CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State Italy for the pesticide active substance propanil and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Regulation (EC) No 1107/2009 of the European Parliament and of the Council. The conclusions were reached on the basis of the evaluation of the representative use of propanil as a herbicide on rice. MRLs were assessed in rice. The reliable endpoints, appropriate for use in regulatory risk assessment and the proposed MRLs, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: propanil, peer review, risk assessment, pesticide, herbicide, maximum residue level

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Summary

Propanil is a new active substance for which, in accordance with Article 7 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council (hereinafter referred to as 'the Regulation'), the rapporteur Member State (RMS), Italy, received an application from United Phosphorus Limited on 28 December 2015 for approval. In accordance with Article 8(1)(g) of the Regulation, United Phosphorus Limited submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 29 February 2016.

The RMS provided its initial evaluation of the dossier on propanil in the draft assessment report (DAR), which was received by the European Food Safety Authority (EFSA) on 14 July 2017. The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 13 September 2017 by dispatching the DAR for consultation to the Member States and the applicant, United Phosphorus Limited.

Following consideration of the comments received on the DAR, 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, environmental fate and behaviour and ecotoxicology.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether propanil can be expected to meet the approval criteria provided for in Article 4 of the Regulation taking into consideration recital (10) of the Regulation and give a reasoned opinion concerning MRL applications, as referred to in Article 10(1) of Regulation (EC) No 396/2005. Furthermore, this conclusion also addresses the assessment required from EFSA under Article 12 of Regulation (EC) No 396/2005, provided the active substance will be approved under Regulation (EC) No 1107/2009 without restrictions affecting the residue assessment.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative use of propanil as a herbicide on rice, as proposed by the applicant. MRL proposals were assessed in rice. Full details of the representative uses and can be found in Appendix A of this report.

The uses of propanil according to the representative uses proposed at the European Union (EU) level result in a sufficient herbicidal efficacy against the target weeds.

A data gap was identified for a search of the scientific peer-reviewed open literature, including the metabolite 3,4-dichloroaniline (3,4-DCA) in the residue section and for further information on the literature review carried out for the ecotoxicology section.

In the area of identity, physical chemical properties and analytical methods, data gaps were identified for data on the self-heating of the Plant Protection Product (PPP), for additional validation data for monitoring methods (pending the decision on the residue definition in food/feed of plant origin), for a monitoring method for food of animal origin, for assessment of the analytical methods used in the dietary toxicological studies for risk assessment and for validation of data generation method in soil.

In the area of mammalian toxicology and non-dietary exposure, data gaps were identified for information on the analytical methods used in all dietary toxicity studies, including the assessment of their validity, characterisation of the toxicokinetics parameters and for data to further investigate the endocrine mode of action for Leydig cell tumours in rats leading to issues that could not be finalised. Data available was not sufficient to conclude on the toxicological profile of the dietary metabolite 3,4-DCA leading to a data gap and issue that could not finalised in the residue area. A data gap for a new gene mutation assay on propanil was set to reduce uncertainty regarding the available gene mutation assays.

In the area of residues, data gaps were set for a sufficient number of residue trials in rice covering the residue definition for risk assessment. In the case that the residue definition for monitoring will be different to that for risk assessment, an additional set of residue trials in rice is needed. The available information is insufficient to propose any MRL for rice. Data on storage stability for the compounds covered by the residue definitions are requested. Furthermore, data on nature of residues in processed commodities and in rotational crops are lacking. Data on residues in pollen and bee products for human consumption need to be provided.

The data available on environmental fate and behaviour were sufficient to carry out the required environmental exposure assessments at EU level for the representative uses. The potential for groundwater exposure above the parametric drinking water limit of 0.1 μg/L by propanil and its metabolites that triggered assessment 3,4-DCA, DCNB and TCAB for these representative uses was assessed as low.

In the area of ecotoxicology, data gaps were identified for further information to address the risk to birds and mammals, aquatic organisms (including amphibians) and soil macroorganisms (Collembola) for both propanil and its metabolite 3,4-DCA. A data gap was set for further information to address sublethal effects on honeybees. Some aspects of the risk assessment for birds and mammals and aquatic organisms could not be finalised. A high risk to birds and mammals from propanil, to soil organisms from propanil and 3,4-DCA was identified for the representative use assessed (critical areas of concern).

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Background

Regulation (EC) No 1107/2009 of the European Parliament and of the Council[1] (hereinafter referred to as 'the Regulation') lays down, *inter alia*, the detailed rules as regards the procedure and conditions for approval of active substances. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States and the applicant(s) for comments on the initial evaluation in the draft assessment report (DAR), provided by the rapporteur Member State (RMS), and the organisation of an expert consultation, where appropriate.

In accordance with Article 12 of the Regulation, EFSA is required to adopt a conclusion on whether an active substance can be expected to meet the approval criteria provided for in Article 4 of the Regulation (also taking into consideration recital (10) of the Regulation) within 120 days from the end of the period provided for the submission of written comments, subject to an extension of 30 days where an expert consultation is necessary, and a further extension of up to 150 days where additional information is required to be submitted by the applicant(s) in accordance with Article 12(3).

Propanil is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, Italy (hereinafter referred to as the 'RMS'), received an application from United Phosphorus Limited on 28 December 2015 for approval of the active substance propanil. A non-approval of propanil had been granted under Commission Implementing Regulation (EU) No 1078/2011[2] after a resubmission application for the inclusion of propanil in Annex I to Directive 91/414/EEC[3] in accordance with the Commission Regulation (EC) No 33/2008[4] following the peer review of the additional data (EFSA, 2011b).

In accordance with Article 8(1)(g) of the Regulation, United Phosphorus Limited submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005.[5] Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 29 February 2016.

The RMS provided its initial evaluation of the dossier on propanil in the DAR, which was received by EFSA on 14 July 2017 (Italy, 2017). The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 13 September 2017 by dispatching the DAR for consultation of the Member States and the applicant, United Phosphorus Limited, for consultation and comments. EFSA also provided comments. In addition, EFSA conducted a public consultation on the DAR. The comments received were collated by EFSA and 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 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 12(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 9 January 2018. 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, environmental fate and behaviour, 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.

[1] 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.

[2] Commission Implementing Regulation (EU) No 1078/2011 of 25 October 2011 concerning the non-approval of the active substance propanil, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 279, 26.10.2011, p. 1–2.

[3] Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1–32. Repealed by Regulation (EC) No 1107/2009.

[4] Commission Regulation (EC) No 33/2008 of 17 January 2008 laying down detailed rules for the application of Council Directive 91/414/EEC as regards a regular and an accelerated procedure for the assessment of active substances which were part of the programme of work referred to in Article 8(2) of that Directive but have not been included into its Annex I. OJ L 15, 18.1.2008, p. 5–12.

