CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance clopyralid

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Finland, and co-rapporteur Member State, Poland, for the pesticide active substance clopyralid are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of clopyralid as a herbicide on winter cereals and grassland. The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: clopyralid, peer review, risk assessment, pesticide, herbicide

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Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Clopyralid is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), Finland, and co-rapporteur Member State (co-RMS), Poland, received an application from Dow AgroSciences S.A.S. for the renewal of approval of the active substance clopyralid. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Poland), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on clopyralid in the renewal assessment report (RAR), which was received by EFSA on 31 May 2017. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Dow AgroSciences S.A.S., for comments on 23 August 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 24 October 2017.

Following consideration of the comments received on the RAR, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether clopyralid can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of clopyralid as a herbicide on winter cereals and grassland, as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

Data were submitted to conclude that the use of clopyralid according to the representative uses proposed at the European Union (EU) level results in a sufficient herbicidal efficacy against the target weeds.

In the area of identity, physical/chemical properties and analytical methods, data gaps were identified for description and validation data for the analytical method used in the developmental toxicity study in rats, validation data for the methods used in water solubility, solubility in organic solvents and octanol/water partition coefficient studies and for verification of the efficiency of the extraction procedures used in the monitoring method for animal products.

In the mammalian toxicology area, data gaps were identified for the analytical method used in the developmental toxicity study in rat (key study to set the acceptable operator exposure level (AOEL)), for an assessment of the toxicological relevance of the impurities present in the technical specification, and to address the skin sensitisation potential of the active substance and representative formulation. Accordingly, the assessment of developmental toxicity in rat could not be finalised and a critical area of concern was identified since the technical material specification proposed was not comparable to the testing material used to derive the toxicological reference values.

In the residue area, clarification is sought on the nature of the 'unknown metabolite B' in the plant metabolism studies and whether it is identical with the 'polar form of clopyralid' and 'clopyralid conjugate'. Rotational crop field trials according to current guidelines should be submitted. Data need to be provided to exclude that pollen/nectar collection by bees might occur in order to exclude potential residues in pollen and bee products for human consumption. The consumer risk assessment as well as the livestock exposure assessment is pending the transparent evaluation of the residue trials data for grass and cereals.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses, with the notable exception that information is missing regarding the effect of the water treatment process chlorination on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. Consequently, the consumer risk assessment from the consumption of drinking water could not be finalised. The potential for groundwater exposure by the active substance clopyralid above the parametric drinking water limit of 0.1 μg/L consequent to the uses assessed, was indicated to be high in up to six out of nine FOCUS groundwater scenarios for the representative use on winter cereals and up to three out of nine of these scenarios for the representative use on grassland.

The risk to birds and mammals, bees, non-target arthropods other than bees, soil dwelling macro-fauna other than earthworms, soil micro-organisms and biological methods of sewage treatment was assessed as low. The risk to aquatic organisms, earthworms and non-target plants was assessed as low for exposure to clopyralid, but needs to be further assessed at Member State level for the formulation.

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Background

Commission Implementing Regulation (EU) No 844/2012[1] (hereinafter referred to as 'the Regulation') lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009[2]. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of an additional 3 months where additional information is required to be submitted by the applicant in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS Finland and co-RMS Poland received an application from Dow AgroSciences S.A.S. for the renewal of approval of the active substance clopyralid. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Poland), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on clopyralid in the RAR, which was received by EFSA on 31 May 2017 (Finland, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Dow AgroSciences S.A.S., for consultation and comments on 23 August 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 24 October 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 11 December 2017. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in June–July 2018.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative uses of clopyralid as a herbicide on winter cereals and grassland, as proposed by the applicant. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2018), which is a compilation of the documentation developed to evaluate and address all issues raised in the

[1] Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

[2] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (11 December 2017);
- the evaluation table (5 July 2018);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Finland, 2018), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Clopyralid is the ISO common name for 3,6-dichloropyridine-2-carboxylic acid or 3,6-dichloropicolinic acid (IUPAC).

The representative formulated product for the evaluation was 'GF-1374', an emulsifiable concentrate (EC) containing 80 g/L clopyralid, 2.5 g/L florasulam and 144.1 g/L fluroxypyr-meptyl (equivalent to 100 g/L fluroxypyr).

