CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, the Netherlands, and co-rapporteur Member State, Spain, for the pesticide active substance chlorpropham and the assessment of applications for maximum residue levels (MRLs) 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 chlorpropham as a plant growth regulator on potatoes and as a herbicide on glasshouse and field lettuce, field onion and field flower bulbs. MRLs were assessed in potato and animal commodities. The reliable end points, 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: chlorpropham, peer review, risk assessment, pesticide, plant growth regulator, herbicide

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Amendment: The dietary risk assessment has been corrected considering the input values agreed during the peer review e.g. variability factor of 7. The acute risk assessment for potatoes has been re-calculated as 797% of the ARfD for chlorpropham and 2360% of the ARfD for 3-chloroaniline. To avoid confusion, the older version has been removed from the EFSA Journal, but is available on request, as is a version showing all the changes made.

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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. Chlorpropham 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), the Netherlands, and co-rapporteur Member State (co-RMS), Spain, received an application from Exponent International Ltd. on behalf of Aceto Agricultural Chemical Corp., Certis Europe B.V. and UPL Europe Ltd. for the renewal of approval of the active substance chlorpropham. In addition, Exponent International Ltd. on behalf of Aceto Agricultural Chemical Corp., Certis Europe B.V. and UPL Europe Ltd. submitted applications for maximum residue levels (MRLs), as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Spain), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on chlorpropham in the renewal assessment report (RAR), which was received by EFSA on 29 April 2016. The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Exponent International Ltd. on behalf of Aceto Agricultural Chemical Corp., Certis Europe B.V. and UPL Europe Ltd., for comments on 22 June 2016. 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 August 2016.

Following consideration of the comments received on the RAR, it was concluded that additional information should be requested from the applicants, and that EFSA should conduct an experts' consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour, and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether chlorpropham 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 and give a reasoned opinion concerning MRL applications as referred to in Article 10(1) of Regulation (EC) No 396/2005.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of chlorpropham as a plant growth regulator on potatoes and as a herbicide on glasshouse and field lettuce, field onion and field flower bulbs, as proposed by the applicants. MRLs were assessed in potato and animal commodities. Full details of the representative uses and the proposed MRLs can be found in Appendix A of this report.

Data were submitted to conclude that the uses of chlorpropham according to the representative uses proposed at European Union (EU) level result in a sufficient plant growth regulatory efficacy to control sprouting and in a sufficient herbicidal efficacy against the target weeds.

There were no data gaps identified in the section identity, physical and chemical properties and analytical methods.

For mammalian toxicology, data gaps are set for further investigations of the immunotoxic potential of chlorpropham, for further assessment of the toxicological relevance of one impurity, and for a resident and bystander exposure assessment during use of Chlorpropham Fog and Chlorpropham 300 EC. In addition, further scientific assessment of the potential endocrine disrupting properties of chlorpropham should be provided, on the basis of the current knowledge (data gap). Regarding the exposure estimates, an exceedance of the acceptable operator exposure level (AOEL) is noted for the operators combining the operating and cleaning tasks during the application of Chlorpropham 300 EC.

As for a number of data gaps, a final consumer risk assessment cannot be performed. However, in an indicative assessment, the highest chronic exposure to chlorpropham residues was exceeding the acceptable daily intake (ADI) (180%) and exposure to residues of metabolite 3-chloroaniline was also exceeding the ADI (195%) set for this compound. A refinement of the assessment using processing factors for potatoes does not appear to be currently possible as the reliability of these processing factors has not been demonstrated. Even if the application of processing factors may reduce intake estimates for chlorpropham, for 3-chloroaniline this is not expected to result in lower intakes given available processing data are indicating formation of 3-chloroaniline from chlorpropham. In an acute risk assessment, exceedance of the acute reference dose (ARfD) was found for potatoes in both

assessments, for chlorpropham and for 3-chloroaniline (797% and 2360% ARfD, respectively). Even if the standard variability factor would be replaced by the lower, still to be confirmed variability factor of 3 for the critical good agricultural practices (GAP) under peer review (data gap), the ARfD will still be exceeded.

Some data requirements identified during the MRL review were addressed and the additional information was assessed; however, in view of the peer review assessment outcome, a revision of the MRLs assessed under the Art. 12 MRL review procedure is recommended while raising the MRLs in potato and animal commodities, as requested in the MRL application, is not proposed since the associated risk assessment is not supportive of the requested MRL of 10 mg/kg in potatoes.

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 an unidentified metabolite formed at levels triggering assessment in the sediment of natural water sediment systems. This resulted in a data gap. A data gap was identified for information on the effect of water treatment processes on the nature of residues potentially present in surface water, when surface water is abstracted for drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses.

In the area of ecotoxicology, the risk assessment for non-target arthropods could not be finalised. In addition data gaps were identified for aquatic organisms and bees.

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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 applicants 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 on additional 3 months where additional information is required to be submitted by the applicants in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS the Netherlands and co-RMS Spain received an application from Exponent International Ltd. on behalf of Aceto Agricultural Chemical Corp., Certis Europe B.V. and UPL Europe Ltd. for the renewal of approval of the active chlorpropham. In addition, Exponent International Ltd. on behalf of Aceto Agricultural Chemical Corp., Certis Europe B.V. and UPL Europe Ltd. submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005[3]. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Spain), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on chlorpropham in the RAR, which was received by EFSA on 29 April 2016 (Netherlands, 2016). The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Exponent International Ltd. on behalf of Aceto Agricultural Chemical Corp, Certis Europe B.V. and UPL Europe Ltd., for consultation and comments on 22 June 2016. 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 August 2016. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicants were invited to respond to the comments in column 3 of the reporting table. The comments and the applicants' response were evaluated by the RMS in column 3.

The need for experts' consultation and the necessity for additional information to be submitted by the applicants in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 6 October 2016. On the basis of the comments received, the applicants' response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicants and that EFSA should conduct an experts' 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.

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

[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.

[3] 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.