[5] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

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 where this took place, were reported in the final column of the evaluation table.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether propanil can be expected to meet the approval criteria provided for in Article 4 of the Regulation, taking into consideration recital (10) of the Regulation, and give a reasoned opinion concerning MRL applications as referred to in Article 10(1) of Regulation (EC) No 396/2005. A final consultation on the conclusions arising from the peer review of the risk assessment and on the MRL assessment took place with Member States via a written procedure in August 2018.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative use of propanil as a herbicide on rice as proposed by the applicant. MRLs were assessed in rice. Furthermore, this conclusion also addresses the assessment required from EFSA under Article 12 of Regulation (EC) No 396/2005, provided the active substance will be approved under Regulation (EC) No 1107/2009 without restrictions affecting the residue assessment. In the event of a non-approval of the active substance or an approval with restrictions that have an impact on the residue assessment, the MRL assessment from this conclusion might no longer be relevant and a new assessment under Article 12 of Regulation (EC) No 396/2005 will be required. A list of the relevant end points for the active substance and the formulation and the MRL assessment 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 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 DAR;
- the reporting table (9 January 2018);
- the evaluation table (4 September 2018);
- the report(s) 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 DAR including its revisions (Italy, 2018) and the peer review report, both documents are considered as background documents to this conclusion.

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

Propanil is the ISO common name for 3′,4′-dichloropropionanilide (IUPAC).

The representative formulated product for the evaluation was 'STAM 480 FLOW', a suspension concentrate (SC) containing 480 g/L propanil.

The representative uses evaluated as herbicide were spray applications to control aquatic weeds in rice in the Southern European zone. Full details of the Good Agricultural Practice (GAP) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the uses of propanil according to the representative uses proposed at EU level result in a sufficient herbicidal efficacy against the target weeds following the guidance document SANCO/10054/2013-rev. 3 (European Commission, 2013).

A data gap has been identified for a search of the scientific peer-reviewed open literature, including the metabolite 3,4-dichloroaniline (3,4-DCA) in the residue section and for further information on the literature review carried out; i.e. a justification for considering the retrieved studies as not relevant, further information on the applied reliability criteria, and the study summaries of the studies considered relevant in the ecotoxicology section reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011a).

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 reference specification for propanil is based on batch data from industrial scale production. The proposed minimum purity of the technical material is 985 g/kg. 2,3-DCA, 3,4-DCA, 3,3′,4,4′-tetrachloroazobenzene (TCAB) and 3,3′,4,4′-tetrachloroazoxybenzene (TCAOB) are considered relevant impurities with maximum limits of 0.5 g/kg, 0.7 g/kg, 2 mg/kg and 0.04 mg/kg, respectively. An FAO Tentative Specification 205/1/ts/5 (205TC/ts/5) under the old procedure is available (AGP:CP/92 Rome, 1980) with a minimum purity of 85%.

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 propanil or the representative formulation. A data gap for data on self-heating of the PPP was identified. The main data regarding the identity of propanil and its physical and chemical properties are given in Appendix A.

Adequate methods were presented for the generation of pre-approval data required for the risk assessment, except the area of human toxicology. A data gap was also identified for a method for the determination of 'total' (base-releasable) 3,4-DCA in soil. Methods of analysis are available for the determination of the active substance in the technical material and formulations. Appropriate methods are available for the quantification of the relevant impurities in the technical material and the representative formulation.

The residue definition for monitoring for food and feed of plant origin was proposed as propanil (by default) or alternatively 'all compounds containing the 3,4-DCA moiety, free and conjugated' (see Section 3). QuEChERS using liquid chromatography with tandem mass spectrometry (LC–MS/MS) with a limit of quantification (LOQ) of 0.013 mg/kg exists for determination of propanil residues in rice grain. Gas chromatography with tandem mass spectrometry (GC–MS/MS) can be used for monitoring of a total 3,4-DCA moiety containing residues in dry commodities with a LOQ of 0.03 mg/kg and in high water content matrices with a LOQ of 0.03 mg/kg. However, it is noted that none of the methods is fully validated as a monitoring method according to SANCO/825/00-rev. 8.1 (European Commission, 2010). Pending the decision on the residue definition for monitoring in food/feed of plant origin, data gaps for both methods were identified and listed in Section 7.

The residue definition for food of animal origin was concluded as propanil (see Section 3), as a consequence a data gap for a monitoring method for determination of residue in animal products was identified.

The residue definition for monitoring in the environmental matrices was defined as propanil and 3,4-DCA. LC–MS/MS methods exist for the determination of propanil and 3,4-DCA in soil, water and air with LOQs of 0.01 mg/kg, 0.1 μg/L and 2 μg/m^3, for each compound, respectively.

LC–MS/MS enforcement methods exist for the determination of residues of propanil and 3,4-DCA by common moiety detection of 3,4-DCA in animal tissues and body fluids with LOQs of 0.1 mg/kg and 0.05 mg/L 3,4-DCA, respectively.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003a), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and Guidance on Dermal Absorption (EFSA PPR Panel, 2012).

Propanil was discussed at the Pesticides Peer Review Experts' Meeting 179 in June 2018.

The previous proposed technical specification is not covered by batches tested in the toxicity studies; however the new specification is covered by the batches tested in the new *in vitro* genotoxicity studies (Italy, 2018, see Table C. 1.2.3-1) lowering the concerns raised by the presence of relevant impurities, it was therefore concluded that the technical specification is supported by the toxicological reference values. Propanil relevant impurities are: 3,4-DCA, 2,3-DCA, TCAB and TCAOB. These impurities are considered not of concern at the levels proposed in the new technical specifications. Information on the analytical methods used in all dietary toxicity studies, including the assessment of their validity was not provided (see Section 1) leading to an issue that could not be finalised.

Propanil was readily and almost completely absorbed (~ 80%), widely distributed and rapidly excreted through urine and faeces. Potential of accumulation was not observed. Propanil is extensively metabolised, primarily to 3,4-dichloroaniline (3,4-DCA), therefore the residue definition for tissues and body fluids should include the parent and this metabolite (3,4-DCA), expressed as 3,4-DCA, for the purpose of human biomonitoring (see also Section 1). No unique human metabolites are expected. Toxicokinetics parameters for propanil and 3,4-DCA are not available and this is considered a data gap.

Propanil showed moderate acute toxicity via oral and inhalation route in rats. Propanil is of low acute dermal toxicity. It is not a skin or eye irritant neither a skin sensitiser. Although not required, a phototoxicity study was provided showing negative results.

In short- and long-term dietary studies, the changes in haematological parameters, specifically related to methaemoglobin levels, are the critical endpoints following oral administration of propanil in the rat, mouse and dog. This effect was in some cases accompanied by histopathological changes (haemosiderosis) in the liver, kidney and spleen. After long-term exposure additional findings in testes, epididymides and prostate were observed in rats (high dose only) and in liver (hepatocyte enlargement) in mouse. The dog is the most sensitive species after short-term exposure, the relevant short-term lowest observable adverse effect level (LOAEL) is $\leq$ 5 mg/kg body weight (bw) per day from the 1-year oral dietary dog study. After long-term exposure the relevant long-term no observed adverse effect level (NOAEL) in mice is 4.39 mg/kg bw per day (2-year mice) and the LOAEL in rats is $\leq$ 9 mg/kg bw per day (2-year rat).

