European Commission

Draft Renewal Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009
and
Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N° 1272/2008

FENPROPIDIN (ISO);
(*R*,*S*)-1-[3-(4-tert-butylphenyl)-2-methylpropyl]piperidine

Volume 1

Rapporteur Member State: Czech Republic
Co-Rapporteur Member State: Germany

May 2021

Version History

When	Version	What
October 2020	Version 1	RMS (CZ) RAR after co-RMS and APPL comments
May 2021	Version 2	RMS (CZ) RAR after EFSA and ECHA completeness check

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Level 1

FENPROPIDIN

1 STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION

1.1 CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED

1.1.1 Purpose for which the draft assessment report was prepared

This Renewal Draft Assessment Report is submitted to support the application for the renewal of approval of the active substance fenpropidin in compliance with Regulation (EC) No 1107/2009.
Fenpropidin was initially included in Annex I of the EU Council Directive 91/414/EEC 1 July 2009 in accordance with Commission regulation EC 2008/66/ES of 30 June 2008 regarding the placement of plant protection products on the market, nowadays is approwed according to the regulation Commision (EU) no. 540/2011 of 25 May 2011. In accordance with regulation Commission (EU) 844/2012 of 18 September 2012 notiffiers Syngenta Crop Protection AG and ADAMA Agriculture B.V. (Fenpropidin Task Force leading by Syngenta) expressed interest in securing approval renewal for fenpropidin. Applicant submitted dossier to the Rapporteur Member State (RMS), the Czech Republic (CZ). The dossier was submitted by June 29, 2016 and after the completeness check it was found complete with regard to the data and information required by the above mentioned Commission regulations.
Change of classification and labelling was required for renewal of fenpropidin. Applicant submitted new data and new proposal for classification.
The application for Classification & Labelling change was submitted to ECHA by Czech Ministry of Environment in January 2017.

1.1.2 Arrangements between rapporteur Member State and co-rapporteur Member State

Czech Republic was the Rapporteur Member State (RMS). Germany was the Co-RMS. The CZ evaluated all aspects of the AIR submission, Co-RMS was as a consultant and participated on commenting of the results. All Co-RMS comments were accepted and RAR proposal was appropriately ammended.

1.1.3 EU Regulatory history for use in Plant Protection Products

This Renewal Draft Assessment Report relied entirely on the dossier from Syngenta Crop Protection AG and ADAMA Agriculture B.V. (Fenpropidin Task Force leading by Syngenta) submitted for the active substance, fenpropidin, and a formulated product Tern 750 EC. The formulated product is a water emulsifiable concentrate [Code: EC] containing 750 g/l fenpropidin. This DRAR provides a discussion of relevant new studies and information submitted and evaluated since Annex I inclusion of fenpropidin, and how these data affect the human health and environmental risk assessments, residue definitions, and MRLs. Studies submitted for the original EU evaluation for Annex I inclusion have not been re-evaluated, but may have been reconsidered for context and to validate previous conclusions and/or calculations. Revisions to the risk assessments and MRLs provided in the original EU evaluation are accompanied by a rationale in support of the changes.

1.1.4 Evaluations carried out under other regulatory contexts

Not applicable.

1.2 APPLICANT INFORMATION

1.2.1 Name and address of applicant(s) for approval of the active substance

Name: Syngenta Crop Protection AG
Address: Postfach
CH-4002 Basel
Switzerland

Name: ADAMA Agriculture B.V.
Address: Arnhemseweg 87
3832 GK Leusden
The Netherlands

1.2.2 Producer or producers of the active substance

Name: Syngenta Crop Protection AG
Address: Postfach
CH 4002 Basel
Switzerland

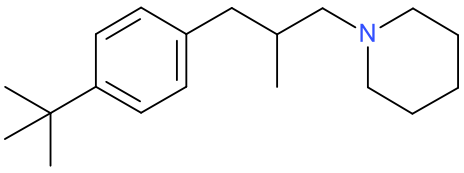
Name: ADAMA Makhteshim Ltd.
Address: P.O. Box 60
Beer Sheva, 8410001
Israel

1.2.3 Information relating to the collective provision of dossiers

Fenpropidin Task Force (Syngenta Crop Protection AG and ADAMA Agriculture B.V.)

Contact Point for the Task Force: Syngenta Crop Protection AG

1.3 IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1 Common name proposed or ISO-accepted and synonyms	Fenpropidin
1.3.2 Chemical name (IUPAC and CA nomenclature)	
IUPAC	(*R*,*S*)-1-[3-(4-tert-butylphenyl)-2-methylpropyl]-piperidine
CA	1-[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropyl]piperidine
1.3.3 Producer's development code number	Syngenta: CGA114900 ADAMA: MCW-273
1.3.4 CAS, EEC and CIPAC numbers	
CAS	67306-00-7
EEC	-
CIPAC	520
1.3.5 Molecular and structural formula, molecular mass	
Molecular formula	$C_{19}H_{31}N$
Structural formula	
Molecular mass	273.5 $g.mol^{-1}$
1.3.6 Method of manufacture (synthesis pathway) of the active substance	Confidential information, data provided in Vol. 4.
1.3.7 Specification of purity of the active substance in g/kg	960.0 g/kg (racemate).
1.3.8 Identity and content of additives (such as stabilisers) and impurities	

1.3.8.1 Additives	Confidential information, data provided in Vol. 4
1.3.8.2 Significant impurities	Confidential information, data provided in Vol. 4
1.3.8.3 Relevant impurities	None identified
1.3.9 Analytical profile of batches	Confidential information, data provided in Vol. 4

1.4 INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1 Applicant	Syngenta Crop Protection AG Address: CH 4002 – Basel, Switzerland
1.4.2 Producer of the plant protection product	Syngenta Crop Protection AG Address: CH 4002 – Basel, Switzerland
1.4.3 Trade name or proposed trade name and producer's development code number of the plant protection product	Trade name: Tern Code number: A7516D
1.4.4 Detailed quantitative and qualitative information on the composition of the plant protection product	
1.4.4.1 Composition of the plant protection product	
1.4.4.2 Information on the active substances	Content of pure fenpropidin: 750 g/L
1.4.4.3 Information on safeners, synergists and co-formulants	Confidential information, data provided in Vol. 4
1.4.5 Type and code of the plant protection product	Type: Emulsifiable concentrate Code: EC
1.4.6 Function	fungicide
1.4.7 Field of use envisaged	Fenpropidin is an agricultural fungicide used to control powdery mildews, rusts and Rynchosprium secalis in cereal crops.
1.4.8 Effects on harmful organisms	Fenpropidin is a piperidine derivative and acts by inhibiting ergosterol biosynthesis, but by a different mechanism to the triazole fungicides. It is a systemic fungicide with both protectant and curative activity.

1.5 DETAILED USES OF THE PLANT PROTECTION PRODUCT

Plese refer to point 1.5.1

1.5.1 Details of representative uses

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc. Fenpropidin. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	g a.s /hL min-max (l)	Water L/ha min-max	g a.s./ha min-max (l)		
Wheat	EU	Tern (A7516D)	F	*Erysiphe graminins*	EC	750 g/L	Foliar spray	BBCH 31-69	2	14	562.5-93.75	100-300	562.5-281.25	-	Min conc. 3g as/L when 281.25g as/ha is used
Barley	EU	Tern (A7516D)	F	*Erysiphe graminins*	EC	750 g/L	Foliar spray	BBCH 31-65	2	14	562.5-93.75	100-300	562.5-281.25	-	Min conc. 3g as/L when 281.25g as/ha is used

(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and sucking insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j) Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of applications possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

1.5.2 Further information on representative uses

Plese refer to point 1.5.1

1.5.3 Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

Not applicable.

1.5.4 Overview on authorisations in EU Member States

Plese refer to CP Dossier, document D2 – list of currently authorised uses and extent of use.

Level 2

FENPROPIDIN

2 SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

Summary of methodology proposed by the applicant for literature review and for all sections

2.1 IDENTITY

2.1.1 Summary or identity

All points of the data requirements regarding Section 1 have been addressed and the information supplied is acceptable. A full scale production 5-batch analyses was provided and was acceptable (please see confidential section for full information). Based on the documentation provided by the both Syngenta and ADAMA for the purpose of renewal, the minimum purity 960 g/kg is proposed. Fenpropidin is the racemic mixture of two enantiomers.

2.2 PHYSICAL AND CHEMICAL PROPERTIES [EQUIVALENT TO SECTION 7 OF THE CLH REPORT TEMPLATE]

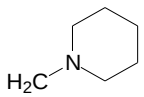
2.2.1 Summary of physical and chemical properties of the active substance

Table 1: Summary of physicochemical properties of the active substance

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	PAS: Pale yellow liquid (Purity 99.5 %) TGAS: Pale yellow liquid (Purity 96.7 %)	Das, 2000 Rodler, 1993	Observed
Melting/freezing point	–64.6°C (Purity 99.5 %)	Nickler, 1999	Measured
Boiling point	Thermal decomposition starts before boiling occurs. Oxidative decomposition starts at 93°C (Purity 99.5 %). Boiling point at 1.1 Pa is 70.2°C	Das, 2000	Measured
Relative density	0.913 (20°C, Purity 99.5 %)	Das, 1999	Measured
Vapour pressure	1.7 x 10^{-2} Pa (25°C, Purity 99.5 %)	Geoffroy, 1993	Measured
Surface tension	65.0 mN/m (90 % saturated solution, 20°C, Purity 99.5 %)	O'Connor B., 2015a	Measured
Water solubility	130 g/L at 25°C (pH 6.0) (Purity 99.3 %) 530 mg/L at 25°C (pH 7.0) (Purity 99.3 %) 6.2 mg/L at 25°C (pH 9.0) (Purity 99.3 %)	Rodler, 1993	Measured
Partition coefficient n-octanol/water	log P_{OW} = 0.83 at 25°C (pH 4.2) (Purity 99.5 %) log P_{OW} = 2.9 at 25°C (pH 7.0) (Purity 99.5 %) log P_{OW} = 4.5 at 25°C (pH 9.0) (Purity 99.5 %)	Stulz, 1998	Measured
Henry's law constant	3.39 Pa. $m^3.mol^{-1}$ (25°C)	Kendall A., 2016	Calculated
Flash point	156°C (Purity 96.7 %) Not classified in terms of its flash point	Schürch, H., 1993	Measured
Flammability	Data not required, the active substance is a liquid		

<table>
<tr><th>Property</th><th>Value</th><th>Reference</th><th>Comment (e.g. measured or estimated)</th></tr>
<tr><td>Explosive properties</td><td>Not an explosive substance (Purity 96.7 %)</td><td>Schürch, H., 1993</td><td>Measured</td></tr>
<tr><td>Self-ignition temperature</td><td>Self-ignition temperature 265 °C (Purity 96.7 %)</td><td>Schürch, H., 1993</td><td>Measured</td></tr>
<tr><td>Oxidising properties</td><td>Fenpropidin is not considered an oxidizing substance</td><td>Angly, H., 1999</td><td>Measured</td></tr>
<tr><td>Granulometry</td><td>Data not required, the active substance is a liquid</td><td></td><td></td></tr>
<tr><td>Solubility in organic solvents and identity of relevant degradation products</td><td>Completely miscible in all tested solvents, Acetone, Dichloromethane, Ethyl Acetate, Hexane, Methanol, Octanol and Toluene (25°C, Purity 97.0 %)</td><td>Kettner, 2000</td><td>Measured</td></tr>
<tr><td>Dissociation constant</td><td>pKa = 9.62 (basic) (Purity 99.5 %)</td><td>O’Connor B., 2015</td><td>Measured</td></tr>
<tr><td>Viscosity</td><td>Not measured</td><td></td><td></td></tr>
<tr><td>Spectra (UV/VIS, IR, NMR, MS), molar extinction at relevant wavelengths, optical purity</td><td>
UV/VIS (Purity: 99.5%):
<table>
<tr><th>solution</th><th>wavelength [nm]</th><th>ε [L / mol · cm]</th></tr>
<tr><td>neutral</td><td>218.2</td><td>10760</td></tr>
<tr><td>acidic</td><td>217.9</td><td>9670</td></tr>
<tr><td>basic</td><td>219</td><td>9440</td></tr>
<tr><td>neutral</td><td>290</td><td>4</td></tr>
</table>
No additional absorption maximum between 340 nm and 750 nm was observed.
IR spectrum (Purity: 99.5 %):
<table>
<tr><th>Wavenumber [cm^{-1}]</th><th>Assigned to</th></tr>
<tr><td>2934</td><td>C-H stretch</td></tr>
<tr><td>2769</td><td>C-H stretch for N-CH_2</td></tr>
<tr><td>1363</td><td>-CH_3 deformation for –C(CH_3)</td></tr>
</table>
All the results support the proposed structure for fenpropidin

^{1}H-NMR (300 MHz, DMSO)
All the results from the spectral analysis support the proposed structure for fenpropidin

MS spectrum of fenpropidin (EI)
<table>
<tr><th>m/z</th><th>Fragment ion</th></tr>
<tr><td>273</td><td>M^+</td></tr>
<tr><td>98</td><td>  </td></tr>
<tr><td>55</td><td>C_4H_7</td></tr>
</table>
All the results support the proposed structure for fenpropidin.
</td><td>Käser, 1997
Heintz K., 2013</td><td>Measured</td></tr>
</table>

2.2.1.1 Evaluation of physical hazards [equivalent to section 8 of the CLH report template]

2.2.1.1.1 Explosives *[equivalent to section 8.1 of the CLH report template]*

Table 2: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
EEC A.14 Effect of a flame Effect of a shock (mechanical)	 not thermally sensitive not shock sensitive	Technical Fenpropidin (batch-no: 5, purity 96.7%)	Schürch, H., 1993
EEC A.14	The test substance did not explode when exposed to heat or mechanical shock.	Fenpropidin (batch id. 14129997, purity 99.7 %)	Jackson W., 2015

2.2.1.1.1.1 Short summary and overall relevance of the provided information on explosive properties

Under the condition of the test, fenpropidin is not explosive. Fenpropidin does not belong to the additional hazard class 'desensitised explosives' in terms of criteria of the 12th ATP and the UN Recommendations on the Transport of Dangerous Goods, Manual of tests and criteria.

2.2.1.1.1.2 Comparison with the CLP criteria

Fenpropidin is not classified as explosive nor a desensitised explosive based on results of the two studies performed as referenced above.
Based on the screening procedure according to Reg (EU) 1272/2008 Annex I 2.1.4.2 and 2.1.4.3, the substance is not classified as explosive if there are no chemical groups associated with explosive properties present in the molecule as given in the Table A6.1 in Appendix 6 of the UN recommendations.
Chemical groups indicating explosive properties in organic materials:

Structural feature	Examples
C-C unsaturation	Acetylenes, acetylides, 1,2-dienes
C-Metal, N-Metal	Grignard reagents, organo-lithium compounds
Contiguous nitrogen atoms	Azides, aliphatic azo compounds, diazonium salts, hydrazines, sulphonylhydrazides
Contiguous oxygen atoms	Peroxides, ozonides
N-O	Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles
N-halogen	Chloramines, fluoroamines
O-halogen	Chlorates, perchlorates, iodosyl compounds

None of these groups associated with explosive properties in the molecule are present in fenpropidin.
With regard to classification procedure for desensitised explosives with reference to 12th ATP and the Reg. (EU) 2019/521, the procedure does not apply if the substances or mixtures contain no explosives according to criteria of section 2.1 of the CLP Reg. (EU) 1272/2008.
Fenpropidin contains no explosives therefore the classification procedure for desensitised explosives does not apply to fenpropidin.

2.2.1.1.1.3 Conclusion on classification and labelling for explosive properties

Not classified.

2.2.1.1.2 Flammable gases (including chemically unstable gases) *[equivalent to section 8.2 of the CLH report template]*

Not relevant: the substance is a liquid.

2.2.1.1.3 Oxidising gases *[equivalent to section 8.3 of the CLH report template]*

Not relevant: the substance is a liquid.

2.2.1.1.4 Gases under pressure *[equivalent to section 8.4 of the CLH report template]*

Not relevant: the substance is a liquid.

2.2.1.1.5 Flammable liquids *[equivalent to section 8.5 of the CLH report template]*

Table 3: Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
EEC A.9 (DIN 51758, Pensky-Martens)	Flash point = 156°C (at 1013 mbar)	Technical Fenpropidin (batch-no: 5, purity 96.7%)	Schürch, H., 1993
EEC A.9 (ASTM D93, Pensky-Martens	Flash point = 158 ± 8 °C (101.2 kPa)	Fenpropidin (batch id. 14129997, purity 99.7 %)	Jackson W., 2015

2.2.1.1.5.1 Short summary and overall relevance of the provided information on flammable liquids

First test was carried out in accordance with EC Test A.9, DIN 51758 for Pensky-Martens closed-cup testing.

Second test was carried out in accordance with EC Test A.9, Reference 5.2, using ASTM D93 for Pensky-Martens closed-cup testing. The test was carried out twice with the same result.

2.2.1.1.5.2 Comparison with the CLP criteria

Flash point is above 60°C. Hence, not flammable according to CLP.

2.2.1.1.5.3 Conclusion on classification and labelling for flammable liquids

The substance is not flammable liquid. Data conclusive but not sufficient for classification.

2.2.1.1.6 Flammable solids *[equivalent to section 8.6 of the CLH report template]*

Not relevant: the substance is a liquid.

2.2.1.1.7 Self-reactive substances *[equivalent to section 8.7 of the CLH report template]*

2.2.1.1.7.1 Short summary and overall relevance of the provided information on self-reactive properties

The classification procedures for self-reactive substances and mixtures need not be applied if there are no chemical groups present in the molecule associated with explosive or self-reactive properties. Examples of such groups are given in the Table A6.3 in Appendix 6 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria:

Structural feature	Examples
Mutually reactive groups	Aminonitriles, haloanilines, organic salts of oxidizing acids
S=O	Sulphonyl halides, sulphonyl cyanides, sulphonyl hydrazides
P-O	Phosphites
Strained rings	Epoxides, aziridines
Unsaturation	Olefins, cyanates

None of these groups associated with self-reactive properties are present in the molecule of fenpropidin.

2.2.1.1.7.2 Comparison with the CLP criteria

Fenpropidin does not contain groups associated with self-reactive properties.

2.2.1.1.7.3 Conclusion on classification and labelling for self-reactive substances

Fenpropidin is not classified as a self-reactive substance.

2.2.1.1.8 Pyrophoric liquids [equivalent to section 8.8 of the CLH report template]

2.2.1.1.8.1 Short summary and overall relevance of the provided information on pyrophoric liquids

No tests have been conducted but safe long-term use of fenpropidin demonstrates that it is not a pyrophoric liquid.
Fenpropidin does not spontaneously ignite in air.

2.2.1.1.8.2 Comparison with the CLP criteria

No tests have been conducted but safe long-term use is evidence that fenpropidin is not liable to ignite in contact with air.
According to the additional classification considerations in CLP Annex I, 2.9.4, the classification procedure for pyrophoric liquids need not be applied when experience in manufacture or handling shows that the liquid does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the liquid is known to be stable at room temperature for prolonged periods of time (days)).

2.2.1.1.8.3 Conclusion on classification and labelling for pyrophoric liquids

Not classified. Fenpropidin is not a pyrophoric liquid.

2.2.1.1.9 Pyrophoric solids [equivalent to section 8.9 of the CLH report template]

Not relevant: the substance is a liquid.

2.2.1.1.10 Self-heating substances *[equivalent to section 8.10 of the CLH report template]*

Table 4: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
EEC A.15 (DIN 51794)	The self-ignition temperature was measured to be 265°C	Fenpropidin (purity 96.7%)	Schürch, H., 1993
EEC A.15	Auto ignition temperature = 265 ± 15°C	Fenpropidin (purity 99.7 %)	Jackson W., 2015

2.2.1.1.10.1 Short summary and overall relevance of the provided information on self-heating substances

Two studies on auto-ignition according to the EC test A.15 were provided. They show a self-heating temperature of 265°C.

2.2.1.1.10.2 Comparison with the CLP criteria

Following CLP guidance (ECHA, 2017), EEC A.15 method is generally inappropriate for a reliable assessment, and the findings do not lead to a classification. However, the result in this case (EEC A15 method), i.e. self-ignition temperature of 265°C, is sufficiently straightforward to conclude that fenpropidin will not be classified as self-heating liquid.

2.2.1.1.10.3 Conclusion on classification and labelling for self-heating substances

Fenpropidin will not be classified as self-heating substance.

2.2.1.1.11 Substances which in contact with water emit flammable gases *[equivalent to section 8.11 of the CLH report template]*

2.2.1.1.11.1 Short summary and overall relevance of the provided information on substances which in contact

with water emit flammable gases
No tests have been conducted but safe long-term use of fenpropidin demonstrates that it does not a emit a gas (flammable or otherwise) when in contact with water.

2.2.1.1.11.2 Comparison with the CLP criteria

Based on provisions of the Reg. (EU) 1272/2008 on the classification criteria for the substances which in contact with water emit flammable gases (Annex I part 2, 2.12.4.1) the classification procedure to fenpropidin for this class does not need to be applied based on the following:
- the chemical structure of fenpropidin does not contain metals of metalloids
- experience in fenpropidin production and handling demonstrates fenpropidin does not react with water
- fenpropidin is soluble in water to form a stable mixture.

2.2.1.1.11.3 Conclusion on classification and labelling for substances which in contact with water emit

flammable gases
Not classified. Fenpropidin does not emit flammable gases in contact with water.

2.2.1.1.12 Oxidising liquids *[equivalent to section 8.12 of the CLH report template]*

Table 5: Summary table of studies on oxidising liquids

Method	Results	Remarks	Reference
Transport of Dangerous Goods, Manual of Tests and Criteria. Part III, section 34. UN 1995	Not considered an oxidising substance according to the test	Fenpropidin (purity 97.0%)	Angly, H., 1999

2.2.1.1.12.1 Short summary and overall relevance of the provided information on oxidising liquids

Mean pressure rise time of a 1:1 mixture of fenpropidin and cellulose is 16.95 s.

2.2.1.1.12.2 Comparison with the CLP criteria

The pressure rise time of a 1:1 mixture of fenpropidin and cellulose is greater than 65% aqueous nitric acid (3.45 s). A substance is classified as an oxidising liquid when the pressure rise time of a sample to cellulose 1:1 mixture is less than or equal to the pressure rise time of 65% aqueous nitric acid. Therefore, the criteria for the classification are not met.

2.2.1.1.12.3 Conclusion on classification and labelling for oxidising liquids

Data conclusive but not sufficient for classification.

2.2.1.1.13 Oxidising solids *[equivalent to section 8.13 of the CLH report template]*

Not relevant: the substance is a liquid.

2.2.1.1.14 Organic peroxides [equivalent to section 8.14 of the CLH report template]

Not relevant as the chemical structure of the active substance does not exhibit a peroxide moiety.

2.2.1.1.15 Corrosive to metals [equivalent to section 8.15 of the CLH report template]

2.2.1.1.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

Fenpropidin is a liquid with a pKa = 9.62 (basic) (Purity 99.5 %). It has no strongly acidic moieties, it does not contain a halogen nor form complexes with metals.

Therefore, fenpropidin is unlikely to be corrosive to metals.

2.2.1.1.15.2 Comparison with the CLP criteria

Based on criteria of the Reg. (EU) 1272/2008 and the CLP guidance 2.16.4.1, fenpropidin is not the substance to be considered for classification of this class, i.e. corrosive to metals. It has no strongly acidic moieties, it does not contain a halogen nor form complexes with metals.

2.2.1.1.15.3 Conclusion on classification and labelling for corrosive to metals

Fenpropidin is not corrosive to metals

2.2.2 Summary of physical and chemical properties of the plant protection product

The plant protection product Tern (code A7516D) is emulsifiable concentrate. The appearance of the product is that of a yellow orange liquid with a thymol like odour. The density of the preparation at a temperature of 20°C is 0.914 g/ml and the pH of a 1% emulsion in water is 10.1. Surface tension of a 1% emulsion in water is 28.7 mN/m; formulation is regarded as surface active. There was no significant physical or chemical change during storage at 54°C for 14 days in f-HDPE packaging material. There was no significant physical or chemical change during storage at 20°C for two years in HDPE/PA and f-HDPE packaging material. The stability data indicate a shelf life of at least 2 years at ambient temperature when stored as recommended. HDPE/PA and f-HDPE packaging proved to be resistant to the product. Technical characteristics of the product are acceptable for an emulsion concentrate.

2.3 DATA ON APPLICATION AND EFFICACY

2.3.1 Summary of effectiveness

TERNTM 750 EC is an agricultural fungicide used to control powdery mildews, rusts and Rynchosprium secalis in cereal crops. Fenpropidin is a piperidine derivative and acts by inhibiting ergosterol biosynthesis, but by a different mechanism to the triazole fungicides. It is a systemic fungicide with both protectant and curative activity.

TERNTM 750 EC is applied at 1 L/ha product in northern Europe and 0.75 L/ha product in southern Europe corresponding to 750 and 562 g ai/ha respectively. A maximum of two applications may be made per year. The

first application will be at the appearance of disease, likely to be close to growth stage 29 (end of tillering, maximum number of tillers detectable), the second application will be made not later than GS 65 (end of flowering, 50% of anthers mature). The interval between applications will typically be 21-35 days.
The product will typically be applied at application volumes of 100-400 L/ha giving concentrations of fenpropidin of 140-750 g ai/hL in the diluted spray.

2.3.2 Summary of information on the development of resistance

Through its good activity fenpropidin provides a valuable anti-resistance strategy for powdery mildew either in mixture or alternation with fungicidal products having a different mode of action. Intensive and exclusive use of fenpropidin for the control of powdery mildew over many years can lead to a gradual decline of the efficacy of the compound. In practice the efficacy of fenpropidin has however, remained stable. To avoid a shift of the pathogen population towards less sensitive strains it is recommended to use fenpropidin in mixture/programs/alternation with compounds with different modes of action.

2.3.3 Summary of adverse effects on treated crops

No report of a particular varietal susceptibility was reported during the commercial use of the product.

2.3.4 Summary of observations on other undesirable or unintended side-effects

TERN^{TM} 750 EC showed no phytotoxicity to a wide range of broad-leaved crops after multiple foliar application.

2.4 FURTHER INFORMATION

2.4.1 Summary of methods and precautions concerning handling, storage, transport or fire

Fenpropidin

Advice for safe handling
No special protective measures against fire required.
Avoid contact with skin and eyes. When using do not eat, drink or smoke.

Conditions for safe storage
No special storage conditions required. Keep containers tightly closed in a dry, cool and well-ventilated place. Keep out of the reach of children. Keep away from food, drink and animal feeding stuffs.

Extinguishing media
Small fires: Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Large fires: Alcohol-resistant foam or water spray

Specific hazards during firefighting
As the product contains combustible organic components, fire will produce dense black smoke containing hazardous products of combustion. Exposure to decomposition products may be a hazard to health

Special protective equipment for firefighters:
Wear full protective clothing and self-contained breathing apparatus.
Transport information
Land transport (ADR/RID)
UN number: UN 3082
UN proper shipping name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (FENPROPIDIN)
Transport hazard class(es): 9
Packing group: III
Labels: 9
Environmental hazards: Environmentally hazardous
Tunnel restriction code: E

Sea transport (IMDG)
UN number: UN 3082
UN proper shipping name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (FENPROPIDIN)
Transport hazard class(es): 9
Packing group: III
Labels: 9
Environmental hazards: Marine pollutant

Air transport (IATA-DGR**)**
UN number: UN 3082
UN proper shipping name: Environmentally hazardous substance, liquid, n.o.s. (FENPROPIDIN)
Transport hazard class(es): 9
Packing group: III
Labels: 9

Tern (product)

Detailed handling procedures for storage:
No special storage conditions required. Keep containers tightly closed in a dry, cool and well-ventilated place. Keep out of the reach of children. Keep away from food, drink and animal feeding stuffs.
No special protective measures against fire required. Avoid contact with skin and eyes. When using do not eat, drink or smoke.

Fire fighting measures
Suitable extinguishing media:
Extinguishing media - small fires: Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Extinguishing media - large fires: alcohol-resistant foam or water spray.
Unsuitable extinguishing media: Do not use a solid water stream as it may scatter and spread fire.
Specific hazards during fire fighting: As the product contains combustible organic components, fire will produce dense black smoke containing hazardous products of combustion.
Exposure to decomposition products may be a hazard to health.
Special protective equipment for firefighters: Wear full protective clothing and self-contained breathing apparatus.

Transport

Land transport
ADR/ RID:
UN-Number: 3082
Class: 9
Labels: 9
Packaging group III
Proper shipping name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (SOLVENT NAPHTHA AND FENPROPIDIN)

Sea transport
IMDG:
UN-Number: 3082
Class: 9
Labels: 9
Packaging group: III
Proper shipping name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (SOLVENT NAPHTHA AND FENPROPIDIN
Marine pollutant: Marine pollutant

Air transport
IATA-DGR
UN-Number: 3082
Class: 9
Labels: 9
Packaging group: III
Proper shipping name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, LIQUID, N.O.S. (SOLVENT NAPHTHA AND FENPROPIDIN)

2.4.2 Summary of procedures for destruction or decontamination

In the event of accidental spillage, neutralisation (with acid or base to neutral pH) is not an effective procedure for the destruction or decontamination of the formulation.
Therefore, the spilled liquid formulation should first be adsorbed onto a solid, such as sand, inert clay filler, saw dust or soil, before being swept up into a safe container to await disposal.

Both, fenpropidin and Tern can be disposed of safely by incineration in a modern incinerator, licensed to treat special contaminated waste, which fulfils the following conditions: > 800°C, minimum residence time within the incinerator, 2 seconds, equipped with a washing unit for flue gases. The ashes have to be disposed of at a suitable, approved waste disposal site. Wash water has to be disposed of via a suitable waste water treatment plant.

Environmental precautions:

Prevent further leakage or spillage if safe to do so. Do not flush into surface water or sanitary sewer system. If the product contaminates rivers and lakes or drains inform respective authorities.

Methods for cleaning up:

Contain spillage, and then collect with non-combustible absorbent material, (e.g. sand, earth, diatomaceous earth, vermiculite) and place in container for disposal according to local / national regulations.

2.4.3 Summary of emergency measures in case of an accident

Acceptable information has been provided, including safety data sheets of fenpropidine technical and TERN^{TM} 750 EC. Please refer to Volume 3 CA and CP, Section B.4.

Containment of spillages:

Prevent entry into drains, waters or soil. Keep in suitable closed containers for disposal.

First aid measures:

Skin contact:	Wash with plenty of water. Use soap if available.
Grossly contaminated clothing:	Remove contaminated clothing. Wash before re-use.
Eye contact:	Rinse immediately with plenty of potable water.
Inhalation:	Move to fresh air.
Ingestion:	Rinse mouth with water. Do not induce vomiting without medical advice.
Medical advice:	Over-exposure symptoms unknown. Only minor local symptoms are expected. No specific antidote. Treat symptomatically.

Protection of emergency workers:

Based on the toxicity of TERN 750 EC no specific protective clothing or equipment is required, however the following are recommended on the basis of good agricultural practice when handling pesticides.
Wear impermeable gloves, suitable protective clothing and suitable eye/face protection.
No information is provided on the suitability of such clothing as its using is recommended on the basis of general advice for all pesticides.

2.5 METHODS OF ANALYSIS

2.5.1 Methods used for the generation of pre-authorisation data

Syngenta technical material and formulation

A validated method for the determination of fenpropidin in the technical material is available. The active substance fenpropidin and impurities are determined using GC with FID detection. Analytical method were considered fully validated in accordance with SANCO/3030/99 rev. 4 for the determination of active substance and impurities content in the technical material. Identity of impurities were confirmed by comparing their retention times to those of reference substances. The MS spectra of active substance and impurities were recorded, confirming their structures.
A GC analytical method with FID detection was considered fully validated in accordance with SANCO/3030/99

rev. 4 for the determination of active substance content in the plant protection product.

ADAMA technical material
A validated method for the determination of fenpropidin in the technical material is available. The active substance fenpropidin is determined using HPLC with DAD detection. Analytical method was considered fully validated in accordance with SANCO/3030/99 rev. 4 for the determination of active substance content in the technical material. A validated method for the determination of impurities in the technical material is available. The impurities are determined using GC with FID detection. Analytical method was considered fully validated in accordance with SANCO/3030/99 rev. 4 for the determination of impurities content in the technical material. The confirmation of identity of the active ingredient and impurities was performed by GC/MS analysis.

Methods for risk assessment
Satisfactory methods of analysis for the detection of fenpropidin and its metabolite CGA 289267, in relevant matrices to support all areas of the risk assessment (including residues, ecotoxicology, mammalian toxicology and environmental fate and behaviour) have been provided. These methods have been assessed in accordance with SANCO/3029/99 rev. 4. The validation evaluation has been conducted in section B5 of the CA RAR documents. The applicability of these methods is addressed in the respective sections for these studies which these methods support.

2.5.2 Methods for post control and monitoring purposes

Active and impurities in the plant protection product: Analytical methods reported in 2.5.1 can be applied.

Methods for monitoring purposes: Satisfactory methods for the determination of all components included in the monitoring residue definition in matrices of plant/animal origin as well as in relevant environmental compartments have been provided. Analytical methods were considered fully validated for the determination of required components' content in the relevant matrices.

Matrix	Analyte	Method	LOQ	ILV	Fully validated
Plant, high water content	Fenpropidin	LC-MS/MS	0.01 mg/kg	Yes	Yes
Plant, acidic commodities	Fenpropidin	LC-MS/MS	0.01 mg/kg	Not required	Yes
Plant, dry commodities	Fenpropidin	LC-MS/MS	0.01 mg/kg	Yes	Yes
Plant, high oil content	Fenpropidin	LC-MS/MS	0.01 mg/kg	Not required	Yes
Commodities which are difficult to analyse	Not required for the intended GAP				
Meat	Fenpropidin and CGA 289267, CGA 289268	LC/MS-MS	0.01 mg/kg	Yes	Yes
Milk	Fenpropidin and CGA 289267, CGA 289268	LC-MS/MS	0.005 mg/kg	Yes	Yes
Eggs	Fenpropidin and CGA 289267, CGA 289268	LC-MS/MS	0.01 mg/kg	Not required	Yes
Fat	Fenpropidin and CGA 289267, CGA 289268	LC-MS/MS	0.01 mg/kg	Yes	Yes
Liver, kidney	Fenpropidin and CGA 289267, CGA 289268	LC-MS/MS	0.01 mg/kg	Not required	Yes
Soil	Fenpropidin	LC-MS/MS	0.01 µg/kg*	Not required	Yes

Matrix	Analyte	Method	LOQ	ILV	Fully validated
Surface water Ground water Drinking water	Fenpropidin	LC/MS-MS	0.05 µg/L**	Yes	Yes
Air	Fenpropidin	LC-MS/MS	0.15 µg/m^3***	Not required	Yes
Body fluids	Fenpropidin and CGA 289267, CGA 289268	LC-MS/MS	0.01 mg/L	Not required	Yes

*The LOQ of the method is in agreement with the NOEC for the most sensitive non-target organism of *Eisenia fetida* (NOEC = 10 mg a.s./kg dry weight soil.

** The LOQ of the method is in agreement with the endpoint for the most sensitive water organism of *Desmodesmus subspicatus* with an E_yC_{50} of 0.7 µg /L.

***LOQ of the method comply with the concentration (15 µg.m-3) calculated from AOEL (0.05 mg/kg).

2.6 EFFECTS ON HUMAN AND ANIMAL HEALTH

More detailed results of the studies are presented in Volume 3, section B.6.

2.6.1 Summary of absorption, distribution, metabolism and excretion in mammals *[equivalent to section 9 of the CLH report template]*

Table 6: Summary table of toxicokinetic studies

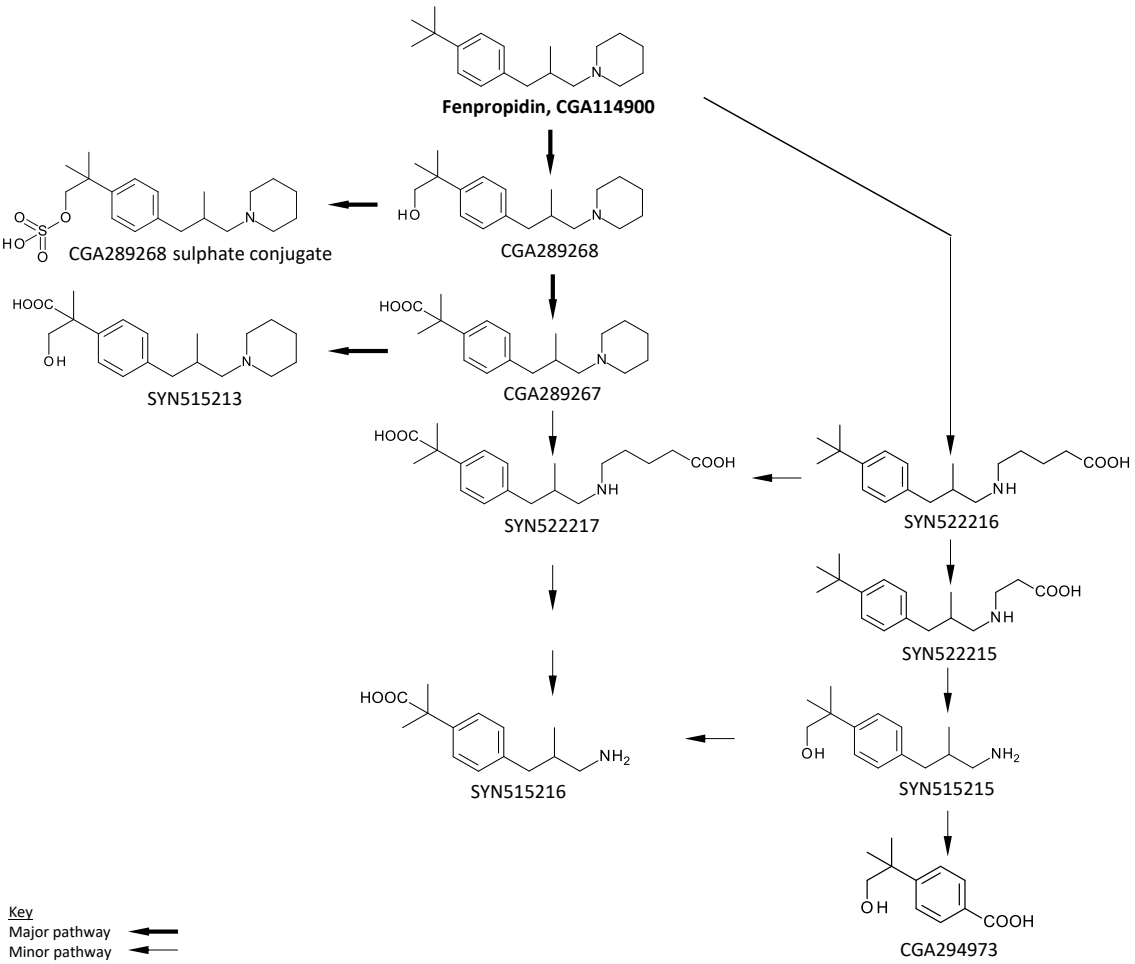
Method	Results	Remarks	Reference
Toxicokinetics Sprague Dawley Rat (males, females, 3 – 12animals/group) Oral route: by gavage, low dose: 0.5 mg/kg bw of ^{14}C-fenpropidin (2.096 MBq/mg); high dose: 100 mg/kg bw of ^{14}C-fenpropidin diluted with non-radiolabelled fenpropidin to achieve a specific activity of 185 kBq/mg Repeated dosing: 14 doses of unlabelled fenpropidin followed by a single radiolabelled dose (0.5 mg/kg bw) Intravenous administration OECD TG 417	C_{max}: 30 min. and 1-2 hours after low and high dose administration, respectively Excretion: 82 – 102% within 48 h, predominantly in urine Residues in tissues: 0.4 – 1.7% of applied dose (7 days after application; predominantly in liver and kidney) Biliary elimination: 12% (low dose females) Single dose absorption: 57 – 93% (only high dose females bellow 80%); the overall estimated absorption: >80%	Test material: ^{14}C-fenpropidin Radiochemical purity: >98% Non-radiolabelled fenpropidin: 99% purity **Acceptable study**	[redacted] (1994)
Metabolism Samples from the [redacted] study (1994) OECD TG 417	No parent substance was found in excreta Urine metabolite pattern: 14 metabolite fractions (major U6: 46-79% of the dose) Faeces metabolite pattern: 16 metabolite fractions (in females major F5: 6-27% ; in males 0.7-1.7% of the dose) Bile metabolite pattern was similar to that of faeces	**Acceptable study**	Muller (1994)
Metabolism Samples from the [redacted] study (1994) OECD TG 417	2 metabolic pathways were proposed for fenpropidin, independent of sex, dose level, dose route and pre-treatment *(see Figure 2.6.1.1-1)*	**Acceptable study**	Molitor (1996)
In vitro comparative metabolism study 10 µM of 2-methylpropyl-3-^{14}C- fenpropidin was incubated with rat, dog and human	No unique human metabolite was identified Interspecies differences in extent of metabolism were observed	Test material: 2-methylpropyl-3-^{14}C-fenpropidin (radiochemical purity: 98.9%, chemical purity: 98.4%)	Sayer (2017)

Method	Results	Remarks	Reference
hepatocytes for 0, 2 and 4 h No OECD TG		Positive control : [^{14}C]-7-ethocycoumarin **Acceptable study**	

2.6.1.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Fenpropidin is rapidly and extensively absorbed after a single oral dose in rats (> 80%, excretion within 48 hours, 79% in urine and 12% via bile). The absorbed dose is distributed mainly between liver and kidney, the principal organs of metabolism and excretion. No tissue accumulation is observed and almost complete excretion of the administered dose occurs within 48 hours, predominantly in urine. Metabolism of fenpropidin is extensive as no parent compound is observed in excreta. The principal urine metabolite is CGA289267, accounting for 46-79% of the administered dose. Other urine metabolites individually account for up to 2.5% of the administered dose and include CGA289268 (≤ 0.3%), and its sulphate ester conjugate (≤ 1.5%) and SYN515213 (≤ 2.5%). The principal faeces and bile metabolite in female rats is the sulphate ester conjugate of CGA289268, accounting for 6-27% and 6% of the administered dose, respectively. Other metabolite fractions in urine, faeces and bile do not exceed 2.5% of the administered dose.

Figure 2.6.1.1-1: **Proposed metabolic pathway of fenpropidin**



In vitro comparative study ([redacted] *2017)* did not reveal any unique human metabolite. In rats as well as dogs, notable metabolism was observed. The proportion of chromatographic radioactivity attributable to the parent compound decreased from 98.7% and 97.6% (0 h) to 0.76% and 2.44% (4h) in male and female rat samples; and from 96.1% and 99.4% to 59.2% and 32.6% in male and female dog samples. On the other hand, in human samples, the proportion of chromatographic radioactivity attributable to the parent compound decreased from 97.0% (0h) to 89.7% (4h). Thus, the extent of metabolism in humans was low.

Table 2.6.1.1-1: **Summary of the notable metabolites (>1% total chromatographic radioactivity) in rats, dogs, and humans**; ND = not detected, *([redacted] 2017)*

Species	Incubation time [hour]	Mean % Chromatogram radioactivity									
		M5	**M7**	**M10**	**M11**	**M12**	**M19**	**M21**	**M22**	**M24**	**Parent**
Male rat	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	98.69
	2	10.78	2.53	0.69	ND	64.80	1.12	1.29	0.98	ND	0.50
	4	7.88	2.96	1.52	ND	64.56	0.98	1.34	0.73	ND	0.76
Female rat	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	97.62
	2	47.76	11.06	1.60	ND	11.17	ND	1.66	5.76	ND	2.49
	4	50.96	8.97	0.57	ND	12.33	1.25	1.63	4.24	ND	2.44
Male dog	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	96.09
	2	ND	ND	4.66	ND	ND	2.29	5.90	8.72	5.30	67.24
	4	0.11	ND	6.24	ND	0.36	2.66	7.78	13.9	3.16	59.21
Female dog	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	99.43
	2	0.62	0.11	8.09	1.25	0.54	4.66	8.09	13.23	10.01	40.37
	4	1.00	0.28	9.18	1.90	0.63	5.29	8.30	17.51	7.42	32.61
Human	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	96.97
	2	ND	ND	3.52	ND	ND	ND	ND	ND	ND	93.27
	4	ND	ND	7.77	ND	ND	ND	ND	0.93	ND	89.65

2.6.2 Summary of acute toxicity

2.6.2.1 Acute toxicity - oral route [equivalent to section 10.1 of the CLH report template]

Table 7: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Acute oral (gavage) Predates, but compliant with, OECD TG 401 Predates GLP certification of laboratories but conducted according to GLP **Acceptable study**	Rat Outbred albino 10/sex/dose (not all dose levels were applied to both sexes)	Fenpropidin technical (purity 94%) Vehicle: gum Arabic 4% aqueous	0, 1872, 2136, 2401, 3205, 4273, or 5341 mg/kg bw (males) 0, 539, 1068, 1333, 1470, 1607, 1872, 2136, 3205 mg/kg bw (females) Single dose followed by 14 day observation period	Males = 2173 mg/kg bw Females = 1452 mg/kg bw Confidence limits not reported	[redacted] (1981)
Acute oral (gavage)	Rat	Fenpropidin	0, 913, 1461, 2283	Males = 2009	[redacted]

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Predates, but compliant with, OECD 401 Deviations : purity of the test substance was not stated Non GLP **Acceptable study**	Sprague Dawley 10/sex/group	technical (purity not stated) Vehicle: distilled water	or 3652 mg/kg bw. Single dose followed by 14 day observation period	mg/kg bw Females = 2009 mg/kg bw (2.2 ml/kg bw 95% confidence limits 2.0 to 2.5 ml/kg bw)	(1981)

Table 8: Summary table of human data on acute oral toxicity

No data available

Table 9: Summary table of other studies relevant for acute oral toxicity

No data available

2.6.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

In an acute oral toxicity study in rats ([redacted] 1981), mortality was observed at doses equivalent to 1872 – 5341 mg/kg bw in males and 1333 – 3205 mg/kg/bw in females. Deaths occurred from day 1 – 10. Clinical observations included rhinorrhoea, dacryorrhoea, lethargy, flaccidity, ataxia and piloerection. Convulsions, diarrhoea and anorexia were seen in some animals prior to death. Body weights were reduced during the first week, in all dose levels which caused mortalities. Surviving animals appeared to have recovered by study termination. Macroscopic findings in animals which were found dead included: gastritis and enteritis; enlarged lymph nodes; spleen adherent to the stomach with a reduced number of lymphocytes, and necrosis in one case. In animals which survived to termination, macroscopic findings included: cellular infiltrates in lungs, liver and/or kidneys; foci of necrosis in liver tissue; reduced numbers of lymphocytes in the spleen (1 female, 1068 mg/kg bw); pneumonitis (1 male, 1872 mg/kg bw). The LD50 of fenpropidin was calculated to be 2.38 and 1.59 mL/kg bw equivalent to 2173 and 1452 mg/kg bw for males and females, respectively.

In another acute oral toxicity study in rats ([redacted] 1981), mortality was observed at doses equivalent to 2283 – 3652 mg/kg bw in males and females. Deaths occurred from day 1 – 7. Clinical observations included piloerection, hunched posture and lethargy. At doses equivalent to 1461 mg/kg bw and above, there were incidences of diarrhoea, reduced respiratory rate, body tremors, ataxia, reduced locomotor activity and collapsed condition. Piloerection was also seen in control animals. All surviving rats had apparently recovered within five days of dosing. Body weights were reduced during the first week in males and females. Macroscopic examination of the decedents revealed slight hyperaemia or congestion of the lungs, congestion of the liver and hyperaemia of the stomach walls. Macroscopic examination of the animals killed at termination revealed slight adherence between the stomach and spleen in 3 males and 3 females dosed at 2283 mg/kg bw. Histopathological examination of tissues from the 3652 mg/kg bw group revealed vacuolisation of liver cells and lesions in the forestomach and the glandular stomach, which are considered to be treatment related. Focal inflammatory lesions of liver, kidney and lung were also seen, but were attributed to a bacterial infection. The acute oral LD50 value of fenpropidin was calculated to be 2.2 mL/kg bw (95% confidence limits 2.0 to 2.5 ml/kg bw) for male and female rats, equivalent to 2009 mg/kg bw.

2.6.2.1.2 Comparison with the CLP criteria regarding acute oral toxicity

According to CLP criteria (Regulation (EC) No. 1272/2008, Annex 1, Table 3.1.1), the last acute toxicity category: Acute Toxicity Category 4, H302: Harmful if swallowed is characterized by the following value of LD_{50}: $300 < LD_{50} \leq 2000$ mg/kg bw. Based on the acute oral toxicity studies, LD_{50} for fenpropidin is in the range 1452 – 2009 mg/kg bw. Therefore, classification is warranted.

2.6.2.1.3 Conclusion on classification and labelling for acute oral toxicity

The proposed classification for fenpropidin is Acute Toxicity Category 4, H302: Harmful if swallowed.

2.6.2.2 Acute toxicity - dermal route [equivalent to section 10.2 of the CLH report template]

Table 10: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Value LD_{50}	Reference
Acute dermal (semi-occlusive) OECD 402 GLP **Acceptable study**	Rat Tif:RAI f (SPF) 5/sex/dose	Fenpropidin technical (purity 97%)	4000 mg/kg bw 24 hour application followed by 19 or 21 day observation period	> 4000 mg/kg bw Males/females	[redacted] (1993)

Table 11: Summary table of human data on acute dermal toxicity

No data available

Table 12: Summary table of other studies relevant for acute dermal toxicity

No data available

2.6.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

In an acute dermal toxicity study in rats ([redacted] 1993), there were no mortalities following a 24 hour application of 4000 mg/kg bw. Clinical signs of piloerection and hunched posture were seen in all animals but did not persist after day 5. Signs of skin irritation at the application site included erythema and oedema and, later on, necrosis. Scaling of the skin was observed only in females. All skin lesions had recovered by day 21. Two females lost weight during the first week but all other animals gained weight during the study. There were no macroscopic abnormalities at necropsy. The acute dermal median lethal dose for male and female rats was >4000 mg/kg bw.

2.6.2.2.2 Comparison with the CLP criteria regarding acute dermal toxicity

According to CLP criteria (Regulation (EC) No. 1272/2008, Annex 1, Table 3.1.1), the last acute toxicity hazard category: Acute Toxicity Category 4, H312: Harmful in contact with skin is characterized by the following value of LD_{50}: $1000 < LD_{50} \leq 2000$ mg/kg bw. Based on the acute dermal toxicity study, LD_{50} for fenpropidin is higher than 2000 mg/kg bw.

2.6.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

As LD_{50} is higher than 2000 mg/kg bw, classification according CLP criteria (Regulation (EC) No.1272/2008) is

not required.

2.6.2.3 Acute toxicity - inhalation route [equivalent to section 10.3 of the CLH report template]

Table 13: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
Acute inhalation (nose-only) Predates, but compliant with, OECD 403 Deviation : purity of the test substance was not stated Non GLP **Acceptable study**	Rat CD (Sprague-Dawley) 8/sex/group	Fenpropidin (purity not reported). Aerosol MMAD: 0.47 mg/L – 1.89 µm, 0.68 mg/L – 1.78 µm 1.09 mg/L – 2.12 µm 1.34 mg/L – 2.32 µm 1.78 mg/L – 2.17 µm 2.39 mg/L – 2.28 µm	0, 0.47, 0.68, 1.09, 1.34, 1.78 or 2.39 mg/L (gravimetric concentration). 4 hour exposure, followed by 14 day observation period	1.22 mg/L (95% CL 1.03-1.44 mg/L) Males /females	[redacted] (1981)

Table 14: Summary table of human data on acute inhalation toxicity

No data available

Table 15: Summary table of other studies relevant for acute inhalation toxicity

No data available

2.6.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In the acute (nose-only) inhalation toxicity study in Sprague Dawley rats ([redacted] 1981), groups of 8 male and 8 female rats were exposed to aerosolised fenpropidin for 4 hours, at gravimetric concentrations of 0.47, 0.68, 1.09, 1.34, 1.78 or 2.39 mg/L. A control group was exposed to filtered air only. Deaths were observed at concentrations of 0.68 mg/L and higher; these generally occurred during exposure on day 1 but at 1.09 male deaths occurred on days 4 – 14. Rats that died during, or shortly after, exposure had respiratory difficulties and body staining. In other animals, clinical signs after exposure included: lethargy, prostration, cold to touch, ataxia and respiratory difficulties. As the study progressed, some animals had dry, scaly skin and body sores. Animals treated with $\geq$ 1.09 mg/L showed skin irritation leading to vocalisation and aggression. All treated animals showed reduced weight gain throughout the study. Macroscopic examination revealed dark patches in the lungs, indicative of pulmonary irritation, and alopecia and skin sores at $\geq$ 1.09 mg//L. Increased lung weights were observed at exposure levels of 1.34 mg/L and higher. Microscopic examination of the animals exposed to 1.78 mg/L that died on the day of exposure, revealed pulmonary congestion, oedema and /or tracheitis, indicative of pulmonary irritation. No significant pulmonary lesions were found in rats exposed to 1.78 mg/L which survived to the end of the study. The LC50 was calculated to be 1.22 mg/L (95% confidence limits 1.44 and 1.03 mg/L).

2.6.2.3.2 Comparison with the CLP criteria regarding acute inhalation toxicity

According to CLP criteria (Regulation (EC) No. 1272/2008, Annex 1, Table 3.1.1), the last acute toxicity hazard category Acute Toxicity Category 4, H332: Harmful if inhaled (dust and mists) is characterized by the following value of LC_{50}: $1< LC_{50} \leq 5$ mg/l. Based on the acute inhalation toxicity study, LC_{50} for fenpropidin is 1.22 mg/l. Therefore, CLP criteria for classification are met.

2.6.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

The proposed classification for fenpropidin is Acute Toxicity Category 4, H332: Harmful if inhaled.

2.6.2.4 Skin corrosion/irritation [equivalent to section 10.4 of the CLH report template]

Table 16: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance**	**Dose levels duration of exposure**	**Results -Observations and time point of onset -Mean scores/animal -Reversibility**	**Reference**
Acute skin irritation (occlusive dressing instead of semi-occlusive; examinations of the application site were at 45 and 68 hours rather than 48 and 72 hours). Predates, but compliant with, OECD 404 GLP **Acceptable study**	Rabbit New Zealand white Male 6/group	Fenpropidin (purity not reported)	0.5 mL applied to shorn flank, under an occlusive dressing 4 hour application Irritation response assessed at 1 hour, 1, 2 & 3 days after removal of dressings and at intervals for up to 14 days	Irritating to skin Signs of skin irritation seen in all rabbits from 1 hour after decontamination which persisted until termination of the study on day 14. Severe oedema was seen in all animals 24 hours after decontamination and moderate skin thickening was present from 6 - 14 days. Mean scores for individual tested animals (calculated from scores at 24, 45 and 68 hours): Erythema: 3.0, 3.7, 3.0, 3.0, 4.0, 4.0 Oedema: 4.0, 4.0, 4.0, 4.0, 4.0, 4.0	[redacted] (1984)
Acute skin irritation (semi-occlusive dressing) OECD 404 GLP **Acceptable study**	Rabbit New Zealand white Female 3/group	Fenpropidin (purity 99.5%)	0.5 mL applied to shorn flank, under a semi-occlusive dressing. Control patch – distilled water 4 hour application. Irritation response assessed at 1 hour, 1, 2 & 3 days after removal of dressings and at intervals for up to 21 days.	Mild irritant to skin. Signs of skin irritation (very slight to well defined erythema and very slight to slight oedema) present in 3/3 animals, all resolved by day 10. Scaling at the application site was seen in all animals on days 10 and 14, with slight scaling still present at day 17. All skin reactions were fully reversed by 21 days after patch removal. Mean scores for individual tested animals (calculated from scores at 24, 48 and 72 hours): Erythema: 2.0, 2.0, 2.0 Oedema: 1.0, 1.3, 1.3	[redacted] (1999)

Table 17: Summary table of human data on skin corrosion/irritation

No data available

Table 18: Summary table of other studies relevant for skin corrosion/irritation

No data available

2.6.2.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

In the first skin irritation study in rabbits ([redacted] 1984), fenpropidin was applied under occlusive conditions to investigate the skin irritation potential. There were no mortalities and no signs of toxicity. Signs of skin irritation were seen in all animals from 1 hour following decontamination (very slight to well defined erythema and moderate to severe oedema). By day 6, all animals had severe erythema. Severe oedema was present in all animals 24 hours after decontamination and persisted until day 6 when moderate skin thickening obscured any oedema. Additional signs of skin irritation were seen in all animals and included scabbing, hardening, cracking, desquamation, staining and areas of blanched skin. Signs of skin irritation had not resolved by day 14 when the study was terminated, however, no full thickness destruction of the skin was observed.
In a subsequent skin irritation study in rabbits ([redacted] 1999), there were no mortalities but a slight weight loss was seen in all 3 rabbits during the first week. Very slight to well-defined erythema and very slight to slight oedema was observed in all animals, but these signs had regressed by day 10. Scaling at the application site was seen in all animals on days 10 and 14, with slight scaling still present at day 17. All skin reactions had resolved by day 21.

2.6.2.4.2 Comparison with the CLP criteria regarding skin corrosion/irritation

According to CLP criteria (Regulation (EC) No. 1272/2008, Annex 1, Table 3.2.1 and 3.2.2) there was no evidence of destruction of skin tissue (visible necrosis through the epidermis and into the dermis) in either study in any animal, classification as skin corrosive is not applicable.
The basis for a positive response with regard to skin irritation is the individual rabbit value averaged over days 1, 2, and 3. The mean score for each individual animal is used as a criterion for classification. Skin irritation Category 2 is used if:

a) In a study with 3 rabbits at least 2 animals show a mean score of 2.3 or above.

b) In case of 6 rabbits if at least 4 out of 6 rabbits show a mean score per animal of $\geq 2.3 \leq 4.0$ for erythema/eschar or for oedema.

In the early study using six rabbits ([redacted] 1984) mean scores in all rabbits were $\geq 2.3 \leq 4.0$ for both erythema and oedema. However, this study is not considered suitable for evaluation of skin irritation as the dressing used was fully occlusive (impermeable rubber sheet wrapped once around the trunk) rather than semi occlusive as specified in test guideline OECD 404. The use of an occlusive dressing rather than a semi occlusive dressing is likely to have a marked impact on the level of skin hydration and absorption characteristics at the application site which would not have been evident under the conditions used in the second study ([redacted] 1999) (gauze patches loosely covered by aluminium foil) and as specified in OECD 404. In the study by [redacted] (1999) mean scores for all rabbits were < 2.3 with scaling and slight scaling between days 10 and 17. All skin reactions had resolved by day 21. Overall, it is concluded that whilst in the [redacted] (1999) study evidence of local irritation was seen at the application site, neither the erythema nor oedema scores were sufficient to trigger classification as a Category 2 skin irritant.

2.6.2.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Classification according to CLP criteria (Regulation (EC) No. 1272/2008) is not required.

2.6.2.5 Serious eye damage/eye irritation [equivalent to section 10.5 of the CLH report template]

Table 19: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Acute eye irritation Predates, but compliant with, OECD 405 except that animals were observed for 14 days and not 21 days and individual body weight data is not provided. Non GLP **Acceptable study**	Rabbit, New Zealand white 3/group	Fenpropidin (purity not reported) Vehicle: none	Single application of undiluted test substance Eyes examined after 1 hour and then at 1, 2, 3, 7 and 14 days after instillation, according to the Draize scheme.	Irritating to eyes Signs of irritation (conjunctival redness, chemosis, corneal opacity and iritis) were present in 3/3 rabbits from 1 – 72 hours after instillation. Mean scores with undiluted test substance at 24, 48 and 72 hours: Cornea: 1.3, 1.3, 1.3 Iris: 1.3, 1.3, 1.3 Conjunctivae (redness): 2.7, 3.0, 3.0 Conjunctivae (chemosis): 1.7, 2.0, 2.0 Signs of irritation had not resolved by day 14 (study termination).	[redacted] and [redacted] (1979)

Table 20: Summary table of human data on serious eye damage/eye irritation

No data available

Table 21: Summary table of other studies relevant for serious eye damage/eye irritation

No data available

2.6.2.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

The eye irritation potential was investigated in a study in rabbits ([redacted] and [redacted] 1979). Following instillation of the undiluted test substance, there was evidence of moderate ocular irritation. Corneal opacity (scores of 1-2) was observed from 1 hour post instillation and persisted until 14 days after instillation in one rabbit. Iritis (scores of 1 – 2) was observed from 1 hour – 72 hours post instillation in all animals. Conjunctival redness and swelling (chemosis) was also seen in all rabbits, from 1 hour – 7 days post instillation. By day 14, conjunctival redness (grade 1-2) persisted in all 3 rabbits and corneal opacity and chemosis was present in 1/3 rabbits.

Medical surveillance data on manufacturing plant personnel and monitoring studies conducted over 20 years indicate no evidence of significant adverse effects. The only reported cases of adverse effects in the eyes were two packing personnel reported smarting in the eyes in 1996.

Table 2.6.2.5.1-1: **Eye irritation scores according to the Draize scheme** (undiluted test substance; [redacted] & [redacted] *1979*).

Time	**Cornea**			**Iris**			**Conjunctiva**					
							Redness			**Chemosis**		
Animal number	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
after 1 hour	1	1	1	1	1	1	2	2	2	1	1	1
after 24 hours	1	1	1	2	2	2	2	3	3	1	2	2
after 48 hours	1	1	1	1	1	1	3	3	3	2	2	2
after 72 hours	2	2	2	1	1	1	3	3	3	2	2	2
mean scores 24-72h	1.3			1.3			2.9			1.9		
after 7 days	1	1	3	0	0	0	3	3	3	2	2	2
after 14 days	0	0	3	0	0	0	1	1	2	0	0	1

2.6.2.5.2 Comparison with the CLP criteria regarding serious eye damage/eye irritation

According to CPL criteria (Regulation (EC) No. 1272/2008 Annex I, Table 3.3.1), an active substance is considered to cause Serious eye damage Category 1, H318 if it produces: at least in one animal, effects on the cornea, iris or conjunctiva that are not expected to reverse or to have not fully reversed within an observation period of 21 days; and/or the following positive response (calculated as the mean scores following grading at 24, 48, and 72 hours after the instillation of the test material) is observed at least in 2 of 3 tested animals: corneal opacity ≥ 3 and/or iritis ≥ 1.5;
In the study of [redacted] and [redacted] (1979), scores for corneal opacity and iritis did not exceed the criteria. However, conjunctival redness was still present in all animals on day 14, while corneal opacity and chemosis in one animal were also present on day 14. As no further observations were made it cannot be excluded that these reaction would have cleared by day 21. Consequently, fenpropidin is considered to cause serious eye damage.

2.6.2.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

The proposed classification for fenpropidin is Serious eye damage Category 1, H318: Causes serious eye damage.

2.6.2.6 Respiratory sensitisation [equivalent to section 10.6 of the CLH report template]

Table 22: Summary table of animal studies on respiratory sensitisation

No studies available

Table 23: Summary table of human data on respiratory sensitisation

No evidence of respiratory sensitisation in humans.

Table 24: Summary table of other studies relevant for respiratory sensitisation

No studies available

2.6.2.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No formally recognised and validated animal tests currently exist for respiratory sensitisation. Although there is evidence of respiratory irritation in single and repeated dose inhalation studies in rats, there was no indication of sensitisation. In humans, based on medical surveillance data on manufacturing plant personnel and monitoring studies conducted over 20 years, no evidence of respiratory sensitisation has been reported.

Manufacturing employees in Switzerland are medically examined by a company physician at the beginning of their employment and then routinely on a regular bases according to the criteria of the Swiss Accident Insurance Institution (SUVA). Routine medical examinations include: anamnesis, physical examination, blood analysis (haemoglobin, erythrocytes, leukocytes, thrombocytes, complete blood count, blood sedimentation rate, blood sugar, blood pressure, cholesterol, triglycerides, ALT, AST, alkaline phosphatase, bilirubine, creatinine, uric acid) and urine analysis. The active ingredient is manufactured on Syngentas behalf by a 3rd Party ([redacted]. No reports of adverse health effects have been made.

Formulation and packaging is located in Syngenta's plant in [redacted] and in [redacted]; in the past also in [redacted] Questionnaires have been sent ou to the managers of the sites and company physicians (last update by March 2003).

Since 1991 about 450 tonnes of fenpropidin per year were used in [redacted], involving 20-50 workers. No adverse health effects have been reported.

Since 1992 about 10 formulations containing fenpropidin were produced in [redacted] Formulation is done in campaigns (e.g. 2 campaigns per year, 1 month per campaign, involving about 30 workers). There was one report of adverse health effects in 1996 involving 4 workers from the packaging line – general itchiness and smarting of eyes in two workers each. Unless other factors (e.g. other formulation ingredients) were involved, the observed effects might be related to fenpropidins well-known irritation potential perhaps in combination with not complete compliance to safety measures.

No adverse health effects have been reported from [redacted], involving 5 persons, 208 tonnes of material was used. In [redacted] formulation of Fenpropidin products was done from 1989 to 1995 in about 10 campaigns per year (each campaign took 11 to 15 days each). A total of 30 persons were involved in the production. No compound related adverse effects were reported.

In summary except a confirmation that potential exposure to fenpropidin can lead to irritation reactions of the skin and eye, no adverse health effects have been observed. Following the report from France in 1996, changes in operating procedures to improve standards of hygiene and reduce exposure have resulted in no further adverse effects being observed in any of the production or formulation.

2.6.2.6.2 Comparison with the CLP criteria regarding respiratory sensitisation

Not relevant. No studies available.

2.6.2.6.3 Conclusion on classification and labelling for respiratory sensitisation

Not relevant. No studies available.

2.6.2.7 Skin sensitisation [equivalent to section 10.7 of the CLH report template]

Table 25: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Maximisation study Predates, but compliant with OECD 406, except that the age of the animals was not reported. GLP **Acceptable study**	Guinea pig: Pirbright white (Tif: DHP) 10/sex –test group 5/sex – control group	Fenpropidin (purity 97%) Vehicle: *oleum arachidis* / vaseline	Induction: Intradermal: 5% in *oleum arachidis*; 5% in FCA / physiological saline; and FCA / physiological saline (1:1). Topical: 30% in vaseline under an occlusive dressing for 48 hours. Challenge: 5% in vaseline under an occlusive dressing for 24 hours.	Sensitising Skin reactions (erythema) following challenge were observed at 24 and 48 hours in 5/20 and 8/20 test animals, respectively. No positive skin reactions were observed in the negative control animals. % of animals with positive reactions at 24 and 48 hours: Controls: Fenpropidin: 0%, 0% Vehicle: 0%, 0% Test group: Fenpropidin: 25%, 40% Vehicle: 0%, 0%	[redacted] (1994a)
Buehler study Predates, but compliant with OECD 406, except that the age of the animals was not reported. GLP **Acceptable study**	Guinea pig Pirbright white (Tif: DHP) 10/sex –test group 5/sex – control group	Fenpropidin (purity 97%) Vehicle: *oleum arachidis*	Induction: Dermal occlusive application for 6 hours in weeks 1, 2 and 3. Test group: 60% fenpropidin in *oleum arachidis* Naive controls: *oleum arachidis* Challenge: dermal occlusive application for 6 hours in week 5 (13-15 days after induction). Test and naive controls - 30% fenpropidin in *oleum arachidis* and vehicle alone.	Sensitising Skin reactions following challenge were observed at 24 and 48 hours in 5/20 and 9/20 test animals, respectively. No positive skin reactions were observed in the negative control animals. % of animals with positive reactions at 24 and 48 hours: Controls: Fenpropidin: 0%, 0% Vehicle: 0%, 0% Test group: Fenpropidin: 25%, 45% Vehicle: 0%, 0%	[redacted] (1994b)

Table 26: Summary table of human data on skin sensitisation

No evidence of skin sensitisation in humans.

Table 27: Summary table of other studies relevant for skin sensitisation

No studies available.

2.6.2.7.1 Short summary and overall relevance of the provided information on skin sensitisation

In a Magnusson and Kligman skin sensitisation study in guinea pigs ([redacted] 1994a), there was no significant skin irritation observed after induction and there were no signs of systemic toxicity. Challenge exposure to 5% fenpropidin in vaseline caused positive skin reactions (erythema) in 25%/40% of the animals 24/48 hours after removal of the dressings. No positive skin reactions were seen in the negative control group. In a separate positive control study with 2-mercaptobenzothiazole, 20/20 test animals exhibited signs of sensitisation, proving the sensitivity of the test system.

In a Buehler sensitisation study in guinea pigs ([redacted] 1994b), there were no signs of systemic toxicity following induction with 60% fenpropidin in *oleum arachidis*. Challenge exposure to 30% fenpropidin in *oleum arachidis* caused positive skin reactions in 9/20 test animals, corresponding to a sensitisation rate of 45%. There were no skin reactions in the naive control animals at challenge. In a separate positive control study with 2-mercaptobenzothiazole, 6/20 test animals showed positive skin reactions (sensitisation rate of 30%), proving the sensitivity of the test system.

2.6.2.7.2 Comparison with the CLP criteria regarding skin sensitisation

Substances are considered to be skin sensitisers and classified in sub-category 1B if in a guinea pig maximisation test ≥ 30% animals respond at > 1% intradermal induction dose. In the study of [redacted] (1994a) 40% of animals responded following intradermal injection at 5%.

For Buehler assays substances are classified in sub-category 1B if ≥ 15% animals respond following a topical dose of > 20%. In the study of [redacted] (1994b), 45% of animals responded following a topical application of 60%.

Both studies meet the criteria for classification and fenpropidin is considered to be a skin sensitiser.

2.6.2.7.3 Conclusion on classification and labelling for skin sensitisation

The proposed classification for fenpropidin is Skin Sensitiser Category 1B, H317: May cause an allergic reaction.

2.6.2.8 Phototoxicity

Table 28: Summary table of studies on phototoxicity

No studies available

Table 29: Summary table of human data on phototoxicity

No data available

Table 30: Summary table of other studies relevant for phototoxicity

No studies available

2.6.2.9 Aspiration hazard [equivalent to section 10.13 of the CLH report template]

Table 31: Summary table of evidence for aspiration hazard

No data available

2.6.2.9.1 Short summary and overall relevance of the provided information on aspiration hazard

No information on aspiration hazard relating to fenpropidin is available.

2.6.2.9.2 Comparison with the CLP criteria regarding aspiration hazard

According to the CLP criteria (Regulation (EC) No. 1272/2008), an active substance is included in the hazard category (Category 1) for aspiration toxicity: (i) based on reliable and good quality human evidence or (ii) if it is a liquid hydrocarbon and has a kinematic viscosity of 20.5 mm^2/s or less, measured at 40°C. Fenpropidin does not meet CLP criteria because no information on aspiration hazard relating to fenpropidin is available and the substance is a liquid of higher kinematic viscosity.

2.6.2.9.3 Conclusion on classification and labelling for aspiration hazard

No classification is proposed.

2.6.2.10 Specific target organ toxicity-single exposure (STOT SE) [equivalent to section 10.11 of the CLH report template]

Table 32: Summary table of animal studies on STOT SE (specific target organ toxicity-single exposure)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results** **- NOAEL/LOAEL** **- target tissue/organ** **- critical effects at the LOAEL**	**Reference**
Acute inhalation Predates, but compliant with, OECD 403 Non GLP Rat: CD (Sprague-Dawley) 8/sex/group **Acceptable study**	Fenpropidin (purity not reported) Aerosol Vehicle: air Nose-only inhalation 0, 0.47, 0.68, 1.09, 1.34, 1.78 or 2.39 mg/L (gravimetric concentration). 4 hour exposure, followed by 14 day observation period	**<u>2.39 mg/L</u>** *Mortality:* 7/8 males and 8/8 females day 1 *Clinical findings:* respiratory difficulties and body staining *Macroscopic examination:* Increased lung weights, evidence of pulmonary irritancy **<u>1.78 mg/L</u>** *Mortality*: 7/8 males (days 1-3), 6/8 females (day 1) *Clinical findings:* decedents: respiratory difficulties and body staining; survivors: lethargy, prostration, cold to touch, ataxia and respiratory difficulties, dry, scaly skin and body sores *Macroscopic examination:* Increased lung weights, evidence of pulmonary and dermal irritancy. *Microscopic examination*: Pulmonary congestion, oedema and /or tracheitis, indicative of pulmonary irritation, dermatitis. **<u>1.34 mg/L</u>** *Mortality*: 8/8 males (day 1), 8/8 females (day 1) *Clinical findings:* respiratory difficulties and body staining *Macroscopic examination:* Increased lung weights,	[redacted] (1981)

		dark patches in the lungs suggestive of pulmonary irritancy. **1.09 mg/L** *Mortality:* 3/7 males (days 4-14), 2/7 females (day 1) *Clinical findings*: decedents: respiratory difficulties and body staining; survivors: lethargy, prostration, cold to touch, ataxia and respiratory difficulties, dry, scaly skin and body sores, vocalisation and aggression *Macroscopic examination:* alopecia and skin sores present **0.68 mg/L** *Mortality:* 1/7 males (day 1), 1/7 females (day 1) *Clinical findings*: decedents: respiratory difficulties and body staining; survivors: lethargy, prostration, cold to touch, ataxia and respiratory difficulties, dry, scaly skin and body sores. **0.47 mg/L** *Mortality:* 0/7 males, 0/7 females *Clinical findings*: lethargy, prostration, cold to touch, ataxia and respiratory difficulties, dry, scaly skin and body sores.	
Acute oral (gavage) Predates, but compliant with, OECD 401 Predates GLP certification of laboratories but conducted according to GLP Rat Outbred albino 10/sex/dose (not all dose levels were applied to both sexes) **Acceptable study**	Fenpropidin technical (purity 94%) Vehicle: gum Arabic 4% aqueous 0, 1872, 2136, 2401, 3205, 4273, or 5341 mg/kg bw (males) 0, 539, 1068, 1333, 1470, 1607, 1872, 2136, 3205 mg/kg bw (females) Single dose followed by 14 day observation period	Mortality : at dose levels of >1333 mg/kg bw Clinical signs: lethargy, ataxia and piloerection (after dosing); rhinorrhoea, dacryorrhoea, , flaccidity; convulsions, diarrhoea and anorexia were seen in some animals prior to death; the majority of survivors appeared normal at the study termination Pathology: cellular infiltrates in lungs (1 ♂ 2401 mg/kg bw); pneumonitis (1 ♂ 1872 mg/kg bw); foci of liver necrosis (1 ♂ 2401 mg/kg bw and 2 ♀ 1607 mg/kg bw); nephritis (1 ♂ 2401 mg/kg bw); In animals found dead: gastritis, enteritis (2 ♀ 2136 mg/kg bw)	[redacted] (1981)
Acute oral (gavage) Predates, but compliant with, OECD 401 Non GLP Rat Sprague Dawley 10/sex/group **Acceptable study**	Fenpropidin technical (purity not stated) Vehicle: distilled water 0, 913, 1461, 2283 or 3652 mg/kg bw. Single dose followed by 14 day observation period	LD_{50} : 2009 mg/kg bw Clinical signs: piloerection, hunched posture and lethargy (in all males and majority of females); diarrhoea, reduced respiratory rate (2283 and 3652 mg/kg bw), body tremors (2283 and 3652 mg/kg bw), ataxia (2283 and 3652 mg/kg bw), reduced locomotor activity (3652 mg/kg bw); recovery complete in survivors within 5 days; Pathology: vacuolisation of liver cells, lesions in the forestomach and glandular stomach (3652 mg/kg bw)	[redacted] (1981)
Acute dermal (semi-occlusive) OECD 402 GLP Rat Tif:RAI f (SPF)	Fenpropidin technical (purity 97%) 4000 mg/kg bw 24 hour application followed by 19 or 21 day observation	No mortality No abnormalities at necropsy Clinical findings during observation period: piloerection and hunched posture	[redacted] (1993)

5/sex/dose **Acceptable study**	period		

Table 33: Summary table of human data on STOT SE (specific target organ toxicity-single exposure)

No evidence of adverse effects

Table 34: Summary table of other studies relevant for STOT SE (specific target organ toxicity-single exposure)

No studies available

2.6.2.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure (STOT SE)

In standard single dose oral and dermal toxicity studies there was not an evidence of specific target organ toxicity. In the acute inhalation study an atmosphere concentration of 1.78 mg/L produced marked signs of pulmonary and dermal irritancy, including microscopic pathology in decedents. Clinical signs of respiratory irritation were observed in all dose groups (≥ 0.47 mg/L), although there was no evidence significant pulmonary lesions in animals that survived to termination.

