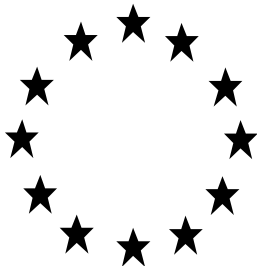
Draft Renewal Assessment Report
under Regulation (EC) 1107/2009



CLOPYRALID

Volume 1

RMS: Finland
Co-RMS: Poland

May 2017

Version History

When	What
2017/May	DRAR - First version submitted to EFSA

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Level 1

CLOPYRALID

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 Draft Renewal Assessment Report (DRAR) has been prepared in accordance with Commission Regulation (EC) No 844/2012 and Guidance Document SANCO/2012/11251 rev. 1.2 in order to evaluate the supplementary dossier submitted by Dow AgroSciences and to allow a decision on the renewal of the approval of the active substance clopyralid.

This DRAR provides a discussion of relevant studies submitted for the original EU evaluation for Annex I inclusion as well as relevant new studies and information generated since the Annex I inclusion of clopyralid in 2007. Where necessary, studies submitted for the original EU evaluation for Annex I inclusion have been re-evaluated to allow risk assessment along current standards, and to validate previous conclusions and/or calculations.
Clopyralid is subject to harmonised classification and the RMS did not find reasons to propose an amendment of this which would have any implications for the considerations of renewal of the approval under Commission Regulation (EC) No. 1107/2009. Therefore, the RMS did not submit any such proposal to ECHA.

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

According to Commission Regulation (EU) No 686/2012 Finland was assigned Rapporteur Member State (RMS) and Poland assigned Co-Rapporteur Member State (Co-RMS).
Finland, as RMS, evaluated the dossier submitted by the applicant and draft the Renewal Assessment Report for all the sections whereas, PL, as Co-RMS, conducted a pre-peer review of this report. The first official version of the DRAR was submitted to the Commission and EFSA in the end of May 2017.

1.1.3. EU Regulatory history for use in Plant Protection Products

Clopyralid was originally included in Annex I of the EU Council Directive 91/414/EEC with Commission Directive 2006/64/EC (entry into force on 1 May 2007). The active substance was subsequently approved under Regulation (EC) 1107/2009 via Implementing Regulation (EU) 540/2011.

EFSA Conclusion was approved on 14 December 2005 and published in the EFSA Journal on 23 January 2006.

The Commission presented a Review Report (SANCO/10012/2006 – rev. 3 4 April 2006) in support to the consideration of Annex I inclusion. Dow AgroSciences was the main data submitter in support of Annex I inclusion. Finland acted as Rapporteur Member State (RMS).

There was a request for confirmatory data to confirm the results on animal metabolism to be submitted after the inclusion in Annex I of EU Council Directive 91/414/EEC. RMS Finland prepared an addendum to DAR which was send for commenting in March 2014. EFSA published the Outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment of Confirmatory Data for the active substance clopyralid (supporting publication 2014:EN-624 27 June 2014)

EFSA has published the following Reasoned Opinion on clopyralid:

> Reasoned opinion of EFSA: Modification of the existing MRLs for clopyralid in various commodities (EFSA Journal 2011;9(10):2418 [40 pp.].)

1.1.4. Evaluations carried out under other regulatory contexts

Clopyralid is used only as herbicide and not regulated by other EU legislations (*e.g.* biocides, flavourings, food additives, cosmetics).
Clopyralid has not been considered by the JMPR.
FAO specification was not found.
The RMS did not find any recent (less than 5 years old) evaluations of clopyralid from US EPA nor PMRA, Canada.

1.2. APPLICANT INFORMATION

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

Central address	Dow AgroSciences Ltd. 3B Park Square, 2nd Floor, Milton Park Abingdon, Oxon. OX14 4RN, UK
Contact:	[redacted]
Telephone	[redacted]
E-mail	[redacted]

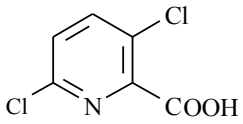
1.2.2. Producer or producers of the active substance

Address:	[redacted]
Telephone	[redacted]
Facsimile	[redacted]
Contact	[redacted]

1.2.3. Information relating to the collective provision of dossiers

Dow AgroScience has been the sole data submitter.

1.3. IDENTITY OF THE ACTIVE SUBSTANCE

1.3.1. Common name proposed or ISO-accepted and synonyms	Clopyralid
1.3.2. Chemical name (IUPAC and CA nomenclature)	
IUPAC	3,6-dichloropyridine-2-carboxylic acid
CA	3,6-dichloro-2-pyridinecarboxylic acid
1.3.3. Producer's development code number	K-038252, X159934, XRD-290, LSN256670, DOWCO 290. The commercial technical active substance may also be referred to as LONTREL** T.
1.3.4. CAS, EEC and CIPAC numbers	
CAS	1702-17-6
EEC	216-935-4
CIPAC	455
1.3.5. Molecular and structural formula, molecular mass	
Molecular formula	$C_6H_3Cl_2NO_2$
Structural formula	
Molecular mass	191.96 g/mol

** Trademark of Dow AgroSciences

1.3.6. Method of manufacture (synthesis pathway) of the active substance	CONFIDENTIAL information - data provided separately (Volume 4)
1.3.7. Specification of purity of the active substance in g/kg	minimum purity 950 g/kg
1.3.8. Identity and content of additives (such as stabilisers) and impurities	
1.3.8.1. *Additives*	CONFIDENTIAL information - data provided separately (Volume 4)
1.3.8.2. *Significant impurities*	CONFIDENTIAL information - data provided separately (Volume 4)
1.3.8.3. *Relevant impurities*	no relevant impurities
1.3.9. Analytical profile of batches	CONFIDENTIAL information - data provided separately (Volume 4)

1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT

1.4.1. Applicant

Central Address	Dow AgroSciences Ltd. 3B Park Square, 2nd Floor, Milton Park Abingdon, Oxon. OX14 4RN, UK
Telephone	[redacted]
Contact	[redacted]
E-mail	[redacted]

Member State Address	[redacted]
Telephone	[redacted]
Contact	[redacted]
E-mail	[redacted]

1.4.2. Producer of the plant protection product

Address	[redacted]
Telephone	[redacted]
Facsimile	[redacted]
Contact	[redacted]
Email	[redacted]

Address	[redacted]
Telephone	[redacted]
Contact	[redacted]

1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product

Trade name(s)	Trevistar, Aka, Kaon, Sekens, Ariane C, Colombus, Galaxy, Praxys, Tapir, Dakota, Bofix FFC
Code number	GF-1374

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**

Active ingredient: Clopyralid

Pure			**Technical (at the minimum purity of 950 g/kg)**		
g /L	**g /L**	**g/L**	**g/L**	**g/L**	**g/L**
Nominal	**Lower limit***	**Upper limit***	**Nominal**	**Lower limit***	**Upper Limit***
80.0	**72.0**	**88.0**	**84.2**	**75.8**	**92.6**

* FAO tolerance limits for nominal declared content of above 25 up to 100g/L is ± 10%

Active ingredient: Florasulam

Pure			**Technical (at the minimum purity of 970 g/kg)**		
g/L	**g/L**	**g/L**	**g/L**	**g/L**	**g /L**
Nominal	**Lower limit***	**Upper limit***	**Nominal**	**Lower limit***	**Upper Limit***
2.50	**2.13**	**2.88**	**2.58**	**2.20**	**2.97**

* FAO tolerance limits for nominal declared content of up to 25g/L is ± 15%

Active ingredient: Fluroxypyr (as fluroxypyr-meptyl)

Pure			**Technical (at the minimum purity of 950 g/kg Fluroxypyr-meptyl)**		
g/L	**g/L**	**g/L**	**g/L**	**g/L**	**g/L**
Nominal	**Lower limit***	**Upper limit***	**Nominal**	**Lower limit***	**Upper Limit***
100.0 (144.1)	**90.0 (129.7)**	**110.0 (158.5)**	**105.3 (151.7)**	**94.7 (136.5)**	**115.8 (166.8)**

* FAO tolerance limits for nominal declared content of 25 up to 100 g/L is ± 10%

Full details of the composition of GF-1374 is CONFIDENTIAL information - data provided separately (Volume 4).

<table>
<tr><td>1.4.4.2. Information on the active substances</td><td>
<table>
<tr><td>Clopyralid</td><td>ISO common name</td><td>Clopyralid</td></tr>
<tr><td></td><td>CAS No.</td><td>1702-17-6</td></tr>
<tr><td></td><td>EINECS No.</td><td>216-935-4</td></tr>
<tr><td></td><td>CIPAC No.</td><td>455</td></tr>
<tr><td></td><td>ELINCS</td><td>216-935-4</td></tr>
<tr><td></td><td>Salt, ester anion or cation present</td><td>The monoethanolamine base combines with the clopyralid acid to form the clopyralid olamine salt.</td></tr>
<tr><td>Florasulam</td><td>ISO common name</td><td>Florasulam</td></tr>
<tr><td></td><td>CAS No.</td><td>145701-23-1</td></tr>
<tr><td></td><td>EINECS No.</td><td>Not available</td></tr>
<tr><td></td><td>CIPAC No.</td><td>616</td></tr>
<tr><td></td><td>ELINCS</td><td>Not available</td></tr>
<tr><td></td><td>Salt, ester anion or cation present</td><td>Not applicable</td></tr>
<tr><td>Fluroxypyr-meptyl</td><td>ISO common name</td><td>Fluroxypyr-meptyl</td></tr>
<tr><td></td><td>CAS No.</td><td>81406-37-3</td></tr>
<tr><td></td><td>EINECS No.</td><td>279-752-9</td></tr>
<tr><td></td><td>CIPAC No.</td><td>431.214</td></tr>
<tr><td></td><td>ELINCS</td><td>279-752-9</td></tr>
<tr><td></td><td>Salt, ester anion or cation present</td><td>Ester</td></tr>
</table>
</td></tr>
<tr><td>1.4.4.3. Information on safeners, synergists and co-formulants</td><td>CONFIDENTIAL information - data provided separately (Volume 4)</td></tr>
<tr><td>1.4.5. Type and code of the plant protection product</td><td>emulsifiable concentrate (EC)</td></tr>
<tr><td>1.4.6. Function</td><td>herbicide</td></tr>
<tr><td>1.4.7. Field of use envisaged</td><td>in cereals and grassland for the control of a range of broad leaf weeds</td></tr>
<tr><td>1.4.8. Effects on harmful organisms</td><td>Clopyralid will mainly be absorbed through green leaves, uptake through roots is of much less importance. Acropetal translocation of clopyralid in xylem into young meristem and youngest leaves as well as basipetal</td></tr>
</table>

	transport in phloem into roots is possible. The MoA is similar to fluroxypyr and not yet completely understood. But it has been shown that clopyralid is being accumulated in merestemic tissue and influencing cell division, cell elongation and cell extension as well as RNA synthesis. Consequently, merestemic tissue dies off. Typical symptoms of susceptible plants are deformation and curling of young leaves and stem followed by growth stop and necrosis. **Florasulam** belongs to a class of herbicides known to inhibit the plant enzyme acetolactate synthase (ALS), also called acetohydroxyacid synthase (AHAS), a key enzyme in the biosynthesis of the branched chained amino acids isoleucine, leucine and valine. **Fluroxypyr 1-methylheptyl ester** will hydrolyse during penetration to form fluroxypyr-acid which acts as an auxin like herbicide causing rapid cell growth within the plant. Once absorbed fluroxypyr acid moves readily through the plant via both the xylem and phloem and is distributed throughout the entire plant to the meristems and other developing parts. In susceptible plant species fluroxypyr induces an epinastic response (ie stimulation of cell elongation and premature senescence, particularly in meristematic tissue) leading to cessation of normal growth and rapid necrosis followed by plant death.

1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

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. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
Winter cereal (wheat, barley oat, rye, triticale, spelt)	CZ/SZ	GF-1374	F	Broad-leaf weeds	EC	80 g/L Clopyralid + 2.5 g/L florasulam + 144 g/L fluroxypyr-metyl (equivalent to 100 g ae/ha fluroxypyr)	Over all broad cast foliar spray	BBCH 13-39 (1st Feb to 30th of June)	1	n/a	Clopyralid: 0.02 to 0.1 kg as/hL + Florasulam 0.0000625 to 0.0003125 kg as/hL + Fluroxypyr meptyl: 0.036 to 0.18 kg as/hL (0.025 to 0.125 kg ae/hL)	80-400	Clopyralid 0.08 kg as/ha + Florasulam 0.0025 kg as/ha + Fluroxypyr-meptyl 0.144 kg as/ha (0.100 kg ae/ha)	n/a	Dose: 1L GF-1374/ha Due to clopyralid content, straw treated with GF-1374 must not be used for compost production (for cultivating susceptible vegetables).
Established permanent pasture	CZ/SZ	GF-1374	F	Broadleaf weeds	EC	80 g/L Clopyralid + 2.5 g/L florasulam + 144 g/L fluroxypyr-metyl (equivalent to 100 g ae/ha fluroxypy	Over all broad cast foliar spray	1st Feb to 30th September	1	n/a	Clopyralid: 0.03 to 0.15 kg as/hL + Florasulam 0.00009375 to 0.00046875 kg as/hL + Fluroxypyr meptyl:	100-400	Clopyralid 0.12 kg as/ha + Florasulam 0.00375 kg as/ha + Fluroxypyr-meptyl 0.216 kg as/ha (0.15kg	7 to 14 days (see note 1)	Dose: 1.5L GF-1374/ha. Note 1: PHI: 7 days for CZ and 14 days for SZ is the interval before any crop cutting or grazing. Fluroxypyr is the limiting factor. Clopyralid residues

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. a.s. (i)	method kind (f-h)	range of growth stages & season (j)	number min-max (k)	Interval between application (min)	kg a.s /hL min-max (l)	Water L/ha min-max	kg a.s./ha min-max (l)		
						r)					0.054 to 0.27 kg as/hL (0.0375 to 0.1875 kg ae/hL)		ae/ha)		in plant tissue (including manure) which has not completely decayed may affect succeeding susceptible crops. Do not use any plant material treated with GF-1374 for composting. Do not use manure from animals fed on crops treated with GF-1374 for composting or mulching.

(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

The representative formulation includes a different product (GF-1374) compared to the product evaluated for the first approval (Lontrel 100 Herbicide). GF-1374 is an emulsifiable concentrate containing the active substance clopyralid at 80 g/l and 2 mixing partners namely Fluroxypyr mepthyl 144 g/l (100 g ae/L) and Florasulam 2.5 g/l.

Clopyralid is used as a post emergence herbicide to control some broadleaf weeds in a range of dicotyledon and monocotyledon crops. The method of application used is a broadcast application with a tractor mounted, self propelled or trailed hydraulic boom sprayer delivering a water volume of 80 l to 400 l/ha in cereals or 100-400l/ha in permanent pasture.

In cereals a maximum of one application per crop may be made between BBCH 13-39 (1st Feb to 30th of June). Only one application may be made per year, a single well timed application will protect a cereal crop to harvest.
In permanent pasture a maximum of one application per year may be made between 1st Feb and 30th September. As a perennial crop growth stage is not relevant. In permanent pasture a single well timed application will suppress weed competition for one growing season.

The representative uses include two uses evaluated during the first approval (cereals and pasture) which also reflect changes in dosage of clopyralid containing products as doses have been reduced. The representative formulation includes a different product (GF-1374) compared to the product evaluated for the first approval (Lontrel 100 Herbicide). GF-1374 is an emulsifiable concentrate containing the active substance clopyralid at 80 g ae/l and 2 mixing partners namely Fluroxypyr mepthyl 144 g/l (100 g ae/L) and Florasulam 2.5 g/l.

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

Not relevant.

1.5.4. Overview on authorisations in EU Member States

Information on the existing approvals for GF-1374

Country	Product name	Regulatory Authority	Registration number	Maximum use rate (L/ha)	Use
Belgium	Trevistar	Belgium	9799B	1.5	BLW's in cereals and grass
Belgium	Trevistar	Netherlands	9799B	1.5 & 1.9 in grass	BLW's in cereals and grass
UK	Galaxy	UK	MAPP 14085	1.5	BLW's in cereals
UK	Praxys	UK	MAPP 13912	2.0	BLW's in Amenity grass, Turf
UK	Dakota	UK	MAPP 16121	1.5	BLW's in cereals
UK	Bofix FFC	UK	MAPP 14179	1.5	BLW's in cereals
Eire	Galaxy	Eire	PCS No. 02948	1.5	BLW's in cereals
Eire	Praxys	Eire	PCS No. 03510	2.0	BLW's in Amenity grass, Turf
Germany	Ariane C	Germany	00621-00/00	1.5	BLW's in cereals
Hungary	Bofix garden	Hungary	02.5/1390/3/2009	1.5	BLW's in grass
Hungary	Colombus EC	Hungary	02.5/235/3/2010	1.5	BLW's in cereals
France	Aka/Kaon/Sekens	France	2110104	1.5	BLW's in cereals

Level 2

CLOPYRALID

2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT

2.1. IDENTITY

Clopyralid is the ISO common name of 3,6-dichloropyridine-2-carboxylic acid.

Clopyralid is a herbicide. Acceptable information has been submitted to establish both the identity of clopyralid and the representative plant protection product. This includes new data on the technical material. The proposed minimum purity following renewal (950 g/kg) remains the same as for the first inclusion.

The active substance as manufactured does not contain any impurities of toxicological / ecotoxicological relevance.

2.2. PHYSICAL AND CHEMICAL PROPERTIES

2.2.1. Summary of physical and chemical properties of the active substance

Clopyralid is a cream powdery solid with a melting point of 149.6°C. The solubility in unbuffered water (pH 1.7) was 0.785 g/100 mL. Clopyralid can be considered to be soluble in most polar solvents (>250 g/L for acetone), and low solubility in non-polar solvent (0.6% for n-hexane). The partition coefficient range at 20°C was $\log K_{ow}$ = -1.81 to -2.55, pH 5-9, respectively. The dissociation constant was 2.01 at 25°C. Clopyralid has a very low volatility (1.02×10^{-5} mmHg or 1.36×10^{-6} kPa at 25°C). The compound is not explosive nor highly flammable. The molar extinction coefficient ε is ~2800-3100 $Lmol^{-1}cm^{-1}$depending on pH.