Based on propanil-mediated haematological changes and methaemoglobin formation, occurring rapidly after single exposure, **STOT-SE category 1** (H370: Causes damage to organs) classification is proposed.[6]

The genotoxic potential of propanil was investigated in *in vitro* and *in vivo* test systems. Equivocal result for gene mutation after metabolic activation in *in vitro* mouse lymphoma assay (MLA) was not confirmed in the repeated *in vitro* MLA using a batch compliant with the new proposed technical specification; however, some uncertainty was raised on the acceptability criterion for selection of the top dose in the repeated gene mutation assay. Propanil was negative in *in vivo* studies. Overall, the experts considered that propanil is unlikely to be genotoxic *in vivo* but further data (i.e. new *in vitro* gene mutation assay, MLA, with further testing up to cytotoxicity concentrations) should be provided to reduce the low uncertainty regarding available gene mutation assays (data gap).[7]

The relevant long term NOAEL for carcinogenicity is 9 mg/kg bw per day from the 2-year study in rats based on an increased incidence of Leydig cells tumours observed in males at mid and high dose. Hepatocellular adenomas in rats and lymphomas in mouse were also observed. Considering the different tumours observed in several organs and in two species, the experts proposed to classify propanil for **carcinogenicity category 2; H351** according to the CLP Regulation (EC) 1272/2008[8].

In the reproduction toxicity study, no adverse effects on reproductive parameters were observed. In the two-generation reproductive toxicity study in rat, the NOAEL for parental and offspring toxicity is 11 mg/kg bw per day and the NOAEL for reproductive toxicity is 43 mg/kg bw per day. In the developmental toxicity studies in rat and rabbit, the NOAEL for developmental toxicity is 20 mg/kg bw per day.

The applicant did not submit neurotoxicity studies, however, no potential for neurotoxicity was observed in the standard toxicity studies.

Propanil is proposed to be classified as carcinogen category 2 and is not classified or proposed to be classified as toxic for reproduction category 2. On this basis, in accordance with the provisions of Regulation (EC) No 1272/2008, 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 properties are not met. From the scientific point of view, on the basis of the occurrence of findings in regulatory studies (i.e. Leydig cells tumours and additional findings in testes, epididymis and prostate in rat long-term toxicity study), in endocrine mechanistic studies (positive competitive androgen receptor (AR) binding, weak positive aryl hydrocarbon receptor (AhR) transactivation and hormonal changes in a 28-day rat study) and current knowledge (OECD GD 150 Conceptual Framework, as analysed in the EFSA Scientific Committee, 2013), the experts concluded that propanil has an endocrine-mediated activity (most likely via anti-androgenic properties). The experts set a data gap to

[6] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.
[7] Refer to experts' consultation 2.2 in the Report of Pesticides Peer Review Experts' Meeting 179.
[8] Refer to experts' consultation 2.3 in the Report of Pesticides Peer Review Experts' Meeting 179.

investigate through additional data (e.g. Hershberger assay/*in vitro* tests or adverse outcome pathway (AOP) key events) the mode of action for Leydig cell tumours in order to have a clear-cut conclusion on the link between Leydig cell tumours and endocrine activity leading to a data gap and an issue that could not be finalised.

The acceptable daily intake (**ADI**) of propanil is 0.02 mg/kg bw per day based on the 1-year study in the dog (LOAEL ≤ 5 mg/kg bw per day) applying an uncertainty factor (UF) of 300. The acceptable operator exposure level (**AOEL**) is 0.02 mg/kg bw per day based on the same 1-year study in dog (LOAEL ≤ 5 mg/kg bw per day) applying an UF of 300 and no correction for oral absorption. The acute reference dose (**ARfD**) of propanil is 0.02 mg/kg bw based on the 1-year study in the dog (LOAEL ≤ 5 mg/kg bw per day) applying an UF of 300. During the first peer review of propanil, ARfD value was set at 0.07 mg/kg bw based on the 30-day dog study (EFSA, 2011b). The acute acceptable operator exposure level (**AAOEL**) is 0.02 mg/kg bw based on the same 1-year study in dog (LOAEL ≤ 5 mg/kg bw per day) applying an UF of 300 and no correction for oral absorption.

Based on human skin *in vitro* dermal absorption study, dermal absorption values for propanil in the representative formulation 'Stam 480 Flow' are 2% for the concentrate and 13% for the dilution. Considering the representative uses with 'Stam 480 Flow' as herbicide in rice the estimated operator exposure was below the AOEL (14.81% of the AOEL) with the use of personal protective equipment (PPE: coverall and sturdy footwear during application and gloves during mixing/loading and application) according to the German Model. Worker exposure was below the AOEL (maximum exposure 77.4% of the AOEL for re-entry a drained paddy field, no PPE). Bystander and resident exposure was below the AOEL (maximum 19% of the AOEL; child bystander, according to German model). It is noted that, according to the EFSA calculator, operators have to use PPE (gloves) to ensure that the AOEL and AAOEL is not exceeded. Also according to the EFSA calculator, the highest residents and bystander' exposure is estimated as 98% of the AOEL and 94% of the AAOEL, respectively (for children).

Available information including toxicity studies on the plant **metabolite** 3,4-DCA, a minor rat metabolite, was not sufficient to conclude on its toxicological profile including genotoxicity leading to a data gap and issue that could not be finalised (see Section 3). It is noted that 3,4-DCA is a common metabolite to other active substances (e.g. linuron; EFSA, 2016). According to harmonised classification of 3,4-DCA (Acute Toxicity, Category 3; H301), the metabolite might be considered of higher acute oral toxicity than propanil. There are some indications that the metabolite might have endocrine activity.

3. Residues

Propanil was discussed at the Pesticides Peer Review meeting 180 in June 2018.

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).

Metabolism of propanil was investigated in rice grown in pots, under greenhouse conditions. A soil application of 3,360 g/ha was followed by a foliar application of 3,800 g/ha (total 7N rate) at BBCH 14-15. Significant total radioactive residues (TRRs) were observed at harvest up to 1.218 mg eq/kg in straw, 1.551 mg eq/kg in bran, 0.703 mg eq/kg in hulls and 0.234 mg eq/kg in grain as well as 7.02 mg eq/kg in immature shoots. The major part of the radioactivity remained unextracted in all plants parts (60% TRR in shoots to 90% TRR in grain) and was released upon enzymatic and chemical treatment leading to the conclusion that the bound residues were incorporated into natural products (e.g. starch, lignin, hemicellulose, etc.). The extracted radioactivity (10–35% TRR) was shown to be composed of numerous fractions where three metabolites were identified: 3,4-DCA (found in bran, hull, straw and shoots at levels of 0.3–7% TRR), 3,4-dichloroglucosylamine (found in hull, straw and shoots at levels of ca. 2–4% TRR) and 3,4-dichloroacetanilide (found in straw at levels of ca 2.5%). The remaining compounds were not identified but some of them could converted into 3,4-DCA.

Critical GAP-compliant residue trials were conducted in Italy and Spain. However, some trials were at the same location and are therefore considered as replicates. In total, five residue trials were considered as independent and valid. Samples were analysed for all the compounds containing the 3,4-DCA moiety, free and conjugated. A data gap is identified to complete the residue dataset for rice analysing the residues in compliance with the agreed risk assessment residue definition.