2.6.2.10.2 Comparison with the CLP criteria regarding STOT SE (specific target organ toxicity-single exposure)

According to CLP criteria (Regulation (EC) No. 1272/2008, Annex 1, Table 3.8.1), an active substance is classified in Specific target organ toxicity after single exposure Category 1, H370 or Category 2, H371, based on the results of animal studies if it elicits significant and/or severe toxic effects of relevance to the human health at generally low or moderate exposure concentrations, respectively. The toxic effects relating to STOT SE include changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism. The Category 3 for STOT SE includes only narcotic effects and respiratory tract irritation. This special classification occurs only when more severe organ effects including in the respiratory system are not observed.

Evidence of significant lung toxicity (i.e. exposure concentrations that produced histopathological damage) was only noted in conjunction with acute mortality. Consequently the data do not warrant classification as Category 1 or 2. However, clinical signs of respiratory tract irritation were noted at a concentration of 0.47 mg/L in the absence of mortality. Therefore, fenpropidin is considered to be a respiratory tract irritant and to meet the criteria for classification.

2.6.2.10.3 Conclusion on classification and labelling for STOT SE (specific target organ toxicity-single exposure)

The proposed classification for fenpropidin is STOT-SE Category 3, H335: May cause respiratory irritation.

2.6.3 Summary of repeated dose toxicity (short-term and long-term toxicity) [section 10.12 of the CLH report]

2.6.3.1 Specific target organ toxicity-repeated exposure (STOT RE) [equivalent to section 10.12 of the CLH report template]

Table 35: Summary table of animal studies on repeated dose toxicity (short-term and long-term toxicity) STOT RE (specific target organ toxicity - repeated exposure)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
28-day range finding study OECD 407 Deviation: brain weight not recorded GLP Rat: Tif: RAIf (SPF) 5/sex/group **Acceptable study**	Fenpropidin technical (purity 97%) Oral (diet) 0, 50, 200, 1000 and 2000 ppm equivalent to 5.40, 20.1, 104.6, 200.1 mg/kg bw/day (males), and 5.62, 19.9, 103.4, 212.2 mg/kg bw/day (females) 28 days continuous in diet	NOAEL: 1000 ppm (104.6 in males and 103.4 mg/kg bw in females) **2000 ppm (males 200.1 mg/kg bw/day, females 212.2 mg/kg bw/day)**: *Body weight*: ↓ 28% males, 14% females at end of study *Food consumption*: ↓ 23% males over course of study *Haematology:* ↑ red cell count: 6.9% males, 5.7% females; ↓ MCV: 6.2% males, 7.8% females; ↓ MCH: 5.9% males, 7.2% females *Clinical chemistry:* ↑ urea: 29.5% males, 25.6% females; ↓ globulin: 6.7% males, 9.7% females; ↑ A/G ratio: 10.1% males, 11.3% females; ↑ ASAT: 55.5% males, 27.1% females; ↑ ALAT: 122.6% males, 131.4% females; ↓ cholesterol: 11.4% males, 24.8% females *Histopathology:* ↑ non glandular stomach hyperkeratosis 5/5 males, 2/5 females (0/5 control) and acanthosis 5/5 males, 0/5 females (0/5 control); ↑ oesophagus hyperkeratosis 5/5 males, 5/5 females (0/5 control) and acanthosis 5/5 males, 0/5 females (0/5 control); ↑ urinary bladder hyperplasia 4/5 males, 4/5 females (0/5 control) and inflammatory cell infiltration 4/5 males, 0/5 females (0/5 control); ↑ lung alveolus foam cell: 4/5 males and 4/5 females (1/5 control) **1000 ppm (males 104.6 mg/kg bw/day, females 103.4 mg/kg bw/day)**: *Body weight:* ↓ 10% males, 7% females at end of study *Food consumption*: ↓ 9% males over course of study *Haematology:* ↑ RBC 6.3% males; ↓ MCV: 4.9% males *Clinical chemistry:* ↑ urea: 40.0% males, ↑ ALAT: 83.2% males, *Histopathology:* ↑ oesophagus hyperkeratosis 5/5 males, 4/5 females (0/5 control); ↑ lung alveolus foam cell: 1/5 male, 4/5 females (1/5 control) **200 ppm (males 20.1 mg/kg bw/day, females 19.9 mg/kg bw/day)**: *Body weight:* ↓ 9% males, 3% females at end of study *Food consumption:* ↓ 10% males over course of study *Haematology:* ↓ MCV: 4.7% females *Histopathology:* ↑ oesophagus hyperkeratosis 3/5 males (0/5 control) **50 ppm (males 5.40 mg/kg bw/day, females 5.62 mg/kg bw/day)**: *Food consumption*: ↓ 11% males over course of study No treatment-related effects.	[redacted] (1994)
90-day oral toxicity study OECD 408, minor deviations: no	Fenpropidin technical (purity 97%). Oral (diet)	NOAEL: 150ppm (9.84 and 10.1 mg/kg bw/day for males and females, respectively) **1500 ppm (89.9 mg/kg bw/day males, 97.3 mg/kg bw/day females)**	[redacted] (1995)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
epididymides or uterus weights, several organs/tissues were not examined GLP Rat: Tif: RAIf (SPF) 15/sex/group 10/sex control and high dose to assess recovery **Acceptable study**	0, 20, 150 and 1500 ppm (1.14, 9.84, 89.9 mg/kg bw/day (males), and 1.24, 10.1, 97.3 mg/kg bw/day (females) 90 day (dietary administration), recovery period for control and high dose 4 weeks	*Clinical observations*: 1/25 females had bilateral opaque eyes from day56 and bilateral limb paralysis from day76. *Body weight:* ↓ 16% males, 8% females week 13 *Body weight gain*: ↓ 29% males, 18% females weeks 1-13 *Food consumption:* ↓ 10% males, 5% females weeks 1-13 *Water consumption*: ↓ 20% males during whole treatment period *Haematology:* ↑ RBC 4.0% males; ↑ Hb 3.3% males; ↑ WBC 22.2% females (29.3% lymphocytes) *Clinical chemistry:* ↓ globulin 9.5% males, 5.8% females, partly reversible after recovery; ↓ glucose 12% males; ↓ triglycerides 29% males similar to control after recovery *Organ weight:* ↑ liver relative to body weight: 12% females *Histopathology:* ↑ oesophagus pathology: hyperkeratosis 10/10 males and 10/10 females (0/10 control) and acanthosis 6/10 males, 2/10 females (0/10 control); ↑ nonglandular stomach pathology: hyperkeratosis 8/10 males, 5/10 females (0/10 and 1/10 control) and acanthosis 7/10 males, 4/10 females (0/10 control); ↑ urinary bladder hyperplasia: 4/10 males, 7/10 females (control 0/10 males and 1/10 females); **demyelination affecting especially nerve roots and spinal tracts** 1/10 females (with hind limb paralysis); ↑ pulmonary foam cells: 9/10 males grading 1.7 (control 7/10 grade 1.3); 7/10 females grade 1.7 (control 6/10 grade 1.3). After 4 weeks there was partial recovery from pathology findings in stomach and oesophagus. **150 ppm (9.84 mg/kg bw/day males, 10.1 mg/kg bw/day females)** *Histopathology:* ↑ oesophagus pathology: hyperkeratosis 4/10 males and 4/10 females (0/10 control); ↑ nonglandular stomach pathology: hyperkeratosis 3/10 males (0/10 control) **20 ppm (1.14 mg/kg bw/day males, 1.24 mg/kg bw/day females)** No treatment related findings	
90-day oral toxicity study OECD 408 Deficiencies: recovery group 6/sex high dose no controls, clinical pathology limited parameter and only 8/sex, not full tissue list for pathology GLP	Fenpropidin (purity 94.7%) Oral (diet) 0, 20, 60, 120 mg/kg bw/day 90-days continuous in diet; high dose only satellite group 14 day recovery	NOAEL: 60mg/kg bw **120 mg/kg bw/day** *Clinical* observations: rough fur, hunched posture, rhagades, loss of hair and necrosis of the tail *Body weight:* ↓ 30% males, 13% females week 13 *Food consumption*: ↓ 18.0% males weeks 1-13, 17.8% females week 1 *Clinical pathology:* ↓ Cholinesterase activity 64.9% females week 13; ↑ GOT (ASAT) 25.8% males, 54.5% females week 7. **60 mg/kg bw/day** *Body weight:* ↓ 15% males, 8% females week 13 *Food consumption:* ↓ 7% males weeks 1-13 *Clinical chemistry*: ↓ Cholinesterase activity 40.9% females	[redacted] (1981)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
Rat: SPF-albino rats (outbred stock) 16/sex/group; satellite recovery group high dose only 6/sex **Acceptable study**		week 13; ↑ GOT (ASAT) 19.4% males, 15.2% females week 7. **20 mg/kg bw/day** *Body weight*: ↓7% males, 6% females week 13 *Clinical chemistry:* ↑ GOT (ASAT) 33.3% females week 7.	
90-day oral toxicity study OECD 408 Deviations: only 8/sex and limited parameters for clinical pathology; thymus and epididymides not weighed; several tissues not examined pathologically. GLP Mouse SPF-albino mice (outbred stock) 16/sex/group **Supportive study**	Fenpropidin (purity 99%) Oral (diet) 0, 625, 1250, 2500 and 5000 ppm; equivalent to 0, 58, 155, 359 and 547 mg/kg bw/day (males), and 0, 87, 179, 361and 566 mg/kg bw/day (females) 90 days continuous in diet Due to mortalities in the 5000 ppm group, additional low dose group added to the study	NOAEL: 1250 ppm (155 in males and 179 mg/kg bw in females) **5000 ppm (547 mg/kg bw/day in males and 566 mg/kg bw/day in females)** All animals died or killed for humane reasons, males by week 7, and females by week 4. In excess of MTD further differences from control not included. **2500 ppm (359 mg/kg bw/day in males and 361 mg/kg bw/day in females)** *Mortality:* 5 females died by week 5, 1 male week 13 *Clinical signs*: ↑ signs of local skin irritation *Body weight*: ↓ 13.8% males, 10.4% females week 13 *Food consumption*: ↑ males (probably wastage) *Clinical chemistry:* ↑ ASAT approximately 100% in both sexes *Macropathology:* ↑ Skin hyperkeratosis **1250 ppm (155 mg/kg bw/day in males and 179 mg/kg bw/day in females)** *Clinical signs:* ↑ Inflammation of the ears and of tail tips. *Body weight:* ↓ 8.3% females week 13 *Food consumption*: ↑ males (probably wastage) **625 ppm (58 mg/kg bw/day in males and 87mg/kg bw/day in females)** *Body weight*: ↓ 10.4% females week 13	[redacted] and [redacted] (1981)
28-day dose ranging finding study in beagle dog. No guideline. non GLP Dog: Beagle 2/sex/group **Supplementary study** (due to limited number of animals and further deviations)	Fenpropidin technical (purity 97%) Oral in capsules 0, 5, 15, 25 mg/kg bw/day 28 days	NOAEL: 5mg/kg bw for males and 15 mg/kg bw for females Body weight differences not statistically significant (small group size), other results significant Jonkheere's trend test) **25 mg/kg bw/day** *Clinical signs:* ↑ vomiting and salivation (transient) males and females *Body weight*: ↓ 9% males and females week 4 *Food consumption*: ↓ 54.9% week 1, 32.3% week 4 females only (note period of feeding extended after week 1) *Clinical chemistry:* ↓ cholesterol 30.9% males, 26.4% females *Organ weights*: ↑ relative kidney 30% males; ↑ relative liver 59% males, 20% females **15 mg/kg bw/day**	[redacted] (1993)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
		Clinical signs: ↑ vomiting and salivation (transient) in females *Body weight*: ↓ 3% males and 5% females week 4 *Food consumption*: ↓ 62.2% week 1 females only (period of feeding extended after week 1) *Clinical chemistry*: ↓ cholesterol 24.4% males *Organ weight*: ↑ relative kidney weights 17% males; ↑ relative liver weight 38% males **5 mg/kg bw/day** No treatment-related effects	
26-week oral toxicity study in dog Pre OECD guideline but similar to OECD 409 GLP Dog: Beagle 4/sex/ group 2/sex/group killed after 26 weeks, 2/sex/group after 4 week recovery **Supportive information** (due to many deviations)	Fenpropidin (purity 94.7%) Oral in capsules 0, 2, 5, 12 mg/kg/day 26 weeks, recovery period 4 weeks	NOAEL: 5mg/kg bw **12 mg/kg bw/day** *Mortality:* One male died week 16 following weight loss from week 11 *Clinical signs:* One female conjunctivitis and keratitis of eye; ↑ salivation in females up to 2 hours after dosing; ↑ vomiting both sexes *Body weight*: ↓ 12% females (week 1-25) *Clinical chemistry:* ↑ ALP 93.6% males, 46.8% females week 26; ↓ cholesterol females weeks 19 and 26, not statistically significant. *Histopathology:* decedent: hepatitis with congestion and slight cholestasis; enteritis and diapedesis bleeding (relation to treatment unknown). **5 mg/kg bw/day** *Clinical signs:* ↑ vomiting (incidence not reported) **2 mg/kg bw/day** No treatment related effects.	[redacted] (1981)
1-year oral toxicity study in dog OECD 452 Deviations: urine volume and ornithine decarboxylase not measured; femur with joint not taken GLP Dog: Beagle 4/sex/group **Acceptable study**	Fenpropidin technical purity 97%) Oral in capsules 0, 2, 5 and 20 mg/kg/day 1 year	NOAEL: 5mg/kg bw **20 mg/kg bw/day** *Mortality:* 1 male with hind limb paresis killed week 38, pathology findings: demyelination of spinal cord *Clinical observations*: ↑ Indurated and inelastic pads 4/4 males and females; vomiting 4/4 females weeks 1-6; scale formation in inguinal and axillary regions 4/4 males and 3/4 females; reddening of skin 1/4 males and females *Ophthalmoscopy*: ↑ opacity of the lens: 4/4 males and females from week 22 *Body weight:* ↓ 15% females week 4, similar to control after initial weeks of study. *Food consumption*: ↓ 27% week 1 and 14% week 4 females *Haematology:* ↑ platelets 53.6% week 13, 40.8% week 26 males *Clinical chemistry*: ↑ ALP 42.4% males week 26, 43.4% and 115.9% females weeks 13 and 52; ↓ albumin:globulin ratio 20.6% males week 13; ↑ globulin 25.4% males and 33.5%	[redacted] (1995)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
		females week 52 *Organ weight:* ↑ relative liver 27% males; ↑ relative kidney 26% females *Histopathology:* cataract of crystalline lens 4/4 males and females (0/4 control); acanthosis of epidermis 3/4 males, 4/4 females (0/4 control); chronic inflammation skin/dermis: 2/4 males, 3/ 4 females (0/4 control); hepatocyte hypertrophy 4/4 males and females (0/4 control); pigmentation of Kupffer cells 4/4 females (1/4 control); liver inflammatory cell infiltration 3/ 4 females (2/4 control); renal tubular pigmentation 4/4 females (1/4 control); inclusion bodies urinary bladder epithelium 4/4 males, 2/4 females (0/4 control); cholesterol granulomas in lung 4/4 males, 1/ 4 females (0/4 control); **demyelination of spinal cord 3/4 males (0/4 control)** **5 mg/kg bw/day** *Clinical chemistry:* ↓ albumin:globulin ratio 12.5% males week 13 *Organ weight*: ↑ relative liver 16% males not significant *Histopathology:* hepatocyte hypertrophy 2/4 males (0/4 control) **2 mg/kg bw/day** No treatment related effects	
21-day dermal toxicity OECD 410 Deviations: some clinical pathology parameters not included, spleen was not examined Non GLP Rabbit: New Zealand white 5/sex/group (intact skin); plus 5/sex/group (abraded skin) **Acceptable study**	Fenpropidin (purity 94.7%) Dermal 0, 0.02, 0.2 and 1-2 mg/kg/day Treatment at 2 mg/kg stopped days 10-13 and continued at 1 mg/kg bw/day day 14 for further 10 days 6 hours/day occlusive dressing, 21 days Vehicle aqueous 0.5% CMC	NOAEL: cannot be stated No evidence of systemic toxicity. No difference in skin irritation response between abraded and intact skin in any group **1-2 mg/kg bw/day** Marked skin irritation with severe fissuring. Epidermal ulceration, marked epidermal thickening, inflammation of the dermis and occasional dermal fibrosis **0.2 mg/kg bw/day** Moderate erythema, oedema and fissuring of the skin. Epidermal ulceration, marked epidermal thickening, inflammation of the dermis and occasional dermal fibrosis **0.02 mg/kg bw/day** Minimal to slight skin irritation was seen in the majority of animals (also controls). Leucocyte infiltration in treated skin	[redacted] (1981)
28-day inhalation study OECD 412 Deviations: some clinical pathology parameters not	Fenpropidin (purity not reported) Inhalation (nose –only) Measured concentration: 0 20.4, 76.8, 237.4	NOAEL: cannot be stated due to pre-term sacrifice of high and intermediate dose level animals **237 mg/m³ and 76.8 mg/m³** Animals were sacrificed after the first week of treatment due to their poor condition. Local irritation in the upper respiratory tract and respiratory distress. Lower body weight and food consumption, some changes in haematology and clinical	[redacted] (1981)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
measured Non GLP Rat: CD (Sprague-Dawley) 15/sex/group; of these 10/sex/group for clinical pathology **Supplementary study**	mg/m^3 6 hours per day for four weeks	chemistry. **20.4 mg/m^3 (measured concentration)** No evidence of systemic toxicity Skin irritation (chronic folliculitis and dermatitis) in nose 1/10 males, 2/10 females; 0/10 controls) and head region (1/10 males, 1/10 females; 0/10 controls)	

Table 36: Summary table of human data on repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

No evidence of adverse effects in humans

Table 37: Summary table of other studies relevant for repeated dose toxicity STOT RE (specific target organ toxicity-repeated exposure)

No studies available

2.6.3.1.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure (short-term and long-term toxicity)

The most consistent effect of fenpropidin observed was irritation. Dietary administration of fenpropidin to rats caused signs of local irritation in the oesophagus, stomach and urinary bladder. Most of these effects were reversible when treatment was discontinued. In mice a dose level of 1250 ppm (155 mg/kg bw/day in males and 179 mg/kg bw/day in females) caused an increased incidence of inflammation of the ears. In dogs signs of local irritation were observed at several locations of the body surface (food pads, ear) in the 1-year study at a dose level of 20 mg/kg bw/day.

Histopathological changes compatible with morphological findings resulting from local irritation were found in treated animals of oral subchronic toxicity studies. The signs of local irritation were hyperkeratosis and acanthosis of keratinised, stratified squamous epithelium (skin, oesophagus, forestomach of rodents) and hyperplasia of the transitional epithelium of the urinary bladder. In addition, inflammation and ulceration were observed in some of these animals.

Systemic effects observed after exposure to fenpropidin were body weight reduction for both males and females in the 28-day study in the rat ([redacted] 1994). In the 90-day study in the rat ([redacted] 1995) reduced body weight development, increased relative liver weight in females and a marginal, non-reversible, increased occurrence of pulmonary foam cells were noted in high dose animals. A demyelination affecting especially nerve roots and spinal tracts was confined to one single high dose female that also had paralysed hind limbs. The same animal developed bilateral cataracts. In the 90-day mouse study ([redacted] and [redacted] 1981) deaths, decreased body weight and changes in aspartate aminotransferase and liver histology were observed in animals administered 2500 ppm.

In the 28-day dog study ([redacted] 1993) clinical signs of vomiting and salivation were observed at dose levels of 15 mg/kg bw/day and above. Increases in absolute and relative liver and kidney weights were observed at dose levels of 15 mg/kg bw/day and above in males only. In females, decreased food consumption and changes in clinical chemistry were observed at 25 mg/kg bw/day. In the 26 week dog study ([redacted] 1981) increased incidences of vomiting, reduced body weight gain and mortality of a single dog was observed at 12 mg/kg bw/day.

In the one-year dog study ([redacted] 1995) liver effects, expressed as increased weight, hepatocyte hypertrophy and increased alkaline phosphatase were observed. In a high dose males (20 mg/kg bw/day) all animals had cataracts of the eyes, in one animal hind limb paralysis was observed and spinal cord toxicity expressed as minimal to marked demyelination was observed in three out of four dogs.
The target organ for fenpropidin was reported as the liver in some studies. In a 90-day rat study there was a small increase in relative liver weight in females at 1500 ppm (97.3 mg/kg bw/day). A more marked increase was noted in dogs after 28 days in both sexes at a dose of 25 mg/kg bw/day and males at 15 mg/kg bw/day and also in a 1 year study at 20 mg/kg bw/day in males. Pathology findings in the liver were confined to the 1-year study in dogs where hepatocyte hypertrophy was evident in all dogs and Kuppfer cell pigmentation in all females at 20 mg/kg bw/day. At a dose of 5 mg/kg bw/day 2/4 males also had hepatocyte hypertrophy. These findings were consistent with adaptive changes and do not represent severe organ toxicity as defined in the CLP guidance (ECHA, 2015).
There was some evidence of demyelination/paralysis and eye effects in two separate studies and species. In a 1 year study in dogs one male treated with 20 mg/kg bw/day was found with hind limb paresis at week 38, which was associated with a demyelination of the thoracic spinal cord. Demyelination of different segments of the spinal cord was also found in the other males of this dose group. All dogs of both sexes developed cataracts (onset of opacity after 22 weeks) at 20 mg/kg bw/day. No cataracts/opacity had been seen in the 26-week study at dose levels up to 12 mg/kg bw/day. In a 90 day rat study one high dose female developed paralysis of the hind limbs after about 11 weeks of treatment with 1500 ppm (97.3 mg/kg bw/day). Histopathological examination revealed demyelination of the spinal cord and peripheral nerves. The same animal showed bilateral cataracts. There was no further evidence for neurological or behavioural effects in any other rat from any other study. It is postulated that both the cataract formation and the demyelination may be linked to impairment of cholesterol biosynthesis.
Percutaneous administration of fenpropidin to rabbits revealed a series of skin irritation reactions at the application site. The irritant properties of the compound precluded the administration of dose levels above 1-2 mg/kg bw/day. Dermal irritation was evident at dose levels of 0.02 and 0.2 mg/kg bw/day. In a rat inhalation study, animals were sacrificed after the first week of treatment at measured concentrations of 76.8 and 237.4 mg/m^3 due to their poor condition. They showed local irritation in the upper respiratory tract and respiratory distress but no effects on the lower airways or lung tissue. In the surviving 20.4 mg/m^3 group, there was no relevant systemic toxicity.

Table 38: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days [if adequate, otherwise please delete]

Study reference	Effective dose (mg/kg/day)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
[redacted] (1995)	20 mg/kg bw (1/4 males paralysis, 4/4 males spinal cord demyelination)	1 year	2.5 – 25 mg/kg bw	STOT-RE Category 2

2.6.3.1.2 Comparison with the CLP criteria regarding STOT RE (specific target organ toxicity-repeated exposure)

According to CLP criteria (Regulation (EC) No. 1272/2008, Annex I, Table 3.9.1), an active substance is classified in Specific target organ toxicity after repeated exposure Category 1, H372 or Category 2, H371 based on the results of animal studies if it elicits significant and/or severe toxic effects of relevance to the human health at generally low or moderate exposure concentrations, respectively. The toxic effects relating to STOT RE include changes which have affected the function or morphology of a tissue/organ (e.g. necrosis, fibrosis, granuloma formation, steatosis), or have produced serious changes in the biochemistry or haematology.
Local irritation is not considered to be evidence of specific target organ toxicity. However, the effects in the nose and upper respiratory tract in the rat inhalation study warrant classification as STOT-SE Cat 3 *(see section 2.6.2.10)*.
Effects in the liver were considered to represent adaptive response rather than evidence of specific target organ toxicity and do not warrant classification.
Cataract was observed in both rats and dogs. Although, it is postulated that the effect may be due to a systemic effect (impairment of cholesterol biosynthesis), there was no other evidence of eye damage and is considered not to represent evidence of significant target organ toxicity.

Evidence of specific target organ toxicity to the nervous system was seen in both the rat and dog characterised by hind-limb paralysis accompanied by demyelination of the spinal cord ([redacted] 1995; [redacted] 1995). The effects are considered to represent significant adverse effects at dose levels below the relevant cut-off value for STOT-RE Category 2 and therefore classification is warranted.

2.6.3.1.3 Conclusion on classification and labelling for STOT RE (specific target organ toxicity-repeated exposure)

The proposed classification for fenpropidin is STOT-RE Category 2, H373: May cause damage to the nervous system through prolonged or repeated oral exposure.

2.6.4 Summary of genotoxicity / germ cell mutagenicity [equivalent to section 10.8 of the CLH report template]

Table 39: Summary table of genotoxicity/germ cell mutagenicity tests *in vitro*

Method, guideline, deviations if any	Test substance	Organisms/strain	Concentrations tested	Observations/Results	Reference
Reverse mutation in bacteria Predates, but compliant with OECD 471 Deviations: the number of cells per culture was not stated GLP **Acceptable study**	Fenpropidin technical (purity 97%) Vehicle: acetone	*Salmonella typhimurium* strains, TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA.	31.25, 62.5, 125, 250 and 500 µg/plate (original experiment) 125, 250, 500, 1000 and 2000 µg/plate (confirmatory experiment). +/- metabolic activation 500 µg/plate initially selected as the highest concentration for the mutagenicity experiment, based on a toxicity test in 2 strains	+S9: negative -S9: negative Cytotoxic effects evident at concentrations of 1000 and 2000 µg/plate in all strains. Positive controls: valid	Hertner (1993a)
Gene mutation assay in mammalian cells Predates, but compliant with OECD 476 (except that only single cultures were used, the required level of toxicity was not achieved in each test and 2-	Fenpropidin technical (purity 91%) Vehicle: dimethylsulfoxide (DMSO)	V79 cells (Chinese hamster lung fibroblasts, clone 66 A/4)	**- S9**: 10-90 µg/mL (exp. 1-3) **+ S9**: 5-50 µg/mL (exp. 1), 20-60 µg/mL (exp. 2).	+S9: negative -S9: negative Positive controls valid. Relative survival was reduced to 10-58% and 8% in the presence and absence of S9, respectively, after treatment with 80 or 60 µg/mL	Strobel (1988)

Method, guideline, deviations if any	Test substance	Organisms/strain	Concentrations tested	Observations/Results	Reference
acetyl aminofluorene was used as a reference substance) GLP **Acceptable study**					
In vitro chromosome aberration test Chinese hamster ovary cells. Predates, but compliant with OECD 473 Deviations: less than 300 well-spread metaphases were scored; a short-term treatment (3-6 hour incubation with test substance; sampling after 18 hours) in the absence of S9 mix was not performed GLP **Acceptable study**	Fenpropidin technical (purity 97%) Vehicle: acetone	Chinese hamster ovary cells (CHO, cell line ATCC CCL 61)	Up to 500 µg/mL, (+/- metabolic activation) in original experiment Up to 62.5 µg/mL, (+/- metabolic activation) concentration 125 µg/mL was included but not scored due to toxicity in confirmatory experiments At least 200 metaphases from 2 cultures scored for mitotic index; 3 concentrations selected for chromosome analysis	+S9: negative -S9: negative Positive controls: valid	Hertner (1993b)
DNA repair (UDS assay) OECD 482 GLP **Acceptable study**	Fenpropidin technical (purity 97%) Vehicle: acetone	Rat hepatocytes freshly isolated from males	0.49/0.48, 0.98/0.97, 1.95/1.94, 3.91/3.88, 7.81/7.75, 15.63/15.5 µg/mL (original/ confirmatory exp. In the confirmatory experiment 31.0µg/mL was included but not scored due to toxicity. 150 cells scored	Negative Positive control: valid	Hertner (1993c)

Method, guideline, deviations if any	Test substance	Organisms/strain	Concentrations tested	Observations/Results	Reference
			from 3 slides. Cells in S-phase excluded.		

Table 40: Summary table of genotoxicity/mutagenicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance	Organisms/strain	Concentrations tested	Observations/Results	Reference
Mouse bone marrow micronucleus test Consistent with OECD 474 except that micronuclei were evaluated at 2 doses only due to mortality. GLP **Acceptable study**	Fenpropidin technical (purity 97%) Vehicle: carboxymethyl cellulose (CMC) 0.5% aqueous solution	Tif: MAGF (SPF) mouse 5/sex/group, including vehicle and positive control groups In addition 3/sex and 2/sex treated with high and intermediate doses, respectively.	385, 770 or 1540 mg/kg bw Highest dose selected as suitable maximum tolerated dose based on a pre-experiment.	Negative Mortality at 1540 mg/kg bw, therefore micronucleus analysis only at 385 and 770 mg/kg bw. Positive and negative control groups valid.	[redacted] (1993d)

Table 41: Summary table of human data relevant for genotoxicity / germ cell mutagenicity

No data available.

2.6.4.1 Short summary and overall relevance of the provided information on genotoxicity / germ cell mutagenicity

Fenpropidin was tested both *in vitro* (in the presence and absence of metabolic activation) and *in vivo* for genotoxicity. Fenpropidin was negative *in vitro* for gene mutation (Ames test and mammalian forward mutation assay), DNA damage (unscheduled DNA synthesis), or chromosome aberrations in the Chinese hamster ovary cells (CHO), and did not show clastogenicity or an aneugenic potential in the *in vivo* mouse bone marrow.

Fenpropidin was negative in a reverse mutagenicity test with and without metabolic activation which indicates that fenpropidin does not induce point mutations by base substitutions or frame shift in the genome of *Salmonella typhimurium* or *Escherichia coli* (Hertner, 1993a).

In gene mutation assays in mammalian cells (Chinese hamster lung fibroblasts and L5178Y mouse lymphoma cells) fenpropidin did not increase the mean mutant frequency in the presence or absence of S9-mix. Fenpropidin is therefore considered non-mutagenic in cultured mammalian cells (Strobel, 1988).

The clastogenic effect of fenpropidin was tested in an *in vitro* chromosome aberration study in Chinese hamster ovary cells (Hertner, 1993b). Fenpropidin did not increase chromosomal aberrations.

Fenpropidin did not cause DNA damage in rat hepatocytes *in vitro* (unscheduled DNA synthesis assay).

In vivo fenpropidin was found negative in a study to detect clastogenicity (mouse bone marrow micronucleus test), there was no evidence of chromosome damage at 770 mg/kg bw (mortality was observed at 1540 mg/kg bw).

Overall the results indicate that fenpropidin does not possess any concern for genotoxicity.

Table 2.6.4.1-1: **Bacterial reverse mutation assay;** Mean of revertant colony counts; Original experiment without^{-} and with^{+} metabolic activation (Hertner, 1993a)

Treatment/Strain	**TA100-**	**TA1535-**	**WP2uvrA-**	**TA98-**	**TA1537-**	**TA100+**	**TA1535+**	**WP2 uvrA+**	**TA98+**	**TA1537+**
31.25 ug/plate	83.3	11.0	23.7	26.7	10.7	120.3	15.0	21.7	51.0	13.0
62.5 ug/plate	101.3	15.7	20.7	23.3	5.0	128.0	13.0	32.3	61.7	10.7
125.0 ug/plate	103.7	13.3	25	26.3	8.7	110.3	17.7	30.7	50.7	11.0
250.0 ug/plate	98.7	12.3	23.7	32.7	18.3	115.0	17.3	31.0	56.7	16.0
500.0 ug/plate	101.7	13.0	23.3	35.3	15.7	124.7	17.0	23.3	46.7	16.3
Negative control	98.3	18.3	23.7	25.3	9.7	120.3	18.7	23.0	52.3	11.3
Positive controls										
Sodium azide	2127.3	1843.7								
4-nitroquinoline-N-oxide			505.0							
2-nitrofluorene				1914.3						
9-aminoacridine					2904.3					
aminoanthracene						2160.7		1035.3	2091.7	207.3
cyclophosphamide							482.0			

Table 2.6.4.1-2: **Bacterial reverse mutation assay;** Mean of revertant colony counts; Confirmatory experiment without^{-} and with^{+} metabolic activation (Hertner, 1993a)

Treatment/Strain	**TA100-**	**TA1535-**	**WP2uvrA-**	**TA98-**	**TA1537-**	**TA100+**	**TA1535+**	**WP2 uvrA+**	**TA98+**	**TA1537+**
125.0 ug/plate	85.0	8.7	18.7	15.7	10.0	109.7	10	29.7	34.7	11.3
250.0 ug/plate	101.0	10	17.7	19.0	7.3	124.0	12.0	22.7	37.0	15.3
500.0 ug/plate	75.0	13.3	19.3	18.0	10.3	109.00	10.7	19.3	54.3	14.3
1000.0 ug/plate	8.0	10.3	11.3	15.0	10.0	35.7	4.3	10.0	16.7	4.7
2000.0 ug/plate	0	5.3	2.0	7.7	1.7	1.0	0.7	2.3	3.0	0
Negative control	107.0	10.0	20.3	15.7	0	119.3	11.0	22.0	30.0	8.0
Positive controls										
Sodium azide	1047.3	933.3								
4-nitroquinoline-N-oxide			646.7							
2-nitrofluorene				1802.3						
9-aminoacridine					2705.0					
aminoanthracene						2198.7		1288.0	1811.3	202.3
cyclophosphamide							450.7			

Table 2.6.4.1-3: **Total numbers of HPRT mutant cells, mutant frequency and viability of V79 cells after 16-hour exposure without metabolic activation;** (Strobel, 1988)

Dose ug/ml	Day 2 Mean Experiment1/Experiment2	RS %	Day 7 Mean Experiment1/Experiment2	Cloning efficiency %	Day 7 HPRT mutations Experiment1/Experiment2
0	146.5/234.3	100/100	162.3/126	81/63	0.6 $^{e-05}$/1.6 $^{e-05}$
10	155.3/240.8	106/100	120.5/166.8	60/83	0/0
60	111.8/143.3	76/61	141.5/173.5	71/87	0/2.3 $^{e-05}$
70	93.3/182.3	64/78	154.3/148.5	77/74	0/4.0 $^{e-05}$
80	47.5/136.3	32/58	141.8/98.8	71/49	0/0
Reference Substance: Ethyl methan sulphonate					
0	146.5/234.4	100/100	162.3/126	81/63	0.6 $^{e-05}$/1.2 $^{e-05}$

100	107.8/226.8	74/97	142.3/155	71/78	28.1 e-05/23.9 e-05

Table 2.6.4.1-4: **Total numbers of HPRT mutant cells, mutant frequency and viability of V79 cells after 5-hour exposure with metabolic activation;** (Strobel, 1988)

Dose ug/ml	Day 2 Mean RS % Experiment1/Experiment2		Day 7 Mean Cloning efficiency % Experiment1/Experiment2		Day 7 HPRT mutations Experiment1/Experiment2
0	105.8/133	100/100	127.5/159.3	64/80	0/1.3 e-05
5	74.8/-	71/-	122.8/-	61/-	0/-
20	120.3/123.3	114/93	128.8/158	64/79	0.8 e-05/1.3 e-05
30	111.8/-	106/-	145.5/-	73/-	1.4 e-05/-
40	99.5/114.3	94/86	160.8/158	80/79	0/1.9 e-05
50	120.5/56.8	114/43	129.3/167.3	65/84	0/1.2 e-05
60	-/10.5	-/8	-/126	-/63	-/0.8 e-05
Reference Substance: 2-acetyl aminofluorene					
0	105.8/133	100/100	127.5/159.3	64/80	0/1.3 e-05
100	96.8/125.8	91/95	158/1141.3	79/71	8.9 e-05/12.7 e-05

Table 2.6.4.1-5: **Chromosomal aberration assay**; TCE: Total number of cells examined; CwA: Cells with aberrations, excluding gaps and numerical alterations (%); gaps: Chromatid and chromosome breaks; ct del: Chromatid deletions; ct exc: Chromatid exchanges; cs del: Chromosome deletions; cs exc: Chromosome exchanges; mab: Multiple aberrations; pol: Polyploid metaphases; end: Endoreduplications; hyp: Hyperploid metaphases; (Hertner, 1993b)

	TCE	CwA	gaps	ct del	ct exc	cs del	cs exc	mab	pol	end	hyp
Treatment: 18h; without metabolic activation											
3.91 ug/ml - Fenpropidin	200	3.0	4	1		3	2		7		1
7.81 ug/ml- Fenpropidin	200	1.5	5	3					5		
15.63 ug/ml- Fenpropidin	200	3.5	5	4		2	1		9		
Negative control	200	4.0	7	7	1	1	2		10		
Mitomycin C	50	32.0	9	9	8		1		2		1
Treatment: 3h, harvest time: 15h after the treatment; with metabolic activation											
15.63 ug/ml- Fenpropidin	200	4.0	5	1	1	3	3		4	2	
31.25 ug/ml- Fenpropidin	200	4.5	12	3	1	3	1	1	5	5	2
62.5 ug/ml - Fenpropidin	200	3.0	4	6		2			5		1
Negative control	200	3.5	9	3		3	1		5		
Cyclophosphamide	50	34.0	4	9	8	3	1				
Confirmatory experiment: Treatment: 18h; without metabolic activation											
7.81 ug/ml - Fenpropidin	200	1.0	4			2			10		
15.63 ug/ml - Fenpropidin	200	1.0	1			1		1	4		
31.25 ug/ml - Fenpropidin	200	1.5	2	2		1			2		1
Negative control	200	2.0	3	1		2	1		3		
Mitomycin C	50	32.0	5	20	10	4	2		1		1
Confirmatory experiment: Treatment: 3h, harvest time: 15h after the treatment; with metabolic activation											
15.63 ug/ml- Fenpropidin	200	6.0		2	1	6	3		4		
31.25 ug/ml- Fenpropidin	200	7.0	12	2	1	8	3		3		
62.5 ug/ml - Fenpropidin	200	6.5	8	6		5	3		6		1
Negative control	200	5.0	6	2		9	1		5	2	1
Cyclophosphamide	50	44.0	9	13	6	11	2		1		
Confirmatory experiment: Treatment: 42h; without metabolic activation											
7.81 ug/ml - Fenpropidin	200	1.0	1	2					3		1
15.63 ug/ml - Fenpropidin	200	1.5	2			2	1		3		

31.25 ug/ml - Fenpropidin	200	2.0	2			3	1		2		
Negative control	200	1.0	4		1	1			4		
Confirmatory experiment: Treatment: 3h, harvest time: 39h after the treatment; with metabolic activation											
15.63 ug/ml- Fenpropidin	200	2.0	5	1		2	1		4	1	1
31.25 ug/ml- Fenpropidin	200	1.5	10	1		1	1		3		
62.5 ug/ml - Fenpropidin	200	1.5	6	1		1	1		44		
Negative control	200	1.0	4			1	1		2		

Table 2.6.4.1-6: **Micronucleus test *in vivo*;** Incidence of micronuclei; CPA = cyclophosphamide; ° from 5 animals (1000 PCE per animal); °° mnPCE per 4000 PCE from 4 animals (1000 PCE per animal); *p<0.05 (Chi-Square test), ([redacted] 1993d)

Concentration	**Sacrifice after [h]**	**PCEs per 1000 erythrocytes**		**PCE/NCE**		**mnPCEs per 5000 PCEs°**		**% mnPCE**		
		M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**pooled**
negative control	16	464	442	0.86	0.79	1	6	0.02	0.12	0.07
	24	431	476	0.76	0.91	1	2	0.02	0.04	0.03
	48	466	470	0.87	0.89	2	1	0.04	0.02	0.03
CPA	24	444	463	0.80	0.86	93	64	1.86*	1.28*	1.57*
770 mg/kg bw	16	472	450	0.89	0.82	3	4	0.06	0.08	0.07
	24	461	467	0.86	0.88	3°°	4	0.08	0.08	0.08
	48	445	463	0.80	0.86	2°°	2	0.05	0.04	0.05
385 mg/kg bw	24	441	454	0.79	0.83	6	5	0.12	0.10	0.11*

2.6.4.2 Comparison with the CLP criteria regarding genotoxicity / germ cell mutagenicity

Germ cell mutagenicity was investigated according to the criteria stated in CLP (Regulation (EC) No. 1272/2008, Annex I, Table 3.5.1. A series of *in vitro* studies and an *in vivo* micronucleus assay for chromosome aberrations have been conducted with fenpropidin. None of the studies revealed any evidence for a mutagenic, clastogenic or aneugenic potential of the compound. Fenpropidin is, therefore, considered not to exert any genotoxic potential in prokaryotic and eukaryotic cells, *in vitro* and *in vivo*. Due to new impurity, further genotoxocity tests were conducted by the notifier, these are provided in the relevant section of VOL.4 – confidential. Following results were obtained - (Ames - negative, HPRT- negative, *In vitro* micronucleus test – Negative)

2.6.4.3 Conclusion on classification and labelling for genotoxicity / germ cell mutagenicity

No classification is proposed.

2.6.5 Summary of long-term toxicity and carcinogenicity [equivalent to section 10.9 of the CLH report template]

Table 42: Summary table of animal studies on long-term toxicity and carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
2-year chronic toxicity/ carcinogenicity study EPA 83-1, consistent with OECD 453 Deviations: dose level changed after 7 weeks, survival below 50% at 2 years GLP Rat: CD-Crl: CD (SD) BR 70/sex/group except high dose 80 sex/group 10/sex/group interim kill after 12 months 10/sex/group for clinical pathology (20/sex for high dose group) **Acceptable study**	Fenpropidin (purity 91%). 0, 5/2, 25/10, 125/50, 625/250 ppm. Higher doses given week 1-7. 2 and 10 ppm from week 8. Groups at 125 and 625 ppm given control diet for 4 weeks and changed to 50 and 250 ppm for remainder of study. Equivalent to average : 0.07, 0.34, 1.68 and 8.53 mg/kg bw/day in males; 0.09, 0.45, 2.27 and 11.83 mg/kg bw/day in females Continuous in the diet for 24 months	NOAEL (systemic): 50 ppm equal to 2.27 mg/kg bw/day in females; no adverse effects in males, thus NOAEL for males cannot be set. **Non-neoplastic findings** **625/250 ppm (8.53 mg/ kg bw/day in males and 11.83 mg/kg bw/day in females)** *Mortality:* No effect on survival. *Clinical signs:* Signs of local irritation until dose decreased and then later in study. *Body weight*: ↓ 12-18% weeks 1-7; 9-14% in females throughout study *Body weight gain:* ↓ 14% females (week 11-80) *Haematology:* ↑ red cell parameters (RBC, Hb and PCV) 13.2-18.3% males week 103. *Clinical chemistry:* ↑ potassium ion concentration 14.3% males and 15.6% females. **125/50 ppm (2.11 mg/ kg bw/day in males and 2.76 mg/kg bw/day in females)** No treatment-related findings **25/10 ppm (0.44 mg/ kg bw/day in males and 0.56 mg/kg bw/day in females)** No treatment-related findings **5/2 ppm (0.09 mg/ kg bw/day in males and 0.11 mg/kg bw/day in females)** No treatment-related findings **Neoplastic findings** No evidence of increased incidence of tumours.	[redacted] (1988)
Carcinogenicity study OECD 451 deviations: aorta and rectum not evaluated, individual clinical observations not reported GLP Mouse: Crl: Crl:CD-1	Fenpropidin (purity not reported) 0, 30, 100, 300 and 1000 ppm corresponding to 0, 4.12, 13.54, 41.90, 143.8 mg/kg bw/day for males and 0, 5.47, 17.70, 51.71, 166.1 mg/kg bw/day for females Continuous in the diet for 80 weeks	NOAEL (systemic): 300 ppm (41.9 mg/ kg bw/day in males and 51.7 mg/kg bw/day in females) **Non-neoplastic findings** **1000 ppm (143.8 mg/ kg bw/day in males and 166.1 mg/kg bw/day in females)** *Mortality:* ↑ in males (45% survival in week 80; 51% survival	[redacted] (1983)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results - NOAEL/LOAEL - target tissue/organ - critical effects at the LOAEL	Reference
(ICR)BR 63/sex/group **Acceptable study**		week 65-76; > 71% in all other groups including control) *Clinical signs*: ↑ incidence of local irritation on forepaws and ears. *Body weight*: ↓ 11% males; 7% females (week 80). *Food consumption*: ↓ 12% in females *Pathology:* ↑ irritation of GI tract (hyperkeratosis of oesophagus and forestomach) **300 ppm (41.9 mg/ kg bw/day in males and 51.7 mg/kg bw/day in females)** No treatment-related findings **100 ppm (13.54 mg/ kg bw/day in males and 17.70 mg/kg bw/day in females)** No treatment-related findings **30 ppm (4.12 mg/ kg bw/day in males and 5.47 mg/kg bw/day in females)** No treatment-related findings **Neoplastic findings** No treatment-related neoplastic findings at any dose level.	

Table 43: Summary table of human data on long-term toxicity and carcinogenicity

No data available

Table 44: Summary table of other studies relevant for long-term toxicity and carcinogenicity

No studies available

2.6.5.1 Short summary and overall relevance of the provided information on long-term toxicity and carcinogenicity

Two long-term toxicity/carcinogenicity studies in mice and rats were conducted with fenpropidin ([redacted] 1989; [redacted] 1983). The long-term exposure produced signs of local irritation expressed as skin irritation in rats and as hyperkeratosis of the oesophagus in mice at doses below those causing systemic toxicity (decreased body weight). Fenpropidin did not induce changes in the incidence and distribution of neoplastic lesions in rats or mice.

Table 2.6.5.1-1: **Tumour incidences** ([redacted] 1989)

	Males					Females				
group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
ppm	**0**	**2°**	**10°**	**50°**	**250°**	**0**	**2°**	**10°**	**50°**	**250°**
Pancreas islet cell adenoma§										
interim sacrifice	0/10	-	-	-	0/10	0/10	-	-	-	0/9
terminal sacrifice	2/17	5/19	4/21	4/17	10/32	6/30	6/31	4/25	1/30	4/40
unscheduled deaths	4/43	3/41	3/39	4/43	8/38	4/30	3/29	2/35	0/30	0/30
total (%)	6 (8.6)	8 (13)	7 (12)	8 (13)	18(23)	10(14)	9 (15)	6 (10)	1 (1.7)	4 (5.1)
Pancreas islet cell carcinoma§										
interim sacrifice	0/10	-	-	-	0/10	0/10	-	-	-	0/9
terminal sacrifice	0/17	0/19	0/21	0/17	0/32	0/30	0/31	1/20	0/30	0/40
unscheduled deaths	1/43	0/41	2/39	0/43	0/38	0/30	0/29	0/35	0/30	0/30
total	1/70	0/60	2/60	0/60	0/80	0/70	0/60	1/60	0/60	0/79
Animals#										
interim sacrifice	10	-	-	-	10	10	-	-	-	9
terminal sacrifice	17	16	18	14	32	30	25	20	24	40
unscheduled deaths	43	34	32	36	38	30	25	30	26	30
total	70	50	50	50	80	70	50	50	50	79
Benign neoplasms#										
interim sacrifice	1	-	-	-	1	2	-	-	-	1
terminal sacrifice	16	12	13	10	22	34	23	19	20	49
unscheduled deaths	41	19	19	25	33	31	24	25	24	29
total (per rat)	58 (0.83)	31 (0.62)	32 (0.64)	35 (0.70)	56 (0.70)	67 (0.96)	47 (0.94)	44 (0.88)	44 (0.88)	79 (1.00)
Malign neoplasms#										
interim sacrifice	2	-	-	-	0	0	-	-	-	0
terminal sacrifice	2	4	5	4	7	9	4	5	4	12
unscheduled deaths	10	10	3	11	9	7	6	10	9	5
total (per rat)	14 (0.20)	14 (0.28)	8 (0.16)	15 (0.30)	16 (0.20)	16 (0.23)	10 (0.20)	15 (0.30)	13 (0.26)	17 (0.21)
Benign + malign neop.#										
interim sacrifice	3	-	-	-	1	2	-	-	-	1
terminal sacrifice	18	16	18	14	29	43	27	24	24	61
unscheduled deaths	51	29	22	36	42	38	30	35	33	34
total (per rat)	72 (1.03)	45 (0.90)	40 (0.80)	50 (1.00)	72 (0.90)	83 (1.19)	57 (1.14)	59 (1.18)	57 (1.14)	96 (1.20)
Animals with neopl.°°										
terminal sacrifice	12/15	13/16	15/18	11/14	21/24	26/26	23/25	20/20	20/24	27/28
unscheduled deaths	30/35	25/34	20/32	29/36	22/26	21/24	24/25	30/30	25/26	21/22
total (%)	42 (84)	38 (76)	35 (70)	40 (80)	43 (86)	47 (94)	47 (94)	50 (100)	45 (90)	48 (96)

° revised dietary levels administered from week 8/12 onwards

§ data from the neoplastic lesion table (carcinogenicity animals) + incidences from result tables for interim sacrifice and clinical pathology animals of groups 1 and 5

data from the tumour summary table (carcinogenicity animals of groups 1-5) + incidences of benign/malign tumours from result tables (not separated between neoplastic and non-neoplastic lesions) for interim sacrifice and clinical pathology animals of groups 1 and 5

°° animals of the carcinogenicity group only (50 per sex and group)

Table 2.6.5.1-2: **Tumour incidences** ([redacted] 1983)

	Males					Females				
group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
ppm	**0**	**30**	**100**	**300**	**1000**	**0**	**30**	**100**	**300**	**1000**
Animals										
interim sacrifice	12	-	-	-	12	12	-	-	-	12
terminal sacrifice	34	-	-	-	23	22	-	-	-	24
unscheduled deaths	17	16	15	14	28	29	17	18	19	27
total	63	16	15	14	63	63	17	18	19	63
Benign neoplasms										
interim sacrifice	2	-	-	-	4	3	-	-	-	0
terminal sacrifice	24	-	-	-	11	14	-	-	-	13
unscheduled deaths	3	3	8	0	4	2	4	11	2	2
total (per rat)	29 (0.46)	3 (0.19)	8 (0.53)	0 (0.00)	19 (0.30)	19 (0.30)	4 (0.24)	11 (0.61)	2 (0.11)	15 (0.24)
Malign neoplasms°										
interim sacrifice	1	-	-	-	0	0	-	-	-	0
terminal sacrifice	0	-	-	-	2	5	-	-	-	1
unscheduled deaths	5	2	4	3	6	13	14	6	12	3
total (per rat)	6 (0.10)	2 (0.13)	4 (0.27)	3 (0.21)	8 (0.13)	18 (0.29)	14 (0.82)	6 (0.33)	12 (0.63)	4 (0.06)
All neoplasms										
Interim sacrifice	3	-	-	-	4	3	-	-	-	0
terminal sacrifice	24	-	-	-	13	19	-	-	-	14
unscheduled deaths	8	5	12	3	10	15	18	17	14	5
total (per rat)	35 (0.56)	5 (0.31)	12 (0.80)	5 (0.21)	27 (0.43)	37 (0.59)	18 (1.06)	17 (0.94)	14 (0.74)	19 (0.30)

° all lymphomas were considered to be malignant; neoplastic 'leucosis' was considered to be equivalent to leukaemia and therefore malignant

2.6.5.2 Comparison with the CLP criteria regarding carcinogenicity

A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as Category 1A or 1B. Category 1A, known to have carcinogenic potential for humans classification is largely based on human evidence. Classification is Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence. The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B. The carcinogenicity was investigated in rats and mice. There was no evidence of a carcinogenic potential in either species. The only effect observed which could be potentially attributed to the carcinogenic potential of the substance was the increased incidence (23%) of pancreatic islet adenoma in the study of [redacted] 1983 in males at top dose. Based on this finding historical controls were requested from the notifier. As presented in the table below, it s true that the mean incidence of 13.9% was exceeded in this study (23%), however DS is of the opinion that this finding should not be considered as treatment related due to following reasons: 1) The incidence range from historical controls is relatively wide, with high extreme incidences of 54%, also as presented in the individual data table, incidences around 20% are not exceptional. 2) It is also important to note, that, at the interim sacrifice, there are no incidences of this finding when comparing top dose and control, therefore DS inclines to the think that this effect is of spontaneous origin related rather to aging rats.

The historical control data (HCD) for the performing laboratory ([redacted] is summarised as per the table below. The historical control data is compiled of studies conducted +/- 5 years of the date of the in-life phase of the 2-year rat study in rats of a similar age and strain. The study was initiated in January 1986 and completed in January 1988. The HCD for the incidence of pancreas islet β-cell adenoma +/-5 years from the date of the study (January 1981- December 1992) are presented in the table below

Historical Cotrol Data for Pancreas Islet Cell Adenoma in CRL:CD (SD) BR Rats from Jan 1981- Dec 1992 – overall values

Year	Sex of animals	No. studies	No. organs examined	Total Incidence of β-cell adenoma (mean)		Incidence Range low		Incidence Range high	
				Number	% incidence	Number	% incidence	Number	% incidence
Jan 1981- Dec 1992	Males	95	5397	751	13.9 %	0/50	0 %	27/50	54.0 %
	Females	95	5405	259	4.8 %	0/60	0 %	11/55	20.0 %

Historical Cotrol Data for Pancreas Islet Cell Adenoma in CRL:CD (SD) BR Rats from Jan 1981- Dec 1992 – invidivual values (frequencies) – Males

code numeber	Study Start	route	supplier	study duration (weeks)	number of animals	Pancreas	B-Isled Cell Adenoma	percentage
						No examined	incidence	
cdr 8102a	Feb-81	dt	crusa	108	100	98	9	9.2%
cdr 8102b	Feb-81	dt	crusa	104	50	50	5	10.0%
cdr 8104a	Apr-81	dt	crusa	112	100	100	12	12.0%
cdr 8104b	Apr-81	dt	crusa	104	100	100	11	11.0%
cdr 8106	Jun-81	dt	crusa	106	50	50	3	6.0%
cdr 8107	Jul-81	dt	crusa	105	100	97	19	19.6%
cdr 8201	Jan-82	og	crusa	104	50	50	7	14.0%
cdr 8203	Mar-82	og	crusa	111	105	104	12	11.5%
cdr 8207	Jul-82	dt	crusa	104	60	60	3	5.0%
cdr 8210a	Oct-82	dt	crusa	110	50	50	6	12.0%
cdr 8210b	Oct-82	dt	crusa	106	50	50	0	0.0%
cdr 8301	Jan-83	dt	crusa	111	50	49	5	10.2%
cdr 8304	Apr-83	og	crusa	104	55	55	10	18.2%
cdr 8305	May-83	dt	crusa	109	50	50	10	20.0%
cdr 8307	Jul-83	dt	crusa	104	50	49	7	14.3%
cdr 8311	Nov-83	dt	crusa	104	50	50	7	14.0%
cdr 8312	Dec-83	og	crusa	104	55	54	7	13.0%
cdr 8402	Feb-84	dt	crusa	104	100	100	12	12.0%
cdr 8407	Jul-84	dt	crusa	107	50	50	5	10.0%
cdr 8409	Sep-84	dt	crusa	102	50	50	7	14.0%
cdr 8409	Sep-84	dt	crusa	102	50	50	13	26.0%
cdr 8410a	Oct-84	dt	crusa	99	50	49	14	28.6%
cdr 8410b	Oct-84	og	crusa	104	55	55	12	21.8%
cdr 8502	Feb-85	dt	crusa	104	50	49	4	8.2%
cdr 8504	Apr-85	og	crusa	104	55	55	8	14.5%
cdr 8504	Apr-85	og	crusa	104	55	55	12	21.8%
cdr 8507	Jul-85	dt	crusa	108	50	50	4	8.0%
cdr 8508	Aug-85	og	crusa	104	60	60	14	23.3%

cdr 8508	Aug-85	og	crusa	104	60	60	15	25.0%
cdr 8509	Sep-85	og	crusa	112	55	51	11	21.6%
cdr 8509	Sep-85	og	crusa	112	55	54	15	27.8%
cdr 8510	Oct-85	dt	crusa	107	50	49	6	12.2%
cdr 8512	Dec-85	dt	crusa	102	50	50	9	18.0%
cdr 8602	Feb-86	og	cruk	104	55	55	4	7.3%
cdr 8602	Feb-86	og	cruk	104	55	55	4	7.3%
cd4 8603	Mar-86	og	crusa	104	50	45	2	4.4%
cdr 8607	Jul-86	ih	crusa	104	100	100	24	24.0%
cdr 8608	Aug-86	dt	crusa	105	50	50	11	22.0%
cdr 8609	Sep-86	ih	crusa	104	60	60	6	10.0%
cdr 8609	Sep-86	ih	crusa	104	60	60	13	21.7%
cdr 8610	Oct-86	dt	crusa	104	50	50	27	54.0%
cdr 8610	Oct-86	dt	crusa	104	50	50	19	38.0%
cdr 8612a	Dec-86	dt	crusa	104	50	50	8	16.0%
cdr 8612b	Dec-86	dt	crusa	104	100	100	15	15.0%
cdr 8704	Apr-87	dt	crusa	106	50	50	3	6.0%
cdr 8704	Apr-87	dt	crusa	106	50	50	4	8.0%
cdr 8707	Jul-87	dt	cruk	104	50	50	4	8.0%
cdr 8708	Aug-87	og	cruk	104	55	55	5	9.1%
cdr 8708	Aug-87	og	cruk	104	55	55	6	10.9%
cdr 8709	Sep-87	dt	cruk	104	50	50	4	8.0%
cdr 8710	Oct-87	og	crusa	104	55	55	12	21.8%
cdr 8710	Oct-87	og	crusa	104	55	55	12	21.8%
cdr 8711	Nov-87	dt	cruk	104	60	60	14	23.3%
cdr 8712a	Dec-87	dt	crusa	110	100	99	8	8.1%
cdr 8712b	Dec-87	dt	crusa	108	50	50	7	14.0%
cdr 8802	Feb-88	dt	crusa	110	50	50	4	8.0%
cdr 8802	Feb-88	dt	crusa	110	50	50	3	6.0%
cdr 8805a	May-88	og	crusa	104	60	60	10	16.7%
cdr 8805b	May-88	og	crusa	104	60	60	4	6.7%
cdr 8808	Aug-88	dt	crusa	101	60	60	9	15.0%
cdr 8905	May-89	dt	crusa	104	50	50	8	16.0%
cdr 8905	May-89	dt	crusa	104	50	50	2	4.0%
cdr 8906a	Jun-89	dt	crusa	107	50	50	5	10.0%
cdr 8906a	Jun-89	dt	crusa	107	50	50	1	2.0%
cdr 8906b	Jun-89	og	crusa	104	55	55	4	7.3%
cdr 8906c	Jun-89	dt	crusa	104	50	50	6	12.0%
cdr 8906c	Jun-89	dt	crusa	104	50	50	5	10.0%
cdr 8906d	Jun-89	dt	crusa	106	50	50	7	14.0%
cdr 8907a	Jul-89	dt	crusa	103	52	52	5	9.6%
cdr 8907b	Jul-89	dt	crusa	106	50	50	5	10.0%

cdr 8909	Sep-89	dt	crusa	105	60	60	8	13.3%
cdr 8911	Nov-89	dt	crusa	104	25	25	4	16.0%
cdr 9002a	Feb-90	dt	crusa	104	60	60	5	8.3%
cdr 9002b	Feb-90	dt	crusa	104	50	50	6	12.0%
cdr 9003	Mar-90	dt	crusa	104	50	49	2	4.1%
cdr 9004	Apr-90	og	crusa	104	70	70	10	14.3%
cdr 9007	Jul-90	dt	crusa	104	50	50	2	4.0%
cdr 9008	Aug-90	dt	crusa	104	50	50	5	10.0%
cdr 9010	Oct-90	dt	crusa	104	55	55	3	5.5%
cdr 9011	Nov-90	dt	crusa	104	51	50	1	2.0%
cdr 9012	Dec-90	dt	crusa	109	50	50	9	18.0%
cdr 9012	Dec-90	dt	crusa	109	50	50	10	20.0%
cdr 9104a	Apr-91	dt	crusa	104	50	50	12	24.0%
cdr 9104b	Apr-91	dt	crusa	107	60	58	3	5.2%
cdr 9105	May-91	dt	crusa	104	50	50	8	16.0%
cdr 9109	Sep-91	dt	crusa	104	50	50	8	16.0%
cdr 9111	Nov-91	dt	crusa	104	60	60	7	11.7%
cdr 9201	Jan-92	dt	crusa	104	50	50	6	12.0%
cdr 9202	Feb-92	dt	crusa	104	56	56	7	12.5%
cdr 9207	Jul-92	dt	crusa	104	50	50	4	8.0%
cdr 9208	Aug-92	dt	crusa	104	55	55	12	21.8%
cdr 9210	Oct-92	og	crusa	104	55	55	7	12.7%
cdr 9211	Nov-92	dt	cruk	104	50	50	11	22.0%
cdr 9212	Dec-92	dt	crusa	103	50	50	10	20.0%
cdr 9212	Dec-92	dt	crusa	103	50	50	7	14.0%
Total					**5424**	**5397**	**751**	**13.92%**
Range of percentages*							**min**	**0.0%**
							max	**54.0%**

Historical Cotrol Data for Pancreas Islet Cell Adenoma in CRL:CD (SD) BR Rats from Jan 1981- Dec 1992 – invidivual values (frequencies) – Females

code numeber	Study Start	route	supplier	study duration (weeks)	number of animals	Pancreas	B-Isled Cell Adenoma	percentage
						No examined	incidence	
cdr 8102a	Feb-81	dt	crusa	108	100	100	6	6.0%
cdr 8102b	Feb-81	dt	crusa	110	50	50	1	2.0%
cdr 8104a	Apr-81	dt	crusa	115	100	99	5	5.1%
cdr 8104b	Apr-81	dt	crusa	104	100	100	3	3.0%
cdr 8106	Jun-81	dt	crusa	107	50	49	3	6.1%
cdr 8107	Jul-81	dt	crusa	105	100	100	6	6.0%
cdr 8201	Jan-82	og	crusa	104	50	50	2	4.0%
cdr 8203	Mar-82	og	crusa	111	105	105	6	5.7%

cdr 8207	Jul-82	dt	crusa	104	61	61	2	3.3%
cdr 8210a	Oct-82	dt	crusa	110	50	50	1	2.0%
cdr 8210b	Oct-82	dt	crusa	106	50	49	0	0.0%
cdr 8301	Jan-83	dt	crusa	111	50	50	2	4.0%
cdr 8304	Apr-83	og	crusa	104	55	55	1	1.8%
cdr 8305	May-83	dt	crusa	109	50	50	8	16.0%
cdr 8307	Jul-83	dt	crusa	104	50	50	3	6.0%
cdr 8311	Nov-83	dt	crusa	104	50	50	4	8.0%
cdr 8312	Dec-83	og	crusa	104	55	55	11	20.0%
cdr 8402	Feb-84	dt	crusa	104	100	100	4	4.0%
cdr 8407	Jul-84	dt	crusa	107	50	50	2	4.0%
cdr 8409	Sep-84	dt	crusa	102	50	50	5	10.0%
cdr 8409	Sep-84	dt	crusa	102	50	50	5	10.0%
cdr 8410a	Oct-84	dt	crusa	99	50	50	6	12.0%
cdr 8410b	Oct-84	og	crusa	104	55	54	1	1.9%
cdr 8502	Feb-85	dt	crusa	104	50	49	4	8.2%
cdr 8504	Apr-85	og	crusa	104	55	54	6	11.1%
cdr 8504	Apr-85	og	crusa	104	55	55	4	7.3%
cdr 8507	Jul-85	dt	crusa	108	50	50	2	4.0%
cdr 8508	Aug-85	og	crusa	104	60	60	4	6.7%
cdr 8508	Aug-85	og	crusa	104	60	60	3	5.0%
cdr 8509	Sep-85	og	crusa	112	55	55	4	7.3%
cdr 8509	Sep-85	og	crusa	112	55	55	2	3.6%
cdr 8510	Oct-85	dt	crusa	107	50	50	0	0.0%
cdr 8512	Dec-85	dt	crusa	102	50	48	2	4.2%
cdr 8602	Feb-86	og	cruk	104	55	55	2	3.6%
cdr 8602	Feb-86	og	cruk	104	55	54	0	0.0%
cd4 8603	Mar-86	og	crusa	104	50	49	4	8.2%
cdr 8607	Jul-86	ih	crusa	104	100	99	4	4.0%
cdr 8608	Aug-86	dt	crusa	105	50	50	5	10.0%
cdr 8609	Sep-86	ih	crusa	104	60	60	3	5.0%
cdr 8609	Sep-86	ih	crusa	104	60	60	3	5.0%
cdr 8610	Oct-86	dt	crusa	104	50	49	5	10.2%
cdr 8610	Oct-86	dt	crusa	104	50	50	8	16.0%
cdr 8612a	Dec-86	dt	crusa	104	50	50	3	6.0%
cdr 8612b	Dec-86	dt	crusa	104	100	100	7	7.0%
cdr 8704	Apr-87	dt	crusa	106	50	50	2	4.0%
cdr 8704	Apr-87	dt	crusa	106	50	50	4	8.0%
cdr 8707	Jul-87	dt	cruk	104	50	50	0	0.0%
cdr 8708	Aug-87	og	cruk	104	55	55	3	5.5%
cdr 8708	Aug-87	og	cruk	104	55	55	0	0.0%
cdr 8709	Sep-87	dt	cruk	104	50	50	2	4.0%
cdr 8710	Oct-87	og	crusa	104	55	55	2	3.6%
cdr 8710	Oct-87	og	crusa	104	55	55	1	1.8%

cdr 8711	Nov-87	dt	cruk	104	60	60	3	5.0%
cdr 8712a	Dec-87	dt	crusa	110	100	100	6	6.0%
cdr 8712b	Dec-87	dt	crusa	108	50	50	5	10.0%
cdr 8802	Feb-88	dt	crusa	110	50	50	3	6.0%
cdr 8802	Feb-88	dt	crusa	110	50	50	2	4.0%
cdr 8805a	May-88	og	crusa	104	60	60	4	6.7%
cdr 8805b	May-88	og	crusa	104	60	60	1	1.7%
cdr 8808	Aug-88	dt	crusa	101	60	60	1	1.7%
cdr 8905	May-89	dt	crusa	104	50	50	2	4.0%
cdr 8905	May-89	dt	crusa	104	50	50	0	0.0%
cdr 8906a	Jun-89	dt	crusa	107	50	49	1	2.0%
cdr 8906a	Jun-89	dt	crusa	107	50	50	0	0.0%
cdr 8906b	Jun-89	og	crusa	104	55	55	0	0.0%
cdr 8906c	Jun-89	dt	crusa	104	50	49	1	2.0%
cdr 8906c	Jun-89	dt	crusa	104	50	49	2	4.1%
cdr 8906d	Jun-89	dt	crusa	106	50	49	2	4.1%
cdr 8907a	Jul-89	dt	crusa	103	52	52	0	0.0%
cdr 8907b	Jul-89	dt	crusa	106	50	50	1	2.0%
cdr 8909	Sep-89	dt	crusa	105	60	60	0	0.0%
cdr 8911	Nov-89	dt	crusa	104	25	25	0	0.0%
cdr 9002a	Feb-90	dt	crusa	104	59	59	3	5.1%
cdr 9002b	Feb-90	dt	crusa	104	50	49	2	4.1%
cdr 9003	Mar-90	dt	crusa	104	50	50	1	2.0%
cdr 9004	Apr-90	og	crusa	104	70	70	5	7.1%
cdr 9007	Jul-90	dt	crusa	104	50	49	2	4.1%
cdr 9008	Aug-90	dt	crusa	104	50	49	1	2.0%
cdr 9010	Oct-90	dt	crusa	104	55	55	1	1.8%
cdr 9011	Nov-90	dt	crusa	104	51	51	2	3.9%
cdr 9012	Dec-90	dt	crusa	109	50	50	6	12.0%
cdr 9012	Dec-90	dt	crusa	109	50	50	3	6.0%
cdr 9104a	Apr-91	dt	crusa	104	50	50	5	10.0%
cdr 9104b	Apr-91	dt	crusa	107	60	60	2	3.3%
cdr 9105	May-91	dt	crusa	104	50	50	0	0.0%
cdr 9109	Sep-91	dt	crusa	104	50	50	0	0.0%
cdr 9111	Nov-91	dt	crusa	104	60	60	0	0.0%
cdr 9201	Jan-92	dt	crusa	104	50	50	1	2.0%
cdr 9202	Feb-92	dt	crusa	104	56	56	2	3.6%
cdr 9207	Jul-92	dt	crusa	104	50	50	5	10.0%
cdr 9208	Aug-92	dt	crusa	104	55	55	2	3.6%
cdr 9210	Oct-92	og	crusa	102	55	55	1	1.8%
cdr 9211	Nov-92	dt	cruk	104	50	50	2	4.0%
cdr 9212	Dec-92	dt	crusa	103	50	50	0	0.0%
cdr 9212	Dec-92	dt	crusa	103	50	50	3	6.0%
Total					**5424**	**5405**	**259**	**4.79%**

Range of percentages*	**min**	**0.0%**
	max	**20.0%**

2.6.5.3 Conclusion on classification and labelling for carcinogenicity

No classification proposed

2.6.6 Summary of reproductive toxicity [equivalent to section 10.10 of the CLH report template]

2.6.6.1 Adverse effects on sexual function and fertility – generational studies [equivalent to section 10.10.1 of the CLH report template]

Table 45: Summary table of animal studies on adverse effects on sexual function and fertility – generational studies

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Reproduction study (two generations/ one litter) OPPTS 870.3800 (1998), OECD 416 (2001) GLP Rat, HanIbm:WIST 30/sex/group **Acceptable study**	Fenpropidin (purity 97%) 0, 25, 100, 500 and 1000 ppm Vehicle: laboratory animal diet Oral (continuous in diet)	NOAEL (parental): 100 ppm (11.4 mg/kg bw) ***Parental toxicity*** **1000 ppm (80 mg/kg bw/day)** F0: ↓ body weight gain males 22%, females 24% (days 1-68); ↓ body weight gain gestation 16% (days 0-21); body weight loss lactation (-12.5 g; control +18.8 g), days 0-21); ↑ relative liver weight (females 21%); ↓ liver lymphohistiocytic infiltration males 8/30 (control 19/30); ↓ spleen extramedullary haematopoiesis males 8/30 (control 20/30), females 2/30 (control 21/30); ↑ adrenal cortical fatty change females 26/30 (control 6/30); ↓ prostate lymphohistiocytic infiltration males 6/30 (control 12/30). F1: ↓ body weight gain (males 24%, females 5%; days 1-68); ↓ body weight gain gestation (19% days 0-21); ↓ body weight gain lactation (93%, days 0-21); ↓ food consumption (males 27%, females 16% pre-mating, 16% gestation, 17% lactation); ↑ relative liver weight (males 7.5%, females 8%); ↓ liver lymphohistiocytic infiltration males 11/30 (control 21/30), females 15/30 (control 22/30); ↓ spleen extramedullary haematopoiesis males 2/30 (control 16/30), females 3/30 (control 28/30); ↑ adrenal cortical fatty change females 21/30 (control 10/30); ↓ prostate lymphohistiocytic infiltration males 4/30 (control 17/30). **500 ppm (42 mg/kg bw/day)** F0: ↓ body weight gain (males 18%, females 17%; days 1-68); ↓ body weight gain gestation (7% days 0-21); ↓ body weight gain	[redacted] (2003)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		lactation (15% days 0-21); ↓ liver lymphocytic infiltration males 9/30 (control 13/30); ↓ spleen extramedullary haematopoiesis females 11/30 (control 21/30); ↑ adrenal cortical fatty change females 14/30 (control 6/30); ↓ prostate lymphohistiocytic infiltration males 2/30 (control 12/30) F1: ↓ body weight gain (males 9% days 1-68); ↓ food consumption (males 7.5% pre-mating); ↑ relative liver weight (males 5%); ↓ spleen extramedullary haematopoiesis males 9/30 (control 16/30) , females 13/30 (control 28/30); ↑ adrenal cortical fatty change females 19/30 (control 10/30); ↓ prostate lymphohistiocytic infiltration males 6/30 (control 17/30) **100 ppm (8 mg/kg bw/day):** No treatment-related findings **25 ppm (2 mg/kg bw/day):** No treatment-related findings ***Reproductive toxicity*** No effects at any dose level ***Offspring toxicity*** NOAEL (offspring): 100 ppm (11.4 mg/kg bw) **1000 ppm (80 mg/kg bw/day)** F1: ↓ body weight gain evident from day 0 (males 37%, females 36%; days 0-21); ↓ sexual maturation males age 28 days (control 25.3 days), body weight 48 g (control 71 g); females age 42 days (control 32.5 days), body weight 106 g (control 102 g); ↓ absolute liver weight (males 37%, females 34%), ↑ relative liver weight females (21%); ↓ liver glycogen deposition males 12/28 (control 28/29); females 4/29 (control 12/28); ↓ liver extramedullary haematopoiesis males 9/28 (control 21/29); females 7/29 (control 18/28); ↓ absolute / relative spleen weight (males 54% / 29%; females 48% / 24%); ↓ grading of spleen extramedullary haematopoiesis males 2.2 (control 2.9) ; females 2.3 (control 3.0); ↓ absolute / relative thymus weight (males 45% / 16%; females 37% / 8%); ↑ thymus atrophy males 8/28 (control 0/29) ; ↑ thymus phagocytic cells males 19/28 (control 5/29) ; ↑ relative brain weight (males 42%, females 36%); ↓	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		absolute brain weight (males 8%, females 8%) F2: ↓ number of implantation sites 10.3 (control 12.4) , mean pups delivered 9.6 (control 11.7) and live birth index 99.3% (control 99.7%); ↓ body weight gain (males 36%, females 36%; days 0-21); ↓ absolute / relative liver weight (males 40% / 7.5%, females 34% / 4%); ↓ liver glycogen deposition males 5/30 (control 18/27); females 2/30 (control 15/27); ↓ liver extramedullary haematopoiesis males 5/30 (control 24/27) females 13/30 (control 25/27); ↓ absolute / relative spleen weight (males 49% / 24%; females 49% / 27%); ↓ grading of spleen extramedullary haematopoiesis males 1.9 (control 2.8); females 2.2 (control 3.1); ↓ absolute thymus weight (males 35%; females 32%); ↑ thymus phagocytic cells males and females 18/30 (control 6/27) both sexes; ↑ relative brain weight (males 40%, females 38%); ↓ absolute brain weight (males 7.5%, females 6%) **<u>500 ppm (42 mg/kg bw/day)</u>** F1: ↓ body weight gain evident from day 4 (males 16%, females 17%; days 0-21); ↓ sexual maturation females age 37.1 days (control 32.5 days), body weight 111 g (control 103 g); ↓ absolute liver weight (males 20%, females 16%); ↓ liver glycogen deposition males 13/24 (control 28/29), females 4/25 (control 12/28); ↓ liver extramedullary haematopoiesis females 11/25 (control 18/28); ↓ absolute / relative spleen weight males 25% / 11%; females 21% / 8%; ↓ grading of spleen extramedullary haematopoiesis males 2.5 (control 2.9); ↓ absolute thymus weight males 19%, females 18%; ↑ thymus phagocytic cells males 10/24 (control 5/29) ; ↑ relative brain weight males 15%, females 15%; ↓ absolute brain weight males 3%. F2: ↓ body weight gain evident from day 4 (males 12%, females 14%; days 0-21); ↓ absolute liver weight (males 16%, females 13%); ↓ liver glycogen deposition (males 8/29 (control 18/27), females 4/29 (control 15/27); ↓ absolute / relative spleen weight (males 17% / 5%; females 20% / 8%); ↓ grading of spleen extramedullary haematopoiesis males 2.3 (control 2.8); ↓ absolute thymus weight (males 14%); ↑ relative brain weight (males 12%, females	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		14%) **100 ppm (8 mg/kg bw/day):** No treatment-related findings **25 ppm (2 mg/kg bw/day):** No treatment-related findings	
Reproduction study (two generations/ one litter) OECD 416 (1983) notable deviation is lack of systemic toxicity at highest dose GLP Oral (continuous in diet) Rat, CD (Sprague Dawley origin) 30/sex/group **Supplementary study**	Fenpropidin (purity 91%) 0, 6.25, 25, 100 ppm corresponding to 0.4, 1.61, 6.43 and 0.50, 2.03, 8.02 mg/kg bw/day for F0 and F1 males respectively. 0.48, 1.91, 7.79 and 0.56, 2.35, 9.31 mg/kg bw/day for F0 and F1 females respectively. These values represent premating period only. Vehicle: laboratory animal diet	***Parental toxicity*** No effects at any dose level ***Reproductive toxicity*** No effects at any dose level ***Offspring toxicity*** No effects at any dose level	[redacted] *et al* (1987)

Table 46: Summary table of human data on adverse effects on sexual function and fertility

No data available

Table 47: Summary table of other studies relevant for toxicity on sexual function and fertility

No studies available

2.6.6.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility – generational studies

Two, two generation reproduction studies of fenpropidin in the rat have been conducted. The most recent study ([redacted] 2003) is the most relevant study since it was conducted according to the more recent OECD guideline. Although conducted after the issue of the current OECD test guideline (OECD 416, 2001), there were a few minor omissions in sperm parameters and tissues examined microscopically and the post lactation ovary was not examined. Nevertheless, these minor omissions/deviations are considered unlikely to alter the conclusions reached. A previous study ([redacted] 1987) has a number of notable deviations from the current test guideline including the lack of systemic toxicity observed in the parental generations. The results of this study are therefore acceptable as supplementary data only.