According to COMMISSION REGULATION (EU) No 283/2013 it is now a requirement to include validation data on the methods used in water, buffer solutions, organic solvents and any additional matrices used in the physical and chemical properties tests. Here only limited or no validation data has been presented for solubility in water and in organic solvents, partition coefficient $\log K_{ow}$ as well as dissociation constant.

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

The product GF-1374 is an emulsion concentrate (EC). All studies have been performed in accordance with the current requirements, the critical GAP and the results are deemed acceptable. The appearance of the product is that of a brown liquid. It is not explosive, has no oxidising properties nor self-ignition temperature below 400°C. In a aqueous solution, it has a pH value of ~2.49. The kinematic viscosity is 7.8×10^{-6} m^2/sec at 40 °C which means that the product has aspiration hazard (see Vol. 4 as well as CLP regulation).

The emulsifiability properties are acceptable. The stability data indicating a shelf life of at least 2 years at ambient temperature in 1 L PET and 1 L f-HDPE packagings is acceptable, as the active ingredient content was

stable, no significant physical changes were observed, and all performance properties remained within acceptable limits. Its technical characteristics are acceptable for an emulsifiable concentrate (EC) formulation.

2.3. DATA ON APPLICATION AND EFFICACY

In accordance with the guidance document (SANCO/12592/2012) on the 'Template Assessment Report' only limited information for efficacy will be provided to address the requirements of Article 4(3) of Regulation (EC) No 1107/2009. Detailed consideration of efficacy will occur in the subsequent product authorisation process at Member State level when a full biological assessment dossier will be provided. Therefore only limited efficacy information is required for clopyralid and has been provided under the appropriate headings in line with the guidance for renewals - Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (SANCO/2012/11251, rev 4).

2.3.1. Summary of effectiveness

Clopyralid and the representative formulation GF1374 are intended for agricultural use. Clopyralid is a contact acting, selective, auxin type herbicide, for post emergence control of broad leaf weeds in cereals and permanent pasture.

GF-1374 is used for the control of broad leaf weeds such *as Galium aparine, Sinapis arvense, Matricaria* spp, *Brassica napus* (oilseed rape), *Centaurea cyanus, Stellaria media, Taraxacum officinalis, Bellis perennis, Ranunculus repens, Plantago major, Plantago lanceolata, Rumex obtusifolius* and *Rumex acetosa*.

2.3.2. Summary of information on the development of resistance

Clopyralid has been in wide scale commercial use in Europe for the control of annual and perennial broad leaved weeds in a wide range of crops since the early 1970's. No reports of resistance in the Europe have been received.

The inherent risk of resistance is very low because of the complex mode of action and besides no cases of resistance to clopyralid have been reported despite being used globally for more than 30 years.

Also, the agronomic risk is very low due to a diversity of available control measures for all the major target weeds including various modes of action. The other reason is that the normal rotation includes grass crops such as wheat. This allows a range of cultural and chemical methods to be employed.

2.3.3. Summary of adverse effects on treated crops

Information about adverse effects on treated crops has not been supplied. When used according to the dose rates and application timings detailed in the directions for use no adverse effects on treated crops are expected.

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

Information about adverse effects on treated crops has not been supplied. When used according to the dose rates and application timings detailed in the directions for use no undesirable or unintended side effects are expected adverse effects on treated crops are expected.

2.4. FURTHER INFORMATION

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

For information on active substance please see Volume 3CA, B4.
For information on representative formulation please see Volume 3CP, B4 – GF1374.

2.4.2. Summary of procedures for destruction or decontamination

For information on active substance please see Volume 3CA, B4.
For information on representative formulation please see Volume 3CP, B4 – GF1374.

2.4.3. Summary of emergency measures in case of an accident

For information on active substance please see Volume 3CA, B4.
For information on representative formulation please see Volume 3CP, B4 – GF1374.

2.5. METHODS OF ANALYSIS

2.5.1. Methods used for the generation of pre-authorisation data

2.5.1.1. Analysis of the active substance as manufactured

Method for the determination of active ingredient in technical Clopyralid: the technical material is dissolved in internal standard and analyzed by gas chromatography applying a flame ionization detector (FID). Quantitation was made by peak area measurements with internal standardization. However, the method is not acceptably validated, because, according to SANCO/3030/99 rev. 4, confirmatory techniques are required to support identification of the a.s when the primary method of determination is not highly specific.

Organic impurities in the technical active substance are determined by GC/FID.

2.5.1.2. Formulation analysis

The method uses a reverse phase liquid chromatographic (LC) system with internal standard quantitation. Peak area was used to determine the weight percent within the formulation. The validation is acceptable, and the method is suitable for the simultaneous determination of the active substances clopyralid, florasulam and fluroxypyr meptyl in the formulation GF-1374.

2.5.1.3. Methods for Risk Assessment

See 2.5.2.

Plants:

Method applying GC/MS:

Determination of Residues of Clopyralid in Grass and Cereal Grain and Straw:

According to SANCO/3029/99 rev. 4, 5 determinations should be made at each fortification level. Although this criteria is not quite fulfilled, the method can be considered to be fit for purpose.

Method applying GC/NCI-MS:

The method is not acceptably validated for the determination of clopyralid in crop matrices. According to SANCO/3029/99 rev. 4, 5 determinations should be made at each fortification level. Here only 1 determination has been performed for every crop.

Food of animal origin

Method applying GC/NCI-MS:

The method is not acceptably validated for the determination of clopyralid in animal matrices. According to SANCO/3029/99 rev. 4, 5 determinations should be made at each fortification level. Here only 1-2 determinations have been performed.

Methods in soil, water, sediment, feed and any additional matrices used in support of ecotoxicology studies: active substance

Method applying HPLC/UV:

The method is acceptably validated for the determination of clopyralid in AAP medium (a freshwater algal medium).

Method applying HPLC/UV:

The method was successfully validated and met the requirements of SANCO/3029/99 rev. 4 for the determination of clopyralid in freshwater algal medium, except for the number of procedural recovery sample replicates. However, the method can be considered to be fit for purpose.

Method applying LC-MS/MS:

The method is acceptably validated for the determination of clopyralid in hard water specimens.

Methods in soil, water, sediment, feed and any additional matrices used in support of ecotoxicology studies: formulation

Determination of clopyralid in GF-1374 spray solutions:

Methods applying HPLC/UV:

According to SANCO/3029/99 rev. 4, 5 determinations should be made at each fortification level. Although this criteria is not quite fulfilled, the methods can be considered to be fit for purpose.

2.5.2. Methods for post control and monitoring purposes

Plants and plant products

Method applying LC-MS/MS:

According to SANCO/825/00 rev. 8.1, recovery and precision data must be reported for the fortification levels LOQ and 10 x LOQ. Here the fortification level 10 x LOQ is missing, and the level 100 x LOQ has been used instead. Otherwise the method is acceptably validated and suitable for the determination of clopyralid in wheat forage (wet crops), wheat grain (dry crops), orange (acidic crops) and canola seed (oily crops). LOQ for clopyralid was established at 0.01 mg/kg for all of them.

The ILV is acceptably validated and suitable for the determination of clopyralid in wheat whole plant (wet crops) and oilseed rape seed (oily crops). LOQ for clopyralid was established at 0.01 mg/kg for both of them.

Food of animal origin

Method applying LC-MS/MS:

According to SANCO/825/00 rev. 8.1, recovery and precision data must be reported for the fortification levels LOQ and 10 x LOQ. Here the fortification level 10 x LOQ is missing, and the level 100 x LOQ has been used

instead. Otherwise the method is acceptably validated and suitable for the determination of clopyralid in bovine muscle, fat, kidney, liver and milk as well as poultry eggs, fat, muscle and liver. LOQ for clopyralid was established at 0.01 mg/kg for all of them.

The ILV is acceptably validated and suitable for the determination of clopyralid in bovine muscle and milk as well as poultry eggs and liver. LOQ for clopyralid was established at 0.01 mg/kg for all of them.

Matrices of Plant and Animal Origin

Multi-residue Method Following the QuEChERS Sample Preparation Technique

According to SANCO/825/00 rev. 8.1, recovery and precision data must be reported for the fortification levels LOQ and 10 x LOQ. Here the fortification level 10 x LOQ is missing, and the level 100 x LOQ has been used instead. Otherwise the method is acceptably validated and suitable for the determination of clopyralid in lettuce, lemon as well as bovine milk and fat. LOQ for clopyralid was established at 0.01 mg/kg for all of them. However, the method is not acceptably validated for the determination of clopyralid in rye, oilseed rape, poultry eggs, bovine muscle and liver as the obtained mean recoveries are too low.

In the ILV, as well, the fortification level 10 x LOQ is missing, and the level 100 x LOQ has been used instead. Otherwise the ILV is acceptably validated and suitable for the determination of clopyralid in lettuce, lemon as well as bovine fat. LOQ for clopyralid was established at 0.01 mg/kg for all of them. However, the method is not acceptably validated for the determination of clopyralid in bovine milk as the obtained mean recoveries are too low.

Soil

Method applying LC-MS/MS:

According to SANCO/825/00 rev. 8.1, recovery and precision data must be reported for the fortification levels LOQ and 10 x LOQ. Here the fortification level 10 x LOQ is missing, and the level 2000 x LOQ has been used instead. Otherwise the method is acceptably validated and suitable for the determination of clopyralid in soil matrices (loamy sand, sandy clay loam, loam, and silt loam soil). LOQ for clopyralid was established at 0.5 µg/kg.

In the ILV, as well, the fortification level 10 x LOQ is missing, and the level 2000 x LOQ has been used instead. Otherwise the ILV is acceptably validated and suitable for the determination of clopyralid in soil matrice (sandy loam). LOQ for clopyralid was established at 0.5 µg/kg.

Water

Method applying LC-MS/MS:

According to SANCO/825/00 rev. 8.1, recovery and precision data must be reported for the fortification levels LOQ and 10 x LOQ. Here the fortification level 10 x LOQ is missing, and the level 200 x LOQ has been used instead. Otherwise the method is acceptably validated and suitable for the determination of clopyralid in water matrices (ground water, drinking water, and surface water). LOQ for clopyralid was established at 0.05 µg/L for the water matrices.

The ILV is acceptably validated and suitable for the determination of clopyralid in water matrices (ground water, drinking water, and surface water). LOQ for clopyralid was established at 0.05 µg/L for the water matrices.

Air

Method applying LC-MS/MS:

According to SANCO/825/00 rev. 8.1, recovery and precision data must be reported for the fortification levels LOQ and 10 x LOQ. Here the fortification level 10 x LOQ is missing, and the level 100 x LOQ has been used instead. Otherwise the method is acceptably validated and suitable for the determination of clopyralid in air (ambient and humid air). LOQ for clopyralid was established at 4.5 µg/m^3 for air.

Body fluids and tissues

According to the new data requirements, these methods are always required.

Body fluids:

Method applying LC-MS/MS:

According to SANCO/825/00 rev. 8.1, recovery and precision data must be reported for the fortification levels LOQ and 10 x LOQ. Here the fortification level 10 x LOQ is missing. Thus the method is not acceptably validated for body fluids (blood and urine),

Body tissues: no method has been given.

2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

2.6.1. Summary of absorption, distribution and excretion in mammals

Clopyralid is rapidly absorbed and eliminated in the rat following single or repeat oral administration at high or low doses and after intravenous administration at low dose. There were no differences in distribution of radioactivity between dose rates, sex, route (oral vs. intravenous) or frequency of administration. Radioactivity in the tissues was less than 0.01% of the applied dose three days after dose administration. The majority of radioactivity (≥ 71.4 % of applied dose) was eliminated as unchanged clopyralid via the urine within 24 hours. Clopyralid was not actively metabolised in the rat. Clopyralid has low potential for accumulation. In the *in vitro* comparative metabolism study no unique human metabolites were formed when compared to rat metabolism and there was no observed metabolism.

2.6.2. Summary of acute toxicity

The acute toxicity of clopyralid was studied by oral, dermal and inhalation routes using rat and rabbit as a test animal. The studies done were briefly described, but according to the study reports, they were conducted in compliance with GLP standards, the methods of USEPA and mainly according to OECD guidelines. Clopyralid was of low toxicity by all routes (Table 2.6-1). The highest attainable concentration achieved in an acute inhalation study after grinding the material was only 1.0 mg/l. An earlier study only succeeded in generating 0.2 mg/l. However, there was no mortality.

Clopyralid did not induce irritation on rabbit skin. However, clopyralid caused marked irritation to eyes of rabbit and symptoms were still present after 21 days. Therefore, clopyralid is to be classified according to regulation 1272/2008 as Eye Dam. 1; H318.

In sensitivity tests, clopyralid was mildly irritating and sensitising in Magnusson & Kligman test but showed no signs of erythema or oedema in Buehler test. The studies were considered supportive. Classification was not possible based on the available data.

There were no studies submitted on phototoxicity and there was not sufficient information to draw the final conclusion.

Table 2.6-1 Summary of acute toxicity of clopyralid

Route/method	Species	Result/Comment	Classification according to regulation 1272/2008	Reference
Oral	Rat	LD_{50} > 5000 mg/kg bw	None	[redacted] *et al*. 1987
Dermal	Rabbit	LD_{50} > 2000 mg/kg bw	None	[redacted] *et al*. 1987
Inhalation	Rat	LC_{50} > 0.2 mg/l/4 h[1)]	- (study for supportive information only)	[redacted] *et al.* 1987
Inhalation	Rat	LC_{50} > 1.0 mg/l/4 h[1)]	None	[redacted] 1991
Dermal	Rabbit	Average scores (24-72 h) for each rabbit is 0 for erythema and 0 for oedema.	None	[redacted] 1987
Eye	Rabbit	Severe irritation; effects still present after 21 days	Eye Dam. 1; H318	[redacted] 1987
Magnusson & Kligman	Guinea pig	Slightly sensitising	- (study for supportive information only)	[redacted] 1996
Buehler test method	Guinea pig	No signs of erythema or oedema	- (study for supportive information only)	[redacted] 1987
Phototoxicity	-	No studies submitted		-

[1)] Highest attainable concentration

2.6.3. Summary of short-term toxicity

In rats, dietary administration of clopyralid in a 4-week study at 500 mg/kg bw/day caused an irritant effect on the stomach characterised as minimal acanthosis and folding of the non-glandular epithelium of the limiting ridge. In a 3-month study at higher doses, liver and kidney weight increases were recorded in males following 300 to 2500 mg/kg bw/day and in females at 2500 mg/kg bw/day. Additionally, males and females at 2500 mg/kg bw/day showed lesions of the gastric limiting ridge. The NOAEL for rat could not be established from the two acceptable studies.

Following oral administration of clopyralid (Table 2.6-2) in the diet to mice in short-term study over 13 weeks, the liver was identified as the target organ based on liver weight increases and microscopic alterations to the centrilobular hepatocytes. Based on the acceptable study, the NOAEL for mouse is 750 mg/kg bw/day.

In a 12-month study in dogs, the NOAEL for dog was 100 mg/kg bw/day. It is based on haematological effects and increases in absolute liver weight observed at the higher dose (320 mg/kg/day).

In rabbits, repeated dermal administration of clopyralid for 15 days in a 21-day rabbit study did not cause systemic toxicity at any dose, and the systemic NOAEL was >1000 mg/kg bw/day.

As the NOAEL for rat could not be established, it is not possible to conclude which species is the most sensitive.