The residue levels expressed as 3,4-DCA found in the field trials were above the trigger of 0.01 mg/kg, but the nature of residues in processed commodities was not investigated with the

argument of the volatility of the substance which is not a valid argument given that most of the residue is bound in the plant matrix (data gap). The magnitude of residues was determined in three studies for effects of industrial processing and/or household preparation on rice grain raw agricultural commodities, but processing factors could not be established. In the first study with 6N application rate, a contamination of control samples occurred and in the other two studies propanil was applied in compliance with the proposed GAP, but the residues of 3,4-DCA in processed commodity were below the LOQ (0.03 mg/kg). A study investigating the magnitude of the residues covered by the residue definition for risk assessment by cooking rice was not presented but might be required should the residues values are above the trigger of 0.1 mg/kg in the outstanding residue trials.

A study investigating uptake from soil and metabolism in the rotational crops grass, soybean and sorghum was presented. ^{14}C-propanil was applied to soil at an exaggerated rate of 6.7 kg a.s./ha (6.7N). At all three crop rotation intervals TRR values above 0.01 mg/kg were found. Highest residues were reported in soybean straw (0.4 mg eq/kg) and sorghum grain (0.3 mg eq/kg) from the first rotation and reached down to 0.04 mg eq/kg in sorghum forage at the third rotation (419 days after treatment (DAT)). Similar to the situation in primary crops most of the residues were bound in the plant matrix and only a small fraction was soluble in organic solvents. However, identification/ characterisation of the residues in cereals (sorghum) as relevant rotational crops in Europe was not performed and a conclusion on a residue definition for rotational crops was not possible (data gap).

Storages stability studies with rice were presented where propanil was spiked to various plant and animal matrices, converted by a caustic hydrolysis step into 3,4-DCA and measured after an extraction step as such. The reporting of the study results in the DAR did not allow to conclude on the stability of propanil (expressed as 3,4-DCA) as results were given only in % recovery (for animal tissues corrected recovery). Therefore, a data gap is set for studies investigating the storage stability for all compounds covered by the residue definition in rice (food and feed commodities) or sufficiently transparent reporting of the presented storage stability data to conclude on the validity and maximum storage stability time in rice.

The residue definition for risk assessment for rice is set as 'All compounds containing the 3,4-DCA moiety free and conjugated'. The experts at the Pesticides Peer Review meeting proposed the decision to set the residue definition for monitoring for rice as propanil or alternatively 'all compounds containing the 3,4-DCA moiety, free and conjugated' be made by risk managers.[9] It was noted that in the framework of the first peer review the residue definition proposed for monitoring (and for risk assessment) was set as 'all compounds containing the common moiety of 3,4-DCA (EFSA, 2011b)'. However, 3,4-DCA is not ideal for the residue definition for monitoring as this is a common metabolite to other substances (e.g. linuron, diuron). However, propanil is not a good marker for monitoring as it will not be present in rice as such except when sampling occurs very soon after any application. In the case that the two residue definitions differ, a data gap for additional residue trials compliant with the critical GAP for the determination of propanil residues according to this residue definition for monitoring would be needed for MRL setting.

The provisional dietary burden calculation with results from the five valid residue field trials triggered a metabolism study in ruminants, which was provided. A metabolism study with hens was also submitted although not triggered for the uses being assessed. Both studies were conducted with propanil whilst exposure to animals will occur in form of compounds containing the 3,4-DCA moiety, free and conjugated. Propanil is extensively metabolised, primarily to 3,4-DCA, therefore the metabolism studies feeding propanil are considered acceptable The study in goats was conducted at ca. 300 N based on the provisional calculated dietary burden. In the goat metabolism study, 3,4 dichloroacetanilide (M15) (up to 49% TRR in muscle) and 3,4-dichloroxaloanilide (M6) (up to 36% TRR in kidney) were found to be predominant in all matrices, except in milk where the dimeric metabolite was major (up to 59% TRR). In the hen metabolism, mainly 3,4-dichloroaniline-*N*-sulfamic acid (M8) and 3,4-dichloroacetanilide (M15) were predominantly present in all matrices. On the basis of these studies the residue definition for animals for risk assessment is defined as 'All compounds containing the 3,4-DCA moiety, free and conjugated'. The animal commodity residue definition for monitoring is set as propanil (by default).

The consumer risk assessment could not be conducted as toxicological reference values are not available for the metabolite 3,4-DCA (see Section 2) and due to the lack of a sufficient valid independent field trials with rice and with lacking information on residues in rotational crops.

A scientific peer-reviewed open literature search was not provided (data gap).

[9] Refer to experts' consultation 3.2 in the Report of Pesticides Peer Review Experts' Meeting 180.

According to EFSA's guidance on bees (EFSA, 2013), rice is generally considered less attractive to bees for pollen but their collection cannot be excluded at all due to controversial information found in literature. Data on residues in pollen and bee products for human consumption is therefore needed (data gap).

Given that the decision on the residue definition for monitoring for rice is pending and that a sufficient number of critical GAP-compliant residue trials is not available (data gap), (neither analysing for whichever residue definition for monitoring as set by risk managers nor analysing for all compounds covered by the residue definition for risk assessment), maximum residue levels for propanil in rice cannot be proposed for the time being.

4. Environmental fate and behaviour

Propanil was discussed at the Pesticides Peer Review Teleconference 186 in June 2018.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. Route and rate of degradation of propanil under aerobic conditions has been investigated in four reliable laboratory experiments in agricultural soils (field capacity pF2 soil moisture) and in two soils under aerobic flooded conditions. In the studies under flooded conditions, propanil exhibited very low to low persistence. Degradation rates of propanil were comparable in the soil investigations available at field capacity soil moisture as occured under aerobic flooded conditions.

Metabolites needing further consideration including for potential groundwater contamination were identified as: 3,4-DCA (max. 83% applied radioactivity (AR) flooded; 80% pF2 soil moisture), DCNB (max. 18% AR pF2) and TCAB (max. 3.6% pF2). Under aerobic flooded conditions 3,4-DCA exhibited medium to high persistence. At pF2, 3,4-DCA exhibited low to high persistence. When not flooded (at soil moisture below field capacity) DCNB and TCAB exhibited low to very high and moderate to very high persistence respectively. Under flooded conditions mineralisation to CO_2 accounted for only 0.9–1.3% AR for the phenyl ring ^{14}C radiolabel all at the end of the studies (after 122 days). Under these conditions non extractable resides (not extracted by acetonitrile/water followed by reflux with acidified acetonitrile) of this radiolabel accounted for 47–54% AR at study end. In rice paddy field dissipation studies carried out at two sites in the USA (Arkansas and Louisiana), dissipation rates of propanil were comparable to the estimates from the flooded soil laboratory incubations. 3,4-DCA declined faster at these trial sites than in the available laboratory investigations. Propanil and 3,4-DCA exhibited medium to low mobility in soil. DCNB exhibited low mobility or was immobile. TCAB was considered to be immobile in soil. There was no indication for pH dependent adsorption for any of these compounds.

Degradation and dissipation of propanil in the aquatic environment was investigated in two water sediment systems. Propanil exhibits very low to low persistence in both systems forming the transformation product 3,4-DCA (max 79%, being present in both the water and sediment exhibiting moderate persistence). Mineralisation to CO_2 accounted for only 0.7–1.1% AR for the phenyl ring ^{14}C radiolabel at the end of the studies (after 100 days). Under these conditions, non extractable residues (not extracted by acetonitrile, then acetonitrile/water followed by reflux with acetonitrile/water) accounted for 59–65% AR at study end.