In the main study ([redacted] 2003), there was a reduction in body weight gain in females during the pre-mating period and during gestation and lactation at the highest dose of 1000 ppm (80 mg/kg bw/day) *(see Table 2.6.6.1.1-1)*. For the F2 litters, there was a reduction in the number of uterine implantations, pups delivered and live born *(see Table 2.6.6.1.1-3)*. For both the F1 and F2 litters, the body weight development of the pups was impaired from birth (day 0) with weight gain over the lactation period being 36% lower than for the control pups. It was this body weight decrement that was considered responsible for the apparent delay in sexual maturation (balanopreputial separation in F1 males and vaginal opening in F1 females; *see Table 2.6.6.1.1-4*) and for a number of differences in organ weights

and microscopic findings in selected tissues examined at weaning *(see Table 2.6.6.1.1-5)*. A similar effect was seen at the lower dose of 500 ppm (42 mg/kg bw/day) although there was no effect on the number of live born pups and the body weight development of the pups was impaired from post-natal day 4.

There was no evidence for a direct effect of fenpropidin on the development of the offspring; all treatment-related changes in offspring occurred in the presence of, and were attributable to, systemic toxicity in the parental generations.

Table 2.6.6.1.1-1: **Parental body weight development** ([redacted] *2003*)

	F0					F1				
ppm	**0**	**25**	**100**	**500**	**1000**	**0**	**25**	**100**	**500**	**1000**
Males: bodyweight [g] / [% of control]										
day 1°	190.3	190.5/100	187.9/ 99	188.7 / 99	188.1 / 99	113.5	115.8/102	107.1/ 94	90.1**/ 79	60.5**/ 53
day 68	413.0	407.6/ 99	399.0/ 97	371.4**/ 90	362.5**/ 88	393.4	399.7/102	380.6/ 97	344.7**/ 88	273.6**/ 70
Cumulative bodyweight gain [g] / [% of control]										
d 1-68°	222.7	217.5/ 98	263.5/ 95	182.8**/ 82	174.399/ 78	279.9	283.9/101	273.5/ 98	254.6**/ 91	213.1**/ 76
Mean food consumption [g/animal/day] / [% pf control]										
d 1-68°	24.1	24.2/ 101	23.7 / 98	23.8 / 99	23.4 / 97	25.2	25.5/ 101	24.0 / 95	23.3 / 93	18.4 / 73
Females: bodyweight [g] / [% of control]										
Prem. day 1°	152.0	152.0/100	151.7/100	151.8/ 100	151.6/ 100	102.1	105.5/103	99.0 / 97	92.6**/ 91	68.0**/ 67
day 68	242.2	239.0/ 99	239.1/ 99	226.5**/ 94	220.5**/ 91	232.8	237.4/102	232.6/100	220.1* / 95	192.1**/ 83
Gest. day 0	242.4	239.3/ 99	241.0/ 99	227.7** 94	221.9**/ 92	235.6	240.2/102	234.6/100	222.4* / 94	193.7**/ 82
day 21	364.6	359.4/ 99	361.8/99	340.7**/ 93	324.7**/ 89	346.1	353.1/102	345.7/100	330.4 / 96	283.5**/ 82
Lact. Day 0	273.2	269.5/ 99	269.3/ 99	257.9**/ 94	240.3**/ 88	265.5	271.5/102	262.9 / 99	254.7 / 96	218.7**/ 82
day 21	292.0	286.1/ 98	286.8/ 98	273.8**/ 94	227.8**/ 78	279.0	282.1/101	272.0 / 98	268.4 / 96	219.6**/ 79
Cumulative bodyweight gain [g] / [% of control]										
Prem. d 1-68°	90.2	85.9 / 95	87.4 / 97	74.7**/ 83	68.8**/ 76	130.7	131.8/101	133.6/102	127.5 / 98	124.1 / 95
Gest. d 0-21	122.2	120.1/ 98	120.8/ 99	113.0 / 93	102.8**/ 84	110.5	112.8/102	111.1/101	106.1 / 96	89.8**/ 81
Lact. d. 0-21	18.8	16.6	17.5	15.9	-12.5**	13.4	10.6	9.2	13.7	0.9**
Mean food consumption [g/animal/day] / [% pf control]										
Prem. d 1-68°	17.4	17.1 / 98	16.9 / 97	17.3 / 99	17.1 / 98	18.7	18.4 / 98	17.6 / 94	17.7 / 95	15.7 / 94
Gest. d 0-21	22.9	22.7 / 99	22.6 / 99	23.5 / 103	23.0 / 101	22.5	22.9 / 102	22.0 / 98	22.1 / 98	18.9 / 84
Lact. d. 0-21	52.3	52.6 / 101	51.7 / 99	51.4 / 98	49.7 / 95	50.3	50.4 / 100	48.8 / 97	48.6 / 97	41.9 / 83

° bw were recorded on day 2 for the F1 generation; prem. = premating, gest. = gestation, lact. = lactation, d = day * p <0.05, ** p<0.01 (Dunnett test)

Table 2.6.6.1.1-2: **Sperm counts** ([redacted] *2003*)

ppm	F0 0	25	100	500	1000	F1 0	25	100	500	1000
Sperm counts [1 x 10^6/g tissue]										
Testis spermatids	82.6	74.6**	76.6	77.9	66.0**	77.6	80.7	82.6*	84.1**	79.2
Cauda epididymides sperm cells	182.6	193.8	204.8	217.7#	158.8#	176.0	162.1	164.2	155.8*	160.9

* p <0.05, ** p<0.01 (Anova + Dunnett test); # p <0.05 (Kruskal-Wallis + Dunnett test)

Table 2.6.6.1.1-3: **F1 litter data** ([redacted] *2003*)

ppm	0	25	100	500	1000
Litters	29	29	29	26	29
with liveborn pups [N / %]	29 / 100	29 / 100	29 / 100	26 / 100	29 / 100
with stillborn pups [N / %]	1 / 3.4	3 / 10.3	3 / 10.3	2 / 7.7	3 / 10.3
Implantation sites [total / mean]	410 / 14.1	361 / 12.4*	374 / 12.9	320 / 12.3*	357 / 12.3**
Pups delivered [total / mean]	381 / 13.1	386 / 13.3	384 / 13.2	313 / 12.0	345 / 11.9
Prenatal loss [%]	7.1	-6.9	-2.7	2.2	3.4
Pups liveborn [N] / Live birth index [%]	380 / 99.7	383 / 99.2	381 / 99.2	309 / 96.7	342 / 99.1
Pups stillborn [N] / Perinatal loss [%]	1 / 0.3	3 / 0.8	3 / 0.8	4 / 1.3	3 / 0.9
Pups d/m/c/es	0 / 3 / 1 / 58	3 / 9 / 0 / 58	2 / 7 / 0 / 58	2 / 6 / 8 / 49	9## / 4 / 0 / 57
Litters not surviving day 21 (es)	0	0	0	1	0
Pups d/sm/m/c [N / %] day 0	0	0	0	0	0
day 1-4	4 / 1.1	12 / 3.1	9 / 2.4	8 / 2.6	13 / 3.8
day 5-7	0	0	0	0	0
day 8-14	0	0	0	8## / 2.6	0
day 15-21	0	0	0	0	0
Pups culled day 4 [N / %]	148 / 38.8	141 / 36.5	140 / 36.5	100 / 31.9	102 / 29.6
Pups surviving day 0-4 [total / mean %]	376 / 98.9	371 / 96.9	372 / 97.6	301 / 97.4	329 / 96.2
Pups surviving day 4-21 [total / mean %]	228 / 100	230 / 100	232 / 100	193** / 96	227 / 100
Live pups per litter: day 0	13.1	13.2	13.1	11.9	11.8
day 4 (preculling)	13.0	12.8	12.8	116.	11.3*
day 4 (postculling)	7.9	7.9	8.0	7.7	7.8
day 21	7.9	7.9	8.0	7.7	7.8
Sex ratio day 0, % live males / females	48.4 / 51.8	46.2 / 53.8	54.1 / 45.9	51.5 / 48.5	50.0 / 50.0
day 21, % live males / females	51.8 / 48.2	50.9 / 49.1	50.4 / 49.6	48.7 / 51.3	48.0 / 52.0

d/m/c/es = died, missing, cannibalised, elected sacrifice; d/sm/m/c = died, sacrificed moribund, missing, cannibalised * p<0.05, ** p <0.01 (Dunnett test); ## p < 0.01 (Chi-Square + Fisher test)

Table 2.6.6.1.1-4: **Bodyweight development and sexual maturation in F1 pups** ([redacted] *2003*)

ppm	Males 0	25	100	500	1000	Females 0	25	100	500	1000
Bodyweight [g] / [% of control]										
day 0	5.7	5.7 /	5.7 /	5.8 /	5.7 /	5.4	5.4 /	5.4 /	5.6 /	5.4 /

		100	100	102	100		100	100	104	100
day 4°	9.7	9.6 / 99	9.5 / 98	9.5 / 98	8.9**/ 92	9.5	9.2 / 97	9.1 / 96	9.2 / 97	8.5* / 89
day 4°°	9.7	9.6 / 99	9.5 / 98	9.5 / 98	8.9**/ 92	9.5	9.3 / 98	9.1 / 96	9.2 / 97	8.5**/ 89
day 7	15.9	15.4 / 97	15.4 / 97	14.9*/ 94	13.0**/ 82	15.5	14.9 / 96	14.8 / 95	14.2 / 92	12.6**/ 81
day 14	32.3	31.6 / 98	30.8 / 95	29.2**/ 90	23.8**/ 74	31.5	30.8 / 98	29.9 / 95	28.1**/ 89	23.2**/ 74
day 21	52.4	51.9 / 99	49.9*/ 95	45.2**/ 86	35.3**/ 67	50.4	50.0 / 99	47.9 / 95	43.1**/ 86	34.0**/ 67
Bodyweight gain [g] / [% of control]										
day 0-4	4.07	3.84 / 94	3.74 / 92	3.74 / 92	3.17**/ 78	4.05	3.82 / 94	3.70 / 91	3.66 / 90	3.16**/ 78
day 4-7	6.16	5.82 / 94	5.92 / 96	5.35**/ 87	4.15**/ 67	5.98	5.64 / 94	5.71 / 95	5.03**/ 84	4.12**/ 69
day 7-14	16.44	16.15/ 98	15.41/ 94	14.27**/ 87	10.75**/ 65	16.24	15.98/ 98	15.25/ 94	13.9**/ 85	10.7**/ 66
day 14-21	20.08	20.32/ 101	19.03/ 95	15.95**/ 79	11.47**/ 57	18.94	19.3/ 102	18.03/ 95	14.9**/ 79	10.9**/ 57
day 0-21	46.74	46.15/ 99	44.14*/ 94	39.39**/ 84	29.54**/ 63	45.00	44.6 / 99	42.52/ 94	37.5**/ 83	28.7**/ 64
Sexual maturation indices										
age [day]	25.3	24.8	25.6	26.1	28.0##	32.5	31.6	33.7	37.1##	42.0##
bw [g]	71.27	69.07	70.33	59.80**	48.37**	102.6	100.3	107.5	111.1*	105.8

* p <0.05, ** p <0.01 (Anova + Dunnett test);## p <0.01 (Kruskal-Wallis + Dunnett test); ° preculling, °° postculling

Table 2.6.6.1.1-5: **Organ weights and histopathological changes in F1 pups (** [redacted] *2003*)

ppm	**Males 0**	**25**	**100**	**500**	**1000**	**Females 0**	**25**	**100**	**500**	**1000**
Carcass [g / % ctr]	53 / 100	53 / 100	51 / 96	45**/ 85	35**/ 66	53 / 100	53 / 100	50 / 94	45**/ 85	36**/ 68
Liver abs [g]	2.455	2.504	2.331	1.970##	1.547##	2.546	2.548	2.436	2.130**	1.677**
relative to bw [‰]	45.76	47.26	45.43	43.78	44.64	39.7	40.3	40.2	41.4	48.1##
rel to bw [% ctr]	100	99	96	92	94	100	102	101	104	121
Thymus abs [mg]	219	221	202	177##	120##	242	230	230	198**	152**
relative to bw [‰]	4.097	4.148	3.946	3.946	3.441**	4.584	4.368	4.568	4.326	4.209
rel to bw [% ctr]	100	101	96	96	84	100	95	100	94	92
Spleen abs [mg]	279	274	258	209**	129**	294	306	270	233##	153##
relative to bw [‰]	5.204	5.169	5.060	4.647*	3.702**	5.573	5.796	5.364	5.107	4.247##
rel to bw [% ctr]	100	99	97	89	71	100	104	96	92	76
Brain abs [g]	1.511	1.521	1.504	1.467*	1.388**	1.468	1.472	1.472	1.438	1.348**
relative to bw [‰]	28.47	28.94	29.57	32.86**	40.47**	27.93	28.11	29.34	32.25##	38.06##
rel to bw [% ctr]	100	102	104	115	142	100	101	105	115	136
Liver: glycogen deposition°	28/29 (2.1)	25/29 (1.9)	24/29 (1.8)	**13/24** (1.7)	**12/28** (1.7)	12/28 (1.6)	15/29 (1.5)	11/29 (1.4)	**4/25** (1.5)	**4/29** (1.3)
extramedullary haematopoiesis°	21/29 (1.4)	17/29 (1.1	20/29 (1.3)	17/24 (1.2)	**9/28** (1.0)	18/28 (1.2)	19/29 (1.3)	19/29 (1.4)	**11/25** (1.1)	**7/29** (1.0)
Spleen: extramed.	29/29	29/29	29/29	24/24	28/28	28/28	29/29	29/29	25/25	29/29

haematopoiesis°	(2.9)	(3.0)	(2.9)	(**2.5**)	(**2.2**)	(3.0)	(3.0)	(2.9)	(2.7)	(**2.3**)
Thymus: atrophy phagocytic cells°	0/29 5/29 (1.2)	0/29 4/29 (1.3)	0/29 6/29 (1.3)	0/24 **10/24** (1.7)	**8/28** **19/28** **(2.1)**	0/28 7/28 (1.9)	0/29 3/29 (2.0)	0/29 1/29 (1.0)	0/25 2/25 (1.5)	0/29 2/29 (1.5)

* p <0.05, ** p <0.01 (Anova + Dunnett test); ## p <0.01 (Kruskal-Wallis + Dunnett test) ° incidence (grading); abs = absolute, rel = relative, ctr = control, extramed. = extramedullary

Table 2.6.6.1.1-6: **Mating indices, survival, gestation, and delivery parameters in F1 females ([redacted] *2003*)**

ppm	**0**	**25**	**100**	**500**	**1000**
Females					
placed with males and mated	30	30	30	30	30
inseminated	28	29	30	30	30
mating index [%]	93.3	96.7	100	100	100
pregnant	28	29	29	29	30
fertility index [%]	100	100	96.7	96.7	100
with defined day 0 pc	27	28	30	29	30
mating after days	2.6	2.8	2.4	2.9	3.0
without evidence of mating:	3	2	0	1	0
pregnant	1	1	0	1	0
non pregnant	2	1	0	0	0
died pregnant / non pregnant	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
pregnant, not delivering	1	0	0	0	0
delivering	27	29	29	29	30
with liveborn pups	27	29	29	29	30
with all pups stillborn	0	0	0	0	0
with stillborn pups	1	2	1	2	2
gestation index [%]	96.4	100	100	100	100
parturition index [%]	96.4	100	100	100	100
duration of gestation [day]	22.1	22.1	22.1	22.0	22.0

Table 2.6.6.1.1-7: **Mating indices in F1 males ([redacted] *2003*)**

Males					
placed with females	30	30	30	30	30
mated	28	29	30	30	30
mating index [%]	93.3	96.7	100	100	100
with females pregnant	28	29	30	29	30
fertility index [%]	100	100	96.7	96.7	100

Table 2.6.6.1.1-8: **Histopathological changes in F1 animals ([redacted] *2003*)**

	Males					Females				
ppm	**0**	**25**	**100**	**500**	**1000**	**0**	**25**	**100**	**500**	**1000**
Liver: lmphohistio-cytic infiltration°	21/30 (1.6)	19/30 (1.6)	17/30 (1.5)	18/30 (1.4)	**11/30** (1.5)	22/30 (1.4)	24/30 (1.5)	21/30 (1.4)	20/30 (1.3)	**15/30** (1.2)
Spleen: extramed. haematopoiesis°	16/30 (1.9)	24/30 (1.9)	20/30 (1.7)	**9/30** (1.6)	**2/30** (**1.5**)	28/30 (1.8)	26/30 (1.9)	24/30 (2.0)	**13/30** (**1.2**)	**3/30** (**1.3**)
Adrenals: cortical fatty change°	23/30 (1.5)	-	-	-	20/30 (1.4)	10/30 (2.0)	15/30 (1.7)	16/30 (2.4)	**19/30** (**2.6**)	**21/30** (**2.8**)
Prostate: lymphoh. infiltration°	17/30 (1.9)	10/30 (2.3)	17/30 (2.0)	**6/30** (2.2)	**4/30** (1.5)	-	-	-	-	-

* p <0.05, ** p <0.01 (Anova + Dunnett test); # p <0.05, ## p <0.01 (Kruskal-Wallis + Dunnett test) ° incidence (grading); abs = absolute, rel = relative, ctr = control, extramed. = extramedullary, lymphoh. = lymphohistiocytic

Table 2.6.6.1.1-9: **F2 litter data** ([redacted] *2003*)

ppm	**0**	**25**	**100**	**500**	**1000**
Litters	27	29	29	29	30
with liveborn pups [N / %]	27 / 100	29 / 100	29 / 100	29 / 100	30 / 100
with stillborn pups [N / %]	1 / 3.7	2 / 6.9	1 / 3.4	2 / 6.9	2 / 6.7
Implantation sites [total / mean]	335 / 12.4	360 / 12.4	370 / 12.8	339 / 11.7	310 / 10.3**
Pups delivered [total / mean]	316 / 11.7	337 / 11.6	352 / 12.1	321 / 11.1	288 / 9.6##
Prenatal loss [%]	5.7	6.4	4.9	5.3	7.1
Pups liveborn [N] / Live birth index [%]	315 / 99.7	334 / 99.1	351 / 99.7	319 / 99.4	286 / 99.3
Pups stillborn [N] / Perinatal loss [%]	1 / 0.3	3 / 0.9	1 / 0.3	2 / 0.6	2 / 0.7
Pups d/m/c/es	1 / 2 / 0 / 54	3 / 3 / 1 / 57	1 / 2 / 0 / 58	1 / 4 / 0 / 58	3 / 2 / 1 / 60
Litters not surviving day 21 (es)	0	0	0	0	0
Pups d/sm/m/c [N / %]:	0	0	0	0	0
day 1-4	2 / 0.6	7 / 2.1	2 / 0.6	5 / 1.6	4 / 1.4
day 5-7	1 / 0.3	0	0	0	0
day 8-14	0	0	1 / 0.3	0	0
day 15-21	0	0	0	0	2 / 0.7
Pups culled day 4 [N / %]	97 / 30.7	105 / 31.2	122 / 34.7	87 / 27.1	50°° / 29.6
Pups surviving day 0-4 [total / mean %]	313 / 99.4	327 / 97.9	349 / 99.4	314 / 98.4	282 / 98.6
Pups surviving day 4-21 [total / mean %]	215 / 99.5	222 / 100	226 / 99.6	227 / 100	230 / 99.1
Live pups per litter:	11.7	11.5	12.1	11.0	9.5##
day 4 (preculling)	11.6	11.3	12.0	10.8	9.4##
day 4 (postculling)	8.0	7.7	7.8	7.8	7.7
day 21	8.0	7.7	7.8	7.8	7.7
Sex ratio day 0, % live males / females	47.3 / 52.7	48.2 / 51.8	45.0 / 55.0	47.0 / 53.0	47.9 / 52.1
day 21, % live males / females	48.4 / 51.6	52.3 / 47.7	47.3 / 52.7	48.0 / 52.0	49.1 / 50.9

d/m/c/es = died, missing, cannibalised, elected sacrifice; d/sm/m/c = died, sacrificed moribund, missing, cannibalised
** p <0.01 (Anova + Dunnett test); ## p <0.01 (Kruskal-Wallis + Dunnett test); °° p < 0.01 (Chi-Square + Fisher test)

Table 2.6.6.1.1-10: **Bodyweight development in F2 pups** ([redacted] *2003*)

	Males					Females				
ppm	**0**	**25**	**100**	**500**	**1000**	**0**	**25**	**100**	**500**	**1000**
Bodyweight [g] / [% of control]										
day 0	5.9	6.0 / 102	6.1 / 103	6.2 / 105	5.9 / 100	5.7	5.7 / 100	5.8 / 102	5.9 / 104	5.7 / 100
day 4°	10.1	9.9 / 98	10.0 / 99	10.3 / 102	9.3$^{\#\#}$/ 92	9.8	9.7 / 99	9.6 / 98	9.9 / 101	9.0$^{\#\#}$/ 92
day 4°°	10.1	10.0 / 99	10.0 / 99	10.4 / 103	9.4$^{\#\#}$/ 93	9.8	9.7 / 99	9.6 / 99	9.9 / 101	9.0$^{\#\#}$/ 92
day 7	16.2	15.8 / 98	16.0 / 99	16.3 / 101	13.7$^{\#\#}$/ 85	15.7	15.4 / 98	15.4 / 98	15.6 / 99	13.3$^{\#\#}$/ 85
day 14	31.9	31.6 / 99	31.4 / 98	30.1 / 94	24.2$^{\#\#}$/ 76	31.3	31.0 / 99	30.6 / 98	28.9$^{\#}$/ 92	23.4$^{\#\#}$/ 75
day 21	51.6	52.0 / 101	49.9 / 97	46.5$^{\#\#}$/ 90	35.3$^{\#\#}$/ 68	50.3	50.4/100	48.5 / 96	44.1$^{\#\#}$/ 88	34.3$^{\#\#}$/ 68
Bodyweight gain [g] / [% of control]										
day 0-4	4.1	4.0 / 98	3.9 / 95	4.1 / 100	3.4$^{\#\#}$/ 83	4.1	4.0 / 98	3.8 / 93	4.1 / 100	3.4$^{\#\#}$/ 83
day 4-7	6.1	5.8 / 95	6.0 / 98	6.0 / 98	4.3$^{\#\#}$/ 70	5.9	5.7 / 97	5.8 / 98	5.6$^{\#}$ / 95	4.3$^{\#\#}$/ 73
day 7-14	15.7	15.8 / 101	15.4 / 98	13.8$^{\#\#}$/ 88	10.5$^{\#\#}$/ 67	15.5	15.6/101	15.1 / 97	13.4$^{\#\#}$/ 86	10.1$^{\#\#}$/ 65
day 14-21	19.7	20.4 / 104	18.5 / 94	16.4**/ 83	11.1**/ 56	19.0	19.4/102	17.9/ 94	15.2**/ 80	10.8**/ 57
day 0-21	45.6	46.0 / 101	43.8 / 96	40.2$^{\#\#}$/ 88	29.3$^{\#\#}$/ 64	44.5	44.7/100	42.7/ 96	38.2$^{\#\#}$/ 86	28.6$^{\#\#}$/ 64

* p <0.05, ** p <0.01 (Anova + Dunnett test); $^{\#\#}$ p <0.01 (Kruskal-Wallis + Dunnett test) ° preculling, °° postculling

Table 2.6.6.1.1-11: **Organ weights and histopathological changes in F2 pups** ([redacted] *2003*)

	Males					Females				
ppm	**0**	**25**	**100**	**500**	**1000**	**0**	**25**	**100**	**500**	**1000**
Carcass[g/ %ctr]	55.0	54.5	52.4	48.3$^{\#\#}$	36.6$^{\#\#}$	51.8	52.9	51.1	45.2$^{\#\#}$	35.8$^{\#\#}$
Liver abs [g]	2.56	2.59	2.38	2.15$^{\#\#}$	1.54$^{\#\#}$	2.32	2.45	2.30	2.01**	1.54**
relative to bw [‰]	45.5	47.3	45.3	44.4	42.1**	44.7	46.3	44.9	44.3	43.0
rel to bw [%ctr]	100	102	97	95	91	100	104	100	99	96
Thymus abs [mg]	237	238	223	204**	153**	236	244	233	211	161**
relative to bw [‰]	4.34	4.34	4.25	4.23	4.16	4.54	4.59	4.56	4.67	4.48
rel to bw [%ctr]	100	100	98	97	96	100	101	100	103	99
Spleen abs [mg]	290	299	266	241	147$^{\#\#}$	279	282	263	224$^{\#\#}$	142$^{\#\#}$
relative to bw [‰]	5.25	5.46	5.07	4.99	3.99$^{\#\#}$	5.38	5.31	5.16	4.96	3.93$^{\#\#}$
rel to bw [%ctr]	100	104	97	95	76	100	99	96	92	73
Brain abs [g]	1.547	1.528	1.524	1.511	1.431**	1.465	1.469	1.475	1.452	1.378**
relative to bw [‰]	28.3	28.5	29.2	31.6$^{\#\#}$	39.6$^{\#\#}$	28.3	28.2	29.1	32.4$^{\#\#}$	39.1$^{\#\#}$
rel to bw [%ctr]	100	101	103	112	140	100	100	103	114	138
Liver:glycogen deposition°	18/27 (1.6)	17/29 (1.9)	18/29 (2.1)	**8/29** (1.6)	**5/30** (1.6) **5/30** (1.0)	15/27 (2.0)	15/28 (2.2)	12/29 (2.2)	**4/29** (2.0)	**2/30** (2.0)
extramedullary haematopoiesis°	24/27 (1.2)	19/29 (1.3)	25/29 (1.7)	20/29 (1.1)		25/27 (1.3)	26/28 (1.5)	28/29 (1.5)	27/29 (1.4)	**13/30** (1.2)
Spleen: extramed. haematopoiesis°	27/27 (2.8)	29/29 (2.8)	29/29 (2.9)	29/29 (**2.3**)	30/30 (**1.9**)	27/27 (3.1)	28/28 (3.3)	29/29 (3.3)	29/29 (2.9)	30/30 (**2.2**)
Thymus: atrophy	0/27	0/29	0/29	0/29	1/30	0/27	0/28	0/29	0/29	0/30

phagocytic cells°	6/27 (1.7)	5/29 (1.6)	4/29 (1.3)	7/29 (1.9)	**18/30** (1.8)	6/27 (2.0)	4/28 (1.8)	7/29 (2.1)	9/29 (2.1)	**18/30** (1.8)

* p <0.05, ** p <0.01 (Anova + Dunnett test); ## p <0.01 (Kruskal-Wallis + Dunnett test) ° incidence (grading); abs = absolute, rel = relative, ctr = control, extramed. = extramedullary

2.6.6.1.2 Comparison with the CLP criteria regarding adverse effects on sexual function and fertility

According to CLP (Regulation (EC) No. 1272/2008, Annex I, Table 3.7.1a), an active substance meets the criteria for classification in relation to sexual function and fertility, if it induces alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems. In two-generation reproduction studies with fenpropidin, no treatment-related adverse effects on sexual function and fertility were observed. The treatment-related effects observed were considered attributable to or a consequence of the systemic toxicity effects.

2.6.6.2 Adverse effects on development [equivalent to section 10.10.4 of the CLH report template]

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Developmental toxicity OECD 414 (1981) Deviations: The test substance was administered only on day 6 to 15 of gestation. Food consumption was recorded with 5 days intervals on day 6, 11, 16 and 21. GLP Oral (gavage) Rat, Tif: RAI f (SPF) 24 mated females/group **Acceptable study**	Fenpropidin (purity 97%) 0, 10, 60 and 90 mg/kg bw/day on gestation days 6-15 Vehicle: 0.5% CMC	***Maternal toxicity*** NOAEL: > 90 mg/kg **90 mg/kg bw/day**: ↓ body weight gain (11% days 6-16, not significant); ↓ food consumption (10% days 11-16) **60 mg/kg bw/day**: No effects **10 mg/kg bw/day**: No effects ***Developmental toxicity*** NOAEL: > 90 mg/kg **90 mg/kg bw/day**: No effects **60 mg/kg bw/day**: No effects **10 mg/kg bw/day**: No effects	[redacted] (1994)
Developmental toxicity Pre OECD 414 (1981) with several significant deviations, e.g. there was 17-18 instead of 20 pregnant rats per group. Food consumption was recorded only during treatment from day 7-16 of gestation. Dosing occurred only for day 7-16. Gravid uterine and cervix weight was not measured. Stability, homogeneity and achieved concentration of test substance in the diet were not reported. GLP Oral (diet) Rat, albino (SPF) 17 females /group with live foetuses (approx. 7 litters for	Fenpropidin (purity not reported) Mean achieved doses were 0, 19.5, 47.5, 87.8 mg/kg bw/day on gestation days 7-16. Vehicle: Nafag 850 diet	NOAEL (maternal): 19.5 mg/kg bw ***Maternal toxicity*** **87.8 mg/kg bw/day**: body weight loss -19.5 g (control +38.1 g) days 7-17; ↓ body weight gain 35% (days 0-21); ↓ food consumption 22% (days 7-9), 58% (days 15-17) **47.5 mg/kg bw/day**: ↓ body weight gain 34% (days 7-17), 9% (days 0-21); ↓ food consumption 16% (days 7-9), 7% (days 15-17) **19.5 mg/kg bw/day**: No effects ***Developmental toxicity*** NOAEL (developmental): 47.5 mg/kg bw **87.8 mg/kg bw/day:** skeletal anomaly: ↑ number of incised neural arches *(see Table 2.6.6.2-7)* **47.5 mg/kg bw/day**: No effects	[redacted] (1981)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
foetal visceral examination and 10 litters for skeletal) **Supplementary study**		**19.5 mg/kg bw/day:** No effects	
Developmental toxicity OECD 414 (2001) GLP Oral (gavage) Rabbit: New Zealand White, Hra:(NZW) SPF 25 mated females/group **Acceptable study**	Fenpropidin (purity 96.9%) 0, 5, 10 and 20 mg/kg bw/day on gestation days 7-28 Vehicle: 0.5% CMC	***Maternal toxicity*** NOAEL (maternal): 10 mg/kg bw **20 mg/kg bw/day:** ↓ defaecation days 16-29, significantly ↓ body weight gain 64% (days 7-29); non-significantly ↓ food consumption 11% (days 7-29) **10 mg/kg bw/day:** No effects **5 mg/kg bw/day**: No effects ***Developmental toxicity*** NOAEL (developmental): 10 mg/kg bw **20 mg/kg bw/day:** ↑ incidence of persistent truncus arteriosus (3/204 foetuses, 3/23 litters within historical control range); ↑ incidence of severely malaligned sternebrae (3/204 foetuses, 3/23 litters outside of historical control range). **10 mg/kg bw/day:** No effects **5 mg/kg bw/day:** No effects	[redacted] (2011)
Developmental toxicity Pre OECD 414 Deviations: Animals were treated only on days 7-19 of gestation. The mortalities were high in the treated groups 15-25% resulting in 15 to 19 pregnant females. Gravid uterine weight was not determined, rationale for dose selection was not given, and details on test formulation (purity was not stated), food and water quality were not reported. Food consumption was not measured. Pre-GLP but with QA Oral (gavage) Rabbit: Swiss hare 20 mated females/group **Supplementary study**	Fenpropidin (purity not reported) 0, 5, 12 and 30 mg/kg bw/day on gestation days 7-19 Vehicle: 4% gum arabic	***Maternal toxicity*** NOAEL (maternal): 12mg/kg bw **30 mg/kg bw/day:** body weight loss 15g (control 129.3 g) days 7-20; ↓ body weight gain 24% (days 1-30) **12 mg/kg bw/day:** No effects **5 mg/kg bw/day:** No effects ***Developmental toxicity*** NOAEL (developmental): 30 mg/kg bw **30 mg/kg bw/day**: ↓ foetal body weight (7%) – possibly a consequence of maternal toxicity or a consequence of larger litter size 7.2 (control 5.7). Latter indicated by inverse relationship **Dose (mg/kg bw/day)** | **0** | **5** | **12** | **30** Mean no. live foetuses | 5.7 | 6.9 | 7.2 | 7.2 Mean foetal body weight (g) | 40.1 | 39.4 | 38.2 | 37.1 **12 mg/kg bw/day:** No effects **5 mg/kg bw/day:** No effects	[redacted] and [redacted] (1981)

Table 48: Summary table of human data on adverse effects on development

No data available.

Table 49: Summary table of other studies relevant for developmental toxicity

No studies available

2.6.6.2.1 Short summary and overall relevance of the provided information on adverse effects on development

The developmental toxicity of fenpropidin was investigated in four prenatal developmental toxicity studies, two in rats (1994; 1981) and two in rabbits (, 2011; and 1981). Three of these studies predate the current OECD Test Guideline Number 414 (2001) and do not include the recommended extended dosing period (i.e. from implantation to one day prior to the day of scheduled kill). However, the rat study of (1994) is considered adequate and relevant for evaluation of the potential of fenpropidin to induce developmental effects in the rat. The other two studies, (1981; and 1981) have notable deviations from the current test guideline and are regarded as supplementary. The rabbit study of (2011) is compliant with the current test guideline requirements, fully adequate and relevant for evaluation of the potential of fenpropidin to induce developmental effects in the rabbit. Therefore, the key developmental toxicity study in the rat is (1994) and in the rabbit (2011).
In the rat study (1994) the highest dose tested of 90 mg/kg bw/day induced maternal toxicity (reduced body weight and food consumption) without a consequential reduction in foetal body weight. Incidental malformations were seen in control (one foetus with encephalocele, protrusion of tongue and open eye; another foetus with acaudia) as well as at top dose (one foetus with anal atresia, hydronephrosis, uteral aplasia and aplasia of urinary bladder); (*see Table 2.6.6.2-1and 2.6.6.2-2).* No treatment-related effects on foetal development were observed and the NOEL for developmental toxicity was therefore set at 90 mg/kg bw/day.

Table 2.6.6.2-1: **Foetal external observations** (1994)

group / **mg/kg bw/day**		**1** **0**	**2** **10**	**3** **60**	**4** **90**
Foetuses / litters examined for external observations		306 / 22	337 / 24	312 / 21	284 / 23
External malformations:					
Encephalocele (head):	foetal incidence: total /%	1 / 0.3	0 / 0	0 / 0	0 / 0
% litter incidence / % affected foetuses per litter		4.5 / 0.3	0 / 0	0 / 0	0 / 0
Protrusion (tongue):	foetal incidence: total /%	1 / 0.3	0 / 0	0 / 0	0 / 0
% litter incidence / % affected foetuses per litter		4.5 / 0.3	0 / 0	0 / 0	0 / 0
Open eye:	foetal incidence: total /%	1 / 0.3	0 / 0	0 / 0	0 / 0
% litter incidence / % affected foetuses per litter		4.5 / 0.3	0 / 0	0 / 0	0 / 0
Anal atresia (trunk):	foetal incidence: total /%	0 / 0	0 / 0	0 / 0	1 / 0.4
% litter incidence / % affected foetuses per litter		0 / 0	0 / 0	0 / 0	4.3 / 0.4
Acaudia missing (tail):	foetal incidence: total /%	1 / 0.3	0 / 0	0 / 0	0 / 0
% litter incidence / % affected foetuses per litter		4.5 / 0.3	0 / 0	0 / 0	0 / 0
External anomalies and variations:	foetal incidence: total / %	0 / 0	0 / 0	0 / 0	0 / 0
	litter incidence: total / %	0 / 0	0 / 0	0 / 0	0 / 0
Total external observations:	foetal incidence: total / %	2 / 0.7	0 / 0	0 / 0	1 / 0.4
	litter incidence: total / %	2 / 9.1	0 / 0	0 / 0	1 / 4.3

Table 2.6.6.2-2: **Foetal visceral observations** ([redacted] 1994)

group **mg/kg bw/day**	**1** **0**	**2** **10**	**3** **60**	**4** **90**
Foetuses / litters examined for visceral observations	148 / 22	163 / 24	150 / 21	137 / 23
Visceral malformations				
Hydronephrosis (kidney): foetal incidence: total /% litter incidence total / % / % affected foetuses per litter	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0	1 / 0.7 1 / 4.3 / 0.9
Aplasia of urinary bladder: foetal incidence: total /% litter incidence total / % / % affected foetuses per litter	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0	1 / 0.7 1 / 4.3 / 0.9
Ureteral aplasia: foetal incidence: total /% litter incidence total / % / % affected foetuses per litter	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0	1 / 0.7 1 / 4.3 / 0.9
Visceral anomalies				
Blood stained fluid (abdom. cavity): foetal incidence: total /% litter incidence total / % / % affected foetuses per litter	0 / 0 0 / 0 / 0	1 / 0.6 1 / 4.3 / 1.4	0 / 0 0 / 0 / 0	1 / 0.7 1 / 4.3 / 1.1
Enlarged liver: foetal incidence: total /% litter incidence total / % / % affected foetuses per litter	1 / 0.7 1 / 4.5 / 0.6	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0
Renal pelvic dilatation (kidney): foetal incidence: total /% litter incidence total / % / % affected foetuses per litter	2 / 1.4 2 / 9.1 / 2.2	2 / 1.2 2 / 8.7 / 1.0	0 / 0 0 / 0 / 0	0 / 0 0 / 0 / 0
Visceral variations				
Enlarged thymus: foetal incidence: total /% litter incidence total / % / % affected foetuses per litter	4 / 2.7 4 / 18.2 / 8.1	9 / 5.5 8 / 34.8 / 4.9	7 / 4.7 5 / 23.8 / 5.5	5 / 3.6 3 / 13.0 / 6.0
Accessory lobulet (liver): foetal incidence: total /% litter incidence total / % / % affected foetuses per litter	0 / 0 0 / 0 / 0	2 / 1.2 2 / 8.7 / 1.0	2 / 1.3 2 / 9.5 / 1.2	2 / 1.5 1 / 4.3 / 1.0
Total visceral observations: foetal incidence: total / % litter incidence: total / %	7 / 4.7 6 / 27.3	14 / 8.6 11 / 47.8	9 / 6.0 7 / 33.3	9 / 6.6 6 / 26.1

Table 2.6.6.2-3: **Foetal skeletal observations** ([redacted] 1994)

mg/kg bw/day	**0**	**10**	**60**	**90**
Foetuses / litters examined for skeletal observations	159 / 22	174 / 24	162 / 21	147 / 23
Total skeletal malformations: foetal incidence: total / % litter incidence: total / %	0 / 0 0 / 0	0 / 0 0 / 0	0 / 0 0 / 0	0 / 0 0 / 0
Total skeletal anomalies: foetal incidence: total / % litter incidence: total / %	8 / 5.0 5 / 22.7	7 / 4.0 7 / 29.2	13 / 8.0 11 / 52.4	12 / 8.2 8 / 34.8
Selected skeletal variations				
Absent ossification of metatarsal-1: foetal incidence: total / % litter incidence total / % / % affected foetuses per litter	17 /10.7 10 /45.5 / 11.2	23 /13.2 9 / 37.5 / 13.4	34* / 21.0 10 / 47.6 / 20.2	13 / 8.8 5 / 21.7 / 8.3
proximal phalanx, anterior digit-2: foetal incidence: total / % litter incidence total / % / % affected foetuses per litter	3 / 1.9 2 / 9.1 / 1.9	5 / 2.9 5 / 20.8 / 3.3	16** / 9.9 7 / 33.3/10.1	6 / 4.1 3 / 13.0 / 4.3
proximal phalanx, anterior digit-5: foetal incidence: total / % litter incidence total / % / % affected foetuses per litter	12 / 7.5 8 / 36.4 / 7.6	11 / 6.3 7 / 29.2 / 7.0	26* / 16.0 9 / 42.9/15.8	11 / 7.5 6 / 26.1 / 7.5
distal phalanx, anterior digit-5: foetal incidence: total / % litter incidence total / % / % affected foetuses per litter	0 / 0 0 / 0 / 0	2 / 1.1 2 / 8.3 / 1.1	12** / 7.4 5 / 23.8 / 8.0	3 / 2.0 3 / 13.0 / 2.2
proximal phalanx, posterior digit-3:				

foetal incidence: total / % litter incidence total / % / % affected foetuses per litter	46 / 28.9 14 / 63.6 / 27.4	39 / 22.4 12 / 50.0 / 22.6	76** / 46.9 17 / 81.0 / 45.0	43 / 29.3 12 / 52.4 / 25.3
proximal phalanx, posterior digit-4:				
foetal incidence: total / % litter incidence total / % / % affected foetuses per litter	44 / 27.7 14 / 63.6 / 26.2	34 / 19.5 12 / 50.0 / 20.2	66* / 40.7 15 / 71.4 / 38.8	33 / 22.4 10 / 43.5 / 19.6
proximal phalanx, posterior digit-2:				
foetal incidence: total / % litter incidence total / % / % affected foetuses per litter	70 / 44.0 20 / 90.9 / 42.6	49** / 28.2 14 / 58.3 / 28.0	84 / 51.9 18 / 85.7 / 49.9	52 / 35.4 13 / 56.5 / 30.3
Poor ossification of proximal phalanx, anterior digit-2: foetal				
incidence: total / % litter incidence total / % / % affected foetuses per litter	1 / 0.6 1 / 4.5 / 0.6	3 / 1.7 2 / 8.3 / 1.5	9* / 5.6 7*/33.3 / 5.2	1 / 0.7 1 / 4.3 / 0.6
Shortened rib 13:				
foetal incidence: total / % litter incidence total / % / % affected foetuses per litter	4 / 2.5 4 / 18.2 / 2.2	15* / 8.6 9 / 37.5 / 7.6	3 / 1.9 2 / 9.5 / 2.0	6 / 4.1 5 / 21.7 / 3.4
Total skeletal variations:				
foetal incidence: total / % litter incidence: total / %	159 / 100 22 / 100	174 / 100 24 / 100	162 / 100 21 / 100	146 / 99.3 23 / 100

In the rabbit study of [redacted] (2011), the highest dose tested (20 mg/kg bw/day) induced maternal toxicity (reduced body weight gain and food consumption). Therefore, the NOAEL for maternal toxicity was set at 10 mg/kg bw/day.

At the top dose, the increased incidence of severely malaligned sternebra(e) as well as persistent truncus arteriosus was observed (3 foetuses/3 litters vs. 0/0 in control; *see Table 2.6.6.2-4)*. According to historical control data provided (studies performed during years 2006 – 2009 in the same laboratory ([redacted]) and with the same strain of rabbits as the study by [redacted] *(2011*); *see Table 2.6.6.2-5*), the skeletal variation malaligned sternebra(e) occurred in the range 0 – 1% per litter (mean 0.1%) and the visceral malformation persistent truncus arteriosus in the range 0 – 2.1% per litter (mean 0.1%). In the study with fenpropidin, the incidence of malaligned sternebra(e) (3 foetuses/3 litters; 1.6% per litter) was outside the historical control data range (0 – 1% per litter; the highest incidence: 2 foetuses/2 litters in 2 studies). Although the incidence of persistent truncus arteriosus (1.7% per litter) was within the historical control data range (0 – 2.1% per litter), it corresponded to the upper observed level, which was obviously rare in the historical control data set (the mean 0.1%, median 0%, 75th quartile 0%). In addition, the applicant admits in the Technical position statement provided, that the maximum observed value 2.1% was attributed to a single study, where the affected litter had only 2 viable foetuses (i.e. 50% incidence). The range without the aforementioned study was 0 – 1.1%, which is similar to the range based on the studies performed during years 2010 – 2014 (i.e. 0 – 1.4% per litter; *see Table 2.6.6.2-5*). Furthermore, the highest observed incidence of persistent truncus arteriosus in historical control data was 2 foetuses in one litter, whereas 3 affected foetuses from 3 litters were found in the study with fenpropidin.

The total number of foetuses with a malformation exerted dose-response relationship and was significantly increased comparing to the control (*see Table 2.6.6.2-4)*. The NOAEL for developmental effects was set at 10 mg/kg bw/day based on the increased incidence of severely malaligned sternebra(e) and persistent truncus arteriosus.

In the Technical position statement of the applicant, two case studies performed in [redacted] focusing on the incidence of persistent truncus arteriosus in the rabbit population are mentioned. In the first case study (2007), 4 foetuses from 4 litters with persistent truncus arteriosus were noted (3 foetuses from 3 litters in the low-dose group and 1 foetus in the mid-dose group). Six months later in the second case study, 3 foetuses from 3 litters with persistent truncus arteriosus in the mid-dose group were noted. The studies are not described in sufficient details (e.g. it is not clear, which doses were used). Based on these studies, the applicant does not consider the increased incidence of persistent truncus arteriosus to be treatment related. However it should be noted that considering both case studies, there were no incidences in the control group animals, therefore it is questionable if this can be considered as relevant for historical controls. It should suggest that the incidence of persistent truncus arteriosus is rather random and generally not treatment related, however this is in our opinion not sufficient evidence. It should be also noted that malaligned sternebrae have been downgraded from malformation to variation (devtox.com)

The statement of applicant on the increased incidence of severely malaligned sternebra(e): *"Although no new data were identified to clarify the occurrence of severely maligned sternebrae, it was considered that the study incidence of 3 foetuses in 3 litters in the 20 mg/kg bw/day group was only just outside the highest historical control incidence of 2 foetuses in 2 litters, seen in two studies. In the absence of any other effect of fenpropidin on the rabbit foetal skeleton, it was considered that the occurrence of maligned sternebrae in isolation was more consistent with a spontaneous event rather than an effect of treatment".*

Table 2.6.6.2-4**: Summary of foetuses and litters with malformations (absolute number),** ([redacted] 2011)

	FOETUSES				**LITTERS**			
Dose (mg/kg bw/day)	0	5	10	20	0	5	10	20
Number examined	222	224	197	204	23	24	20	23
Carpal and/or tarsal flexure	0	1	0	0	0	1	0	0
Microphthalmia and/or anophthalmia	0	0	1	0	0	0	1	0
Hydrocephaly	0	1	0	0	0	1	0	0
Persistent truncus arteriosus (% per litter)	**0**	**0**	**0**	**3**	**0**	**0**	**0**	**3 (1.7 %)**
Interventricular septal defect	1	0	0	0	1	0	0	0
Lungs – lobular agenesis	0	0	2	0	0	0	1	0
Vertebral anomaly with/without associated rib anomaly	0	1	0	1	0	1	0	1
Sternebra(e) malaligned (severe) ** ***(% per litter)***	***0***	***0***	***0***	***3***	***0***	***0***	***0***	***3 (1.6%)***
Total number of malformations (excluding Malaligned strenbrae (variation)	**1**	**3**	**3**	**4**	**1**	**3**	**2**	**4**

*significantly different from the control group at 0.05 using Fisher´s exact test

**downgraded to variation

Historical control data

Table 2.6.6.2-5**: Summary Incidence of Malformations and Variations in Developmental Toxicity Studies Conducted in the New Zealand White [Hra: (NZW) SPF] (CRP, Kalamazoo) between August 2006 and December 2009**

NO. OF DATASETS	65	
Total No. of fetuses/litters examined externally		
Total No. of fetuses/litters examined viscerally	12086	1375
Total No. of fetuses/litters examined skeletally	12086	1375

MALFORMATIONS (% per litter)	Mean	S.D.	SEM	Median	Min	Max	25th Quartile	75th Quartile	Number	
									Fetuses	Litters
TOTAL VISCERAL MALFORMATIONS	0.86	0.868	0.108	0.6	0	3.16	0	1.34		
TOTAL SKELETAL MALFORMATIONS	0.94	0.893	0.111	0.84	0	5.07	0.41	1.28		
VISCERAL										
Persistent Truncus Arteriosus	0.13	0.339	0.042	0	0	2.08	0	0	12	11
SKELETAL										
Sternebra(e)- Malaligned (Severe)	0.1	0.245	0.03	0	0	1.01	0	0	12	12

Table 2.6.6.2-6**: Summary Incidence of Malformations and Variations in Developmental Toxicity Studies Conducted in the New Zealand White [Hra: (NZW) SPF] (CRP, Kalamazoo) between January 2010 and November 2014**

NO. OF DATASETS	62	
Total No. of fetuses/litters examined externally		
Total No. of fetuses/litters examined viscerally	11415	1300
Total No. of fetuses/litters examined skeletally	11415	1300

MALFORMATIONS (% per litter)	Mean	S.D.	SEM	Median	Min	Max	25th Quartile	75th Quartile	Number	
									Fetuses	Litters
TOTAL VISCERAL MALFORMATIONS	1.05	1.031	0.131	0.69	0	4.26	0.1	1.63		
TOTAL SKELETAL MALFORMATIONS	0.93	0.774	0.098	0.96	0	3.54	0.1	1.41		
VISCERAL										
Persistent Truncus Arteriosus	0.04	0.171	0.022	0	0	1.14	0	0	3	3
SKELETAL										
Sternebra(e)- Malaligned (Severe)	0.07	0.229	0.029	0	0	1.06	0	0	7	7

Table 2.6.6.2-7: **Individial historical control data for persistent truncus arteriosus and malaligned sternebrae conducted in the New Zealand White [Hra:(NZW)SPF] (CRP, Kalamazoo) between August 2006 and December 2009**

				VISCERAL					SKELETAL				
				Persistent Truncus Arteriosus					Sternebra - Malaligned (Severe)				
Study Number	Day 0 of Gestation	Necropsy Date	Route of Administration	Number of Affected Foetuses	Number of Affected Litters	% per Litter	Total Fetuses Examined	Total Litters Examined	Number of Affected Foetuses	Number of Affected Litters	% per Litter	Total Fetuses Examined	Total Litters Examined
1	10/15/2006	11/17/2006	Gavage	0	0	0.000	209	23	0	0	0.000	209	23
2	10/15/2006	11/17/2006	Gavage	0	0	0.000	214	24	0	0	0.000	214	24
3	8/22/2006	9/22/2006	Gavage	0	0	0.000	183	20	0	0	0.000	183	20
4	9/19/2006	10/20/2006	Gavage	0	0	0.000	204	22	0	0	0.000	204	22
5	09/12/2006	10/13/2006	Gavage	0	0	0.000	205	23	1	1	0.543	205	23
6	1/29/2007	03/02/2007	Gavage	0	0	0.000	169	20	0	0	0.000	169	20
7	01/09/2007	02/09/2007	Gavage	0	0	0.000	204	23	1	1	0.395	204	23
8	11/17/2006	12/15/2006	Subcutaneous	0	0	0.000	177	19	0	0	0.000	177	19
9	03/11/2007	04/11/2007	Gavage	0	0	0.000	128	16	0	0	0.000	128	16
10	02/12/2007	3/16/2007	Gavage	0	0	0.000	219	25	0	0	0.000	219	25
11	04/08/2007	05/10/2007	Gavage	0	0	0.000	202	21	0	0	0.000	202	21
12	05/08/2007	06/10/2007	Gavage	1	1	0.952	182	21	2	2	1.005	182	21
13	4/16/2007	5/18/2007	IV	1	1	2.083	194	24	0	0	0.000	194	24
14	04/10/2007	05/11/2007	Gavage	0	0	0.000	146	17	0	0	0.000	146	17
15	06/01/2007	6/29/2007	Gavage	1	1	0.476	183	21	0	0	0.000	183	21

				VISCERAL					SKELETAL				
				Persistent Truncus Arteriosus					Sternebra - Malaligned (Severe)				
Study Number	Day 0 of Gestation	Necropsy Date	Route of Administration	Number of Affected Foetuses	Number of Affected Litters	% per Litter	Total Fetuses Examined	Total Litters Examined	Number of Affected Foetuses	Number of Affected Litters	% per Litter	Total Fetuses Examined	Total Litters Examined
16	06/10/2007	07/11/2007	Gavage	0	0	0.000	199	22	0	0	0.000	199	22
17	6/22/2007	7/20/2007	Gavage	0	0	0.000	163	20	0	0	0.000	163	20
18	07/06/2007	08/03/2007	Gavage	0	0	0.000	193	22	0	0	0.000	193	22
19	08/07/2007	8/31/2007	Gavage	1	1	0.595	195	21	0	0	0.000	195	21
20	08/01/2007	8/29/2007	Gavage	0	0	0.000	160	19	0	0	0.000	160	19
21	8/17/2007	9/14/2007	Subcutaneous	1	1	0.500	166	20	0	0	0.000	166	20
22	10/01/2007	10/26/2007	Gavage	0	0	0.000	200	23	0	0	0.000	200	23
23	9/21/2007	10/19/2007	Gavage	0	0	0.000	162	19	0	0	0.000	162	19
24	10/05/2007	11/02/2007	Dermal	0	0	0.000	178	20	0	0	0.000	178	20
25	10/12/2007	11/09/2007	Gavage	1	1	0.585	154	19	1	1	0.752	154	19
26	10/19/2007	11/16/2007	Gavage	0	0	0.000	208	23	1	1	0.483	208	23
27	10/24/2007	11/21/2007	Gavage	0	0	0.000	191	21	0	0	0.000	191	21
28	11/02/2007	11/30/2007	IV	0	0	0.000	211	23	0	0	0.000	211	23
29	11/09/2007	12/07/2007	Gavage	0	0	0.000	175	21	0	0	0.000	175	21
32	12/26/2007	01/10/2008	Dermal	0	0	0.000	165	20	0	0	0.000	165	20
34	8/13/2007	09/06/2007	Gavage	0	0	0.000	220	25	0	0	0.000	220	25
35	12/23/2007	1/15/2008	Gavage	0	0	0.000	166	22	1	1	0.758	166	22
36	12/04/2007	12/28/2007	Gavage	0	0	0.000	200	22	0	0	0.000	200	22
37	03/11/2008	04/11/2008	Gavage	0	0	0.000	188	21	0	0	0.000	188	21
38	1/13/2009	02/06/2009	Gavage	0	0	0.000	188	22	0	0	0.000	188	22
43	3/31/2009	4/24/2009	Gavage	0	0	0.000	168	20	0	0	0.000	168	20
44	02/12/2008	03/07/2008	Gavage	0	0	0.000	188	21	1	1	0.595	188	21
45	03/04/2008	3/28/2008	Gavage	0	0	0.000	186	21	0	0	0.000	186	21
46	05/06/2008	5/30/2008	Gavage	0	0	0.000	187	22	0	0	0.000	187	22
47	02/01/2008	2/27/2008	Gavage	0	0	0.000	137	17	0	0	0.000	137	17
48	09/05/2008	10/03/2008	Subcutaneous	2	1	0.784	151	17	0	0	0.000	151	17
50	03/04/2009	3/30/2009	Gavage	0	0	0.000	158	18	0	0	0.000	158	18
51	4/15/2008	05/09/2008	Gavage	0	0	0.000	182	21	0	0	0.000	182	21
52	7/21/2008	8/22/2008	Subcutaneous	0	0	0.000	164	19	0	0	0.000	164	19
54	5/21/2008	6/20/2008	Gavage	0	0	0.000	207	21	0	0	0.000	207	21
55	11/25/2008	12/19/2008	Subcutaneous	1	1	0.649	185	22	1	1	0.649	185	22
56	04/01/2008	4/25/2008	Gavage	0	0	0.000	190	22	0	0	0.000	190	22
57	07/07/2008	7/31/2008	Gavage	0	0	0.000	192	23	0	0	0.000	192	23
58	02/03/2009	2/27/2009	Subcutaneous	0	0	0.000	184	21	0	0	0.000	184	21
59	6/22/2008	7/16/2008	Subcutaneous	0	0	0.000	188	22	0	0	0.000	188	22
60	11/18/2008	12/12/2008	Gavage	0	0	0.000	183	22	0	0	0.000	183	22
61	4/22/2008	5/16/2008	Gavage	0	0	0.000	182	23	1	1	0.483	182	23
62	01/11/2009	02/04/2009	Gavage	0	0	0.000	211	25	0	0	0.000	211	25
63	12/09/2008	01/09/2009	Gavage	1	1	0.543	212	23	0	0	0.000	212	23
67	5/29/2009	6/26/2009	Subcutaneous	0	0	0.000	193	19	0	0	0.000	193	19
68	05/01/2009	5/29/2009	Gavage	0	0	0.000	171	19	0	0	0.000	171	19
69	05/10/2009	06/03/2009	Gavage	0	0	0.000	184	19	1	1	0.752	184	19
70	9/23/2008	10/17/2008	Gavage	0	0	0.000	217	24	0	0	0.000	217	24
72	1/20/2008	2/13/2008	Gavage	0	0	0.000	223	24	1	1	0.379	223	24
73	1/15/2008	02/09/2008	Gavage	0	0	0.000	198	21	0	0	0.000	198	21
74	8/19/2008	09/12/2008	Gavage	1	1	0.455	186	20	0	0	0.000	186	20
75	6/17/2008	07/11/2008	Gavage	1	1	0.680	203	21	0	0	0.000	203	21
86	10/09/2009	11/05/2009	GAVAGE	0	0	0.000	165	20	0	0	0.000	165	20
89	10/27/2009	11/20/2009	GAVAGE	0	0	0.000	221	24	0	0	0.000	221	24
97	12/22/2009	1/15/2010	GAVAGE	0	0	0.000	169	20	0	0	0.000	169	20

Table 2.6.6.2-8**: Individual historical control data for persistent truncus arteriosus and malaligned sternebrae Conducted in the New Zealand White [Hra:(NZW)SPF] (CRP, Kalamazoo) between January 2010 and November 2014**

				VISCERAL					SKELETAL				
				Persistent Truncus Arteriosus					Sternebra - Malaligned (Severe)				
Study Number	Day 0 of Gestation	Necropsy Date	Route of Administration	Number of Affected Foetuses	Number of Affected Litters	% per Litter	Total Fetuses Examined	Total Litters Examined	Number of Affected Foetuses	Number of Affeceted Litters	% per litter	Total fetuses examined	Total litters examined
82	8/17/2010	09/01/2010	Subcutaneous	0	0	0	148	19	0	0	0	148	19
84	10/31/2010	11/24/2010	Gavage	0	0	0	221	25	0	0	0	221	25
85	8/17/2010	09/10/2010	Gavage	0	0	0	164	20	1	1	1	164	20
87	01/05/2010	02/03/2010	Gavage	0	0	0	151	17	0	0	0	151	17
88	7/20/2010	8/13/2010	Gavage	0	0	0	176	20	2	2	1	176	20
90	8/24/2010	9/17/2010	Gavage	0	0	0	193	23	0	0	0	193	23
92	01/04/2010	1/28/2010	Intravenous	0	0	0	169	22	0	0	0	169	22
93	07/06/2010	7/30/2010	Gavage	0	0	0	214	22	0	0	0	214	22
94	08/09/2010	09/02/2010	Gavage	0	0	0	169	20	0	0	0	169	20
95	10/12/2010	11/05/2010	Gavage	1	1	1.136	179	22	0	0	0	179	22
99	4/18/2011	5/13/2011	Subcutaneous	0	0	0	182	20	1	1	1	182	20
100	5/24/2011	6/17/2011	Gavage	0	0	0	195	21	0	0	0	195	21
101	8/30/2011	9/23/2011	Gavage	0	0	0	163	19	0	0	0	163	19
102	2/21/2011	4/15/2011	Intravenous	0	0	0	203	23	0	0	0	203	23
103	1/18/2011	3/30/2011	Gavage	0	0	0	157	19	0	0	0	157	19
104	07/05/2011	8/31/2011	Intravenous	1	1	0.505	189	22	0	0	0	189	22
105	06/07/2011	7/29/2011	Intravenous	0	0	0	212	22	0	0	0	212	22
106	6/24/2011	8/16/2011	Gavage	0	0	0	154	20	0	0	0	154	20
107	6/14/2011	8/15/2011	Gavage	0	0	0	170	20	0	0	0	170	20
108	02/08/2011	03/04/2011	Gavage	0	0	0	177	21	0	0	0	177	21
109	3/15/2011	04/08/2011	Gavage	0	0	0	192	22	0	0	0	192	22
110	08/02/2011	8/16/2011	Gavage	0	0	0	157	19	0	0	0	157	19
112	10/30/2011	11/23/2011	Intravenous	0	0	0	176	21	0	0	0	176	21
114	3/20/2011	4/15/2011	Gavage	0	0	0	176	21	0	0	0	176	21
115	2/14/2012	03/09/2012	Gavage	0	0	0	152	20	0	0	0	152	20
116	10/18/2011	11/11/2011	Intravenous	0	0	0	172	20	0	0	0	172	20
117	03/11/2012	04/04/2012	Gavage	0	0	0	187	21	0	0	0	187	21
119	02/07/2012	03/02/2012	Gavage	0	0	0	173	20	0	0	0	173	20
120	11/22/2011	12/16/2011	Gavage	0	0	0	182	21	0	0	0	182	21
121	09/07/2011	11/02/2011	Whole-Body	0	0	0	94	12	0	0	0	94	12
122	1/17/2012	02/10/2012	Subcutaneous	0	0	0	179	20	0	0	0	179	20
123	11/07/2011	12/02/2011	Dermal	0	0	0	214	25	0	0	0	214	25
128	10/02/2012	10/25/2012	Gavage	0	0	0	207	23	0	0	0	207	23
132	4/16/2013	05/10/2013	Intravenous	0	0	0	163	19	0	0	0	163	19

133	7/29/2012	8/22/2012	Gavage	0	0	0	186	21	0	0	0	186	21
134	01/09/2013	03/08/2013	Whole-Body	0	0	0	214	23	0	0	0	214	23
135	8/27/2013	9/20/2013	Gavage	0	0	0	187	21	0	0	0	187	21
136	11/27/2012	12/28/2012	Gavage	0	0	0	220	25	0	0	0	220	25
138	10/12/2012	05/03/2013	Gavage	0	0	0	163	19	0	0	0	163	19
139	01/11/2013	3/15/2013	Gavage	0	0	0	167	19	0	0	0	167	19
145	1/28/2013	2/22/2013	Gavage	0	0	0	210	24	0	0	0	210	24
146	04/03/2012	4/27/2012	Gavage	0	0	0	186	21	0	0	0	186	21
147	8/14/2012	09/07/2012	Gavage	0	0	0	174	18	0	0	0	174	18
148	05/08/2012	06/01/2012	Gavage	0	0	0	195	23	0	0	0	195	23
149	10/09/2013	11/01/2013	Subcutaneous	0	0	0	170	19	0	0	0	170	19
150	09/10/2013	10/04/2013	Gavage	0	0	0	192	22	0	0	0	192	22
151	07/08/2013	08/01/2013	Gavage	0	0	0	200	22	0	0	0	200	22
152	12/11/2012	01/04/2013	Gavage	0	0	0	220	22	0	0	0	220	22
153	8/25/2014	9/18/2014	Gavage	0	0	0	220	25	0	0	0	220	25
154	9/15/2014	10/09/2014	Gavage	0	0	0	162	18	0	0	0	162	18

				VISCERAL					SKELETAL				
				Persistent Truncus Arteriosus					Sternebra - Malaligned (Severe)				
Study Number	Day 0 of Gestation	Necropsy Date	Route of Administration	Number of Affected Foetuses	Number of Affected Litters	% per Litter	Total Fetuses Examined	Total Litters Examined	Number of Affected Foetuses	Number of Affeceted Litters	% per litter	Total fetuses examined	Total litters examined
155	02/11/2014	4/17/2014	Gavage	0	0	0	203	24	0	0	0	203	24
156	02/04/2014	2/28/2014	Gavage	0	0	0	213	22	0	0	0	213	22
157	2/26/2014	05/01/2014	Subcutaneous	0	0	0	234	25	0	0	0	234	25
158	6/30/2014	7/24/2014	Gavage	0	0	0	193	21	0	0	0	193	21
160	5/13/2014	06/06/2014	Subcutaneous	0	0	0	201	22	0	0	0	201	22
161	6/30/2014	7/25/2014	Gavage	1	1	0.568	192	22	0	0	0	192	22
162	09/02/2014	9/17/2014	Gavage	0	0	0	194	21	0	0	0	194	21
163	3/24/2014	04/09/2014	Gavage	0	0	0	166	18	0	0	0	166	18
164	08/11/2014	8/26/2014	Gavage	0	0	0	177	19	1	1	1	177	19
165	12/16/2013	01/10/2014	Intravenous	0	0	0	173	19	1	1	1	173	19
166	11/10/2014	12/04/2014	Gavage	0	0	0	212	23	0	0	0	212	23
167	5/27/2014	6/20/2014	Intravenous	0	0	0	181	21	1	1	0	181	21

The original rat study ([redacted] 1981) was conducted in 1980 prior to OECD Guideline 414 issued in 1981. With respect to the study design, the dietary route of administration was selected and food consumption was recorded for the treatment period only, days 7-16 of gestation. The main guideline deviations relate to the lack of a full necropsy for the maternal animals, the use of only 7 litters per group for foetal visceral examination and 10 litters per group for skeletal examination. The achieved dose levels were 19.5, 47.5 and 87.8 mg/kg bw/day. At the two highest doses, a reduction in food consumption resulted in body weight loss (top dose) or decreased body weight gain during the treatment period (partly compensated after treatment between days 17-21). The marginal decrease in foetal body weights did not follow dose dependency and were therefore not considered as adverse *(see Table 2.6.6.2-5)*. In treated rats, increased number of incised neural arches was observed with dose-response relationship. However, at the low dose increased number of incised neural arches lay within historical control data presented by the notifier. At the top dose increased numbers of split, poorly ossified and/or half present neural arches were also seen *(see Table 2.6.6.2-6)*. The NOAEL (developmental) was set at 47.5 mg/kg based on the skeletal effects on neural arches. However due to the unknown purity, this study is considered only as supplementary material.

Table 2.6.6.2-9: **Caesarean section data** ([redacted] *1981*)

mg/kg bw/day	**0**	**19.5**	**47.5**	**87.8**
Corpora Lutea: total / mean per dam	214 / 12.6	249 / 13.8	210 / 12.4	224 / 13.2
Implantation sites: total / mean per dam	212 / 12.5	222 / 12.3	195 / 11.5	225 / 13.2
Live foetuses: total / mean per litter	195 / 11.5	200 / 11.1	177 / 10.4	196 / 11.5
Dead foetuses: total	0	0	0	0
Early resorptions°: total / mean per dam	16 / 0.9	20 / 1.1	18 / 1.1	29 / 1.7
% of implantations	7.5	9.0	9.2	12.9
Late resorptions°°: total / mean per dam	1 / 0.1	2 / 0.1	0 / 0	0 / 0
% of implantations	0.5	0.9	0	0
Total resorptions: total / mean per dam	17 / 1.0	22 / 1.0	18 / 1.1	29 / 1.7
% of implantations	8.0	9.9	9.2	12.9
Ratio male / female foetuses (% males)	107 / 88 (54.9)	94 / 106 (47.0)	81 / 96 (45.8)	89 / 107 (45.4)
mean foetal body weight [g]	3.4	3.2**	3.5	3.3*
crown – rump length [cm]	3.8	3.7	3.8	3.7

Table 2.6.6.2-10: **Foetal examinations** ([redacted] *1981*)

mg/kg bw/day		**0**	**19.5**	**47.5**	**87.8**
Foetuses / litters examined for **skeletal** observations		104 / 10	120 / 11	105 / 10	112 / 10
Neural arches:	half present	0	0	0	15
	poorly ossified	4	1	0	20
	split	2	7	2	32
	incised	64	100	147	276
Foetuses / litters examined for **visceral** observations		91 / 7	80 / 7	72 / 7	84 / 7
renal pelvis enlarged		0	2	1	2
testicles rudimentary		0	0	1	0
hydrocephalus internal		0	0	0	1

The rabbit study of [redacted] and [redacted] (1981) was conducted in 1980 prior to the issue of OECD Guideline 414 in 1981. The study was conducted using the oral gavage route of exposure. Although 20 mated females per group were allocated to the study, there were non-treatment-related deaths in all groups (1, 5, 3 and 4 in the control, 5, 12 and 30 mg/kg/day group, respectively) and 4 occurrences of total resorption in the control group. Some of the deaths were due to application errors (3 for the 5 mg/kg/day group, one dam each for the 12 and 30 mg/kg/day groups), broken vertebral column (1 dam each for the 12 and 30 mg/kg/day groups) or unknown causes. The high dose group had a significantly reduced body weight gain between days 7-20 of gestation (they lost weight compared to initial body weight). No maternal food consumption data were recorded. Whether or not this dose had an effect of foetal body weight is uncertain due to the imbalance in litter size; the weight of evidence suggests that the difference in foetal body weight is most likely attributable to the difference in litter size.

