPont-32709 GLP: Yes Published: No	Y	DuPont

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Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
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Arnie, J.R., Kendall, T.Z., Porch, J.R.	2013b	DPX-QGU42 technical: A 96-hour toxicity test with the freshwater diatom (*Navicula pelliculosa*) Wildlife International Ltd (USA) DuPont-35843 GLP: Yes Published: No	Y	DuPont
Claude, M.B., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2012	DPX-QGU42 technical: A follow-through life-cycle toxicity test with the saltwater mysid (*Americamysis bahia*) Wildlife International Ltd (USA) DuPont-32456 GLP: Yes Published: No	Y	DuPont
Kley, A., Deierling, T.	2010a	DPX-QGU42 technical: Effects on growth to the green algae *Pseudokirchneriella subcapitata* in a static test IBACON DuPont-29275 GLP: Yes Published: No	Y	DuPont
Kley, A., Deierling, T.	2010b	DPX-QGU42 technical: Effects on growth to the blue-green algae *Anabaena flos-aquae* in a static test IBACON DuPont-29320 GLP: Yes Published: No	Y	DuPont
Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2011a	DPX-QGU42 technical a 96-hour static acute toxicity test with the bluegill (*Lepomis macrochirus*) Wildlife International Ltd (USA) DuPont-32818 GLP: Yes Published: No	Y	DuPont
Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2011b	DPX-QGU42 technical: A 96-hour static acute toxicity test with the sheepshead minnow Wildlife International Ltd (USA) DuPont-32819 GLP: Yes Published: No	Y	DuPont

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
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Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2011d	DPX-QGU42 technical: A semi-static life-cycle toxicity test with the cladoceran (*Daphnia magna*) Wildlife International Ltd (USA) DuPont-32455 GLP: Yes Published: No	Y	DuPont
Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2011e	DPX-QGU42 technical: A 48-hour static acute toxicity test with the cladoceran (*Daphnia magna*) Wildlife International Ltd (USA) DuPont-32484 GLP: Yes Published: No	Y	DuPont
Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2012a	DPX-QGU42 technical: A 96-hour static acute toxicity test with the rainbow trout (*Oncorhynchus mykiss*) Wildlife International Ltd (USA) DuPont-32481, Revision No. 1 GLP: Yes Published: No	Y	DuPont
Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2012b	DPX-QGU42 technical: An early life-stage toxicity test with the sheepshead minnow (*Cyprinodon variegatus*) Wildlife International Ltd (USA) DuPont-32820 GLP: Yes Published: No	Y	DuPont
Minderhout, T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2012c	DPX-QGU42 technical: A 96-hour shell deposition test with the eastern oyster (*Crassostrea virginica*) Wildlife International Ltd (USA) DuPont-32453 GLP: Yes Published: No	Y	DuPont
Minderhout, T., Kendall, T.Z., Krueger, H.O.	2012	DPX-QGU42 technical: An early life-stage toxicity test with the rainbow trout (*Oncorhynchus mykiss*) Wildlife International Ltd (USA) DuPont-32482 GLP: Yes Published: No	Y	DuPont

Author(s)	Year	Title Source Company Report No. GLP or GEP Status (where relevant) Published or not	Data Protection Claimed (Y/N) according to Regulation (EC) 1107/2009	Owner
Nabb, D.L.	2013	DPX-QGU42 technical: *In vitro* trout hepatocyte screen DuPont Haskell Laboratory DuPont-29276, Revision No. 2 GLP: No Published: No	N	DuPont
Porch, J.R., Kendall, T.Z., Krueger, H.O.	2011	DPX-QGU42 technical: A 7-day static-renewal toxicity test with duckweed (*Lemna gibba* G3) Wildlife International Ltd (USA) DuPont-32480 GLP: Yes Published: No	Y	DuPont
Thomas, S.T., Kendall, T.Z., Gallagher, S.P., Krueger, H.O.	2012	DPX-QGU42 technical: A 48-hour static acute toxicity test with *Chironomus riparius* Wildlife International Ltd (USA) DuPont-32454 GLP: Yes Published: No	Y	DuPont
Thomas, S.T., Kendall, T.Z., Martin, K.H., Gallagher, S.P., Krueger, H.O.	2013a	DPX-QGU42 technical: A bioconcentration test with the bluegill (*Lepomis macrochirus*) Wildlife International Ltd (USA) DuPont-32483 GLP: Yes Published: No	Y	DuPont
Thomas, S.T., Kendall, T.Z., Martin, K.H., Gallagher, S.P., Krueger, H.O	2013b	^{14}C DPX-QGU42: A prolonged sediment toxicity test with *Chironomus riparius* using spiked sediment Wildlife International Ltd (USA) DuPont-35835 GLP: Yes Published: No	Y	DuPont
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8 ANNEXES

For confidential information, see IUCLID6 Section 13, Record: "DAR Confidential Section May 2016" for the word document, or IUCLID6 Section 13, Record: "DAR Confidential Section May 2016 PDF".