MEDRICE guidance (European Commission, 2003b) was used to calculate predicted environmental concentrations (PEC) in surface water and sediment for propanil and 3,4-DCA. Higher tier surface water modelling was carried out using the RICEWQ/RIVWQ models for three Italian scenarios (Mantova, Padova and average), four Spanish scenarios (Extramadura, Tarragona, Sevilla and Valencia), three Portuguese scenarios (Mondego, Sado and Tejo) and a Greek scenario. The scenario parameterisation followed an approach that Member States had accepted previously in the assessment of the rice herbicide penoxsulam. Note that the RMS disagrees with the single first-order DT_{50} for foliage for both propanil and 3,4-DCA used in the calculations that underpin this EFSA conclusion (that was derived from available field experiments). Their final view was that a (default, longer, more conservative) value of 10 days represents the input values that should be used in such calculations.

Groundwater exposure of propanil and 3,4-DCA have been assessed using the MEDRICE guidance document (European Commission, 2003b). Calculations for 3,4-DCA were completed considering a maximum annual total dose and maximum formation percentage. Propanil and 3,4-DCA did not exceed the parametric drinking water limit of 0.1 μg/L in the two MEDRICE scenarios. As 3,4-DCA has the potential to still be present in soil after rice has been harvested and following crops other than rice (which will not be grown under flooded conditions) can be cultivated, PEC groundwater were also calculated using the FOCUS (2009) groundwater guidance on spring cereals as a representative crop. These simulations were carried out for the soil metabolites DCNB and TCBA in addition to propanil and

3,4-DCA. None of the compounds were predicted to exceed the limit of 0.1 μg/L in any of the 7 FOCUS groundwater scenarios defined for spring cereals.

In relation to the effect of water treatments processes on the nature of the residues present in raw water, when surface water or groundwater are abstracted for drinking water; the RICEWQ/RIVWQ calculations predict that surface water bodies receiving paddy outflow will have concentrations of up to 0.0022 μg/L for propanil and 0.0821 μg/L for 3,4-DCA, i.e. below the parametric drinking water limit of 0.1 μg/L.[10] As indicated in the paragraph above, the same situation pertains to groundwater in the situations represented by the two MEDRICE scenarios. Therefore for the representative uses assessed, in the situations represented by the scenarios assessed, concentrations at raw water abstraction points used as drinking water resources will be low and an assessment of the effect of water treatments processes on the nature of these residues below 0.1 μg/L was considered unnecessary.

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, 2003b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013). According to Regulation (EU) No 283/2013[11], data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002a) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to European Commission (2002a), the risk to adult honeybees from chronic toxicity and the risk to bee brood, could not be finalised due to the lack of a risk assessment scheme. Therefore, the EFSA (2013) was used for risk assessment in order to reach a conclusion for the representative uses.

The available information was not sufficient to confirm whether the batches used in the ecotoxicity studies are compliant with the old technical specifications, nevertheless, the new technical specifications are expected to cover the batches used in the ecotoxicological studies (see also Section 2).

An acute toxicity study on bobwhite quail and a reproductive toxicity study on mallard duck were available. Short-term toxicity tests on mallard duck and bobwhite quail were available, providing a lower endpoint for bobwhite quail. Noting the above and the limitations in the study design of the short-term toxicity studies (EFSA, 2009), some uncertainties remain in relation to the endpoint used for the long-term risk assessment for birds. This endpoint was based on a study performed with mallard duck and this species seemed to be less sensitive than bobwhite quail in the available short-term test. The dietary risk assessment for propanil for **birds** and **mammals** was discussed at the Pesticide Peer Review meeting 181.[12] The experts at the meeting agreed that the scenarios for cereals could be used as a surrogate for rice at the screening level only and that further consideration was still needed for the situations where the screening assessment showed a high risk. In the latter cases, the experts agreed to use the mallard duck (herbivorous bird) and the black-winged stilt (insectivorous bird) as focal species for birds and water vole (herbivorous mammals) as focal species for mammals and to use a worst-case PD (composition of diet from treated area). It was, however, noted that additional feeding guilds should be covered in the risk assessment for which focal species were not identified, i.e. omnivorous and amphibian-eating birds and mammals and insectivorous mammals (data gap and issue that could not be finalised). A high acute risk to herbivorous birds and a high long-term risk to insectivorous birds and herbivorous birds and mammals were concluded for all the representative uses. Acceptable refinements were not available to refine the risk to birds and mammals (data gap and critical area of concern). A low risk to birds and mammals via exposure to contaminated paddy water was concluded. The available information was not sufficient to address the risk to birds and mammals via exposure to the plant metabolite 3,4 DCA and via exposure to contaminated (paddy) water with the same metabolite, it is noted that there are indications that this metabolite may be more toxic than the parent compound (see Section 2), data gap and issue that could not be finalised (see also evaluation table, data requirement 5.3).

[10] Where measured field experiment values for single first order DT_{50} for foliage are employed in simulations, rather than the default value for this substance property of 10 days.

[11] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market Text with EEA relevance. OJ L 93, 3.4.2013, p. 1–84.

[12] Refer to experts' consultation 5.2 and 5.3 in the Report of Pesticides Peer Review Experts' Meeting 181.

Valid acute and chronic toxicity studies on **aquatic organisms** were available for propanil. By using the available endpoints for the risk assessment, a low acute and chronic risk to fish and aquatic invertebrates and a low risk to aquatic plants could be concluded. It is noted that in the available full life cycle toxicity test on fish, the endpoint setting for fecundity was uncertain due to the high variability in the results of the treatments and due to the low performance of the controls. The chronic risk assessment was nevertheless performed with the endpoint derived from this study and based on other parameters (hatching success, survival, total length, wet weight) being lower than the one derived from the early life stage test though there are still some uncertainties.[13] It is further noted that in the case of algae only a study on *Skeletonema costatum* was available while, considering the herbicidal activity of propanil, a second species should have been tested (data gap). A low risk to aquatic invertebrates (acute and chronic) and to fish (acute) and a low risk to algae and aquatic plants was concluded for the surface water metabolite 3,4-DCA. It is, however, noted that a no observed effect concentration (NOEC) on fish for this metabolite could not be set in the available full life cycle test, therefore, a risk assessment could not be performed (data gap and issue that could not be finalised). It is noted that some indications of endocrine activity for this metabolite were available (*in vitro* binding to the androgen receptor and reduction of 11-ketotestosterone in fish testis). This might need to be taken into account while addressing the chronic risk to fish for this metabolite. A low risk to sediment dwellers via exposure to sediments in receiving water bodies was concluded for both propanil and metabolite 3,4-DCA. It is noted that a study on sediment dwellers (spiked-water) was available for propanil. The endpoint derived from this study was not considered in the risk assessment since it was not considered reliable, instead the risk assessment was based on the endpoint derived from the spiked-sediment study. The RMS disagreed with this and considered the endpoint based on the spiked-water study as reliable. The outcome of the risk assessment is unchanged.