Table 2.6-2 Summary of short-term toxicity of clopyralid

Study	Dose levels	NOAEL	LOAEL	Effects at LOAEL	Reference
4-week oral (dietary) rat	0, 150, 500, 1500 mg/kg bw/day	Males: 150 mg/kg bw/day Females: < 150 mg/kg bw/day	Males: 500 mg/kg bw/day Females: 150 mg/kg bw/day	Males: Changes in clinical biochemistry parameters, histopathological changes on stomach. Females: Kidney weight↑.	[redacted] *et al*., 1986 **Acceptable**
2-week oral (dietary) $B_6C_3F_1$ mouse	0, 0.2%, 1%, 2.5%, 5%, 10% dietary concentrations (about 0, 500, 2300, 5500, 9600, 19200) mg/kg bw/day	Males: <500 mg/kg bw/day Females: 500 mg/kg bw/day	Males: 500 mg/kg bw/day Females: 2300 mg/kg bw/day	Reduction in food consumption and slight histopathological alteration in the liver, increase of relative liver weight (males).	[redacted] *et al.* 1982 Supportive
13-day oral New Zealand White rabbit (Female)	0, 350, 500, 750 mg/kg bw/day	< 350 mg/kg bw/day	350 mg/kg bw/day	Multifocal erosions and/or ulcers of the stomach.	[redacted] *et al*., 1990 Supportive
3-month oral (dietary) rat	0, 300, 1500, 2500 mg/kg bw/day	Males: <300 mg/kg bw/day Females: 300 mg/kg bw/day	Males: 300 mg/kg bw/day Females: 1500 mg/kg bw/day	Males: Mean relative liver and kidney weights significantly↑, serum chemistry value (alkaline phosphase) ↓, microscopical investigations on liver. Females: Mean body weight and bodyweight gain ↓, serum chemistry value (alkaline phosphase) ↓, microscopical investigations on liver.	[redacted] *et al.*, 1983 **Acceptable**

Study	Dose levels	NOAEL	LOAEL	Effects at LOAEL	Reference
90-day oral (dietary) Sprague-Dawley rat	0, 5, 15, 50, 150 mg/kg bw/day	>150 mg/kg bw/day	>150 mg/kg bw/day	No toxicologically significant effects.	[redacted] *et al.,* 1973 Supportive
13-week oral (dietary) $B_6C_3F_1$ mouse	0, 200, 750, 2000, 5000 mg/kg bw/day	Males: 2000 mg/kg bw/day Females: 750 mg/kg bw/day	Males: 5000 mg/kg bw/day Females: 2000 mg/kg bw/day	Microscopical changes in the liver, mean relative liver weights ↑ (males).	[redacted] *et al.*, 1983 **Acceptable**
12-month oral (dietary) Beagle dog	0, 100, 320, 1000 mg/kg bw/day	100 mg/kg bw/day	320 mg/kg bw/day	Haematological effects, liver weights ↑(males).	[redacted] *et al.*, 1984 **Acceptable**
6-month oral (dietary) Beagle dog	0, 15, 50, 150 mg/kg bw/day	Males: >150 mg/kg bw/day Females: 50 mg/kg bw/day	Males: >150 mg/kg bw/day Females: 150 mg/kg bw/day	Males: No treatment related toxicological effects. Females: Increase in relative liver weight.	[redacted] *et al*., 1976 Supportive
180-day oral (dietary) Beagle dog	0, 15, 50, 150 mg/kg bw/day	>150 mg/kg bw/day	>150 mg/kg bw/day	No treatment related toxicological effects.	[redacted] 1975 Supportive
21-day dermal New Zealand White rabbit	0, 100, 500, 1000 mg/kg bw/day	Systemic NOAEL >1000 mg/kg bw/day	>1000 mg/kg bw/day	No treatment related systemic toxic effects.	[redacted] *et al.,* 1990 **Acceptable**

2.6.4. Summary of genotoxicity

There are two Ames tests (*Salmonella* typhimurium reverse mutation assay) in the original DAR (Richold *et al*., 1981, Bruce and Gollapudi, 1987). Clopyralid did not induce gene mutations in these tests where no bacterial strain capable of detecting cross-linking mutagens was included. *In vitro* host mediated assay with *Salmonella* typhimurium strains TA 1530 and G-46 and *Saccharomyces cerevisiae* strain D-3 (Sibinovic, 1973) was performed using no official guideline or test method, and it was not done under GLP. The study is supportive only. *In vitro* mammalian cell gene mutation assay in Chinese hamster ovary cells ([redacted] and [redacted] 1987) gave a negative result.

In the *in vitro* chromosome aberration test in cultured rat lymphocytes ([redacted] *et al*., 2001) frequency of aberrant cells was increased significantly although the frequency was within the historical control range. As this highest tested concentration (697.5 µg/mL) does not fulfil the OECD Guideline 473 requirement for the dose selection and neither does the reduction in mitotic index show that the dose was high enough, no definite evidence for the positive or negative result can be indicated. Hence, the result of the study is considered equivocal. Clopyralid did not demonstrate genotoxic activity in an *in vitro* test of unscheduled DNA synthesis (UDS) performed in isolated rat hepatocytes ([redacted] and [redacted] 1985). Because of the deviations in relation to the OECD Test Guideline, the study is considered supportive only.

In an *in vivo* micronucleus test ([redacted] *et al*., 1991), the highest dose exceeded the maximum tolerated dose and was thus useless for evaluation. The remaining two doses did not fulfill the OECD Test Guideline requirements for the proper dose selection with three analysable dose levels covering a range from the maximum to little or no toxicity. Dose selection was inappropriate also in an acute and subacute *in vivo* cytogenetic non-GLP study in rats ([redacted] 1973). Because of the wrong dose selection, both the *in vivo* micronucleus test and the acute and subacute *in vivo* cytogenetic study were not acceptable.

In vivo dominant lethal mutagenesis assay (non-GLP) ([redacted] 1973) is not acceptable as test substance concentrations have been too low in the study and the procedure did not cover all phases of male germ cell maturation in rat.

There is no acceptable chromosome test in the whole dossier and hence, a data gap for addressing clastogenic and aneugenic end point is identified.

Table 2.6-3 Summary of *in vitro* and *in vivo* genotoxicity studies

Test	Test Object	Concentration	Result	Reference
In vitro gene mutation assays				
In vitro bacterial reverse mutation (Ames)	*Salmonella* typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538	125, 250, 500 and 1000 µg/plate in the presence and absence of S9 mix	Negative	Richold, M. *et al*., 1981
In vitro bacterial reverse mutation (Ames)	*Salmonella* typhimurium TA 98, TA 100, TA 1535, TA 1537	50, 158, 500, 1580 and 5000 µg/plate in the presence and absence of S9 mix	Negative	Bruce, R. & Gollapudi, B., 1987
In vitro host mediated assay	*Salmonella* typhimurium TA 1530, G-46; *Saccharomyces cerevisiae* D-3	10%, 20% or 50% saturated solution of clopyralid	Negative Study supportive	Sibinovic, K., 1973
In vitro mammalian cell forward mutation	Chinese hamster ovary cells (CHO/HGPRT)	125, 250, 500, 700, 750, 1000 and 1500 µg/ml in the absence of S9 mix; 1750, 2000, 2250, 2500 and 2750 µg/ml in the presence of S9 mix	Negative	[redacted] 1987
In vitro cytogenetic assay				
In vitro chromosome aberration	Cultured rat lymphocytes	43.6 to 2790 µg/ml in the presence and absence of S9 mix	Equivocal	[redacted] *et al*., 2001
Unscheduled DNA synthesis (UDS)				
In vitro mammalian UDS	Rat hepatocytes	5 x 10^{-5}, 1.56 x 10^{-4}, 5 x 10^{-4}, 1.56 x 10^{-3}, 5 x 10^{-3}, 1.56 x 10^{-2}, 5 x 10^{-2} M	Negative Study supportive	[redacted] 1985
In vivo studies in somatic cells				
In vivo micronucleus test	Mouse bone marrow	500, 1667 or 5000 mg/kg bw, single administration by gavage	Study not acceptable	[redacted] *et al*., 1991
In vivo chromosome aberration	Rat bone marrow	4, 40 or 400 mg/kg bw, single administration by gavage (acute study); 4, 40 or 400 mg/kg bw/day administration by gavage once daily for five days (subacute study) to males	Study not acceptable	[redacted] 1973

Test	Test Object	Concentration	Result	Reference
In vivo studies in germ cells				
In vivo dominant lethal mutagenesis assay	Sprague-Dawley CD rats	4, 40 or 400 mg/kg bw/day administration by gavage once daily for five days to males	Study not acceptable	[redacted] 1973

2.6.5. Summary of long-term toxicity and carcinogenicity

Oral administration of clopyralid at 150 and 1500 mg/kg bw/day to Fischer-344 rats caused hyperplasia and thickening of the epithelium of the anterior surface of the gastric limiting ridge. The effect in gastric limiting ridge was more frequently recorded in animals treated at 1500 mg/kg bw/day and this dose level was also associated with reduced body weight, decreased food consumption, increased relative liver and kidney weight, and a grossly visible increase in the size of the gastric limiting ridge. Although the gastric limiting ridge is not present in human's stomach, the lesions detected in animals characterize the irritant nature of clopyralid rather than being species specific effect. There was no evidence that clopyralid caused increased incidence of malignant or non-malignant tumours in the rat. The NOAEL for rat is 15 mg/kg bw/day. In the supplementary study, no toxicologically significant effects were associated with ingestion of Dowco 290 for 2 years. The only finding which was detected and may be related to the ingestion of Dowco 290 in the diet was a reduction in the mean body weight of female rats at the high dose level, 150 mg/kg bw/day.

In a 2-year study in $B_6C_3F_1$ mice, dietary administration of clopyralid at 2000 mg/kg bw/day led to a reduction in body weight in males. No other significant toxicological effects were recorded in males or in female mice. There was no evidence that clopyralid caused increased incidence of malignant or non-malignant tumours in the mouse. The NOAEL for mice is 500 mg/kg bw/day.

Table 2.6-4 Summary of long term toxicity and carcinogenicity of clopyralid

STUDY (ROUTE)	SPECIES/ STRAIN	DOSAGES	NOAEL	LOAEL	EFFECTS AT LOAEL	REFERENCE
2-year chronic toxicity and oncogenicity study (diet)	Rat/ Fischer-344 (male/female)	15, 150, 1500 mg/kg bw/day	15 mg/kg bw/day	150 mg/kg bw/day	Lesions of the gastric limiting ridge, slightly reduced food consumption	[redacted] *et al.*, 1985 and 1986 **Acceptable**
2-year combined toxicity and carcinogenicity (dietary)	Rat/ Sprague-Dawley (male)	5, 15, 50, 150 mg/kg bw/day	>150 mg/kg bw/day	> 150 mg/kg bw/day	ND	[redacted] *et al.*, 1977 **Supplementary**
	Rat/ Sprague-Dawley (female)	5, 15, 50, 150 mg/kg bw/day	50 mg/kg bw/day	150 mg/kg bw/day	Reduction in body weight	[redacted] *et al.*, 1978 [redacted] 1985
2-year dietary chronic toxicity-oncogenicity study (diet)	Mouse/ $B_6C_3F_1$ (male)	100, 500, 2000 mg/kg bw/day	500 mg/kg bw/day	2000 mg/kg bw/day	Reduction in body weight	[redacted] *et al.*, 1984 [redacted] et al., 1986 **Acceptable**
	Mouse/ $B_6C_3F_1$ (female)	100, 500, 2000 mg/kg bw/day	2000 mg/kg bw/day	>2000 mg/kg bw/day	ND	
18-month carcinogenicity (dietary)	Mouse/ CR strain (male/female)	35, 100, 350 ppm	>350 ppm (> 52,5 mg/kg bw/day)	> 350 ppm (> 52,5 mg/kg bw/day)	ND	[redacted] 1976 **Supportive**

ND: Not determined: no adverse effects

2.6.6. Summary of reproductive toxicity

In the two-generation toxicity study (Table 2.6-5), the NOAEL for adults was 150 mg/kg bw/day based on the reduction in parental body weight and food consumption, and induced stomach lesions. The NOAEL for offspring was higher, 500 mg/kg bw/day, based on the reduction in F1 pup weights and increased liver weight. However, because the dietary concentrations were reduced during mating, pregnancy and lactation periods, but the food consumption was not recorded, lower NOAELs may be possible. Originally, in the DAR the conclusion was that based on this two-generation study in rats, the toxicity for reproduction cannot be evaluated comprehensively. Need for a new study should be considered. This study was discussed also in the Addendum 1 (2004) to DAR where the conclusion was that the results do not suggest any harm in the fertility of dams or in the offspring and that a specific reproductive risk is most unlikely. In this AIR 3 evaluation the study is considered supportive, however, a potential of reproductive toxicity is unlikely.

In teratogenicity studies, clopyralid did not induce specific malformations or increased the incidence of spontaneous malformations at nonmaternotoxic dose level.

There was no dose-relationship in foetal effects in F344 rats. Number of malformed foetuses increased (statistically nonsignificant) at maternotoxic dose level of 250 mg/kg bw/day. However, these malformations (polydactyly and hemivertebra) were considered incidental because no major malformations were observed in an additional group of animals dosed to 250 mg/kg bw/day. The number of resorptions did not increase at the high dose level. The NOAEL for developmental effects was >250 mg/kg bw/day. The maternal NOAEL was 15 mg/kg bw/day based on decreased liver weight and food consumption.

In rabbits, increased incidence of resorptions, malformations and alterations were seen at maternotoxic dose level of 250 mg/kg bw/day (NOAEL 110 mg/kg bw/day) in the acceptable study. The observed maternal toxicity i.e. morbidity, clinical signs, gastric lesions, reductions in body weight and body weight gain may have caused the observed malformations and resorptions. However, mortality and abortions were observed already at the lowest dose level.

Table 2.6-5 Summary of reproduction and developmental toxicity studies conducted in rats and rabbits

Species Strain	Test material	Application dates: day of gestation	Doses tested/ Route	NOAELs/LOAELs	Reference
Rat, Fischer 344	DOWCO 290 96.7%	Two-generation study	0, 150, 500, 1500 mg/kg bw/day Dietary	**Adults:** NOAEL 150 mg/kg bw/day (females) and 500 mg/kg bw/day (males), based on decreased body weight, reduced food consumption, stomach lesions **Offspring:** NOAEL 500 mg/kg bw/day based on decreased pup weights and increased pup liver weights in F1 generations. **Reproduction:** NOAEL >1500 mg/kg bw/day	[redacted] *et al*., 1983 Supportive

Species Strain	Test material	Application dates: day of gestation	Doses tested/ Route	NOAELs/LOAELs	Reference
				Supplementary histopathological examinations on samples collected in the above study No treatment-related histopathological effects in reproductive organs and accessory sex glands in randomly selected adult F0 and F1 rats/sex at 1500 mg/kg bw/day or in major organs of randomly selected F2B weanlings/sex at 1500 mg/kg bw/day	[redacted] 1984 **Acceptable**
Rat, Fischer 344	DOWCO 290 97%	6-15	0, 15, 75, 250 mg/kg bw/day Oral gavage	**Maternal:** NOAEL 15 mg/kg bw/day based on decreased liver weight and food consumption **Embryotoxicity/teratogenicity**: NOAEL >250 mg/kg bw/day, no LOAEL (malformed foetuses detected were considered incidental)	[redacted] *et al.*, 1981 **Acceptable**
Rabbit, New Zealand White	DOWCO 290 96.4%	7-19	0, 50, 110, 250 mg/kg bw/day Oral gavage	**Maternal**: NOAEL 110 mg/kg bw/day based on decreased body weight and body weight gain, gastric lesions, clinical signs and morbidity **Embryotoxicity/teratogenicity:** NOAEL 110 mg/kg bw/day based on decreased mean foetal weight, slightly increased spontaneous malformations	[redacted] *et al.,* 1990 **Acceptable**
Rabbit, New Zealand White	DOWCO 290 96%	6-18	0, 110, 250, mg/kg bw/day Oral gavage	**Maternal**: NOAEL >250 mg/kg bw/day, no LOAEL **Embryotoxicity/teratogenicity**: NOAEL 250 mg/kg bw/day, no LOAEL	[redacted] *et al.*, 1974 Additional information

2.6.7. Summary of neurotoxicity

No study submitted. The results from toxicological studies on clopyralid suggest that there are no specific neurotoxic effects

2.6.8. Summary of further toxicological studies on the active substance

Clopyralid was first manufactured before 1980. The method of manufacture changed from the so-called 'Hydrazino' process to the so-called 'Penta' process in 1987. The toxicity of the technical material produced by the two production processes is essentially similar.

In a study where immunotoxic potential of clopyralid was investigated after 28 day exposure to rats, the NOAEL was 150 mg/kg bw/day based on the increased thymus weight at dose levels 500 and 1000 mg/kg bw/day. No other treatment related effects were observed.

The overall picture shows that clopyralid has no endocrine disrupting properties. The search on open literature provided no articles with relevance for toxicology section.

2.6.9. Summary of toxicological data on impurities and metabolites

No studies submitted.

2.6.10. Summary of medical data and information

Surveillance data indicated that workers involved in the production of clopyralid were healthy and did not show any acute or chronic medical problems. One worker developed an allergic reaction, which subsided after he was transferred to another manufacturing plant but the reaction was not positively correlated with exposure to clopyralid.

According to the applicant clopyralid is considered to be of low overall systemic toxicity, and there is no specific antidote. Mild exposures or small ingestions are unlikely to cause significant systemic toxicity, and first aid measures are, for the most part, generic to such products and related to supportive care relative to any symptoms.

2.6.11. Toxicological end point for assessment of risk following long-term dietary exposure – ADI

The ADI for clopyralid is based on the most relevant NOAEL from long-term toxicity, carcinogenicity, reproductive and developmental toxicity studies. Relevant studies with the resulting NOAELs are presented in the table 2.6-6.

Long-term exposure to clopyralid was tolerated well by rats and mice. The major effects were decreased food consumption, body weight reduction and/or increased liver and kidney weights. The lowest relevant NOAEL was 15 mg/kg bw/day in a 2-year rat chronic toxicity and oncogenicity study by [redacted] *et al.* (1985, 1986). The LOAEL was 150 mg/kg bw/day in this study, based on decreased food consumption and lesions on the gastric limiting ridge. These lesions were also detected in subchronic studies in rat. Although the gastric limiting ridge is not present in human's stomach, the lesions detected in animals characterize the irritant nature of clopyralid rather than being species specific effect. The lowest NOAEL in the developmental study was also 15 mg/kg bw/day recorded in the female rat ([redacted] *et al*., 1981). Using a NOAEL of 15 mg/kg bw/day and a 100-fold safety factor, the ADI for clopyralid is 0.15 mg/kg bw/day.

Table 2.6-6 Summary of relevant NOAELs for deriving ADI

Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Effects at LOAEL
Dog, 12-month oral toxicity (diet)	100	320	Haematological effects, liver weights ↑(males).
Rat, 2-year chronic toxicity and oncogenicity (diet)	**15**	**150**	Lesions of the gastric limiting ridge, slightly reduced food consumption.
Mouse, 2-year dietary chronic toxicity-oncogenicity study (diet, males)	500	2000	Reduction in body weight.
Rat, two-generation reproduction study (Parental toxicity, females)	150	500	NOAEL based on decreased body weight, reduced food consumption, stomach lesions.
Rat, developmental study (maternal toxicity)	**15**	75	NOAEL 15 mg/kg bw/day based on decreased liver

Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Effects at LOAEL
			weight and food consumption.
Rabbit, developmental study (maternal and embryotoxicity)	110	250	Maternal: NOAEL based on decreased body weight and body weight gain, gastric lesions, clinical signs and morbidity Embryotoxicity/teratogenicity: NOAEL based on decreased mean foetal weight, slightly increased spontaneous malformations.