The representative uses evaluated were broadcast foliar spray against broad leaf weed species such as *Circium arvensis*, *Scenecio vulgaris*, *Matricaria chamomilla* and *Matricaria inodorum* in winter cereals and grass. Full details of the good agricultural practices (GAPs) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the uses of clopyralid according to the representative uses proposed at EU level result in a sufficient herbicidal efficacy against the target weeds, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b)

Conclusions of the evaluation

1. Identity, physical/chemical/technical properties and methods of analysis

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

The proposed new reference specification for clopyralid is based on batch data from industrial plant and quality control (QC) data. The proposed minimum purity of the technical material is 950 g/kg. It should be noted that the evaluation of the relevance of the impurities is not finalised (see Section 2). The batches used in the toxicological assessment support neither the original nor the proposed new reference specification (See Section 2). There is no FAO specification available for clopyralid.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of clopyralid or the representative formulations. The main data regarding the identity of clopyralid and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. However, data gaps for description and validation data for the analytical method used in developmental toxicity study in rats and for validation data for the methods used in water solubility, solubility in organic solvents and octanol/water partition coefficient studies were identified. Methods of analysis are available for the determination of the active substance in the technical material and in the representative formulation and for the determination of the respective impurities in the technical material.

Clopyralid, its salts and conjugates can be monitored in food and feed of plant origin by liquid chromatography with tandem mass spectrometry (LC–MS/MS) with a limit of quantification (LOQ) of

0.01 mg/kg in each commodity group. Residues of clopyralid and its salts in food of animal origin can be determined by LC–MS/MS with a LOQ of 0.01 mg/kg in all animal matrices. However, it should be noted that the efficiency of the extraction procedures used in this method was not verified. In addition, there is a validated multiresidue quick, easy, cheap, effective and safe (QuEChERS) method using LC–MS/MS which can be used for monitoring of the clopyralid residues in high water and high acid content plant commodities and fat and milk with a LOQ of 0.01 mg/kg. It should be noted that also for this method efficiency of the extraction procedures used for animal products was not verified, therefore a data gap has been identified.

Clopyralid residues in environmental matrices can be monitored by LC–MS/MS with LOQs 0.5 μg/kg in soil, 0.05 μg/L in water and 4.5 μg/m^3 in air.

The LC-MS/MS method can be used for monitoring of clopyralid residues in body fluids (urine and blood) with a LOQ of 0.05 mg/L. Clopyralid residues in body tissues can be determined by using the monitoring methods for residues in food of animal origin.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on dermal absorption (EFSA PPR Panel, 2012) and Guidance on the Application of the CLP Criteria (ECHA, 2017).

Clopyralid was discussed at the Pesticides Peer Review Experts' Meeting 175 in April 2018.

The technical specifications (either the current one or the one newly proposed during the peer review) are not supported by the batches used in the toxicological studies; it was, however, noted that the newly proposed technical specification raises less concern since lower levels of impurities are specified. The toxicity of some individual impurities in comparison with the toxicological profile of the parent compound has not been fully addressed and therefore a data gap has been identified to address the relevance of the impurities present in the technical specifications. Since the technical material specification proposed was not comparable to the testing material used to derive the toxicological reference values and the presence of relevant impurities could not be excluded, a critical area of concern was raised. The analytical methods used in the toxicological studies were considered fit-for-purpose for most relevant studies, except for the developmental toxicity study in rats (data gap), this was considered an issue that could not be finalised since the study was used to set the acceptable operator exposure level (AOEL).

Clopyralid is extensively absorbed after oral administration, rapidly eliminated mostly through urine within 48 h and is largely excreted as parent material. The residue definition for body fluids and tissues is therefore set as the parent compound alone. No unique human metabolites were observed.

Low acute toxicity was observed when clopyralid is administered by the oral, dermal or inhalation routes; no skin irritation was observed after single application of the substance, but clopyralid caused epidermal hyperplasia and inflammation of the dermis at all dose levels (lowest observed adverse effect level (LOAEL) 100 mg/kg body weight (bw) per day) in a 21-day dermal toxicity study in rabbits and caused marked irritation to eyes of rabbit. Accordingly, classification as Skin Irrit. 2, H315 'causes skin irritation' according to Regulation (EU) No 1272/2008[3] was proposed by the peer review,[4] in addition to the harmonised classification as Eye Dam. 1, H318 'causes serious eye damage'. It was not possible to conclude on the skin sensitisation potential of the active substance and representative formulation due to limitations identified in the two studies provided and equivocal sensitisation potential seen in one of them (data gap). No phototoxicity study was provided. The phototoxicity (and photogenotoxicity) of the substance needs to be investigated according to the UV/VIS absorption of the substance (data gap); however, since absorption occurs below 313 nm, it is acknowledged that there is no validated test guideline to address this requirement.