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 and on the proposed MRLs took place with Member States via a written procedure in May-June 2017.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulations, evaluated on the basis of the representative uses of chlorpropham as a plant growth regulator on potatoes and as a herbicide on glasshouse and field lettuce, field onion and field flower bulbs, as proposed by the applicants. MRLs were assessed in potato and animal commodities. A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2017), 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 RAR;
- the reporting table (6 October 2016);
- the evaluation table (15 June 2017);
- 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 (Netherlands, 2017), 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

Chlorpropham is the ISO common name for isopropyl 3-chlorocarbanilate (IUPAC).

The representative formulated products for the evaluation were 'Chlorpropham Fog', (Aceto Agricultural Chemicals Corp.), a hot fogging concentrate (HN), containing 975 g/kg chlorpropham; 'Chlorpropham 300 EC' (Certis Europe B.V.) and 'Chlorpropham 400 EC' (UPL Europe Ltd.), both emulsifiable concentrates (EC) containing 300 and 400 g/L chlorpropham, respectively.

The representative uses evaluated were applications by hot fogging equipment or by in-store conveyor spraying to control sprouting in potatoes during storage, and spray applications to control annual and perennial broadleaved weeds and annual grasses in field and protected lettuce, field onion (northern EU) and flower bulbs. 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 chlorpropham according to the representative uses proposed at EU level result in a sufficient plant growth regulatory efficacy to control sprouting in potatoes and in a sufficient herbicidal efficacy against the target weeds following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014).

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 specification is based on batch data from industrial scale production and is common to all applicants. It should be mentioned, however, that during the peer review applicant Certis withdrew one manufacturing source from consideration for the renewal of chlorpropham. The minimum purity of the technical material is 975 g/kg. 3-Chloroaniline is considered a relevant impurity

for all chlorpropham sources with a maximum content of 0.1 g/kg (see Section 2). The minimum purity and the maximum content of the relevant impurity are meeting the requirements of the FAO specification available for chlorpropham (AGP: CP/73, Rome, 1977) developed under the old procedure. It should be noted, however, that the maximum value for the relevant impurity in the FAO specification applies only to chlorpropham applied pre-emergent or to growing crops and is unacceptable for application to harvested potatoes for sprout inhibition.

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 chlorpropham or the representative formulations. The main data regarding the identity of chlorpropham 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. Methods of analysis are available for the determination of the active substance in the technical material and representative formulations and also for the determination of the relevant impurity.

Chlorpropham can be monitored in food and feed of plant origin by the Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) method using high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) with a limit of quantification (LOQ) of 0.01 mg/kg in all commodity groups. The residue definition for monitoring for animal matrices was set to sum of chlorpropham and 4′-hydroxychlorpropham-*O*-sulfonic acid (4-HSA), expressed as chlorpropham in mammals and to chlorpropham in poultry. Monitoring the compounds of the residue definition in animal matrices can be done by the QuEChERS method using HPLC–MS/MS with LOQs of 0.01 mg/kg for both compounds in all matrices.

HPLC–MS/MS methods are available enabling the determination of residues of chlorpropham in the environmental matrices with LOQs of 0.01 mg/kg in soil, 0.1 μg/L in surface water and drinking water, and 1.5 $\mu g/m^3$ in the air, respectively. 3-Chloroaniline can be monitored in drinking and surface water by HPLC–MS/MS with a LOQ of 0.1 μg/L.

Chlorpropham and 3-chloroaniline can be monitored in body fluids and tissues by HPLC–MS/MS with a LOQ of 0.05 mg/L in urine and with a LOQ of 0.1 mg/kg in muscle, for each compound.

2. Mammalian toxicity

The toxicological profile of the active substance chlorpropham and its metabolites was discussed at the Pesticides Peer Review experts' meeting 151 (February 2017) and assessed based on the following guidance documents: SANCO/221/2000-rev. 10 final (European Commission, 2003a), 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, 2015).

To assess the toxicological profile of the active substance, the applicant submitted a complete set of valid toxicity studies. The batches used in the toxicity studies were concluded as being representative of the proposed technical specification for the active substance. 3-Chloroaniline is identified as a relevant impurity (max. of 0.1 g/kg). For one impurity, limited results of quantitative structure–activity relationship (QSAR) data are reported in the RAR and are not sufficient to conclude on its (non)-toxicological relevance (data gap).

In the toxicokinetic studies, oral absorption is estimated to be 90%. Chlorpropham is widely distributed (highest residues in liver, kidney and plasma), without evidence of accumulation, extensively metabolised and rapidly excreted (predominantly via urine). None of the metabolites observed in the comparative *in vitro* metabolism study are unique to the human material. All of the regions of radioactivity observed in the human hepatocyte profiles were also observed at comparable or higher levels in the profile from at least one other species.

In the acute toxicity studies, chlorpropham was of low toxicity (orally, dermally or by inhalation), not a skin or eye irritant nor a skin sensitiser. Phototoxicity and photomutagenicity studies are not required as the molar absorption coefficient of the active substance is less than 10 L/mol cm.

In an acute oral toxicity study in dogs, a no observed adverse effect level (NOAEL) of 50 mg/kg body weight (bw) was identified based on haematological findings. Based on the observed narcotic effects in two acute oral toxicity studies (in rats and dogs), the majority of experts proposed a classification[4] with STOT SE category 3 (H336): may cause drowsiness or dizziness.

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

The most sensitive species is the dog. The relevant short-term oral NOAELs are 5 mg/kg bw per day in the 60-week dog study and 10 mg/kg bw per day in the 90-day rat study. These values are based on haematological effects in both species and thyroid effects in dogs. On this basis, the harmonised classification STOT RE 2 (H373)[5]: may cause damage to organs through prolonged or repeated exposure is still supported. By dermal route, a NOAEL for systemic and local effects is set at 104 mg/kg bw per day in 21-day rabbit study and at 30 mg/kg bw per day in 28-day rat study. Based on the absence of toxic effects in the acute inhalation study, no further repeat dose toxicity test by inhalation is required.

In the long-term studies, the relevant lowest observable adverse effect levels (LOAELs) are 24 mg/kg bw per day in the 2-year rat study, and 40 mg/kg bw per day in the 18-month mouse study, based on haematological effects, spleen and bone marrow changes.