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

According to Guidance for the Setting of an Acute Reference Dose (ARfD) (European Commission, 7199/VI/99 rev. 5, 05/07/2001) the following categories of toxicological alerts should suggest the need to establish an ARfD (FAO/WHO, 2000):

- Lethality after administration of a single low dose orally
- Developmental effects, except when these are clearly a consequence of maternal toxicity
- Clinical signs, other pharmacological effects, or effects on target organs observed early in studies with repeated doses, including effects on behaviour or on the gastrointestinal, cardiovascular or respiratory system
- Acute neurotoxicity, including that due to exposure to organophosphates and carbamates.
- Hormonal or other biochemical alterations observed in studies with repeated doses, which might conceivably be elicited by a single dose.

As the criteria are not met there is no need to establish ARfD for clopyralid.

2.6.13. Toxicological end point for assessment of occupational, bystander and residents risks – AOEL

The AOEL for clopyralid is based on the most relevant NOAEL recorded in short-term toxicity, reproduction and developmental toxicity studies in the rat, mouse, rabbit and dog. The most relevant NOAEL is the one derived from the most sensitive relevant effect in the most sensitive relevant animal model. Relevant studies with the resulting NOAELs are summarised in Table 2.6-7.

Short-term exposure to clopyralid was tolerated well by rats, mice, rabbits and dogs. The major effects were increased liver and/or kidney weights or microscopic alterations in liver or haematological effects. In mice the liver was identified as the major target organ. Thickening of the epithelium of the gastric limiting ridge was detected in rats. The NOAEL for rats could not be established from the two acceptable studies.

In the previous evaluation, from studies regarded as acceptable, a NOAEL of 100 mg/kg bw/day from 12-month dog study, based on increased liver weight and haematological effects, was regarded as most relevant for setting AOEL. The conclusion of 4-week rat study ([redacted] *et al*., 1986) changed during AIR 3 evaluation and therefore it was not possible to establish NOAEL from rat studies. Based on this, it was not possible to conclude which species was the most sensitive in the short-term studies.

Therefore, it was decided that the lowest NOAEL 15 mg/kg bw/day recorded in the developmental study in the rat (based on maternal decreased liver weight and food consumption) should be used for setting AOEL even though clopyralid was not teratogenic, decreased liver weight is considered as uncharacteristic symptom and higher doses were tolerated without adverse effects in other studies.

Oral absorption of clopyralid is high (>80%) and therefore no correction for bioavailability is necessary. Using a NOAEL of 15 mg/kg bw/day and a 100-fold safety factor the AOEL for clopyralid is 0.15 mg/kg bw/day.

Table 2.6-7 Summary of relevant NOAELs for deriving AOEL

Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Effects at LOAEL
Rat, 4-week oral (diet, females)	< 150	150	Kidney weight ↑.
Rat, 3-month oral (diet, males)	<300	300	Mean relative liver and kidney weights significantly↑, serum chemistry value (alkaline phosphase) ↓, microscopical investigations on liver.
Mouse, 13-week oral (diet, females)	750	2000	Microscopical changes in the liver.
Dog, 12-month oral toxicity (diet)	100	320	Haematological effects, liver weights ↑(males).
Rabbit, 21-day dermal	>1000	>1000	No treatment related systemic toxic effects.
Rat, developmental study (maternal toxicity)	15	75	NOAEL 15 mg/kg bw/day based on decreased liver weight and food consumption.
Rabbit, developmental study (maternal and embryotoxicity)	110	250	Maternal: NOAEL based on decreased body weight and body weight gain, gastric lesions, clinical signs and morbidity Embryotoxicity/teratogenicity: NOAEL based on decreased mean foetal weight, slightly increased spontaneous malformations.

2.6.14. Summary of product exposure and risk assessment

Based on the studies the product GF-1374, containing 80 g/L clopyralid, 2.5 g/L florasulam and 144 g/L fluroxypyr-meptyl (100 g a.e./L fluroxypyr), is of low acute toxicity by oral and dermal route but it is harmful if inhaled. GF-1374 is irritating to skin and eyes. The product is classified as Asp. Tox. 1; H304. The studies are presented in more detail in Volume 3 Annex B.6 (PPP).

Table 2.6-8 Summary of acute toxicity studies of GF-1374

Route/method	Species	Result/ Comment	Classification according to Regulation (EC) No. 1272/2008	Reference
Acute oral	Rat (Female)	LD_{50} = 3378 mg/kg	Not Classified	[redacted] (2005) Acceptable
Acute dermal	Rat	LD_{50} > 5000 mg/kg	Not Classified	[redacted] (2005) Acceptable
Acute inhalation	Rat	LC_{50} (males) = 4.58 mg/L LC_{50} (females) = 3.35 mg/L	Acute Tox. 4; H332	[redacted] *et al.* (2005) Acceptable

Route/method	Species	Result/ Comment	Classification according to Regulation (EC) No. 1272/2008	Reference
Skin irritation	Rabbit	Irritating to skin	Skin Irrit. 2; H315	[redacted] (2005) Acceptable
Eye irritation	Rabbit	Irritating to eyes	Eye Irrit. 2; H319	[redacted] (2005) Acceptable
Skin sensitisation (M&K)	Guinea pig	No result	Not classified, based on concentration limits.	[redacted] (2005) Supportive

GF-1374 (EC) is intended to be used on winter cereal and established permanent pasture as a herbicide. Critical use pattern used in the exposure assessment is presented below. Detailed modeling on exposure assessment is presented in Volume 3 Annex B.6 (PPP). Default dermal absorption values were used for all active substances.

Table 2.6-9 Summary of critical use pattern (i.e. worst case) for use of GF-1374.

Crop	Application equipment	Application rate per treatment		Spray volume (L/ha)	Number of applications
		kg a.s./ha	L product/ ha		
Established permanent pasture	Tractor mounted sprayer, overall broadcast foliar spray	Clopyralid 0.120 Florasulam 0.00375 Fluroxypyr-meptyl 0.216	1.5	100-400	1

Operator exposure, resulting from the proposed uses of GF-1374, has been evaluated by the German model (75th percentile), UK POEM and EFSA model. The estimated exposure of operators was estimated to be under the respective AOEL for florasulam, when no PPE is considered. Regarding fluroxypyr-meptyl, according to UK POEM the estimated exposure is below AOEL only when PPE (gloves during mixing, loading and application) is considered. For clopyralid the exposure is below AOEL only when PPE (gloves during mixing, loading and application, coverall and sturdy footwear during application or gloves and work wear (arms, body and legs covered) during mixing, loading and application) is considered.

Based on the results of the estimated combined exposure (based on results by German model and EFSA model) PPE (gloves or gloves and work wear during mixing, loading and application/ Gloves during mixing, loading and application, coverall and sturdy footwear during application) is required in order to the combined exposure to be below 100%. Based on calculations by UK POEM the combined exposure is above 100% even when PPE (gloves during mixing, loading and application) is considered.

When taking into account also the classification of the product as Asp. Tox. 1; H304, Acute Tox. 4; H332, Eye Irrit. 2; H319 and Skin Irrit. 2; H315 relevant PPE (respiratory protection equipment, goggles, cap) in addition to gloves, coverall and sturdy footwear is needed.

The bystander exposure was evaluated by EUROPOEM II and Martin et al. and resident exposure by Martin et al and EFSA model. Worker exposure was modelled by Europoem II and EFSA model. According to model calculations, the estimated exposure of a bystander, resident and worker is below the respective AOEL for each active substance (without PPE for workers). The combined exposure % is clearly below 100 %.

It is concluded that operators (with relevant PPE), bystanders, residents and workers (no PPE) are not anticipated to be exposed for unacceptable high levels of clopyralid, florasulam and fluroxypyr-meptyl, also when combined exposure is considered.

2.7. RESIDUE

2.7.1. Summary of storage stability of residues

The residue definition is comprised of parent clopyralid. its conjugates and salts for risk assessment. Storage stability has only been studied with the unconjugated parent compound. The methods are capable to analyse the conjugates, but they have been fully validated only by using unconjugated parent compound.

In order to demonstrate storage stability of plant commodities with high protein content, Clements (1996) and Foster et al. (1996) studied clopyralid stability in corn grain, straw and fodder, indicating that clopyralid is stable in pasture for 520 days. Maize fractions were shown to be stable for 385 days.

In these previously assessed studies results were corrected with concomitant recovery levels, which is not in line with current guidelines and recommendations, and may give rise to erroneous results.

The data (Allen 2013) indicates that residues of clopyralid are stable for at least 305 days (10 months) in orange peel, orange fruit, olive oil and pitted, jarred olives in brine olive fruit stored under frozen conditions.

Storage stability of clopyralid was demonstrated for up to 305 days (10 months) in orange peel, orange fruit, olive oil and olive fruit.The data by [redacted] (2015) indicates that residues of clopyralid are stable in representative bovine fat for at least 24 months when stored at 20 ± 10°C. Samples were properly generated and stored at frozen temperatures. Any fluctuations in temperature as a result of defrosting or removal of samples from freezer for analyses were negligible and had no effect on the study results. Samples were analyzed for clopyralid residues using well controlled and appropriate methods. No unusual analytical events were experienced during the conduct of this study.

The data by [redacted] (2004) indicates that residues of clopyralid are stable in bovine muscle, liver, kidney, milk and poultry eggs for up to 18 months when stored at -20 ± 10°C. Samples were properly generated and stored at frozen temperatures. Any fluctuations in temperature as a result of defrosting or removal of samples from freezer for analyses were negligible and had no effect on the study results. Samples were analyzed for clopyralid residues using well-controlled and appropriate methods.

The edible commodities covered by stability studies comprise of orange fruit (high acid content), olive fruit and olive oil (high oil content).

Of the plant matrices listed in the OECD guideline document submitted studies cover high starch content (maize fractions), while matrices with high starch content. high protein content and high water content.

For olive data only covers processed olives and, consequently no data are available to demonstrate storage stability in edible plant commodities with high oil content in general. Applied processing may destroy metabolising enzymes. Hydrolysis studies revealed that clopyralid was otherwise stable, but was not tested at basic pH levels, which may be employed in production of jarred olives.

For maize (corn) and pasture procedural recoveries were used to adjust results from storage samples, a procedure, which does not meet current guidelines.

Consequently the available data does not cover plant derived edible commodities with high water, high starch and high oil content in a GLP compliant way.

Clopyralid conjugates are major residue species in oilseed rape representing 19% - 29% of TRR.

Since conjugates have been taken into residue definition, the storage stability of clopyralid conjugates (mainly glycine conjugate) should be assessed, since the spiking has only been carried out with parent compound. As such the methods employed are capable to determine also clopyralid conjugates.

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

The metabolism of clopyralid has been studied in four different crops: sugarbeet (crop group R), oilseed rape (crop group P/O), cabbage (crop group L) and pasture (C/G crop group). Aside from the latter, a GLP noncompliant study on pasture, the studies are considered acceptable and the metabolic pathways of clopyralid in plants can be regarded sufficiently studied in three crop groups

Clopyralid, in its unconjugated and conjugated forms, was found to be the major residue species, thus the residue definition in plants for risk assessment purposes is clopyralid and its salts and conjugates expressed as clopyralid equivalents. The data allow universal residue definitions for edible plant derived commodities to be established, since three crop groups were studied with consistent results.

The study on pasture (Bauriedel and Miller, 1981) predated OECD GLP requirements and the documentation was not fully worked out. In the study, residue decreased from a 1-week concentration of 100 ppm to an 18-week concentration of 0.6 ppm (both values given on dry-weight basis). The data indicated a half-life of about 2.3 weeks. The study lend support to the notion that clopyralid metabolism in pasture is limited as the residue in all samples consisted of only unchanged 3,6 dichloropicolinic acid.

Uncertainty remains, however whether the samples were kept in a fridge or not. The only known detail relating to sample storage, is that at some stage the samples were dried and the analyses were carried out from the dried material. Another deficient issue in this study is the high application rate, approx. 10N. Using high application rates tend to overestimate the relative amount of the parent substance. Thus this study should only be regarded as supportive information.

Otherwise all previous plant metabolism studies evaluated meet also the current requirements and a more recent (1991) study is available for pasture:

Study	Crop	Status
Chapelo and Caley (2002a)	Sugar Beet	acceptable
Chapelo and Caley (2002b)	Oilseed Rape	acceptable
Wright (1996)	Cabbage	acceptable
Bauriedel and Miller (1981)	Pasture Grass	Supportive data. The study does not meet OECD GLP requirements and has deficiencies in documentation.

The only new clopyralid metabolism study, submitted (Gourlay 2015) to support the AIR3 renewal, was rather a study on biodistribution and uptake of clopyralid in oilseed rape and wheat in hydroponic conditions than a metabolism study. Regarding current guidelines and requirements, the study has very limited value in assessing plant metabolism. The study has been evaluated as a part of the Vol 3 Section B.8 ‘Fate and Behaviour’.

In studies on the sugar beets and rape plants most of the recovered radioactivity was removed by surface washing on the day of application. At maturity of the crop most of the radioactivity was taken up into plants. At this time point the major radioactive compound in the crop was unchanged parent compound and polar and conjugated forms of parent. Together these fractions accounted for 89 – 97 % of TRR. No other significant metabolites were detected. In sugar beets clopyralid accounted for 0.36 –0.38 mg/kg in both beets and shoots.

In oilseed rape clopyralid accounted for 0.71mg/kg in straw and 0.059 mg/kg in seeds. Unchanged clopyralid was also found to be the major residue species, accounting for 0.321 mg/kg in cabbage heads and 1.21 mg/kg in

wrapper leaves. The presence of residues in the cabbage hearts indicates translocation from the immature leaves with the residue level being diluted by growth.

The study on cabbage shows that clopyralid does not undergo significant metabolism. Unchanged clopyralid was found to be the major component of the residue, accounting for 91,5% TRR (0.321 mg/kg) in cabbage heads and 99% TRR (1.21 mg/kg) in wrapper leaves. It was stated that the presence of residues in the cabbage hearts indicates translocation from the immature leaves with the residue level being diluted by growth. Study is acceptable.

The metabolism of clopyralid in grass is also very limited and the reduction of residue levels (from 13.1 mg/kg to 0.16 mg/kg) is due to the growth dilution.

In the metabolism studies no positive identification was made for any of the components. The identification of the residue species was based on co-chromatography and the presence of the radio label. This is not considered as a deficiency on basis of total radioactivity, which could almost all be assigned to the parent.

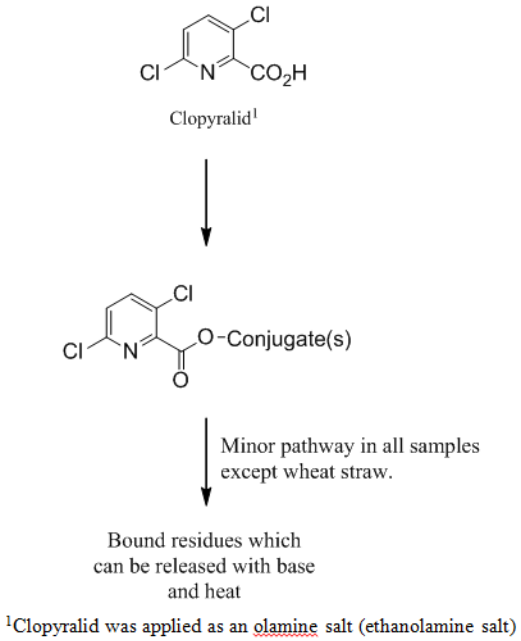
All the metabolism data has been summed up in the following Table. A simple picture of clopyralid metabolism is emerged: unchanged clopyralid is the major residue species and if conjugates are taken into account, amount of clopyralid ranges from 89.5 %TRR in sugar beet shoots up to 99.2 %TRR in cabbage leaves. Conjugates corresponded to 39.1 %TRR in sugar beet roots highest levels being in oilseed rape leaves i.e. 61.7 %TRR.

The table below sums up all the data obtained in plant metabolism studies:

	Sugar beet roots		Sugar beet shoots		Cabbage head		Cabbage wrapper leaf		Oilseed rape Maturity			
									Straw		Seeds	
	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR
Identified components	0.356	96.9	0.381	89.5	0.321	91.5	1.21	99.2	0.711	94.1	0.059	89
Clopyralid	0.212	57.8	0.218	51.3	0.321	91.5	1.21	99.2	0.245	32.4	0.029	43.4
Polar form of clopyralid (acid hydrolysis)	0.144	39.1	0.159	37.3				0.41	0.244	32.3	0.018	27.5
Clopyralid conjugates	-	-	0.004	0.9				0.9	0.222	29.4	0.012	18.1
Ether fractions												
Unknown 1 (3 min)					ND	ND	0.005	0.41				
Unknown 2 (11-12)					0.015	4.27	0.011	0.9				
Unknown 3 (14)					ND	ND	0.004	0.33				
Unknown 4 (18-19)					0.004	1.14	0.002	0.16				
Unknown 5 (20-20.5)					ND	ND	0.007	0.57				
Dichloromethane surface wash									0.009	1.2	-	-
Organic surface wash	0	0	0.002	0.5								
Aqueous surface wash	0.004	1.2	0.001	0.3					-	-	-	-
Aqueous residue	0.025	6.7	0.023	5.5					0.011	1.5	0.002	2.4
Acid ectractable (6M HCl)	0.02	5.4	0.014	3.3					0.045	6	0.002	3.8
URR	0.002	0.6	0.006	1.4	0.008	2.28	0.029	2.38	0.009	1.2	0.004	5.6
ERR					0.340	96.9	1.24	102				
Recovery	0.407	110.8	0.427	100.5	0.351	100	1.22	100	0.785	104	0.067	110.8

Biodistribution is one of the issues, which is to be studied to clarify metabolism. The study by Gourlay (2015) was the only new plant metabolism study submitted. The study gives information on uptake, but metabolism as such is not covered by this type of study and therefore has only supportive value.

The proposed metabolic pathway in plants is shown below.



[1]Clopyralid was applied as an olamine salt (ethanolamine salt)

2.7.2.2. Animal metabolism

2.7.2.2.1. Proposed Metabolic Pathway for ^{14}C -Clopyralid in Laying Hen

Majority of the residues present in livestock was clopyralid and a very small amount of glycine conjugate (X36538) of clopyralid was present.