In short-term dietary studies, the main critical effects were attributed to the irritant properties of the substance such as stomach lesions (rats and rabbits); other target organs included the liver (in mice and dogs) and kidneys (rats). The relevant short-term no observed adverse effect level (NOAEL) is 100 mg/kg bw per day from the 1-year study in dogs, based on haematological effects and

[3] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.

[4] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

increased liver weight. Clopyralid did not present genotoxic potential *in vitro* and no evidence of clastogenicity and aneugenicity was found in *in vitro* or *in vivo* tests. The relevant long-term NOAEL is 15 mg/kg bw per day from the 2-year study in rats, based on lesions of the gastric limiting ridge at 150 mg/kg bw per day. No evidence of carcinogenicity was observed in either rats or mice.

The two-generation reproductive toxicity study in rat raised concerns due to deviations from the test guidelines, such as reduction of the dose levels during the course of the study and lack of analysis or reporting of a number of parameters.[5] However, considering the toxicological profile of the substance (irritant properties leading to gastric lesions), the majority of the experts considered that the study should not be repeated. The RMS re-assessed the study in agreement with the discussion held during the experts' consultation and presented a worst case approach with regards to the dose levels administered. The resulting parental NOAEL was reconsidered by the RMS to be 825 mg/kg bw per day (the highest dose) based on no clear parental systemic effects: the reduction in parental body weight was statistically significant but less than 10% compared to control; only for high dose P1 females body weight gain was reduced by 12% compared to control animals. The NOAEL for the offspring is 275 mg/kg bw per day (equivalent to the mid dose) based on slight reductions in F1 organ weights (heart, kidney, ovaries) and reduced terminal body weight of F1b males (as concluded during the experts' consultation). The reproductive NOAEL is 825 mg/kg bw per day (high dose) based on no effects on reproductive parameters (also in line with the conclusion of the experts). In EFSA's view, the parental NOAEL should remain as was concluded by the experts at the mid-dose level since the reduction of body weight was above 10% for P1 females, but this does not have an impact on the overall risk assessment.

The maternal NOAEL of the developmental toxicity study in rat is 15 mg/kg bw per day based on decreased maternal body weight gain; the developmental NOAEL is 75 mg/kg bw per day based on malformations (hemivertebrae and polydactyly) observed at the high dose. In rabbits, the maternal and developmental LOAEL is 50 mg/kg bw per day based on early reduction of maternal body weight gain, and reduced fetal body weight and delayed ossification observed at all dose levels; at higher dose levels, malformations were also seen in rabbits (hydrocephaly and forelimb flexure). The experts considered that classification as Repr. 2, H361d 'suspected of damaging the unborn child' may be appropriate, based on the malformations observed in rat and rabbit. The basis for no classification with regard to the developmental toxicity in the Annex VI of Regulation (EC) No 1272/2008 is unknown to EFSA. Based on the mortality observed in dams in the developmental toxicity studies in rat and rabbit at 250 mg/kg bw per day, classification as STOT RE 2, H373 'may cause damage to organs through prolonged or repeated exposure' may also be applicable.

Clopyralid is proposed to be classified by the peer review as toxic for reproduction category 2 in accordance with the provisions of Regulation (EC) No 1272/2008, and no toxic effects on endocrine organs have been observed in the available data. On this basis, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine-disrupting (ED) properties would not be met. As discussed by the experts during the peer review meeting 175, despite weaknesses of the database it was considered that clopyralid is unlikely to have endocrine mediated adverse effects since typically endocrine organs are not target of the active substance. There was no evidence of neurotoxic or immunotoxic effects induced by clopyralid administration in the studies provided.

The acceptable daily intake (ADI) of clopyralid is 0.15 mg/kg bw per day[6] based on the NOAEL of 15 mg/kg bw per day for stomach lesions from the 2-year rat study and applying an uncertainty factor (UF) of 100. The AOEL is 0.15 mg/kg bw per day[7] based on the developmental toxicity study in rat with a maternal NOAEL of 15 mg/kg bw per day for reduced maternal body weight gain, applying an UF of 100; no correction for oral absorption is needed. The acute acceptable operator exposure level (AAOEL) and acute reference dose (ARfD)[8] are 0.17 mg/kg bw per day based on the developmental toxicity study in rabbits with a maternal LOAEL at 50 mg/kg bw per day based on early reduction of maternal body weight and an additional UF of 3 (total 300) applied due to the basis of a LOAEL.