The risk assessment for amphibians was discussed at the Pesticide Peer Review meeting 181.[14] From the available literature data, the acute toxicity of propanil seemed to be comparable with respect to the acute toxicity to fish. Nevertheless, the risk assessment for fish may not cover the risk to amphibians in term of exposure; amphibians are expected to be exposed both to paddy water and ditch water in the case of uses on rice. While recognising the absence of a risk assessment scheme for amphibians and noting the shortcomings in the study from which the amphibian acute endpoint was derived, an illustrative acute risk assessment was performed considering the PEC paddy water and the available acute endpoint. On this basis, a high acute risk to amphibians could not be excluded (data gap). Regarding the chronic risk assessment, it could not be concluded whether propanil would be more toxic to amphibians since a chronic endpoint could not be derived in the available literature studies. In consideration of this, the risk to amphibians could not be finalised; therefore, the experts at the Pesticide Peer Review meeting 181 considered necessary to request an additional toxicity study on amphibians (data gap and issue that could not be finalised). It is noted that during the meeting concerns were raised also for the potential risk to amphibians for the metabolite 3,4-DCA. Nevertheless, due to the properties of propanil the toxicity of this metabolite may be covered by the requested LAGDA test (Larval Amphibian Growth and Development Assay, OECD 241).

Suitable acute (oral and contact) and chronic (adult) toxicity studies on honey**bees** were available. It is noted that only a single exposure study was available for larvae; considering the margin of safety in the provided risk assessment, this was considered sufficient. Information on potential sublethal effects on honeybees (e.g. effects on hypopharyngeal glands (HPG)) was not available (data gap). A suitable assessment for accumulative effects was not available. Using the available data in a risk assessment in line with EFSA (2013) a low risk to honeybees was concluded for all the routes of exposure (including exposure via paddy water). It is noted that a risk assessment for exposure to guttation water was not presented, however, when a screening assessment in line with EFSA (2013) is performed, a low risk could be concluded. The same conclusion with respect to the acute risk to bees could be reached with European Commission (2002a). Considering the available information (acute toxicity studies on the major plant metabolite 3,4-DCA), a low risk via exposure to metabolites formed in pollen and nectar is expected.

It is noted that for **non-target arthropods**, only extended laboratory studies were available. On the basis of these studies, a low risk to non-target arthropods could be concluded.

The risk assessment for **soil macroorganisms (including earthworms)** was discussed at the Pesticide Peer Review expert meeting 181. In line with European Commission (2002a), a high risk to

[13] Refer to open point 5.8 in the evaluation table.
[14] Refer to experts' consultation 5.1 in the Report of Pesticides Peer Review Experts' Meeting 181.

Collembola was identified for both propanil and its metabolite 3,4 DCA (data gap and critical area of concern) while a low risk was concluded for the remaining soil organisms. The experts at the meeting agreed that the relevance of soil organisms in the risk assessment for rice uses may depend on the agricultural management practices which may vary at Member State level. Any refinement of the risk to soil organisms should, therefore, be considered taking into account the specific agricultural practices and occurrence of dry and flooded soil periods. During the meeting, it was also seen relevant to perform a risk to sediment dwellers in the paddy water, considering the specific conditions of the rice fields. It is, however, noted that there are uncertainties in the available endpoint for sediment dwellers (spiked-water) for the parent; therefore, the risk assessment was performed considering the endpoint from the spiked-sediment study and the PEC_{soil} (paddy). Although there are uncertainties in this approach, a low risk could be concluded. In the case of the metabolite 3,4-DCA, a high risk to sediment dwellers when exposed to paddy water was concluded based on an illustrative risk assessment (data gap). A low risk to soil organisms for the soil metabolites DCNB and TCAB could be concluded for the representative use under assessment since these metabolites are expected to be formed only in not flooded soils. Further consideration of these metabolites may be needed at Member States level pending on the specific agricultural practices and occurrence of dry and flooded soil periods.

A low risk to **soil microorganisms** was concluded for propanil its pertinent metabolites for all the representative uses.

A low risk to **non-target terrestrial** plants and to organisms used in **biological methods of sewage treatment** was concluded for all the representative uses.

Regarding the endocrine-disrupting properties, positive endocrine activity (androgen antagonist activity) was observed in the *in vitro* tests performed with propanil. The available full life cycle toxicity study on fish did not include parameters relevant for the endocrine disruptor assessment. Additionally, effects on fecundity could not be excluded on the basis of this study (see above). Pending on the data gap identified in Section 2, further data may be needed to address the potential endocrine-disrupting properties of propanil for 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
Propanil	Very low to low persistence Single first-order DT_{50} 0.25–1.8 days (20°C flooded soil)	High risk
3,4-dichloroaniline (3,4-DCA)	Medium to high persistence Single first-order DT_{50} 99–140 days (20°C flooded soil)	High risk
DCNB (only in not flooded soil)	Low to very high persistence Single first-order DT_{50} 9–> 1,000 days (20°C 30–60% MWHC or pF2 soil moisture)	Low risk
TCAB (only in not flooded soil)	Moderate to very high persistence Single first-order DT_{50} 55–> 1,000 days (20°C 30–60% MWHC or pF2 soil moisture)	Low risk

DT_{50}: period required for 50% dissipation; MWHC: maximum water-holding capacity.

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
Propanil	Medium to low mobility K_{Foc} 239–800 mL/g	No	Yes	Yes
3,4-dichloroaniline (3,4-DCA)	Medium to low mobility K_{Foc} 326–585 mL/g	No	Assessment not triggered	Assessment not triggered
DCNB	Low mobility to immobile K_{Foc} 1,332–7,697 mL/g	No	Assessment not triggered	Assessment not triggered
TCAB	Immobile K_{doc} 57,230 mL/g	No	Assessment not triggered	Assessment not triggered

K_{Foc}: Freundlich organic carbon adsorption coefficient; K_{doc}: organic carbon linear adsorption coefficient.
(a): At least one FOCUS scenario or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Propanil	Data gap
3,4-dichloroaniline (3,4-DCA)	Data gap

Table 4: Air

Compound (name and/or code)	Toxicology
Propanil	Rat LC_{50} inhalation LC_{50} > 2.13 mg/L air/4 h (whole body) (classification as Acute Toxicity Category 4: H332 – 'Harmful if inhaled' is proposed)
3,4-dichloroaniline (3,4-DCA)	Rat LC_{50} inhalation LC_{50} > 3.3 mg/L air/4 h (harmonised classification as Acute Toxicity Category 3: H331 – 'Toxic if Inhaled')

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 the Regulation concerning information on potentially harmful effects).