Multiple defects were noted in one foetus from each of the 5 mg/kg and 30 mg/kg dose group; these were considered by the notifier to be spontaneous as they are observed quite frequently in control animals of this strain (no historical control data were presented). The findings were for the 5 mg/kg animal: omphalocele (liver and intestine), missing left ear, missing tail, rudimentary eyelid and maxilla, aplastic left forepaw, multiple skeletal anomalies and the 30 mg/kg animal: ectopia (liver, stomach, intestine), missing tail, torsion of left hindpaw at the knee-joint, skeletal anomalies. There were no significant findings (brain anomalies) in the foetal heads examined by the modified Wilson technique. The NOAEL developmental effects was set at 30 mg/kg based (top dose).

Table 2.6.6.2-11: **Caesarean section data (***[redacted]* *and* *[redacted]* *1981)*

group **mg/kg bw/day**	**1** **0**	**2** **5**	**3** **12**	**4** **30**
Corpora Lutea: total / mean per dam	185 / 9.7	153 / 10.2	164 / 9.6	163 / 10.2
Implantation sites: total / mean per dam	151 / 7.9	124 / 8.3	136 / 8.0	126 / 7.9
Live foetuses: total / mean per litter	108 / 5.7	104 / 6.9	123 / 7.2	115 / 7.2
Dead foetuses: total / mean per litter	8 / 0.4	0 / 0	0 / 0	1 / 0.1
Early resorptions°: total / mean per dam	30 / 1.6	15 / 1.0	12 / 0.7	6 / 0.4
% of implantations	19.9	12.1	8.8	4.8
Late resorptions°°: total / mean per dam	5 / 0.3	5 / 0.3	1 / 0.1	4 / 0.3
% of implantations	3.3	4.0	0.7	3.2
Total resorptions: total / mean per dam	35 / 1.8	20 / 1.3	13 / 0.8	10 / 0.6
% of implantations	23.2	16.1	9.6	7.9
Ratio male / female foetuses (% males)	62 / 54 (53.4)	55 / 49 (52.9)	55 / 68 (44.7)	63 / 53 (54.3)
mean foetal body weight [g] / [% of control]	40.1 / 100	39.4 / 98	38.2 / 95	37.1 / 93
crown – rump length [cm] / [% of control]	8.0 / 100	7.9 / 99	7.8 / 98	7.7 / 96
Survival rate 24 h incubation [%]	95.4	93.3	95.1	93.0

° embryonic, °° foetal

2.6.6.2.2 Comparison with the CLP criteria regarding adverse effects on development

According to CLP criteria (Regulation (EC) No. 1272/2008, Annex I, Table 3.7.1a), the major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

In the rabbit developmental toxicity study with fenpropidin ([redacted] (2011), the increased incidence of severely malaligned sternebra(e) and persistent truncus arteriosus (skeletal variation and visceral malformation, respectively) was observed at the top dose (20 mg/kg bw/day). In the rat study with fenpropidin ([redacted] *1981*), increased number of incised neural arches was observed in treated animals with dose-response relationship. In addition, at the top dose (87.8 mg/kg bw) increased numbers of split, poorly ossified and/or half present neural arches were seen. Since the study of [redacted] was considered as supplementary it should not be considered for classification purposes

According to CLP criteria (Regulation (EC) No. 1272/2008), the classification of a substance in Category 1B (presumed human reproductive toxicant) is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on development in the absence of other toxic effects, or if occurring together with other toxic effects, the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate. Based on the results of developmental studies with fenpropidin, classification as a reproductive toxicant Category 2 (H361d: Suspected to damaging unborn child) is proposed. However, the DS is of the opinion that observed effects which could be clearly attributed to the test substance are not convincing and generally are the results borderline between the category 2 and no classification for development.

2.6.6.3 Adverse effects on or via lactation [equivalent to section 10.10.7 of the CLH report template]

Table 50: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Reproduction study (two generations/ one litter) OPPTS 870.3800 (1998), OECD 416 (2001) GLP Rat, HanIbm:WIST 30/sex/group **Acceptable study**	Fenpropidin (purity 97%) 0, 25, 100, 500 and 1000 ppm Vehicle: laboratory animal diet Oral (continuous in diet)	***Parental toxicity*** NOAEL (parental): 100 ppm (11.4 mg/kg bw) **1000 ppm (80 mg/kg bw/day)** F0: ↓ body weight gain males 22%, females 24% (days 1-68); ↓ body weight gain gestation 16% (days 0-21); body weight loss lactation (-12.5 g (control +18.8 g), days 0-21); ↑ relative liver weight (females 21%); ↓ liver lymphohistiocytic infiltration males 8/30 (control 19/30); ↓ spleen extramedullary haematopoiesis males 8/30 (control 20/30), females 2/30 (control 21/30); ↑ adrenal cortical fatty change females 26/30 (control 6/30); ↓ prostate lymphohistiocytic infiltration males 6/30 (control 12/30).	[redacted] (2003)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		F1: ↓ body weight gain (males 24%, females 5%; days 1-68); ↓ body weight gain gestation (19% days 0-21); ↓ body weight gain lactation (93%, days 0-21); ↓ food consumption (males 27%, females 16% pre-mating, 16% gestation, 17% lactation); ↑ relative liver weight (males 7.5%, females 8%); ↓ liver lymphohistiocytic infiltration males 11/30 (control 21/30), females 15/30 (control 22/30); ↓ spleen extramedullary haematopoiesis males 2/30 (control 16/30), females 3/30 (control 28/30); ↑ adrenal cortical fatty change females 21/30 (control 10/30); ↓ prostate lymphohistiocytic infiltration males 4/30 (control 17/30). **500 ppm (42 mg/kg bw/day)** F0: ↓ body weight gain (males 18%, females 17%; days 1-68); ↓ body weight gain gestation (7% days 0-21); ↓ body weight gain lactation (15% days 0-21); ↓ liver lymphocytic infiltration males 9/30 (control 13/30); ↓ spleen extramedullary haematopoiesis females 11/30 (control 21/30); ↑ adrenal cortical fatty change females 14/30 (control 6/30); ↓ prostate lymphohistiocytic infiltration males 2/30 (control 12/30) F1: ↓ body weight gain (males 9% days 1-68); ↓ food consumption (males 7.5% pre-mating); ↑ relative liver weight (males 5%); ↓ spleen extramedullary haematopoiesis males 9/30 (control 16/30) , females 13/30 (control 28/30); ↑ adrenal cortical fatty change females 19/30 (control 10/30); ↓ prostate lymphohistiocytic infiltration males 6/30 (control 17/30) **100 ppm (8 mg/kg bw/day)**:	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		No treatment-related effects **<u>25 ppm (2 mg/kg bw/day):</u>** No treatment-related effects ***Reproductive toxicity*** No effects at any dose level ***Offspring toxicity*** <u>NOAEL (offspring):</u> 100 ppm (11.4 mg/kg bw) **<u>1000 ppm (80 mg/kg bw/day)</u>** F1: ↓ body weight gain evident from day 0 (males 37%, females 36%; days 0-21); ↓ sexual maturation males age 28 days (control 25.3 days) , body weight 48 g (control 71 g); females age 42 days (control 32.5 days), body weight 106 g. (control 102 g); ↓ absolute liver weight (males 37%, females 34%), ↑ relative liver weight females (21%); ↓ liver glycogen deposition males 12/28 (control 28/29); females 4/29 (control 12/28); ↓ liver extramedullary haematopoiesis males 9/28 (control 21/29); females 7/29 (control 18/28); ↓ absolute / relative spleen weight (males 54% / 29%; females 48% / 24%); ↓ grading of spleen extramedullary haematopoiesis males 2.2 (control 2.9) ; females 2.3 (control 3.0); ↓ absolute / relative thymus weight (males 45% / 16%; females 37% / 8%); ↑ thymus atrophy males 8/28 (control 0/29) ; ↑ thymus phagocytic cells males 19/28 (control 5/29 ; ↑ relative brain weight (males 42%, females 36%); ↓ absolute brain weight (males 8%, females 8%) F2: ↓ number of implantation sites 10.3 (control 12.4) , mean pups delivered 9.6 (control 11.7) and live birth index 99.3% (control 99.7%); ↓ body weight gain (males	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		36%, females 36%; days 0-21); ↓ absolute / relative liver weight (males 40% / 7.5%, females 34% / 4%); ↓ liver glycogen deposition males 5/30 (control 18/27); females 2/30 (control 15/27); ↓ liver extramedullary haematopoiesis males 5/30 (control 24/27) females 13/30 (control 25/27); ↓ absolute / relative spleen weight (males 49% / 24%; females 49% / 27%); ↓ grading of spleen extramedullary haematopoiesis males 1.9 (control 2.8); females 2.2 (control 3.1); ↓ absolute thymus weight (males 35%; females 32%); ↑ thymus phagocytic cells males and females 18/30 (control 6/27) both sexes; ↑ relative brain weight (males 40%, females 38%); ↓ absolute brain weight (males 7.5%, females 6%) **500 ppm (42 mg/kg bw/day)** F1: ↓ body weight gain evident from day 4 (males 16%, females 17%; days 0-21); ↓ sexual maturation females age 37.1 days (control 32.5 days), body weight 111 g (control 103 g); ↓ absolute liver weight (males 20%, females 16%); ↓ liver glycogen deposition males 13/24 (control 28/29); females 4/25 (control 12/28); ↓ liver extramedullary haematopoiesis females 11/25 (control 18/28); ↓ absolute / relative spleen weight males 25% / 11%; females 21% / 8%; ↓ grading of spleen extramedullary haematopoiesis males 2.5 (control 2.9); ↓ absolute thymus weight males 19%; females 18%; ↑ thymus phagocytic cells males 10/24 (control 5/29) ; ↑ relative brain weight males 15%, females 15%; ↓ absolute brain weight males 3%. F2: ↓ body weight gain evident from day 4 (males 12%, females	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		14%; days 0-21); ↓ absolute liver weight (males 16%, females 13%); ↓ liver glycogen deposition (males 8/29 (control 18/27), females 4/29 (control 15/27); ↓ absolute / relative spleen weight (males 17% / 5%; females 20% / 8%); ↓ grading of spleen extramedullary haematopoiesis males 2.3 (control 2.8); ↓ absolute thymus weight (males 14%); ↑ relative brain weight (males 12%, females 14%) **100 ppm (8 mg/kg bw/day):** No treatment related findings **25 ppm (2 mg/kg bw/day):** No treatment related findings	
Reproduction study (two generations/ one litter) OECD 416 (1983) notable deviation is lack of systemic toxicity at highest dose GLP Oral (continuous in diet) Rat, CD (Sprague Dawley origin) 30/sex/group **Supplementary study**	Fenpropidin (purity 91%) 0, 6.25, 25, 100 ppm corresponding to 0.4, 1.61, 6.43 and 0.50, 2.03, 8.02 mg/kg bw/day for F0 and F1 males respectively. 0.48, 1.91, 7.79 and 0.56, 2.35, 9.31 mg/kg bw/day for F0 and F1 females respectively. These values represent premating period only. Vehicle: laboratory animal diet	***Parental toxicity*** No effects at any dose level ***Reproductive toxicity*** No effects at any dose level ***Offspring toxicity*** No effects at any dose level	[redacted] *et al* (1987)
Developmental toxicity Pre OECD 414 (1981) with several significant deviations, e.g. there was 17-18 instead of 20 pregnant rats per group. Food consumption was recorded only during treatment from day 7-16 of gestation. Dosing occurred only for day 7-16. Gravid uterine and cervix weight was not measured. Stability, homogeneity and achieved concentration of test substance in the diet were not reported. GLP Oral (diet)	Fenpropidin (purity not reported) Mean achieved doses were 0, 19.5, 47.5, 87.8 mg/kg bw/day on gestation days 7-16. Vehicle: Nafag 850 diet	***Maternal toxicity*** NOAEL (maternal): 19.5 mg/kg bw **87.8 mg/kg bw/day**: body weight loss -19.5 g days 7-17 (control +38.1 g); ↓ body weight gain (35% days 0-21); ↓ food consumption (22% days 7-9, 58% days 15-17) **47.5 mg/kg bw/day**: ↓ body weight gain (34% days 7-17, 9% days 0-21); ↓ food consumption (16% days 7-9, 7% days 15-17) **19.5 mg/kg bw/day**: No effects ***Developmental toxicity*** NOAEL (developmental): 47.5	[redacted] (1981)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Rat, albino (SPF) 17 females /group with live foetuses (approx. 7 litters for foetal visceral examination and 10 litters for skeletal) **Supplementary study**		mg/kg bw **87.8 mg/kg bw/day:** skeletal anomaly: ↑ number of incised neural arches *(see Table 2.6.6.2-6)* **47.5 mg/kg bw/day**: No effects **19.5 mg/kg bw/day:** No effects	

Table 51: Summary table of human data on effects on or via lactation

No evidence of adverse effects on or via lactation in humans

Table 52: Summary table of other studies relevant for effects on or via lactation

No relevant studies

2.6.6.3.1 Short summary and overall relevance of the provided information on effects on or via lactation

The rat two generation study of fenpropidin ([redacted] 2003) and the systemic toxicity induced in parental animals has been described earlier in this section *(2.6.6.1)*. Systemic parental toxicity was observed at 500 and 1000 ppm (42 and 80 mg/kg bw/day) which in turn resulted in impaired pup growth. Although the effect on pup growth was apparent from day 0 at 1000 ppm and from day 4 at 500 ppm there was no indication of decreased pup viability during lactation. For the high dose F0 females during lactation, a body weight loss of 12.5 g was noted compared with a gain of 18.8 g in control animals (days 0-21) and for the high dose F1 females, body weight gain was 93% lower than controls. Despite these significant effects on the lactating females, the quality of the milk and the ability of the mothers to nurse their young were not impaired.
The results of a rat developmental toxicity study ([redacted] 1981) with a littering phase did not provide evidence of an adverse effect on lactation due to fenpropidin at dose levels up to 87.8 mg/kg bw/day.

2.6.6.3.2 Comparison with the CLP criteria regarding effects on or via lactation

According to CLP criteria (Regulation (EC) No. 1272/2008, Annex I, Table 3.7.1b). The classification is intended to indicate when a substance may cause harm due to its effects on or via lactation and is independent of consideration of the reproductive or developmental toxicity of the substance. There were no effects to warrant classification of fenpropidin for effects on or via lactation.

2.6.6.4 Conclusion on classification and labelling for reproductive toxicity

Based on the results of the developmental studies, i.e. increased incidence of malformation in rabbits (persistent truncus arteriosus) and in compliance with CLP criteria (Regulation (EC) No. 1272/2008), fenpropidin is proposed to be classified to as a reproductive toxicant Category 2 (H361d: Suspected to damaging unborn child).

2.6.7 Summary of neurotoxicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results:** **- NOAEL/LOAEL** **- target tissue/organ** **-critical effect at LOAEL**	**Reference**
Developmental neurotoxicity study OECD TG 426 30 Crl:WI (Han) female rats/group **Acceptable study**	Fenpropidin (96.9%) 0, 40, 100, 400 ppm (equal to 0, 3, 7, 27 mg/kg bw) in diet Duration of exposure: from gestation day 6 to lactation day 21	NOAEL (maternal neurotoxicity): ≥400 ppm (27 mg/kg bw) NOAEL (developmental neurotoxicity): ≥ 400 ppm (27 mg/kg bw) **No effects on nervous system: no changes in brain weights, dimensions; no histopathological alterations in central or peripheral nervous system tissues.** Maternal toxicity: no effect on survival, bw (gain), food consumption, gestation length, number of implantations; no findings at necropsy; Offspring: no effect on the mean number of born pups, litter size, postnatal survival; mean pup body weight slightly ↓ (by 6.96% compared to controls, days 7-21); no findings at necropsy	[redacted] (2011)
90-day oral toxicity study OECD 408, Deviations: no epididymides or uterus weights, several organs/tissues were not examined GLP Rat: Tif: RAIf (SPF) 15/sex/group 10/sex control and high dose to assess recovery **Acceptable study**	Fenpropidin technical (purity 97%). Oral (diet) 0, 20, 150 and 1500 ppm (1.14, 9.84, 89.9 mg/kg bw/day (males), and 1.24, 10.1, 97.3 mg/kg bw/day (females) 90 day (dietary administration), recovery period for control and high dose 4 weeks	NOAEL: 150ppm (9.84 and 10.1 mg/kg bw/day for males and females, respectively) **1500 ppm (89.9 mg/kg bw/day males, 97.3 mg/kg bw/day females)** *Clinical observations*: 1/25 females had bilateral opaque eyes from day56 and bilateral limb paralysis from day76. *Body weight:* ↓ 16% males, 8% females week 13 *Body weight gain*: ↓ 29% males, 18% females weeks 1-13 *Food consumption:* ↓ 10% males, 5% females weeks 1-13 *Water consumption*: ↓ 20% males during whole treatment period *Haematology:* ↑ RBC 4.0% males; ↑ Hb 3.3% males; ↑ WBC 22.2% females (29.3% lymphocytes) *Clinical chemistry:* ↓ globulin 9.5% males, 5.8% females, partly reversible after recovery; ↓ glucose 12% males; ↓ triglycerides 29% males similar to control after recovery *Organ weight:* ↑ liver relative to body weight: 12% females	[redacted] (1995)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results:** **- NOAEL/LOAEL** **- target tissue/organ** **-critical effect at LOAEL**	**Reference**
		Histopathology: ↑ oesophagus pathology: hyperkeratosis 10/10 males and 10/10 females (0/10 control) and acanthosis 6/10 males, 2/10 females (0/10 control); ↑ nonglandular stomach pathology: hyperkeratosis 8/10 males, 5/10 females (0/10 and 1/10 control) and acanthosis 7/10 males, 4/10 females (0/10 control); ↑ urinary bladder hyperplasia: 4/10 males, 7/10 females (control 0/10 males and 1/10 females); **demyelination affecting especially nerve roots and spinal tracts** 1/10 females (with hind limb paralysis); ↑ pulmonary foam cells: 9/10 males grading 1.7 (control 7/10 grade 1.3); 7/10 females grade 1.7 (control 6/10 grade 1.3). After 4 weeks there was partial recovery from pathology findings in stomach and oesophagus. **150 ppm (9.84 mg/kg bw/day males, 10.1 mg/kg bw/day females)** *Histopathology:* ↑ oesophagus pathology: hyperkeratosis 4/10 males and 4/10 females (0/10 control); ↑ nonglandular stomach pathology: hyperkeratosis 3/10 males (0/10 control) **20 ppm (1.14 mg/kg bw/day males, 1.24 mg/kg bw/day females)** No treatment related findings	
1-year oral toxicity study in dog OECD 452 Deviations: urine volume and ornithine decarboxylase not measured; femur with joint not taken GLP Dog: Beagle 4/sex/group **Acceptable study**	Fenpropidin technical purity 97%) Oral in capsules 0, 2, 5 and 20 mg/kg/day 1 year	NOAEL: 5mg/kg bw **20 mg/kg bw/day** *Mortality:* 1 male with hind limb paresis killed week 38, pathology findings: demyelination of spinal cord *Clinical observations*: ↑ Indurated and inelastic pads 4/4 males and females; vomiting 4/4 females weeks 1-6; scale formation in inguinal and axillary regions 4/4 males and 3/4 females; reddening of skin 1/4 males and females *Ophthalmoscopy*: ↑ opacity of the lens: 4/4 males and females from week 22 *Body weight:* ↓ 15% females week 4, similar to control after initial weeks of study. *Food consumption*: ↓ 27% week 1 and 14% week 4 females *Haematology:* ↑ platelets 53.6% week 13, 40.8% week 26 males *Clinical chemistry*: ↑ ALP 42.4% males week 26,	[redacted] (1995)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results: - NOAEL/LOAEL - target tissue/organ -critical effect at LOAEL	Reference
		43.4% and 115.9% females weeks 13 and 52; ↓ albumin:globulin ratio 20.6% males week 13; ↑ globulin 25.4% males and 33.5% females week 52 *Organ weight:* ↑ relative liver 27% males; ↑ relative kidney 26% females *Histopathology:* cataract of crystalline lens 4/4 males and females (0/4 control); acanthosis of epidermis 3/4 males, 4/4 females (0/4 control); chronic inflammation skin/dermis: 2/4 males, 3/ 4 females (0/4 control); hepatocyte hypertrophy 4/4 males and females (0/4 control); pigmentation of Kupffer cells 4/4 females (1/4 control); liver inflammatory cell infiltration 3/ 4 females (2/4 control); renal tubular pigmentation 4/4 females (1/4 control); inclusion bodies urinary bladder epithelium 4/4 males, 2/4 females (0/4 control); cholesterol granulomas in lung 4/4 males, 1/ 4 females (0/4 control); **demyelination of spinal cord 3/4 males (0/4 control)** **5 mg/kg bw/day** *Clinical chemistry:* ↓ albumin:globulin ratio 12.5% males week 13 *Organ weight*: ↑ relative liver 16% males not significant *Histopathology:* hepatocyte hypertrophy 2/4 males (0/4 control) **2 mg/kg bw/day** No treatment related effects	

Fenpropidin does not belong to a chemical class, which is suspected to cause delayed neurotoxic effects (e.g. organophosphates, carbamates). Therefore, specific studies on delayed neurotoxicity were not deemed necessary. No acute neurotoxicity study was performed, since the toxicity studies conducted with fenpropidin did not indicate that such a study was necessary. 90-day oral toxicity study in the rat ([redacted] *1995*) and 1-year oral toxicity study in dog *([redacted] 1995), described in more detail in section 2.6.3.1.1*, revealed the specific toxicity to the nervous system characterised by hind-limb paralysis accompanied by demyelination of the spinal cord. The effects were observed at dose levels below the CLP cut-off values, therefore classification STOT-RE Category 2 (H373: May cause damage to the nervous system through prolonged or repeated oral exposure) was proposed *(see 2.6.3.1.2)*.

One developmental neurotoxicity study in rats is available *([redacted] 2011)*. In this new study, fenpropidin-related effects were not present. NOAEL in this study was set to ≥400 ppm (equal to 27 mg/kg bw), representing the top dose evaluated.

2.6.8 Summary of other toxicological studies

2.6.8.1 Toxicity studies of metabolites and impurities

Genotoxicity studies on GW metabolite CGA289267 have been performed to support an assessment of the toxicological relevance of the metabolite in groundwater. These studies have not been previously submitted for EU review.

All three genotoxicity studies met the requirements for a clearly negative response therefore CGA289267 is not considered to be toxicologically relevant. The results are summarised below. For further details, please refer to section B.6.8.1 in CA B6

Assay(Guideline)	Test System	Result	Reference
In vitro bacterial reverse mutation assay (Ames; OECD 471, 1997)	*S. typhimurium* strains TA1535, TA1537, TA98 and TA100, and *E. coli* strain WP2 uvrA pKM101	Negative +/- S9	Woods I. (2017).
Gene mutation assay (HPRT; OECD 476, 2016)	(Chinese hamster ovary CHO cells)	Negative +/-S9	Gilby B. (2017)
In vitro micronucleus (OECD 487, 2016)	Human lymphocytes	Negative +/- S9	Gilby B (2017)

2.6.8.2 Supplementary studies on the active substance

An immunotoxicity study with fenpropidin *(Eapen, 2011)* evaluating anti-sheep red blood cell response in mice is available. Fenpropidin (purity: 96.9%) at the concentration of 125, 400, and 1250 ppm (equal to 0, 26, 90, and 258 mg/kg) was administered to CD-1 female mice (10 animals/group) in diet for 28 consecutive days. On Day 24, all animals were immunized with a single intravenous dose of sheep red blood cells (SRBCs). The concurrent negative control group as well as positive control group were offered the basal diet on a comparable regimen to the fenpropidin-treated groups. Cyclophosphamide, the immunomodulatory positive control, was injected to animals intraperitoneally during days 24 – 28. All animals were euthanized on study day 28.
Clinical examinations were performed once daily for all animals. Detailed physical examinations were performed once weekly and on the day of the scheduled necropsy. Individual body weights were recorded twice weekly and food consumption was recorded approximately weekly. Complete necropsies were conducted on all animals. The mesenteric lymph node, Peyer's patches, spleen, and thymus were collected at the scheduled necropsy. Spleen and thymus was weighed. Spleen cell suspensions were prepared, spleen cell counts performed, and the number of specific IgM antibody-forming cells directed towards the SRBC antigen determined to measure the humoral immune response (splenic Antibody-Forming Cell (AFC) assay).
All animals survived to the scheduled necropsy with the exception of an early death at 1250 ppm that was not considered treatment-related. There were no fenpropidin-related clinical observations, macroscopic findings, or effects on body weight, food consumption, or organ weights. There were no significant effects on spleen cell number, and fenpropidin did not suppress significantly the humoral immune response when evaluated as

either specific activity (AFC/10^6 Spleen Cells) or as total activity (AFC/Spleen) of splenic IgM to the T-cell dependent antigen SRBC. In the positive control group, statistically significantly lower spleen weight, spleen cell numbers (35%), specific activity (100%), and total spleen activity (100%) of IgM antibody-forming cells were noted when compared to the vehicle control group. These effects were consistent with the known immunosuppressive effects of cyclophosphamide and validated the functionality of the assay. Based on the results of this study, the NOAEL for the AFC assay (humoral immune response) was set at 1250 ppm (equivalent to 258 mg/kg of body weight/day), which was the top dose group evaluated.

In addition, a detailed review of parameters related to immune function has been conducted on the toxicity database for fenpropidin. Repeat-dose studies in rats, mice and dogs were reviewed for any treatment-related changes in a variety of indicators of potential immunotoxicity including leukocyte counts, lymphocyte counts, globulin concentration, macroscopic findings (adrenals, lymph nodes, thymus, and spleen), organ weights (spleen, thymus and adrenals), and microscopic findings (bone marrow, lymph nodes, spleen, thymus and adrenals).

A thorough review of the toxicology database for fenpropidin has shown no evidence of adverse effects on the immune system in rats, mice or dogs. In addition, fenpropidin does not belong to a class of chemicals (e.g., the organotoxins, heavy metals, or halogenated aromatic hydrocarbons) that would be expected to be immunotoxic. Therefore, it can be concluded that fenpropidin has no immunotoxic potential.

2.6.8.3 Endocrine disrupting properties

The assessment strategy is based on the three conditions stipulated in the ED criteria (adversity, endocrine activity and a biologically plausible link between the two) and the grouping of the parameters described above, as recommended in the EFSA-ECHA (2018) Guidance. The assessment strategy is applicable to both humans and non-target organisms, and is illustrated in Figure 2.1. The remainder of this report is structured as follows:

Gather information & assess the evidence

Data reviews

Integration and assessment of lines of evidence

Initial analysis of the evidence (WoE)

MoA analysis

Conclusion on the ED criteria

Following an outline of the methodology (Section 3), the data reviews in Section 4 are organised around the OECD's Conceptual Framework for the Testing and Assessment of Endocrine Disrupting Chemicals (Table 2.1 and Table 2.2). In accordance with the Guidance (EFSA-ECHA, 2018), data from the various Conceptual Framework levels have differing applications and implications, e.g. providing mechanistic information (Levels 2 and 3) or providing data on adverse effects on endocrine relevant endpoints (Levels 4 and 5). Section 5 integrates and assesses the lines of evidence, whereas Section 6 evaluates all of the available evidence in a weight of evidence assessment, considering the availability of "EATS mediated" parameters. Where EATS mediated parameters are not sufficiently investigated according to the EFSA-ECHA Guidance (2018), potential endocrine modalities and testing strategies are outlined in Section 7. Section 8 provides a conclusion on the ED criteria.

Each Section considers effects relevant to both human health and non-target organisms. It should be noted that non-EATS modalities and potential for endocrine disrupting properties in invertebrate organisms are not currently within the scope of the Guidance (EFSA-ECHA 2018).

Table 6.8.3-1 OECD Conceptual Framework for Testing and Assessment of Endocrine Disruptors relevant for mammalian toxicology

Level 1 Existing data and non-test information	• Physical & chemical properties, e.g., MW reactivity, volatility, biodegradability. • All available toxicological data from standardized or non-standardized tests. • Read across, chemical categories, QSARs and other *in silico* predictions, and ADME model predictions.
Level 2 *In vitro* assays providing data about selected endocrine mechanism(s)/pathways(s)	• Estrogen or androgen receptor binding affinity • Estrogen receptor transactivation (OECD TG 455) • Androgen or thyroid transactivation (If/when TGs are available) • Steroidogenesis *in vitro* (OECD TG 456) • MCF-7 cell proliferation assays (ER ant/agonist) • Other assays as appropriate
Level 3 – Mammalian Species *In vivo* assays providing data about selected endocrine mechanism(s)/pathway(s)	• Uterotrophic assay (OECD TG 440) • Hershberger assay (OECD TG 441)
Level 4 – Mammalian Species *In vivo* assays providing data on adverse effects on endocrine relevant endpoints	• Repeated dose 28-day study (OECD TG 407) • Repeated dose 90-day study (OECD TG 408) • 1-generation reproduction toxicity study (OECD TG 415) • Male pubertal assay (see GD 150 Chapter C4.3) • Female pubertal assay (see GD 150 Chapter C4.4) • Intact adult male endocrine screening assay (see GD 150 Chapter

	Annex 2.5) • Prenatal developmental toxicity study (OECD TG 414) • Chronic toxicity and carcinogenicity studies (OECD TG 451-3) • Reproductive screening test (OECD TG 421 if enhanced) • Combined 28-day/reproductive screening assay (OECD TG 422 if enhanced) • Developmental neurotoxicity (OECD TG 426)
Level 5 – Mammalian Species *In vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism	• Extended one-generation reproductive toxicity study (OECD TG 443) • 2-Generation reproduction toxicity study (OECD TG 416)

This section assembles all the lines of evidence for endocrine activity and adversity.

Following the OECD Conceptual Framework and the four groupings specified in the EFSA-ECHA (2018) Guidance, the lines of evidence are organised according to their contribution to their assessment. The available data for fenpropidin has been compiled using the spreadsheet recommended by the EFSA-ECHA (2018) Guidance (appendix E in that document), and is supplied alongside this report.

***In Vitro* and *In Silico* Mechanistic Data**

***In silico* data in OECD Conceptual Framework level 1**

Reference:	Devillers J. *et al*., 2015. Prediction of the endocrine disruption profile of pesticides. *SAR QSAR Environ. Res.* **26(10)**: 831-852.

Guidelines: Not applicable.

GLP: No.

Study design: The ability of fenprodidin to bind and act as an agonist/antagonist of androgen receptor (AR), oestrogen receptor α (ERα), oestrogen receptor β (ERβ), thyroid hormone receptor α (TRα) and thyroid hormone receptor β (TRβ) was predicted using an *in silico* molecular docking approach. The authors provide limited information on the methodology, protein preparation or protocol generation (i.e. docking target). Predicted binding potentials were scored 1 to 4, with 1 representing a low probability of binding and 4 representing a high probability of binding. The degree of inappropriate penetration into the docking site (i.e. crash score) was not considered, the sensitivity and specificity of the models were not detailed and bootstrap analysis was not conducted.

Binding affinities with receptors not directly involved with the endocrine system were also estimated. These data are outside the scope of this review and are not discussed further.

Results:

Receptor:	**AR**	**ARa***	**ERα**	**ERαa***	**ERβ**	**ERβa***	**TRα**	**TRβ**
Score:	1	3	1	1	1	1	2	2-3**

*: ‘a’ denotes antagonist mode

**: When the different runs led to various probability values, the most frequent one was reported first. Thus, the code 2-3 means that the studied chemical showed more frequently binding scores leading to its allocation in class 2 rather than in class 3.

Overall, the results of these *in silico* predictions indicate that fenpropidin has a low potential to interact with the estrogen (α, β) receptors, but may bind to the thyroid (α, β) receptorsand may have antagonistic activity on the androgen receptor. It is important to note that these scores reflect theoretical binding potential, calculated via *in silico* docking to protein structures and are of questionable relevance to *in vitro* and *in vivo* activity. X-ray crystallography selectively favours the protein confirmations most likely to crystalise. Consequently, most structures are ligand-bound dimers (LBD) with associated cofactors, rather than monomeric ligand binding domains stabilised by heat-shock proteins (HSP). Thus, cofactors and ligands should be removed and the protein

structure optimised for physiological pH. The authors also failed to minimise and prepare the database for screening, which can lead to docking performance scores worse than random (Jain 2007; Peng *et al*. 1996).

CONCLUSIONS

Reliability score	**2**: Reliable with restrictions
Relevance score	**Medium** (Endpoint is based on simulated receptor binding potential in an *in silico* model). Note: The CEFIC EMSG does not give criteria for relevance of *in silico* data. Relevance has been assigned in line with the criteria for *in vitro* data.
Overall significance	**Low – Limited evidence of effects relevant to the assessment of the A and T pathways.**

***In vitro* data in OECD Conceptual Framework level 2**

No *in vitro* mechanistic data in OECD conceptual framework level 2 was identified for inclusion in this review.

In Vivo Mechanistic Data – Mammalian Species

Short term mechanistic studies in OECD Conceptual Framework level 3

No *in vivo* mechanistic data in OECD conceptual framework level 3 was identified for inclusion in this review

In Vivo Data – Mammalian Species

Short term studies in OECD Conceptual Framework level 4

Report:	[redacted] 1980. Ro 12-3049/000 - 21 Day percutaneous toxicity study in the rabbit. Report number: [redacted]. Syngenta file number: CGA114900_0128.

Guidelines: OECD 410.

GLP: Yes.

Study design: Fenpropidin was administered dermally to groups of 5 New Zealand White rabbits/sex/dose for 21 days at inclusion levels of 0 (control), 0.02, 0.2 and 2 (reduced to 1) mg/kg/day.

Endpoints relevant for assessment of potential for endocrine disruption

Gross macroscopic observations

Organ weights: Adrenal glands, ovary, pituitary gland, testes and thyroid

Histopathological evaluation: Adrenal glands, ovary, pituitary gland, prostate, testes and thyroid

Deviations from the current guideline relevant for assessment of potential for endocrine disruption: None.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	**1**: Reliable without restrictions
Relevance score	**Medium** (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	**Indicative – No evidence of an effect relevant to the assessment of endocrine disruption**

Report:	[redacted] 1981. 28 Day inhalation study in the rat with Ro 12-3049/000. Report number: [redacted]. Syngenta file number: CGA114900_0126.

Guidelines: OECD 412.

GLP: Yes.

Study design: Group of 15 Sprague Dawley rats/sex/dose were exposed daily to fenpropidin via inhalation (nose-only) for 6 hours per day for 28 days at dose levels of 0 (control), 20, 80 and 240 mg/m^3.

Endpoints relevant for assessment of potential for endocrine disruption

Gross macroscopic observations

Organ weights: Adrenal glands, ovary, pituitary gland and testes

Histopathological evaluation: Adrenal glands, epididymis, mammary gland, ovary, pituitary gland, prostate, seminal vesicles, testes, thyroid and uterus

Deviations from the current guideline: No weights of the thyroid and the uterus were recorded in this study. However, histopathology was performed on these organs. Therefore, the lack of these organ weights is not considered to affect the validity of this GLP and Guideline compliant study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Lower mean absolute and relative to brain testes weights were noted in males exposed to 240 mg/m^3. These differences reflected the lower bodyweights in this group and not a direct effect on the testes as there was no statistically significant difference in organ/body weight ratio and there were no correlating histopathological findings.

Higher mean relative to brain adrenal glands weights were noted in females exposed to 240 mg/m^3. As there were statistically significant effects on absolute adrenal glands weight and no correlating histopathological findings,

these differences reflect the lower body and absolute brain weights noted for this group and not a direct effect on the adrenal glands.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report: [redacted] 1994. 28-days range finding study in rats (administration in food). Report number: [redacted]. Syngenta file number: CGA114900_0316.

Guidelines: OECD 407.

GLP: Yes.

Study design: Fenpropidin was administered to groups of 5 Tif: RAIf (SPF) rats/sex/dose for 28 days via the diet at inclusion levels of 0 (control), 50, 200, 1000 and 2000 ppm. Animals were sacrificed at the end of the treatment period and all animals were subject to a detailed gross pathological examination. Specified organ weights and selected tissues were examined histopathologically.

Endpoints relevant for assessment of potential for endocrine disruption

Gross macroscopic observations

Organ weights: Adrenal glands, ovary, testes and thyroid (with parathyroid)

Histopathological evaluation: Adrenal glands, epididymis, ovary, pituitary gland, testes, thyroid (with parathyroid), uterus and vagina.

Deviations from the current guideline: The OECD 407 guideline was updated on 3 October 2008, to include endocrine organs, vaginal lavage at necropsy and optional thyroid hormone measurements (T3, T4 and TSH). Relative to the current guideline, the current study omitted histopathological examination of the prostate and seminal vesicles with coagulating glands and did not stage the oestrous cycle at termination via an assessment of vaginal cytology.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Increased adrenal weights relative to body weight were noted at 2000 ppm in males and females and increased testis and thyroid weights relative to body weight were observed at 2000 ppm in males. The corresponding absolute organ weights were within the expected range. The changes in relative organ weights are a consequence of the decreased body weight of high dose group (28 % lower body weights in males, 14% lower in females) and, therefore not considered treatment related.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 1981. Tolerance study following an oral administration of the plant fungicide Ro 12-3049/000 in rats during 13 weeks. Report number: [redacted] Syngenta file number: CGA114900_0108.

Guidelines: OECD 408.

GLP: Yes.

Study design: Fenpropidin was administered to groups of 16 SPF albino rats /sex/dose for 13 weeks via the diet at nominal dose levels of 0 (control), 20, 60 and 120 mg/kg/day.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Organ weights: Adrenal glands, ovary, pituitary gland, prostate, seminal vesicles, testes, thyroid and uterus.

Histopathological evaluation: Adrenal glands, epididymis, ovary, pituitary gland, prostate, seminal vesicles, testes, thyroid and uterus.

Deviations from the current guideline: The OECD 408 guideline was updated on 25 June 2018, to include thyroid hormones (T_3, T_4 and TSH), sperm parameters and vaginal cytology, none of which were considered. The tissues preserved for histopathological examination were limited, omitting the mammary glands and the vagina.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 1995. CGA 114900 tech: 3-Month oral toxicity study in rats (administration in food). Report number: [redacted]. Syngenta file number: CGA114900_0388.

Guidelines: OECD 408.

GLP: Yes.

Study design: Fenpropidin was administered to groups of 15 Tif: RAIf (SPF) rats/sex/dose for 3 months via the diet at inclusion levels of 0 (control), 20, 150 and 1500 ppm. An additional 10 animals per sex of the control group and the high dose group were kept on control diet for a 4 week recovery period before sacrifice.

Endpoints relevant for assessment of potential for endocrine disruption

Gross macroscopic observations

Organ weight: Adrenal glands, ovary, testes and thyroid (with parathyroid)

Histopathological evaluation: Adrenal glands, epididymis, ovary, pituitary gland, testes, thyroid (with parathyroid), uterus and vagina.

Deviations from the current guideline: The OECD 408 guideline was updated on 25 June 2018, to include thyroid hormones (T_3, T_4 and TSH), sperm parameters and vaginal cytology, none of which were considered. The recorded weights of organs were limited, omitting the epididymis, the pituitary gland, the uterus and the prostate. Histopathological examination did not include the prostate (including seminal vesicles) and the mammary gland.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Small testes with corresponding tubular atrophy was noted in two high dose males. These effects were considered to be incidental and unrelated to treatment. This conclusion is supported by the lack of effects on the testes in a previously conducted 13 week rat dietary study ([redacted] 1981, see above) at dose levels up to 120 mg/kg/day, i.e. up to higher doses than those used in this study (the dietary inclusion level of 1500 ppm in this study corresponded to an estimated achieved intake of 89.9 mg/kg/day).

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] and [redacted] 1981. Tolerance study with Ro 12-3049/000 administered orally as feed admixture to mice over 13 weeks. Report number: [redacted]. Syngenta file number: CGA114900_0107.

Guidelines: OECD 408.

GLP: Yes.

Study design: Fenpropidin was administered to groups of 16 SPF albino mice /sex/dose for 13 weeks via the diet at inclusion levels of 0 (control), 625, 1250, 2500 and 5000 ppm.

Endpoints relevant for assessment of potential for endocrine disruption

Gross macroscopic observations

Organ weights: Adrenal glands, ovary, prostate (including seminal vesicles), testes, and uterus.

Histopathological evaluation: Adrenal glands, epididymis, ovary, prostate, seminal vesicles, testes, and uterus.

Deviations from the current guideline: The OECD 408 guideline was updated on 25 June 2018, to include thyroid hormones (T_3, T_4 and TSH), sperm parameters and vaginal cytology, none of which were considered. The recorded weights of organs were limited, omitting the epididymis, the thyroid and the pituitary gland. Histopathological examination did not include the pituitary, the thyroid and the vagina.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Statistically significantly lower mean absolute prostate weights (males) and adrenal glands and ovary weights (females) were noted in animals receiving 2500 ppm (highest surviving dose level). These differences reflected the lower bodyweights in these groups and were not direct effects on these organs as there were no statistically significant differences in organ/body weight ratios (Table 4.3-1) and there were no correlating histopathological findings.

Table 6.8.3-2 90-day mouse study with fenpropidin: selected organ weights

		Males				Females			
	ppm	0	625	1250	2500	0	625	1250	2500
Adrenals	absolute [mg]	8.0	9.1	9.5	11.1	16.5	15.7	15.0	13.2**
	relative to bw [‰]	0.127	0.142	0.153	0.198	0.344	0.374	0.341	0.307
Ovaries	absolute [mg]	-	-	-	-	45.5	43.3	39.7	37.4*
	relative to bw [‰]					0.95	1.03	0.90	0.87
Prostate°	absolute [mg]	559	651	649	477*	-	-	-	-
	relative to bw [‰]	8.87	10.17	10.47	8.52				

* p<0.05, **p<0.01 (Student's t-test, difference from control group mean) ° including seminal vesicles

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 1993. 28-Day range finding toxicity study in Beagle dogs. Report number: [redacted]. Syngenta file number: CGA114900_0270.

Guidelines: None, adapted from OECD 409

GLP: No. The study was performed according to GLP-principles, but without Quality Assurance.

Study design: Fenpropidin was administered to groups of 2 Beagle dogs/sex/dose for 28 days via gelatine capsules at dose levels of 0 (control), 5, 15 and 25 mg/kg/day.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Organ weights: Adrenals glands, ovary, testes and thyroid (with parathyroid)

Histopathological evaluation: Adrenal glands, ovary, testes and thyroid (with parathyroid)

Deviations from the current guideline: Deviations from the current OECD guideline 409 include the lack of organ weights of epididymides and uterus. Histopathological evaluation was limited, omitting the pituitary, uterus, accessory sex organs and the prostate.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 1981. Toxicity study following oral administration of Ro 12-3049/000 to dogs for a period of 26 weeks. Report number: [redacted]. Syngenta file number: CGA114900_0120.

Guidelines: OECD 409.

GLP: Yes.

Study design: Fenpropidin was administered to groups of 4 Beagle dogs/sex/dose for 26 weeks via gelatine capsules at dose levels of 0 (control), 2, 5 and 12 mg/kg/day.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Organ weights: Adrenal glands, ovary, pituitary gland, prostate, testes, thyroid and uterus

Histopathological evaluation: Adrenal glands, epididymis, mammary area, ovary, pituitary gland, prostate, testes, thyroid and uterus

Deviations from the current guideline: Deviations from the current OECD guideline 409 include the lack of organ weights of epididymides. Histopathological evaluation was did not consider accessory sex organs.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Chronic and carcinogenicity studies in OECD Conceptual Framework level 4

Report:	[redacted] 1995. Fenpropidin: 12-Month chronic oral toxicity study in Beagle dogs. Report number: [redacted]. Syngenta file number: CGA114900_0427.

Guidelines: OECD 452.

GLP: Yes.

Study design: Fenpropidin was administered to groups of 4 Beagle dogs/sex/dose for 52 weeks via gelatine capsules at dose levels of 0 (control), 2, 5 and 20 mg/kg/day.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Organ weights: Adrenal glands, ovary, testes and thyroid (with parathyroid).

Histopathological evaluation: Adrenal glands, epididymis, ovary, pituitary gland, prostate, testes, thyroid (with parathyroid), uterus and vagina

Deviations from the current guideline: Deviations from the current OECD guideline 452 include the lack of organ weights of epididymides and uterus.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Increased adrenal weights in the low and mid dose group males as well as increased absolute thyroid weights in high dose males are not considered of toxicological relevance in the absence of a dose-response and pathological correlates.

Table 6.8.3-3 12-month dog study with fenpropidin: selected organ weights

		Males				**Females**			
		0	**2**	**5**	**20**	**0**	**2**	**5**	**20**
Carcass [kg]		10.85	11.55	10.63	11.25	11.53	10.55*	11.16	10.44
Adrenal	absolute [g]	1.399	1.282	1.712*	1.619	1.697	1.825	2.054	1.967
	relative to bw [‰]	0.130	0.111*	0.161*	0.144	0.147	0.173	0.185	0.188
Thyroid	absolute [g]	0.801	0.843	0.875	1.080*	0.957	0.860	1.156	1.062
	relative to bw [‰]	0.076	0.073	0.083	0.096	0.083	0.091	0.103	0.105

* $p<0.05$ (Wilcoxon test, difference from control group mean)

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] *et al*. 1989. Ro 12-3049/000 - Potential tumorigenic and toxic effects in prolonged dietary administration to rats (according to OECD and EPA guidelines). Report number: [redacted]. Syngenta file number: CGA114900_0109.

Guidelines: OECD 453.

GLP: Yes.

Study design: Fenpropidin was administered to groups of 70 (80 at high dose) Crl:CD (SD) BR rats/sex/dose for up to 104 weeks via the diet at inclusion levels of 0 (control), 5, 25, 125 and 625 ppm. Owing to excessive toxicity at the high dose, the dose levels were reduced to 2, 10, 50 and 250 ppm from week 8 onwards. 10 animals/sex/group were used for an interim kill at 52 weeks, 10 animals/sex/group were used for blood sampling and urine analysis, the remaining animals were sacrificed at the end of the study.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Organ weights: Adrenal glands, ovary, pituitary gland, testes and thyroid (with parathyroid)

Histopathological evaluation: Adrenal glands, epididymis, mammary gland, ovary, pituitary gland, prostate, seminal vesicles, testes, thyroid (with parathyroid) and uterus.

Deviations from the current guideline: The recorded weights of organs were limited, omitting the epididymis, and uterus. Histopathological examination did not include the vagina.

Effects on endpoints relevant for assessment of potential for endocrine disruption

None.

At the terminal sacrifice lower pituitary weights were noted in 50 and 250 ppm females and significantly lower when adjusted for body weight. The absolute values had a broad range (11-406 mg, 17-451 mg, 17-301 mg, 8-376 mg, 12-272 mg for the individual groups of females). However, in absence of any corroborative histopathological changes in the pituitary gland, the observed weight variations are considered to be of no toxicological relevance.

Higher mean absolute ovary weights compared to control were noted in females of the three highest dose groups. There was no apparent dose-response and the weights were demonstrated to be within the historical control range for this organ. Therefore, these apparent differences were considered incidental and unrelated to treatment.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard chronic toxicity/carcinogenicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 1983. Ro-12-3049/000: 80 Week oral (dietary) combined carcinogenicity and toxicity study in the mouse. Report number: [redacted]. Syngenta file number: CGA114900_0110.

Guidelines: OECD 453.

GLP: Yes.

Study design: Fenpropidin was administered to groups of 63 Crl:CD-1(ICR)BR mice/sex/dose for up to 80 (males) / 90 (females) weeks via the diet at inclusion levels of 0 (control), 30, 100, 300 and 1000 ppm. 12 animals/sex/group were sacrificed after 52 weeks of treatment and the same parameters were investigated as for the terminal kill.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Organ weights: Ovary and testes

Histopathological evaluation: Adrenal glands, epididymis, mammary gland, ovary, pituitary gland, prostate, seminal vesicles, testes, thyroid (with parathyroid) and uterus

Deviations from the current guideline: Relative to the current OCED 453 guideline, the organ weights of adrenals, thyroid, epididymis, ovaries and uterus were not recorded.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard chronic toxicity/carcinogenicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Developmental studies in OECD Conceptual Framework level 4

Report:	[redacted] 1981. Embryotoxicity study in rats with oral administration of Ro 12-3049/000 - Phase II teratology study. Report number: [redacted] Syngenta file number: CGA114900_0124.

Guidelines: Equivalent to OECD 414 (1981).

GLP: No. This study was performed prior to the GLP certification of laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance statement is included in the report.

Study design: Groups of 40 mated female Füllinsdorf albino (SPF) rats/dose were administered fenpropidin via the diet at nominal dose levels of 0 (control), 20, 50 and 125 mg/kg/day from gestation days 7-16, inclusive to assess pre- and post- natal development. The dams were divided into 2 subgroups. One cohort was sacrificed on gestation day 21 for full examinations of the uterine contents and foetal examination (external, visceral and skeletal). The other subgroup was allowed to litter and dams and pups were sacrificed on postnatal day 23.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Pregnancy parameters (e.g. % pregnant)

Number of *corpora lutea*

Number of implantations

Number of abortions/resorptions/intra-uterine deaths

Sex ratio

Foetal abnormalities

Deviations from the current guideline: The OECD 414 guideline was updated on 25 June 2018, to include measurement of maternal thyroid hormones (T4, T3 and TSH) and ano-genital distance (AGD) in rats, neither of which were considered in the current study. Gravid uterus weights were not recorded. Furthermore, there were some deviations relative to the contemporaneous 2001 guideline, including the length of treatment, which

considered the major period of organogenesis rather than the full length of gestation. The skeletons were also only singly stained with Alizarin red, rather than double stained with Alcian blue. However, any significant changes in cartilage development would have been detected under light microscope. Furthermore, contrary to the current guideline, the study provided a robust assessment of postnatal development, as cohorts of animals were maintained to weaning.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

An increased number of incised neural arches compared to controls was observed at the mid and high dose. Although the low dose was also increased compared to controls, it was within historical control limits according to historical data. These findings can be considered as signs of a retarded ossification as a results of a decreased body weight gain in the dams. The bodyweight development of the mid dose dams was moderately reduced during treatment (gestation day 7-16), whereas the high dose dams lost bodyweight (the absolute body weights day 0-21were decreased by 3 and 10% for mid and high dose, respectively, when compared to controls).

In the second subgroup no effects were observed on the reproductive parameters, body weights, weight development, or viability. Organ weights were not affected by treatment.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard developmental toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 1994. CGA 114900 Technical: rat oral teratogenicity. Report number: [redacted]. Syngenta file number: CGA114900_0324.

Guidelines: OECD 414.

GLP: Yes.

Study design: Groups of 24 pregnant female Tif:RAIf (SPF) rats/dose were administered fenpropidin by oral gavage at dose levels of 0 (control), 10, 60 and 90 mg/kg/day from gestation days 6-15, inclusive. Dams were sacrificed on gestation day 21 and there were full examinations of the uterine contents/pups.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Pregnancy parameters (e.g. % pregnant)

Number of *corpora lutea*

Number of implantations

Number of abortions/resorptions/intra-uterine deaths

Sex ratio

Foetal abnormalities

Deviations from the current guideline: The OECD 414 guideline was updated on 25 June 2018, to include measurement of maternal thyroid hormones (T4, T3 and TSH) and ano-genital distance (AGD) in rats, neither of which were considered in the current study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard developmental toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] and [redacted] 1981. Embryotoxicity study in rabbits with oral administration of Ro 12-3049/000. Phase II – teratological study. Report number: [redacted]. Syngenta file number: CGA114900_0123.

Guidelines: OECD 414.

GLP: No. This study was performed prior to the GLP certification of laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance statement is included in the report.

Study design: Groups of 20 time-mated female Swiss Hare rabbits/dose were administered fenpropidin by oral gavage at dose levels of 0 (control), 5, 12 and 30 mg/kg/day from gestation days 7-19, inclusive. Dams were sacrificed on gestation day 30 and there were full examinations of the uterine contents/pups.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

Pregnancy parameters (e.g. % pregnant)

Number of *corpora lutea*

Number of implantations

Number of abortions/resorptions/intra-uterine deaths

Sex ratio

Foetal abnormalities

Deviations from the current guideline: There were some deviations relative to the contemporaneous 2001 guideline, including the length of treatment, which considered the major period of organogenesis rather than the full length of gestation. The skeletons were also only singly stained with Alizarin red, rather than double stained with Alcian blue. Despite the lack of cartilage staining in this study, any significant changes would have been detected under light microscope.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard developmental toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 2011. Fenpropidin - A prenatal developmental toxicity study in New Zealand White rabbits. Report number: [redacted]. Syngenta file number: CGA114900_10474.

Guidelines: OECD 414.

GLP: Yes.

Study design: Groups of 25 time-mated female New Zealand White rabbits/dose were administered fenpropidin by oral gavage at dose levels of 0 (control), 5, 10 and 20 mg/kg/day from gestation days 7-28, inclusive. Dams were sacrificed on gestation day 29 and there were full examinations of the uterine contents/pups.

Endpoints relevant for assessment of potential for endocrine disruption

Gross macroscopic observations

Pregnancy parameters (e.g. % pregnant)

Number of *corpora lutea*

Number of implantations

Number of abortions/resorptions/intra-uterine deaths

Sex

Foetal abnormalities

Deviations from the current guideline: None.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

Skeletal malformations were noted in 0 (0), 1 (1), 0 (0), and 4 (4) foetuses (litters) in the control, 5, 10, and 20 mg/kg bw/day groups, respectively. Three foetuses in the 20 mg/kg bw/day group had severely malaligned sternebra(e). The foetal and litter incidences of this finding were not statistically significant when compared to the concurrent control group, however, the mean litter proportion of this finding in the 20 mg/kg bw/day group (1.6 % per litter) exceeded the maximum mean value in the WIL historical control data for definitive studies (1.0% per litter). None-the-less, the incidence of this single finding is only slightly outside the background range, is occurring in the absence of any other foetal malformations, and was not observed in the original developmental toxicity studies in Swiss Hare rabbits ([redacted] and [redacted] 1981). It can therefore be concluded that the incidence of this finding in this study is very unlikely to be related to treatment and can be considered to be a spontaneous finding.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard developmental toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 2011. Fenpropidin - A dietary developmental neurotoxicity study in Wistar Han rats. Report number: [redacted]. Syngenta file number: CGA114900_50018.

Guidelines: OECD 426.

GLP: Yes.

Study design: Fenpropidin was offered on a continuous basis as a dietary admixture to 3 groups of female Crl:WI(Han) rats (consisting of up to 30 rats/group) from gestation day 6 through lactation day 21 at dietary concentrations of 0 (control) 40, 100, and 400 ppm. All females were allowed to deliver and rear their offspring to lactation day 21.

Endpoints relevant for assessment of potential for endocrine disruption:

Gross macroscopic observations

% Pregnant

Duration of gestation

Parturition

Implantation sites

Litter size (reductions in litter size can be indicative of abortions/resorptions/intra-uterine deaths)

Sex ratio

Sexual maturation

Age and weight at preputial separation

Age and weight at vaginal opening

Motor activity (including habituation), motor and sensory function, learning and memory in offspring

Deviations from the current guideline: None.

Effects on endpoints relevant for assessment of potential for endocrine disruption

None.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard developmental neurotoxicity toxicity study, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Reproductive studies in OECD Conceptual Framework level 5

Report:	[redacted] *et al.* 1987. RO 12-3049/000: Effects upon reproduction performance of rats treated continuously throughout two successive generations. Report number: [redacted]. Syngenta file number: CGA114900_0125.

Guidelines: OECD 416.

GLP: Yes.

Study design: Groups of 30 Sprague-Dawley derived CD rats/sex/dose were fed diet containing 0, 6.25, 25 or 100 ppm fenpropidin. Exposure started about 13 weeks (92 and 100 days for the F0 and F1, respectively) before the first mating period in both generations (1:1 mating). The F1A and F2A pups were reared to day 25 *post partum*. Then the parental animals were given at least 10 days before second mating. The F1 parental generation

was selected from the F1B litters. To standardize litter size, litters with more than 9 pups were culled by random selection to yield 4 males and 4 females per litter, whenever possible on day 4 *post partum*.

Endpoints relevant for assessment of potential for endocrine disruption

Gross macroscopic observations

Reproductive performance:

Pre-coital interval

Mating

Fertility

Duration of gestation

Parturition

Litter size (reductions in litter size can be indicative of abortions/resorptions/intra-uterine deaths)

Oestrus cyclicity

Sex ratio

Organ weights: Adrenal glands, epididymis, ovary, pituitary gland, prostate, seminal vesicles, testes, thyroid, uterus and vagina

Histopathological evaluation: Epididymis, ovary, prostate, seminal vesicles, testes, thyroid, uterus and vagina

Deviations from the current guideline: Relative to OECD 416 (2001), no systemic effects were accomplished at the highest dose (which is in disagreement with the guideline). Food consumption was only recorded during the premating period. Number of implantations, corpora lutea and post-implantation loss was not investigated. Ovarian primordial follicle count, sperm parameters and sexual maturation were not specifically investigated in this study.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

None.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity test, with endpoints that may be influenced by the endocrine system, but are also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	Indicative – No evidence of an effect relevant to the assessment of endocrine disruption

Report:	[redacted] 2003. Rat dietary two-generation reproduction study. Report number: [redacted]. Syngenta file number: CGA114900_4693.

Guidelines: OECD 416.

GLP: Yes.

Study design: Groups of 30 HanIbm: WIST rats/sex/dose were fed diet containing 0, 25, 100, 500 and 1000 ppm fenpropidin. Animals were exposed continuously in two successive generations. Exposure started 10 weeks before the mating period in both generations (1:1 mating). The F1 generation was selected from the litters of the F0 generation. To standardize litter size, litters with more than 9 pups were culled by random selection to yield 4 males and 4 females per litter, when ever possible on day 4 *post partum*.

Endpoints relevant for assessment of potential for endocrine disruption

Gross macroscopic observations

Reproductive performance:

Pre-coital interval

Mating

Fertility

Duration of gestation

Parturition

Litter size (reductions in litter size can be indicative of abortions/resorptions/intra-uterine deaths)

Sexual maturation

Age and weight at preputial separation

Age and weight at vaginal opening

Oestrus cyclicity

Sperm analysis

Motility

Count (spermatids per testis weight, sperm per cauda epididymis)

Morphology

Sex ratio

Organ weights: Adrenal glands, epididymis, ovary, pituitary gland, prostate, seminal vesicles, testes, thyroid (with parathyroid) and uterus

Histopathological evaluation: Adrenal glands, epididymis, ovary, pituitary gland, prostate, seminal vesicles, testes, thyroid (with parathyroid), vagina and uterus

Deviations from the current guideline: Only minor deviations i.e body weights of F1 generation was first recorded day 2 instead of day 1, data on food efficiency and *corpora lutea* was not included in the report.

Effects on endpoints relevant for assessment of potential for endocrine disruption:

In F1 male pups, balanopreputial separation was statistically significantly delayed at 1000ppm (25.3 days for control and 28.0 days). At PND 21 mean bodyweights of the high dose group were 33% lower than controls and these pups were still lighter than controls at the time of maturation. In F1 female pups of the 500ppm and 1000 ppm groups, a delay in vaginal opening was noted (32.5 days for control and 37.1 and 42.0 days for 500 ppm and 1000ppm, respectively). The mean bodyweight gains of these dose groups were significantly lower during lactation, resulting in reduced bodyweights of 14% and 33% below controls at PND21. At the day of vaginal opening, bodyweights were not relevantly different between controls and treated groups. Therefore, the observed delays in sexual maturation are considered secondary to the lower bodyweight in these groups. This is further discussed in the assessment of lines of evidence in section 5.1.

Changes in absolute and relative organs weights were observed in F0 and F1 high dose animals and were mainly related to decreased bodyweight in these animals. No histopathological correlates were observed and therefore, these changes are not considered to have toxicologically significance.

Increased incidences and severity of cortical fatty change of the adrenal glands were noted in F0 and F1 adult females receiving 500 and 1000 ppm. This most likely represents a stress response, with significant reductions in body weight gain noted for females in these groups, particularly throughout lactation (i.e. the period immediately prior to termination and collection of tissue for histopathology). The lack of any direct effect on the adrenals on this study is supported by the lack of any effect on adrenal histopathology in adult males and the lack of any effects on adrenal pathology in F1 and F2 pups of either sex (Table 4.3-3).

Lymphohistiocytic infiltration in the prostate was decreased in F0 and F1 adult males receiving 500 and 1000 ppm and considered to be secondary to the depressed bodyweight development.

Table 6.8.3-4 Two generation reproduction study with fenpropidin: histopathological findings in endocrine organs in adult F0 and F1 animals

			males					**females**				
		ppm	**0**	**25**	**100**	**500**	**1000**	**0**	**25**	**100**	**500**	**1000**
F0	adrenals: cortical fatty change	incidence	12/30	11/30	8/30	9/30	9/30	6/30	7/30	8/30	**14/30**	**26/30**
		grading	(2.3)	(1.8)	(1.9)	(1.7)	(2.1)	(1.5)	(1.7)	(2.1)	(2.3)	(2.1)
	Prostate: lymph. Inflitration	incidence	12/30	12/30	10/30	**2/30**	**6/30**					
		grading	(2.3)	(2.1)	(2.8)	(2.0)	(2.0)					
F1	adrenals: cortical fatty change	incidence	23/30	-	-	-	20/30	10/30	15/30	16/30	**19/30**	**21/30**
		grading	(1.5)	-	-	-	(1.4)	(2.0)	(1.7)	(2.4)	(2.6)	(2.8)

	Prostate: lymph. Inflitration	incidence	17/30	10/30	17/30	**6/30**	**4/30**	
		grading	(1.9)	(2.3)	(2.0)	(2.2)	(1.5)	

Lower mean sperm counts noted for F0 males (lower spermatids per gram testis in the 25 and 1000 ppm groups and lower sperms per epididymis in the 1000 ppm group) were attributed to the higher than normal mean values for the control animals (compared to control data from previous studies which reported 71.9 million spermatids per g testis and 134.2 million sperms per g cauda epidermis) and not considered an effect of treatment. This is supported by the lack of any effects on sperm motility and morphology, any histopathological effects on the testes and the absence of any treatment-related effects on sperm counts of F1 males (Table 4.3-4).

Table 6.8.3-5 Two generation reproduction study with fenpropidin: sperm counts

	F0					**F1**				
ppm	**0**	**25**	**100**	**500**	**1000**	**0**	**25**	**100**	**500**	**1000**
Sperm counts [1 x 106/g tissue]										
Testis (spermatids)	82.6	74.6**	76.6	77.9	66.0**	77.6	80.7	82.6*	84.1**	79.2
Causa epididymides (sperm cells)	182.6	193.8	204.8	217.7#	158.8#	176	162.1	164.2	155.8*	160.9

* p <0.05, ** p<0.01 (Anova + Dunnett test); # p <0.05 (Kruskal-Wallis + Dunnett test)

Lower implantation sites compared to control were noted in F0 dams receiving 25, 500 and 1000 ppm. This was not considered an effect of treatment as they were within the range of historical controls, while the concurrent control is near the upper limit of historical controls (14.1 vs. 12.2-14.2) and all the treatment groups towards the lower end with no dose-response (12.4, 12.3 and 12.3 for 25, 500 and 1000ppm, respectively). In addition the mean number of pups delivered in the 25, 100 ppm groups was higher than the mean implantation sites, due to a few uncountable *corpora lutea* in these groups. The slightly higher incidence of pup loss during days 1-4 *post partum* in the high dose group was mainly due to one dam that lost 8 pups and is therefore considered unrelated to treatment. The lower number of pups surviving from day 4 to 21 *post partum* in the 500 ppm group was due to one total litter loss and was therefore considered to be unrelated to treatment.

Lower implantation sites and a corresponding lower number of pups delivered compared to control were noted in F1 dams receiving 1000 ppm. However, owing to the lack of any effect on any other reproductive parameters, including number of successful matings/pregnant animals, fertility index, live birth index and pup survival, this was not considered an effect of treatment.

CONCLUSIONS

Reliability score	1: Reliable without restrictions
Relevance score	Medium (Standard repeat dose toxicity test, with endpoints that may be influenced by the endocrine system, but are also known to be affected by

	other factors, e.g. toxicity, etc.)
Overall significance	Indicative –Evidence of an effect potentially relevant to the assessment of endocrine disruption
Effects of potential relevance	Delay in sexual maturation

INTEGRATION AND ASSESSMENT OF LINES OF EVIDENCE

Lines of evidence for endocrine disrupting potential relevant to humans

The following line of evidence has been assembled through interrogation of the data assessed in Section 4 of this document:

Delay in sexual maturation in a two-generation reproductive toxicity study

Sexual maturation was delayed with statistical significance for male F1 pups in the 1000 ppm dose group (25.3 days for control and 28.0 days for 1000 ppm). F1 males in the 1000 ppm group had consistently lower body weights compared with controls in the period leading up to the point of sexual maturation At weaning on day 21 *post partum* mean bodyweights of males F1 pups were 14% and 33% below control levels at 500 and 1000 ppm, respectively. F1 male pups were lighter than controls at the time of maturation (group mean body weight of 71.27 g and 48.37 g for control and 1000 ppm males respectively). Therefore, the observed delays are considered secondary to bodyweight effects. Figures 5.1-1 and 5.1-2 show the mean group bodyweight development of F1 males pups before and after.

Figure 6.8.3-1 Two-generation reproduction study with fenpropidin: bodyweight development in F1 male pups pre-weaning ([redacted] 2003)

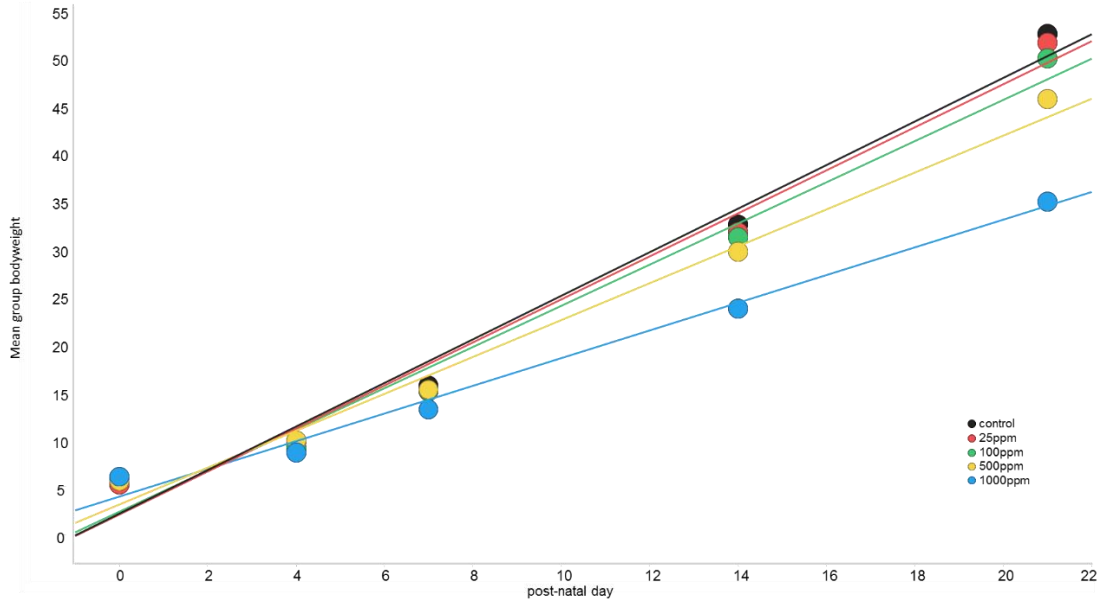
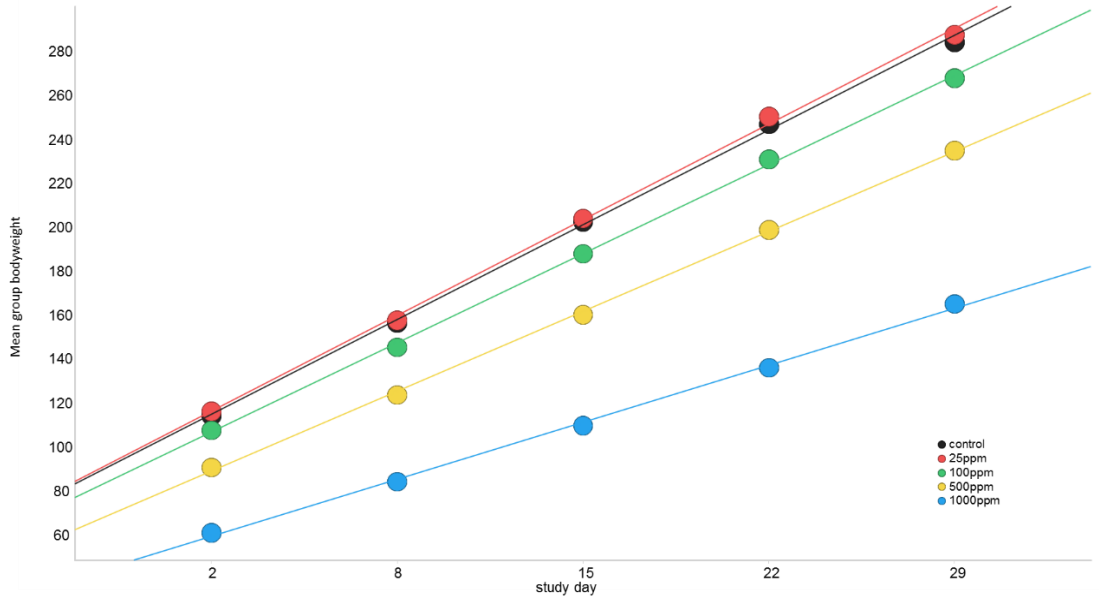


Figure 6.8.3-2 Two-generation reproduction study with fenpropidin: bodyweight development in F1 male post-weaning selected for mating ([redacted] 2003)



A delay in vaginal opening in female F1 pups in the 500ppm and 1000 ppm groups was observed (32.5 days for control and 37.1 and 42.0 days for 500 ppm and 1000ppm, respectively). This is considered to be secondary to a reduction in body weight gain during the lactation phase (i.e. postnatal day (PND) 1 to 21), which showed a statistically significant reduction from PND 4 onwards for 500ppm and from PND 0 for 1000ppm ($p<0.01$). The group mean pup body weight at weaning was 14% and 33% below control levels at 500 and 1000 ppm, respectively. At the day of sexual maturation the bodyweights in these F1 females were not relevantly higher than controls (102.6 g for control and 111.1 g and 105.8 g for 500 ppm and 1000ppm, respectively). Figure 6.1-2 shows the mean group bodyweight development of F1 females pups and the mean age and bodyweight at vaginal opening. Therefore, the observed delays reflect excessive reductions in bodyweight. Figures 5.1-3 and 5.1-4 show the mean group bodyweight development of F1 males pups before and after.

Figure 6.8.3-3 Two-generation reproduction study with fenpropidin: bodyweight development in F1 female pups pre-weaning ([redacted] 2003)

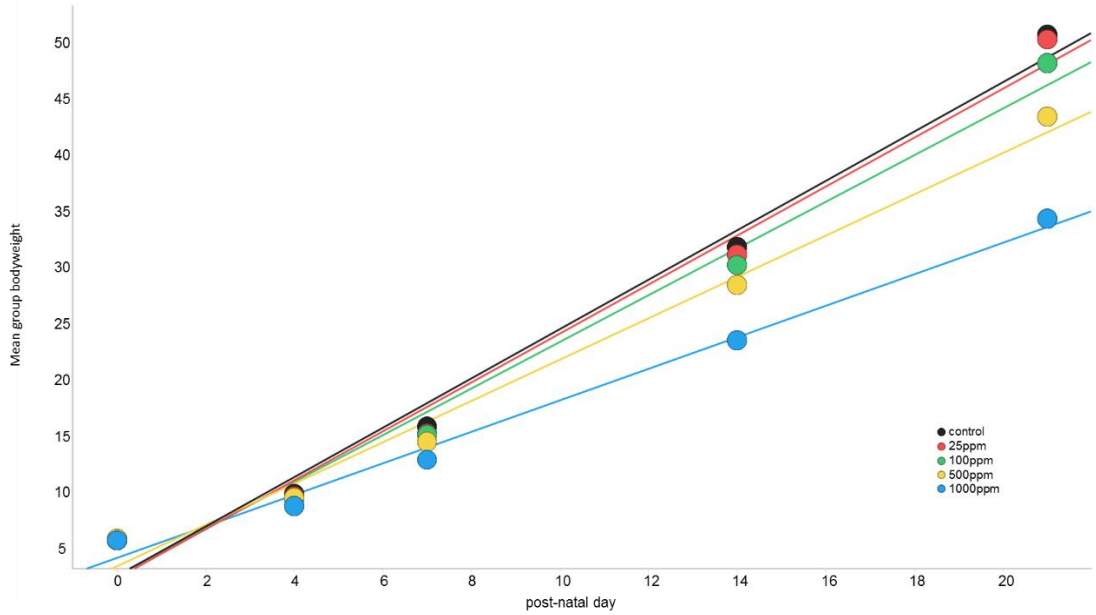
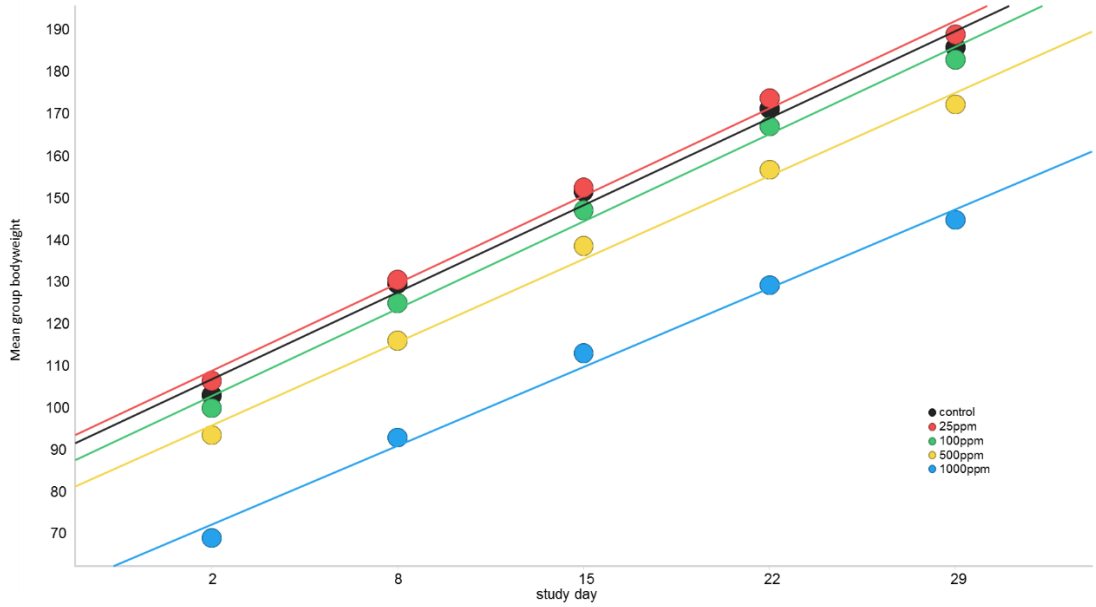


Figure 6.8.3-4 Two-generation reproduction study with fenpropidin: bodyweight development in F1 females post-weaning selected for mating ([redacted] 2003)



The delay in sexual maturation is secondary to a reduction in bodyweight, rather than a direct influence of fenpropidin. Bodyweight and growth rate play a significant role in the onset of puberty (Goldman *et al*. 2000; Glass *et al*. 1976) and pubertal delays are induced by dietary restriction in rats (Wilen & Naftolin 1978; Holehan & Merry 1985). Sexual development is initiated by a shift in the frequency of electrical activity in gonadotropin-releasing hormone expressing (GnRH) neurons of the hypothalamus, which control the release of reproductive hormones from the pituitary. The strongest activators of GnRH neurons are Kisspeptin, Neuropeptide Y, Adiponectin, and white adipose tissue (leptin), which have been demonstrated to positively feedback at the hypothalamus, triggering sexual development in humans and rodents (Pinilla *et al*. 2012). Consequently, the reductions in bodyweight and nutritional status are considered the most plausible mechanism for the apparent delay in sexual development observed in fenpropidin treated rats. This is supported by the lack of effects on reproduction parameter, notably mating and fertility indices. Furthermore, in the developmental neurotoxicity study by [redacted] (2011) no influence of fenpropidin on sexual maturation was observed in the absence of significant bodyweight effects.