Chlorpropham is unlikely to be genotoxic based on available genotoxicity studies: bacterial reverse mutation, *in vitro* chromosomal aberration, *in vitro* mammalian cell gene mutation assays and *in vivo* micronucleus study. In a chronic/carcinogenicity study in rat, Leydig cell tumours are observed and the harmonised classification carcinogen Cat 2 (H351): suspected of causing cancer is supported by the experts.

In the two-generation rat studies, the overall agreed parental LOAEL is 20.5 mg/kg bw per day based on decreased bodyweight, changes in spleen, liver, kidneys and bone marrow. The NOAEL for the offspring is 44.5 mg/kg bw per day based on spleen changes. In the absence of adverse effects on reproduction, the reproductive NOAEL is 208.4 mg/kg bw per day.

For the developmental rat studies, the overall maternal NOAEL is 50 mg/kg bw per day based on decreased body weight gain. The developmental NOAEL is 200 mg/kg bw per day based on retarded ossification and reduced fetal weight. For the developmental rabbit toxicity studies, the overall maternal NOAEL is 125 mg/kg bw per day based on the mortality observed in dams, and the developmental NOAEL is 250 mg/kg bw per day based on the delayed ossification and decreased foetal weight.

Neurotoxicity studies are not required as no neurotoxic potential has been observed in the available data package. EFSA notes that, for completeness with regard to the approval criteria, further assessment of the immunotoxic potential of chlorpropham should be provided (data gap).

Chlorpropham is classified carcinogenic category 2 but not toxic for reproduction category 2, in accordance with the provisions of Regulation (EC) No 1272/2008[5], and therefore, 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.

The majority of the experts agreed that an endocrine-mediated mode of action could not be excluded for the effects in Leydig cells (uncertainty exists regarding the androgen antagonism activity in rats) and in thyroid (dogs) while the RMS did consider that the data indicate dopamine agonism as the most probable mode of action for the Leydig cell tumours and pregnane X receptor (PXR)-mediated liver enzyme induction as the most probable mode of action for the thyroid findings. Considering the uncertainties, it was agreed to ask for further investigations on the basis of the current scientific knowledge (OECD Conceptual Framework, as analysed in the EFSA Scientific Committee, 2013) (data gap).

The acceptable daily intake (ADI) is the same as the one set during the first review (European Commission, 2003c), i.e. 0.05 mg/kg bw per day based on the 60-week dog and applying an uncertainty factor (UF) of 100. The acceptable operator exposure level (AOEL) is 0.05 mg/kg bw per day based on the 60-week dog study supported by the 28-day dog study, applying an UF of 100 and considering an oral absorption of 100%.

The acute reference dose (ARfD) is the same as the one set during the first review (European Commission, 2003c) but the study from which it is derived is different. An ARfD of 0.5 mg/kg bw and an acute AOEL (AAOEL) of 0.5 mg/kg bw per day are derived based on the acute oral dog study supported by the rat developmental study, based on the NOAEL of 50 mg/kg bw per day (haematological findings) and applying an UF of 100, considering an oral absorption of 100%.

For **Chlorpropham Fog**, used in fogging potato stores, the operator exposure estimates during loading of the machine are below the AOEL without use of personal protective equipment (PPE) (RISKOFDERM model).

[5] 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.

For **Chlorpropham 300 EC**, considering the combination of the operating and cleaning activities, the operator exposure estimates are 147% of the AOEL even with the use of PPE.

For both products, the exposure of residents and bystanders cannot be concluded on the basis of limited field study results (non-good laboratory practice (GLP) study for which individual results were not reported and units of the measured values could not be confirmed) (data gap). The worker exposure during inspection (30 min) is below the AOEL without use of PPE, whereas the use of PPE (gloves and coverall) is needed for transportation of stored potatoes (8 h).

For **Chlorpropham 400 EC**, for the field use on low crops, the use of PPE is needed in the German model to obtain exposure estimates below the AOEL. For the greenhouse use, the Southern Greenhouse model provides exposure estimates below the AOEL with the use of PPE, whereas with the Dutch greenhouse model, no prediction is below the AOEL, even with the use of PPE. It is noted that there is no harmonised model for the greenhouse applications. In the case of residents and bystanders, the exposure estimates are below the AOEL. For workers (calculations provided during the written procedure), the exposure estimates for field and greenhouse re-entry are below the AOEL with the use of PPE.

Concerning the **metabolites**, 3-chloroaniline is unlikely to be genotoxic based on the available data package. The majority of the experts agreed on an ADI of 0.007 mg/kg bw per day based on the 90-day rat study, with the application of an increased UF of 1,000 to cover extrapolation from subchronic to chronic toxicity, from LOAEL to NOAEL, use of a limited data package and adjustment for an exposure of 5 days per week. The ARfD is 0.03 mg/kg bw based on the 90-day rat study (acute effect on MetHb), applying an UF of 300 to extrapolate from LOAEL to NOAEL.

The metabolite 3-chloro-4-hydroxyaniline is concluded as having no genotoxic potential on the basis of the available data. Considering the structural similarity with 3-chloroaniline, the reference values set for 3-chloroaniline can also apply to 3-chloro-4-hydroxyaniline.

The metabolite 4-OH-chlorpropham, proposed as intermediate in the rat metabolic pathway towards the major metabolite 4-HSA, could also be considered as covered by the toxicological profile of chlorpropham.

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).

The metabolism of chlorpropham was investigated in stored potatoes upon post-harvest treatment and in carrots, lettuce and onions upon pre-emergence or/and foliar treatment and covers the categories root/tuber crops and leafy crops.