Regarding the formulation 'GF-1374' (an EC formulation containing 80 g clopyralid/L, 2.5 g florasulam/L and 144.1 g fluroxypyr-meptyl/L), a combined exposure to the three active substances

[5] See experts' consultation 2.9 of the report Pesticides Peer Review 175_04 Clopyralid (EFSA, 2018).
[6] No changes of the ADI value with regards to the previous review (EFSA, 2006 and European Commission, 2006).
[7] The previously set AOEL was 1 mg/kg bw per day based on the 1-year dog study (EFSA, 2006 and European Commission, 2006).
[8] ARfD previously not allocated (EFSA, 2006 and European Commission, 2006).

has been calculated as the sum of the component exposures (as percentage of the respective AOELs) without regard to the mode of action or target of toxicity considered as a first Tier estimate (Northern Zone, 2018). In the absence of a dermal absorption study with the representative formulation, the default dermal absorption values of 25% for the concentrate and 75% for all dilutions are applicable according to the Guidance on Dermal Absorption (EFSA PPR Panel, 2012).

Considering exposure to clopyralid alone, according to the UK POEM, German model and EFSA calculator, operators have to use personal protective equipment (PPE) such as gloves and work wear during mixing, loading and application to ensure that the (A)AOEL is not exceeded. According to the EUROPOEM II model and the EFSA calculator, the exposure estimates for workers inspecting treated crops (without PPE) are below the AOEL. Bystander and residents' exposure is estimated to remain below the (A)AOEL according to either the EUROPOEM II model or the EFSA calculator. Cumulative exposure to the three active substances in the formulation indicate the need for operators to use PPE (as indicated from exposure to clopyralid alone) to ensure that the sum of exposure does not exceed 100% of the AOELs, according to the German model and EFSA calculator. Worker, bystander and resident's cumulative exposure to the three active substances does not exceed 100% of the AOELs (even when no PPE are considered in the case of workers). An acute cumulative exposure risk assessment is not needed for 'GF-1374' since the setting of an AAOEL would not be required for florasulam and fluroxypyr-meptyl.

3. Residues

The assessment in the residue section is based on the OECD guidance document on overview of residue chemistry studies (OECD, 2009), the OECD publication on MRL calculations (OECD, 2011), the European Commission guideline document on MRL setting (European Commission, 2011) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

Clopyralid was discussed at the Pesticides Peer Review Experts' Meeting 176 in April 2018.

Three Good Laboratory Practice (GLP) and guideline-compliant metabolism studies with foliar application of ^{14}C clopyralid are available for root crop, leafy vegetable and pulses/oilseeds.

The extraction with caustic methanol employed in the cabbage study has led to cleavage of the conjugates and resulted in the presence of free clopyralid at maturity up to 92% and 99% total radioactive residue (TRR) in head and wrapper leaves, respectively. In the studies with oilseed rape and sugar beet, a first extraction was performed with acetonitrile/water and followed with a caustic extraction allowing for investigation of the presence of eventual conjugates. In sugar beet, clopyralid was initially the major residue in the plant (97% TRR at day 0 and 85% TRR at day 28). At maturity, it decreased to 51% TRR in the shoot and to 58% TRR in the root. A 'polar form of clopyralid' was observed in shoots and roots up to 37% TRR and 39% TRR, respectively, but only in the mature plant parts. In oilseed rape clopyralid was present at 63% TRR in immature plant and at 32% and 43% TRR in mature straw and seed, respectively. A 'polar form of clopyralid' was reported to 32% and 28% TRR in mature straw and seed, respectively and an unknown metabolite B also referred to as 'clopyralid conjugates' to 29% and 18% TRR in mature straw and seed, respectively. From the analytical protocol it can be assumed that the 'polar clopyralid' refers to the protonated form (clopyralid acid). However, a confirmation that the observed results in the different metabolism studies are consistent with the analytical conditions (pH) used and an explanation why in mature samples of sugar beet and oilseed rape 'polar clopyralid' and clopyralid were observed while 'polar clopyralid' was not observed in immature samples as the analytical procedure used was always the same within one study is outstanding (data gap). A clarification is also needed whether the term 'polar clopyralid' is referring always to a single structure (and not different polar compounds) and that this structure of 'polar clopyralid' is identical across all metabolism studies where it has been identified (data gap).