The age and weight of F1 pups reaching sexual maturation landmarks is presented in Table 5.1-1. Table 5.1-2 presents the reproduction parameter of the F1 parental generation. Table 5.1-3 assembles the lines of evidence for delays in sexual maturation and EAS-mediated adversity in accordance with the ECHA-EFSA (2018) guidance.

Table 6.8.3-6 Two-generation reproduction study with fenpropidin: bodyweight development and sexual maturation in F1 pups ([redacted] 2003)

		males					**females**				
ppm		**0**	**25**	**100**	**500**	**1000**	**0**	**25**	**100**	**500**	**1000**
Bodyweight											
day 0	bodyweight [g]	5.7	5.7	5.7	5.8	5.7	5.4	5.4	5.4	5.6	5.4
	% of control		100	100	102	100		100	100	104	100
day 4°	bodyweight [g]	9.7	9.6	9.5	9.5	8.9**	9.5	9.2	9.1	9.2	8.5*
	% of control		99	98	98	92		97	96	97	89
day 4°°	bodyweight [g]	9.7	9.6	9.5	9.5	8.9**	9.5	9.3	9.1	9.2	8.5**
	% of control		99	98	98	92		98	96	97	89
day 7	bodyweight [g]	15.9	15.4	15.4	14.9*	13.0**	15.5	14.9	14.8	14.2	12.6**
	% of control		97	97	94	82		96	95	92	81
day 14	bodyweight [g]	32.3	31.6	30.8	29.2**	23.8**	31.5	30.8	29.9	28.1**	23.2**
	% of control		98	95	90	74		98	95	89	74
day 21	bodyweight [g]	52.4	51.9	49.9*	45.2**	35.3**	50.4	50	47.9	43.1**	34.0**
	% of control		99	95	86	67		99	95	86	67
bodyweight gain											
day 0-4	bodyweight gain [g]	4.07	3.84	3.74	3.74	3.17**	4.05	3.82	3.7	3.66	3.16**
	% of control		94	92	92	78		94	91	90	78
day 4-7	bodyweight gain [g]	6.16	5.82	5.92	5.35**	4.15**	5.98	5.64	5.71	5.03**	4.12**
	% of control		94	96	87	67		94	95	84	69
day 7-14	bodyweight gain [g]	16.44	16.15	15.41	14.27**	10.75**	16.24	15.98	15.25	13.9**	10.7**
	% of control		98	94	87	65		98	94	85	66
day 14-21	bodyweight gain [g]	20.08	20.32	19.03	15.95**	11.47**	18.94	19.3	18.03	14.9**	10.9**
	% of control		101	95	79	57		102	95	79	57
day 0-	bodyweight gain [g]	46.74	46.15	44.14*	39.39**	29.54**	45	44.6	42.52	37.5**	28.7**

21	% of control		99	94	84	63		99	94	83	64
sexual maturation											
age [days]		25.3	24.8	25.6	26.1	28.0##	32.5	31.6	33.7	37.1##	42.0##
bodyweight [g]		71.27	69.07	70.33	59.80**	48.37**	102.6	100.3	107.5	111.1*	105.8

* p <0.05, ** p <0.01 (Anova + Dunnett test); ## p <0.01 (Kruskal-Wallis + Dunnett test); ° preculling, °° postculling

Table 6.8.3-7 Two-generation reproduction study with fenpropidin: F1 - mating indices, survival, gestation and delivery parameters females ([redacted] 2003)

ppm	**0**	**25**	**100**	**500**	**1000**
Females					
placed with males and mated	30	30	30	30	30
inseminated	28	29	30	30	30
mating index [%]	93.3	96.7	100	100	100
pregnant	28	29	29	29	30
fertility index [%]	100	100	96.7	96.7	100
with defined day 0 pc	27	28	30	29	30
mating after days	2.6	2.8	2.4	2.9	3.0
without evidence of mating:	3	2	0	1	0
pregnant non pregnant	1	1	0	1	0
died pregnant / non pregnant	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
pregnant, not delivering	1	0	0	0	0
delivering	27	29	29	29	30
with liveborn pups with all pups	27	29	29	29	30
stillborn with stillborn pups	0	0	0	0	0
gestation index [%]	96.4	100	100	100	100
parturition index [%]	96.4	100	100	100	100
duration of gestation [day]	22.1	22.1	22.1	22.0	22.0
Males					
placed with females					
mated	28	29	30	30	30
mating index [%]	93.3	96.7	100	100	100
with females pregnant	28	29	30	29	30
fertility index [%]	100	100	96.7	96.7	100

Integrating and assembling the lines of evidence for delays in sexual maturation and EAS-mediated adversity can be found in Appendix_E

Dataset sufficiency in mammals

A dataset is considered to have sufficiently investigated EAS related adversity in relation to mammals if the parameters investigated in a two-generation reproductive toxicity study (OECD TG 416) conducted to the 2001 revision of this guideline have been assessed (EFSA-ECHA, 2018). A compliant study is available for fenpropidin. In conclusion, the potential of EAS related adversity is sufficiently investigated for fenpropidin.

Table 6.8.3-8: Comparison of the parameters sensitive to perturbation of the endocrine system required in the 2001 revision of OECD 416 and the two-generation toxicity study with fenpropidin.

Parameter	**Assessed in the two-generation study with fenpropidin**
Gross necropsy (macroscopic) observations	Yes
Reproductive performance: Pre-coital interval Mating (copulation indices) Fertility Gestation index Duration of gestation Parturition Litter size (reductions in litter size can be indicative of abortions/resorptions/intra-uterine deaths) Number of implantations	Yes
Number of *corpora lutea*	Yes
Sex ratio	Yes
Oestrus cyclicity	Yes
Sexual maturation (vaginal opening and preputial separation)	Yes

Parameter	**Assessed in the two-generation study with fenpropidin**
Ano-genital distance	Not triggered (delay in sexual maturation was considered bodyweight related)
Sperm analysis (number, motility and morphology)	Yes
Organ weights: uterus, ovaries, testes, epididymides, prostate, seminal vesicles with coagulating glands, pituitary, thyroid and adrenal glands	Yes
Histopathological examination: vagina, uterus (with cervix), ovaries, testis, epididymis, seminal vesicles, prostate (and coagulating gland)	Yes

A dataset is considered to have sufficiently investigated thyroid related adversity in relation to mammals if the parameters investigated in OECD TG 407, 408, 409 (and/or the one-year dog study, if available), 416, and 453 have been assessed. Assessment of the potential for fenpropidin to alter thyroid related parameters (histology and/or weight) has been conducted in studies spanning a range of durations (from 28-days to 104-weeks), in the mouse, rat and dog, and through multiple exposure routes (see data reviews in Section 4). It is therefore determined that the potential for thyroid related effects in relation to mammals has been sufficiently addressed.

Assessment of endocrine related adversity in mammals

Overall, no adversity based on EATS-mediated parameters is observed and thus, the first condition of the ED criteria is not met. Therefore, it is possible to conclude that the substance does not meet the ED criteria according to scenario 1a of the EFSA-ECHA guidance (2018).

Moa analysis

Not relevant. No effect on any parameter described as *'EATS-mediated'* or '*sensitive to, but not diagnostic of EATS'* in the guidance document was identified in the fenpropidin mammalian database.

Conclusions

The available data on fenpropidin do not indicate effects consistent with endocrine disruption. In accordance with the EFSA-ECHA (2018) Guidance, EATS-mediated parameters have been sufficiently investigated *in vivo*. Applying this Guidance Document, the conclusion can be drawn that fenpropidin does not meet the criteria for endocrine disruption with respect to humans.

RMS comments and conclusion: Regarding the data sufficiency, the RMS agrees with the notifier´s conclusion, that the ED data set can be considered as complete. The RMS is also in agreement with the conclusion that the ED criteria are not met and therefore Fenpropidin can be considered as non-ED substance.

NON-MAMMALIAN SPECIES

1. Data review

1.1 Existing Data in OECD Conceptual Framework level 1

The following studies conducted as part of the regulatory data package for registration of fenpropidin were not specifically designed for detection of endocrine disrupting properties, but as they cover life stages and endpoints relevant to growth and development they have been included in the current evaluation.

Report:	[redacted] (1989) The prolonged toxicity of RO12-3049/000 to Rainbow trout (*Salmo gairdneri*)., Project number [redacted] Syngenta File Number CGA114900/0071

Guidelines: OECD 204

GLP: Yes

Study design: Rainbow trout were exposed in groups of 10 to nominal concentrations of 0.032, 0.1, 0.32, 1.0 and 3.2 mg fenpropidin/L in a flow-through test system for 21 days at 14.0 °C. A dilution water control group and a solvent control group were also employed. Actual concentrations of fenpropidin were determined by chemical analysis on 9 occasions during the 21-day study. Mortality and symptoms of toxicity were recorded daily.

Endpoints relevant for assessment of potential for endocrine disruption

- growth

Effects on endpoints relevant for assessment of potential for endocrine disruption

None

CONCLUSIONS

Reliability score	1 – Reliable without restrictions
Relevance score	Medium (endpoint in a repeat dose toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity)
Overall significance	Low

Report:	[redacted] 2016. Fenpropidin T. G. Early Life-Stage Toxicity Test with Fathead Minnow (*Pimephales promelas*). Study No. [redacted]. [redacted] (Syngenta File No. CGA114900/10666)

Guidelines: OCSPP 850.1400, OECD 210, ASTM 1241-05

GLP: Yes

Study design: Newly fertilised *Pimephales promelas* embryos (30 per replicate, 4 replicates) were exposed under flow-through conditions to fenpropidin technical at nominal concentrations of 0.15, 0.38, 0.96, 2.4, 6.0 and 15 µg a.s/L (measured 0.079, 0.26, 0.82, 1.6, 3.8 and 10 µg a.s./L – 52 to 86% of nominal) as well as a dilution water control. Embryos were exposed for 4 days and after hatching thinned to 20 fry per replicate and exposed for a further 28 days. Effects on embryo survival, larval survival and larval growth (length and wet/dry weight) were recorded.

Endpoints relevant for assessment of potential for endocrine disruption

- Hatching success
- Larval growth (length and wet/dry weight)

Effects on endpoints relevant for assessment of potential for endocrine disruption

- Larval growth (length only) was significantly reduced at 10 µg/L

Effects on larval growth (length only) were observed the highest concentration tested of 10 µg/L without associated effects on survival.

CONCLUSIONS

Reliability score	**1** – Reliable without restriction
Relevance score	**Medium** (Endpoint in a multi-generation test, or other repeat dose standard toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	**Indicative for evidence of effects relevant for the assessment of endocrine disruption** (Screening assay studies of medium relevance and with reliability scores of 1 or 2)
Effects of potential relevance	**Reduced growth**

A mesocosm study conducted with a solo formulation of fenpropidin (A-7516 A) is also considered, as fish included in the study underwent chronic exposure to the active ingredient.

Report:	Neumann CH. 1997. CGA 114900 EC 750 (A-7516 A): Outdoor aquatic mesocosm study of the environmental fate and ecological effects. Report No. 95N001. Novartis Crop Protection AG, Basle, Switzerland (Syngenta File No. CGA114900/0500)

Guidelines:

Guidance Document on Testing Procedures for Pesticides in Freshwater Mesocosms. From the Workshop "A meeting of Experts on Guidelines for Static Field Mesocosm Tests", held at Monks Wood Experimental Station, Huntingdon, UK, July 3-4, 1991.

Workshop on Aquatic Microcosms for Ecological Assessment of Pesticides held at Wintergreen, Virginia, USA, Oct. 6-11, 1991.

European Workshop on Freshwater Field Tests (EWOFFT) held in Potsdam, Germany, June 25-26, 1991.

Draft OECD TG; Proposal for Freshwater lentic Field Testing of Xenobiotic Chemicals, issued by the Aquatic Model Ecosystem Advisory Commitee under the auspices of SETAC Foundation for Environmental Education, Pensacola, Florida, USA, 1993.

GLP: Yes

Study design: Ecological effects mesocosm study conducted in 12 foil-basins coated with clay (10 cm) buried in the ground, each with a volume of about 20 000 l, length 6 m (surface)/1 m (bottom), width 6 m (surface)/1 m (bottom), height: about 1.5 m (deep water zone)/0.5 m (shallow water zone). Three mesocosms were used as controls, one mesocosm for the highest test concentration, the other treatment groups consisted of two replicates. The mesocosms were randomly assigned to treatment. The mesocosms were filled with water and sediment from a natural pond. Sediment and water in the microcosm was introduced from a nearby supply pond. The sediment of each mesocosm and microcosm was characterised separately. Algae, zooplankton and other organisms were introduced with the water from the supply pond. Periphyton developed from natural populations on glass slides about 30-40 cm below the surface of each mesocosm (introduced March, 28). Macrophytes (*Myriophyllum spicatum*, *Potamogeton natans*, *Chara intermedia*) developed from rhizomes left from a study one year before or grew from the border of each pond where they had not been removed. Macroinvertebrates entered the mesocosms via egg deposition of adult insects. Invertebrate refugia were placed in the center of each mesocosm (April, 11) to allow colonisation. 20 juvenile bluegill sunfish (*Lepomis macrochirus*) about 2.0-2.5 cm in size were stocked into the meso/microcosms (April, 11). The test substance was applied to mesocosms as over-spray using a Knapsack sprayer, in sequence from the lowest to the highest treatment level. The study duration was 25 weeks after 1st application (i.e. from April until October).

Endpoints relevant for assessment of potential for endocrine disruption

- Fish length and weight
- Gonadal weight/gonadosomatic index

Effects on endpoints relevant for assessment of potential for endocrine disruption

- none

While the study was conducted with a (solo) formulation containing fenpropidin, the study was of a duration where it can be expected that chronic exposure of the fish was predominantly to the active substance, and the study can be considered to be 'as a.s.'. There were no effects on fish growth (length and weight) or gonadosomatic index, though the degree of variability in this parameter (combined with the low degree of replication in the study) means that it is likely only large effects on this parameter could have been detected. The study did not report sex (and consequently sex ratio) of the fish sampled at the end of the study, and it is not clear from the report whether the fish had undergone sexual maturation. Combining gonadosomatic index for mixed sex groups would increase variability in this parameter. In conclusion, the responses reported for Bluegill sunfish from this chronic study did not indicate any endocrine-mediated adversity, though the endpoints measured lacked the diagnostic capacity that would be expected of a study designed for assessing endocrine effects.

CONCLUSIONS

Reliability score	**1** – Reliable without restriction
Relevance score	**Medium** (Endpoint in a multi-generation test, or other repeat dose standard toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	**Indicative for no evidence of effects relevant for the assessment of endocrine disruption** (repeat dose studies of medium relevance and with reliability scores of 1 or 2)
Effects of potential relevance	**none**

1.2. Non-mammalian studies in OECD Level 4

Report:	[redacted] and [redacted] 1992. Ro 12-3049/000 The Effect of Dietary Inclusion on Reproduction in the Bobwhite Quail Volume I. Study report no. [redacted]. [redacted] (Syngenta File No. CGA114900/0133)

Guidelines: OECD 206

GLP: Yes

Study design: Adult 40 week old bobwhite quails (*Colinus virginianus*) were exposed to dietary concentrations of fenpropidin (nominal 0, 30, 180 and 1080 ppm). Measured concentrations in diets were stable at 93.0-100.1% of nominal. Birds were exposed for 21 weeks (11 weeks prior to egg production and 10 weeks during

egg production). Twenty replicates per treatment with 1 male:1 female per replicate. Birds were observed for signs of mortality, abnormal behaviour (daily), body weight, egg production, egg shell thickness, egg quality, viability of embryos, hatchability, number and weight of hatchlings, hatchling survival and gross pathology.

Endpoints relevant for assessment of potential for endocrine disruption

- Egg production, egg shell thickness, egg quality
- Viability of embryos
- Hatchability, number and weight of hatchlings
- Gross pathology

Effects on endpoints relevant for assessment of potential for endocrine disruption

- Egg production, mean egg weight, viable embryos as a proportion of eggs set, hatchlings of eggs set, 14 day survivors per female and initial bodyweight of hatchlings were all significantly reduced at the top concentration of 1080 ppm
- The proportion of female birds laying eggs showed a decreasing trend across the dose range

Observations of reduced reproduction were seen in the highest concentration tested of 1080 ppm without associated effects on systemic toxicity. The day 14 chick body weights were also significantly reduced at 30, 180 and 1080 ppm, although the significance level at 30 and 180 ppm was reduced, compared to the significance level at 1080 ppm. Since the differences reported between the 30 and 180 ppm groups and the control were relatively small and no differences were observed in any of the other reproductive parameters, these effects were not considered as biologically significant, with a NOEL of 180 ppm reported.

CONCLUSIONS

Reliability score	**1** – Reliable without restrictions
Relevance score	**Medium** (Endpoint in a multi-generation test, or other repeat dose standard toxicity test, which may be influenced by the endocrine system, but is also known to be affected by other factors, e.g. toxicity, etc.)
Overall significance	**Indicative for evidence of effects relevant for the assessment of endocrine disruption** (Screening assay studies of medium relevance and with reliability scores of 1 or 2)
Effects of potential relevance	**Reduced reproduction**

2. Integration and assessment of lines of evidence for endocrine disrupting potential relevant to non-target organisms

2.1 Lines of evidence for adversity

According to the Criteria an adverse effect relevant to non-target organisms *"is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences"*

Effect on endpoints relevant to survival, growth, development and reproduction in available ecotoxicology studies may therefore be regarded as relevant to establishing evidence for adverse effects. However, as indicated in the Guidance document with respect to validated test guidelines informative for endocrine disrupting properties (Table 15), such endpoints can only be considered '*Sensitive to, but not diagnostic of, EATS'*.

2.1.1 Survival

One avian reproduction study (OECD 206) is available for fenpropidin, in the Bobwhite quail ([redacted] and [redacted] 1992). No effects on parental survival were reported at any dose, while in offspring there were reductions in % viable embryos/eggs set, % hatchlings/eggs set, and number of 14 day survivors per female in the top dose, 1080 ppm.

Three studies in fish are available: a prolonged toxicity study (OECD 204) in Rainbow trout ([redacted] 1989), a fish early life stage (ELS, OECD 210) study in the Fathead minnow ([redacted] 2016), and the mesocosm study including Bluegill sunfish (Neumann 1997). In the prolonged toxicity test by [redacted] (1989), survival was significantly affected at the top two test concentration (1.0 and 3.2 mg/L). Behaviour was also affected at these test concentrations, with observations of lethargy and increased pigmentation. These observations indicate that the reduced survival in fish exposed to fenpropidin test was due to overt/systemic toxicity, in a study designed to determine NOEC/LOECs for risk assessment. In the early life stage test in the Fathead minnow there was no effect on survival reported, which is not inconsistent with the OECD 204 test, considering the concentration range tested. No mortality or behavioural alterations in the Bluegill sunfish exposed for 25 weeks in the mesocosm study was reported by Neumann (1997)

2.1.2 Growth

Hatchling body weight is the apical endpoint relevant to growth in avian reproduction studies (OECD 206 and similar). In the study on effects of fenpropidin on Bobwhite quail ([redacted] and [redacted] 1992), there was a significant reduction in hatchling bodyweight at the top test concentration (1080 ppm) on day 0 (hatching) and day 14. This was concurrent with a reduction in hatchling survival at this test concentration (see above), and is clearly an indication of the onset of systemic toxicity in the offspring.

Length and wet/dry weight are the apical endpoints relevant to growth in the fish prolonged toxicity test (OECD 204). In the study in Rainbow trout by [redacted] (1989), no effects on length or body weight were reported at

any test concentration. In contrast, in the fish early life-stage test (OECD 210) by [redacted] (2016), there was a significant reduction in body length, but not wet weight, at the top test concentration (10 ¯g/L). Differences in growth/survival responses in these two studies may represent different life stage and or species sensitivity, and should be considered as part of a continuum of indications of systemic toxicity (growth, behaviour, survival) with increasing exposure to fenpropidin. No effects on length or weight of fishes were observed in the mesocosm study by Neumann (1997).

Growth was therefore affected by fenpropidin in birds and fish, but in studies not specifically designed for identification of endocrine disrupting properties. Moreover, the growth endpoints in these ecotoxicity test guidelines are well established indicators of systemic toxicity, and toxicity through other non-endocrine modes of action, as acknowledged by the classification of such endpoints in the Appendix E spreadsheet as 'Sensitive to but not diagnostic of'. These studies therefore provide no evidence of effects of fenpropidin on growth in fish or birds through endocrine disruption.

2.1.3 Development

Hatchability is the apical endpoint relevant to development in the avian reproduction test (OECD 206), though this endpoint also integrates embryonic survival. In the study in Bobwhite quail ([redacted] and [redacted] 1992) there was a reduction in the percentage eggs hatched/eggs set, though no significant reduction in the absolute number of eggs hatched, at the top test concentration. This correlated with the % of viable embryos/eggs set and the reduction in hatchling body weight, suggesting that the response was indicative of offspring systemic toxicity.

Hatching success is the apical endpoint relevant to development in the fish early life-stage test (OECD 210). In the study in the Fathead minnow ([redacted] 2016), there was no effect of fenpropidin exposure on hatching success at any of the test concentrations.

The available studies in fish and birds therefore provide no evidence of effects of fenpropidin on development through endocrine disruption.

2.1.4 Reproduction

Apical endpoints relevant to reproduction in the avian studies include egg production, egg viability, egg quality (size, cracking), and gross pathology. In the study in the Bobwhite quail, there were reduced numbers of eggs laid, number eggs per female and reduced numbers of females laying at the top test concentration.

The fish early life stage study (FIFRA 72-4) does not cover the relevant life stage to be informative on reproduction. Reproductive activity and sex ratio of fish in the mesocosm study were not reported, and there were no effects on gonadosomatic index in the fish sampled at the end of the study (Neumann 1997)

The only available information on reproductive effects of fenpropidin in non-target organisms is therefore the single bird reproduction study. Considering the dose-concordance of effects on egg laying in the parental

generation with effects on offspring viability, it is reasonable to assume that these responses are collectively indicative of systemic toxicity.

Table 2.6.8.3-9 Assembled lines of evidence non-target organisms

	Grouping	Line(s) of Evidence	Species	Exposure	Route of exposure	Effect Concentration	Observed effects	Assessment	Assessment of integrated line of evidence	Modality
Integrated line of evidence for endocrine activity	No data available									
Integrated line of evidence for adversity	**EATS-mediated parameters**	None available								
	Sensitive-to-but not diagnostic of EATS	Growth	*Colinus virginianus*	21 w	Diet	1080 ppm	Reduced chick bodyweights on Day 0 and Day 14 at 1080 ppm; highest dose 1080 ppm	Not indicative of endocrine disruption – endpoint is sensitive to but not diagnostic of endocrine mediated effect, concurrent with reduced embryo viability, hatching rate and 14 day survival	No evidence for endocrine mediated adverse effects – all effects occurring in context of systemic toxicity	-
			Pimephales promelas	32 d	Water	10 µg/L	Decreased mean total length of surviving larvae at 10 ¯ g/L; no effect on body weight; highest dose 10 ¯ g/L	Endpoint is sensitive to but not diagnostic of endocrine mediated effect		
			Oncorhynchus mykiss	21 d	Water	n/a	No effect on body weight and length; highest dose 3.2 mg/L	No evidence		
			Lepomic macrochirus	25 w	Water	n/a	No effect on body weight or length of fish sampled at the end of the study	No evidence		

		Development	*Colinus virginianus*	21 w	Diet	1080 ppm	Reduction in the %hatchlings of eggs set at 1080 ppm; highest dose 1080 ppm	Not indicative of endocrine disruption – endpoint is sensitive to but not diagnostic of endocrine mediated effect, concurrent with reduced embryo viability, hatchling bodyweight and 14 day survival		
			Pimephales promelas	32 d	Water	n/a	No effect on the hatching success; highest dose 1080 ppm	No evidence		
		Reproduction (fecundity)	*Colinus virginianus*	21 w	Diet	1080 ppm	Reduced egg production at 1080 ppm; highest dose 1080 ppm	Not indicative of endocrine disruption – endpoint is sensitive to but not diagnostic of endocrine mediated effect, concurrent with reduced embryo viability, hatching rate, hatchling bodyweight and 14 day survival		
		Reproduction (fertility)	*Colinus virginianus*	21 w	Diet	1080 ppm	Reduction in the % of viable embryos of egg set and in the number of 14-day survivors per female and mean egg weight (g) at 1080 ppm; highest dose 1080 ppm	Not indicative of endocrine disruption – endpoint is sensitive to but not diagnostic of endocrine mediated effect, concurrent with reduced hatching rate, hatchling bodyweight and 14 day survival		
		Reproduction	*Lepomis macrochirus*	25 w	Water	n/a	No effect on gonadosomatic index	No evidence		
Evidence of general toxicity	Mortality		*Colinus virginianus*	21 w	Diet	n/a	No mortality (F0); highest dose 1080 ppm	No evidence		
						1080 ppm	Decreased embryo	Indicates that embryo/hatchling MTC is lower than for adults		

						viability and 14 d survival of offspring at highest dose 1080 ppm		Sufficient evidence of systemic toxicity to exclude endocrine mechanism as plausible mode of action for observed effects on development (embryo viability, hatching), reproduction and growth.
		Pimephales promelas	32 d	Water	n/a	No effect on the larvae survival at test termination; highest dose 10 ¯g/L	No evidence	
		Oncorhynchus mykiss	21 d	Water	1 mg/L	Increased mortality at 1.0 and 3.2 mg/L; 100% mortality at 3.2 mg/L; highest dose 3.2 mg/L	Test concentration evidently around/above MTC	
	Behaviour	*Colinus virginianus*	21 w	Diet	n/a	No abnormal behaviour; highest dose 1080 ppm	No evidence	
		Oncorhynchus mykiss	21 d	Water	1 mg/L	Increased lethargy and pigmentation at 1.0 and 3.2 mg/L; highest dose 3.2 mg/L	Test concentration evidently around/above MTC	

2.2 Lines of evidence for EATS-related endocrine activity

No *in vivo* mechanistic studies in non-target organisms are available for fenpropidin.

3. Analysis of evidence relevant to ED potential in non-target organisms

Studies recommended in the guidance document as sufficient for investigation of 'EATS-mediated adversity' in non-target organisms: fish full life study (MEOGRTS or equivalent and LAGDA) are not available for fenpropidin. Consequently, with reference to Figure 1 in the Guidance document, it is not possible to conclude from the available dataset that fenpropidin does not meet the ED criteria (Scenario 1a).

In assembling the lines of evidence for adversity in non-target organisms in the preceding section, it is clear that there is no evidence of EATS-mediated adversity in the available ecotoxicology studies. Parameters relevant to survival, growth, development and reproduction in the fish prolonged toxicity and early life stage toxicity studies, and the bird reproduction study may be considered 'sensitive to, but not diagnostic of, EATS', and were evidently indicative of systemic/overt toxicity. With reference to Figure 1, Scenario 2b is not relevant in the present evaluation.

As noted in Section 2, endocrine activity has not been observed in non-target organisms. With reference to Figure 2.1, Scenario 2b is not relevant in the present evaluation.

The Guidance states in Section 3.4.2. that 'to consider the EAS modalities for non-target organisms sufficiently investigated, preferably the fish short-term reproduction assay (FSTRA; OECD 229) should have been conducted, and to consider the T-modality sufficiently investigated, an Amphibian Metamorphosis Assay (AMA; OECD 231), should have been conducted.

4. MOA Analysis – Non-Target Organisms

Not relevant at present time. No effect on any parameter described as "EATS-mediated" in the guidance document was identified in the fenpropidin ecotoxicology database currently available.

5. Conclusions – Non-Target Organisms

Available ecotoxicology data do not indicate effects consistent with endocrine disruption, however, considering the available data in accordance with the EFSA-ECHA Guidance document (2018), there is not currently a fully adequate dataset to conclude on whether fenpropidin exhibits endocrine disrupting properties in non-target organisms according to the Endocrine Disruption Criteria (2018/605).

As first steps to make sufficient data available to reach a conclusion, Syngenta proposes to conduct the following studies:

1) Fish short-term reproduction assay (OECD 229) in the Fathead minnow.

2) Amphibian Metamorphosis Assay (OECD 231).

RMS comments and conclusion (RAR 2020):

Wild mammals

For the ED assessment for humans provided in Volume 3 CA B.6, it was concluded that EATS mediated parameters were sufficiently investigated and fenpropidin does not meet ED criteria.
This also applies to wild mammals as non-target organisms.

Non-target organisms other than mammals

1) T-modality

For the ED assessment through the T-modality for non-target organisms other than mammals, no specific studies were available. According to OECD 150, the ELS study with fish can provide some information for the T-modality when parameters like swim bladder inflation and time to metamorphosis are measured and reported. In the case of fenpropidin, time to hatch was measured and reported, however, no delays in hatch were observed at any treatment level.
Based on available information, it is concluded that the available evidence is not sufficient to conclude either on T-mediated endocrine activity or on the T-mediated adversity. Further data need to be generated.
According to the ECHA/EFSA GD (2018), scenario 2a (iii) should be selected:

Adversity based on T-mediated parameters	**Positive mechanistic OECD CF level 2/3 Test**	**Scenario**	**Next step of the assessment**	**Scenario selected** *(indicate with an "x" the scenario selected based on the assessed lines of evidence)*
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	X

According to the guidance, additional information should be generated. A level 3 study according to OECD TG 231 (AMA) is required.
However, considering that no T-mediated adversity was observed in mammals based on a complete dataset, a Xenopus Eleutheroembryonic Thyroid Assay (XETA) according to OECD TG 248 might be sufficient, instead of the AMA.

2) EAS-modality

For the ED assessment through the EAS-modality for non-target organisms other than mammals, one reproductive toxicity studies on birds (OECD TG 206), one prolonged toxicity study on fish (OECD TG 204) and one toxicity study with early life stages of fish (ELS) (OECD TG 210) was available.
However, these studies are only considered supportive for the lack of EAS-related adversity since they provide little information concerning potential EAS-related effects. Parameters relevant to survival, growth, development and reproduction in the fish prolonged toxicity and early life stage toxicity studies, and the bird reproduction study may be considered 'sensitive to, but not diagnostic of, EATS',
Overall, for EAS-modalities, in line with ECHA/EFSA GD (2018), the dataset is considered not sufficient for the assessment of E, A and S rndocrine activity and adversity.

According to the ECHA/EFSA GD (2018), scenario 2a (iii) should be selected:

Adversity based on T-mediated parameters	**Positive mechanistic OECD CF level 2/3 Test**	**Scenario**	**Next step of the assessment**	**Scenario selected** *(indicate with an "x" the scenario selected based on the assessed lines of evidence)*
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	X

According to the guidance, additional information should be generated (Scenario 2a(iii)). A level 3 study according to OECD TG 229 (FSTRA) is required.

2.6.9 Summary of medical data and information

Manufacturing employees in Switzerland are medically examined by a company physician at the beginning of their employment and then routinely on a regular bases according to the criteria of the Swiss Accident Insurance Institution (SUVA). Routine medical examinations include: anamnesis, physical examination, blood analysis (haemoglobin, erythrocytes, leukocytes, thrombocytes, complete blood count, blood sedimentation rate, blood sugar, blood pressure, cholesterol, triglycerides, ALT, AST, alkaline phosphatase, bilirubin, and creatinine) and urine analysis. The active ingredient is manufactured on Syngentas behalf by a 3rd Party ([redacted]. No reports of adverse health effects have been made.

Formulation and packaging is located in Syngenta's plant in [redacted] and in [redacted]; in the past also in [redacted]. Questionnaires have been sent out to the managers of the sites and company physicians (last update by March 2003).

Since 1991 about 450 tonnes of fenpropidin per year were used in [redacted], involving 20-50 workers. No adverse health effects have been reported.

Since 1992 about 10 formulations containing fenpropidin were produced in [redacted]. Formulation is done in campaigns (e.g. 2 campaigns per year, 1 month per campaign, involving about 30 workers). There was one report of adverse health effects in 1996 involving 4 workers from the packaging line – general itchiness and smarting of eyes in two workers each. Unless other factors (e.g. other formulation ingredients) were involved, the observed effects might be related to fenpropidins well-known irritation potential perhaps in combination with not complete compliance to safety measures.

No adverse health effects have been reported from [redacted], involving 5 persons, 208 tonnes of material was used. In [redacted] formulation of Fenpropidin products was done from 1989 to 1995 in about 10 campaigns per year (each campaign took 11 to 15 days each). A total of 30 persons were involved in the production. No compound related adverse effects were reported.

In summary, except a confirmation that potential exposure to fenpropidin can lead to irritation reactions of the skin and eye, no adverse health effects have been observed. Following the report from France in 1996, changes in operating procedures to improve standards of hygiene and reduce exposure have resulted in no further adverse effects being observed in any of the production or formulation.

No case of poisoning has been reported to the company. No cases of poisoning have been reported to the company.

In 1986 a survey of the use of Patrol 750 EC (A-7516 A; contains 750 g/L fenpropidin) among 65 farmers was performed in the UK. A questionnaire was sent to the farmers asking for information about use rates, mixing partners, description of activity (e.g. mixing and/or spraying; area sprayed), safety measures and whether adverse health effects were observed. While compliance to the recommended safety measures was relatively good – e.g. 78% and 32% of the farmers wore gloves and eye protection, respectively, during mixing/loading - none of the farmers reported any adverse health effect.

A literature search on human data / human exposure for fenpropidin has been performed.

In summary no cases of poisoning by exposure to fenpropidin or adverse health effects associated with exposure to the compound were found in the public literature. There is also no investigation published, reporting health effects on the general population due to exposure to fenpropidin.

2.6.10 Toxicological end points for risk assessment (reference values)

Table 53: Overview of relevant studies for derivation of reference values for risk assessment

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Rat	28-day oral toxicity study Oral route: in diet	Fenpropidin (purity: 97%) Dose levels: 0, 50, 200, 1000, 2000 ppm (5.40, 20.1, 104.6, 200.1 mg/kg bw/day in M and 5.62, 19.9, 103.4, 212.2 mg/kg bw/day in F)	Increased hyperkeratosis of Esophagus (5/5 males, 5/5 females, 0/5 control) and non-glandular stomach (5/5 males, 2/5 females, 0/5 control); body weight reduction (28% males, 14% females at end of study); decreased food consumption (23% males over course of study)	1000 ppm (104.6 and 103.4 mg/kg bw/day in males and females, respectively)	2000 ppm (200.1 and 212.2 mg/kg bw/day in males and females, respectively)	[redacted] *(1994)*
Dog	28-day oral toxicity study Oral route: in capsules	Fenpropidin (purity: 97%) Dose levels: 0, 5, 15, 25 mg/kg bw/day	Males: Mean relative liver weight (↑ 38%); mean relative kidney weight (↑ 17%); clinical chemistry parameters (↓ cholesterol 24.4%); vomiting, salivation Females: Decreased food consumption (54.9% week 1, 32.3% week 4); changes in clinical chemistry (↓ cholesterol 26.4%); vomiting, salivation	Males: 5 mg/kg bw/day Females: 15 mg/kg bw/day	Males: 15 mg/kg bw/day Females: 25 mg/kg bw/day	[redacted] *(1993)*

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
Rat	90-day oral toxicity study Oral route: in diet	Fenpropidin (purity: 94.7%) Dose levels: 0, 20, 60, 120 mg/kg bw/day	Body weight decrease (↓ 30% males, 13% females week 13)	60 mg/kg bw/day	120 mg/kg bw/day	[redacted] *(1981)*
Rat	90-day oral toxicity study Oral route: in diet	Fenpropidin Dose levels: 0, 20, 150, 1500 ppm (1.14, 9.84, 89.9 mg/kg bw/day in males and 1.24, 10.1, 97.3 mg/kg bw/day in females)	Food consumption(↓ 10% males, 5% females weeks 1-13); body weight (↓ 16% males, 8% females week 13); demyelination of spinal cord (one female), hindlimb paralysis (one female), cataracts (one female); pulmonary foam cells; changes in blood parameters and clinical chemistry parameters; relative liver weight (↑ 12% females)	150 ppm (9.84 and 10.1 mg/kg/day for males and females, respectively)	1500 ppm (89.9 and 97.3 mg/kg/day for males and females, respectively)	[redacted] *(1995)*
Mouse	90-day oral toxicity study Oral route: in diet	Fenpropidin (purity: 99%) Dose levels: 0, 625, 1250, 2500, 5000 ppm (58, 155, 359, 547 mg/kg bw/day in males and 87, 179, 361and 566 mg/kg bw/day in females)	Deaths (5 females died by week 5, 1 male week 13); reduced body weight (13.8% males, 10.4% females) week 13; enzyme change (↑ ASAT approximately 100% in both sexes)	1250 ppm (155 and 179 mg/kg bw/day for males and females, respectively)	2500 ppm (359 and 361 mg/kg bw/day for males and females, respectively)	[redacted] *and* [redacted] *(1981)*
Dog	26-week oral toxicity study Oral route: in capsules	Fenpropidin Dose levels: 0, 2, 5, 12	Mortalities (one male); conjunctivitis and keratitis of	5 mg/kg/day	12 mg/kg/day	[redacted] *(1981)*

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
		mg/kg/day	eye (one female); body weight development (↓ 12% females, week 1-25); overall body weight gain; vomiting; salivation			
Dog	1-year oral toxicity study Oral route: in capsules	Fenpropidin Dose levels: 0, 2, 5 and 20 mg/kg/day	Hind limb paresis and demyelination of spinal cord (one male); indurated and inelastic pads (4/4 males and females); vomiting (4/4 females weeks 1-6); opacity of the lens (4/4 males and females from week 22); food consumption (↓ 27% week 1 and 14% week 4 females); relative renal weight (↑26% females); pigmentation of renal cells; granuloma of the lungs; skin irritation	5 mg/kg/day	20 mg/kg/day	[redacted] *(1995)*
Rat	2-year chronic toxicity/carcinogenicity study Oral route: in diet	Fenpropidin Dose levels: 0, 5/2, 25/10, 125/50, 625/250 ppm (0.07, 0.34, 1.68, 8.53 mg/kg bw/day in males; 0.09, 0.45, 2.27, 11.83 mg/kg bw/day in females	Decreased body weight in females (12-18% weeks 1-7; 9-14% throughout the study)	NOAEL (systemic): 50 ppm equal to 2.27 mg/kg bw/day for females; for males not stated	LOAEL (systemic): 250 ppm (equal to 11.83 mg/kg bw/day) in females	[redacted] *(1989)*
Mouse	80-week	Fenpropidin	Mortality: in	NOAEL (systemic):	LOAEL (systemic):	[redacted]

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
	carcinogenicity study Oral route: in diet	(purity not reported) Dose levels: 0, 30, 100, 300 and 1000 ppm (0, 4.12, 13.54, 41.90, 143.8 mg/kg bw/day for males and 0, 5.47, 17.70, 51.71, 166.1 mg/kg bw/day for females)	males (45% survival in week 80; 51% survival week 65-76; > 71% in all other groups including control) local irritation of upper gastro-intestinal tract and skin; reduced bodyweight development (11% males, 7% females, week 80)	300 ppm (41.9 mg/ kg bw/day in males and 51.7 mg/kg bw/day in females)	1000 ppm (143.8 mg/ kg bw/day in males and 166.1 mg/kg bw/day in females)	*(1983)*
Rat	two-generation study Oral route: in diet	Fenpropidin (purity 97%) 0, 25, 100, 500 and 1000 ppm (0, 2, 8, 42, 80 mg/kg bw/day)	Absolute body weight and body weight gain reduction, organ weights and histopathology changes (↑ adrenal cortical fatty change females 14/30 (control 6/30); delayed sexual maturation	Parental and offspring: 100 ppm (12 mg/kg bw/day)	Parental and offspring: 500 ppm (80 mg/kg bw/day)	[redacted] *(2003)*
Rat	Developmental toxicity study Oral route: in diet	Fenpropidin (purity not reported) 0, 19.5, 47.5, 87.8 mg/kg bw/day	Decreased body weight and body weight gain (34% days 7-17; 9% days 0-21); decreased skeletal ossification on neural arches	Maternal: 19.5 mg/kg bw Developmental:47.5 mg/kg bw	Maternal: 47.5 mg/kg bw Developmental:87.8 mg/kg bw	[redacted] *(1981)*
Rat	Developmental toxicity study Oral route: by gavage	Fenpropidin (purity 97%) 0, 10, 60, 90 mg/kg bw/day	decreased body weight gain (11% days 6-16, not significant); decreased food consumption (10% days 11-16)	Parental: > 90 mg/kg bw/d Offspring: > 90 mg/kg bw/d	-	[redacted] *(1994)*
Rabbit	Developmental toxicity	Fenpropidin	Maternal	Maternal: 10 mg/kg	Maternal: 20 mg/kg	[redacted]

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
	study Oral route: by gavage	(purity 96.9%) 0, 5, 10 and 20 mg/kg bw/day	toxicity: Decreased food consumption (11% days 7-29), body weight gain (64% days 7-29), defaecation Developmental toxicity: ↑ incidence of persistent truncus arteriosus (3/204 foetuses, 3/23 litters) and incidence of severely malaligned sternebrae (3/204 foetuses, 3/23 litters outside of historical control range)	bw Developmental: 10 mg/kg bw	bw Developmental: 20 mg/kg bw	[redacted] *(2011)*
Rabbit	Developmental toxicity study Oral route: by gavage	Fenpropidin (purity not reported) 0, 5, 12 and 30 mg/kg bw/day	Reduced body weight gain (24% days 1-30), reduced foetal body weight (7% possibly a consequence of maternal toxicity or a consequence of larger litter size 7.2 vs. 5.7 in control)	Maternal: 12mg/kg bw Developmental: 30 mg/kg bw	Maternal: 30 mg/kg bw Developmental: > 30 mg/kg bw	[redacted] *and* [redacted] *(1981)*
Rat	Developmental neurotoxicity study Oral route: in diet	Fenpropidin (96.9%) 0, 40, 100, 400 ppm (0, 3, 7, 27 mg/kg bw)	No adverse effects	Maternal neurotoxicity: ≥400 ppm (27 mg/kg bw) Developmental neurotoxicity: ≥400 ppm (27 mg/kg bw)	-	[redacted] *(2011)*
Mouse	Immunotoxicity study Oral route: in diet	Fenpropidin (purity: 96.9%) 125, 400, and 1250 ppm (0, 26,	No adverse effects	Immunotoxicity: 1250 ppm (258 mg/kg)	Immunotoxicity: >1250 ppm (258 mg/kg)	[redacted] *(2011)*

Species	Study (method/type, length, route of exposure)	Test substance	Critical effect	NOAEL	LOAEL	Cross reference
		90, and 258 mg/kg)				

2.6.10.1 Toxicological end point for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake)

The estimation of the Acceptable Daily Intake (ADI) is based on the lowest no observed adverse effect level (NOAEL) estimated from chronic toxicity/carcinogenicity studies. The lowest NOAEL was obtained from rat chronic toxicity/carcinogenicity study with a NOAEL of 2.27 mg/kg bw/day for females. This with an assement factor of 100 gives an ADI of 0.02 mg/kg bw/day. Therefore t**he ADI is proposed to be 0.02 mg/kg bw/day.**

2.6.10.2 Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)

The acute effects after ingestion of fenpropidin is expected to be related to fenpropidins irritative potential. Several studies strengthen this assumption. Hyperkeratosis of the esophagus was observed in the 28-days oral treatment of rats with fenpropidin with a NOAEL of 5.40 mg/kg bw/day. Vomiting and salivations occur in dogs after administration with fenpropidin in capsules in both the 28 days study and the 26 weeks study with a NOAEL of 5 mg/kg bw/day. In view of the fact that 28 day and 26 week studies in dogs are both considered as supplementary, the ARFD is derived from 28 day oral study in rats. Lowest local NOAEL from this study was 5.4 mg/kg bw/day, this with an assesment factor of 100 gives an **ARfD of 0.05 mg/kg bw/day**.

2.6.10.3 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL (acceptable operator exposure level)

AOEL is based on the results from one year dog study. At top dose 20 mg/kg a spinal chord demyelination and hind limb paralysis were observed and were considered as critical effects for setting the NOAEL. Thus, the NOAEL was set at 5 mg/kg/bw, the second highest dose group evaluated. At this dose some effects in the liver are noted (increased liver weight, hepatocyte hypertrophy), however these effects are considered not to be adverse and are rather adaptive to the administration of the test substance. Thus, AOEL is based on NOAEL of 5 mg/kg/bw. This together with an assessment factor of 100 gives the **proposed AOEL of 0.05 mg/kg bw/day**. No correction factor for systemic availability is used since the oral absorption is considered to be more than 80 %.

2.6.10.4 Toxicological end point for assessment of occupational, bystander and residents risks – AAOEL (acute acceptable operator exposure level)

Acute AOEL is based on the NOAEL of 5.4 mg/kg bw/day from the 28 day oral rat study = the same basis as ARFD. No correction factor for systemic availability is used, therefore the proposed AAOEL is 0.05 mg/kg bw/day.

2.6.11 Summary of product exposure and risk assessment

The representative uses of fenpropidin in the EU for renewal of Annex I approval are cereals. The representative product A7516D (TERN 750 EC) will be applied as foliar spray with tractor mounted equipment and will be used with a rate of 562.5 g/ha of fenpropidin equal to 0.75 L/ha of the product. The worst case scenario is given by two treatments per season.

Operator exposure

The operator risk assessment was estimated using the EFSA AOEM model. Predicted systemic longer term and acute operator exposure to fenpropidin is acceptable (3.9 and 41 % of AOEL) when gloves and workwear are used

during mixing/loading

Worker exposure

The worker exposure was estimated using the EFSA AOEM model. According to the risk assessment, it can be concluded that the risk for workers performing inspection of cereal crops treated with A7516D is acceptable (49 % of AOEL without PPE (with adequate work clothing, but no gloves). As a standard rule, it should be mentioned on the label that treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried.

Bystander and resident exposure

Estimates of bystander and resident exposure have been made using the EFSA model and a UK DEFRA study. It is concluded that there is no undue risk to bystanders or residents during and following field applications of A7516D.

2.7 RESIDUE

2.7.1 Summary of storage stability of residues

The potential for degradation of residues during storage has been previously assessed in the framework of the peer review for fenpropidin (Sweden, 2005) and in the case of eggs, a new study ([redacted] ***2016***) was performed. Fenpropidin is the only component of the proposed residue definitions for monitoring and risk assessment with food of plant origin, and stability has been demonstrated in representative uses (wheat grain and straw). Fenpropidin and the metabolite CGA 289267 comprise the proposed residue definition for monitoring with food of animal origin. The stability of fenpropidin and CGA 289267 in cattle and egg commodities has been demonstrated with other components of the proposed residue definition for monitoring with food of animal origin accounted for through conversion factors based on metabolism studies.

Stability of relevant fenpropidin residues in plant and animal comodities is presented in Table 2.7.1-1.

Table 2.7.1-1 Summary of the stability of fenpropidin residues in plant and animal comodities

Plant products (Category)	**Commodity**	**T** (°C)	**Stability** (Months)		
			Fenpropidin		
High Water Content	Banana	< -18	24		
High Starch Content	Wheat, ears	< -18°	24		
High Acid Content	Grapes	< -18°	24		
Dry	Wheat, straw	< -18°	24		
Processed products	Wine	< -18°	24		
Animal	**Animal commodity**	**T** (°C)	**Stability**		
			Fenpropidin	CGA 289267	CGA 289268
Cattle	Muscle	< -18°	112 days	24 months	30 months
Cattle	Liver	< -18°	118 days	24 months	30 months
Cattle	Milk	< -18°	69 days	24 months	30 months
Poultry	Egg	< -18°	136 days	136 days	136 days
Cattle	Kidney	< -18°	117 days	24 months	30 months
Cattle	Blood	< -18°	29 days	24 months	30 months
Cattle	Fat	< -18°	101 days	24 months	30 months

2.7.2 Summary of metabolism, distribution and expression of residues in plants, poultry,

lactating ruminants, pigs and fish

2.7.2.1. Plant metabolism

Foliar applied fenpropidin plant metabolism studies have been undertaken in four crops, representing three crop groupings - cereals (spring wheat), root vegetable (sugar beet) and fruits (grape and banana). The representative use for fenpropidin in the EU is cereals.

Spring wheat metabolism studies have been conducted using two study designs. The first of these designs involved two applications of fenpropidin (500g ai/ha per application separated by 20 days) at rates and timings which were generally representative of the proposed GAP in the EU (study data previously evaluated during the 91/414/EEC review). The second design involved a single early application of 1125 g ai/ha which was not representative of the proposed GAP in the EU (new study data not previously reviewed).

In the first wheat study design total radioactive residues in the human edible portion of the wheat crop (grain) were 0.185-0.202 mg fenpropidin equivalents/kg and in the straw (animal feed) were 14.5-19.1 mg fenpropidin equivalents/kg. Fenpropidin was well metabolised and accounted for 37.5-55.7% TRR (0.076-0.103 mg/kg) in grain. Significant proportions of the remaining grain residue, comprising mainly of solvent unextractable components, was demonstrated to be associated with naturally incorporated radioactivity (starch). No individual extractable metabolite in grain exceeded 2.5% TRR (0.005 mg/kg) with the largest identified metabolite, CGA289263, accounting for 2.0-2.4% TRR (0.004 mg/kg).

The proportions of the total radioactive residue present as parent fenpropidin in forage (74-79% TRR; 4.97-7.02 mg/kg) and straw (52-54% TRR; 7.58-10.32 mg/kg) were higher than for grain. The remainder of the residue comprised either numerous minor metabolites, the largest identified residue of which was CGA289263 (forage: 1.8-2.0% TRR; 0.121-0.177 mg/kg; straw: 6.8-6.9% TRR; 0.987-1.319 mg/kg), or solvent unextractable residue.

In the second wheat study design total radioactive residues in the human edible portion of the wheat crop (grain) were 0.025-0.224 mg/kg and in the straw (animal feed) were 7.10-8.52 mg/kg. Fenpropidin was extensively metabolised and accounted for only 0.7 TRR (0.002 mg/kg) in grain. As in the first study design significant proportions of the remaining grain residue were associated with the unextractable components which were likely to be similarly associated with naturally incorporated radioactivity within endogenous material. The largest identified metabolite in grain, CGA289263, accounted for 1% TRR (0.004 mg/kg).

Residue levels of fenpropidin in wheat forage (19.5-26.3% TRR; 0.664-1.78 mg/kg) and straw (4.8-4.9% TRR; 0.346-0.401 mg/kg) were higher than that of grain. The remainder of the residue in these commodities comprised numerous metabolites, the largest identified residue of which was CGA289268, present in forage and straw at levels of 13.7-28.4% TRR (0.925-0.965 mg/kg) and 8.0-12.8% TRR (0.679-0.903 mg/kg) respectively and was found in both the free and glycoside conjugated forms of the metabolite.

More minor metabolites identified in forage and straw were CGA289263 (4.4-4.5% TRR; 0.145-0.304 mg/kg and 6.9-7.6% TRR; 0.581-0.539 mg/kg respectively), a dihydroxy CGA289267 metabolite (3.1-7.1% TRR; 0.216-0.455 mg/kg found, exclusively in its acyl glycoside conjugated form in both commodities), and a monohydroxylated CGA289267 metabolite (1.8-2.4% TRR; 0.081-0.158 mg/kg; found exclusively in the free form of the metabolite).

Fenpropidin was similarly metabolised in the other three crop metabolism studies undertaken (sugar beet, grape and banana), with fenpropidin being the predominant residue component detected in commodities in each case. Levels of metabolites were generally one order of magnitude lower than the amount of parent compound. In sugar beet roots approximately 20% of the radioactivity was due to the incorporation of radioactive carbon into natural plant sugars.

Metabolic processes observed in the four crops involved:

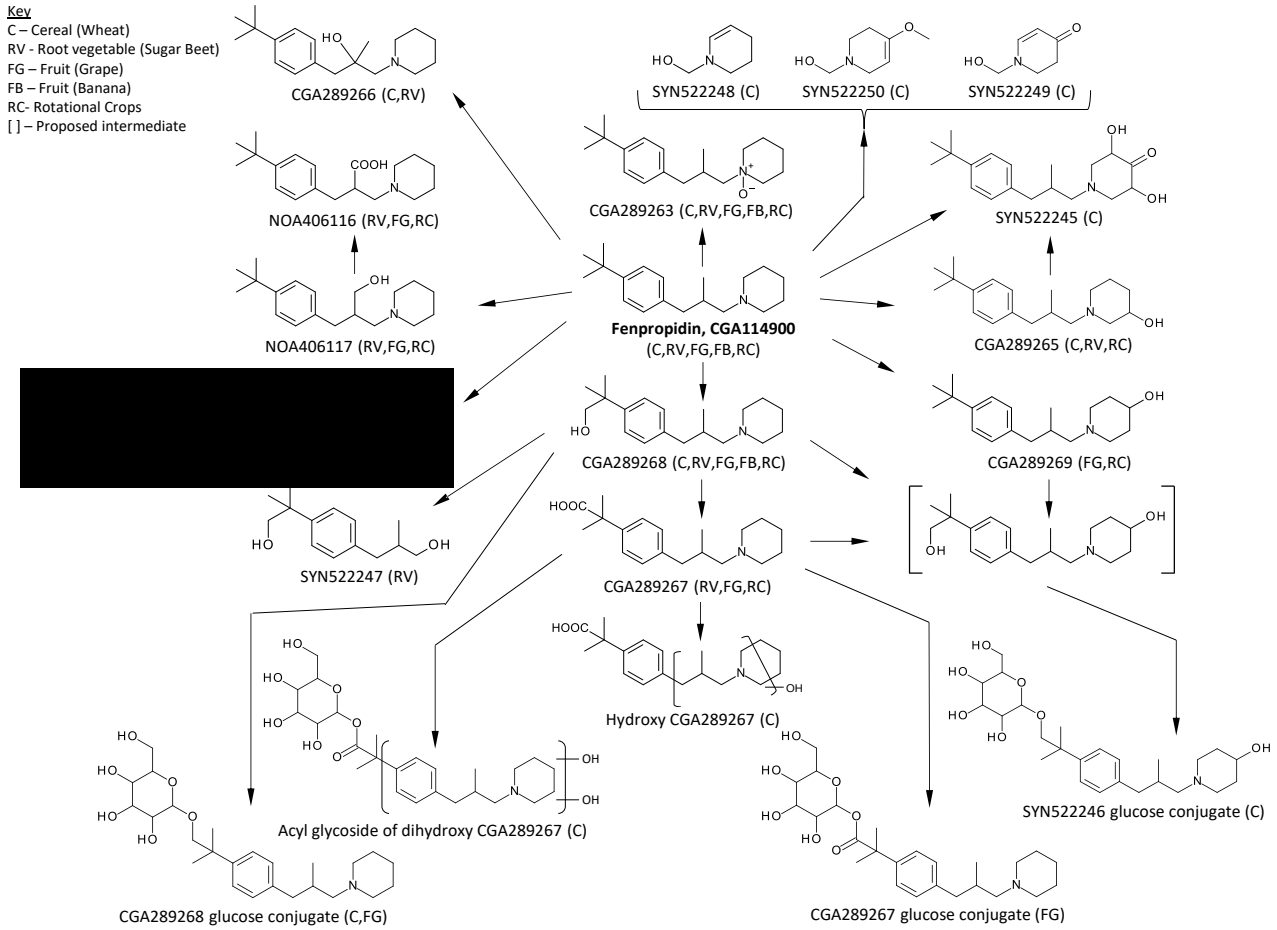
- oxidations of the piperidinyl ring to CGA289263, CGA289269, CGA289265 and SYN522245
- successive oxidations of the tertiary butyl sidechain to CGA289268 and CGA289267
- oxidation of the 2-methylpropyl chain to CGA289266, NOA406117 and NOA406116
- additional non-specified hydroxylations

- cleavage of the piperidinyl bond (a minor process) to form [redacted] SYN522247, [redacted] SYN522249, SYN522248 and SYN522250

Glucose conjugation of the tertiary butyl oxidation metabolites was also observed.

The proposed metabolic pathway for the biotransformation of fenpropidin in plants is given in Figure 2.7.2.1-1.

Figure 2.7.2.1-1: Proposed metabolic pathway of fenpropidin in plants



2.7.2.2. Livestock metabolism

Fenpropidin is extensively metabolised and rapidly excreted in the lactating goat. Following oral dosing for four consecutive days with fenpropidin at a level of 150 mg ai equivalents per day (3.06 mg/kg bw/d; 87.4x the maximum dairy cows dietary burden), the majority of the administered dose was found in urine and faeces (63.3%). Only small amounts of the dosed radioactivity were found in milk (0.09%) and edible tissues (1.2%) demonstrating that fenpropidin and its metabolites do not bioaccumulate and are rapidly excreted.

Total radioactive residue levels were highest in the principal metabolising and excretion organs, liver (7.65 mg/kg) and kidney (4.37 mg/kg) but were lower in milk (0.196 mg/kg), muscle (0.164 mg/kg) and fat (0.042 mg/kg).

Parent fenpropidin was detected in the liver and fat only, at concentrations of 0.084 mg/kg and 0.003 mg/kg respectively.

The principal primary metabolites found in all tissues and milk were CGA289267 (8.4-38.4% TRR; 0.007-0.645 mg/kg) and SYN515213 (6.5-30.0% TRR; 0.007-0.713 mg/kg).

The major secondary metabolites observed were the sulphate ester conjugates of SYN515213, CGA289286 and SYN515215, accounting individually for 5.2-13.0% TRR (0.228-0.568 mg/kg) in kidney, ≤ 33.4% TRR (≤ 0.066 mg/kg) in milk (predominantly as the CGA289268 conjugate) and 12.6-13.3% TRR (0.961-1.02 mg/kg) in liver. A glucuronide conjugate of CGA289267 was also observed in liver and fat at low levels (ca 1% TRR).

Other primary metabolites, including CGA289268 (present in fat only:1.2% TRR; 0.001 mg/kg), SYN515214 (≤ 3.7% TRR) and SYN515216 (liver and kidney: 8.3-9.8% TRR; 0.427-0.631 mg/kg, muscle and fat: 0.8-3.7% TRR; ≤0.006 mg/kg), were also detected but were present at generally low proportions of the total radioactive residue.

In laying hens, fenpropidin is also extensively metabolised and rapidly excreted. Following oral dosing for four consecutive days with fenpropidin at levels of 1.16 - 1.319 mg ai equivalents per day (0.77 and 0.88 mg/kg bw/d; 22.7 and 25.9x the maximum laying hens dietary burden), the majority of the administered dose (88-92%) was found in the excreta. Only small amounts of the administered dose were found in the eggs (0.1%) and tissues (1%) demonstrating that fenpropidin and its metabolites do not bioaccumulate and are rapidly excreted.

Total radioactivie residue levels were highest in the principal metabolising and excretion organs, liver (0.46-0.52 mg/kg) and kidney (0.61-0.62 mg/kg) but were lower in muscle (0.076-0.083 mg/kg), fat+skin (0.041-0.046 mg/kg), egg white (0.039-0.053 mg/kg) and egg yolk (0.028 mg/kg).

Parent was detected in eggs and all tissues. The highest absolute residues were detected in liver (0.037-0.045 mg/kg) with the remaining tissues and eggs containing only lower levels (< 0.01 mg/kg). The principal metabolite found was CGA289267 accounting for 35.5-91.7% TRR in eggs and all tissues. The highest absolute residues of CGA289267 were greatest in liver (0.182-0.212 mg/kg; 35.5-46.5% TRR) but were lower in other tissues and eggs (0.017-0.067 mg/kg). Other metabolites (including CGA289268: 2.7-2.8% TRR; 0.013-0.014) were found at generally significantly lower proportions of the total radioactive residue. Identified residues were found exclusively in their free (unconjugated) form of the residue.

The primary metabolic processes in hens and goats involved:

- Successive oxidations of the tertiary butyl sidechain to CGA289268, CGA289267, SYN515213 and SYN515214 (goat only)
- Successive oxidations of the piperidinyl ring to SYN522217, SYN515216 and SYN515215

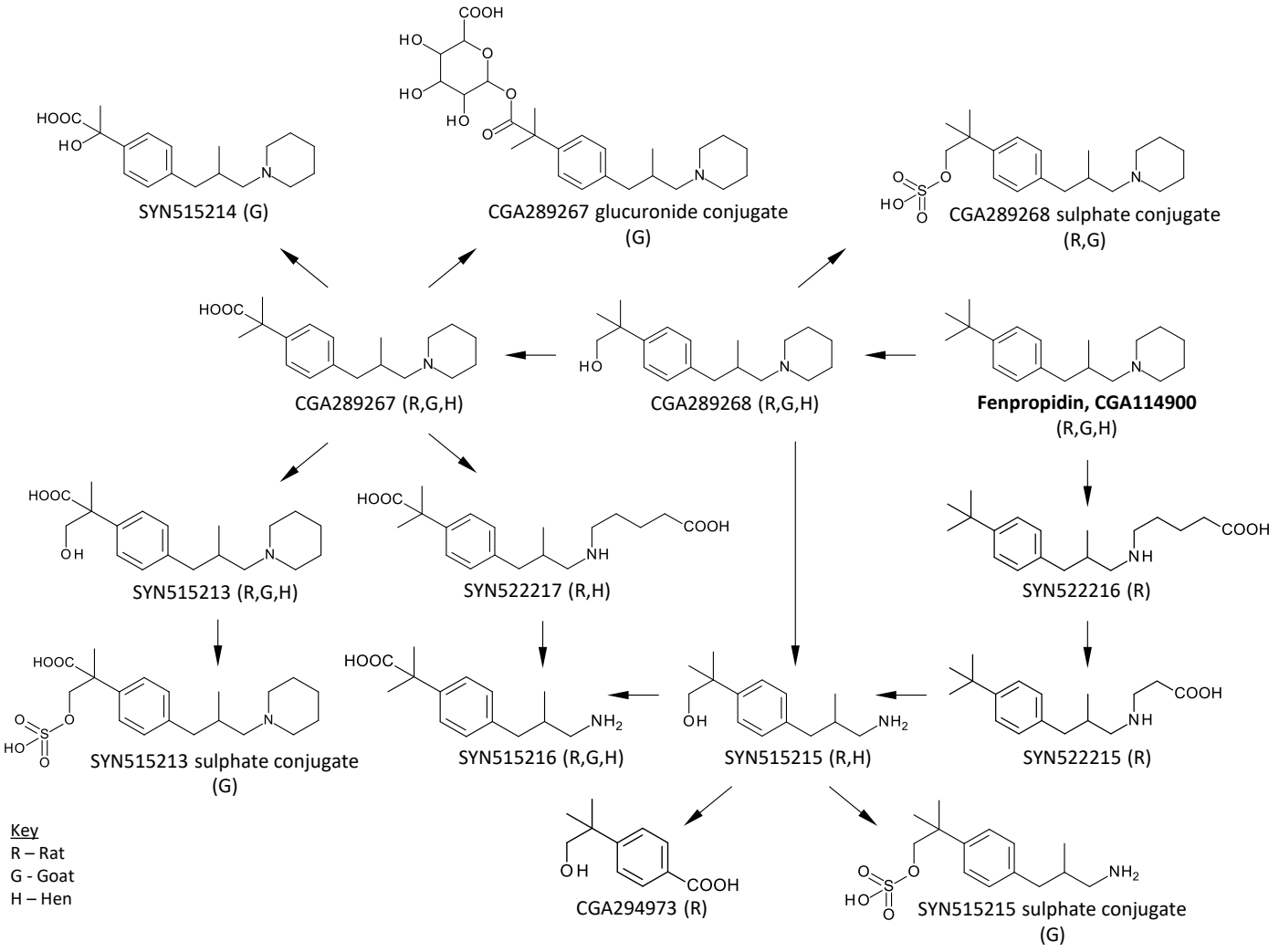
Suphate ester and glucuronide conjugation were observed as secondary metabolism processes in the lactating goat.

The proposed metabolic pathway for the biotransformation of fenpropidin in animals is given in Figure 2.7.2.2-1.

As the metabolism of fenpropidin in the lactating goat and laying hen does not significantly differ from the rat, a pig study was not required.

There are currently no definitive triggers in Regulation (EC) No. 283/2013 on which to base a decision as to whether a "fish metabolism" study is required or not. Consequently no fish metabolism studies have been conducted for fenpropidin.

Figure 2.7.2.2-1: Proposed metabolic pathway of fenpropidin in livestock animals


SYN515214 (G)
CGA289267 glucuronide conjugate (G)
CGA289268 sulphate conjugate (R,G)
CGA289267 (R,G,H)
CGA289268 (R,G,H)
Fenpropidin, CGA114900 (R,G,H)
SYN515213 (R,G,H)
SYN522217 (R,H)
SYN522216 (R)
SYN515213 sulphate conjugate (G)
SYN515216 (R,G,H)
SYN515215 (R,H)
SYN522215 (R)
CGA294973 (R)
SYN515215 sulphate conjugate (G)
Key
R – Rat
G - Goat
H – Hen

APPENDIX 1

Consumer Risk Assessments for Fenpropidin

FENPROPIDIN

Prepare workbook for refined calculations

Undo refined calculations

Status of the active substance:	AIR 3	Code no.	
LOQ (mg/kg bw):	0.01	proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw/day):	0,02	ARfD (mg/kg bw):	0,02
Source of ADI:	Dir 08/66	Source of ARfD:	Dir 08/66
Year of evaluation:	2007	Year of evaluation:	2007

Explain choice of toxicological reference values.

The risk assessment has been performed on the basis of the MRLs collected from Member States in April 2006. For each pesticide/commodity the highest national MRL was identified (proposed temporary MRL = pTMRL).
The pTMRLs have been submitted to EFSA in September 2006.

Chronic risk assessment

TMDI (range) in % of ADI minimum - maximum	
	15
No of diets exceeding ADI:	---

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
14,7	UK Infant	12,2	Milk and cream,	1,3	Wheat	1,0	Bovine: Liver	
14,3	FR toddler	12,5	Milk and cream,	1,3	Wheat	0,2	Bovine: Meat	
13,4	NL child	9,3	Milk and cream,	2,4	Wheat	0,8	Bovine: Liver	
8,8	UK Toddler	6,5	Milk and cream,	2,0	Wheat	0,2	Bovine: Liver	
8,7	FR infant	8,1	Milk and cream,	0,4	Wheat	0,1	Bovine: Meat	
8,3	IE adult	3,7	Barley	2,4	Sheep: Liver	1,1	Wheat	
8,2	DK child	4,0	Milk and cream,	2,8	Wheat	1,3	Bovine: Liver	
7,4	WHO Cluster diet B	4,3	Wheat	1,0	Milk and cream,	0,8	Barley	
7,2	ES child	4,0	Milk and cream,	2,2	Wheat	0,3	Swine: Liver	
6,9	DE child	4,5	Milk and cream,	2,1	Wheat	0,1	Birds' eggs	
5,9	WHO cluster diet E	2,4	Barley	2,0	Wheat	0,9	Milk and cream,	
5,9	WHO cluster diet D	3,3	Wheat	1,6	Milk and cream,	0,7	Barley	
5,6	SE general population 90th percentile	3,9	Milk and cream,	1,6	Wheat	0,1	Birds' eggs	
5,4	WHO Cluster diet F	1,8	Barley	1,8	Wheat	1,3	Milk and cream,	
4,8	NL general	2,1	Milk and cream,	1,1	Barley	1,0	Wheat	
4,8	ES adult	1,6	Milk and cream,	1,5	Barley	1,2	Wheat	
4,6	WHO regional European diet	1,5	Milk and cream,	1,5	Wheat	1,0	Barley	
3,4	DK adult	1,7	Milk and cream,	1,0	Wheat	0,6	Bovine: Liver	
3,4	IT kids/toddler	3,3	Wheat	0,0	Barley		FRUIT (FRESH OR FROZEN)	
2,7	FR all population	1,6	Wheat	0,8	Milk and cream,	0,1	Bovine: Meat	
2,5	LT adult	1,3	Milk and cream,	0,5	Wheat	0,2	Barley	
2,4	FI adult	1,8	Milk and cream,	0,5	Wheat	0,1	Barley	
2,2	UK vegetarian	1,0	Milk and cream,	1,0	Wheat	0,1	Barley	
2,1	IT adult	2,1	Wheat	0,0	Barley		FRUIT (FRESH OR FROZEN)	
2,0	PT General population	2,0	Wheat	0,1	Barley		FRUIT (FRESH OR FROZEN)	
2,0	UK Adult	0,9	Milk and cream,	0,8	Wheat	0,1	Bovine: Liver	
	PL general population		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	

Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.
A long-term intake of residues of FENPROPIDIN is unlikely to present a public health concern.

Acute risk assessment /children

Acute risk assessment / adults / general population

The acute risk assessment is based on the ARfD.

For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.

In the **IESTI 1** calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used.
In the **IESTI 2** calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variabilty factor of 3.

Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100 % of the ARfD.

Unprocessed commodities

No of commodities for which ARfD/ADI is exceeded (IESTI 1):		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 1):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---
IESTI 1	***)**	****)**	**IESTI 2**	***)**	****)**	**IESTI 1**	***)**	****)**	**IESTI 2**	***)**	****)**
Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
2,9	Wheat	0,04 / -	2,9	Wheat	0,04 / -	3,3	Barley	0,09 / -	3,3	Barley	0,09 / -
1,2	Bovine: Liver	0,0286 / -	1,2	Bovine: Liver	0,0286 / -	1,7	Sheep: Liver	0,5 / -	1,7	Sheep: Liver	0,5 / -
1,1	Birds' eggs	0,0179 / -	1,1	Birds' eggs	0,0179 / -	1,6	Wheat	0,04 / -	1,6	Wheat	0,04 / -
1,0	Milk and milk	0,0016 / -	1,0	Milk and milk	0,0016 / -	1,0	Poultry: Meat	0,0168 / -	1,0	Poultry: Meat	0,0168 / -
0,9	Poultry: Meat	0,0168 / -	0,9	Poultry: Meat	0,0168 / -	0,4	Bovine: Liver	0,0286 / -	0,4	Bovine: Liver	0,0286 / -
No of critical MRLs (IESTI 1)			---			**No of critical MRLs (IESTI 2)**			---		

Processed commodities

No of commodities for which ARfD/ADI is exceeded:		---				**No of commodities for which ARfD/ADI is exceeded:**		---			
		*****)**						*****)**			
Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)				Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)			
2,4	Wheat flour	0,04 / -				0,9	Bread/pizza	0,04 / -			

*) The results of the IESTI calculations are reported for at least 5 commodities. If the ARfD is exceeded for more than 5 commodities, all IESTI values > 90% of ARfD are reported.
**) pTMRL: provisional temporary MRL
***) pTMRL: provisional temporary MRL for unprocessed commodity

Conclusion:

For FENPROPIDIN IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.
No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

For processed commodities, no exceedance of the ARfD/ADI was identified.

2.7.3 Definition of the residue

Proposed residue definition (food of plant origin)

Endpoint	Proposed EU endpoints
Residue definition in food of plant origin for monitoring purposes	sum of fenpropidin and its salts, expressed as fenpropidin
Residue definition in food of plant origin for risk assessment purposes	sum of fenpropidin and its salts, expressed as fenpropidin

Proposed residue definition (food of animal origin)

Endpoint	Proposed EU endpoints
Residue definition in food of animal origin for monitoring purposes	sum of fenpropidin, CGA 289267, and their salts, expressed as fenpropidin
Residue definition in food of animal origin for risk assessment purposes	sum of fenpropidin, CGA 289267, SYN515213, CGA 289268 and their conjugates, expressed as fenpropidin

2.7.4 Summary of residue trials in plants and identification of critical GAP

Critical GAP:

Critical GAP for the proposed uses for fenpropidin in the EU is presented in Table 2.7.4-1.

- **Table 2.7.4-1 Summary of the critical GAP for the proposed uses for fenpropidin**

Crop	Outdoor/ Protected	Growth stage	Maximum number of applications	Minimum application interval (days)	Maximum Rate per application (g a.s./ha)	Water (L/ha)	Minimum PHI (days)
Wheat	Outdoor	BBCH 31-69	2	14	562.5	100-300	-
Barley	Outdoor	BBCH 31-65	2	14	562.5	100-300	-

Residue trials:

Residue trials quantifying parent fenpropidin in barley and wheat conducted in the EU to support the proposed EU GAP are presented in Table 2.7.4-2.