In post-harvest treated potato tubers, chlorpropham and 4′-hydroxychlorpropham (or 4-OH-chlorpropham) mainly in its conjugated form were found to be the predominant compounds. In field-grown carrots and onions chlorpropham was ranging between 2.1% and 45% total radioactive residue (TRR) while 3-chloroaniline free and conjugated (0.3–2.8% TRR) was recovered only in onions. Identification remained limited to the aforementioned compounds. In older studies in lettuce, significant proportions of residues remained unidentified (31–55% TRR) as only chlorpropham (7–15% TRR) and very low amounts of conjugated 3-chloroaniline (< 1% TRR) could be determined. In a newly submitted lettuce study (2016), upon a combination of soil and foliar treatment and quick analysis of harvest samples, chlorpropham was recovered at only 8% TRR while the predominant compounds of the total residues were 3-chloroaniline free (19% TRR) and hydroxychlorpropham (U3) (38% TRR). A data gap was set to identify the exact position of the hydroxyl group given the significant amount of U3.

It is noted that available data indicate limited stability of aniline, 3-chloroaniline and 4′-hydroxychlorpropham in freezer storage and thus uncertainty remains over the reported quantities and proportions of metabolites in most of the metabolism studies with exception of the new lettuce study.

The major metabolic pathway in all investigated crops consisted of hydroxylation of the phenyl ring of the parent molecule (hydroxychlorpropham) conjugated to amino acids or oligosaccharides and the formation of 3-chloroaniline with further N-glucosylamine conjugation. Public literature indicated a general potential for microbial-induced dechlorination of chloroanilines leading to aniline formation. As 3-chloroaniline was a major plant metabolite such processes cannot be generally excluded for

chlorpropham. Aniline was sought after but not found above the LOQ in the new lettuce study and two lettuce residue trials; however, this is a very limited number of investigations to rule out the relevance of dechlorination of chlorpropham with certainty. It is acknowledged that the issue is not specific to chlorpropham alone but to all compounds bearing/releasing a chloroaniline structure, and this indication may have to be followed up further in future.

Chlorpropham was considered a suitable marker compound and therefore included in the residue definition for monitoring. The residue definition for risk assessment for root and tuber crops, and leafy crops was set as (1) chlorpropham and 4′-hydroxychlorpropham (free and conjugated), expressed as chlorpropham and (2) 3-chloroaniline (free and conjugated) separately for its different toxicological profile. Part (1) of the residue definition is pending confirmation for leafy crops upon clarification of the identity of the hydroxychlorpropham found as the major residue in lettuce (data gap). Based on the current data, a robust conversion factor for monitoring to risk assessment cannot be derived. For risk assessment purposes in the scope of peer review, conversion factors of 1.85 for potato and 5.6 for lettuce were tentatively derived from the respective metabolism studies.

As the DT_{90} of chlorpropham and the major soil metabolite 3-chloroaniline is exceeding the 100 days trigger value, investigation of residues in rotational crops is required for the uses in onion and lettuce but no specific study was submitted (data gap).

Under standard hydrolysis conditions simulating the most common industrial and household processes only little degradation of chlorpropham occurred, however with formation of 3-chloroaniline (up to 1.3%). Significantly higher levels of 3-chloroaniline can be formed at higher temperatures (170–200°C) as demonstrated by processing data with unpeeled potato commodities (e.g. French fries, crisps, baked potato). This backed up the postulation from published literature which suggested that the higher the heating temperature (up to 250°C), the more chlorpropham degraded while 3-chloroaniline was formed. The behaviour of the major potato metabolite 4′-hydroxychlorpropham and of 3-chloroaniline under hydrolysis conditions representative of food processing should be further addressed and an additional processing trial on potato involving higher temperatures (> 120°C) should be conducted (data gaps). It is noted that several studies on the magnitude of residues in processed potato commodities are currently available, but samples in these processing trials had unknown length of storage. The reliability of the derived processing factors should be reconsidered in view of the additional processing studies requested on the nature and magnitude of residues and in view of the unknown length of storage of the residue samples from the available processing residue trials (data gap).

Residue trials in potato, lettuce and onion are available; however, in view of the demonstrated instability of 3-chloroaniline, the results may not be relied on as in the majority of residue trials analysis of 3-chloroaniline had either not been conducted, or had not been done immediately after sampling. Therefore, a completed residue data package is required on onions and lettuce with immediate residue analysis and covering the residue definition for risk assessment (data gaps).

For post-harvest treated potatoes, different GAPs have been applied for, involving spray treatment and fogging, separately or in combination. The available residue trials using only spray treatments may therefore not reflect the most critical use scenario. As for an inappropriate sampling regime, residue trials that studied a fogging treatment of bulked potatoes were considered not acceptable. Residue trials are required on potato, addressing critical good agricultural practices (cGAP) conditions and a suitable and realistic time period following applications. These trials should analyse potatoes for all compounds included in the residue definitions. Pending the requested data on the unit to unit variability in order to demonstrate a variability factor (VF) of 3 can be applied to the cGAP for potato, the variability factor of 7 should be used. Residue trials in a commercial scale setting with bulked and boxed potatoes, available at Member State (MS) level, demonstrated even higher residues of chlorpropham than the data submitted in the dossier by the applicant. These trials were evaluated as adverse data during the peer review and, where relevant, considered for the consumer risk assessment.

Available livestock metabolism data with chlorpropham in goat and hen were deemed acceptable to depict the general metabolic behaviour of chlorpropham in animals, yet they should not be relied on for quantification purposes as for the unknown storage time of the samples and possible significant degradation of residues. Chlorpropham was predominant in the fatty tissues and 4-HSA was a major metabolite. Although not detected in the metabolism studies it cannot be excluded that 3-chloroaniline is formed and metabolised into different compounds recovered in significant proportions in goat and laying hen, i.e. 3-chloro-4-hydroxyaniline and its conjugates and 3-chloroacetanilide.

The residue definition for monitoring was proposed as chlorpropham and 4-HSA expressed as chlorpropham for ruminant and as chlorpropham alone for poultry. The potential inclusion of 3-chloro-

4-hydroxyaniline conjugates should be considered for monitoring pending analysis of releasable residues from bound residues in liver and eggs (data gap). For risk assessment, the residue definition was set considering the different toxicological properties of the major residues. For goat, (1) chlorpropham and 4-HSA expressed as chlorpropham and (2) 3-chloroaniline (provisional) were included for risk assessment, while for poultry, (1) chlorpropham and (2) 3-chloroaniline and 3-chloro-4-hydroxyaniline (free and conjugated) expressed as 3-chloroaniline (provisional) have to be considered. To finalise the residue definitions in livestock, data gaps regarding storage stability of 3-chloroaniline and 3-chloro-4-hydroxyaniline conjugates in animal matrices and further analysis of the bound residues in poultry commodities have to be fulfilled.