A new poultry nature of residue (NOR) study was conducted according to the current guideline requirements and also performed complete characterization on the tissues. Findings in this study for the tissue residues and the excretion and metabolite profiles were consistent with findings in a prior goat nature of residue study. Unchanged clopyralid was the major residue with a minor amount of X36538 in both studies.

In eggs plateau was not reached at the end of the experiment, and consequently the studies should be continued.

Results indicate that clopyralid is minimally metabolized in laying hens. The majority of clopyralid is excreted unchanged. While a diminutive amount, 2.0% TRR and 0.0002 mg eq./kg is metabolized in eggs to the unidentified Metabolite 1.

The study is acceptable.

2.7.2.2.2. Proposed Metabolic Pathway for 14C -Clopyralid in ruminants

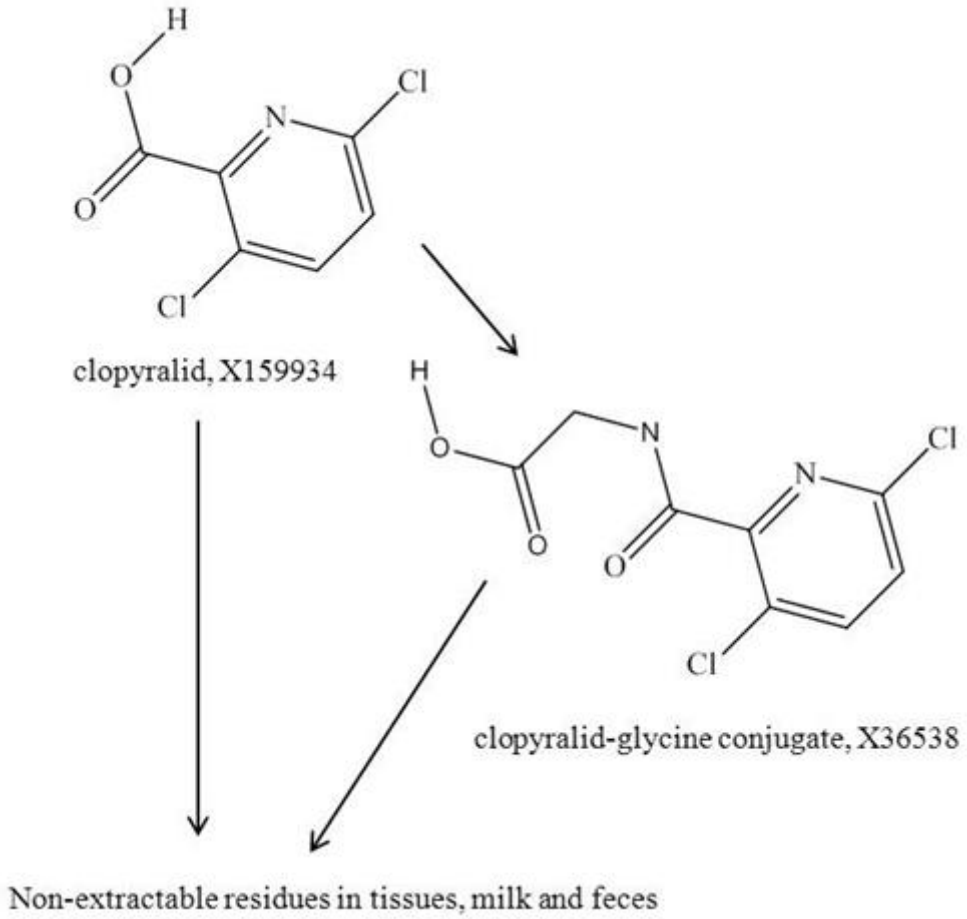
In a new submitted metabolism study by [redacted] and [redacted] (2015) clopyralid and its glycine conjugate were present as the primary residue in milk, in all tissues, in feces and in urine corresponding from 54 to over 112% of the TRR. X36538 was present only in subcutaneous fat, urine and feces at less than 2% of the TRR and in milk at from 11 to 22% of the TRR.

Clopyralid was identified by co-chromatography with a reference standard by HPLC and confirmed by LC/MS. There was no reference standard for X36538, and its identity was tentatively assigned by results obtained from LC/MS analysis and by reference to an earlier study in which it was observed.

Clopyralid is not metabolized in the goat, except for formation of small amounts of clopyralid glycine conjugate, X36538. Non-extractable or bound radioactivity in kidney was liberated as only clopyralid after treatment using base and acid treatment. While the non-extractable radioactivity from no samples other than kidney was treated with base and acid to release clopyralid, it was proposed that those non-extractable residues were likely to contain clopyralid and/or X36538.

In this study positive identification using HPLC MS/MS had been carried out. In contrast to the previous studies this study meets the GLP requirements of OECD. The study is acceptable and has high quality.

Proposed metabolic profile of active substance in domestic animals:



2.7.3. Definition of the residue

The EFSA peer review report (EFSA Scientific Report (2005) 50, 1–65, Conclusion on the peer review of clopyralid) decided that the plant and animal residue definitions for both monitoring and consumer risk assessment should be clopyralid, its salts and conjugates, expressed as clopyralid.

This residue definition is not in line with the existing enforcement residue definition in Reg. (EU) 396/2005, which has set the residue definitions both for risk assessment and monitoring as parent clopyralid only.

In the section 2.7.7 'Summary of residues in rotational crops' a notion has been made of an unknown metabolite. This metabolite found in wheat grain is driven by soil metabolism as it occurs in rotational crops only.

Food of plant origin:
the plant residue definition for risk assessment is sum of clopyralid, its salts and conjugates, expressed as clopyralid.

NOTE: Rotational crops studies revealed an unidentified metabolite in wheat grain, which may have an impact on the residue definitions.

For monitoring: the plant and animal residue definitions for monitoring is clopyralid, its salts and conjugates, expressed as clopyralid.

Food of animal origin: the animal residue definitions for monitoring is clopyralid, its salts and conjugates, expressed as clopyralid.

The residue definition for animal derived edible commodities to be used in risk assessment is sum of clopyralid, its salts and conjugates, expressed as clopyralid

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

The representative uses considered for clopyralid Annex I Renewal include use on pasture grass in established grass pastures and use on cereals (wheat (including triticale), barley, oats and rye).

The critical GAP for use of clopyralid in pasture grass / established grass pasture in both Northern and Southern Europe is based on one application at a maximum rate of 120 g a.i./ha with a 7-day PHI or 7-day interval before grazing treated grass. The critical GAP for use of clopyralid in cereals in both Northern and Southern Europe is based on a single application at a maximum rate of 80 g a.i./ha with application at a maximum growth stage of BBCH 39. The maximum growth stage at application is to define the latest timing for application rather than a PHI. Therefore, no PHI for use of clopyralid in cereals is proposed. A summary of the critical GAPs for clopyralid in pasture and cereals are presented in the table below.

Summary of the critical GAPs proposed for clopyralid Annex I Renewal

Crop	Maximum rate g a.i./ha	Number of applications (minimum interval in days)	PHI (days)	Growth stage at latest application (BBCH)
Pasture grass / Established pasture	120	1	7 days (Note: for one of the formulated products, GF-1374, a PHI of 14 days is used due to requirements associated with fluroxypyr).	N/A – Minimum interval between application and harvest (cutting or grazing) is to be based on PHI rather than on maximum growth stage.
Cereals: wheat (including triticale and spelt), barley, oat and rye	80	1	N/A - latest timing for application is defined by maximum growth stage rather than PHI as such.	BBCH 39

All the residue trials, which were conducted with formulation Bofix* BP (EF-1403) that contains 27 g a.i./L clopyralid, were performed at 3 L/ha, which corresponds to 80 g a.i./ha. This application rate, 80 g a.i./ha, is the same as the cGAP used for cereals. The same formulation also contains 54 g a.i./L fluroxypyr present as the butoxypropyl ester and 267 g as/L MCPA was employed in a study on winter barley (Butler , 1998).

According to *SANCO 7525/VI/95 - rev.9*, trials with increases up to 25% in the application rate (under otherwise identical conditions) are assumed to be comparable, following the statistical approach by Lundehn et al. 1990. In the guideline rials with an increased application rate more than 25% of the proposed by the applicant GAP are not considered comparable with those conducted according to the GAP as these trials may lead to higher residue levels, and consequently higher than appropriate MRLs.

In RMS opinion overdose trials can be used as to support an authorization, provided that residue levels of the overdosed trials are covered by the current MRLs and no other parameters are modified.

In general overdosed trials may be used to support a less critical GAP, when they indicate that no residues above the LOQ are to be expected provided that no other parameters have been modified.

Analytical Procedures for Plant matrixes

The primary metabolic path for clopyralid in all crops is the formation of conjugates that can be hydrolysed to parent. Therefore it is important that the analytical methods employed are capable to determine not only the unchanged clopyralid, but also the clopyralid conjugates.

Bound residues were only significant in wheat straw (10.6% TRR) and the majority of these "bound" residues was solubilized using 1 N NaOH and heat (9.2% TRR).

The crop methods ERC 97.10, GRM 01.16 and 120610 have a common analytical extraction and hydrolysis procedure with caustic methanol solution with overnight hydrolysis.

In the confined rotational crops study (Hall, L. R., 2015, DAS 130733) a specific assessment of the extraction and hydrolysis efficiency included in the listed method above was conducted using aged residues in wheat forage, straw, grain and immature cabbage to validate the procedure. The overall results of the metabolism study demonstrated that the majority of the residue(s) in the plant tissue were either clopyralid or conjugates that readily hydrolysed to clopyralid.

Pasture Grass / Established Pasture:

The critical GAP supported for clopyralid use in pasture grass for Annex I Renewal (AIR) has changed and is less critical compared to the critical GAP accepted during Active Approval. The critical GAP for pasture grass proposed for clopyralid AIR is based on an application of clopyralid at a maximum rate of 0.12 kg ae/ha with a 7-day PHI in both the N-EU and S-EU (although for the representative formulation, GF-1374, there is a 14-day PHI in the S-EU due to limitation of the PHI for fluroxypyr). For Active Approval the critical GAP in the S-EU was 0.24 kg ae/ha, 7-day PHI and in the N-EU the critical GAP was 0.12 kg ae/ha, 7-day PHI. For the N-EU, trials available during Active Approval had been carried out using rates above the critical GAP (carried out at 0.2 – 0.24 kg ae/ha), but were accepted to provide a conservative, worst case evaluation of potential livestock dietary burden from treated grass.

Results from the new pasture residue trials are presented in this dossier which provide a full set of 8 trials in the S-EU that are compliant with the critical GAP proposed for clopyralid AIR and it is proposed that these trials are accepted for use to support clopyralid AIR in the S-EU. The new S-EU trials were treated with clopyralid at a nominal rate of 105 g ae/ha (actual reate ranged from 104 g ae/ha to 112 g ae/ha). Clopyralid residue in grass in the S-EU trials at a 7-day PHI ranged from 1.66 mg/kg to 4.09 mg/kg. The additional 4 trials for the N-EU available from the new study were carried out at 0.2 kg ae/ha and were therefore at a rate higher than proposed for clopyralid AIR. However, it is proposed that results from these additional 4 trials be combined with the 6 trials accepted during Active Approval to provide a conservative, worst case evaluation of potential livestock dietary burden for the N-EU. The clopyralid residues in grass in the combined group of 10 N-EU trials ranged from 2.49 mg/kg to 6.95 mg/kg.

It is concluded that results from pasture grass trials, accepted during Active Approval together with trials from a new study included in this submission, are adequate to provide a conservative, worst case evaluation of potential dietary burden for livestock consuming treated grass.

Cereals (Wheat and Barley):

The critical GAP supported for clopyralid use in cereals for Annex I Renewal (AIR) has changed and is less critical compared to the critical GAP accepted during Active Approval. The critical GAP for cereals proposed for clopyralid AIR is based on an application of clopyralid at a maximum rate of 0.05 kg ae/ha with application at a latest growth stage of BBCH 39 in both the N-EU and S-EU. For Active Approval, the critical GAP that was supported was application at a maximum rate of 0.127 kg ae/ha in both the N-EU and S-EU with application at a latest growth stage of BBCH 39 and BBCH 45 in the N-EU and S-EU, respectively.

Since the critical GAP supported for Active Approval and upon which current EU MRLs in cereals are based is more critical than the GAP proposed for Annex I Renewal, the residue trial data supporting the Active Approval and the EU MRLs also covers the less critical GAP proposed for Annex I Renewal.

Although residue data for cereals from the more critical GAPs accepted for Active Approval are expected to equal or exceed residue levels from the less critical GAP proposed for Annex I Renewal, results from a limited number of available barley and wheat trials having GAPs considered equivalent to the critical GAP proposed for Annex I Renewal (e.g. ± 25% of the cGAP rate) have been summarized and presented in this document as confirmatory information.

Although the application rates are within 25% of the cGAP for Annex I Renewal, most of the available trials had application at a somewhat earlier stage of growth (BBCH 32) rather than BBCH 39, but these were considered comparable since the plants in these growth stages are in similar stages of development and occur well before development of the grain / consumable part of the plant. As expected, residues from trials considered to be in compliance with the GAP proposed for clopyralid Annex I Renewal are considered to be within the range of residue values from trials accepted for Active Approval that were conducted under a more critical GAP. Therefore, it is proposed that the exiting residue data for cereals that was accepted during Active Approval and upon which EU MRLs are based is adequate to also support the less critical GAP proposed for Annex I Renewal.

In conclusion, the GAPs proposed for clopyralid AIR are less critical than the GAPs and the associated residue data for wheat and barley accepted for Active Approval and the existing EU MRLs in cereals are based on these trial results.

Therefore, it was proposed that the data and associated MRLs as presented in the EFSA Scientific Report (2005) 50, 1-65, 'Conclusion on the peer review of clopyralid' also be used to support the clopyralid AIR. Results from these trials accepted for Active Approval are presented to support the use of clopyralid in cereals for clopyralid AIR. Results from the wheat and barley trials are to be extrapolated to support MRLs for oats and rye as well.

The representative formulation for Annex I Renewal (AIR) is GF-1374, an emulsifiable concentrate containing the active substance clopyralid at 80 g a.i./L and 2 mixing partners namely fluroxypyr mepthyl 144 g/l (100 g as/L) and florasulam 2.5 g/l.

Bofix* BP (EF-1403). This formulation contains 27 g as/L clopyralid, 54 g a.i./L fluroxypyr present as the butoxypropyl ester and 267 g as/L MCPA was employed in a study on winter barley (Butler , 1998).

According to SANCO 7525/VI/95 - rev.9, trials with increases up to 25% in the application rate (under otherwise identical conditions) are assumed to be comparable, following the statistical approach by Lundehn et al. 1990. tIn the guideline rials with an increased application rate more than 25% of the proposed by the applicant GAP are not considered comparable with those conducted according to the GAP as these trials may lead to higher residue levels, and consequently higher than appropiate MRLs.

In RMS opinion overdose trials can be used as to support an authorization, provided that residue levels of the overdosed trials are covered by the current MRLs and no other parameters are modified.

In general overdosed trials may be used to support a less critical GAP, when they indicate that no residues above the LOQ are to be expected provided that no other parameters have been modified.

The analytical methods used in these residue trials did not necessarily use a hydrolysis step prior to analysis of clopyralid and therefore it is not clear whether conjugates of clopyralid were analysed.

None of the studies give separate results for the conjugates.

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

Analytical

The analytical methods for residue in animal tissues, GRM 02.14 and 120483, have a common analytical extraction and hydrolysis procedure with caustic solution with 2 hours heat to complete hydrolysis of the conjugates. The nature of the residues in livestock was previously assessed in the original Annex I evaluation under EFSA scientific report (2005) 50, 1-65 where it was agreed that glycine conjugates of clopyralid is hydrolysed under alkaline conditions which is lately comprised in the analytical methods of livestock.

Laying hen

Results from a poultry feeding study have previously been evaluated during Annex I inclusion / Active Approval (Clopyralid Draft Assessment Report, Vol.3, B7.8, February, 2005). These data were considered valid for decision making, but there were some unresolved questions on certain experimental details. A new poultry feeding study was conducted since some experimental details were not well documented in the earlier study and since the study was not GLP and did not follow current study guidelines because the study was conducted prior to initiation of GLP requirements and development of study guidelines. Additionally, residues were generally found at equal ot greater levels in the new study than in the previous study. Therefore, it is proposed that the new poultry feeding study be used to evaluate transfer of clopyralid residues from the diet to eggs and tissues.

In the new poultry feeding study, laying hens were dosed orally for 28 or 29 consecutive days via gelatine capsules containing clopyralid. Based on actual feed consumption during the period of dosing, the average dose levels of clopyralid based on concentration in the diet (DM feed basis) were 4.90 mg/kg (1x), 10.26 mg/kg (2x), 19.82 mg/kg (4x) and 50.50 mg/kg (10x). If the daily dosage of clopyralid is expressed on the basis of bodyweight of the individual hens (mg/kg bw/day), the average dosage over the four weeks of dosing was 0.280 mg/kg bw/day, 0.571 mg/kg bw/day, 1.086 mg/kg bw/day and 2.779 mg/kg bw/day, for the 1x, 2x, 4x and 10x treatment groups, respectively.

No adverse treatment-related effects were observed on body weight, feed consumption or egg production. No treatment-related behavioural reactions or systemic signs of toxicity were noted and gross necropsies showed no effects that appeared to be treatment-related.

Residues of clopyralid in eggs and tissues were measured using an analytical method based on LC-MS/MS with a limit of detection (LOD) and limit of quantitation (LOQ) in each of the sample matrices of 0.003 mg/kg and 0.01 mg/kg, respectively. Overall average procedural recovery for clopyralid in all matrices ranged from 75% to 87%.