Residue trials were conducted and presented for all representative uses and it seems that a sufficient number of valid trials for grass, barley and wheat for each zone is available. However, the reporting of the trials in the RAR in an inconsistent manner renders a transparent risk assessment not feasible (data gap). During the commenting period on the draft conclusion, the RMS has presented an updated RAR in which the field trials were re-evaluated and new values for highest residue and supervised trials median residue were calculated. However, it is still not clear on which basis the RMS has rejected the application of the proportionality principle to the field trials. EFSA therefore reiterates its request for a transparent presentation of the residue trials data for grass, barley and wheat for each zone.

Storage stability data for cereals (grain and forage/fodder), grass, olives, oilseeds and oranges are available. It seems that most of the residue trials were performed within periods covered by storage stability data.[9]

Three nature of residues studies in three rotational crops covering the plant-back interval (PBI) of ca 30, 120 and 365 days are available. Only in the most recent study covering PBI of 30 days, identification of residues was performed and besides the parent only conjugated clopyralid is found in wheat, cabbage and radish. As residues in rotational crops cannot be excluded based on the available data, rotational crop field trials according to current guidelines should be submitted (data gap).

Clopyralid proved to be stable under pasteurisation, baking, brewing, boiling and sterilisation conditions. Processing factors have been established. Validity is pending the evaluation of the underlying residue field trials.

Although the metabolism studies are not performed with crop groups covering the representative uses in cereals and grass, they are sufficient to derive a general residue definition for primary and rotational crops for risk assessment and monitoring as 'clopyralid common moiety (sum of clopyralid, its salts and conjugates expressed as clopyralid)' – pending the outstanding clarification on the nature of 'polar clopyralid'.

Metabolism studies both for ruminants and poultry are submitted indicating that conjugation is the major pathway; however, significant amounts of glycine conjugates were only found in milk. The conversion factor of 1.3 for monitoring to risk assessment is only relevant for milk and is based on the new ruminant metabolism study.

The residue definition in products of animal origin for risk assessment is proposed as 'clopyralid common moiety (sum of clopyralid, its salts and glycine conjugates expressed as clopyralid)' and 'clopyralid and its salts' for monitoring. The plateau in eggs was reached at ca 7 days and in milk at day 1.

GLP- and guideline-compliant feeding studies with poultry and cattle analysing for all compounds covered by the residue definition for risk assessment and within a time period covered by storage stability data were presented. Residues in poultry matrices at the highest dose group at sampling day 28 were highest in eggs (up to 0.046 mg/kg), followed by liver (up to 0.034 mg/kg) and muscle (up to 0.017 mg/kg), whereas very little residue were quantified in fat (0.005 mg/kg). Residues in cow's milk were in the highest dosing group already at day 2 (up to 0.0175 mg/kg) and remained at this level. Residue levels at the highest dose group were observed also in all other organs (up to 0.484 mg/kg in muscle, up to 1.962 mg/kg in liver, up to 25.3 mg/kg in kidney and up to 2.131 mg/kg in average fat).

Data need to be provided to exclude that pollen/nectar collection by bees might occur in order to exclude potential residues in pollen and bee products for human consumption (data gap).

The consumer risk assessment could not be performed and is awaiting the outcome of the evaluation of the residue trial data for grass and cereals which will impact the animal dietary burden calculation and the exposure assessment. Also, information on residues resulting from water treatment processes is missing and results in the consumer risk assessment not being finalised (see Sections 4 and 9).

4. Environmental fate and behaviour

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, clopyralid exhibited low to medium persistence, forming no metabolites at levels triggering identification or further assessment (i.e. all chromatographically resolved radiolabelled components accounted for < 5% applied radioactivity (AR)). Mineralisation of the 2,6-pyridinyl ^{14}C radiolabel to carbon dioxide accounted for 47–70% AR after 90–92 days. The formation of unextractable residues (not extracted by sequential use of aqueous calcium chloride followed by acidified acetone and aqueous sodium hydroxide or just acidified acetonitrile) for this radiolabel accounted for 11–35% AR after 90–92 days. In anaerobic soil incubations, clopyralid was essentially stable. Clopyralid exhibited very high mobility in soil. It was concluded that the adsorption of clopyralid was not pH dependent. In satisfactory field dissipation studies carried out at four sites in France, three in Germany, and one each in the UK, Denmark and Spain (spray application to the soil surface on bare soil plots in late spring or in autumn), clopyralid exhibited low to moderate persistence. Field study DegT50 values were derived following normalisation to FOCUS reference conditions (20°C and pF2 soil moisture) following the EFSA (2014) DegT50 guidance. The field data endpoints were not combined with lab values to derive modelling endpoints when following the statistical test specified in this guidance.