Considering the levels of chlorpropham and 3-chloroaniline in residue trials on potato, the livestock dietary burden is significant for both compounds. While behaviour of chlorpropham in livestock has been addressed by several studies, the metabolic pathway and the potential transfer of 3-chloroaniline and/or its degradation products in animal matrices has to be investigated (data gap).

Feeding studies are available with chlorpropham in ruminant and poultry; however, the level of residues of relevant analytes in different poultry and ruminant matrices was not consistently understood from the available studies (data gap). The reliability of the determined residue levels in animal commodities is therefore pending confirmation and is pertinent to finalisation of the residue definitions in livestock. In addition, further analysis of the bound residues in poultry liver and eggs in the new feeding study is requested to release 3-chloro-4-hydroxyaniline residues (data gap). The residues assessment in animal products can therefore not be concluded.

A study was assessed in the section on ecotoxicology with fish and there was no indication for bioaccumulation of significant residues in fish, and therefore further investigation of residues in fish is not required. Further, a case was made to waive investigation on residue levels in pollen and in bee products for human consumption with regard to the representative uses and a waiver was accepted.

As for a number of data gaps, a final consumer risk assessment cannot be performed; however, an indicative assessment was attempted by the RMS using the EFSA Pesticide Residues Intake Model (PRIMo) and the toxicological reference values agreed for chlorpropham and 3-chloroaniline. The highest chronic exposure to chlorpropham was calculated for Dutch children, representing 180% of the ADI of chlorpropham. The dietary exposure to 3-chloroaniline was resulting in 195% of the ADI for 3-chloroaniline. A refinement of the assessment using processing factors for potatoes does not appear to be currently possible as the reliability of these processing factors has not been demonstrated (data gap). Even if the application of processing factors may reduce intake estimates for chlorpropham, for 3-chloroaniline this is not expected to result in lower intakes given the processing data indicating formation of 3-chloroaniline. Moreover, no input value could be derived for 3-chloroaniline in onions and full consideration of residues of 3-chloroaniline and 3-chloro-4-hydroxyaniline in poultry matrices in the consumer intake calculation was not possible due to the identified data gaps.

In an acute risk assessment, significant exceedance of the ARfD was found for potatoes in both tentative assessments, for chlorpropham and for 3-chloroaniline (797% and 2360% ARfD, respectively). Even if the standard variability factor would be replaced by the lower variability factor of 3 proposed by the applicant but not agreed on during the peer review without the availability of further data (data gap), the ARfD will still be exceeded.

Data requirements identified during the MRL review were addressed in the dossier submission and the additional information was assessed, however in view of the peer review assessment outcome a review of the MRLs assessed under the Art. 12 MRL review procedure is recommended while raising the MRLs in potato and animal commodities, as requested in the submitted MRL application, is not proposed since the associated risk assessment is not supportive of the requested MRL of 10 mg/kg in potatoes.

4. Environmental fate and behaviour

Chlorpropham was discussed at the Pesticides Peer Review Meeting 152 in February 2017.

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, chlorpropham exhibited low to moderate persistence, forming the major (> 10% applied radioactivity (AR)) metabolite 3-chloroaniline (max. 19% AR), which exhibited moderate persistence. Mineralisation of the phenyl ring ^{14}C radiolabel to carbon dioxide accounted for 8–30% AR after 120 days. The formation of unextractable residues (not extracted by acidified acetonitrile followed by soxhlet extraction with acetonitrile/water) for this radiolabel accounted for 38–81% AR after 120 days.

In anaerobic soil incubations, chlorpropham degraded at a comparable rate to under aerobic conditions with 3-chloroaniline being formed in higher amounts (max. 34% AR). Chlorpropham was stable under the conditions of a laboratory soil photolysis study. Chlorpropham exhibited medium to low mobility in soil. 3-chloroaniline exhibited high to medium soil mobility.

In laboratory incubations in dark aerobic natural sediment water systems, chlorpropham exhibited moderate to medium persistence, forming an unidentified metabolite 'A' in sediment (max. 8.6% AR after 8 days, also being present at 7.3% after 6 days in 1 of the 4 systems investigated). Consequently, a data gap was identified for the identification of this metabolite and the calculation of sediment exposure estimates (see Section 7). The unextractable sediment fraction (not extracted by acetonitrile or acidified acetone/water) was a major sink for the phenyl ring ^{14}C radiolabel, accounting for 28–53% AR at 105–120 days). Mineralisation of this radiolabel accounted for 16–49% AR at study end (105–169 days). In a laboratory sterile aqueous photolysis experiment, chlorpropham was stable.

For the herbicide uses, the necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for both chlorpropham and the metabolite 3-chloroaniline, using the FOCUS (2001) step 1 and step 2 approach (version 1.1 of the Steps 1–2 in FOCUS calculator). For the active substance chlorpropham and 3-chloroaniline, appropriate steps 3 and 4 (FOCUS, 2001) calculations were available.[6] The step 4 calculations appropriately followed the FOCUS (2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 91–93% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% and erosion runoff of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. Volatilisation, short range transport and deposition were appropriately accounted for in the step 4 calculations in accordance with FOCUS (2008) air guidance using the EVA tool (version 3). The SWAN tool (version 3.0.0) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that while run-off mitigation is included in the step 4 calculations available, the FOCUS (2007) report acknowledges that for substances with K_{Foc} < 2,000 mL/g (i.e. chlorpropham), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds.