Table 2.7.4-2: Summary of residues data from the supervised residue trials

Crop	Region/ Indoor (a)	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs (b)	MRL calculation (mg/kg) (c)	HR (mg/kg) (c,d)	STMR (mg/kg) (c,e)
Wheat grain (500090)	NEU	5× <0.01, 2× 0.01, 0.04	0.06	0.04	0.01
	SEU	4× <0.01, 2× 0.01, 2× 0.02, 0.03, 0.04	0.06	0.04	0.01
	Combined	9× <0.01, 4× 0.01, 2x 0.02, 0.03, 2x 0.04	0.06	0.04	0.01
Barley grain (500010)	NEU	5 × <0.01; 2 × 0.01; 0.04	0.15	0.07	0.05
	SEU	<0.01, 2× 0.03, 0.05, 2× 0.06, 2× 0.07, 0.08, 0.09	0.2	0.09	0.06
	Combined	<0.01, 2× 0.02, 2× 0.03, 2× 0.04, 0.05, 4× 0.06, 4× 0.07, 0.08, 0.09	0.15	0.09	0.06
Wheat straw	NEU	0.40, 0.46, 0.48, 0.61, 0.62, 0.91, 1.1, 2.5	-	2.5	0.62
	SEU	0.26, 0.40, 0.46, 0.65, 0.77, 0.92, 0.95, 1.0,	-	3.71	0.85

Crop	Region/ Indoor (a)	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs (b)	MRL calculation (mg/kg) (c)	HR (mg/kg) (c,d)	STMR (mg/kg) (c,e)
		1.19, 3.71			
	Combined	0.26, 2× 0.40, 2× 0.46, 0.48, 0.61, 0.62, 0.65, 0.77, 0.91, 0.92, 0.95, 1.0, 1.1, 1.19, 2.5, 3.71	-	3.71	0.71
Barley straw	NEU	0.30, 0.51, 0.62, 2× 0.74, 0.82, 1.5, 2.2	-	2.2	0.74
	SEU	0.01, 0.13, 0.45, 0.47, 0.55, 0.67, 0.72, 0.79, 1.29, 1.56	-	1.56	0.61
	Combined	0.01, 0.13, 0.30, 0.45, 0.47, 0.51, 0.55, 0.62, 0.67, 0.72, 2× 0.74, 0.79, 0.82, 1.29, 1.5, 1.56, 2.2	-	2.2	0.70

(a): **NEU** or **SEU** for northern or southern **outdoor** trials in EU member states (**combined** merges both zones).
(b): Residue levels in trials conducted according to GAP; proposed residue definitions for monitoring and risk assessment are the same.
(c): Proposed STMRs, HRs and MRLs (underlined values) are derived from the combined datasets, after determining NEU and SEU residue values were similar.
(d): **HR**: Highest residue.
(e): **STMR:** Supervised Trials Median Residue.

2.7.5 Summary of feeding studies in poultry, ruminants, pigs and fish

The maximum dietary burden of fenpropidin in poultry (laying hens) is shown to be 0.034 mg/kg bw/day (equivalent to 0.50 mg/kg dry matter). The magnitude of fenpropidin in poultry was investigated in a new feeding study with laying hens presented in Volume 3 CA – B.7.4.1. The mean fenpropidin residue in liver specimens from hens in Group D (42N rate) was 0.04 mg/kg. A fenpropidin residue of 0.01 mg/kg was detected in a single replicate of hens in Group C (12N), but the mean fenpropidin residue in liver from the hens in Group C was below the LOQ. No fenpropidin residues above the LOQ were detected in any other tissue specimens, or in eggs from any of the treatment groups.

Residues of CGA289267 were found in egg specimens from hens in Group D only with a maximum mean level of 0.02 mg/kg. The mean CGA289267 residue in muscle specimens from hens from Group D was 0.02 mg/kg. Mean CGA289267 residues in liver were 0.02 mg/kg in hens from Group B (3.9N), 0.06 mg/kg in hens from Group C and 0.08 mg/kg in hens from Group D. A CGA289267 residue in skin/fat of 0.01 mg/kg was detected in a single replicate of hens from Group D, but the mean CGA289267 residue in skin/fat was below the LOQ in hens from Group D. No CGA289267 residues above the LOQ were detected in any other tissue specimens. No residues of CGA289268 were detected in egg or tissue specimens from the hens in any treatment group. Residues of fenpropidin and CGA289267 in eggs and tissues from hens in the depuration group declined rapidly after withdrawal of fenpropidin from the hens' diet. Residues were below the LOQ in eggs after 3 days and in tissues after 5 days following withdrawal of fenpropidin from the hens' diet.

The maximum dietary burden of fenpropidin in cattle (dairy) and sheep (lambs) were shown to be 0.035 and 0.075 mg/kg bw/day, respectively (equivalent to 0.91 and 1.77 mg/kg dry matter, respectively). The magnitude of fenpropidin in ruminants was investigated in a previously-reviewed feeding study with lactating cows but in line with the conclusions of the Review of existing MRLs (EFSA Journal 2011;9(8):2333), this submission utilises the previous-reviewed goat metabolism study for risk assessment purposes (see conclusion below, Volume 3 CA – B.7.4.2, and section 2.7.2.2 above).

Parent fenpropidin was detected in the liver and fat only, at concentrations of 0.084 and 0.003 mg/kg, respectively. The major primary metabolites found were CGA 289267 and SYN 515213, which occurred at levels up to 38.4% TRR (0.063 mg/kg) and 30.0% TRR (0.049 mg/kg), respectively in muscle. The major secondary metabolites observed were sulphate ester conjugates of SYN 515213, CGA 289268 and SYN 515215, accounting individually for up to 13.0% TRR (0.568 mg/kg) in kidney, 33.4% TRR (0.066 mg/kg) in milk and 12.7% TRR (0.975 mg/kg) in liver. A glucuronide conjugate of CGA 289267 was also observed in liver and fat at low levels (*ca* 1% TRR). Other metabolites, including CGA 289268, SYN 515214 and SYN 515216, also occurred at low levels, less than 10% of the TRR (maximum 0.631 mg/kg).
In regard to swine, the maximum dietary burden of fenpropidin (finishing swine) was shown to be below the threshold of 0.004 mg/kg bw/d (0.0024 mg/kg bw/day; equivalent to 0.08 mg/kg dry matter).

Table 2.7.5-1: Results of the dietary burden calculation

Animals	**Median burden** / mg/kg bw (mg/kg DM)	**Maximum burden** / mg/kg bw (mg/kg DM)	**Above 0.004 mg/kg bw/d?**	**Highest contributing commodities**
Beef cattle	0.007 (0.303)	0.022 (0.918)	Yes	Wheat straw
Dairy cattle	0.012 (0.303)	0.035 (0.91)	Yes	Wheat straw
Ram/Ewe	0.018 (0.539)	0.059 (1.767)	Yes	Wheat straw
Lamb	0.023 (0.539)	0.075 (1.767)	Yes	Wheat straw
Pig (breeding)	0.002 (0.08)	0.002 (0.08)	No	Wheat milled bypdts
Pig (finishing)	0.002 (0.08)	0.002 (0.08)	No	Wheat milled bypdts
Poultry broiler	0.005 (0.068)	0.005 (0.068)	Yes	Wheat gluten meal
Poultry layer	0.011 (0.155)	0.034 (0.496)	Yes	Wheat straw
Turkey	0.004 (0.054)	0.004 (0.054)	No	Wheat gluten meal

2.7.6 Summary of effects of processing

The effects of processing on the nature (see Table 2.7.6-1) and magnitude (see Table 2.7.6-2) of fenpropidin residues have been investigated and previous reviewed (Sweden, 2005).

Table 2.7.6-1: Summary of nature of residue studies

Conditions	**Relative occurrence level of identified chemical species (%TRR)**
Pasteurisation (20 min, 90 °C, pH 4.3)	Fenpropidin (97.1%)
Baking, boiling, brewing (60 min, 100 °C, pH 5.1)	Fenpropidin (97.1%)
Sterilisation (20 min, 120 °C, pH 6.3)	Fenpropidin (96.1%)

Table 2.7.6-2: Summary of processing studies

Crop (RAC)/Edible part or Crop (RAC)/Processed product	**Number of studies**	**Processing Factor** (PF)	
		Individual values	Median PF

Crop (RAC)/Edible part or Crop (RAC)/Processed product	**Number of studies**	**Processing Factor** (PF)	
		Individual values	Median PF
Wheat, whole-meal flour	4	1.20, 1.00, 1.20, 1.00	1.10
Wheat, whole meal bread	4	1.00, 0.90, 1.10, 1.00	1.00
Wheat, white flour	4	0.20, 0.20, 0.20, 0.20	0.20
Wheat, bran	4	4.30, 4.40, 3.90, 4.00	4.15
Barley, brewing malt	2	1.5, 0.8	1.15 [(a)]
Barley, beer	2	0.2, 0.5	0.35

[(a)]: Residues of fenpropidin were slightly higher in the processed malt (1.5, 0.8) and the calculated mean transfer factor was 1.15. However, this factor cannot be considered as an increase of fenpropidin residues in processed malt, since the residues in unprocessed grain and processed malt were close to the LOQ in the commodities (grain: 0.05, 0.02; malt: 0.04, 0.03).

2.7.7 Summary of residues in rotational crops

Following two applications of 750 g a.s./ha to bare soil (separated by a 21 day interval reflecting the proposed GAP), total radioactive residues in rotated crops planted 28 to 365 days after the second application (DA2A) ranged from 0.003 – 3.1 mg/kg.
Residues present in 28 DA2A commodities in general decreased progressively and markedly in commodities of subsequent rotational intervals, the one exception being wheat grain where the residue level in the 28 DA2A plantback wheat grain increased in the subsequent 76 DA2A commodity before markedly reducing in the 365 DA2A grain.
Residues levels were greatest in cereal (spring wheat) commodities of mature straw (0.023-3.1 mg/kg), immature wheat plants (0.004-0.568 mg/kg) and mature grain (0.007-0.039 mg/kg) and were lower in root crop (radish) foliage (0.007-0.090 mg/kg) and root (0.003-0.029 mg/kg) commodities and leafy (lettuce) foliage (0.005-0.070 mg/kg).
The metabolic pattern observed in residues was similar to that observed in primary crops with fenpropidin being the major constituent of the residue accompanied by a complex mixture of more minor metabolites.
Residue extractability was high (73-87% TRR) for most 28 DA2A harvested commodities with the exception of wheat straw (slightly lower; 67-71 %TRR) and wheat grain (lower still; 23% TRR).
In spring wheat, the extractable radioactivity comprised mainly fenpropidin and up to 19 discrete metabolites including CGA289268, CGA289263, CGA289269, CGA289267, NOA406117, CGA289265, [redacted] and (tentatively) NOA406116.
In radish commodities, extractable radioactivity comprised mainly fenpropidin together with smaller residues of NOA406117, NOA406116, CGA289263, CGA289268, CGA289267 and CGA289269.
In lettuce, extractable radioactivity comprised mainly fenpropidin together with smaller residues of NOA406117, CGA289268 and CGA289267.
Identified metabolites were present in the free (unconjugated) form of the residue.
Major proportions of the unextracted residue present in wheat grain and straw were characterised to comprise naturally incorporated radioactivity.
The proposed metabolic pathway for the biotransformation of fenpropidin in rotated crops is given in Figure 2.7.2.1-1.
Due to the very low residue levels observed in the confined rotational crop studies, limited field studies are not required.

2.7.8 Summary of other studies

No further studies have been conducted.

2.7.9 Estimation of the potential and actual exposure through diet and other sources

Chronic (long-term) and acute (short-term) exposure calculations for all crops proposed for fenpropidin were performed using revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo). Guidance on pairing estimated dietary burdens with appropriate domestic animal species within EFSA (2015a) was followed when calculating HRs and STMRs for animal commodities.
For the TMDI (Theoretical Maximum Daily Intake) calculation, and IESTI (International Estimate of Short-Term Intake) calculations with mammalian commodities, animal metabolism studies were used to derive CFs for calculating animal commodity residues according to the $RD_{(RA)}$ from residues according to the $RD_{(Mo)}$. Although a CF-approach was not necessary for IESTIs with mammalian commodities, due to them being based on the goat metabolism study scaled to the 1N rate, the CF approach was taken to support monitoring. For IESTI calculations with poultry commodities, the hen feeding study was used to derive CFs for calculating residues according to the $RD_{(RA)}$, from residues according to the sum of the $RD_{(Mo)}$ and CGA289268 (measured alongside $RD_{(Mo)}$ structures by the method used in the feeding study).
The TMDI calculation is derived based on existing EU MRLs for the representative uses (barley and wheat grain) and edible animal products. The chronic risk assessment (TMDI) results ranged to a maximum value representing 14.7% of the ADI (for the UK Infant consumer group). The IESTI calculations are based on residue levels assumed to be present at the value of the highest residues (HR) observed in barley and wheat supervised field trials and highest residues (HR) for livestock commodities. Only the representative uses and animal commodities are considered for the calculation. The highest acute exposure was calculated for barley at 3.3% of the ARfD (for the NL Adults consumer group). Thus it can be concluded that unacceptable acute or chronic risks to human health arise from the application of fenpropidin to barley and wheat in accordance with the uses considered.

2.7.10 Proposed MRLs and compliance with existing MRLs

EU MRLs for fenpropidin are currently detailed in Annex II of Regulation (EC) No 396/2005. No changes are proposed to the MRLs for representative uses and animal commodities.

2.7.11 Proposed import tolerances and compliance with existing import tolerances

No import tolerances proposed.

2.7.12 Pre-harvest intervals for envisaged uses

The applications of plant protection products containing fenpropidin in accordance with representative uses are growth stage-dependent and therefore a pre-harvest interval (PHI) in days is not applicable for these crop types.

2.7.13 Re-entry period (in days) for livestock, to area to be grazed

Livestock grazing is not relevant to field crops.

2.7.14 Re-entry period (in hours or days) for man to crops, buildings, or spaces treated

Under practical conditions of use, there is no reason for workers to enter the crop shortly after treatment. Assessments conducted for the representative formulation demonstrate that exposure is within the level which does not pose a risk to human safety without any additional re-entry interval. The general approach of avoiding re-entry until the spray solution has dried is recommended.

2.7.15 Withholding period (in days) for animal feedingstuffs

A dietary burden calculation has been performed; taking into account the highest residues in animal feed items at harvest. Therefore a withholding period is not necessary.

2.7.16 Waiting period (in days) between last application and sowing or planting the crops to be protected

Not applicable since application is made after sowing.

2.7.17 Waiting period (in days) between application and handling treated product

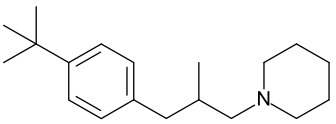
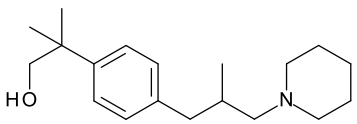
The general approach of avoiding handling until the spray solution has dried is recommended.

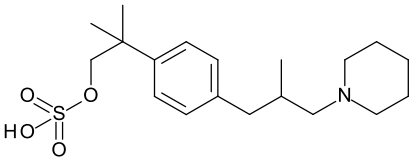
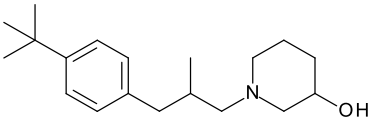
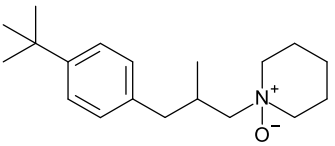
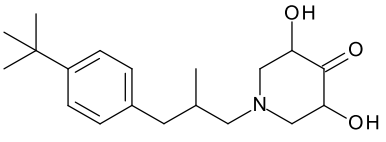
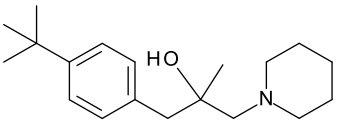
2.7.18 Waiting period (in days) between last application and sowing or planting succeeding crops

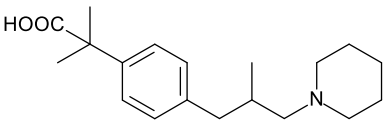
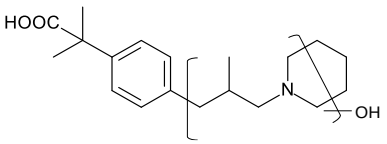
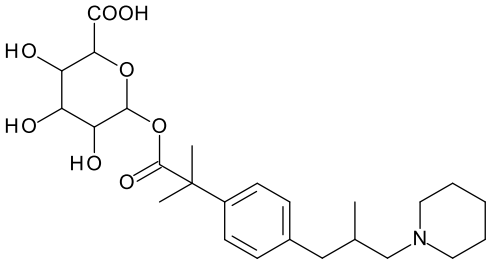
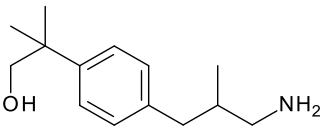
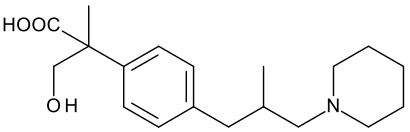
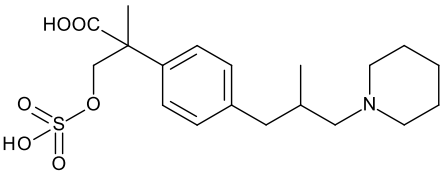
No specific plant-back restriction is required when fenpropidin is applied according to GAP.

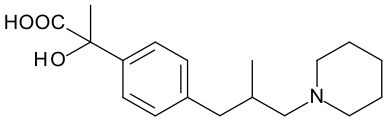
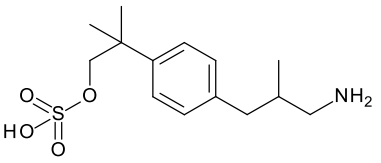
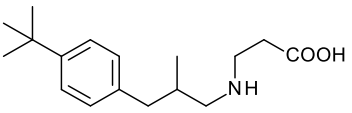
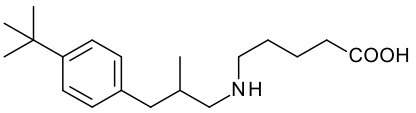
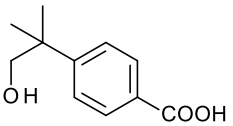
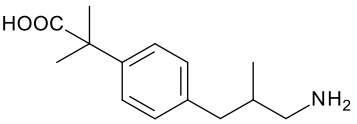
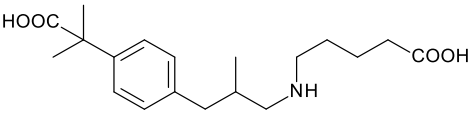
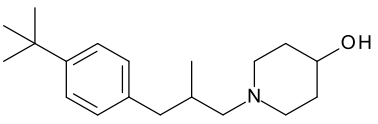
APPENDIX 2

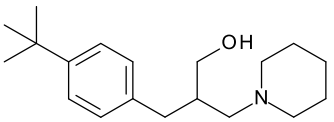
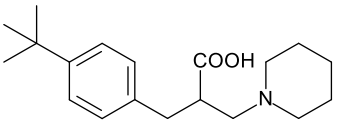
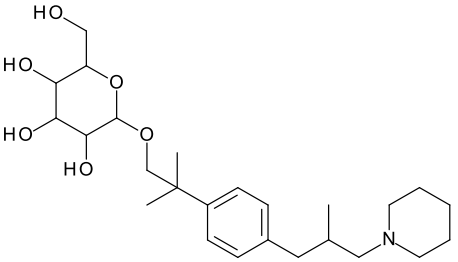
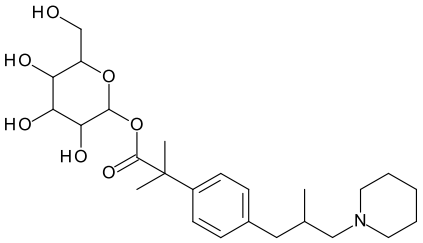
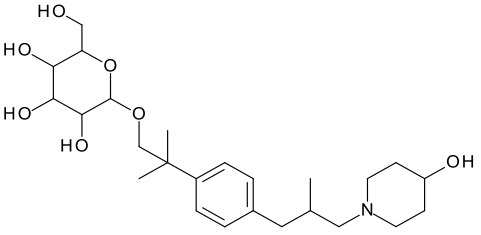
Codes, chemical names and chemical structures of fenpropidin its metabolites and their occurence

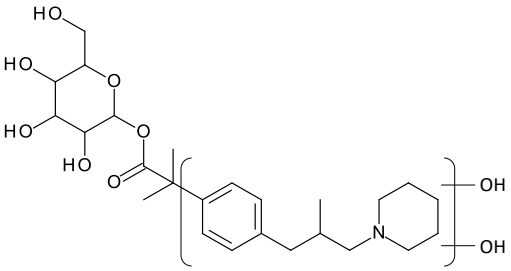
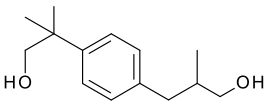
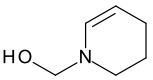
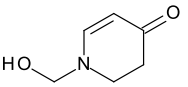
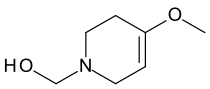
Code Number (Synonyms)	Description	Compound found in:	Structure
ISO common name: Fenpropidin Development codes: CGA114900 (Ciba Geigy) Ro 12-3049 (Maag) I_{11} I_{16} IA_7 M18	IUPAC name: 1-[3-(4-*tert*.-butylphenyl)-2-methylpropyl]-piperidine Chemical Abstracts name: 1-[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropyl]-piperidine [CAS 67306-00-7]	**Wheat** (immature crop, mature straw, grain) **Sugar beet** (foliage, root) Grape (fruit, leaves) **Banana** (pulp, leaves) **Rotational crops** (cereal, root vegetable and leafy) **Goat** (liver, fat) **Hen** (liver, muscle, skin+fat, egg white, egg yolk) **Rat** **Soil** **Aerobic mineralization** **Aerobic aquatic sediment**	
CGA289268 Ro 15-6046 Metabolite I_4 Metabolite I_{13} Metabolite I_{13a} Metabolite IA_{6a} Metabolite 4U	IUPAC name: 2-methyl-2-[4-(2-methyl-3-piperidin-1-yl-propyl)-phenyl]-propan-1-ol [CAS not available]	**Wheat** (immature crop, mature straw) **Sugar beet** (foliage) **Grape** (fruit, leaves) **Banana** (leaves) **Rotational crops**	

Code Number (Synonyms)	Description	Compound found in:	Structure
Metabolite M19		(cereal, root vegetable and leafy) **Goat** (fat) **Hen** (liver, muscle, skin+fat, egg white, egg yolk) **Rat** **Soil** **Aerobic mineralization** **Aerobic aquatic sediment**	
CGA289268 sulphate conjugate Metabolite M10 Metabolite 2U	IUPAC name: 2-methyl-2-[4-(2-methyl-3-piperidin-1-yl-propyl)-phenyl]-propan-1-ol sulphate conjugate [CAS not available]	**Goat** (liver, kidney, muscle, fat, milk) **Rat**	
CGA289265 Metabolite I_6 Metabolite I_{14}	1-[3-(4-*tert*.-butylphenyl)-2-methylpropyl]-piperidin-3-ol [CAS not available]	**Wheat** (immature crop, mature straw) **Sugar beet** (foliage) **Rotational crops** (cereal)	
CGA289263 Ro 12-7124 Metabolite I_7 Metabolite I_{12}	IUPAC name: 1-[3-(4-*tert*.-butylphenyl)-2-methylpropyl]-piperidine-1-oxide Chemical Abstracts name: 1-[3-[4-(1,1-dimethylethyl)phenyl]-2-methylpropyl]-piperidine-1-oxide [CAS 67306-64-3]	**Wheat** (immature crop, mature straw, grain) **Sugar beet** (foliage) **Grape** (fruit, leaves) **Banana** (pulp, leaves) **Rotational crops** (cereal, root vegetable and leafy) **Soil**	
SYN522245 Metabolite I_9	IUPAC name: 1-[3-(4-*tert*.-butylphenyl)-2-methylpropyl]-3,5-dihydroxy-piperidin-4-one [CAS not available]	**Wheat** (immature crop, mature straw, grain)	
CGA289266 Metabolite I_{10}	IUPAC name: 1-(4-*tert*.-butylphenyl)-2-methyl-3-piperidinyl-1-yl-propan-2-ol [CAS not available]	**Wheat** (immature crop, mature straw) **Sugar beet** (foliage)	

Code Number (Synonyms)	Description	Compound found in:	Structure
CGA289267 Metabolite I_6 Metabolite IA_{5a} Metabolite 1U Metabolite M20	IUPAC name: 2-methyl-2-[4-(2-methyl-3-piperidin-1-yl-propyl)-phenyl]-propionic acid [CAS not available]	**Sugar beet** (foliage) **Grape** (fruit, leaves) **Rotational crop** (cereal, root vegetable and leafy) **Goat** (liver, kidney, muscle, fat, milk) **Hen** (liver, muscle, skin+fat, egg white, egg yolk) **Rat** **Soil** **Aerobic mineralization** **Aerobic aquatic sediment**	
Hydroxy CGA289267 (location of hydroxylation unspecified)	-	**Wheat** (immature crop, mature straw)	
CGA289267 glucuronide conjugate Metabolite I_4	IUPAC name: 2-methyl-2-[4-(2-methyl-3-piperidin-1-yl-propyl)-phenyl]-propionic acid glucuronide conjugate [CAS not available]	**Goat** (liver, fat)	
SYN515215 Metabolite IA_{3a} Metabolite 7U	IUPAC name: 2-[4-(3-amino-2-methyl-propyl)-phenyl]-2-methyl-propyl-1-ol [CAS not available]	**Hen** (liver, egg white, egg yolk) **Rat**	
SYN515213 Metabolite IA_{4a2} Metabolite 8U Metabolite M12	IUPAC name: 3-hydroxy-2-methyl-2-[4-(2-methyl-3-piperidin-1-yl-propyl)-phenyl]-propionic acid [CAS not available]	**Goat** (liver, kidney, muscle, fat, milk) **Hen** (liver, skin+fat) **Rat**	
SYN515213 sulphate conjugate Metabolite M5	IUPAC name: 3-hydroxy-2-methyl-2-[4-(2-methyl-3-piperidin-1-yl-propyl)-phenyl]-propionic acid sulphate conjugate [CAS not available]	**Goat** (liver, kidney, muscle, fat, milk)	

Code Number (Synonyms)	Description	Compound found in:	Structure
SYN515214 Metabolite M11	IUPAC name: 2-hydroxy-2-[4-(2-methyl-3-piperidin-1-yl-propyl)-phenyl]-propionic acid [CAS not available]	**Goat** (liver, kidney, muscle, fat, milk)	
SYN515215 sulphate conjugate	IUPAC name: 2-[4-(3-amino-2-methyl-propyl)-phenyl]-2-methyl-propyl-1-ol sulphate conjugate [CAS not available]	**Goat** (liver, kidney)	
SYN522215 Metabolite 3U	IUPAC name: 3-[3-(4-*tert*.-butylphenyl)-2-methyl-propylamino]-propionic acid [CAS not available]	**Rat**	
SYN5222216 Metabolite 5U	IUPAC name: 5-[3-(4-tert-butylphenyl)-2-methyl-propylamino]-pentanoic acid [CAS not available]	**Rat**	
CGA294973 Metabolite 11U	IUPAC name: 4-(2-hydroxy-1,1-dimethyl-ethyl)-benzoic acid [CAS not available]	**Rat**	
SYN515216 Metabolite IA_{4a1} Metabolite 9U Metabolite M28	IUPAC name: 2-[4-(3-amino-2-methyl-propyl)-phenyl]-2-methyl-proprionic acid [CAS not available]	**Goat** (liver, kidney, muscle, fat) **Hen** (liver, skin+fat, egg white) Rat	
SYN522217 Metabolite IA4b Metabolite 10U	IUPAC name: 5-(3-[4-(1-carboxy-1-methyl-ethyl)-phenyl]-2-methyl-propylamino)-pentanoic acid [CAS not available]	**Hen** (liver, muscle, skin+fat, egg white) **Rat**	
CGA289269 Metabolite I_{13b}	IUPAC name: 1-[3-(4-*tert*.-butylphenyl)-2-methylpropyl]-piperidin-4-ol [CAS not available]	**Grape** (fruit) **Rotational crops** (cereal, root vegetable and leafy) **Soil**	

Code Number (Synonyms)	Description	Compound found in:	Structure
NOA406117 Metabolite I_{15}	IUPAC name: 3-[4-*tert.*-butylphenyl]-2-piperidin-1-ylmethyl-propan-1-ol [CAS not available]	**Sugar beet** (foliage) **Grape** (leaves) **Rotational crops** (cereal, root vegetable and leafy) **Soil**	
NOA406116 Metabolite I_{11} Metabolite I_{10a}	IUPAC name: 3-[4-*tert.*-butylphenyl]-2-piperidin-1-ylmethyl-propionic [CAS not available]	**Sugar beet** (foliage) **Grape** (leaves) **Rotational crops** (cereal and root vegetable) **Soil**	
[redacted] Metabolite I_{6a}	IUPAC name: [redacted] [CAS not available]	**Wheat** **Rotational crops** (cereal) **Soil**	[redacted]
CGA289268 glucose conjugate Metabolite I_{2a}	IUPAC name: 2-hydroxymethyl-6-{2-methyl-2-[4-(2-methyl-3-piperidin-1-ylpropyl)-phenyl]-propoxy}-tetrahydro-pyran-3,4,5-triol [CAS not available]	**Wheat** (immature crop, mature straw) **Grape** (leaves)	
CGA289267 glucose conjugate	IUPAC name: 2-methyl-2-[4-(2-methyl-3-piperidin-1-yl-propyl)-phenyl]-propionic acid glucose conjugate [CAS not available]	**Grape** (leaves)	
SYN522246 glucose conjugate Metabolite I_{2b}	IUPAC name: 1-[3-[4-(2-hydroxy-1,1-dimethyl-ethyl)phenyl]-2-methyl-propyl]piperidin-4-ol glucose conjugate [CAS not available]	**Wheat** (mature straw)	
[redacted] Metabolite I_{19} Lilial	IUPAC name: [redacted] [CAS not available]	**Grape** (leaves) **Sugar beet** (foliage) **Soil** (tentative assignment)	[redacted]

Code Number (Synonyms)	Description	Compound found in:	Structure
Acyl glycoside of dihydroxy CGA289267	-	**Wheat** (immature crop, mature straw)	
SYN522247 Metabolite H-12	IUPAC name: 2-[4-(2-hydroxypropyl)-phenyl]-2-methyl-propan-1-ol [CAS not available]	**Sugar beet** (foliage)	
SYN522248 Metabolite I_{13b}	IUPAC name: (3,4-dihydro-*2H*-pyridin-1-yl)-methanol [CAS not available]	**Wheat** (immature crop, mature straw)	
SYN522249 Metabolite I_{13c}	IUPAC name: 1-hydroxymethyl-2,3-dihydro-*1H*-pyridin-4-one [CAS not available]	**Wheat** (immature crop, mature straw)	
SYN522250 Metabolite I_3	IUPAC name: (4-methoxy-3,6-dihydro-*2H*-pyridin-1-yl)-methanol [CAS not available]	**Wheat** (immature crop, mature straw)	

2.8 FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1 Summary of fate and behaviour in soil

The comparative aerobic and anaerobic metabolism study and the sterile degradation study demonstrated that biodegradation occurs mainly under oxidative conditions; photochemical transformation is not an important route of degradation on soil. This is consistent with the range of metabolites identified in the aerobic studies. CGA 289269 (4-hydroxy derivative of fenpropidin) and CGA 289263 (N-oxide derivative of fenpropidin) were characterised as products of oxidation of the piperidine ring. The hydroxylated intermediate metabolite CGA 289268 and which is subsequently oxidised to CGA 289267 were both characterised as oxidative products of the tertiary butyl side chain. In all cases the majority of the residue was subsequently mineralised to carbon dioxide. CGA 289269, CGA 289263 and CGA 289268 were identified but none of them represented > 5% of applied radioactivity in viable soils at standard laboratory conditions. The metabolite CGA 289267 was identified at > 10% of applied radioactivity in a test system incubated at 8 °C. At 22 °C it was identified at a maximum of 4.6% of applied radioactivity.

A scheme on the proposed route of degradation is given in Figure 2.8.1-1.

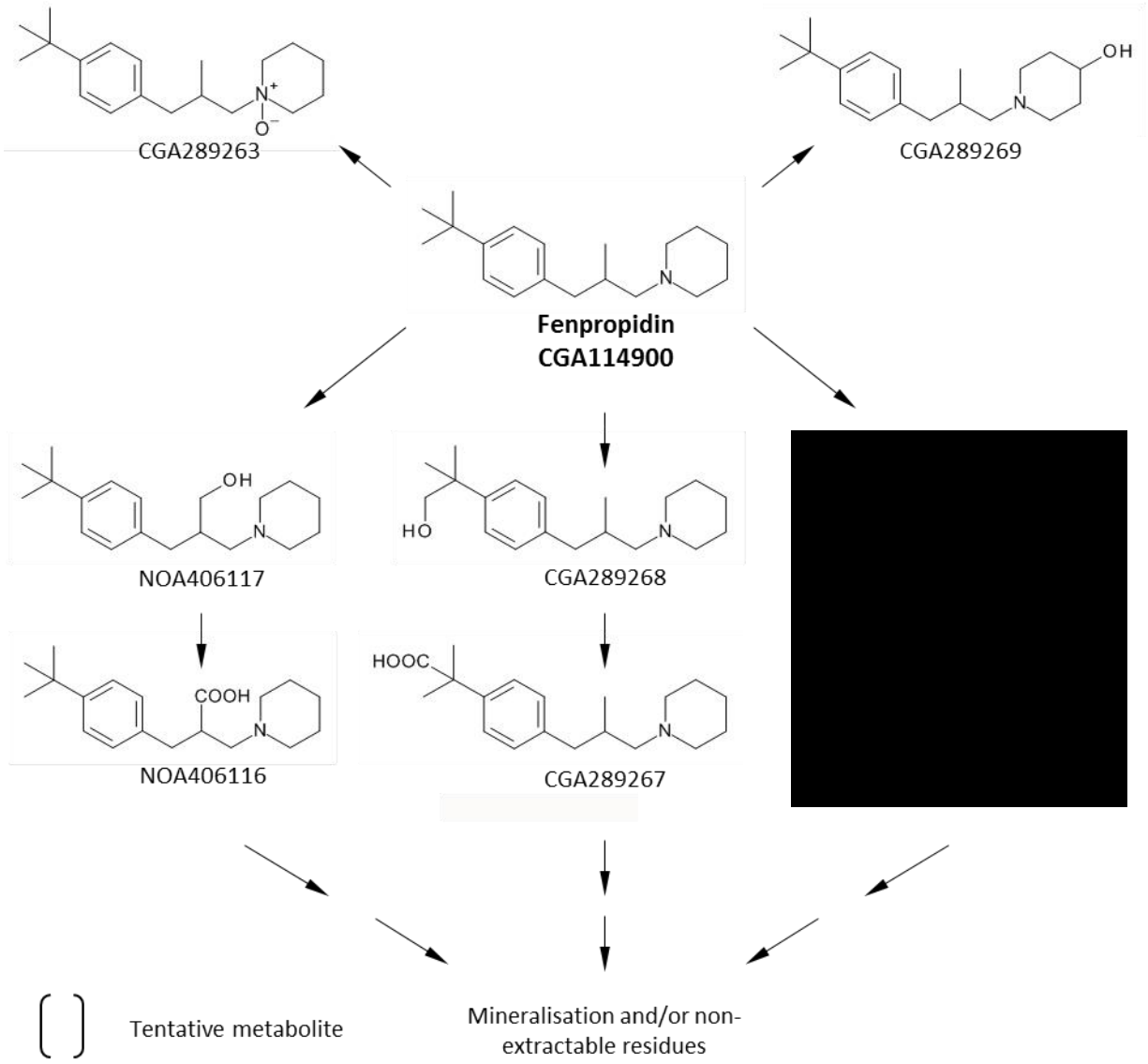


Figure 2.8.1-1: Proposed route of degradation of fenpropidin in soil

2.8.2 Summary of fate and behaviour in water and sediment [equivalent to section 11.1 of the

Under sterile aquatic conditions, fenpropidin was stable to hydrolysis at pH 3, 7 and 9. The photolytic degradation of fenpropidin in water has been investigated under sterile conditions in aqueous buffer solution at pH 6. Photochemical transformation in water is not considered to be a significant route of degradation of fenpropidin.
In a new aerobic mineralisation study (OECD 309) the fate of fenpropidin was investigated in natural water at pH 8.4. The degradation rate was dependent on concentration and slower in the sterile system than the biotic systems. The only major degradate of fenpropidin was found to be CGA289267 which reached a maximum mean level of 25.5% of applied radioactivity at the higher rate treatment. CGA289267 was not detected in sterilised samples. Mineralization was a minor route of degradation.
In four water / sediment systems (pH of water phases between 6.5 and 7.4) fenpropidin rapidly dissipated from the water phase to the sediment in all systems. Degradation of fenpropidin in the whole water/sediment systems was relatively slow. Once deposited in the sediment, parent remained relatively stable maximum as evidenced by the slow degradation over time and the lack of formation of significant metabolites. Fenpropidin reached a maximum of 58.2% of applied radioactivity in the sediment at day 44 before declining to 28.5% at 106 days. The only major degradate of fenpropidin was found to be CGA289267 which reached a maximum mean level of 19.4% of applied radioactivity in the water phase and 7.8% in the sediment phase. Carbon dioxide was a major product of metabolism in all systems reaching a maximum value of 45.4%.

2.8.2.1 Rapid degradability of organic substances

Table 54: Summary of relevant information on rapid degradability

Method	**Results***	**Key or Supportive study**	**Reference**
Aerobic Mineralisation of ^{14}C- Fenpropidin in Surface Water, OECD 309	Mineralisation of fenpropidin not significant, mean $^{14}CO_2$ levels never exceeded 6.2% AR for all of the incubation groups tested.	Key	Williams, D. (2016)
Aerobic transformation of ^{14}C-labelled Fenpropidin in water/sediment	DT50 = 53.7 – 129 days in whole system for fenpropidin	Key	Klöppel, H. (2006c)
Aerobic Aquatic-Sediment Metabolism of ^{14}C-Fenpropidin, Aerobic Aquatic-Sediment Metabolism of ^{14}C-Fenpropidin: Additional Confirmatory Analyses, OECD 308	DT50 = 27.8 days in whole system for fenpropidin	Key	Adam, D. (2016), Adam, D. (2016a)
Degradation of Ro 12-3049/031 in soil/aquatic systems. RCC, Itingen, Switzerland	The current value of the unknown metabolite of 5.7 % AR is only slightly above 5 % AR, therefore, it is likely that this would be below 5% AR if the	Key	Van Dijk, A. (1987)

Method	Results*	Key or Supportive study	Reference
	entire chromatogram had been quantified.		

** data on full mineralization should be reported*

2.8.2.1.1 Ready biodegradability

Fenpropidin seemed to be degraded in at least two steps, seen as two lag phases. A plateau of the biodegradation curve was not reached at day 41. The shapes of the curves were similar at both test concentrations, but degradation was slower at the higher test concentration. Since >20% biodegradability was observed fenpropidin may be classified as "inherently biodegradable". The positive control was degraded by 87% within 141 hours.

Table 55: Summary of relevant information on ready degradability

Method	Results	Remarks	Reference
Ready Biodegradability (modified Sturm Test) of Ro 12-3049 {1-(3-[p-tert-butylphenyl]-2-methylpropyl)-piperidene} according to OECD Test Guideline 301B.	Not readily biodegradable according to the OECD criteria	Key study	Lebertz, H. (1990)

2.8.2.1.2 BOD5/COD

Data not available

2.8.2.2 Other convincing scientific evidence

Data not available

2.8.2.2.1 Aquatic simulation tests

Data not available

2.8.2.2.2 Field investigations and monitoring data (if relevant for C&L)

Data not available

2.8.2.2.3 Inherent and enhanced ready biodegradability tests

Data not available

2.8.2.2.4 Soil and sediment degradation data

Data on soil degradation are reported under 2.8.1, whilst sediment degradation data are presented under 2.8.2

2.8.2.2.5 Hydrolysis

Data on hydrolysis are reported under 2.8.2.

2.8.2.2.6 Photochemical degradation

Data on photochemical degradation are reported under 2.8.1 and 2.8.2.

2.8.2.2.7 Other / Weight of evidence

None

2.8.3 Summary of fate and behaviour in air

The photochemical-oxidative half-life of fenpropidin in air is 3.4 hours. The vapour pressure of fenpropidin is 0.019 Pa, which is in excess of the triggers for volatilisation of 10^{-5} Pa from plants and 10^{-4} Pa from soil. The volatilisation of fenpropidin from plant and soils surfaces has therefore been investigated as well as the deposition of fenpropidin following volatilisation in wind tunnels under semi field conditions. As the vapour pressure of fenpropidin is in excess of the triggers for volatilisation from plant and soil surfaces, the volatilisation/re-deposition values of fenpropidin have been used for the aquatic risk assessment.

2.8.3.1 Hazardous to the ozone layer

Data not available

2.8.3.1.1 Short summary and overall relevance of the provided information on hazards to the ozone layer

Data not available

2.8.3.1.2 Comparison with the CLP criteria

The substance is not mentioned in Annexes of the Montreal Protocol.

2.8.3.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

Not classified

2.8.4 Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

No monitoring data are available for fenpropidin

2.8.5 Definition of the residues in the environment requiring further assessment

The residue definition relevant for environmental risk assessment is as follows:

Soil	Fenpropidin and CGA289267
Groundwater	Fenpropidin and CGA289267
Surface water	Fenpropidin and CGA289267
Sediment	Fenpropidin and CGA289267
Air	Fenpropidin

2.8.6 Summary of exposure calculations and product assessment

Exposure via Soil

The predicted environmental concentrations in soil (PEC_{soil}) for the active substance fenpropidin and its metabolite CGA289267 were calculated based on a simple first tier approach (Microsoft® Excel spreadsheet) assuming even distribution of the compound in the upper 0-5 cm soil layer. A standard soil density of 1.5 g/cm^3 was assumed. The interception rates follow the recommendations of the FOCUS groundwater guidance paper (FOCUS 2014) for cereals (BBCH 31-69): 80/90% interception). According to the use pattern, multiple foliar spray applications of fenpropidin at rates of 281.25 and 562.5 g fenpropidin/ha to winter and spring cereals between BBCH 31 and 69 were considered.

The new kinetic evaluations of field studies resulted in a maximum DT_{50} for fenpropidin of 1000 days (SFO, un-normalised); hence the calculation of a $PEC_{plateau}$ is triggered.

For the metabolite CGA289267 the max DT_{50} was 55.8 days (SFO, un-normalised); a $PEC_{plateau}$ calculation was also calculated.

Details of the calculations are given in Volume 3_CP_B-8, Section B.8.2 for fenpropidin.

Exposure via Groundwater

Predicted environmental concentrations in groundwater (PEC_{gw}) for fenpropidin and its metabolite CGA 289267 were calculated for the use in Europe, using the simulation model FOCUS PEARL (version 4.4.4), PELMO (version 5.5.3) and MACRO (version 5.5.4). PEC_{gw} were evaluated as the 80th percentile of the mean annual leachate concentration at 1 m soil depth. Model parameters and scenarios consisting of weather, soil, and crop data were used as proposed by FOCUS.

All PEC_{gw} values for fenpropidin for use in spring and winter cereals were <0.1µg/L. Based on FOCUS groundwater calculations with PEARL and PELMO models, it can be concluded that the representative use of fenpropidn on cereals poses no unacceptable risk to groundwater at 1 m depth. The metabolite CGA289267, present a PECgw values clearly above the 0.1 µg/L.

Details of the calculations are given in Volume 3_CP_B-8, Section B.8.3 for fenpropidin.

Table 2.8.6-1: PEC_{gw} at 1 m soil depth for fenpropidin following two applications of fenpropidin to winter and spring cereals (FOCUS-PELMO)

Scenario	FOCUS-PELMO			
	Application to winter cereals 2 x 562.5g a.s./ha (80/90% CI)		Application to spring cereals 2 x 562.5 g a.s./ha (80/90% CI)	
	Fenpropidin	CGA 289267	Fenpropidin	CGA 289267
	PEC_{gw} [µg/L]	PEC_{gw} [µg/L]	PEC_{gw} [µg/L]	PEC_{gw} [µg/L]
Châteaudun	< 0.001	0.023	< 0.001	0.017
Hamburg	< 0.001	0.376	< 0.001	0.338
Jokioinen	< 0.001	0.223	< 0.001	0.160
Kremsmönster	< 0.001	0.224	< 0.001	0.211
Okehampton	< 0.001	0.421	< 0.001	0.386
Piacenza	< 0.001	0.221	-	-
Porto	< 0.001	0.346	< 0.001	0.315
Sevilla	< 0.001	0.004	-	-
Thiva	< 0.001	0.014	-	-

- Scenario not relevant for the crop

Table 2.8.6-2: PEC_{gw} at 1 m soil depth for fenpropidin following two applications of fenpropidin to winter and spring cereals (FOCUS-PEARL)

Scenario	FOCUS-PEARL			
	Application to winter cereals 2 x 562.5g a.s./ha (80/90% CI)		Application to spring cereals 2 x 562.5 g a.s./ha (80/90% CI)	
	Fenpropidin	CGA 289267	Fenpropidin	CGA 289267
	PEC_{gw} [µg/L]	PEC_{gw} [µg/L]	PEC_{gw} [µg/L]	PEC_{gw} [µg/L]
Châteaudun	< 0.001	0.035	< 0.001	0.030
Hamburg	< 0.001	0.389	< 0.001	0.430
Jokioinen	< 0.001	0.189	< 0.001	0.189
Kremsmönster	< 0.001	0.224	< 0.001	0.242
Okehampton	< 0.001	0.418	< 0.001	0.391
Piacenza	< 0.001	0.134	-	-
Porto	< 0.001	0.208	< 0.001	0.288
Sevilla	< 0.001	0.005	-	-
Thiva	< 0.001	0.015	-	-

- Scenario not relevant for the crop

Table 2.8.6-3: PEC_{GW} of fenpropidin and CGA289267 following two applications of fenpropidin to winter and spring cereals (FOCUS-MACRO)

Application rate [g a.s./ha]	Number of applications	Scenario	PEC_{GW} at 1 m soil depth [µg/L]			
			Winter cereals		Spring cereals	
			Fenpropidin	CGA 289267	Fenpropidin	CGA 289267
562.5	2	Châteaudun	< 0.001	< 0.001	< 0.001	< 0.001

Exposure via Surface Water and Sediment

Predicted environmental concentrations of the active substance fenpropidin and its metabolite CGA289267 in surface water (PEC_{sw}) and sediment (PEC_{sed}) were calculated for the use in Europe, employing the tiered FOCUS Surface Water (SW) approach (FOCUS 2001, 2015). All relevant entry routes of a compound into surface water (principally a combination of spray drift and runoff/erosion or drain flow) were considered in these calculations.

The FOCUS tool SWASH (v 5.3), including the operational models FOCUS-MACRO (v 5.5.4), FOCUS-PRZM (v 4.3.1) and FOCUS-TOXSWA (v 4.4.3), were used in the modelling study for Step 3 simulations. The ECPA tool SWAN (v 4.0.1) was used to implement mitigation options at Step 4. With a vapour pressure of 0.019 Pa dry deposition of fenpropidin following volatilisation was included in the Step 4 calculations.

For the use of fenpropidin on cereals (winter and spring), FOCUS Steps 1-4 were performed for its metabolite CGA289267, FOCUS steps 1-2 were performed.

According to the use pattern, multiple foliar spray applications of fenpropidin at rates of 281.25 and 562.5 g fenpropidin/ha to winter and spring cereals between BBCH 31 and 69 were considered.

Details of the calculations are given in Volume 3_CP_B-8, Section B.8.5 for fenpropidin.

Other routes of exposure

There are no other routes of exposure if the product is used according to good agricultural practice.

2.9 EFFECTS ON NON-TARGET SPECIES

Metabolites

According to the results presented in Volume 3 CA B.7 (7.1 – 7.3), the only metabolite considered requiring an ecotoxicological risk assessment is CGA289267:

Fenpropidin metabolites identified as requiring an ecotoxicological risk assessment

Compartment	Metabolite
Soil	Fenpropidin, CGA289267
Surface water	Fenpropidin, CGA289267
Sediment	Fenpropidin, CGA289267
Groundwater	Fenpropidin, CGA289267

2.9.1 Summary of effects on birds and other terrestrial vertebrates

Effects on birds

The results of avian toxicity studies for fenpropidin are summarised in the table below.

Table 2.9.1-1 Summary of avian toxicity studies for fenpropidin

Test species	Test substance	Test system	Endpoint	Toxicity (mg/kg bw/day)	Reference[a]
Mallard duck (*Anas platyrhynchos*) [#]	Fenpropidin	Acute, oral 14 d	LD_{50}	1899 mg/kg bw	[redacted] (1980a) CGA114900/0062
Pheasant (*Phasianus colchicus*) [#]	Fenpropidin	Acute, oral 14 d	LD_{50}	n.a.	[redacted] (1980b) CGA114900/0063
Japanese quail (*Coturnix coturnix japonica*)	Fenpropidin	Acute, oral 14 d	LD_{50}	n.a.	[redacted] (1997a) CGA114900/1061 8
Bobwhite quail (*Colinus virginianus*) [#]	A7516B	Acute, oral 14 d	LD_{50}	568 mg form./kg bw **431 mg a.s./kg bw**	[redacted] et al. (2001) CGA114900/4652
Bobwhite quail (*Colinus virginianus*) [# a]	Fenpropidin	Short-term dietary, 5 day feeding	LC_{50} LDD_{50}	>6594 ppm >1417 mg/kg bw/d	[redacted] & [redacted] (1986) CGA114900/0065
Mallard duck (*Anas platyrhynchos*) [# a]	Fenpropidin	Short-term dietary, 5 day feeding	LC_{50} NOEL [2]	3762 ppm 103 mg/kg bw/d	[redacted] et al. (1986) CGA114900/0064
Japanese quail (*Coturnix coturnix japonica*)	Fenpropidin	Short-term dietary, 5 day feeding	LC_{50} LDD_{50}	>5000 ppm >630 mg/kg bw/d	[redacted] (1997a) CGA114900/1062 1
Bobwhite quail (*Colinus virginianus*) [#]	Fenpropidin	Subchronic and reproductive, 21 weeks feeding	NOEC NOEL	180 ppm **14.6 mg/kg bw/d**	[redacted] & [redacted] (1992) CGA114900/0133

[#] Study evaluated in old DAR (2005).
[a] Study evaluated or re-evaluated in old Addendum (2007)
[1] The study is not considered valid or suitable for regulatory use.
[2] The NOEL of 103 mg/kg bw/day based on mortality was set as an endpoint to replace the LDD50 which could not be reliably calculated due to high mortality at higher tested doses.
n.a. not applicable
Endpoints used in the regulatory risk assessment included in bold.

Effects on terrestrial vertebrates other than birds

A summary of the key mammalian toxicity studies relevant to the ecotoxicological risk assessment is given in the table below. These data were evaluated in Section B.6 where further discussion can be found.

Table 2.9.1-2 A summary of the key mammalian toxicity studies relevant to the ecotoxicological risk assessment

Substance	Species	Type of study, dose range tested	Study endpoint	Value, adverse effects at LOAEL	Reference
Acute oral toxicity					
Fenpropidin	Rat	Acute oral, OECD 401; Males: 2.05, 2.34, 2.63, 3.51, 4.68, 5.85 ml/kg bw (1872, 2136, 2401, 3205, 4273, 5341 mg/kg bw) Females: 0.59, 1.17, 1.46, 1.61, 1.76, 2.05, 2.34, 3.51 ml/kg bw (539, 1068, 1333, 1470, 1607, 1872, 2136, 3205 mg/kg bw)	LD_{50}	2173 mg/kg bw (2.38 ml/kg bw) (M) **1452 mg/kg bw** (1.59 ml/kg) (F)	[redacted] 1981
Fenpropidin	Rat	Acute oral, OECD 401; 0, 1.0, 1.6, 2.5, 4.0 ml/kg bw (corresponding to 913, 1461, 2283, 3652 mg/kg bw)	LD_{50}	2009 mg/kg bw (2.2 ml/kg)	[redacted] 1987
Long-term toxicity					
Fenpropidin	Rat	Two-generation reproduction,; OECD 416; 0, 25, 100, 500 and 1000 ppm M: 2-3, 8-10, 42-58 and 80-126 mg/kg bw/d F: 2-5, 8-18, 45-96 and 88-205 mg/kg bw/d Overall grand mean values (mean of grand means per period, sex and generation): 2.9, 11.4, 60.3 and 123 mg/kg bw/day	NOAEL [NOAEC]	Parental toxicity: **11.4 mg/kg bw/d** [100 ppm] Body weight gain reduction, decreased food consumption, organ weights and histopathology changes, Reproductive toxicity: 123 mg/kg bw/d [1000 ppm] No effects at any dose level. Offspring toxicity: **11.4 mg/kg bw/d** [100 ppm] Body weight gain reduction, delayed sexual	[redacted] (2003)

				maturation.	
Fenpropidin [1]	Rat	Two-generation reproduction,; OECD 416; 0, 6.25, 25, 100 ppm corresponding to 0.4, 1.61, 6.43 and 0.50, 2.03, 8.02 mg/kg bw/day for F0 and F1 males respectively. 0.48, 1.91, 7.79 and 0.56, 2.35, 9.31 mg/kg bw/day for F0 and F1 females respectively (premating period only).	NOAEL [NOAEC]	Parental, reproductive and offspring toxicity: 7.9 mg/kg bw/d [2] (overall mean value for both sexes) [100 ppm] No effects at any dose level.	[redacted] et al (1987)
Fenpropidin [1]	Rat	Developmental (in diet), OECD 414, F: 0, 19.5, 47.5 and 87.8 mg/kg bw/d	NOAEL	Maternal: 47.5 mg/kg bw/d Decreased body weights and body weight gain. Developmental: 47.5 mg/kg bw/d Skeletal effects on neural arches.	[redacted] (1981)
Fenpropidin	Rat	Developmental (gavage), OECD 414, F: 0, 10, 60, 90 mg/kg bw/d	NOAEL	Maternal and developmental: 90 mg/kg bw/d Not significant decrease in maternal body weight gain and significant decrease of food consumption but no treatment-related foetal abnormalities.	[redacted] (1994)
Fenpropidin [1]	Rabbit	Developmental (gavage), OECD 414, F: 0, 5, 12, 30 mg/kg bw/d	NOAEL	Maternal: 12 mg/kg bw/d Reduced body weight gain. Developmental: 30 mg/kg bw/d Reduced mean litter weight.	[redacted] and [redacted] (1981)
Fenpropidin	Rabbit	Developmental (gavage), OECD 414, F: 0, 5, 10, 20 mg/kg bw/d	NOAEL	Maternal: 10 mg/kg bw/d Reduced body weight gain. Developmental: 10 mg/kg bw/d	[redacted] (2011)

				Increased incidence of persistent truncus arteriosus and severely malaligned sternebrae.	

[1] Supplementary study.
[2] No effects observed up to the highest dose tested in this study. It is not the defining study in this area, because there was similar and more robust study testing to higher doses.

Selection of acute toxicity endpoint
The lowest acute endpoint LD_{50} of 1452 mg a.s./kg bw determined for female rats from the study by [redacted] (1981) is used in the acute risk assessment.Since the difference in acute LD_{50} between male and female rats in this study was greater than 25 % the geometric mean could not be taken into account.

Selection of reproductive toxicity endpoint
For the long-term risk assessment, the Notifier suggested the endpoint of 500 ppm (calculated as mean 60.25 mg a.s./kg bw/d) from 2-generation rat study ([redacted] 2003) based on the EFSA report for fenpropidin (EFSA Scientific Report No. 124, 2007) where the following was concluded:
"The endpoint NOAEL of 60.25 mg/kg bw/d from a 2-generation reproduction study in rats was discussed since effects on body weight gain were observed. No other adverse effects were observed in the study at this concentration. The experts agreed to the use of the endpoint since the magnitude of effects was low and at least partly caused by reduced maternal food consumption."

However, based on the RMS evaluation of the study by [redacted] (2003) in Volume 3 B.6 CA, the following conclusion was provided:
"The only effect on reproduction was a significant delay in sexual maturation at doses above 500 ppm for F1 females and 1000 ppm for F1 males. The number of pups delivered and the number of implantations was significantly reduced at 1000 ppm for the F2 pups only. **The NOAEL for effects on offspring and reproduction is 100 ppm.**
The body weights, both absolute and relative were reduced for all generations at doses above 500 ppm. Effects on organ weights and histopathology were also observed at doses above 500 ppm for all generations. The **NOAEL for the parental effects is 100 ppm.**
The effects on thymus weights and spleen weights that occurred in all generations and the histological evidences of reduced extramedullary hematopoesis, reduced lymphohistiocytic infiltration of the liver, and atrophy of phagocytic cells in thymus might indicate an immunosuppressive effect of fenpropidin. However, the effects were less severe in the F1 pups generation than in the F1 parent generation. Also no consistent similar effects were observed in any of the sub chronic toxicity studies in rats (or mice) at similar dose levels. In the 90 day rat study decreased thymus weights occurred but without histopathological evidence of damage. Since these effects were confined to this study and only at high doses in the presence of reduced body weights, these effects are considered as incidental."
Hence, taking into account effects on sexual maturation which are considered as relevant for reproductive performance according to EFSA GD (2009), RMS has proposed the ecotoxicologically relevant endpoint derived from this study NOEL of 11.4 mg a.s./kg bw/day from 2-generation rat study ([redacted] 2003).

In addition, a new developmental study in rabbit was submitted ([redacted] 2011). The maternal and developmental NOAEL derived from this study is 10 mg a.s./kg bw/day, based on reduced body weight gain of mothers and on increased incidence of persistent truncus arteriosus and severely malaligned sternebrae. All these adverse effects are considered as ecotoxicologically relevant.

Overall, RMS has proposed as the ecotoxicologically relevant endpoint to be used in the reproductive risk assessment for wild mammals **NOEL of 10 mg a.s./kg bw/day** from developmental study in rabbit ([redacted] 2011).

For details see Volume 3 CP B.9, Section B.9.1.2.

The selection of ecotoxicologically relevant endpoint to be used in the reproductive risk assessment for wild mammals should be discussed in peer review.

2.9.2 Summary of effects on aquatic organisms [section 11.5 of the CLH report]

2.9.2.1 Bioaccumulation [equivalent to section 11.4 of the CLH report template]

Table 56: Summary of relevant information on bioaccumulation

Method	Species	Results	Key or Supportive study*	Remarks	Reference
Not stated	*Lepomis macrochirus*	BCF 163	Acceptable Key study	-	[redacted] (1989)
OECD 305	*Danio rerio*	BCF 62 – 14 (mean 103.5)	Acceptable Key study	-	[redacted] (2006)

2.9.2.1.1 Estimated bioaccumulation

No data available.

2.9.2.1.2 Measured partition coefficient and bioaccumulation test data

[redacted] **(1989):** In a bio-concentration study, groups of Bluegill sunfish (*Lepomis macrochirus)* (50 in the control and 60 in each of the duplicate test substance treatment) were exposed to 0.19 mg/L of ^{14}C-fenpropidin for a period of 28 days under flow-through conditions (uptake phase), followed by a period of 14 days in test medium without test substance (depuration phase). An untreated control group was run concurrently.
Mortality and behaviour of the fish were recorded. Temperature, pH and oxygen concentrations were measured daily in all test vessels. From the treatment tanks 10 fish, 5 from each tank, were sampled at day 0 (1 hour after start of treatment), 3, 7, 14, 21 and 28 of the exposure phase. During the depuration phase 6 fish per sampling interval were taken at day 1, 3, 7, 10 and 14. From the control tank fish were taken at day 0 (1 hour after treatment) and 28 of the exposure phase, and at day 14 of the depuration phase.. Water samples were taken at day 0 (1 hour after start of treatment), 1, 3, 7, 14, 21 and 28 of the exposure phase and at day 1, 7 and 14 of the depuration phase. From the control tank water samples were taken at day 0 (1 hour after start of treatment), 14 and 28 of the exposure phase.. The test concentrations in the water phase were within ± 20 % of nominal values throughout the uptake phase.
Steady state concentrations were reached within 3 days of exposure. The steady state residue values divided by the average concentration in both tanks, 0.19 mg parent equivalents/l, resulted in BCF of 25, 259 and 163 for edible parts, non-edible parts and whole fish respectively. The half-lives calculated from the slope of the line passing through the points corresponding to day 0 and day 1 of the depuration phase were 17.3, 14.6 and 16.8 hours for edible, non-edible and whole fish tissues, respectively.
The study is considered valid and acceptable for regulatory use.

[redacted] **(2006):** In a bio-concentration study, groups of 50 zebra fish were exposed to 42 and 140 µg/L of ^{14}C-fenpropidin for a period of 4 days under flow-through conditions (uptake phase), followed by a period of 4 days in test medium without test substance (depuration phase). An untreated control group was run concurrently.
Mortality and behaviour of the fish were recorded. Temperature, pH and oxygen concentrations were measured daily in all test vessels. Four fish per group were sampled during the uptake phase at 0, 7, 14, 28, 48, 56, 72 , 76, 84, 96 and 100 hours and during the depuration phase at 7, 20, 35 and 70 hours. Water samples were taken concurrently during the uptake phase and at the first sampling time of the depuration phase. The test concentrations in the water phase were within ± 20 % of nominal values throughout the uptake phase.
BCF values related to whole body weight were calculated as mean BCF derived from BCF_{SS} and BCF_k values at 62 and 145 for environmental concentrations around 40 µg/L and 120 µg/L, respectively. The BCF was dependent on the exposure concentration due to slow net uptake which is counteracted by fast test item depuration and metabolism. Depuration and/or metabolic degradation in fish is rapid as demonstrated by a mean clearance rate DT_{95} = 0.85 days.
The study is considered valid and acceptable for regulatory use.

The fish bioconcentration studies showed a rapid depuration of residues of the active substance. The results do not indicate a potential for bioaccumulation of fenpropidin (BCF in fish < 500).

2.9.2.2 Acute aquatic hazard [equivalent to section 11.5 of the CLH report template]

Table 57: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results[1]	Key or Supportive study*	Remarks	Reference
Not stated	Rainbow trout (*Oncorhynchus mykiss*)	Fenpropidin	96 h LC_{50} 2.57 mg/L (mm)	Acceptable Key study	-	[redacted] (1981b)
EU method C.1 (92/69/EEC)	Rainbow trout (*Oncorhynchus mykiss*)	Fenpropidin	96 h LC_{50} 2.84 mg/L (mm)	Acceptable Key study	-	[redacted] (2006)
Not stated	Bluegill sunfish (*Lepomis macrochirus*)	Fenpropidin	96 h LC_{50} 1.93 mg/L (mm)	Acceptable Key study	-	[redacted] (1981a)
Not stated	Common carp (*Cyprinus carpio*)	Fenpropidin	96 h LC_{50} 3.55 mg/L (mm)	Acceptable Key study	-	[redacted] (1981c)
EU method C.1 (92/69/EEC)	Zebra fish (*Danio rerio*)	Fenpropidin	96 h LC_{50} 5.37 mg/L (mm)	Acceptable Key study	-	[redacted] (2006a)
Not stated	*Daphnia magna*	Fenpropidin	48 h EC_{50} 0.54 mg/L (mm)	Acceptable Key study	-	Hill (1981d)
OECD 202	*Daphnia magna*	Fenpropidin	48 h EC_{50} 6.15 mg/L (mm)	Acceptable Key study	-	Noack (2007a)
OECD 201	Freshwater green (*Desmodesmus subspicatus*)	Fenpropidin	96 h E_rC_{50} n.a. 96 h E_bC_{50} n.a.	Not valid	Validity criteria not met for the mean coefficient of variation for section-by section specific growth rate and for the specific growth rate in control	Handley (1989)
ASTM guideline E 1218-90	Freshwater green (*Microcystis aeruginosa*)	Fenpropidin	96 h E_rC_{50} n.a. 96 h E_bC_{50} n.a.	Not valid	Validity criteria not met for the mean coefficient of variation for section-by section specific growth rate and for the specific growth rate in control	Grade (1993a)
OECD 201	Freshwater green (*Desmodesmus subspicatus*)	Fenpropidin	96 h E_rC_{50} >0.001 mg/L 96 h E_bC_{50} n.d.	Acceptable Key study	-	Pupp & Wydra (2008)
OECD 201	Freshwater green (*Desmodesmus subspicatus*)	Fenpropidin	72 h E_rC_{50} 0.000688 mg/L	Acceptable Key study	-	Scheerbaum (2007a) Pickering &

			72 h E_yC_{50} 0.000044 mg/L (mm)			Allen (2018a)
OECD 221	Duckweed *(Lemna gibba)*	Fenpropidin	Frond number: 7 d E_rC_{50} 0.0789 mg/L 7 d E_yC_{50} 0.00367 mg/L Dry weight: 7 d E_rC_{50} 0.293 mg/L 7 d E_yC_{50} 0.00819 mg/L (mm)	Acceptable Key study	-	Bebon & Wydra (2017)
OECD 239	*Myriophyllum spicatum*	Fenpropidin	Shoot length: 14 d E_rC_{50} 2.0 mg/L 14 d E_yC_{50} 1.8 mg/L Shoot wet weight: 14 d E_rC_{50} 0.77 mg/L 14 d E_yC_{50} 0.77 mg/L Shoot dry weight: 14 d E_rC_{50} 0.91 mg/L 14 d E_yC_{50} 0.88 mg/L (mm)	Acceptable Key study	-	Kirkwood (2018)

Acute toxicity studies on fish, daphnia and alga were available also for metabolite CGA289267, indicating that its toxicity is considerably lower than the toxicity of parent (100-100000x lower). For details see Table 9.4.1-1 in Volume 3 CP B.9 of RAR.

2.9.2.2.1 Acute (short-term) toxicity to fish

Five valid studies performed with active substance fenpropidin were available:

[redacted] (1981b):
A 96 hours test on the acute toxicity of fenpropidin (purity: 94.7 % w/w) to the rainbow trout was performed under flow-through conditions at eight nominal test concentrations (0.32, 0.56, 0.75, 1.0, 1.8, 2.4, 3.2, and 5.6 mg a.s./L), one control and one solvent control (acetone). Twenty fishes were exposed to each test concentration. Observations of mortality only were made at 24, 48, 72, and 96 hours. In addition, observations of mortality and sublethal effects (loss of equilibrium, quiescence, surfacing, darkening in colour, laboured respiration, coughing) were made at 5.25, 21.5, 29.25, 45.5, 53.25, 69.5, 77.25, and 93.5 hours, respectively. Analytical determinations of the test substance concentrations were made daily throughout the exposure period (except following 100%

mortality).
The mean measured test substance concentrations were in the range of 74-88% of nominal. The mean measured concentrations were used in the calculation and reporting of results. The concentrations in the controls were below the detection limit (< 0.01 mg a.s./l).
The study is considered valid and acceptable for regulatory use.
The 96-hour LC_{50} is 2.57 mg fenpropidin /L and the 96-hour no-observed-effect concentration (NOEC) is 0.26 mg fenpropidin /L, based on mean measured concentrations.

[redacted] (2006):
Groups of 7 rainbow trout were exposed to 0.50, 0.89, 1.58, 2.81 and 5.00 mg/L fenpropidin technical (purity: 97.8 %) for 96 hours under static conditions. The fish were observed for symptoms of intoxication and mortality after approximately 3, 24, 48, 72 and 96 hours.
Analytical verification of test item concentrations was performed at test start and test end. The recovery rates were in a range of 102 – 114 % of nominal at test start and 59 – 89 % at test end.
The study is considered valid and acceptable for regulatory use.

The 96-hour LC_{50} is 2.84 mg fenpropidin /L and the 96-hour no-observed-effect concentration (NOEC) is 0.745 mg fenpropidin /L, based on mean measured concentrations.

[redacted] (1981a):
A 96 hours test on the acute toxicity of fenpropidin (purity: 94.7 % w/w) to the bluegill sunfish (*Lepomis macrochirus*) was performed under flow-through conditions at six nominal test concentrations (0.56, 0.75, 1.0, 1.8, 3.2, and 5.6 mg a.s./L), one control and one solvent control. Twenty fishes were exposed to each test concentration. Analytical determinations of the test substance concentrations were made daily throughout the exposure period (except following 100% mortality). Observations of mortality only were made at 24, 48, 72, and 96 hours. In addition, observations of mortality and sublethal effects (e.g. loss of equilibrium, quiescence, surfacing, weak fish, darkening in colour, decrease in respiration rates) were made at 4, 21, 28, 45, 52, 69, 76, and 93 hours, respectively.
The mean measured test substance concentrations were in the range of 73-90.6% of nominal. The mean measured concentrations were used in the calculation and reporting of results. The concentrations in the controls were below the detection limit (< 0.02 mg a.s./l).
The study is considered valid and acceptable for regulatory use.
The 96-hour LC_{50} is 1.93 mg fenpropidin /L and the 96-hour no-observed-effect concentration (NOEC) is <0.44 mg fenpropidin /L, based on mean measured concentrations.

[redacted] (1981c):
A 96 hours test on the acute toxicity of fenpropidin (purity: 94.7 % w/w) to the mirror carp (*Cyprinus carpio*) was performed under flow-through conditions at eight nominal test concentrations (0.56, 1.0, 1.8, 2.4, 3.2, 5.6, 7.5, and 10 mg a.s./L), one control and one solvent control. Ten fishes were exposed to each test concentration. Analytical determinations of the test substance concentrations were made daily throughout the exposure period (except following 100% mortality). Observations of mortality only were made at 24, 48, 72, and 96 hours. In addition, observations of mortality and sublethal effects (loss of equilibrium, quiescence, surfacing, weak fish, darkening in colour, decrease in respiration rates) were made at 4.5, 21, 28.5, 45, 52.5, 69, 76, and after 93 hours, respectively.
The mean measured test substance concentrations were in the range of 78-90.9% of nominal. The mean measured concentrations were used in the calculation and reporting of results. The concentrations in the controls were below the detection limit (< 0.02 mg a.s./l).
The study is considered valid and acceptable for regulatory use.
The 96-hour LC_{50} is 3.55 mg fenpropidin /L and the 96-hour no-observed-effect concentration (NOEC) is 0.46 mg fenpropidin /L, based on mean measured concentrations.

[redacted] (2006a):
Groups of 7 zebrafish were exposed to 1, 2, 4, 8 and 16 mg/L fenpropidin technical (purity: 97.8 %) for 96 hours under static conditions. The fish were observed for symptoms of intoxication and mortality after approximately 3, 24, 48, 72 and 96 hours.
Analytical verification of test item concentrations was performed at test start and test end. The recovery rates were in a range of 95 – 118 % of nominal at test start and 89 – 120 % at test end.
The study is considered valid and acceptable for regulatory use.
The 96-hour LC_{50} is 5.37 mg fenpropidin /L and the 96-hour no-observed-effect concentration (NOEC) is 1.60 mg fenpropidin /L, based on mean measured concentrations.

2.9.2.2.2 Acute (short-term) toxicity to aquatic invertebrates

Two valid studies performed with active substance fenpropidin were available:

Hill RW (1981d):
Groups of 20 *Daphnia magna* (4 replicates of 5 animals per test concentration) were exposed to 0.056, 0.1, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2 and 5.6 mg/L of fenpropidin for 48 hours under static conditions. The invertebrates were observed for immobilisation after 24 and 48 hours of exposure.
Analytical verification of test item concentrations was performed at test start and test end. At the start of the test the measured concentrations ranged from 80.6-100% of the nominal values and at the end of the test they ranged from 78.6-97.2% of the nominal values (overall mean 85.0-96.3%). Mean measured concentrations were used in the calculation and reporting of results.
The study is considered valid and acceptable for regulatory use.
The 48-hour LC_{50} is 0.54 mg fenpropidin /L and the 48-hour no-observed-effect concentration (NOEC) is 0.048 mg fenpropidin /L, based on mean measured concentrations.

Noack M. (2007a):
Groups of 20 *Daphnia magna* were exposed to 1.03, 2.07, 4.03, 8.70 and 16.6 mg/L of fenpropidin technical for 48 hours under static conditions. The invertebrates were observed for immobilisation after 24 and 48 hours of exposure.
Analytical verification of test item concentrations was performed at test start and test end. The results showed that the test concentrations were maintained above 80 % of initial concentrations.
The study is considered valid and acceptable for regulatory use.
The 48-hour EC_{50} is 6.15 mg fenpropidin /L and the 48-hour no-observed-effect concentration (NOEC) is 2.07 mg fenpropidin /L, based on mean measured concentrations.

2.9.2.2.3 Acute (short-term) toxicity to algae or aquatic plants

Two valid studies on algae (delivering EC_{50}) and two valid study on aquatic plants performed with active substance fenpropidin were available:

Pupp & Wydra (2008):
The toxicity of fenpropidin to the green alga *Desmodesmus subspicatus* was determined. Algae were exposed to nominal concentrations of 0.001, 0.0032, 0.01, 0.032, 0.1, 0.32 and 1.0 µg test item/L alongside a medium control. The algal cell densities were measured at 24, 48, 72 and 96 hours and the mean biomass (are under the growth curve), growth rate and yield calculated. At the start of the test, test item concentrations were measured in the range 105 to 115 % of the nominal concentrations, after 96 hours, values were 81 – 93 % of nominal concentrations. The lower test concentrations were below the limit of detection or limit of quantification. All reported results are related to nominal concentrations of the test item.
The algal growth inhibition based on the average growth rate was less than 50% at all treatment levels up to and including the highest nominal test concentration of 1.0 µg/L, after 72 and 96 hours test duration. Therefore it was concluded that the 72-hour and 96-hour E_rC_{50} values were greater than the highest test concentration of 1.0 µg/L, as confirmed by the analytical measurement of the test item concentration.
The study is considered valid and acceptable for regulatory use.
96-hour E_rC_{50} is greater than 1.0 µg a.s./L.
Due to the issue of fenpropidin concentrations insufficiently maintained in most of the test concentrations, no other endpoint could be derived from the study (neither NOEC or EC_{10}, nor E_yC_{50}).