7.1. Data gaps identified for the representative uses evaluated

- A search of the scientific peer-reviewed open literature, including the metabolite 3,4-DCA should be conducted in the residue section and further information on the performed literature review should be reported in the ecotoxicology section, i.e. a justification for considering the retrieved studies as not relevant, further information on the applied reliability criteria, and the study summaries of the studies considered relevant, in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011a; relevant for all representative uses evaluated i.e. in rice; submission date proposed by the applicant unknown; see Sections 3 and 5).
- Data on the self-heating of the PPP (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 1).
- Monitoring method in acidic and oily plant commodities, addressing the extraction efficiency and the efficiency of the hydrolysis step (relevant for all representative uses evaluated, i.e. in rice providing that the residue definition for monitoring in food/feed of plant origin is concluded as 'all compounds containing the 3,4-DCA moiety, free and conjugated'; submission date proposed by the applicant: unknown; see Section 1).
- Independent laboratory validation (ILV) of the monitoring method in plants (relevant for all representative uses evaluated, i.e. in rice providing that the residue definition for monitoring in food/feed of plant origin is concluded as 'all compounds containing the 3,4-DCA moiety, free and conjugated'; submission date proposed by the applicant: unknown; see Section 1).
- Monitoring method in high water content, acidic and oily plant commodities, addressing the extraction efficiency (relevant for all representative uses evaluated, i.e. in rice providing that the residue definition for monitoring in food/feed of plant origin is concluded as propanil; submission date proposed by the applicant: unknown; see Section 1).
- ILV of the monitoring method in plants (relevant for all representative uses evaluated, i.e. in rice providing that the residue definition for monitoring in food/feed of plant origin is concluded as propanil; submission date proposed by the applicant: unknown; see Section 1).
- Monitoring method in food of animal origin (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 1).
- Method for the determination of 'total' (base-releasable) 3,4-DCA in soil validated according to guideline SANCO/3029/99 rev. 4 (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Sections 1 and 4).
- Identification of the analytical methods used in the dietary toxicological studies for risk assessment, including the assessment of their validity (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Sections 1 and 2).
- Toxicokinetics parameters (plasma bioavailability, C_{max}, T_{max}, half-life, area under the curve (AUC) for propanil and the metabolite 3,4-DCA are not available (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 2).
- A new gene mutation assay, i.e. MLA on the active substance propanil with further testing up to cytotoxic concentrations is needed to decrease uncertainty on available gene mutation assays (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 2).
- The toxicological profile of the metabolite 3,4-DCA, including investigation of the clastogenic/ aneugenic potential, needs to be assessed (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Sections 2 and 3).

- Toxicokinetics parameters (plasma bioavailability, C_{max}, T_{max}, half-life, AUC) for propanil and the metabolite 3,4-DCA are not available (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 2).
- The endocrine-disrupting mode of action has to be confirmed with appropriate studies (e.g. Hershberger assay/*in vitro* tests, AOP key events), with regard to findings (Leydig cell tumours in rats) observed in regulatory studies and in mechanistic investigations, indicating a possible anti-androgenic effect (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 2).
- The residue dataset for rice analysing for 'All compounds containing the 3,4-DCA moiety, free and conjugated' according to the residue definition for risk assessment should be completed by three additional residue trials. In case the residue definition for monitoring differs, an additional set of field trials should be provided to establish an MRL (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 3).
- A nature of residue study in processed commodities for all compounds covered by the RD for RA is required (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 3).
- Identification/characterisation of the residues in rotational crops relevant for Europe (e.g. cereals) in order to conclude on a residue definition of risk assessment for rotational crop (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 3)
- A study investigating the storage stability for all compounds covered by the residue definition for risk assessment in rice (food and feed commodities) or sufficiently transparent reporting of the presented storage stability data to conclude on the validity of the study and maximum storage stability time in rice (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 3).
- Data on residue levels in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom. (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant: unknown; see Section 3).
- Further information to address the acute risk to herbivorous birds and the long-term risk to insectivorous and herbivorous birds and herbivorous mammals. Further information to address the risk to omnivorous and amphibian-eating birds and mammals and to insectivorous mammals (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant unknown; see Section 5).
- Further information to address the risk to birds and mammals for metabolite 3,4-DCA (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant unknown; see Section 5).
- An additional study of propanil on a second algal species relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant unknown; see Section 5).
- Further information to address the chronic risk to fish of metabolite 3,4-DCA (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant unknown; see Section 5).
- Further information to address the chronic toxicity (i.e. a study in line with OECD TG 241) and risk to amphibians for propanil. Further consideration on the risk to amphibians for metabolite 3,4-DCA (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant unknown; see Section 5).
- Further information on potential sublethal effects on honeybees (e.g. effects on HPG) of propanil (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant unknown; see Section 5).
- Further information to address the risk to soil organisms (i.e. Collembola) of propanil and 3,4-DCA (relevant for all representative uses evaluated, i.e. in rice; submission date proposed by the applicant unknown; see Section 5).
- Further information to address the risk to sediment dwellers for 3,4-DCA via exposure to paddy water (relevant for all representative uses evaluated, i.e. in rice; 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 should use coverall and sturdy footwear during application and gloves during mixing/loading and application to reduce exposure below the AOEL according to the German model (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 the Regulation and as set out in Commission Regulation (EU) No 546/2011[15] 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 the Regulation.

1) Information on the analytical methods used in all dietary toxicity studies, including the assessment of their validity was not provided (see Sections 1 and 2).
2) Propanil is proposed to be classified as carcinogen category 2 and is not classified or proposed to be classified as toxic for reproduction category 2. On this basis, in accordance with the provisions of Regulation (EC) No 1272/2008, 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 properties are not met. Based on findings observed in the regulatory studies and in mechanistic studies, it was concluded that propanil has an endocrine-mediated activity (most likely via anti-androgenic properties). However, additional data to further investigate the mode of action for Leydig cell tumours should be provided in order to have a clear-cut conclusion on the link between Leydig cell tumours and endocrine activity (see Section 2).
3) The consumer risk assessment could not be conducted as no toxicological reference values are available for the metabolite 3,4-DCA (see Section 2) and due to lack of sufficient number of valid field trials with rice and with rotational crops (see Section 3).
4) The risk assessment for omnivorous and amphibian-eating birds and mammals and insectivorous mammals could not be finalised (see Section 5).
5) The risk to birds and mammals for metabolite 3,4-DCA could not be finalised (see Section 5).
6) The chronic risk to fish for metabolite 3,4-DCA could not be finalised (see Section 5).
7) The risk to amphibians could not be finalised. It is acknowledged that a risk assessment scheme addressing the risk to amphibians is not yet available (see Section 5).

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 the Regulation 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 a 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.

[15] 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.

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 the Regulation.

8) A high acute risk to herbivorous birds and a high long-term risk to insectivorous birds and herbivorous birds and mammals were concluded for all the representative uses (see Section 5).
9) A high risk to soil organisms for propanil and metabolite 3,4-DCA (i.e. Collembola) was identified. It is acknowledged that the relevance of soil organisms in the risk assessment for rice uses may depend on the agricultural management practices which may vary at Member State level (see Section 5).

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.)

Table 5: Overview of concerns

Representative use		Rice
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[3]
Risk to wild non-target terrestrial vertebrates	Risk identified	X[8]
	Assessment not finalised	X[4,5]
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[9(c)]
	Assessment not finalised	
Risk to aquatic organisms	Risk identified	
	Assessment not finalised	X[6,7]
Groundwater exposure to active substance	Legal parametric value breached	
	Assessment not finalised	
Groundwater exposure to metabolites	Legal parametric value breached[(a)]	
	Parametric value of 10 μg/L[(b)] breached	
	Assessment not finalised	

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.
(a): Based on classification made in the context of this evaluation procedure under Regulation (EC) No 1107/2009. It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.
(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003a.
(c): The relevance of soil organisms in the risk assessment for rice uses may depend on the agricultural management practices which may vary at Member State level.