Annex 1
2-Year Rat Historical Control Data: Pancreas Islet Cell Neoplasms

MPI Research
Historical Control Pancreas Selected Tumor Neoplastic Data
Female Sprague Dawley Rat - Charles River Laboratories
2 Year Studies
4/1/2006 to 3/1/2013

Study	**A**	**B**	**C**	**D**	**E**	**E**	**F**	
Experimental Start Date	5/4/2004	12/22/2004	1/13/2005	3/17/2005	5/20/2005	5/20/2005	10/7/2005	12/1/2005
Experimental Termination Date	5/3/2006	12/20/2006	1/15/2007	3/9/2007	5/24/2007	5/24/2007	10/8/2007	12/4/2007
Control Group	C-1	C-1	C-1	C-1	C-1	C-2	C-1	C-1
Number of Animals	60	60	60	60	60	60	75	
				Protocol Tissues				
Pancreas								
Total Number Examined	60	60	60	60	60	60	75	
Adenoma, islet cell, benign								
Inc.	1	0	0	5	0	1	1	
% Inc.	1.7	0.0	0.0	8.3	0.0	1.7	1.3	5.0
Carcinoma, islet cell, malignant								
Inc.	0	1	0	0	0	0	1	
% Inc.	0.0	1.7	0.0	0.0	0.0	0.0	1.3	0.0
Tumor, islet cell (adenoma + carcinoma pooled)								
Inc.	1	1	0	5	0	1	2	
% Inc.	1.7	1.7	0.0	8.3	0.0	1.7	2.7	5.0

Inc. - Incidence
Formula = Inc./Total Number Examined

MPI Research
Historical Control Pancreas Selected Tumor Neoplastic Data
Female Sprague Dawley Rat - Charles River Laboratories
2 Year Studies
4/1/2006 to 3/1/2013

Study	**G**	**H**	**I**	**I**	**J**	**K**	**L**	
Experimental Start Date	12/1/2005	12/13/2005	1/21/2006	1/21/2006	3/17/2006	7/19/2006	8/3/2006	8/3/2006
Experimental Termination Date	12/4/2007	12/13/2007	1/22/2008	1/22/2008	3/17/2008	7/17/2008	8/5/2008	8/5/2008
Control Group	C-2	C-1	C-1	C-2	C-1	C-1	C-1	C-2
Number of Animals	60	60	60	60	65	60	70	
				Protocol Tissues				
Pancreas								
Total Number Examined	59	59	60	59	65	60	70	
Adenoma, islet cell, benign								
Inc.	2	1	2	1	1	0	1	
% Inc.	3.4	1.7	3.3	1.7	1.5	0.0	1.4	0.0
Carcinoma, islet cell, malignant								
Inc.	0	0	2	2	0	2	0	
% Inc.	0.0	0.0	3.3	3.4	0.0	3.3	0.0	1.4
Tumor, islet cell (adenoma + carcinoma pooled)								
Inc.	2	1	4	3	1	2	1	
% Inc.	3.4	1.7	6.7	5.1	1.5	3.3	1.4	1.4

Inc. - Incidence
Formula = Inc./Total Number Examined

MPI Research
Historical Control Pancreas Selected Tumor Neoplastic Data
Female Sprague Dawley Rat - Charles River Laboratories
2 Year Studies
4/1/2006 to 3/1/2013

Study	**M**	**M**	**N**	**O**	**P**	**P**	**Q**	
Experimental Start Date	8/11/2006	8/11/2006	9/15/2006	9/20/2006	10/16/2006	10/16/2006	11/21/2006	11/21/2006
Experimental Termination Date	8/14/2008	8/14/2008	9/17/2008	9/22/2008	10/15/2008	10/15/2008	11/12/2008	11/12/2008
Control Group	C-1	C-2	C-1	C-1	C-1	C-2	C-1	C-2
Number of Animals	69	70	60	60	65	65	60	
				Protocol Tissues				
Pancreas								
Total Number Examined	69	70	60	60	64	65	60	
Adenoma, islet cell, benign								
Inc.	1	3	1	0	0	1	1	
% Inc.	1.4	4.3	1.7	0.0	0.0	1.5	1.7	1.7
Carcinoma, islet cell, malignant								
Inc.	0	0	0	0	0	3	1	
% Inc.	0.0	0.0	0.0	0.0	0.0	4.6	1.7	0.0
Tumor, islet cell (adenoma + carcinoma pooled)								
Inc.	1	3	1	0	0	4	2	
% Inc.	1.4	4.3	1.7	0.0	0.0	6.2	3.3	1.7