Results showed that residues of clopyralid above the LOQ transfer into eggs in hens from the 2x, 4x and 10x dose groups. Residues of clopyralid in eggs appeared to reach a plateau within the first 7 days of dosing.

Residues of clopyralid above the LOQ were found in muscle in hens from the 1x, 2x and 10x dose groups and in liver in hens from the 1x, 2x, 4x and 10x dose groups. Residues of clopyralid were below the LOQ in fat in hens from all dose groups.

Regression analysis shows a generally linear relationship between dosing level and residue in eggs, muscle and liver, although in liver and to a lesser degree in muscle variability in residue levels among replicates in the 1x, 2x and 4x dose levels affected the analysis. Regression analysis has not been performed for fat, as in all cases the residues were below the LOQ.

Depuration data generated using hens in the 10x dose level showed that residues of clopyralid declined rapidly following withdrawal of the test item from the hens' diet. All residues were below the LOQ by 3 days of depuration (i.e. 3 days after the end of the dosing period).

Estimated dietary burden was only 30% of lowest dose employed in the feeding study. Consequently there is uncertainty in the MRL extrapolation. It is concluded by the RMS that on basis of the data available the current MRLs in force, i.e. 0.05 mg/kg cover edible commodities derived from hen, as far as the representative uses are concerned.71

Lactating cow

Results from cattle feeding studies have previously been evaluated during Annex I inclusion / Active Approval (Clopyralid Draft Assessment Report, Vol.3, B7.8, February, 2005). These data were considered valid for decision making, but there were some unresolved questions on certain experimental details, including confirmation of whether or not dose levels in the diet were expressed on a dry matter basis.

A new cattle feeding study was conducted since some experimental detail were not well documented in the earlier studies and since these previous studies did not meet neither the GLP requirements and current study guidelines. The studies were conducted prior to initiation of GLP requirements and development of guidelines. Additionally, residues were generally found at equal or greater levels in the new study than in the previous studies. Therefore, it is proposed that the new cattle feeding study be used to evaluate transfer of clopyralid residues from the diet to milk and tissues.

In the new cattle feeding study lactating dairy cows were dosed orally for 28 or 29 consecutive days via gelatine feeding capsules containing clopyralid. Gelatine capsules containing the test item were administered to each cow on two occasions each day (AM and PM feeding). Based on actual feed consumption during the period of dosing, the average dose levels of clopyralid based on concentration in the diet (DM feed basis) were 16.7 mg/kg (0.3x), 56.6 mg/kg (1x), 309.8 mg/kg (5x) and 1019.5 mg/kg (18x). If the daily dosage of clopyralid is expressed on the basis of bodyweight of the individual cows (mg/kg bw/day), the average dosage over the four weeks of dosing was 0.451 mg/kg bw/day, 1.670 mg/kg bw/day, 8.517 mg/kg bw/day and 30.538 mg/kg bw/day, for the 0.3x, 1x, 5x and 18x treatment groups, respectively.

No adverse treatment-related effects were observed on body weight, feed consumption or milk production. No treatment-related behavioural reactions or systemic signs of toxicity were noted and gross necropsies showed no effects that appeared to be treatment-related.

Residues of clopyralid were measured using an analytical method based on LC-MS/MS with a limit of detection (LOD) and limit of quantitation (LOQ) in all sample matrices of 0.003 mg/kg and 0.01 mg/kg, respectively. Overall average procedural recovery for clopyralid in all matrices ranged from 71% to 82%.

Residues of clopyralid above the LOQ of 0.01 mg/kg were found in muscle samples from cows in the 1x, 5x and 18x treatment groups and in the liver, kidney, subcutaneous fat, mesenteric fat and perirenal fat from cows in the 0.3x, 1x, 5x and 18x treatment groups. Residues of clopyralid in whole milk appeared to reach a plateau within the first 2 days of dosing. The average level of clopyralid in whole milk from samples collected from the second day of dosing (Study Day 2) until the end of the dosing period was ND, <0.01 mg/kg, 0.040 mg/kg and 0.153 mg/kg for the 0.3x, 1x, 5x and 18x treatment groups, respectively.

Regression analysis of clopyralid in milk, skimmed milk, cream and tissues (muscle, liver, kidney and fat) demonstrated a generally linear relationship between the dose level and the resulting residue concentration.

Depuration data generated using the 12 cows in the 18x dose level showed that residues of clopyralid declined rapidly following withdrawal of the test items from the cows' diet

Pig

The metabolism of clopyralid in ruminants (goats) and non-ruminants (rats, poultry) is similar, and therefore metabolism and feeding studies in pigs are not required. It is possible to extrapolate results from the cattle feeding study to pigs, consequently further studies are not required.

No supplementary study or data are required or submitted.

Fish

A fish feeding study is not considered presently as there are currently no final, approved guidance documents or test guidelines for determining dietary burden / potential residue intake in the diet or methodology for conducting a fish feeding study.

Furthermore, clopyralid is not expected to bioaccumulate in animal tissues as indicated by a log P_{ow} of -2.63 and a fish BCF < 1

2.7.6. Summary of effects of processing

Clopyralid is stable to processing hydrolysis under all conditions tested. Therefore, the nature of the residue is not expected to be altered during processing.

Any test regarding the behaviour of clopyralid conjugates has not been conducted, which would also serve as a validation for the common extraction step of conjugates, which employ high temperatures and high pH and are utilised in all analytical methods of clopyralid. As such these methods are capable of determining conjugates, but does any losses occur has not been fully worked out. It is true, however, that in many cases conjugates are assumed to be stable.

Processing trials were carried out in wheat and barley to determine if residues concentrate in processed commodities. Although carried out on a laboratory scale, the processing procedures used in the wheat and barley processing studies were representative of commercial processing procedures and conditions.

In wheat, clopyralid residues were found to concentrate in wheat germ and bran. Compared to the residue level in grain, concentration of clopyralid was found to decrease in white flour, white bread and wholemeal bread.

In barley, there was no concentration of clopyralid residues in any of the malting / brewing products collected. Compared to the residue level in gain, clopyralid residues decreased in malt sprouts, brewing malt, spent grain and flocs, brewer's yeast and beer.

2.7.7. Summary of residues in rotational crops

The metabolism of clopyralid was shown to proceed in rotational crops in a similar fashion as in the primary crops. Consequently, the same definition of residue can be maintained.

In rotational crop intervals majority of the residue identified was clopyralid. Free and conjugated clopyralid were the most abundant residue species at all PBIs. Clopyralid taken up by the plants possibly as a glucose conjugate of clopyralid.

A magnitude of residue study in rotational crops was not carried out for use during the Active Approval. A magnitude of residue in rotational crops study is currently on-going to provide further information, but no data from the study is available at the time of writing. However, further consideration of the available data from the confined rotational crop residue study is discussed below.

Data from a confined rotational crop residue study indicated that following application of clopyralid at 280 g ae/ha to bare soil, significant residues in rotational crops planted approximately 125 days later are not expected. With regard to the GAPs proposed for clopyralid AIR, these results provide an overly conservative assessment of the potential for residues above the MRL in rotational crops since the maximum application rate considered for cereals in this submission is 80 g active substance/ha, which is less than 30% of the rate used in the confined rotational crop residue study. Additionally, since the only use of clopyralid considered for cereals is a post emergence foliar application, the soil loading with clopyralid residues would be further reduced due to crop interception compared to the bare soil condition used in the confined rotational crop residue study. Use in established pasture would not normally be considered as relevant for rotational crop residues as crops are not normally grown in rotation with established grass pasture. However, even if rotation is considered, the maximum rate considered in pasture in this submission is 120 g ae/ha, which is less than 50% of the rate evaluated in the confined rotational crop residue study.

Additionally, in application to pasture, there would be a very high level of interception of clopyralid by the grass foliage with little of the spray reaching the soil. Another consideration is that existing EU MRLs in essentially all crops have been set at 0.5 mg/kg or higher. Consequently, an interval appreciably shorter than 125 days would be expected to be adequate to avoid significant residues in rotational crops or residues that would exceed existing MRLs. For clopyralid use in cereals, it is proposed that no further waiting period is required for sowing or planting succeeding crops after normal crop maturity and harvest. The latest growth stage for application to

cereals is BBCH 39. Based on the GAPs proposed in this submission, the interval between application at BBCH 39 and normal crop maturity and harvest is expected to be adequate to ensure that residues are not found in rotational crops in significant levels.

Since conjugates corresponds upto 52% of TRR in succeeding wheat forage, 59% in wheat hay and even in grains more than 34% of TRR, it is clear that conjugates should to be included in residue definitions out as well as for primary crops as for rotational crops.

The rotational crop study by Hall(2015) reveals an unknown component in wheat grain at a high level (20%TRR) triggering the requirement of identification of this metabolite and, if needed, a clarification of its toxicological properties.

2.7.8. Summary of other studies

2.7.8.1. Effects on the residue level in pollen and bee products

This is a new data requirement under Regulation EU 1107/2009 therefore no data have previously been considered.

Additionally, the representative uses evaluated in this submission involve application to grass pasture and cereals which are not considerd to be crops that are attractive to bees.

There are a wide range of other supported uses of clopyralid containing products in production of various melliferous plants.

Bearing this issue and future MRL settings in mind, storage stability of honey should be set as a data gap, since such studies take considerable amount of time. As far as rotational crops are concerned, EFSA guideline states that some crops (e.g. cauliflower, carrots, chicory) which usually do not flower during normal production, are indicated as attractive to bees because, in some cases, they can be cultivated for seed production.

Same likely holds true for raddish, a crop which has been evaluated in the present document as a rotational or succeeding crop.

Consequently:

- Crops, such as cabbage, are attractive to honeybees.
- Clopyralid is a selective systemic herbicide belonging to the chemical class of pyridines and its residues are likely to be present in the pollen.
- Application before or during attractive period (flower – honeydew)
- The MRLs of clopyralid in the honey have been set at the limit of quantification 0.05 mg/kg as any data have not been made available.

Considering plants, which do not attract bees, such as the representative uses of the present document, it can be stated that the pollen content in honey is low. Puusepp and Koff (2014) reported an average concentration of 10,000 grains/gram honey and considering that 2000 pollen grains weigth one milligram (Porter, 1981), the pollen content in honey is around 0.5%.

2.7.8.2. Other studies

Kucharski et al. (2006) studied residues of clopyralid in mustard seeds, following treatment according to a less critical use than considered in the DAR for oilseed rape, ranged from <0.001 (non-detected) to 0.005 mg/kg. As expected the levels are significantly below the existing EU MRL of 0.5 mg/kg for mustard seeds and therefore no further consideration is required.

Kucharski et al. (2009) studied effect of soil contamination with herbicides on the nitrification process. The study does not follow an appropriate guideline but methodology is comprehensively described. The study is relevant, but does not alter the existing risk assessment.

In the studies by Sadowski et al. (2010) residues of clopyralid in oilseed rape were measured, but rates and timings of application were not provided. The levels are significantly below the existing EU MRL.

Kucharski et al. (2005) studied degradation dynamics and residues of clopyralid in surface and groundwater on fields of Lower Silesia. The objective of the study is is environmental. Also other submitted studies had environmental scope and will not be evaluated in this Section.

2.7.9. Estimation of the potential and actual exposure through diet and other sources

The ADI for clopyralid is 0.15 mg/kg bw/day. Predicted dietary intakes of clopyralid using the EFSA PRIMo model (ver 2.0) indicate that the intended use (representative use) does not lead to unacceptable risk for consumers. The TMDI calculation shows that potential exposure to clopyralid using MRL data is very low (≤ 27, 0.5, or 1.4 % of the ADI for any subpopulation, respectively). Taking data, which only covers the representative uses and STMRs the highest intake occurs with WHO cluster diet D (7.0 %ADI) and the second highest is DK children with 6.3 %ADI utilisation.

Acute reference doses (ARfDs) for clopyralid, were not allocated by EFSA*, therefore acute risk assessment is not required.

ADI usage evaluated with EFSA PRIM over 2.0 using STMRs.

Highest calculated TMDI values as %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
6,4	UK Toddler	5,3	Sugar beet (root)	1,1	Wheat	0,0	Head cabbage
3,1	UK Infant	2,3	Sugar beet (root)	0,7	Wheat	0,0	Maize
2,8	WHO Cluster diet B	2,4	Wheat	0,2	Sugar beet (root)	0,1	Maize
2,8	DK child	1,5	Wheat	1,2	Rye	0,0	Head cabbage
2,1	WHO cluster diet D	1,8	Wheat	0,1	Rye	0,1	Barley
1,9	IT kids/toddler	1,9	Wheat	0,0	Barley	0,0	Maize
1,5	WHO cluster diet E	1,1	Wheat	0,2	Barley	0,1	Rye
1,5	NL child	1,3	Wheat	0,1	Milk and milk products: Cattle	0,0	Rye
1,5	UK vegetarian	0,9	Sugar beet (root)	0,6	Wheat	0,0	Head cabbage
1,4	WHO Cluster diet F	1,0	Wheat	0,2	Rye	0,2	Barley
1,4	DE child	1,2	Wheat	0,2	Rye	0,0	Milk and milk products: Cattle
1,4	UK Adult	0,9	Sugar beet (root)	0,5	Wheat	0,0	Head cabbage
1,3	ES child	1,2	Wheat	0,0	Milk and milk products: Cattle	0,0	Maize
1,2	IT adult	1,2	Wheat	0,0	Head cabbage	0,0	Barley
1,2	PT General population	1,1	Wheat	0,0	Rye	0,0	Maize
1,1	IE adult	0,6	Wheat	0,3	Barley	0,1	Maize
1,1	SE general population 90th percentile	0,9	Wheat	0,1	Head cabbage	0,1	Rye
1,0	WHO regional European diet	0,8	Wheat	0,1	Barley	0,1	Head cabbage
0,9	FR all population	0,9	Wheat	0,0	Milk and milk products: Cattle	0,0	Head cabbage
0,8	ES adult	0,7	Wheat	0,1	Barley	0,0	Milk and milk products: Cattle
0,8	DK adult	0,6	Wheat	0,2	Rye	0,0	Head cabbage
0,8	FR toddler	0,7	Wheat	0,0	Head cabbage	0,0	Bovine: Meat
0,8	NL general	0,6	Wheat	0,1	Barley	0,0	Head cabbage
0,7	LT adult	0,3	Wheat	0,3	Rye	0,1	Head cabbage

Highest calculated TMDI values as %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
0,5	FI adult	0,3	Wheat	0,2	Rye	0,0	Head cabbage
0,3	FR infant	0,2	Wheat	0,1	Milk and milk products: Cattle	0,0	Bovine: Meat
0,1	PL general population	0,1	Head cabbage	0,0	Maize		FRUIT (FRESH OR FROZEN)

2.7.10. Proposed MRLs and compliance with existing MRLs

Cereal grain (wheat and barley with extrapolation to oats and rye):
As the existing residue data from Active Approval is used, it is proposed to retain the existing EU MRL for cereals (wheat, barley, oat and rye) at 2 mg/kg.

Food commodities of animal origin:

MRLs for clopyralid based on the use in pasture grass and cereals and associated dietary burden are proposed below. Due to results from the new cattle feeding study there is a need to propose increased MRLs in some instances. Where there was no need to increase the MRL, it is proposed to maintain the MRL at the current level even if the data suggests that a lower MRL might be adequate. The reason for not reducing the MRLs is that other existing uses of clopyralid other than grass and cereals were not considered in this submission. A summary of proposed MRLs in commodities of animal origin is presented below and the MRL value is displayed in bold when an increase in the MRL value is proposed.

RD monitoring Sum of clopyralid, its conjugates and salts, expressed as clopyralid							
RD risk assessment Sum of clopyralid, its conjugates and salts, expressed as clopyralid							
Bovine							
Closest level[(a)] 15 mg/kg DM 0,8 N Dairy C. 0,9 N Beef C.	Residues at the closest feeding level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg) RMS	Existing MRL Reg. (EU) No 322/2012 : 17.4.2012)	MRL value proposed by the Notifier in the MRL application
	Mean	Highest	STMR[(b)] (mg/kg)	HR (mg/kg)			
Meat	-	-	0.0098	0.0138	-		
Muscle	0.007	0.007	0.007	0.010	0.01	0.08	
Fat	0.023	0.041	0.073	0.090	0.09	0.05*	0.07
Liver	0.032	0.036	0.026	0.055	0.06	0.06	
Kidney	0.429	0.606	0.305	0.755	0.8	0.4	1
Milk[(c)]	0.004	0.005	0.004	0.005	0.005	0.05*	
Sheep							
Closest level[(a)] 0.451 mg/kg bw 0.5 N Ewe 0.6 N Lamb	Residues at the closest feeding level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg)		
	Mean	Highest	STMR[(b)] (mg/kg)	HR (mg/kg)			
Meat	-	-	0.0098	0.0138	-		
Muscle	0.007	0.007	0.009	0.015	0.015	0.08	
Fat	0.023	0.041	0.082	0.134	0.15	0.05*	0.09
Liver	0.032	0.036	0.038	0.078	0.08	0.06	0.08
Kidney	0.429	0.606	0.445	1.197	1.5	0.4	1.5
Milk[(c)]	0.004	0.005	0.005	0.007	0.007	0.05*	

Swine							
Closest level[(a)]	Residues at the closest feeding level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg)		
0.451 mg/kg bw							
2.2 N Breeding			STMR[(b)] (mg/kg)	HR (mg/kg)			
4.1 N Finishing	Mean	Highest					
Meat	-	-	0.0098	0.0138	-		
Muscle	0.007	0.007	0.005	0.005	0.005	0.05*	
Fat	0.023	0.041	0.069	0.067	0.07	0.05*	
Liver	0.032	0.036	0.020	0.035	0.04	0.05*	
Kidney	0.429	0.606	0.161	0.281	0.3	0.05*	0.3
Milk[(c)]	0.004	0.005	0.004	0.004	0.004	0.05*	
Poultry							
Closest level[(a)]	Residues at the closest feeding level (mg/kg)		Estimated value at 1N level		MRL proposal (mg/kg)		
0.280 mg/kg bw							
1.9 N Layer			STMR[(b)] (mg/kg)	HR (mg/kg)			
2.0 N Layer	Mean	Highest					
Meat	-	-	0.00815	0.0104	-	0.05*	
Muscle	0.006	0.011	0.003	0.00578	0.006	0.05*	
Fat	0.003	0.003	0.002	0.001576	0.002	0.05*	
Liver	0.01867	0.032	0.010	0.016816	0.02	0.05*	
Kidney	0	0.000				0.05 *	
Eggs[(c)]	0.003	0.003	0.002	0.002275	0.003	0.05*	

It is proposed that the MRLs for bovine be extrapolated to equine and that MRLs for sheep be extrapolated to goats since the OECD guidance on residues in livestock does not address diets or body weight for equine or sheep.