[9] See experts' consultation 3.1 in the evaluation table (EFSA, 2018).

In BBA guideline lysimeter studies of 3 years duration where applications were made in the first 2 years, using marginally increased doses compared to the representative uses being assessed here, that were planted with oilseed rape followed by winter wheat or with sugar beet, all chromatographically resolved components in leachate moving below 1 m (on an annual or biennial average basis) accounted for < 0.078 μg/L.

In laboratory incubations in dark aerobic natural sediment water systems, clopyralid exhibited very high persistence, forming no chromatographically resolved metabolites at levels triggering identification or further assessment. The unextractable sediment fraction (not extracted by acetonitrile followed by acidified acetonitrile) was a small sink for the 2,6-pyridinyl ^{14}C radiolabel, accounting for 5% AR at study end (100 days). Mineralisation of this radiolabel accounted for 2–5% AR at the end of the study. Clopyralid was stable under the conditions of a laboratory sterile aqueous photolysis experiment. Surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for clopyralid using the FOCUS (2001) step 1 and step 2 approach (version 3.2 of the Steps 1-2 in FOCUS calculator). Appropriate step 3 (FOCUS, 2001) calculations were also available.[10]

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4.[9] The potential for groundwater exposure from the representative uses by clopyralid above the parametric drinking water limit of 0.1 μg/L (as estimated by annual average recharge concentrations in water moving below 1 m soil depth) was concluded to be high in geoclimatic situations that are represented by varying proportions of the FOCUS groundwater scenarios depending on the month of the year that applications are made in the simulations. For the representative use on winter cereals: with application on 1 February and 1 March, six out of nine FOCUS scenarios were above the parametric drinking water limit. When applications were simulated on 1 April, this reduced to five out of nine. When applications were simulated on 1 May and 1 June, this reduced again to four out of nine FOCUS scenarios being above the parametric drinking water limit. For the representative use on grassland: with application on 1 February, three out of nine FOCUS scenarios were above the parametric drinking water limit. When applications were simulated on 1 March and 1 August this reduced to two out of nine. When applications were simulated on 1 April, May, June and July, no FOCUS scenario was indicated to have concentrations above the parametric drinking water limit.

The applicant provided appropriate information to address the low likelihood of water treatment processes to produce nitrosamine compounds when surface water containing clopyralid is abstracted to produce drinking water (note: conditions of any approval and or product authorisation would need to preclude that groundwater exposure would occur above the parametric drinking water limit). However, the potential for surface water containing clopyralid to form chlorinated transformation products at the disinfection stage of usual water treatment processes was not addressed by the information available. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013), EFSA (2013).

Clopyralid was discussed at the Pesticides Peer Review Experts' teleconference 173 in April 2018.

The acute and long-term risk to **birds and mammals** from oral exposure via residues in food items and contaminated drinking water was assessed as low. No risk assessment for secondary poisoning was triggered because the log P_{ow} is < 3.

The risk to **fish and aquatic invertebrates** was assessed as low for the representative uses. The risk to **algae and aquatic plants** was assessed as low for exposure to the active substance clopyralid alone. However, the studies with the formulation containing also the active substances florasulam and fluroxypyr-meptyl were not considered appropriate for use in the risk assessment due to uncertainty around the exposure in the test system as the concentration of clopyralid in the test systems was not measured. As aquatic plants are the most sensitive group of aquatic organisms, further studies should be provided at Member State level. The study with *Myriophyllum* should be

[10] Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

conducted in accordance with OECD 239 and the root weight and the shoot weight should be measured separately. The content of all three active substances should be measured and fluroxypyr-meptyl and acid should be measured separately. A final conclusion on the risk to the aquatic environment from the formulation can only be drawn after the studies with the formulation and aquatic plants are made available. This should be addressed during product authorisation at Member State level. A section by section coefficient of variation was provided only for some of the algae studies. However, this should be provided for all algae studies which are considered for the risk assessment and hence a data gap was identified.

The acute risk assessment according to European Commission (2002a) resulted in a low acute risk to **honeybees**. A chronic adult honeybee study and a honeybee larvae study were submitted and evaluated by the RMS using EFSA (2013). The acute and chronic risk to adult bees and the risk to larvae were assessed as low. No data were available for bumble bees and solitary bees.