Scheerbaum, D. (2007a) (for further details see Volume 3 CA B.9 of RAR, Section B.9.2.6.1.1 iv))

A growth inhibition test was performed with the green algae (*Desmodesmus subspicatus*). Three replicates with $2 – 5 \times 10^3$ algal cells per mL test medium were exposed to fenpropidin technical (purity: 97.8 %) at mean measured concentrations of 1.29, 0.639, 0.288, 0.097, 0.049 and 0.024 µg test item/L for 72 hours under static conditions (for the two lowest dilution levels no measured concentrations are available since the concentrations were below the LOQ). Therefore, fenpropidin concentrations were calculated under consideration of the mean measured concentration of the lowest measured dosage level and the dilution factor of 2. Cell densities in defined volumes of algal suspensions from all replicates were determined after 24, 48 and 72 hours of exposure. The inhibition of algae growth was determined from the average specific growth rate µ and the yield (= biomass

at the end of the test minus the starting biomass).
Analytical verification was performed at test start and test end. Recovery rates in were in the range of 76 – 107 % of initial concentrations. For the two lowest dilution levels no measured concentrations are available since the concentrations were below the LOQ. Therefore, fenpropidin concentrations were calculated under consideration of the mean measured concentration of the lowest measured dosage level and the dilution factor of 2 but this approach was not accepted by RMS. All effect concentrations were based on mean measured test concentrations.
The results of the study were re-calculated by Pickering & Allen (2018a) using top four concentrations only as mean measured concentrations. It is noted that E_yC_{50} should be considered with caution because the inhibition of yield was 66% at the lowest treatment level in which the fenpropidin concentration could be measured. However, it seems to be low enough to be sufficiently protective. This approach was accepted by RMS.
The study is considered valid and acceptable for regulatory use.
72-hour E_rC_{50} is 0.688 µg a.s./L, 72-hour E_yC_{50} is 0.044 µg a.s./L.
Due to the issue of fenpropidin concentrations insufficiently maintained in the two lowest dilution levels, neither NOEC nor EC_{10} could be derived from the study.

Bebon R. & Wydra V. (2017): (for further details see Volume 3 CA B.9 of RAR, Section B.9.2.7 i))
The toxicity of fenpropidin to the aquatic plant *Lemna gibba* was determined in a 7-day semi-static test followed by testing for recovery of growth. *Lemna* plants were exposed to nominal concentrations of fenpropidin of 1000, 320, 100, 32, 10, 3.2 and 1.0 µg/L for 7 days alongside a dilution water control and a solvent control. The biological results were based on the geometric mean measured concentrations which were 981, 317, 92.6, 29.7, 8.77, 2.71 and 0.599 µg/L, respectively.
The study is considered valid. Endpoints based on the exposure phase can only be considered for regulatory use.
The 7-day E_rC_{50} based on frond number is 78.9 µg a.s./L , the 7-day E_yC_{50} based on frond number is 3.67 µg a.s./L, the 7-day E_rC_{50} based on dry weight is 293 µg a.s./L , the 7-day E_yC_{50} based on dry weight is 8.19 µg a.s./L. The 7-day NOEC based on growth rates (frond number and dry weight) is 0.599 µg a.s./L, all based on mean measured concentrations. The 7-day NOEC based on yield (frond number and dry weight) could not be determined.

Kirkwood, A. (2018):
The toxicity of fenpropidin to the aquatic macrophyte *Myriophyllum spicatum* was determined in a 14 day static test. *Myriophyllum* plants were exposed to nominal concentrations of fenpropidin of 0.12, 0.37, 1.1, 3.3, and 10 mg/L equivalent to 0.0013, 0.0045, 0.025, 0.14, and 2.0 mg/L, respectively, based on geometric mean measured concentrations.
The study is considered valid and acceptable for regulatory use.
The 14-day E_rC_{50} based on shoot length is 2.0 mg a.s./L , the 14-day E_yC_{50} based on shoot length is 1.8 mg a.s./L a.s./L, the 14-day E_rC_{50} and E_yC_{50} based on shoot wet weight is 0.77 mg a.s./L, the 14-day E_rC_{50} based on shoot dry weight is 0.91 mga.s./L, the 14-day E_yC_{50} based on shoot dry weight is 0.88 mg a.s./L. The 14-day NOEC for all parameters is 0.14 mg a.s./L, all based on mean measured concentrations.

2.9.2.2.4 Acute (short-term) toxicity to other aquatic organisms

No relevant study was available.

2.9.2.3 Long-term aquatic hazard [equivalent to section 11.6 of the CLH report template]

Table 58: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results[1]	Key or Supportive study*	Remarks	Reference
OECD 204	Rainbow trout (*Oncorhynchus mykiss*)	Fenpropidin	21 d NOEC 0.32 mg/L (nom)	Acceptable Key study	-	[redacted] (1989a)
OECD 210, EPA OPPTS 850.1400	Rainbow trout (*Oncorhynchus mykiss*)	Fenpropidin	32 d NOEC 0.0038 mg/L (mm)	Acceptable Key study	-	[redacted] (2016)

OECD 202, Part II (1984)	*Daphnia magna*	Fenpropidin	21 d NOEC 0.32 mg/L (nom)	Acceptable Key study	-	Handley (1989b)
OECD 211	*Daphnia magna*	Fenpropidin	21 d NOEC 0.050 mg/L (nom)	Acceptable Key study	-	Noack (2007b)
BBA - Guideline Proposal 1995, OECD (1998)	*Chironomus riparius*	Fenpropidin	28 d NOEC 1.0 mg/L (ini nom)	Acceptable Key study	spiked water	Grade (1999a)
BBA - Guideline Proposal 1995, OECD (1998)	*Chironomus riparius*	Fenpropidin	28 d NOEC 40 mg/kg dw (ini nom)	Acceptable Key study	spiked sediment	Grade (1999a)
OECD 218	*Chironomus riparius*	Fenpropidin	28 d NOEC 47.06 mg/kg dw 28 d EC_{10} 67.1 mg/kg dw (mm)	Acceptable Key study	spiked sediment	Scheerbaum (2007) Pickering & Allen (2018)
OECD 201	Freshwater diatom (*Navicula pelliculosa*)	Fenpropidin	72 h NOE_rC 0.0008 mg/L 72 h NOE_yC 0.0008 mg/L (mm)	Acceptable Key study	-	Grade (1993b) Taylor & Howells (2015b)
OECD 221	Duckweed *(Lemna gibba)*	Fenpropidin	7 d NOErC 0.000599 mg/L 7 d NOEyC <0.000599 mg/L (mm)	Acceptable Key study	-	Bebon & Wydra (2017)
OECD 239	*Myriophyllum spicatum*	Fenpropidin	14 d NOE_rC 0.14 mg/L 14 d NOE_yC 0.14mg/L (mm)	Acceptable Key study	-	Kirkwood (2018)

A chronic toxicity study on alga was available also for metabolite CGA289267, indicating that its toxicity is considerably lower than the toxicity of parent (cca 100000x lower). For details see Table 9.4.1-1 in Volume 3 CP B.9 of RAR.

2.9.2.3.1 Chronic toxicity to fish

Two valid studies performed with active substance fenpropidin were available:

[redacted] (1989a):
The toxicity of fenpropidin to rainbow trout was assessed under flow through conditions over a 21-day exposure period. The study was conducted according to OECD 204 TG. The juvenile fishes were exposed to five nominal concentrations (0.032, 0.10, 0.32, 1.0, and 3.2 mg/L), one dilution water control and one solvent control. Ten trouts were used per treatment and control. Observations of mortality, and sublethal effects (increased pigmentation and lethargy) were made on a daily basis throughout the study. Analytical determinations of the test substance concentrations were made on days 0, 4, 6, 8, 11, 13, 15, 18 and 21. Mean measured concentrations

ranged from 98 – 145% of the nominal concentrations. Therefore, the nominal concentrations were used in the calculation and reporting of results.
The study is considered valid and acceptable for regulatory use.
The 21-day no-observed-effect concentration (NOEC) is 0.32 mg fenpropidin/L, based on nominal concentration. No reliable EC_x values could be calculated for survival, length and weight.

[redacted] (2016):
The toxicity of fenpropidin to early-life stages of fathead minnow (*Pimephales promelas*) was determined. Fish were exposed to the following range of nominal concentrations of 0.15, 0.38, 0.96, 2.4, 6.0 and 15 µg/L (0.079, 0.26, 0.82, 1.6, 3.8 and 10 µg/L mean measured), and a dilution water control. Four replicates with 30 embryos each per treatment were used. Observations for time to hatch, hatching success, larval mortality, deformed larvae and other symptoms of toxicity were made daily during the pre and post-hatch phases, as appropriate. At the end of the test, lengths and dry weights of the surviving fry were measured. The concentrations of fenpropidin in test solutions were measured at 0, 4, 13, 19, 25 and 32 days. Mean measured concentrations ranged from 52 to 86 % of nominal concentration. The results are based on mean measured concentrations.
The study is considered valid and acceptable for regulatory use. The no-observed-effect concentration (NOEC) is 0.0038 mg fenpropidin /L, based on mean measured concentrations. No reliable EC_x value could be calculated for for any parameter.

2.9.2.3.2 Chronic toxicity to aquatic invertebrates

Two valid studies on *Daphnia* and two valid studies on *Chironomus* performed with active substance fenpropidin were available:

Handley JW (1989b):
The chronic effects of fenpropidin on the survival, growth and reproduction of *Daphnia magna* were determined. Four replicates of 10 daphnids (< 24 hours old) were incubated under semi-static conditions for 21 days. Immobility, general condition and size of the parental (P_1) *Daphnia* were recorded daily. The number of *Daphnia* with eggs or young in the brood pouch was determined at each test media renewal together with the numbers of live and dead filial *Daphnia* (F_1). The number of discarded unhatched eggs was also recorded at this time. Test substance concentrations were measured day 0 in fresh media and day 2, 5, 7, 9, 12, 14, 16, 19 and 21 in old media. The medium was renewed 3 times/week (days 2, 5, 7, 9, 12, 14, 16 and 19). Mean measured concentrations were 0.034, 0.10, 0.28, 1.08 and 2.25 mg/l, i.e. 106, 102, 88.2, 101 and 70.4% of the nominal values respectively. The measured concentrations in 0.032, 0.10 and.3.2 mg/l treatment group were below 80% of the nominal values but there was no impact on the results of the study since the 0.32 mg/l (NOEC) and 1.0 mg/l (LOEC) test concentrations remained near nominal.
The study is considered valid and acceptable for regulatory use.
The 21-day no-observed-effect concentration (NOEC) is 0.32 mg fenpropidin /L, based on nominal concentrations.
No reliable ECx values could be calculated for number of surviving adults, number of gravid adults and number of living offspring.

Noack M. (2007b) :
Ten *Daphnia* per test group were exposed for 21 days under semi-static conditions to fenpropidin technical (purity: 97.8 %) at nominal concentrations of 0.050, 0.100, 0.200 and 0.400 mg test item/L. A control with test medium without test substance was run concurrently. Ten animals per treatment group were used. Immobilisation, abnormalities (e.g. swimming behaviour, number of males and winter eggs), the appearance of juveniles, the number of neonates (alive and dead) and the number of aborted eggs were recorded regularly during the study. Upon study termination total length and body weight of surviving parental *Daphnia* were determined. Analytical verification was performed in fresh media (day 2, 7, 14, 19) and old media (day 5, 9, 16, 21) of all test concentrations. The results showed that the test concentrations were maintained above 80 % of nominal concentrations.
The study is considered valid and acceptable for regulatory use.
The 21-day no-observed-effect concentration (NOEC) is 0.050 mg fenpropidin /L, based on nominal concentrations.
No reliable ECx values could be calculated for the number of offspring per replicate, adult mortality, length and dry weight.

Grade R (1999a):
Exposure scenario A: Control, solvent control (0.05 ml DMF/l) and nominal test concentrations of 1.0, 2.0, 4.0,

8.0 and 16 mg/l.

Exposure scenario B: Control (aged sediment), solvent control (aged sediment with acetone treated sand) and nominal concentrations of 5.0, 10, 20, 40, 80 and 160 mg/kg d.w. sediment.

20 midge larvae (2-3 days old) per test vessel were used. Duration of the test was 28 days.

Two exposure scenarios were tested separately in a water/sediment system. In scenario A, fenpropidin was applied to the water phase. In scenario B, fenpropidin was added to the sediment.

The tests were performed in a static test system with 1 l glass beakers containing 1-2 cm artificial sediment and reconstituted bi-distilled water of approximately 8 cm height.

Samples for analytical determinations of the test substance concentrations in the water column were taken after 0, 2, 7, 14 and 28 days, for both exposure scenarios. At the beginning, after 7 days and at the end of the test, the concentration of the test substance in the sediment was determined in the two highest concentrations for both exposure scenarios A and B.

The test vessels were visually inspected daily for larval behaviour, mortality and emergence of midges (except day 3, 4, 6, 8, 10, 11, 18, 23 and 25 for scenario A and day 3, 4, 6, 8, 10, 11, 18 and 25 for scenario B). The number, time and the sex of emerged adults were recorded, and the adults were removed afterwards. Biological parameters observed were: gender rate, emergence rate, mean development time, mean development rate, mean weight of larvae on day 9.

Exposure scenario A: The measured test concentrations in the water phase were 1.12, 2.07, 3.13, 6.18 and 8.45 mg/l at day 0 (1-3 hours after application) corresponding to 112, 104, 78, 77 and 53% of the nominal concentrations. At the end of the test (day 28) water concentrations had decreased to <LOD, < LOD, 0.04, 0.17 and 0.66 mg/l, respectively. Fenpropidin concentrations in sediment were analysed from the two highest nominal concentrations. For the nominal concentration of 8.0 mg/l, at day 0, 7 and 28 the measured concentrations in the sediment (including interstitial water, water just above the sediment and test substance adsorbed on the inner surface of the test vessel) were 0.3, 1.8 and 1.9 mg per 0.12 kg wet sediment respectively. For the nominal concentration of 16 mg/l, at day 0, 7 and 28 the measured concentrations in the sediment were 0.41, 2.8 and 3.5 mg per 0.12 kg wet sediment, respectively. Calculations of effect concentrations for the rate of emergence, the development time and the rate of the development (reciprocal of the development time) were based on nominal concentrations in the water phase.

Exposure scenario B: The measured test concentrations in the water phase were <LOD, <LOD, <LOD, 0.1, 0.2 and 0.6 mg/l at day 0. At the end of the test (day 28) water concentrations were <LOD in all treatments except at the highest nominal concentration where 0.3 mg/l was measured. Fenpropidin concentrations in sediment were analysed from the two highest nominal concentrations. For the nominal concentration of 80 mg/kg dry weight (equivalent to 61 mg/kg sediment wet weight) at day 0, 7 and 28 the mean measured concentrations in the sediment (including interstitial water) were 8.0, 7.5 and 7.2 mg per 0.16 kg wet sediment, respectively (50, 47 and 45 mg/kg sediment wet weight, respectively). For the nominal concentration of 160 mg/kg dry weight (equivalent to 122 mg/kg sediment wet weight) at day 0, 7 and 28 the mean measured concentrations in the sediment were 10.4, 6.5 and 15.0 mg per 0.16 kg wet sediment, respectively (65, 41 and 94 mg/kg sediment wet weight, respectively). Calculations of effect concentrations for the rate of emergence, the development time and the rate of the development (reciprocal of the development time) were based on nominal concentrations in the spiked sediment.

The main part of the study is judged to be of acceptable quality but there are some shortcomings. The concentration changes in water and sediment during the study were only described and not satisfactorily discussed in the report. The determinations of EC_{50} (logit analysis) were not reliable. In scenario A the mortality was high in all test groups including controls (i.e., few larvae found), obviously not reflected in the main test system determining development and emergence. No conclusion regarding weight could be drawn. In scenario B the mortality was much lower in all test groups (i.e., high number of larvae found), except for the highest test concentration (160 mg/kg sediment) where no larvae could be found. However, no influence of the test substance on weight could be established by the test.

However, the derived NOEC values are considered sufficiently conservative to be used in the risk assessment. The study is still considered valid and acceptable for regulatory use.

The 28-day no-observed-effect concentration (NOEC) is 1.0 mg fenpropidin/L for spiked water exposure scenario and 40 mg fenpropidin/kg dw for spiked sediment exposure scenario, based on initial nominal concentrations.

Scheerbaum D. (2007):

Sixty first instar larvae of Chironomus riparius were exposed to fenpropidin technical (purity: 97.8 %) for 28 days under static conditions in a water/sediment system. The artificial sediment was spiked at nominal concentrations of 10, 20, 40, 80, 160 and 320 mg test item/kg dw. A control and a solvent control without test substance were run concurrently. Water quality parameters (pH value, oxygen concentration, temperature) were measured weekly. Observations for behaviour of the larvae and emergence were made daily from day 14

onwards.

Samples of water, pore water and sediment for test item analysis were taken after 0, 7 and 28 days and the concentrations of fenpropidin were determined by LC-MS/MS. Test item concentrations in the water layer and in the pore-water were negligible throughout the test. Excluding the 20 mg/kg dw treatment (due to an application error), initial test concentrations in the sediment layer were in a range of 69 to 92 % of the applied concentrations, and recoveries on day 28 were in a range of 26 – 40 %. The effect concentrations were based on nominal concentrations in the sediment layer.

After 28 days of exposure, a corrected mortality of 79.5 % was observed in the 320 mg/kg dw treatment, whereas mortalities in the lower treatments were < 10 % and statistically not significantly different from the control. Statistically significant effects on emergence were found at 320 mg/kg dw and the development rate was significantly reduced at 320 mg/kg dw and 160 mg/kg dw.

The study is considered valid and acceptable for regulatory use.

The 21-day no-observed-effect concentration (NOEC) is 80 mg/kg dw, based on nominal concentrations, equivalent to 47.06 fenpropidin /kg dw, based on mean measured concentrations.

Based on re-analysis of the results by Pickering, F. & Allen, M. (2018), only the EC_{10} of 67.1 mg/kg dw for development rate could be reliably determined. EC_{20} and EC_{50} values for development rate and EC_{10}, EC_{20} and EC_{50} values for emergence rate could not be reliably calculated due to the lack of suitable responses to treatment.

2.9.2.3.3 Chronic toxicity to algae or aquatic plants

One valid study on algae (delivering NOEC) and two valid study on aquatic plants performed with active substance fenpropidin were available:

Grade R (1993b) :

The toxicity of fenpropidin to the diatom *Navicula pelliculosa* was determined. Algae were exposed to nominal concentrations of 0.4, 1.2, 3.7, 11, 33 and 100 µg /L alongside a medium control and solvent control. The algal cell densities were measured at 24, 48, 72 and 96 hours. The measured concentrations at test start could not be determined because a background signal was present. The measured concentration after 96 h was not quantifiable in the lowest test concentration and ranged between 45-65% of the nominal concentrations in the other test concentrations (see the table below). The results were therefore based on measured concentrations.

The dose response curve was very steep therefore the E_rC_{50} value could be underestimated. E_rC_{10} at 72 and 96 hours could not be calculated.

The 96-hour NOE_rC and NOE_yC is 0.8 µg a.s./L, based on final measured concentrations.

Bebon R. & Wydra V. (2017):

For summary see point 2.9.2.2.3 above.

The 7-day NOEC based on growth rates (frond number and dry weight) is 0.599 µg a.s./L, all based on mean measured concentrations. The 7-day NOEC based on yield (frond number and dry weight) could not be determined.

Kirkwood, A. (2018):

For summary see point 2.9.2.2.3 above

The 14-day NOEC for all parameters is 0.14 mg a.s./L, all based on mean measured concentrations.

2.9.2.3.4 Chronic toxicity to other aquatic organisms

No relevant study was available.

2.9.2.4 Comparison with the CLP criteria

2.9.2.4.1 Acute aquatic hazard

Table 59: Summary of information on acute aquatic toxicity relevant for classification

Method	Species	Test material	Results[1]	Remarks	Reference
Not stated	Bluegill sunfish (*Lepomis macrochirus*)	Fenpropidin	96 h LC_{50} 1.93 mg/L (mm)	-	[redacted] (1981a)
Not stated	*Daphnia magna*	Fenpropidin	48 h EC_{50} 0.54 mg/L	-	Hill (1981d)

			(mm)		
OECD 201	Freshwater green (*Desmodesmus subspicatus*)	Fenpropidin	72 h E_rC_{50} 0.000688 mg/L 72 h E_yC_{50} 0.000044 mg/L (mm)	-	Scheerbaum (2007a) Pickering & Allen (2018a)

Aquatic acute toxicity data for all three trophic levels were available for active substance fenpropidin. Based on the lowest acute endpoint EC50 < 1 mg a.s./L (*Desmodesmus subspicatus* E_rC_{50} = 0.000688 mg a.s./L), aquatic acute category 1 (H400) is required. A M-factor of 1000 is applicable based on 0.0001 < E_rC_{50} ≤ 0.001 mg/L.

2.9.2.4.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Table 60: Summary of information on long-term aquatic toxicity relevant for classification

Method	Species	Test material	Results[1]	Remarks	Reference
OECD 210, EPA OPPTS 850.1400	Rainbow trout (*Oncorhynchus mykiss*)	Fenpropidin	32 d NOEC 0.0038 mg/L (mm)	-	[redacted] (2016)
OECD 211	*Daphnia magna*	Fenpropidin	21 d NOEC 0.050 mg/L (nom)	-	Noack (2007b)
OECD 221	Duckweed *(Lemna gibba)*	Fenpropidin	7 d NOErC 0.000599 mg/L 7 d NOEyC <0.000599 mg/L (mm)	-	Bebon & Wydra

Aquatic long-term toxicity data for all three trophic levels were available for active substance fenpropidin. Based on the lowest long-term endpoint NOEC ≤ 0.1 mg a.s./L (*Lemna gibba* NOE_rC = 0.000599 mg a.s./L) and the fact that the active substance is not rapidly degradable, aquatic chronic category 1 (H410) is required. A M-factor of 100 is applicable based on 0.0001 < NOE_rC ≤ 0.001 mg/L.

2.9.2.5 Conclusion on classification and labelling for environmental hazards

Classification for acute aquatic hazards:

Classification categories:	**Aquatic acute 1**
M-factor (acute/chronic)	**1000**
Hazard statements	**H400: Very toxic to aquatic life**

Classification for chronic aquatic hazards:

Classification categories:	**Aquatic chronic 1**
M-factor (acute)	**100**
Hazard statements	**H410: Very toxic to aquatic life with long lasting effects.**
Pictogram	

Signal word	**Warning**
Precautionary statements	**P273 Avoid release to the environment** **P501 Dispose of contents/ container to ... (in accordance with local/ regional/ national/ international regulation (to be specified))**

2.9.3 Summary of effects on arthropods

Effects on bees

Table 2.9.3-1 Summary of reported laboratory bee toxicity studies with technical and formulated fenpropidin

Species	Test substance	Time scale/type of endpoint	End point	Toxicity	Reference
Laboratory tests					
Apis mellifera #	Fenpropidin	Acute	Oral toxicity (LD_{50})	>10 µg a.s./bee	Gough et al. (1984) CGA114900/0176
Apis mellifera #	Fenpropidin	Acute	Contact toxicity (LD_{50})	**46.0 µg a.s./bee**	
Apis mellifera #	A7516 A	Acute	Oral toxicity (LD_{50})	**99.9 µg a.s./bee**	
Apis mellifera #	A7516 A	Acute	Contact toxicity (LD_{50})	55.3 µg a.s./bee	
Apis mellifera	A7516 D	Chronic	10 d chronic toxicity (LDD_{50})	0.174 µg form./bee/day **0.144 µg a.s/bee/day**	Noël (2016) A7516D/10257
Apis mellifera	A7516 D	Chronic, repeated exposure	Oral toxicity (LD_{50}) (NOED)	>150 µg form./larva* >124.5 µg a.s./larva* 1.86 µg form./larva* **1.544 µg a.s./larva***	Deslandes (2016) A7516D/10264
Semi-field tests					
BBA VI, 23-1 (1991) Honey bee (*Apis mellifera*) cage test in *Phacelia tanacetifolia* in Germany Test substance: CGD 20160 F (fenpropidin 750 g/L EC) Application rate: 1.5 L product/ha, corresponding to 1125 g a.s./ha, applied on flowering crop during daily bee flight Duration: 72 hours Assessment: Mortality, flight density and behaviour. No residue measurements. Results: Increased adult mortality was observed in the first repetition on first day after					Kleiner (1992) # CGA114900/0512

treatment but not in the second repetition. Otherwise, no adverse effects on mortality, foraging activity and behaviour were noted. RMS: The study is only short-term (72 hours) and only mortality, foraging activity and behaviour was assessed, therefore, the results can only be used as additional information for evaluation of acute risk to adult honeybees.	
BBA VI, 23-1 (1991) Honey bee (*Apis mellifera*) cage test in *Phacelia tanacetifolia* in Germany Test substance: CGD 20160 F (fenpropidin 750 g/L EC) Application rate: 1.5 L product/ha, corresponding to 1125 g a.s./ha, applied on flowering crop during daily bee flight Duration: 5-11 days Assessment: Mortality, flight density and behaviour. No residue measurements. Results: No adverse effects on mortality, foraging activity and behaviour were noted. RMS: Since the study is only short-term (5-11 days) and only mortality, foraging activity and behaviour was assessed, the results can only be used as additional information for evaluation of acute risk to adult honeybees.	Tornier (1993) [#] CGA114900/0511
BBA VI, 23-1 (1991) Honey bee (*Apis mellifera*) cage test in *Phacelia tanacetifolia* in Germany Test substance: CGD 20160 F (fenpropidin 750 g/L EC) Application rate: 1.5 L product/ha, corresponding to 1125 g a.s./ha, applied on flowering crop during daily bee flight Duration: 3 days Assessment: Mortality, flight density and behaviour. No residue measurements. Results: Increased adult mortality was observed in the second repetition after treatment but not in the first repetition. RMS: The study is only short-term (3 days) and only mortality, foraging activity and behaviour was assessed, therefore, the results can only be used as additional information for evaluation of acute risk to adult honeybees.	Muehlen et al. (1993) [#] CGA114900/0510

[#] Study evaluated in old DAR (2005)
* Per developmental period

Effects on non-target arthropods other than bees

Table 2.9.3-2 Laboratory and semi-field tests with non-target arthropods

Species	Life stage	Test substance	Study type	Dose (L/ha)[2]	Mortality/ Corr. mortality (%)	Sublethal effects	References
Laboratory tests							
Aphidius rhopalosiphi [#]	Adult	A7516A	Tier I Glass plate Limit test	 Control 1.0 L form. (750 g a.s.)	 6.7 100 LR_{50} <1.0 L form./ha (<750 g a.s.)	No. of pupae / % adverse effects[3] - -	Mead-Briggs (1995); CGA114900/0373 (ext. lab. test also included in the report)

Species	Life stage	Test substance	Study type	Dose (L/ha)[2]	Mortality/ Corr. mortality (%)	Sublethal effects	References
Aleochara bilineata #	Adult	A7516B	Tier I Sand	Control 0.04 L form. (30 g a.s.) 0.5 L form. (375 g a.s.) 1.0 L form. (750 g a.s.) 2.0 L form. (1500 g a.s.)	36 28 / 0 25 / 0 39 / 5 33 / 0 n.a.	No. of eggs per female / % adverse effects[2] 70 66 / 5% 58 / 16% 58 / 16% 61 / 12% ER_{50} >2.0 L form./ha (>1500 g a.s./ha)	Taruza (2002) CGA114900/4683
Chrysoperla carnea #	Larva	A7516B	Tier I Glass plate	Control 0.04 L form. (30 g a.s.) 1.0 L form. (750 g a.s.)	3.3 10.0 / 6.9 86.7 / 86.2 LR_{50} >0.040 and <1.0 L form./ha (>30 and <750 g a.s./ha)	No. of eggs per female per day / % adverse effects: 29.4 26.1 / 11.2 26.8 / 8.8 ER_{50} >1.0 L form./ha (>750 g a.s./ha)	Kemmeter (2000a) CGA114900/4632
Coccinella septempunctata#	Larva	A7516B	Tier I Glass plate	Control 0.04 L form. (30 g a.s.) 1.0 L form. (750 g a.s.) 2.0 L form. (1500 g a.s.)	2.2 6.7 / 4.6 26.7 / 25.0 80.0 / 79.6 LR_{50} >1.0 and <2.0 L form./ha (>750 and <1500 g a.s./ha)	No. of eggs per female per day / % adverse effects: 7.6 6.1 / 19.7% 6.5 / 14.5% 0.7 / 90.8% ER_{50} >1.0 and <2.0 L form./ha (>750 and <1500 g a.s./ha)	Kemmeter (2000b) CGA114900/4634
	Larva	A7516A	Tier I Glass plate Limit test	Control 0.75 L form. (562.5 g a.s.)	11.1 6.7 / -4.9 LR_{50} >0.75 L form./ha (>562.5 g a.s./ha)	No. of eggs per female per day / % adverse effects: 2.24 2.7 / -20.5% ER_{50} >0.75 L form./ha (>562.5 g a.s./ha)	Kühner (1992) CGA114900/0215

Species	Life stage	Test substance	Study type	Dose (L/ha)[2]	Mortality/ Corr. mortality (%)	Sublethal effects	References
Bembidion tetracolum [#]	Adult	A7516A	Tier I Sand Limit test	Control 1.0 L form. (750 g a.s.)	0 43.3 LR_{50} >1.0 L form./ha (>750 g a.s.)	No. of pupae consumed / % adverse effects[3] 10.6 11.3 / -6.0% ER_{50} >1.0 L form./ha (>750 g a.s.)	Mead-Briggs (1994) CGA114900/0312
Poecilus cupreus [#]	Adult	A7516A	Tier I Sand Limit test	Control 0.75 L form. (562.5 g a.s.)	0 0 LR_{50} >0.75 L form./ha (>562.5 g a.s./ha)	No. of larvae consumed / % adverse effects[3] 5.33 5.49 / -3.0% ER_{50} >0.75 L form./ha (>562.5 g a.s./ha)	Pietrzik (1991) CGA114900/0212
Poecilus cupreus [#]	Adult	A7516B	Tier I Sand	Control 0.04 L form. (30 g a.s.) 1.0 L form. (750 g a.s.) 2.0 L form. (1500 g a.s.)	3.3 0 / -3.4 0 / -3.4 0 / -3.4 LR_{50} >2.0 L form./ha (>1500 g a.s./ha)	No. of larvae consumed / % adverse effects[3] 6.0 6.0 / 0% 6.0 / 0% 6.0 / 0% ER_{50} >2.0 L form./ha (>1500 g a.s./ha)	Schmitzer (2000) CGA114900/4630
Extended laboratory tests							
Aphidius rhopalosiphi[#]	Adult	A7516A	Tier II Barley seedlings (3-D)	Control 1.0 L form. (750 g a.s.)	0 13.3 LR_{50} >1.0 L form./ha (>750 g a.s.)	No. of pupae / % adverse effects[3] 4.6 5.1 /-10.9% ER_{50} >1.0 L form./ha (>750 g a.s.)	Mead-Briggs (1995); CGA114900/0373 (lab. test also included in the report)

Species	Life stage	Test substance	Study type	Dose (L/ha)[2]	Mortality/ Corr. mortality (%)	Sublethal effects	References
Aphidius rhopalosiphi[#]	Adult	A7516B	Tier II Barley seedlings (3-D)	Control 0.1 L form. (75 g a.s.) 0.5 L form. (375 g a.s.) 1.0 L form. (750 g a.s.) 2.0 L form. (1500 g a.s.)	4 20 / 17 8 / 4 5 / 1 16 / 13 LR_{50} >2.0 L form./ha (>1500 g a.s./ha)	No. of pupae / % adverse effects[3] 10.8 10.5 /2.7% 10.9 /-1.0% 9.5 /-12.0% 10.3 /4.6% ER_{50} >2.0 L form./ha (>1500 g a.s./ha)	Vinall (2001a) CGA114900/4650
Typhlodromus pyri [#1]	Protonymph	A7516A	Tier II Bean leaves (2-D)	Control 0.53 L form. (400 g a.s.)	18.3 88.3 / 85.7 LR_{50} <0.53 L form./ha (<400 g a.s./ha)	No. of eggs per female / % adverse effects[3] 3.03 2.20 / 27.4 The reproduction part of the test not considered reliable	Kleiner (1992a) CGA114900/0533
Phytoseiulus persimilis [#]	Protonymph	A7516A	Tier II Bean leaves (2-D)	Control 0.53 L form. (400 g a.s.)	1.7 85 / 84.7 LR_{50} <0.53 L form./ha (<400 g a.s./ha)	No. of eggs per female / % adverse effects[3] 16.9 11.1 / 34.3 ER_{50} >0.53 L form./ha (>400 g a.s./ha)	Kleiner (1992b) CGA114900/0262

Species	Life stage	Test substance	Study type	Dose (L/ha)[2]	Mortality/ Corr. mortality (%)	Sublethal effects	References
Phytoseiulus persimilis	Protonymph	A7516D	Tier II Bean leaves (2-D)			No. of eggs per female / % adverse effects[3]	Vinall (2010) A7516D/10000
				Control	18	16.1	
				0.0404 L form. (30.8 g a.s.)	18 / 0	16.3 / -1%	
				0.1039 L form. (77.9 g a.s.)	27 / 10	13.8 / 15%	
				0.1385 L form. (103.9 g a.s.)	42 / 29	13.0 / 20%	
				0.2023 L form. (151.7 g a.s.)	60 / 51	11.6 / 28%	
				0.750 L form. (562.5 g a.s.)	48 / 37	16.2 / 0%	
				1.0 L form. (750 g a.s.)	63 / 55	14.5 / 10%	
					LR_{50} = 0.3771 L form./ha (282.8 g a.s./ha)	ER_{50} >1.0 L form./ha (>750 g a.s./ha)	
Bembidion tetracolum #	Adult	A7516A	Tier II Sandy soil			No. of pupae consumed / % adverse effects[3]	Vinall (2001b) CGA114900/4659
				Control	0	7.77	
				2 x 0.04 L form. (2 x 30 g a.s.)	6.7	7.30 / 6.0%	
				2 x 1.0 L form. (2 x 750 g a.s.)	3.3	8.07 / -3.9%	
					LR_{50} >2 x 1.0 L form./ha (>2 x 750 g a.s.)	ER_{50} >2 x 1.0 L form./ha (>2 x 750 g a.s.)	
Extended laboratory / aged residue							

Species	Life stage	Test substance	Study type	Dose (L/ha)[2]	Mortality/ Corr. mortality (%)	Sublethal effects	References
Typhlodromus pyri [#]	Protonymph	A7516B	Barley seedlings			No. of eggs per female / % adverse effects[3]	Taruza (2001) CGA114900/4660
				0 DAT			
				Control	26	6.2	
				1 x 1.0 L form. (1 x 750 g a.s.)	26 / 0	4.1 / 34%	
				2 x 0.04 L form. (2 x 30 g a.s.)	31 / 7	6.2 / 0%	
				2 x 1.0 L form. (2 x 750 g a.s.)	36 / 14	5.7 / 8%	
				1 DAT			
				Control	34	4.9	
				1 x 1.0 L form.	40 / 9	4.7 / 4%	
				2 x 0.04 L form.	27 / 0	4.6 / 4%	
				2 x 1.0 L form.	15 / 0	5.8 / -18%	
				3 DAT			
				Control	27	6.5	
				1 x 1.0 L form.	29 / 3	2.8 / 57%	
				2 x 0.04 L form.	30 / 4	7.1 / -9%	
				2 x 1.0 L form.	31 / 6	6.8 / -5%	
				5 DAT			
				Control	37	4.3	
				1 x 1.0 L form.	35 / 0	6.2 / -44%	
				2 x 0.04 L form.	35 / 0	4.5 / -5%	
				2 x 1.0 L form.	14 / 0	4.8 / -12%	
				8 DAT			
				Control	25	4.9	
				1 x 1.0 L form.	36 / 15	3.9 / 20%	
				2 x 0.04 L form.	28 / 4	4.6 / 6%	
				2 x 1.0 L form.	21 / 0	3.5 / 29%	

Species	Life stage	Test substance	Study type	Dose (L/ha)[2]	Mortality/ Corr. mortality (%)	Sublethal effects	References
Phytoseiulus persimilis[#]	Protonymph	A7516B	Tier II with aged residues Sweet pepper plants			No. of eggs per female / % adverse effects[3]	Vinall (2002) CGA114900/4674
				0 DAT			
				Control	36	17.7	
				1 x 1.0 L form. (1 x 750 g a.s.)	75 / 60	n.a.	
				2 x 0.04 L form. (2 x 30 g a.s.)	59 / 35	15.6 / 11.9%	
				2 x 1.0 L form. (2 x 750 g a.s.)	85 / 77	n.a.	
				1 DAT			
				Control	32	14.5	
				1 x 1.0 L form.	40 / 12	16.3 / -12.4%	
				2 x 0.04 L form.	36 / 6	15.8 / -9.0%	
				2 x 1.0 L form.	48 / 24	18.7 / -29.0%	
				3 DAT			
				Control	24	15.0	
				1 x 1.0 L form.	31 / 9	15.9 / -6.0%	
				2 x 0.04 L form.	21 / 0	15.7 / -4.7%	
				2 x 1.0 L form.	37 / 18	18.2 / -21.3%	
				5 DAT			
				Control	34	14.3	
				1 x 1.0 L form.	36 / 3	15.8 / -10.5%	
				2 x 0.04 L form.	24 / 0	15.4 / -7.7%	
				2 x 1.0 L form.	30 / 0	15.8 / -10.5%	
				8 DAT			
				Control	38	16.1	
				1 x 1.0 L form.	28 / 0	16.2 / -0.6%	
				2 x 0.04 L form.	36 / 0	14.5 / 9.9%	
				2 x 1.0 L form.	24 / 0	12.8 / 20.5%	
Field tests -							

[#] Study evaluated in old DAR (2005).
[1] the reproduction part of the test not considered reliable
[2] form. – formulation; a.s. - active substance
[3] positive percentages relate to adverse effects in comparison with control
n.a. – not applicable

2.9.4 Summary of effects on non-target soil meso- and macrofauna

Effects on earthworms

Table 2.9.4-1 Summary of studies on toxicity to earthworms

Test organism	Test substance	Application method of test a.s./ OM content	Time scale	End point	Toxicity	Reference
Eisenia fetida [#]	Fenpropidin	Mixed through soil / 10% OM	Acute	Mortality	1000 < LC_{50} < 3200 mg a.s./kg dws	Edwards (1984) CGA114900/0070
	A7516A	Mixed through soil / 10% OM	Acute	Mortality	1000 < LC_{50} < 3200 mg form./kg dws	
Eisenia fetida [#]	Metabolite CGA289267	Mixed through soil / 10% OM	Acute	Mortality	LC_{50} < 1000 mg/kg dws	Candolfi & Grimm (1998) CGA289267/0006
Eisenia fetida [#]	A7516B	Mixed through soil / 10% OM	Chronic	Growth, reproduction, behaviour	NOEC = 13.3 mg form./kg dws NOEC = 10 mg a.s./kg dws [1] **NOECcorr = 5 mg a.s./kg dws [1]**	Gillham (2002) CGA114900/4662
Eisenia fetida	Metabolite CGA289267	Mixed through soil / 10% OM	Chronic	Growth, reproduction, behaviour	**NOEC = 1000 mg/kg dws**	McCormac (2015) CGA289267/10003
Field tests						
-						

[#] Study evaluated in old DAR (2005).
[1] EPPO correction factor is required as fenpropidin has log Pow value >2
Endpoints in bold have been considered in the risk assessment

Table 2.9.4-2: Summary of studies on toxicity to soil meso- and macrofauna (other than earthworms)

Test organism	Test substance	Application method of test a.s./ OM[1]	Time scale	End point	Toxicity	Reference
Folsomia candida [#]	A7516B	Mixed through soil / 10% OM	Chronic	Mortality, reproduction, behaviour	NOEC = 124 mg form./kg soil dw EC_{10} = 121.52 mg form./kg soil dw NOEC = 93 mg a.s./kg soil dw $NOEC_{corr}$ = 46.5 mg a.s./kg soil dw EC_{10} = 91.37 mg a.s./kg soil dw **EC_{10corr} = 45.69 mg a.s./kg soil dw**	Barth (2001) CGA114900/4684 EC_x estimate by: Taylor & Allen (2015a) A7516B/10020
Folsomia candida	Metabolite CGA289267	Mixed through soil / 5% OM	Chronic	Mortality, reproduction, behaviour	**NOEC = 1000 mg/kg soil dw**	Geary (2015) CGA289267/10002
Hypoaspis aculeifer	A7516D	Mixed through soil / 5% OM	Chronic	Mortality, reproduction, behaviour	NOEC = 1000 mg form./kg soil dw NOEC = 830 mg a.s./kg soil dw **$NOEC_{corr}$ = 415 mg a.s./kg soil dw**	Parsons (2015) A7516D/10235
Hypoaspis aculeifer	Metabolite CGA289267	Mixed through soil / 5% OM	Chronic	Mortality, reproduction, behaviour	**NOEC = 1000 mg/kg soil dw**	Vinall (2015) CGA289267/10004

[#] Study evaluated in old DAR (2005).
[a] Estimated using the actual active substance content of 83 % (w/w) fenpropidin
Endpoints in bold have been considered in the risk assessment

2.9.5 Summary of effects on soil nitrogen transformation

Table 2.9.5-1 EU Endpoint: Effects on soil nitrogen transformation - Ecotoxicological endpoints for soil micro-organisms

Test item	Test type	Endpoint	Reference
A7516A #	C & N trans-formation	No significant effect >25 % at up to 5.6-6.0 mg a.s./kg soil	Askew et al (1985) CGA114900/0046
A7516B #	N trans-formation & dehydrogenase activity	Short-term transient effect on N transformation (27 %) at 1.0 mg a.s./kg. No significant effect >25 % on dehydrogenase activity up to 2.5 mg a.s./kg soil	Lang (1993) CGA114900/0513
Metabolite CGA289267 #	C & N trans-formation	No significant effect >25 % up to 10 mg/kg soil	Grade (1999b) CGA289267/0007
Metabolite CGA289267 (fenpropidin acid)	C & N trans-formation	No significant effect >25 % up to 10.36 mg/kg soil	Schulz (2008) CGA289267/10011

Study evaluated in old DAR (2005).

2.9.6 Summary of effects on terrestrial non-target higher plants

Test substance	Species	Test type	Endpoint	Proposed endpoint for risk assessment	Reference
A7516B #	Cucumber, wild oat, onion, sugar beet, oilseed rape, soybean	Screening, seedling emergence (dose-response)	No significant effects on seedling emergence at rates up to 1000 mL product/ha	Seedling emergence: NOER = 1000 mL product/ha (750 g a.s./ha) ER_{50} >1000 mL product/ha (>750 a.s./ha)	Waelder (2003) CGA114900/4788
		Screening, vegetative vigour (dose-response)	Some effects on vegetative vigour noted at all rates. Effects >50 % at the rate of 1000 mL product/ha	Vegetative vigour: ER_{50} >500 mL product/ha (>375 g a.s/ha)	
MCW-273 750 EC	Oilseed rape, sugar beet, soybean, carrot, onion, oat	Vegetative vigour (dose-response)	NOER = 93.8 mL product/ha (70.3 g a.s./ha) ER_{50} = 1495 mL product/ha (1121 g a.s./ha)	Vegetative vigour: ER_{50} = 1495 mL product/ha (1121 g a.s./ha)	Siemoneit-Gast (2007) CGA114900/10883

Study evaluated in old DAR (2005).

2.9.7 Summary of effects on other terrestrial organisms (flora and fauna)

Not applicable.

2.9.8 Summary of effects on biological methods for sewage treatment

Test type/organism	Test substance	end point

Activated sludge	Fenpropidin	EC_{50} (3 h) > 100 mg a.s./L
Activated sludge	A7516B	EC_{50} (3 h) = 228 mg A7516B/L (171 g a.s./L).

2.9.9 Summary of product exposure and risk assessment

2.9.9.1 Risk assessment for birds and other terrestrial vertebrates

An ecological risk assessment in relation to the risk to birds has been undertaken in accordance with the 'Guidance of EFSA Risk Assessment for Birds and Mammals', EFSA Journal 2009 7(12):1438.
Intended application pattern relevant to the use of fenpropidin is given in the table below.

Table 2.9.9-1 Intended application pattern

Crop	Application				Application rate	
	Method/kind [a]	Growth stage	Maximum number of applications	Minimum application interval (days)	Individual application rate (L product/ha)	Individual application rate (g a.s./ha)
Wheat	Foliar spray (F)	BBCH 31-69	2	14	0.750 - 0.375	**562.5** - 281.25
Barley	Foliar spray (F)	BBCH 31-65	2	14	0.750 - 0.375	**562.5** - 281.25

[a] Field (F)
In bold maximum individual application rate

2.9.9.1.1 Risk assessment for birds

Screening assessment

Table 2.9.9-2 Screening level estimates of the acute and long-term exposure to fenpropidin

Crop	Indicator species	No. of applica-tions x application rate (kg a.s./ha)	Risk	Shortcut value	TWA	DDD for a single application(mg a.s./kg bw/day)	MAF	DDD for a multiple application(mg a.s./kg bw/day)
Cereals	Small omnivorous bird	2 x 0.5625	**Acute**	158.8	-	89.3	1.2	107.2
			Long-term	64.8	0.53	19.3	1.4	27.1

Table 2.9.9-3 Screening TER calculations for the acute and long-term exposure to fenpropidin

Crop	Indicator species	Risk	Toxicity value (mg a.s./kg b.w./day)	DDD for a multiple application(mg a.s./kg bw/day)	TER	Trigger value
Cereals	Small omnivorous bird	**Acute**	LD_{50} 431	107.2	**4.02**	10
		Long-term	NOEL 14.6	27.1	**0.54**	5

Since TER values remain below the relevant triggers, Tier 1 assessment is required.

Tier 1 assessment

A Tier 1 acute and long-term risk assessment has been conducted and the TER values for the generic focal species are presented in the tables below.

Table 2.9.9-4 Tier 1 acute risk assessment for birds

Crop Application rate	Scenario	Generic focal species	Shortcut value	MAF	TWA	DDD (mg/kg bw)	TER_A	Trigger value
Cereals 2 x 0.5625 kg a.s./ha	Cereals BBCH 30-39	Small omnivorous bird 'lark'	12.0	1.2	-	8.1	53.2	10
	Cereals BBCH ≥ 40	Small omnivorous bird 'lark'	7.2	1.2	-	4.86	88.7	

Table 2.9.9-5 Tier 1 reproductive risk assessment for birds

Crop Application rate	Scenario	Generic focal species	Shortcut value	MAF	TWA	DDD (mg/kg bw)	TER_{LT}	Trigger value
Cereals 2 x 0.5625 kg a.s./ha	Cereals BBCH 30-39	Small omnivorous bird 'lark'	5.4	1.4	0.53	2.25	6.5	5
	Cereals BBCH ≥ 40	Small omnivorous bird 'lark'	3.3	1.4	0.53	1.38	10.6	

All TER values for fenpropidin exceed the relevant trigger values, indicating low acute and long-term dietary risk to birds.

Risk assessment for drinking water exposures

Puddle scenario

Table 2.9.9-6 Screening step for drinking water acute risk assessment (puddle scenario) - ratio of effective application rate to relevant endpoint for birds

Crop group	Compound	Soil DT_{50} [a] (days)	K_{oc}** (L/kg)	AR (g a.s./ha)	MAF_m	AR_{eff} (g a.s./ha)	LD_{50} (mg a.s./kg bw)	Ratio (AR_{eff} / LD_{50})	No concern ratio
Cereals	Fenpropidin	84.9	3770	562.5	1.89	1063	431	2.47	≤3000

[a] Soil DT_{50} based on laboratory studies (geomean), as used for PECgw and PECsw calculation (refer to Volume 3 CP B.8)
**Geomean Koc value (refer to Volume 3 CP B.8)

Table 2.9.9-7 Screening step for drinking water long-term risk assessment (puddle scenario) - ratio of effective application rate to relevant endpoint for birds

Crop group	Compound	Soil DT_{50} [a] (days)	K_{oc}** (L/kg))	AR (g a.s./ha)	MAF_m	AR_{eff} (g a.s./ha)	NOAEL (mg a.s./kg bw/day)	Ratio (AR_{eff} / NOAEL)	No concern ratio
Cereals	Fenpropidin	84.9	3770	562.5	1.89	1063	14.6	72.8	≤3000

[a] Soil DT_{50} based on laboratory studies (geomean), as used for PECgw and PECsw calculation (refer to Volume 3 CP B.8)
**Geomean Koc value (refer to Volume 3 CP B.8)

The ratios of the application rates to the toxicity endpoints are clearly less than 3000 indicating low concern for acute and long-term exposure to birds drinking water from puddles and hence there is no need to carry out further calculations of exposure in puddle water.
In conclusion, the risk through drinking water from the intended use of fenpropidin according to the use pattern is acceptable.

Risk for Bioaccumulation and Secondary Poisoning
Fenpropidin has a log P_{OW} of 4.5 (at pH 9.0) indicating a potential risk of secondary poisoning, therefore a risk assessment is provided.
The main soil and water metabolite of fenpropidin (CGA289267) has a log P_{OW} value in the range from -0.1 to 0.1 indicating low potential for bioaccumulation. Given that the metabolite will be found at lower concentrations in soil than the parent active substance, the risk assessment for the parent is considered to cover the metabolite.

1) Risk to earthworm-eating birds

Table 2.9.9-8 Long-term risk from secondary poisoning to earthworm-eating birds

Compound	Appl. rate (g a.s./ha)	PEC_{soil} (mg a.s./kg)	K_{ow}	f_{oc}	K_{OC}	BCF	PEC_{worm} (mg a.s./kg)	DDD (mg a.s./kg bw/day)	NOAEL (mg a.s./kg bw/day)	TER_{worm}
Fenpropidin	562.5	0.420	794	0.02	3770	0.138	0.0578	0.0606	14.6	241

The TER value exceeds the long-term trigger value of 5, indicating that A7516D poses an acceptable risk to earthworm eating birds.

2) Risk to fish eating birds

Table 2.9.9-9 Long-term risk from secondary poisoning to fish-eating birds

Compound	Application rate (g a.s./ha)	$PEC_{sw,\ max}$ Step 3 (mg a.s./L)	BCF_{fish}	PEC_{fish} (mg a.s./kg)	DDD (mg a.s./kg bw/day)	NOAEL (mg a.s./kg bw/day)	TER_{fish}
Fenpropidin	562.5	0.00356	163 [a]	0.580	0.0923	14.6	158

[a] The lowest BCF (whole fish) determined in bluegill sunfish.

The TER value exceeds the long-term trigger value of 5, indicating that A7516D poses an acceptable risk to fish eating birds.

Dietary risk to birds from metabolites

Plant metabolism studies in wheat, sugar beet, grape and banana showed that fenpropidin was extensively metabolised in the plants (refer to Volume 3 CP B.7). The pathway of metabolism was very similar in these crops with fenpropidin being the main compound detected. Twenty metabolites were identified in forage, straw or grain at low levels. The maximum residues were found for CGA289268 (max. 9.2 % of total radioactive residue in wheat straw) and its glycoside (max. 22 % in immature wheat) in a wheat metabolism study. The residues of other individual metabolites in treated plants did not exceed 7.6 % of applied parent compound. Further studies in rotational crops showed that residues of formed metabolites in succeeding crops are low.
In fish, the main compounds detected in the whole fish extracts were fenpropidin (18.8 % of radioactive residues) and the metabolite CGA289268 (16.1 %). The radioactivity in the water phase could not be extracted indicating that fenpropidin had been metabolised extensively to very polar metabolites or conjugates (Point B.9.2.3 of the DAR (2006).
Several metabolites were identified in soil, but only CGA289267 was detected at a maximum amount of 10.4 % of the applied radioactivity in one study (refer to Volume 3 CP B.8). All other individual metabolites in soil represent less than 10 % of applied fenpropidin. In water, the only major metabolite was found to be CGA289267 at the maximum of 27.2 % of applied fenpropidin in water-sediment systems. Thus, CGA289267 is the only metabolite that occurs in environmental compartments and birds and mammals could potentially be exposed to.
Metabolism studies in hen, rat and goat showed that fenpropidin is rapidly metabolised and excreted in birds and mammals (refer to Volume 3 CP B.6 and B.7). The primary metabolic process in each animal involved oxidation

of the tertiary-butyl side chain of the fenpropidin molecule to CGA289268 and subsequent formation of CGA289267, SYN515213 and other metabolites or conjugates. Thus, the metabolite CGA289268 found as residue in plants and fish, and CGA289267 and SYN515213 (and its conjugates) that may occur as metabolites in prey animals are part of the major metabolic pathway of fenpropidin in birds and mammals, and occurred at significant levels in the animal metabolism studies. The glycoside of CGA289268 that was found at the maximum of 22 % in wheat plants is expected to be rapidly broken down in birds and mammals to CGA289268 that is further metabolised to CGA289267 and other compounds.
According to the EFSA GD (2009) it can be assumed that these metabolites observed in the hen metabolism study were present in the avian toxicity tests with the parent and thus the studies with the parent fenpropidin adequately covers the potential toxicity of these metabolites.
It can therefore be concluded that the risk posed by the metabolites to birds will be covered by the risk assessment for the parent and hence is low and no further risk assessment is required.

Conclusion – risk to birds:
Low acute and long-term risks to birds can be concluded following applications of fenpropidin according to the proposed GAP. Low risk to birds is also expected from fenpropidin metabolites.

2.9.9.1.2 Risk assessment for mammals

Screening assessment

Table 2.9.9-10 Screening level estimates of the acute and long-term exposure to fenpropidin

Crop	Indicator species	No. of applica-tions x application rate (kg a.s./ha)	Risk	Shortcut value	TWA	DDD for a single application(mg a.s./kg bw/day)	MAF	DDD for a multiple application(mg a.s./kg bw/day)
Cereals	Small herbivorous mammal	2 x 0.5625	**Acute**	118.4	-	66.6	1.2	79.9
			Long-term	48.3	0.53	14.4	1.4	20.2

Table 2.9.9-11 Screening TER calculations for the acute and long-term exposure to fenpropidin

Crop	Indicator species	Risk	Toxicity value (mg a.s./kg b.w./day)	DDD for a multiple application(mg a.s./kg bw/day)	TER	Trigger value
Cereals	Small herbivorous mammal	**Acute**	LD_{50} 1452	79.9	18.2	10
		Long-term	NOAEL 10	20.2	**0.50**	5

Acute TER value is above the trigger of 10 indicating low acute risk to mammals from application of fenpropidin according to proposed GAP. However, long-term TER value remain below the triggers of 5, indicating high long-term risk. Therefore, the Tier 1 reproductive assessment is required.

Tier 1 assessment

Table 2.9.9-12 Tier 1 reproductive risk assessment for mammals

Crop Application rate	Scenario	Generic focal species	Shortcut value	MAF	TWA	DDD (mg/kg bw)	TER_{LT}	Trigger value
Cereals 2 x 0.5625 kg a.s./ha	Cereals BBCH ≥ 20	Small insectivorous mammal 'shrew'	1.9	1.4	0.53	0.793	12.6	5
	Cereals BBCH ≥ 40	Small herbivorous mammal 'vole'	21.7			9.06	**1.1**	

	Cereals BBCH 30-39	Small omnivorous mammal 'mouse'	3.9			1.63	6.1	
	Cereals BBCH ≥ 40	Small omnivorous mammal 'mouse'	2.3			0.960	10.4	

All TER_{LT} values for fenpropidin exceeded the trigger values of 5, except for the TER_{LT} value for the small herbivorous mammal scenario "vole". Further consideration is needed.

The Notifier proposed the refinement of the deposition factor. In default shortcut value, the deposition factor of 0.3 is incorporated. According to the FOCUS ground water guidance document (version 2.2, May 2014), interception of 90% should be considered for winter cereals, BBCH 40-69. Therefore, the relevant deposition factor is 0.1. The refined calculation of DDD and TER is provided below.

Refined vole risk assessment using FOCUSgw crop interception for cereals at BBCH >40

Generic focal species	RUD (mg a.s./kg)	FIR/bw	App. rate (kg a.s./ha)	MAF_m	f_{twa}	DF	DDD (mg a.s./kg bw/day)	NOEL	TER
Small herbivorous mammal 'vole' – cereals BBCH >40	54.2	1.33	0.563	1.4	0.53	0.1	3.01	10	3.32

DF: Deposition factor based on FOCUSgw crop interception (90% interception for cereals at BBCH 40-69)

The refined TER_{LT} value for fenpropidin for the small herbivorous mammal scenario "vole" remains below the trigger of 5, when the maximum intended application rate of fenpropidin (i.e. 2 x 562.5 g a.s./ha) was used in the risk assessment. No further refinement was available.
Therefore, the minimum intended application rate (i.e. 2 x 281.25 g a.s./ha) was also considered in the long-term risk assessment for mammals, for small herbivorous mammal scenario. The calculation is provided below.

Refined vole risk assessment using FOCUSgw crop interception for cereals at BBCH >40 (2 x 281.25 g a.s./ha)

Generic focal species	RUD (mg a.s./kg)	FIR/bw	App. rate (kg a.s./ha)	MAF_m	f_{twa}	DF	DDD (mg a.s./kg bw/day)	NOEL	TER
Small herbivorous mammal 'vole' – cereals BBCH >40	54.2	1.33	0.28125	1.4	0.53	0.1	1.50	10	6.67

DF: Deposition factor based on FOCUSgw crop interception (90% interception for cereals at BBCH 40-69)

The TER_{LT} value for fenpropidin for the small herbivorous mammal scenario "vole"exceeded the trigger value of 5, when the minimum intended application rate of fenpropidin (i.e. 2 x 281.25 g a.s./ha) was used in the risk assessment..

The selection of ecotoxicologically relevant endpoint to be used in the reproductive risk assessment for wild mammals will be discussed in peer review.

Risk assessment for drinking water exposures

Puddle scenario

Table 2.9.9-13 Screening step for drinking water acute risk assessment (puddle scenario) - ratio of effective application rate to relevant endpoint for mammals

Crop group	Compound	Soil DT_{50} [a] (days)	K_{oc}** (L/kg)	AR (g a.s./ha)	MAF_m	AR_{eff} (g a.s./ha)	LD_{50} (mg a.s./kg bw)	Ratio (AR_{eff} / LD_{50})	No concern ratio
Cereals	Fenpropidin	84.9	3770	562.5	1.89	1063	1452	0.73	≤3000

[a] Soil DT_{50} geometric mean of normalised (pF 2, 20 °C) laboratory and field DT50 (n =17), as used for PECgw and PECsw calculation (refer to Volume 3 CP B.8)
**Geomean Koc value (refer to Volume 3 CP B.8)

Table 2.9.9-14 Screening step for drinking water long-term risk assessment (puddle scenario) - ratio of effective application rate to relevant endpoint for mammals

Crop group	Compound	Soil DT_{50} [a] (days)	K_{oc}** (L/kg))	AR (g a.s./ha)	MAF_m	AR_{eff} (g a.s./ha)	NOAEL (mg a.s./kg bw/day)	Ratio (AR_{eff} / NOAEL)	No concern ratio
Cereals	Fenpropidin	84.9	3770	562.5	1.89	1063	10	106	≤3000

[a] Soil DT_{50} geometric mean of normalised (pF 2, 20 °C) laboratory and field DT50 (n =17), as used for PECgw and PECsw calculation (refer to Volume 3 CP B.8)
**Geomean Koc value (refer to Volume 3 CP B.8)

The ratios of the application rates to the toxicity endpoints are below 3000 indicating low concern for acute and long-term exposure to mammals in drinking water from puddles and hence there is no need to carry out further calculations of exposure in puddle water.

In conclusion, the risk through drinking water from the intended use of fenpropidin according to the use pattern is acceptable.

Risk for Bioaccumulation and Secondary Poisoning

Fenpropidin has a log P_{OW} of 4.5 (at pH 9.0) indicating a potential risk of secondary poisoning, therefore a risk assessment is provided.
The main soil and water metabolite of fenpropidin (CGA289267) has a log P_{OW} value in the range from -0.1 to 0.1 indicating low potential for bioaccumulation. Given that the metabolite will be found at lower concentrations in soil than the parent active substance, the risk assessment for the parent is considered to cover the metabolite.

1) Risk to earthworm-eating mammals

Table 2.9.9-15 Long-term risk from secondary poisoning to earthworm-eating mammals

Compound	Appl. rate (g a.s./ha)	PEC_{soil} (mg a.s./kg)	K_{ow}	f_{oc}	K_{OC}	BCF	PEC_{worm} (mg a.s./kg)	DDD (mg a.s./kg bw/day)	NOAEL (mg a.s./kg bw/day)	TER_{worm}
Fenpropidin	562.5	0.420	794	0.02	3770	0.138	0.0578	0.0739	10	135

The TER value exceeds the long-term trigger value of 5, indicating that A7516D poses an acceptable risk to earthworm eating mammals.

2) Risk to fish eating mammals

Table 2.9.9-16 Long-term risk from secondary poisoning to fish-eating mammals

Compound	Application rate (g a.s./ha)	$PEC_{sw, max}$ Step 3 (mg a.s./L)	BCF_{fish}	PEC_{fish} (mg a.s./kg)	DDD (mg a.s./kg bw/day)	NOAEL (mg a.s./kg bw/day)	TER_{fish}
Fenpropidin	562.5	0.00356	163 [a]	0.580	0.0824	10	121

[a] The lowest BCF (whole fish) determined in bluegill sunfish.

The TER value exceeds the long-term trigger value of 5, indicating that A7516D poses an acceptable risk to fish eating mammals.

Risk to mammals from metabolites
Metabolites of fenpropidin that were found in potential food items for wild mammals (CGA289267, CGA289268 (glycoside) and SYN515213) are part of the major metabolic pathway of fenpropidin in mammals and occurred at significant levels in the rat and goat metabolism studies (see B.9.2.1 for further details).
According to the EFSA GD (2009) it can be assumed that these metabolites observed in the rat and goat metabolism studies were present in the mammalian toxicity tests with the parent compound and thus the studies with the parent fenpropidin adequately covers the potential toxicity of these metabolites.

It can therefore be concluded that the risk to wild mammals will be covered by the risk assessment for the parent and hence is low and no further risk assessment is required.

Conclusion – risk to vertebrates other than birds:
Low acute and long-term risks to mammals can be concluded following applications of fenpropidin according to the proposed GAP, except for long-term dietary risk to small herbivorous mammal scenario "vole". Low risk to mammals is expected from fenpropidin metabolites.

It is noted that the selection of ecotoxicologically relevant endpoint to be used in the reproductive risk assessment for wild mammals will be discussed in peer review.

2.9.9.2 Risk assessment for aquatic organisms

Endpoints of technical and formulated fenpropidin and its metabolite used in risk assessment

Test organism	Test substance	Time scale, study type	Endpoint	Toxicity (mg a.s./L)	Reference
FISH					
Bluegill sunfish (*Lepomis macrochirus*)	Fenpropidin	Acute, 96h (flow-through)	Mortality, LC_{50}	1.93 (mm)	[redacted] (1981a) CGA114900/0069
Rainbow trout (*Oncorhynchus mykiss*)	Metabolite CGA289267	Acute, 96h (static)	Mortality, LC_{50}	>100 (nom)	[redacted] (1995) CGA289267/0003
Rainbow trout (*Oncorhynchus mykiss*)	Fenpropidin	Chronic, 32d ELS (flow-through)	Growth and mortality, NOEC	0.0038 (mm)	[redacted] (2016) CGA114900/10666
AQUATIC INVERTEBRATES					
Daphnia magna	Fenpropidin	Acute, 48h (static)	Immobility, EC_{50}	0.54 (mm)	Hill (1981d) CGA114900/0074
Daphnia magna	Metabolite CGA289267	Acute, 48h (static)	Immobility, EC_{50}	>123.45 (mm)	Grade (1994a) CGA289267/0002
Daphnia magna	Fenpropidin	Chronic, 21d (semi-static)	Reproduction and development, NOEC	0.050 (nom)	Noack (2007b) CGA114900/10626
SEDIMENT-DWELLING INVERTEBRATES					
Chironomus riparius	Fenpropidin	Chronic, 28 d (static) spiked water	Development, NOEC	1.0 (ini nom)	Grade (1999a) CGA114900/4591
		Chronic, 28 d (static) spiked sediment	Development, NOEC	40 mg/kg dw (ini nom)	
ALGAE					
Freshwater green (*Desmodesmus subspicatus*)	Fenpropidin	72 h (static)	Growth rate: E_rC_{50}	0.000688 (mm)	Scheerbaum (2007a) CGA114900/10620 Pickering & Allen

Test organism	Test substance	Time scale, study type	Endpoint	Toxicity (mg a.s./L)	Reference
					(2018a) CGA114900/10915
Freshwater green (*Desmodesmus subspicatus*)	Metabolite CGA289267	72 h (static)	Growth rate: E_rC_{50}	69 (mm)	Grade (1994b) CGA289267/0001 Taylor & Radford (2015a) CGA289267/10009
AQUATIC PLANTS					
Duckweed *(Lemna gibba)*	Fenpropidin	7 d (static-renewal)	Frond number: E_rC_{50}	0.0789 (mm)	Bebon & Wydra (2017) CGA114900/10897
Further testing on aquatic organisms *[To report a short summary of mesocosms and SSD assessments and to include the associated AF for the representative use and explain the reason (briefly)]*					
Mesoocosm (phytoplankton, periphyton, macrophytes, zooplankton, macroinvertebrates, fish)	A7516A (750 g/L fenpropidin)	2 applications, 14 d interval, 177 d (static)	NOEC NOEAEC	0.00013 0.00039 (initial mm)	Neumann (1997) Statistical analysis: Ashwell et al. (2007) Stat. re-analysis: Stegger (2016a)
Mesoocosm (phytoplankton, periphyton, macrophytes, zooplankton, macroinvertebrates)	MCW-273 750 EC (750 g/L fenpropidin)	2 applications, 14 d interval, 84 d (static)	NOEAEC	0.001* (initial nom)	Wellmann (2007) Stat. re-analysis: Stegger (2016b)
Potential endocrine disrupting properties (Annex Part A, point 8.2.3) -					

(nom) nominal concentration; (ini nom) initial nominal concentration; (mm) mean measured concentration; (initial mm) initial measured concentration; form.: formulation; a.s.: active substance
n.a. not applicable
* The NOEAEC considered in deriving of the overall NOEAEC from mesocosms but finaly not used in the risk assessment, see the explanation below.

Mesocosm studies - RMS Overall summary and conclusion on mesocosm endpoints and RACs for aquatic organisms (RAR 2018):

Three mesocosm studies were available. Two of them are considered suitable for regulatory use (Neumann, 1997 and Wellmann, 2006). Both studies are considered as being reliable and of high quality. The results of both studies indicate that there are species of algae that are very sensitive to fenpropidin also at low concentrations.

A **NOEC** could only be derived from the study by **Neumann (1997)**:

NOEC = 0.13 µg a.s./L

The study by Neumann (1997) is considered as being reliable and of high quality. Parameters related to phytoplankton community and populations were identified as being the most sensitive. Some uncertainty is connected with presence of fish that might have fed on zooplankton. It is noted that considering the ecological relevance and richness of species of the community tested the study by Neumann is considered as substantially more valuable than the study by Wellmann based on a rich number of sensitive/vulnerable taxa classified as Category 1.

Further it is noted the endpoints derived from the study by Neumann (1997) are considered as rather conservative since they are based on initial measured concentrations sampled few hours after first and second application.

As mentioned above, no NOEC could be derived from the other mesocosm study Wellmann (2007). However, this study indicates that the NOEC is below the lowest concentration tested (i.e. < 0.3 µg a.s./L), which confirms result of the study Neumann (1997).

Taking these into account **assessment factor of 2 is proposed by RMS in combination with NOEC of 0.13 µg a.s./L, resulting in ETO-RAC of 0.065 µg a.s./L**.

A **NOEAEC** could be derived from both studies (Neumann, 1997 and Wellmann, 2007).
Neumann (1997) : NOEAEC = 0.39 µg a.s./L (LOEAEC = 1.4 µg a.s./L);
Wellman (2007): NOEAEC = 1.0 µg a.s./L (LOEAEC = 3.0 µg a.s./L)
The study by Wellmann (2007) is considered as being reliable and of high quality. Phytoplankton and periphyton taxa were identified as being the most sensitive. The endpoint is based on nominal concentrations since measured concentrations in mesocosms were 84-133% of nominal values after first and second application.

It is noted that the lowest available NOEAECof 0.39 µg a.s./L from the study by Neumann (1997) is considered as rather conservative since it is based on initial mean measured concentrations sampled few hours after first and second application.
Further, the highest NOEAEC of 1.0 µg a.s./L from the study by Wellmann (2007) is lower than the lowest LOEAEC of 1.4 µg a.s./L from the study by Neumann (1997). However, it is noted that the study by Wellmann does not have the same value as the study by Neumann, considering the ecological relevance and richness of species of the community tested. The study by Wellmann has only the minimum of 8 sensitive/vulnerable taxa (i.e. algal taxa) with acceptable MDD, while the study by Neumann includes much more such taxa. As regards to green algae, only 3 taxa with acceptable MDD were included in the study by Wellman (2007) while 9 taxa were included in the study by Neumann (1997). However, it is noted that the results of the study by Wellmann (2007) indicates that the NOEC is below the lowest concentration tested (i.e. < 0.3 µg/L), which confirms the result of the study by Neumann (1997).
Overall, considering the concerns mentioned about the limited richness of the community most at risk in study Wellmann (2007), it seems thus more appropriate in terms of protectiveness to select the most conservative of the 2 different NOEAEC derived from these two mesocosm studies.

Thus, the **overall NOEAEC of 0.39 µg a.s./L is proposed by RMS**.

Since two reliable and high quality mesocosm studies were available, it is assumed that very little uncertainty is associated with the overall NOEAEC of 0.39 µg a.s./L. Therefore, **an assessment factor of 3 is proposed by RMS, resulting in ERO-RAC of 0.13 µg a.s./L**.

The selection of endpoints from mesocosm studies and their use in the risk assessment should be discussed in peer-review.

PEC/RAC comparisons for aquatic species for active substance and its metabolites

PEC/RAC comparisons for aquatic organisms based on FOCUSsw Step 1, 2 and 3

Table 2.9.9-17 FOCUS$_{sw}$ step 1-3 - PEC/RAC comparisons for fenpropidin – winter cereals at 562.5 g a.s./ha x 2

Scenario	PEC global max (µg /L)	fish acute	fish chronic	Aquatic invertebrates	Aquatic invertebrates prolonged	Algae	Higher plant	Sed. dweller prolonged Spiked water	Sed. dweller prolonged Spiked sediment	Microcosm / Mesocosm	
		Lepomis macrochirus	*Oncorhynchuss mykiss*	*Daphnia magna*	*Daphnia magna*	*Desmodesmus subspicatus*	*Lemna gibba*	*Chironomus riparius*	*Chironomus riparius*	Mesocosm	
		LC_{50}	NOEC	EC_{50}	NOEC	E_rC_{50}	ErC_{50}	NOEC	NOEC	NOEC	NOEAEC
		1930 µg/L	3.8 µg/L	540 µg/L	50 µg/L	0.688 µg/L	78.9 µg/L	1000 µg/L	40000 µg/kg	0.13 µg/L	0.39 µg/L
RAC		**19.3 µg/L**	**0.38 µg/L**	**5.4 µg/L**	**5.0 µg/L**	**0.0688 µg/L**	**7.89 µg/L**	**100 µg/L**	**4000 µg/kg**	**0.065 µg/L**	**0.13 µg/L**
Assessment factor**		100	10	100	10	10	10	10	10	2	3
FOCUS Step 1	72.57 µg/L /2350 µg/kg	**72.57**	**72.57**	**72.57**	**72.57**	**72.57**	**72.57**	72.57	2350	-	-
FOCUS Step 2											
North Europe	11.19	11.19	**11.19**	**11.19**	**11.19**	**11.19**	**11.19**	-	-	-	-
South Europe	20.30	**20.30**	**20.30**	**20.30**	**20.30**	**20.30**	**20.30**	-	-	-	-
FOCUS Step 3*											
D1 / ditch	3.560 [a]	3.560	**3.560**	3.560	3.560	**3.560**	3.560	-	-	**3.560**	**3.560**
D1 / stream	3.039 [a]	3.039	**3.039**	3.039	3.039	**3.039**	3.039	-	-	**3.039**	**3.039**
D2 / ditch	3.555 [a]	3.555	**3.555**	3.555	3.555	**3.555**	3.555	-	-	**3.555**	**3.555**
D2 / stream	2.978 [a]	2.978	**2.978**	2.978	2.978	**2.978**	2.978	-	-	**2.978**	**2.978**
D3 / ditch	3.521 [a]	3.521	**3.521**	3.521	3.521	**3.521**	3.521	-	-	**3.521**	**3.521**
D4 / pond	0.136	0.136	0.136	0.136	0.136	**0.136**	0.136	-	-	**0.136**	**0.136**
D4 / stream	2.781 [a]	2.781	**2.781**	2.781	2.781	**2.781**	2.781	-	-	**2.781**	**2.781**
D5 / pond	0.161	0.161	0.161	0.161	0.161	**0.161**	0.161	-	-	**0.161**	**0.161**
D5 / stream	2.811 [a]	2.811	**2.811**	2.811	2.811	**2.811**	2.811	-	-	**2.811**	**2.811**
D6 / ditch	3.543 [a]	3.543	**3.543**	3.543	3.543	**3.543**	3.543	-	-	**3.543**	**3.543**
R1 / pond	0.190	0.190	0.190	0.190	0.190	**0.190**	0.190	-	-	**0.190**	**0.190**
R1 / stream	2.319 [a]	2.319	**2.319**	2.319	2.319	**2.319**	2.319	-	-	**2.319**	**2.319**
R3 / stream	3.260 [a]	3.260	**3.260**	3.260	3.260	**3.260**	3.260	-	-	**3.260**	**3.260**
R4 / stream	2.319 [a]	2.319	**2.319**	2.319	2.319	**2.319**	2.319	-	-	**2.319**	**2.319**

values in bold exceed the relevant RAC, indicating an unacceptable risk

[a] PEC_{sw} for a single application as a worse case

*[Only scenarios where the trigger is not met at FOCUSsw step 1-2 should be included in step 3.]