The MRL in force, have been taken from Reg. (EU) No 322/2012.

In evaluation carried out under directive 91/414 a MRL of 0.5 mg/kg for ruminant kidney was proposed.

In feeding studies fat tissues were collected in different locations. If the levels were different the highest one was chosen.

Current MRLs for eggs are for all bird species 0.05 mg/kg.

2.7.11. Proposed import tolerances and compliance with existing import tolerances

No EU Import Tolerances are neither proposed nor applied for in this submission. Additionally, there are no CXLs since clopyralid has not been reviewed by the JMPR.

2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT

2.8.1. Summary of fate and behaviour in soil

The degradation of clopyralid in soil is fairly rapid. In laboratory studies clopyralid mineralized to CO_2 under aerobic conditions whereas in anaerobic conditions very minimal degradation occured and no transformation products were formed. CO_2 accounted for 47.5% to 65.5% after 92 days in the aerobic soil studies. Degradation via photolysis can be considered as negligible.

Degradation of clopyralid was investigated in 10 different laboratory soils under aerobic conditions in the dark (CA 7.1.2.1). DT_{50} were in the range of 4.9-64.6 (non-normalised). The aerobic degradation of clopyralid followed SFO kinetics in all soils studied. Following normalisation (20°C, pF2), DT_{50} was determined to be between 4.9 and 64.6, resulting in a geometric mean of 18.4 days. No pH correlation was observed.

Under field conditions in Europe, rapid dissipation of clopyralid was observed, with DT_{50} (20°C, pF2) between 2.07 and 13.5 days. The geometric mean DT_{50} was determined to be 6.76 days (n = 8, CA 7.1.2.2). In January 2017 the Dow AgroSciences informed the RMS about two new field dissipation studies in Markgröningen, Germany, and Meauzac, S-France, for which the final study reports are expected in March, 2017 (Ahrens, C. and Kröger, F. 2017: Field soil dissipation study with one spring application of GF-1966 (Clopyralid) at one site in North EU and one site in South EU to bare soil in 2016 – 2017. DAS Study ID 160394). The two new trials consolidate the existing data package. After consultation with EFSA, the RMS could not postpone submitting the dRAR in order to include these sites in the kinetic evaluation of soil dissipation studies at this stage, but recognized that further data exists, which should be taken into account to finalise the kinetic evaluation of field degradation of clopyralid.

Clopyralid soil adsorption K_{FOC} values range between 0.26 and 4.1 mL/g (n = 9), and 1/n values are between 0.3881- 1.047 (CA 7.1.3). For modelling purposes some of the 1/n had to be replaced by the default value of 0.9 according to reliability criterion presented in the OECD 106 guidance, resulting in an arithmetic mean 1/n of 0.836 used in modelling, together with the geometric mean K_{FOC} of 1.41 mL/g.

2.8.2. Summary of fate and behaviour in water and sediment

Clopyralid is stable to hydrolysis in sterile buffer solution at 50ºC for five days (DT_{50} >1 year) at environmental relevant pH 4 to 9. Therefore, clopyralid is expected to be stable to hydrolysis for more than 30 d at 20ºC. Photolysis is not a significant route of degradation of clopyralid in water.

In the aerobic mineralisation study, no degradation of clopyralid was determined.

In water/sediment system studies it was only possible to determine the DT_{50} for the water phase (148 d, geometric mean, n = 2). Mineralization of CO_2 reached a maximum of 5.3% AR after 100 days, while NER accounted for 5.85 %AR.

2.8.3. Summary of fate and behaviour in air

Clopyralid has a low vapour pressure of 1.02×10^{-5} mm Hg at 25°C (CA 2.2). As the vapour pressure does not exceed the trigger for volatilisation no further evaluation is required.

The evaporation of clopyralid from soil and plant surfaces is minimal, and therefore clopyralid is not expected to be present in air in significant quantities. Its Henry's law constant (3.28×10^{-10} Pa m^3 /mol) also indicates that its volatilisation into air is not probable. Therefore the risk of long range transport of clopyralid is acceptable.

2.8.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

Clopyralid was monitored in surface freshwater in eleven countries (Austria, Belgium (Wallonia), Czech Republic, Finland, France, Norway, Slovakia, Sweden, Switzerland, the Netherlands and the United Kingdom) in 2006-2015. It was generally more frequently found and at higher concentrations than in groundwater, though with more variability as is typical of surface freshwater. More than 1,678 sites were monitored and 21,159 samples analysed. Clopyralid was detected and exceeded 0.1 µg/L in ≥4,172 samples which represented ≤19.71% of all samples. However, there were LoDs >0.1 µg l^{-1} and this has exaggerated the number of samples exceeding the limit. Maximum concentrations in excess of the 0.1 µg/L drinking water limit were reported in the Czech Republic, Finland, France, Norway, Slovakia, Sweden, Switzerland and the United Kingdom (England, and Scotland).

Clopyralid was monitored in groundwater in eight countries (Austria, Belgium (Wallonia), Czech Republic, Ireland, Norway, Slovakia, Sweden and the United Kingdom) in 2007-2015. There were more than 4,459 sites and over 24,538 samples. Clopyralid was detected and exceeded the 0.1 µg/L drinking water limit in ≤0.35% of groundwater samples (≤85 samples). Maximum concentrations in excess of 0.1 µg/L were reported in Belgium (Wallonia), Czech Republic, Slovakia, Sweden and the United Kingdom (England and Wales). A maximum clopyralid concentration of 17.1 µg/L was reported in the Czech Republic.

2.8.5. Definition of the residues in the environment requiring further assessment

Definition of the residues in soil, ground water, surface water and air is clopyralid only. This is based on the data in soil degradation studies, lysimeter and water/sediment studies, where no aerobic or anaerobic metabolites except CO_2 were formed, and also on hydrolysis or photolysis studies, where no degradation products were found > 10 % of AR. According to the calculation of the photochemical stability in air, clopyralid is expected to be the only residue in air.

2.8.6. Summary of exposure calculations and product assessment

Soil

The maximum non-normalised field DT_{50} (23.7 days) was used for PEC_{soil} calculations. The initial PEC_{soil} following application on winter cereals and grassland was calculated according to the GAP for GF-1374 assuming that clopyralid is evenly distributed in the top 5 cm horizon with a soil bulk density of 1.5 g/cm3 (CP 9.1.3). $PEC_{plateau}$ calculations were not required as the $DT_{90,field}$ does not exceed the trigger value (1 year).

No relevant soil metabolites have been identified. Therefore, PEC_{soil} values for soil metabolites are not required and have not been calculated.

Groundwater

FOCUS PEARL, PELMO and MACRO groundwater scenarios and models were used to model active substance PEC_{GW} based on the GAP recommended for GF-1374 (CP 9.2.4). The 80th percentile annual average leachate concentrations for clopyralid at 1 m depth (PEC_{GW}) were estimated employing the field DT_{50} values.

For Approval Renewal purposes sufficient safe uses (scenario/application date combinations) for annual application of clopyralid on winter cereals and grassland for the entire application period could be demonstrated. However, the detailed results are as follows: For winter cereals, all model scenarios resulted in PEC_{GW} <0.1 µg/L with an annual application in May. For applications from February through April and in June, bi-annual or tri-annual application was required for some scenarios, it was not possible to show a safe use for some of the scenario/application date combinations following application of clopyralid every third year. For grassland, PEC_{GW} <0.1 µg/L was demonstrated for all model scenarios with an annual application occurring from April. For applications in February and March, a bi-annual or tri-annual application was required for some scenarios.

No relevant soil metabolites were identified (see section 2.11), and hence PEC_{GW} simulations for metabolites were not required.

Surface water and sediment

PEC_{SW} and PEC_{SED} values for clopyralid following application to winter cereals and grassland have been calculated using the surface water models FOCUS STEPS 1-2 and FOCUS SWASH (CP 9.2.5). Safe uses for aquatic organisms were demonstrated using FOCUS STEP 1-2 PECsw and PECsed values.

No relevant metabolites in surface water or sediment were identified.

Air

Clopyralid is not expected to occur in significant amounts in air, due to its low vapour pressure. Therefore, exposure via air has not been estimated.

Other routes of exposure

Due to the nature of the recommended use of GF-1374 as spray application on winter cereals and grassland, exposure via other routes (e.g. by deposition of dust; indirect exposure or surface water from sewage treatment plant) can be excluded.

2.9. EFFECTS ON NON-TARGET SPECIES

2.9.1. Summary of effects on birds and other terrestrial vertebrates

Considering the worst-case shortcut values of the screening risk assessment, all TER_A values are in excess of their corresponding Annex VI trigger of 10, indicating acceptable acute risks to birds and mammals after application of GF-1374 at rates up to 120 g a.s./ha on grassland and 80 g a.s./ha on cereals. For long term exposure assessment of birds and mammals, application scenarios for grassland and cereals both resulted in TER_{LT} values greater than the Annex VI trigger of 5 indicating low long-term risk to birds and mammals. Overall acute and chronic risk is low for applications of GF-1374 and clopyralid to both grassland and cereals at proposed use rates.

2.9.2. Summary of effects on aquatic organisms

TER calculations based on the FOCUS STEP 1-2 PECsw and PECsed values demonstrate that, overall, there is acceptable acute and long-term risks to fish, aquatic invertebrates, sediment-dwellers and algae from the use of clopyralid (applied as GF-1374) to cereals and pasture with one application per year. Based on these results, no acute or long-term risk to aquatic organisms is expected for GF-1374 applications at rates up to 1.5 L formulation/ha on pasture and 1.0 L formulation/ha on cereals. No risk mitigation measures beyond 1 m buffer are necessary to protect the aquatic organisms, if the product GF-1374 is used according to these GAPs.

2.9.3. Summary of effects on arthropods

Clopyralid is an herbicide with no known insecticidal properties and it exhibits low acute oral and contact toxicity to honey bees. The HQ values for acute oral and contact exposure, calculated in accordance with current risk assessment guidance (SANCO/10329/202 rev 2 final), are both below the trigger value of 50. However, because no studies on the effects of clopyralid on honey bee development and other life stages were submitted according to current data requirements, the risk assessment on pollinating insects is inconclusive for the time being, and a data gap is identified.

The proposed use of clopyralid on pasture and cereal crops, in accordance with Good Agricultural Practice, will present no unacceptable acute risk to other non-target arthropods.

2.9.4. Summary of effects on non-target soil meso- and macrofauna

Using the maximum initial PEC_{soil} values resulting from the total annual application rate of GF-1374 on pasture and cereals, the TER_A and TER_{LT} values for the formulation and active ingredient pass the Annex VI recommended trigger values of 10 and 5 for acute and long term exposure of earthworms and other soil macro-organisms. Consequently, acceptable risk of acute and long term toxicity for earthworms and soil macro-organisms at an application rate of 120 g clopyralid/ha on pasture and 0.80 kg clopyralid/ha on cereals was calculated.

2.9.5. Summary of effects on soil nitrogen transformation

No long-term effects on soil micro-organisms were observed at treatment levels equivalent to > 6.68 times the maximum application rate of GF-1374 to cereals and pastures. Overall, an acceptable risk to soil micro-organisms is therefore expected following the use of clopyralid and GF-1374. Based on these results, no risk to soil micro-organisms is expected for applications up to 1.5 L/ha to pasture and 1.0 L/ha to cereals.

2.9.6. Summary of effects on terrestrial non-target higher plants

A low risk to terrestrial non-target plants was identified for clopyralid after applications of GF-1374 at rates up to 1.5 L product/ha on pasture and amenity grassland with the use of a 1m buffer zone with 75% drift reducing nozzles or 5 m buffer zone from the edge of the field during applications based on probabilistic assessment. Based on these results, the risks to terrestrial plants from GF-1374 applications to pasture and amenity grasslands are considered acceptable with appropriate risk mitigation measures and if the GAP is assumed.

2.9.7. Summary of effects on other terrestrial organisms (flora and fauna)

No additional data on the effects of GF-1374 on other terrestrial organisms has been generated due to the lack of effects on terrestrial organisms. Due to this reason, no further information is provided.

2.9.8. Summary of effects on biological methods for sewage treatment

No adverse effects on activated sewage sludge was observed at 100 mg/L resulting in the 3 h EC_{50} for the inhibition of respiration of activated sludge reported as > 100 mg/L. Therefore no risk is expected following applications of 120 g clopyralid/ha to grassland and 80 g clopyralid/ha to cereals.

2.9.9. Summary of product exposure and risk assessment

GF-1365 demonstrated low acute and chronic risk to birds and mammals. Also, the formulated product showed little or no risk to aquatic species, non-target arthropods, soil microorganisms, earthworms, and soil macrofauna. However, a 5m buffer zone must be implemented following applications of GF-1374 to protect non-target plants. Overall, GF-1374 demonstrated low acute and chronic risk to all non-target species evaluated.

2.10. CLASSIFICATION AND LABELLING

Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				
2.2.	Flammable gases				
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids				
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquids				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases				
2.13.	Oxidising liquids				
2.14.	Oxidising solids				
2.15.	Organic peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity - oral				Data conclusive but not sufficient for classification
	Acute toxicity - dermal				Data conclusive but not sufficient for classification
	Acute toxicity - inhalation				Data conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation				Data conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	Eye Dam. 1; H318		Eye Dam. 1; H318	
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation				Data inconclusive
3.5.	Germ cell mutagenicity				Data inconclusive
3.6.	Carcinogenicity				Data conclusive but not sufficient for

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
					classification
3.7.	Reproductive toxicity				Data (partly) inconclusive
3.8.	Specific target organ toxicity –single exposure				Data conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				Data conclusive but not sufficient for classification
3.10.	Aspiration hazard				Data conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	H410 Very toxic to aquatic life with long lasting effects		H410 Very toxic to aquatic life with long lasting effects	Triggered by study data.
5.1.	Hazardous to the ozone layer				

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Hazard pictograms: **GHS05, GHS09**

Signal word: Danger
Hazard statements: H318 Causes serious eye damage.
H410 Very toxic to aquatic life with long lasting effects H410
Precautionary statements: P280, P305+P351+P338, P310, P273, P501

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Proposed classification according to Dangerous Substances Directive (Directive 67/548/EEC)

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification [1)]**	**Reason for no classification [2)]**
Explosiveness				
Oxidising properties				
Flammability				
Other physico-chemical properties *[Add rows when relevant]*				
Thermal stability				
Acute toxicity				
Acute toxicity – irreversible damage after single exposure				
Repeated dose toxicity				
Irritation / Corrosion				
Sensitisation				
Carcinogenicity				
Mutagenicity – Genetic toxicity				
Toxicity to reproduction – fertility				
Toxicity to reproduction – development				
Toxicity to reproduction – breastfed babies. Effects on or via lactation				
Environment				

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger:
R-phrases:
S-phrases:

2.11. RELEVANCE OF METABOLITES IN GROUNDWATER

2.11.1. STEP 1: Exclusion of degradation products of no concern

No groundwater metabolites identified. Therefore the further steps of assessment are not necessary.

Appendix 1: Metabolites formed from active substance and their occurrence

Code Number (Synonyms)	Description	Compound found in:	Structure
Not applicable	None	Not applicable	Not applicable

2.11.2. STEP 2: Quantification of potential groundwater contamination

-

2.11.3. STEP 3: Hazard assessment – identification of relevant metabolites

-

2.11.3.1 STEP 3, Stage 1: screening for biological activity

-

2.11.3.2 STEP 3, Stage 2: screening for genotoxicity

-

2.11.3.3 STEP 3, Stage 3: screening for toxicity

-

2.11.4. STEP 4: Exposure assessment – threshold of concern approach

-

2.11.5. STEP 5: Refined risk assessment

-

2.11.6. Overall conclusion

No relevance of metabolites in groundwater.

2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT

Active is not of isomeric composition therefore no data/information are presented.

2.12.1. Identity and physical chemical properties

2.12.2. Methods of analysis

2.12.3. Mammalian toxicity

2.12.4. Operator, Worker, Bystander and Resident exposure

2.12.5. Residues and Consumer risk assessment

Predicted dietary intakes of clopyralid using the EFSA PRIMo model indicate that the intended use (representative use) does not result in unacceptable risk for consumers.

Acute reference doses (ARfDs) for clopyralid, were not allocated by EFSA*, therefore acute risk assessment is not required.

2.12.6. Environmental fate

2.12.7. Ecotoxicology

2.13. RESIDUE DEFINITIONS

2.13.1. Definition of residues for exposure/risk assessment

Food of plant origin:
the plant and animal residue definition for consumer risk assessment is clopyralid, its salts and conjugates, expressed as clopyralid.

For rotational crops an unidentified metabolite was observed in wheat grain, which may have an impact on the residue definitions.

Food of animal origin:
the animal residue definition for consumer risk assessment is clopyralid, its salts and conjugates, expressed as clopyralid.

Soil: clopyralid

Groundwater: clopyralid

Surface water: clopyralid

Sediment: clopyralid

Air: clopyralid

2.13.2. Definition of residues for monitoring

Food of plant origin:
the plant and animal residue definitions for monitoring is clopyralid, its salts and conjugates, expressed as clopyralid..