For the representative herbicides uses in glasshouses, the necessary surface water and sediment exposure assessments PEC for chlorpropham were appropriately carried out using the FOCUS (2001) steps 1 and 2 approach (version 1.1) of the steps 1–2 in FOCUS calculator), which was then modified by post-processing the spray drift input results (option 'no runoff' or 'drainage' was selected) to obtain a 0.1% emission of chlorpropham from glasshouses being re-deposited on adjacent surface water bodies. This approach has been accepted by Member State experts as an assumption that can be used in EU level surface water exposure assessments for glasshouse uses and is referred to in FOCUS (2008) guidance as being appropriate, except when applications are made with ultra low volume application techniques when 0.2% emission is prescribed.

For the representative uses as a plant growth regulator to suppress sprouting in potato stores, the necessary surface water and sediment exposure assessments were carried out for chlorpropham using 0.05% emission from the store being deposited to an adjacent surface water body in line with FOCUS (2008) air guidance. An assessment was also completed using the European Commission (2003b) technical guidance document on risk assessment and the model EUSES (version 2.1.2) to address the exposure route from the disposal of wash water in the potato processing industry when this passes through a sewage treatment or waste water treatment plant before being discharged into a surface water body.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (2009) scenarios and the models PEARL 4.4.4 and PELMO 5.5.4[6] for the active substance chlorpropham and its soil metabolite 3-chloroaniline. The potential for groundwater exposure from the representative uses by chlorpropham and 3-chloroaniline above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios.

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. 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).

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

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, 2013) and EFSA PPR Panel (2013). According to Commission Regulation (EU) No 283/2013[7], 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 Guidance Document (EFSA PPR Panel, 2013) was used for risk assessment in order to reach a conclusion for the representative uses.

For the indoor representative uses on potatoes during storage, the exposure to birds and mammals, bees, non-target arthropods and non-target terrestrial plants, is considered negligible and therefore no assessment was performed. This is also applicable to the representative uses on lettuce in permanent glasshouse.

For the representative outdoor uses on lettuce, onion and flower bulbs, based on the available data, low acute risk was concluded for **birds and mammals**. High long-term risk was identified to medium herbivorous/granivorous birds and to large herbivorous mammals for the representative use on lettuce.

Available refinements were discussed at the Peer Review Experts' meeting 154. The experts agreed to use refined residue per unit dose (RUD) values based on tailored residue trials (35) done on lettuce according to the GAP. Overall, low long-term risk was concluded on birds and mammals.

The risk to birds and mammals through consumption of contaminated water was low.

The risk via secondary poisoning was high at Tier 1. Suitable refinements (e.g. refined bioconcentration factor (BCF), PEC_{worms}) were proposed and a low risk was concluded.

Toxicity data were available with all the standard **aquatic** taxonomic groups for chlorpropham. For algae, however, only data on diatom were present (data gap). Two of the representative formulations were tested on fish, invertebrates and algae. No toxicity studies were available on Chlorpropham Fog; however, the formulated product only contains the active substances and therefore, the toxicity of the formulation can be predicted by using the data of the active substance.

Based on the available data, low risk to aquatic organisms was concluded for the representative use on lettuce in permanent greenhouse by using FOCUS (2008) air guidance for the exposure estimate (see Section 4). For the outdoor representative uses (lettuce, onion and flower bulbs), low risk was identified by using PEC_{sw} Steps 3 and 4 when mitigation measures up to 20 m no-spray buffer zone and 20 m vegetative buffer strip are applied. For the indoor representative uses on potato during storage, low risk to aquatic organisms was concluded for the non-recycled wastewater scenario (STP scenario) and recycled wastewater scenario (WWTP scenario) but high risk was identified for the venting scenario (data gap).

For the pertinent metabolite 3-chloroaniline, low risk to aquatic organisms was identified for all the relevant FOCUS exposure scenarios by using PEC_{sw} Steps 3 and 4 with the application of mitigation measures up to 20 m no-spray buffer zone and 20 m vegetative buffer strip with the exception of situations represented by the scenarios D6, R3 and R4 (data gap). Exposure of aquatic organisms to the pertinent metabolite following indoor application to potatoes is considered low. No data on sediment organisms were available to assess the risk to the unidentified metabolite 'A' (data gap).

Toxicity data on adult **honeybee** and larvae were only available with the active substance. The acute risk assessment was performed in accordance with European Commission (2002a). The Tier 1 risk assessment according to EFSA Guidance Document (EFSA, 2013) was performed by the applicant but could not be appropriately peer reviewed because it was not transparently reported in the RAR, i.e. only the outcome was reported (data gap). According to the available information, chronic Tier 1 risk to adult bees was identified when exposed to the treated crops. This is, however, only considered

[7] 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. OJ L 93, 3.4.2013, p. 1–84.

relevant for flower bulbs which flowers after the application, assuming lettuce and onions are not harvested for seed production.

High risk to honeybees (adult and larvae) was also identified from exposure to contaminated weeds. However, chlorpropham is a herbicide applied in pre-emergence and up to BBCH 14, therefore, the relevance of the exposure scenario 'flowering weeds' may be considered low, by also taking into account the persistence of the substance in soil. No assessment was available for effects on hypopharyngeal glands (HPG) (data gap). No assessment for accumulative effects and no risk assessment were available for contaminated water (surface water, guttation and puddle). No information was available regarding metabolites occurring in pollen and nectar (data gap).

No data were available for bumblebees and solitary bees.

For **non-target arthropods,** Tier 1 toxicity data for chlorpropham were not available. Therefore, the risk assessment could not be finalised due to the lack of toxicity data on the two standard species (data gap).

Low risk was concluded on **earthworms**, **soil macroorganisms** other than earthworms, **soil microorganisms**, **non-target terrestrial plants** and for **biological methods of sewage treatment**.

The potential for **endocrine disruption** of chlorpropham was discussed at the Peer Review experts' meeting 154. In light of the available data, showing (i) effects on thyroid in only one species at the highest tested dose (dog) and (ii) only slight effects regarding the androgen antagonism activity (rat) (see Section 2), the experts agreed that no further data are considered necessary.