Standard first tier studies with **non-target arthropods** other than bees were available with technical clopyralid but not for the representative formulation 'GF 1374'. The formulation was tested in extended laboratory studies with *Aphidius rhopalosiphi*, *Typhlodromus pyri* and *Chrysoperla carnea*. This approach was considered acceptable as a comprehensive first tier database with technical clopyralid was available. The risk to non-target arthropods was assessed as low for the representative uses.

The risk from clopyralid alone was assessed as low for **earthworms**. However, the available long-term reproduction study with earthworms and the representative formulation was discussed by the experts. Concerns were raised with regard to exposure of earthworms since the product was applied on the soil surface instead of mixing it into the soil as required by Regulation (EU) No 284/2013. This would have led to exposure of earthworms only when they come to the surface for feeding and hence exposure may not be as high as when the substance would have been mixed into the soil. The experts were of the opinion that the study is not appropriate as a first tier study and therefore this needs to be further considered at Member State level.

The risk to **other soil macrofauna** and **soil nitrogen transformation** was assessed as low.

Concerns were raised regarding the reliability of the non-target plant studies as the planting density was higher than what is recommended in the test guideline (OECD 227) which could have led to masking of effects due to competition and also to reduced exposure of individual plants. The planting density was too high especially in the study with the formulation. The experts agreed that no new study with the active substance is needed as the deviation was not as severe as in the study with the formulation. The risk to non-target plants was assessed as low for exposure to the active substance clopyralid alone. A data gap was identified for a new study with non-target plants for the formulation which should be addressed at Member States level. The study should also include tomato as it may be the most sensitive test species for fluroxypyr.

The risk to **biological methods of sewage treatment** was assessed as low.

Based on the information in Section 2, it is unlikely that clopyralid is an endocrine disruptor for mammals. However, further data might be necessary to address the potential endocrine disrupting properties for other vertebrate non-target organisms.

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Clopyralid	Low to medium persistence Single first-order DT_{50} 4.9–64.6 days (20°C pF 2 soil moisture) Field dissipation studies single first-order and biphasic kinetics DT_{50} 0.16–23.7 days (DT_{90} 12.1–78.7 days)	The risk to soil micro-organism and soil dwelling macro-organisms from the active substance clopyralid alone was assessed as low

DT_{50}: period required for 50% dissipation; DT_{90}: period required for 90% dissipation.

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
Clopyralid	Very high mobility K_{Foc} 0.26–4.1 mL/g	Winter cereals: 6/9 FOCUS scenarios application in February and March, 5/9 application in April, 4/9 application in May and June Grassland; 3/9 FOCUS scenarios application in February, 2/9 application in March and August. No exceedances for application in April, May, June and July	Yes	Yes

K_{Foc}: Freundlich organic carbon adsorption coefficient; FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use.
(a): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Clopyralid	The risk to aquatic organisms from the active substance clopyralid alone was assessed as low

Table 4: Air

Compound (name and/or code)	Toxicology
Clopyralid	Rat LC_{50} inhalation > 1.0 mg/L air per 4 h (nose only, highest attainable concentration – no classification required)

LC_{50}: lethal concentration, median.

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- Validation data for the methods used in water solubility, solubility in organic solvents and octanol/water partition coefficient studies (relevant for all representative uses evaluated; submission date proposed by the applicant: end 2018; see Section 1).
- Verification of the efficiency of the extraction procedures used in monitoring methods for animal products (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- An assessment of the toxicological relevance of the individual impurities present in the technical specification in comparison with the toxicity profile of the parent compound (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Analytical method used in the developmental toxicity study in rats (key study in setting the AOEL (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 1 and 2).
- Skin sensitisation potential of the active substance and of the representative formulation (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Phototoxicity and photogenotoxicity potential of the active substance (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; it is acknowledged that there is no validated test guideline available to address these endpoints; see Section 2).
- Clarification on the nature of the 'unknown metabolite B' in the plant metabolism studies and whether it is identical with the 'polar form of clopyralid' and 'clopyralid conjugates'. Furthermore, an explanation why in mature samples of sugar beet and oilseed rape 'polar clopyralid' and clopyralid were observed while 'polar clopyralid' was not observed in immature samples as the analytical procedure used was always the same within one study (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Residue trials were conducted and presented for all representative uses and it seems that a sufficient number of valid trials for grass, barley and wheat for each zone is available. However, the reporting of the trials in the RAR in an inconsistent manner renders a transparent risk assessment not feasible therefore the trials should be re-evaluated and the results reported in a transparent manner (relevant for all representative uses evaluated; submission date proposed by the applicant: not applicable; see Section 3).
- Rotational crop field trials according to current guidelines should be submitted (relevant for representative use on cereals; submission date proposed by the applicant: unknown; see Section 3).
- Data need to be provided to exclude that pollen/nectar collection by bees might occur in order to exclude potential residues in pollen and bee products for human consumption (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Information to address the effect of the water treatment process chlorination on the nature of residues present in surface water, when surface water is abstracted for drinking water regarding potential chlorination reaction products was not available excluding that the formation of nitrosamines was demonstrated to be unlikely. Should any further consideration of this topic indicate novel compounds might be expected to be formed from chlorination, the risk to human or animal health through the consumption of drinking water containing them should be addressed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- A section by section coefficient of variation should be provided for all algae studies (relevant for all representative uses evaluated, submission date proposed by the applicant: unknown, see Section 5).