Food of animal origin: the animal residue definition for monitoring is clopyralid, its salts and conjugates, expressed as clopyralid..

Soil: clopyralid

Groundwater: clopyralid

Surface water: clopyralid

Sediment: clopyralid

Air: clopyralid

Level 3

CLOPYRALID

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.	Y		It is considered that Article 4 of Regulation(EC) No 1107/2009 is complied with Clopyralid for the representative uses (please refer to Section 1.5.1 Level 1 for details of representative uses).
3.1.1.2. Submission of further information				
		Yes	No	
i)	It is considered that a complete dossier has been submitted	Y		With regards to the submission made, a complete dossier is considered to have been submitted, which enables a regulatory decision of Clopyralid to be made. Data gaps were identified . Please see the point 3.1.4. and 3.1.5
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.			

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.	Y		a) The minimum purity should remain unchanged as 950 g/kg. *(c)* For protecting terrestrial non-target plants appropriate risk mitigation measures are necessary, as for instance 1m buffer zone with 75% drift reducing nozzles or 5 m buffer zone from the edge of the field during applications of GF-1374 at rates up to 1.5 L product/ha on pasture and amenity grassland. *(f)* Further studies on sub-lethal effects on pollinating insects, to honey bee development and other honeybee life stages, according to current data requirement regulations 283/2013 and 284/2013, are required.
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).		N	As the clastogenicity and aneugenicity of clopyralid has not been excluded, ADI and AOEL are not applicable until the question of mutagenicity is solved.
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for 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			• a) Metabolism studies have been conducted with three crop groups allowing universal residue definition for risk assessment and monitoring. • b) Concerns have been raised with regard to analytical methods of clopyralid conjugates. None of the residue methods has been validated with clopyralid conjugates. The methods as such are capable for conjugate analysis, but the amount of lossess during the procedure have not been clarified. • c) Hydrolytic stability of parent clopyralid mimicking home processes, such as baking brewing, boiling and sterilisation have been studied. The parent compound was shown to be stable, but any information of the behaviour of its conjugates have not been

	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.			submitted. Predicted dietary intakes of clopyralid using the EFSA PRIMo model indicate that the intended use (representative use) does not lead to unacceptable risk for consumers. The TMDI calculation shows that potential exposure to clopyralid using MRL data is very low (≤ 27, 0.5, or 1.4 % of the ADI for any subpopulation, respectively). Acute reference doses (ARfDs) for clopyralid, were not allocated by EFSA*, therefore acute risk assessment is not required. This applies to all representative uses, i.e. to cereals and pasture. There are a plethora of other uses not taken into account in the present evaluation. While the residue data have been produced using a set of different formulations, any bridging data have not been submitted.
	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.	Y		This applies to all representative uses, i.e. to cereals and pasture. There are a plethora of other uses not taken into account in the present evaluation.
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.	Y		Sufficient information on efficacy of clopyralid was provided by applicant. For details please see Level 2, Section 2.3.
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.	Y		This applies to all representative uses, i.e. to cereals and pasture. There are a plethora of other uses not taken into account in the present evaluation.
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 impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.	Y		Proposed specification of clopyralid is acceptable, and the analytical methods provided are acceptable. Proposed representative formulation is acceptable.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such			n.a.

	specification exists.			
	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			n.a.
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.		N	The provided analytical method for the determination of the active substance in technical material is not acceptably validated, because, according to SANCO/3030/99 rev. 4, confirmatory techniques are required to support identification of the a.s when the primary method of determination is not highly specific. The provided analytical method for the determination of the impurities in technical material is acceptable.
	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.	Y		The provided analytical methods for post control and monitoring residue analysis in plants and plant products, foodstuffs and feeding stuffs, soil, water and air are acceptable. However, some methods for risk assessment of plants and of food of animal origin have not been acceptably validated.
	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.	Y		
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.			An ADI of 0.15 mg/kg bw/day has been established based on a NOAEL of 15 mg/kg bw/day determined in a 2-year rat chronic toxicity and oncogenicity study and in a rat developmental study and a 100- fold safety factor (Level 2, Section 2.6.11). ARfD is not necessary as the criteria given in Guidance for the Setting of an Acute Reference Dose (ARfD) are not met (Level 2, Section 2.6.12). An AOEL of 0.15 mg/kg bw/day is derived from a NOAEL of

				15 mg/kg bw/day in a developmental study in the rat by applying a standard safety factor of 100 (Level 2, Section 2.6.13).
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.**			The acceptable *in vitro* bacterial and mammalian gene mutation tests gave negative result. *In vitro* chromosome aberration test in cultured rat lymphocytes is not considered acceptable anymore. The supportive *in vitro* test of unscheduled DNA synthesis (UDS) performed in isolated rat hepatocytes gave negative result. Because of the wrong dose selection, both the *in vivo* micronucleus test and the acute and subacute *in vivo* cytogenetic study were not acceptable. The i*n vivo* dominant lethal mutagenesis assay is considered as not acceptable as well. There is no acceptable chromosome test in the whole dossier and hence, a data gap for addressing clastogenic and aneugenic end point is identified. (Level 2, Section 2.6.4)
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.**		N	There was no evidence that clopyralid caused increased incidence of malignant or non-malignant tumours in the rat or in the mouse. Therefore clopyralid is unlikely to pose a carcinogenic hazard to humans. (Level 2, Section 2.6.5)
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.	n/a	n/a	Not applicable. Clopyralid is not classified or proposed for classification for carcinogenicity.

Impact on human health – proposed reproductive toxicity classification				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive 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.**		N	The two-generation toxicity study is considered as supportive only because of the deviations, e.g. in the doses. However, the results do not suggest any harm in the fertility of dams or in the offspring and when taking into account the whole toxicological profile of clopyralid, a potential of reproductive toxicity is unlikely. In teratogenicity studies, clopyralid did not induce specific malformations or increased the incidence of spontaneous malformations at nonmaternotoxic dose level in rat. The observed malformations (polydactyly and hemivertebra) at maternotoxic dose level were considered incidental. In rabbits, increased incidence of resorptions, malformations and alterations were seen at maternotoxic dose level. The observed maternal toxicity i.e. morbidity, clinical signs, gastric lesions, reductions in body weight and body weight gain may have caused the observed malformations and resorptions. Potential of teratogenicity is unlikely. (Level 2, Section 2.6.6)
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.	n/a	n/a	Not applicable. Clopyralid is not classified or proposed for classification as toxic for reproduction category 1A or 1B.
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**		N	Clopyralid is not classified or proposed for classification as carcinogenic category 2 and toxic for reproduction category 2. It does not fulfill the interim criteria for endocrine disruptive criteria. (Level 2, Section 2.6.8)

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**		N	Clopyralid is not classified or proposed for classification as toxic for reproduction category 2. It has not been shown beyond any doubt that clopyralid has toxic effects on endocrine organs. It does not fulfill the interim criteria for endocrine disruptive criteria. (Level 2, Section 2.6.8)
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.	n/a	n/a	Not applicable. Clopyralid is not classified or proposed for classification as carcinogenic category 2 and toxic for reproduction category 2. It has not been shown beyond any doubt that clopyralid has toxic effects on endocrine organs. It does not fulfill the interim criteria for endocrine disruptive criteria.
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.		N	
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.		N	
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.		N	

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.	Y		In the terrestrial vertebrate risk assessment, all TER_A and TER_{LT} values are in excess of their corresponding Annex VI triggers, indicating acceptable acute and long term risks to birds and mammals after application of GF-1374 at rates up to 120 g a.s./ha on grassland and 80 g a.s./ha on cereals. Based on the FOCUS STEP 1-2 PECsw and PECsed values, the acute and long-term are acceptable to fish, aquatic invertebrates, sediment-dwellers and algae from the use of clopyralid (applied as GF-1374) to cereals and pasture with one application per year at rates up to 1.5 L formulation/ha on pasture and 1.0 L formulation/ha on cereals. No risk mitigation measures beyond 1 m buffer are necessary to protect the aquatic organisms, if the product GF-1374 is used according to these GAPs. Clopyralid is an herbicide with no known insecticidal properties and it exhibits low acute oral and contact toxicity to honey bees. The HQ values for acute oral and contact exposure, calculated in accordance with the guidance of SANCO/10329/202 rev 2 final, are both below the trigger value of 50. However, because no studies on the effects of clopyralid on honey bee development and other life stages were submitted according to current data requirements, the risk assessment on pollinating insects is inconclusive for the time being, and a data gap is identified. The proposed use of clopyralid on pasture and cereal crops, in accordance with Good Agricultural Practice, will present no unacceptable acute risk to other non-target arthropods. Acceptable risk of acute and long term toxicity for earthworms and soil macro-organisms at an application rate of 120 g clopyralid/ha on pasture and 0.80 kg clopyralid/ha on cereals was calculated. The risk to soil micro-organisms is negligible for applications up to 1.5 L/ha to pasture and 1.0 L/ha to cereals. A low risk to terrestrial non-target plants was identified for clopyralid after applications of GF-1374 at rates up to 1.5 L product/ha on pasture and amenity grassland with the use of a 1m buffer zone with 75% drift reducing

				nozzles or 5 m buffer zone from the edge of the field during applications based on probabilistic assessment. Based on these results, the risks to terrestrial plants from GF-1374 applications to pasture and amenity grasslands are considered acceptable with appropriate risk mitigation measures and if the GAP is assumed. No other uses in addition to the representative uses of the formulation GF-1374 on cereals and grassland have been considered in the risk assessment.
	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.		N	
	Linked to the consideration of the endocrine properties immediately 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.	Y		
	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.			Due to insufficient data available, the chronic and sub-lethal risk assessment on honeybee development and colony survival is inconclusive for the time being. Data gap is identified and further data according to regulations 283/2013 and 284/2013 are required.
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.		No	The residue definition is clopyralid only in all environmental compartments. No degradation products are formed. **Food of plant origin:** the plant residue definition for risk assessment is sum of clopyralid, its salts and conjugates, expressed as clopyralid.

				NOTE: Rotational crops studies revealed an unidentified metabolite in wheat grain, which may have an impact on the residue definitions. the plant and animal residue definitions for monitoring is clopyralid, its salts and conjugates, expressed as clopyralid. **Food of animal origin:** the animal residue definitions for monitoring is clopyralid, its salts and conjugates, expressed as clopyralid.
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.	Y		The PECgw values are below the trigger of <0.1 µg/L in most European scenarios, thus indicating that safe uses of clopyralid can be identified. In certain vulnerable conditions and use patterns, appropriate risk mitigation may be applied at Member State level, as for instance restricting the yearly use to seasons with least vulnerable soil hydrological conditions or bi-annual or tri-annual applications.

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		N	

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.		N	

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				
3.1.4.2. Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
Only limited or no validation data has been presented for solubility in water and in organic solvents, partition coefficient logK_{ow} as well as dissociation constant.	relevant for all uses	X		
3.1.4.3. Data on uses and efficacy				
3.1.4.4. Data on handling, storage, transport, packaging and labelling				

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**
3.1.4.5. Methods of analysis				
The provided analytical method for the determination of the active substance in technical material is not acceptably validated, because a confirmatory method is missing.	relevant for all uses	X		
Some methods for risk assessment of plants and of food of animal origin have not been acceptably validated.	relevant for all uses	X		
Body fluids: the method given is not acceptably validated for body fluids (blood and urine), **Body tissues**: no method has been given.	For the new data requirements this method is always required.	X		
3.1.4.6. Toxicology and metabolism				
3.1.4.7. Residue data				
The residue definition for monitoring of plant derived edible commodities has been changed to include clopyralid, its salts and conjugates.	Risk assessment. Enforcement methods. MRL setting.	X		

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
The presence of an unknown metabolite in rotational wheat grain should be clarified for its structure and potential toxicity.	Residue definitions	X		
3.1.4.8. Environmental fate and behaviour				
In January 2017 the Dow AgroSciences informed the RMS about two new field dissipation studies in Markgröningen, Germany, and Meauzac, S-France, for which the final study reports are expected in March, 2017, and offered to update the risk assessments accordingly. The two new trials consolidate the existing data package. After consultation with EFSA, the RMS could not postpone submitting the dRAR in order to include these sites in the kinetic evaluation of soil dissipation studies at this stage, but recognized that further data exists, which should be taken into account later, for which an appropriate evaluation period has to be ensured.	Relevant data concerning the both uses of the representative formulation GF-1374 on cereals and grassland.			Ahrens, C. and Kröger, F. 2017: Field soil dissipation study with one spring application of GF-1966 (Clopyralid) at one site in North EU and one site in South EU to bare soil in 2016 – 2017. DAS Study ID 160394
3.1.4.9. Ecotoxicology				
Further studies on sub-lethal effects on pollinating insects, to honey bee development and other honeybee life stages, according to current data requirement regulations 283/2013 and 284/2013, are required.	Relevant data concerning the both uses of the representative formulation GF-1374 on cereals and grassland.	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)
Risk assessment according to the new guidance on pollinating insects is inconclusive due to the data gaps identified.	Data is relevant for both supported uses of the representative formulation GF-1374 on cereals and grassland.
Kinetic evaluation of soil dissipation studies should be updated to include the two new field trial sites in Europe (Ahrens & Kröger 2017). Consequently, the updates of environmental fate and ecotoxicological risk assessments are necessary.	Data is relevant for both supported uses of the representative formulation GF-1374 on cereals and grassland.
Clastogenicity and aneugenicity of clopyralid has not been excluded.	ADI and AOEL are not applicable until the question of mutagenicity is solved.
Skin sensitization properties could not be concluded because of the adequate data is lacking.	Relevant for all uses.
Phototoxicity could not be concluded because of the adequate data is lacking.	Relevant for all uses.

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)
	[specify if concern relates to all or specific representative use/use scenario/product or to all uses/products]

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" (cereals)	Use "B" (grassland)
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		
	Assessment not finalised		
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised	x	x
Risk to aquatic organisms	Risk identified		
	Assessment not finalised		
Groundwater exposure active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure metabolites	Legal parametric value breached		
	Parametric value of 10µg/L[(a)] breached		
	Assessment not finalised		
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 organise a consultation of experts on the following parts of the assessment report:

Area(s) where expert consultation is considered necessary	**Justification**
	[specify the reasons why expert consultation is considered necessary]

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**

3.2. PROPOSED DECISION

It is proposed that:

[redacted]

3.3. RATIONAL FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPORVAL 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

Volume 3 – B1: Identity

None

Volume 3 - B2: Physicochemical properties

None

Volume 3 - B5: Analytical methods

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)

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)

Guidance document on pesticide residue analytical methods
(SANCO/825/00 rev. 8.1)

Volume 3 - B6: Toxicology and metabolism of the active substance

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

EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665

Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labeling and packaging (CLP) of substances and mixtures. Version 4.1, June 2015.

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

EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

Volume 3 - B7: Residues

EC (European Commission), 2011. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs; 7525/VI/95-rev.9

EFSA (2011). 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

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

OECD Guidance Document 502 Metabolism in Rotational Crops

OECD Guidance Document 503 for Metabolism in Livestock (Issued 8 January 2007)

OECD Guidance Document on Residues in Livestock (Series on Pesticides No. 73, ENV/JM/MONO(2013)8, 10-Jul-2013).

OECD Guidance Document: Overview for Residue Chemistry Studies (As Revised in 2009), OECD Guidelines for the Testing of Chemicals, No. 505: Residues in Livestock (2007),

OECD 506, EC Guideline 1607/VI/97 rev.2, Appendix H 7032/VI/95 rev.5

OECD Guidance Document 506: Stability of Pesticide Residues in Stored Commodities

EC Guideline 1607/VI/97 rev.2, Appendix H 7032/VI/95 rev.5

OECD Guidance Document 507 : Nature of the Pesticide Residues in Processed Commodities - High Temperature Hydrolysis

Guidance Document 508 : Magnitude of the Pesticide Residues in Processed Commodities

Guidance Document 5089: Crop Field Trial

OECD Environment, Health and Safety Publications Series on Testing and Assessment
No. 63 and Series on Pesticides No. 31 GUIDANCE DOCUMENT ON THE DEFINITION OF RESIDUE (AS REVISED IN 2009)

OECD (Organisation for Economic Co-operation and Development), 2011; OECD MRL Calculator:User Guide. In: Series on Pesticides No 56. ENV/JM/MONO(2011)2, 01 March 2011.

H. Bleiholder E. Weber, M. Hess, H. Wicke, T. van den Boom, P. D. Lancashire, L. Buhr, H. Hack, R. Klose, R. Stauss, and R. Stauss Uwe Meier (editor). BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4

Volume 3 - B8: Environmental Fate and Behaviour

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 (2009). 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 1, 604 pp.

FOCUS (2003) FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC. Report prepared by the FOCUS Working Group on Surface Water Scenarios. SANCO/4802/2001-rev.2 final (May 2003).

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 v2.0. 169 pp.

EFSA (2011). 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.

Volume 3 - B9: Ecotoxicology

Risk Assessment for Birds and Mammals, EFSA Journal 2009;7(12):1438
Guidance Document on Aquatic Ecotoxicology in the context of the Directive 91/414/EEC, SANCO/3268/2001 rev. 4 (final), 17 October 2002.
Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290.
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

Candolfi et al., 2000, Guidance Document on Regulatory Testing and Risk Assessment Procedures for Plant Protection Products with Non-Target Arthropods, ESCORT 2 SETAC Workshop

Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/141/EEC, SANCO/10329/2002, 17 October 2002 rev. 2 final

EFSA (2011). 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

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

Volume 4 Annex C:

Guidance document on the assessment of the equivalence of technical materials of substances regulated under regulation (EC) No 1107/2009 (SANCO/10597/2003 –rev. 10)
Guidance document on significant and non-significant changes of the chemical composition of authorised plant protection products under Regulation (EC) No 1107/2009 of the EU Parliament and Council on placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.
(SANCO/12638/2011 20 November 2012 rev. 2)

3.5. REFERENCE LIST

No references specifically cited in Volume 1.