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
Chlorpropham	Low to moderate persistence Single first-order DT_{50} 2.8–42.8 days (20°C pF 2.5 or 40% MWHC soil moisture)	Low risk to soil organisms
3-Chloroaniline	Moderate persistence Single first-order DT_{50} 11.5–33.6 days (20°C pF 2.5 soil moisture)	Low risk to soil organisms

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
Chlorpropham	Medium to low mobility K_{Foc} 260–774 mL/g	No	Yes	Yes
3-Chloroaniline	High to medium mobility K_{Foc} 101–356 mL/g	No	Assessment not triggered ADI of 0.007 mg/kg bw per day is below that of chlorpropham	Assessment not triggered

K_{Foc}: Freundlich organic carbon adsorption coefficient; ADI: acceptable daily intake; bw: body weight.
(a): At least one FOCUS scenario or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Chlorpropham	High risk for aquatic organisms for the venting scenario (potato)
3-Chloroaniline	High risk for aquatic organisms for 1 out of 7 (field lettuce) and 2 out of 7 (onions and flower bulbs)
Unidentified metabolite 'A' (sediment only)	Data gap

Table 4: Air

Compound (name and/or code)	Toxicology
Chlorpropham	Rat LC_{50} inhalation > 0.467 mg/L air/4 h (nose only)

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).

- Immunotoxicity potential of chlorpropham should be further addressed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Further scientific assessment of the potential endocrine disrupting properties of chlorpropham should be provided, on the basis of the current knowledge (OECD Conceptual Framework, as analysed in the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors, 2013) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- A validated exposure assessment for bystanders and residents during the uses of Chlorpropham Fog and Chlorpropham 300 EC should be provided (relevant for the representative uses of Chlorpropham Fog and Chlorpropham 300 EC; submission date proposed by the applicant: unknown; see Section 2).
- Further detailed data on toxicological relevance of one impurity should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Information on the position of the hydroxyl group on the hydroxychlorpropham metabolite U3 found in the lettuce metabolism study (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Storage stability data for 3-chloroaniline and conjugates of 3-chloro-4-hydroxyaniline in the relevant animal matrices, for chlorpropham storage stability data in eggs plus information demonstrating that the available data for ruminant muscle and liver cover the maximum length of storage of poultry muscle and liver samples in the feeding study, otherwise chlorpropham storage stability to validate the results in poultry muscle and liver in the feeding study are required (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Further analysis of the bound residues – including an enzymatic hydrolysis step – to release 3-chloro-4-hydroxyaniline residues in poultry liver and eggs from the feeding studies (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Information on the metabolic pathway of 3-chloroaniline and the potential transfer of 3-chloroaniline and/or its degradation products in animal matrices (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Unit-to-unit variability information on the commercial scale bulk and box stored potatoes to confirm the proposed variability factor of three (relevant for the representative uses in potato; submission date proposed by the applicant: unknown; see Section 3).
- Sufficient acceptable residue trials on potato analysing for chlorpropham, 3-chloroaniline (free and conjugated) and 4-OH-chlorpropham (free and conjugated) using a sampling strategy/design that permits the establishment of a parent/metabolites ratio, with immediate analysis after sampling (relevant for the representative uses in potato; submission date proposed by the applicant: unknown; see Section 3).
- A complete residue data package on onions in accordance with the agreed residue definitions, with immediate analysis after sampling (relevant for the representative uses in onions; submission date proposed by the applicant: unknown; see Section 3).
- A complete residue data package on lettuce in accordance with the agreed residue definitions, with immediate analysis after sampling (relevant for the representative uses in lettuce; submission date proposed by the applicant: unknown; see Section 3).
- The behaviour of 3-CA and 4-OH-chlorpropham under hydrolysis conditions representative of processing (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- An additional processing trial on potato and involving higher temperatures (> 120°C) analysing residues in accordance with the residue definition in processed commodities and taking into

account potential new information in studies with investigating the nature of the residues upon processing for the metabolites (relevant for the representative uses in potato; submission date proposed by the applicant: unknown; see Section 3).

- The reliability of the derived processing factors for potatoes should be addressed in view of the additional processing studies requested on the nature and magnitude of residues and in view of the unknown length of storage of the residue samples from the available processing residue trials (relevant for the representative uses in potato; submission date proposed by the applicant: unknown; see Section 3).
- Investigation of residues in rotational crops is required or further justification for a waiver of rotational crop data, respectively (relevant for uses in onion and lettuce; submission date proposed by the applicant: unknown; see Section 3).
- An assessment of the effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking water is not available. In the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. If an argumentation is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in surface water as well as the active substance (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Metabolite 'A' in sediment at > 5% AR at two time points in the sediment water study De Vette & Hanstveit (1999) has not been identified and reaches levels that trigger an exposure and risk assessment, but such an assessment is not available (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 4 and 5).
- Further toxicity data with chlorpropham on green algae (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to refine the risk to aquatic organisms exposed to 3-chloroaniline in situations represented by the FOCUS exposure scenarios R3 and D6, R4 (relevant for the representative uses on lettuce (field) and onions and flower bulbs, respectively; submission date proposed by the applicant: unknown; see Section 5).
- Further information to refine the risk to aquatic organisms exposed to chlorpropham in situations represented by venting exposure scenarios (relevant the representative uses on potato; submission date proposed by the applicant: unknown; see Section 5).
- A detailed and transparent risk assessment according to EFSA (2013) was not reported in the RAR and should be presented for (i) chronic data with adult honeybees, (ii) data on larvae and brood, (iii) all relevant exposure routes and metabolites occurring in pollen and nectar (relevant for all the representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further toxicity data with chlorpropham on non-target arthropods (relevant for the outdoor representative uses evaluated (lettuce, onion and flower bulbs); 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

- Gloves and coverall are needed for transportation of store potatoes (8 h) by the worker with Chlorpropham 300 EC (section 2).
- For Chlorpropham 400 EC, for the field use on low crops, the use of PPE is needed in the German model to obtain exposure estimates below the AOEL. For the greenhouse use, the Southern Greenhouse model provides exposure estimates below the AOEL with the use of PPE.
- Measures equivalent to 20 m no-spray buffer and 20 m vegetative buffer strip are needed for mitigating the risk to aquatic organisms when exposed to chlorpropham and 3-chloroaniline for the outdoor representative uses evaluated (lettuce, onion and flower bulbs) (see Section 5).