**[If the Trigger value has been adjusted during the risk assessment, it should always be clear on what basis the risk assessment has been performed, i.e. what the AF value is and for which organism and endpoint it refers.]

Table 2.9.9-18 FOCUS$_{sw}$ step 1-3 - PEC/RAC comparisons for fenpropidin – spring cereals at 562.5 g a.s./ha x 2

Scenario	PEC global max (µg /L)	fish acute	fish chronic	Aquatic invertebrates	Aquatic invertebrates prolonged	Algae	Higher plant	Sed. dweller prolonged Spiked water	Sed. dweller prolonged Spiked sediment	Microcosm / Mesocosm	
		Lepomis macrochirus	*Oncorhynchus mykiss*	*Daphnia magna*	*Daphnia magna*	*Desmodesmus subspicatus*	*Lemna gibba*	*Chironomus riparius*	*Chironomus riparius*	Mesocosm	
		LC_{50}	NOEC	EC_{50}	NOEC	E_rC_{50}	ErC_{50}	NOEC	NOEC	NOEC	NOEAEC
		1930 µg/L	3.8 µg/L	540 µg/L	50 µg/L	0.688 µg/L	78.9 µg/L	1000 µg/L	40000 µg/kg	0.13 µg/L	0.39 µg/L
RAC		**19.3 µg/L**	**0.38 µg/L**	**5.4 µg/L**	**5.0 µg/L**	**0.0688 µg/L**	**7.89 µg/L**	**100 µg/L**	**4000 µg/kg**	**0.065 µg/L**	**0.13 µg/L**
Assessment factor**		100	10	100	10	10	10	10	10	2	3
FOCUS Step 1	72.57 µg/L /2350 µg/kg	**72.57**	**72.57**	**72.57**	**72.57**	**72.57**	**72.57**	**72.57**	2350	-	-
FOCUS Step 2											
North Europe	11.19	11.19	**11.19**	**11.19**	**11.19**	**11.19**	**11.19**	-	-	-	-
South Europe	20.30	**20.30**	**20.30**	**20.30**	**20.30**	**20.30**	**20.30**	-	-	-	-
FOCUS Step 3*											
D1 / ditch	4.111	4.111	**4.111**	4.111	4.111	**4.111**	4.111	-	-	**4.111**	**4.111**
D1 / stream	3.119 [a]	3.119	**3.119**	3.119	3.119	**3.119**	3.119	-	-	**3.119**	**3.119**
D3 / ditch	3.528 [a]	3.528	**3.528**	3.528	3.528	**3.528**	3.528	-	-	**3.528**	**3.528**
D4 / pond	0.136	0.136	0.136	0.136	0.136	**0.136**	0.136	-	-	**0.136**	**0.136**
D4 / stream	2.882 [a]	2.882	**2.882**	2.882	2.882	**2.882**	2.882	-	-	**2.882**	**2.882**
D5 / pond	0.153	0.153	0.153	0.153	0.153	**0.153**	0.153	-	-	**0.153**	**0.153**
D5 / stream	3.064 [a]	3.064	**3.064**	3.064	3.064	**3.064**	3.064	-	-	**3.064**	**3.064**
R4 / stream	2.329 [a]	2.329	**2.329**	2.329	2.329	**2.329**	2.329	-	-	**2.329**	**2.329**

values in bold exceed the relevant RAC, indicating an unacceptable risk

[a] PEC_{sw} for a single application as a worse case

*[Only scenarios where the trigger is not met at FOCUSsw step 1-2 should be included in step 3.]

Table 2.9.9-19 FOCUS$_{sw}$ step 1-3 - PEC/RAC comparisons for fenpropidin – winter cereals at 281.25 g a.s./ha x 2

Scenario	PEC global max (µg /L)	fish acute	fish chronic	Aquatic invertebrates	Aquatic invertebrates prolonged	Algae	Higher plant	Sed. dweller prolonged Spiked water	Sed. dweller prolonged Spiked sediment	Microcosm / Mesocosm	
		Lepomis macrochirus	*Oncorhynchuss mykiss*	*Daphnia magna*	*Daphnia magna*	*Desmodesmus subspicatus*	*Lemna gibba*	*Chironomus riparius*	*Chironomus riparius*	Mesocosm	
		LC_{50}	NOEC	EC_{50}	NOEC	E_rC_{50}	ErC_{50}	NOEC	NOEC	NOEC	NOEAEC
		1930 µg/L	3.8 µg/L	540 µg/L	50 µg/L	0.688 µg/L	78.9 µg/L	1000 µg/L	40000 µg/kg	0.13 µg/L	0.39 µg/L
RAC		**19.3 µg/L**	**0.38 µg/L**	**5.4 µg/L**	**5.0 µg/L**	**0.0688 µg/L**	**7.89 µg/L**	**100 µg/L**	**4000 µg/kg**	**0.065 µg/L**	**0.13 µg/L**
Assessment factor**		100	10	100	10	10	10	10	10	2	3
FOCUS Step 1	36.29 µg/L /1170 µg/kg	**36.29**	**36.29**	**36.29**	**36.29**	**36.29**	**36.29**	36.29	1170	-	-
FOCUS Step 2											
North Europe	5.59	5.59	**5.59**	**5.59**	**5.59**	**5.59**	5.59	-	-	-	-
South Europe	10.15	10.15	**10.15**	**10.15**	**10.15**	**10.15**	**10.15**	-	-	-	-
FOCUS Step 3*											
D1 / ditch	1.777 [a]	-	**1.777**	1.777	1.777	**1.777**	1.777	-	-	**1.777**	**1.777**
D1 / stream	1.516 [a]	-	**1.516**	1.516	1.516	**1.516**	1.516	-	-	**1.516**	**1.516**
D2 / ditch	1.774 [a]	-	**1.774**	1.774	1.774	**1.774**	1.774	-	-	**1.774**	**1.774**
D2 / stream	1.486 [a]	-	**1.486**	1.486	1.486	**1.486**	1.486	-	-	**1.486**	**1.486**
D3 / ditch	1.757 [a]	-	**1.757**	1.757	1.757	**1.757**	1.757	-	-	**1.757**	**1.757**
D4 / pond	0.067	-	0.067	0.067	0.067	0.067	0.067	-	-	**0.067**	0.067
D4 / stream	1.408 [a]	-	**1.408**	1.408	1.408	**1.408**	1.408	-	-	**1.408**	**1.408**
D5 / pond	0.080	-	0.080	0.080	0.080	**0.080**	0.080	-	-	**0.080**	0.080
D5 / stream	1.403 [a]	-	**1.403**	1.403	1.403	**1.403**	1.403	-	-	**1.403**	**1.403**
D6 / ditch	1.768 [a]	-	**1.768**	1.768	1.768	**1.768**	1.768	-	-	**1.768**	**1.768**
R1 / pond	0.081	-	0.081	0.081	0.081	**0.081**	0.081	-	-	**0.081**	0.081
R1 / stream	1.157 [a]	-	**1.157**	1.157	1.157	**1.157**	1.157	-	-	**1.157**	**1.157**
R3 / stream	1.627 [a]	-	**1.627**	1.627	1.627	**1.627**	1.627	-	-	**1.627**	**1.627**
R4 / stream	1.157 [a]	-	**1.157**	1.157	1.157	**1.157**	1.157	-	-	**1.157**	**1.157**

values in bold exceed the relevant RAC, indicating an unacceptable risk

[a] PEC_{sw} for a single application as a worse case

*[Only scenarios where the trigger is not met at FOCUSsw step 1-2 should be included in step 3.]

**[If the Trigger value has been adjusted during the risk assessment, it should always be clear on what basis the risk assessment has been performed, i.e. what the AF value is and for which organism and endpoint it refers.]

Table 2.9.9-20 FOCUS$_{sw}$ step 1-3 - PEC/RAC comparisons for fenpropidin – spring cereals at 281.25 g a.s./ha x 2

Scenario	PEC global max (µg /L)	fish acute	fish chronic	Aquatic invertebrates	Aquatic invertebrates prolonged	Algae	Higher plant	Sed. dweller prolonged Spiked water	Sed. dweller prolonged Spiked sediment	Microcosm / Mesocosm	
		Lepomis macrochirus	*Oncorhynchus mykiss*	*Daphnia magna*	*Daphnia magna*	*Desmodesmus subspicatus*	*Lemna gibba*	*Chironomus riparius*	*Chironomus riparius*	Mesocosm	
		LC_{50}	NOEC	EC_{50}	NOEC	E_rC_{50}	ErC_{50}	NOEC	NOEC	NOEC	NOEAEC
		1930 µg/L	3.8 µg/L	540 µg/L	50 µg/L	0.688 µg/L	78.9 µg/L	1000 µg/L	40000 µg/kg	0.13 µg/L	0.39 µg/L
RAC		**19.3 µg/L**	**0.38 µg/L**	**5.4 µg/L**	**5.0 µg/L**	**0.0688 µg/L**	**7.89 µg/L**	**100 µg/L**	**4000 µg/kg**	**0.065 µg/L**	**0.13 µg/L**
Assessment factor**		100	10	100	10	10	10	10	10	2	3
FOCUS Step 1	36.29 µg/L /1170 µg/kg	**36.29**	**36.29**	**36.29**	**36.29**	**36.29**	**36.29**	36.29	1170	-	-
FOCUS Step 2											
North Europe	5.59	5.59	**5.59**	**5.59**	**5.59**	**5.59**	5.59	-	-	-	-
South Europe	10.15	10.15	**10.15**	**10.15**	**10.15**	**10.15**	**10.15**	-	-	-	-
FOCUS Step 3*											
D1 / ditch	2.028	2.028	**2.028**	2.028	2.028	**2.028**	2.028	-	-	**2.028**	**2.028**
D1 / stream	1.556 [a]	1.556	**1.556**	1.556	1.556	**1.556**	1.556	-	-	**1.556**	**1.556**
D3 / ditch	1.761 [a]	1.761	**1.761**	1.761	1.761	**1.761**	1.761	-	-	**1.761**	**1.761**
D4 / pond	0.067	0.067	0.067	0.067	0.067	0.067	0.067	-	-	**0.067**	0.067
D4 / stream	1.438 [a]	1.438	**1.438**	1.438	1.438	**1.438**	1.438	-	-	**1.438**	**1.438**
D5 / pond	0.076	0.076	0.076	0.076	0.076	**0.076**	0.076	-	-	**0.076**	0.076
D5 / stream	1.529 [a]	1.529	**1.529**	1.529	1.529	**1.529**	1.529	-	-	**1.529**	**1.529**
R4 / stream	1.162 [a]	1.162	**1.162**	1.162	1.162	**1.162**	1.162	-	-	**1.162**	**1.162**

values in bold exceed the relevant RAC, indicating an unacceptable risk

[a] PEC_{sw} for a single application as a worse case

*[Only scenarios where the trigger is not met at FOCUSsw step 1-2 should be included in step 3.]

Based on a comparison of the results of the standard laboratory toxicity studies with FOCUS Step 3 maximum PEC_{sw} values for fenpropidin for use on winter and spring cereals, the long-term TER values for fish and algae remain below the relevant triggers, indicating that further consideration of the risk is required (see below).

The TER calculations for metabolite CGA289267 are presented in the tables below.

Table 2.9.9-21 PEC/RAC comparisons for the most sensitive aquatic organisms (Regulation (EU) N° 284/2013, Annex Part A, point 10.2): $FOCUS_{sw}$ step 1 - TERs for metabolite CGA289267– winter/spring cereals at 562.5 g a.s./ha x 2

Scenario	PEC global max (µg L)	fish acute	fish chronic	Aquatic invertebrates	Aquatic invertebrates prolonged	Algae	Higher plant	Sed. dweller prolonged	Microcosm / Mesocosm
		Oncorhynchus mykiss	-	*Daphnia magna*	-	*Desmodesmus subspicatus*	-	-	
		LC_{50}	NOEC	EC_{50}	NOEC	E_rC_{50}	E_yC_{50}	NOEC	NOEC
		>100 000 µg/L	-	>123 450 µg/L	-	69 000 µg/L	-	-	-
RAC		**>1 000 µg/L**	-	**>1234.5 µg/L**	-	**6 900 µg/L**	-	-	-
Assessment factor**		100	-	100	-	10	-	-	-
FOCUS Step 1									
	148.0	148.0	-	148.0	-	148.0	--	-	-

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 1-2 should be included in step 3.]

Based on a comparison of the results of the standard laboratory toxicity studies with FOCUS Step 1 maximum PEC_{sw} values for metabolite CGA289267, all TER values are greater than the relevant triggers for all uses, indicating low risk.

Table 2.9.9-22 $FOCUS_{sw}$ step 4 - PEC/RAC comparisons for fenpropidin – winter cereals at 562.5 g a.s./ha x 2 – Mesocosm ETO-RAC 0.065 µg a.s./L

Organisms: Mesocosm
Toxicity endpoint: NOEC 0.13 µg a.s /L, AF: 2
RAC: 0.065 µg a.s./L

Mitigation options	[x] m non-spray buffer zone (corresponding to ≤ 95 % drift reduction)	[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)	PECsw (x.xx µg/L)
FOCUS Step 4*			
D1 / ditch	20	-	**0.264** [a]
D1 / stream	20	-	**0.303** [a]
D2 / ditch	20	-	**0.263** [a]
D2 / stream	20	-	**0.297** [a]
D3 / ditch	20	-	**0.261** [a]
D4 / pond	15	-	0.0646
D4 / stream	20	-	**0.278** [a]
D5 / pond	20	-	0.0640
D5 / stream	20	-	**0.281** [a]
D6 / ditch	20	-	**0.262** [a]
R1 / pond	20	20	0.0602
R1 / stream	20	20	**0.2627**
R3 / stream	20	20	**0.326** [a]
R4 / stream	20	20	**1.784**

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 3 should be included in step 4].
[a] PEC_{sw} for a single application as a worse case

Table 2.9.9-23 $FOCUS_{sw}$ step 4 - PEC/RAC comparisons for fenpropidin – winter cereals at 562.5 g a.s./ha x 2 – Mesocosm ETO-RAC 0.13 µg a.s./L

Organisms: Mesocosm
Toxicity endpoint: NOEAEC 0.39 µg a.s /L, AF: 3
RAC: 0.13 µg a.s./L

Mitigation options	[x] m non-spray buffer zone (corresponding to ≤ 95 % drift reduction)	[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)	PECsw (x.xx µg/L)
FOCUS Step 4*			
D1 / ditch	20	-	**0.264** [a]
D1 / stream	20	-	**0.303** [a]
D2 / ditch	20	-	**0.263** [a]
D2 / stream	20	-	**0.297** [a]
D3 / ditch	20	-	**0.261** [a]
D4 / pond	15	-	0.0646
D4 / stream	20	-	**0.278** [a]
D5 / pond	15	-	0.0769
D5 / stream	20	-	**0.281** [a]
D6 / ditch	20	-	**0.262** [a]
R1 / pond	20	-	0.0602
R1 / stream	20	20	**0.2627**
R3 / stream	20	20	**0.326** [a]
R4 / stream	20	20	**1.784**

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 3 should be included in step 4].
[a] PEC_{sw} for a single application as a worse case

Table 2.9.9-24 $FOCUS_{sw}$ step 4 - PEC/RAC comparisons for fenpropidin – spring cereals at 562.5 g a.s./ha x 2 – Mesocosm ETO-RAC 0.065 µg a.s./L

Organisms: Mesocosm
Toxicity endpoint: NOEC 0.13 µg a.s /L, AF: 2
RAC: 0.065 µg a.s./L

Mitigation options	[x] m non-spray buffer zone (corresponding to ≤ 95 % drift reduction)	[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)	PECsw (x.xx µg/L)
FOCUS Step 4*			
D1 / ditch	20	-	**0.269**
D1 / stream	20	-	**0.311** [a]
D3 / ditch	20	-	**0.261** [a]
D4 / pond	20	-	0.054
D4 / stream	20	-	**0.288** [a]
D5 / pond	20	-	0.061
D5 / stream	20	-	**0.306** [a]
R4 / stream	20	20	**0.232**

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 3 should be included in step 4].
[a] PEC_{sw} for a single application as a worse case

Table 2.9.9-25 $FOCUS_{sw}$ step 4 - PEC/RAC comparisons for fenpropidin – spring cereals at 562.5 g a.s./ha x 2 – Mesocosm ETO-RAC 0.13 µg a.s./L

Organisms: Mesocosm
Toxicity endpoint: NOEAEC 0.39 µg a.s /L, AF: 3
RAC: 0.13 µg a.s./L

Mitigation options	[x] m non-spray buffer zone (corresponding to ≤ 95 % drift reduction)	[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)	PECsw (x.xx µg/L)
FOCUS Step 4*			
D1 / ditch	20	-	**0.269**
D1 / stream	20	-	**0.311** [a]
D3 / ditch	20	-	**0.261** [a]
D4 / pond	15	-	0.065

D4 / stream	20	-	**0.288** [a]
D5 / pond	15	-	0.073
D5 / stream	20	-	**0.306** [a]
R4 / stream	20	20	**0.232**

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 3 should be included in step 4].
[a] PEC_{sw} for a single application as a worse case

Table 2.9.9-26 FOCUS$_{sw}$ step 4 - PEC/RAC comparisons for fenpropidin – winter cereals at 281.25 g a.s./ha x 2 – Mesocosm ETO-RAC 0.065 µg a.s./L

Organisms: Mesocosm
Toxicity endpoint: NOEC 0.13 µg a.s /L, AF: 2
RAC: 0.065 µg a.s./L

Mitigation options	**[x] m non-spray buffer zone (corresponding to ≤ 95 % drift reduction)**	**[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)**	**PECsw (x.xx µg/L)**
FOCUS Step 4*			
D1 / ditch	20	-	**0.131** [a]
D1 / stream	20	-	**0.151** [a]
D2 / ditch	20	-	**0.131** [a]
D2 / stream	20	-	**0.148** [a]
D3 / ditch	20	-	**0.130** [a]
D4 / pond	15	-	0.032
D4 / stream	20	-	**0.138** [a]
D5 / pond	15	-	0.038
D5 / stream	20	-	**0.140** [a]
D6 / ditch	20	-	**0.131** [a]
R1 / pond	10	10	0.046
R1 / stream	20	20	**0.115** [a]
R3 / stream	20	20	**0.162** [a]
R4 / stream	20	20	**0.175**

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 3 should be included in step 4].
[a] PEC_{sw} for a single application as a worse case

Table 2.9.9-27 $FOCUS_{sw}$ step 4 - PEC/RAC comparisons for fenpropidin – winter cereals at 281.25 g a.s./ha x 2 – Mesocosm ETO-RAC 0.13 µg a.s./L

Organisms: Mesocosm
Toxicity endpoint: NOEAEC 0.39 µg a.s /L, AF: 3
RAC: 0.13 µg a.s./L

Mitigation options	[x] m non-spray buffer zone (corresponding to ≤ 95 % drift reduction)	[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)	PECsw (x.xx µg/L)
FOCUS Step 4*			
D1 / ditch	20	-	**0.131** [a]
D1 / stream	20	-	**0.151** [a]
D2 / ditch	20	-	**0.131** [a]
D2 / stream	20	-	**0.148** [a]
D3 / ditch	20	-	**0.130** [a]
D4 / stream	20	-	**0.138** [a]
D5 / stream	20	-	**0.140** [a]
D6 / ditch	20	-	**0.131** [a]
R1 / stream	20	20	0.115 [a]
R3 / stream	20	20	**0.162** [a]
R4 / stream	20	20	**0.175**

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 3 should be included in step 4].
[a] PEC_{sw} for a single application as a worse case

Table 2.9.9-28 $FOCUS_{sw}$ step 4 - PEC/RAC comparisons for fenpropidin – spring cereals at 281.25 g a.s./ha x 2 – Mesocosm ETO-RAC 0.065 µg a.s./L

Organisms: Mesocosm
Toxicity endpoint: NOEC 0.13 µg a.s /L, AF: 2
RAC: 0.065 µg a.s./L

Mitigation options	[x] m non-spray buffer zone (corresponding to ≤ 95 % drift reduction)	[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)	PECsw (x.xx µg/L)
FOCUS Step 4*			
D1 / ditch	20	-	**0.133**
D1 / stream	20	-	**0.155** [a]
D3 / ditch	20	-	**0.130** [a]
D4 / pond	5	-	0.058
D4 / stream	20	-	**0.143** [a]
D5 / pond	10	-	0.046
D5 / stream	20	-	**0.152** [a]
R4 / stream	20	20	**0.116** [a]

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 3 should be included in step 4].
[a] PEC_{sw} for a single application as a worse case

Table 2.9.9-29 $FOCUS_{sw}$ step 4 - PEC/RAC comparisons for fenpropidin – winter cereals at 281.25 g a.s./ha x 2 – Mesocosm ETO-RAC 0.13 µg a.s./L

Organisms: Mesocosm
Toxicity endpoint: NOEAEC 0.39 µg a.s /L, AF: 3
RAC: 0.13 µg a.s./L

Mitigation options	[x] m non-spray buffer zone (corresponding to ≤ 95 % drift reduction)	[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)	PECsw (x.xx µg/L)
FOCUS Step 4*			
D1 / ditch	20	-	**0.133**
D1 / stream	20	-	**0.155** [a]
D3 / ditch	20	-	**0.130** [a]
D4 / stream	20	-	**0.143** [a]
D5 / stream	20	-	**0.152** [a]
R4 / stream	20	20	0.116 [a]

Bold figures fall below the Regulation (EU) 546/2011trigger value
*[Only scenarios where the trigger is not met at FOCUSsw step 3 should be included in step 4].
[a] PEC_{sw} for a single application as a worse case

Conclusion – risk to aquatic organisms
No risks were identified for fish, aquatic invertebrates and aquatic macrophytes. Algae were identified as the most sensitive group of organisms and two mesocosm studies were used to refine the risk for them. Two RAC options were proposed by the RMS and should be discussed in peer-review:

- Mesocosm ETO-RAC 0.065 µg a.s./L
- Mesocosm ERO-RAC 0.13 µg a.s./L

Considering **ETO-RAC 0.065 µg a.s./L**, the following scenarios passed:

Scenario	**FOCUS Step 4**	
	[x] m non-spray buffer zone	**[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)**
Winter cereals at 562.5 g a.s./ha x 2		
D4 / pond	15	.
D5 / pond	20	.
R1 / pond	20	20
Spring cereals at 562.5 g a.s./ha x 2		
D4 / pond	20	.
D5 / pond	20	.
Winter cereals at 281.25 g a.s./ha x 2		
D4 / pond	15	.
D5 / pond	15	.
R1 / pond	10	10
Spring cereals at 281.25 g a.s./ha x 2		
D4 / pond	5	.
D5 / pond	10	.

Considering **ERO-RAC 0.13 µg a.s./L**, the following scenarios passed:

Scenario	**FOCUS Step 4**	
	[x] m non-spray buffer zone	**[x] m vegetated buffer strip (corresponding to ≤ 90 % run-off reduction)**
Winter cereals at 562.5 g a.s./ha x 2		
D4 / pond	15	.
D5 / pond	15	.
R1 / pond	20	20
Spring cereals at 562.5 g a.s./ha x 2		
D4 / pond	15	.
D5 / pond	15	.
Winter cereals at 281.25 g a.s./ha x 2		
D4 / pond	Step 3	.
D5 / pond	Step 3	.
R1 / pond	Step 3	.

R1 / stream	20	20
Spring cereals at 281.25 g a.s./ha x 2		
D4 / pond	Step 3	.
D5 / pond	Step 3	.
R4 / stream	20	20

2.9.9.3 Risk assessment for arthropods

2.9.9.3.1 Risk assessment for bees

Risk assessment for honeybees from contact and oral dietary exposure for cereals at 562.5 g a.s./ha x 2, BBCH 31-69

Species	Test substance	Scenario	Risk quotient	HQ/ETR	Trigger
Screening level assessment					
Apis mellifera	a.s.	Not relevant	$HQ_{contact}$	12.2	42
Apis mellifera	a.s.	Not relevant	$ETR_{acute\ adult\ oral}$	0.04	0.2
Apis mellifera	a.s.	Not relevant	$ETR_{chronic\ adult\ oral}$	**29.69**	0.03
Apis mellifera	a.s.	Not relevant	$ETR_{chronic\ larva\ oral}$	**1.60**	0.2
Tier 1 level assessment – BBCH 30-39					
Apis mellifera	a.s.	treated crop	$ETR_{chronic\ adult\ oral}$	**2.588**	0.03
Apis mellifera	a.s.	weeds	$ETR_{chronic\ adult\ oral}$	**4.078**	0.03
Apis mellifera	a.s.	field margin	$ETR_{chronic\ adult\ oral}$	**0.075**	0.03
Apis mellifera	a.s.	adjacent crop	$ETR_{chronic\ adult\ oral}$	**0.054**	0.03
Apis mellifera	a.s.	succeeding crop	$ETR_{chronic\ adult\ oral}$	**1.519**	0.03
Apis mellifera	a.s.	treated crop	$ETR_{chronic\ larva\ oral}$	0.05	0.2
Apis mellifera	a.s.	weeds	$ETR_{chronic\ larva\ oral}$	**0.34**	0.2
Apis mellifera	a.s.	field margin	$ETR_{chronic\ larva\ oral}$	0.01	0.2
Apis mellifera	a.s.	adjacent crop	$ETR_{chronic\ larva\ oral}$	0.00	0.2
Apis mellifera	a.s.	succeeding crop	$ETR_{chronic\ larva\ oral}$	0.12	0.2
Tier 1 level assessment – BBCH 40-69					
Apis mellifera	a.s.	treated crop	$ETR_{chronic\ adult\ oral}$	**2.588**	0.03
Apis mellifera	a.s.	weeds	$ETR_{chronic\ adult\ oral}$	**2.447**	0.03
Apis mellifera	a.s.	field margin	$ETR_{chronic\ adult\ oral}$	**0.075**	0.03
Apis mellifera	a.s.	adjacent crop	$ETR_{chronic\ adult\ oral}$	**0.054**	0.03
Apis mellifera	a.s.	succeeding crop	$ETR_{chronic\ adult\ oral}$	**1.519**	0.03
Apis mellifera	a.s.	treated crop	$ETR_{chronic\ larva\ oral}$	0.05	0.2
Apis mellifera	a.s.	weeds	$ETR_{chronic\ larva\ oral}$	**0.20**	0.2
Apis mellifera	a.s.	field margin	$ETR_{chronic\ larva\ oral}$	0.01	0.2
Apis mellifera	a.s.	adjacent crop	$ETR_{chronic\ larva\ oral}$	0.00	0.2
Apis mellifera	a.s.	succeeding crop	$ETR_{chronic\ larva\ oral}$	0.12	0.2

Risk assessment for honeybees from consumption of contaminated water

Species	Test substance	Risk quotient	ETR	Trigger
Risk assessment from exposure to residues in guttation fluid (water solubility = 530 mg/L)				
Apis mellifera	a.s.	$ETR_{acute\ adult\ oral}$	0.06	0.2
Apis mellifera	a.s.	$ETR_{chronic\ adult\ oral}$	**22.658**	0.03
Apis mellifera	a.s.	$ETR_{chronic\ larva\ oral}$	**27.43**	0.2
Risk assessment from exposure to residues in surface water (FOCUS Step 3 PECsw of 0.003562 mg/L)				
Apis mellifera	a.s.	$ETR_{acute\ adult\ oral}$	0.00	0.2
Apis mellifera	a.s.	$ETR_{chronic\ adult\ oral}$	0.000	0.03
Apis mellifera	a.s.	$ETR_{chronic\ larva\ oral}$	0.00	0.2
Risk assessment from exposure to residues in puddle water (FOCUS Step 3 PECsw of 0.003262 mg/L)				
Apis mellifera	a.s.	$ETR_{acute\ adult\ oral}$	0.00	0.2
Apis mellifera	a.s.	$ETR_{chronic\ adult\ oral}$	0.00	0.03
Apis mellifera	a.s.	$ETR_{chronic\ larva\ oral}$	0.00	0.2

* value not calculated by excel sheet

Risk assessment for honeybees from contact and oral dietary exposure for cereals at 281.25 g a.s./ha x 2, BBCH 31-69

Species	Test substance	Scenario	Risk quotient	HQ/ETR	Trigger
Screening level assessment					
Apis mellifera	a.s.	Not relevant	$HQ_{contact}$	6.1	42
Apis mellifera	a.s.	Not relevant	$ETR_{acute\ adult\ oral}$	0.02	0.2
Apis mellifera	a.s.	Not relevant	$ETR_{chronic\ adult\ oral}$	**14.84**	0.03
Apis mellifera	a.s.	Not relevant	$ETR_{chronic\ larva\ oral}$	**0.80**	0.2
Tier 1 level assessment – BBCH 30-39					
Apis mellifera	a.s.	treated crop	$ETR_{chronic\ adult\ oral}$	**1.294**	0.03
Apis mellifera	a.s.	weeds	$ETR_{chronic\ adult\ oral}$	**2.039**	0.03
Apis mellifera	a.s.	field margin	$ETR_{chronic\ adult\ oral}$	**0.039**	0.03
Apis mellifera	a.s.	adjacent crop	$ETR_{chronic\ adult\ oral}$	0.027	0.03
Apis mellifera	a.s.	succeeding crop	$ETR_{chronic\ adult\ oral}$	**0.759**	0.03
Apis mellifera	a.s.	treated crop	$ETR_{chronic\ larva\ oral}$	0.02	0.2
Apis mellifera	a.s.	weeds	$ETR_{chronic\ larva\ oral}$	0.17	0.2
Apis mellifera	a.s.	field margin	$ETR_{chronic\ larva\ oral}$	0.00	0.2
Apis mellifera	a.s.	adjacent crop	$ETR_{chronic\ larva\ oral}$	0.00	0.2
Apis mellifera	a.s.	succeeding crop	$ETR_{chronic\ larva\ oral}$	0.16	0.2

Tier 1 level assessment – BBCH 40-69					
Apis mellifera	a.s.	treated crop	$ETR_{chronic\ adult\ oral}$	**1.294**	0.03
Apis mellifera	a.s.	weeds	$ETR_{chronic\ adult\ oral}$	**1.223**	0.03
Apis mellifera	a.s.	field margin	$ETR_{chronic\ adult\ oral}$	**0.038**	0.03
Apis mellifera	a.s.	adjacent crop	$ETR_{chronic\ adult\ oral}$	0.027	0.03
Apis mellifera	a.s.	succeeding crop	$ETR_{chronic\ adult\ oral}$	**0.759**	0.03
Apis mellifera	a.s.	treated crop	$ETR_{chronic\ larva\ oral}$	0.02	0.2
Apis mellifera	a.s.	weeds	$ETR_{chronic\ larva\ oral}$	0.10	0.2
Apis mellifera	a.s.	field margin	$ETR_{chronic\ larva\ oral}$	0.00	0.2
Apis mellifera	a.s.	adjacent crop	$ETR_{chronic\ larva\ oral}$	0.00	0.2
Apis mellifera	a.s.	succeeding crop	$ETR_{chronic\ larva\ oral}$	0.06	0.2

Risk assessment for honeybees from consumption of contaminated water

Species	**Test substance**	**Risk quotient**	**ETR**	**Trigger**
Risk assessment from exposure to residues in guttation fluid (water solubility = 530 mg/L)				
Apis mellifera	a.s.	$ETR_{acute\ adult\ oral}$	0.06	0.2
Apis mellifera	a.s.	$ETR_{chronic\ adult\ oral}$	**22.658**	0.03
Apis mellifera	a.s.	$ETR_{chronic\ larva\ oral}$	**27.43**	0.2
Risk assessment from exposure to residues in surface water (FOCUS Step 3 PECsw of 0.003562 mg/L)				
Apis mellifera	a.s.	$ETR_{acute\ adult\ oral}$	0.00	0.2
Apis mellifera	a.s.	$ETR_{chronic\ adult\ oral}$	0.000	0.03
Apis mellifera	a.s.	$ETR_{chronic\ larva\ oral}$	0.00	0.2
Risk assessment from exposure to residues in puddle water (FOCUS Step 3 PECsw of 0.003262 mg/L)				
Apis mellifera	a.s.	$ETR_{acute\ adult\ oral}$	0.00	0.2
Apis mellifera	a.s.	$ETR_{chronic\ adult\ oral}$	0.00	0.03
Apis mellifera	a.s.	$ETR_{chronic\ larva\ oral}$	0.00	0.2

The HQ and ETR values met the relevant triggers at screening assessment, except for the chronic oral risk to adult honeybees and chronic oral risk to honeybee larvae. Therefore, Tier 1 assessment was performed, for both maximum (i.e. 2 x 562.5 g a.s./ha) and minimum (i.e. 2 x 281.25 g a.s./ha) intended application rate of fenpropidin.

All the ETR values for honeybee larvae met the relevant triggers at Tier 1 assessment, except for scenario "weeds" for application rate 562.5 g a.s./ha x 2.

No chronic ETR value for adult honeybees met the relevant triggers at Tier 1 assessment, except for the scenario "adjacent crop" for application rate 281.25 g a.s./ha x 2, indicating high chronic risk to adult honeybees.

Moreover, based on the risk assessment from exposure to residues in guttation fluid, the ETR values do not met the relevant triggers for the chronic oral risk to adult honeybees and chronic oral risk to honeybee larvae, for both maximum and minimum intended application rate.

It is noted that the exposure to bees via flowering weeds scenario in cereals is considered of rather low relevance (see EFSA Conclusion on confirmatory data for clothianidin and imidacloprid, EFSA Journal 2016;14(11):4606, EFSA Journal 2016;14(11):4607). Therefore, the chronic risk to honeybee larvae is considered to be low also for scenario "weeds".

However, further consideration is needed for chronic risk to adult honeybees and the risk from exposure to residues in guttation fluid.

Higher tier studies
In addition to the laboratory tests, three semi-field studies (tunnel tests) were conducted according to BBA VI, 23-1 (1991). However, the studies are only short-term (observation period: 72 hours, 5-11 days and 3 days) and mortality, foraging activity and behaviour was only assessed . Therefore, the results can only be used as additional information for evaluation of acute risk to adult honeybees and cannot be used for refinement of the chronic risk to adult honeybees.

Risk assessment for bumblebees and solitary bees:
No data were available and no risk assessment was performed by RMS.

Risk assessment for exposure to metabolites
No data were available and no risk assessment was performed by RMS.

Conclusion – risk to bees:
Based on the results of the standard laboratory toxicity studies and screening calculations, low risk was concluded for acute contact and oral risk to adult honeybees for all bee exposure scenarios considered.
Based on Tier 1 calculations, low risk was concluded for chronic risk to honeybee larvae for all bee exposure scenarios considered, except for scenario "weeds". However, since the exposure to bees via flowering weeds scenario in cereals is considered of rather low relevance (see EFSA Conclusion on confirmatory data for clothianidin and imidacloprid, EFSA Journal 2016;14(11):4606, EFSA Journal 2016;14(11):4607), the chronic risk to honeybee larvae is considered to be low also for scenario "weeds".
No chronic ETR value for adult honeybees met the relevant triggers at Tier 1 assessment, indicating high chronic risk to adult honeybees.
Moreover, the risk assessment from exposure to residues in guttation fluid indicated high risk to honeybees.
In addition to the laboratory tests, three semi-field studies (tunnel tests) were conducted according to BBA guideline. However, the studies are only short-term (observation period: 72 hours, 5-11 days and 3 days) and mortality, foraging activity and behaviour was only assessed. Therefore, the results can only be used as additional information for evaluation of acute risk to adult honeybees and cannot be used for refinement of the chronic risk to adult honeybees.
To refine the risk to bees, the Notifier provided the consideration based on the EPPO 2010 scheme.

It is concluded the that chronic risk assessment for adult honeybees and risk assessment for honeybees from consumption of guttation fluid and from metabolites could not be finalized, as well as the risk assessment for bumblebees and solitary bees.

The risk assessment for bees should be discussed in peer review.

2.9.9.3.2 Risk assessment for non-target arthropods other than bees

Ter 1 risk assessment

According to ESCORT 2 guidance (2001) and Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002) details should be provided for glass plate residue toxicity tests conducted with the indicator species *Aphidius rhopalosiphi* and *Typhlodromus pyri*. The Tier 1 study for *Aphidius rhopalosiphi* was only available. However, it was performed as a limit test and resulted in 100% mortality in test substance treatment, indicated high risk.
Thus, no Tier 1 quantitative risk assessment could be performed for standard indicator species *Aphidius rhopalosiphi* and *Typhlodromus pyri*. Further consideration is needed.

Higher Tier risk assessment
Extended laboratory studies

Table 2.9.9-30 In-field risk assessment based on extended laboratory studies

Crop	Species	Appl. rate [g a.s./ha]	MAF	$PER_{in\text{-}field}$ [g a.s./ha]	LR_{50}; ER_{50} [g a.s./ha]	Risk acceptable?
Cereals	*Phytoseiulus persimilis*	2 x 562.5	1.7	956	282.8	**No**
	Aphidius rhopalosiphi				>1500	Yes

Table 2.9.9-31 Off-field risk assessment based on extended laboratory studies

Crop	Species	Appl. rate [g/ha]	MAF	Drift factor[a]	VDF	Correc-tion factor	$PER_{off\text{-}filed}$ [g a.s./ha]	LR_{50}; ER_{50} [g a.s./ha]	Risk acceptable?
Cereals	*Phytoseiulus persimilis*	2 x 562.5	1.7	0.0238 (1 m)	1 (3-D)	5	113.8	282.8	Yes
	Aphidius rhopalosiphi						113.8	>1500	Yes

[a] An overall 90th percentile drift value was used and hence for each application an 82nd percentile drift was considered

Based on comparison of toxicity endpoints for *Aphidius rhopalosiphi* and *Phytoseiulus persimilis* and in-field and off-field predicted exposure rate, low in-field and off-field risk for *Aphidius rhopalosiphi* and low off-field risk for *Phytoseiulus persimilis* has been concluded. However, high in-field risk for *Phytoseiulus persimilis* has been indicated and further consideration is required.

Additional species tested - Tier 1 risk assessment

In addition to laboratory and/or extended laboratoty studies on *Aphidius rhopalosiphi*, *Typhlodromus pyri* and *Phytoseiulus persimilis*, laboratory studies on *Aleochara bilineata, Chrysoperla carnea, Coccinella septempunctata, Bembidion tetracolum* and *Poecilus cupreus* were available.

Table 2.9.9-32 In-field and off-field Tier 1 hazard quotients (HQs) for terrestrial arthropods other than *T. pyri* and *A. rhopalosiphi*

Crop	Test species	LR_{50}/ ER_{50} (g a.s./ha)	Exposure scenario	Estimated exposure (L/ha)	HQ [Trigger = 2]
Cereals	*Aleochara bilineata*	>1500	In-field	956	<0.64
			Off-field	11.4	<0.015
	Chrysoperla carnea	>30 and <750	In-field	956	**<31.87 and >1.37**
			Off-field	11.4	<0.76 and >0.03
	Coccinella septempunctata	>750 and <1500	In-field	956	<1.27 and >0.64
			Off-field	11.4	<0.03 and >0.015
	Bembidion tetracolum	>750	In-field	956	<1.27
			Off-field	11.4	<0.03
	Poecilus cupreus	>1500	In-field	956	<0.64
			Off-field	11.4	<0.015

All HQ values for *Aleochara bilineata*, *Coccinella septempunctata*, *Bembidion tetracolum* and *Poecilus cupreus* met the trigger of 2, indicating low in-field and off-field risk. For *Chrysoperla carnea*, HQ value for off-field risk met the trigger only, while HQ value for in-field risk was not met. Therefore, further consideration is required for in-field risk for *Chrysoperla carnea.*

Refined in-field risk assessment for *Typhlodromus pyri, Phytoseiulus persimilis* and *Chrysoperla carnea*

Aged residue study on *Typhlodromus pyri* and *Phytoseiulus persimilis*

Extended laboratory studies with aged residues were performed in which *Typhlodromus pyri* (Taruza, 2001) or *Phytoseiulus persimilis* (Vinall, 2002*)* were exposed to intact sweet pepper plant leaves after 2 applications of A7516B, each at 750 g a.s./ha and a 14 day interval between applications. Exposure just after the maximum recommended number of applications per season and with a spray interval recommended resulted in < 50% lethal and sub-lethal effects of *T. pyri*. Therefore a low risk to this indicator species is expected following the recommended use of fenpropidin. Subsequent bioassays starting 1, 3, 5 and 8 days after the second application and bioassays commencing after only one application yielded results that are consistent with an estimation of low risk.

Exposure of *P. persimilis* commencing just after the maximum recommended number of applications per season resulted in > 50% lethal effects. However, in subsequent bioassays conducted 1, 3, 5 and 8 days after the second application <50% lethal and sub-lethal effects were observed. Therefore within 1 day of the final application of A7516B, the predatory mites, *P. persimilis* demonstrated a potential for recolonisation of in-field habitats. Bioassays commencing after only one application yielded results that are consistent with this potential for recolonisation of *P. persimilis*.

Regarding in-field risk to *Chrysoperla carnea*, no additional data were available. However, the results of Tier 1 studies showed that *A. rhopalosiphi* (also a leaf-dwelling insect) is similarly or slightly more sensitive than *C. carnea*, therefore, the risk assessment for *A. rhopalosiphi* can be considered as sufficiently protective also for *C.carnea*. Moreover, extended laboratory studies with aged residues discussed above indicated that he residues of fenpropidin dropped to acceptable levels very rapidly.

Taking all this information into account, the in-field risk to *Typhlodromus pyri, Phytoseiulus persimilis and Chrysoperla carnea* can be considered as low.

Conclusion - risk to non-target arthropods other than bees:
Low in-field and off-field risk to non-target arthropods can be concluded for A7516D following the proposed use pattern.

The risk assessment for non-target arthropods should be discussed in peer review.

2.9.9.4 Risk assessment for non-target soil meso- and macrofauna

2.9.9.4.1 Risk assessment for earthworms

Table 2.9.9-33 Long-term TER values for earthworms

Application rate	Compound	NOEC (mg/kg)	$NOEC_{corr}$ (mg/kg)	Maximum PEC_S (mg/kg)	TER_{LT}	Trigger
562.5 g a.s./h)	Fenpropidin [a]	10	5	0.420	1.19	5
	CGA289267	1000	-	0.0236	42373	

[a] Tested as A7516B

The long-term TER values exceed the trigger value of 5, indicating that low risk to earthworms following use of A7516D according to the proposed use pattern.

Conclusion – risk to earthworms
Low risk to earthworms for use of fenpropidin according to proposed GAP can be concluded.

2.9.9.4.2 Risk assessment for non-target soil meso- and macrofauna (other than earthworms)

Table 2.9.9-34 Long-term TER values for *Folsomia candida* and *Hypoaspis aculeifer*

Test organisms	Test substance	NOEC / EC_{10} (mg/kg)	$NOEC_{corr}$ / EC_{10corr} (mg/kg)	Maximum PEC_S (mg/kg)	TER_{LT}	Trigger
Folsomia candida	Fenpropidin [a]	91.37	45.69	0.420	109	5
	CGA289267	1000	-	0.024	41667	
Hypoaspis aculeifer	Fenpropidin [a]	830	415	0.420	993	
	CGA289267	1000	-	0.024	41667	

[a] Tested as A7516B

The long-term TER values exceed the trigger value of 5, indicating that low risk to *Folsomia candida* and *Hypoaspis aculeifer* following use of A7516D according to the proposed use pattern.

Conclusion – risk to soil meso- and macrofauna (other than earthworms)

Low risk to non-target soil meso- and macrofauna (other than earthworms) for use of fenpropidin according to proposed GAP can be concluded.

2.9.9.5 Risk assessment for soil nitrogen transformation

Table 2.9.9-35 Risk assessment for effects on soil micro-organisms

Application rate (g a.s./ha)	Compound	NOEC (mg/kg)	Maximum PEC_S (mg/kg)	Ratio of NOEC:PEC_S
562.5	Fenpropidin [a]	6.0	0.420	14
	CGA289267	10	0.0236	424

[a] Tested as A7516A

Fenpropidin had no significant effect on soil micro-organisms at 6.0 mg a.s./kg soil. This is approximately 14 times higher than the maximum PEC_S of 0.420 mg a.s/kg when accounting multi-year uses of A7516D. This indicates that the risk to non-target soil micro-organisms is acceptable following use of A7516D according to the proposed use pattern.
Furthermore, the NOEC for the soil metabolite CGA289267 is 420 times higher than the maximum soil concentration.

It is concluded that the use of A7516D will not pose an unacceptable risk to non-target soil micro-organisms, if applied according to the recommended use pattern.

2.9.9.6 Risk assessment for non-target plants

TER value for effects of A7516D on non-target plants

Application rate (g a.s./ha)	Endpoints		$PER_{off\text{-}field}$ (g a.s./ha)	TER	Trigger
	ER_{50} Vegetative vigour (g a.s. /ha)	ER_{50} Seedling emergence (g a.s./ha)			
562.5	>375	>750	15.6	>24	5

The TER values are well in excess of the trigger value of 5, indicating that the risk to non-target plants is acceptable following use of A7516D according to the proposed use pattern.

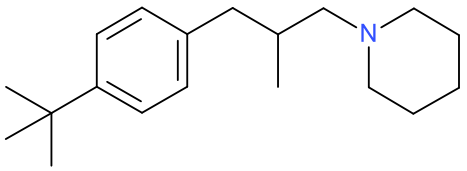
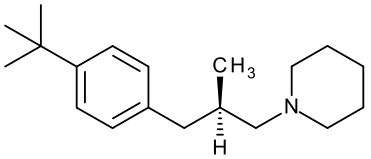
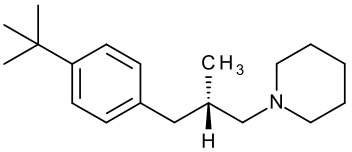
In conclusion, A7516D poses no unacceptable risk to terrestrial non-target plants in off-crop areas following the proposed uses.

2.10 PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA *[SECTIONS 1-6 OF THE CLH REPORT]*

2.10.1 Identity of the substance [section 1 of the CLH report]

2.10.1.1 Name and other identifiers of the substance

Table 61: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	(*R*,*S*)-1-[3-(4-tert-butylphenyl)-2-methylpropyl]-piperidine
Other names (usual name, trade name, abbreviation)	Fenpropidin
ISO common name (if available and appropriate)	Fenpropidin (ISO)
EC number (if available and appropriate)	-
EC name (if available and appropriate)	-
CAS number (if available)	67306-00-7
Other identity code (if available)	CIPAC No. 520 Development codes: Syngenta: CGA114900 ADAMA: MCW-273
Molecular formula	$C_{19}H_{31}N$
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	273.5 g.mol^{-1}
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Fenpropidin has two enantiomers, R (CGA344628) and S (CGA276059). The R-enantiomer has the following stereochemistry:  The S-enantiomer has the following stereochemistry:  The R and S enantiomers are non-superimposable mirror images that have identical physicochemical properties.
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not relevant

Degree of purity (%) (if relevant for the entry in Annex VI)	min. 960 g/kg

2.10.1.2 Composition of the substance

Table 62: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
None			

Table 63: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
None				

Table 64: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
None					

Table 65: Test substances (non-confidential information)

Identification of test substance	**Purity**	**Impurities and additives (identity, %, classification if available)**	**Other information**	**The study(ies) in which the test substance is used**

The purity of the material tested is stated in the relevant sections of the dossier.

2.10.2 Proposed harmonized classification and labelling

2.10.2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 66: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal		**Fenpropidin (ISO); (*R*,*S*)-1-[3-(4-tert-butylphenyl)-2-methylpropyl]piperidine**	-	67306-00-7	Acute tox 4 Acute tox 4 Eye Dam. 1 Skin Sens 1B STOT SE 3 STOT RE 2 Repr. 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H332 H318 H317 H335 H373 (nervous system) H361d H400 H410	GHS08 GHS09 Dgr	H302 H332 H318 H317 H335 H373 (nervous system) H361d H410		M-factor (acute/chronic) 1000/100	
Resulting Annex VI entry if agreed by RAC and COM		**Fenpropidin (ISO); (*R*,*S*)-1-[3-(4-tert-butylphenyl)-2-methylpropyl]pip**	-	67306-00-7	Acute tox 4 Acute tox 4 Eye Dam. 1	H302 H332 H318	GHS08 GHS09 Dgr	H302 H332 H318		M-factor (acute/chronic) 1000/100	

		eridine			Skin Sens. 1B STOT SE 3 STOT RE 2 Repr. 2 Aquatic Acute 1 Aquatic Chronic 1	H317 H335 H373 (nervous system) H361d H400 H410		H317 H335 H373 (nervous system) H361d H410			

2.10.2.2 Additional hazard statements / labelling

Table 67: Reason for not proposing harmonised classification and status under CLH public consultation

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Explosives	data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	hazard class not applicable	No
Oxidising gases	hazard class not applicable	No
Gases under pressure	hazard class not applicable	No
Flammable liquids	data conclusive but not sufficient for classification	Yes
Flammable solids	hazard class not applicable	No
Self-reactive substances	data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	data conclusive but not sufficient for classification	Yes
Pyrophoric solids	hazard class not applicable	No
Self-heating substances	data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	data conclusive but not sufficient for classification	Yes
Oxidising liquids	data conclusive but not sufficient for classification	Yes
Oxidising solids	hazard class not applicable	No
Organic peroxides	hazard class not applicable	No
Corrosive to metals	data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	-	Yes
Acute toxicity via dermal route	Conclusive, but not sufficient for classification	Yes
Acute toxicity via inhalation route	-	Yes
Skin corrosion/irritation	Conclusive, but not sufficient for classification	Yes
Serious eye damage/eye irritation	-	Yes
Respiratory sensitisation	Conclusive, but not sufficient for classification	Yes
Skin sensitisation	-	Yes
Germ cell mutagenicity	Conclusive, but not sufficient for classification	Yes
Carcinogenicity	Conclusive, but not sufficient for classification	Yes
Reproductive toxicity	-	Yes
Specific target organ toxicity-single exposure	-	Yes
Specific target organ toxicity-repeated exposure	-	Yes
Aspiration hazard	Hazard class not applicable	Yes

Hazard class	Reason for no classification	Within the scope of CLH public consultation
Hazardous to the aquatic environment	-	Yes
Hazardous to the ozone layer	Data not available	None

2.10.3 History of the previous classification and labelling

Not applicable. Fenpropidin has no previous CLP classification and labelling.

2.10.4 Identified uses

Fenpropidin is an agricultural fungicide used to control powdery mildews, rusts and Rynchosprium secalis in cereal crops.
Fenpropidin is a piperidine derivative and acts by inhibiting ergosterol biosynthesis, but by a different mechanism to the triazole fungicides. It is a systemic fungicide with both protectant and curative activity.

2.10.5 Data sources

The data submitted in the context of renewal of pesticide active substances under Regulation no. 1107/2009 concerning the placing of plant protection products on the market. The data was evaluated in the Renewal Assessment Report (RAR) Vol. 1-4.

2.11 RELEVANCE OF METABOLITES IN GROUNDWATER

Predicted environmental concentrations in groundwater (PEC_{gw}) for fenpropidin and its metabolite CGA 289267 were calculated for the use in Europe, using the simulation model FOCUS PEARL (version 4.4.4), PELMO (version 5.5.3) and MACRO (version 5.5.4). PEC_{gw} were evaluated as the 80^{th} percentile of the mean annual leachate concentration at 1 m soil depth. Model parameters and scenarios consisting of weather, soil, and crop data were used as proposed by FOCUS.
The metabolite CGA289267, present a PECgw values clearly above the 0.1 µg/L.
No data were submitted by the applicant for the evaluation of relevance of the metabolite CGA289267.
Data requirement.

2.11.1 STEP 1: Exclusion of degradation products of no concern

Metabolite CGA289267 does not meet the criteria for products of no concern as defined in step 1 of the guidance and therefore needs further assessment.

2.11.2 STEP 2: Quantification of potential groundwater contamination

PECgw calculations after leaching from soil for metabolite CGA289267 were performed (see Volume 3_CP_B-8, Section B.8.3 for fenpropidin). The critical GAP leads to PECGW exceeding 0.1 µg/L for the metabolite. Details are given in Volume 3_CP_B-8, Section B.8.3 for fenpropidin.

2.11.3 STEP 3: Hazard assessment – identification of relevant metabolites

2.11.3.1 STEP 3, Stage 1: screening for biological activity

No data were submitted by the applicant for the evaluation of relevance of the metabolite CGA289267.
Data requirement.

2.11.3.2 STEP 3, Stage 2: screening for genotoxicity

Genotoxicity studies on GW metabolite CGA289267 have been performed to support an assessment of the toxicological relevance of the metabolite in groundwater. These studies have not been previously submitted for EU review.

All three genotoxicity studies met the requirements for a clearly negative response therefore CGA289267 is not considered to be toxicologically relevant. The results are summarised below. For further details, please refer to section B.6.8.1 in CA B6

Assay(Guideline)	Test System	Result	Reference
In vitro bacterial reverse mutation assay (Ames; OECD 471, 1997)	*S. typhimurium* strains TA1535, TA1537, TA98 and TA100, and *E. coli* strain WP2 uvrA pKM101	Negative +/- S9	Woods I. (2017).
Gene mutation assay (HPRT; OECD 476, 2016)	(Chinese hamster ovary CHO cells)	Negative +/-S9	Gilby B. (2017)
In vitro micronucleus (OECD 487, 2016)	Human lymphocytes	Negative +/- S9	Gilby B (2017)

2.11.3.3 STEP 3, Stage 3: screening for toxicity

No data were submitted by the applicant for the evaluation of relevance of the metabolite CGA289267, however based on the proposed classification CGA 289 267 can be considered as preliminarily relevant metabolite.

2.11.4 STEP 4: Exposure assessment – threshold of concern approach

No data were submitted by the applicant for the evaluation of relevance of the metabolite CGA289267

2.11.5 STEP 5: Refined risk assessment

No data were submitted by the applicant for the evaluation of relevance of the metabolite CGA289267

2.11.6 Overall conclusion

No data were submitted by the applicant for the evaluation of relevance of the metabolite CGA289267

2.12 CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

2.12.1 Identity and physical chemical properties

Not relevant.

2.12.2 Methods of analysis

Not relevant.

2.12.3 Mammalian toxicity

The R and S enantiomers are non-superimposable mirror images that have identical physicochemical as well as toxicological properties.

2.12.4 Operator, Worker, Bystander and Resident exposure

Not relevant

2.12.5 Residues and Consumer risk assessment

Not relevant.

2.12.6 Environmental fate

The R and S enantiomers are non-superimposable mirror images that have identical physicochemical as well as EFATE properties.

2.12.7 Ecotoxicology

The R and S enantiomers are non-superimposable mirror images that have identical physicochemical as well as ecotoxicological properties.

2.13 RESIDUE DEFINITIONS

2.13.1 Definition of residues for exposure/risk assessment

Food of plant origin: Sum of fenpropidin and its salts, expressed as fenpropidin.

Food of animal origin: Sum of fenpropidin, CGA 289267, SYN515213, CGA 289268 and their conjugates, expressed as fenpropidin.

Soil: Fenpropidin

Groundwater: Fenpropidin

Surface water: Fenpropidin

Sediment: Fenpropidin

Air: Fenpropidin

2.13.2 Definition of residues for monitoring

Food of plant origin: Sum of fenpropidin and its salts, expressed as fenpropidin.

Food of animal origin: Sum of fenpropidin, CGA 289267, and their salts, expressed as fenpropidin

Soil: Fenpropidin

Groundwater: Fenpropidin

Surface water: Fenpropidin

Sediment: Fenpropidin

Air: Fenpropidin

Level 3

FENPROPIDIN

3 PROPOSED DECISION WITH RESPECT TO THE APPLICATION

3.1 BACKGROUND TO THE PROPOSED DECISION

3.1.1 Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

3.1.1.1 Article 4				
		Yes	No	
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	X		
3.1.1.2 Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	X		
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or (b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.			Not relevant.
3.1.1.3 Restrictions on approval				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.			the minimum degree of purity of the active substance is 960 g/kg
3.1.1.4 Criteria for the approval of an active substance				
Dossier				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	X		The provided data are sufficient for establishing reference values.
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for	X		The provided data are sufficient for risk assessment.

	substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.			The information provided is sufficient to describe the fate and behaviour of fenpropidin in soil, water and air, and to estimate the exposure in soil, groundwater, surface water, sediment and air for all sustained uses. Appropriate mitigation measures should be considered to protect aquatic organisms.
Efficacy				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.			The required information has been presented and deemed acceptable.
Relevance of metabolites				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	X		
Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of	Yes		Sufficient information has been provided to satisfactorily establish the identity of Fenpropidin, the nature and levels of impurities in the technical material (refer to Volume 4 – Confidential Information sections).

	impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.			
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.			No FAO specification
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted			No FAO specification
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	Yes		Adequate methods are available to analyze fenpropidin and impurities in technical material.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	Yes		Adequate methods are available to monitor the respective current residue definition in plant material, food of animal origin, soil, drinking water, surface water, air and body fluids and tissues.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.			
Impact on human health				
Impact on human health - ADI, AOEL, ARfD				
		Yes	No	
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	X		The estimation of the Acceptable Daily Intake (ADI) is based on the lowest no observed adverse effect level (NOAEL) estimated from chronic toxicity/carcinogenicity studies. The lowest NOAEL was obtained from rat chronic toxicity/carcinogenicity study with a NOAEL of 2.27 mg/kg bw/day for females. This with an assement factor of 100 gives an ADI of 0.02 mg/kg bw/day. Therefore t**he ADI is proposed to be 0.02 mg/kg bw/day** AOEL is based on the results from one year dog study. AOEL is based on NOAEL of 5 mg/kg/bw. This together with an assessment factor of 100 gives the **proposed AOEL of 0.05 mg/kg bw/day**. No correction factor for systemic availability is used since the oral absorption is considered to be more

				than 80 %. The acute effects after ingestion of fenpropidin is expected to be related to fenpropidins irritative potential. Several studies strengthen this assumption. Hyperkeratosis of the esophagus was observed in the 28-days oral treatment of rats with fenpropidin with a NOAEL of 5.40 mg/kg bw/day, this with an assesment factor of 100 gives an **ARfD of 0.05 mg/kg bw/day**
Impact on human health – proposed genotoxicity classification				
		Yes	No	
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as mutagen category 1A or 1B.**		X	Test results are not indicative to genotoxic potential.
Impact on human health – proposed carcinogenicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as carcinogen category 1A or 1B.**		X	Test results are not indicative to carcinogenic potential.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.		X	
Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive		X	There were no effects observed in relevant studies to justify this classification.

	toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, **the substance SHOULD BE classified or proposed for classification**, in accordance with the provisions of Regulation (EC) No 1272/2008, **as toxic for reproduction category 1A or 1B.**			
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.		X	
Impact on human health – proposed endocrine disrupting properties classification				
		Yes	No	
i)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties**		X	Fenpropidin is proposed for Repr. 2 (H361d) only. ED criteria are not met in complete dataset.
ii)	It is considered that **the substance SHOULD BE classified or proposed for classification** in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and** in addition the RMS considers the substance **has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties**		X	Fenpropidin is proposed for Repr. 2 (H361d) only. ED criteria are not met in complete dataset.
iii)	Linked to either i) or ii) immediately above. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.		X	

Fate and behaviour in the environment				
Persistent organic pollutant (POP)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.	X	X	3.7.1.1 Persistence: Yes Normalised laboratory soil DT50 to 12°C = 21.2 – 1171.5 days Trigger un-normalised field soil DT50 = 5.58 – 94 days Normalised field soil DegT50 (20°C) = 26.3 – 233 days Whole system trigger water/sediment DT50 = 59.1 – 274.1 days (normalised to 12°C) Aerobic mineralisation in surface water = 51 – 87.1 days (normalised to 12°C) 3.7.1.3 Potential for long-range environmental transport: No DT50 in air: 3.4 hours 3.7.1.2 Bioaccumulation: Bioaccumulation criterion not fulfilled: The bioconcentration factor (BCFfish = 163) and the partition co-efficient (log POW = 4.5) are below the trigger of 5000 and > 5, respectively.
Persistent, bioaccumulative and toxic substance (PBT)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.	X		3.7.2.1 Persistence: Yes Normalised laboratory soil DT50 to 12°C = 21.2 – 1171.5 days Trigger un-normalised field soil DT50 = 5.58 – 94 days Normalised field soil DegT50 (20°C) = 26.3 – 233 days Whole system trigger water/sediment DT50 = 59.1 – 274.1 days (normalised to 12°C) Aerobic mineralisation in surface water = 51 – 87.1 days (normalised to 12°C) 3.7.2.2 Bioaccumulation: Bioaccumulation criterion not fulfilled: The bioconcentration factor (BCFfish = 163) is below the trigger of 2000. 3.7.2.3 Toxicity: The toxicity criterion (T) fulfilled: The NOEC values for marine and freshwater species are below the trigger of 0.01 mg a.s./L (*Oncorhynchus mykiss* NOEC = 0.0038 mg a.s./L; *Desmodesmus subspicatus* NOEC <0.000688 mg a.s./L).
Very persistent and very bioaccumulative substance (vPvB).				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.	X		3.7.3.1 Persistence: Yes Normalised laboratory soil DT50 to 12°C = 21.2 – 1171.5 days Trigger un-normalised field soil DT50 = 5.58 – 94 days Normalised field soil DegT50 (20°C) = 26.3 – 233 days

				Whole system trigger water/sediment DT50 = 59.1 – 274.1 days (normalised to 12°C) Aerobic mineralisation in surface water = 51 – 87.1 days (normalised to 12°C) 3.7.3.2 Bioaccumulation: Bioaccumulation criterion not fulfilled: The bioconcentration factor is below the trigger of 5000 (BCFfish = 163).
Ecotoxicology				
		Yes	No	
	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.			No acute or reproductive risks were identified for birds. No acute risk was identified for mammals. High reproductive dietary risk was identified for small herbivorous mammal scenario "vole". No reproductive risk was identified for other mammal scenarios. No risks were identified for fish, aquatic invertebrates and aquatic macrophytes. Algae were identified as the most sensitive group of organisms and two mesocosm studies were used to refine the risk for them. Two RAC options were proposed by the RMS and should be discussed in peer-review. Considering these two options most of scenarios failed based on comparison with FOCUS Step 4 PEC values. No acute risk to adult honeybees and no chronic risk to honeybee larvae was identified High chronic risk to adult honeybees and high risk from exposure to residues in guttation fluid was identified. In addition, the risk assessment from metabolites could not be finalized, as well as the risk assessment for bumblebees and solitary bees. No risks to non-target arthropods other than bees were identified. No risks were identified for earthworms and other macro soil dwelling organisms. No risks were identified for soil micro-organisms. Risks to other non-target flora were concluded to be low. For further information on risks to non-target flora and fauna, see Vol 1 Level 2.6.
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance **HAS** endocrine disrupting properties that may cause adverse effects on non-target organisms.		X	Based on the provided datasest, the substance is not ED.
	Linked to the consideration of the endocrine properties immediately			Not relevant.

	above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			
	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist: — will result in a negligible exposure of honeybees, or — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.			The risk assessment for honeybees could not be finalized. The risk assessment for bees should be discussed in peer review.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X		<u>Definition of residues for exposure/risk assessment:</u> Soil: Fenpropidin and CGA289267 Surface water: Fenpropidin and CGA289267 Sediment: Fenpropidin and CGA289267 Ground water: Fenpropidin and CGA289267 Air: Fenpropidin
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	X		PECgw values for fenpropidin were <0.1 µg/L in all scenarios, for all intended uses. Max. PECgw value for fenpropidin metabolite CGA289267 is 0.421 µg/L in Okehampton scenario for use in winter cereals. A relevance assessment for CGA289267 is therefore required.

3.1.2 Proposal – Candidate for substitution

Candidate for substitution				
		Yes	No	
	It is considered that the active substance shall be approved as a candidate for substitution		X	

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		X	Fenpropidin is persistent in soil Normalised laboratory soil DT50 to 12°C = 21.2 – 1171.5 days Trigger un-normalised field soil DT50 = 5.58 – 94 days Normalised field soil DegT50 (20°C) = 26.3 – 233 days The bioconcentration factor (BCFfish = 163) is above the trigger of 100.

3.1.4 List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1 Identity of the active substance or formulation				
None				
3.1.4.2 Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
None				
3.1.4.3 Data on uses and efficacy				
None				
3.1.4.4 Data on handling, storage, transport, packaging and labelling				
None				
3.1.4.5 Methods of analysis				
None				
3.1.4.6 Toxicology and metabolism				
None				
3.1.4.7 Residue data				
None				

3.1.4.8 Environmental fate and behaviour				
Assessment of relevance of metabolite CGA 289267 in groundwater	all	x		
Address the effect of water treatment processes on the nature of residues present in surface and groundwater, when surface water or groundwater is abstracted for drinking water	all	x		
3.1.4.9 Ecotoxicology				
Further studies addressing ED properties should be performed.	all	x		

3.1.5 Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	**Relevance in relation to representative use(s)**
EFATE: Effect of water treatment processes on the nature of residues present in surface and groundwater, when surface water or groundwater are abstracted for drinking water.	All
ECOTOX: Reproductive dietary risk assessment for wild mammals.	All
ECOTOX: Chronic risk to adult honeybees, risk from exposure to residues in guttation fluid and metabolites, risk to solitary bees and bumblebees.	All

3.1.6 Critical areas of concern

An issue is listed as a critical area of concern:
(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or
(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	**Relevance in relation to representative use(s)**
None	

3.1.7 Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)
All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		Use "A" (X[1])	Use "B" (X[1])
Operator risk	Risk identified	-	-
	Assessment not finalised	-	-
Worker risk	Risk identified	-	-
	Assessment not finalised	-	-
Bystander risk	Risk identified	-	-
	Assessment not finalised	-	-
Consumer risk	Risk identified	-	-
	Assessment not finalised	-	-
Risk to wild non target terrestrial vertebrates	Risk identified	X	X
	Assessment not finalised	X	X
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified	X	X
	Assessment not finalised	X	X
Risk to aquatic organisms	Risk identified	-	-
	Assessment not finalised	-	-
Groundwater exposure active substance	Legal parametric value breached	no	no
	Assessment not finalised	no	no
Groundwater exposure metabolites	Legal parametric value breached	y	y
	Parametric value of 10µg/L[(a)] breached	no	no
	Assessment not finalised	y	y
Comments/Remarks			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.
(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

3.1.8 Area(s) where expert consultation is considered necessary

It is recommended to organize a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	**Justification**

ECOTOX	Reproductive dietary risk assessment for wild mammals- the selection of ecotoxicologically relevant endpoint to be used in the reproductive risk assessment for wild mammals.
ECOTOX	Mesocosm studies - the endpoints from mesocosm studies and their use in the risk assessment.
ECOTOX	Risk assessment for bees and other non-target arthropods

3.1.9 Critical issues on which the Co RMS did not agree with the assessment by the RMS

Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

Issue on which Co-RMS disagrees with RMS	**Opinion of Co-RMS**	**Opinion of RMS**
None		

3.2 PROPOSED DECISION

[redacted]

[redacted]

3.3 RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE

3.3.1 Particular conditions proposed to be taken into account to manage the risks identified

[redacted]

3.4 APPENDICES

GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

General

COMMISSION IMPLEMENTING REGULATION (EU) No 844/2012 of 18 September 2012
setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (L 252/26, Official Journal of the European Union)

COMMISSION IMPLEMENTING REGULATION (EU) No 686/2012 of 26 July 2012
allocating to Member States, for the purposes of the renewal procedure, the evaluation of the active substances whose approval expires by 31 December 2018 at the latest (L 200/5, Official Journal of the European Union)

COMMISSION REGULATION (EU) No 283/2013 of 1 March 2013
setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (L 93/1, Official Journal of the European Union)

COMMISSION REGULATION (EU) No 284/2013 of 1 March 2013
setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market (L 93/85, Official Journal of the European Union)

Section identity, physical chemical and analytical methods

Section physico chemical properties

None

Section analytical methods

European Commission, 2000. Residues: Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 (SANCO/3029/99 rev. 4)

European Commission, 2000. Technical Material and Preparations: Guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 (SANCO/3030/99 rev. 4)

European Commission, 2010. Guidance document on pesticide residue analytical methods (SANCO/825/00 rev. 8.1)

Section Data on application and efficacy

None

Section Toxicology

OECD Test guideline 401: Acute oral Toxicity

OECG Test guideline 402: Acute Dermal Toxicity

OECD Test guideline 403: Acute Inhalation toxicity

OECD Test Guideline 404: Acute Dermal Irritaton/Corrosion

OECD Test Guideline 405: AcuteEye Irritation/Corrosion

OECD Test Guideline 406: Skin Sensitisatin

OECD Test Guideline 408: Subchronic Oral Toxicity – Rodent: 90 day Study

OECD Test Guideline 409: Subchronic Oral Toxicity – Non-rodent: 90 day Study

OECD Test Guideline 412: Repeated Dose Inhalation Toxicity: 28-day or 14-day study

OECD Test Guideline 410: Repeated Dermal Toxicity 21/28 day Study

OECD Test Guideline 414: Teratogenicity

OECD Test Guideline 416: Two-Generation Reproduction Toxicity

OECD Test Guideline 417: Toxicokinetcs

OECD Test Guideline 424: Neurotoxicity Study In Rodents

OECD Test Guideline 425: Acute Oral Toxicity – Up-and-Down Procedure

OECD Test Guideline 451 Carcinogenicity studies

OECD Test Guideline 453: Combined Chronic Toxicity/Carcinogenicity Studies

OECD Test Guideline 471: Genetic Toxicology: Salmonella typhimurium, Reverse mutation Assay

OECD Test Guideline 472: Genetic Toxicology: Escherichia coli, Reverse mutation Assay

OECD Test Guideline 473: Genetic Toxicology: *In vitro* Mammalian Cytogenetic Test

OECD Test Guideline 474 Genetic Toxicology: Micronucleus test

OECD Test Guideline 476: Genetic Toxicology: *In vitro* Mammalian Cell Gene Mutation Tests

OECD Test Guideline 486: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo

OPPTS 870.7800: Immunotoxicity

Section Residue and consumer risk assessment

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 501: Metabolism in Crops (adopted in 2007)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 502: Metabolism in Rotational Crops (adopted in 2007)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 503: Metabolism in Livestock (adopted in 2007)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 504: Residues in Rotational Crops (Limited Field Studies) (adopted in 2007)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 505: Residues in Livestock (adopted in 2007)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 506: Stability of Pesticide Residues in Stored Commodities (adopted in 2007)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 507: Nature of the Pesticide Residues in Processed Commodities - High Temperature Hydrolysis (adopted in 2007)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 508: Magnitude of the Pesticide Residues in Processed Commodities (adopted in 2008)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS 509: Crop Field Trial (adopted in 2009)

OECD GUIDANCE DOCUMENT ON THE DEFINITION OF RESIDUE (as revised in 2009), SERIES ON TESTING AND ASSESSMENT No. 63 and SERIES ON PESTICIDES No. 31 (ENV/JM/MONO(2009)30)

OECD Guidance Document on Magnitude of Pesticide Residues in Processed Commodities Series on Testing and Assessment, No. 96 (ENV/JM/MONO(2008)23)

OECD Guidance Document on Residues in Livestock Series on Pesticides No. 73 (ENV/JM/MONO(2013)8)

GUIDANCE DOCUMENT SANCO 7525/VI/95, Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs, Rev. 10.3, 13 June 2017

Section fate and behavior in environment

European Commission, 2003. Guidance Document on Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev. 10 - final, 25 February 2003.

EC (2014). Assessing Potential for Movement of Active Substances and their Metabolites to Ground Water in the EU. Report of the FOCUS Ground Water Work Group, EC Document Reference SANCO/13144/2010, version 3

EC (2014). Generic Guidance for Tier 1 FOCUS Ground Water Assessments. Version 2.2

EC (2015). Generic Guidance for FOCUS surface water scenarios. Version: 1.4

EC (2015). Generic Guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies in Pesticides in EU Registration. Version 1.1

EFSA (2014). EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014;12(5):3662

FOCUS (2007). Landscape and Mitigation Factors in Aquatic Risk Assessment. Volume 1. Extended Summary and Recommendations. Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment, EC Document Reference SANCO/10422/2005, version 2.0

FOCUS, 2006. "Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration" Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp.

FOCUS, 2000. "FOCUS Groundwater Scenarios in the EU review of active substances". Report of the FOCUS Groundwater Scenarios Workgroup, EC Document Reference SANCO/321/2000-rev.2. 202 pp, as updated by the Generic Guidance for FOCUS groundwater scenarios, version 1.1 dated April 2002.

FOCUS, 2001. "FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC". Report of the FOCUS Working Group on Surface Water Scenarios, EC Document Reference SANCO/4802/2001-rev.2. 245 pp., as updated by the Generic Guidance for FOCUS surface water scenarios, version 1.1 dated March 2012

European Food Safety Authority; Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092.

Section ecotoxicology

EFSA (European Food Safety Authority), 2009. Guidance Document on Risk Assessment for Birds and Mammals on request of EFSA. EFSA Journal 2009; 7(12):1438.

European Commission, 2002a. Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002 rev.2 final, 17 October 2002.

European Commission, 2002b. Guidance Document on Aquatic Ecotoxicology Under Council Directive 91/414/EEC. SANCO/3268/2001 rev 4 (final), 17 October 2002.

European Commission, 2003. Guidance Document on Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev. 10 - final, 25 February 2003.

SETAC (Society of Environmental Toxicology and Chemistry), 2001. Guidance Document on Regulatory Testing and Risk Assessment procedures for Plant Protection Products with Non-Target Arthropods. ESCORT 2.

European Food Safety Authority, 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera*, *Bombus* spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp., doi:10.2903/j.efsa.2013.3295

3.5 REFERENCE LIST

Section identity, physical chemical and analytical methods
No references should be included

Section data on application and efficacy
No references should be included

Section toxicology
No references should be included

Section residue and consumer risk assessment
No references should be included

Section fate and behavior in environment
No references should be included

Section ecotoxicology
No references should be included