8. Particular conditions proposed to be taken into account to manage the risk(s) identified

- Operators have to wear PPE to ensure that the AOEL is not exceeded (see Section 2).

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if 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 in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[11] and if 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).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

1) No validated analytical methods were reported for the developmental toxicity study in rats (key study in setting the AOEL) therefore the reliability of the study is questioned and the developmental toxicity endpoint in rat could not be finalised (see Section 2).
2) The consumer risk assessment could not be finalised because residue trials data for grass and cereals were not reported in a transparent manner allowing for the transparent calculation of the animal dietary burden and human exposure (see Section 3).
3) The consumer risk assessment from the consumption of drinking water could not be finalised because satisfactory information was not available to address the effect of the water treatment process chlorination on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (see Section 4).

9.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion 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 if the assessment at the higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion 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 if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

4) The technical material specification proposed was not comparable to the material used in the testing used to derive the toxicological reference values and the presence of relevant impurities could not be excluded (see Section 2).

9.3. Overview 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 Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

[11] Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.

All columns are grey, as the technical material specification proposed was not comparable to the material used in the testing that was used to derive the toxicological reference values.

Table 5: Overview of concerns

Representative use		Winter cereals	Grassland
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Resident/bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised	X[2,3]	X[2,3]
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		
Risk to aquatic organisms	Risk identified		
	Assessment not finalised		
Groundwater exposure to active substance	Legal parametric value breached	6/9 FOCUS scenarios[(a)]	3/9 FOCUS scenarios[(b)]
	Assessment not finalised		
Groundwater exposure to metabolites	Legal parametric value breached		
	Parametric value of 10 µg/L breached		
	Assessment not finalised		

FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use.
Columns are grey if no safe use can be identified. The superscript numbers without parenthesis relate to the numbered points indicated in Section 9.1. Where there is no superscript number, see Sections 2–6 for further information.
(a): 6/9 FOCUS scenarios application in February and March, 5/9 application in April, 4/9 application in May and June.
(b): 3/9 FOCUS scenarios application in February, 2/9 application in March and August. No exceedances for application in April, May, June and July.

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Abbreviations

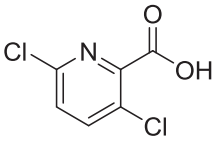
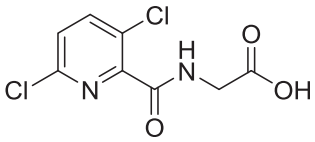
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake

AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
DAR	draft assessment report
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
EC	emulsifiable concentrate, also used for European Commission
ECHA	European Chemicals Agency
ED	endocrine-disrupting
EEC	European Economic Community
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MRL	maximum residue level
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
P_{ow}	partition coefficient between *n*-octanol and water
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
PPE	personal protective equipment
QC	quality control
QuEChERS	quick, easy, cheap, effective and safe
RAR	Renewal Assessment Report
RMS	rapporteur Member State
SMILES	simplified molecular-input line-entry system
TRR	total radioactive residue
UF	uncertainty factor
WHO	World Health Organization

Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5389

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
clopyralid	3,6-dichloropyridine-2-carboxylic acid or 3,6-dichloropicolinic acid O=C(C1=NC(Cl)=CC=C1Cl)O HUBANNPOLNYSAD-UHFFFAOYSA-N	
X36538 **clopyralid glycine conjugate**	*N*-(3,6-dichloropyridine-2-carbonyl)glycine O=C(O)CNC(C1=NC(Cl)=CC=C1Cl)=O QONCEWHCVBAIBS-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ChemBioDraw v. 13.0.2.3021.
(c): ChemBioDraw v. 13.0.2.3021.