Inc. - Incidence
Formula = Inc./Total Number Examined

MPI Research
Historical Control Pancreas Selected Tumor Neoplastic Data
Female Sprague Dawley Rat - Charles River Laboratories
2 Year Studies
4/1/2006 to 3/1/2013

Study	**R**	**R**	**S**	**T**	**U**	**V**	**V**	
Experimental Start Date	2/27/2007	2/27/2007	4/17/2007	4/18/2007	5/3/2007	5/31/2007	5/31/2007	6/19/2007
Experimental Termination Date	2/24/2009	2/24/2009	4/14/2009	4/16/2009	5/27/2009	6/2/2009	6/2/2009	6/18/2009
Control Group	C-1	C-2	C-1	C-1	C-1	C-1	C-2	C-1
Number of Animals	60	60	60	60	60	70	70	
				Protocol Tissues				
Pancreas								
Total Number Examined	60	45	60	60	60	70	70	
Adenoma, islet cell, benign								
Inc.	0	0	3	0	1	1	2	
% Inc.	0.0	0.0	5.0	0.0	1.7	1.4	2.9	1.7
Carcinoma, islet cell, malignant								
Inc.	3	2	1	0	1	1	2	
% Inc.	5.0	4.4	1.7	0.0	1.7	1.4	2.9	0.0
Tumor, islet cell (adenoma + carcinoma pooled)								
Inc.	3	2	4	0	2	2	4	
% Inc.	5.0	4.4	6.7	0.0	3.3	2.9	5.7	1.7

Inc. - Incidence
Formula = Inc./Total Number Examined

MPI Research
Historical Control Pancreas Selected Tumor Neoplastic Data
Female Sprague Dawley Rat - Charles River Laboratories
2 Year Studies
4/1/2006 to 3/1/2013

Study	**X**	**Y**	**Z**	**AA**	**AA**	**AB**	**AC**	**AC**
Experimental Start Date	8/30/2007	9/25/2007	1/14/2008	4/3/2008	4/3/2008	6/25/2008	7/30/2008	7/30/2008
Experimental Termination Date	8/31/2009	9/23/2009	1/13/2010	2/26/2010	2/26/2010	6/24/2010	7/30/2010	7/30/2010
Control Group	C-1	C-1	C-1	C-1	C-2	C-1	C-1	C-2
Number of Animals	60	60	60	65	65	70	65	
				Protocol Tissues				
Pancreas								
Total Number Examined	60	60	60	65	65	70	65	
Adenoma, islet cell, benign								
Inc.	0	3	0	2	1	3	4	
% Inc.	0.0	5.0	0.0	3.1	1.5	4.3	6.2	6.2
Carcinoma, islet cell, malignant								
Inc.	0	1	2	3	0	0	3	
% Inc.	0.0	1.7	3.3	4.6	0.0	0.0	4.6	0.0
Tumor, islet cell (adenoma + carcinoma pooled)								
Inc.	0	4	2	5	1	3	7	
% Inc.	0.0	6.7	3.3	7.7	1.5	4.3	10.8	6.2

Inc. - Incidence
Formula = Inc./Total Number Examined

MPI Research
Historical Control Pancreas Selected Tumor Neoplastic Data
Female Sprague Dawley Rat - Charles River Laboratories
2 Year Studies
4/1/2006 to 3/1/2013

Study	AD	AE	AF	AF	AG
Experimental Start Date	8/26/2008	12/3/2008	5/20/2009	5/20/2009	7/24/2009
Experimental Termination Date	8/27/2010	12/6/2010	5/23/2011	5/23/2011	7/22/2011
Control Group	C-1	C-1	C-1	C-2	C-1
Number of Animals	60	60	60	60	85
			Protocol Tissues		
Pancreas					
Total Number Examined	60	60	60	60	85
Adenoma, islet cell, benign					
Inc.	0	3	2	2	3
% Inc.	0.0	5.0	3.3	3.3	3.5
Carcinoma, islet cell, malignant					
Inc.	2	1	3	1	0
% Inc.	3.3	1.7	5.0	1.7	0.0
Tumor, islet cell (adenoma + carcinoma pooled)					
Inc.	2	4	5	3	3
% Inc.	3.3	6.7	8.3	5.0	3.5

Inc. - Incidence
Formula = Inc./Total Number Examined