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Abbreviations

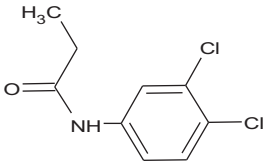
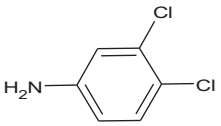
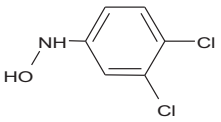
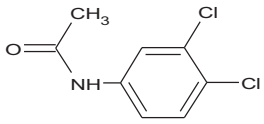
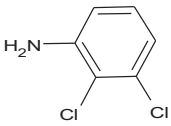
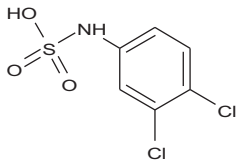
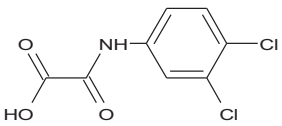
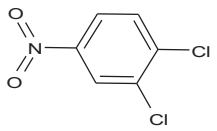
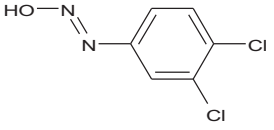
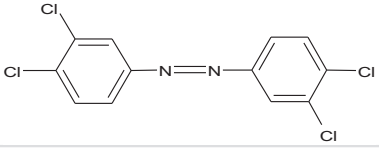
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AhR	aryl hydrocarbon receptor
AOEL	acceptable operator exposure level
AOP	adverse outcome pathway
AP	alkaline phosphatase
AR	applied radioactivity
AR	androgen receptor
ARfD	acute reference dose
AUC	area under the blood concentration/time curve
bw	body weight
C_{max}	concentration achieved at peak blood level
DAR	draft assessment report
DAT	days after treatment
3,4-DCA	3,4-dichloroaniline
DT_{50}	period required for 50% dissipation (define method of estimation)
EEC	European Economic Community
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
GC–MS/MS	gas chromatography with tandem mass spectrometry
HPG	hypopharyngeal glands
InChiKey	International Chemical Identifier Keys
ILV	independent laboratory validation
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint Meeting on 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_{doc}	organic carbon linear adsorption coefficient
K_{Foc}	Freundlich organic carbon adsorption coefficient
LAGDA	Larval Amphibian Growth and Development Assay
LC_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MLA	mouse lymphoma assay
MS	mass spectrometry
MWHC	maximum water-holding capacity
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PD	proportion of different food types
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
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PPE	personal protective equipment
PPP	Plant Protection Product
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation

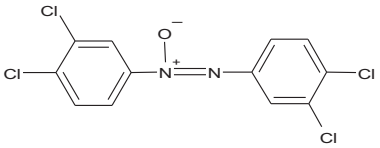
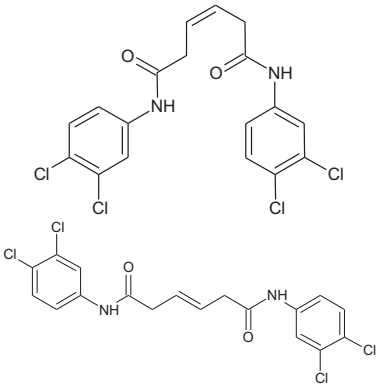
RMS	rapporteur Member State
SC	suspension concentrate
SFO	single first-order
SMILES	simplified molecular-input line-entry system
T_{max}	time until peak blood levels achieved
TRR	total radioactive residue
TWA	time-weighted average
UF	uncertainty factor
UV	ultraviolet
WHO	World Health Organization

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.2018.5418

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
propanil	3′,4′-dichloropropionanilide Clc1ccc(NC(=O)CC)cc1Cl LFULEKSKNZEWOE-UHFFFAOYSA-N	
3,4-dichloroaniline (3,4-DCA)	3,4-dichloroaniline Nc1cc(Cl)c(Cl)cc1 SDYWXFYBZPNOFX-UHFFFAOYSA-N	
***N*-hydroxy-3,4-dichloroaniline**	3,4-dichloro-*N*-hydroxyaniline Clc1ccc(NO)cc1Cl AKSIQQBEDAZPLD-UHFFFAOYSA-N	
3,4-dichloroacetanilide (M15)	*N*-(3,4-dichlorophenyl)acetamide Clc1ccc(NC(C)=O)cc1Cl SCYGGCAQZFJGRF-UHFFFAOYSA-N	
2,3-dichloroaniline (2,3-DCA)	2,3-dichloroaniline Nc1cccc(Cl)c1Cl BRPSAOUFIJSKOT-UHFFFAOYSA-N	
3,4-dichloroaniline-*N*-sulfamic acid (M8)	(3,4-dichlorophenyl)sulfamic acid Clc1ccc(NS(=O)(=O)O)cc1Cl WOBZEFNSIXMTAG-UHFFFAOYSA-N	
3,4-dichloroxaloanilide (M6)	(3,4-dichloroanilino)(oxo)acetic acid Clc1ccc(NC(=O)C(=O)O)cc1Cl SWKJJZISAXATCK-UHFFFAOYSA-N	
DCNB	1,2-dichloro-4-nitrobenzene Clc1ccc(cc1Cl)N(=O)=O NTBYINQTYWZXLH-UHFFFAOYSA-N	
DCAB	(*EZ*)-(3,4-dichlorophenyl)diazen-1-ol Clc1ccc(/N=N/O)cc1Cl GRBXOCFHPXMGLJ-UHFFFAOYSA-N	
TCAB 3,3′,4,4′-tetrachloro-azobenzene	(*EZ*)-bis(3,4-dichlorophenyl)diazene Clc1ccc(/N=N/c2ccc(Cl)c(Cl)c2)cc1Cl SOBGIMQKWDUEPY-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
TCAOB 3,3′,4,4′-tetrachloroazoxybenzene	1,2-dichloro-4-[(*EZ*)-(3,4-dichlorophenyl)-*NNO*-azoxy]benzene Clc1ccc(\N=[N+](/[O-])c2ccc(Cl)c(Cl)c2)cc1Cl BCOVXBPXQLIGEV-UHFFFAOYSA-N	
propanil dimer	(3*Z*)-*N*,*N*′-bis(3,4-dichlorophenyl)hex-3-enediamide Clc2ccc(NC(=O)C/C=C\CC(=O)Nc1ccc(Cl)c(Cl)c1)cc2Cl APGNMOOOGHDWSO-UPHRSURJBX (3*E*)-*N*,*N*′-bis(3,4-dichlorophenyl)hex-3-enediamide Clc2ccc(NC(=O)C\C=C\CC(=O)Nc1ccc(Cl)c(Cl)c1)cc2Cl APGNMOOOGHDWSO-OWOJBTEDBW	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Keys.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2017.2.1 ACD/Labs 2017 Release (File version N40E41, Build 96719, 6 September 2017).
(c): ACD/ChemSketch 2017.2.1 ACD/Labs 2017 Release (File version C40H41, Build 99535, 14 February 2018).