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[8] 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) Further scientific assessment of the potential endocrine disrupting properties of chlorpropham should be provided, on the basis of the current knowledge (OECD Conceptual Framework, as analysed in the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors, 2013) (see Section 2).
2) The bystander and resident exposure assessment during the representative uses of Chlorpropham Fog and Chlorpropham 300 EC could not be finalised, on the basis of a non GLP study for which individual results were not reported and units of the measured values could not be confirmed (see Section 2).
3) The consumer risk assessment from the consumption of water could not be finalised, while satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (see Section 4).
4) The risk to non-target arthropods for the field uses (lettuce, onion and flower bulbs) could not be finalised due to the lack of toxicity data on one of the two standard species (see Section 5).
5) A final consumer risk assessment cannot be performed due to a number of data gaps identified for the food crop uses. The indicative lower tier level assessment is resulting in an exceedance of the toxicological reference values triggered by the exposure from potato consumption, is surrounded by uncertainties (see Section 3).

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 a higher tier level could not be finalised due to lack of information, and if the assessment performed at a 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.

6) In an indicative risk assessment, the highest chronic exposure to chlorpropham residues was calculated for Dutch children, representing 180% of the ADI of chlorpropham. The dietary exposure to 3-chloroaniline was resulting in 195% of the ADI for 3-chloroaniline. A

[8] 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.

refinement of the assessment using processing factors for potatoes does not appear to be currently possible as the reliability of these processing factors has not been demonstrated. Even if the application of processing factors may reduce intake estimates for chlorpropham this is not expected to result in lower intakes for 3-chloroaniline given the processing data indicating formation of 3-chloroaniline from chlorpropham. Moreover, no input value could be derived for 3-chloroaniline in onions and full consideration of residues of 3-chloroaniline and 3-chloro-4-hydroxyaniline in poultry matrices in the consumer intake calculation has not yet been possible due to identified data gaps (see Section 3). In addition, an exceedance of the ARfD was identified for potatoes for chlorpropham and for 3-chloroaniline in individual assessments (797% and 2360% of the ARfD, respectively). Even if the standard variability factor would be replaced by the lower variability factor of 3 proposed by the applicant but not agreed on during the peer review, the ARfD will still be exceeded for potato.

9.3. Overview of the concerns identified for each representative use considered (Table 5)

Table 5: Overview of concerns

Representative use		Lettuce (field)	Lettuce (greenhouse)	Onion (field)	Flower bulbs (field)	Ware and starch potato (in-store)
Operator risk	Risk identified					X (only for Chlorpropham 300 EC)
	Assessment not finalised					
Worker risk	Risk identified					
	Assessment not finalised					
Resident/ bystander risk	Risk identified					
	Assessment not finalised					X[2]
Consumer risk	Risk identified	X[6]	X[6]	X[6]		X[6]
	Assessment not finalised	X[3,5]	X[3,5]	X[3,5]	X[3]	X[3,5]
Risk to wild non-target terrestrial vertebrates	Risk identified					
	Assessment not finalised					
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified					
	Assessment not finalised	X[4]		X[4]	X[4]	
Risk to aquatic organisms	Risk identified	X		X	X	X
	Assessment not finalised					
Groundwater exposure to active substance	Legal parametric value breached					
	Assessment not finalised					
Groundwater exposure to metabolites	Legal parametric value breached					
	Parametric value of 10 µg/L 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.

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Abbreviations

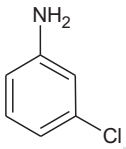
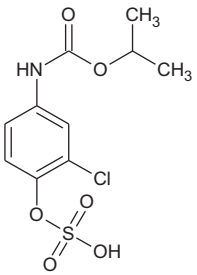
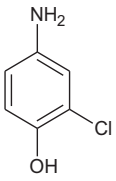
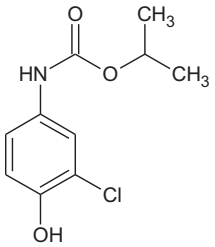
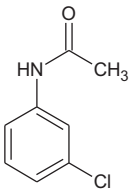
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
CLP	classification, labelling and packaging
DAR	draft assessment report
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
EC	emulsifiable concentrate
ECHA	European Chemicals Agency
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
HPG	hypopharyngeal glands
HPLC–MS/MS	high–performance liquid chromatography with tandem mass spectrometry
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
LABC	levator ani-bulbocavernosus
LC_{50}	lethal concentration, median
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MRL	maximum residue level
MS	Member State
MWHC	maximum water-holding capacity
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration

PEC_{sw}	predicted environmental concentration in surface water
PPE	personal protective equipment
PRIMo	(EFSA) Pesticide Residues Intake Model
PXR	pregnane X receptor
QSAR	quantitative structure–activity relationship
QuEChERS	Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)
RAR	Renewal Assessment Report
RMS	rapporteur Member State
RUD	residue per unit dose
SMILES	simplified molecular-input line-entry system
STP	sewage treatment plant
TRR	total radioactive residue
UF	uncertainty factor
VF	variability factor
WHO	World Health Organization
WWTP	wastewater treatment plant

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.2017.4903

Appendix B – Used compound codes

Code/trivial name	Chemical name/SMILES notation	Structural formula
3-chloroaniline	3-chloroaniline Nc1cc(Cl)ccc1	
4-HAS **or** **4′-hydroxychlorpropham-*O*-sulfonic acid**	Isopropyl [3-chloro-4-(sulfooxy)phenyl]carbamate Clc1cc(ccc1OS(=O)(=O)O)NC(=O)OC(C)C	
3-chloro-4-hydroxyaniline	4-amino-2-chlorophenol Nc1cc(Cl)c(O)cc1	
4-OH-chlorpropham **or** **4′-hydroxychlorpropham**	Isopropyl (3-chloro-4-hydroxyphenyl)carbamate Oc1ccc(NC(=O)OC(C)C)cc1Cl	
3-chloroacetanilide	*N*-(3-chlorophenyl)acetamide Clc1cc(NC(C)=O)ccc1	

SMILES: simplified molecular-input line-entry system.